Allyl- and Benzylindium Reagents. Carboindation of Carbon−Carbon and Carbon−Nitrogen Triple Bonds

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The reaction of unactivated simple terminal alkynes **1** with allylindiums in THF proceeded smoothly to give the corresponding allylation products **2** in good to high yields. This result is in marked contrast to that of the reaction carried out in DMF, where the allylation of unactivated alkynes was very sluggish. The allylic group of the reagent was attached to the internal carbon of the triple bond, and indium was attached to the less substituted terminal carbon, except for the case of TMS substituted acetylenes **1j** and **1k** in which the allyl group went to the less substituted carbon of the triple bond. The reaction of unactivated simple terminal and certain internal acetylenes with benzylindium in THF proceeded smoothly to afford the corresponding benzylation products **18** in good to high yields. The benzyl group was attached to the less substituted unhindered carbon of the triple bond, and indium was attached to the more sterically congested carbon. The reaction of activated nitriles **3** with allylindiums in THF at 70 °C gave the corresponding allylation−enamination products **4** in high to excellent yields. This reaction provides a useful method for the synthesis of highly functionalized enamines, which are not easily available via conventional methods. The mechanisms on the above three indation reactions are discussed.

Introduction

Since the first carbometalation discovered by Ziegler and Bähr in 1927,[1] a number of additions of organometallics to the *carbon−carbon triple bond* (−C≡C−) have been reported.[2] Although the carbometalation of activated alkynes, such as alkynyl ketones (Michael acceptor) and alkynols (functional group substituted alkynes), and/or the intramolecular carbometalation proceed smoothly with various allylmetals,[2] the carbometalation of simple unactivated alkynes **1** is not so easy and only a limited number of allylmetals are available for this purpose.[3] More recently, Araki and co-workers reported that the reaction of allylindium[4] with terminal alkynols[5a] and allenols[5b] *in DMF* at 100−140 °C gave the corresponding allylation products in good to high yields. However, the presence of a hydroxy group was essential for facilitating the addition and the allylation of simple unactivated alkynes was sluggish even at higher temperatures (150−180 °C), giving the allylation products in low yields (12−28%).[5a] In the meantime, it is well-known that the reaction of nitriles (*carbon−nitrogen triple bond*, R−C≡N) with organometallics (R′−ML_n, M = Li, Mg, Zn, and others) including allylic compounds gives the corresponding metalated imines R(R′)C═NM, which produces ketones R(R′)C═O after hydrolysis.[6]

We previously reported that allylindium reagents react with simple unactivated alkynes **1** very readily *in THF*[7] to give the corresponding allylation product **2** in good to high yields (eq 1)[8] and that those allylindium reagents also react with certain activated nitriles **3** to afford in good to high yields the allylation−enamination products **4** that are not easily available via the reaction of conventional allylating reagents with nitriles (eq 2).[9] Herein, we describe in detail the reaction of carbon−carbon and carbon−nitrogen triple bonds with allyl- and benzylindium reagents.

Results and Discussion

Allylation of Unactivated and/or Functionalized Alkynes with Allylindiums. Allylindium reagents were

(1) Ziegler, K.; Bähr, K. *Chem. Ber.* **1928**, *61*, 253.

(2) For reviews, see: (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841 (organo-Li, Mg, Zn, B, Al, and Cu compounds). (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38 (stoichiometric organo-Li, Mg, Zn and catalytic Ni, Pd, Pt compounds). (c) Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333 (organo-Al/Ti and Al/Zr system). (d) Knochel, P. *Comprehensive Organometallic Chemistry II*; Able, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 11, p 159 (organo-Li, Mg, Zn, B, Al, Cu, Hg/Pd, Ni, Mn compounds). (e) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 865. (f) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207 (organo-Li, Mg, Zn, B, Al compounds).

(3) (a) Takai, K.; Yamada, M.; Odaka, H.; Utimoto, K.; Fujii, T.; Furukawa, I. *Chem. Lett.* **1995**, 315 (allyl-Ta). (b) Takahashi, T.; Kotora, M.; Kasai, K.; Suzuki, N. *Tetrahedron Lett.* **1994**, *35*, 5685 (allyl-Zr). (c) Chatani, N.; Amishiro, N.; Morii, T.; Yamashita, T.; Murai, S. *J. Org. Chem.* **1995**, *60*, 1834 (allyl-Zn). (d) Molander, G. A. *J. Org. Chem.* **1983**, *48*, 5409 (allyl-Zn). (e) Miller, J. A.; Negishi, E. *Tetrahedron Lett.* **1984**, *25*, 5863 (allyl-Al). (f) Negishi, E.; Miller, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 6761 (allyl-Zn). (g) Eisch, J. J.; Boleslawski, M. P. *J. Organomet. Chem.* **1987**, *334*, C1 (allyl-Ti). (h) Yeon, S. H.; Han, J. S.; Hong, E.; Do, Y.; Jung, I. N. *J. Organomet. Chem.* **1995**, *499*, 159 (Lewis acid-catalyzed allyl-Si). (i) Asao, N.; Matsukawa, Y.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 1513 (Lewis acid-catalyzed allyl-Sn). (j) Asao, N.; Yoshikawa, E.; Yamamoto, Y. *J. Org. Chem.* **1996**, 4874 (Lewis acid-catalyzed allyl-Si).

(4) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831.

(5) (a) Araki, S.; Imai, A.; Shimizu, K.; Yamada, M.; Mori, A.; Butsugan, Y. *J. Org. Chem.* **1995**, *60*, 1841. (b) Araki, S.; Usui, H.; Kato, M.; Butsugan, Y. *J. Am. Chem. Soc.* **1996**, *118*, 4699.

(6) Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1.

(7) The allylindium reagent was prepared originally in DMF (ref 4). Since then, the allylindation reactions of acetylenes have been carried out in this solvent. Now, it is clear that the reagent can be prepared in THF, and this finding expands the scope of this reagent to the carboindation. The reactions of α- and/or *β*-oxy aldehydes with allylindiums in H_2O and aqueous/dry THF have been studied: (a) Paquette, L. A.; Mitzel, T. M. *Tetrahedron Lett.* **1995**, *36*, 6863. (b) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931. (c) Paquette, L. A.; Mitzel, T. M. *J. Org. Chem.* **1996**, *61*, 8799.

(8) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2318. See also: Ranu, B. C.; Majee, A. *J. Chem. Soc., Chem. Commun.* **1997**, 1225.

(9) Fujiwara, N.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 4729.

10.1021/jo990160x CCC: $18.00
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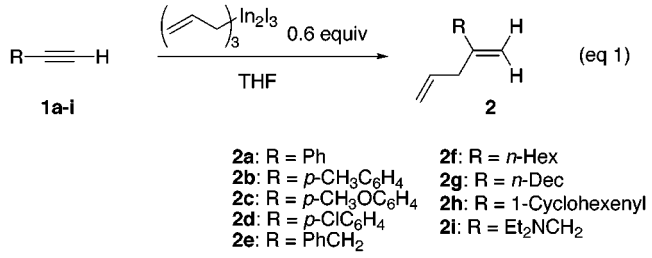
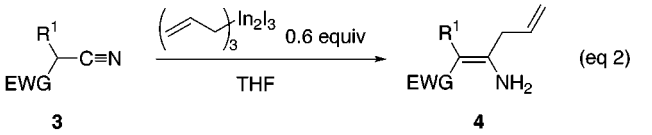
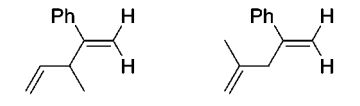
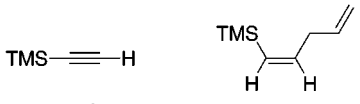




prepared by mixing In powder (1.2 equiv) with allyl iodide (1.8 equiv) or crotyl- and methallyl bromides (1.8 equiv) in *dry THF* at room temperature for 1 h. The results on the reaction of the allylindiums with various acetylenes are summarized in Table 1. The reaction of phenylacetylene **1a** with 0.6 equiv of allylindium,[10] generated in situ, gave the allylation product **2a** regioselectively in 94% yield (entry 1). The reactions of various para-substituted aryl alkynes **1b**, **1c**, and **1d** and of benzylacetylene **1e** proceeded smoothly to give **2b**−**e**, respectively, in high to good yields (entries 2−5). The reactions shown in entries 1−5 were complete within 2 h at 70 °C. The reactions of 1-octyne **1f** and 1-dodecyne **1g** gave **2f** and **2g**, respectively, in good yields (entries 6 and 7). The allylation of the enyne **1h** also proceeded smoothly to give the corresponding allylation product **2h** in excellent yield (entry 8). The allylations in entries 6−8 were complete within 1 h at 70 °C. The amino-substituted alkyne **1i**, which was inert to the Lewis acid-catalyzed allylsilylation[3j] due to the coordination of Lewis acid to the nitrogen atom,[11] reacted with allylindium at 70 °C for 2 h, giving the corresponding allylation product **2i** in 75% yield (entry 9). It should be noted that the regioselectivity of the allylation of **1i** is opposite to that of propargyl alcohol and related hydroxy-substituted alkynes;[5a] chelation-promoted allylation[5] is not involved in the allylation of **1i**. In addition, the reaction of **1a** with crotylindium, prepared from In powder (1.2 equiv) and crotyl bromide (1.8 equiv) in THF, gave the γ-adduct **5** in 88% yield (entry 10); the straight-chain α-adduct was not detected. The reaction of **1a** with methallylindium, generated in situ from In powder (1.2 equiv) and metallyl bromide (1.8 equiv) in THF, gave **6** in 90% yield (entry 11).





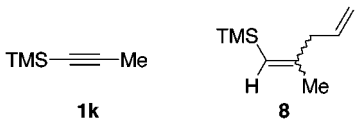
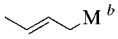
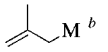


Table 1. Allylation of Simple Terminal Alkynes 1 with Allyl-, Crotyl-, and Methallylindiums

entry	alkynes 1	alkynes R	allyl-M	product	yield[a] (%)
1	**1a**	Ph		**2a**	94
2	**1b**	*p*-$CH_3C_6H_4$		**2b**	81
3	**1c**	*p*-$CH_3OC_6H_4$		**2c**	66
4	**1d**	*p*-ClC_6H_4		**2d**	85
5	**1e**	$PhCH_2$		**2e**	72
6	**1f**	*n*-Hex		**2f**	60
7	**1g**	*n*-Dec		**2g**	70
8	**1h**			**2h**	93
9	**1i**	Et_2NCH_2		**2i**	75
10	**1a**	Ph	 [b]	**5**	88
11	**1a**	Ph	 [b]	**6**	90

[a] Isolated yield. [b] Bromides were used as starting materials instead of iodide for the preparation of allylindium reagents.

Interestingly, the use of silyl-substituted alkynes brought a regioselectivity different from the cases shown above. The allylation of trimethylsilylacetylene **1j** occurred on the terminal carbon,[12] giving the (*Z*)-allylation product **7** stereoselectively in 75% yield. The reaction of silyl-substituted internal alkyne, 1-trimethylsilyl-1-propyne **1k**, gave a mixture of trans- and cis-allylation products **8** in 50% yield. In the case of the silyl-substitued alkynes **1j** and **1k**, an exceptionally longer reaction time (~36 h) was necessary to complete the allylation reaction, compared to the ordinary terminal acetylenes **1a**−**1i**. The usual internal alkynes, such as 1-phenyl-1-propyne and 4-octyne, did not react at all with allylindium reagents.

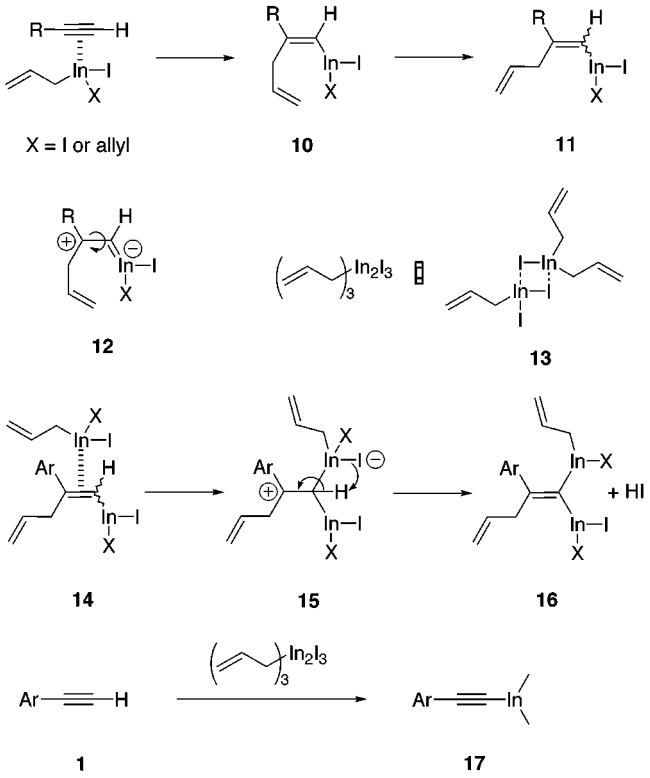
To help clarify the mechanism of the allylindation, the reaction of **1a** (1 equiv) with allylindium reagent (0.6 equiv) was quenched with DCl (20 wt % solution in D_2O), giving the d_1-allylation product **2a**-d_1 (95% D content) in 85% yield: the ratio of *E* to *Z* was 32:68 (eq 3). As mentioned above, concerning the stoichiometry of the allylindation, 0.5 equiv of $(allyl)_3In_2I_3$ corresponds to 1 equiv of acetylenes. The reaction of **1j** with 0.6 equiv of allylindium reagent was quenched similarly, affording **7**-d_1 (89% D content) in 82% yield: only *Z* isomer was obtained (eq 4). These two results clearly indicate that

(10) Two allyl (or $PhCH_2$) groups of the indium reagents $(allyl)_3In_2I_3$ [or $(PhCH_2)_3In_2I_3$] are used for the allylation (or benzylation) reaction, and the third allyl (or $PhCH_2$) group acts as a ligand of the In complex (ref 4). Accordingly, if the addition of the indium reagents to acetylenes proceeds in quantitative yield, 0.5 equiv of the reagents are needed for 1 equiv of acetylenes. Normally, we used 0.6 equiv of the reagents toward 1 equiv of acetylenes.

(11) Yamamoto, Y.; Yoshikawa, E. Unpublished result.

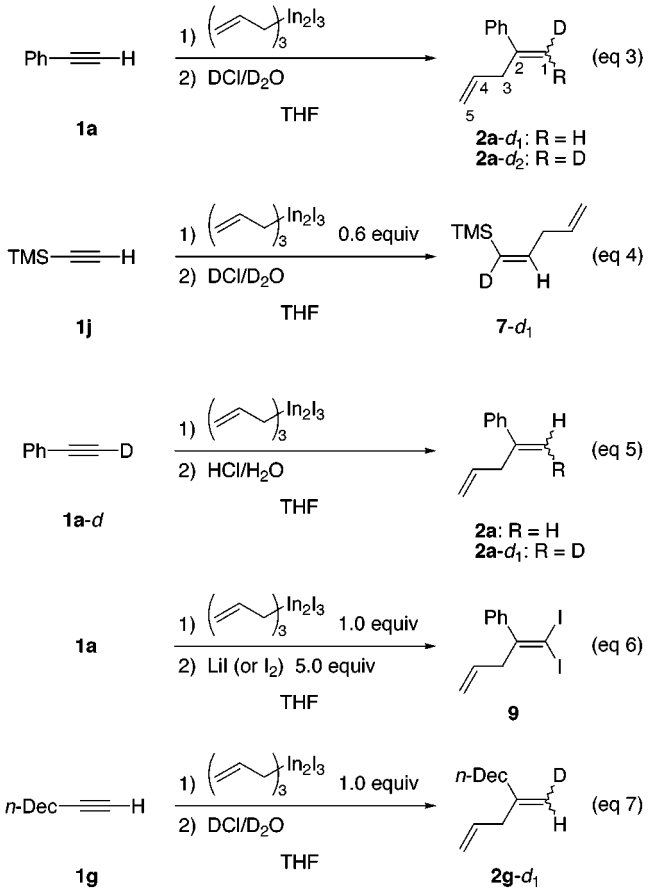
(12) The allylation of TMS-substituted alkynes with allylzinc bromide gives the same regioselectivity as the present allylindation (ref 3d).

Scheme 1



two of the three allyl groups of the reagent $(allyl)_3In_2I_3$ were transferred to the triple bond and indium metal was bonded to the vinyl carbon to which deuterium was attached. However, the observation became complicated was made when an excess amount (1 equiv) of allylindium reagent was used.

The reaction of **1a** with 1 equiv of allylindium was quenched with DCl (20 wt % solution in D_2O), giving the d_2-allylation product **2a**-d_2 (>95% D content) in which two deuteriums were incorporated at the C-1 position (eq 3). The reaction of phenylacetylene-*d* **1a**-*d* with 1 equiv of allylindium followed by the usual workup using HCl/H_2O afforded **2a**, in which no deuterium was incorporated, in 91% yield (eq 5). However, as mentioned above, the use of 0.6 equiv of allylindium toward **1a**-*d* gave **2a**-d_1 in 85% yield (eq 5). Furthermore, the allylation of **1a** with 1.0 equiv of allylindium followed by treatment with LiI or I_2 (5.0 equiv) at room temperature gave the diiodinated product **9** in 65−74% yield (eq 6). These results indicate that the allylation of **1a** with excess amounts of allylindium gave the geminal diindation product,[13] which produced **2a**-d_2 upon deuteriolysis or produced diiodinated **9** upon treatment with I_2. The deuterium loss in the case of **1a**-*d* (eq 5) also indicates that the C−D bond was cleaved in a certain stage of the allylindation with excess amounts of the indium reagent, but not cleaved with 0.6 equiv amount of the reagent (eq 5). The acetylenic hydrogen of aromatic acetylenes is more acidic than that of aliphatic acetylenes. We examined the deuteriolysis of the products from allylindation of **1g**. The reaction of **1g** with 1.0 equiv of allylindium followed by treatment with D_2O/DCl gave the monodeuterated product **2g**-d_1 (93% D content) in 81% yield; the ratio of *E* to *Z* was 49:51 (eq 7). Accordingly, it is clear that the formation of the dideuterated product takes place only in the case of **1a**. Actually, rather acidic aromatic acetylenes **1b** and **1d** behaved similarly, but no dideuteration occurred in the case of other aliphatic acetylenes such as **1e** and **1f**.



When 0.6 equiv of allylindium (which is approximately stoichiometric amount toward 1 equiv of an acetylene) was used, the allylindation would occur as shown in Scheme 1; the coordination of Lewis acidic indium to an electron-rich triple bond followed by allylindation would give the vinylindium **10**, which would undergo *E*−*Z* isomerization under the reaction conditions to give an *E*/*Z* mixture of **11**; the isomerization would occur via the intermediate **12**. Since the structure of the allylindium reagent is assumed to be a sesquidimeric **13**,[4] X in **10**−**12** is either I or allyl. In the case of aromatic acetylenes, the vinylindium intermediate would coordinate to the indium metal of the reagent once more (**14**), producing the diindated compound **16** through a cationic intermediate **15**. Perhaps the cation stabilization of aliphatic derivatives is weaker in comparison with that of aromatic cases (**15**), and therefore, no double indation takes place in the case of aliphatic acetylenes although the further coordination of allylindium reagent to aliphatic vinylindium may take place. Actually, the dideuteration took place in the reaction of **1h** with 1.0 equiv of allylindium; an allylic cation is involved in the intermediate derived from the reaction of **1h**, and thus, the cation intermediate would be stabilized. When 2,4-hexadiene (5 equiv) was added, to detect HI, at the beginning of the reaction of **1a** with 1 equiv of the allylindium, 2-iodo-3-hexene was

(13) A double-zincation intermediate was proposed in the allylzincation of terminal alkynes: Frangin, Y.; Gaudemar, M. *J. Organomet. Chem.* **1977**, *142*, 9. See also: Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 883.

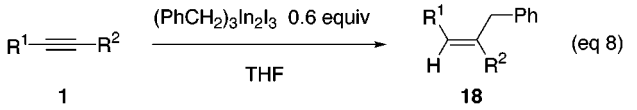
Table 2. Benzylation of Simple Alkynes with Benzylindiums

entry	alkynes			product	yield[a] (%)
	1	R^1	R^2		
1	**1a**	Ph	H	**18a**	91
2	**1b**	*p*-$CH_3C_6H_4$	H	**18b**	83
3	**1h**		H	**18c**	89
4	**1l**	Ph	CH_3	**18d** (15:85)[b]	64 (30)
5	**1g**	*n*-Dec	H	**18e** (34:66)[b]	48 (39)
6	**1m**	*n*-1-Hexynyl	*n*-Bu	**18f** (37:63)[b]	61 (15)
7	**1j**	$(CH_3)_3Si$	H	**18g** (37:63)[b]	57 (22)

[a] Isolated yield. Yields in parentheses are the recovery yields of **1**. [b] Benzylation products are given as mixtures of *E*/*Z* isomers, and the ratio of *E*/*Z* isomers are given in parentheses.

obtained, strongly supporting the reaction course shown in Scheme 1. One may think that an acidic acetylenic hydrogen reacts with allylindium reagent prior to the allylindation to liberate either HI or 1-propene and to produce the acetylenic indium reagent **17**, which undergoes the allylindation in the presence of excess allylindium reagent. If this mechanism is involved for the reaction of aromatic acetylenes, the reaction of **1a** with 0.6 equiv of allylindium reagent followed by quenching with D_2O should produce the dideuterated allylation product **2a**-d_2 (see eq 3): only monodeuterated **2a**-d_1 was obtained. Therefore, the mechanism through acetylenic indium intermediate **17** is not operative.

Benzylation of Simple Alkynes with Benzylindium. We investigated the addition of other organoindium reagents, such as benzyl-, propargyl-, methyl-, and ethylindium reagents, to alkynes. However, among these reagents only benzylindium underwent the addition to alkynes. Benzylindium sesquiiodide [$(PhCH_2)_3In_2I_3$] was prepared in situ by mixing In powder (1.2 equiv) with benzyl iodide (1.8 equiv) in THF at room temperature. Simple terminal and *internal* alkynes **1** readily reacted with benzylindium to give the corresponding benzylation products **18** in good to high yields (eq 8). This is the first example of the direct carbometalation of organometallics to *both simple terminal and internal* alkynes.[3] Allylindiums did not react with the ordinary internal alkynes (see above), but benzylindium reacts with them.

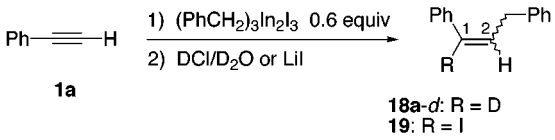


(eq 8)

18a: R^1 = Ph, R^2 = H
18b: R^1 = *p*-$CH_3C_6H_4$, R^2 = H
18c: R^1 = 1-Cyclohexenyl, R^2 = H
18d: R^1 = Ph, R^2 = CH_3
18e: R^1 = *n*-Dec, R^2 = H
18f: R^1 = *n*-1-Hexynyl, R^2 = *n*-Bu
18g: R^1 = $(CH_3)_3Si$, R^2 = H

The results are summarized in Table 2. The reaction of phenylacetylene **1a** (1.0 equiv) with 0.6 equiv of

Scheme 2



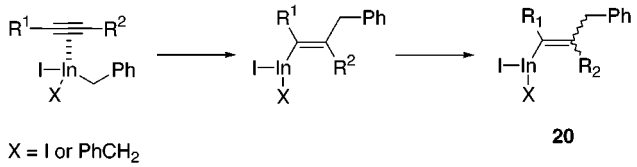
benzylindium,[10] generated in situ by mixing In powder (1.2 equiv) with benzyl iodide (1.8 equiv) in THF, gave the benzylation product **18a** regio- and *Z*-stereoselectively[14] in 91% yield (entry 1). The reactions of *p*-tolylacetylene **1b** and the enyne **1h** proceeded smoothly to give **18b** and **18c**, respectively, in high yields (entries 2 and 3). The *Z* configurations of **18a**−**c** were determined by the coupling constants between the vinylic protons (J_{HandR^2} = 11.0−11.5 Hz). The benzylation of the internal alkyne **1l** proceeded significantly slowly, compared to the reaction of terminal alkynes, to give the corresponding benzylation product **18d** regio- and *Z*-stereoselectively in 64% yield along with small amounts of the recovered **1l** (entry 4). No regio- and stereoisomers were detected by the ^1H NMR and GC−MS analysis of the crude reaction mixture. The *Z*-configuration of **18d** was confirmed by a 400 MHz NOE experiment where signal enhancement (6.0%) of the vinylic proton was observed when the methyl protons were irradiated. The reactions shown in entries 1−4 were carried out at 100 °C in sealed reaction vials for 2−3 days, and the reaction progress was monitored by TLC analysis of the reaction mixture.

In addition, we also tried the reaction with some aliphatic and silyl-substituted alkynes. The benzylation of 1-dodecyne **1g** gave the corresponding benzylation product **18e** in 48% along with the recovered **1g** (39%) (entry 5). The reaction of dodeca-5,7-diyne **1m**, where there are two possible sites of alkynyl moieties, gave only monobenzylation product **18f** exclusively, and no dibenzylation product was obtained (entry 6). The reaction of trimethylsilylacetylene **1j** gave the benzylation product **18g** (entry 7). Since the reactions shown in entries 5−7 were rather sluggish, longer reaction times (4−6 d) were needed to consume the benzylindium reagent and even at the stage when the reagent was consumed completely significant amounts of the starting acetylenes remained unreacted. Another point different from the case of aromatic and conjugated acetylenes, the products **18e**−**g** were obtained as a mixture of *E*,*Z*-isomers (entries 5−7).

To help clarify the mechanism of the benzylindation, the reaction of **1a** with 0.6 equiv of benzylindium was quenched with DCl (20 wt % solution in D_2O), giving the *d*-benzylation product **18a**-*d* (91% D content) in which a deuterium was incorporated at the C-1 position (Scheme 2); in this case, no dideuteration occurred when even 1 equiv of benzylindium was used. Furthermore, the benzylation of **1a** with 0.6 equiv of the reagent, followed by treatment with excess lithium iodide, gave the benzylation−iodination product **19** in 80% yield as a mixture of *E*,*Z* stereoisomers (*E*/*Z* = 57:43). These results clearly indicate that the benzylation of simple alkynes **1** gives the vinyl indium intermediate **20** via the benzylindation of alkynes (Scheme 3). In the case of aromatic and conjugated alkynes, the benzylindium proceeds in a

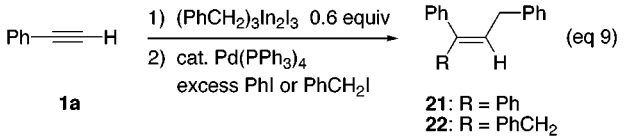
(14) The stereoselectivity of the addition of aluminum hydride to alkynes was precisely studied. According to the study, the trans-carbometalation product is favored thermodynamically under high-temperature reaction conditions: Eisch, J. J.; Rhee, S.-G. *J. Am. Chem. Soc.* **1975**, *97*, 4673. See also ref 2d, p 280.

Scheme 3



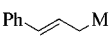
trans-addition manner, while that of aliphatic alkynes proceeds in a nonstereoselective fashion. Also, the treatment with LiI of the vinylindium intermediate derived from **1a** gave a trans and cis mixture of **19**. Perhaps the isomerization would take place in the presence of LiI.

It occurred to us that **20** would undergo the palladium-catalyzed cross coupling with organic halides.[15] If this is the case, a "one-shot" three-component coupling reaction between phenylacetylene **1a**, benzylindium, and iodobenzene would become possible. Actually, the three component coupling reaction took place in the presence of 10 mol % of $Pd(PPh_3)_4$, giving **21** in low yield (eq 9).[16] The reaction of **1a** with 0.6 equiv of $(PhCH_2)In_2I_3$ followed by the addition of 2.0 equiv of benzyl iodide and 10 mol % of $Pd(PPh_3)_4$ gave the three-component coupling product **22** in 49% yield (eq 9).[17,18]



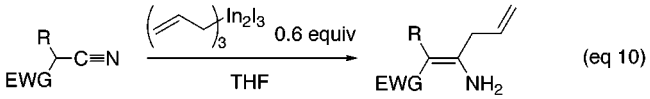
A New Enamine Synthesis: Allylation−Enamination Reaction of Nitriles with Allylindiums. Allylindium reagents were prepared as described above. The results on the reaction of the allylindiums with various activated nitriles are summarized in Table 3.[19] The reaction of methyl cyanoacetate **3a** with 0.6 equiv of allylindium[10] gave the allylation−enamination product **4a** regio- and (*Z*)-stereoselectively in essentially quantitative yield (entry 1). The *Z* configuration was confirmed by a 400 MHz NOE experiment where signal enhancement (6.1%) of the olefinic proton next to the ester group was observed when the methylene protons of the allyl group were irradiated. The reactions of malononitrile **3b** and cyanoacetylpiperidine **3c** proceeded smoothly to give **4b** and **4c**, respectively, in high to good yields (entries 2 and 3). The reaction of ethyl phenylcyanoacetate **3d**, which has a bulky phenyl group at the position α to the cyano group, also proceeded smoothly to give the corresponding enamine product **4d** in good yield (entry 4). The

Table 3. Allylation−Enamination Reaction of Nitriles with Allylindiums

entry	nitriles 3	R	EWG	allyl-M	product	yield[a] (%)
1	**3a**	H	CO_2CH_3		**4a**	100
2	**3b**	H	CN		**4b**	77
3	**3c**	H			**4c**	55
4	**3d**	Ph	$CO_2C_2H_5$		**4d**	65
5	**3a**	H	CO_2CH_3		**23**	93
6	**3a**	H	CO_2CH_3		**24**	90
7	**3a**	H	CO_2CH_3		**25**	64
8	**3a**	H	CO_2CH_3		**26**	75

[a] Isolated yield. [b] Bromides were used as starting materials instead of iodide for the preparation of allylindium reagents.

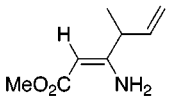
reactions shown in entries 1−4 were completed within 2 h at 70 °C. The reaction of **3a** with crotylindium, prepared from In powder and crotyl bromide in THF, gave the γ-adduct **23** in 93% yield (entry 5); the regioisomeric α-adduct was not detected. The reactions of **3a** with methallyl-, prenyl-, and cinnamylindium gave **24**−**26**, respectively, in high to good yields (entries 6−8). Here also, the branched γ-adducts **25** and **26** were obtained exclusively in the reactions of prenyl- and cinnamylindiums, respectively. The reactions shown in entries 5−8 were completed in longer reaction time depending upon the substituents in the allyl group (2−36 h).



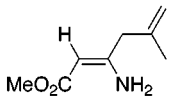
EWG = CO_2R', CN, COR'
R = H, Ph

3a-d **4a-d, 23-26**

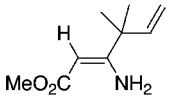
4a: EWG = CO_2Me, R = H
4b: EWG = CN, R = H
4c: EWG = COPip, R = H (Pip = )
4d: EWG = CO_2Et, R = Ph



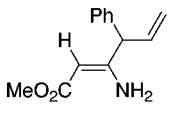
23



24



25



26

A plausible mechanism of this allylation−enamination reaction is shown in Scheme 4. The nitrile may coordinate to the Lewis acidic indium of allylindium reagent, making the protons next to the coordinated nitrile more acidic and facilitating the formation of the intermediate **27**. The allyl transfer to the carbon of the C=N double bond would produce **28**, which upon hydrolysis[20] would give the

(15) Negishi et al. reported the palladium-catalyzed coupling reaction of vinylic bromides and alkenylalane, which was prepared in situ from alkynes and alkylaluminum hydride (ref 2c).

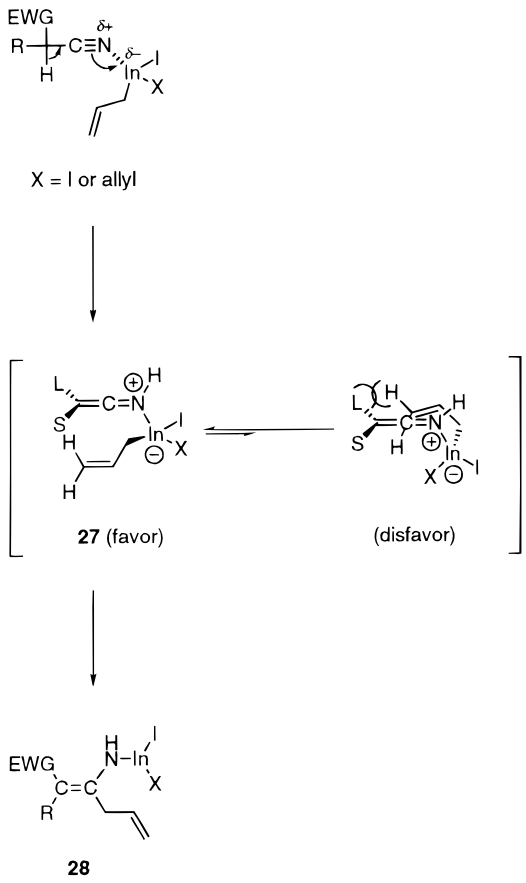
(16) In the three-component coupling reaction, a fair amount of byproducts (mono- and dibenzylation products **18a** and **22**, respectively) were formed along with **21**.

(17) The stereochemistry of the dibenzylation product **22** was not determined clearly because no apparent signal enhancement between the two benzyl protons was observed by 400 MHz NOE. Analysis with ^{1}H NMR and GC−MS showed that **22** was obtained as a single stereoisomer. The *Z*-conformation were assigned by the analogy from the result of **18a**-*d* (Scheme 2).

(18) The three-component coupling reaction would proceed as follows: oxidative insertion of Pd(0) into R^3-X' would produce $R^2-Pd(II)X'$ species, which would undergo the transmetalation reaction with the vinylindium **20** to give the vinylpalladium intermediate. Reductive elimination would give the three-component coupling product along with the Pd(0) catalyst.

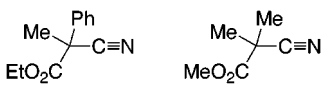
(19) Araki and co-workers reported that allylindiums are inert to nitriles in DMF.[4]

Scheme 4



allylation−enamination product **4**. Here again, two of the three allyl groups of allylindium reagent $(allyl)_3In_2I_3$ were used for the allylation−enamination reaction and the third allyl group must remain in the resulting monoallylindium reagent; it is assumed from the stoichiometry of the reaction that $(allyl)InI_2$ is produced, as a byproduct, along with InI. Actually, when the allylation−enamination reaction using 0.6 equiv of cinnamylindium was quenched with DCl/D_2O, allylbenzene-*d* ($PhCHDCH{=}CH_2$, 96% D content) was obtained, strongly suggesting that the third cinnamyl group remained as a cinnamylindium species.

The reaction of 1.2 equiv of allylmagnesium chloride with **3a** resulted in recovery of **3a** and the allylation−enamination product was not obtained,[21] showing that the present allylation−enamination reaction takes place only with less basic allylindium reagents, and failure of the Grignard reagent to react with **3a** is presumably due to deprotonation from the activated methylene position.[22] The reactions of **29** and **30** with allylindium and allylmagnesium reagents were carried out. However, both substrates were recovered after a prolonged reaction time, irrespective of the reagent type. No reactions with allylindium are reasonable since there is no activated methyne proton in both substrates. No reactions with allylmagnesium chloride are presumably due to the steric bulkiness at the α-position of nitriles **29** and **30**; it seems that even $(Me)_2C(CO_2Me)$ of **30** is sterically demanding. Enamines are important synthetic intermediates in organic synthesis since the discovery of the Stork reaction.[22] Nevertheless, fewer reactions are available for their preparation.[23,24] The present procedure with allylindiums may be useful for the synthesis of certain functionalized enamines since such enamines are not easily available via conventional methods.



29 **30**

Conclusion

Although further study is needed to settle the mechanism of allylation and benzylation, we are now in a position to carry out the allyl- and benzylindation of simple unactivated alkynes in good to high yields and to synthesize various 2-substituted 1,4-pentadiene and 1-substituted 3-phenyl-1-propene derivatives in regio- and stereocontrolled manner. In addition, nitriles having another electron-withdrawing group at the α-position can be converted to allylated enamines with allylindiums, providing a new procedure for the synthesis of highly functionalized enamines.

Experimental Section

The following materials were commercially available and used as such: phenylacetylene (**1a**), *p*-tolylacetylene (**1b**), *p*-chlorophenylacetylene (**1d**), 3-phenyl-1-propyne (**1e**), 1-octyne (**1f**), 1-dodecyne (**1g**), 1-ethynyl-1-cyclohexene (**1h**), 3-diethylamino-1-propyne (**1i**), trimethylsilylacetylene (**1j**), 1-trimethylsilyl-1-propyne (**1k**), 1-phenyl-1-propyne (**1l**), dodeca-5,7-diyne (**1m**), methyl cyanoacetate (**3a**), malononitrile (**3b**), cyanoacetylpiperidine (**3c**), ethyl phenylcyanoacetate (**3d**), indium powder, allyl iodide, crotyl bromide, methallyl bromide, prenyl bromide, cinnamyl bromide, iodine, hydrochloric acid, and deuterium chloride (as 20 wt % solution in D_2O). Benzyl iodide was prepared according to the known procedures.[25]

Preparation of Allylindium Sesquiiodide. In powder (69 mg, 0.60 mmol) was placed in a reaction vial under Ar, followed by the addition of THF (1.0 mL) and allyl iodide (82 μL, 0.9 mmol) at room temperature. After being stirred for 1 h, the THF suspension of In powder turned into a white solution of allylindium sesquiiodide. The allylindium reagent was used without any further purification. The crotyl(or metallyl)indium sesquibromide was prepared with the same procedure from In powder and crotyl(or metallyl) bromide.

Preparation of Benzylindium Sesquiiodide. In powder (69 mg, 0.60 mmol) was placed in a reaction vial under Ar, followed by the addition of THF (1.0 mL) and benzyl iodide (0.20 g, 0.90 mmol) at room temperature. After being stirred for 1 h, the THF suspension of In powder turned into white

(20) The protonation would take place at the workup stage: normally, an acidic silica gel column was used (see Experimental Section). On the other hand, when the reaction was quenched with diluted HCl, the desired allylation−enamination product was not obtained.

(21) Only abstraction of activated methylene hydrogen due to the basicity of allylmagnesium chloride was observed in this case (pK_a of the methylene hydrogen of **3a** ≈ 9; see: Peason, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 2439).

(22) Stork, G.; Terrell, R.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1954**, *76*, 2029.

(23) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975.

(24) (a) Leonard, N. J.; Hay, A. S.; Fulmer, R. W.; Gash, V. W. *J. Am. Chem. Soc.* **1955**, *77*, 439. (b) Katritzky, A. R.; Long, Q.-H.; Lue, P.; Jozwiak, A. *Tetrahedron* **1990**, *46*, 8153. (c) Broekhof, N. L. J. M.; Jonkers, F. L.; van der Gen, A. *Tetrahedron Lett.* **1979**, 2433. (d) Broekhof, N. L. J. M.; Jonkers, F. L.; van der Gen, A. *Tetrahedron Lett.* **1980**, *21*, 2671. (e) Bekker, B. H.; A-Lim, D. S. T.; van der Gen, A. *Tetrahedron Lett.* **1984**, *25*, 4259. (f) Comi, R.; Franck, R. W.; Reitano, M.; Weinreb, S. M. *Tetrahedron Lett.* **1973**, 3107. (g) White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213. (h) Kuo, S. C.; Daly, W. H. *J. Org. Chem.* **1970**, *35*, 1861.

(25) Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* **1984**, *25*, 1103.

solution of benzylindium sesquiiodide. The benzylindium reagent was used without any further purification.

Preparation of (4-Methoxyphenyl)acetylene (1c). *n*-BuLi (1.48 mL of 1.56 N in *n*-hexane, 2.3 mmol) was added to a mixture of ether (1.5 mL) and THF (1.5 mL) at −40 °C under Ar. 1,1-Dichloro-2-(4-methoxyphenyl)ethene (214 mg, 1.1 mmol) was introduced at −78 °C, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was quenched with aqueous 2 N sulfuric acid. The organic layer was extracted with pentane, washed with water, dried with anhyd Mg_2SO_4, and concentrated under reduced pressure. The crude mixture was separated with column chromatography on silica gel (hexane/ethyl acetate = 10/1), giving the alkyne **1c** (60%, 83 mg).

Preparation of 2a from 1a. Allylindium was prepared by mixing In powder (69 mg, 0.60 mmol) with allyl iodide (82 μL, 0.90 mmol) in THF (1.0 mL) at room temperature for 1 h. To a THF solution of allylindium was added phenylacetylene **1a** (55 μL, 0.50 mmol) at room temperature. The reaction mixture was heated to 70 °C and stirred for 2 h. The reaction was quenched with diluted aqueous hydrochloric acid solution (15 v/v %, 2.0 mL) at room temperature. The reaction product was extracted with ether, washed with brine, dried with anhyd Mg_2SO_4, concentrated under reduced pressure, and separated with silica gel column chromatography using hexane as an eluent, giving the allylation product **2a** in 94% yield (68 mg) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.20 (m, 5H), 5.91 (ddt, J = 6.5, 10.0, 16.6 Hz, 1H), 5.39 (d, J = 1.1 Hz, 1H), 5.11 (ddt, J = 1.6, 1.6, 16.6 Hz, 1H), 5.10 (dt, J = 1.1, 1.4 Hz, 1H), 5.07 (ddt, J = 1.6, 1.6, 10.0 Hz, 1H), 3.25 (ddt, J = 1.4, 1.6, 6.5 Hz, 2H). Anal. Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.39. Found: C, 91.72; H, 8.28.

Preparation of 18a from 1a. Benzylindium was prepared by mixing In powder (69 mg, 0.60 mmol) with benzyl iodide (0.20 g, 0.90 mmol) in THF (1.0 mL) at room temperature for 1 h. To a THF solution of benzylindium was added phenylacetylene **1a** (55 μL, 0.50 mmol) at room temperature. The reaction vial containing the reaction mixture was sealed and stirred for 2 d at 100 °C. The reaction was quenched with diluted aqueous hydrochloric acid solution (15 v/v %, 2.0 mL) at room temperature. The reaction product was extracted with ether, washed with brine, dried with anhyd Mg_2SO_4, concentrated under reduced pressure, and separated with silica gel column chromatography (eluent: hexane/ethyl acetate = 30/1), giving the benzylation product **18a** in 91% yield (88 mg) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46−7.17 (m, 10H), 6.60 (dt, J = 2.0, 11.5 Hz, 1H), 5.86 (dt, J = 7.0, 11.5 Hz, 1H), 3.68 (dt, J = 2.0, 7.0 Hz, 2H). Anal. Calcd for $C_{15}H_{14}$: C, 92.74; H, 7.26. Found: C, 92.97; H, 7.03.

Preparation of 4a from 3a. Allylindium was prepared by mixing In powder (69 mg, 0.60 mmol) with allyl iodide (82 μL, 0.90 mmol) in THF (1.0 mL) at room temperature for 1 h. To a THF solution of allylindium was added methyl cyanoacetate **3a** (44 μL, 0.50 mmol) at room temperature. The reaction mixture was heated to 70 °C, stirred for 2 h, and then cooled to room temperature. THF was removed under vacuo, and the reaction product was separated with column chromatography on silica gel (hexane/ethyl acetate = 8/1), giving the allylation−enamination product **4a** in 100% yield (70 mg) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86 (br s, 2H), 5.81 (ddt, J = 7.0, 10.0, 17.5 Hz, 1H), 5.22 (ddt, J = 1.5, 1.5, 17.5 Hz, 1H), 5.21 (ddt, J = 1.5, 1.5, 10.0 Hz, 1H), 4.58 (br s, 1H), 3.65 (s, 3H), 2.90 (br d, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.61, 160.82, 132.90, 119.32, 83.70, 50.18, 40.51; IR (neat) 3450, 3340, 2950, 1670, 1620, 1560, 1270, 1170, 1040, 790 cm^{-1}; HRMS calcd for $C_7H_{11}NO_2$ (m/z, M^+) 141.0790, found 141.0782. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.72; H, 8.00; N, 9.87.

Supporting Information Available: Characterization data of **2b**−**i**, **5**−**8**, **18b**−**g**, **22**, **4b**−**d**, and **23**−**26** and copies of ^{1}H and ^{13}C NMR spectra for reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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