Synthetic Methods

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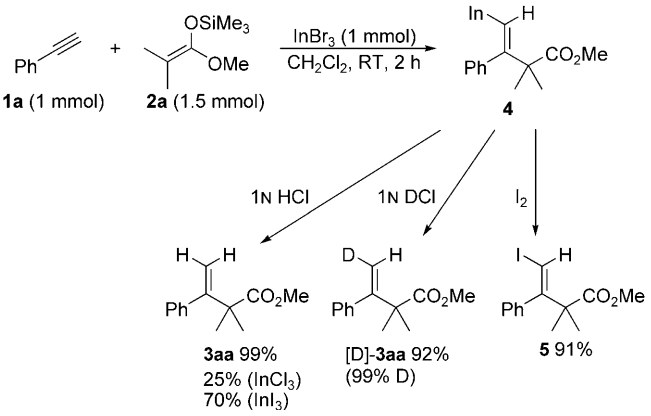
Regio- and Stereoselective Generation of Alkenylindium Compounds from Indium Tribromide, Alkynes, and Ketene Silyl Acetals**

*Yoshihiro Nishimoto, Ryosuke Moritoh, Makoto Yasuda, and Akio Baba**

The synthesis of alkenylmetals by the Lewis acid promoted addition of organometallic compounds to alkynes is an important process in organic chemistry because of the application of this class of compounds in coupling reactions. Despite extensive investigation of addition reactions using alkyl, allyl, alkenyl, and aryl nucleophiles,[1] the use of heteroatom-containing organometallic compounds has rarely been used because a coordinative heteroatom disturbs the weak interaction between an alkyne and a Lewis acid. Therefore, the reaction using silyl enolate has not been developed. Meanwhile, reaction systems promoted by $GaCl_3$, $HgCl_2$, $W(CO)_5$, and $EtAlCl_2$ have been reported.[2] However, the $GaCl_3$-mediated system has been limited to silylacetylene substrates and other metals systems limit the method to intramolecular cyclization. In addition, there have been no examples of coupling reactions that employ alkenylmetal species generated in situ. Herein, we report the $InBr_3$-mediated addition of ketene silyl acetals to alkynes to give alkenylindiums with high regio- and stereoselectivity. This reaction proceeds in an *anti* fashion as opposed to the general *syn* addition of carboindation using organoindium substrates.[3,4] We determined the X-ray structure of alkenylindium adducts, which furnishes experimental evidence for our proposed mechanism. To the best of our knowledge, this is the first crystallographic characterization of alkenylindium species as a carboindation product. Additionally, the resulting alkenylindiums were subsequently coupled with iodobenzene using a palladium catalyst in a one-pot reaction.

We have reported the reaction of alkyl chlorides with silyl enolates in which $InBr_3$ selectively activated an alkyl chloride irrespective of the oxygen moiety on the enolates.[5] This result prompted us to attempt the intermolecular addition of silyl enolates to alkynes, in which selective activation of the alkyne by indium halides was expected.[6] At first, we examined the reaction of $InBr_3$, phenylacetylene (**1a**), and dimethylketene methyl silyl acetal **2a**, which afforded the olefin **3aa** as a single isomer in quantitative yield after work-up with 1N HCl (Scheme 1). $InCl_3$ and InI_3 gave lower yields



Scheme 1. Reaction with $InBr_3$, alkyne **1a**, and ketene silyl acetal **2a**.

than $InBr_3$. Typical Lewis acids such as $BF_3{\cdot}OEt_2$, $AlCl_3$, and $TiCl_4$ yielded no product, while $GaCl_3$ gave a low yield (23%) because highly oxophilic Lewis acids are strongly coordinated by the oxygen atom.[7] Work-up with DCl gave the product [D]-**3aa**, which was deuterated at the *cis* position relative to the phenyl group. The iodolysis also afforded the iodoalkene **5** as a single isomer. These results strongly indicate that carboindation took place in an anti fashion with high regio- and stereoselectivity to yield the alkenylindium **4**.

We observed the generation of alkenylindium **4** using NMR spectroscopy by varying the amount of $InBr_3$ added (Figure 1). When 1 equivalent of $InBr_3$ was used the reaction gave two types of products that were assigned as monoalkenylindium **6** and dialkenylindium **7** (spectrum a). The signals corresponding to **6** decreased when 0.5 equivalents of $InBr_3$ was used (spectrum b). Meanwhile, 0.3 equivalents of $InBr_3$ afforded only **7** (spectrum c). The structures of **6** and **7** were confirmed by X-ray analysis.[8,9] When 0.75 equivalent of $InBr_3$ was used, compound **6** adopts a distorted trigonal bipyramidal coordination geometry with an alkenyl group and two bromine atoms in equatorial positions, while the two axial positions are occupied by a bromine atom and the carbonyl oxygen of another molecule in the unit cell (Figure 2a). The equatorial and axial bromine atoms bridge between two indium centers as shown in Figure 2b. Interestingly, by exploiting this bridging and coordination, six

[*] Y. Nishimoto, R. Moritoh, Dr. M. Yasuda, Prof. Dr. A. Baba
Department of Applied Chemistry
Center for Atomic and Molecular Technologies (CAMT)
Graduate School of Engineering
Osaka University, 2-1, Yamada-oka, Suita, Osaka (Japan)
Fax: (+81) 6-6879-7387
E-mail: baba@chem.eng.osaka-u.ac.jp

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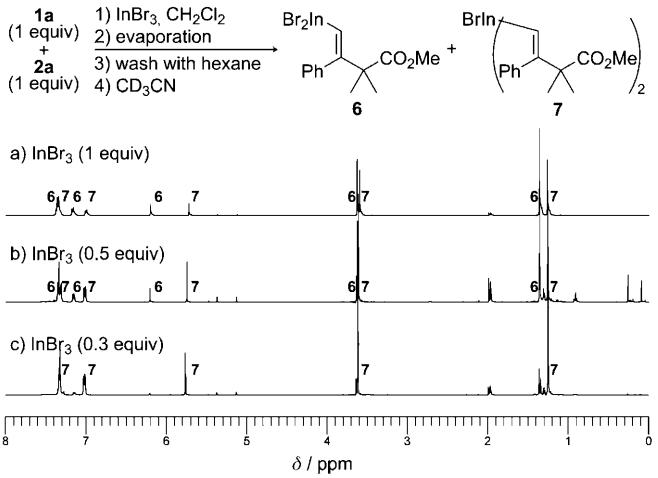
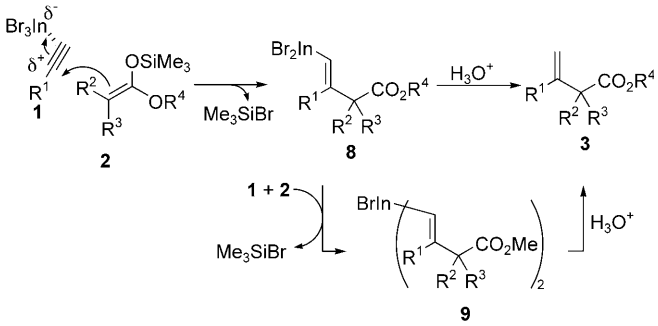


Figure 1. ^{1}H NMR spectra of alkenylindium derivatives.

molecules of **6** form a 28-membered macrocycle (Figure 2c), and the crystal structure of **6** shows the formation of a two-dimensional coordination polymer.[10] Dialkenylindium **7** dimerized with a bromine bridge (Figure 2d and e). Two alkenyl groups and two bromine atoms around the indium center are arranged in distorted tetrahedral environments. As expected, both **6** and **7** were confirmed to have *cis* conformations of indium and phenyl moieties around the double bond (see Scheme 1).

A plausible reaction mechanism for the formation of **3** is illustrated in Scheme 2. The chemoselective activation of alkyne **1** by $InBr_3$ takes place irrespective of the oxygen moieties of ketene silyl acetal **2** in order to increases the positive charge on the internal carbon atom of the alkyne **1** because the R^1 group stabilizes the charge. Ketene silyl acetal **2** attacks the internal carbon atom from the opposite side of the coordinated $InBr_3$ to give the monoalkenylindium **8**, which is a carboindation adduct that forms in a *anti* fashion.[11] The subsequent addition of **8** to another alkyne **1** affords the



Scheme 2. Plausible mechanism.

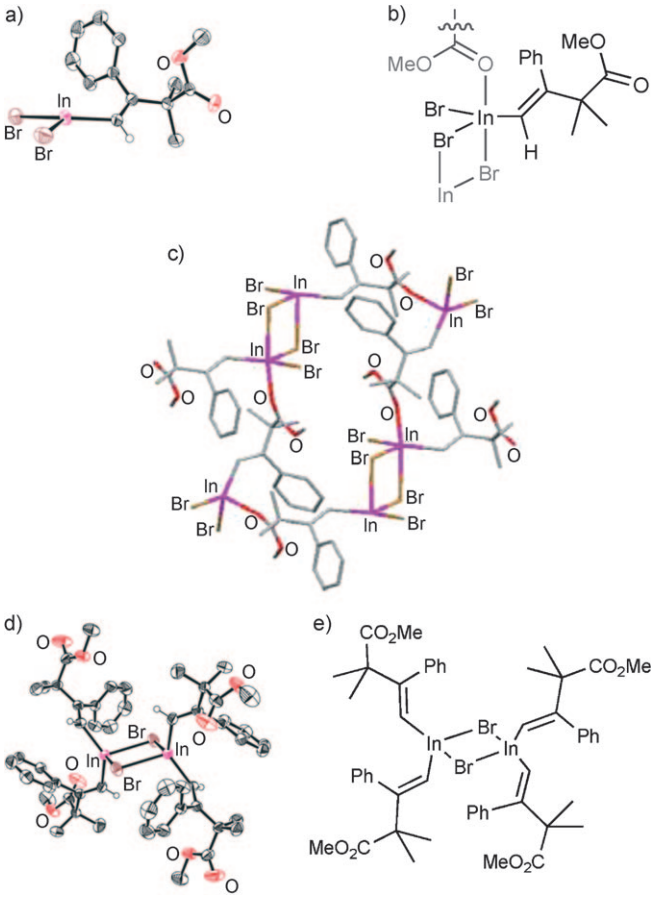


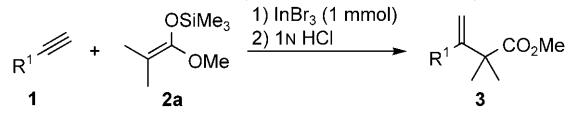
Figure 2. Molecular structure of **6** (a, b, and c) and **7** (d and e).

dialkeynylindium **9**. The hydrolysis of **8** and **9** gives β,γ-unsaturated ester **3**. The soft Lewis acidity of $InBr_3$ plays an important role in the activation of alkynes to promote the reaction between alkynes and ketene silyl acetals. In contrast, the use of strong Lewis acids such as $AlCl_3$ and $BF_3{\cdot}OEt_2$, which predominantly interact with oxygen-containing ketene silyl acetals, resulted in no reaction. The alternative route, which includes indium enolates, was excluded at this stage because no transmetalation between $InBr_3$ and silyl enolates was observed under the reaction conditions.

The scope of applicable alkynes was investigated (Table 1). Aromatic alkynes **1b–d** bearing electron-donating and -withdrawing groups gave high yields (Table 1, entries 1–3). The aliphatic alkyne **1e** afforded the desired product **3ea** (Table 1, entry 4), and the methyl ether moiety also tolerated these reaction conditions (Table 1, entry 5). In the reaction with the conjugated enyne **1g**, the addition proceeded selectively at the alkyne moiety (Table 1, entry 6). Overall, the alkynes in entries 1, 3, and 6 of Table 1 gave high yields, even in the presence of 0.5 equivalents of $InBr_3$.

Table 2 shows the results of addition reactions using various ketene silyl acetals. Dialkyl- and alkylarylketene silyl acetals **2b–d** gave desired products in high yields (Table 2, entries 1–3). Monosubstituted ketene silyl acetals **2e** and **2f** afforded their corresponding products in 58% and 97% yields, respectively (Table 2, entries 4 and 5). Unfortunately, unsubstituted ketene silyl acetal **2g** was not applicable to this reaction system because it easily isomerizes to the corresponding α-silyl ester under these reaction conditions (Table 2, entry 6).[12]

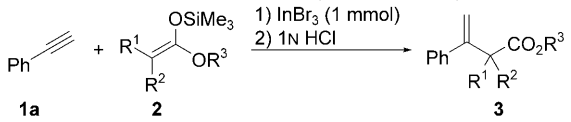
Table 1: Additions of ketene silyl acetal **2a** to various alkynes.[a]



Entry	Alkyne	R^1	Product	Yield [%][b]
1	**1b**	4-MeC_6H_4	**3ba**	94 (80)[c]
2	**1c**	4-$tBuC_6H_4$	**3ca**	71
3	**1d**	4-ClC_6H_4	**3da**	99 (97)[c]
4	**1e**	C_6H_{13}	**3ea**	71
5	**1f**	$MeOCH_2(CH_2)_3$	**3fa**	61
6	**1g**		**3ga**	83 (82)[c]

[a] Reaction conditions: **1** (1.0 mmol), **2a** (1.5 mmol), $InBr_3$ (1.0 mmol), CH_2Cl_2 (1 mL), RT, 2 h. [b] Yields were determined by ^1H NMR analysis. [c] Yield of product in a reaction using 0.5 mmol of $InBr_3$.

Table 2: Additions of various ketene silyl acetals to alkyne **1a**.[a]

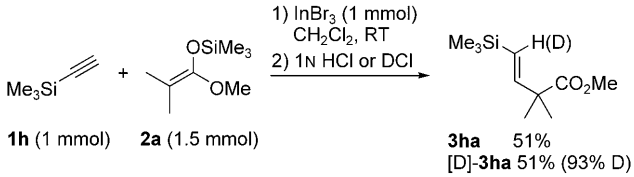


Entry	Silyl ketene acetal	R^1	R^2	R^3	Product	Yield [%][b]
1	**2b**	Et	Et	Et	**3ab**	87
2	**2c**	$-(CH_2)_5-$	–	Me	**3ac**	99
3	**2d**[c]	Me	Ph	Me	**3ad**	98
4	**2e**[d]	H	*n*Bu	Me	**3ae**	58
5	**2f**[e]	H	Ph	Me	**3af**	97
6	**2g**	H	H	Me	**3ag**	0

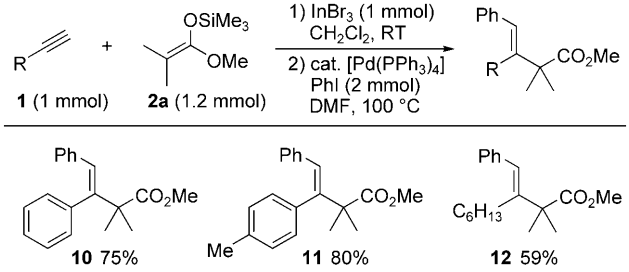
[a] Reaction conditions: **1a** (1.0 mmol), **2** (1.5 mmol), $InBr_3$ (1 mmol), CH_2Cl_2 (1 mL), room temperature, 2 hours. [b] Yields were determined by ^1H NMR analysis. [c] $E/Z = 66:34$. [d] $E/Z = 89:11$. [e] $E/Z = 70:30$.

The reaction with trimethylsilyl acetylene gave reverse regio- and stereoselectivity, in which **2a** attacked the terminal carbon atom of **1h** to afford the carboindation adduct in a *syn* fashion (Scheme 3). This regioselectivity may depend on the stability of the positive charge at the β position to the silyl group.[13] The *Z*-isomer **3ha** seems to be formed by the isomerization of the unstable *E* isomer, which is generated by *anti* carboindation.[14]

Finally, we examined the coupling reaction of the resulting alkenylindium using an aryl halide in a one-pot procedure (Scheme 4).[15] After the treatment of **2a** with **1a**, the subsequent addition of $[Pd(PPh_3)_4]$, PhI, and DMF to the resulting CH_2Cl_2 solution afforded the coupling product **10** as



Scheme 3. Reverse regio- and stereoselectivity to afford the carboindation adduct in a *syn* fashion.



Scheme 4. One-pot addition/coupling reaction. DMF = *N*,*N*-dimethylformamide.

a single isomer in high yield. The other aromatic alkyne **1b** and the aliphatic alkyne **1e** gave the trisubstituted olefins **11** and **12**, respectively. The geometry of the olefinic double bond was confirmed by X-ray analysis of the carboxylic acid obtained by the hydrolysis of **10**[16] (see the Supporting Information), which showed that the coupling reaction proceeded with retention of configuration of the corresponding alkenylindiums.

In summary, we have developed a synthetic method for the preparation of alkenylindiums by the regio- and stereoselective addition of ketene silyl acetals to $InBr_3$-activated alkynes. Further application of this method in the synthesis of more elaborately functionalized alkenylindiums is now in progress.

Experimental Section

Typical procedure for the addition reaction of **1a** with **2a** (Scheme 1): **1a** (1.0 mmol) was added to a mixture of $InBr_3$ (1.0 mmol) and **2a** (1.5 mmol) in CH_2Cl_2 (1 mL) under nitrogen. The reaction mixture was stirred under the reaction conditions noted in the text. The resulting mixture was poured into Et_2O (10 mL) and 1N HCl (5 mL). The solution was extracted with Et_2O and the organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to afford the crude product, which was analyzed by NMR spectroscopy.

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