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Regioselective Carboindation of Simple Alkenes with Indium Tribromide and Ketene Silyl Acetals

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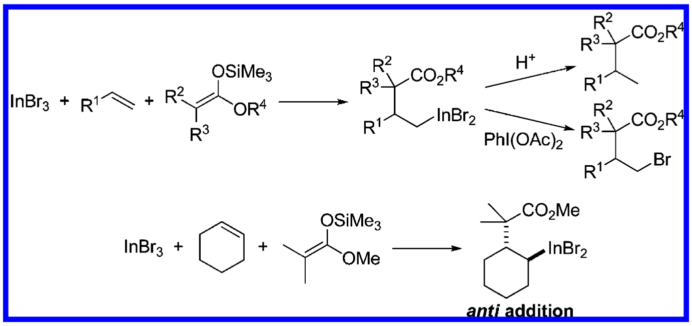
ABSTRACT



The regioselective carboindation of simple alkenes with indium tribromide and ketene silyl acetals was accomplished. Various alkenes such as ethylene, 1-alkenes, and cyclic alkenes were applicable for this reaction system. The alkylindium product from the carboindation of cyclohexene revealed an *anti* addition mechanism.

The carbometalation of alkenes has an important role in organic chemistry, because the resulting alkylmetals are fundamental materials for diverse organic transformations.[1] In particular, the use of simple and easily accessible alkenes in the petrochemical industry would be quite practical. However, almost all carbometalations of simple alkenes, in contrast to other unsaturated compounds such as alkynes and allenes, are restricted to the addition of feasible alkylmetal nucleophiles like Grignard and organolithium reagents, which strictly narrows the scope of both alkenes and nucleophiles.[2] In addition, preparation of the starting alkylmetal substrates is considerably taxing. Therefore, the development of carbometalation that can introduce functional groups has been highly desired. Especially, carbometalation with metal enolates has significant value, because it could furnish organometallic compounds bearing carbonyl groups. However, there are only a few examples of intramolecular reactions perhaps to avoid undesired over-reactions.[3,4] Herein, we describe the intermolecular carbometalation of simple alkenes using indium tribromide and ketene silyl acetals, wherein no preparation of organoindium nucleophiles is required.

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(1) For reviews, see: (a) Knochel, P. In *Comprehensive Organometallic Chemistry III*; Mingos, D. M. P., Crabtree, R. H., Eds.; Elsevier: Oxford, UK, 2007; Vol. 9. (b) Hiyama, T. In *Comprehensive Organometallic Chemistry III*; Mingos, D. M. P., Crabtree, R. H., Eds.; Elsevier: Oxford, UK, 2007; Vol. 11.

(2) For reviews, see: (a) Semmelhack, M. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 4. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Negishi, E.; Kondakov, D. Y. *Chem. Soc. Rev.* **1996**, *25*, 417. (d) Marek, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 535. (e) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899. (f) Ojima, I. In *Comprehensive Organometallic Chemistry III*; Mingos, D. M. P., Crabtree, R. H., Eds.; Elsevier: Oxford, UK, 2007; Vol. 10.

(3) (a) Lorthiois, E.; Marek, I.; Normant, J. F. *J. Org. Chem.* **1998**, *63*, 2442. (b) Kitagawa, O.; Suzuki, T.; Inoue, T.; Watanabe, Y.; Taguchi, T. *J. Org. Chem.* **1998**, *63*, 9470. (c) Kitagawa, O.; Fujiwara, H.; Suzuki, T.; Taguchi, T.; Shiro, M. *J. Org. Chem.* **2000**, *65*, 6819.

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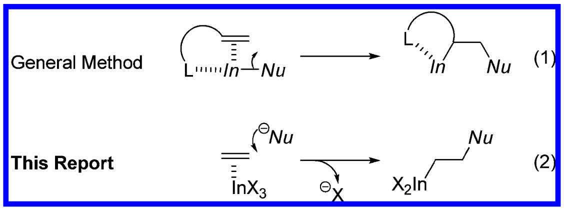
A variety of allylindations of alkynes has been examined due to high compatibility of indium species with functional groups, in which effective activation of alkynes by generated allylindium halide species is plausible.[5] In contrast to alkynes, carboindation of alkenes has been strictly limited to the reaction with cyclopropenes or norbornenes bearing directing groups (L) like a hydroxy one (eq 1).[6] These facts indicate that the activation of alkenes by allylindium halide species is insufficient and that stronger Lewis acidity is required for the activation. The introduction of organic ligands is the reason for decreasing the Lewis acidity. Therefore, the formation of organoindium nucleophiles should be avoided to achieve a practical carboindation of alkenes, which promotes the type of reaction as shown in eq 2. In eq 2, it is an important point that the activation of alkenes by indium trihalide is followed by the reaction of nucleophiles. Quite recently, we reported the carboindation of terminal alkynes on the basis of a similar strategy.[7] It was very surprising and fortunate that the same concept could be applied to a variety of alkenes, including internal ones, because the reactivity of alkene had been considered to be far lower than that of alkynes. To the best of our knowledge, this is the first example of the carboindation of simple alkenes.



First, we treated $InBr_3$ (1 mmol) with 1-octene **1a** (3 mmol) and dimethylketene silyl acetal **2a** (1.5 mmol) in CH_2Cl_2 (2 mL) at room temperature. To our delight, the desired carboindation smoothly proceeded in 2 h. After the solvent was evaporated and the residue was washed with hexane, the carboindation product **3aa** was isolated as a white solid in 70% yield based on $InBr_3$ (eq 3). The structure of **3aa** was successfully confirmed by X-ray crystallographic analysis, which showed that indium added selectively at the terminal olefin carbon (Figure 1). The geometry around the indium atom is a distorted trigonal bipyramid, in which one alkyl group and two bromine atoms occupy equatorial positions, and a carbonyl oxygen atom and a bromine atom of another molecule occupy axial positions. Bromine bridges are used to construct the alkylindium dimer.

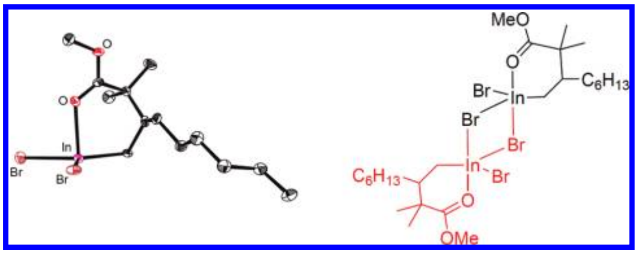
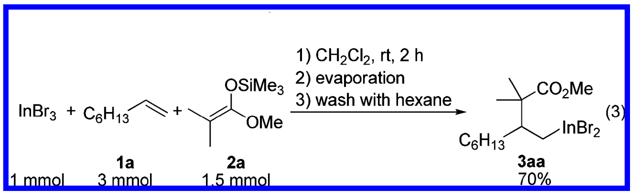
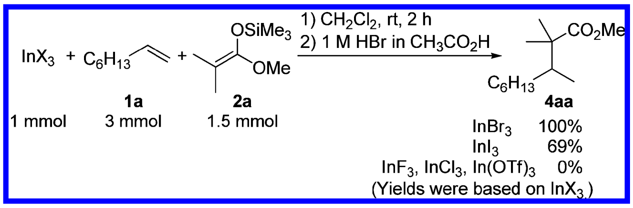


Figure 1. X-ray crystallographic analysis and dimeric structure of alkylindium **3aa**. (In the dimeric structure, one molecule is shown in black and the other is shown in red.)



This carboindation strongly depended on the counteranion of indium(III). $InBr_3$ gave the desired ester **4aa** quantitatively after the treatment with 1 M HBr of CH_3COOH solution (Scheme 1). InI_3 also gave **4aa** in 69% yield, while InF_3, $InCl_3$, and $In(OTf)_3$ had no effect on the carboindation. Other Lewis acids, such as boron, aluminum, and gallium trihalides, gave no product because these harder Lewis acids strongly interact with oxygen moieties in preference to alkenes.[8] This compatibility with functional groups is an advantage of indium halides. These results showed that $InBr_3$ has the most suitable π-electrophilic Lewis acidity.

Scheme 1. Effect of Indium Trihalides



As shown in Table 1, various types of 1-alkenes were applicable to this reaction system. Styrene **1b** gave the

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[4] For a pioneering work of carbometalation of alkenes with zinc enamides, see: (a) Kubota, K.; Nakamura, E. *Angew. Chem., Int. Ed.* **1997**, *36*, 2491. (b) Nakamura, E.; Kubota, K.; Sakata, G. *J. Am. Chem. Soc.* **1997**, *119*, 5457. For a review, see: (c) Pérez-Luna, A.; Botuha, C.; Ferreira, F.; Chemla, F. *New J. Chem.* **2008**, *32*, 594.

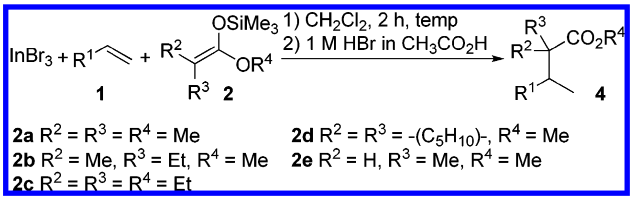
[5] For carboindation of alkynes and allenes, see: (a) Araki, S.; Imai, A.; Shimizu, K.; Butsugan, Y. *Tetrahedron Lett.* **1992**, *33*, 2581. (b) Araki, S.; Imai, A.; Shimizu, K.; Yamada, M.; Mori, A.; Butsugan, Y. *J. Org. Chem.* **1995**, *60*, 1841. (c) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2318. (d) Ranu, B. C.; Majee, A. *Chem. Commun.* **1997**, 1225. (e) Fujiwara, N.; Yoshinori, Y. *J. Org. Chem.* **1999**, *64*, 4095. (f) Klaps, E.; Schmid, W. *J. Org. Chem.* **1999**, *64*, 7537. (g) Salter, M. M.; Sardo-Inffiri, S. *Synlett* **2002**, 2068. (h) Lee, P. H.; Kim, S.; Lee, K.; Seomoon, D.; Kim, H.; Lee, S.; Kim, M.; Han, M.; Noh, K.; Livinghouse, T. *Org. Lett.* **2004**, *6*, 4825. (i) Miura, K.; Fujisawa, N.; Hosomi, A. *J. Org. Chem.* **2004**, *69*, 2427. (j) Yanada, R.; Obika, S.; Kobayashi, Y.; Inokuma, T.; Oyama, M.; Yanada, K.; Takemoto, Y. *Adv. Synth. Catal.* **2005**, *347*, 1632. (k) Goeta, A.; Salter, M. M.; Shah, H. *Tetrahedron* **2006**, *62*, 3582. (l) Miura, K.; Fujisawa, N.; Toyohara, S.; Hosomi, A. *Synlett* **2006**, 1883.

[6] For carboindation of activated alkenes, see: (a) Araki, S.; Nakano, H.; Subburaj, K.; Hirashita, T.; Shibutani, K.; Yamamura, H.; Kawai, M.; Butsugan, Y. *Tetrahedron Lett.* **1998**, *39*, 6327. (b) Araki, S.; Kamei, T.; Igarashi, Y.; Hirashita, T.; Yamamura, H.; Kawai, M. *Tetrahedron Lett.* **1999**, *40*, 7999. (c) Araki, S.; Shiraki, F.; Tanaka, T.; Nakano, H.; Subburaj, K.; Hirashita, T.; Yamamura, H.; Kawai, M. *Chem.—Eur. J.* **2001**, *7*, 2784.

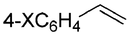
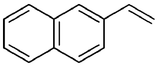
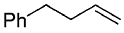
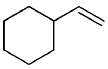
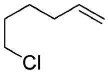
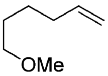
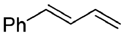
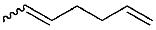
[7] Nishimoto, Y.; Moritoh, R.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4577.

[8] The results of other Lewis acids are shown in the Supporting Information.

Table 1. Scope and Limitations of Alkenes **1** and Silyl Ketene Acetals **2**[a]

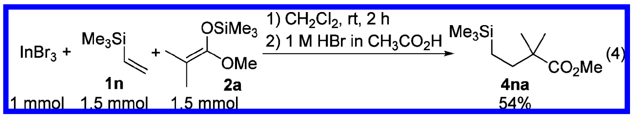


2a $R^2 = R^3 = R^4 = Me$
2b $R^2 = Me$, $R^3 = Et$, $R^4 = Me$
2c $R^2 = R^3 = R^4 = Et$
2d $R^2 = R^3 = \text{-}(C_5H_{10})\text{-}$, $R^4 = Me$
2e $R^2 = H$, $R^3 = Me$, $R^4 = Me$

entry	1		2	temp	4	yield (%)[g]
						
1	X = H	**1b**	**2a**	rt	**4ba**	100
2[b]	OMe	**1c**	**2a**	-20 ºC	**4ca**	100
3[c]	Me	**1d**	**2a**	rt	**4da**	100
4	Cl	**1e**	**2a**	rt	**4ea**	95
5	NO$_2$	**1f**	**2a**	80 ºC	**4fa**	0
6[b]		**1g**	**2a**	rt	**4ga**	74
7		**1h**	**2a**	rt	**4ha**	70
8		**1i**	**2a**	rt	**4ia**	36
9[d]		**1j**	**2a**	rt	**4ja**	93
10		**1k**	**2a**	rt	**4ka**	42
11[e]		**1l**	**2a**	rt	**4la**	59
12[d,e,f]		**1m**	**2a**	rt	**4ma**	95
13[d]	**1b**		**2b**	rt	**4bb**	81[h]
14[d]	**1b**		**2c**	rt	**4bc**	69
15[d]	**1b**		**2d**	rt	**4bd**	73
16[d]	**1b**		**2e**	50 ºC	**4be**	61[i]

[a] InBr$_3$ (1 mmol), **1** (1.5 mmol), **2** (1.5 mmol), CH$_2$Cl$_2$ (2 mL), 2 h. [b] **2a** (3 mmol). [c] **1d** was added slowly for 10 min. [d] **1** (3 mmol). [e] Quench by 1 M HCl of diethyl ether solution. [f] **1m** (*E*/*Z* = 88:12), **4ma** (*E*/*Z* = 92:8). [g] Yields based on InBr$_3$ were determined by ^{1}H NMR spectroscopy. [h] Diastereomer ratio 66:34. [i] Diastereomer ratio 57:43.

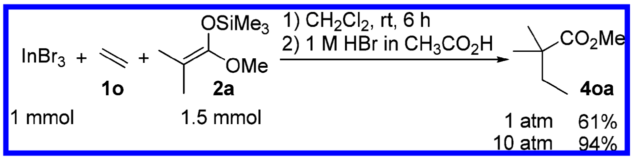
desired product **4ba** in a quantitative yield (entry 1). Reactions with other aromatic alkenes, **1c**−**e**, successfully proceeded with the exception of the nitro-substituted one, **1f** (entries 2−5). Electron-rich alkene **1c** quantitatively yielded **4ca** even at −20 °C. Vinyl naphthalene **1g** and 4-phenyl-but-1-ene **1h** also underwent carboindation to furnish the corresponding esters in 74% and 70% yields, respectively (entries 6 and 7). The use of vinyl cyclohexane **1i** resulted in a low yield due to its steric hindrance (entry 8). Chloride and ether moieties tolerated the reaction conditions (entries 9 and 10). In the reaction with 1,3-diene **1*l***, a 1,2-addition selectively took place (entry 11). When using 1,5-diene **1m**, a carboindation of the terminal alkene moiety occurred to give the predictable product **4ma** in 95% yield (entry 12). Diverse disubstituted ketene silyl acetals **2b**−**d** gave satisfactory results (entries 13−15). The reaction of the monosubstituted ketene silyl acetal **2e** with **1b** at 50 °C yielded **4be** in a 61% yield (entry 16), while unsubstituted ketene silyl acetal was found be inapplicable to this reaction system perhaps due to its low nucleophilicity.[9] Notably, the carboindation of vinylsilane **1n** proceeded with reverse regioselectivity to furnish the product **4na** (eq 4).



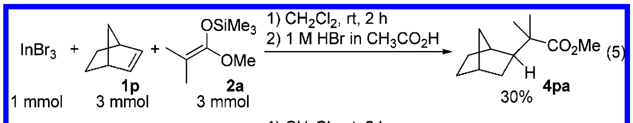
(4)

Selective carbometalation of ethylene remains a challenging problem because of a lack of polarity despite the fact that ethylene is obviously the most fundamental alkene. Notably, when InBr$_3$ was treated with **2a** under 1 and 10 atom of ethylene in CH$_2$Cl$_2$ at room temperature, carboindation of ethylene took place in 61% and 94% yields, respectively, without polymerization of ethylene (Scheme 2).

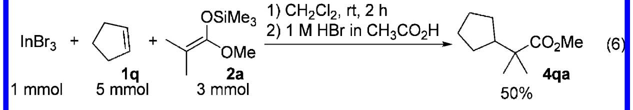
Scheme 2. Carboindation of Ethylene



After an extensive survey of diverse multisubstituted alkenes, we found that cyclic ones were applicable to this reaction system, although acyclic ones could not been used in this stage. Norbornene **1p** gave stereoselectively the *exo* product **4pa** in 30% yield (eq 5).[10] Cyclopentene **1q** and cyclohexene **1r** also gave the desired products in 50% and 20% yields, respectively (eqs 6 and 7). To gain insight into the reaction mechanism, we examined the X-ray crystallographic analysis of alkylindium **3ra**, which was obtained as a white solid in 18% yield from the reaction under the same conditions as eq 7 without the acid treatment.[11] The structure indicates that carboindation proceeds in an *anti* addition manner (Figure 2). Complex **3ra** as well as **3aa**



(5)



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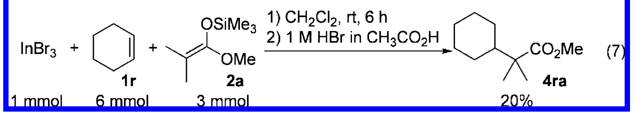


(7)

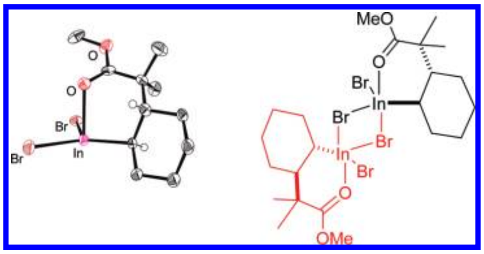
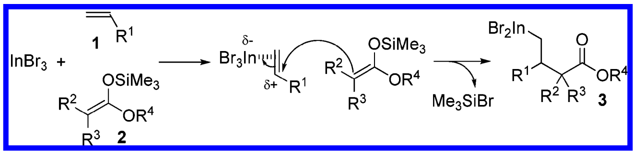


Figure 2. X-ray crystallographic analysis and dimeric structure of alkylindium **3ra**. (In the dimeric structure, one molecule is shown in black and the other is shown in red.)

has a distorted trigonal bipyramidal structure, and bromine bridges are used to construct the alkylindium dimer.

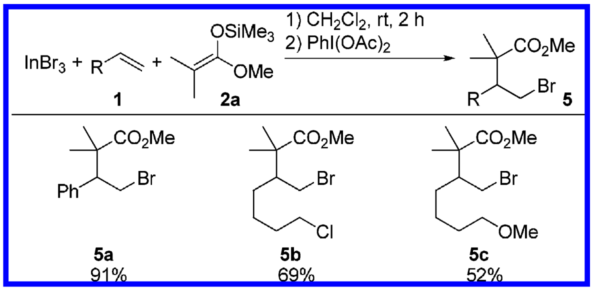
A plausible mechanism for the formation of alkylindium **3** is illustrated in Scheme 3. $InBr_3$ effectively activates alkene **1** irrespective of the oxygen atoms of ketene silyl acetal **2**. The positive charge, which is stabilized by the R^1 group, on the internal carbon atom of the double bond was increased to accept the nucleophilic attack of **2** from the opposite side of $InBr_3$, and then alkylindium product **3** and Me_3SiBr are generated. In the carboindation of vinylsilane **1n**, the stability of the positive charge at the β-position to the silyl group reversed the regioselectivity (eq 4). This anti addition is supported by the structure of **3ra**. At this stage, syn addition via an indium enolate species followed by isomerization to alkylindium **3ra** was ruled out because transmetalation between $InBr_3$ and **2** was not observed under the reaction conditions. No transmetalation is an important point in terms of the fact that an organoindium species would not be so highly π-electrophilic to activate alkenes.[7,12] In addition, $InBr_3$ would have a low oxophilicity and a high π-electrophilicity in contrast to harder Lewis acids such as $In(OTf)_3$, which interact preferentially with oxygen moieties of ketene silyl acetals or produced esters.

Scheme 3. Plausible Mechanism



Finally, we developed the transformation of alkylindium compounds to the corresponding alkyl bromides. After examining various bromination reagents, $PhI(OAc)_2$ was found to cause the bromination of alkylindium under mild conditions (Scheme 4).[13] Even alkenes bearing functional groups afforded the corresponding alkyl bromides **5a**−**c**. This method provided convenient access to functionalized compounds that have been traditionally difficult to synthesize.

Scheme 4. Bromination of Alkylindium



In summary, we have accomplished the carboindation of simple alkenes using $InBr_3$ and ketene silyl acetals, in which $InBr_3$ directly activates an alkene without the generation of organoindium species via transmetalation between $InBr_3$ and a ketene silyl acetal. Successful application of internal alkenes is a cornerstone of carboindation. In addition, $PhI(OAc)_2$ smoothly transformed produced alkylindiums to the corresponding alkyl bromides. The mechanistic study is currently underway in our laboratory.

Acknowledgment. This work was supported by Grant-in-Aid for Scientific Research on Priority Areas (No. 18065015, “Chemistry of Concerto Catalysis” and No. 20036036, “Synergistic Effects for Creation of Functional Molecules”) and for Scientific Research (No. 19550038) from Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank Dr. Nobuko Kanehisa (Osaka University) for the valuable advice regarding X-ray crystallography.

Supporting Information Available: Experimental procedures, and characterization data for all new compounds, and CIF of **3aa**, **3ra**, and **s1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

(10) The stereochemistry of **4qa** was confirmed by X-ray analysis of the amide obtained by the reaction of **4qa** with aniline.

(11) Reaction conditions: $InBr_3$ (2 mmol), **1s** (12 mmol), **2a** (6 mmol), CH_2Cl_2 (4 mL), rt, 6 h. Experimental procedures are shown in the Supporting Information.

(12) (a) Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2007**, *72*, 8588. (b) Nishimoto, Y.; Yasuda, M.; Baba, A. *Org. Lett.* **2007**, *9*, 4931. (c) Nishimoto, Y.; Saito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2009**, *65*, 5462.

(13) A bromonium ion generated from the reaction of $PhI(OAc)_2$ with a bromide ion probably caused the bromination of alkylindiums. NBS, Br_2, and $PhIBr_2$ as well as $PhI(OAc)_2$ gave the corresponding alkyl bromides, although yields were low or moderate.