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Synthetic Methods

Regio- and Stereoselective Carbobismuthination of Alkynes**

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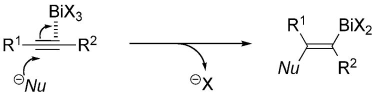
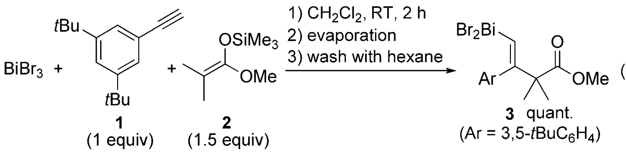
The carbometalation of carbon–carbon triple bonds is of excellent value as a synthetic method for alkenylmetal compounds and is accompanied by the formation of both carbon–carbon and carbon–metal bonds. Therefore, carbometalations using a variety of metal elements have been developed by many chemists.[1] As far as we could ascertain, however, carbobismuthination has never been reported.[2–4] Many inorganic bismuth compounds are used in various applications, including as medicinal chemicals, because bismuth is a virtually nontoxic heavy element in contrast with other heavy elements such as arsenic, antimony, lead, and thallium.[5] However, the use of organobismuth compounds in synthetic chemistry has been mostly limited to the introduction of aryl moieties by an arylbismuth compound,[6] perhaps because practical synthetic methods of other organobismuth compounds are scarce. Only transmetalation between a bismuth halide and an organometallic compound has been generally applied, thus limiting the number of compatible functional groups.[7] Herein, we wish to report the first carbobismuthination of an alkyne. In contrast with general carbometalations, the separate introduction of a carbon nucleophile and a metal without the preformation of organometallic nucleophiles resulted in carbobismuthination [Eq (1)]. In addition, the present study was an effort to expand carbometalation based on this concept, which has recently been reported for carboindation and carbogallation.[8,9] The present reaction system requires only a simple mixture of $BiBr_3$, an alkyne, and a ketene silyl acetal to produce an alkenylbismuth bearing an ester moiety with high stereo- and regioselectivity.



(1)

First, the achievement of a carbobismuthination was confirmed by X-ray crystallographic analysis of the alkenylbismuth compound. The reaction of $BiBr_3$ with 3,5-di(*tert*-butyl)phenylacetylene **1** and dimethylketene trimethylsilyl methyl acetal **2** in CH_2Cl_2 at room temperature gave monoalkenylbismuth dibromide **3** as a white solid in a quantitative yield [Eq. (2)]. X-ray crystallographic analysis of **3** revealed the *cis* conformation of bismuth and aromatic moieties around the double bond; this conformation showed that the carbobismuthination took place regio- and stereoselectively in an *anti* addition manner (Figure 1 a). The tetramer of **3** resulted from the formation of bromine bridges, as shown in Figure 1 b. The geometry around the bismuth atom in **3** is a distorted trigonal bipyramidal with two bromines in axial positions. An alkenyl group and a bromine occupied two equatorial positions, and the other was vacant.[7] The obtained alkenylbismuth **3** easily reacted with I_2, furnishing alkenyl iodide **4** with retention of stereochemistry [Eq. (3)].



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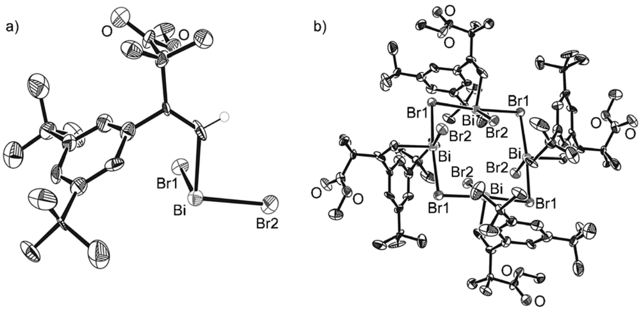

Figure 1. X-Ray crystallographic analysis of alkenylbismuth dibromide **3** (the thermal ellipsoids are shown at 50% probability.[17]

Table 1 shows the comparison of $BiBr_3$ with other bismuth(III) salts in carbobismuthination/iodination using phenylacetylene **5** and ketene silyl acetal **2**. To our surprise,

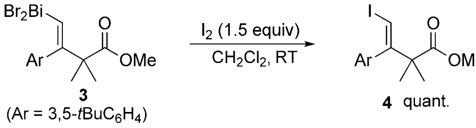

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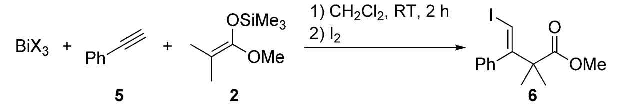
Table 1: Comparison of $BiBr_3$ with other bismuth(III) salts.[a]

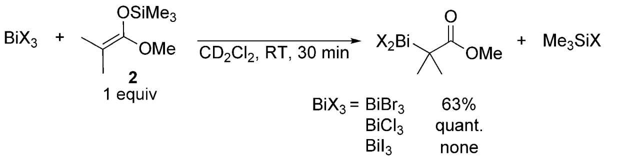


Entry	BiX_3	Yield of **6** [%][b]
1	$BiBr_3$	quant.
2	BiF_3	0
3	$BiCl_3$	0
4	BiI_3	0
5	$Bi(OTf)_3$	0

[a] 1) BiX_3 (1 mmol), **5** (1 mmol), **2** (1.5 mmol), CH_2Cl_2 (2 mL), RT, 2 h; 2) I_2 (2 mmol). [b] Yields were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Tf = trifluoromethanesulfonyl.

only $BiBr_3$ characteristically gave the desired alkenyliodide **6** in a quantitative yield (Table 1, entry 1), and the other bismuth(III) salts such as BiF_3, $BiCl_3$, BiI_3, and $Bi(OTf)_3$ gave no product at all (Table 1, entries 2, 3, 4, and 5).

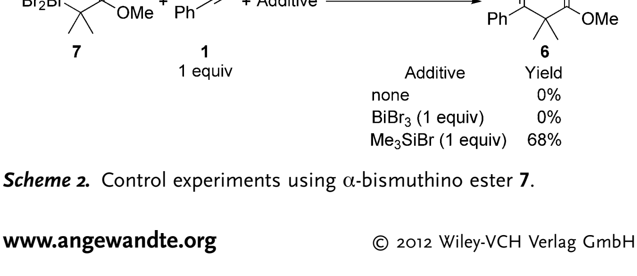
To examine the reaction mechanism, we monitored CD_2Cl_2 solutions of bismuth trihalides and ketene silyl acetal **2** by ^1H, ^{13}C, and ^{29}Si NMR spectroscopy (Scheme 1).



Scheme 1. Transmetalation between a bismuth trihalide and ketene silyl acetal **2**.

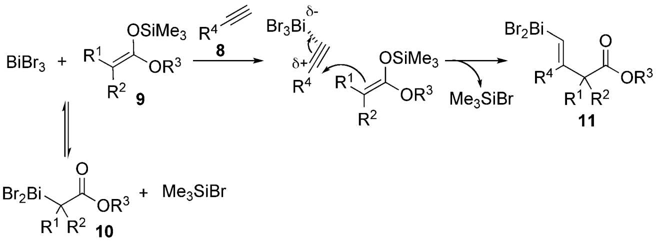
Moderate transmetalation occured between $BiBr_3$ and **2** to give α-dibromobismuthino ester **7** and Me_3SiBr. This result indicated the involvement of **7** in the carbobismuthination. A similar transmetalation, however, took place even in the case of $BiCl_3$, which promoted no production of an alkenylbismuth (Table 1, entry 3). In contrast, BiI_3, which also gave no product (Table 1, entry 4), caused no transmetalation with ketene silyl acetal **2**. These results lend uncertainty to the involvement of α-bismuthino esters as an intermediate.

Next, control experiments using the isolated α-bismuthino ester **7** were performed (Scheme 2).[10] α-Bismuthino ester **7** did not react with phenylacetylene **1** at all, even in the presence of equimolar amounts of $BiBr_3$. In contrast, the addition of Me_3SiBr promoted carbobismuthination to furnish alkenyliodide **6** in 90 % yield. In addition, monitoring the mixture of **7** and Me_3SiBr by ^1H NMR spectroscopy revealed a regeneration of the starting ketene silyl acetal **2**, which indicated that **7** is a resting state rather than an intermediate.



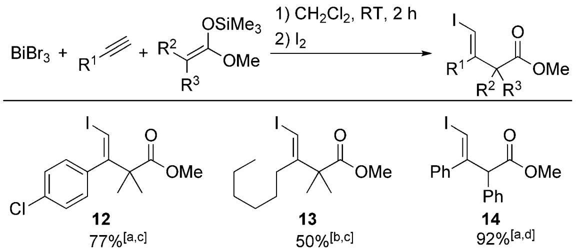
Scheme 2. Control experiments using α-bismuthino ester **7**.

A plausible reaction mechanism is illustrated in Scheme 3. It is similar to the mechanism proposed for carbometallation using indium and gallium trihalides, with exception of the transmetalation between $BiBr_3$ and ketene silyl acetal **9**.[8,9] The interaction between $BiBr_3$ and alkyne **8** results in a positive charge at the internal carbon of the triple bond, which is stabilized by the R^1 group.[11] Then, the internal carbon is attacked by ketene silyl acetal **9** *anti* to $BiBr_3$ to furnish monoalkenylbismuth **11** with regio- and stereoselectivity. α-Bismuthino ester **10** is not an active species, although the reversible transmetalation between $BiBr_3$ and **9** occurs to generate **10** and Me_3SiBr. $BiCl_3$, which promoted no carbobismuthination, irreversibly transmetalates with **9**. In fact, no formation of **9** was observed by ^1H NMR in the mixture of an isolated α-dichlorobismuthino ester and Me_3SiCl.[12] Although BiI_3 does not promote the transmetalation side reaction its Lewis acidity is too low to activate an alkyne.[13]



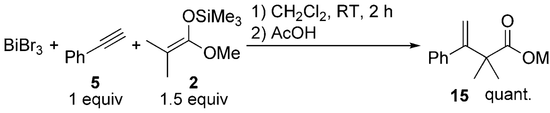
Scheme 3. Plausible mechanism.

Some representative alkynes and ketene silyl acetals were examined (Scheme 4). 4-Chlorophenylacetylene gave a slightly lower yield than phenylacetylene **5** because of the lower electron density of the alkyne moiety owing to the presence of the chloro group (**12**). An aliphatic alkyne also furnished the desired alkene **13** in 50 % yield at 55 °C. The use of a monophenyl-substituted ketene silyl acetal led to effective carbobismuthination at room temperature (**14**).



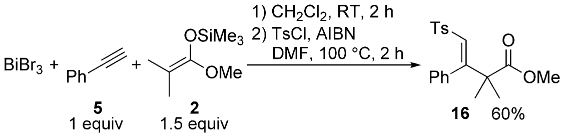
Scheme 4. Scope of alkenes and ketene silyl acetals. Reaction conditions: [a] $BiBr_3$ (1 mmol), alkyne (1 mmol), ketene silyl acetal (1.5 mmol), CH_2Cl_2 (2 mL), 2 h, RT. [b] $BiBr_3$ (1 mmol), alkyne (5 mmol), ketene silyl acetal (3 mmol), CH_2Cl_2 (2 mL), 2 h, 50 °C. [c] Yields determined by ^1H NMR spetroscopy. [d] Yield of the isolated product.

We investigated the transformation of the produced alkenylbismuth compounds. Acetic acid quantitatively protonolyzed alkenylbismuth under mild reaction conditions to furnish the corresponding disubstituted alkene **15** [Eq. (4)].



(4)

The substitution of a Br_2Bi group was successfully performed with *p*-toluenesulfonyl chloride and diphenyldisulfide in the presence of 2,2′-azoisobutyronitrile (AIBN) to give alkenylsulfone **16** and alkenylsulfide **17**, respectively [Eqs. (5) and (6); DMF = *N*,*N*′-dimethylformamide, Ts = *p*-toluenesulfonyl].[14] It is noteworthy that the stereochemistry of the carbon atom attached to the bismuth atom was retained after the introduction of a sulfur atom. This is the first example of the substitution of the bismuth atom in bismuth(III) compounds with a sulfur atom.[15]



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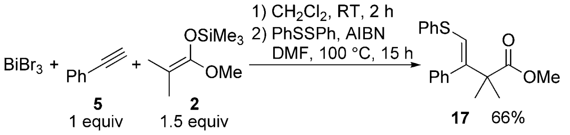
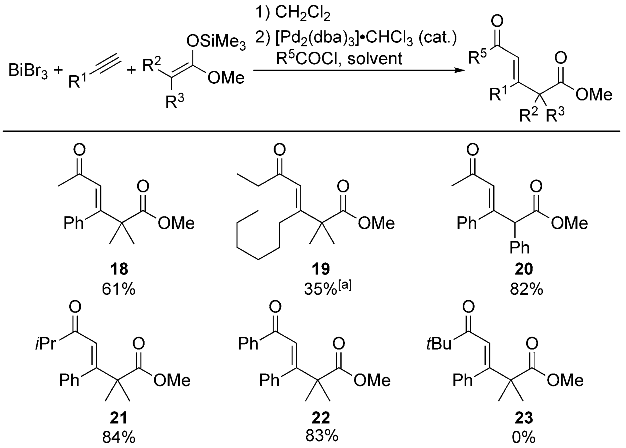


(6)

Finally, we developed a coupling reaction between the synthesized alkenylbismuth compounds and acid chlorides; as far as we could ascertain this reaction has been never reported (Scheme 5).[16] After the carbobismuthination using phenylacetylene **5** and ketene silyl acetal **2**, the successive addition of $[Pd_2(dba)_3]\cdot CHCl_3$, acetyl chloride, and DMF to the resultant CH_2Cl_2 solution afforded coupling product **18** as a single isomer in 61 % yield. The geometry of the olefinic double bond showed that the stereochemistry of the corresponding alkenylbismuth was retained. The alkenylbismuth produced from octyne gave the desired enone **19** in 35 % yield. Monophenyl-substituted ketene silyl acetal was also applicable (**20**). Coupling reactions using isobutyryl chloride and benzoyl chloride gave excellent results (**21** and **22**), although the bulky pivaloyl chloride could not be employed (**23**).



Scheme 5. One-pot formation of functionalized enones by coupling reactions between alkenylbismuth compounds and acid chlorides. Reaction conditions: 1) $BiBr_3$, alkyne (1 equiv), ketene silyl acetal (1.5 equiv), CH_2Cl_2 1 mL), RT, 2 h; 2) $[Pd_2(dba)_3]\cdot CHCl_3$ (0.1 equiv), acid chloride (2 equiv), solvent (DMF or HMPA; 2.5 mL), RT, 7 h. Yields of the isolated products are shown. [a] 1) $BiBr_3$, alkyne (5 equiv), ketene silyl acetal (3 equiv), CH_2Cl_2 (1 mL), 2 h, 50°C; 2) $[Pd_2(dba)_3]\cdot CHCl_3$ (0.05 equiv), acid chloride (2 equiv), solvent (HMPA; 2.5 mL), 7 h, 50°C. dba = dibenzylideneacetone, HMPA = hexamethylphosphorylamide.

In summary, we achieved the carbobismuthination of alkynes using $BiBr_3$ and ketene silyl acetals. X-ray crystallographic analysis of the alkenylbismuth product and control experiments revealed the reaction mechanism whereby $BiBr_3$ and a ketene silyl acetal add to an alkyne in an *anti* manner. In addition, the Br_2Bi group in the alkenylbismuth compounds was substituted by I, Ts, and SPh groups to obtain heteroatom-substituted alkenes. The Pd-catalyzed cross-coupling of alkenylbismuth compounds with acid chlorides achieved the synthesis of regio- and stereoselectively functionalized enones. Applications to other nucleophiles are currently underway.

Experimental Section

Typical Procedure (Table 1, entry 1): Ketene silyl acetal **2** (1 mmol) added to a suspension of $BiBr_3$ (1 mmol) and alkyne **1** (1.5 mmol) in dichloromethane (1 mL). The reaction mixture was stirred for 2 h at room temperature and then was quenched by I_2 (2 mmol). The resultant mixture was poured into $Na_2S_2O_3$ (aq) and extracted with Et_2O. The organic layer was dried over $MgSO_4$, and volatiles were removed under reduced pressure to afford the crude product, which was confirmed by ^1H NMR spectroscopy.

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Keywords: alkynes · bismuth · carbobismuthination · ketene silyl acetals · synthetic methods

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[17] CCDC 836576 (**3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.