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Highly Regio- and Stereoselective Carbostannylation Reaction of Fluorine-Containing Internal Acetylenes with Allylstannanes

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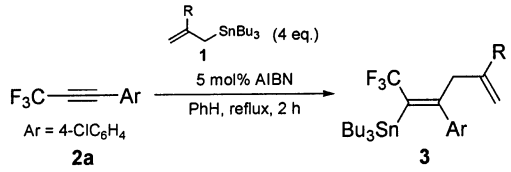
Abstract: Carbostannylation of fluoroalkylated alkynes with various allylstannanes in the presence of AIBN was investigated. In the case of the allylstannane having an electron-withdrawing group at the β position, the reaction proceeded highly regio- and stereoselectively to give the corresponding allylstannylated products in high yields. Even in the absence of AIBN, the reaction took place smoothly in a highly regio- and stereoselective manner under an atmosphere of air. Thus-obtained vinylstannanes were subjected to the Migita−Kosugi−Stille coupling reaction conditions, affording the tetrasubstituted alkenes in excellent yields.

Carbostannylation of alkynes has become a powerful synthetic tool in organic synthesis, because the C−C and C−Sn bonds are simultaneously introduced across a triple bond in a stereoselective fashion to give alkenylstannanes that can be converted into variously substituted ethenes with retention of configuration through the Migita−Kosugi−Stille coupling reaction.[1] Furthermore, the high chemoselectivity and mild reactivity of organostannanes, as compared with other organometallic reagents, make the carbostannylation and subsequent reactions extremely useful and applicable for preparing a wide variety of substances. Although the carbostannylation of alkynes, promoted by various mediators such as Lewis acid,[2] radical initiator,[3] nickel complex,[4] palladium complex,[5] etc., has been developed and studied extensively in *nonfluorinated* chemistry, the carbostannylation of *fluorine-containing* alkynes has attracted little attention so far. Herein, we wish to describe the highly regio- and stereoselective carbostannylation reaction of fluoroalkylated internal acetylene derivatives via a radical chain process.

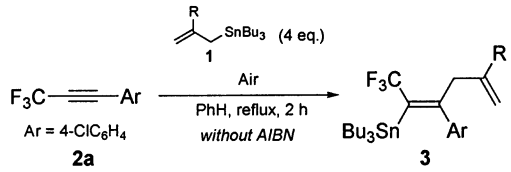
TABLE 1. Carbostannylation in the Presence of AIBN



entry	R	product	yield[a] (% of **3**)	recovery[a] (% of **2a**)
1[b]	CO_2Me (**a**)	**3a**	62	4
2[c]	CO_2Me (**a**)	**3a**	71	5
3	CO_2Me (**a**)	**3a**	80 (60)	1
4	CN (**b**)	**3b**	67	3
5	H (**c**)		tr	12
6	Me (**d**)		tr	9

[a] Determined by ^{19}F NMR. Value in parentheses is of isolated yield. [b] 1.2 equiv of allylstannane was employed. [c] 2.0 equiv of allylstannane was employed.

TABLE 2. Carbostannylation in the Absence of AIBN



entry	R	product	yield[a] (% of **3**)	recovery[a] (% of **2a**)
1	CO_2Me (**a**)	**3a**	(92)	0
2	CN (**b**)	**3b**	37	63
3	H (**c**)		0	99
4	Me (**d**)		0	99

[a] Determined by ^{19}F NMR. Value in parentheses is of isolated yield.

Initially, the addition of allylstannane **1a**−**d**[6] to trifluoromethylated alkyne **2a**[7] was examined in the presence of 5 mol % of AIBN at the reflux temperature of benzene, and the results are summarized in Table 1. Treatment of **2a** with 1.2 equiv of allylstannane **1a** gave the desired product **3a** in 62% yield, the starting material being recovered in 4% yield (entry 1). Increase of the amount of allylstannane improved the yield of **3a**. As a result, we found that the reaction with 4.0 equiv of **1a** proceeded smoothly to give **3a** in 80% yield as a sole product (entry 3). No regio- and stereoisomers were detected. We also examined the allylstannylation reaction using various allylstannanes **1b**−**d**. It should be noted that the substituent at the β position of **1** significantly affects efficiency of the reaction. Thus, allylstannane **1b**

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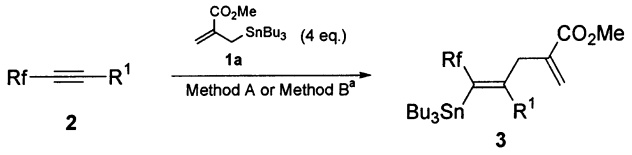
TABLE 3. Carbostannylation of Various Fluorinated Internal Acetylenes with Allylstannane 1a



				in the presence of AIBN (method A)		in the absence of AIBN (method B)	
entry	Rf	R^1	product	yield[b] (% of **3**)	recovery[b] (% of **2a**)	yield[b] (% of **3**)	recovery[b] (% of **2a**)
1	CF_3	Ph	**3c**	79	0	(90)	0
2	CF_3	*p*-ClC_6H_4	**3a**	80 (60)	0	(92)[c]	0
3	CF_3	*m*-ClC_6H_4	**3d**	81	0	(83)	0
4	CF_3	*o*-ClC_6H_4	**3e**	85	0	(83)	0
5	CF_3	*p*-$MeOC_6H_4$	**3f**	84	0	(86)	0
6	CF_3	*p*-MeC_6H_4	**3g**	91	0	(94)	0
7	CF_3	*p*-$EtO_2CC_6H_4$	**3h**	90	0	(86)	0
8	CF_3	*p*-$MeOC_6H_4CH_2$	**3i**	44 (44)	48	0	99
9	HCF_2	*p*-ClC_6H_4	**3j**	99 (99)	1	73[c]	8
10	$HCF_2CF_2CF_2$	*p*-ClC_6H_4	**3k**	84 (78)	0	28	53

[a] Method A: The reaction was carried out for 2 h at the reflux temperature of benzene in the presence of AIBN under the atmosphere of argon. Method B: The reaction was carried out for 12 h at the reflux temperature of benzene in the absence of AIBN under the atmosphere of the air. [b] Determined by ^{19}F NMR. Value in parentheses is of isolated yield. [c] Stirred for 2 h.

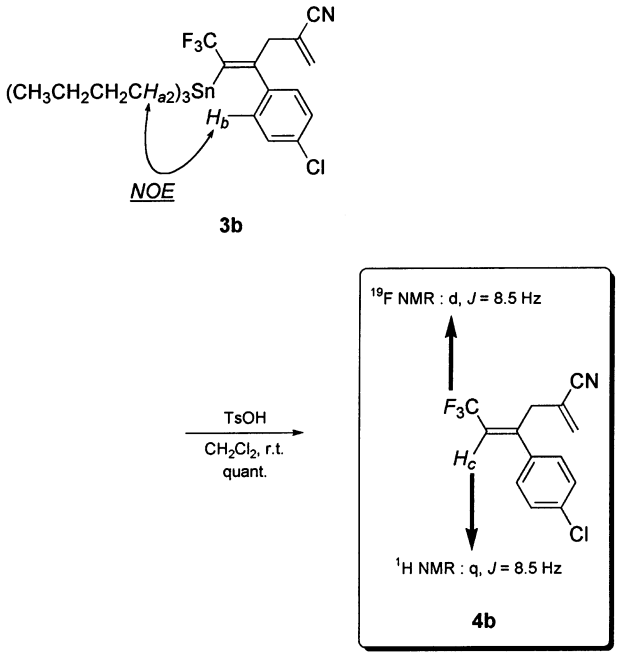
bearing an electron-withdrawing group (CN) at the β position efficiently reacted with **2a** to afford the vinylstannane **3b** in 67% yield (entry 4), whereas the reaction with allylstannane **1c** or **1d** having a H or Me moiety at the β position gave a complex mixture (entries 5 and 6).

It is interesting to note that the carbostannylation reaction of **2a** with **1a** proceeded smoothly even in the absence of AIBN, as shown in Table 2. Thus, treatment of **2a** with **1a** under an atmosphere of air for 2 h gave the vinylstannane **3a** in 92% isolated yield as a single isomer,[8] no regio- and stereoisomers being detected. The reaction with allylstannane **1b**, on the other hand, provided **3b** in only 37% yield. In the case of allylstannane **1c** or **1d**, the starting material was recovered quantitatively.

To examine the limitation of the allylstannylation reaction, a variety of fluoroalkylated internal acetylenes were subjected to the reaction with **1a** both in the presence and absence of AIBN. The results are collected in Table 3.

Generally, the allylstannylation proceeded smoothly to give the corresponding vinylstannanes **3** in high yields *in the presence of AIBN*. As shown in entries 1, 2, and 5−7, the alkynes having an aromatic ring with either an electron-donating group (MeO, Me) or an electron-withdrawing group (EtO_2C) were found to be good substrates. To be noted is that the position of the substituent on the benzene ring of **2** did not affect the yield at all (entries 2−4). In contrast, the use of an alkyl side chain as R^1 resulted in a significant decrease of the reaction rate (**3i**: 44% yield, 48% recovery of **2**), although the reaction proceeded with high regio- and stereoselectivity (entry 8). The substrates bearing various fluoroalkyl groups could participate well in the reaction to give the corresponding vinylstananes **3** in high yields (entries 9 and 10).

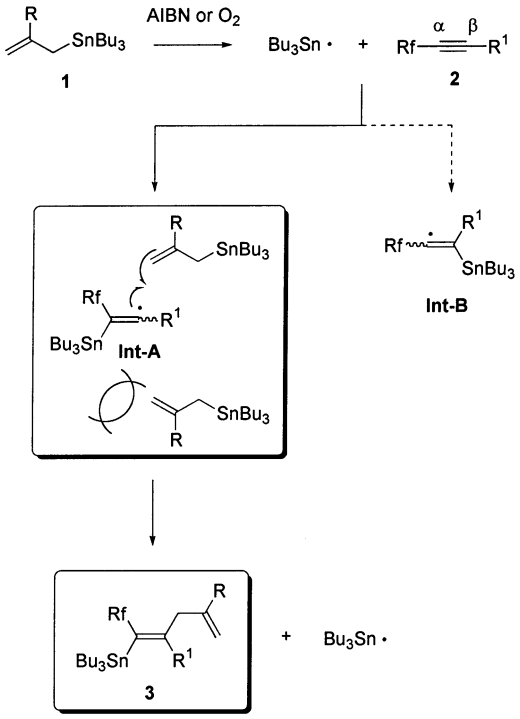
SCHEME 1. Stereochemistry of Carbostannylated Products 3



As shown in entries 1−7, the allylstannylation *without AIBN* (under an atmosphere of air) also proceeded smoothly to give the desired products **3** in excellent yields, comparable with the yields in the presence of AIBN, though a longer reaction period (12 h) was needed for completion of the reaction. Interestingly, the use of an alkyl side chain as R^1 led to the complete recovery of the starting material (entry 8). It is noteworthy that the difference of a fluoroalkyl group in **2** significantly influenced the reaction. Thus, the substrate with a difluoromethyl group gave **3j** in only 73% yield (Entry 9). Additionally, changing the fluoroalkyl group from a

(8) Under an atmosphere of argon, the reaction of **2a** with **1a** without AIBN was carried out several times; however, the result was not reproducible. In contrast, the allylstannylation under an atmosphere of the air proceeded very smoothly. Additionally, the reaction in the presence of 20 mol % BHT (2,6-di-*tert*-butyl-4-methylphenol, the radical inhibitor) without AIBN was performed under an atmosphere of the air at the reflux temperature of benzene for 12 h. As a result, the desired allylstannylated product **3a** was obtained in only 14% yield, together with the starting material in 86% yield. These results may indicate that the AIBN-free reaction also takes place via a radical chain process and the radical initiator is oxygen.

SCHEME 2. Mechanism

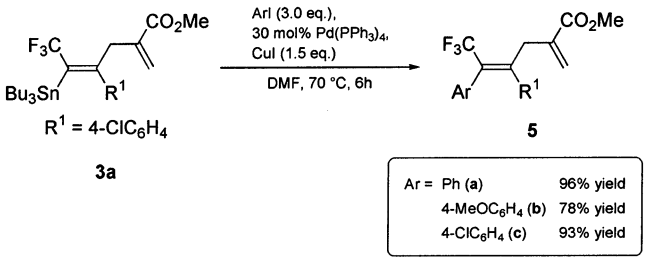


difluoromethyl group to a hexafluoropropyl group caused a significant decrease of the yield (entry 10).

The stereochemistry of the carbostannylated product **3** was determined as follows. Thus, the NOE between Ha and Hb in **3b** was observed in the NOESY, strongly indicating that the tributylstannyl group and the aromatic ring were situated in the *cis* configuration. Protolysis of **3b** with TsOH gave the corresponding destannylated product **4b**. ^{1}H and ^{19}F NMR spectra of **4b** showed a quartet signal due to the vinylic proton Hc and a doublet signal due to the CF_3 group, respectively (Scheme 1). These spectral data of **4b** suggest that the tributylstannyl group is attached with the carbon having the CF_3 group in **3b**. These results may allow us to draw the reaction mechanism as described in Scheme 2.[9]

In the initiation step, the radical generated from AIBN or the oxygen biradical reacts with allylstannane **1** to generate the tributylstannyl radical. As this stannyl radical is nucleophilic, the addition of the tributylstannyl radical to the alkyne **2** would take place at the more electrophilic α carbon as a result of the electron-withdrawing fluoroalkyl group,[10] leading to the vinyl radical, **Int-A** exclusively. The allylstannane favors the attack from the side occupied by a fluoroalkyl group, avoiding a bulkier tributylstannyl group because of large steric repulsion. Therefore, the vinylstannane **3** was formed in a highly stereoselective manner.

SCHEME 3. Palladium-Catalyzed Cross-Coupling Reaction



Finally, we confirmed the utility of the carbostannylation products by the transformation of **3a** to tetrasubstituted ethenes (Scheme 3). Thus, the palladium-catalyzed cross-coupling reaction with iodobenzene, *p*-methoxyiodobenzene, and *p*-chloroiodobenzene gave the corresponding tetrasubstituted alkenes with complete retention of the olefinic geometry in 96%, 78%, and 93% yield, respectively.

In summary, we have developed a highly regio- and stereoselective radical allylstannylation reaction to give the corresponding fluoroalkylated vinylstannane in excellent yields. Thus-obtained vinylstannane smoothly underwent the Kosugi−Migita−Stille cross-coupling, affording the tetrasubstituted alkenes in high yields.[11]

Supporting Information Available: Experimental procedure, characterization data, ^{1}H NMR and ^{13}C NMR spectra of **3a**−**k**, **4b**, **5a**, and NOESY of **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) A similar reaction mechanism has been proposed; see: Chae, J.; Konno, T.; Kanda, M.; Ishihara, T.; Yamanaka, H. *J. Fluorine Chem.* **2003**, *120*, 33−39.

(10) It has been reported that on treating 1-phenyl-1-hexyne with allylstannane in the presence of AIBN for 6 h, the corresponding vinylstannane was obtained in only 19% yield, whereas the allylstannylation of 6-dodecyne did not proceed at all (see ref 3a). It is apparent that fluoroalkyl groups promoted the allylstannylation both in the presence and absence of AIBN.

(11) This methodology for the preparation of various multisubstituted alkenes having a fluoroalkyl group is complementary to Ramachandran's, which involves the radical addition of a fluoroalkyl radical to the terminal alkynes, followed by Suzuki−Miyaura cross-coupling, the trisubstituted alkenes being produced. See: Jennings, M. P.; Cork, E. A.; Ramachandran, P. V. *J. Org. Chem.* **2000**, *65*, 8763−8766.