Facile Synthesis of Trifluoromethyl-substituted Enynes: Remarkable Reactivity and Stereoselectivity of Tributyl(3,3,3-trifluoropropynyl)stannane in Carbostannylation of Alkynes

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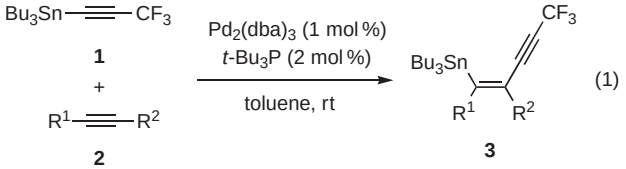
Carbostannylation of alkynes with tributyl(3,3,3-trifluoropropynyl)stannane is found to proceed at *room temperature* in a syn-manner, giving rise to the corresponding CF_3-substituted enynes as *a single stereoisomer* in good yields. Both terminal and, CF_3- or RO_2C-substituted internal alkynes are applicable to the addition reaction. Synthetic applications of the adduct are also demonstrated.

Since carbon–carbon triple bonds can undergo various kinds of transformations, 3,3,3-trifluoropropynyl-containing compounds[1] serve as versatile building blocks for the preparation of trifluoromethylated molecules, to which much attention has been paid in the fields of pharmaceuticals, agrochemicals, and organic materials.[2] Hence, generation and reactions of 3,3,3-trifluoropropynyllithium, -magnesium, -silyl, and -zinc reagents have been studied well.[3] Meanwhile, transition metal-catalyzed carbostannylation of alkynes with alkynylstannanes has emerged as a powerful synthetic tool because an alkynyl and stannyl groups are simultaneously incorporated into alkynes in a syn-manner to afford stereodefined alkenyltins, which can further be transformed into a variety of alkenes via stereospecific carbon–carbon and carbon–heteroatom bond formations with the aid of the tin functionality.[4] Therefore, carbostannylation of alkynes with 3,3,3-trifluoropropynylstannanes is highly attractive for the preparation of diverse trifluoromethylated enynes. We report here palladium-catalyzed carbostannylation of alkynes with tributyl(3,3,3-trifluoropropynyl)stannane (**1**),[5] which proceeds smoothly at room temperature to give CF_3-substituted enynes **3** as a single stereoisomer in good yields (Eq 1).



(1)

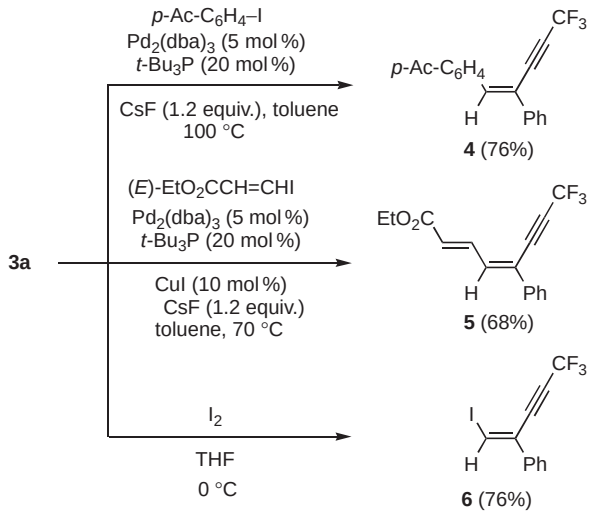
In the course of our synthetic study utilizing **1**, we attempted cross-coupling reaction of **1** with iodobenzene to prepare 3,3,3-trifluoro-1-phenylpropyne. Thus, a toluene solution of **1** and iodobenzene in the presence of $Pd_2(dba)_3$ (1 mol %) and t-Bu_3P (2 mol %) was stirred at room temperature.[6] The isolated product unexpectedly turned out to be alkenylstannane **3** ($R^1 = CF_3$, $R^2 = Ph$) as a single stereoisomer in 40% yield, which was considered to form via carbostannylation of the cross-coupled product with **1**. This result prompted us to investigate generality of the carbostannylation with **1**. The results are summarized in Table 1. Under the same conditions, aryl acetylenes **2a**–**2d** were carbostannylated with **1** at room temperature to give **3a**–**3d** as a stereochemically pure form in good yields (Entries 1–4),[7] respectively. *Z*-Stereochemistry of **3b** determined by NOE data of the vinyl hydrogen and protonolysis of the C–Sn bond[8] indicated that the reaction proceeded via syn-addition and the Bu_3Sn group that was bulkier than a CF_3CC group added to the less hindered sp carbon. Methyl propiolate (**2e**) and *N*,*N*-dimethyl propiolamide (**2f**) also reacted with **1** to afford stereochemically pure **3e** and **3f**, whose stereochemistries were deduced by protonolysis, with the opposite regioselectivity (Entries 5 and 6).[8] Since these stereochemical outcome is consistent with typical carbostannylation, the present reaction is considered to proceed via the well-accepted reaction mechanism,[4] which involves oxidative addition of **1** to the Pd(0) complex and successive insertion of an alkyne to the Pd–C bond followed by reductive elimination, resulting in production of **3** and regeneration of the Pd(0) complex.

Furthermore, the reaction of internal alkynes, which was usually difficult to achieve in the typical alkynylstannylation chemistry,[4] was scrutinized. The results are shown in entries 7–17 in Table 1. To our delight, the addition to CF_3-substituted aryl acetylenes **2g**–**2n** occurred also at room temperature under the same conditions to give **3g**–**3n** as a sole product (Entries 7–14). Various functional groups were tolerant under the conditions. Phenyl- and methyl-substituted propiolate derivatives **2o** and **2p** as well as dimethyl acetylenic dicarboxylate (**2q**) reacted

Table 1. Carbostannylation of alkynes **2** with **1**[a]

Entry	**2**	R^1	R^2	**3**	Yield/%
1	**2a**	H	C_6H_5	**3a**	79
2	**2b**	H	p-MeO-C_6H_4	**3b**	73
3	**2c**	H	p-C_6H_5-C_6H_4	**3c**	82
4	**2d**	H	p-CF_3-C_6H_4	**3d**	79
5	**2e**	CO_2Me	H	**3e**	78
6	**2f**	$CONMe_2$	H	**3f**	58
7	**2g**	CF_3	Ph	**3g**	76
8	**2h**	CF_3	p-Me-C_6H_4	**3h**	52
9	**2i**	CF_3	p-MeO-C_6H_4	**3i**	67
10	**2j**	CF_3	p-Cl-C_6H_4	**3j**	62
11	**2k**	CF_3	p-Ac-C_6H_4	**3k**	68
12	**2l**	CF_3	p-EtO_2C-C_6H_4	**3l**	57
13	**2m**	CF_3	p-O_2N-C_6H_4	**3m**	58
14	**2n**	CF_3	p-CF_3-C_6H_4	**3n**	67
15	**2o**	CO_2Et	Ph	**3o**	87
16	**2p**	CO_2Et	Me	**3p**	77
17	**2q**	CO_2Me	CO_2Me	**3q**	71

[a]Reagents and conditions: **1** (0.6 mmol), **2** (0.9 mmol), $Pd_2(dba)_3$ (6.0 μmol), t-Bu_3P (12 μmol), toluene (1.6 mL), and rt.



Scheme 1. Synthetic application of **3a**.

in a Michael fashion to afford **3o–3q** as a single stereoisomer in good yields, respectively (Entries 15–17). Since diphenylacetylene and 4-octyne did not react with **1** at all, the presence of such an electron-withdrawing group as CF_3 and CO_2R appears to be essential for the realization.

The fact that all the reactions took place at *room temperature* definitely shows remarkably higher reactivity of **1** than those of common alkynyltins which require heating at 50 or 90 °C to effect the carbostannylation reaction.[4] Strong electron-withdrawing effect by a CF_3 group may induce acceleration of the oxidative addition step to undergo the reaction at room temperature, which lead to perfect stereoselectivity.[9]

Alkenyltin functionality of **3** can be readily utilized for further transformation.[10] Representative examples with **3a** are demonstrated in Scheme 1. Pd-catalyzed cross-coupling reaction with aryl and alkenyl iodides gave CF_3-substituted enyne **4** and dienyne **5**, while iodinated enyne **6** was prepared in good yield by treatment with I_2 in THF.

In summary, we have demonstrated that carbostannylation of alkynes with tributyl(3,3,3-trifluoropropynyl)stannane constitutes facile and stereoselective synthesis of 1-tributylstannyl-5,5,5-trifluoropent-1-en-3-ynes. Both terminal and internal alkynes are applicable to the reaction. Synthetic application of the CF_3-substituted enynes is in progress in our laboratory.

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References and Notes

1 a) M. G. Barlow, S. Tajammal, and A. E. Tipping, *Chem. Commun.*, **1989**, 1637. b) N. Yoneda, S. Matsuoka, N. Miyaura, T. Fukuhara, and A. Suzuki, *Bull. Chem. Soc. Jpn.*, **63**, 2124 (1990). c) M. G. Barlow, S. Tajammal, and A. E. Tipping, *J. Fluorine Chem.*, **63**, 139 (1993). d) M. N. Bobrovnikov, E. S. Turbanova, and A. A. Petrov, *Russ. J. Org. Chem.*, **29**, 1445 (1993). e) M. G. Barlow, N. N. E. Suliman, and A. E. Tipping, *J. Fluorine Chem.*, **70**, 109 (1995). f) T. Yamazaki, K. Mizutani, and T. Kitazume, *J. Org. Chem.*, **60**, 6046 (1995). g) A. K. Brisdon, I. R. Crossley, K. R. Flower, R. G. Pritchard, and J. E. Warren, *Angew. Chem., Int. Ed.*, **42**, 2399 (2003). h) A. K. Brisdon, I. R. Crossley, R. G. Pritchard, G. Sadiq, and J. E. Warren, *Organometallics*, **22**, 5534 (2003). i) I. H. Jeong, S. L. Jeon, and B. T. Kim, *Tetrahedron Lett.*, **44**, 7213 (2003). j) J. Chae, T. Konno, T. Ishihara, and H. Yamanaka, *Chem. Lett.*, **33**, 314 (2004). k) T. Konno, J. Chae, T. Ishihara, and H. Yamanaka, *Tetrahedron*, **60**, 11695 (2004). l) T. Konno, J. Chae, T. Tanaka, T. Ishihara, and H. Yamanaka, *Chem. Commun.*, **2004**, 690. m) T. Konno, T. Daitoh, A. Noiri, J. Chae, T. Ishihara, and H. Yamanaka, *Org. Lett.*, **6**, 933 (2004). n) T. Konno, T. Takehana, J. Chae, T. Ishihara, and H. Yamanaka, *J. Org. Chem.*, **69**, 2188 (2004).

2 a) J. T. Welch, *Tetrahedron*, **43**, 3123 (1987). b) J. F. Liebman, A. Greenberg, and J. W. R. Dolbier, "Fluorine-containing Molecules: Structure, Reactivity, Synthesis, and Applications," VCH, New York (1988). c) J.-P. Begue and D. Bonnet-Delpon, *Tetrahedron*, **47**, 3207 (1991). d) M. A. McClinton and D. A. McClinton, *Tetrahedron*, **48**, 6555 (1992). e) R. E. Banks, B. E. Smart, and J. C. Tatlow, "Organofluorine Chemistry. Principles and Commercial Applications," Plenum Press, New York (1994). f) M. Hudlicky and A. E. Pavlath, "Chemistry of Organic Fluorine Compounds II A Critical Review," American Chemical Society-ACS Monograph 187, Washington, DC (1995). g) T. Hiyama, "Organofluorine Compounds-Chemistry and Applications," Springer, Berlin (2000). h) M. Shimizu and T. Hiyama, *Angew. Chem., Int. Ed.*, **44**, 214 (2005).

3 a) A. L. Henne and M. Nager, *J. Am. Chem. Soc.*, **74**, 650 (1952). b) F. G. Drakesmith, O. J. Stewart, and P. Tarrant, *J. Org. Chem.*, **33**, 280 (1968). c) J. E. Bunch and C. L. Bumgardner, *J. Fluorine Chem.*, **36**, 313 (1987). d) A. R. Katritzky, M. Qi, and A. P. Wells, *J. Fluorine Chem.*, **80**, 145 (1996). e) A. K. Brisdon and I. R. Crossley, *Chem. Commun.*, **2002**, 2420. f) T. Konno, J. Chae, M. Kanda, G. Nagai, K. Tamura, T. Ishihara, and H. Yamanaka, *Tetrahedron*, **59**, 7571 (2003).

4 a) E. Shirakawa, H. Yoshida, T. Kurahashi, Y. Nakao, and T. Hiyama, *J. Am. Chem. Soc.*, **120**, 2975 (1998). b) E. Shirakawa and T. Hiyama, *J. Organomet. Chem.*, **576**, 169 (1999). c) E. Shirakawa, H. Yoshida, Y. Nakao, and T. Hiyama, *J. Am. Chem. Soc.*, **121**, 4290 (1999). d) E. Shirakawa, K. Yamasaki, H. Yoshida, and T. Hiyama, *J. Am. Chem. Soc.*, **121**, 10221 (1999). e) E. Shirakawa, H. Yoshida, Y. Nakao, and T. Hiyama, *Org. Lett.*, **2**, 2209 (2000). f) H. Yoshida, E. Shirakawa, T. Kurahashi, Y. Nakao, and T. Hiyama, *Organometallics*, **19**, 5671 (2000). g) E. Shirakawa, Y. Nakao, H. Yoshida, and T. Hiyama, *J. Am. Chem. Soc.*, **122**, 9030 (2000). h) E. Shirakawa, Y. Nakao, and T. Hiyama, *Chem. Commun.*, **2001**, 263. i) H. Yoshida, E. Shirakawa, Y. Nakao, Y. Honda, and T. Hiyama, *Bull. Chem. Soc. Jpn.*, **74**, 637 (2001). j) H. Yoshida, Y. Honda, E. Shirakawa, and T. Hiyama, *Chem. Commun.*, **2001**, 1880. k) E. Shirakawa and T. Hiyama, *J. Organomet. Chem.*, **653**, 114 (2002). l) E. Shirakawa and T. Hiyama, *Bull. Chem. Soc. Jpn.*, **75**, 1435 (2002). m) E. Shirakawa, Y. Yamamoto, Y. Nakao, S. Oda, T. Tsuchimoto, and T. Hiyama, *Angew. Chem., Int. Ed.*, **43**, 3448 (2004).

5 T. Hanamoto, Y. Hakoshima, and M. Egashira, *Tetrahedron Lett.*, **45**, 7573 (2004).

6 No carbostannylated product formed when *N*-[2-(diphenylphosphino)benzylidene]cyclohexylamine, which was essential for conventional carbostannylation of alkynes, or PPh_3 was employed as a phosphine ligand with $Pd_2(dba)_3$ complex.

7 Reaction of alkyl acetylenes with **1** failed to give the carbostannylation products under the conditions.

8 See Supporting Information.

9 In marked contrast, no reaction took place with tributylpropynylstannane under the same conditions, suggesting that the fluorine atoms played a crucial role in the reaction of **1**.

10 a) M. Pereyre, J.-P. Quintard, and A. Rahm, "Tin in Organic Synthesis," Butterworth, London (1987). b) A. G. Davies, "Organotin Chemistry," VCH, Weinheim (1997).

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