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An Efficient Protocol for the Stereoselective Construction of Multisubstituted Fluorine-Containing Alkenes. A Palladium-Catalyzed Bisstannylation of Fluorinated Internal Alkynes

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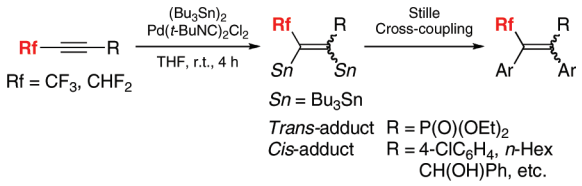

On treatment of various fluorinated internal alkynes with 1.2 equiv of hexabutylditin under the influence of 2.5 mol % of Pd(*t*-BuNC)$_2$Cl$_2$ in THF at room temperature for 4 h, the bisstannylation proceeded smoothly to afford the corresponding bisstannylated cis-adducts in high yields. Thus obtained adducts were subjected to the Stille cross-coupling reaction to give the corresponding tetrasubstituted fluorine-containing alkenes with defined stereochemistry in good yields.

Bisstannylation of alkynes has become a powerful synthetic tool in view of versatile elaborations: two C−Sn bonds are simultaneously introduced across the triple bonds of alkynes in a *syn*-selective manner to give vinylstannane, which can be converted into variously multisubstituted ethenes with retention of configuration through the Migita−Kosugi−Stille cross-coupling reaction.[1] Furthermore, high chemoselectivity and mild reactivity of organostannanes as compared with other organometallics, such as organolithium reagents, Grignard reagents, and so on, make the reactions extremely useful and applicable to a wide variety of substrates. Although the bisstannylation of various *nonfluorinated* alkynes has been published,[2] thus far there have been no studies on the reaction of *fluorinated* alkynes. Herein we wish to describe the first bisstannylation of fluorine-containing internal alkynes in detail.

Initially, the bisstannylation of the alkyne **1a**[3] with hexabutylditin was examined (Table 1). Thus, treatment of **1a** with 1.2 equiv of hexabutylditin in the absence of palladium catalyst in THF at room temperature for 4 h led to quantitative recovery of the starting alkyne (Table 1, entry 1). The use of Pd(PPh$_3$)$_4$ (2.5 mol %) did not provide a satisfactory result (Table 1, entry 2). In sharp contrast, the reaction in the presence of Pd(*t*-BuNC)$_2$Cl$_2$ took place smoothly to give the corresponding bisstannylated product **2a** in 86% yield as a sole product (entry 3). The obtained product was found to be the trans-adduct only. With this catalyst, the bisstannylation of various alkynes **1** was investigated.

As shown in entry 4 of Table 1, changing a fluoroalkyl group from a CF_3 to a CHF_2 group did not cause a significant influence on the reaction, the corresponding trans-adduct **2b** being obtained exclusively in 85% yield. The reaction of the alkynyl ester **1c** afforded the desired product in only 48% yield as an isomeric mixture in a ratio of 82:18, while the alkynes having an aryl group, such as *p*-ClC$_6$H$_4$, *p*-MeOC$_6$H$_4$, *p*-EtO$_2$CC$_6$H$_4$, and *p*-NCC$_6$H$_4$ groups, could participate in the reaction nicely to give the corresponding adducts in excellent yields (Table 1, entries 6, 7, 10, and 11). In these cases, the products were all cis-adducts. As shown in entries 7−9 of Table 1, the position of the substituent on the benzene ring of the alkynes did not affect the reaction at all, leading to the exclusive formation of the cis-adducts in high yields. However, the alkyne bearing a *p*-NO$_2$-substituted aryl group or a styryl group as R could not be applied for the reaction successfully (Table 1, entries 12 and 13).

We also investigated the bisstannylation of various γ-fluoroalkylated propargyl alcohols as well as amines in detail.[4] As listed in entries 14, 16, 17, 20, and 21 of Table 1, various propargyl alcohols **1*l***, **1n**, **1o**, **1r**, and **1s** having various aromatic substituents, such as phenyl, *p*-MeOC$_6$H$_4$, *p*-ClC$_6$H$_4$, 1-naphthyl, and 2-furyl moieties, could participate well in the bisstannylation to give the corresponding adducts **2*l***, **2n**, **2o**, **2r**, and **2s**, respectively, in high to excellent yields in a highly cis-selective manner. Additionally, the position of the substituent on the benzene ring of the alkynes did not influence the reaction at all, the cis-adducts **2o**−**q** being afforded in high yields (Table 1, entries 17−19). Various aliphatic substituents, such as *n*-hexyl, cyclohexyl, and β-styryl groups, did not bring about a significant change on the reaction (Table 1, entries 22−24). However, the alkynes having a bulky substituent,

(1) For a review on the bisstannylation of alkynes, see: Beletskaya, I.; Moberg, C. *Chem. Rev.* **1999**, *99*, 3435–3462.

(2) (a) Mancuso, J.; Lauten, M. *Org. Lett.* **2003**, *5*, 1653–1655. (b) Carter, N.; Mabon, R.; Richecoeur, A. M. E.; Sweeney, J. B. *Tetrahedron* **2002**, *58*, 9117–9129. (c) Beaudet, I.; Parrain, J.-L.; Quintard, J.-P. *Tetrahedron Lett.* **1991**, *32*, 6333–6336. (d) Mabon, R.; Richecoeur, A. M. E.; Sweeney, J. B. *J. Org. Chem.* **1999**, *64*, 328–329. (e) Casson, S.; Kocienski, P.; Reid, G.; Smith, N.; Street, J. M.; Webster, M. *Synthesis* **1994**, 1301–1309. (f) Piers, E.; Skerlj, R. T. *Can. J. Chem.* **1994**, *72*, 2468–2482. (g) Piers, E.; Skerlj, R. T. *J. Chem. Soc., Chem. Commun.* **1986**, 626–627. (h) Mitchell, T. N.; Amamria, A.; Killing, H.; Rutchow, D. *J. Organomet. Chem.* **1986**, *304*, 257–265.

(3) (a) Konno, T.; Morigaki, A.; Ninomiya, K.; Miyabe, T.; Ishihara, T. *Synthesis* **2008**, 564–572. For the synthetic methods for other fluorine-containing alkynes, see: (b) Konno, T.; Chae, J.; Kanda, M.; Nagai, G.; Tamura, K.; Ishihara, T.; Yamanaka, H. *Tetrahedron* **2003**, *59*, 7571–7580.

(4) (a) Konno, T.; Moriyasu, K.; Ishihara, T. *Synthesis* **2009**, 1087–1094. (b) Yamazaki, T.; Mizutani, K.; Kitazume, T. *J. Org. Chem.* **1995**, *60*, 6046–6056. (c) Mizutani, K.; Yamazaki, T.; Kitazume, T. *J. Chem. Soc., Chem. Commun.* **1995**, 51–52.

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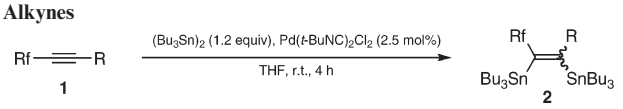
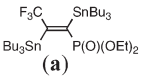
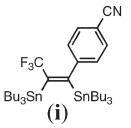
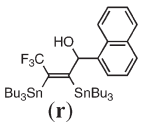
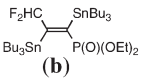
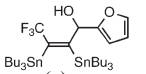
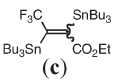
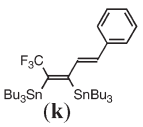
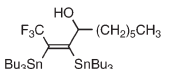
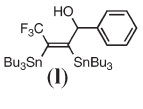
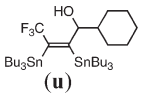
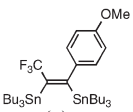
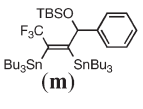
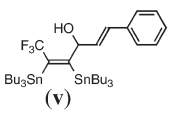
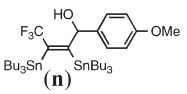
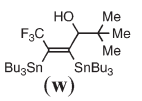
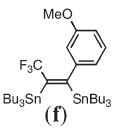
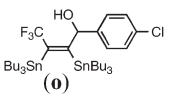
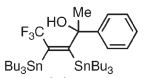
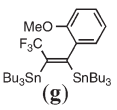
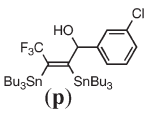
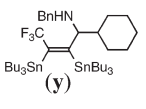
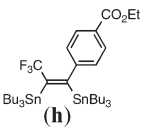
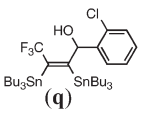
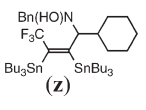
TABLE 1. Bisstannylation of Various Alkynes



entry	product	yield[a]/%	entry	product	yield[a]/%	entry	product	yield[a]/%
1		0[b]						
2		0[c]	11		81 (68)	20		63 (50)
3	(**a**)	86		(**i**)			(**r**)	
4	 (**b**)	85	12	 (**j**)	0	21	 (**s**)	91 (70)
5	 (**c**)	48 (30[d])	13	 (**k**)	19	22	 (**t**)	92 (76)
6	 (**d**)	99 (69)	14	 (**l**)	87 (87)	23	 (**u**)	83 (65)
7	 (**e**)	95 (84)	15	 (**m**)	26	24	 (**v**)	65
			16	 (**n**)	85 (71)	25	 (**w**)	0
8	 (**f**)	87 (82)	17	 (**o**)	quant. (92)	26	 (**x**)	0
9	 (**g**)	98 (86)	18	 (**p**)	91 (73)	27	 (**y**)	0
10	 (**h**)	95 (83)	19	 (**q**)	95 (89)	28	 (**z**)	0

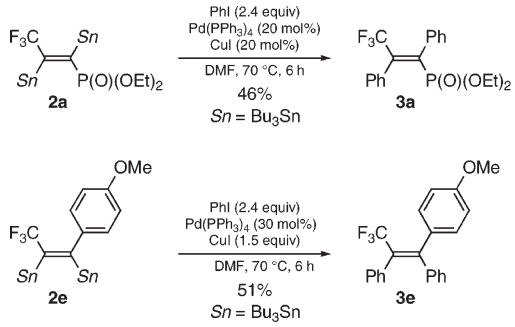
[a]Determined by ^{19}FNMR. Values in parentheses are of isolated yield. [b]In the absence of palladium catalyst. [c]$Pd(PPh_3)_4$ was used instead of $Pd(t\text{-BuNC})_2Cl_2$. [d]The isomeric ratio was 82:18.

such as *tert*-butyldimethylsilyloxy, *tert*-butyl, and 1-hydroxy-1-phenylethyl groups, did not react with hexabutylditin, the starting alkynes being recovered in high yields (Table 1, entries 15, 25, and 26). Neither propargylamine **1y** nor hydroxylamine **1z** underwent the bisstannylation at all, resulting in quantitative recovery of the starting amine (Table 1, entries 27 and 28).

As synthetic applications of the bisstannylated adducts, **2a** and **2e** were subjected to the Stille cross-coupling reaction to synthesize the multisubstituted fluorine-containing alkenes (Scheme 1).[5] Thus, treatment of **2a** or **2e** with 2.4 equiv of

(5) (a) Konno, T.; Takehana, T.; Chae, J.; Ishihara, T.; Yamanaka, H. *J. Org. Chem.* **2004**, *69*, 2188–2190. (b) Huang, X.; Xiong, Z.-C. *Synth. Commun.* **2003**, *33*, 2511–2517.

SCHEME 1. The Stille Cross-Coupling Reaction



iodobenzene in the presence of 20 mol % each of $Pd(PPh_3)_4$ and CuI[6] in DMF at 70 °C for 6 h gave the corresponding tetrasubstituted fluorine-containing alkene **3a** or **3e** in 46% or 51% yield, respectively.[7]

The structures of all new bisstannylated adducts **2a**−**v** were confirmed as follows (Figure 1).

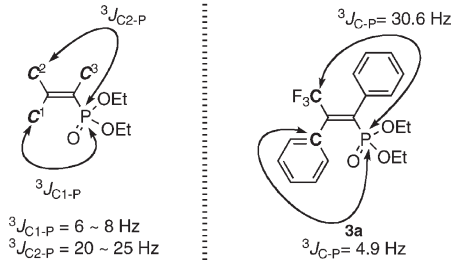
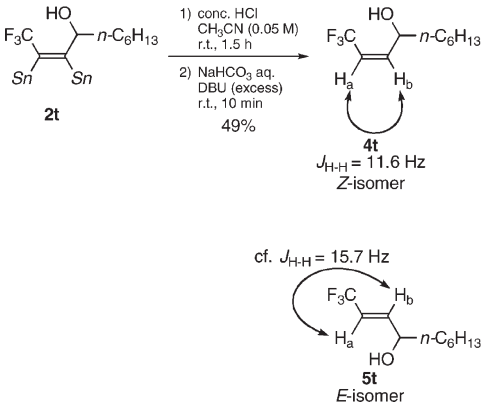


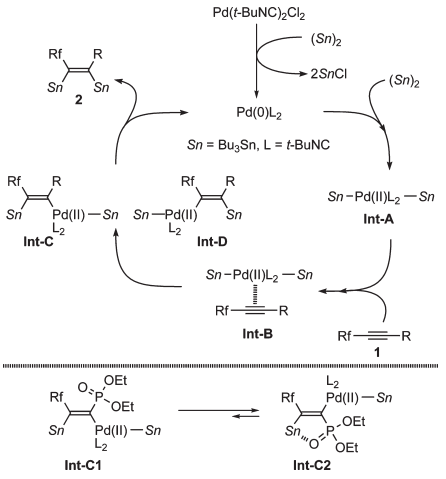
FIGURE 1. Determination of the Stereochemistry with the C−P Coupling Constants.

It is recognized that for various vinylphosphonates, the $^3J_{C1-P}$ coupling constant is generally smaller than $^3J_{C2-P}$ in the ^{13}C NMR, and that $^3J_{C1-P}$ and $^3J_{C2-P}$ are 6−8 and 20−25 Hz, respectively.[5b,8] Therefore, the small $^3J_{C1-P}$ (4.9 Hz) and the large $^3J_{C2-P}$ coupling constant (30.6 Hz) of **3a** are consistent with the cis and trans configuration of Ph or CF_3 with respect to phosphorus, respectively. This fact suggests that the bisstannylation of **1a** proceeded in a trans-selective fashion. On the other hand, **3e**, bearing a *p*-methoxyphenyl group is the known compound,[9] of which the stereochemistry was determined as *Z*. This means that the bisstannylation of **1e** took place in a cis-selective manner. Additionally, treatment of **2t**, derived from the bisstannylation of the propargyl alcohol **1t**, with concd HCl in CH_3CN at room temperature for 1.5 h, followed by the addition of $NaHCO_3$ and DBU, gave the corresponding destannylated product **4t** in 49% yield (Scheme 2).[10] The coupling constant

SCHEME 2. Determination of the Stereochemistry



SCHEME 3. A Proposed Mechanism



of H_a-H_b of **4t** in ^1H NMR was found to be 11.6 Hz, while that of the known *E* isomer **5t** has been reported as 15.7 Hz.[11] Therefore, the stereochemistry of **4t** is assigned as the cis configuration, suggesting that the bisstannylation of **1t** occurred in an exclusively cis-selective manner.

The structures of the other products were determined on the basis of the comparison with the chemical shifts of **2a**, **2e**, and **2t** in ^{19}F NMR.

These results may allow us to draw the reaction mechanism as described in Scheme 3. Thus, the present bisstannylation presumably proceeds via (1) generation of Pd(0)$(t\text{-BuNC})_2$ through the reduction of $Pd(t\text{-BuNC})_2Cl_2$ by $(Bu_3Sn)_2$, (2) oxidative addition of $(Bu_3Sn)_2$ to Pd(0)$(t\text{-BuNC})_2$ to form the stannylpalladium intermediate **Int-A**, (3) coordination of the alkyne **1** to the palladium center of **Int-A** (as shown by **Int-B**) and subsequent insertion into the Sn−Pd bond giving rise to the vinylpalladium intermediate **Int-C** and/or **Int-D**, and (4) reductive elimination of **Int-C** and/or **Int-D** to afford the bisstannylated cis-product **2** and regeneration of Pd(0)$(t\text{-BuNC})_2$.

In the case of **1a**,**b**, it is highly possible that **Int-C1** and **Int-C2** are in equilibrium,[12] in which **Int-C2** is more stable due to

(6) For the effect of copper(I) salt, see: (a) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905–5911. (b) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359–5364.

(7) Treatment of **2e** with 2.4 equiv of Ph_2ICl instead of PhI in the presence of 20 mol % of $Pd(PPh_3)_4$ and 1.5 equiv of CuI in DMF at room temperature for 6 h gave the corresponding Stille cross-coupling product **3e** in higher yield (75% yield).

(8) (a) Drag, M.; Kafarski, P.; Pirat, J.-L.; Cristau, H.-J. *Phosphorus, Sulfur Silicon* **2002**, *177*, 1153–1156. (b) Cristau, H.-J.; Mbianda, X. Y.; Beziat, Y.; Gasc, M.-B. *J. Organomet. Chem.* **1997**, *529*, 301–311. (c) Cristau, H.-J.; Gasc, M.-B.; Mbianda, X. Y. *J. Organomet. Chem.* **1994**, *474*, C14–C15.

(9) Konno, T.; Taku, K.; Ishihara, T. *J. Fluorine Chem.* **2006**, *127*, 966–972.

(10) Miura, K.; Saito, H.; Fujisawa, N.; Hosomi, A. *J. Org. Chem.* **2000**, *65*, 8119–8122.

(11) Yamazaki, T.; Ichige, T.; Kitazume, T. *Org. Lett.* **2004**, *6*, 4073–4076.

(12) It has been reported that (*Z*)-2,3-bis(trimethylstannyl)alk-2-enoates are thermally unstable, and that they easily isomerize into the (*E*) isomer at 75−95 °C. See ref 2g.

the interaction between tin and the phosphonyl oxygen atom. Then, the reductive elimination takes place from **Int-C2**, giving the corresponding trans-adduct exclusively.[13]

In conclusion, we have demonstrated the bisstannylation of various fluorine-containing internal alkynes with hexabutylditin in the presence of Pd(*t*-BuNC)$_2$Cl$_2$ in THF at room temperature. The reaction proceeded smoothly in a highly cis-selective manner to give the corresponding adducts in good to high yields. The obtained vinylstannanes were subjected to the Stille cross-coupling reaction conditions, the corresponding tetrasubstituted alkenes being afforded with high stereoselectivity in good yields.

Experimental Section

Typical Procedure for Bisstannylation. To a solution of 1-(4-chlorophenyl)-3,3,3-trifluoropropyne (**1d**) (0.051 g, 0.25 mmol) and Pd(*t*-BuNC)$_2$Cl$_2$ (0.002 g, 0.00625 mmol, 2.5 mol %) in THF (2.5 mL) was added a THF solution of hexabutylditin (0.176 g, 0.30 mmol) at room temperature. The whole mixture was stirred for 4 h at room temperature. The reaction was then quenched with H_2O. The resulting mixture was extracted three times with Et_2O. The combined ethereal layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:EtOAc 30:1) to afford (*Z*)-1,2-bis(tributylstannyl)-1-(4-chlorophenyl)-3,3,3-trifluoropropene (**2d**) (0.14 g, 0.17 mmol, 69% yield). ^{1}H NMR ($CDCl_3$) δ 0.79−1.55 (m, 54H), 6.73 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.9 (d, J = 1.6 Hz), 12.1, 13.2, 13.3, 13.4, 13.5, 27.0, 27.1, 27.2, 28.1, 30.3, 124.5 (q, J = 281.0 Hz), 130.4, 145.5, 146.5 (q, J = 28.1 Hz), 172.5 (q, J = 7.5 Hz); ^{19}F NMR ($CDCl_3$) δ −49.2 (s, 3F); IR (neat) 2957, 2871, 1481, 1463, 1377, 1227, 1180, 1135, 960, 864 cm^{-1}. Anal. Calcd for $C_{33}H_{58}ClF_3Sn_2$: C, 50.51; H, 7.45. Found: C, 50.25; H, 7.67.

Supporting Information Available: Characterization data, ^{1}H and/or ^{13}C NMR spectra of **2a**−**i**, **2*l***, **2n**−**v**, **3a**, and **4t**. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) To clarify the reaction mechanism, we attampted the bisstannylation of **1a** with hexabutylditin in the presence of 20 mol % of 4-*tert*-butyl-2,6-dimethylphenol and 2.5 mol % of Pd(*t*-BuNC)$_2$Cl$_2$ in THF at room temperature for 4 h. As a result, the corresponding bisstannylated trans-adduct **2a** was obtained in 90% yield. This means that the radical mechanism is excluded.