Preliminary Note

Palladium-catalyzed cross-coupling of (*E*)-(3-trifluoromethyl-1,3-butadienyl)di-isopropoxyborane with vinyl halides. An efficient stereospecific synthesis of trifluoromethylated 1,3,5-trienes

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Abstract

1,3,5-Trienes containing a CF_3 group have been synthesized stereospecifically in good yield via the palladium-catalyzed cross-coupling of (*E*)-(3-trifluoromethyl-1,3-butadienyl)di-isopropoxyborane with vinyl halides. As a synthetic application, a novel CF_3-containing nucleoside derivative was synthesized via this methodology.

Preparations of trifluoromethylated compounds are in great demand because of their biological activities and high performance as materials [1]. Aromatic compounds with a CF_3 group can be obtained quite readily via direct trifluoromethylation using such reagents as trifluoromethyl copper and related organometallics [2], and by transformation of the trichloromethyl group with hydrogen fluoride and of carboxy groups with sulfur tetrafluoride [3]. In contrast, the direct introduction of CF_3 groups into aliphatic molecules is often difficult because of the requirement for milder reaction conditions and the limited intrinsic reactivity of various trifluoromethylating reagents. Hence, the preparation of CF_3-containing intermediates and their utilization as building blocks has become an important strategy for the construction of trifluoromethylated aliphatic molecules [4].

Recently, we have reported the preparation of (*E*)-(3-trifluoromethyl-1,3-butadienyl)di-isopropoxyborane(**1**) and its application as a versatile CF_3-containing building block for the synthesis of (*E*)-1-aryl-3-trifluoromethyl-1,3-butadienes (Scheme 1) [5]. As a part of our continuing studies on expanding the scope of this CF_3-containing building block, we now wish to report our results on the palladium-catalyzed cross-coupling of **1** with vinyl halides to afford stereospecifically the 1,3,5-trienes bearing a CF_3 group (Scheme 2).

The results are summarized in Table 1. ^{19}F NMR and ^1H NMR spectra showed that the coupling reaction proceeded with retention of configuration for both the vinyl halide (entry 2, 6) and **1** without any contamination by other isomers. It is noteworthy that, in the presence of aqueous LiOH, the coupling reaction could take place with steroid halides (**2g**, **2h**) and **1**. Much effort has been paid to fluorine-modified steroids, such as fluorinated vitamin D_3, for their unique biological activity [6]. Hence, the present reaction provides a potentially useful approach to steroid compounds with a CF_3-containing side-chain. It should be mentioned that, using ethanolic NaOEt as the base, only reduction products could be obtained in the case of such steroid vinyl halides. From the mechanistic viewpoint, LiOH and NaOEt are quite different bases; LiOH only pro-

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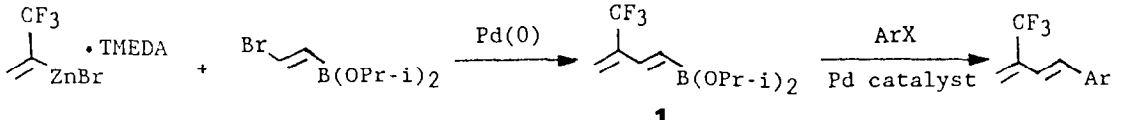

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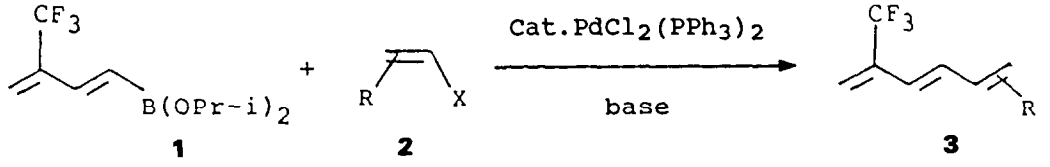
Scheme 1.



1 **2** **3**

Scheme 2.

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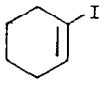
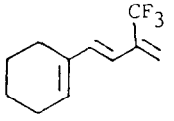
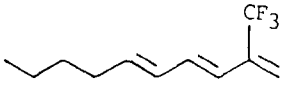
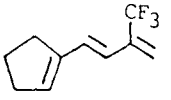
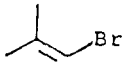
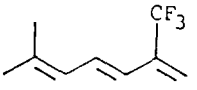
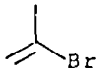
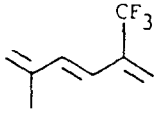
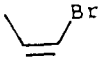
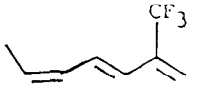
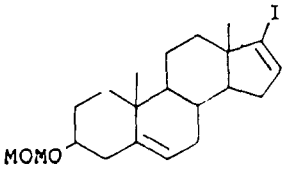
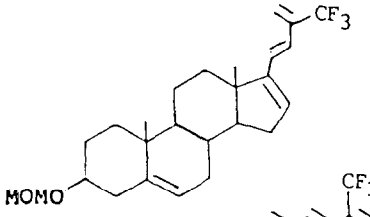
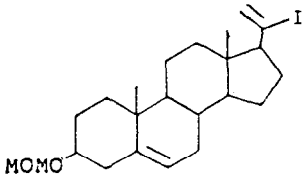
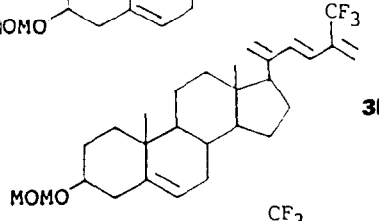
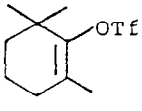
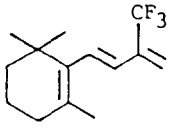
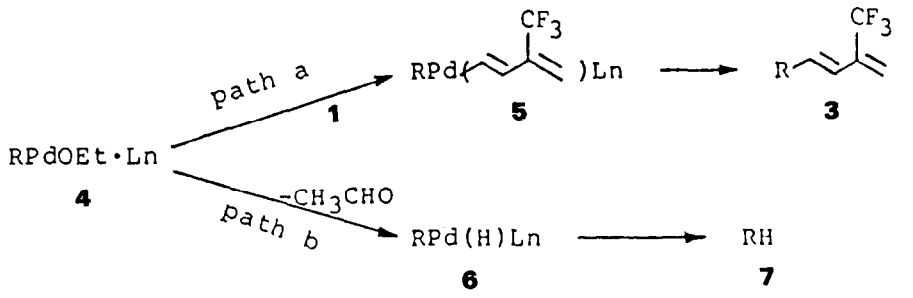
TABLE 1. Cross-coupling of (*E*)-(3-trifluoromethyl-1,3-butadienyl)di-isopropoxyborane(**1**) with vinyl halides

Entry No.	Vinyl halides (2)		Reaction conditions[a] Temp.(°C)/time(h)	Products (3)[d]		Yields[e] (%)
1		**2a**	60/3		**3a**	84
2		**2b**	60/3		**3b**	68
3		**2c**	60/3		**3c**	89
4		**2d**	80/3		**3d**	77
5		**2e**	80/4		**3e**	81
6		**2f**	70/4		**3f**	79
7		**2g**	70/4[b]		**3g**	61
8		**2h**	70/3[b]		**3h**	75
9		**2i**	85/4[c]		**3i**	63

[a]Mole ratio of **1** to vinyl halides = 1.1:1, 3 mol% of $PdCl_2(PPh_3)_2$ (based on vinyl halide) was used as catalyst and 2 equiv. of ethanolic NaOEt (2 M) as base. Benzene was the solvent unless otherwise stated.
[b]Aqueous LiOH (2 M, 2 equiv.) was used as base and THF as solvent.
[c]$Na_3PO_4 \cdot 12H_2O$ (solid, 2 equiv.) was used as base and 1,4-dioxan as solvent.
[d]All products were fully characterized by ^1H, ^{19}F and IR spectroscopy, by C, H, F elemental analyses of HRMS.
[e]Isolated yield based on vinyl halide.

motes the normal coupling reaction whereas NaOEt mediates both the coupling (Scheme 3, path a) and reduction (Scheme 3, path b) reactions [7]. In the case of steroid vinyl halides, the extremely bulky steroidal group largely suppresses transmetallation between the boron reagent **1** and the palladium complex **4** (Scheme 3, path a). Thus, when using ethanolic NaOEt as the base, the competitive reduction process occurs relatively easily, thereby resulting only in the formation of a reduction product. Under the same conditions reported

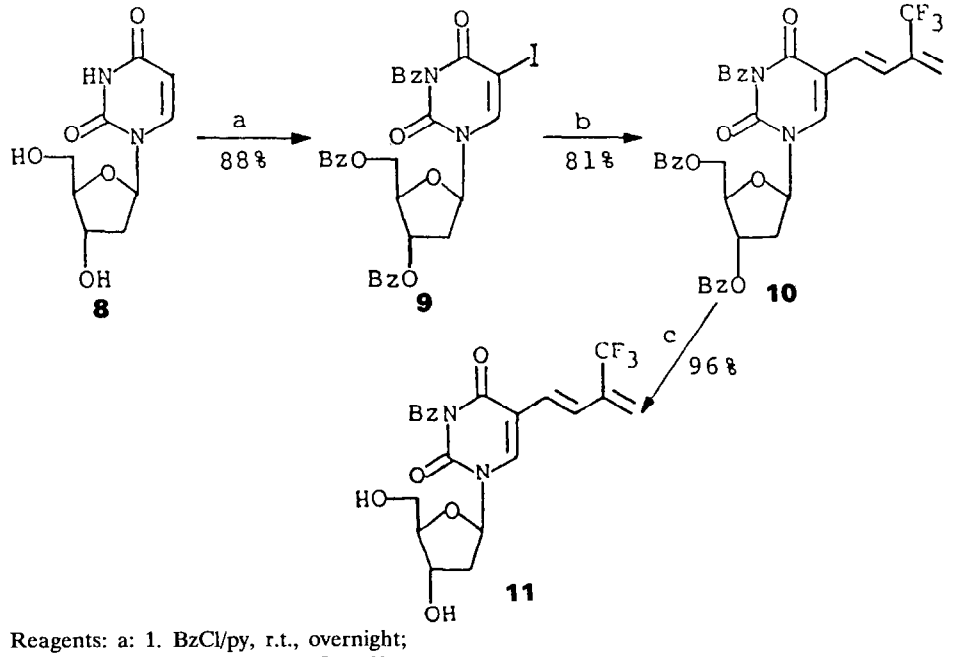


Scheme 3.

by Suzuki *et al.* [8], coupling of **1** with an enol triflate could proceed as usual (Table 1, entry 9).

It is well known that 5-substituted pyrimidine nucleosides are potent antivirus and anticancer agents. Thus, to date, 5-(*E*)-(2-bromovinyl)-2′-deoxyuridine [9] and 5-(*E*)-(2-trifluoromethyl-vinyl)-2′-deoxyuridine [10] exhibit the highest inhibitory activity against herpes simplex virus type-1 (HSV-1) of all the antiviral compounds. We have found that coupling could also take place between **1** and a 5-halogen-substituted uridine, affording an interesting 5-(*E*)-(ν-CF_3-α,ν-butadienyl)-substituted uridine derivative. 2′-Deoxyuridine(**8**) was first converted into the iodo derivative **9** by protective benzoylation and subsequent treatment with iodine chloride. Coupling of **9** with **1** in the presence of palladium catalyst and aqueous LiOH gave compound **10** in 81% yield. Finally, alkaline hydrolysis of **10** at room temperature afforded the 3-benzoyl-5-(*E*)-(ν-CF_3-α,ν-butadienyl)-2′-deoxyuridine (**11**) (Scheme 4).

In a typical experiment, to a stirred solution of iodide **2h** (234 mg, 0.5 mmol) in 6 ml of THF was added $PdCl_2(PPh_3)_2$ (11 mg) followed by the introduction of (*E*)-(3-trifluoromethyl-1,3-butadienyl)di-isopropoxyborane (**1**, 138 mg, 0.55 mmol) and an aqueous solution of LiOH (1 ml, 2 M). The reaction mixture was heated at 70 °C for 3 h. Usual work-up, followed by chromatography on silica gel using a mixture of petroleum ether (60–90 °C) and acetone (9:1) as the eluent, gave **3h** in 75% yield as an amorphous solid. IR(KCl) (cm^{-1}): 2900; 1710; 1600; 1100; 740. ^1H NMR ($CDCl_3$) δ: 0.60 (s, 3H); 1.00 (s, 3H); 3.38 (s, 3H); 3.46 (m, 1H); 4.70 (s, 2H); 5.10 (m, 1H); 5.38 (m, 2H); 5.56 (s, 1H); 5.68 (s, 1H); 6.26 (d, J=17 Hz, 1H); 6.56 (d, J=17 Hz, 1H) ppm. ^{19}F NMR(CCl_4) δ_{TFA}: −9.3 (downfield, s)



Reagents: a: 1. BzCl/py, r.t., overnight;
2. ICl/CH_2Cl_2, reflux, 2h
b: **1**, 3 mol% $PdCl_2(PPh_3)_2$, 2 equiv. LiOH, THF reflux
c: 2.5% KOH/MeOH, 1 h, r.t.

Scheme 4.

ppm. MS, *m/z* (relative intensity): 464 (M, 3.24); 463 (M − 1, 3.26); 257 (25.1); 45 (100). Analysis: Calc. for $C_{28}H_{39}F_3O_2$: C, 72.38; H, 8.46; F, 12.27%. Found: C, 72.69; H, 8.50; F, 12.36%.

Acknowledgements

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References

1 (a) R. Filler and Y. Kobayashi, *Biomedicinal Aspects of Fluorine Chemistry,* Kodansha, Tokyo, 1982; (b) M. Hudlicky, *Chemistry of Organic Fluorine Compounds,* Ellis Horwood, New York, 1976.

2 (a) Y. Kobayashi and I. Kumadaki, *Tetrahedron Lett.,* (1969) 4095; (b) D.M. Wiemers and D.J. Burton, *J. Am. Chem. Soc., 108* (1986) 823; (c) J.H. Clark, M.A. McClinton and R.J. Blade, *J. Chem. Soc., Chem. Commun.,* (1988) 638.

3 (a) C.W. Tullock, F.S. Fawcett, W.C. Smith and D.D. Coffman, *J. Am. Chem. Soc., 82* (1960) 539; (b) R. Filler, *Adv. Fluorine Chem., 6* (1970) 1; (c) M.R.C. Gerstenberger and A. Hans, *Angew. Chem., Int. Ed. Engl., 20* (1981) 647; (d) G.A. Bosswell, Jr., W.C. Ripka, R.M. Scribner and C.W. Tullock, *Org. React., 21* (1974) 1.

4 (a) K. Tanaka, S. Maeno and K. Mitsuhashi, *Chem. Lett.,* (1982) 543; (b) T. Taguchi, R. Namba, M. Nakazuwa, M. Nakajima, Y. Nakama, Y. Kobayashi, N. Hara and N. Ikekawa, *Tetrahedron Lett., 29* (1988) 27; (c) T.E. Nickson, *J. Org. Chem., 53* (1988) 3870; (d) Y. Kanitori, M. Hojo, R. Masuda, T. Yishida, S. Ohara, K. Yamada and N. Yoshikawa, *J. Org. Chem., 53* (1988) 519; (e) K. Tanaka, *J. Syn. Org. Chem. Jpn., 48* (1990) 16.

5 F. Jin, Y.-Y. Xu and B. Jiang, *J. Fluorine Chem., 65* (1993) 111.

6 Y. Kobayashi and T. Taguchi, *J. Synth. Org. Chem. Jpn., 43* (1985) 1073.

7 N. Miyaura, K. Yamada, H. Suginome and A. Suzuki, *J. Am. Chem. Soc., 107* (1985) 972.

8 Takayuki Oh-e, N. Miyaura and A. Suzuki, *Synlett.,* (1990) 221.

9 (a) E. De Clercq, J. Descamps, G. Vechels, R.T. Walker, A.S. Jones, P.F. Tonence and D. Shugar, *J. Infect. Dis., 141* (1980) 563; (b) E. De Clercq, E. Verhelst, J. Descamps and D.E. Bergstorm, *Acta Microbiol. Acad. Sic. Hung., 28* (1981) 307.

10 D.E. Bergstorm, J.T. Ruth, P.A. Reddy and E. De Clercq, *J. Med. Chem., 27* (1984) 279.