

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

Fuqiang Jin and Yuan-Yao Xu*

Shanghai Institute of Organic Chemistry, Academia Sinica,
345 Lingling Lu, Shanghai 200032 (China)

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Abstract

1,3,5-Trienes containing a CF₃ 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 CF₃-containing nucleoside derivative was synthesized via this methodology.

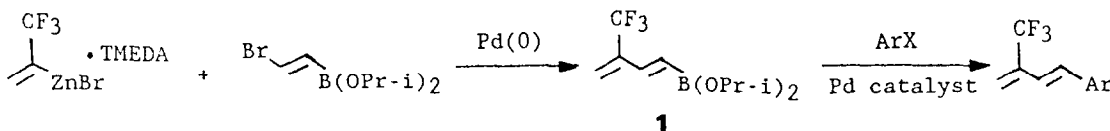
Preparations of trifluoromethylated compounds are in great demand because of their biological activities and high performance as materials [1]. Aromatic compounds with a CF₃ group can be obtained quite readily via direct trifluoromethylation using such reagents as trifluoromethyl copper and related organometallics [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 CF₃ 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 CF₃-containing intermediates and their utilization as building blocks has become an important strategy for the construction of trifluoromethylated aliphatic molecules [4].

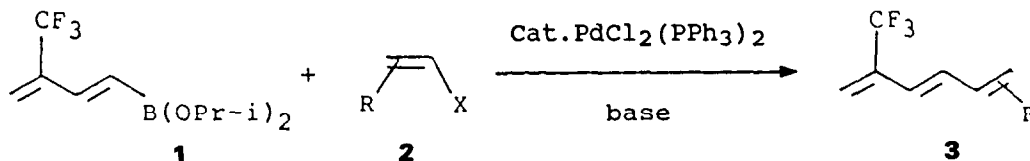
Recently, we have reported the preparation of (*E*)-(3-trifluoromethyl-1,3-butadienyl)di-isopropoxyborane (**1**) and its application as a versatile CF₃-containing building block for the synthesis of (*E*)-1-aryl-3-trifluoromethyl-1,3-butadienes (Scheme 1) [5]. As a part of our continuing studies on expanding the scope of this CF₃-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 CF₃ group (Scheme 2).

The results are summarized in Table 1. ¹⁹F 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 D₃, for their unique biological activity [6]. Hence, the present reaction provides a potentially useful approach to steroid compounds with a CF₃-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-

*Author to whom correspondence should be addressed.

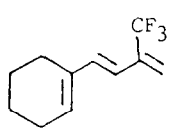
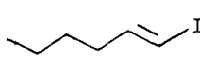
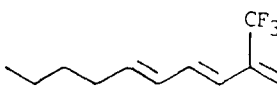
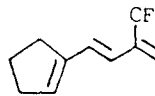
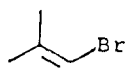
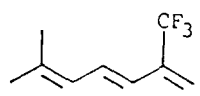
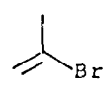
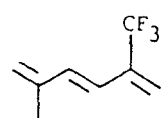
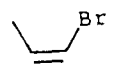
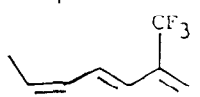
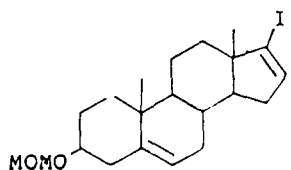
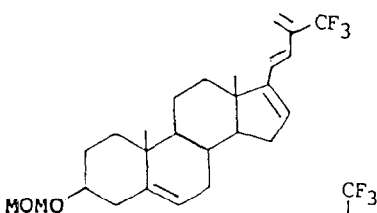
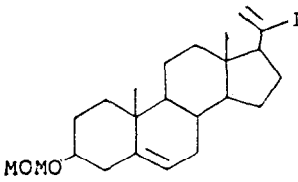
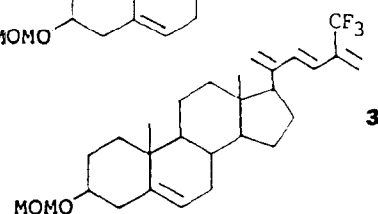
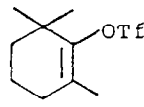
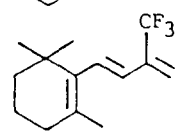


Scheme 1.



Scheme 2.

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		Products (3) ^d	Yields ^e (%)
			Temp.(°C)/time(h)			
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

^aMole ratio of **1** to vinyl halides = 1.1:1, 3 mol% of PdCl₂(PPh₃)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.

^bAqueous LiOH (2 M, 2 equiv.) was used as base and THF as solvent.

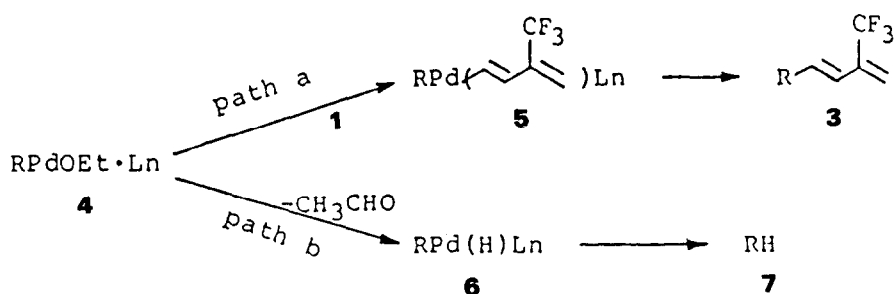
^cNa₃PO₄·12H₂O (solid, 2 equiv.) was used as base and 1,4-dioxan as solvent.

^dAll products were fully characterized by ¹H, ¹⁹F and IR spectroscopy, by C, H, F elemental analyses of HRMS.

^eIsolated 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 transmetalation 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



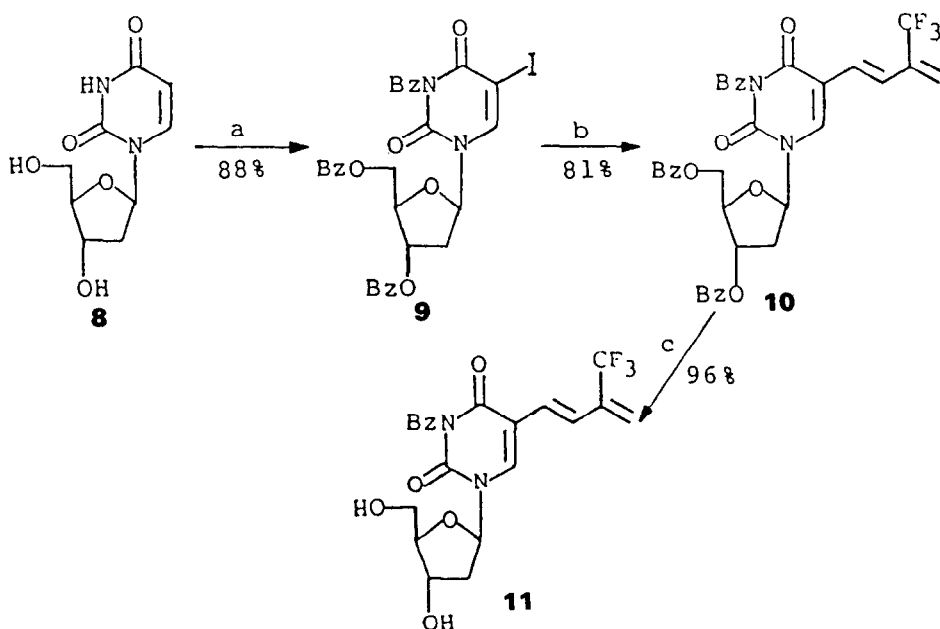
Scheme 3.

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 antiviral 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-CF₃-α,ν-butadienyl)-substituted uridine derivative. 2'-Deoxyuridine (**8**) was first converted into the iodo derivative **9** by protective benzylation 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-CF₃-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 PdCl₂(PPh₃)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 (CDCl₃) 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. ¹⁹F NMR(CCl₄) δ_{TFA}: -9.3 (downfield, s)



Reagents: a: 1. BzCl/py, r.t., overnight;
2. ICl/CH₂Cl₂, reflux, 2h
b: **1**, 3 mol% PdCl₂(PPh₃)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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