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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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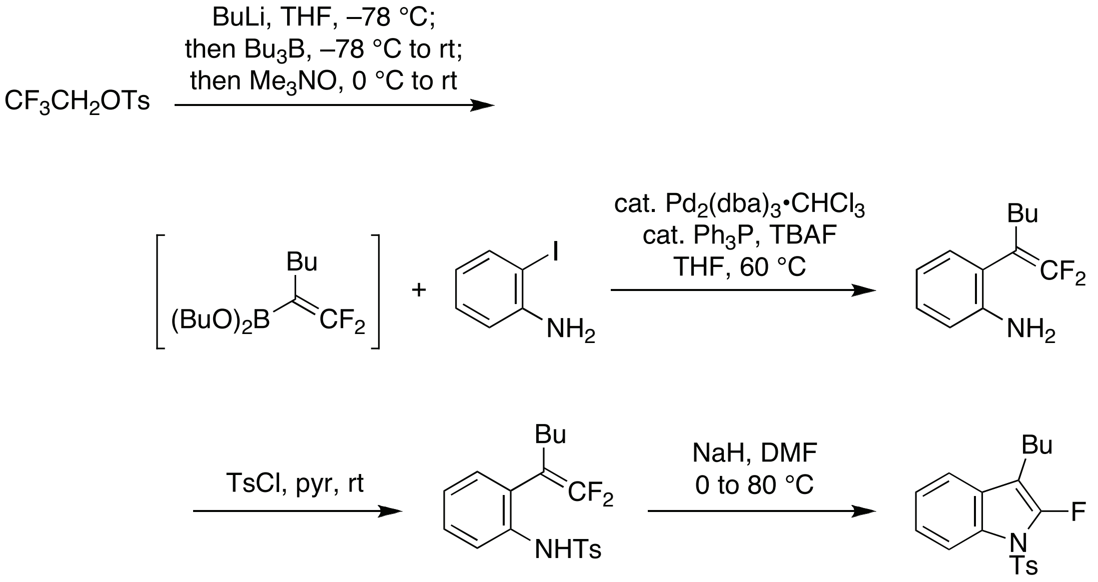
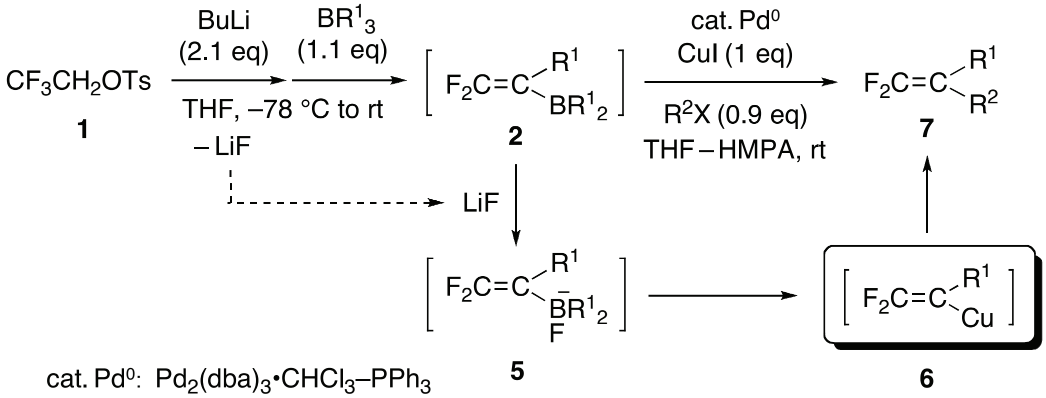
Discussion Addendum for:

5-*ENDO-TRIG* CYCLIZATION OF 1,1-DIFLUORO-1-ALKENES: SYNTHESIS OF 3-BUTYL-2-FLUORO-1-TOSYLINDOLE (1*H*-INDOLE, 3-BUTYL-2-FLUORO-1-[(4-METHYLPHENYL)SULFONYL]-)



Prepared by Junji Ichikawa.*[1]
Original article: Ichikawa, J.; Nadano, R.; Mori, T.; Wada, Y. *Org. Synth.* **2006**, *83*, 111.

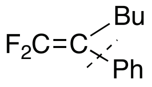
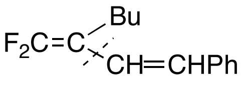
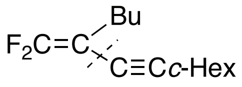
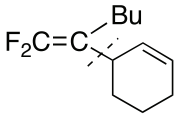
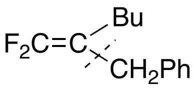
The precursors of 2-fluoroindoles, β,β-difluorostyrenes, are prepared by the palladium-catalyzed coupling reaction of 2,2-difluorovinylboron compounds with aryl iodides. The reaction of dialkyl(2,2-difluorovinyl)boranes **2** (Scheme 1) with an aryl iodide resulted in the coupling of not only the difluorovinyl but also the alkyl moieties on the boron. The contamination by alkyl-coupling product was suppressed by using fluoride salt as a base,[2a,3] and eventually overcome by the selective oxidation of the alkyl–boron bonds leading to the boronates prior to the coupling reaction as shown in the above scheme. Another way is a vinyl-selective transmetalation from boron to palladium via copper(I) species **6** (Scheme 1). On treatment of *in-situ* generated **2** with aryl iodides in the presence of cuprous iodide and a palladium catalyst, disubstituted difluoroalkenes **7** are obtained in excellent yield (Table 1).[2b,2c,4b]



Scheme 1

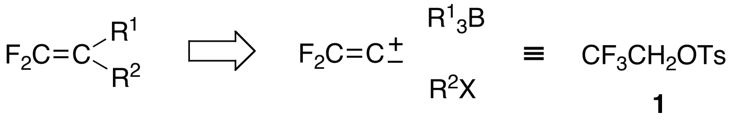
Alkenyl iodides and bromides,[5] and benzyl bromides[2c] are also successfully employed in the cross-coupling reaction. The configuration of 1-alkenyl halides is completely preserved during the reaction. The coupling reaction with alkynyl iodides[6] and allyl bromides[2c] proceeds without the palladium catalyst. These reactions provide important synthetic intermediates such as 1,1-difluoro-1,3- and -1,4-dienes and 1,1-difluoro-1,3-enyenes (Scheme 1, Table 1).

Table 1. Synthesis of Disubstituted 1,1-Difluoro-1-alkenes

Product, Time (Halide); Yield from **1**		
		
1 h (I); 90%	1 h (Br); 86%	1 h (I); 77%[a,b]
		
1 h (Br); 66%[b]	15 h (Br); 61%	

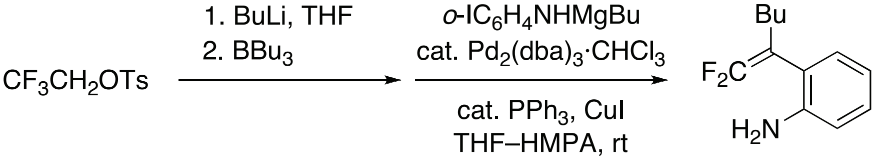
[a] CuCl•SMe$_2$ (1 eq) was employed instead of CuI.
[b] The reaction was carried out in the absence of the Pd catalyst.

The sequence of reactions: (i) the 1,2-migration via borate complexes and (ii) the coupling reaction via difluorovinylcoppers **6** provides a general synthetic method for unsymmetrically disubstituted 1,1-difluoro-1-alkenes **7** by the introduction of two different carbon substituents (R^1 and R^2) onto *difluorovinylidene* (CF$_2$=C) unit in opposite polarities. That is, the carbon framework of difluoroalkenes can be constructed at will in this onepot operation, where 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**) functions as a synthon of *difluorovinylidene* ambiphile (Scheme 2).



Scheme 2

Thus, procedure A in the original article, providing *o*-(1,1-difluorohex-1-en-2-yl)aniline, can be replaced with the following sequence (Scheme 3) on the same scale.[4a] The solution of 2,2-difluorovinylborane, generated from **1** (15.3 g, 60 mmol), is treated with hexamethylphosphoric triamide (HMPA, 20 mL), PPh_3 (1.26 g, 4.8 mmol), and $Pd_2(dba)_3{\cdot}CHCl_3$ (1.24 g, 1.20 mmol). To the solution is added *N*-butylmagnesio-*o*-iodoaniline, which is generated *in situ* from *o*-iodoaniline (9.20 g, 42.0 mmol) and dibutylmagnesium (42 mL, 1.0 M in heptane, 42 mmol). MeMgI can be also used for deprotonation of the amino group. Copper(I) iodide (11.4 g, 60 mmol) is then added, and the reaction mixture is stirred at room temperature. After quenching the reaction with phosphate buffer, the mixture is treated with hydrogen peroxide (100 mL, 30% in water) at 0 °C and then at room temperature for 1 h. The mixture is filtered through a pad of Celite, and organic materials are extracted with ethyl acetate. After removing HMPA by short column chromatography on silica gel, the crude product is distilled under reduced pressure to give *o*-(1,1-difluorohex-1-en-2-yl)aniline (5.76 g, 65%). The coupling reaction of difluorovinylcoppers **6** can be also conducted with *o*-iodo-*p*-toluenesufonanilide without its deprotonation to give the indole precursors with an *N*-tosyl group directly, albeit in slightly lower yield.

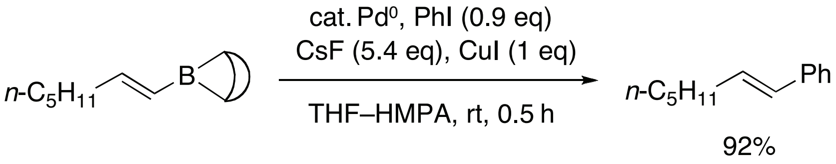


Scheme 3

Moreover, difluorovinylcoppers **6** react as alkyl-substituted difluorovinyl anion with various electrophiles, such as acyl chlorides,[7] chlorodiphenylphosphine,[8] iodine,[9] NBS,[2c] and (methylene)ammonium iodides,[2c] which allows introduction of acyl, phosphine, iodine, bromine, and aminomethyl substituents to the difluorovinylic position. The directly-functionalized 1,1-difluoro-1-alkenes are readily supplied by this methodology.

While several methods for the activation of vinylboron compounds by transmetalation to copper have been reported,[10] all of them require a strong nucleophilic species, such as methylcopper, alkyllithium, or sodium methoxide, to induce borate-complex formation. In the above-mentioned transmetalation, the lithium fluoride formed *in situ* acts as the nucleophile, which allows the selective activation of the vinyl group on boron under mild conditions (Scheme 1).

Furthermore, this type of activation with fluoride ion and copper(I) salt can also be applied to fluorine-free alkenylboranes.[2b] The cross-coupling reaction of a *B*-(1-alkenyl)-9-borabicyclo[3.3.1]nonane (BBN), generated *in situ* via hydroboration of the corresponding 1-alkyene with 9-BBN, readily proceeds at room temperature within 1 h in the presence of cesium fluoride, cuprous iodide, and a palladium catalyst, while high temperature is normally required for efficient reaction rates in the Suzuki–Miyaura coupling (Scheme 4).[2b,2c,11] This is a useful activation method of alkenylboranes, which increases their reactivity as carbon nucleophiles.



cat. Pd^0: $Pd_2(dba)_3\cdot CHCl_3$–P(2-furyl)$_3$

Scheme 4

1. Department of Chemistry, Graduate School of Pure and Applied Sciences, University of Tsukuba, Tsukuba, 305-8571, Japan. junji@chem.tsukuba.ac.jp
2. For the original reports on the synthesis of 1,1,-difluoro-1-alkenes, see: (a) Ichikawa, J.; Moriya, T.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1991**, 961. (b) Ichikawa, J.; Minami, T.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1992**, *33*, 3779. (c) Ichikawa, J. *J. Fluorine Chem.* **2000**, *105*, 257 and references cited therein.
3. Since our report in 1991,[2a] *fluoride*-activation strategy has been widely

applied in the Suzuki–Miyaura coupling. See for example: (a) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095. (b) Desurmont, G.; Dalton, S.; Giolando, D. M.; Srebnik, S. *J. Org. Chem.* **1997**, *62*, 8907. (c) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (d) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (e) Kotha, S.; Behera, M.; Shah, V. R. *Synlett* **2005**, 1877. (f) Korenaga, T.; Kosaki, T.; Fukumura, R.; Ema, T.; Sakai, T. *Org. Lett.* **2005**, *7*, 4915. (g) Ishikawa, S.; Manabe, K. *Chem. Lett.* **2006**, *35*, 164. (h) Molander, G. A.; Sandrock, D. L. *Org. Lett.* **2009**, *11*, 2369. (i) Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G. C.; Murray, P. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 5156.

4. For the original reports on the synthesis of 2-fluoroindoles, see: (a) Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. *Synthesis* **2002**, 1917. (b) Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun.* **1997**, 1537. See also: (c) Ichikawa, J.; Fujiwara, M.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun.* **2000**, 1887.

5. Ichikawa, J.; Ikeura, C.; Minami, T. *Synlett* **1992**, 739.

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8. Ichikawa, J.; Yonemaru, S.; Minami, T. *Synlett* **1992**, 833.

9. Ichikawa, J.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1989**, *30*, 6379.

10. For a review, see: Wipf, P. *Synthesis* **1993**, 537. For a recent example, see: Gerard, J.; Hevesi, L. *Tetrahedron* **2004**, *60*, 367.

11. For the recent reports on the room-temperature Suzuki–Miyaura coupling, see: (a) He, Y.; Cai, C. *Catal. Lett.* **2010**, *140*, 153. (b) Rahimi, A.; Schmidt, A. *Synlett* **2010**, 1327. (c) Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. *Chem. Eur. J.* **2006**, *12*, 5142. (d) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685 and references therein. (e) Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 2149. For a review, see: (f) Lipshutz, B. H.; Ghorai, S. *Aldrichim. Acta*, **2008**, *41*, 59.

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