Tetrahedron Letters, Vol. 33, No. 26, pp. 3779-3782, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

A Facile Synthesis of Disubstituted 1,1-Difluoro-1-alkenes *via* Double Transmetalation of 2,2-Difluorovinylboranes

Junji ICHIKAWA* and Toru MINAMI

Department of Applied Chemistry, Kyushu Institute of Technology, Sensui-cho, Tobata,
Kitakyushu 804, Japan

Takaaki SONODA and Hiroshi KOBAYASHI

Institute of Advanced Material Study, Kyushu University, Kasuga, Fukuoka 816, Japan

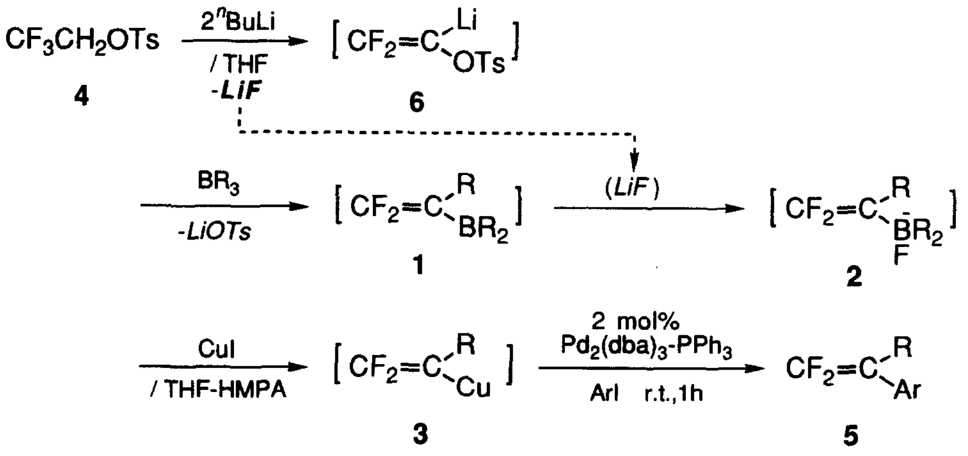
Key Words: Difluoroalkene; Difluorovinylborane; Transmetalation; Coupling reaction; Palladium catalyst

Abstract: *2,2,2-Trifluoroethyl p-toluenesulfonate is treated with butyllithium and trialkylboranes successively to generate 1-alkyl-2,2-difluorovinylboranes, which couple with aryl iodides in the presence of cuprous iodide and palladium catalyst to afford 1,1-difluoro-1-alkenes in excellent yields.*

Terminal fluoroalkenes have a unique unsaturated system reactive toward nucleophiles, which fact produces their diverse utilities not only as building blocks for fluorinated compounds and polymers,[1] but recently as a new type of enzyme inhibitors designed with a mechanism-based concept.[2] Because of their versatility, there have been reported a number of examples on the preparation of disubstituted 1,1-difluoro-1-alkenes.[3,4] Most of them are, however, confined to the introduction of *difluorometylene* unit (CF_2).[3a-c]

On the other hand, we have recently reported the first and still only method for introducing *difluorovinylidene* unit ($CF_2=C$), which provides a useful synthetic route to unsymmetrically disubstituted 1,1-difluoro-1-alkenes by attaching two different carbon substituents to difluorovinylidene group *via* i) a boron-mediated alkylation and ii) a palladium-catalyzed coupling reaction.[4] In the latter process, the coupling reaction of dialkyl-2,2-difluorovinylboranes **1** with aryl iodides, a problem was the participation of the alkyl groups on boron other than the desired difluorovinyl group. This difficulty was eventually overcome by the oxidation of alkyl-boron bonds in **1** with trimethylamine oxide prior to the coupling reaction, unfortunately which can be a drawback in manipulation.

In our previous paper, we have noted that the addition of copper(I) salt to **1** activates only the 2,2-difluorovinyl group, which in turn reacts as a vinyl anion.[5] This vinyl-selective activation presumably consists of two stages: i) the formation of boron ate-complex **2** by the fluoride anion formed *in situ* and ii) the subsequent generation of difluorovinylcopper **3** *via* transmetalation. It was also reported that 1-alkenyl- and 1-alkynylcopper derivatives were effectively employed in a coupling reaction catalyzed by palladium.[6] On the



basis of these considerations, we attempted to apply the copper-mediated activation method to the coupling reaction mentioned above, which turned out to be quite selective toward the difluorovinyl group and offered a facile procedure without the tedious oxidation step. Herein, we report a versatile one-pot synthesis of disubstituted 1,1-difluoro-1-alkenes in excellent yields by using palladium-catalyzed coupling reaction *via* the sequential transmetalation of boron-copper-palladium.

Dibutyl(1-butyl-2,2-difluorovinyl)borane (**1a**, R=^{n}Bu) was generated *in situ* from 2,2,2-trifluoroetyl *p*-toluenesulfonate (**4**) by treating with butyllithium and tributylborane successively.[5] Then, the reaction of **1a** with iodobenzene was attempted in the presence of 1 equiv. of cuprous iodide and a catalytic amount of dichlorobis(triphenylphosphine)palladium. The desired coupling reaction of the difluorovinyl moiety on boron proceeded smoothly even at room temperature to afford the corresponding difluoroalkene, 1,1-difluoro-2-phenyl-1-hexene (**5a**) in 44% yield.

After screening on palladium catalysts, we found that the palladium(0) complex, formed *in situ* from tris(dibenzylideneacetonyl)bispalladium (Pd$_2$(dba)$_3$) and triphenylphosphine in a palladium : phosphine ratio of 1 : 2,[7] brought about 100% conversion of iodobenzene to raise the yield of **5a** up to 94%. The GLC analysis of this reaction revealed no formation of butylbenzene, the coupling product of the alkyl moieties in **1a**, which indicates that the vinyl-group transfer was exclusively accomplished.

Moreover, the coupling reactions were examined under similar conditions in the absence of cuprous iodide or the palladium complex to yield no coupling products. Although cuprous iodide have seemed to act as a cocatalyst, its use of 0.2 equiv. induced the formation of **5a** only in 24% yield. Thus, both of the copper salt (1 equiv.) and the palladium catalyst are essential in the present reaction, and the double transmetalation from boron to copper and then to palladium promotes the coupling of vinyl group effectively.[8]

Under the reaction conditions defined above, several other disubstituted 1,1-difluoro-1-alkenes were synthesized by using trialkylboranes and aryl iodides. The yields are excellent as shown in Table 1. In the case of *p*-iodoanisole, the reaction was slowed down probably due to its poor ability of oxidative addition to palladium, and also did not go to completion. A palladium : phosphine ratio of 1 : 4 gave an acceptable rate here and the reaction afforded the corresponding alkene in 94% yield (Entry 7).

Table 1. One-pot Synthesis of 1,1-Difluoro-1-alkenes[a]

Entry	R	Ar	Pd catalyst[b]	Yield of **5**/%[c]
1	^{n}Bu	Ph	A	90 (94)
2		p-$NO_2C_6H_4$	A	90
3		m-$NO_2C_6H_4$	A	91
4		p-AcC_6H_4	A	94 (quant)
5		p-$EtO_2CC_6H_4$	A	93
6		p-ClC_6H_4	A	91
7		p-$MeOC_6H_4$	B	94
8		1-Naphthyl	A	91
9	^{sec}Bu	Ph	A	83 (91)

[a] Unless otherwise noted, all reactions were carried out under the conditions described in the text. Molar ratio of **4** : BR_3 : ArI = 1 : 1.1 : 0.9.

[b] A: $Pd_2(dba)_3 \bullet CHCl_3$: PPh_3 = 1 : 4; B: $Pd_2(dba)_3 \bullet CHCl_3$: PPh_3 = 1 : 8.

[c] Isolated yields. Numbers in parentheses show the yields determined by ^{19}F NMR relative to internal $C_6H_5CF_3$ standard. All compounds were fully characterized by ^{1}H NMR, ^{19}F NMR, ^{13}C NMR, IR, and mass spectra.

It should be noted that this sequence of reactions includes two carbon-carbon bond formations in one-pot operation and that the latter coupling reaction of vinylboranes is completed in about 10 min at room temperature, while prolonged heating is required in similar reactions of vinylboron compounds.[9] The double transmetalation procedure using cesium fluoride, cuprous iodide, and palladium catalyst can be actually employed in the coupling reaction of non-fluorinated 1-alkenylboranes, which proceeds smoothly at room temperature.

A typical reaction procedure is as follows: To 2,2,2-trifluoroethyl p-toluenesulfonate (**4**, 160 mg, 0.63 mmol) in tetrahydrofuran (THF, 2 ml) was added butyllithium (0.81 ml, 1.63 M in hexane, 1.32 mmol) at -78 °C over 10 min under an argon atmosphere. The reaction mixture was stirred for 30 min at -78 °C to generate **6**,[5] and then treated with tributylborane (0.69 ml, 1.0 M in THF, 0.69 mmol) at -78 °C. After being stirred for 1 h at -78 °C, the mixture was brought to room temperature and stirred for an additional 3 h. The vinylborane solution thus obtained was treated with hexamethylphosphoric triamide (HMPA, 0.7 ml), triphenylphosphine (13 mg, 0.050 mmol), and tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (13 mg, 0.013 mmol)[7] and stirred for 10 min. To the resulting solution was added 4'-iodoacetophenone (141 mg, 0.57 mmol) and cuprous iodide (120 mg, 0.63 mmol). After the mixture was stirred for 1 h at room temperature, water was added to quench the reaction. Usual workup followed by column chromatography on silica gel (Et_2O-hexane 1 : 7) gave 1,1-difluoro-2-(4-acetylphenyl)-1-hexene (**5b**, 128 mg, 94%).[10]

We gratefully acknowledge the financial support for this research by a grant from Izumi Science and Technology Foundation to J. I., and also appreciate a generous gift of 2,2,2-trifluoroethanol from Central Glass Co., Ltd.

REFERENCES AND NOTES

1. (a) Sheppard, W. A.; Sharts, C. M. *Organic Fluorine Chemistry*; W. A. Benjamin: New York. 1969; Chaps. 3, 6, and 7. (b) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed; Ellis Horwood: Chichester. 1976; Chap. 5. (c) Chambers, R. D.; Mobbs, R. H. *Advances in Fluorine Chemistry*; Stacey, M.; Tatlow, J. C.; Sharpe, A. G. Eds.; Butterworths: London, 1965; Vol. 4, pp. 50-112. (d) Chambers, R. D.; James, S. R. *Comprehensive Organic Chemistry*; Stoddart, J. F. Ed.; Pergamon Press: Oxford, 1979; Vol. 1, pp. 545-547.
2. McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439-7440 and references cited therein.
3. For the synthesis of disubstituted 1,1-difluoro-1-alkenes, see: The introduction of *difluoromethylene* unit: (a) Burton, D. J.; Kesling, H. S.; Naae, D. G. *J. Fluorine Chem.* **1981**, *18*, 293-298 and references therein. (b) Edwards, M. L.; Stemerick, D. M.; Jarvi, E. T.; Matthews, D. P.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 5571-5574 and references therein. (c) Wheaton, G. A.; Burton, D. J. *J. Org. Chem.* **1983**, *48*, 917-927 and references therein. The introduction of *difluorovinyl* unit: (d) Gillet, J. P.; Normant, J. F. *Synthesis* **1986**, 538-543. (e) Ishihara,T.; Yamana, M.; Ando,T. *Tetrahedron Lett.*, **1983**, *24*, 5657-5660. The introduction of *difluorovinylidene* unit: (f) Ichikawa, J.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1989**, *30*, 6379-6382.
4. Ichikawa, J.; Moriya, T; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1991**, 961-964. For the synthesis of symmetrically disubstituted 1,1-difluoro-1-alkenes, see also: Ref. 3f.
5. Ichikawa, J.; Hamada, S; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1992**, *33*, 337-340.
6. (a) Jabri, N.; Alexakis, A.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1983**, 332-338. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467-4470.
7. Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, Jr., C. *J. Org. Chem.* **1990**, *55*, 5833-5847 and references therein.
8. For a paper on the concept of double transmetalation , see: Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254-2256. For the effect of copper salt, see also: Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359-5364 and references therein.
9. Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221-223 and references therein. For a paper on exceptional conditions without heating, see: Uenishi, J.; Beau, J. -M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756-4758.
10. **5b** (R=^{n}Bu, Ar=*p*-AcC_6H_4): IR (neat) 1715, 1680, 1605, 1355, 1265, 1235, 955, 835, and 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.87 (3H, m), 1.12-1.48 (4H, m), 2.23-2.52 (2H, m), 2.59 (3H, s), 7.42 (2H, br d, J=9 Hz), and 7.94 (2H, dm, J=9 Hz); ^{19}F NMR ($CDCl_3/C_6F_6$) 72.0 ppm (1F, d, J_{FF}=40 Hz) and 72.5 ppm (1F, d, J_{FF}=40 Hz); ^{13}C NMR ($CDCl_3$) δ=13.8, 22.1, 26.6, 27.2, 30.0, 92.3 (dd, J_{CF}=23 Hz, 12 Hz), 128.4 (t, J_{CF}=3 Hz), 128.5, 135.8, 139.0 (t, J_{CF}=4 Hz), 153.9 (dd, J_{CF}=292 Hz, 288 Hz), and 197.5; MS (75 eV) *m/z* (rel intensity) 238 (M$^+$; 45), 223 (100), 181 (31), and 43 (30); Found: *m/z* 238.1170. Calcd for $C_{14}H_{16}OF_2$: M, 238.1168.

(Received in Japan 6 March 1992)