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A sequential highly stereoselective hydroboration and Suzuki–Miyaura cross-coupling reaction of fluoroalkylated internal acetylenes: a practical one-pot synthesis of fluoroalkylated trisubstituted alkenes

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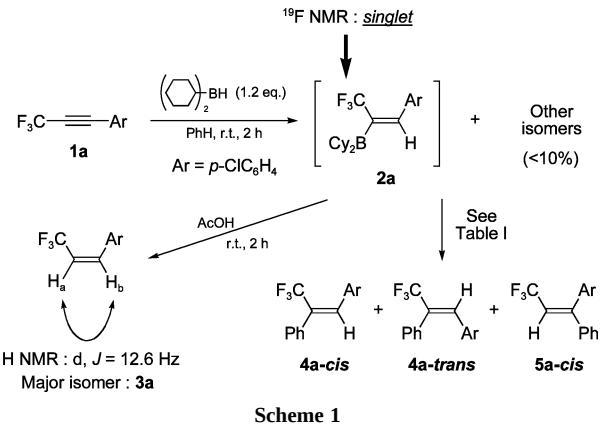
The one-pot synthesis of trisubstituted alkenes starting from fluoroalkylated internal alkynes was investigated. Hydroboration of the alkynes proceeded in a highly regio- and stereoselective manner to give the corresponding vinylboranes in excellent yields. Without isolation, treatment of the vinylboranes with various aryl halides under the Suzuki–Miyaura cross-coupling conditions gave the fluoroalkylated trisubstituted alkenes in high yields with complete retention of the olefinic geometry.

Considerable attention has been paid to fluorine-containing materials due to their unique properties arising from altered electron density, acidity, and hydrogen-bonding patterns.[1] Fluoroalkyl groups increase lipophilicity allowing for easier drug transportation, cellular absorption, blood–brain barrier penetration, and improved binding within hydrophobic pockets of receptors.[1] Accordingly, the development of novel methods for the synthesis of fluoroalkylated molecules has been becoming more and more important in fluorine chemistry.

Among various types of fluoroalkylated molecules, alkenes possessing a fluoroalkyl group are well known as one of the most important synthetic targets because they are found in the framework of biologically active compounds such as panomifene.[2] Though several synthetic methods for such molecules have been reported thus far,[3] the hydrometallation of fluoroalkylated alkynes is potentially attractive because the hydrometallation reaction very often proceeds in a stereoselective fashion and the resulting vinylmetal intermediates can be transformed further to variously substituted ethylenes under the influence of a transition metal catalyst. Despite such great utility, little attention has been paid to such reaction of fluorine-containing alkynes so far.[4] Herein we wish to describe a highly regio- and stereoselective hydroboration reaction of fluorine-containing internal alkynes, followed by Suzuki–Miyaura cross-coupling reaction, which realized the one-pot synthesis of fluoroalkylated alkenes in high yields.

Initially, the reaction of trifluoromethylated internal alkyne **1a**[5] with dicyclohexylborane was examined (Scheme 1). On treating **1a** with 1.2 equiv. of dicyclohexylborane (prepared by stirring cyclohexene (2.4 equiv.) with borane·THF complex (1.2 equiv.) in benzene at room temperature for 2 h), the vinylborane **2a** was formed selectively, together with a small amount of other isomers



Scheme 1

(< 10%). ^{19}F NMR spectra of **2a** showed a singlet peak, strongly suggesting that a dicyclohexylboryl group is attached to a carbon bearing a trifluoromethyl group.[6] Without product isolation, the reaction mixture was subjected to acid hydrolysis to afford the disubstituted alkene **3a** as a major product. The analysis of the ^{1}H NMR of **3a** showed the coupling constant of H_a and H_b to be 12.6 Hz, indicating that **3a** has the *Z* configuration.[7] Accordingly, it was revealed that the present hydroboration proceeded in a highly *cis* addition manner.

Next, we attempted the Suzuki–Miyaura cross-coupling reaction[8] of vinylborane **2a** with iodobenzene in the presence of palladium catalyst. Thus, a benzene solution of the vinylborane **2a** was treated with 5 mol% of $Pd(PPh_3)_4$ and 3 equiv. of NaOEt, and the whole was refluxed for 4 h. After quenching the reaction with acetic acid, ^{19}F NMR analysis indicated that the desired coupling product **4a** was formed in 23% yield, together with 76% of **3a** (Table 1, Entry 1). Prolonged reaction time led to the significant decrease of the yield (Entry 2). Switching the palladium catalyst from $Pd(PPh_3)_4$ to $Pd(PPh_3)_2Cl_2$ brought about a slight increase of the yield (Entry 3). It is interesting to note that the base used in this reaction was crucial for the high yield. Thus, changing the base from NaOEt to NaOH resulted in a dramatic increase of the yield as described in Entry 4. In this case, 10% of **3a** was recovered unchanged. The use of 10 mol% of the palladium catalyst led to the complete consumption of the vinylborane **2a**, giving the desired product in 89% yield (Entry 5). In Entries 4 and 5, high regioselectivity (**4a-*cis*** + **4a-*trans*** : **5a-*cis*** = 94 : 6) and high stereoselectivity (**4a-*cis*** : **4a-*trans*** = 98 : 2) were observed.

With the optimized reaction conditions in hand, the scope of the one-pot reaction was investigated with various alkynes in detail (Table 2). As shown in Entries 1-4 and 6, various types of alkynes carrying an electron-donating group (Me, MeO) or an electron-withdrawing group (EtO_2C) on the benzene ring could participate well in the reaction to give the corresponding trisubstituted alkenes in high yields. However, a significant decrease of the yield was observed when an alkyne having a nitro group on the benzene ring was used (Entry 5). The regioselectivity was also decreased slightly. Additionally, a fluoroalkylated alkyne having an aliphatic side chain (p-$MeOC_6H_4CH_2$-) was not a good substrate, a low regioselectivity (**4** : **5** = 58 : 42) being obtained and **6** being produced in 26% yield (Entry 7, Fig. 1). We also examined the effect of the coupling reagents (R^1I) on the reaction as shown in Entries 8–14. The position of the substituent on the benzene ring significantly influenced the coupling reaction. Thus, the dimer **7**

Table 1 Examination of the reaction conditions

Entry	Catalyst (5 mol%)	Base	Time/h	Yield[a] of **4a** + **5a** (%)	Yield[a] of **3a** (%)
1	$Pd(PPh_3)_4$	NaOEt	4	23	76
2	$Pd(PPh_3)_4$	NaOEt	20	7	35
3	$Pd(PPh_3)_2Cl_2$	NaOEt	4	37	63
4	$Pd(PPh_3)_2Cl_2$	NaOH	4	80[b]	10
5	$Pd(PPh_3)_2Cl_2$[c]	NaOH	4	89 (64)[b]	0

[a] Determined by ^{19}F NMR. Value in parentheses is of isolated yield. [b] **4a** : **5a** = 94 : 6; **4a-*cis*** : **4a-*trans*** = 98 : 2. [c] Ten mol% of $Pd(PPh_3)_2Cl_2$ was employed.

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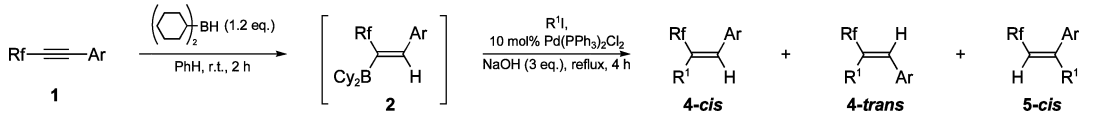
Table 2 The synthesis of a variety of trisubstituted alkenes



Entry	Rf	Ar	R^1	Yield[a,b] of **4**+**5** (%)	**4** (*cis* : *trans*) : **5**[a]
1	CF_3 (**a**)	C_6H_5	C_6H_5	85 (73)	95 (100 : 0) : 5
2	CF_3 (**a**)	*p*-ClC_6H_4	C_6H_5	89 (64)	94 (98 : 2) : 6
3	CF_3 (**a**)	*p*-MeC_6H_4	C_6H_5	83 (66)	94 (100 : 0) : 6
4	CF_3 (**a**)	*p*-$MeOC_6H_4$	C_6H_5	99 (88)	96 (100 : 0) : 4
5	CF_3 (**a**)	*p*-$O_2NC_6H_4$	C_6H_5	25	88 (100 : 0) :12
6	CF_3 (**a**)	*p*-$EtO_2CC_6H_4$	C_6H_5	99	95 (100 : 0) : 5
7	CF_3 (**a**)	*p*-$MeOC_6H_4CH_2$	C_6H_5	62[c]	58 (100 : 0) :42
8	CF_3 (**a**)	*p*-ClC_6H_4	*o*-ClC_6H_4	53[d]	92 (100 : 0) : 8
9	CF_3 (**a**)	*p*-ClC_6H_4	*m*-ClC_6H_4	74	93 (100 : 0) : 7
10	CF_3 (**a**)	*p*-ClC_6H_4	*p*-ClC_6H_4	83 (74)	96 (100 : 0) : 4
11	CF_3 (**a**)	*p*-ClC_6H_4	*p*-MeC_6H_4	86 (55)	94 (99 : 1) : 6
12	CF_3 (**a**)	*p*-ClC_6H_4	*p*-$MeOC_6H_4$	68 (56)	98 (93 : 7) : 2
13	CF_3 (**a**)	*p*-ClC_6H_4	*p*-$O_2NC_6H_4$	54	100 (91 : 9) : 0
14	CF_3 (**a**)	*p*-ClC_6H_4	*p*-$EtO_2CC_6H_4$	99	91 (100 : 0) : 9
15	CHF_2 (**b**)	*p*-ClC_6H_4	C_6H_5	67	84 (100 : 0) :16
16	$HCF_2CF_2CF_2$ (**c**)	*p*-ClC_6H_4	C_6H_5	78	83 (100 : 0) :17

[a] Determined by ^{19}F NMR. [b] Values in parentheses are of isolated yields. [c] The product **6** was obtained in 26% yield, together with 8% of **1**. [d] The dimer **7** was obtained in 20% yield.

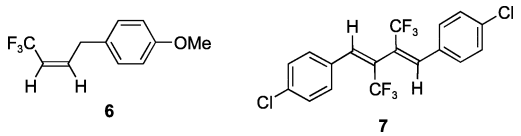


Fig. 1 Byproducts.

was formed in 20% yield when *o*-chloroiodobenzene was used as R^1I (Entry 8, Fig. 1), while a satisfactory result was obtained in the case of *m*-chloroiodobenzene. The reaction using coupling reagents having various types of substituents such as chloro, methyl, methoxy, and ethoxycarbonyl groups proceeded smoothly to afford the trisubstituted alkenes in a highly regio- and stereoselective manner (Entries 10–12 and 14). However the use of *p*-nitroiodobenzene resulted in a decrease of the yield (Entry 13). It should also be noted that changing the fluoroalkyl group from a trifluoromethyl group to a difluoromethyl or hexafluoropropyl group did not have a significant influence on the reaction (Entries 15 and 16).

In summary, we have developed a practical one-pot method for the preparation of fluoroalkylated trisubstituted alkenes, starting from a variety of fluoroalkylated alkynes.[9] Various types of alkynes were demonstrated to be suitable for the present reaction, affording the desired compounds in excellent yields. In almost all cases, over 95% regio- and stereoselectivity were observed.

Notes and references

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4 The hydroboration reaction of γ-trifluoromethylated propargylic alcohol is reported to proceed in a highly stereoselective manner. See Y. Hanzawa, K. Kawagoe, N. Tanahashi and Y. Kobayashi, *Tetrahedron Lett.*, 1984, **25**, 4749.

5 Fluoroalkylated alkynes were prepared according to our recently reported methods. See T. Konno, J. Chae, M. Kanda, G. Nagai, K. Tamura, T. Ishihara and H. Yamanaka, *Tetrahedron*, 2003, **59**, 7571.

6 A similar effect due to an electron-withdrawing trifluoromethyl group was observed. See J. Chae, T. Konno, M. Kanda, T. Ishihara and H. Yamanaka, *J. Fluorine Chem.*, 2003, **120**, 185.

7 In our previous study, the coupling constants of **3a-*cis*** and **3a-*trans*** were observed to be 12.5 and 16.5 Hz, respectively. See ref. 6.

8 (*a*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (*b*) A. Suzuki, *Acc. Chem. Res.*, 1994, **66**, 213.

9 A typical procedure is as follows: To a solution of cyclohexene (0.12 mL, 1.18 mmol) in benzene (2 mL) was added a THF solution of borane–THF complex (0.59 mL, 1 M THF solution, 0.59 mmol) at 0 °C. After stirring of the reaction mixture for 20 min followed by the addition of **1a** (100 mg, 0.49 mmol), the reaction mixture was allowed to warm to room temperature, then stirred for 2 h. To this reaction mixture was added iodobenzene (119 mg, 0.59 mmol), $Pd(PPh_3)_2Cl_2$ (34 mg, 0.049 mmol), and 10% NaOH aq. (1.71 mL, 1.46 mmol) in this order. After refluxing of the mixture for 4 h, the reaction was cooled to room temperature, and the whole was extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous Na_2SO_4, then evaporated *in vacuo*. The residue was purified by silica gel column chromatography to give the corresponding alkenes **4a-*cis***, **4a-*trans***, and **5a-*cis*** as an inseparable mixture.