Synthesis of *gem*-Difluoroalkenes via β-Fluoride Elimination of Organorhodium(I)

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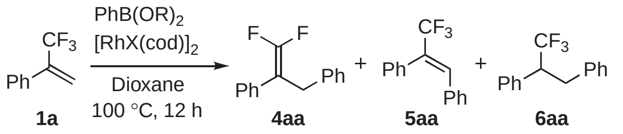
Treatment of α-(trifluoromethyl)styrenes with arylboronic esters and MeMgCl in the presence of a rhodium(I) catalyst affords *gem*-difluoroalkenes. The reaction proceeds through the addition of arylrhodium(I) species across the electron-deficient carbon–carbon double bond and the subsequent β-fluoride elimination.

The rhodium-catalyzed addition reactions of organoboron reagents to unsaturated functionalities have grown dramatically in organic synthesis.[1] The reaction generally proceeds via a transmetalation step generating an organorhodium(I) species from Rh^I–OR (OR = hydroxy or alkoxy) and organoboron followed by a carborhodation step onto various unsaturated functional groups. For regeneration of the Rh^I–OR species, there are two major elementary steps available. One is protodemetalation by a proton source, i.e., water or an alcohol that is present as a co-solvent or an additive,[2] and the other is β-oxygen elimination from a β-oxy-substituted organorhodium(I) intermediate.[3] We have described a variety of catalytic reactions which proceed through a sequential carborhodation/β-oxygen elimination pathway.[4] As a continuation of our studies on rhodium-catalyzed addition reactions, we report herein a new rhodium-catalyzed addition reaction of arylboronic esters to α-(trifluoromethyl)styrenes,[5] in which an organorhodium(I) intermediate undergoes β-fluoride elimination[6] to afford *gem*-difluoroalkenes.[7]

A mixture of α-(trifluoromethyl)styrene (**1a**) and phenylboronic acid (**2a**, 3 equiv) in 1,4-dioxane was heated at 100 °C in the presence of $[Rh(OH)(cod)]_2$ (5 mol % Rh, cod = cycloocta-1,5-diene). An aqueous workup afforded a mixture of products **4aa** (39%), **5aa** (2%), and **6aa** (22%) (Table 1, Entry 1). Scheme 1 depicts the pathways conceivable for the formation of the products. Initially, an alkylrhodium(I) intermediate **A** arises from regioselective 1,2-addition of phenylrhodium(I) species across the electron-deficient carbon–carbon double bond of **1a**. Whereas β-fluoride elimination takes place with **A** to afford the product **4aa**, β-hydride elimination of **A** gives the product **5aa**.[8] On the other hand, protodemetalation of **A** by H_2O or **2a** forms **6aa**.

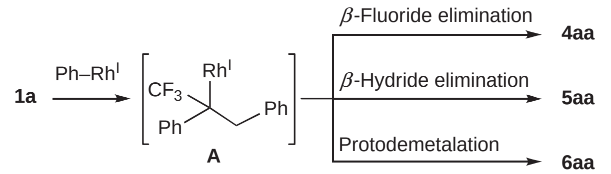
When phenylboronic ester **3a** (PhBneo = 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane) was used in place of phenylboronic acid (**2a**), the formation of **6aa** was diminished and the yield of **4aa** increased to 60% (Table 1, Entry 2). Next, the effect of several additives was examined (Entries 3–7). Among them, the use of methylmagnesium chloride gave a better yield of **4aa**.[9] We assume that the Mg–F interaction activates the C–F bond to promote the β-fluoride elimination step.[10] The product **4aa** was obtained in 73% yield even with 1.5 equiv of phenylboronate **3a** (Entry 8).

Table 1. Optimization of reaction conditions[a]



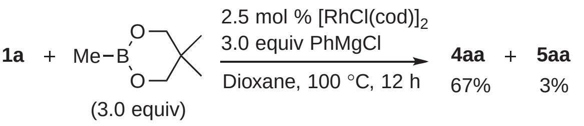
Entry	X	**2a** or **3a** $PhB(OR)_2$ (equiv)	Additive (3 equiv)	GC yield/%[b]		
				4aa	**5aa**	**6aa**
1	OH	$PhB(OH)_2$ (3.0)	none	39	2	22
2	OH	PhBneo (3.0)	none	60	5	8
3	OH	PhBneo (3.0)	CsF	55	1	4
4	Cl	PhBneo (3.0)	CsF	51	4	4
5	Cl	PhBneo (3.0)	NaOEt	37	3	0
6	Cl	PhBneo (3.0)	MeLi	60	5	0
7	Cl	PhBneo (3.0)	MeMgCl	72	2	0
8	Cl	PhBneo (1.5)	MeMgCl	73	1	0

[a]Reaction conditions: **la** (0.2 mmol), **2a** or **3a**, additive (0.6 mmol), $[RhX(cod)]_2$ (5.0 µmol, 5 mol % Rh) in dioxane (4 mL) at 100 °C for 12 h. [b]GC analysis (J&W DB-1).



Scheme 1. Plausible reaction pathways.

A control experiment was carried out using a combination of methylboronic ester and phenylmagnesium chloride (eq 1). The sequential arylation/β-fluoride elimination reaction proceeded under similar conditions to give **4aa** in 67% yield. This result indicated generation of magnesium methyl(phenyl)borate from organoboronic esters and Grignard reagents.[11]



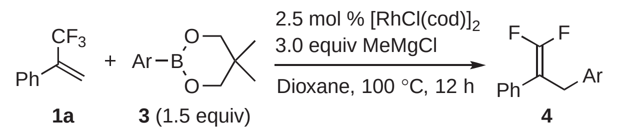
(1)

Under the optimized reaction conditions using MeMgCl as the activator, a wide range of arylboronic esters **3b**–**3i** participated in the reaction with **1a** to furnish *gem*-difluoroalkenes **4ab**–**4ai** (Table 2).

The scope of the substrate **1** was also examined (Table 3). The methoxy-substituted substrate **1b** was more reactive than the substrates having electron-withdrawing substituents **1c**–**1e** (Entries 1–4). No reaction took place with alkyl-substituted substrate **1g** (Entry 6).

When α-(difluoromethyl)styrenes **7a** and **7b** were subjected to similar reaction conditions, β-fluoride elimination occurred

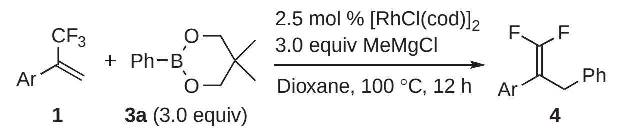
Table 2. Scope of arylboronate reagents **3**[a]



Entry		Ar	Product	Yield/%[b]
1	**3b**	4-Me–C_6H_4	**4ab**	78
2	**3c**	4-F–C_6H_4	**4ac**	77
3	**3d**	3-Cl–C_6H_4	**4ad**	79
4	**3e**	3-MeO–C_6H_4	**4ae**	77
5	**3f**	3-CN–C_6H_4	**4af**	55[c]
6	**3g**	3-MeO_2C–C_6H_4	**4ag**	74[c]
7	**3h**	2-Me–C_6H_4	**4ah**	75
8	**3i**	2-Cl–C_6H_4	**4ai**	48

[a]Reaction conditions: **1a** (0.5 mmol), **3** (0.75 mmol), MeMgCl (1.5 mmol), $[RhCl(cod)]_2$ (12.5 µmol, 5 mol % Rh) in dioxane (10 mL) at 100 °C for 12 h unless otherwise noted. [b]Isolated material of >95% purity. [c]**3** (1.5 mmol).

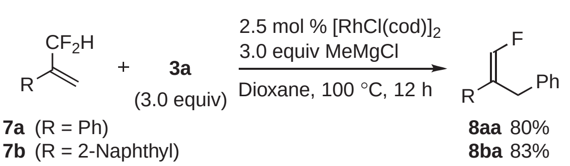
Table 3. Scope of substrates **1**[a]



Entry		Ar	Product	Yield/%[b]
1	**1b**	4-MeO–C_6H_4	**4ba**	80
2	**1c**	4-F–C_6H_4	**4ca**	60
3	**1d**	4-Br–C_6H_4	**4da**	61
4	**1e**	4-CN–C_6H_4	**4ea**	54
5	**1f**	2-Naphthyl	**4fa**	88
6	**1g**	n-$C_{10}H_{21}$	**4ga**	0

[a]Reaction conditions: **1a** (0.2 mmol), **3a** (0.6 mmol), MeMgCl (0.6 mmol), $[RhCl(cod)]_2$ (5.0 µmol, 5 mol % Rh) in dioxane (4 mL) at 100 °C for 12 h unless otherwise noted. [b]Isolated material of >95% purity.

selectively to produce fluoroalkenes **8aa** and **8ba** in good yield as a single stereoisomer (E/Z = >95 : 5, eq 2).[12]



(2)

In summary, we have demonstrated that the rhodium-catalyzed addition of arylboronic esters to α-(trifluoromethyl)-styrenes provides a new synthetic route to *gem*-difluoroalkenes.[13] This catalytic process presents a rare example of β-fluoride elimination of an organorhodium(I) complex.

This research was partly supported by Grant-in-Aids for Young Scientists (B) No. 18750084 and Scientific Research on Priority Areas No. 18032040 from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

References and Notes

1 For reviews, see: a) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169. b) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829. c) T. Miura, M. Murakami, *Chem. Commun.* **2007**, 217.

2 a) T. Hayashi, M. Takahashi, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **2002**, *124*, 5052. b) P. Zhao, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 1876.

3 a) M. Lautens, C. Dockendorff, K. Fagnou, A. Malicki, *Org. Lett.* **2002**, *4*, 1311. b) L. Navarre, S. Darses, J.-P. Genêt, *Chem. Commun.* **2004**, 1108. c) L. Dong, Y.-J. Xu, L.-F. Cun, X. Cui, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Org. Lett.* **2005**, *7*, 4285. d) F. Menard, T. M. Chapman, C. Dockendorff, M. Lautens, *Org. Lett.* **2006**, *8*, 4569.

4 a) T. Miura, M. Shimada, S.-Y. Ku, T. Tamai, M. Murakami, *Angew. Chem., Int. Ed.* **2007**, *46*, 7101. b) M. Shimada, T. Harumashi, T. Miura, M. Murakami, *Chem. Asian J.* **2008**, *3*, 1035, and references therein.

5 For addition of organolithium reagents to α-(trifluoromethyl)styrenes, see: a) R. Fontanelli, D. Sianesi, *Ann. Chim. (Roma)* **1965**, *55*, 862. b) J.-P. Bégué, D. Bonnet-Delpon, M. H. Rock, *J. Chem. Soc., Perkin Trans. 1* **1996**, 1409.

6 For β-fluoride elimination of transition-metal complexes, see: [Rh]: a) A. A. Peterson, K. McNeill, *Organometallics* **2006**, *25*, 4938. [Pd]: b) W. Heitz, A. Knebelkamp, *Makromol. Chem. Rapid Commun.* **1991**, *12*, 69. c) K. Sakoda, J. Mihara, J. Ichikawa, *Chem. Commun.* **2005**, 4684. d) J. Ichikawa, R. Nadano, N. Ito, *Chem. Commun.* **2006**, 4425. e) M. Yokota, D. Fujita, J. Ichikawa, *Org. Lett.* **2007**, *9*, 4639.

7 For other synthetic methods of *gem*-difluoroalkenes, see: a) J. Ichikawa, *J. Fluorine Chem.* **2000**, *105*, 257. b) J. Ichikawa, H. Fukui, Y. Ishibashi, *J. Org. Chem.* **2003**, *68*, 7800, and references therein.

8 M. Lautens, A. Roy, K. Fukuoka, K. Fagnou, B. Martín-Matute, *J. Am. Chem. Soc.* **2001**, *123*, 5358.

9 No reaction took place when the substrate **1a** was heated with phenylboronic ester and methylmagnesium chloride in the absence of a rhodium catalyst. Other Grignard reagents such as methylmagnesium bromide and iodide gave lower yields.

10 a) J. Terao, H. Watabe, N. Kambe, *J. Am. Chem. Soc.* **2005**, *127*, 3656. b) N. Yoshikai, H. Mashima, E. Nakamura, *J. Am. Chem. Soc.* **2005**, *127*, 17978.

11 For a reaction of lithium methyl(phenyl)borates generated from phenylboronic esters and MeLi, see: Y. Kobayashi, R. Mizojiri, E. Ikeda, *J. Org. Chem.* **1996**, *61*, 5391.

12 The geometrical configurations of fluoroalkenes were assigned based upon a previous paper: R. Ocampo, W. R. Dolbier, Jr., F. Zuluaga, *Collect. Czech. Chem. Commun.* **2002**, *67*, 1325.

13 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

Published on the web (Advance View) September 5, 2008; doi:10.1246/cl.2008.1006