ORGANIC LETTERS

2009
Vol. 11, No. 23
5406−5409

# Stereocontrolled Access to Unsymmetrical 1,1-Diaryl-2-fluoroethenes

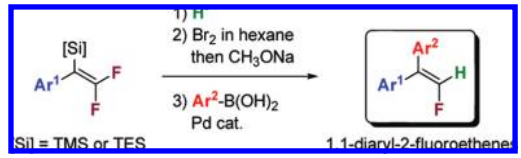
**Grégory Landelle, Marc-Olivier Turcotte-Savard, Judikaëlle Marterer, Pier Alexandre Champagne, and Jean-François Paquin***

*Canada Research Chair in Organic and Medicinal Chemistry, Département de chimie, 1045 avenue de la Médecine, Université Laval, Québec, QC, Canada G1V 0A6*

*jean-francois.paquin@chm.ulaval.ca*

**Received September 30, 2009**

## ABSTRACT




**A simple and effective method for stereocontrolled preparation of 1,1-diaryl-2-fluoroethenes is reported. First, 1-aryl-1-bromo-2-fluoroethenes are generated using an addition/elimination reaction of hydride to silylated $\beta,\beta$-difluorostyrene derivatives followed by a bromination/desilicobromination reaction. Subsequent Suzuki−Miyaura coupling with a variety of boronic acids gives access to the desired 1,1-diaryl-2-fluoroethenes.**

1,1-Disubstituted-2-fluoroethenes (**1**−**3** in Figure 1) are of interest in medicinal chemistry because they can be used, for example, in the design of mechanism-based enzyme inhibitors.[1] Although a few methods for the stereoselective preparation of **1** ($R^1 \neq R^2$)[2−4] and **2**[5,6] exist, to the best of our knowledge, no method for the stereoselective preparation of **3** ($R^1 \neq R^2$) has been reported.[7] Regardless of this synthetic shortcoming, bioactive 1,1-diaryl-2-fluoroethenes (i.e., **4** and **5** in Figure 1) have been reported (as a *E*/*Z* mixture).[8]

We have recently reported an addition/elimination reaction of organolithium reagents to silylated $\beta,\beta$-difluorostyrene derivatives (**6** or **7** in Scheme 1) followed by a bromination/desilicobromination reaction as a simple and effective synthetic approach to a wide range of bromofluoroalkenes (*Z*/*E* up to >97/3). These were then submitted to a number of Pd-catalyzed transformations giving access to both tri- and tetrasubstituted fluoroalkenes.[9] On the basis of these

(1) (a) McDonald, I. A.; Lacoste, J. M.; Bey, P.; Wagner, J.; Zreika, M.; Palfreyman, M. G. *J. Am. Chem. Soc.* **1984**, *106*, 3354–3356. (b) McCarthy, J. R.; Jarvi, E. T.; Matthews, D. P.; Edwards, M. L.; Prakash, N. J.; Bowlin, T. L.; Mehdi, S.; Sunkara, P. S.; Bey, P. *J. Am. Chem. Soc.* **1989**, *111*, 1127–1128. (c) Kirsh, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004. (d) Berlowitz, D. B.; Karukurichi, K. R.; de la Salud-Bea, R.; Nelson, D. L.; McCune, C. D. *J. Fluorine Chem.* **2008**, *129*, 731–742. (e) Bégué, J.-P.; Bonnet-Delphon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley & Sons: Hoboken, 2008.

(2) (a) 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. (b) McCarthy, J. R.; Huber, E. W.; Le, T.-B.; Laskovics, M.; Matthews, D. P. *Tetrahedron* **1996**, *52*, 45–58.

(3) For a nonselective method for the preparation of **1** ($R^1 \neq R^2$), see: Tius, M. A.; Kawakami, J. K. *Tetrahedron* **1995**, *51*, 3997–4010.

(4) For the preparation of **1** with $R^1 = R^2$, see: Du, Z.; Haglund, M. J.; Pratt, L. A.; Erickson, K. L. *J. Org. Chem.* **1998**, *63*, 8880–8887.

(5) (a) Reference 1a. (b) Miura, T.; Ito, Y.; Murakami, M. *Chem. Lett.* **2008**, *37*, 1006–1007.

(6) For nonselective or moderately selective methods for the preparation of **2**, see: (a) Burton, D. J.; Greenlimb, P. E. *J. Org. Chem.* **1975**, *40*, 2796–2801. (b) Hayashi, S.-i.; Nakai, T.; Ishikawa, N.; Burton, D. J.; Naae, D. G.; Kesling, H. S. *Chem. Lett.* **1979**, 983–986. (c) Purrington, S. T.; Pittman, J. H. *Tetrahedron Lett.* **1987**, *28*, 3901–3904. (d) Reference 3. (e) Greedy, B.; Gouverneur, V. *Chem. Commun.* **2001**, 233–234. (f) Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. *Synthesis* **2002**, 1917–1936.

(7) For examples of methodology for the preparation of **3** with $R^1 = R^2$, see: (a) Bornstein, J.; Blum, M. S.; Pratt, J. J., Jr. *J. Org. Chem.* **1957**, *22*, 1210–1213. (b) Bergmann, E. D.; Moses, P.; Neeman, N.; Cohen, S.; Kaluszyner, A.; Reuter, S. *J. Am. Chem. Soc.* **1957**, *79*, 4174–4178. (c) Silversmith, E. F.; Smith, D. *J. Org. Chem.* **1958**, *23*, 427–430. (d) Beltrame, P.; Beltrame, P. L.; Cereda, M. L.; Lazzerini, G. *J. Chem. Soc. B* **1969**, 1100–1102. (e) Boys, M. L.; Collington, E. W.; Finch, H.; Swanson, S.; Whitehead, J. F. *Tetrahedron Lett.* **1988**, *29*, 3365–3368. (f) Matthews, D. P.; Miller, S. C.; Jarvi, E. T.; Sabol, J. S.; McCarthy, J. R. *Tetrahedron Lett.* **1993**, *34*, 3057–3060. (g) Satoh, T.; Takano, K.; Someya, H.; Matsuda, K. *Tetrahedron Lett.* **1995**, *36*, 7097–7100. (h) Asakura, N.; Usuki, Y.; Iio, H. *J. Fluorine Chem.* **2003**, *124*, 81–88.

(8) (a) Coghlan, M. J.; Green, J. E.; Grese, T. A.; Jadhav, P. K.; Matthews, D. P.; Steinberg, M. I.; Fales, K. R.; Bell, M. G. *WO 2004052847 A2*, 2004. (b) Katsuta, Y.; Hirobe, H.; Namite, Y. *JP 60209503 A*, 1985.

(9) Landelle, G.; Champagne, P. A.; Barbeau, X.; Paquin, J.-F. *Org. Lett.* **2009**, *11*, 681–684.

10.1021/ol9022672 CCC: $40.75 
**Published on Web 11/04/2009**

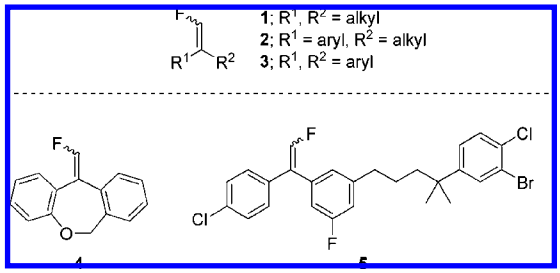
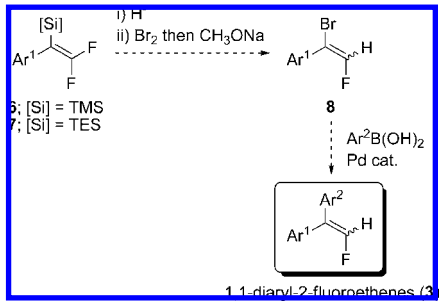



**Figure 1.** Terminal fluoroalkenes and bioactive 1,1-diaryl-2-fluoroethenes.

results, we envisoned that the addition/elimination reaction of hydride nucleophile followed by a bromination/desilicobromination reaction could potentially generate stereoselectively 1-aryl-1-bromo-2-fluoroethenes (**8**)[10] (Scheme 1). A Suzuki−Miyaura coupling with a variety of boronic acids would give access to the desired 1,1-diaryl-2-fluoroethenes (**3**). Herein, we report the first stereocontrolled method for the preparation of 1,1-diaryl-2-fluoroethenes. This short and simple synthetic sequence (only five steps from commercially available $CF_3CH_2I$) provides an effective synthetic approach to a wide range of 1,1-diaryl-2-fluoroethenes with good to excellent stereocontrol (up to 97/3).

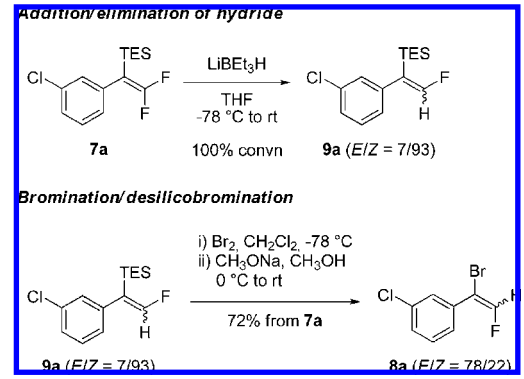
**Scheme 1.** Stereoselective Approach to 1,1-Diaryl-2-fluoroethenes




The idea was initially tested on compound **7a** (Scheme 2). The addition, using $LiBEt_3H$ as the hydride source, proceeded smoothly to afford a crude mixture of the desired fluoroalkene **9a** with complete conversion and with an excellent selectivity of 7/93 in favor of the (*Z*)-isomer.[11] The preference for the (*Z*)-isomer was expected on the basis of our previous work on the addition of organolithium reagents to **6** or **7**.[9] However, it is difficult at this point to rationalize the fact that a higher selectivity is observed with a hydride nucleophile as compared to an organolithium reagent, and experiments are underway in order to understand this trend.

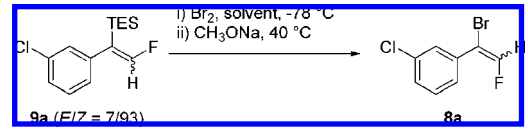
Submission of the mixture to bromination/desilicobromination conditions[12] resulted in inversion of the stereochemistry with loss of selectivity (**9a**; *E*/*Z* = 7/93 → **8a**; *E*/*Z* = 78/22). This result follows the stereochemical path expected for this transformation[12] but is in clear contrast with our previous work where retention was observed with isomeric enrichment.[9]

**Scheme 2.** Initial Results




Solvent is known to influence the stereoselectivity in the bromination of styrene derivatives.[13] We therefore decided to examine various solvents as shown in Table 1 with the hope of finding a solvent that would not result in a lost of selectivity. The use of MeOH resulted in a complete loss of selectivity (entry 2), while using $Et_2O$ gave **8a** with retention of configuration and loss of selectivity (entry 3). Finally, hexane was found to be the solvent of choice for the

**Table 1.** Optimization of the Bromination/Desilicobromination Step[a]




| | | result | |
|---|---|---|---|
| entry | solvent | convn (%)[b] | *E*/*Z*[b] |
| 1 | $CH_2Cl_2$ | 100 | 78/22 |
| 2 | MeOH | 28 | 50/50 |
| 3 | $Et_2O$ | 30 | 37/63 |
| 4 | hexane | 100 | 92/8 |

[a] See Supporting Information for details concerning the reaction conditions. [b] Determined by $^{19}F$ NMR and/or $^{1}H$ NMR spectroscopic analysis of the crude product.

(10) The synthesis of **8** ($Ar^1$ = Ph) as a 50/50 *E*/*Z* mixture has been reported; see: Petasis, N. A.; Yudin, A. K.; Zavialov, I. A.; Prakash, G. K. S.; Olah, G. A. *Synlett* **1997**, 606–608.

(11) The stereochemistry of the major product was confirmed by $^{1}H-^{19}F$ NOESY (HOESY) experiment. See Supporting Information for more details.

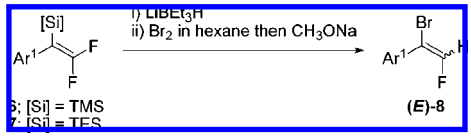
(12) Fisher, R. P.; On, H. P.; Snow, J. T.; Zweifel, G. *Synthesis* **1982**, 127–129.

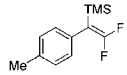
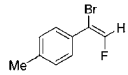
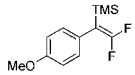
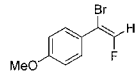
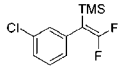
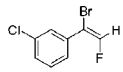
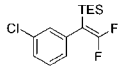
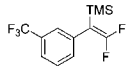
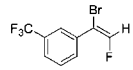
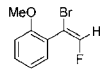
(13) (a) Ruasse, M.-F.; Dubois, J.-E. *J. Am. Chem. Soc.* **1975**, *97*, 1977–1978. (b) Ruasse, M.-F.; Zhang, B. L. *J. Org. Chem.* **1984**, *49*, 3207–3210. (c) Ruasse, M.-F.; Lefebvre, E. *J. Org. Chem.* **1984**, *49*, 3210–3214. (d) Ruasse, M.-F.; Motallebi, S. *J. Phys. Org. Chem.* **1991**, *4*, 527–535.

bromination/desilicobromination step since inversion was observed with little stereochemical erosion (entry 4). The variation in selectivity for the bromination/desilicobromination reaction might be due to a change in mechanism in the bromination step (bromonium-like vs carbocation-like),[14] and we are currently investigating this reaction in more details.

Having optimized the bromination/desilicobromination step, we next investigated the scope of the addition/elimination reaction of hydride followed by a bromination/desilicobromination reaction as presented in Table 2. In general, the bromofluoroalkenes were isolated in good to excellent yield (up to 86% for 2 steps) with good to excellent stereocontrol (up to 97/3) in favor of the (*E*)-isomer.[11] It is important to note that in most cases both geometrical isomers were easily separable by simple flash chromatography. The reaction is applicable to a number of substrates with either an electron-rich or electron-poor aryl substituent, although silylated $\beta$, $\beta$-difluorostyrene derivatives with a substituent

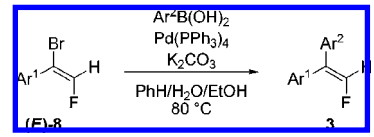
**Table 2.** Formation of 1-Aryl-1-bromo-2-fluoroethenes (**8**)[a]

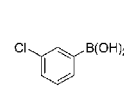
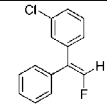
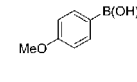
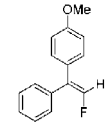
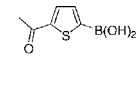
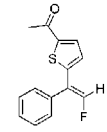
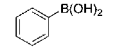
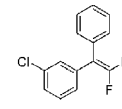
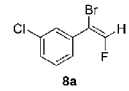
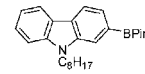
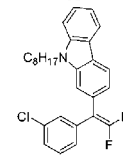
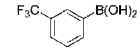
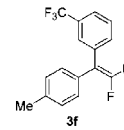
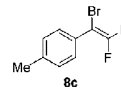
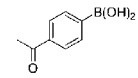
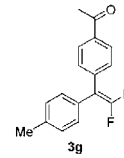
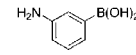
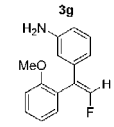
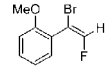
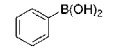
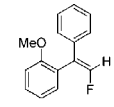



| entry | substrate | product | yield (%)[b] | *E*/*Z*[c] |
|---|---|---|---|---|
| 1 |  **6b** |  **8b** | 73 | 95/5 |
| 2 |  **7b** | | 61 | 94/6 |
| 3 |  **6c** |  **8c** | 51 | 89/11 |
| 4 |  **6d** |  **8d** | 0 (68)[d] | (92/8)[d] |
| 5 |  **6a** |  **8a** | 78 | 97/3 |
| 6 |  **7a** | | 86 | 92/8 |
| 7 |  **6e** |  **8e** | 60 | 93/7 |
| 8 |  **6f** |  **8f** | 57 | 78/22 |
| 9 |  **6g** |  **8g** | 68 | 86/14 |

[a] See Supporting Information for details concerning the reaction conditions. [b] Isolated yield of the combined isomers for the 2 steps. [c] Determined by $^{19}$F NMR and/or $^{1}$H NMR spectroscopic analysis of the crude product. [d] The desired bromofluoroalkene **8d** (*E*/*Z* = 92/8) was contaminated by 32% of an unidentified and inseparable side-product.

**Table 3.** Synthesis of 1,1-Diaryl-2-fluoroethenes (**3**)[a]




| entry | substrate | $ArB(OH)_2$ | product | yield (%)[b] |
|---|---|---|---|---|
| 1 | |  |  **3a** | 69 |
| 2 |  **8b** |  |  **3b** | 67 |
| 3 | |  |  **3c** | 65 |
| 4 | |  |  **3d** | 88 |
| |  **8a** | | | |
| 5 | |  |  **3e** | 64 |
| 6[c] | |  |  **3f** | 71[d] |
| |  **8c** | | | |
| 7[c] | |  |  **3g** | 66[e] |
| 8 | |  |  **3h** | 73 |
| |  **8g** | | | |
| 9 | |  |  | 61 |

[a] See Supporting Information for details concerning the reaction conditions. [b] Isolated yield. [c] Compound **8c** with *E*/*Z* = 89/11 was used. [d] Isolated as a *E*/*Z* mixture (98/2). [e] Isolated as a *E*/*Z* mixture (92/8).

(14) (a) Brook, A. G; Duff, J. M.; Reynolds, W. F. *J. Organomet. Chem.* **1976**, *121*, 293–306. (b) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1978**, *43*, 4424–4431. (c) Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press Limited: London, 1988.

at the 2 position of the aryl group resulted in slightly reduced selectivity (entries 8 and 9). Practically, whereas the bromofluoroalkenes (**8**) with an electron-neutral or electron-rich aryl group were stable upon storage at room temperature, the ones with an electron-poor aryl had the tendency to decompose upon standing at room temperature. Nevertheless, they could be used successively in a Suzuki−Miyaura cross-coupling if they were used promptly (*vide infra*).

The 1-aryl-1-bromo-2-fluoroethenes (**8**) were then subjected to standard Suzuki−Miyaura conditions[15] with a variety of arylboronic acids giving access to a wide range of 1,1-diaryl-2-fluoroethenes (**3**) in moderate to excellent yields (Table 3).[11] It is interesting to note that this approach permits the stereocontrolled preparation of 1,1-diaryl-2-fluoroethenes with little steric differentiation at the aryl groups (e.g., entry 2 or 7) that would be challenging to discriminate otherwise. In addition, the versatility of this methodology allows the synthesis of both stereoisomers (e.g., **3a**/**3d**) by simple changes in the synthetic sequence.

In conclusion, we have described the first stereocontrolled method for the preparation of 1,1-diaryl-2-fluoroethenes. This short and simple synthetic sequence (only five steps from commercially available $CF_3CH_2I$) provides an effective synthetic approach to a wide range of 1,1-diaryl-2-fluoroethenes with good to excellent stereocontrol (up to 97/3). First, 1-aryl-1-bromo-2-fluoroethenes are generated using an addition/elimination reaction of hydride to silylated $\beta,\beta$-difluorostyrene derivatives followed by a bromination/desilicobromination reaction. For the latter transformation, hexane was found to be the key solvent for the conservation of the selectivity. Subsequent Suzuki−Miyaura coupling with a variety of boronic acids gives access to the desired 1,1-diaryl-2-fluoroethenes. Further expansion of the scope, mechanistic studies and application of this methodology for the synthesis of bioactive compounds are currently underway.

**Acknowledgment.** This work was supported by the Canada Research Chair Program, the Natural Sciences and Engineering Research Council of Canada, the Canada Foundation for Innovation, Merck Frosst Centre for Therapeutic Research, the Fonds de recherche sur la nature et les technologies, and the Université Laval. We thank Pierre-Luc T. Boudreault (Research group of Prof. Mario Leclerc, Université Laval) for a generous donation of *N*-octyl-9*H*-carbazole-2-boronic acid pinacol ester.

**Supporting Information Available:** General experimental procedures, specific details for representative reactions, and isolation and spectroscopic information for the new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9022672

(15) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.