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

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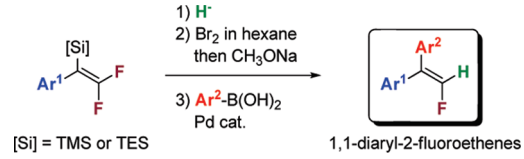
ABSTRACT



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 β,β-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 β,β-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 Fluororganic 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.

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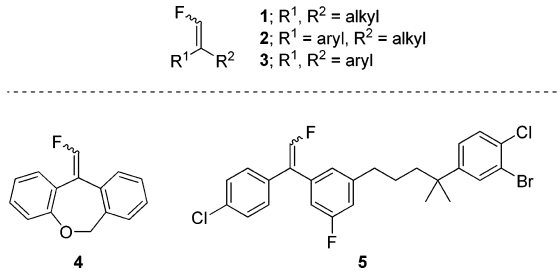
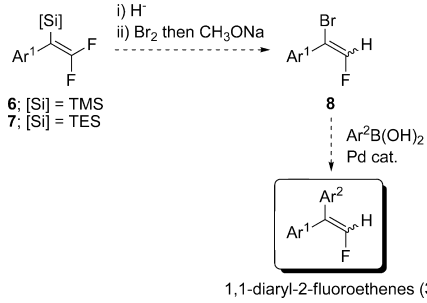


Figure 1. Terminal fluoroalkenes and bioactive 1,1-diaryl-2-fluoroethenes.

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).

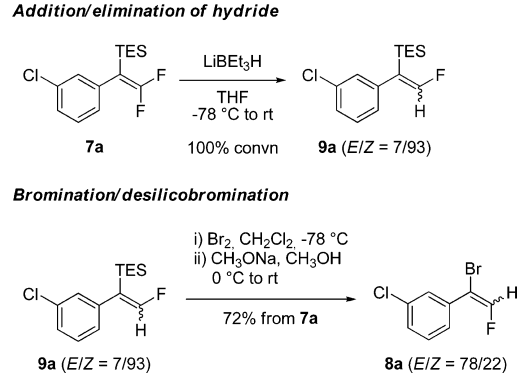
Scheme 1. Stereoselective Approach to 1,1-Diaryl-2-fluoroethenes



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.

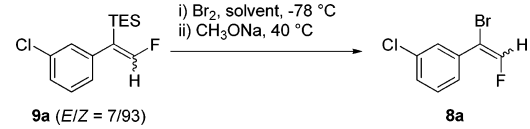
Submission of the mixture to bromination/desilicobromination conditions[12] resulted in inversion of the stereochemistry with loss of selectivity (**9a**; *E*/*Z* = 7/93 → **8a**; *E*/*Z* = 78/22). This result follows the stereochemical path expected for this transformation[12] but is in clear contrast 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 ^1H 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 $^1H-^{19}F$ NOESY (HOESY) experiment. See Supporting Information for more details.

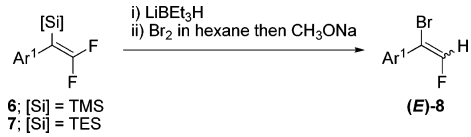
(12) Fisher, R. P.; On, H. P.; Snow, J. T.; Zweifel, G. *Synthesis* **1982**, 127–129.

(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.

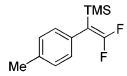
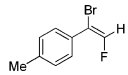
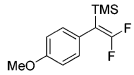
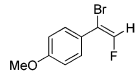
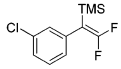
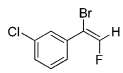
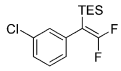
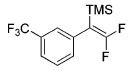
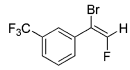
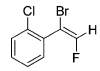
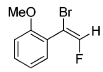
bromination/desilicobromination step since inversion was observed with little stereochemical erosion (entry 4). The variation in selectivity for the bromination/desilicobromination reaction might be due to a change in mechanism in the bromination step (bromonium-like vs carbocation-like),[14] and we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

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

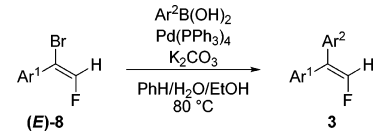


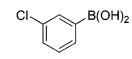
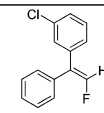
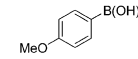
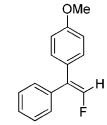
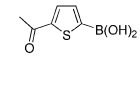
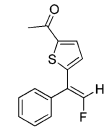
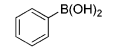
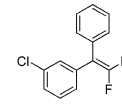
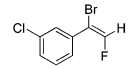
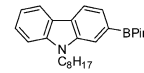
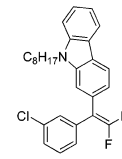
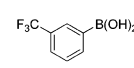
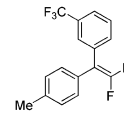
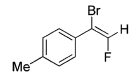
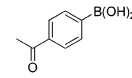
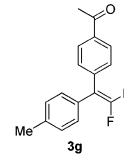
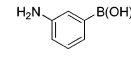
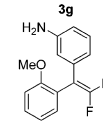
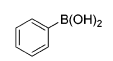
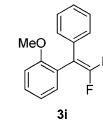
6; [Si] = TMS
7; [Si] = TES
(*E*)-**8**

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
5	 **8a**		 **3e**	64
6[c]			 **3f**	71[d]
7[c]	 **8c**		 **3g**	66[e]
8	 **8g**		 **3h**	73
9			 **3i**	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).

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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 β,β-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.

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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

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