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Stereocontrolled Approach to Bromofluoroalkenes and Their Use for the Synthesis of Tri- and Tetrasubstituted Fluoroalkenes

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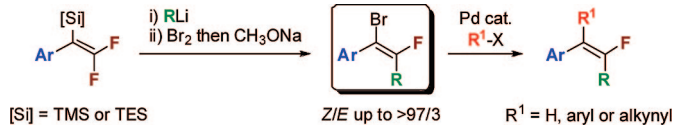
ABSTRACT



An addition/elimination reaction of organolithium reagents to silylated β,β-difluorostyrene derivatives followed by a bromination/desilicobromination reaction provides a simple and effective synthetic approach to a wide range of bromofluoroalkenes (up to >97/3). In addition, the bromofluoroalkenes can be used in Pd-catalyzed transformations giving access to both tri- and tetrasubstituted fluoroalkenes.

The properties of a bioactive molecule can often be modulated by adding fluorine atoms since this leads to changes in solubility, lipophilicity, metabolic stability, conformation, hydrogen-bonding ability, or chemical reactivity.[1] Consequently, much effort has been devoted to the development of novel methods for the synthesis of fluorinated molecules.[1a,2,3] Among the vast array of fluorine-containing functionalities, fluoroalkenes are of particular interest since they have potential applications in material sciences,[4] medicinal chemistry,[5] and organic chemistry where they can be utilized as synthons for further functionalization.[6]

The stereoselective synthesis of nonfluorinated tri- and tetrasubstituted alkenes represents a synthetic challenge even though more approaches have been developed recently.[7] However, only a few of these methods are applicable for

(1) (a) Hiyama, T. In *Organofluorine Compounds; Chemistry and Applications*; Yamamoto, H., Ed.; Springer: New York, 2000; and references therein. (b) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3–11. (c) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15–24. (d) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013–1029. (e) Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992–1012. (f) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886. (g) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330.

(2) For recent reviews in this area, see: (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119–6146. (b) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2004**, *44*, 214–231. (c) Bobbio, C.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 2065–2075. (d) Surya Prakash, G. K.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921–930. (e) Pacheco, M. C.; Purser, S.; Gouverneur, V. *Chem. Rev.* **2008**, *108*, 1943–1981.

(3) For our own work in this area, see: (a) Bélanger, É.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. *J. Am. Chem. Soc.* **2007**, *129*, 1034–1035. (b) Bélanger, E.; Houzé, C.; Guimond, N.; Cantin, K.; Paquin, J.-F. *Chem. Commun.* **2008**, 3251–3253.

(4) For recent examples, see: (a) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. *Chem. Commun.* **2007**, 1003–1022. (b) Babudri, F.; Cardone, A.; Farinola, G. M.; Martinelli, C.; Mendichi, R.; Naso, F.; Striccoli, M. *Eur. J. Org. Chem.* **2008**, 1977–1982.

(5) For recent examples, see: (a) Sciotti, R. J.; Pliushchev, M.; Wiedeman, P. E.; Balli, D.; Flamm, R.; Nilius, A. M.; Marsh, K.; Stolarik, D.; Jolly, R.; Ulrich, R.; Djuric, S. W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2121–2123. (b) Van der Veken, P.; Senten, K.; Kertèsz, I.; De Meester, I.; Lambeir, A.-M.; Maes, M.-B.; Scharpé, S.; Haemers, A.; Augustyns, K. *J. Med. Chem.* **2005**, *48*, 1768–1780. (c) Niida, A.; Tomita, K.; Mizumoto, M.; Tanigaki, H.; Terada, T.; Oishi, S.; Otaka, A.; Inui, K.-i.; Fuji, N. *Org. Lett.* **2006**, *8*, 613–616. (d) Alloatti, D.; Giannini, G.; Cabri, W.; Lustrati, I.; Marzi, M.; Ciacci, A.; Gallo, G.; Tinti, M. O.; Marcellini, M.; Riccioni, T.; Guglielmi, M. B.; Carminati, P.; Pisano, C. *J. Med. Chem.* **2008**, *51*, 2708–2721.

(6) For example, see: (a) Hara, S. In *Fluorine-Containing Synthons*; Soloshonok, V. A., Ed.; ACS Symposium Series 911; American Chemical Society: Washington, DC, 2005; pp 121−172, and references therein. (b) Dutheuil, G.; Couve-Bonnaire, S.; Pannecoucke, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 1290–1292.

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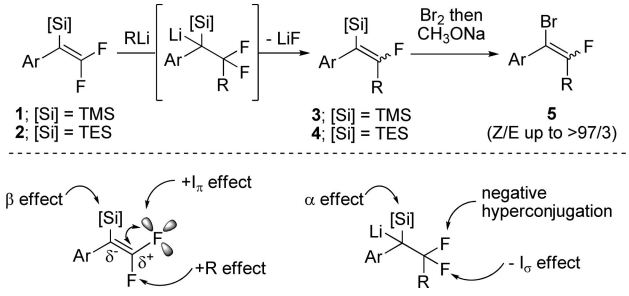
the preparation of tri- or tetrasubstituted fluoroalkenes. Consequently, stereocontrolled and practical access to tri- and tetratetrasubstituted fluoroalkenes remains a synthetic challenge, in particular when one or more of the substituents are aryl groups.[6a,8−10]

Herein, we document a novel stereocontrolled method for the preparation of tri- and tetrasubstituted fluoroalkenes using an addition/elimination reaction of organolithium reagents to silylated β,β-difluorostyrene derivatives (**1** or **2**) followed by a bromination/desilicobromination reaction (Scheme 1).

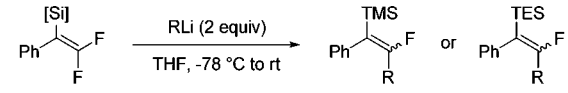
Scheme 1. Stereoselective Approach to Bromofluoroalkenes



This sequence provides an effective synthetic approach to a wide range of bromofluoroalkenes (**5**) with moderate to excellent stereocontrol (up to >97/3). In addition, the bromofluoroalkenes can be used in Pd-catalyzed transformations giving access to both tri- and tetrasubstituted fluoroalkenes.

In our initial plan, we envisioned that silylated β,β-difluorostyrene derivatives (**1** or **2**) would be suitable substrates for an addition/elimination reaction with organolithium reagents. Various derivatives of **1** and **2** are readily available in two steps from commercially available CF_3CH_2I.[11] These alkenes are ideal substrates to undergo carbolithiation for the following reasons: (a) electron-deficient character and (b) polarization due to the $+I_\pi$ effect of the fluorine atoms,[1a] the resonance effect (+R) of fluorine,[1a] as well as the β-effect of the silicon.[12] Upon carbolithiation, the generated carbanion is stabilized by the α effect of the silicon[12] and the inductive effect ($-I_\sigma$)[1a] and negative hyperconjugation of fluorine.[1a,13] Finally, the loss of a fluorine atom as a leaving group via β elimination would produce silylated fluoroalkenes (**3** or **4**). While literature precedence indicated that this would be a viable strategy,[9e,14,15] questions remained as to whether or not this reaction would present useful selectivity and if it would be possible to later substitute the silyl group with a more versatile substituent.

Table 1. Initial Results: Addition/Elimination Sequence[a]



entry	substrate	R	product	yield[b] (%)	*Z*/*E*[c]
1	**1a**	*t*-Bu	**3a**	81	87/13
2		*n*-Bu	**3b**	86	80/20
3		Ph	**3c**	76	50/50
4	**2a**	*t*-Bu	**4a**	72	90/10
5		*n*-Bu	**4b**	61	83/17
6		Ph	**4c**	63	75/25

[a] Reaction conditions: **1** or **2** (1 mmol), RLi (2 mmol), THF (7 mL) at −78 °C to rt for 1 h (see the Supporting Information for details); [b] Isolated yield of the combined isomers; [c] Determined by ^{19}F NMR and/or ^{1}H NMR spectroscopic analysis of the crude product.

In our initial screening experiments, we found that the addition/elimination proceeded readily at −78 °C in THF with different organolithium reagents (Table 1).[15−17] In all cases, both geometrical isomers were easily separable by

(7) Review: Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698–4745. Highlights: Reiser, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 2838–2840.

(8) For access to trisubstituted fluoroalkenes, see, for example: (a) Okada, M.; Nakamura, Y.; Saito, A.; Sato, A.; Horikawa, H.; Taguchi, T. *Tetrahedron Lett.* **2002**, *43*, 5845–5847. (b) Pacheco, C.; Gouverneur, V. *Org. Lett.* **2005**, *7*, 1267–1270. (c) Dutheuil, G.; Paturel, C.; Lei, X.; Couve-Bonnaire, S.; Pannecouke, X. *J. Org. Chem.* **2006**, *71*, 4316–4319. (d) Andrei, D.; Wnuk, S. F. *J. Org. Chem.* **2006**, *71*, 405–408. (e) Akana, J. A.; Bhattacharya, K. X.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 7736–7737.

(9) For access to tetrasubstituted fluoroalkenes, see: (a) Fish, P. V.; Reddy, S. P.; Lee, C. H.; Johnson, W. S. *Tetrahedron Lett.* **1992**, *33*, 8001–8004. (b) Kim, B. T.; Min, Y. K.; Asami, T.; Park, N. K.; Kwon, O. Y.; Cho, K. Y.; Yoshida, S. *Tetrahedron Lett.* **1997**, *38*, 1797–1800. (c) Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1997**, *53*, 14749–14762. (d) Lin, J.; Welch, J. T. *Tetrahedron Lett.* **1998**, *39*, 9613–9616. (e) Huang, X.-h.; He, P.-y.; Shi, G.-q. *J. Org. Chem.* **2000**, *65*, 627–629. (f) Jin, Y.; Williams, D. C.; Croteau, R.; Coates, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 7834–7842. (g) Zoute, L.; Dutheuil, G.; Quirion, J.-C.; Jubault, P.; Pannecoucke, X. *Synthesis* **2006**, 3409–3418. (h) Hara, S.; Guan, T.; Yoshida, M. *Org. Lett.* **2006**, *8*, 2639–2641. (i) Guan, T.; Yoshida, M.; Hara, S. *J. Org. Chem.* **2007**, *72*, 9617–9621. (j) Pomeisl, K.; Èejka, J.; Kvíèala, J.; Paleta, O. *Eur. J. Org. Chem.* **2007**, 5917–5925.

(10) A notable exception is when the fluoroalkene is part of a cyclic system; see, for example: (a) Hossain, M. A. *Tetrahedron Lett.* **1997**, *38*, 49–52. (b) Ichikawa, J.; Wada, Y.; Kuroki, H.; Mihara, J.; Nadano, R. *Org. Biomol. Chem.* **2007**, *5*, 3956–3962.

(11) (a) Anilkumar, R.; Burton, D. J. *J. Fluorine Chem.* **2005**, *126*, 457–463. (b) Okano, T.; Ito, K.; Ueda, T.; Muramatsu, H. *J. Fluorine Chem.* **1986**, *32*, 377–388.

(12) (a) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761–786. (b) Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press Limited: London, 1988;. and references therein.

(13) Dixon, D. A.; Fukunaga, T.; Smart, B. E. *J. Am. Chem. Soc.* **1986**, *108*, 4027–4031.

(14) (a) Hayashi, S.-i.; Nakai, T.; Ishikawa, N. *Chem. Lett.* **1980**, 935–938. (b) Martin, S.; Sauvêtre, R.; Normant, J.-F. *Tetrahedron Lett.* **1983**, *24*, 5616–5618. (c) Martin, S.; Sauvêtre, R.; Normant, J.-F. *J. Organomet. Chem.* **1984**, *264*, 155–161. (d) Lee, J.; Tsukazaki, M.; Snieckus, V. *Tetrahedron Lett.* **1993**, *34*, 415–418. (e) Bégué, J.-P.; Bonnet-Delphon, D.; Bouvet, D.; Rock, M. H. *J. Org. Chem.* **1996**, *61*, 9111–9114. (f) Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. *Synthesis* **2002**, 1917–1936.

(15) Ichikawa, J.; Fukui, H.; Ishibashi, Y. *J. Org. Chem.* **2003**, *68*, 7800–7805.

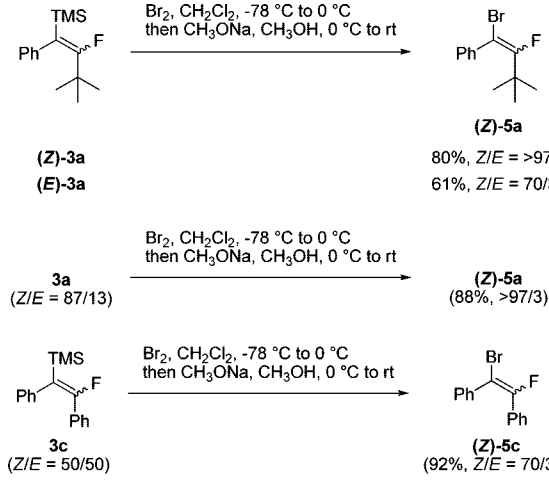
(16) The reaction also proceeds in Et_2O with similar results.

(17) Other nucleophiles such as Grignard or organozinc reagents do not react under these conditions.

simple flash chromatography.[18] From these initial results, it can be seen that using a bulkier RLi and/or silyl group results in increased selectivity (up to 90/10 = *Z*/*E* ratio).[19]

Having established the basic reactivity of this class of substrate, we then sought to investigate the transformation of the silyl group. In particular, we were interested in finding a reaction that would transform the silyl group into a halide, thus opening the way to a wide range of metal-catalyzed transformations. We first evaluated a bromination/desilicobromination reaction.[15,20] This two step/one-pot procedure allows for the conversion of vinylsilanes into vinyl bromides with inversion of configuration at the carbon bearing the silyl group due to the geometrical requirement for both steps (*trans* bromination followed by *anti* elimination). Unexpectedly, when the reaction was tested on **(*Z*)-3a**, the desired product **5a** was isolated in 80% yield but as the *Z* isomer (*Z*/*E* = >97/3) instead of the expected *E* isomer, as confirmed by single-crystal X-ray analysis (Scheme 2).[18]

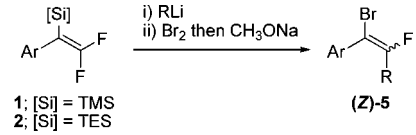
Scheme 2. Isomeric Enrichment via Bromination/Desilicobromination

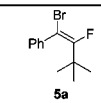
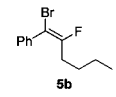
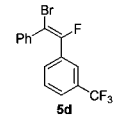
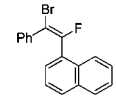
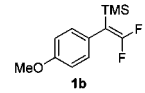
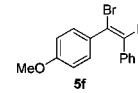
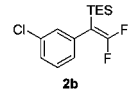
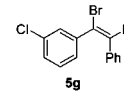
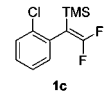
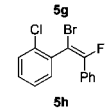
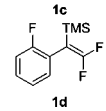
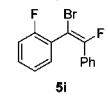


More surprisingly, reaction of **(*E*)-3a** occurred with partial inversion furnishing **5a** as a mixture (*Z*/*E* = 70/30). The unexpected selectivity of the bromination/desilicobromination reaction might be due to a change in mechanism for the bromination step, and we are currently investigating this reaction in more detail.[12b,21] Nevertheless, these results open the way to isomeric enrichment since the opposite geometrical isomer of the silylated fluoroalkene **3** (or **4**) is converted to the same *Z* isomer of the bromofluoroalkene **5**. This idea was tested on an isomeric mixture of **3a** (*Z*/*E* = 87/13), which upon reaction gave the desired product **(*Z*)-5a** as a single isomer (*Z*/*E* = >97/3). Similarly, reaction of isomeric mixture of **3c** (*Z*/*E* = 50/50) gave the bromofluoroalkene **5c** as an enriched mixture in favor of the *Z* isomer (*Z*/*E* = 70/30).

This interesting aspect of the reaction has been further exploited by carrying out the entire transformation (**1** (or **2**) → **5**) as a one-pot sequence, thus avoiding the purification of the intermediate (**3** or **4**) while generating C−C and C−Br bonds in a single flask. The scope of the addition/elimination reaction of organolithium reagents followed by a bromination/desilicobromination reaction is presented in Table 2. In

Table 2. Stereoselective Preparation of **(*Z*)-5** from **1** or **2** in the One-Pot Procedure[a]



entry	substrate	product	yield (%)[b]	*Z*/*E*[c]
1		 **5a**	76	>97/3
2		 **5b**	68	96/4
3	 **1a**	 **5c**	90	76/24
4		 **5d**	72	88/12
5		 **5e**	69	93/7
6	 **2a**	 **5c**	81	88/12
7	 **1b**	 **5f**	72	85/15
8	 **2b**	 **5g**	72	81/19
9	 **1c**	 **5h**	65	78/22
10	 **1d**	 **5i**	24[d]	85/15

[a] See the Supporting Information for details concerning the reaction conditions. [b] Isolated yield of the combined isomers. [c] Determined by ^{19}F NMR and/or ^{1}H NMR spectroscopic analysis of the crude product. [d] A number of unidentified nonfluorinated side products were also isolated.

(18) The stereochemistry of the major product was unambiguously confirmed by single-crystal X-ray analysis. See the Supporting Information for more details.

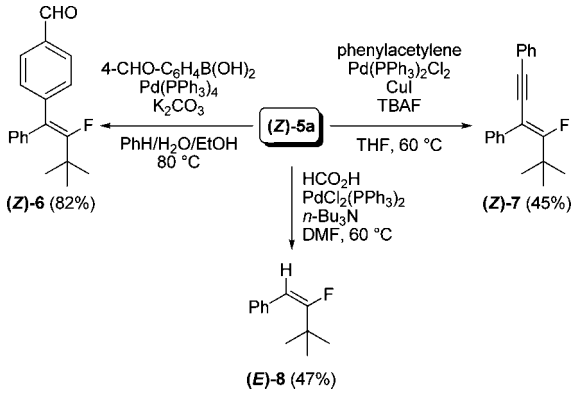
(19) Silylated β,β-difluorostyrene with [Si] = TBS has been prepared but is unreactive under these conditions with either *t*-BuLi or PhLi.

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

(21) (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.

all the cases, the bromofluoroalkenes were isolated in good to excellent yield (up to 90%) with good to excellent stereocontrol (up to >97:3) in favor of the (*Z*)-isomer. A number of substrates (**1a**−**d**, **2a**−**b**) can be used including two bearing a chlorine atom (entries 8 and 9), a useful synthetic handle for further elaboration. From the point of view of the organolithium reagent, various alkyl- and aryllithiums can be used including a functionalized one such as 3-lithiotrifluoromethylbenzene (entry 4).[22] It is important to note that, in most cases, both geometrical isomers were easily separable by simple flash chromatography.

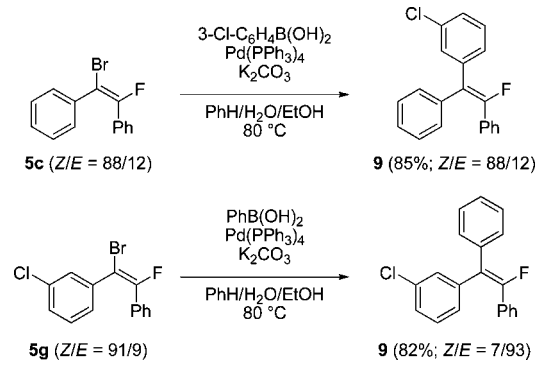
Scheme 3. Synthetic Elaboration of **(*Z*)-5a**



To illustrate the utility of these bromofluoroalkenes, we carried out a number of synthetic transformations on **(*Z*)-5a** as demonstrated in Scheme 3. For example, **(*Z*)-5a** can be converted into single isomers of tetrasubstituted fluoroalkenes **6** and **7** via Suzuki−Miyaura or Sonoghashira cross-coupling in 82% and 45% yields (nonoptimized), respectively. Similarly, the bromine atom can be reduced to produce the trisubstituted fluoroalkene **8** as a single isomer in 47% yield (nonoptimized).[23]

Finally, the versatility of this methodology can be illustrated by the fact that, in the case of 1,1-diaryl-2-fluoroethene derivatives, both stereoisomers can be obtained by a simple change in the synthetic sequence (Scheme 4). For example, both **2a** and **2b** can be obtained from the same precursor, CF_3CH_2I, in two steps by using the proper aryl iodide (PhI vs 3-Cl-C_6H_4I).[11] These compounds can then be submitted to the one-pot procedure (addition/elimination reaction of PhLi followed by a bromination/desilicobromination reaction) to furnish the (*Z*)-bromofluoroalkenes **5c** and **5g** in good yield and selectivity (Table 2, entries 6 and 8). In the last step, a Suzuki reaction is performed on the bromofluoroalkene with the proper arylboronic acid partner (i.e., 3-Cl-$C_6H_4B(OH)_2$ and $PhB(OH)_2$, respectively) to give both stereoisomers of the tetrasubstituted fluoroalkene **9** in excellent yields. Thus, both stereoisomers can be selectively obtained in four steps from commercially available CF_3CH_2I.

Scheme 4. Stereoselective Preparation of Both Geometrical Isomer of **9**



In conclusion, we have described a novel, stereocontrolled method for the preparation of tri- and tetrasubstituted fluoroalkenes using an addition/elimination reaction of organolithium reagents to silylated β,β-difluorostyrene derivatives followed by a bromination/desilicobromination reaction. This short and simple synthetic sequence provides an effective synthetic approach to a wide range of bromofluoroalkenes with moderate to excellent stereocontrol (up to >97/3). In addition, the bromofluoroalkenes can be used in Pd-catalyzed transformations giving access to both tri- and tetrasubstituted fluoroalkenes. 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.

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