ORGANIC LETTERS

2011
Vol. 13, No. 6
1568–1571

Stereoselective Synthesis of Both Stereoisomers of β-Fluorostyrene Derivatives from a Common Intermediate

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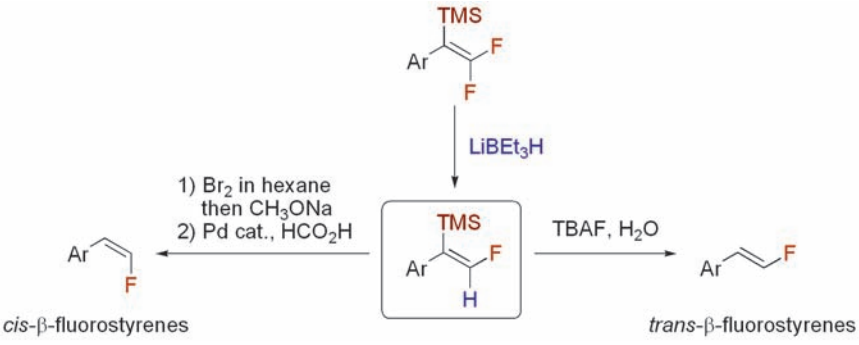
Received January 31, 2011

ABSTRACT



The stereoselective synthesis of both *cis*- and *trans*-β-fluorostyrene derivatives from a common intermediate, (*Z*)-1-aryl-2-fluoro-1-(trimethylsilyl)ethenes, is described. The *trans* isomers are obtained by a stereospecific replacement of the silyl group in the presence of water and a fluoride source, whereas the preparation of the *cis* isomers is achieved by a bromination/desilicobromination sequence followed by reduction of the newly created C−Br bond. A stereoselective transformation of both stereoisomers of β-fluorostyrene is also presented.

Addition of fluorine atoms on a bioactive molecule is often used to modulate its solubility, lipophilicity, metabolic stability, conformation, hydrogen-bonding ability, or chemical reactivity. Thus, the number of drugs or agrochemicals with at least one fluorine atom has increased dramatically over the past decade.[1,2] It is therefore not surprising that a parallel interest in the development of novel methods for the synthesis of organofluorine compounds has been observed. For this purpose, two complementary approaches are generally employed: formation of a C−F bond from a suitable functional group with a fluorinating reagent or functionalization of simple and readily available fluorinated synthons.[1a]

In regard to the second approach, one simple fluorinated synthon that is surprisingly missing from the toolbox is β-fluorostyrene (*trans* or *cis*) and its derivatives. Indeed, a wide range of diversified fluorinated synthons could be obtained from β-fluorostyrenes if a practical and stereoselective access to them was available. While numerous

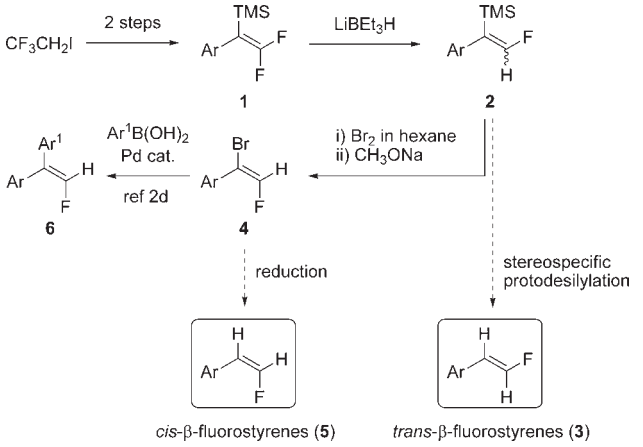
(1) For selected book/reviews/accounts, see: (a) Hiyama, T. In *Organofluorine Compounds; Chemistry and Applications*; Yamamoto, H., Ed.; Springer: 2000 and references therein. (b) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3–11. (c) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *106*, 6119–6146. (d) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214–231. (e) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15–24. (f) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013–1029. (g) Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992–1012. (h) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921–930. (i) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886. (j) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330. (k) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369. (l) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1–PR43.

(2) For our own efforts in this area, see: (a) Bélanger, É.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. *J. Am. Chem. Soc.* **2007**, *129*, 1034–125. (b) Bélanger, É.; Houzé, C.; Guimond, N.; Cantin, K.; Paquin, J.-F. *Chem. Commun.* **2008**, 3251–3253. (c) Landelle, G.; Champagne, P. A.; Barbeau, X.; Paquin, J.-F. *Org. Lett.* **2009**, *11*, 681–684. (d) Landelle, G.; Turcotte-Savard, M.-O.; Marterer, J.; Champagne, P. A.; Paquin, J.-F. *Org. Lett.* **2009**, *11*, 5406–5409. (e) Pigeon, X.; Bergeron, M.; Barabé, F.; Dubé, P.; Frost, H. N.; Paquin, J.-F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1123–1127.

(3) For a review on the synthesis of terminal monofluoroalkenes including β-fluorostyrenes, see: van Steenis, J. H.; van der Gen, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2117–2133.

10.1021/ol200302h
Published on Web 02/21/2011

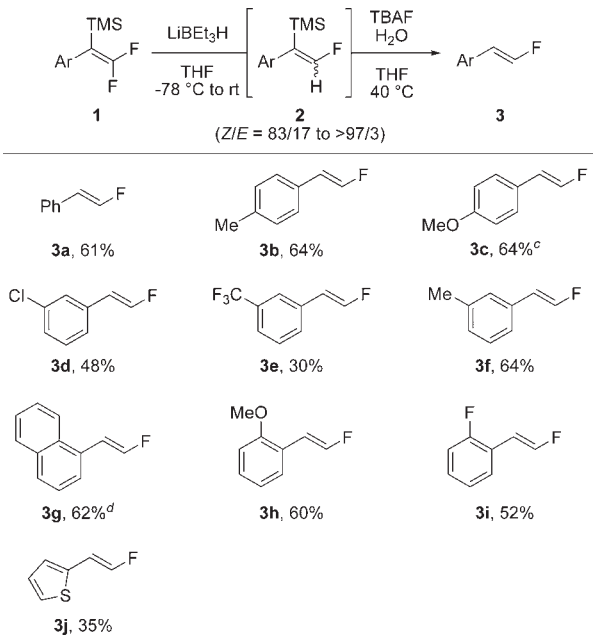
Scheme 1. Stereoselective Approaches to Both Isomers of β-Fluorostyrenes



synthetic routes to β-fluorostyrenes[3] have been described, the majority are either nonselective[4] or display low to high selectivity.[5] This is problematic since, in most cases, it is impossible to separate the isomers by flash chromatography, and this mixture of geometrical isomers may impact the stereochemical purity of the product generated by a further transformation. Methods providing exclusively one isomer are rare with two notable exceptions.[6,7] Indeed, while the fluorination of *trans*-β-lithiostyrene generated from *trans*-β-iodostyrene with $PhSO_2N(F)t$-Bu is a known transformation,[6] when we tried to reproduce this result using NFSI instead,[8] we obtained a moderate conversion (55%) of an inseparable mixture (ca. 1:1) of *trans*-β-fluorostyrene and styrene.[9] More recently, a silver(I) triflate mediated transformation of styrylboronic acid into *trans*-β-fluorostyrene using Selectfluor was reported by Ritter.[7] To the best of our knowledge, no stereocontrolled access to the *cis* isomer has ever been reported.

We have recently described the first stereocontrolled method for the preparation of 1,1-diaryl-2-fluoroethenes (**6**, Scheme 1).[2d] First, 1-aryl-1-bromo-2-fluoroethenes (**4**) are generated using an addition/elimination reaction of hydride to silylated β,β-difluorostyrene derivatives (**1**) followed by a bromination/desilicobromination sequence. Subsequent Suzuki−Miyaura coupling with a variety of boronic acids gives access to the desired 1,1-diaryl-2-fluoroethenes. Based on these results, we envisioned that the intermediate **2** could potentially be used as a common precursor to give direct and stereoselective access to both isomers of β-fluorostyrene derivatives. We report herein that the *trans*-β-fluorostyrene derivatives (**3**) can be prepared by a stereospecific replacement of the silyl group in the presence of water and a fluoride source whereas the preparation of *cis*-β-fluorostyrenes (**5**) can be achieved by the reduction of the C−Br bond created from the bromination/desilicobromination sequence of **2** (Scheme 1).

Scheme 2. Synthesis of *trans*-β-Fluorostyrene Derivatives [a,b]



[a] See Supporting Information for details concerning the reaction conditions. [b] Isolated yield of the fluorostryrene for 2 steps (from **1**). [c] The product is contaminated with ca. 2% of 4-ethynylanisole. [d] Estimated yield by NMR as the product is contaminated with ca. 30% of 1-ethynylnaphthalene.

Our stategy for the synthesis of *trans*-β-fluorostyrenes relied on protodesilylation of **2** with retention of the alkene geometry.[10] The requisite (*Z*)-1-aryl-2-fluoro-1-(trimethylsilyl)ethenes (**2**) were prepared using an addition/elimination reaction of hydride to silylated β,β-difluorostyrene derivatives (**1**) as described previously[2d] and were used crude after an aqueous workup. A survey of various

(4) (a) Schlosser, M.; Zimmermann, M. *Synthesis* **1969**, 75–76. (b) Inbasekaran, M.; Peet, N. P.; McCarthy, J. R.; LeTourneau, M. E. *J. Chem. Soc., Chem. Commun.* **1985**, 678–679. (c) Petasis, N. A.; Yudin, A. K.; Zavialov, I. A.; Prakash, G. K. S.; Olah, G. A. *Synlett* **1997**, 606–608. (d) Wang, Q.; Wei, H.-x.; Schlosser, M. *Eur. J. Org. Chem.* **1999**, 3263–3268. (e) Zhu, L.; Ni, C.; Zhao, Y.; Hu, J. *Tetrahedron* **2010**, *66*, 5089–5100. (f) Prakash, G. K. S; Shakhmin, A.; Zibinsky, M.; Ledneczki, I.; Chacko, S.; Olah, G. A. *J. Fluorine Chem.* **2010**, *131*, 1192–1197.

(5) (a) Schlosser, M.; Christmann, K.-F. *Synthesis* **1969**, 38–39. (b) Burton, D. J.; Greenlimb, P. E. *J. Org. Chem.* **1975**, *40*, 2796–2801. (c) Hayashi, S.-i.; Nakai, T.; Ishikawa, N.; Burton, D. J.; Naae, D. G.; Kesling, H. S. *Chem. Lett.* **1979**, 983–986. (d) Cox, D. G.; Gurusamy, N.; Burton, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 2811–2812. (e) Purrington, S. T.; Pittman, J. H. *Tetrahedron Lett.* **1987**, *28*, 3901–3904. (f) Uno, H.; Sakamoto, K.; Semba, F.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 210–217. (g) Galli, C.; Guarnieri, A.; Koch, H.; Mencarelli, P.; Rappoport, Z. *J. Org. Chem.* **1997**, *62*, 4072–4077. (h) Kataoka, K.; Tsuboi, S. *Synthesis* **2000**, 452–456. (i) van Steenis, J. H.; van der Gen, A. *Eur. J. Org. Chem.* **2001**, 897–910. (j) Greedy, B.; Gouverneur, V. *Chem. Commun.* **2001**, 233–234.

(6) (a) Lee, S.-H.; Schwartz, J. *J. Am. Chem. Soc.* **1986**, *108*, 2445–2447. (b) Lee, S.-H.; Riediker, M.; Schwartz, J. *Bull. Korean Chem. Soc.* **1998**, *19*, 760–766.

(7) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860–2863.

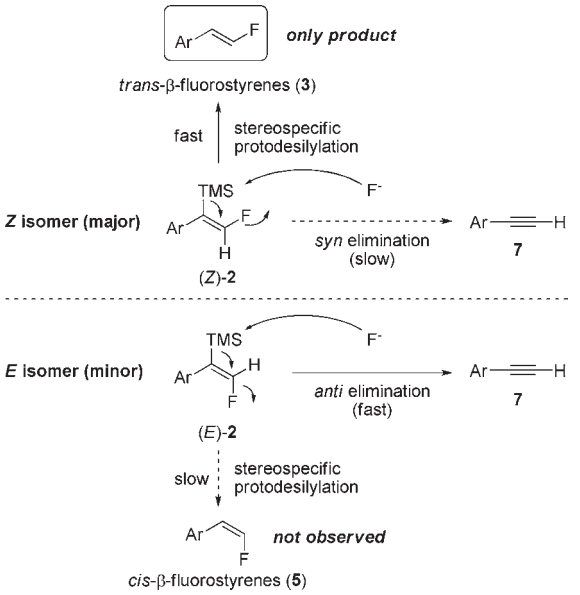
(8) $PhSO_2N(F)t$-Bu is not commercially available and has to be prepared using elemental fluorine.

(9) Marterer, J.; Paquin, J.-F. *Unpublished results.*

(10) (a) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761–786. (b) Oda, H.; Sato, M.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3257–3268. (c) Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press Limited: London, 1988 and references therein.

experimental conditions for the stereospecific protodesilylation led to the finding of the optimal conditions [TBAF, H_2O (2 equiv), THF, 40 °C]. The scope of the addition/elimination reaction of a hydride followed by a stereospecific protodesilylation is presented in Scheme 2. In all the cases, the β-fluorostyrenes were isolated in moderate to good yields in two steps (averages of 55−80% per step) as the *trans* isomer only (*vide infra*). Notably, with the exception of **3a**, the synthesis of pure *trans* isomers of **3b**−**h** have not been reported before while **3i** and **3j** were unknown compounds though potentially interesting fluorinated synthons. It should be noted that all of these compounds display significant volatility rendering their isolation on a small scale (0.4−1.4 mmol) challenging.

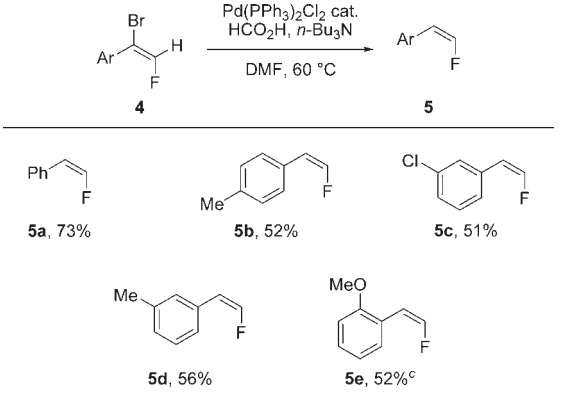
Scheme 3. Mechanistic Hypothesis



The only side products isolated are the corresponding alkynes (**7**). Interestingly, the fluorostyrenes were always isolated as single isomers even though the crude intermediates **2** were not totally isomerically pure (Z/E = 83/17 to >97/3) depending on the substitution pattern.[11] A possible explanation for this phenomenon is found in Scheme 3 where we postulate that the minor isomer ((*E*)-**2**) is kinetically destroyed under the reaction conditions. Indeed, the fact that we do not observe the *cis* isomer seems to indicate that the *anti*-elimination between the silyl group and the fluorine atom is facile[12] under those conditions and kinetically overrides the stereospecific protodesilylation. On the contrary, in (*Z*)-**2**, the silyl group and the fluorine atom are *cis* to one another which would disfavor the elimination over the stereospecific protodesilylation. However, the fact that the amount of alkyne (**7**) isolated exceeds the percentage of (*E*)-**2** detected in the crude mixture indicates that the elimination is still a competing process.

For the preparation of the *cis*-fluorostyrenes, we envisioned a palladium-catalyzed reduction of the C−Br bond[13] of 1-aryl-1-bromo-2-fluoroethenes (**4**). The latter were prepared using an addition/elimination reaction of hydride to silylated β,β-difluorostyrene derivatives (**1**) followed by a bromination/desilicobromination reaction to afford **4** in 51−86% yields (**1** → **4**, Scheme 1).[2d]

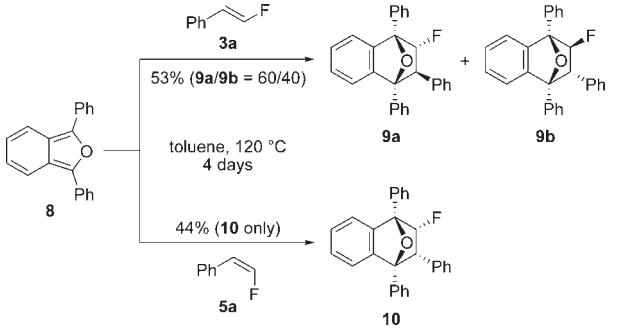
Scheme 4. Synthesis of *cis*-β-Fluorostyrene Derivatives[a,b]



[a] See Supporting Information for details concerning the reaction conditions. [b] Isolated yield of the fluorostyrene. [c] The product is contaminated with ca. 3% of the *trans* isomer.

The scope of the synthesis of *cis*-β-fluorostyrenes (**5**) from the reduction of 1-aryl-1-bromo-2-fluoroethenes (**4**) is presented in Scheme 4. In all the cases, the β-fluorostyrenes were isolated in moderate to good yields (56−73%) as the *cis* isomer only indicating that no scrambling of the geometry occurred at the reduction with the exception of **5e** where ca. 3% of the *trans* isomer was observed. Here again, with the exception of **5a**,[14] the synthesis of the pure *cis* isomer of **5b**−**e** had not been reported before.

Scheme 5. Diels−Alder of Both Isomers of β-Fluorostyrene with 1,3-Diphenylisobenzofuran



To illustrate the potential utility of *trans*- and *cis*-β-fluorostyrenes as fluorinated synthons, their Diels−Alder

(11) See Supporting Information for more details.

(12) (a) Bach, R. D.; Evans, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 1374–1379 and references therein. (b) Cho, B. R.; Cho, N. S.; Lee, S. K. *J. Org. Chem.* **1997**, *62*, 2230–2233 and references therein.

(13) Xu, J.; Burton, D. J. *Org. Lett.* **2002**, *4*, 831–833.

(14) Goumans, T. P. M.; van Alem, K.; Lodder, G. *Eur. J. Org. Chem.* **2008**, 435–443.

reaction with 1,3-diphenylisobenzofuran (**8**) was examined (Scheme 5).[15] When *trans*-β-fluorostyrene (**3a**) was used, a moderate yield of the cycloadduct (**9**) was isolated as an *endo*/*exo* mixture (60/40) with respect to the fluorine atom.[16] Using *cis*-β-fluorostyrene (**5a**) led to the pure *endo* isomer (**10**) in 44% yield. This transformation illustrates the rationale for a stereoselective access to both isomers of β-fluorostyrene without which diastereoselective preparation of the cycloadducts (**9** and **10**) would have been difficult.

In conclusion, we have described a stereoselective method for the preparation of both *cis*- and *trans*-β-fluorostyrene derivatives from a common intermediate, (*Z*)-1-aryl-2-fluoro-1-(trimethylsilyl)ethenes. The short and simple synthetic sequences provide an effective synthetic approach to both stereoisomers of a wide range of β-fluorostyrene derivatives with excellent stereocontrol. Further expansion of the scope and application of this methodology for the preparation of novel fluorinated synthons 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, the Fonds de recherche sur la nature et les technologies (FQRNT), Merck Frosst Centre for Therapeutic Research, FQRNT Centre in Green Chemistry and Catalysis, and the Université Laval.

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.

(15) (a) Ernet, T.; Haufe, G. *Tetrahedron Lett*. **1996**, *37*, 7251–7252. (b) Ernet, T.; Maulitz, A. H.; Würthwein, E.-U.; Haufe, G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1929–1938.

(16) For other examples where the selectivity of a Diels−Alder reaction is influenced by the presence of a fluorine atom, see: (a) Crowley, P. J.; Percy, J. M.; Stansfield, K. *Tetrahedron Lett*. **1996**, *37*, 8237–8240. (b) Percy, J. M. *Top. Curr. Chem*. **1997**, *193*, 131–195. (c) Ito, H.; Saito, A.; Taguchi, T. *Tetrahedron Lett*. **1998**, *9*, 1979–1987. (d) Ito, H.; Saito, A.; Taguchi, T. *Tetrahedron Lett*. **1998**, *9*, 1988–1994. (e) Haufe, G. In *Vinyl Fluorides in Cycloadditions, in Fluorinated Synthons*; Soloshonok, V., Ed.; ACS Symposium Series 911; American Chemical Society: Washington, D.C., 2005; pp 155−172.