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Stereoselective Preparation of (*E*)-(1,2-Difluoro-1,2-ethenediyl) Bis[tributylstannane] and Stereospecific Synthesis of (*E*)-1,2-Difluorostilbenes

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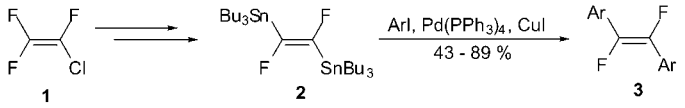
ABSTRACT



The novel bisstannane (*E*)-(1,2-difluoro-1,2-ethenediyl) bis[tributylstannane] 2 was stereoselectively prepared in a high overall yield through a sequential synthetic route from chlorotrifluoroethylene 1. The synthetic application of this novel bisstannane 2 was exemplified in the Pd(PPh$_3$)$_4$/CuI-catalyzed cross-coupling reactions with aryl iodides, yielding (*E*)-1,2-difluorostilbenes 3 in moderate to high yields.

The symmetrical (*E*)-1,2-difluoroethylene synthon is a fundamental building block in numerous organic compounds. Some aromatic derivatives have been found to possess liquid crystal properties and are usable in LC electrooptical devices.[1,2] Other classes of compounds containing the (*E*)-1,2-difluoro-1,2-ethenediyl unit have been rarely studied, mainly because of the lack of efficient and stereoselective synthetic methods for these materials.[3] On the other hand, the (*E*)-1,2-difluoro-1,2-ethenediyl organometallics have never been reported. The only practical method for the preparation of (*E*)-1,2-difluoro-stilbenes **3** is the addition−elimination reaction between tetrafluoroethylene (TFE) and aryllithium reagents.[2,4,5] An alternative reaction using α,α-bromofluorotoluene to form the disubstituted stilbene was also reported, but with low yield and essentially no stereoselectivity.[6] In general, the addition−elimination reaction has been successfully applied to prepare a number of symmetrical (*E*)-1,2-difluorostilbenes **3**. However, because of the reaction of aryllithium reagents with many functional groups, its scope of application is limited. Furthermore, both the explosive nature of TFE and the requirement of low-temperature reaction conditions deter the industrial application of this method.

In our research group, one of the approaches utilized for the incorporation of fluorinated synthons is via fluorinated organometallic reagents.[7] This previously reported methodology using organozinc or cadmium synthons stereospecifically permitted monofunctionalization of the organometallic intermediate. To successfully achieve bis-functionalization processes in one step, we have attempted to develop a stable 1,2-difluoro-bisorgano-metallic reagent. The requirements that we demanded of such a reagent are that (1) it could be prepared from a commercially available reagent; (2) it could be prepared stereospecifically or stereoselectively; (3) it

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(2) Inoue, S.; Asahi, M.; Honda, K. *Rep. Asahi. Glass Found*. **1995**, 37.
(3) Jing, N.; Lemal, D. M. *J. Org. Chem.* **1994**, *59*, 1844.
(4) McGrath, T. F.; Levine, R. *J. Am. Chem. Soc.* **1955**, *77*, 4168.
(5) Dixon, S. *J. Org. Chem.* **1956**, *21*, 400.
(6) Kam, T.; Lim, T. *J. Chem. Soc., Perkin Trans. 2* **1993**, 147.

(7) For selected papers for the synthesis and synthetic applications of fluorinated organometallic reagents, see: (a) Burton, D. J.; Yang, Z.; Morken, P. A. *Tetrahedron* **1994**, *50*, 2993. (b) Burton, D. J. In *Synthetic Fluorine Chemistry*; Olah, G. A., Chambers, R. D., Prakash, G. K. S., Eds.; Wiley: New York, 1992; pp 205−206. (c) Burton, D. J.; Yang, Z. In *Chemistry of Organic Fluorine Compounds II*; Hudlicky, M., Pavlath, A. E., Eds.; Washington, DC; 1995; pp 670−728. (d) Burton, D. J.; Yang, Z. *Tetrahedron* **1992**, *48*, 189. (e) Xue, L.; Lu, L.; Pedersen, S.; Liu, Q.; Narske, R.; Burton, D. J., *Tetrahedron Lett.* **1996**, *37*, 1921. (f) Xue, L.; Lu, L.; Pedersen, S.; Liu, Q.; Narske, R.; Burton, D. J. *J. Org. Chem.* **1997**, *62*, 1064. (g) Fontana, S. A.; Davis, C. R.; He, Y.; Burton, D. J. *Tetrahedron* **1996**, *52*, 37. (h) Davis, C. R.; Burton, D. J. *Tetrahedron Lett.* **1996**, *37*, 7237. (i) Davis, C. R.; Burton, D. J. *J. Org. Chem.* **1997**, *62*, 9217. (j) Liu, Q.; Burton, D. J. *Tetrahedron Lett.* **2000**, *41*, 8045.

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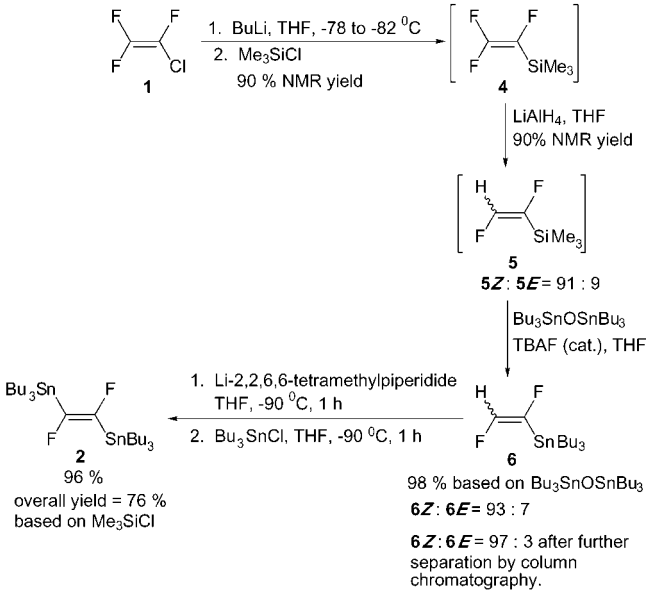
would be stable at room temperature or above; and (4) it could be readily functionalized. A reagent that met these requirements could be utilized by any workers (not just specialists) and could be readily adopted to scale-up.

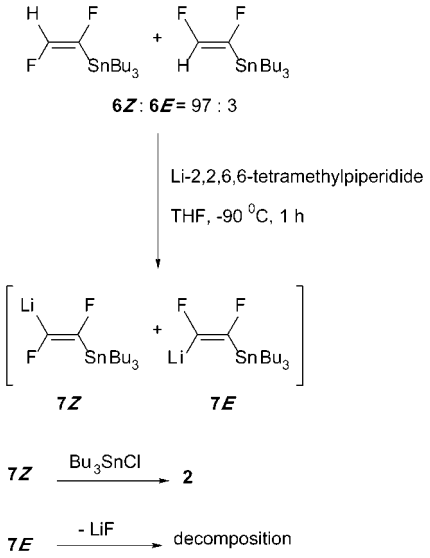
The stereoselective synthesis of (*E*)-(1,2-difluoro-1,2-ethenediyl) bis[tributylstannane] **2** is described in Scheme 1. Chlorotrifluoroethylene **1** was treated with an *n*-butyl-

Scheme 1



lithium/hexanes solution and quenched in situ with chlorotrimethylsilane to give the trifluorovinyltrimethylsilane **4** as a crude product. The crude **4** in THF and hexanes was reduced to an isomeric mixture of 91:9 of *Z*/*E* **5** with $LiAlH_4$. Both the isomeric ratio and yields were determined from ^{19}F NMR integration using $PhCF_3$ as an internal standard. We could not separate completely either **4** or **5** from the solvents since their boiling points are too close to those of the solvents. However, these solvents never caused any problems in subsequent reactions. On the contrary, the simplified procedures led to higher efficiency and were much more convenient. When **5** was reacted in THF with $Bu_3SnOSnBu_3$ in the presence of catalytic amount of tetrabutylammonium fluoride, a 93:7 *Z*/*E* mixture of difluorostannanes **6** was isolated in nearly quantitative yield.[7f] The isomeric ratio of **6** was enhanced from 93:7 *Z*/*E* to 97:3 after chromatographic separation. It is worth mentioning that the chromatographic separation of the two isomers is not required, because as illustrated in Scheme 2 the (*E*)-isomer **6*E*** decomposes during the metalation step with *n*-BuLi, presumably as a result of a LiF anti elimination. The 1,2-difluoroethenyltributylstannanes (**6*Z***:**6*E*** = 97:3) were treated with a bulky base, lithium 2,2,6,6-tetramethylpiperidide to form the corresponding vinyllithium reagent **7*Z***. Subsequent trapping of the lithium intermediate **7*Z*** with tributyltin chloride yields the bis-stannane **2** in 100% isomeric purity and nearly quantitative isolated yield. The bis-stannane **2** is a stable, colorless liquid.

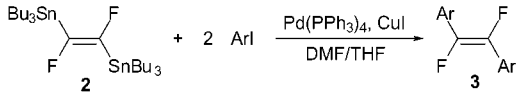
Scheme 2



It was found that this organometallic reagent may be stored at room temperature indefinitely without decomposition.

To evaluate the potential of **2** for bis-functionalization, we attempted the coupling of **2** with aryl iodides. As summarized in Table 1, (*E*)-1,2-difluorostilbenes **3** may be

Table 1. Preparation of (*E*)-1,2-Diflurostilbenes



entry	ArI	conditions	isolated yield[a] (%)
1	C_6H_4I	rt/2 h	86
2	*m*-$CF_3C_6H_4I$	rt/2 h	85
3	*p*-$EtOOCC_6H_4I$	rt/0.5 h	83
4	*p*-$CH_3C_6H_4I$	rt/2 h	89
5	*p*-$MeOC_6H_4I$	60 °C/8 h	70
6	*o*-ClC_6H_4I	rt/20 h	63
7	*o*-BrC_6H_4I	rt/20 h	62
8	*o*-$MeOC_6H_4I$	rt/24 h	51

[a] The isolation process consists of flash chromatography and crystallization of the (*E*)-1,2-difluorostilbenes from the by-product, Bu_3SnI. Further recrystallization of the crude crystals from ethanol or ether gave the product as fine crystals.

stereospecifically synthesized from the $Pd(PPh_3)_4$/CuI-catalyzed cross-coupling reaction between the bis-stannane **2** and aryl iodides.[8] The cross-coupling reaction is sluggish

(8) **Typical Procedure for (*E*)-(1,2-Difluoro-1,2-ethenediyl) Bis[3′-trifluoromethylbenzene], 3-(2).** A one-neck 10-mL round-bottom flask equipped with a Teflon-coated stir bar and attached to a nitrogen tee was charged with 0.64 g (1.0 mmol) of (*E*)-(1,2-difluoro-1,2-ethenediyl) bis-[tributylstannane], 0.54 g (2.0 mmol) of 3-iodobenzotrifluoride, 1.5 mL of THF, 1.5 mL of DMF, 0.19 g (1 mmol) of CuI, and 0.11 g (5 mol %) of $Pd(PPh_3)_4$. The reaction mixture was stirred at room temperature. An

without the CuI cocatalyst and gives lower yields of stilbenes. In the literature, the current preparative method employed aryllithium reagents in an addition−elimination reaction at low temperature to generate the corresponding (*E*)-1,2-difluorostilbenes **3**.[2,4,5] In contrast to the current preparative method via reaction of aryllithium reagents with TFE, our bisstannane strategy has a wider scope of functional group tolerance and is carried out under mild reaction conditions.

In summary, we have reported the first synthesis of (*E*)-(1,2-difluoro-1,2-ethenediyl) bis[tributylstannane] **2** and its synthetic application in the stereospecific preparation of (*E*)-1,2-difluorostilbenes **3**.[9] We anticipate that this novel fluorinated organometallic reagent **2** will play an important role in future synthetic organofluorine chemistry.[10,11]

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Supporting Information Available: Complete experimental details for the synthesis outlined in Scheme 1 and Table 1 and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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exothermic reaction occurred, and the reaction mixture quickly turned to a dark homogeneous solution. ^{19}F NMR analysis was employed to monitor the progress of the reaction. After the reaction mixture had been stirred for 2 h, the ^{19}F NMR signal of the (*E*)-(1,2-difluoro-1,2-ethenediyl) bis-[tributylstannane] had disappeared and two new singlets (−63 and −151 ppm) were observed. The dark reaction mixture was poured onto a silica gel column and eluted with pentane, $R_f = 0.5$. Removal of most of the solvent via rotary evaporation yielded a liquid, which gave colorless crystals after being stored at room temperature overnight. These crystals were further purified via recrystallization from ethanol. Removal of the solvent at rt/1 mmHg yielded 0.29 g (85%) of colorless crystals, mp 55−56 °C. ^{19}F NMR δ −63.45 (s, 6 F), −151.32 (s, 2 F); ^{1}H NMR δ 8.02 (s, 2 H), 7.93 (d, J = 8 Hz, 2 H), 7.65 (d, J = 8 Hz, 2 H), 7.58 (dd as t, J = 8 Hz, 2 H); {^{1}H}^{13}C NMR δ 148.13 (2nd order due to virtual coupling), 131.38 (q, J = 33.0 Hz), 130.60 (t, J = 9.3 Hz), 129.27 (s), 129.05 (tq, J = 9.1, 1.1 Hz), 126.06 (q, J = 3.6 Hz), 123.92 (q, J = 272.3 Hz), 122.84 (tq, J = 7.5, 4.0 Hz); FTIR (CCl_4, cm^{-1}) 3086.0 (vw), 1495.3 (w), 1442.7 (w), 1335.8 (s), 1311.6 (w), 1267.8 (w), 1250.0 (m), 1183.6 (m), 1173.1 (s), 1139.9 (s), 1079.4 (m); GC−MS (*m*/*e*) 352 (M^+, 100), 333 (28), 282(27), 263 (29), 233 (44), 214 (88); UV ($CHCl_3$) 259 nm (ϵ = 10800 cm^{-1} M^{-1}), 314 nm (ϵ = 12200 cm^{-1}M^{-1}); HRMS calcd for $C_{16}H_8F_8$ 352.0498, obsd 352.0511.

(9) Attempts to prepare unsymmetrical stilbenes via sequential coupling of the bis-stannane were unsuccessful.

(10) In a preliminary experiment, **2** reacted with (*E*)-C_6H_5CH═$CHBr$ under similar conditions to stereospecifically give (1*E*,3*E*,5*E*)-3,4-difluoro-1,6-diphenylhexatriene in 52% yield.[11]

(11) Liu, Q. The University of Iowa, unpublished work.