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Stereospecific preparation of (*Z*)-α-fluorostilbenes via a kinetically controlled palladium-catalyzed cross-coupling reaction of high *E*/*Z* ratio 1-bromo-1-fluorostyrenes and aryl stannanes

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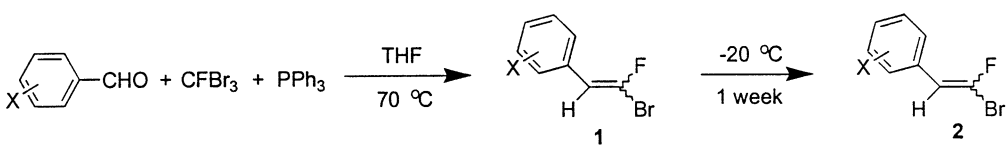
Abstract—High *E*/*Z* ratios were obtained for 1-bromo-1-fluorostyrenes by isomerization from the original *E*/*Z* ratios of approximately 1:1. The palladium-catalyzed cross-coupling reaction of high *E*/*Z* ratio 1-bromo-1-fluorostyrenes with aryl stannanes gives (*Z*)-α-fluorostilbenes stereospecifically in good yields. © 2002 Elsevier Science Ltd. All rights reserved.

Fluoroorganic compounds have exhibited increased interest as agrochemical and pharmaceutical agents in recent years[1] since it has been found that fluorine modifies biological activity by altering the physiochemical properties of organic compounds.[2] Monofluorinated stilbenes, especially α-fluorostilbenes ArCH=CFAr,[1] attracted our interest because they, as an important class of fluorinated olefins,[3] are potential enzyme inhibitors.[4] The stereospecific preparation of α-fluorostilbenes continues to be a challenge, however. Base-promoted dehydrofluorination of 1,2-difluoro-1,2-diphenylethanes leads to (*E*),(*Z*) α-fluorostilbene mixtures[5] although under a certain reaction condition (*E*)-α-fluorostilbenes may dominate.[5c] The Wadsworth–Emmons–Horner olefination of $[(RO)_2P(O)CFPh]^-$ with substituted benzaldehydes also gives a mixture of (*E*),(*Z*)-α-fluorostilbenes.[6] McCarthy and co-workers have described the stereospecific preparation of 1-fluorovinyl stannanes and their coupling reaction with aryl halides and showed the potential of this approach for the synthesis of (*Z*)-α-fluorostilbenes, although it takes several steps to prepare the starting (*E*)-1-fluorovinyl stannanes.[7] Recently McCarthy and co-workers also reported the palladium-catalyzed cross-coupling reaction of 1-bromo-1-fluorostyrenes with organoboranes and aromatic stannanes.[8] This methodology is more straightforward compared to the previous coupling reaction between 1-fluorovinyl stannanes and aryl halides.[7] A limitation of this method, however, is the availability of pure (*E*)- and (*Z*)-1-bromo-1-fluorostyrenes. These isomeric 1-bromo-1-fluorostyrenes were separated by gas chromatography[8] from the corresponding *E*,*Z* isomeric mixtures.[9] This methodology is unlikely to be useful for large scale preparative synthetic purposes. A multi-step route to (*Z*)-1-bromo-1-fluorostyrenes includes bromination of (*E*)-2-fluoro-3-phenylacrylic acid followed by debromocarboxylation.[10] Rolando's isomerization from (*Z*) to a high *E*/*Z* ratio of 1-bromo-1-fluorostyrenes was only partially successful.[11] McCarthy and co-workers briefly mentioned another isomerization method from (*Z*) isomers to *E*/*Z*=92:8 isomer mixtures using a catalytic amount of bromine in chloroform.[8a] In our hands this isomerization by Br_2 was found to be low-yielding (<20%) due to competitive addition of bromine to the alkene. Herein we report our approach to a high *E*/*Z* ratio 1-bromo-1-fluorostyrenes and the kinetic sep-



Scheme 1.

Keywords: fluorostilbenes; palladium-catalyzed cross-coupling; stereospecific; isomerization; bromofluoroalkenes; kinetic separation.
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aration methodology in their palladium-catalyzed cross-coupling reactions with aryl stannanes.

Isomerization was observed when 1-bromo-1-fluorostyrenes (neat, $E/Z \approx 1{:}1$) were stored at −20°C. 1-Bromo-1-fluorostyrenes ($E/Z \approx 1{:}1$), which were readily prepared by the literature method,[9a] were found to have a higher E/Z ratio after storage at −20°C (Scheme 1). For example, 1-bromo-1-fluorostyrene changed from an E/Z ratio of 44:56 to 85:15 after 1 week at −20°C. This ratio increased to 88:12 when the product was kept at −20°C for 3 months. Similar E/Z ratio changes were also observed at room temperature. Presumably this isomerization was catalyzed by a trace amount of bromine in the mixture (Table 1).[12]

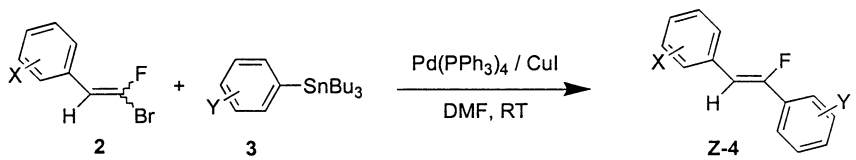
The palladium-catalyzed cross-coupling reactions between high E/Z ratio 1-bromo-1-fluorostyrenes and aryl stannanes were studied. Aryl stannanes reacted stereoselectively with the (E) isomers[13] and very high Z/E ratios were obtained for the resulting α-fluorostilbenes (Scheme 2). Most (Z) isomers of **2**, however, remained unreacted, as detected by ^{19}F NMR analysis of the reaction mixture when the reactions were completed. Pure (Z)-α-fluorostilbenes Z-**4a**–**h** were separated in good yields (Table 2), by column chromatography or column chromatography followed by recrystallization.

A variety of pure (Z) α-fluorostilbenes can be prepared by this method as the starting materials are easy to prepare and the reaction conditions are very mild. Various combinations of functional groups on both phenyl rings are available and permutation is also possible, as demonstrated by Z-**4b** and Z-**4f**. We have also tested the coupling reaction of 1-bromo-1-fluorostyrenes ($E/Z = 88{:}12$) and phenylboronic acid in the presence of 4% $Pd(PPh_3)_4$ under Suzuki conditions.[8] At room temperature, the reaction proceeded very slowly, after 5 days, only 2/3 of the starting E isomers had reacted and the E/Z ratio of the resulting α-fluorostilbenes was 95:5. When above Suzuki reaction was carried out at reflux temperature the reaction proceeded to completion and the Z/E ratio of α-fluorostilbenes in the mixture was 94:6. Similar coupling reaction under Stille conditions at room temperature gave a Z/E ratio of 98:2. Therefore, although both routes gave similar results, Stille coupling reaction conditions are preferred for the preparation of (Z)-α-fluorostilbenes.

Table 1. The preparation[a] and isomerization (at −20°C, 1 week) of X-C_6H_4CH=CFBr

X	Time (h)	Yield (%)	E/Z after reaction	E/Z after isomerization
H	6	77	**1a** 44:56	**2a** 85:15[b]
o-Cl	6	67	**1b** 48:52	**2b** 82:18
p-MeO	6	62	**1c** 66:34	**2c** 81:19[c]
p-F	6	45	**1d** 72:28	**2d** 87:13
m-NO_2	8	53	**1e** 63:37	**2e** 76:24[d]

[a] Typical reaction condition: same as in Ref. 9a except that THF was used as solvent.
[b] E/Z ratio increased to 88:12 after 3 months.
[c] E/Z ratio increased to 83:17 after 3 months.
[d] E/Z ratio increased to 81:19 after 3 months.



Scheme 2.

Table 2. Synthesis of (Z)-α-fluorostilbenes from high E/Z ratio 1-bromo-1-fluorostyrenes and aryl stannanes

Entry	X	Y	E/Z of vinylbromide	Time (h)	Product[a] (Z/E)[b]	Mixture Z/E[c]	Yield (conversion)[d]
1	**2a** H	**3a** H	88:12	20	Z-**4a** (100:0)	98:2	73 (83)
2	**2a** H	**3b** *p*-F	88:12	16	Z-**4b** (100:0)	98:2	67 (76)
3	**2b** *o*-Cl	**3a** H	82:18	15	Z-**4c** (100:0)	94:6	71 (87)
4	**2b** *o*-Cl	**3b** *p*-F	82:18	16	Z-**4d** (100:0)	94:6	52 (63)
5	**2c** *p*-MeO	**3a** H	83:17	22	Z-**4e** (100:0)	93:7	61 (74)
6	**2d** *p*-F	**3a** H	87:13	16	Z-**4f** (100:0)	96:4	69 (80)
7	**2e** *m*-NO_2	**3a** H	76:24	16	Z-**4g** (100:0)	87:13	53 (70)
8	**2f** *p*-Cl	**3a** *p*-F	88:12	12	Z-**4h** (100:0)	98:2	72 (82)

[a] All products gave satisfactory ^{19}F, ^{1}H, ^{13}C NMR and HRMS data.
[b] Z/E ratio of isolated product.
[c] Z/E ratios of α-fluorostilbenes were determined by ^{19}F NMR analysis of the reaction mixture when the reaction was completed.
[d] Isolated yield. Conversion was calculated based on the amount of (E)-1-bromo-1-fluorostyrenes in the starting E,Z mixtures.

In a typical experiment, $Pd(PPh_3)_4$ (0.08 g, 0.07 mmol) and dry DMF (4 ml) were added to a 25 ml dry round-bottom flask equipped with a magnetic stirring bar and a N_2 tee. 1-Bromo-1-fluoro-2-(4-methoxyphenyl)-ethylene (0.46 g, 2.0 mmol, $E/Z=83:17$) was added and the resulting solution was stirred at room temperature for 15 min. CuI (0.16 g, 0.83 mmol) and phenyltributylstannane (0.85 g, 2.32 mmol) were added to the mixture sequentially, and the reaction mixture was stirred at room temperature for 22 h. ^{19}F NMR analysis of the reaction mixture showed that the reaction was completed. The reaction mixture was directly added to a silica gel column (ethyl acetate:hexanes = 5:95, $R_f=0.33$) and the white solid collected was further purified by recrystallization from hexanes to give *Z*-**4e**, white crystal, mp 97–99°C, 0.28 g (61%). The conversion was 74% based on the amount of (*E*)-1-bromo-1-fluorostyrene in the starting *E*,*Z* mixture. ^{19}F NMR ($CDCl_3$) δ −117.7 (d, $^3J_{FH(trans)}=39.9$ Hz, 1F) ppm; ^1H NMR ($CDCl_3$) δ 7.61 (tm, $J=8.2$ Hz, 4H), 7.30–7.42 (m, 3H), 6.91 (dm, $J=8.8$ Hz, 2H), 6.26 (d, $^3J_{HF(trans)}=39.9$ Hz, 1H), 3.83 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 158.7 (d, $J=1.7$ Hz), 155.9 (d, $^1J_{CF}=255.3$ Hz), 133.1 (d, $J=28.2$ Hz), 130.2 (d, $J=8.2$ Hz), 128.51, 128.47, 126.3 (d, $J=4.3$ Hz), 123.9 ($J=7.2$ Hz), 114.0, 105.4 (d, $J=10.9$ Hz), 55.2 ppm; GC–MS, *m*/*z* (relative intensity): 230 (M^++ 2, 3), 229 (4), 228 (M^+, 100), 213 (69), 196 (13), 185 (25), 183 (51), 170 (35), 165 (75), 133 (19), 114 (15); HRMS calcd 228.0950 for $C_{15}H_{13}OF$, found 228.0945.

In conclusion, we have described the isomerization of 1-bromo-1-fluorostyrenes (from $E/Z\approx1:1$ to high E/Z ratios). Room temperature coupling reactions of these high E/Z ratio 1-bromo-1-fluorostyrenes with aryl stannanes in the presence of $Pd(PPh_3)_4$/CuI stereospecifically gave (*Z*)-α-fluorostilbenes in good yields via kinetic separation.

Acknowledgements

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12. Subsequently, we found that the isomerization could be facilitated by photolysis of the E/Z mixture at 254 nm. For example, an E/Z mixture of *o*-Cl-C_6H_4CH=CFBr ($E/Z=63:37$) cleanly isomerized to an E/Z mixture of 78:22 after photolysis at 254 nm for 1 h. Longer photolysis time produced increasing amounts of impurities.
13. The kinetic separation of the E/Z 1-bromo-1-fluorostyrenes has been demonstrated to occur in the oxidative addition step of the reaction between the 1-bromo-1-fluorostyrenes and Pd(0).[14,15]
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