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Stereospecific preparation of symmetrical (1*Z*,3*Z*) 2,3-difluoro-1,4-disubstituted-buta-1,3-dienes by the coupling reaction between bis(tributyltin) and high *E*/*Z* 1-bromo-1-fluoroalkenes

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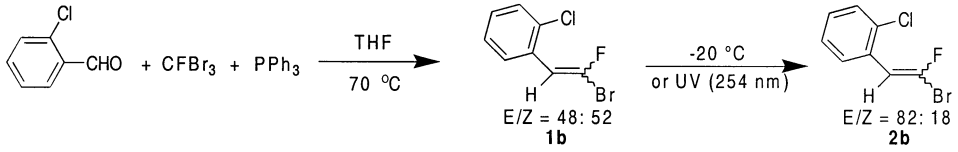
Abstract—When the palladium-catalyzed coupling reaction of $Bu_3SnSnBu_3$ and high *E*/*Z* 1-bromo-1-fluoroalkenes is carried out at room temperature, symmetrical (1*Z*,3*Z*) 2,3-difluorinated-1,4-disubstituted-buta-1,3-dienes are successfully prepared in good yields.

Fluoroorganic compounds continue to be of interest to polymer chemists, pharmaceutical chemists and agriculture chemists because of the unique properties these compounds exhibited when fluorine atoms were strategically placed in the molecule.[1] As conjugated dienes and polyenes widely exit as the essential features of many natural products, such as pheromones and juvenile hormones,[2] there is increased research interest in the synthesis and biological activity of their fluorinated analogues.[3] Popular methodologies for the preparation of fluorinated dienes include: (1) palladium/copper(I) halide catalyzed coupling reactions between 1,2-difluorovinylstannanes and vinyl halides;[4] (2) the coupling reaction between fluorinated vinyl zinc reagents and vinyl halides;[5] (3) the coupling reaction between fluorinated vinyl copper reagents and fluorinated vinyl halides;[6] and (4) the recently developed copper(II) salt-mediated homo-coupling of 1,2-difluorovinylstannanes.[7] Herein we wish to report the preparation of symmetrical (1*Z*,3*Z*) 2,3-difluoro-buta-1,3-dienes via the bis(tributyltin)-mediated homo-coupling of high *E*/*Z* 1-bromo-1-fluoroalkenes.

1-Bromo-1-fluoroalkenes **1** (*E*/*Z* ≈ 1:1), readily available from $CFBr_3$, PPh_3 and RCHO,[8] could potentially serve as a useful monofluorinated synthon in the preparation of fluorinated olefins. Recently, we found that the *E*/*Z* ratio of **1** could be increased via isomerization of **1** either by storage at –20°C or by photolysis at 254 nm for 1 h (Scheme 1).

We recently reported that at room temperature the (*E*) isomer of **1** reacts faster than the corresponding (*Z*) isomer in palladium-catalyzed coupling reactions.[9] This reactivity difference occurred in the first step of oxidative addition between the (*E*) or (*Z*) isomer of **1** and Pd(0). This kinetic separation strategy was successfully utilized to synthesize (*E*) and (*Z*) α-fluorovinylphosphonates[9a] and (*E*) and (*Z*) monofluoroenynes.[9b] In an effort to prepare (*E*) 1-fluoro-2-phenylvinyltributyltin, which is a



Scheme 1. An example of the preparation and isomerization of 1-bromo-1-fluoroalkenes.

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Table 1. Preparation of symmetrical (1*Z*,3*Z*) 2,3-difluoro-buta-1,3-dienes from high *E*/*Z* 1-bromo-1-fluoroalkenes

Entry	R	S.M. #	*E*/*Z* of 1-bromo-1-fluoroalkenes	Time (h)	Isolated yield (%)[a]	Prod. #
1	Ph-	**2a**	85:15	68[b]	64 (75)	**3a**
2	*o*-ClC_6H_4-	**2b**	82:18	45	71 (86)	**3b**
3	*p*-$MeOC_6H_4$-	**2c**	81:19	40	43 (53)	**3c**
4	*p*-ClC_6H_4-	**2d**	88:12	41	72 (82)	**3d**
5	$PhCH(CH_3)$-	**2e**	83:17[c]	46	67 (81)	**3e**

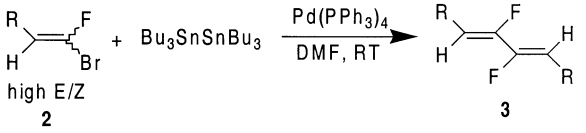
[a] All products gave satisfactory ^{19}F, ^{1}H, ^{13}C NMR and GC–MS, HRMS data; the number in the bracket is the conversion which was calculated based on the amount of the starting (*E*) isomer in **2**.
[b] The reaction of **2a** was carried out in THF instead of DMF.
[c] The starting material was obtained by an alternative method other than isomerization.

useful synthon[10], high *E*/*Z* 1-bromo-1-fluorostyrene (*E*/*Z* = 85:15) was reacted with $Bu_3SnSnBu_3$ (1.2 equiv.) and $Pd(PPh_3)_4$ (4 mol%) in THF at room temperature.[11] To our surprise, (*E*) 1-fluoro-2-phenylvinyltributyltin was not obtained. Instead, (1*Z*,3*Z*) 2,3-difluoro-1,4-diphenyl-buta-1,3-diene (**3a**) was isolated in 64% yield (the conversion is 75% on the basis of the consumed (*E*) 1-bromo-1-fluorostyrene). A trace amount of the (1*Z*,3*E*) isomeric diene was also detected in the reaction mixture by ^{19}F NMR analysis of the reaction mixture and could be successfully separated from the major product.

A similar symmetrical 2,3-difluoro-butadiene had also been observed by McCarthy and co-workers as a side reaction in the coupling reaction between 1-fluorovinyltin and phenyl triflate, oxalyl chloride and ethyl chloroformate.[10b] Although biaryls have been occasionally prepared via the coupling reaction between aryl halide and $Bu_3SnSnBu_3/Pd(0)$,[12] to the best of our knowledge the methodology to prepare fluorinated symmetrical dienes mediated by $Pd(PPh_3)_4/Bu_3SnSnBu_3$ has not been reported.

Similar reaction between other high *E*/*Z* 1-bromo-1-fluoroalkenes and $Bu_3SnSnBu_3$ catalyzed by $Pd(PPh_3)_4$ in DMF also occurred successfully. It is noteworthy that for both 1-bromo-1-fluorostyrenes (R = aryl groups) and other 1-bromo-1-fluoroalkenes (R = alkyl groups) symmetrical (1*Z*,3*Z*) dienes **3b–e** were obtained in good yields (Table 1, Scheme 2).

Since a trace amount of 1-fluoro-2-phenylvinyltributyltin was detected by ^{19}F NMR analysis of the reaction mixture, the symmetrical diene could be formed by the palladium-catalyzed coupling reaction between 1-fluoro-2-phenylvinyltributyltin intermediate and the (*E*) 1-bromo-1-fluoroalkene (Scheme 3). A similar mechanism to form biaryls has been reported.[12c]



Scheme 2.

In a typical experiment, a 25 mL dry round-bottom flask equipped with a stirring bar and an N_2 tee, was charged with $Pd(PPh_3)_4$ (0.08 g, 0.07 mmol) and dry DMF (5 mL). 1-Bromo-1-fluoro-2-(2-chlorophenyl)-ethylene (0.47 g, 2.0 mmol, *E*/*Z* = 82:18) was added and the solution was stirred at room temperature for 15 minutes. After the addition of $Bu_3SnSnBu_3$ (1.14 g, 1.97 mmol), the reaction mixture was stirred at room temperature for 45 h. $Co(OAc)_2{\cdot}4H_2O$ (1.25 g, 5.0 mmol) was added to remove tributyltin halide from the reaction mixture.[13] The mixture was separated by silica gel column chromatography (hexanes 100%, $R_f = 0.33$), followed by recrystallization from hexanes to give (1*Z*,3*Z*) 1,4-di(2-chloro-phenyl)-2,3-difluoro-buta-1,3-diene (**3b**) as white crystals (0.22 g, mp 144–145°C) in 71% yield (86% conversion based on the consumed (*E*) 1-bromo-1-fluoroalkene). (1*Z*,3*Z*) 100%. ^{19}F NMR ($CDCl_3$) δ –127.7 ppm (dd, $^{3}J_{FH(trans)} = 26.5$ Hz, $^{4}J_{FH} = 14.0$ Hz, 2F) ppm; ^{1}H NMR ($CDCl_3$) δ 7.90 (dd, $J = 7.7$ Hz, $J = 1.5$ Hz, 2H), 7.42 (dd, $J = 7.8$ Hz, $J = 1.2$ Hz, 2H), 7.29 (t, $J = 7.2$ Hz, 2H), 7.22 (td, $J = 7.8$ Hz, $J = 1.3$ Hz, 2H), 6.73 (dd, $^{3}J_{HF(trans)} = 27.8$ Hz, $^{4}J_{FH} = 13.9$ Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 150.9 (dd, $^{1}J_{CF} = 260.0$ Hz, $^{2}J_{CF} = 43.3$ Hz), 133.8, 130.8 (t, $J = 6.5$ Hz), 130.5, 129.9, 129.4, 127.2, 104.0 (t, $J = 3.0$ Hz) ppm; GC MS, *m*/*z* (relative intensity): 314 (M^++4, 7), 312 (M^++2, 40), 310 (M^+, 61), 277 (22). 275 (63), 155 (14), 240 (66), 239 (77), 238 (100), 221 (18), 220 (88), 219 (17), 218 (14), 199 (13), 198 (10), 164 (34), 163 (14), 119 (94), 109 (26), 97 (20); HRMS calcd 310.0128 for $C_{16}H_{10}{}^{35}Cl_2F_2$, observed 310.0138.

In summary, high *E*/*Z* 1-bromo-1-fluoroalkenes were found to react with $Bu_3SnSnBu_3$ and $Pd(PPh_3)_4$ at room temperature in DMF to stereoselectively give (1*Z*,3*Z*) 2,3-difluoro-1,4-disubstituted-buta-1,3-dienes. This methodology provides a straightforward route to symmetrical 2,3-difluorinated dienes from readily available starting materials.

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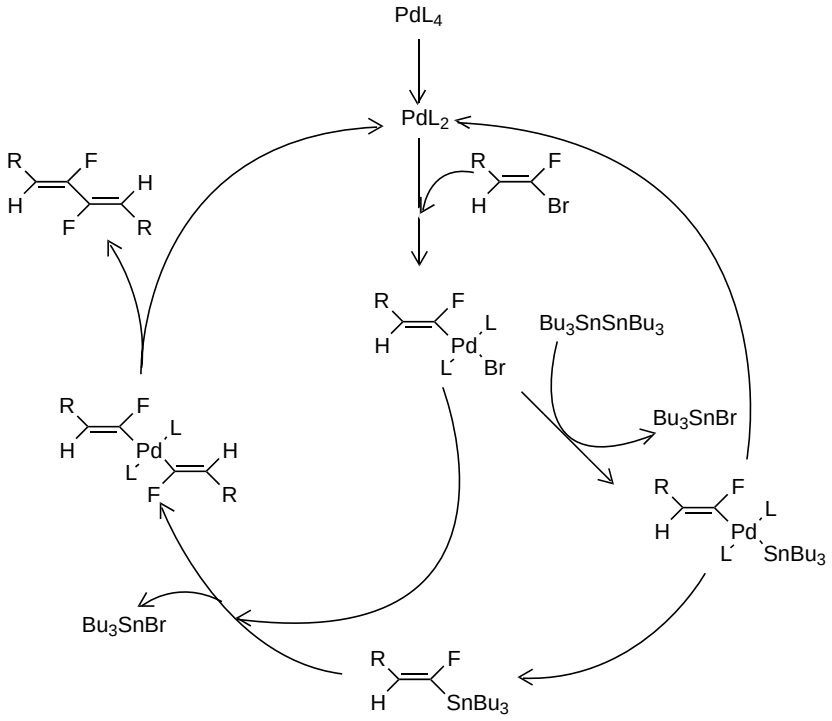

Scheme 3. Proposed mechanism for the formation of symmetrical (1*Z*,3*Z*) dienes.

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