



# Building block synthesis of predominantly (*E*) symmetrical and unsymmetrical 1,2-difluorostilbenes from 1,2-dibromo-1,2-difluoroethene



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## ABSTRACT

An efficient synthesis of predominantly (*E*) symmetrical or unsymmetrical 1,2-difluorostilbenes based on the Suzuki–Miyaura palladium-catalyzed cross-coupling reaction of arylboronic acids with predominantly (*E*)-1,2-dibromo-1,2-difluoroethene in the presence of Cs<sub>2</sub>CO<sub>3</sub> in toluene is described. The reaction preserved the stereochemistry of the building block and performed in good yield independently of the electron-withdrawing or electron-donating character of the substituents.

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## 1. Introduction

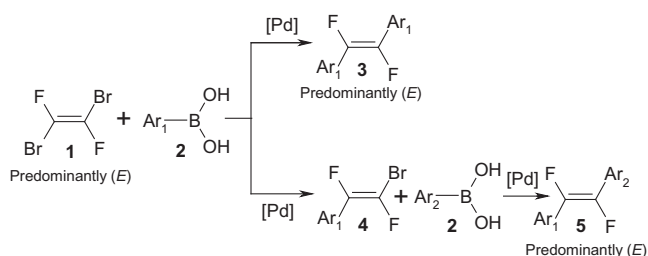
Introducing a fluorine atom in an organic compound very often brings different properties either for biological or in material science applications. The special properties of fluorine, such as strong electronegativity, small size (comparable to hydrogen) and low polarizability of the C–F bond are responsible for these effects. Indeed, an increasing number of drugs or photoelectronic devices contain fluorine, the presence of which often is of major importance to their activity. There are by far fewer reports in the literature on disubstituted-1,2-difluorinated olefins when compared to disubstituted monofluorinated olefins, which have found numerous applications, especially in biology. Analogues of combrestatin, a natural oxygenated stilbene bearing two fluorine-atoms on the central double bond, have been synthesized as tubulin aggregation inhibitors. In most of the cases, the difluorinated analogues were shown to be as efficient for tubulin aggregation inhibition as their unfluorinated counterpart but proved to be by far less toxic.<sup>1a</sup> Very recently, Dalvit and Vulpetti proposed 1,2-difluoroethene as an amide (O=C–NH) structural analogue for building peptidomimetics by a QSAR approach based on <sup>19</sup>F NMR displacement.<sup>1b</sup> On

the other hand, the photochemistry of 1,2-difluorostilbenes has received much attention: they isomerize very efficiently in the *Z* isomer by photo-irradiation, as their non-fluorinated analogues but with little halogen elimination, unlike others halogens, especially Br and I.<sup>2a,2b</sup> (*Z*) 1,2-Difluorostilbenes are also less prone under irradiation to phenanthrene formation and are thermally more stable than their non-fluorinated analogues.<sup>2c,2d</sup> These properties led to the introduction of difluoroethene bridges in many conjugated molecules or materials designed to have opto-electronic properties. Substituted difluorostilbenes resulted in nematic crystals, the properties of which can be optimized.<sup>3a</sup> For example, (*E*)-1-(*trans*-4-alkylcyclohexyl)-2-(4-chlorophenyl)-difluoroethylene has been shown to grow into nematic crystals that show great promise for super twisted nematic displays due to their high contrast and rapid response time, but also due to their improved UV stability.<sup>3b–e</sup> Substituted 1,4-bis(1,2-difluoro-2-phenylethenyl)-benzene show electro-optical properties.<sup>4a</sup> Due to their enhanced stability they have found applications as sensors.<sup>4b</sup> Cyanin dyes linked by a perfluorinated polymethine chain, which implies the 1,2-difluoroethene bridge, have been synthesized.<sup>5</sup> Theoretical calculations have shown that 1,2-bis-(3-thienyl)-1,2-difluoroethene derivatives exhibit non-linear optical properties and can act as photoswitches like their non-fluorinated analogues with modulated properties.<sup>6</sup> (*E*)-1,2-Difluoro-1,2-di-2-thienylethene, (*E*)-1,2-difluoro-1,2-bis(5-

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trimethylsilyl-2-thienyl)ethene and (*E*)-1,2-difluoro-1,2-bis(4-methoxy-5-trimethylsilyl-2-thienyl)-ethene monomers were prepared and polymerized under controlled oxidation.<sup>7a,7b</sup> The introduction of fluorine-atoms in the vinylene units yields a blue optical band gap in the obtained thin films.<sup>7c,7d</sup> Poly[5,5-(5',6'-di-octy-loxy-4',7'-di-2-thienyl-2',1',3'-benzothiadiazole)-*alt*-1,2-difluorovinylene]polymer have been synthesized and exhibited also a higher band gap. This material have found applications in polymer solar cells.<sup>8</sup> Difluorinated olefins have also been used as bridging ligands between organometallic centers.<sup>9</sup>

These various applications push us to report a novel synthesis of 1,2-difluorostilbenes, symmetrical **3** and unsymmetrical **5** from the 1,2-dibromo-1,2-difluoroethene **1** building block. The cross-coupling reaction of predominantly (*E*) 1,2-dibromo-1,2-difluoroethene with arylboronic acids **2** using palladium(0) as the catalyst in toluene and cesium carbonate as a base affords, following the protocol established for synthesizing monofluoroolefins from 1,1-bromofluoroolefins by Burton group<sup>10</sup> and our group<sup>11</sup> (for reviews see Ref. 12), the expected 1,2-difluorostilbenes either symmetrical or unsymmetrical in good yield (Scheme 1).



Scheme 1. Synthesis of 1,2-difluorostilbenes.

## 2. Results and discussion

In the literature only a few studies have described the synthesis of 1,2-difluoroolefins in a simple, versatile, and stereoselective manner. The most important syntheses are summarized below. Dixon first reported the preparation of symmetrical (*E*)-1,2-difluorostilbenes via the reaction of tetrafluoroethene with phenyllithium in ether at  $-60\text{ }^{\circ}\text{C}$ .<sup>13</sup> Unsymmetrical (*E*)-1,2-difluorostilbenes have been obtained via the reaction of trifluorostyrenes and aryllithiums in hexane at  $-80\text{ }^{\circ}\text{C}$ .<sup>14</sup> Trifluorostyrene precursors were obtained by treatment of iodobenzenes with tetrafluoroethylene in the presence of *n*-butyl lithium in a mixture of *n*-hexane and diethyl ether at  $-80\text{ }^{\circ}\text{C}$ . Recently, trifluorostyrenes have been obtained by the reaction of phenyl boronic acids with chloro- or bromotrifluoroethylene catalyzed by palladium.<sup>15</sup> The Dixon synthesis has been employed for the synthesis of opto-electronic materials and in the polymer field.<sup>7b,16</sup>

Shimizu and Kuroboshi et al. have developed a highly stereoselective synthesis of (*E*) and (*Z*)  $\beta$ -bromo- $\alpha,\beta$ -difluorostyrene ( $\text{ArCF}=\text{CFBr}$ ) from  $\text{ArCH}(\text{OH})\text{CFBr}_2$ .<sup>17</sup> The treatment of tribromofluoromethane ( $\text{CBr}_3\text{F}$ ) with BuLi in a mixture of THF and Et<sub>2</sub>O at  $-130\text{ }^{\circ}\text{C}$  afforded dibromofluoromethyl lithium, which was reacted with an aldehyde to give the fluorinated alcohol ( $\text{ArCH}(\text{OH})\text{CFBr}_2$ ). This alcohol was stereoselectively converted to pure (*E*)-1-bromo-1,2-difluoroolefin via fluorination with Et<sub>2</sub>NSF<sub>3</sub>, followed by dehydrobromination with lithium 2,2,6,6-tetramethylpiperidide (LiTMP), in THF at  $-98\text{ }^{\circ}\text{C}$  for 10 min. The use of less crowded organic bases or superbases (DBU, Bu<sub>4</sub>N<sup>+</sup>OH<sup>-</sup>, BEMP) on the same intermediate led to a mixture that was predominantly (*Z*). The obtained (*E*)-1-bromo-1,2-difluoroolefins ( $\text{RCF}=\text{CFBr}$ ) were coupled with silanes, stannanes or boronic acids under palladium

catalysis to afford in good yield (*Z*) difluoroolefins ( $\text{RCF}=\text{CFR}$ ) with a complete retention of the geometry of the double bond. The obtained (*E*)-1-bromo-1,2-difluoroolefins ( $\text{RCF}=\text{CFBr}$ ) could also be transformed in lithium reagents ( $\text{RCF}=\text{CFLi}$ ) by treatment with butyllithium in THF/Et<sub>2</sub>O at  $-130\text{ }^{\circ}\text{C}$ , then condensed with electrophiles at the same temperature, with preservation of the double bond geometry. Recently Giannini et al. used this method to prepare (*Z*)-difluorocombretastin analogues by coupling conveniently substituted (*E*)- $\beta$ -bromo- $\alpha,\beta$ -difluorostyrenes with 3,4,5-trimethoxybenzenboronic acid in presence of palladium.<sup>1a</sup>

Burton et al. developed several methods for the preparation of symmetrical or unsymmetrical (*E*) (and, recently, (*Z*)) 1,2-difluorostilbenes. The key compounds in their approach of (*E*) isomers are (*Z*)-(1,2-difluoroethenyl)-tributylstannane ( $\text{HFC}=\text{CFSnBu}_3$ ) and (*E*)-(1,2-difluoro-1,2-ethenediyl)-bis-[tributylstannane], which are obtained in three or four steps. In the first step chlorotrifluoroethylene ( $\text{F}_2\text{C}=\text{CFCl}$ ) was metalated by *n*-butyl lithium in THF at  $-80\text{ }^{\circ}\text{C}$ , then reacted with chlorotrimethylsilane to afford (1,2,2-trifluoroethenyl)-trimethylsilane ( $\text{F}_2\text{C}=\text{CFSiMe}_3$ ), which was not isolated. In the second step (1,2,2-trifluoroethenyl)-trimethylsilane was reduced in situ by LiAlH<sub>4</sub> in THF to afford a mixture containing predominantly (*Z*)-(1,2-difluoroethenyl)-trimethylsilane ( $\text{HFC}=\text{CFSiMe}_3$ ) (*Z*:*E*, 91:9), which was isolated by flash distillation. Then (1,2-difluoroethenyl)-trimethylsilane was reacted in THF with bis(tributyltin)oxide ( $\text{Bu}_3\text{SnOSnBu}_3$ ) in the presence of a catalytic amount of tetrabutylammonium fluoride to give the desired, predominantly (*Z*), (1,2-difluoroethenyl)-tributylstannane ( $\text{HFC}=\text{CFSnBu}_3$ ), which could be further purified by chromatography. Finally (*E*)-(1,2-difluoro-1,2-ethenediyl)-bis-[tributylstannane] ( $\text{Bu}_3\text{SnFC}=\text{CFSnBu}_3$ ) was obtained by metalating the monostannane by lithium, 2,2,6,6-tetramethylpiperidide (LiTMP) in THF at  $-90\text{ }^{\circ}\text{C}$  and trapping the intermediate with tributyltin chloride.<sup>18a</sup> Symmetrical (*E*)-1,2-difluorostilbenes were readily obtained via stereospecific Pd(0) coupling of (*E*)-(1,2-difluoro-1,2-ethenediyl)-bis-[tributylstannane] ( $\text{Bu}_3\text{SnFC}=\text{CFSnBu}_3$ ) with aryl iodides using Pd(PPh<sub>3</sub>)<sub>4</sub>/CuI as a catalyst in Stille–Liebeskind conditions.<sup>18b</sup> Unfortunately (*Z*)-(1,2-difluoro-1,2-ethenediyl)-bis-[tributylstannane] stereoisomers afforded no coupling products in the same conditions. Nevertheless, unsymmetrical (*Z*)-1,2-distilbenes were obtained using a combination of the previously described protocols. First, (*E*)-(1,2-difluoroethenyl)-trimethylsilane, obtained by the photoisomerization of the (*Z*) isomer by UV light in presence of a catalytic amount of phenyldisulfide, (*E*)-(1,2-Difluoroethenyl)-trimethylsilane was converted into (*E*)-1,2-difluorovinyl iodide ( $\text{HFC}=\text{CFI}$ ) by iodine at room temperature.<sup>18c</sup> (*E*)-1,2-difluorovinyl iodide ( $\text{HFC}=\text{CFI}$ ) was treated with zinc and coupled with aryl iodide using palladium catalysis affording (*Z*)- $\alpha,\beta$ -difluorostyrene ( $\text{PhFC}=\text{CHF}$ ). In turn (*Z*)- $\alpha,\beta$ -difluorostyrene was transformed into (*E*)-1,2-difluoro-2-aryl-tributylstannylethenes by metalation by lithium 2,2,6,6-tetramethylpiperidide (LiTMP) and trapping at  $-78\text{ }^{\circ}\text{C}$  with tributyltin chloride.<sup>18d</sup> Then (*E*)-1,2-difluoro-2-aryl-tributylstannylethenes were coupled with the second aryl iodide in the Stille–Liebeskind conditions described above to afford (*Z*)-1,2-difluorostilbenes.<sup>18e</sup>

We described here an original method for the stereoselective synthesis of (*E*)-1,2-difluorostilbenes in only two steps for unsymmetrical 1,2-difluorostilbenes and in a single step for symmetrical 1,2-difluorostilbenes. The starting reagent **1** 1,2-dibromo-1,2-difluoroethene is a non-volatile liquid product (boiling point about  $85\text{ }^{\circ}\text{C}$ ), which is perfectly stable and which is commercially available as a mixture of stereoisomers (*E*/*Z*: 85/15). When 1,2-dibromo-1,2-difluoroethene **1** was reacted with 2.3 equiv of phenyl boronic acids using tetrakis(triphenylphosphine)palladium(0) as the catalyst in toluene and cesium carbonate ( $\text{Cs}_2\text{CO}_3$ ) as a base in ethanol/water at  $110\text{ }^{\circ}\text{C}$  during 3 h, symmetrical 1,2-

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