## An Easy Stereoselective Copper(I)-Catalyzed Synthesis of (*E*)-3-Trifluoromethylbut-2-en-3-ynoate via Palladium-Free Stille Coupling Reaction

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**Abstract:** A general and efficient Cu(I)-catalyzed cross-coupling reaction of alkynyl bromides and  $\beta$ -tributylstannyl- $\alpha$ , $\beta$ -unsaturated ester bearing a trifluoromethyl group in  $\beta$ -position was developed under very mild conditions. This method provides easy access to a variety of 2,3-enynoate bearing a trifluoromethyl group from good to excellent yields with excellent stereoselectivity. This procedure does not require the use of any expensive supplementary additives and is palladium-free.

**Key words:**  $\beta$ -tributylstannyl- $\alpha$ , $\beta$ -unsaturated ester, palladiumfree, copper-catalyst, trifluoromethylbut-2-en-3-ynoate

Organic compounds containing one or more fluorine atoms have received increasing attention in medicinal, agricultural, and material sciences.<sup>1</sup> They often confer significant changes in their chemical and physical properties. The introduction of a fluorine or perfluoroalkyl group into organic compounds often dramatically changes their structure, stability, lipophilicity, reactivity, and biological activity.<sup>2</sup> The development of a simple method to obtain perfluoroalkylated building blocks for their subsequent utilization in the synthesis of fluoroalkyl-containing compounds is therefore essential to organofluorine chemistry.<sup>3,4</sup> Perfluoroalkylated vinyl metals constitute an important class of these building blocks.

Perfluoroalkylated vinyl metals have been demonstrated in which lithium,<sup>5</sup> magnesium,<sup>6</sup> zinc,<sup>7</sup> silver,<sup>8</sup> and palladium<sup>9</sup> species were prepared and alkylated with electrophiles specific to the carbon attached to the metal. Vinylstannanes bearing a perfluoroalkyl group also opened the way for the preparation of these types of compounds.<sup>10</sup> Vinylstannanes are the reagents of choice for the synthesis of enyne structures by Stille coupling reaction.<sup>11</sup>

Enyne systems have attracted much attention from synthetic organic chemists as enynes show interesting chemical and biological activities.<sup>12</sup> Conjugated enynes are important synthetic intermediates since the conjugated 1,3-enyne moiety can be readily converted in a stereospecific manner into the corresponding diene system.<sup>13</sup> Many methods can be used for the stereocontrolled synthesis of conjugated enynes.<sup>10d,14</sup>

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Scheme 1 Preparation of  $\beta$ -stannyl-4,4,4-trifluorobutenoate

However, to the best of our knowledge, no palladium-free Stille coupling of  $\beta$ -stannyltrifluoromethylbutenoate (*Z*)-**1** $\beta$  using alkynyl bromides has yet been described. We recently reported the preparation of the first highly regioselective metal-free hydrostannylation of ethyl 4,4,4trifluorobutynoate (**1**)<sup>15</sup> without any additive (Scheme 1). These new reagents reacted with a wide range of allyl and propargyl bromides, leading to polyfunctional products bearing a fluoroalkyl group.<sup>16</sup>

As a continuation of our previous research on the method for preparing various derivatives bearing the trifluoromethyl group, we report here the first stereoselective coppercatalyzed coupling reaction of  $\beta$ -stannyl-4,4,4-trifluorobutenoate (*Z*)-**1** $\beta$  with alkynyl bromides without any additive. More systematic investigations of Pd-catalyzed alkynylation with alkynylstannanes were performed in the early 1980's by Bumagin, Beletskaya, and their colleages<sup>17</sup> and later by Stille.<sup>18</sup> On the other hand, few reports of the Pd-catalyzed alkynylation with alkenylstannanes have been described.<sup>11</sup>

Although Stille reported that Pd(PPh<sub>3</sub>)<sub>4</sub> alone catalyzed the coupling reaction of vinylstannanes and alkynyl bromides,<sup>11</sup> no coupling reaction between (*Z*)-**1** $\beta$  and 1-bromo-2-phenylacetylene was observed when Pd(PPh<sub>3</sub>)<sub>4</sub> was used alone. Under Liebeskind conditions<sup>19</sup> [5 mol% of Pd(PPh<sub>3</sub>)<sub>4</sub> and 10 mol% of CuI], the desired product was formed with moderate yield (60%). In contrast, on the basis of transmetalation from the organotin compound to the organocopper intermediate,<sup>20</sup> we investigated a palladium-free cross-coupling of vinylstannane (*Z*)-**1** $\beta$  with alkyne bromides in the presence of a catalytic amount of CuI (10 mol%). A very clean reaction was observed, and good yields of the desired product were obtained. It was discovered that the reaction was complete within five hours using 10 mol% of CuI at 20 °C (Scheme 2).



Scheme 2 Preparation of (E)-3-trifluoromethylbut-2-en-3-ynoate

The use of CuBr instead of CuI provided similar results. To investigate the scope of the copper-alkylynated reaction, several alkynyl bromides were tested to react with (*Z*)-**1** $\beta$ , and the reaction provided stereospecifically the isomerically pure *E*-conjugated enynes.<sup>21</sup> The results are summarized in Table 1.

Table 1 CuI-Catalyzed Coupling of (Z)-1β with Alkynyl Bromides





<sup>a</sup> Yield of isolated product.

<sup>b</sup> E/Z = 70:30 (ratio determined on crude <sup>1</sup>H and <sup>19</sup>F NMR spectrum). <sup>c</sup> E/Z = 60:40 (ratio determined on crude <sup>1</sup>H and <sup>19</sup>F NMR spectrum).

As shown in Table 1, compounds (Z)-1 $\beta$  underwent reactions with a variety of alkynyl bromides to provide the 3alkynylated products 2a-l with good yields and with a clean E configuration of the double bond in the most of the cases, demonstrating that the copper(I) catalyst coupling reaction occurred with retention of configuration (Scheme 2 and Table 1). Both aromatic and aliphatic alkynyl bromides worked well. The coupling reactions were not affected by the presence of either electron-donating group on the aromatic ring (Table 1, entries 3–5). However, the presence of an electron-withdrawing group on the aromatic ring provided moderate yields of the desired product (51%; Table 1, entry 6). The reaction proceeded cleanly with retention of configuration of the starting vinylstannanes (Z)- $1\beta$ , except in the case of the aromatic ring substituted by electron-donating groups

(Table 1, entries 4 and 5) where partial isomerization of the double bond was observed (E/Z = ca. 60:40). The partial E/Z isomerization of activated 1,3-enynes has already been reported by Gevorgyan.<sup>14e,22</sup> In our case, we supposed that this isomerization may occur under these reaction conditions. It may be due to an equilibrium involving the formation of an enolate stabilized by the electron-donating group. Nevertheless, both isomers were separated by column chromatography.

The presence of a trimethylsilyl group as substituent in the terminal alkyne was not successful in this cross-coupling reaction (Table 1, entry 13), only the starting material and product **4** of dimerization were recovered.

Finally, this new coupling method tolerated the presence of a variety of functional groups (including hydroxy, alkoxy, phenyl, ester, etc.) present in the acetylenic compounds. Indeed, the ester, alcohol, and ketal functions were highly tolerated in this cross-coupling reaction (Table 1, entries 9–12).

The retention of the double-bond configuration in most of the cases indicated that the presumed intermediate copper reagent  $3^{10a,16b,23}$  formed after catalytic transmetalation of vinyltin reagents with copper iodide was configurationally stable and reacted stereoselectively with alkynyl bromide substrates. No coupling reaction was observed in the absence of Cu(I) catalyst, and the starting material was entirely recovered. Similarly, no homocoupling product (diynes) was observed under the conditions employed.<sup>24</sup> In addition, no cyclization reaction producing butenolides or  $\alpha$ -pyrones was observed.<sup>25</sup>

The Bu<sub>3</sub>Sn/CuI transmetalation step was confirmed by the experiment in which the vinyl stannane (*Z*)-1 $\beta$  was treated with 10 mol% of CuI at room temperature in DMF, which yielded 80% of the homocoupling product 4 (Scheme 3).<sup>16b,26</sup> Spectroscopic analyses (<sup>1</sup>H NMR and <sup>13</sup>C NMR) of product 4 were in perfect agreement with those previously described by our group for the same product. These findings were also confirmed by iodod-



Scheme 3

estannylation of (*Z*)-**1** $\beta$  using a stoichiometric amount of CuI and one equivalent of iodine in diethyl ether, which provided good yields of the known iodinated product **5** (72%).<sup>27</sup> However, no iododestannylation of (*Z*)-**1** $\beta$  occurred in the absence of a CuI catalyst, and the starting material was recovered. The stability of the *cis* copper intermediate **3** was presumably attributable to the coordination<sup>28</sup> between copper and oxygen of the ester group (Scheme 3).

Interestingly, the use of vinyltin compound (*Z*)-**6** under the same reaction conditions in the presence of bromoethynylbenzene did not provide the expected conjugated enyne. Indeed, only starting material and a mixture of dienes **7** resulted from the homocoupling reaction were recovered after 16 hours of stirring (Scheme 4).<sup>26</sup> This result shows the importance of the presence of the trifluoromethyl group to facilitate the Bu<sub>3</sub>Sn/Cu transmetalation reaction and, more particularly, the cross-coupling reaction with bromoalkyne.

One-pot hydrostannylation reaction of 4,4,4-trifluorobut-2-ynoate (1) followed by cross-coupling of vinyltin formed (*Z*)-1 $\beta$  with 1-bromophenyl acetylene were attempted, but, unfortunately, only a low yield of the desired product 2b was isolated (27%).

A plausible mechanism can be proposed for the copper (I)-catalyzed coupling reaction that would proceed as follows: copper(I) iodide would transmetalate the vinyltin reagent (*Z*)- $1\beta$ ,<sup>19</sup> leading to a vinyl copper species, which then would react with alkynebromide to generate a copper(III) intermediate. Finally, the expected enyne **2** would be obtained via a reductive elimination step giving the active Cu(I) species.

In summary, we investigated the transition-metal-free cross-coupling reaction of  $\beta$ -stannylated alkenoate bearing a trifluoromethyl group with alkynyl bromides. The copper(I)-catalyzed coupling reaction offered a versatile useful procedure for the preparation of substituted functionalized enynes and provided good yields of the corresponding acrylate esters with a clean olefinic configuration. This method provided a new and efficient means of entry to this important class of compounds. Many extensions of this work can be envisaged. Furthermore, the structurally novel enyne products would appear to be worthy intermediates for future investigations in organic synthesis. We are actively pursuing a number of possibilities.

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**Scheme 4** Tentative of cross-coupling reaction between (*Z*)-6 and bromoalkyne

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- (21) Typical Experimental Procedure for the Preparation of 2a–l: Synthesis of (*E*)-Ethyl 3-(Trifluoromethyl)undec-2en-4-ynoate (2a)

Compound 1ß (200 mg, 0.437 mmol), 1-bromooct-1-yne (83 mg,0.437 mmol), and dry DMF (5 mL) were introduced into a dry Schlenk flask under argon. The mixture was degassed under agitation (10 min), then CuI (8 mg, 0.04 mmol) was introduced under argon flux. The mixture was brought to r.t. and left for 5 h under stirring. The reaction mixture was diluted with Et<sub>2</sub>O, washed with aq KF solution (1 M, 10 mL) and the ether layer was separated, dried over MgSO<sub>4</sub>, concentrated, and separated on a silica gel column (pentane- $Et_2O = 95:5$ ) to provide 100 mg (83%) of enyne **2a** as a colorless liquid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 0.91$  (t, J = 7.2 Hz, 3 H), 1.22–1.66 (m, 11 H), 2.48 (d, J = 7.1 Hz, 2 H), 4.26 (q, J = 7.2 Hz, 2 H), 6.54 (s, 1 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 13.6, 14.1, 20.0, 22.4, 27.9, 28.4, 31.2, 61.1, 72.3, 106.8, 120.9 (q,  $J_{C-F}$  = 273.4 Hz), 126.4 (q,  $J_{C-F}$ <sub>F</sub> = 34.6 Hz), 127.1 (q,  $J_{C-F}$  = 4.4 Hz), 163.5. <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):  $\delta = -67.9$ . IR (ATR): v = 2955, 2926, 2856,2219 1734, 1634 cm<sup>-1</sup>.

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