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Palladium-Catalyzed Cross-Coupling of Fluorinated Vinyl Chlorides with Terminal Alkynes: A General Protocol to Fluorinated Enynes

Sheng Chen, Chunfa Xu, Long Lu,* and Qilong Shen*

Key Laboratory of Organofluorine Chemistry, *Shanghai Institute of Organic Chemistry*, *Chinese Academy of Sciences*, *Shanghai 200032*, *China*

An efficient and cost-effective method for the preparation of fluorinated conjugated enynes was described. The method was compatible with a variety of functional groups such as chloride, amine, cyano and ester group. The method could also be extended to the coupling of (*R*,*Z*)-3-(2-chloro-1,2-difluorovinyl)-4-alkyloxazolidin-2-one (**3**) with moderate yields.

Keywords fluorine, enyne, palladium, chlorotrifluoroethylene

Introduction

Conjugated enynes are important structural motifs in medicinal chemistry and in conjugated polymers with optoelectronic application.[1] For example, Terbinafine (Lamisil™),[1d] an enyne derivative, is currently in clinical use as an antifungal medicine and carbazole-substituted phenyl enynes has been shown to be an excellent single-emitting component for white organic light-emitting devices (WOLEDs).[1e] In addition, conjugated enynes are valuable building blocks in organic synthesis that can be converted into a variety of different functional groups.[2] On the other hand, it is well-known that incorporation of fluorine into small molecules will result in significant changes in their physical, chemical and biological properties.[3] Thus, fluorinated conjugated enynes are expected to be versatile building blocks in the preparation of partially fluorinated molecules that might find applications in medicinal chemistry or materials science. Consequently, development of new methods for the preparation of fluorinated conjugated enynes is of great interest.

In 1987, Normant *et al*.[4] reported the first palladium-catalyzed coupling of fluorinated vinyl iodides with terminal alkynylzinc reagents for the preparation of fluorinated conjugated enynes. Although moderate to good yields were achieved in this approach, the prior generation of the requisite alkynyl zinc reagent was necessary. To circumvent the using of the alkynyl zinc reagent, Yang and Burton improved the reaction conditions by using the combination of $Pd(PPh_3)_2Cl_2$ and CuI as the catalyst in the presence of Et_3N as the base.[5] Under these conditions, a number of alkynes were directly coupled with fluorinated vinyl iodides to give the desired fluorinated enynes in good yields. Nevertheless, both of these methods involved fluorinated vinyl iodides as the substrates that typically required multiple steps for their synthesis.

More recently, we reported a palladium catalyzed Suzuki-Miyaura coupling reaction of chlorotrifluoroethylene with a variety of aryl boronic acids for the formation of trifluorostyrene derivatives.[6] As part of our ongoing programs with the aim to utilize cheap and easily available chlorotrifluoroethylene as starting material, we wondered if it could be possible to realize the Sonogashira reaction of chlorotrifluoroethylene with terminal alkynes. In general, carbon-chloride bond is much stronger than carbon-bromide and carbon-iodide bond, as a consequence, the activation of carbon-chloride bond is more difficult.[7] Few coupling reaction of fluorinated vinyl chlorides has been reported previously.[8] Herein, we reported a palladium/copper-catalyzed direct coupling of chlorotrifluoroethylene with terminal alkynes in good to excellent yields.

Experimental

General procedure for preparation of compound 3

A Schlenk-type tube (with a condenser) equipped with a magnetic stir bar charged with oxazolidinone (1.0 mmol) was vacuumed and recharged with argon three times. THF (2.0 mL) was added and the solution was cooled to −78 ℃. *n*-BuLi (1.1 mmol) solution was then added slowly. The reaction mixture was stirred for 4 h at

* E-mail: shenql@sioc.ac.cn
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this temperature. 5.0 mmol of chlorotrifluoroethylene in a balloon was condensed into the tube. And the tube was stirred for another 6 h at room temperature. The reaction was quenched with water when the oxazolidinone disappeared as determined by TLC. The mixture was separated and the water phase was extracted with ethyl acetate three times. The organic phase was combined and concentrated. The resulting residue was purified by silica gel flash column chromatography to give 189.5 mg (84%) of (*R*,*Z*)-3-(2-chloro-1,2-difluorovinyl)-4-isopropyloxazolidin-2-one (**3a**) and 238.1 mg (87%) of (*R*,*Z*)-3-(2-chloro-1,2-difluorovinyl)-4-benzyloxazolidin-2-one (**3b**) as pale yellow solid.

(*Z*)-3-(2-Chloro-1,2-difluorovinyl)-4-isopropyloxazolidin-2-one (3a) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 4.47−4.41 (m, 1H), 4.24−4.20 (m, 1H), 4.06−4.01 (m, 1H), 2.05−2.00 (m, 1H), 1.00−0.93 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −116.9 (dd, J=116.7, 7.9 Hz, 1F), −127.9 (d, J=124.6 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 154.2, 137.6 (m), 134.9 (m), 64.9, 60.2, 29.6, 17.3, 15.1. MS (EI) *m/z* (%): 225 (100). HRMS: Calculated for $C_8H_{10}F_2O_2NCl$: 225.0368, found 225.0370.

(*Z*)-4-Benzyl-3-(2-chloro-1,2-difluorovinyl)oxazolidin-2-one (3b) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.37−7.30 (m, 3H), 7.21−7.19 (m, 2H), 4.42−4.34 (m, 2H), 4.21−4.18 (m, 1H), 3.17−3.12 (m, 1H), 2.89−2.83 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −113.8 (d, J=124.6 Hz, 1F), −124.9 (d, J=126.6 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 153.6, 137.5 (dd, J=291.5, 68.9 Hz), 134.8 (dd, J=211.5, 46.2 Hz), 134.2, 129.0, 128.9, 127.6, 68.2, 56.6, 39.0. MS (EI) *m/z* (%): 273 (100). HRMS: Calculated for $C_{12}H_{10}F_2O_2NCl$: 273.0368, found 273.0372.

General procedure A for preparation of fluorinated enynes (2a−2f, 2h, 2k, 2n, 2o)

A Schlenk-type tube (with a condenser) equipped with a magnetic stir bar was charged with the alkyne (1.0 mmol), $Pd(PPh_3)_4$ (116 mg, 0.10 mmol), CuI (19.1 mg, 0.10 mmol), tributylamine (37 mg, 0.20 mmol), K_3PO_4 (637 mg, 3.0 mmol). And the reaction tube was added benzene (2.0 mL) and water (0.7 mL). The tube was equipped with a dry ice/acetone condenser, and then evacuated briefly under high vacuum and charged with argon three times. 5 mmol of chlorotrifluoroethylene in a ballon was plunged into the tube. Then the reaction mixture was stirred at 80 ℃ for 10 h. The reaction was then cooled to room temperature. The mixture was extracted with 20 mL of diethyl ether three times. The organic phase was combined, dried with anhydrous Na_2SO_4. Silica gel (10.0 g) was added to the solution. The solvent was then evacuated under rotaty evaporator. The residue was purified by silica gel flash column chromatography using hexane as eluent. Further purification was conducted by Kugelrohr distillation.

General procedure B for preparation of fluorinated enynes (2g, 2i, 2j, 2l, 2m)

A Schlenk-type tube equipped with a magnetic stir bar was charged with the alkyne (1.0 mmol), $Pd(PPh_3)_4$ (116 mg, 0.10 mmol), CuI (191 mg, 1.0 mmol), K_3PO_4 (637 mg, 3 mmol). The reaction tube was capped, then evacuated briefly under high vacuum and charged with argon for three times. Benzene (4.0 mL) and deionized water (1.4 mL) was added. Chlorotrifluoroethylene was bubbled for 5.0 min. The reaction mixture was stirred at 80 ℃ for 10 h. The mixture was cooled to room temperature and was extracted with 20 mL of diethyl ether for three times. The organic phase was combined, dried over anhydrous Na_2SO_4. Silica gel (10.0 g) was added to the solution. The solvent was then evacuated under rotaty evaporator. The residue was purified by silica gel flash column chromatography using hexane as eluent.

General procedure C for preparation of fluorinated enynes (4a−4g)

A Schlenk-type tube equipped with a magnetic stir bar was charged with the alkyne (1 mmol), compound **3** (1.0 mmol), $Pd(PPh_3)_2Cl_2$ (70.1 mg, 0.1 mmol), CuI (19.1 mg, 0.1 mmol). The reaction tube was evacuated briefly under high vacuum and charged with argon for three times. Triethylamine (96 mg, 1.0 mmol) and DMSO (2.0 mL) was then added. The reaction mixture was stirred at 45 ℃ for 10 h. The mixture was cooled to room temperature. The mixture was concentrated and the residue was purified by silica gel flash column chromatography to give the corresponding coupling product.

1-Fluoro-4-(3,4,4-trifluorobut-3-en-1-ynyl)benzene (Table 2, 2a) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.48−7.45 (m, 2H), 7.06−7.02 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −90.1−90.3 (m, 1F), −108.1−108.2 (m, 1F), −110.1−110.6 (m, 1F), −172.0 (dd, J=115.0, 26.8 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 163.3 (d, J=288 Hz), 157.7 (td, J=297.5, 52.3 Hz), 133.7 (m), 128.2 (d, J=0.8 Hz), 115.9 (m), 115.7 (m), 101.1 (m), 73.1 (m). MS (EI) *m/z* (%): 200 (100). HRMS: Calculated for $C_{10}H_4F_4$: 200.0249, found 200.0253.

1-Methyl-4-(3,4,4-trifluorobut-3-en-1-ynyl)benzene (Table 2, 2b) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.39 (d, J=8.0 Hz, 2H), 7.17 (d, J=8.0 Hz, 2H), 2.37 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −91.2 (dd, J=47.6, 27.9 Hz, 1F), −110.7 (dd, J=114.8, 47.6 Hz, 1F), −171.5 (dd, J=114.8, 27.9 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 157.6 (ddd, J=296.5, 285.4, 52.7 Hz), 140.2, 131.5, 129.2, 128.3, 116.0 (ddd, J=222.1, 53.3, 30.8 Hz), 102.5 (m), 72.7 (ddd, J=32.2, 10.1, 3.0 Hz), 21.4. MS (EI) *m/z* (%): 196 (100). HRMS: Calculated for $C_{11}H_7F_3$: 196.0500, found 196.0504.

1-Propyl-4-(3,4,4-trifluorobut-3-en-1-ynyl)benzene (Table 2, 2c) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.43−7.41 (m, 2H), 7.19−7.17 (m, 2H), 2.65

(t, J=7.6 Hz, 2H), 1.68−1.62 (m, 2H), 0.95 (t, J=7.6 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −91.2 (dd, J=47.6, 27.9 Hz, 1F), −111.2 (dd, J=114.7, 47.6 Hz, 1F), −171.5 (dd, J=114.7, 47.6 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 157.6 (ddd, J=296.5, 285.4, 53.3 Hz), 144.9, 131.5, 128.7, 118.0 (ddd, J=222.1, 53.3, 31.2 Hz), 115.9 (m), 102.5, 72.7 (ddd, J=32.2, 10.1, 3.1 Hz), 38.0, 24.2, 13.6. MS (EI) *m/z* (%): 224 (100). HRMS: Calculated for $C_{13}H_{11}F_3$: 224.0813, found 224.0817.

1-*tert*-Butyl-4-(3,4,4-trifluorobut-3-en-1-ynyl)benzene (Table 2, 2d) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.45−7.37 (m, 4H), 1.32 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −90.8 (dd, J=47.6, 27.4 Hz, 1F), −110.7 (dd, J=114.7, 47.2 Hz, 1F), −171.2 (dd, J=114.7, 47.2 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 157.6 (ddd, J=296.5, 285.4, 52.7 Hz), 153.3, 131.4, 125.5, 117.8, 115.9 (ddd, J=274.4, 53.3, 30.8 Hz), 102.5 (m), 72.7 (ddd, J=32.2, 10.1, 3.1 Hz), 34.9, 31.0. MS (EI) *m/z* (%): 238 (100). HRMS: Calculated for $C_{14}H_{13}F_3$: 238.0969, found 238.0973.

1-Methoxy-4-(3,4,4-trifluorobut-3-en-1-ynyl)benzene (Table 2, 2e) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.42 (d, J=8.8 Hz, 2H), 6.86 (d, J=8.8 Hz 2H), 3.81 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −91.1 (dd, J=48.0, 26.6 Hz, 1F), −110.9 (dd, J=114.7, 47.7 Hz, 1F), −170.7 (dd, J=114.3, 26.6 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 160.8, 157.5 (ddd, J=296.5, 285.4, 53.2 Hz), 133.3, 115.8 (ddd, J=279.4, 58.3, 27.3 Hz), 114.1, 112.8, 102.4 (m), 72.1 (ddd, J=31.6, 9.6, 2.5 Hz), 55.3. MS (EI) *m/z* (%): 212 (100). HRMS: Calculated for $C_{11}H_7F_3O$: 212.0449, found 212.0451.

4-(3,4,4-Trifluorobut-3-en-1-ynyl)benzonitrile (Table 2, 2f) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.64 (d, J=8.0 Hz, 2H), 7.56 (d, J=8.4 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −87.6 (dd, J=40.1, 28.5 Hz, 1F), −108.1 (dd, J=114.7, 40.5 Hz, 1F), −173.3 (dd, J=114.7, 28.5 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 157.8 (ddd, J=298.5, 287.4, 50.6 Hz), 132.2, 131.8, 125.4, 117.9, 115.4 (ddd, J=223.1, 53.3, 31.2 Hz), 113.1, 100.2 (m), 77.3 (m). MS (EI) *m/z* (%): 207 (100). HRMS: Calculated for $C_{11}H_4F_3N$: 207.0296, found 207.0299.

Methyl 4-(3,4,4-trifluorobut-3-en-1-ynyl)benzoate (Table 2, 2g) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 8.02 (d, J=8.2 Hz, 2H), 7.54 (d, J=8.2 Hz, 2H), 3.89 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ: −89.2 (dd, J=42.7, 27.8 Hz, 1F), −109.5 (dd, J=114.8, 42.7 Hz, 1F), −173.1 (dd, J=114.7, 27.8 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ: 166.0, 157.6 (ddd, J=297.5, 286.5, 51.5 Hz), 131.2, 130.7, 129.5, 125.0, 115.3 (ddd, J=80.8, 54.1, 27.1 Hz), 101.2 (m), 75.7 (ddd, J=31.7, 9.9, 2.7 Hz), 52.2. MS(EI) *m/z* (%): 209.1 (100). HRMS: Calculated for $C_{12}H_7F_3O_2$: 2240.0398, found 240.0395.

1-Fluoro-2-(3,4,4-trifluorobut-3-en-1-ynyl)benzene (Table 2, 2h) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.48−7.35 (m, 2H), 7.15−7.07 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −89.4−89.6 (m, 1F), −108.6 (m, 1F), −109.2−109.7 (m, 1F), −172.4 −172.8 (m, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 162.4 (d, J=296.5 Hz), 157.7 (ddd, J=297.5, 286.5, 51.5 Hz), 133.2, 131.7, 128.8, 124.1, 115.7 (d, J=20.7 Hz), 115.6 (ddd, J=232.2, 54.3, 30.2 Hz), 95.7 (m), 77.9 (m). MS (EI) *m/z* (%): 200 (100). HRMS: Calculated for $C_{10}H_4F_3$: 200.0249, found 200.0247.

1-Chloro-2-(3,4,4-trifluorobut-3-en-1-ynyl)benzene (Table 2, 2i) ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS) δ: 7.88−6.71 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$, 293 K) δ: −89.2 (dd, J=43.0, 27.8 Hz, 1F), −109.2 (dd, J=114.7, 43.3 Hz, 1F), −172.6 (dd, J=114.9, 27.8 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 157.70 (ddd, J=297.4, 286.5, 51.5 Hz), 133.17, 130.73, 129.47, 128.29, 126.56, 120.99, 115.66 (ddd, J=221.4, 53.0, 30.6 Hz), 98.80 (ddd, J=10.2, 8.4, 5.3 Hz), 78.03 (ddd, J=31.9, 9.9, 2.8 Hz). MS (EI) *m/z* (%): 216 (100). HRMS: Calculated for $C_{10}H_4F_3Cl$: 215.9954, found 215.9957.

1-Chloro-3-(3,4,4-trifluorobut-3-en-1-ynyl)benzene (Table 2, 2j) ^{1}H NMR (400 MHz, $CDCl_3$, 293 K, TMS) δ: 7.70−6.90 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$, 293 K) δ: −89.3 (dd, J=44.0, 27.9 Hz, 1F), −109.6 (dd, J=114.9, 43.9 Hz, 1F), −172.6 (dd, J=114.9, 27.9 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 157.73 (ddd, J=297.3, 286.2, 51.5 Hz), 134.47, 131.28 (m), 130.02, 129.75, 129.60 (m), 128.31, 115.6 (ddd, J=222.2, 53.5, 30.6 Hz), 100.64 (ddd, J=10.1, 8.3, 5.2 Hz), 74.38 (ddd, J=12.9, 9.6, 2.7 Hz). MS (EI) *m/z* (%): 216 (100). HRMS: Calculated for $C_{10}H_4F_3Cl$: 215.9954, found 215.9949.

3-(3,4,4-Trifluorobut-3-en-1-ynyl)aniline (Table 2, 2k) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.20 (t, J=8.0 Hz, 1H), 6.87 (d, J=7.6 Hz, 1H), 6.77 (s, 1H), 6.70−6.67 (m, 1H), 3.70 (s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −90.4 (dd, J=46.1, 27.4 Hz, 1F), −110.4 (dd, J=114.0, 46.1 Hz, 1F), −171.4 (dd, J=114.7, 27.4 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 157.4 (ddd, J=297.3, 286.2, 51.5 Hz), 146.4, 129.4, 121.8, 121.4, 117.4, 116.6 (m), 116.2, 102.5 (m), 72.7 (m). MS (EI) *m/z* (%): 197 (100). HRMS: Calculated for $C_{10}H_6F_3N$: 197.0452, found 197.0449.

2-(3,4,4-Trifluorobut-3-en-1-ynyl)thiophene (Table 2, 2l) ^{1}H NMR (400 MHz, $CDCl_3$, 293 K) δ: 7.61 (d, J=2.0 Hz, 1H), 7.32 (dd, J=4.9, 2.9 Hz, 1H), 7.17 (d, J=4.7 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$, 293 K) δ: −90.1 (dd, J=46.0, 27.2 Hz, 1F), −110.2 (dd, J=115.1, 46.1 Hz, 1F), −171.6 (dd, J=115.1, 27.2 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 158.1 (ddd, J=299.9, 292.9, 54.5 Hz), 130.99, 129.48, 125.96, 119.94, 115.80 (ddd, J=221.3, 52.6, 30.5 Hz), 97.47 (ddd, J=9.9, 8.1, 5.0 Hz), 72.97 (ddd, J=12.8, 9.6, 2.7 Hz). MS (EI) *m/z* (%): 188 (100). HRMS: Calculated

for $C_8H_3F_3S$: 187.9908, found 187.9912.

2-Methoxy-6-(3,4,4-trifluorobut-3-en-1-ynyl)naphthalene (Table 2, 2m) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.95－7.11 (m, 6H), 3.93 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −90.4 (dd, J=46.8, 27.4 Hz, 1F), −110.4 (dd, J=114.7, 46.8 Hz, 1F), −171.1 (dd, J=114.7, 26.6 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 168.9, 157.6, 149.1, 134.9, 132.0, 129.6, 128.9, 128.2, 127.0, 119.8, 115.6, 105.8, 98.7, 73.5 (m), 55.3. MS (EI) *m/z* (%): 262 (100). HRMS: Calculated for $C_{15}H_9F_3O$: 262.0605, found 262.0604.

4,5,5-Trifluoropent-4-en-2-ynyl benzoate (Table 2, 2n) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 8.08－8.03 (m, 2H), 7.57－7.55 (m, 1H), 7.46－7.42 (m, 2H), 5.12－5.10 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −87.9－88.0 (m, 1F), −108.9－109.3 (m, 1F), −173.5－173.9 (m, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 165.6, 158.2 (ddd, J= 297.3, 286.2, 51.5 Hz), 133.5, 129.8, 129.0, 128.5, 115.1 (m), 97.4 (m), 71.4 (m), 52.4. MS (EI) *m/z* (%): 240 (100). HRMS: Calculated for $C_{12}H_7F_3O_2$: 240.0398, found 240.0400.

(4,5,5-Trifluoropent-4-en-2-ynyl)benzene (Table 2, 2o) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.34－7.23 (m, 5H), 3.84－3.82 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −91.2－91.4 (m, 1F), −112.1－112.5 (m, 1F), −171.4－171.8 (m, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 157.9 (ddd, J=290.5, 289.4, 52.3 Hz), 128.7, 128.3, 127.9, 127.0, 115.0, 101.9 (m), 67.3 (m), 25.8. MS (EI) *m/z* (%): 196 (100). HRMS: Calculated for $C_{11}H_7F_3$: 196.0500, found 196.0499.

(*E*)-3-(1,2-Difluoro-4-phenyl-but-1-en-3-ynyl)-4-isopropyloxazolidin-2-one (Table 3, 4a) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.47－7.25 (m, 5H), 6.95－6.76 (m, 2H), 4.48－4.43 (m, 1H), 4.25－4.08 (m, 2H), 2.08－2.04 (m, 1H), 1.02－0.96 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −131.9 (dd, J=128.6, 1.5 Hz, 1F), −157.6 (d, J=128.2 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 135.5, 131.1, 128.8, 127.0, 113.2, 113.0, 64.8, 60.5, 29.6, 17.4, 15.2; MS (EI) *m/z* (%): 291 (100). HRMS: Calculated for $C_{16}H_{15}F_2O_2N$: 291.1071, found 291.1068.

(*E*)-3-(1,2-Difluoro-4-*p*-tolylbut-1-en-3-ynyl)-4-isopropyloxazolidin-2-one (Table 3, 4b) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.47－7.19 (m, 4H), 4.49－4.45 (m, 1H), 4.26－4.11 (m, 2H), 2.38 (s, 3H), 2.09－2.05 (m, 1H), 1.02－0.97 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −127.8 (d, J=121.2 Hz, 1F), −149.9 (d, J=118.4 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 154.8, 145.3, 138.6, 130.5, 128.4, 128.0, 126.2, 122.9, 102.4, 72.1, 64.9, 60.6, 29.7, 21.4, 17.5, 15.3. MS (EI) *m/z* (%): 305 (100). HRMS: Calculated for $C_{17}H_{17}F_2O_2N$: 305.1227, found 305.1231.

(*E*)-3-(1,2-Difluoro-4-(4-methoxyphenyl)but-1-en-3-ynyl)-4-isopropyloxazolidin-2-one (Table 3, 4c) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.61－6.93 (m, 4H), 4.47－4.44 (m, 1H), 4.27－4.08 (m, 2H), 3.85 (s, 3H), 2.13－2.02 (m, 1H), 1.03－0.96 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −130.6 (d, J=128.9 Hz, 1F), −144.2 (d, J=128.6 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 135.5, 131.1, 128.8, 127.0, 113.2, 113.0, 64.8, 60.5, 55.2, 29.6, 17.4, 15.2. MS (EI) *m/z* (%): 321 (100). HRMS: Calculated for $C_{17}H_{17}F_2O_3N$: 321.1176, found 321.1181.

(*E*)-3-(1,2-Difluoro-4-*m*-tolylbut-1-en-3-ynyl)-4-isopropyloxazolidin-2-one (Table 3, 4d) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.58－7.22 (m, 4H), 4.51－4.45 (m, 1H), 4.27－4.13 (m, 2H), 2.41－2.40 (m, 3H), 2.11－2.06 (m, 1H), 1.04－0.97 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −128.2 (d, J=118.4 Hz, 1F), −149.6 (d, J=121.2 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 154.9, 139.9, 134.6, 129.2, 125.6, 102.4, 72.1, 65.0, 60.0, 29.7, 21.3, 17.5, 15.3. MS (EI) *m/z* (%): 305 (100). HRMS: Calculated for $C_{17}H_{17}F_2O_2N$: 305.1227, found 305.1225.

(*E*)-3-(1,2-Difluoro-4-(6-methoxynaphthalen-2-yl)-but-1-en-3-ynyl)-4-isopropyloxazolidin-2-one (Table 3, 4e) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.98－7.48 (m, 4H), 7.19－7.11 (m, 2H), 4.48－4.42 (m, 1H), 4.26－4.11 (m, 2H), 3.93 (s, 3H), 2.44－2.41 (m, 3H), 2.11－2.07 (m, 1H), 1.02－0.98 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −122.4 (d, J=121.6 Hz, 1F), −144.8 (d, J=126.8 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 158.9, 149.1, 134.9, 132.1, 129.6, 128.2, 127.1, 123.9, 119.8, 115.5, 105.8, 98.7, 74.8, 64.9, 60.4, 55.4, 29.7, 17.4, 15.2. MS (EI) *m/z* (%): 371 (100). HRMS: Calculated for $C_{21}H_{19}F_2O_3N$: 371.1333, found 371.1329.

(*E*)-4-Benzyl-3-(1,2-difluoro-4-*p*-tolylbut-1-en-3-ynyl)oxazolidin-2-one (Table 3, 4f) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.42－7.17 (m, 9H), 4.41－4.34 (m, 2H), 4.21－4.18 (m, 1H), 3.23－3.18 (m, 1H), 2.88－2.82 (m, 1H), 2.38 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −122.7 (d, J=181.0 Hz, 1F), −144.4 (d, J=180.8 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 153.5, 149.1, 143.3 (dd, J=261.3, 51.4 Hz), 140.4, 134.3, 131.7, 131.3 (dd, J= 230.2, 65.1 Hz), 129.3, 129.0, 127.5, 117.6, 102.6, 74.6, 68.1, 56.9, 38.9, 21.6. MS (EI) *m/z* (%): 353 (100). HRMS: Calculated for $C_{21}H_{17}F_2O_2N$: 353.1227, found 353.1222.

(*E*)-4-Benzyl-3-(1,2-difluoro-4-(4-methoxyphenyl)-but-1-en-3-ynyl)oxazolidin-2-one (Table 3, 4g) ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ: 7.47－6.87 (m, 9H), 4.37－4.34 (m, 2H), 4.21－4.18 (m, 1H), 3.68 (s, 3H), 3.23－3.18 (m, 1H), 2.88－2.82 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$, 293 K, TMS) δ: −122.7 (d, J=128.9 Hz, 1F), −144.4 (d, J=130.6 Hz, 1F); ^{13}C NMR (100.5 MHz, $CDCl_3$, 293 K, TMS) δ: 153.5, 149.1, 143.3 (m), 134.3, 133.5, 132.7, 131.2 (m), 129.0, 127.5, 123.9, 117.6, 102.6 (m), 74.6 (m), 68.1, 56.9, 55.8, 38.9. MS (EI) *m/z* (%): 369 (100). HRMS: Calculated for $C_{21}H_{17}F_2O_3N$: 369.1176, found 369.1180.

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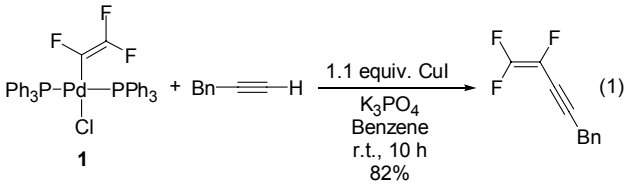
Results and Discussion

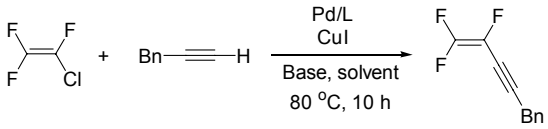
We began our investigation by studying the stoichiometric reaction of previously isolated [*trans*-$(PPh_3)_2$-Pd(CF=CF_2)(Cl)][9] **1** with 3-phenyl-1-propyne under various conditions. Heating of [*trans*-$(PPh_3)_2$Pd(CF=CF_2)(Cl)] **1** with 3-phenyl-1-propyne in THF, benzene or toluene in the present of 5 mol% CuI as additive and 1.0 equivalent of Et_3N or K_3PO_4 as the base generated the corresponding fluorinated enyne in less than 5% yield. Interestingly, the yield was increased to 58% when the reaction was conducted in benzene with 1.1 equivalent of CuI as the additive and K_3PO_4 as the base. Lowering the reaction temperature to room temperature led to higher yield (82%) (Eq. 1), possibly due to the slowing down of the unwanted competition dimerization of the alkyne. Since we have determined previously that oxidative addition of chlorotrifluoroethylene to Pd(0) occurred at 80 ℃,[6] the stoichiometric reaction indicated that that oxidative-addition of chlorotrifluoroethylene to Pd(0) species was much slower than those of transmetalation and reductive-elimination steps. Thus, if a suitable ligand can be identified to facilitate the oxidative-addition of chlorotrifluoroethylene to Pd(0) species,[8] the efficient Pd-catalyzed cross-coupling of chlorotrifluoroethylene and terminal alkynes might be accomplished under mild conditions.



(1)

Guided by these stoichiometric investigations, we first examined various supporting ligands, especially those known to accelerate the oxidative-addition step for the model reaction between chlorotrifluoroethylene and 3-phenyl-1-propyne. Surprisingly, no desired fluorinated conjugated enyne was observed when tri-*o*-tolylphosphine (P(*o*-tol)$_3$), butyl-di-1-adamantyl phosphine (Ad_2PBu), tri-*tert*-butylphosphine, 2-(dicyclohexylphosphino)biphenyl (CyJohnPhos), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (DavePhos) or 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos)[10] was used as the ligand when the reaction was conducted in benzene with 1.1 equivalent of CuI as the additive and K_3PO_4 as the base (Table 1, Entries 1—6). In contrast, when triphenylphosphine was used as the ligand, the desired product was formed in 69% yield under otherwise identical conditions (Table 1, Entry 7). Replacing $Pd(dba)_2$ with $Pd(OAc)_2$ resulted in completely shutting down the reaction (Table 1, Entry 8). Using $Pd(PPh_3)_2Cl_2$ as the catalyst formed the product in lower 33% yield while using $Pd(PPh_3)_4$ led to much higher 82% yield (Table 1, Entries 9 and 10). The effect of the solvent and the base was further evaluated. Reaction in THF was less efficient than those in benzene (Table 1, Entry 11). Reaction using Et_3N or *i*-Pr_2NH as the base was not effective at all (Table 1, Entries 12 and 13). When the amount of CuI was reduced to 20 mol%, the yield of the fluorinated conjugated enyne was decreased to 20 mol% (Table 1, Entry 14). Interestingly, the yield was significantly improved to 87% when 20 mol% of Bu_3N was used as an additive and a mixed solvent of benzene/water (3/1, *V*/*V*) was used (Table 1, Entries 15—17). Reaction in a mixed solvent of toluene/water under otherwise same conditions gave the product in 85% yield (Table 1, Entry 18). It is likely that the presence of water increased the solubility of K_3PO_4 that facilitated the transmetalation step of the catalytic cycle.[11]

Table 1 Optimization for Pd-catalyzed coupling of chlorotrifluoroethylene with 3-phenyl-1-propyne[a]



Entry	Pd source	Ligand	Solvent	CuI	Base	Yield[b]/%
1	$Pd(dba)_2$	P(*o*Tol)$_3$	Benzene	1.1 equiv.	K_3PO_4	—
2	$Pd(dba)_2$	Ad_2PBu	Benzene	1.1 equiv.	K_3PO_4	—
3	$Pd(dba)_2$	*t*-Bu_3P	Benzene	1.1 equiv.	K_3PO_4	—
4	$Pd(dba)^2$	CyJohnPhos	Benzene	1.1 equiv.	K_3PO_4	—
5	$Pd(dba)_2$	DavePhos	Benzene	1.1 equiv.	K_3PO_4	—
6	$Pd(dba)_2$	SPhos	Benzene	1.1 equiv.	K_3PO_4	—
7	$Pd(dba)_2$	PPh_3	Benzene	1.1 equiv.	K_3PO_4	69
8	$Pd(OAc)_2$	PPh_3	Benzene	1.1 equiv.	K_3PO_4	—
9	$Pd(PPh_3)_4$	—	Benzene	1.1 equiv.	K_3PO_4	82
10	$Pd(PPh_3)_2Cl_2$	—	Benzene	1.1 equiv.	K_3PO_4	33

Continued

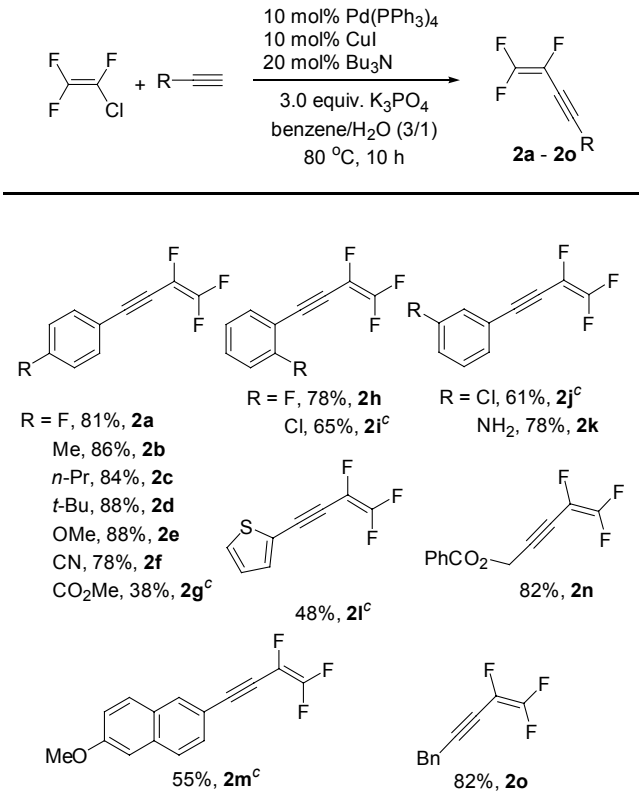
Entry	Pd source	Ligand	Solvent	CuI	Base	Yield[b]/%
11	$Pd(PPh_3)_4$	—	THF	1.1 equiv.	K_3PO_4	52
12	$Pd(PPh_3)_4$	—	Benzene	1.1 equiv.	Et_3N	—
13	$Pd(PPh_3)_4$	—	Benzene	1.1 equiv.	*i*-Pr_2NH	—
14	$Pd(PPh_3)_4$	—	Benzene	10 mol%	K_3PO_4	20
15	$Pd(PPh_3)_4$	—	Benzene/H_2O (5/1)	10 mol%	K_3PO_4	43[c]
16	$Pd(PPh_3)_4$	—	Benzene/H_2O (3/1)	10 mol%	K_3PO_4	87[c]
17	$Pd(PPh_3)_4$	—	Benzene/H_2O (1/1)	10 mol%	K_3PO_4	71[c]
18	$Pd(PPh_3)_4$	—	Toluene/H_2O (3/1)	10 mol%	K_3PO_4	85[c]

[a] Reaction conditions: 3-phenyl-1-propyne (1.0 mmol), excess chlorotrifluoroethylene, palladium precursor (10 mol%), ligand (20 mol%), base (3.0 mmol) in 2.0 mL solvent. [b] The yield was determined by ^{19}F NMR spectroscopy with fluorobezene as an internal standard. [c] 20 mol% Bu_3N was added as additive.

The scope of Sonogashira reaction of a variety of alkynes with chlorotrifluoroethylene in the presence of palladium catalyst and CuI as additive is shown in Table 2. A wide range of alkynes were readily converted to the corresponding fluorinated conjugated enynes in moderate to excellent yields. Reactions of both electron-rich and electron-poor aryl substituted alkynes gave the corresponding products in good to excellent yields (Table 2, **2a**—**2m**). It was found that the reaction conditions were compatible with various functional groups such as ester, amine, cyano group (Table 2, **2f**, **2g**, **2i** and **2n**). Notably, 2- or 3-chlorophenylethyne also coupled with chlorotrifluoroethylene to give the corresponding enynes in 65% and 61% yield, respectively (Table 2, Entries **2i** and **2j**), which indicated that C—Cl bond in chlorotrifluoroethylene is more reactive than those in aryl chlorides that has been observed in the palladium-catalyzed Suzuki-coupling of chlorotrifluoroethylene with aryl boronic acids. The presence of chloride in the products is very useful for further synthetic manipulations. Reaction of heteroaryl alkyne such as 2-thiophenylethyne occurred smoothly to give the corresponding product in 48% yield (Table 2, **2l**). Reactions of alkyl alkynes generated the corresponding enynes in excellent yields (Table 2, **2n** and **2o**).

To further expand the scope of the reaction, we further studied the reaction of (*R*,*Z*)-3-(2-chloro-1,2-difluorovinyl)-4-alkyloxazolidin-2-one (**3a** and **3b**) with alkynes. After careful investigation of various reaction parameters, it was found that reaction of compound **3a** with phenylacetylene occurred smoothly to give the coupled product in 64% yield when 10 mol% of $Pd(PPh_3)_2Cl_2$ was used as the catalyst, 20 mol% of CuI was used as cocatalyst and Et_3N was used as base in DMSO. A variety of aryl alkynes were subjected to the catalytic conditions to give the product in moderate to good yield, as summarized in Table 4. In general, these reactions were faster than those of chlorotrifluoroethylene and the reaction typically required 10 h at 45 ℃. At higher temperature, the yields dropped significantly.

Table 2 Scope of Pd-catalyzed coupling of chlorotrifluoroethylene with alkynes[a,b]



[a] Reaction conditions: alkyne (1.0 mmol), excess chlorotrifluoroethylene, $Pd(PPh_3)_4$ (10 mol%), CuI (10 mol%), *n*-Bu_3N (20 mol%), K_3PO_4 (3.0 mmol) in 2.0 mL of benzene/H_2O (3/1) at 80 ℃ for 10 h. [b] Isolated yields. [c] 1.0 equivalent of CuI was used.

Conclusions

In summary, an efficient and cost-effective method for the preparation of fluorinated conjugated enynes has been successfully developed. The method was compatible with a variety of functional groups such as chloride, amine, cyano and ester group. The method could also be extended to the coupling of (*R*,*Z*)-3-(2-chloro-1,2-di-

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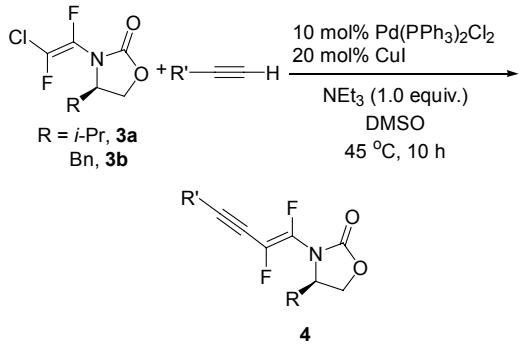
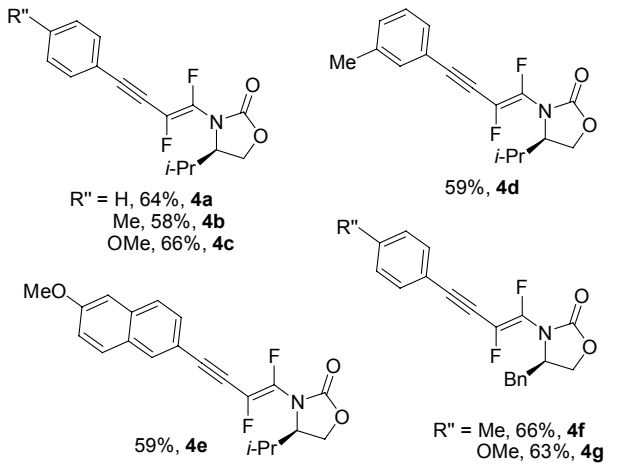
Table 3 Scope of Pd-catalyzed coupling of (*R*,*Z*)-3-(2-chloro-1,2-difluorovinyl)-4-alkyloxazolidin-2-one **3** with alkynes[a,b]





[a] Reaction conditions: alkyne (1.2 mmol), (*R*,*Z*)-3-(2-chloro-1,2-difluorovinyl)-4-alkyloxazolidin-2-one (**3**) (1.0 mmol), $Pd(PPh_3)_2Cl_2$ (10 mol%), CuI (10 mol%), Et_3N (20 mol%) in 2.0 mL of DMSO at 45 ℃ for 10 h. [b] Isolated yields.

fluorovinyl)-4-alkyloxazolidin-2-one (**3**) with moderate yields. Work is ongoing to elucidate the mechanism of the reaction and to further explore the reactivity of chlorotrifluoroethylene.

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(Pan, B.; Qin, X.)

