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Novel synthesis of 3-(3,3,3-trifluoroprop-1-en-2-yl)furans via stereoselective processing and palladium-catalyzed cycloisomerization

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Abstract—The 3,3,3-trifluoroprop-1-en-2-yl-substituted furans (**4**) were synthesized via palladium-catalyzed cyclization–isomerization of 1,1,1-trifluoro-2-[(*tert*-butyldimethylsilyloxy)methyl]-3-alkynylbut-2-en-1-ols (**3**), which were readily obtained from 1,1,1-trifluoro-2-[(*tert*-butyldimethylsilyloxy)methyl]-3,3-dibromoprop-2-ene (**1**) in three steps.

Furan is not only a useful fragment in naturally occurring products and biologically active compounds but also a key building block in organic synthesis.[1] In addition, introduction of fluorine atom into organic compounds has been known as one of the major strategies for the enhancement or modification of their original biological activities.[2] Hence, it is desirable to develop efficient methods for the synthesis of fluorinated furans. In fact, there are a few reports on the fluorinated furans.[3] However, as far as we know, 3,3,3-trifluoroprop-1-en-2-yl-substituted furans have not been documented, in which the 3,3,3-trifluoroprop-1-en-2-yl may be utilized for further functional group transformations. Some methods for the synthesis of substituted furans from 3 or 2-alkynyl allylic alcohols under Pd[4], Ag[5] or Ru-catalyzed[6] and basic condition[7] have been documented. Based on our previous work,[8] we present here an efficient approach towards a family of 3,3,3-trifluoroprop-1-en-2-yl-substituted furans (**4**) from 1,1,1-trifluoro-2-[(*tert*-butyldimethylsilyloxy)methyl]-3-alkynylbut-2-en-1-ols (**3**) through Pd-catalyzed cyclization–isomerization.

Our previous investigations focused on the highly stereoselective lithium–bromine exchange reaction of 1,1,1-trifluoro-2-[(*tert*-butyldimethylsilyloxy)methyl]-3,3-dibromo-prop-2-ene (**1**).[8a] After the lithium–bromine exchange, the carbenoid of **1** was quenched with benzaldehyde, furan-2-carbaldehyde and butyraldehyde to give the corresponding **2a**–**c** in 73–82% yields, respectively (Table 1).

The reaction of **2a**–**c** with a series of terminal alkynes under Sonogashira reaction conditions gave the corresponding coupling products, 1,1,1-trifluoro-2-[(*tert*-butyldimethylsilyloxy)methyl]-3-alkynylbut-2-en-1-ols (**3a**–**i**) in 58–87% yields. The preliminary results are summarized in Table 2.

The construction of fluorinated furans substituted with various functional groups is of our current interest.[9] With **3a**–**i** in our hands, we first attempted Pd-catalyzed cyclization of **3a** by means of several palladium complexes. Among the catalysts tested, only $PdCl_2(CH_3CN)_2$ could catalyze the cyclization of **3a** to give 3,3,3-trifluoroprop-1-en-2-yl-substituted furan (**4a**) in 99% yield, whereas $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$ and $PdCl_2(PPh_3)_2$ were inactive under the similar reaction conditions. The structure of **4a** was supported by ^1H, ^{13}C and ^{19}F NMR spectra,[10,11] and further confirmed by a single crystal X-ray diffraction study (Fig. 1).[12]

Other substrates (**3b**–**i**) also readily underwent Pd-catalyzed intramolecular cyclization under similar reaction conditions. The corresponding fluorinated furans (**4b**–**i**) were obtained in 87–99% yields, except for **4d** that was formed in 58% yield in two steps (Table 3). Their

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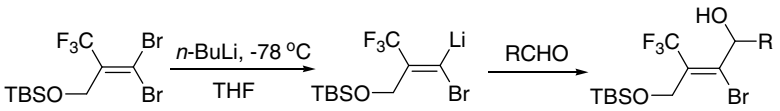
Table 1. Reaction of **1** with aldehydes

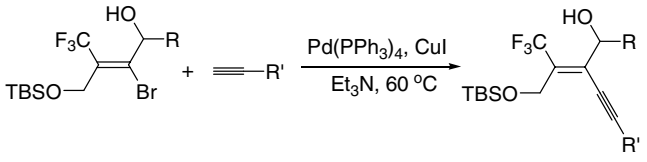


1 **2**

Entry	R	Product	Yield[a] (%)
1	Phenyl	**2a**	82
2	α-Furyl	**2b**	78
3	*n*-Propyl	**2c**	73

[a] Isolated yield based on **1**.

Table 2. Pd-Catalyzed reaction of **2** with terminal alkynes

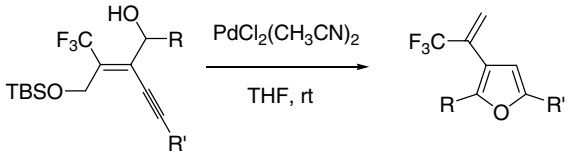


2 **3**

Entry	Substrate	R	R′	Product	Yield[a] (%)
1	**2a**	Phenyl	Phenyl	**3a**	69
2	**2a**	Phenyl	*p*-MeO–phenyl	**3b**	67
3	**2a**	Phenyl	*p*-MeO_2C–phenyl	**3c**	58
4	**2a**	Phenyl	*n*-Pentyl	**3d**	—[b]
5	**2b**	α-Furyl	Phenyl	**3e**	70
6	**2b**	α-Furyl	*p*-MeO_2C–phenyl	**3f**	71
7	**2c**	*n*-Propyl	Phenyl	**3g**	87
8	**2c**	*n*-Propyl	*p*-MeO–phenyl	**3h**	86
9	**2c**	*n*-Propyl	*p*-MeO_2C–phenyl	**3i**	74

[a] Isolated yield based on **2a**–**c**.
[b] Pure product could not be purified.

Table 3. Palladium-catalyzed preparation of fluorinated furans **4** from **3**



3 **4**

Entry	Substrate	Product	Yield[a] (%)
1	**3a**	**4a**	99
2	**3b**	**4b**	93
3	**3c**	**4c**	98
4	**3d**	**4d**	58[b]
5	**3e**	**4e**	92
6	**3f**	**4f**	87
7	**3g**	**4g**	93
8	**3h**	**4h**	91
9	**3i**	**4i**	89

[a] Isolated yield based on **3a**–**i**.
[b] Two steps in one pot.

structures were established by their ^{1}H, ^{13}C and ^{19}F NMR spectra, respectively.

A possible mechanism was proposed in Scheme 1. First, Pd(II) mediated and activated the triple bond of substrate **3**, then hydroxyl group intramolecularly attacked the triple bond to form a vinylpalladium intermediate **5**

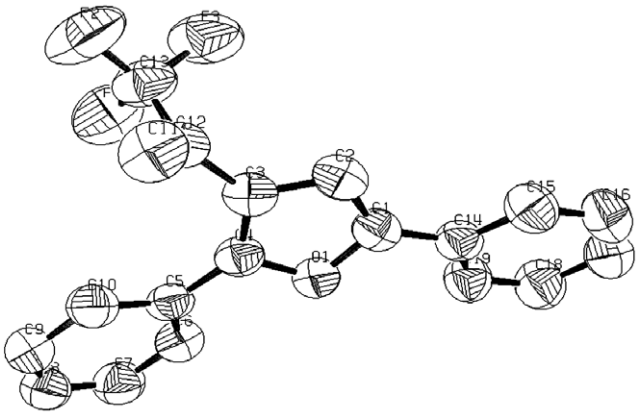
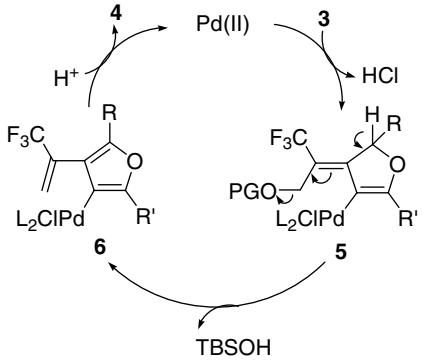


Figure 1. An ORTEP drawing of **4a** with all H atoms omitted for clarity.



Scheme 1. Proposed mechanism for the formation of **4**.

in 5-*endo*-*dig* mode. Subsequently, **5** proceeds an aromatizing reaction via an elimination of the TBSOH to give an intermediate **6**, which further produces the final product by protonolysis.

In summary, a new synthetic method of 3,3,3-trifluoroprop-1-en-2-yl-substiuted furans has been developed, which may be used to synthesize CF_3-containing analogues of naturally occurring products or biologically

active compounds. Further studies in this area are being pursued in our laboratory.

Acknowledgement

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10. ^{19}F NMR spectra were recorded on a Bruker AM300 spectrometer using $CFCl_3$ as the external standard, and downfield shifts being designed as negative.
11. *Typical experimental procedure for* **4a**–**i**: A solution of **3a** (170 mg, 0.38 mmol) and $PdCl_2(CH_3CN)_2$ (10 mg, 0.038 mmol) in THF (4 mL) was stirred at room temperature under argon. The reaction was completed in 20 min (TLC), then the solvent was removed under reduced pressure. The crude product was purified by chromatography with petroleum as the eluant to give 2,5-diphenyl-3-(3,3,3-trifluoroprop-1-en-2-yl)furan as a white solid (118 mg, 99%, **4a**). IR (thin film) υ_{max} 3107, 1592, 1494, 1447, 1386, 1468, 1128 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.79–7.32 (m, 10H), 6.78 (s, 1H), 6.06 (s, 1H), 5.72 (s, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ: 67.3 (s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 152.8, 150.7, 132.0 (q, $J = 27.2$ Hz), 130.2, 130.1, 128.8, 128.6, 128.2, 127.9, 126.4, 124.0, 123.4 (q, $J = 4.2$ Hz), 123.1 (q, $J = 274.6$ Hz), 116.2, 108.5; MS (EI) m/z 314 (M^+, 100); HRMS Calcd for $C_{19}H_{13}F_3O$: 314.0919. Found: 314.0930.
12. Crystallographic data for X-ray structure have been deposited with the Cambridge Crystallographic Centre as CCDC 258472. Copies of the data can be obtained free of charge via from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk.