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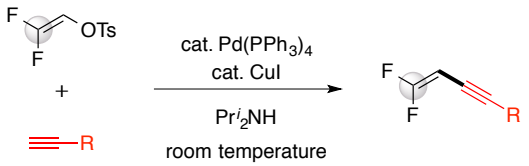
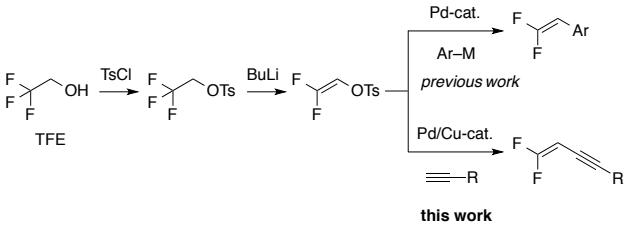
Supporting Information Placeholder



ABSTRACT: The Sonogashira-type coupling of 2,2-difluoroethenyl tosylate with a variety of aliphatic and aromatic terminal alkynes proceeds smoothly even at room temperature to produce the corresponding difluorinated enyne derivatives. 2,2-Difluoroethenyl tosylate is a useful difluoroethenyl source because of its ready availability from 2,2,2-trifluoroethanol. Some of obtained enynes exhibits strong fluorescence in the solid state. Further derivatization of a difluorinated enyne through Rh(III)-catalyzed oxidative coupling has also been examined.

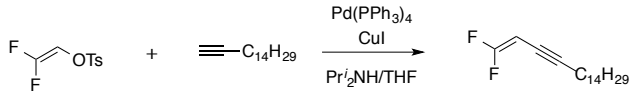
gem-Difluoroalkenyl units can be seen in a variety of biologically active compounds and their synthetic intermediates.[1] Recently, π-conjugated molecules containing *gem*-difluoroalkenyl functions have attracted attention because of their optical and electrochemical properties.[2] Therefore, development of synthetic methods for introducing the *gem*-difluoroalkenyl groups on organic molecules regioselectively under mild conditions has been desired. The cross-coupling reactions of 2,2-difluoroethenyl tosylate appear to be promising approaches toward such functionalized π-conjugated molecules, because the tosylate is readily available even in high-volume from 2,2,2-trifluoroethanol (TFE) (Scheme 1),[3] which has become widely employed as a solvent in organic chemistry laboratories. However, the utilization of the tosylate in cross-coupling reactions has been limited to only Suzuki-Miyaura coupling.[4,5] In the context of our studies on the synthesis of fluorine-containing functionalized molecules,[6] we have found that the tosylate also undergoes Sonogashira-type coupling[7] upon treatment with terminal alkynes in the presence of a palladium-copper catalyst system to produce difluorinated enyne derivatives selectively.[8] In contrast to the previous Suzuki-Miyaura coupling,[4] the present reaction proceeds efficiently even at room temperature and without any alkylphosphine ligands. Notably, some of obtained enynes exhibit solid-state fluorescence. Further derivatization of the difluorinated enyne has also been examined. These new findings are described herein.

Scheme 1. Preparation and Cross-Coupling of 2,2-Difluoroethenyl Tosylate



In an initial attempt, 2,2-difluoroethenyl tosylate (**1**) (0.25 mmol) was treated with 1-hexadecyne (**2a**) (0.25 mmol) in the presence of $Pd(PPh_3)_4$ (0.013 mmol) and CuI (0.038 mmol) as catalysts under argon in Pr^i_2NH/THF (1:1) at 85 °C for 1 h. As expected, Sonogashira-type coupling took place to produce 1,1-difluorooctadec-1-en-3-yne (**3a**) in 69% yield (entry 1 in Table 1). Increasing the amount of **2a** to 0.38 mmol somewhat improved the yield of **3a** to 75% (entry 2). While reducing the amount of CuI by half did not affect the reaction efficiency significantly (entry 3), the yield of **3a** markedly decreased to 30% in the absence of CuI (entry 4). It should be noted that the reaction could be conducted efficiently under milder conditions. Even at room temperature, **3a** was obtained in 80% yield by extending the reaction time to 2 h (entry 6).

Table 1. Reaction of 2,2-Difluoroethenyl Tosylate (1) with 1-Hexadecyne (2a)[a]



1 2a 3a

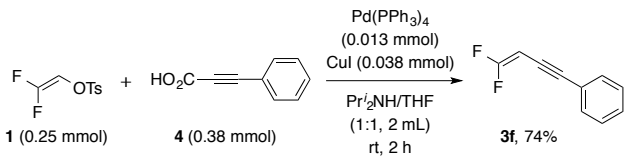
entry	CuI (mmol)	temp (°C)	time (h)	yield (%)[b]
1[c]	0.038	85	1	69
2	0.038	85	1	75
3	0.019	85	2	71
4	0	85	2	30
5	0.038	50	2	80
6	0.038	rt	2	80 (74)

[a] Reaction conditions: **1** (0.25 mmol), **2a** (0.38 mmol), $Pd(PPh_3)_4$ (0.013 mmol) in Pr^i_2NH/THF (1:1, 2 mL) under Ar, unless otherwise noted. [b] GC yield based on the amount of **1a** used. Value in parentheses indicates yield after purification. [c] With **2a** (0.25 mmol).

We next examined the reactions of a variety of terminal alkynes **2** with tosylate **1** under the conditions used in entry 6 of Table 1 (Table 2). The reactions using linear aliphatic alkynes, 1-pentadecyne (**2b**) and 1-dodecyne (**2c**), in place of **2a** proceeded efficiently to produce the corresponding enynes **3b** and **3c** in 76 and 74% yields, respectively, within 2 h. Oct-7-yn-1-ol (**2d**) and 1,1-diphenylprop-2-yn-1-ol (**2e**) underwent the coupling with **1** to give enynes **3d** and **3e**, showing the tolerance of hydroxy groups. For the present coupling, a series of aromatic alkynes can also be employed. Thus, in addition to unsubstituted phenylacetylene (**2f**), 4-methoxyl (**2g**), -phenyl (**2h**), -chloro (**2i**), and -bromo (**2j**) substituted phenylacetylenes coupled with **1** to afford **3f-j** in 39-68% yields. Electron deficient substrates tend to need longer reaction times and afford lower yields. Besides these phenylacetylenes, 2-naphthyl (**2k**), 9-anthryl (**2l**), and 9-phenanthryl (**2m**) acetylenes reacted with **1** in a similar manner to produce **3k-m** in 47-82% yields.

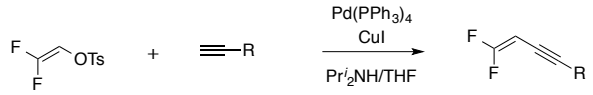
The rather high yield preparation of enyne **3f** was achieved by decarboxylative coupling[9] of readily available phenylpropiolic acid (**4**) with **1**. Thus, treatment of **1** (0.25 mmol) with **4** (0.38 mmol) in the presence of $Pd(PPh_3)_4$ (0.013 mmol) and CuI (0.038 mmol) under argon in Pr^i_2NH/THF (1:1) at room temperature for 2 h gave **3f** in 74% yield (Scheme 2). Since a series of arylpropiolic acids can be easily prepared through Sonogashira coupling of aryl halides with propiolic acid itself without bothersome protection/deprotection processes,[9a] the decarboxylative coupling provides a powerful alternative for preparation of difluorinated enynes.

Scheme 2. Decarboxylative Coupling of Phenylpropiolic Acid (4) with 2,2-Difluoroethenyl Tosylate (1)



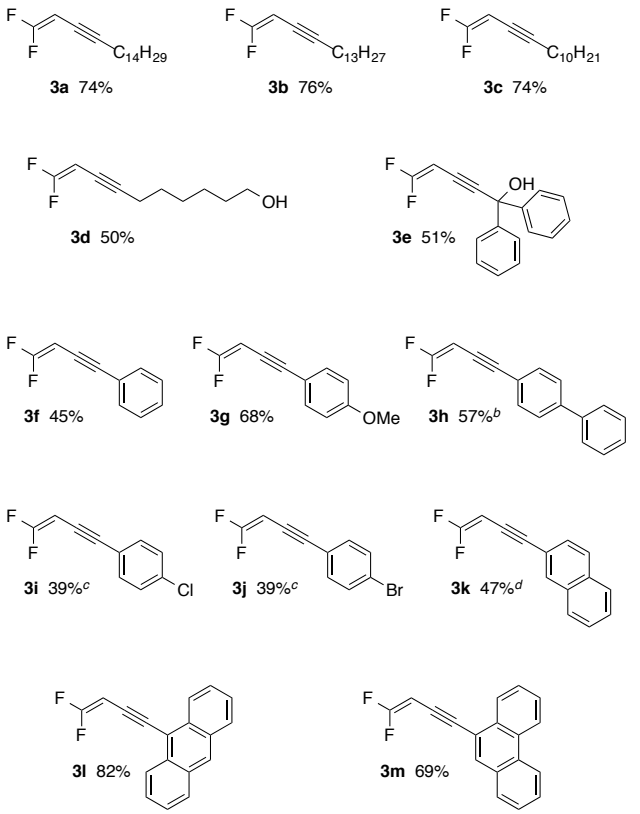
1 (0.25 mmol) **4** (0.38 mmol) **3f**, 74%

Table 2. Reaction of 2,2-Difluoroethenyl Tosylate (1) with Alkynes 2[a]



1 **2** **3**

product yield (%)



[a] Reaction conditions: **1** (0.25 mmol), **2** (0.38 mmol), $Pd(PPh_3)_4$ (0.013 mmol), CuI (0.038 mmol) in Pr^i_2NH/THF (1:1, 2 mL) under Ar at rt for 2 h. [b] For 6 h. [c] For 8 h. [d] For 5 h.

Finally, we conducted preliminary investigations on the properties and applications of newly prepared difluorinated enynes. Anthryl-substituted enyne **3l** showed strong fluorescence in the solid state at 485 nm (excited at 365 nm) (Figure 1). The largely red-shifted fluorescence compared with that in the liquid state (417 nm) is attributed to the π-stacked structure of **3l** in the solid state (for single crystal and crystal packing structures, see the Supporting Information). The quantum efficiency of the solid-state fluorescence was determined to be an absolute value of 0.35.

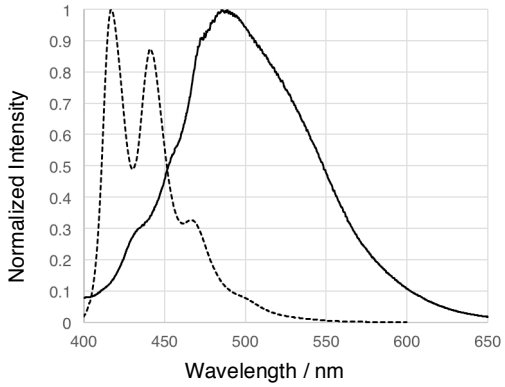
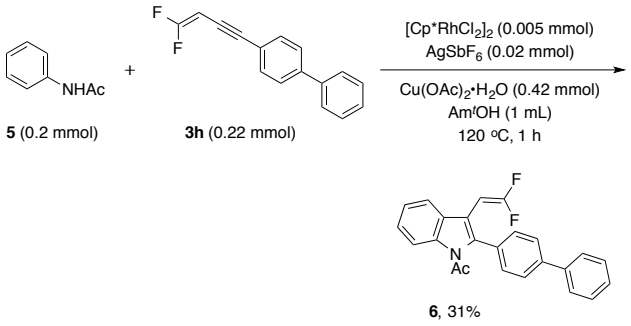


Figure 1. Normalized photoluminescence spectra (excited at 365 nm) of **3l** in hexane solution (1.0×10^{-5} M) (dotted line) and solid state (solid line).

In addition, difluorinated enynes can be building blocks in construction for more structurally complicated π-conjugated molecules through further coupling reactions. For example, we and other groups have developed the rhodium(III)-catalyzed oxidative coupling reactions of various aromatic substrates with alkynes via regioselective C–H bond cleavage to form annulated products.[10,11] Expectedly, enyne **3h** was found to undergo this kind of oxidative coupling with *N*-acetylaniline (**5**).[12] Although the reaction conditions have not been optimized yet, a difluoroethenyl-substituted indole derivative **6** was obtained in a moderate yield (Scheme 3). It has been reported that this type of *gem*-difluoroethenyl(hetero)arenes can be readily transformed to β,β,β-trifluoroethyl(hetero)arenes upon treatment with TBAF.[13] A range of β,β,β-trifluoroethyl(hetero)arenes including 3-(β,β,β-trifluoroethyl)indoles have been known to show unique biological activities.[14]

Scheme 3. Rh(III)-Catalyzed Oxidative Coupling of Enyne 3h with *N*-Acetylaniline (5)



In summary, we have demonstrated that the synthesis of difluorinated enynes can be achieved through the palladium-catalyzed coupling of 2,2-difluoroethenyl tosylate with terminal alkynes. The tosylate is readily preparable even in high-volume from an organic solvent, 2,2,2-trifluoroethanol. Moreover, the synthesized enynes are expected to undergo further coupling with various aromatic substrates. Therefore, the reaction sequence provides cost-effective, simple synthetic routes toward fluorinated π-conjugated molecules. Work is underway toward the further development of the procedures.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.
Experimental procedures and characterization data of products (PDF)
Crystallographic data for **3l** and **6** (CIF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was partly supported by JSPS KAKENHI Grant Number JP16H01037 in Precisely Designed Catalysts with Customized Scaffolding, JST (ACT-C), and NEDO, Japan.

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