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Synthesis of Difluorinated Enynes through Sonogashira-Type Coupling

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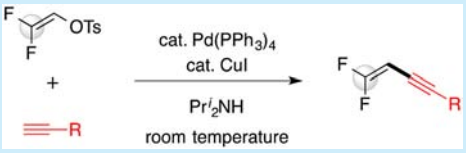
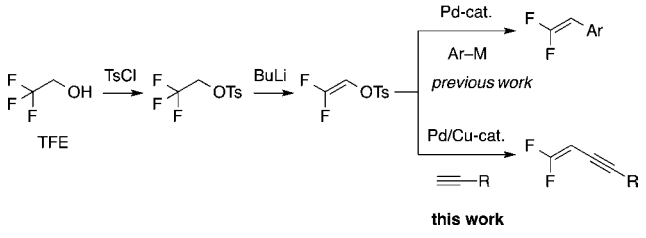
Supporting Information

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 the obtained enynes exhibit strong fluorescence in the solid state. Further derivatization of a difluorinated enyne through Rh(III)-catalyzed oxidative coupling has also been examined.



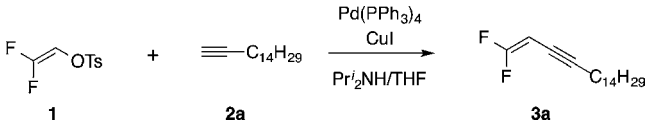
gem-Difluoroalkenyl units can be seen in a variety of biologically active compounds and their synthetic intermediates.[1] Recently, π-conjugated molecules containing *gem*-difluoroalkenyl functions have attracted attention because of their optical and electrochemical properties.[2] Therefore, development 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

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).

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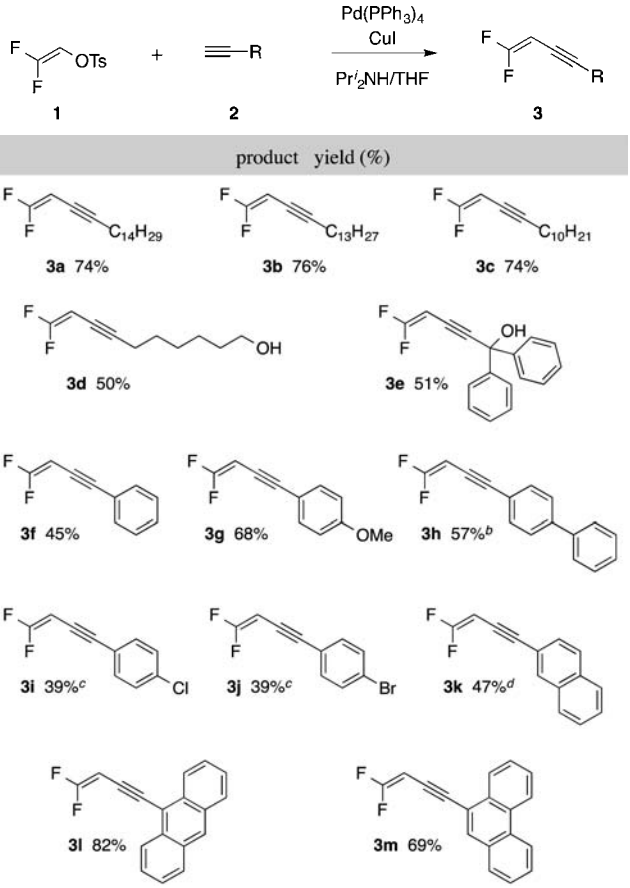
conditions. Even at room temperature, **3a** was obtained in 80% yield by extending the reaction time to 2 h (entry 6).

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

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

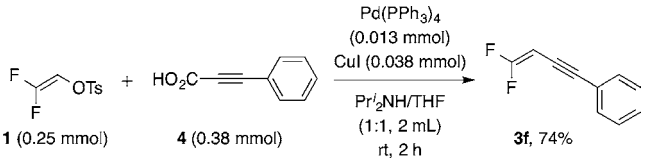


[a]Reaction conditions: **1** (0.25 mmol), **2** (0.38 mmol), $Pd(PPh_3)_4$ (0.013 mmol), CuI (0.038 mmol) in Pr^i_2NH/THF (1:1, 2 mL) under Ar at rt for 2 h. [b]For 6 h. [c]For 8 h. [d]For 5 h.

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 tolerance for 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 require 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

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



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.

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

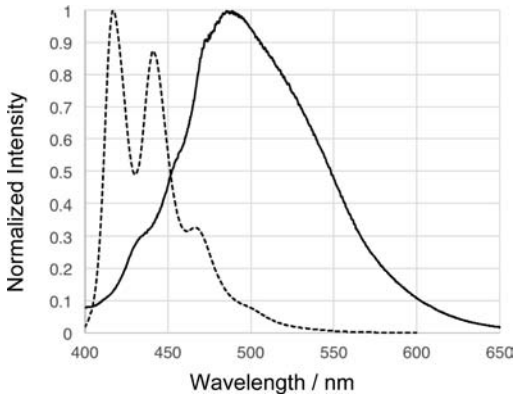


Figure 1. Normalized photoluminescence spectra (excited at 365 nm) of **3l** in hexane solution (1.0×10^{-5} M) (dotted line) and solid state (solid line).

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.

In addition, difluorinated enynes can be building blocks in the construction of 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]

In summary, we have demonstrated that the synthesis of difluorinated enynes can be achieved through the palladium-

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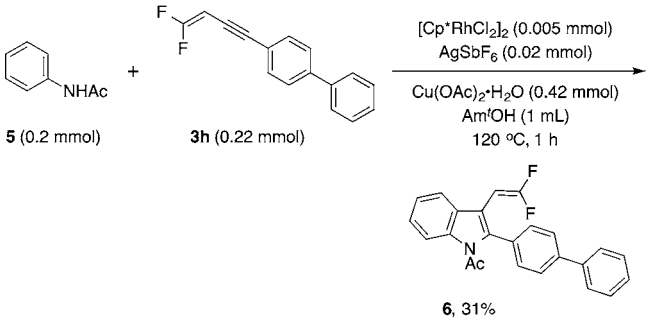
Scheme 3. Rh(III)-Catalyzed Oxidative Coupling of Enyne 3h with *N*-Acetylaniline (5)



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.6b02919.

Crystallographic data for **3l** (CIF)
Crystallographic data for **6** (CIF)
Experimental procedures and characterization data of products (PDF)

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Notes

The authors declare no competing financial interest.

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