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A novel method for (*Z*)-stereoselective preparation of CF_3-substituted enediynes and their coupling reactions

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Abstract—Trifluoromethylated enynyl sulfones **3** were reacted with 2–4 equiv of phenyl, *n*-hexyl, trimethylsilyl, or triisopropylsilyl substituted ethynyllithium reagents in THF or ether at 0 °C to give trifluoromethylated enediynes **6** (*Z*)-stereoselectively in 41–96% yields. The reactions of β-fluoro-β-trifluoromethylvinyl sulfone **5** with same ethynyllithium reagents (4 equiv) afforded the corresponding enediynes **6** in 41–90% yields. The cross-coupling reactions of **6** bearing TMS group with aryl iodides in the presence of $Pd(PPh_3)_2Cl_2$, Ag_2CO_3, and $n\text{-}Bu_4NBr$ provided the corresponding enediynes **6** in 20–71% yields. Dimerization of (*Z*)-**6** bearing TMS group in the presence of $CuBr_2$ and K_2CO_3 yielded dimer (*Z*,*Z*)-**7** in good yield.

Recently, enediyne compounds have attracted much interest since they can be used not only to study on the mechanism for their function in antitumor antibiotics[1–3] such as dynemicin, neocarzinostatin, and esperamicin, but also utilize in the synthesis of oligoenynes and oligoenediynes as well as π-conjugated polymers for electronic and photonic applications.[4–7] Although numerous methods for the preparation of nonfluorinated enediyne derivatives and their applications to the synthesis of benzene derivatives and π-conjugated oligomers have been well documented in the previous literatures,[8–15] there has been quite limited reports on the preparation of trifluoromethylated enediynes, which are valuable building blocks in the synthesis of trifluoromethylated oligoenediynes, in which the presence of trifluoromethyl group sometimes causes their properties to change dramatically as compared to nonfluorinated ones. Hong prepared (*E*)-trifluoromethylated enediyne from the Pd-catalyzed Sonogashira coupling reaction of (*Z*)-1,2-dibromo-3,3,3-fluoropropene with terminal alkynes.[16] (*Z*)-Trifluoromethylated enediyne was also prepared from the reaction of trifluoromethylated oxiranyllithiums with (pinacolato)borane, in which trifluoromethylated oxiranyllithiums were synthesized from the treatment of trifluoromethylated dichlorohydrines with 2 equiv of alkyllithium at a low temperature.[17] However, the previous methods have some drawbacks such as lack of novelity and generality, and tedious procedure. Herein, we wish to report a novel and general preparation of (*Z*)-stereoselective trifluoromethylated enediynes and their coupling reactions to give a variety of trifluoromethylated enediynes and their dimers.

Trifluoromethylated enynyl sulfones **3a**–**b** ($E/Z = 9/91$) as precursors to enediynes were prepared in quantitative yields from the oxidation of trifluoromethylated enynyl sulfides **2a**–**b** ($E/Z = 9/91$), which were synthesized from the reaction of pentafluoroethyl phenyl dithioketal **1** with phenyl or *n*-hexyl substituted ethynyllithium reagents (2.5 equiv).[18] The assignment of *E* and *Z* isomers of **3a**–**b** was made by the comparison of chemical shift of authentic sample in ^{19}F NMR spectroscopy.[19] It has been established that ^{19}F NMR signal (~ -55.70 ppm) in the *Z*-isomer is less shielded than that (~ -59.00 ppm) in the *E*-isomer. Since **1** was not reacted with trimethylsilyl or triisopropylsilyl substituted ethynyllithium reagents, enynyl sulfones **3c**–**d** were prepared from the reaction of β-fluoro-β-trifluoromethylvinyl sulfone **5**, formed by oxidation of β-fluoro-β-trifluoromethylvinyl sulfide **4**,[20] with trimethylsilyl or triisopropylsilyl substituted ethynyllithium reagents.

Further reactions of **3a**–**b** with ethynyllithium reagents (2–4 equiv) in THF or ether at 0 °C for 1–2 h afforded

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Keywords: Trifluoromethylated enynyl sulfones; Trifluoromethylated enediynes; (*Z*)-Stereoselectivity; Cross-coupling reaction; Dimerization.

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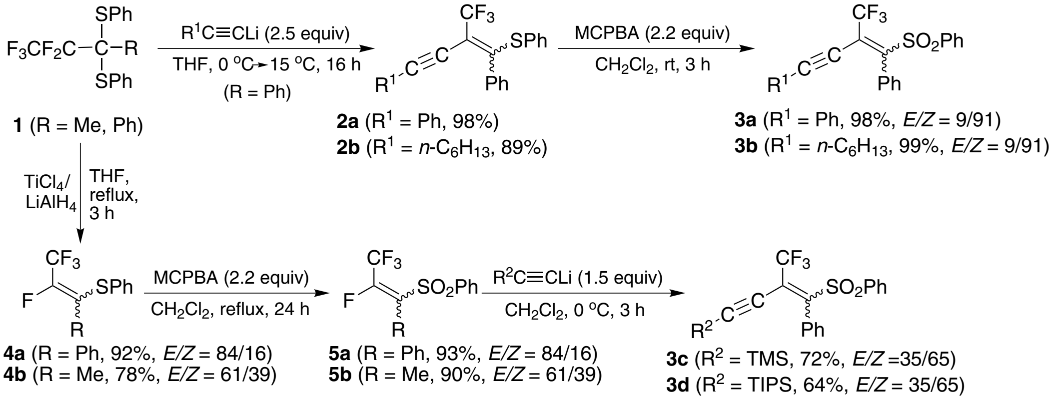


1 (R = Me, Ph)

2a (R^1 = Ph, 98%)
2b (R^1 = n-$\mathrm{C_6H_{13}}$, 89%)

3a (R^1 = Ph, 98%, E/Z = 9/91)
3b (R^1 = n-$\mathrm{C_6H_{13}}$, 99%, E/Z = 9/91)

4a (R = Ph, 92%, E/Z = 84/16)
4b (R = Me, 78%, E/Z = 61/39)

5a (R = Ph, 93%, E/Z = 84/16)
5b (R = Me, 90%, E/Z = 61/39)

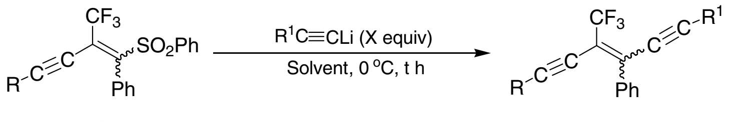
3c (R^2 = TMS, 72%, E/Z =35/65)
3d (R^2 = TIPS, 64%, E/Z = 35/65)

the corresponding enediynes **6a–f** (*Z*)-stereoselectively in 41–96% yields. The reactions of **3c–d** with trimethylsilyl or triisopropylsilyl substituted ethynyllithium reagents also yielded enediynes **6g–i** (*Z*)-stereoselectively in high yields under the same reaction condition. (*Z*)-Isomers of enediynes **6f–j** were used after isolation by column chromatography, but the separation of (*Z*)-isomer of **6a** was not successful. We assigned *E* and *Z* isomers of **6a–i** by the comparison of chemical shift of (*Z*)-1-phenyl-4-phenylethynyl-3-trifluoromethyl-oct-3-en-1-yne in ^{19}F NMR spectroscopy, in which signal appeared at −61.1 ppm.[17] Since the chemical shift of one isomer of **6a** in the ^{19}F NMR spectra is −61.08 ppm, this isomer should be (*Z*)-isomer and thus a signal at −57.01 ppm will be (*E*)-isomer. The use of ether as a solvent in the reactions of **3a–d** with trimethylsilyl or triisopropylsilyl substituted ethynyllithium reagent provided a better result than did the use of THF. The results of these reactions are summarized in Table 1. (*Z*)-Stereoselectivity in these reactions can be rationalized by the formation of stable carbanion intermediates followed by the elimination of sulfonyl group. The conformational intermediates [A] and [B] could be formed from top and bottom attack of the substituted ethynyllithium on (*Z*)-**3**, respectively. Rotation of these two intermediates by 60° would result in two reasonably stable conformational intermediates [C] and [D], which quickly undergo the elimination of the sulfonyl group to give (*Z*)-**6** in a high stereoselectiviy. The other isomer, (*E*)-**3** could provide (*E*)-**6** in a high stereoselectively in a similar manner. However, the reaction of **3b** with ethynyllithium reagents showed relatively less stereoselectivity because of presumably steric effect of flexible hexyl group.

Vinyl sulfones **5a–b** are very reactive species to react with phenyl, *n*-hexyl or trimethylsilyl ethynyllithium reagents to give the corresponding enediynes **6a**, **6e**, **6g**, and **6j–m** in 41–90% yields whose results are summarized in Table 2. (*Z*)-Stereoselectivity in these reactions was decreased dramatically as compared to the reaction as shown in Table 1. This low stereoselectivity can be explained by the reaction process involving a different intermediate. We actually examined the reaction of **5a** with 2.5 equiv of phenylethynyllithium at 0 °C, in which **3a**, **3e**, and **6a** were obtained as a mixture. This result indicated that the reaction of **5a** with ethynyllithium did not proceed only via intermediate **3a**. In other words, **6a** was also obtained via intermediate **3e**.

We carried out the palladium-catalyzed cross-coupling reaction of **6c**, **6f**, and **6g** with aryl iodides to introduce an aromatic group at the trimethylsilyl (TMS) site.[21]

Table 1. Preparation of trifluoromethylated enediynes **6** from trifluoromethylated enynyl sulfones **3**



3 **6**

Compound	R	R^1	X	Solvent	*t*	Yield[a] (%)	*E*/*Z*[b]
6a	Ph	Ph	2	THF	1	87	9/91
6b	Ph	n-$\mathrm{C_6H_{13}}$	2	THF	1	96	9/91
6c	Ph	TMS	3	Ether	2	92	7/93
6d	n-$\mathrm{C_6H_{13}}$	Ph	4	THF	1	68	18/82
6e	n-$\mathrm{C_6H_{13}}$	n-$\mathrm{C_6H_{13}}$	4	THF	1	64	25/75
6f	n-$\mathrm{C_6H_{13}}$	TMS	4	Ether	2	41	7/93
6g	TMS	TMS	3	Ether	2	82	35/65
6h	TMS	TIPS	3	Ether	2	84	35/65
6i	TIPS	TMS	3	Ether	2	73	37/63

[a] Isolated yield.

[b] *E*/*Z* ratio was determined by ^{19}F NMR spectrum.

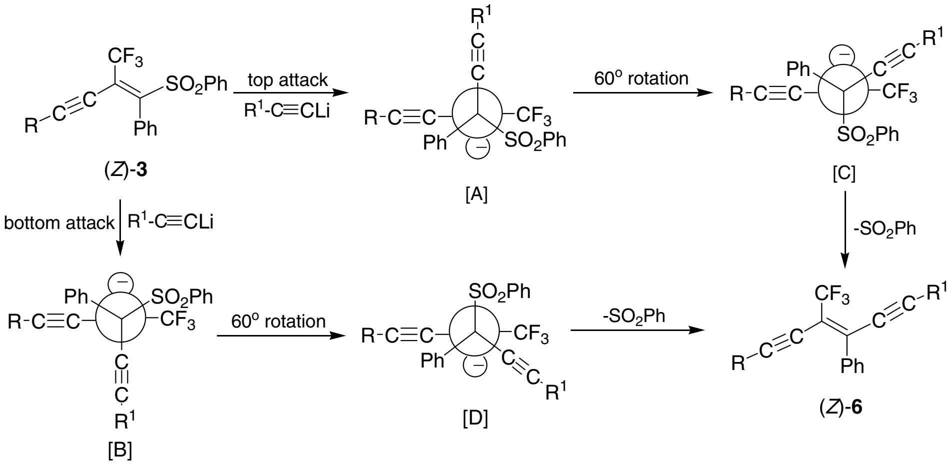
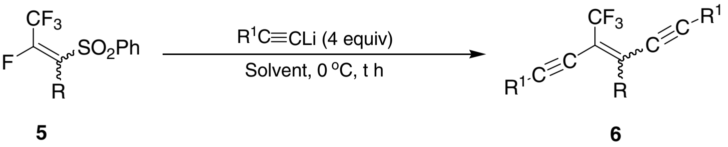


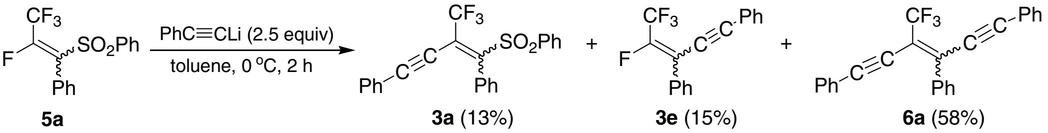
Table 2. Preparation of trifluoromethylated enediynes **6** from trifluoromethylated vinyl sulfones **5**



Compound	R	R^1	Solvent	*t*	Yield[a] (%)	*E*/*Z*[b]
6a	Ph	Ph	Toluene	2	72	37/63
6e	Ph	*n*-C_6H_{13}	Toluene	1	66	42/58
6g	Ph	TMS	Ether	2	90	42/58
6j	Ph	TIPS	Ether	2	69	37/63
6k	Me	Ph	Toluene	4	64	64/36
6l	Me	*n*-C_6H_{13}	Toluene	4	41	66/34
6m	Me	TMS	Ether	4	84	64/36

[a] Isolated yield.

[b] *E*/*Z* ratio was determined by ^{19}F NMR spectrum.



When **6c** ($E/Z = 9/91$) was treated with phenyl iodide in the presence of $Pd(PPh_3)_2Cl_2$ (10 mol %), Ag_2CO_3 (0.5 equiv) and *n*-Bu_4NBr (1.0 equiv) in toluene at room temperature for 12 h, the cross-coupled product **6a** ($E/Z = 9/91$) was formed in 55% yield along with a large amount of self-coupled product (36%). The use of other Pd catalysts such as $Pd(PPh_3)_4$ and $Pd(OAc)_2$ and other bases such as K_2CO_3, Ce_2CO_3, and KF did not improve the yield of **6a**. Toluene is the best solvent in this reaction among THF, DMF, $CHCl_3$, CH_2Cl_2, CH_3CN, and benzene. The cross-coupling reaction of **6c** with various phenyl iodides bearing methoxy, methyl, fluoro, chloro, bromo, trifluoromethyl, and nitro on *para* position under the same reaction condition afforded the cross-coupled products **6n–t** in 20–71% yields. Similar experiments were performed with (*Z*)-**6f** and the cross-coupled products (*Z*)-**6d** and (*Z*)-**6u–v** were obtained in 40–46% yields. The results of the cross-coupling reaction are summarized in Table 3. Double cross-coupling reaction of (*Z*)-**6g** under the same reaction condition also yielded the corresponding enediynes (*Z*)-**6a** and (*Z*)-**6w–x** in low yields.

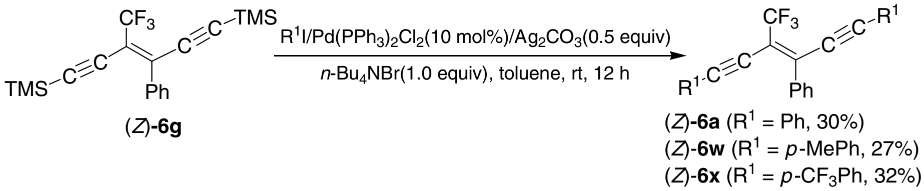
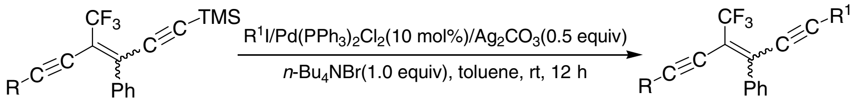


Table 3. The cross-coupling reaction of **6c** and **6f** with aryl iodides in the presence of the Pd catalyst



6c, **6f** → **6**

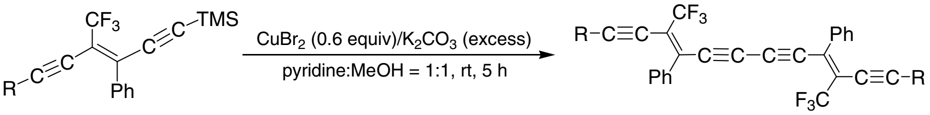
Compound	R	R^1	Yield[a] (%)	E/Z[b]
6a	Ph	Ph	55	9/91
6n	Ph	*p*-MeOPh	20	9/91
6o	Ph	*p*-MePh	44	10/90
6p	Ph	*p*-FPh	41	10/90
6q	Ph	*p*-ClPh	51	9/91
6r	Ph	*p*-BrPh	50	10/90
6s	Ph	*p*-CF_3Ph	71	8/92
6t	Ph	*p*-NO_2Ph	45	10/90
6d	*n*-C_6H_{13}	Ph	55	0/100[c]
6u	*n*-C_6H_{13}	*p*-MePh	40	0/100[c]
6v	*n*-C_6H_{13}	*p*-CF_3Ph	46	0/100[c]

[a] Isolated yield.

[b] E/Z ratio was determined by ^{19}F NMR spectrum.

[c] (Z)-Isomer of **6f** was used.

Dimerization reaction of (Z)-**6f** and (Z)-**6i** was performed in the presence of $CuBr_2$ and K_2CO_3 in a 1:1 ratio of pyridine and methanol, and thus oligoenediyne dimers **7a** and **7b**[22] were obtained in 78% and 77% isolated yields, respectively.



(Z)-**6f** (R = *n*-C_6H_{13})
(Z)-**6i** (R = TIPS)

7a (R = *n*-C_6H_{13}, 78%)
7b (R = TIPS, 77%)

A typical reaction procedure for the preparation of **6i** is as follows. A 25 mL two-neck round bottomed flask equipped with a magnetic stirrer bar, a septum and nitrogen tee connected to an argon source was charged with (trimethylsilyl) acetylene (0.304 g, 3.1 mmol) and 4 mL ether. Methyllithium (1.6 M solution, 1.9 mL, 3.0 mmol) was added into the mixture at 0 °C. After stirring the reaction mixture at 0 °C for 30 min, ether solution of enynyl sulfone **3d** (0.492 g, 1.0 mmol) was added to the mixture at 0 °C and then the mixture was stirred at 0 °C for 2 h. The reaction mixture was extracted with diethyl ether twice and then the diethyl ether solution was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on SiO_2 column. Elution with *n*-hexane provided 0.327 g of **6i** ($E/Z = 37/63$) in 73% yield. **6i**: yellow oil: ^1H NMR ($CDCl_3$) δ 7.83–7.26 (m, 10H, E and Z-isomer), 1.14 (m, 21H, E-isomer), 1.00 (m, 21H, Z-isomer), 0.22 (s, 9H, Z-isomer), 0.15 (s, 9H, E-isomer): ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ -57.36 (s, 3F, E-isomer), -61.41 (s, 3F, Z-isomer); MS, m/z (relative intensity) 448 (M^+, 12), 405 (100), 289 (15), 223 (11), 203 (16), 189 (21), 175 (11), 165 (12), 127 (21), 77 (35), 73 (14); IR (neat) 3060, 2945, 2894, 2867, 2139, 1557, 1492, 1463, 1446, 1385, 1367, 1329, 1251, 1194, 1075, 1041, 1020, 998, 894, 770, 760, 697 cm^{-1}. Anal. Calcd for $C_{25}H_{35}F_3Si_2$: C, 66.92; H, 7.86. Found: C, 66.79; H, 7.77.

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22. Spectroscopic data of **7b**: mp 114–116 °C: ^{1}H NMR ($CDCl_3$) δ 7.76–7.26 (m, 10H), 1.06 (s, 6H), 0.99 (s, 36H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −61.67 (s, 6F); MS, *m/z* (relative intensity) 750 (M^+, 100), 707 (28), 531 (37), 362 (6), 157 (14), 127 (41), 77 (53); IR (KBr) 3060, 2945, 2892, 2867, 2124, 1733, 1548, 1493, 1463, 1364, 1330, 1255, 1183, 1118, 1062, 997, 882, 849, 764, 692 cm^{-1}. Anal. Calcd for $C_{44}H_{52}F_6Si_2$: C, 70.37; H, 6.98. Found: C, 70.18; H, 6.88.