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Synthesis of 2-Phenylated 1,1-difluoro-1,3-enynes *via* Alkynylation of β,β-Difluoro-α-phenylvinylstannane

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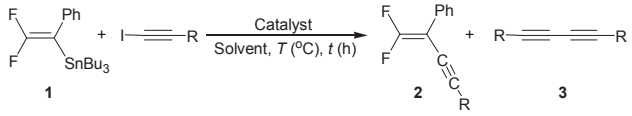
1,3-Enynes represent a class of important synthetic intermediates and have been utilized as essential components in the synthesis of multifunctional molecules[1-5] and natural products.[6-8] Of particular interests in 1,3-enynes are fluorine-containing conjugated enynes which would be important building blocks for the synthesis of fluorinated compounds having unique biological and physical properties.[9-12] Although various methods for the preparation of nonfluorinated 1,3-enynes have been well documented in the previous literature,[13] there are only limited reports on the synthesis of fluorinated 1,3-enynes and most of them covered the synthesis of 1,2-difluorinated[14-15] or monofluorinated 1,3-enynes.[16-22] Moreover, only three examples on the synthesis of 1,1-difluoro-1,3-enyne derivatives having high reactivity toward nucleophiles were reported. Burton *et al*. prepared 1,1-difluoro-2-phenyl-1,3-enynes in low yield as a mixture *via* the hydrolysis of the trifluoromethylated allenic phosphonium salt.[23] Direct coupling reactions of 1,1-difluorovinyl iodides with alkynylzinc chloride in the presence of Pd catalysis afforded the 1,1-difluoro-1,3-enynes in moderate yields.[24] Ichikawa *et al*. synthesized 2-alkylated 1,1-difluoro-1,3-enynes in good yields *via* the coupling reaction of 1-alkyl-2,2-difluorovinylboranes, formed from the reaction of 2,2,2-trifluoroethyl *p*-toluenesulfonate with *n*-butyllithium and trialkylboranes, with 1-halo-1-alkynes in the presence of cuprous iodides.[25] However, the previous methods have some drawbacks such as low yield preparation, the use of unisolable vinylmetal reagents and lack of generality. Herein, we wish to report first preparation of 2-phenylated 1,1-difluoro-1,3-enynes *via* the direct coupling reaction of the thermostable and isolable β,β-difluoro-α-phenylvinylstannane with alkynyl iodides in the presence of Pd catalysis.

In the course our studies on the coupling reaction of **1**,[26] we examined the reactivity of carbon-carbon bond formation between **1** and alkynyl iodides to afford 1,1-difluoro-2-phenyl-1,3-enynes. The results of the coupling reaction between **1** and 1-iodo-1-octyne or phenylethynyl iodide were summarized in Table 1. When **1** was treated with 1-iodo-1-octyne in refluxing THF for 1.5 hours in the presence of $Pd(PPh_3)_4$ (10 mol %) and CuI (10 mol %), unreacted starting material **1** was recovered and only homocoupled diynes **3** of 1-iodo-1-octyne was obtained in 76% yield based on the conversion of starting material. The use of toluene as a solvent under the same reaction condition resulted in the similar result. When the same reaction was performed in DMF at 80 °C for 1.5 hours, however, the desired enyne **2b** was obtained in 80% yield without diyne **3** (Table 1, entry 3). The longer reaction time or different reaction temperature decreased the yield of **2b**. The use of only CuI (10 mol %) as a catalyst in this reaction resulted in the formation of only 2,2-difluoro-1-phenylethenyl iodide **4** as a major product, whereas the use of only $Pd(PPh_3)_4$ (10 mol %) as a catalyst caused the homocoupling reaction of 1-iodo-1-octyne to give diyne **3**. The reaction of **1** with phenylethynyl iodide under the optimized reaction condition provided the corresponding enyne **2f** in only 44% yield (Table 1, entry 9). When the same reaction was performed at 50 °C, the desired product **2f** was obtained in increased yield (65%). However, the reaction at room temperature afforded the homocoupled product **3** in 66% yield along with **4**.

The reactions with different alkynes such as 1-iodo-1-pentyne, 1-iodo-1-nonyne, 1-iodo-1-decyne, and 1-iodo-3-*t*-butyldimethylsiloxyl-1-propyne in DMF at 80 °C for 0.5 - 1.5 hours in the presence of $Pd(PPh_3)_4$ (10 mol %) and CuI (10 mol %) gave the corresponding 1,3-enynes **2a**, **2c-2e** in 45 - 80% yields. When 1-iodo-2-phenylethyne was used as an coupling partner under the same reaction condition except for reaction temperature such as 50 °C, the corresponding 1,3-enyne **2f** was obtained in 65% yield. The reaction with 1-iodo-2-phenylethyne having substituent such as fluoro, methyl, methoxy, trifluoromethyl and chloro at meta or para position of the benzene ring provid-

Table 1. Coupling reaction of **1** with 1-iodo-1-octyne or phenylethynyl iodide at the different reaction conditions

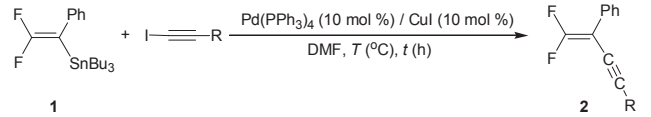


1 2 3

Entry	R	Catalyst[a]	Solvent	T (°C)	t (h)	Yield[b] (%)	
						2	**3**
1	C_6H_{13}	$Pd(PPh_3)_4$/CuI	THF	reflux	1.5	0	76
2	C_6H_{13}	$Pd(PPh_3)_4$/CuI	Toluene	reflux	1.5	0	68
3	C_6H_{13}	$Pd(PPh_3)_4$/CuI	DMF	80	1.5	80	0
4	C_6H_{13}	$Pd(PPh_3)_4$/CuI	DMF	80	4	55	0
5	C_6H_{13}	$Pd(PPh_3)_4$/CuI	DMF	25	4	0	78
6	C_6H_{13}	$Pd(PPh_3)_4$/CuI	DMF	100	1.5	48	0
7	C_6H_{13}	$Pd(PPh_3)_4$	DMF	80	1.5	0	81
8	C_6H_{13}	CuI[c]	DMF	80	1.5	0	0
9	C_6H_5	$Pd(PPh_3)_4$/CuI	DMF	80	2	44	0
10	C_6H_5	$Pd(PPh_3)_4$/CuI	DMF	50	2	65	0
11	C_6H_5	$Pd(PPh_3)_4$/CuI	DMF	25	4	0	66

[a]10 mol % of catalyst was used. [b]Isolated yield. [c]2,2-Difluoro-1-phenylethenyl iodide was obtained as a major product.

Table 2. Preparation of 1,1-difluoro-2-phenyl-1,3-enynes **2** *via* the coupling reactions of **1** with 1-iodo-1-alkynes



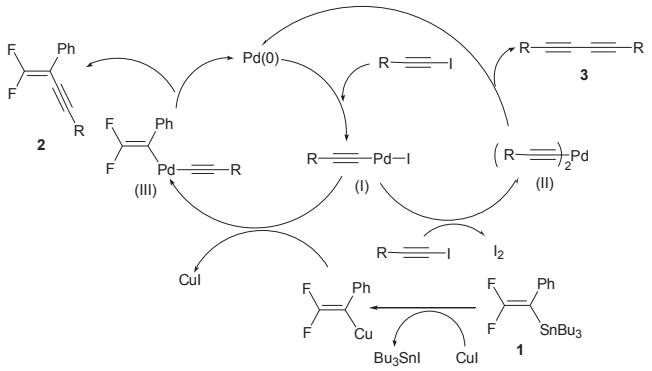
Compound	R	T (°C)	t (h)	Yield[a] (%)
2a	n-C_5H_{11}	80	1.5	80
2b	n-C_6H_{13}	80	1.5	80
2c	n-C_7H_{15}	80	1.5	75
2d	n-C_8H_{17}	80	1.5	78
2e	$CH_2OTBDMS$	80	0.5	45
2f	C_6H_5	50	2.0	65
2g	p-FC_6H_4	50	1.5	67
2h	p-ClC_6H_4	50	1.5	64
2i	p-$CH_3C_6H_4$	50	1.0	53
2j	p-$CH_3OC_6H_4$	50	1.5	55
2k	m-FC_6H_4	50	1.0	40
2l	3,5-$(CF_3)_2C_6H_3$	50	1.0	67
2m	TMS	50	1.0	48
2n	3-SC_4H_3	50	0.5	59

[a]Isolated yield.

ed the corresponding 1,3-enynes **2g-2l** in 40 - 67% yields. The reaction of **1** with 1-iodo-2-trimethysilylethyne and 1-iodo-2-(3-thiophenyl)ethyne under the same reaction condition afforded the corresponding 1,3-enynes **2m** and **2n** in 48% and 59% yields, respectively. The results of these reactions are summarized in Table 2.

Although the reaction mechanism of coupling reaction of **1** with 1-iodoalkyne is not clear, we assume that oxidative addition intermediate (I) reacts with β,β-difluoro-α-phenylvinylcopper, generated from the reaction of **1** with CuI, to give an intermediate (III) which undergoes reductive elimination to produce the 1,3-enynes **2** (Scheme 1). In the cases of the reactions of **1** with alkyl-substituted ethynyl iodides, a mechanism in Scheme 1 would be favored at 80 °C, but room temperature reaction provided the 1,3-diynes **3** *via* the formation of dialkynylpalladium intermediate (II) followed by reductive elimination. Aryl-substituted ethynyl iodides underwent the coupling reaction smoothly at 50 °C to give the 1,3-enynes **2** in maximum yields, whereas the higher reaction temperature than 50 °C caused to reduce the yield of **2**. Room temperature reaction of **1** with aryl-substituted ethynyl iodides yielded the 1,3-diynes **3** in high yields,[27] which indicates the formation of dialkynylpalladium intermediate (II) would be faster than that of intermediate (III).

A typical reaction procedure for the preparation of **2a** is as follows. To a DMF (5 mL) solution of β,β-difluoro-α-phenylvinylstannane (0.100 g, 0.230 mmol) and 1-iodo-1-heptyne (0.063 g, 0.270 mmol) was added $Pd(PPh_3)_4$ (0.023 mmol) and CuI (0.023 mmol), and the reaction mixture was heated at 80 °C for 1.5 hours. After the reaction mixture was quenched with water, the solution was extracted with ether (15 mL × 2). The ether solution was dried and chromatographed on SiO_2 column. Elution with n-hexane and EtOAc (20 : 1) provided 0.043 g of **2a** in 80% yield. **2a**: oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.53 (m, 2H), 7.38-7.34 (m, 2H), 7.30-7.26 (m, 1H), 2.42-2.38 (m, 2H), 2.24 (t, J = 7.3 Hz, 2H), 0.94-0.88 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (dd, J = 298 Hz), 128.9, 128.4, 127.7, 127.6, 95.7 (t, J = 6 Hz), 31.0, 28.1, 22.2, 19.3, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$, internal standard $CFCl_3$) δ −77.90 (d, J = 9.4 Hz, 1F), −82.01 (d, J = 9.4 Hz, 1F); MS, m/z (relative intensity) 234 (M^+, 68); Anal. Calcd for $C_{15}H_{16}F_2$: C, 76.90; H, 6.88. Found: C, 76.68; H, 6.85.



Scheme 1. A plausible mechanism for the formation of **2** and **3**

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