

Cross-coupling Reaction of β,β -Difluoro- α -phenylvinylstannane with Alkenyl Iodides: Novel Approach to 2-Phenyl-1,1-difluoro-1,3-butadienes

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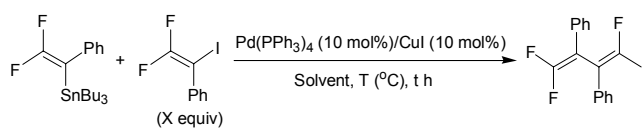
Key Words: Cross-coupling reaction, β,β -Difluoro- α -phenylvinylstannane, Alkenyl iodides, 2-Phenyl-1,1-difluoro-1,3-butadienes

1,3-Butadienes have received much attention because they are valuable synthetic intermediates for the formation of carbocyclic and multifunctionalized system in organic synthesis.¹ Especially, 1,1-difluoro-1,3-butadienes are useful building blocks for the introduction of difluoromethylene (CF_2) and monofluoromethylene (CFH) unit into organic molecules.²⁻⁵ However, there are only limited reports on the synthesis of 1,1-difluorinated 1,3-butadienes which were prepared mainly *via* the β -defluorination, dehalogenation and Wittig reactions. Huang *et al.* prepared 1,1-difluoro-2-siloxy-1,3-butadiene from the reaction of trifluoroacetyltriphenylsilane with vinylmagnesium bromide followed by a sequence Brook rearrangement of triphenylsilyl group and β -defluorination.⁶ Mg(0)-Promoted selective C-F bond cleavage of trifluoromethyl enones afforded 1-methoxy-4,4-difluoro-3-(trimethylsiloxy)-1,3-butadienes.⁵ Double dehydrobromination of 1,3-dibromo-1,1-difluoro compounds with DBU afforded 1,1-difluoro-1,3-butadienes.⁷ We also reported the preparation of 2,3-disubstituted 1,1-difluoro-1,3-butadienes *via* 1,4-debromofluorination reaction.^{8,9} Wittig reaction of 3,3-difluoroallyltriphenylphosphonium bromide with aldehydes also gave 1,1-difluoro-1,3-butadienes.¹⁰ 1,1-Difluoro-4,4-bis(dimethylamino)-1,3-butadienes were synthesized from the treatment of 1,1-difluoro-4,4-bis(dimethylamino)ethane with ethyl propiolate.¹¹ However, we are interested in the straightforward method for the synthesis of 1,1-difluoro-1,3-butadienes from the cross-coupling reaction of 2,2-difluoroalkenylmetal reagent with alkenyl halides, which should be a simple and efficient method. Palladium-catalyzed cross-coupling reactions of 1,1-difluorohomoallyl bromide with aryl bromides and iodides and aryl boronic acids provided the corresponding 1,1-difluoro-1,3-butadienes.¹² Ichikawa *et al.* prepared 1,1-difluoro-1,3-butadienes from the reaction of 2,2-difluorovinylboranes with 1-alkenyl halides in the presence of copper(I) iodide and a palladium catalyst.¹³ The use of 2,2-difluorovinylzinc reagent¹⁴ as a coupling partner also gave the 1,1-difluoro-1,3-butadienes. Recently, Burton *et al.* reported that 1,1-difluoro-1,3-butadienes were prepared from the Sonogashira type of coupling reactions of α -bromo- β,β -difluorostyrenes with vinylboronic acid in the presence of Pd catalyst.¹⁵ However, the previous methods have main drawbacks such as the use of unisolable vinylmetal reagents in solution, moisture sensitivity and lack of generality. Herein, we wish to report first preparation of 1,1-difluoro-2-phenyl-1,3-butadienes *via* the direct coupling reaction of the thermostable and isolable β,β -

difluoro- α -phenylvinylstannane with alkenyl iodides in the presence of Pd and CuI catalyst.

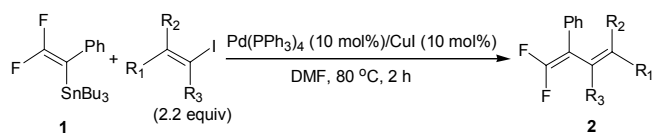
Recently, we reported a novel method for the synthesis of β,β -difluoro- α -phenylvinylstannane **1** and its coupling reaction with aryl iodides in the presence of catalyst to give 2,2-diaryl-1,1-difluoroethenes.¹⁶ In the course our studies on the coupling reaction of **1**, we examined the reactivity of carbon-carbon bond formation between **1** and alkenyl halides to afford 2-phenyl-1,1-difluoro-1,3-butadienes (Table 1). When **1** was treated with 1.1 equiv of 1,1-difluoro-2-iodo-2-phenylethene in refluxing THF for 4 hours in the presence of Pd(PPh₃)₄ (10 mol%) and CuI (10 mol%), unreacted starting material **1** was recovered (entry 1). When the same reaction was performed in DMF at 80 °C for 2 hours, however, the desired diene **2a** was obtained in 38% yield (entry 2). The use of 2.2 equiv of 1,1-difluoro-2-iodo-2-phenylethene under the same reaction condition resulted in the formation of the desired product **2a** in 73% yield (entry 4). The same reaction was performed at 50 °C for 5 hours, but no reaction occurred. The reaction at 100 °C resulted in the decomposition of all reagents and no desired product was obtained. Increase of equivalence of 1,1-difluoro-2-iodo-2-phenylethene caused to decrease the formation of product **2a** dramatically. We also tried the reaction between **1** and 2-bromo-1,1-difluoro-2-phenylethene under the optimized reaction con-

Table 1. Optimization for the coupling reaction between **1** and 1,1-difluoro-2-iodo-2-phenylethene

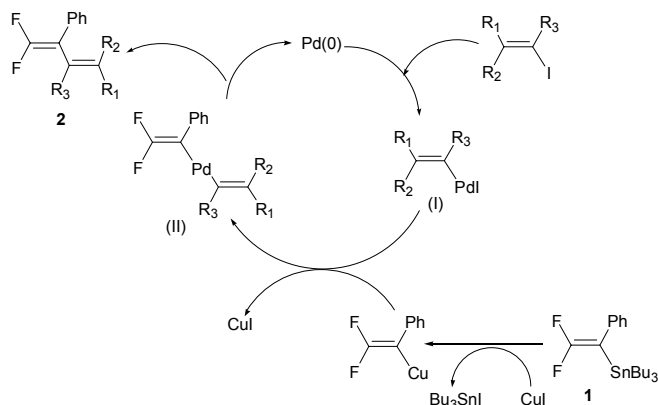


Entry	X (equiv)	Solvent	T (°C)	t (hours)	Yield (%) ^a
1	1.1	THF	reflux	4	0
2	1.1	DMF	80	2	38
3	2.2	THF	reflux	4	0
4	2.2	DMF	80	2	73
5	2.2	DMF	100	1	- ^b
6	2.2	DMF	50	5	0
7	3.0	DMF	80	1	55
8	4.0	DMF	80	1	15
9	6.0	DMF	80	1	< 5

^aIsolated yield. ^bAll reagents were decomposed.

Table 2. Preparation of fluorinated 1,3-dienes **2** via the coupling reactions of **1** with various types of alkenyl iodides


Entry	R ₁	R ₂	R ₃	Yield (%) ^a
1	F	F	C ₆ H ₅	2a (73)
2	F	F	F	2b (77)
3	C ₆ H ₅	F	F	2c (71)
4	F	C ₄ H ₉	F	2d (68)
5	C ₆ H ₅	H	F	2e (78)
6	C ₆ H ₅	CH ₃	F	2f (70)
7	CF ₃	C ₆ H ₅	C ₆ H ₅	2g (54)
8	C ₆ H ₅	CF ₃	C ₆ H ₅	2h (45)
9	CF ₃	F	C ₆ H ₅	2i (21)
10	C ₆ H ₅	H	H	2j (82)
11	C ₃ H ₇	H	H	2k (75)

^aIsolated yield.**Scheme 1.** A proposed mechanism for the coupling reactions of **1** with alkenyl iodides

dition, but the desired product **2a** was obtained in 27% yield.

The reactions of **1** with a various types of alkenyl iodides in DMF at 80 °C for 2 hours in the presence of Pd(PPh₃)₄ (10 mol%) and CuI (10 mol%) gave the corresponding 1,3-butadienes **2b-2k** in 21 - 82% yields (Table 2). It seems likely that the coupling reaction was not influenced by the steric effect of substituent attached to reactive vinyl carbon site (entry 1). On the other hand, electronic and steric effect caused by trifluoromethyl group (CF₃) at β-vinyl carbon was a main factor for the decrease of yield of the coupling products **2** (entry 7-9) Alkenyl iodides having proton, fluoro, phenyl and alkyl substituent at α or β position of reactive vinyl carbon afforded the corresponding 1,3-butadienes **2** in high yields (entry 2-6, 10, 11).

Although the reaction mechanism of coupling reaction of **1** with alkenyl iodides is not clear, we assume that intermediate (I) formed by oxidative addition of alkenyl iodides with Pd(PPh₃)₄ reacts with β,β-difluoro-α-phenylvinylcopper, generated from the reaction of **1** with CuI, to give an intermediate (II) which undergoes reductive elimination to produce the 1,3-butadienes **2** (Scheme 1). Although role of CuI in the

coupling reaction is obscure, it was suggested that copper iodide facilitates the transmetalation step in the cross-coupling mechanism cycle and thus speeds the cross-coupling in the presence of Pd catalyst.¹⁷ One experimental result showed that the decomposition of **1** was observed from the reaction of **1** with the same equivalent of CuI only, which indicates that vinylcopper reagent was formed.

A typical reaction procedure for the preparation of **2a** is as follows. A 15 mL two-neck round bottom flask equipped with a reflux condenser, a magnetic stirrer bar, a septum and argon tee connected to an argon source was charged with β,β-difluoro-α-phenylvinylstannane (0.100 g, 0.230 mmol), 1,1-difluoro-2-iodo-2-phenylethene (0.136 g, 0.510 mmol) and 5 mL DMF. After Pd(PPh₃)₄ (0.023 mmol) and CuI (0.023 mmol) were added, the mixture was heated at 80 °C for 2 hours and then quenched with water. The reaction mixture was extracted with diethyl ether (30 mL × 2). The diethyl ether solution was dried with anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. Elution with *n*-hexane and EtOAc (20 : 1) provided 0.047 g of **2a** in 73% yield. **2a**: oil: ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.30 (m, 4H), 7.28-7.20 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 154.7 (t, *J* = 294.8 Hz), 129.6, 128.6, 128.4, 127.7, 127.5, 88.5 (dd, *J* = 20.6, 15.5 Hz); ¹⁹F NMR (376 MHz, CDCl₃, internal standard CFCl₃) δ -82.45 (d, 2F, *J* = 24.8 Hz), -86.36 (d, 2F, *J* = 24.8 Hz); MS *m/z* (relative intensity) 278 (M⁺, 100), 258 (40), 238 (42), 227 (33), 209 (30), 178 (16), 151 (37), 127 (80), 119 (28); Anal. Calcd for C₁₆H₁₀F₄: C, 69.07; H, 3.62. Found: C, 68.94; H, 3.60.

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References

- Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990.
- Matsuo, N.; Kende, A. S. *J. Org. Chem.* **1988**, *53*, 2304-2308.
- Jin, F.; Xu, Y.; Huang, W. *J. Chem. Soc. Chem. Commun.* **1993**, 814-816.
- Jin, F.; Xu, Y.; Huang, W. *J. Fluorine Chem.* **1995**, *71*, 1-4.
- Amii, H.; Kobayashi, T.; Terasawa, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 3103-3105.
- Jin, F.; Xu, Y.; Huang, W. *J. Chem. Soc. Perkin Trans. 1* **1993**, 795-800.
- Elsheimer, S.; Foti, C. J.; Bartberger, M. D. *J. Org. Chem.* **1996**, *61*, 6252-6255.
- Jeong, I. H.; Park, Y. S.; Chung, M. W.; Kim, B. T. *Synth. Commun.* **2001**, *31*, 2261-2270.
- Son, J. B.; Cho, J. A.; Choi, J. H.; Jeong, I. H. *Bull Korean Chem. Soc.* **2008**, *29*, 31-32.
- Qiu, W.; Burton, D. J. *J. Fluorine Chem.* **1993**, *65*, 143-147.
- Xu, Y.; Tian, F.; Dolbier, W. R., Jr. *J. Org. Chem.* **1999**, *64*, 5599-5602.
- Shen, Q.; Hammond, G. B. *Org. Lett.* **2001**, *3*, 2213-2215.
- Ichikawa, J.; Ikeura, C.; Minami, T. *Synlett* **1992**, 739-740.
- Tellier, F.; Sauvetre, R.; Normant, J.-F. *J. Organomet. Chem.* **1986**, *303*, 309-315.
- Raghavanpillai, A.; Burton, D. J. *J. Org. Chem.* **2006**, *71*, 194-201.
- Choi, J. H.; Jeong, I. H. *Tetrahedron Lett.* **2008**, *49*, 952-955.
- Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L. *J. Am. Chem. Soc.* **1988**, *110*, 2641-2643.