ORGANIC LETTERS

2010
Vol. 12, No. 23
5518−5521

Efficient Synthesis of 2,2-Diaryl-1,1-difluoroethenes via Consecutive Cross-Coupling Reactions of 2,2-Difluoro-1-tributylstannylethenyl *p*-Toluenesulfonate

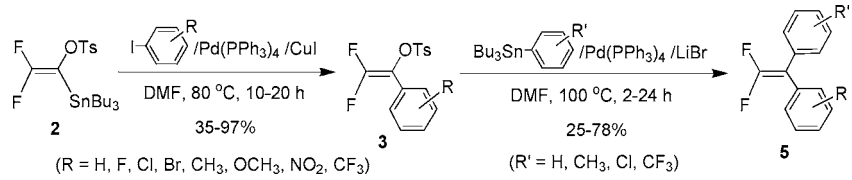
Seung Yeon Han and In Howa Jeong*

Department of Chemistry and Medical Chemistry, Yonsei University, Wonju 220-710, Korea

jeongih@yonsei.ac.kr

Received October 5, 2010

ABSTRACT



2,2-Difluoro-1-tributylstannylethenyl *p*-toluenesulfonate (2) was reacted with aryl iodides in the presence of 10 mol % of $Pd(PPh_3)_4$ and 10 mol % of CuI in DMF at 80 °C for 10−20 h to give the cross-coupled products 3 in 35−97% yields. Further coupling reaction of 3 with arylstannanes in the presence of 5 mol % of $Pd(PPh_3)_4$ and 3 equiv of LiBr in DMF at 100 °C for 2−24 h afforded the desired products 5 in 25−78% yields.

The synthesis of 1,1-difluoroolefins is an important aspect of organofluorine chemistry since they exhibit chemical reactivities toward nucleophiles[1] and can be utilized as valuable intermediates for the synthesis of fluorinated organic molecules via an addition−elimination reaction.[2] They are also known to act as a bioisostere for the carbonyl group,[3] and they are important to many biologically active compounds such as mechanism-based enzyme inhibitors.[1a,4] Despite their important applications, approaches for the synthesis of 2,2-diaryl-1,1-difluoroethenes among 1,1-difluoroolefins have been quite limited in the previous literature[5] since the Wittig methodology was not suitable for the synthesis of 2,2-diaryl-1,1-difluoroethenes due to the poor reactivity of the diaryl ketones toward the difluoromethylene ylide, and unsymmetrical diaryl ketones are not readily

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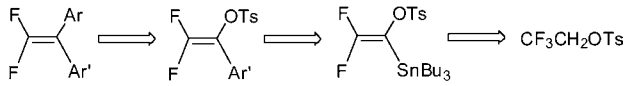
10.1021/ol1024037
Published on Web 11/02/2010

available.[6] The organometallic approaches for the synthesis of various 1,1-difluoroalkenes also cannot be utilized to prepare 2,2-diaryl-1,1-difluoroalkenes. Specific 1,1-difluoro-2,2-diphenylethene was prepared from the modified Wittig reactions of diphenyl ketone with (diethylphosphinyl)-difluoromethyllithium[5a] or difluoromethyl diphenylphosphine oxide.[5b] Nowak and Robins also prepared 1,1-difluoro-2,2-diphenylethene from the reaction of diphenyl ketone with difluoromethylene ylide generated in situ by heating $(CF_3)_2Hg$ and NaI with triphenylphosphine.[5c] Burton et al. reported a general and efficient method for the synthesis of 2,2-diaryl-1,1-difluoroethenes, in which α-aryl-α-halo-*β*,*β*-difluorostyrenes synthesized by the coupling reaction of the corresponding α-halo-*β*,*β*-difluoroethenylzinc reagents with aryl iodides were functionalized at the halogen site via Suzuki−Miyaura coupling reactions.[5d] Recently, we prepared *β*,*β*-difluoro-α-phenylvinylstannane that was functionalized to give 2,2-diaryl-1,1-difluoroethenes via Pd(0)/CuI-catalyzed coupling reaction with aryl iodides.[5e] However, the previous methods have some drawbacks such as lack of generality,[5a−c] tedious procedure,[5a,b,e] the use of expensive starting material,[5d,e] and moisture-sensitive vinylmetal reagents.[5a,b,d] Herein, we report a concise and efficient method for 2,2-diaryl-1,1-difluorethenes via a consecutive cross-coupling reaction of 2,2-difluoro-1-tributylstannylethenyl *p*-toluenesulfonate.

2,2-Difluoro-1-tributylstannylethenyl *p*-toluenesulfonate could be a remarkable precursor of 2,2-diaryl-1,1-difluoroethenes because it has two functionally different coupling partners at the same position such as the nucleophilic tributylstannyl and electrophilic tosylate groups. The retrosynthetic pathway for 2,2-diaryl-1,1-difluoroethenes is outlined in Scheme 1.

Scheme 1

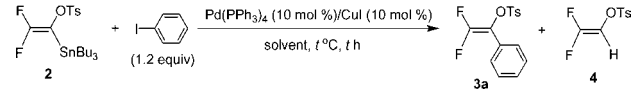


Surprisingly, given the extensive use of 2,2-difluoroethenylstannane having a carbamate[7] or OMEM group[8] at the α-position, there was no report of a synthesis of 2,2-difluoro-1-tributylstannylethenyl *p*-toluenesulfonate in the previous literature.

2,2-Difluoro-1-tributylstannylethenyl *p*-toluenesulfonate (**2**) was easily prepared in 90% yield from the reaction of 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**) with 2 equiv of LDA in THF at −78 °C, followed by treatment with tributylstannyl chloride. Then, we attempted the palladium-catalyzed cross-coupling reaction of **2** with aryl iodides to introduce an aromatic group at the stannane site.

When **2** was reacted with iodobenzene in the presence of 10 mol % of $Pd(PPh_3)_4$ and 10 mol % of CuI in THF at reflux temperature for 10 h, the cross-coupled product **3a** was obtained in 56% yield along with the reducing product **4** in 24% yield. The longer reaction time (24 h) promoted the yield of **3a** up to 70%. After monitoring of the reaction under the different solvents and reaction temperature and time (Table 1), we found that the use of DMF at 80 °C for

Table 1. Optimization Reaction of **2** with Iodobenzene



				yield (%)[a]	
entry	solvent	*t* (°C)	*t* (h)	**3a**	**4**
1[b]	THF	reflux	10	56	24
2	DMF	50	10	43	45
3	DMF	80	3	70	20
4	DMF	80	5	79	10
5	DMF	80	10	94	0
6[c]	DMF	80	10	40	50

[a] Isolated yield. [b] Starting material (10%) was recovered. [c] Only $Pd(PPh_3)_4$ was used.

10 h provided **3a** in 94% yield without any detected **4** (entry 5). It seems likely that **3a** was formed not only from **2** but also from **4**. The use of only $Pd(PPh_3)_4$ as catalyst under the same reaction condition resulted in the formation of **3a** in only 40% yield along with 50% yield of **4**. A similar result was obtained by using a mixture of $Pd(PPh_3)_2Cl_2$ and CuI as catalyst. Although the role of CuI in this coupling is not clear, CuI may facilitate the transmetalation process to give vinylcopper which speeds the cross-coupling reaction in the presence of Pd catalyst.[9] Coupling reaction of **2** with bromobenzene under the same reaction condition afforded the only reducing product **4**.

Optimized reaction conditions (reaction time is 10−20 h) were applied to prepare a variety of cross-coupled products **3b**−**o** via reaction between **2** and aryl iodides having fluoro, chloro, bromo, methoxy, methyl, trifluoromethyl, and nitro on the benzene ring. Except for aryl iodides having an ortho substituent (CH_3, OCH_3) or electron-withdrawing group (NO_2, CF_3), the coupling reactions provided excellent yields (81−97%) of **3**. (Table 2). The longer reaction time (18−20 h) was required for the reaction with aryl iodides having the *m*-CF_3, *o*-OCH_3, or *o*-CH_3 substituent, giving relatively low yields (58−68%).

Heteroaryl iodides such as 2-iodothiophene and 3-iodothiophene also underwent coupling reactions with **2** under

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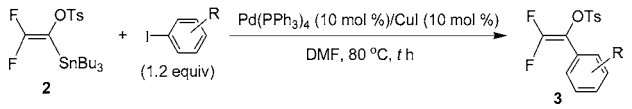
Table 2. Preparation of 2,2-Difluoro-1-arylethenyl *p*-Tolunenesulfonate (**3**)

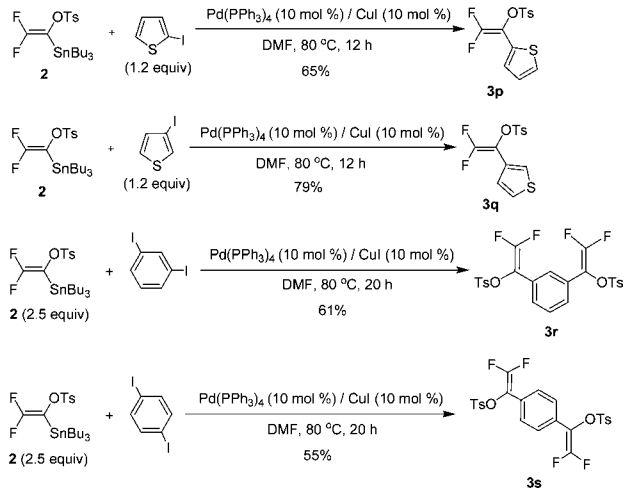


compound no.	R	*t* (h)	yield (%)[a]
3a	H	10	94
3b	*p*-F	12	97
3c	*p*-Cl	12	96
3d	*p*-Br	14	93
3e	*p*-OCH_3	12	85
3f	*p*-CH_3	12	88
3g	*p*-NO_2	14	35
3h	*m*-F	12	95
3i	*m*-Cl	12	96
3j	*m*-Br	14	94
3k	*m*-OCH_3	12	90
3l	*m*-CH_3	12	81
3m	*m*-CF_3	20	68
3n	*o*-OCH_3	18	68
3o	*o*-CH_3	18	58

[a] Isolated yield.

similar conditions to give the cross-coupled products **3p** and **3q** in 65% and 79% yields, respectively (Scheme 2).

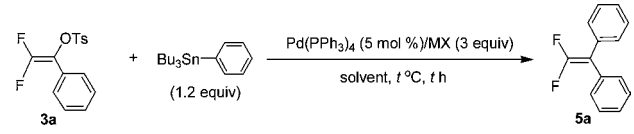
Scheme 2



However, product **3p** slowly underwent the polymerization after isolation of product. When **2** (2.5 equiv) was reacted with *m*-diiodobenzene and *p*-diiodobenzene having two reaction sites under the similar conditions, the cross-coupled products **3r** and **3s** were obtained in 61% and 55% yields, respectively.

We chose 2,2-difluoro-1-phenylethenyl *p*-toluenesulfonate (**3a**) as a second coupling partner. The Stille coupling reaction using vinyl triflate is of great practical importance in carbon−carbon bond formation.[10] However, vinyl tosylates which are relatively unreactive compared to vinyl triflate would be of significant interest because tosylates are more easily handled and considerably less expensive than vinyl triflates. Although there were several examples of the palladium-catalyzed cross-coupling reactions of vinyl tosylates derived from only α,β-unsaturated esters with aryl or vinyl boronic acids,[11] arylstannane,[12] or organozinc reagents,[13] to our knowledge there are no reports of coupling fluorinated vinyl tosylate with organometallic reagents. Therefore, we investigated the coupling reaction of vinyl tosylate **3a** with phenyl boronic acid or tributylphenylstannane as a coupling partner. First, when Suzuki−Miyaura cross-coupling reaction of **3a** was performed with phenyl boronic acid in the presence of 5 mol % of $Pd(PPh_3)_2Cl_2$ and Na_2CO_3 or Cs_2CO_3 in THF at reflux temperature for 28 h, conversion of **3a** was incomplete, and extensive formation of biphenyl via self-coupling reaction of the boronic acid was observed. We then turned our attention to arylstannane as a coupling partner of **3a** (Table 3).

Table 3. Optimization Reaction of **3a** with Tributylphenyl Stannane



entry	MX	solvent	*t* (°C)	*t* (h)	yield (%)[a]
1	LiCl	THF	reflux	24	60
2	LiCl	DME	reflux	24	62
3	LiCl	Dioxane	reflux	24	61
4	LiCl	DMF	25	24	NR[b]
5	LiCl	DMF	50	24	73
6	LiCl	DMF	80	18	73
7	LiCl	DMF	100	8	74
8	LiBr	DMF	100	2	78

[a] Isolated yield. [b] No reaction occurred.

When **3a** was reacted with tributylphenylstannane (1.2 equiv) in the presence of $Pd(PPh_3)_4$ (5 mol %) and LiCl (3 equiv) in THF at reflux temperature for 24 h, the desired product **5a** was obtained in 60% yield (entry 1). Similar results were obtained with DME or dioxane as a solvent (entries 2 and 3). The use of DMF as a solvent at 100 °C in this reaction caused an increase in the yield of **5a** with relatively short reaction time (entries 5−7). The best result for the formation of coupling product **5a** was established with the use of catalyst derived from 5 mol % of $Pd(PPh_3)_4$ and 3 equiv of LiBr in DMF (entry 8). In this case, the reaction was complete in 2 h at 100 °C. However, arylstannanes, having an electron-withdrawing group in the aromatic

(10) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040.
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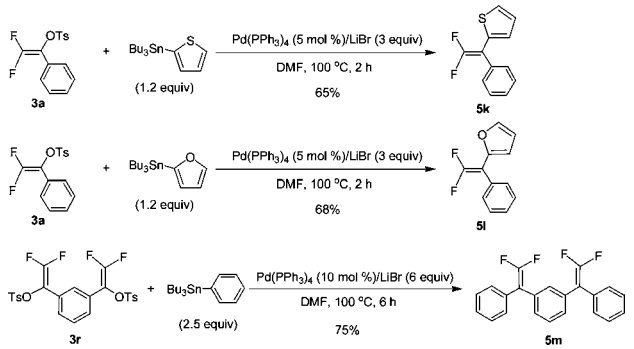
(12) Schio, L.; Chatreaux, F.; Klich, M. *Tetrahedron Lett.* **2000**, *41*, 1543–1547.
(13) Wu, J.; Liao, Y.; Yang, Z. *J. Org. Chem.* **2001**, *66*, 3642–3645.

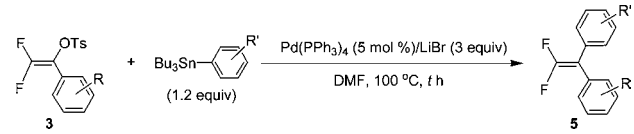
ring, underwent the coupling reaction in much longer reaction time to produce the corresponding cross-coupled product **5j**. The coupling reaction was also slower in the case of arylstannanes having a substituent in the ortho position of the benzene ring (synthesis of **5d**). To check the reactivity of **3** in the coupling reaction with arylstannane, we attempted the reaction of 2,2-difluoro-1-arylethenyl *p*-toluenesulfonate **3** having an electron-donating or electron-withdrawing group. Vinyl tosylates **3e** and **3f** having an electron-donating group underwent coupling reaction in 20−24 h to give the coupling products **5e** and **5f**, whereas the coupling reactions of vinyl tosylate **3m** having an electron-withdrawing group were complete in 3 h. Vinyl tosylates **3r** having two tosylate groups as coupling partners also underwent the coupling reaction with 2.5 equiv of tributylphenylstannane in 6 h to give the cross-coupled product **5m** in 75% yield (Scheme 3). Finally, heteroarylstannanes such as 2-(tributylstannyl)

Scheme 3



thiophene and 2-(tributylstannyl) furan are also successfully reacted with **3a** under similar reaction conditions to produce the cross-coupled products **5k** and **5l** in 65% and 68% yields, respectively (Scheme 3). The cross-coupling reactions of **3** with a variety of arylstannanes under the optimized conditions were summarized in Table 4. The plausible mechanism involves the initial oxidative addition of **3** to the palladium(0) catalyst followed by transmetalation of the arylstannane to

Table 4. Preparation of 2,2-Diaryl-1,1-difluoroethenes (**5**)



compound no.	R	R′	*t* (h)	yield (%)[a]
5a	H	H	2	78
5b	H	*p*-CH_3	3	75
5c	H	*p*-Cl	6	60
5d	H	*o*-CH_3	24	25
5e	*m*-CH_3	H	20	58
5f	*p*-OCH_3	H	24	53
5g	*m*-CF_3	H	3	55
5h	*m*-CF_3	*p*-CH_3	3	61
5i	*p*-Cl	*m*-CH_3	3	75
5j	*p*-Cl	*m*-CF_3	24	57

[a] Isolated yield.

yield the corresponding bis(organo)palladium(II) complex, which quickly undergoes reductive elimination to give the coupled product **5**.

In summary, we have developed a new and efficient method for the synthesis of 2,2-diaryl-1,1-difluoroethenes from the consecutive coupling reactions of 2,2-difluoro-1-tributylstannylethenyl *p*-toluenesulfonate. This method has several advantages such as satisfaction of generality, use of inexpensive starting material, relatively simple procedure, and easy handling of reagents.

Acknowledgment. This work was supported by the Basic Research Grant (2009-0073839) funded by the National Research Foundation of Korea.

Supporting Information Available: Experimental details and characterization data of **2**, **3a**−**3s**, and **5a**−**5m**, and ^{1}H, ^{13}C, and ^{19}F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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