Palladium-Catalyzed Coupling Reaction of Fluoroalkylated Propargyl Mesylates with Organozinc Reagents: Novel Synthesis of Optically Active Fluorine-Containing Trisubstituted Allenes

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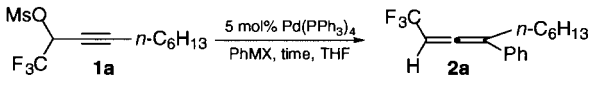
In the presence of 5 mol% of tetrakis(triphenylphosphine)-palladium(0), the reaction of chiral fluorinated propargyl mesylates with a variety of organozinc reagents proceeded smoothly in a highly stereoselective fashion to give the corresponding optically active fluorine-containing trisubstituted allenes in good yields without any loss of optical purity through the reaction.

Allenes have been recognized to be capable of participating efficiently in various types of regio- and stereo-controlled carbon–carbon bond formation reactions.[1] Therefore, they have attracted much attention as an exceedingly useful building blocks in organic synthesis and are frequently employed as versatile precursors in the synthesis of various naturally-occurring substances.[2] In contrast to such cumulative information of nonfluorinated allenic compounds, there have found a limited studies on the preparations and reactions of fluorine-containing counterparts in the literature.[3] The great importance of fluorinated allene chemistry has strongly urged the development of new methods, particularly stereocontrolled ones for the preparation of fluorinated allenic compounds. In this communication, we wish to disclose our preliminary results on the coupling reaction between fluoroalkylated propargyl esters and organometallic reagents, which is mediated catalytically by an allenylpalladium complex. To our best knowledge, the present reaction sequence is the first example of a highly effective and stereospecific route to the synthesis of optically enriched fluorine-containing allenic compounds.

The fluoroalkylated mesylates **1** required as starting materials were readily prepared from polyfluoroalkanoic acid ethyl esters and lithium acetylides in three steps (1. $R^1C{\equiv}CLi$, then $RfCO_2Et$; 2. $NaBH_4$; 3. MsCl, Et_3N). Initially, **1a** was treated with 5 mol% of $Pd(PPh_3)_4$ at room temperature for 10 min, followed by the addition of 2 equiv of PhMgBr and stirring at that temperature for 24 h, but no desired allene **2a** was obtained and the starting ester was recovered in 37% yield (Table 1; Entry 1). Even use of 3 equiv of PhMgBr provided only a trace amount of the product (7%), along with a lower recovery of the starting ester (8%) (Entry 2). On the other hand, organozinc reagent was found to participate more efficiently in the reaction than Grignard reagent did. Two equiv of zinc reagent, prepared from PhMgBr and $ZnCl_2$, was allowed to react with **1a** under the influence of the Pd(0) catalyst to produce **2a** in 47% yield, though the starting ester **1a** still remained unchanged (Entry 3). Three equiv of the zinc reagent was sufficient to completion of the reaction, in which **2a** was given in 63% yield (Entry 4). $ZnCl_2$·TMEDA complex was employed in place of $ZnCl_2$ for the preparation of organozinc reagent, in view of very easy handling due to its low moisture-sensitivity. On treating **1a** with PhZnCl prepared from PhMgBr and $ZnCl_2$·TMEDA complex in the presence of the Pd(0) catalyst for 6 h at 0 °C to room temperature, the reaction proceeded smoothly to afford **2a** in good yields (Entries 5–8). Eventually, the use of 2 equiv of the zinc reagent led to the best results (77% yield) as shown in Entry 7. Thus, the reactions of fluoroalkylated propargyl esters **1** with various organozinc reagents were carried out as summarized in Table 2.

Table 1. Investigation of the reaction conditions

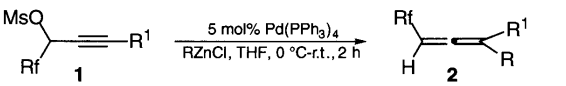


Entry[a]	PhMX (equiv)	Time/h	Yield/%[b]	Recovery of **1a**/%[c]
1	PhMgBr (2.0)	24	0	37
2	PhMgBr (3.0)	24	7	8
3	PhMgBr/$ZnCl_2$ (2.0)	24	47	17
4	PhMgBr/$ZnCl_2$ (3.0)	24	63	0
5	PhMgBr/$ZnCl_2$•TMEDA (1.5)	6	67	0
6[d]	PhMgBr/$ZnCl_2$•TMEDA (1.5)	6	70	0
7[d]	PhMgBr/$ZnCl_2$•TMEDA (2.0)	2	77	0
8[d]	PhMgBr/$ZnCl_2$•TMEDA (3.0)	1	76	0

[a]All reactions were carried out at room temperature, unless otherwise noted. [b]Isolated yields. [c]Determined by ^{19}F NMR. [d]Zinc reagent was added to the reaction mixture at 0 °C, then the whole was stirred at room temperature.

In the case of arylzinc reagents as shown in Entries 1–4, the desired allenes **2** were obtained in excellent yields. With (*E*)-styrylzinc reagent, however, the yield of **2** was decreased due to instability of the product (Entry 5). The reaction of **1a** with 1-alkynylzinc reagent, prepared from the corresponding lithium acetylide and $ZnCl_2$·TMEDA, gave the desired allene in less than 10% yield. Even use of 3 equiv of zinc reagent did not cause any

Table 2. Palladium-catalyzed reaction of various types of mesylates **1** with organozinc reagents



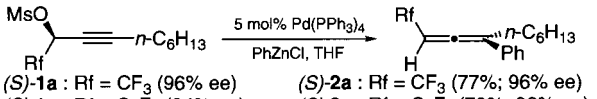
Entry	Rf	R^1	RZnCl	Yield/%[a]
1	CF_3 (**a**)	*n*-C_6H_{13}	PhZnCl	83 (77)
2			*p*-MeC_6H_4ZnCl	89 (81)
3			*p*-$MeOC_6H_4ZnCl$	86
4			1-$C_{10}H_7ZnCl$	80
5[b]			PhCH=CHZnCl	50
6[c]			*n*-$C_6H_{13}C{\equiv}CZnCl$	78 (50)
7		CH_2OTBS	PhZnCl	(86)
8		CH_2OBn		73
9		*t*-Bu		tr
10		TMS		tr
11	CF_2H (**b**)	*n*-C_6H_{13}	PhZnCl	0
12			*p*-MeC_6H_4ZnCl	0
13	CF_3CF_2 (**c**)	*n*-C_6H_{13}	PhZnCl	(70)
14			*p*-MeC_6H_4ZnCl	(79)

[a]Determined by ^{19}F NMR. In parentheses are shown isolated yields. [b]Carried out for 4 h. [c]The reaction was performed at room temperature for 24 h by using three equiv of zinc reagent which was prepared from the corresponding lithium acetylide and $ZnCl_2$.

dramatic improvement. It should be noted that 3 equiv of zinc reagent prepared from lithium acetylide and anhydrous $ZnCl_2$ allowed the smooth reaction of **1a**, giving the desired allene **2** in 78% yield, though the reaction period was elongated to 24 h (Entry 6). As shown in Entries 1, 7–10, the propargyl esters **1a** carring a straight side chain R^1 participated readily in the reaction, but the esters having a bulky side chain such as a *t*-Bu or TMS group did not.

Very interestingly, it was found that the pentafluoroethylated ester **1c** underwent the present reaction as effectively as the trifluoromethylated esters **1a** (Entries 13 and 14), while the difluoromethylated ester **1b** did not react at all; no trace of the desired product could be observed and the starting material could be recovered almost quantitatively (Entries 11 and 12).

Our attention was thus directed to the preparation of optically active fluorine-containing allenes as described in Scheme 1.



(*S*)-**1a** : Rf = CF_3 (96% ee) (*S*)-**2a** : Rf = CF_3 (77%; 96% ee)
(*S*)-**1c** : Rf = C_2F_5 (94% ee) (*S*)-**2c** : Rf = C_2F_5 (70%; 96% ee)

Scheme 1.

The starting optically active mesylate esters (*S*)-**1a** and (*S*)-**1c** were easily prepared according to the literature method.[4] Their optical purities were determined as 96% ee and 94% ee, respectively, by gas chromatography after the conversion to the MTPA esters.[5] When these non-racemic mesylates (*S*)-**1a** and (*S*)-**1c** were allowed to react with PhZnCl in the presence of 5 mol% $Pd(PPh_3)_4$ at room temperature for 2 h, the corresponding allenes (*S*)-**2a** and (*S*)-**2c** were obtained in 77 and 70% yields, respectively, with high enantiomeric excess (96% ee), which was measured by HPLC using a chiral column (DAICEL, CHIRALCEL OD).[6] Of great synthetic value is that no loss of the optical purities occurs, strongly suggestive of the present reaction proceeding in a completely stereoselective manner.

Although the absolute configurations of the above-obtained chiral allenes have not been established conclusively, the origin of the *anti* substitution products (*S*)-**2a** and (*S*)-**2c** is conceivable by assuming the reaction sequence shown in Figure 1.[2e] Thus, the oxidative insertion of the Pd(0) catalyst into the mesylate **1** gives rise to the allenylpalladium intermediate **3** (inversion), which is in turn transformed into **4** (retention) via nucleophilic displacement of the mesylate ligand by organozinc reagent. The resultant intermediate undergoes the reductive elimination to produce the allenic compound **2** (retention), along with the regeneration of the Pd(0) species. For the nonfluorinated series, it is proposed that depending on the starting propargyl ester used, an

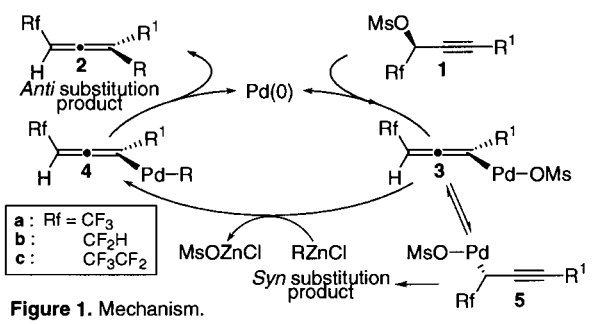


Figure 1. Mechanism.

intermediary allenylpalladium complex, like **3**, is in equilibrium with a propargylpalladium intermediate, like **5**, which is displaced directly by a nucleophile to afford the *syn* substitution product, resulting in the decrease in stereoselectivity of the reaction, i.e., optical purity of the product. The extremely high stereoselectivity observed in this study enables us to consider that no isomerization of **3** to **5** occurs in the reaction of **1a** or **1c**. The difficulty in this isomerization can be ascribed to a large steric bulk of the perfluoroalkyl group, such as the CF_3 or C_2F_5 group. It is possible that the allenylpalladium complex **3b** generated initially from the difluoromethylated ester **1b** will isomerize more easily to the propargylic palladium intermediate **5b** than the complexes **3a** and **3c**, because the CF_2H group is not so bulky as the CF_3 and C_2F_5 groups,[7] and the resulting propargylpalladium intermediate **5b** seems to be stabilized by the electronegative CF_2H group to fail in the coupling reaction,[8] so that the relevant catalytic cycle is entirely prohibited to leave the starting ester **1b** substantially.

In summary, we have developed the palladium(0)-catalyzed coupling reaction of the fluoroalkylated propargyl mesylates **1** with organozinc reagents leading to the fluorinated allenic compounds **2** in high yields. More significantly, it has also been demonstrated that utilization of the chiral starting mesylates **1** leads to the formation of chiral fluorinated allenes with an excellent level of stereoselection. Further studies to extend the synthetic utility of the fluorine-containing allenylpalladium complexes and related intermediates are currently underway in our laboratory.

References and Notes

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6 The retention time in HPLC (haxane/2-propanol = 99.5/0.5, 0.7 mL/min) is as follows; compound **2a** : *R* isomer, 6.1 min, *S* isomer, 7.1 min. compound **2c** : *R* isomer, 5.9 min, *S* isomer, 6.5 min.

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8 The mesylate **1b** was treated with an equimolar amount of $Pd(PPh_3)_4$ at 0 °C in THF-d_8 for 10 min, and then ^{19}F NMR and ^1H NMR analysis of the reaction mixture was carried out. The formation of a sole product was detected in ^{19}F NMR. Furthermore, only two peaks were observed (δ 4.0 (br s, 1H, CF_2HCH), 4.78 (dt, J = 6.7, 57.1 Hz, 1H, CF_2H)) in the range of 4–7 ppm in ^1H NMR, and any olefinic proton peaks were not found. This strongly suggests that the propargylpalladium complex **5** was formed exclusively, not allenylpalladium complex **3**.