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Highly regio- and stereo-controlled Pd(0)-catalyzed nucleophilic substitution reaction for the synthesis of optically active γ-fluoroalkylated allylic alcohols

Tsutomu Konno,* Takashi Ishihara and Hiroki Yamanaka

Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Sakyo-ku, Kyoto 606-8585, Japan

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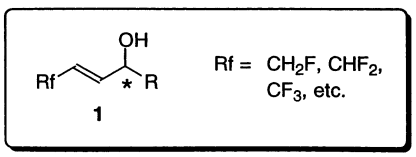
Abstract

Pd(0)-catalyzed nucleophilic substitution reaction of optically active α-(fluoroalkyl)allyl mesylates with various types of carboxylates proceeded regioselectively to afford the corresponding chiral γ-fluoroalkylated allylic alcohol derivatives in excellent yields without any loss of optical purities.

Keywords: γ-fluoroalkylated allylic alcohols; palladium-catalyzed reaction.

Fluorine-containing organic molecules are well known to often exhibit unique chemical and biological properties due to the electron-withdrawing effect of a fluorine atom.[1] Practically, they have widely been utilized as ferroelectric liquid crystals,[2] pharmaceuticals,[3] agrochemicals,[4] and so on. Therefore, fluorinated materials have attracted much attention from many scientists in various fields, and much effort has been devoted to the development of general and convenient methods for synthesizing such compounds.[5]



γ-Fluoroalkylated allylic alcohols **1** have frequently been employed as one of the most valuable starting materials in the preparation of fluoroorganic compounds with a more

* Corresponding author.

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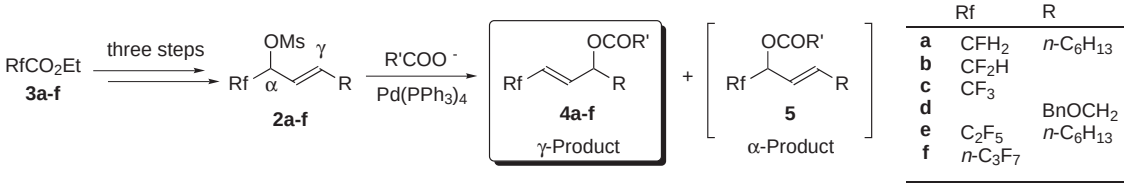
complicated framework, such as naturally occurring compounds.[6] Although several synthetic methods for racemic allylic alcohols are already known,[7] only quite limited methods have been found thus far for the preparation of their non-racemic counterparts. The enzymatic kinetic resolution of the racemic alcohols **1** has been reported as the most convenient way to obtain both enantiomers with high optical purities.[6c,e] However, this method suffers at least one serious disadvantage in that the yields of the chiral alcohols are not more than 50%. On the other hand, the asymmetric synthesis provides us with the great advantage that the transformation can be carried out to completion, i.e. 100% maximum yield. Surprisingly, no examples of the asymmetric synthesis of optically active γ-fluoroalkylated allylic alcohols **1** have appeared. Herein we wish to disclose a novel nucleophilic substitution reaction of various fluorinated allyl mesylates **2** with carboxylates under the influence of a catalytic Pd(0) complex, which can serve as a general and efficient route to the preparation of non-racemic alcohols **1**.

At first, we attempted the Pd-catalyzed reaction using racemic α-(fluoroalkyl)allyl mesylates **2a**–**f** as the starting materials, prepared readily from the corresponding perfluoroalkanoic acid ethyl esters **3a**–**f** in three steps ((1) RC≡CLi, then $RfCO_2Et$; (2) Red–Al; (3) MsCl, Et_3N) (Scheme 1). Except for **2b**–**f**, monofluorinated mesylate **2a** was too unstable to be purified by silica gel column chromatography. Therefore, **2a** was used for the reaction without any purification.



Scheme 1.

Several examinations of the reaction conditions led us to the conclusion that the best yield of **4c** was obtained by the reaction of **2c** performed in the following manner: the mesylate **2c** was treated with 5 mol% of tetrakis(triphenylphosphine)palladium(0) in THF at 0°C for 5 min, followed by the addition of 2 equiv. each of benzoic acid and triethylamine at that temperature. After stirring for several hours at 0°C and an unusual workup, the desired γ-trifluoromethylated allylic alcohol derivative **4c** (γ-product) was obtained in 91% isolated yield as a sole product. High *E* selectivity was observed at the newly created olefinic bond in **4c**, and no regioisomer **5** (α-product) was detected.[8]

With this successful result in hand, we carried out the Pd-catalyzed reactions between various types of the substrates **2** and carboxylic acids under the same reaction conditions. The results of these reactions are summarized in Table 1. Although the crude mesylate **2a**, as noted above, was employed as such for the Pd-catalyzed process, the desired allylic alcohol derivative **4a** was obtained in 56% two-step yield as a single isomer (entry 1). As shown in entries 2, 3, 10, and 11, the Rf groups of **2** did not exert any influence on the regio- and stereochemical course of the reaction, with all the cases leading to γ-products with the *E* configuration. A variety of carboxylic acids, such as benzoic acid, acetic acid, propionic acid, chloro-, and methoxyacetic acid, participated nicely in the reaction, giving rise to the corresponding γ-products **4** exclusively (entries 3–7). It was found that the differences in the side chain R largely affected the reaction.

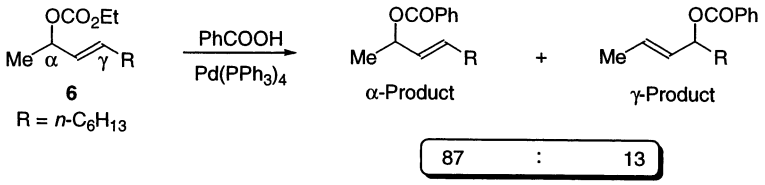
Thus, a slight decrease in the stereoselectivity at the newly formed olefinic bond was observed with the benzyloxymethyl group (entry 8). Furthermore, the *t*-butyl group completely prevented the reaction from proceeding (entry 9).

Table 1
Pd(0)-catalyzed reaction of fluorinated allyl mesylates **2** with various carboxylates

Entry[a]	Rf	R	RCO_2H	Yield (%)[b,c]
1	CH_2F	*n*-C_6H_{13}	BzOH	56
2	CHF_2	*n*-C_6H_{13}	BzOH	89
3	CF_3	*n*-C_6H_{13}	BzOH	91
4	CF_3	*n*-C_6H_{13}	CH_3CO_2H	80
5	CF_3	*n*-C_6H_{13}	$CH_3CH_2CO_2H$	74
6	CF_3	*n*-C_6H_{13}	$ClCH_2CO_2H$	99
7	CF_3	*n*-C_6H_{13}	$MeOCH_2CO_2H$	96
8	CF_3	$BnOCH_2$	BzOH	93[d]
9	CF_3	*t*-Bu	BzOH	0
10	CF_3CF_2	*n*-C_6H_{13}	BzOH	87
11	$CF_3(CF_2)_2$	*n*-C_6H_{13}	BzOH	99

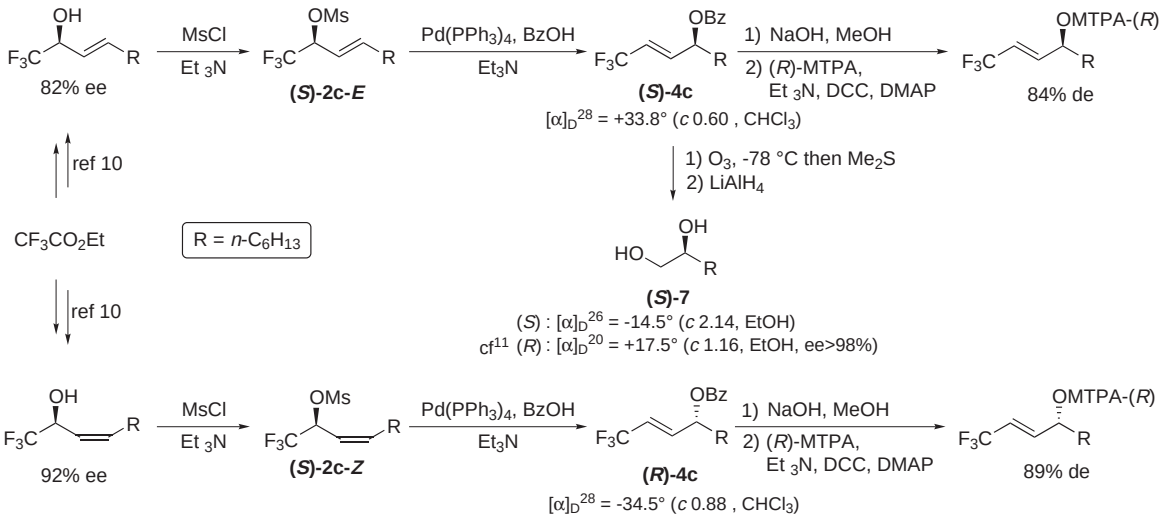
[a] All reactions were performed at 0°C by using 2 equiv. each of Et_3N, carboxylic acid and 5 mol% of $Pd(PPh_3)_4$.
[b] Isolated yield.
[c] The *E* isomer was produced exclusively in all cases, unless otherwise noted.
[d] The stereoisomers of *E* and *Z* forms were obtained in a ratio of 94:6.

In order to evaluate the influence of an Rf group upon the reaction, we examined the reaction of a nonfluorinated counterpart (Scheme 2). Ethyl carbonate **6** was used as the starting ester because the corresponding allyl mesylate was so thermally unstable that it could not be prepared. The ester **6** was treated with 5 mol% of $Pd(PPh_3)_4$ and 2 equiv. of benzoic acid at room temperature, and the reaction mixture was stirred at that temperature for 24 h. HPLC of the reaction mixture indicated that a large amount of the substrate **6** remained unreacted, and that the α- and γ-products were obtained in only 16% yield in a ratio of 87:13, respectively.[9] It should be emphasized that the α-product was given preferentially, not γ-product. This is totally different from the results of the reaction of the fluorinated substrates **2**.



Scheme 2.

The access to chiral γ-fluoroalkylated allylic alcohols **1** was undertaken as outlined in Scheme 3. Thus, on treating chiral (*E*)-substrate (*S*)-**2c**-*E*[10] with benzoic acid and Et_3N under the same conditions as described above, the optically active product (*S*)-**4c** was obtained in 91% yield. The ester (*S*)-**4c**, after hydrolysis, was converted into the MTPA ester, whose diastereomeric excess was measured to be 84% by gas chromatography. This clearly indicates that the reaction proceeds without any loss of optical purity throughout the reaction. The transformation of (*S*)-**4c** into the known compound (*S*)-**7** and comparison between their optical rotations[11] made it possible to determine its absolute configuration as *S*.



Scheme 3.

Similarly, the reaction of chiral (*Z*)-substrate (*S*)-**2c**-*Z*[10] was conducted under the same conditions, leading to the corresponding chiral allylic alcohol derivative (*R*)-**4c** in 88% yield. The optical rotation of the product was opposite to the (*S*)-enantiomer, and thereby its absolute configuration was assigned as *R*. In addition, this ester was transformed into the MTPA ester, followed by gas chromatography, which was determined to be 89% de. This fact strongly suggests that the reaction of the (*Z*)-substrate takes place in an entirely stereoselective fashion.

The mechanism of the present reaction may be proposed as indicated in Fig. 1. Thus, when the Pd complex coordinates on the face of the olefin distal to the mesyloxy group, the Pd species

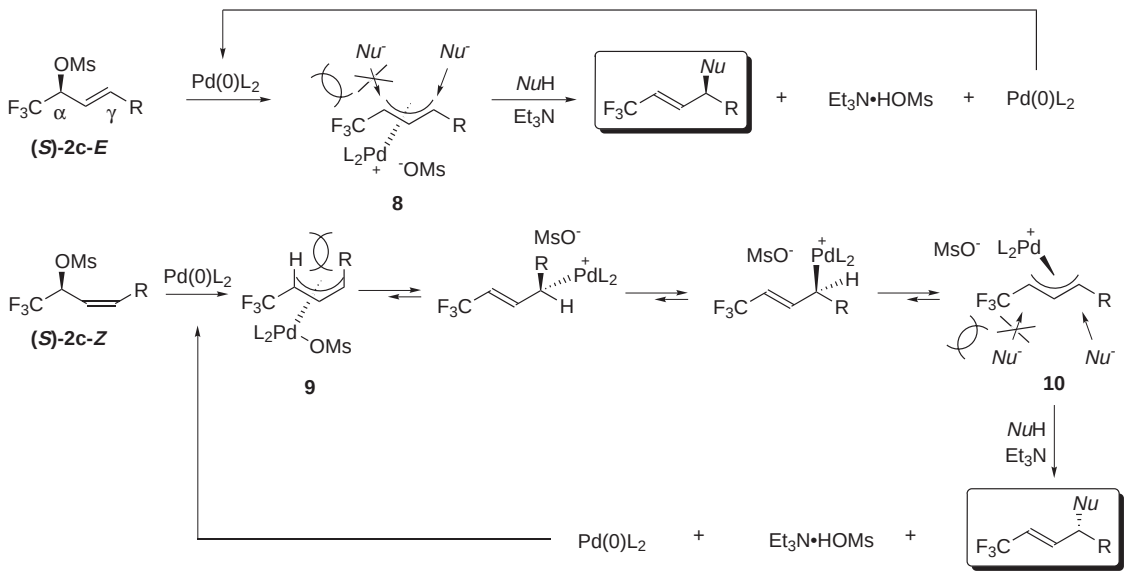
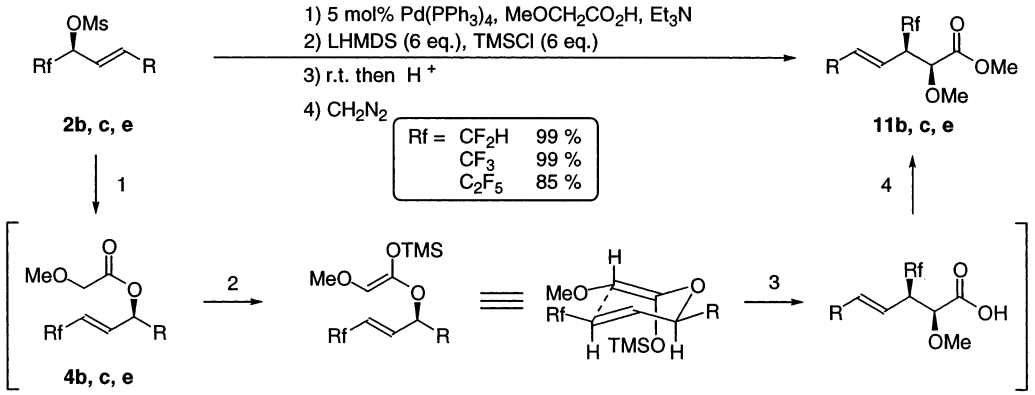


Figure 1.

displaces the mesylate with inversion to give a π-allyl complex **8**. The carboxylate nucleophile attacks complex **8** on the face opposite to that occupied by Pd. The double inversion results in a net retention for these processes.[12] In this case, the Pd moiety might be closer to the Rf group than the R due to the electron-withdrawing effect of the Rf group.[13] Therefore, the nucleophile attacks preferentially at the less hindered γ-carbon to give the γ-fluoroalkylated allylic alcohol derivative **4**.

On the other hand, oxidative addition of Pd(0) to the (*Z*)-substrate generates the π-allylpalladium complex **9**, which is less stable than **10** due to a ^{1,3}A strain, so that **9** could be converted into **10** via π-σ-π equilibrium with inversion. The nucleophilic attack occurs with inversion, as mentioned in the (*E*)-substrate. Thus, the reaction of the (*Z*)-substrate involves three inversion processes, which creates a net inversion.

Finally, we investigated the application of the present reaction combined with an Ireland–Claisen rearrangement (Scheme 4).



Scheme 4.

Thus, the Pd-catalyzed reactions of chiral mesylates **2b**,**c**,**e** with methoxyacetic acid gave the corresponding allylic alcohol derivatives **4b**,**c**,**e** in situ, which were treated successively with 6 equiv. each of trimethylsilyl chloride and lithium hexamethyldisilazide at −50°C. After stirring at that temperature for 30 min, the whole was gradually warmed up to room temperature over 2 h and then stirred at ambient temperature for 3 h. The usual workup gave the corresponding rearranged products, which were subjected to esterification with diazomethane to afford α-methoxy-β-trifluoromethyl ester **11b**,**c**,**e** in 85–99% overall yields as single stereoisomers.

Although the stereochemistry and enantiomeic excess of these esters have not been confirmed, our precedent work[6c] allows us to expect that the reaction proceeds via an energetically stable six-membered cyclic transition state, where the R group occupies the equatorial position, without any loss of optical purities throughout the reaction.

In conclusion, we have investigated the Pd-catalyzed nucleophilic substitution reaction of chiral α-(fluoroalkyl)allyl mesylates **2** with carboxylates affording the corresponding chiral γ-fluoroalkylated allylic alcohol derivatives **4** in excellent yields. This reaction can serve as a general and expedient means for synthesizing optically active fluorinated allylic alcohols. We have also demonstrated that the sequential Pd-catalyzed allylic substitution reaction and Ireland–Claisen rearrangement leads efficiently to optically enriched α-methoxy-β-(fluoroalkyl)-γ,δ-unsaturated esters in excellent yields.

Further studies on the synthetic utilizations of fluorine-containing palladium complexes are now under way in our laboratory.

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