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Palladium-Catalyzed Regio- and Stereoselective Formate Reduction of Fluorine-Containing Allylic Mesylates. A New Entry for the Construction of a Tertiary Carbon Attached with a Fluoroalkyl Group

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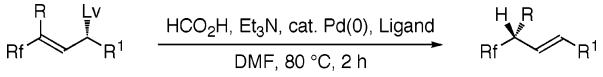

The regioselective palladium-catalyzed formate reduction of γ-fluoroalkylated allylic esters is described. Reduction of the allylic esters under the influence of palladium with a monodentate phosphine ligand proceeded preferentially at the γ position, the corresponding reduction products with a fluoroalkyl group at the tertiary carbon being afforded in high yields. When the chiral allylic ester was employed, complete chirality transfer was observed, leading to the optically active materials in high yields.

Introduction

Introduction of a fluoroalkyl group into an asymmetric carbon center (Figure 1) constitutes a major interest in organofluorine chemistry owing to the recent outstanding applications of optically active fluoroalkylated compounds in the medicinal, pharmaceutical, and agricultural fields, such as Efavirenz (non-nucleoside transcriptase inhibitor), KW-7158 (a agent for treating urinary incontinence), and so on.[1]

Consequently, much effort has been put forth toward the development of a new synthetic approach to various classes of chiral fluoroalkylated compounds thus far.[2] Herein, we wish to describe a new entry to such chiral organic molecules **1** via highly regio- and stereoselective palladium-catalyzed formate reduction of γ-fluoroalkylated allylic esters **2** in detail (Scheme 1).[3,4]

Results and Discussion

Palladium-Catalyzed Formate Reduction of Nonchiral Allyl Mesylates. Our initial studies were performed using nonchiral allyl mesylates **2a**−**f**,**h** as a substrate which could be easily prepared as a mixture of *E* and *Z* isomers in four steps from commercially available poly- or perfluoroalkanoic acid ethyl esters **3** (Scheme 2).[5] Thus, treatment of **3** with Grignard reagents at −78 °C gave the corresponding polyfluoroalkyl ketones **4** in good yields, which underwent the efficient Horner−Wadsworth−Emmons reaction to afford the α,β-unsaturated esters **5** in excellent yields. Reduction of **5** with DIBAL-H followed by mesylation produced fluoroalkylated allyl mesylates

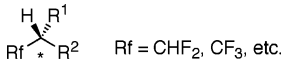

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FIGURE 1. Chiral fluoroalkylated compounds.

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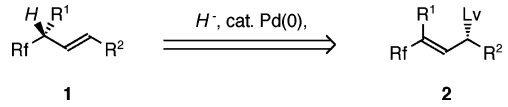
SCHEME 1



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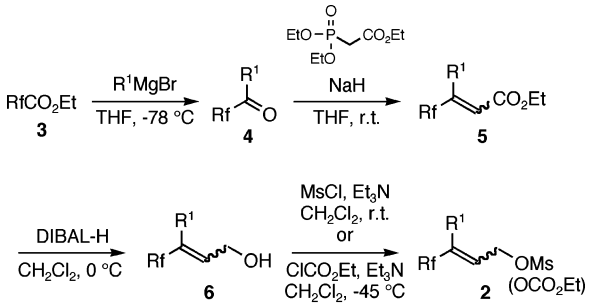
SCHEME 2



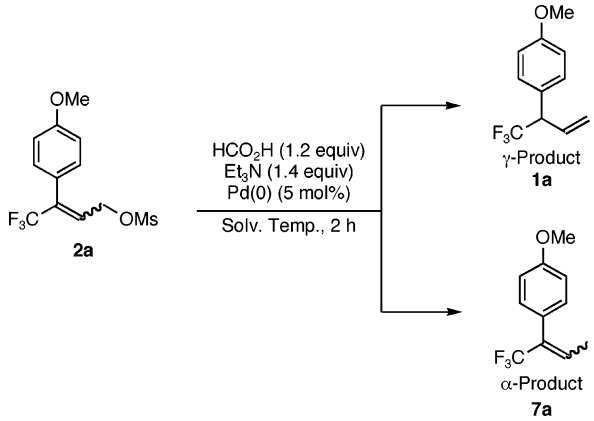
a : Rf = CF_3, R^1 = *p*-$MeOC_6H_4$
b : Rf = CF_3, R^1 = *m*-$MeOC_6H_4$
c : Rf = CF_3, R^1 = *o*-$MeOC_6H_4$
d : Rf = CF_3, R^1 = *p*-*t*-BuC_6H_4
e : Rf = CF_3, R^1 = α-Naphthyl
f : Rf = CF_3, R^1 = *n*-$C_{10}H_{21}$
g : Rf = CHF_2, R^1 = *p*-$MeOC_6H_4$
h : Rf = CF_3CF_2, R^1 = *p*-$MeOC_6H_4$

2 in good combined yields. Difluoromethylated allyl mesylate was too unstable to be prepared, so that the corresponding allyl carbonate **2g** was used for the next reaction.

Treatment of **2a** (*E*/*Z* = 76/24) with $HCO_2^-NEt_3H^+$ (1.2 equiv) in the presence of $Pd(PPh_3)_4$ in THF at room temperature for 24 h afforded the desired γ-product **1a** in 66% yield preferentially, together with 20% of the α-product **7a** (Scheme 3, Table 1, entry 1). The reaction in benzene resulted in a slight increase of the chemical yield (entry 2). In contrast to these solvents, more polar solvents, such as 1,4-dioxane and DMF, were found to be less effective for the reaction at room temperature, **1a** being obtained in only 45% and 25% yields, respectively (entries 3 and 4). Interestingly, higher reaction temperatures caused a significant increase of the yield as shown in entries 5−8. In particular, the reaction in DMF at 80 °C for 2 h gave **1a** in 89% yield (entry 8).

We also examined the effect of the ligand on palladium as shown in entries 9−17. When a phosphine ligand was not employed, **7a** was formed preferentially (entry 9). A series of monodentate phosphine ligands, such as PPh_3, $P(o\text{-Tol})_3$, $P(OPh)_3$, and $P(n\text{-Bu})_3$, were found to be very effective to afford the desired **1a** in high yields with a satisfactory regioselectivity.

SCHEME 3



In particular, the use of $Pd_2(dba)_3CHCl_3$ + $4PPh_3$ led to optimum regioselectivity (entry 10). On the contrary, a bulky and monodentate trialkylphosphine ligand, like PCy_3, decreased the regioselectivity significantly. More interestingly, bidentate ligands, such as dppe, dppf, and BINAP, resulted in a high reverse regioselectivity, the α-product **7a** being afforded in 75−97% yields.

With the optimized reaction conditions (Table 1, entry 10), we investigated the present palladium-catalyzed formate reduction of various types of allyl mesylates **2** as shown in Scheme 4 and Table 2.

Generally, all substrates could participate nicely in the reaction to give the reduction products **1** and **7** in excellent combined yields. The reaction of allyl mesylate bearing para- and meta-substituted aromatic rings as R^1 proceeded in a highly regioselective manner (entries 1, 2, and 4); however, ortho-substitution on the aromatic ring in R^1 slightly decreased the regioselectivity (entries 3 and 5). The use of an alkyl group as R^1 also led to a high regioselectivity. It should be noted that various types of fluoroalkyl groups did not influence on the yield and regioselectivity.

Formate Reduction of α-Substituted-Allyl Mesylates. We next investigated the palladium-catalyzed formate reduction of (α-substituted)allyl esters **2i**−**o**, which could be easily prepared as described in Schemes 5 and 6. Thus, **2i**,**j**,**l**−**n** could be prepared from **3** by a similar procedure as shown in Scheme 2, though phosphonium salts **8** were used for the Wittig reaction, instead of Horner−Wadsworth−Emmons reagents (Scheme 5). The fluoroalkylated allylic mesylate with a phenyl group as R^2 was too unstable to be prepared, so that the corresponding allyl acetate **2k** was used for the next formate reduction. On the other hand, propargylic alcohol **9**, which could be prepared from 2-bromo-3,3,3-trifluoropropene **10** according to the literature,[6] was reduced with an excess amount of Red-Al followed by treatment of I_2, leading to vinyl iodide **11**. The Suzuki−Miyaura cross-coupling reaction of **11**[7] and the subsequent mesylation of the resultant allylic alcohol **12** gave the desired allylic mesylate **2o** in good yield (Scheme 6).

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TABLE 1. Investigation of the Reaction Conditions Using 2a

entry[a]	Pd(0)/(Pd = 5 mol %)	solvent	yield[d]/% of **1a**	yield[d]/% of **7a** (*E*/*Z*)
1[b]	$Pd(PPh_3)_4$	THF	66	20 (100:0)
2[b]	$Pd(PPh_3)_4$	PhH	70	12 (99:1)
3[b]	$Pd(PPh_3)_4$	1,4-dioxane	45	15 (93:7)
4[b]	$Pd(PPh_3)_4$	DMF	25	6 (67:33)
5[c]	$Pd(PPh_3)_4$	THF	66	16 (100:0)
6[c]	$Pd(PPh_3)_4$	PhH	86	7 (100:0)
7[c]	$Pd(PPh_3)_4$	1,4-dioxane	79	6 (100:0)
8	$Pd(PPh_3)_4$	DMF	89	9 (100:0)
9	$Pd_2(dba)_3{\cdot}CHCl_3$	DMF	29	69 (90:10)
10	$Pd_2(dba)_3{\cdot}CHCl_3 + 4PPh_3$	DMF	86 (82)[c]	7 (100:0)
11	$Pd_2(dba)_3{\cdot}CHCl_3 + 8P(o\text{-Tol})_3$	DMF	85	12 (86:14)
12	$Pd_2(dba)_3{\cdot}CHCl_3 + 8P(OPh)_3$	DMF	77	20 (95:5)
13	$Pd_2(dba)_3{\cdot}CHCl_3 + 8P(n\text{-Bu})_3$	DMF	80	16 (88:12)
14	$Pd_2(dba)_3{\cdot}CHCl_3 + 8PCy_3$[f]	DMF	47	50 (90:10)
15	$Pd_2(dba)_3{\cdot}CHCl_3$ + 4dppe[g]	DMF	0	97 (82)[c] (97:3)
16	$Pd_2(dba)_3{\cdot}CHCl_3$ + 4dppf[h]	DMF	0	83 (94:6)
17	$Pd_2(dba)_3{\cdot}CHCl_3$ + 4(*S*)-BINAP[i]	DMF	7	75 (91:9)

[a] Unless otherwise noted, the reaction was carried out at 80 °C. [b] Stirred at rt for 24 h. [c] Stirred at the reflux temperature for 2 h. [d] Determined by ^{19}F NMR. [e] Isolated yields. [f] Cy = cyclohexyl. [g] dppe = 1,2-bis(diphenylphosphino)ethane. [h] 1,1′-Bis(diphenylphosphino)ferrocene. [i] BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

SCHEME 4

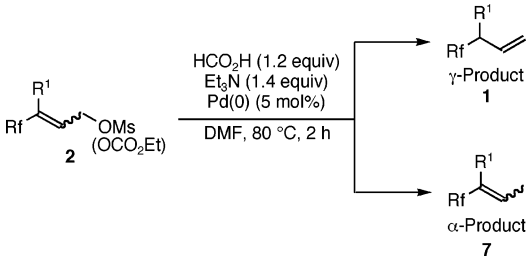


TABLE 2. Palladium-Catalyzed Formate Reduction of Various Mesylates

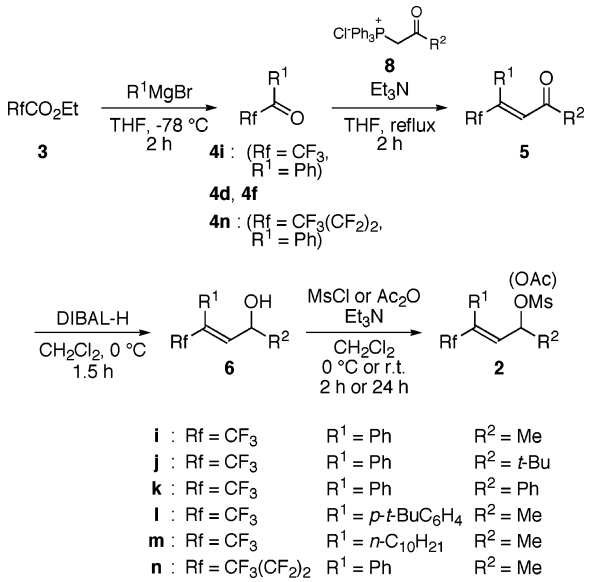
entry	substrate (*E*/*Z*)	yield[a]/% of **1**	yield[b]/% of **7** (*E*:*Z*)
1	**2a** (76/24)	86 (82)	7 (100:0)
2	**2b** (95/5)	86 (46)	8 (100:0)
3	**2c** (88/12)	61 (54)	12 (100:0)
4	**2d** (97/3)	73 (52)	10 (100:0)
5	**2e** (31/69)	69 (26)	22 (59:41)
6	**2f** (94/6)	84	9 (100:0)
7[c]	**2g** (16/84)	91 (88)	0
8	**2h** (95/5)	78 (62)	13 (100:0)

[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yield. [b] Determined by ^{19}F NMR. [c] Difluoromethylated allyl carbonate was used.

With allylic mesylate **2i** (Rf = CF_3, R^1 = Ph, R^2 = Me), the palladium-catalyzed formate reduction was attempted under the same reaction conditions as in the case of **2a** (Scheme 7). Thus, to a solution of formic acid (1.2 equiv) and Et_3N (1.4 equiv) in the presence of $Pd_2(dba)_3CHCl_3$ (2.5 mol %) and PPh_3(10 mol %) in DMF was added the starting ester **2i**, and then the whole was heated at 80 °C for 2 h. As a result, the desired γ-product **1i** was formed in only 47% yield as an *E* and *Z* mixture in a ratio of 83:17, together with 5% of the α-product **7i**. Additionally, fluoroalkylated diene **13i** was given in 46% yield (Table 3, entry 1). The unsatisfactory results prompted us to reexamine the reaction of **2i** in detail as described in entries 2−10.

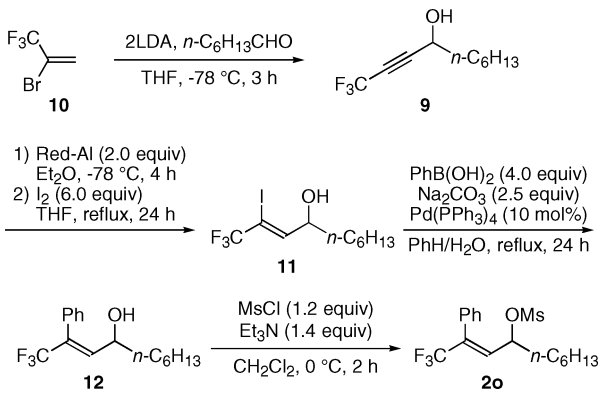
As shown in entry 2, the reaction at room temperature for 24 h did not give rise to any change in the ratio of **1i**/**7i**/**13i**, the starting material being recovered in only 16% yield. Even use of 20 mol % of PPh_3 did not lead to a satisfactory result (entry 3). On the other hand, P(*o*-Tol)$_3$ caused an increase of the yield of **1i** and a decrease of the yield of **13i**, though the

SCHEME 5



α-product was formed in 28% yield. Then the γ-product **1i** was afforded in 57% yield when P(*p*-Tol)$_3$ was employed. Eventually, the best yield was given when more electron-donating ligand, P(*p*-MeOC$_6$H$_4$)$_3$, was used. In this case, the γ-product was obtained in 72% yield as a mixture of *E* and *Z* isomer in

SCHEME 6



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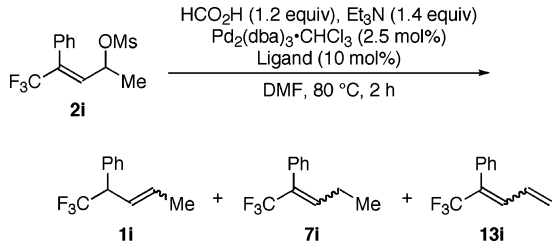


TABLE 3. Palladium-Catalyzed Formate Reduction of 2i

entry	ligand (10 mol %)	yield/% of **1i** (*E*/*Z*)[a]	yield/% of **7i**[a,b]	yield/% of **13i**[a]
1	PPh_3	47 (83:17)	5	46
2[c]	PPh_3	37 (100:0)	3	32
3[d]	PPh_3	41 (93:7)	4	51
4	P(*o*-Tol)$_3$	59 (83:17)	28	6
5	P(*p*-Tol)$_3$	57 (82:18)	6	37
6	P(*p*-MeOC$_6$H$_4$)$_3$	72 (84:16)	5	23
7	P(*n*-Bu)$_3$	36 (100:0)	21	0
8	PCy_3	45 (100:0)	55	0
9	dppe	29 (100:0)	35	21
10	bpy	15 (100:0)	64	17

[a] Determined by ^{19}F NMR. [b] The stereochemistry was not determined. [c] Stirred at rt for 24 h. [d] Twenty mol % of ligand was employed.

SCHEME 8

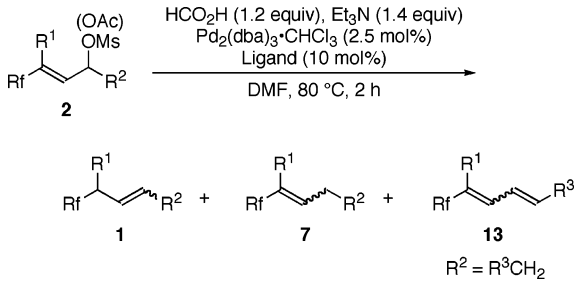


TABLE 4. Palladium-Catalyzed Formate Reduction of Various Mesylates

entry	substrate	yield/% of **1** (*E*/*Z*)[a]	yield/% of **7**[a,b]	yield/% of **13**[a,b]
1	**2i**	72 (84:16)	5	23
2	**2o**	62 (100:0)	22	16
3	**2j**	48 (100:0)	38	
4	**2k**	80 (89:11)	9	
5	**2l**	68 (87:13)	7	21
6	**2m**	45 (100:0)	3	11
7	**2n**	67[c]	11[d]	23[d]

[a] Determined by ^{19}F NMR. [b] The stereochemistry was not determined. [c] The stereochemistry was not determined. [d] Determined by ^{1}H NMR.

a ratio of 84:16, together with 5% of **7i** and 23% of **13i** (entry 6). Additional studies on the ligand effect revealed that trialkylphosphines and bidentate phosphine were not suitable for obtaining the γ-product largely (entries 7−9) and that the use of bpy ligand gave the α-product preferentially (entry 10).

With the best reaction conditions (entry 6 in Table 3), we performed the reaction of various allyl mesylates having a side chain R^2 at the α position (Scheme 8). The results are summarized in Table 4.

Switching the side chain R^2 from a methyl group to an *n*-hexyl group led to a decrease of the α-/γ-product ratio, **1** and **7** being obtained in 62% and 22% yield, respectively (entry 2) (Scheme 8). Furthermore, a *t*-Bu group resulted in the formation of

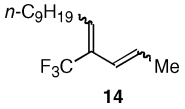
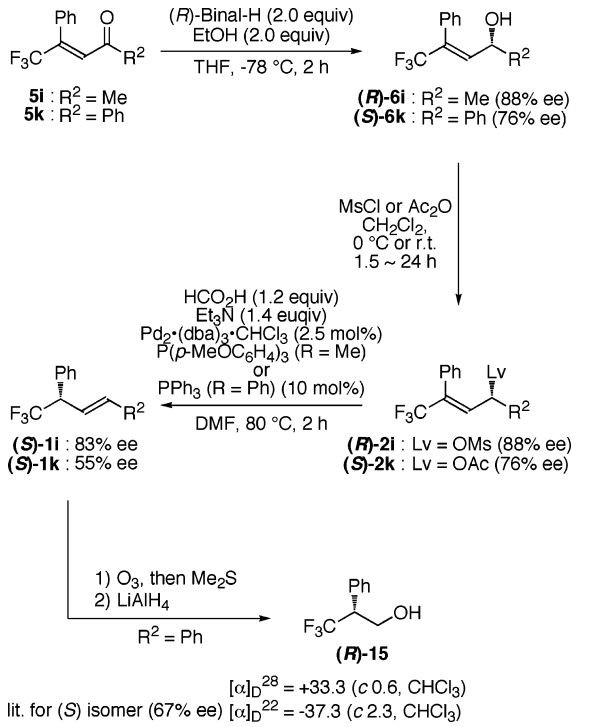


FIGURE 2. A byproduct.

SCHEME 9



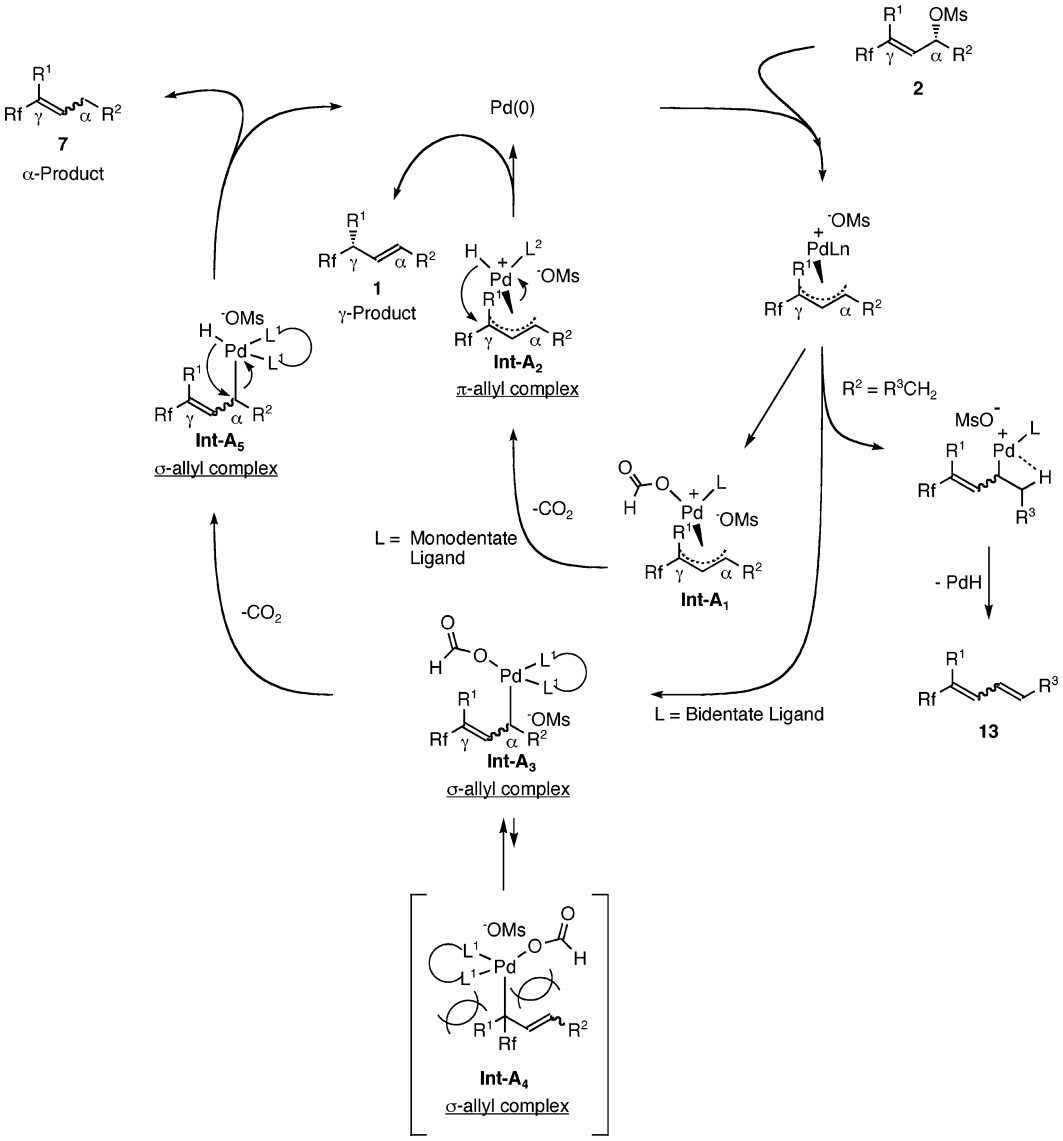
the α-product in 38% yield (entry 3), while the high regioselectivity was observed in the case of a phenyl group as R^2 (entry 4).

It was also found that the R^1 group influenced the present reaction significantly. Thus, when an alkyl group, such as the *n*-$C_{10}H_{21}$ substituent, was employed as R^1, the α- or γ-product was afforded in only 45 or 3% yield, respectively, together with the byproduct **14** (entry 6, Figure 2), though changing the R^1 group from a phenyl to a 4-(*t*-Bu)C_6H_4 group did not affect the reaction (entry 5). Use of a pentafluoroethyl group as a fluoroalkyl group did not influence the reaction significantly (entry 7).

Synthesis of Optically Active Fluorine-Containing Materials. Our attention was thus directed to the preparation of optically active compounds as described in Scheme 9. The optically active starting ester (*R*)-**2i** or (*S*)-**2k** was easily prepared via the enantioselective reduction of **5i** or **5k**, followed by the usual mesylation or acetylation according to the literature method.[8] The optical purity of (*R*)-**6i** or (*S*)-**6k** was determined as 88% ee or 76% ee by HPLC using a chiral column (DAICEL, CHIRALPAK AD-H, and CHIRALPAK OD). When the nonracemic fluoroalkylated ester, (*R*)-**2i** or (*S*)-**2k**, was subjected to the palladium-catalyzed formate reduction as described above, the corresponding γ-product (*S*)-**1i** or (*S*)-**1k** was obtained in 72% or 80% yield, respectively. The stereochemical assignment of **1k** was made as follows. The ozonolysis of **1k** produced crude α-trifluoromethyl aldehyde, which

(8) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709−6706.

SCHEME 10



was immediately reduced with an excess amount of lithium aluminum hydride to give the known compound **15**. Comparison of the observed optical rotation of (*R*)-**15** with its literature value[9] made it possible to determine the absolute configuration of **15** as *R*. Analysis of the optical purity of reduction products by HPLC revealed that (*S*)-**1i** or (*S*)-**1k** had 83% ee or 55% ee. Of great synthetic value is that almost no loss of the optical purity occurs in the reaction of (*R*)-**2i**, strongly suggestive of the present reaction proceeding in an almost complete stereoselective manner. However, the formate reduction of (*S*)-**2k** resulted in a significant decrease of the chirality transfer

Mechanism. A possible reaction mechanism for the Pd(0)-catalyzed formate reduction is outlined in Scheme 10. Thus, the oxidative addition of allyl mesylate to Pd(0), followed by the attack of formate to a palladium center, gives the corresponding π-allylpalladium complex **Int-A$_1$**. In the case of a monodentate ligand as L, the subsequent decarbonation (**Int-A$_2$**) followed by the reductive elimination affords the reduction product. In this process, a palladium metal would be closer to the γ-carbon attached with an Rf group than the α-carbon, due to an extremely electron-withdrawing Rf group.[10] Accordingly, the reductive elimination takes place at the γ-carbon preferentially to give the corresponding γ-product **1**. In the case of a bidentate ligand as L, on the other hand, the palladium has already four ligands, indicating that the double bond in the allylic part cannot coordinate with the palladium anymore, the palladium complex being in a σ-allyl form. In this case, **Int-A$_3$** is more stable than **Int-A$_4$** due to a large steric repulsion between a bulky CF_3, R groups and a palladium moiety. Accordingly, **Int-A$_3$** can be transformed into **Int-A$_5$** via decarbonation, followed by the reductive elimination, giving the corresponding α-product **7** preferentially.

In the case of the substrate **2i**−**o** (except **2j**,**k**) carrying a side chain R^2 ($R^2 = CH_2R^3$), a cationic π-allylpalladium complex may easily be converted into the diene **13** via β-elimination before the attack of the formate ion to the palladium center, when the electron-donating ability of the ligand L on palladium is weak (i.e., L = PPh_3). The use of

(9) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 961−974.

(10) The similar effect was observed in our previous work. See ref 3a,b.

$P(4\text{-}MeOC_6H_4)_3$ as the ligand L, on the other hand, makes the cationic π-allylpalladium complex stable due to its strongly electron-donating ability. As a result, the nucleophilic attack of the formate ion to the palladium center proceeds smoothly, followed by decarbonation and reductive elimination, the α- or γ-product being afforded in good yield.

Conclusion

In summary, we have developed the palladium(0)-catalyzed formate reduction of various allyl mesylates **2**, leading to the desired compounds **1** attached with a fluoroalkyl group at the tertiary carbon. More significantly, the use of chiral allyl mesylate (*R*)-**2i** resulted in the formation of chiral (*S*)-**1i** with almost complete chiralty transfer.

Experimental Section

Typical Procedure for the Palladium-Catalyzed Formate Reduction of Fluoroalkylated Allyl Mesylates. To a DMF solution of palladium catalyst prepared *in situ* by mixing $Pd_2(dba)_3{\cdot}CHCl_3$ (8 mg, 0.008 mmol) and PPh_3 (8 mg, 0.032 mmol) was added 4,4,4-trifluoro-3-(4-methoxyphenyl)-2-butenyl mesylate **2a** (100 mg, 0.32 mmol) at 0 °C. After the reaction mixture was stirred for 10 min at that temperature, a DMF solution of triethylammonium formate, prepared from formic acid (18 mg, 0.38 mmol) and triethylamine (0.06 mL, 0.45 mmol), was added to the reaction mixture, and the solution was stirred for 2 h at 80 °C. The reaction was quenched with NH_4Cl aq, and the whole was extracted with ether three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography with hexane/benzene (10/1) as an eluent to give 1,1,1-trifluoro-2-(4-methoxyphenyl)-3-butene **1a** (57 mg, 82%).

4,4,4-Trifluoro-3-(4-methoxyphenyl)-1-butene (1a): yield 82%. ^1H NMR ($CDCl_3$) δ 3.81 (3H, s), 3.94 (1H, dq, J = 7.4, 9.2 Hz), 5.27 (1H, d, J = 17.3 Hz), 5.35 (1H, d, J = 10.4 Hz), 6.11 (1H, ddd, J = 7.4, 10.4, 17.3 Hz), 6.89 ~ 6.90 (2H, m), 7.23 ~ 7.25 (2H, m); ^{13}C NMR ($CDCl_3$) δ 53.1 (q, J = 27.6 Hz), 55.2, 114.1, 120.4, 126.0 (q, J = 279.9 Hz), 126.4 (q, J = 1.5 Hz), 130.1, 131.7 (q, J = 2.3 Hz), 159.4; ^{19}F NMR ($CDCl_3$) δ −70.0 (3F, d, J = 9.2 Hz); HRMS (EI) calcd for $C_{11}H_{11}F_3O$ (M^+) 216.0762, found 216.0769; IR (neat) ν 1612, 1516, 1252, 1167 cm^{-1}.

Typical Procedure for the Palladium-Catalyzed Formate Reduction of α-Substituted Fluoroalkylated Allyl Mesylates. To a DMF solution of palladium catalyst, prepared *in situ* by mixing $Pd_2(dba)_3{\cdot}CHCl_3$ (65 mg, 0.063 mmol) and $P(p\text{-}MeOC_6H_4)_3$ (88 mg, 0.25 mmol), was added (*R*)-(*E*)-5,5,5-trifluoro-4-phenyl-3-penten-2-yl methansulfonate (**(*R*)-2i**) (736 mg 2.5 mmol) at 0 °C. After the reaction mixture was stirred for 10 min at that temperature, a DMF solution of triethylammonium formate, prepared from formic acid (138 mg, 3.0 mmol) and triethylamine (0.49 mL, 3.5 mmol), was added to the reaction mixture, and the solution was stirred for 2 h at 80 °C. The reaction was quenched with NH_4Cl aq and the whole was extracted with ether three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using hexane to give 5,5,5-trifluoro-4-phenyl-2-pentene ((*S*)-**1i**) in 72% yield.

(*S*)-(*E*)-5,5,5-Trifluoro-4-phenyl-2-pentene (1i): yield 72% (determined by ^{19}F NMR); ^1H NMR ($CDCl_3$) δ 1.74 (3H, d, J = 5.6 Hz), 3.89−3.96 (1H, m), 5.67−5.79 (2H, m), 7.30−7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ 18.0, 53.3 (q, J = 18.2 Hz), 124.4 (q, J = 2.7 Hz), 126.2 (q, J = 279.9 Hz), 128.0, 128.7, 128.8, 132.0, 135.3; ^{19}F NMR ($CDCl_3$) δ −69.8 (3F, d, J = 9.3 Hz); HRMS calcd for $C_{11}H_{10}F_3$ (M − H) 199.0735, found 199.0735; IR (neat) ν 3036, 2922, 1499, 1456 cm^{-1}. This compound was found to be very volatile, so that it could not be purified completely. Therefore, the optical rotation value could not be measured.

Supporting Information Available: ^1H NMR and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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