JOC*Article*

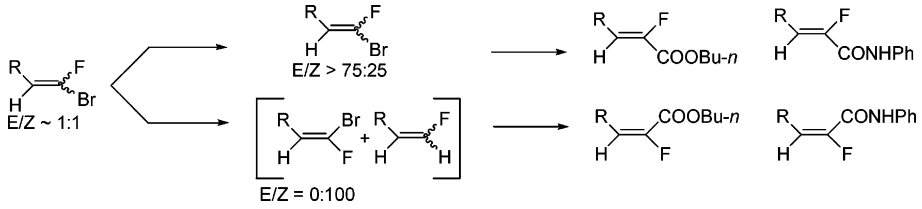
Highly Stereoselective Synthesis of (*E*)- and (*Z*)-α-Fluoro-α,*β*-unsaturated Esters and (*E*)- and (*Z*)-α-Fluoro-α,*β*-unsaturated Amides from 1-Bromo-1-fluoroalkenes via Palladium-Catalyzed Carbonylation Reactions

Jianjun Xu and Donald J. Burton*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242

donald-burton@uiowa.edu

Received February 18, 2005



The highly stereoselective synthesis of (*E*)- and (*Z*)-α-fluoro-α,*β*-unsaturated esters and (*E*)- and (Z)-α-fluoro-α,*β*-unsaturated amides is described. 1-Bromo-1-fluoroalkenes (*E*/*Z* ≈ 1:1), which are readily available starting materials, have been found to isomerize to high *E*/*Z* ratios after storage at −20 °C for 1 week or by photolysis at 254 nm. Since the (*E*)-isomers have been found to react faster than the corresponding (*Z*)-isomers at room temperature in Pd(0)-catalyzed reactions, the palladium-catalyzed carboalkoxylation of high *E*/*Z* 1-bromo-1-fluoroalkenes lead to a high *Z*/*E* (*Z*/*E* ≥ 98:2) ratio of the α-fluoro-α,*β*-unsaturated esters. When 1-bromo-1-fluoroalkenes (*E*/*Z* ≈ 1:1) were reacted with HCOOH/NBu_3/Pd(II)/DMF, the (*E*)-isomer was selectively reduced, and the remaining (*Z*)-1-bromo-1-fluoroalkenes were recovered in essentially pure isomeric form. The resulting mixture of (*Z*)-1-bromo-1-fluoroalkenes and the reduced products underwent similar palladium-catalyzed carboalkoxylation reactions at 70 °C, and the (*E*)-α-fluoro-α,*β*-unsaturated esters were stereospecifically obtained. This methodology was also successfully applied for the stereospecific synthesis of (*Z*)- and (*E*)-α-fluoro-α,*β*-unsaturated amides: the palladium-catalyzed carboamidation reaction of high *E*/*Z* and (*Z*)-1-bromo-1-fluoroalkenes lead to pure (*Z*)- and (*E*)-α-fluoro-α,*β*-unsaturated amides, respectively.

Introduction

α-Fluoro-α,*β*-unsaturated esters have attracted increased interest since they can serve as useful intermediates in the synthesis of a variety of biologically active compounds.[1,2] Substitution of a fluorine atom adjacent to the ester functionality usually increases the biological activity of these compounds significantly, as exemplified in vitamin A and pheromone chemistry.[2] Therefore, α-fluoro-α,*β*-unsaturated esters have been widely employed as precursors in the preparation of monofluorinated retinoids,[3] fluorinated analogues of insect sex pheromones,[4] and pyrethroids.[5] This class of α,*β*-unsaturated esters has also been converted into high ee 2-fluoroalkanoic acids via asymmetric hydrogenation;[6] therefore, the preparation of isomerically pure (*E*)- and (*Z*)-α-fluoro-α,*β*-unsaturated esters has become a key challenge for synthetic chemists.

α,*β*-Unsaturated amides can serve as Michael acceptors to afford an important method of carbon−carbon bond formation.[7] The Michael addition reactions of cuprate reagents[8] or Grignard reagents[9] to α,*β*-unsaturated amides have been reported. Some compounds that con-

(1) Shen, Y.; Zhou, Y. *J. Fluorine Chem.* **1993**, *61*, 247−251.
(2) Fieler, R.; Kobayashi, Y. *Biomedical Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1982.
(3) Liu, R. S. H.; Matsumoto, H.; Asato, A. E.; Denny, M.; Schichida, Y.; Yoshizawa, T.; Dahlquist, F. W. *J. Am. Chem. Soc.* **1981**, *103*, 7195−7201.
(4) Camps, F.; Coll, J.; Fabrias, G.; Guerrero, A. *Tetrahedron* **1984**, *40*, 2871−2878.
(5) Arlt, D.; Jautelat, M.; Lantzsch, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 703−818.
(6) Saburi, M.; Shao, L.; Sakurai, T.; Uchida, Y. *Tetrahedron Lett.* **1992**, *33*, 7877−7880.
(7) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series Vol. 9; Pergamon Press: Oxford, 1992.

10.1021/jo050314a CCC: $30.25 © 2005 American Chemical Society
Published on Web 04/21/2005

tain α,β-unsaturated amide moieties have been shown to be irreversible inhibitors of guinea pig liver transglutaminase (TGase)[10] or potential ACE (angiotensin converting enzyme) inhibitors.[11] Due to the introduction of fluorine neighboring the amide structure unit, α-fluoro-α,β-unsaturated amides have shown very important applications in medicinal chemistry: for example, α-fluoro-α,β-unsaturated amide derivatives have been studied as potential anticonvulsants,[12] glucagon antagonists,[13] CCR5 receptor modulators,[14] IMPDH enzyme inhibitors,[15] and retinoid metabolism inhibitors.[16] However, to the best of our knowledge, no systematic synthetic method for α-fluoro-α,β-unsaturated amides has been reported, although there are some methods describing the synthesis of nonfluorinated α,β-unsaturated amides.[17,18] The lack of a reliable, convenient, and stereospecific synthetic method of α-fluoro-α,β-unsaturated amides has inhibited further medicinal chemistry studies of this category of compounds.

A variety of synthetic methods have been reported on the stereoselective synthesis of (*Z*)-α-fluoro-α,β-unsaturated esters. Some examples include Cr(II)-mediated olefination of aldehydes with trifluoroacetates,[19] Pommelet's method by Durst reaction from 3-hydroxy-2-fluoro-2-sulfinyl esters,[20] the tandem reduction−olefination of α-fluoro-α-acylphosphonoesters,[21] the Wittig reaction between aldehydes and trifluorinated ylides,[22] the heteropoly acid-medicated ethanolysis of α-substituted β,γ,γ-trifluoroallyl alcohols,[23] dehydroxylation of α-fluoro-β-hydroxy esters,[24] thermal elimination reaction from α-fluorosulfoxide,[25] the condensation reaction between 2-fluoro-3-oxo-succinnates and aldehydes,[26] multistep preparation from trifluorovinyl compounds,[27] the reaction between α-azoesters and phenylselenenyl fluoride equivalent, followed by oxidation by H_2O_2,[28] Peterson olefination,[29] one-pot reaction between aldehydes or ketones and diethyl chloromalonate in the "spray-dried" KF-sulfolane system,[30] reductive coupling-elimination reaction between methyl dichlorofluoroacetate and carbonyl compounds in the presence of zinc(0)−copper(I) chloride,[31] and reaction between β,β′-dihydroxy carboxylic acid esters and vanadium(V) trichloride oxide.[32]

Fewer methods have been documented for the stereoselective synthesis of (*E*)-α-fluoro-α,β-unsaturated esters. The Wadsworth−Horner−Emmons reaction between fluorocarboalkoxy-substituted dialkylphosphonate anion and carbonyl compounds has been the most popular choice.[33] Preparation from α-halo-β-mesyloxy sulfoxides has also been reported.[34]

Although many of these methods provide a convenient route to prepare either the (*E*)- or (*Z*)-α-fluoro-α,β-unsaturated esters stereoselectively, there is no general method that can offer a straightforward route to *both* (*E*)- and (*Z*)-isomers. Therefore, we explored our methodology for the stereoselective synthesis of (*E*)- and (*Z*)-α-fluoro-α,β-unsaturated esters and amides from high *E*/*Z* and (*Z*)-1-bromo-1-fluoroalkenes via palladium-catalyzed carboalkoxylation/carboamidation reactions. A portion of this work has been reported as a preliminary communication.[35]

Results and Discussion

1-Bromo-1-fluoroalkenes (*E*/*Z* ≈ 1:1) **1**, which can be readily prepared from $CFBr_3$, PPh_3, and RCHO,[36] are potential synthons for the preparation of (*Z*)- and (*E*)-α-fluoro-α,β-unsaturated esters. However, the (*E*)- and (*Z*)-isomers are difficult to separate by either simple distillation or column chromatography.

McCarthy and co-workers have separated (*E*)- and (*Z*)-1-bromo-1-fluoro-2-phenylethylene by gas chromatography (the (*E*)-isomer has an *E*/*Z* ratio of 92:8).[37] As most of the reactions were carried out on a millimolar scale, it is unlikely to be of practical use for large-scale

(8) Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem*. **1993**, *58*, 766−770. (b) Melnyk, O.; Stephan, E.; Pourcelot, G.; Cresson, P. *Tetrahedron* **1992**, *48*, 841−850. (c) Oppolzer, W.; Kingma, A. J.; Poli, G. *Tetrahedron* **1989**, *45*, 479−488. (d) Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett*. **1986**, *27*, 369−372.

(9) Mukaiyama, T.; Iwasawa, N. *Chem. Lett*. **1981**, 913−916.

(10) Marrano, C.; de Macedo, P.; Keillor, J. W. *Bioorg. Med. Chem*. **2001**, *9*, 1923−1928.

(11) Choo, H. Y. P.; Peak, K. H.; Park, J.; Kim, D. H.; Chung, H. S. *Eur. J. Med. Chem*. **2000**, *35*, 643−648.

(12) Coulton, S.; Harling J. D.; Porter, R. A.; Thompson, M. WO PCT 2000/007 993, 2000.

(13) (a) Ling, A.; Gregor, V.; Gonzalez, J.; Hong, Y.; Kiel, D.; Kuki, A.; Shi, S.; Naerum, L.; Madsen, P.; Sams, C.; Lau, J.; Plewe, M. B.; Feng, J.; Teng, M.; Johnson, M. D.; Teston, K. A.; Sidelmann, U. G.; Knudsen, L. B. US Patent 107 400, 2003. (b) Gonzales, J.; Sams, C.; Teng, M.; Ling, A.; Gregor, V.; Hong, Y.; Kiel, D.; Kuki, A.; Shi, S.; Naerum, L.; Madsen, P.; Lau, J.; Plewe, M. B.; Feng, J.; Johnson, M. D.; Teston, K. A.; Sidelmann, U. G.; Knudsen, L. B. WO PCT 99/01 423, 1999.

(14) Bondinell, W. E. WO PCT 2000/006 153, 2000.

(15) Gu, H. H.; Dhar, T. G.; Murali, I. E.; WO PCT 2000/026 197, 2000.

(16) Mabire, D.; Adelinet, C. D.; Csoka, I. C.; Venet, M. G. WO PCT 99/29 674, 1999.

(17) Choi, T. L.; Chatterjee, A. K.; Grubbs, R. H. *Abstracts of Papers*, 222nd American Chemical Society National Meeting, Chicago, IL, Aug 26−30, 2001; American Chemical Society: Washington, DC, 2001; 303-ORGN, Part 2.

(18) Kojima, S.; Inai, H.; Hidaka, T.; Ohkata, K. *Chem. Commun*. **2000**, 1795−1796.

(19) Barma, D. K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falck, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 3218−3219.

(20) (a) Chevrie, D.; Lequeux, T.; Pommelet, J. C. *Org. Lett*. **1999**, *1*, 1539−1541. (b) Jouen, C.; Lemaitre, S.; Lequeux, T.; Pommelet J. C. *Tetrahedron* **1998**, *54*, 10801−10810.

(21) Sano, S.; Saito, K.; Nagao, Y. *Tetrahedron Lett.* **2003**, *44*, 3987−3990.

(22) Suzuki, Y.; Sato, M.; *Tetrahedron Lett.* **2004**, *45*, 1679−1681.

(23) Funabiki, K.; Sawa, K.-i.; Shibata, K.; Mitsui, M. *Synlett* **2002**, *7*, 1134−1136.

(24) Elkik, E.; Francesch, C. *Bull. Soc. Chim. Fr*. **1986**, *3*, 423−428.

(25) Allmendinger, T. *Tetrahedron* **1991**, *47*, 4905−4914.

(26) (a) Bergmann, E. D.; Shahak, I. *J. Chem. Soc*. **1961**, 4033−4038. (b) Clemenceau, D.; Cousseau, J. *Tetrahedron Lett*. **1993**, *34*, 6903−6906.

(27) Park, H. M.; Uegaki, T.; Konno, T.; Ishihara, T.; Yamanaka, H. *Tetrahedron Lett*. **1999**, *40*, 2985−2988.

(28) Usuki, Y.; Iwaoka, M.; Tomoda, S. *J. Chem. Soc., Chem. Commun*. **1992**, 1148−1150.

(29) Lin, J.; Welch, J. T. *Tetrahedron Lett*. **1998**, *39*, 9613−9616.

(30) Kitazume, T.; Ishikawa, N. *Chem. Lett*. **1981**, 1259−1260.

(31) Ishihara, T.; Kuroboshi, M. *Chem. Lett*. **1987**, 1145−1148.

(32) Ishihara, T.; Shintani, A.; Yamanaka, H.; *Tetrahedron Lett*. **1998**, *39*, 4865−4868.

(33) (a) Thenappan, A.; Burton, D. J. *J. Org. Chem*. **1990**, *55*, 4639−4642. (b) Machleidt, H.; Wessendorf, R. *Liebig Ann. Chem*. **1964**, *674*, 1−10. (c) Daubresse, N.; Chupeau, Y.; Francesch, C.; Lapierre, C.; Pollet, B.; Rolando, C. *Chem. Comm*. **1997**, 1489−1490. (d) Sano, S.; Ando, T.; Yokoyama, K.; Nagao, Y. *Synlett* **1998**, *7*, 777−779.

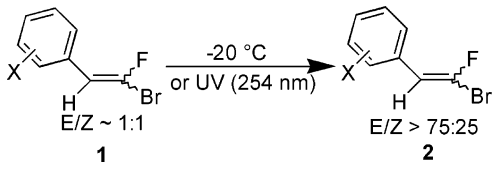
(34) Satoh, T.; Itoh, N.; Onda, K.-i.; Kitoh, Y.; Yamakawa, K. *Tetrahedron Lett*. **1992**, *33*, 1483−1484.

(35) Xu, J.; Burton, D. J. *Org. Lett*. **2002**, *4*, 831−833.

(36) (a) Vanderhaar, R. W.; Burton, D. J.; Naae, D. G. *J. Fluorine Chem*. **1971/72**, *1*, 381−383. (b) Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev*. **1996**, *96*, 1641−1715. (c) Burton, D. J. *J. Fluorine Chem*. **1983**, *23*, 339−357.

(37) Chen, C.; Wilcoxen, K.; Strack, N.; McCarthy, J. R. *Tetrahedron Lett*. **1999**, *40*, 827−830.

SCHEME 1. Preparation and Isomerization of 1-Bromo-1-fluoroalkenes



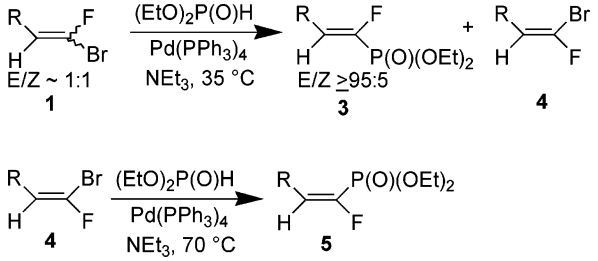
preparative purposes. It has been reported that a few (*Z*)-1-bromo-1-fluoroalkenes could be prepared by bromination of (*E*)-2-fluoro-3-phenylacrylic acid followed by debromocarboxylation,[38] although this route takes several steps.[24,39] Rolando and co-workers also reported the isomerization of (Z)-1-bromo-1-fluoroalkenes to high *E*/*Z* ratios catalyzed by $Pd(OAc)_2$ at 110 °C; however, this route was not thoroughly studied and was only partially successful.[38] Recently, McCarthy and co-workers noted the isomerization of (*Z*)-1-bromo-1-fluoro-2-phenylethylene to an *E*/*Z* ratio of 92:8.[37] In our hands, the addition of Br_2 to 1-bromo-1-fluoro-2-phenylethylene was only partially successful, and the saturated addition product dominated. Only low yields (<20%) of high *E*/*Z* ratio 1-bromo-1-fluoro-2-phenylethylene could be obtained by this procedure.

Recently, we found that 1-bromo-1-fluoroalkenes (1:1) **1** isomerize to high *E*/*Z* ratio (*E*/*Z* ≥ 75:25) **2** when they are stored at −20 °C (Scheme 1).[40] Presumably, this isomerization is caused by a trace amount of bromine in the products.[35,40] For 1-bromo-1-fluoroalkenes (R = phenyl or substituted phenyl groups), the isomerization proceeded smoothly; for others (R = 1-naphthyl or alkyl groups), no obvious isomerization was observed. Alternatively, a similar isomerization was found to occur by photolysis of the *E*/*Z* mixture at 254 nm.[40] For example, an *E*/*Z* mixture of *o*-$ClC_6H_4CH{=}CFBr$ (*E*/*Z* = 63:37) isomerized to an *E*/*Z* mixture of 78:22 cleanly after photolysis at 254 nm for 1 h.

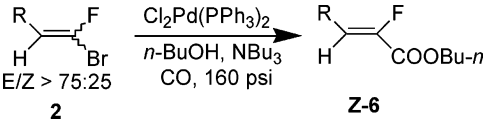
These high *E*/*Z* ratio 1-bromo-1-fluoroalkenes are utilized in the preparation of (*Z*)-α-fluoro-α,β-unsaturated esters. Recently, we reported that the (*E*)-isomer in **1** reacts faster than the corresponding (*Z*)-isomer at room temperature.[41] For example, when **1** was reacted with $Pd(PPh_3)_4$, $(EtO)_2P(O)H$, and NEt_3 at 35 °C, high *E*/*Z* ratio (*E*/*Z* = 95:5) α-fluorovinyl phosphonates were formed and pure (*E*)-α-fluorovinyl phosphonate was isolated. At the same time, most of the (*Z*)-1-bromo-1-fluoroalkene **4** could be recovered. Similar coupling reaction of recovered **4** at 70 °C led to (*Z*)-α-fluorovinyl phosphonates **5** stereospecifically (Scheme 2).[41a]

A stereospecific palladium-catalyzed carboalkoxylation of 2-substituted-1,2-difluorovinyl iodides has been developed in this research group.[42] Therefore, we tested similar palladium-catalyzed carboalkoxylation of **2** at room temperature (Scheme 3). When **2** was reacted with $Cl_2Pd(PPh_3)_2$ (4 mol %), NBu_3, *n*-BuOH, and CO (160 psi) at room temperature, the (*E*)-isomers, which dominated in **2**, reacted faster than the corresponding (*Z*)-isomers at room temperature, and high *Z*/*E* ratios were obtained for the corresponding α-fluoro-α,β-unsaturated esters in the reaction mixture. The products (*Z*)-α-fluoro-α,β-unsaturated esters **Z-6** could be separated pure or obtained in very high *Z*/*E* ratios (Table 1). For example, after the reaction of the 1-bromo-1-fluoro-2-(4-chlorophenyl)alkenes (*E*/*Z* = 87:13) with *n*-BuOH, NBu_3, $Cl_2Pd(PPh_3)_2$, and CO (160 psi) for 144 h at room temperature, ^{19}F NMR analysis of the reaction mixture showed that the resulting product, (*Z*)-*n*-butyl 3-(4-chlorophenyl)-2-fluoropropenoate (**Z-6d**), had a *Z*/*E* ratio of 99:1. After workup and purification by column chromatography, pure **Z-6d** was obtained in 78% yield. The conversion, which was calculated on the basis of the amount of (*E*)-isomer in the starting 1-bromo-1-fluoroalkenes, was 89%.

SCHEME 2. Preparation of (*E*)- and (*Z*)-α-Fluorovinyl Phosphonates by Kinetic Separation Methodology



SCHEME 3. Preparation of (*Z*)-α-Fluoro-α,β-unsaturated Esters



A new kinetic separation methodology was developed for the separation of (*Z*)-1-bromo-1-fluoroalkene from its *E*/*Z* mixture. Presumably, similar palladium-catalyzed carboalkoxylation of (*Z*)-1-bromo-1-fluoroalkenes at higher temperature could lead to (*E*)-α-fluoro-α,β-unsaturated esters stereospecifically. The separation of **4** from an *E*/*Z* mixture **1** is the key problem. Therefore, we decided to selectively reduce the (*E*)-isomers by a palladium-catalyzed reaction, so that the (*Z*)-1-bromo-1-fluoroalkenes **4** could be recovered. For that purpose, the reducing system of HCOOH/NBu_3/Pd(II)/DMF was examined. This system has been used in the reduction of vinyl triflate[43] and aryl halides.[44] Similar reduction using HCOONa/Pd(II)/DMF has also been reported.[45]

The reduction of **1** was successful; all of the (*E*)-isomer (as well as a small amount of (*Z*)-isomer) was reduced, and most of the (*Z*)-1-bromo-1-fluoroalkenes **4** remained unreacted. This reaction could be used to recover **4** from **1** (Scheme 4). For example, the reaction of 1-bromo-1-fluoro-2-phenylethylene **1a** (*E*/*Z* = 44:56) with formic acid, tributylamine, and $Cl_2Pd(PPh_3)_2$ in DMF at 35 °C

(38) Eddarir, S.; Francesch, C.; Mestdagh, H.; Rolando, C. *Bull. Soc. Chim. Fr*. **1997**, *134*, 741−755.
(39) (a) Elkik, E.; Francesch, C. *Bull. Soc. Chim. Fr*. **1973**, 1277−1280; 1281−1285. (b) Etemad-Moghadam, G.; Seyden-Penne, J. *Bull. Soc. Chim. Fr*. **1985**, 448−454.
(40) Xu, J.; Burton, D. J. *Tetrahedron Lett*. **2002**, *43*, 2877−2879.
(41) (a) Zhang, X.; Burton, D. J. *J. Fluorine Chem*. **2001**, *112*, 47−54. (b) Zhang, X.; Burton, D. J. *J. Fluorine Chem*. **2001**, *112*, 317−324.
(42) Wesolowski, C. A.; Burton, D. J. *Tetrahedron Lett*. **1999**, *40*, 2243−2246.
(43) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett*. **1984**, *25*, 4821−4824.
(44) Cortese, N. A.; Heck, R. F. *J. Org. Chem*. **1977**, *42*, 3491−3498.
(45) Leung, S. H.; Edington, D. G.; Griffith, T. E.; James, J. J. *Tetrahedron Lett*. **1999**, *40*, 7189−7191.

TABLE 1. Preparation of (Z)-α-Fluoro-α,β-unsaturated Esters from High *E/Z* 1-Bromo-1-fluoroalkenes (Scheme 3)

entry	R	*E/Z* of **2**	*T* (°C)	time (h)	*Z/E* of isolated **Z-6**[a]	*Z/E* in the mixture[b]	yield (%) (conversion, %)[c]
1	Ph (**2a**)	88:12	rt	57	99:1 **Z-6a**	99:1	72 (82)
2	*o*-ClC_6H_4 (**2b**)	82:18	rt	96	99:1 **Z-6b**	99:1	78 (95)
3	*p*-$OMeC_6H_4$ (**2c**)	81:19	rt	258	100:0 **Z-6c**	98:2	73 (91)
4	*p*-ClC_6H_4 (**2d**)	88:12	rt	134	100:0 **Z-6d**	99:1	78 (89)
5	*p*-FC_6H_4 (**2e**)	87:13	rt	144	100:0 **Z-6e**	96:4	75 (86)
6	*m*-$NO_2C_6H_4$ (**2f**)	81:19	rt	96	100:0 **Z-6f**	97:3	67 (83)
7	$PhC(CH_3)H$ (**2g**)	83:17	45	115	98:2 **Z-6 g**	98:2	56 (67)

[a] All products gave satisfactory ^{19}F, ^1H, and ^{13}C NMR and GC−MS, HRMS (or elemental analysis) data. [b] *Z/E* ratios were determined by ^{19}F NMR analysis of the reaction mixtures when the reactions were completed. [c] Conversion was calculated on the basis of the amount of (*E*)-1-bromo-1-fluoroalkenes in **2**.

SCHEME 4

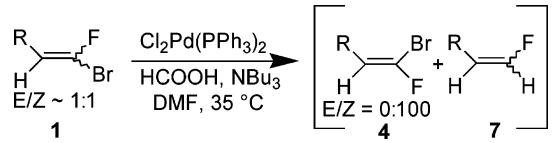


TABLE 2. Kinetic Separation of (Z)-1-Bromo-1-fluoroalkenes from *E/Z* Mixtures (Scheme 4)

entry	R	time (h)	*E/Z* of **1**	yield (recovery) of **4**[a] (%)	*E/Z* of **4**
1	Ph (**1a**)	75	44:56	21 (38)[b]	2:98 **4a**
2	Ph (**1a**)	143	43:57	(83)	0:100 **4a**
3	*o*-ClC_6H_4 (**1b**)	141	48:52	(81)	0:100 **4b**
4	*o*-ClC_6H_4 (**1b**)	171	26:74	(57)	0:100 **4b**
5	*p*-$MeOC_6H_4$ (**1c**)	135	51:49	22 (45)[b]	0.5:99.5 **4c**
6	*p*-$MeOC_6H_4$ (**1c**)	110	51:49	(75)	0:100 **4c**
7	PhC(Me)H (**1g**)	156	36:64	(82)	0:100 **4g**
8	1-naphthyl (**1h**)	129	48:52	(77)	0:100 **4h**
9	*n*-C_7H_5 (**1i**)	121	43:57	(37)	0:100 **4i**

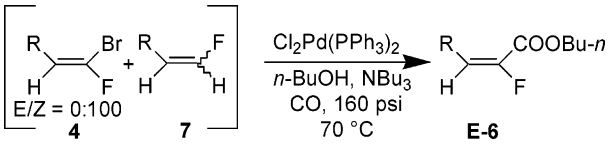
[a] Recovery (number in the parentheses) was calculated on the basis of the amount of **4** obtained and the amount of the (*Z*)-isomer in the starting *E/Z* mixture **1**. [b] **4** was separated from **7** by distillation using a Vigreux column.

for 75 h gave 21% (*Z*)-1-bromo-1-fluoro-2-phenylethylene (*E/Z* = 2:98, recovery 38%) as well as the reduced products (Table 2, entry 1).

Problems arose when we applied this method to the preparation of **4** in larger quantities (>100 mmol). The reactions went smoothly; however, when we tried to separate pure **4** from the mixture by silica gel column chromatography, it proved to be difficult for most substrates. A repeated distillation of the E/Z mixture of 1-bromo-1-fluoroalkenes using a Vigreux column under full vacuum led to pure (*Z*)-1-bromo-1-fluoroalkenes; however, we noticed the formation of 1% or 2% of the (*E*)-isomer, formed by isomerization of the (*Z*)-isomer in the process of distillation (Table 2, entries 1 and 5). The isolation of (*Z*)-1-bromo-1-fluoroalkenes was time-consuming, and the yields were lowered accordingly.

An effective solution to this problem was not to separate **4** from **7** at this stage. Instead, we directly used the mixture of **4** and **7** in the palladium-catalyzed reactions and separated the product from **7** at that time. This decision was based on the following considerations: the reduced products **7** generally do not participate in further palladium-catalyzed reactions (such as carboalkoxylation); the products of the reaction (for example, (*E*)-α-fluoro-α,β-unsaturated esters) can easily be separated from **7** by column chromatography; and the relative molar

SCHEME 5



ratios of **4** and **7** in the mixture can be easily determined by ^{19}F NMR analysis, which was utilized to calculate the weight percentage of **4** in a mixture of **4** and **7**. This kinetic separation method successfully led to several 1-bromo-1-fluoroalkenes (*E/Z* = 0:100) **4** and **7** (Table 2).

The methodology to prepare (*E*)-α-fluoro-α,β-unsaturated esters **E-6** from **4** was tested. First, **4a** (*E/Z* = 2:98) was used as the starting material. It was reacted with *n*-BuOH, NBu_3, $Cl_2Pd(PPh_3)_2$, and CO (160 psi) at 70 °C (Scheme 5). After 81 h, ^{19}F NMR analysis of the reaction mixture showed that the reaction was completed and that the products had a *Z/E* ratio of 98:2. The reaction was presumably stereospecific since the starting *E/Z* ratio was 2:98. After workup and purification by silica gel column chromatography, the corresponding *n*-butyl 2-fluoro-3-phenylpropenoate (*Z/E* = 98:2) was obtained in 81% yield (Table 3).

Therefore, we directly utilized the mixtures of **4** and **7** as the starting materials in the carboalkoxylation reaction. Their reactions with *n*-BuOH, NBu_3, $Cl_2Pd(PPh_3)_2$, and CO (160 psi) at 70 °C were also successful (Table 3). When these reactions were completed, ^{19}F NMR analysis showed that the products had a *Z/E* ratio of 100:0. Again, this palladium-catalyzed carboalkoxylation reaction was shown to be stereospecific, since the starting 1-bromo-1-fluoroalkenes had *E/Z* ratios of 0:100. The products **E-6** could be obtained pure; some products, however, were shown to partially isomerize in the process of isolation. For example, the mixture of **4c** (*E/Z* = 0:100) and **7** gave a *Z/E* ratio of 100:0 by ^{19}F NMR analysis of the reaction mixture when the reaction was completed. After workup and purification by silica gel column chromatography, *n*-butyl 2-fluoro-3-(4-methoxyphenyl)propenoate **E-6c** (*Z/E* = 98:2) was obtained; 2% of the product had isomerized in the process of purification.

The carboalkoxylation reaction of (*Z*)-1-bromo-1-fluoroalkenes is stereospecific; this is similar to the carboalkoxylation reactions of 2-substituted-1,2-difluoro-1-iodoalkenes and α,β-difluoro-β-iodostyrenes.[42] However, it has been reported by Heck and co-workers that nonfluorinated vinyl halides can suffer from isomerization problems in similar carboalkoxylation reactions.[46] For example, (Z) *n*-BuCH=CHI leads to (Z) *n*-BuCH=CHCOOBu-*n* and (E) *n*-BuCH=CHCOOBu-*n* in 79% and 6% yield, respectively.[46]

TABLE 3. Preparation of (*E*)-α-Fluoro-α,β-unsaturated Esters (Scheme 5)

entry	R	*E*/*Z* of **4**	*T* (°C)	time (h)	*Z*/*E* of **E-6**[a]	yield[b] (%)
1	Ph (**4a**)	2:98[c]	70	81	2:98 **E-6a**	81
2	Ph (**4a**)	0:100	70	180	0:100 **E-6a**	90
3	*o*-ClC_6H_4 (**4b**)	0:100	70	125	0:100 **E-6b**	94
4	*p*-$OMeC_6H_4$ (**4c**)	0:100	70	155	2:98[d] **E-6c**	79
5	$PhC(CH_3)H$ (**4g**)	0:100	70	161	0:100 **E-6g**	92
6	1-naphthyl (**4h**)	0:100	70	160	7:93[d] **E-6h**	81
7	*n*-C_7H_{15} (**4i**)	0:100	70	160	inseparable	inseparable

[a] All products gave satisfactory ^{19}F, ^{1}H, and ^{13}C NMR and GC−MS, HRMS data. [b] Isolated yield. [c] The starting material did not contain reduced products. [d] *Z*/*E* ratio was 100:0 when the reaction was completed; isomerization happened to the product in the process of separation.

TABLE 4. Preparation of (*Z*)-α-Fluoro-α,β-unsaturated Amides (Scheme 6)

entry	R	*E*/*Z* of **2**	*T* (°C)	time (h)	*Z*/*E* of **Z-8**[a]	*Z*/*E* in mixture[b]	yield (%) (conversion, %)[c]
1	Ph (**2a**)	85:15	rt	90[d]	100:0 **Z-8a**	94:6	46 (54)
2	*o*-ClC_6H_4 (**2b**)	82:18	rt	148	100:0 **Z-8b**	89:11	74 (90)
3	*p*-$MeOC_6H_4$ (**2c**)	81:19	rt	336	100:0 **Z-8c**	96:4	70 (87)
4	*p*-ClC_6H_4 (**2d**)	88:12	rt	94	100:0 **Z-8d**	95:5	44 (50)
5	*p*-FC_6H_4 (**2e**)	87:13	rt	140	100:0 **Z-8e**	95:5	77 (89)
6	*m*-$NO_2C_6H_4$ (**2f**)	81:19	rt	110	100:0 **Z-8f**	98:2	46 (57)
7	$PhC(CH_3)H$ (**2g**)	83:17	50	117	100:0 **Z-8g**	97:3	55 (64)

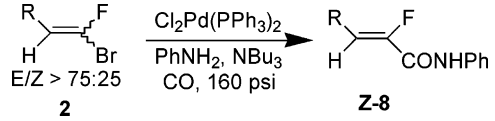
[a] All products gave satisfactory ^{19}F, ^{1}H, and ^{13}C NMR and GC−MS, HRMS data. [b] *Z*/*E* was obtained by ^{19}F NMR analysis of the reaction mixture when the reaction was completed. [c] The conversion was calculated on the basis of the amount of (*E*)-1-bromo-1-fluoroalkenes in the starting materials. [d] NEt_3 was used instead of NBu_3.

TABLE 5. Preparation of (*E*)-α-Fluoro-α,β-unsaturated Amides (Scheme 7)

entry		*E*/*Z* of **4**	*T* (°C)	time (h)	*Z*/*E* of **E-8**[a]	yield (%)
1	Ph (**4a**)	0:100	70	182	0:100 **E-8a**	25
2	o-ClC_6H_4 (**4b**)	0:100	70	140	0:100 **E-8b**	27
3	*p*-$MeOC_6H_4$ (**4c**)	0:100	70	139	inseparable	inseparable
4	$PhC(CH_3)H$ (**4g**)	0:100	70	109	0:100 **E-8g**	74
5	1-naphthyl (**4h**)	0:100	70	175	0:100 **E-8h**	42
6	*n*-C_7H_{15} (**4i**)	0:100	70	122	inseparable	inseparable

[a] All products gave satisfactory ^{19}F, ^{1}H, and ^{13}C NMR and GC−MS and HRMS data.

SCHEME 6

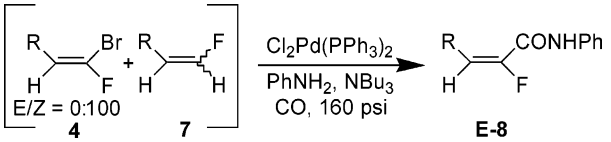


High *E*/*Z* ratios and (*Z*)-1-bromo-1-fluoroalkenes were also used as the starting material in the preparation of (*Z*)-and (*E*)-α-fluoro-α,β-unsaturated amides. Following the success with the highly stereoselective preparation of (*Z*)- and (*E*)-α-fluoro-α,β-unsaturated esters, we begun to explore the preparation of (*Z*)- and (*E*)-α-fluoro-α,β-unsaturated amides by similar methodology. Therefore, aniline replaced the *n*-BuOH in above palladium-catalyzed reactions of high *E*/*Z* and (*Z*)-1-bromo-1-fluoroalkenes.

The reactions between **2** and aniline, NBu_3, $Cl_2Pd(PPh_3)_2$, and CO (160 psi) at room temperature (except 50 °C for **2g**) were carried out smoothly, and high *Z*/*E* ratios were detected for the corresponding amide products by ^{19}F NMR analysis of the reaction mixture (Scheme 6). After separation by silica gel column chromatography followed by recrystallization, pure (*Z*)-α-fluoro-α,β-unsaturated amide **Z-8** was obtained (Table 4).

Starting from the mixtures of **4** and **7**, similar reactions with aniline, NBu_3, $Cl_2Pd(PPh_3)_2$, and CO (160 psi) at

SCHEME 7



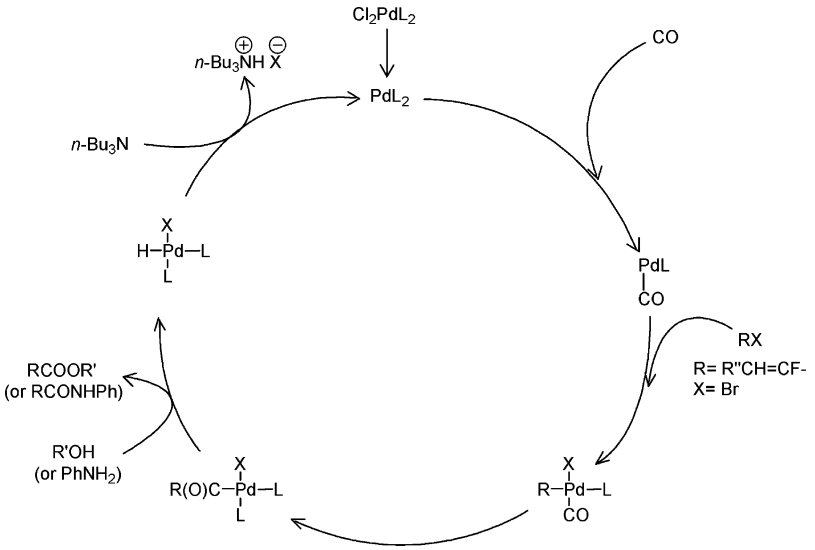
70 °C gave (*E*)-α-fluoro-α,β-unsaturated amides **E-8** (Scheme 7). When the reactions were completed, ^{19}F NMR analysis of the mixture showed that *Z*/*E* ratios of the products were 0:100. Most products were successfully separated pure in moderate yields (Table 5). However, in certain cases, an unknown impurity in the mixture made it difficult to separate the desired products (R = *p*-$MeOC_6H_4$−, *n*-C_7H_{15}−). When R = *o*-ClC_6H_4−, the yield of the desired product was very low. A side product, which had very close chemical shift and the same coupling patterns with the desired product, was observed by ^{19}F NMR. Attempts to separate this side product failed. This side product could be (E) RCH=CFC(O)C(O)NHPh which was formed at high temperature.[47]

Most **Z-8** and **E-8** showed a doublet of doublet (dd) pattern in their ^{19}F NMR spectra in $CDCl_3$. The second doublet (with typical coupling constants of 3−6 Hz) is presumably due to the intramolecular coupling between F and HN. To test this hypothesis, (*Z*)-2-fluoro-3,*N*-

(46) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318−3326.

(47) Uozumi, Y.; Arii, T.; Watanabe, T. *J. Org. Chem.* **2001**, *66*, 5272−5274.

SCHEME 8. Proposed Mechanism for the Carboalkoxylation and Carboamidation Reaction



diphenylacrylamide was used as a representative of these amides. ^{19}F NMR of this amide in $CDCl_3$ showed a doublet of doublet pattern; when one drop of D_2O was added to the NMR solution, ^{19}F NMR analysis of this mixture gave a sharp doublet. Most probably, NH had underwent a fast exchange with D_2O so that the intramolecular coupling between F and HN was no longer detectable.

The carboalkoxylation and carboamidation reactions presumably follow the mechanism proposed by Heck and co-workers (Scheme 8):[46] Cl_2PdL_2 (L = PPh_3) is first reduced to PdL_2; CO is added to PdL_2 and Pd(CO)L is formed; oxidative addition of vinyl halide (RX) to Pd(CO)L leads to the formation of the complex RPdX(CO)L; CO is inserted to the R−Pd bond and $RC(O)PdXL_2$ is formed; R′OH (R′ = *n*-Bu) or $PhNH_2$ attacks the carbonyl group, and the product RCOOR′ (or RCONHPh) leaves; reductive elimination of $HPdXL_2$ by NBu_3 recovers the active catalyst PdL_2. Again, as shown in our previous report,[41] (*Z*)-1-bromo-1-fluoroalkene only participates in the oxidative addition step at higher temperature (70 °C).

Conclusion

1-Bromo-1-fluoroalkenes were successfully employed to prepare (*E*)- and (*Z*)-α-fluoro-α,β-unsaturated esters and (*E*)- and (*Z*)-α-fluoro-α,β-unsaturated amides in high stereoselectivity. 1-Bromo-1-fluoroalkenes were found to isomerize to high *E*/*Z* ratios when stored at −20 °C or by photolysis at 254 nm. Kinetic separation strategy was successfully utilized to prepare (*Z*)-1-bromo-1-fluoroalkenes (*E*/*Z* = 0:100).

Room-temperature palladium-catalyzed carboalkoxylation of high *E*/*Z* 1-bromo-1-fluoroalkenes led to (*Z*)-α-fluoro-α,β-unsaturated esters in high *Z*/*E* ratios; similar carboalkoxylation of (*Z*)-1-bromo-1-fluoroalkenes led to (*E*)-α-fluoro-α,β-unsaturated esters stereospecifically. Starting from high *E*/*Z* and (*Z*)-1-bromo-1-fluoroalkenes, (*Z*)- and (*E*)-α-fluoro-α,β-unsaturated amides were stereospecifically prepared, respectively.

Experimental Section

The preparation and characterization of **Z-6a**, **Z-6b**, **Z-6c**, **Z-6g**, **E-6a**, **E-6b**, **E-6c**, and **E-6g** were described in the preliminary communication;[35] their ^1H and ^{13}C NMR spectra are included in the Supporting Information.

General Procedures for the Preparation of (*Z*)-α-Fluoro-α,β-unsaturated Esters Z-6. An oven-dried 120 mL Hastelloy Parr pressure reactor equipped with a stirring bar was charged with 0.07 g (0.10 mmol) of $Cl_2Pd(PPh_3)_2$, 5 mL of *n*-butanol, and 0.59 g (3.2 mmol) of tri-*n*-butylamine. 1-Bromo-1-fluoroalkene (3.0 mmol, high *E*/*Z* ratio) was added, and the pressure reactor was closed. (*Caution: All reactions should be carried out behind a safety shield in a well-ventilated hood.*) The pressure reactor was pressurized to 160 psi with carbon monoxide, and the pressure was released. This process was repeated four times to rid the system of air. Finally, the pressure reactor was pressurized to 160 psi and was allowed to stir at room temperature (for 1-bromo-1-fluoroalkenes, R = aryl) or in an oil bath at 45 °C (for 1-bromo-1-fluoroalkenes, R = alkyl). The consumption of carbon monoxide could be roughly determined by the reading on the gauge. When the reaction was completed, the reactor was allowed to cool to room temperature (if necessary) and the pressure was carefully released. The reaction mixture was transferred to a separatory funnel containing 100 mL of ethyl acetate. The organic layer was washed with aqueous 10% hydrochloric acid (3 × 15 mL), saturated sodium bicarbonate (2 × 15 mL), and brine (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation, and the crude product was further purified by silica gel column chromatography.

(Z)-*n*-Butyl 3-(4-Chlorophenyl)-2-fluoropropenoate (Z-6d). Similarly, a mixture of 1-bromo-1-fluoro-2-(4-chlorophenyl)ethylene (0.24 g, 1.0 mmol, *E*/*Z* = 88:12), NBu_3 (0.78 g, 1.14 mmol), and $Cl_2Pd(PPh_3)_2$ (0.03 g, 0.04 mmol) in *n*-butanol (6 mL) was reacted with CO at room temperature for 134 h. When the reaction was completed, ^{19}F NMR analysis of the mixture showed that the *Z*/*E* ratio of the crude product was 99:1. Silica gel column chromatography (ethyl acetate/hexanes = 5:95, R_f = 0.35) followed by recrystallization from hexanes gave white crystals: mp 63−65 °C; 0.20 g, yield 78% (conversion 89% based on the consumed (*E*)-1-bromo-1-fluoro-2-(4-chlorophenyl)ethylene), *Z*/*E* = 100:0; ^{19}F NMR ($CDCl_3$) δ −124.6 (d, $^3J_{FH(trans)}$ = 33.8 Hz, 1 F) ppm; ^1H NMR ($CDCl_3$) δ 7.58 (dm, J = 8.5 Hz, 2 H), 7.37 (dm, J = 8.6 Hz, 2 H), 6.86 (d, $^3J_{HF(trans)}$ = 34.7 Hz, 1 H), 4.29 (t, J = 6.6 Hz, 2 H), 1.73 (pentet, J = 7.1 Hz, 2 H), 1.45 (sextet, J = 7.4 Hz, 2 H), 0.98 (t, J = 7.3 Hz, 3 H) ppm; ^{13}C NMR ($CDCl_3$) δ 161.0 (d, J = 34.2 Hz), 147.2 (d, J = 268.0 Hz), 135.4 (d, J = 3.6 Hz), 131.3 (d, J =

(48) King, A. O.; Negishi, E.-i.; Villani, F. J., Jr.; Silveira, A., Jr. *J. Org. Chem.* **1978**, *43*, 358−360.

8.8 Hz), 129.5 (d, J = 5.8 Hz), 128.9, 116.0 (d, J = 4.2 Hz), 65.6, 30.4, 19.0, 13.5 ppm; GC−MS m/z (relative intensity): 258 (M^+ + 2, 11), 257 (4), 256 (M^+, 33), 236 (2), 202 (45), 200 (100), 183 (29), 180 (55), 165 (9), 163 (10), 154 (16), 152 (16), 136 (7), 135 (10), 120 (80), 99 (23); HRMS calcd 256.0666 for $C_{13}H_{14}O_2{}^{35}ClF$, obsd 256.0656.

General Procedures for the Preparation of the Mixture of 4 and 7 from 1. A 100 mL dry flask equipped with a stirring bar and N_2 tee was charged with 0.074 g (0.106 mmol) of $Cl_2Pd(PPh_3)_2$ and 8 mL of dry DMF. Then 6.00 mmol of 1-bromo-1-fluoroalkene ($E/Z \approx$ 1:1, includes (E)-isomer 3.0 mmol) was added, and the solution was stirred at room temperature for 15 min. After the addition of 1.67 g (9.00 mmol, 3.0 equiv) of NBu_3, the reaction mixture was allowed to stir for 5 min and 0.23 g (5.1 mmol, 1.7 equiv) of HCOOH was added. The mixture was stirred at 35 °C. The reaction progress was monitored by ^{19}F NMR analysis of the mixture. When the reaction was completed, the reaction mixture was added directly to a silica gel column and a mixture of **4** and **7** was obtained.

General Procedures for the Preparation of (*E*)-α-Fluoro-α,*β*-unsaturated Esters E-6. An oven-dried 120 mL Hastelloy Parr pressure reactor equipped with a stirring bar was charged with 0.07 g (0.10 mmol) of $Cl_2Pd(PPh_3)_2$, 5 mL of n-butanol, and tri-n-butylamine (0.48 g, 2.6 mmol). A mixture of (Z)-1-bromo-1-fluoroalkene (2.0 mmol) and the reduced olefins was added, and the pressure reactor was closed. (*Caution: All reactions should be carried out behind a safety shield in a well-ventilated hood.*) The pressure reactor was pressurized to 160 psi with carbon monoxide, and the pressure was released. This process was repeated four times to rid the system of air. Finally, this pressure reactor was pressurized to 160 psi and was allowed to stir in an oil bath at 70 °C. The consumption of carbon monoxide could be roughly determined by the reading on the gauge. When the reaction was completed, the reactor was allowed to cool to room temperature and the pressure was carefully released. The reaction mixture was transferred to a separatory funnel containing 100 mL of ethyl acetate. The organic layer was washed with aqueous 10% hydrochloric acid (3 × 15 mL), saturated sodium bicarbonate (2 × 15 mL), and brine (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation, and the crude product was further purified by silica gel column chromatography.

(E)-*n*-Butyl 2-Fluoro-3-(1-naphthyl)propenoate (E-6h). Similarly, a mixture of (Z)-1-bromo-1-fluoro-2-(1-naphthyl)-ethylene (contains 1-bromo-1-fluoro-2-(1-naphthyl)ethylene 0.25 g, 1.0 mmol, E/Z = 0:100) and the reduced olefins, tri-n-butylamine (0.24 g, 1.3 mmol), and $Cl_2Pd(PPh_3)_2$ (0.03 g, 0.04 mmol) in n-butanol (4 mL) was reacted with CO at 70 °C for 160 h. ^{19}F NMR analysis of the reaction mixture showed that the Z/E ratio of the product was 0:100. A colorless liquid was obtained after silica gel column chromatography (ethyl acetate/hexanes = 5:95, R_f = 0.31): 0.22 g, 81% yield, Z/E = 7:93; ^{19}F NMR ($CDCl_3$) δ −116.0 (d, $^3J_{FH(cis)}$ = 19.2 Hz, 1 F) ppm; ^1H NMR ($CDCl_3$) δ 7.81−7.88 (m, 3 H), 7.48−7.51 (m, 2 H), 7.42−7.44 (m, 2 H), 7.33 (d, $^3J_{HF(cis)}$ = 19.3 Hz, 1 H), 3.95 (t, J = 6.4 Hz, 2 H), 1.17 (m, 2 H), 0.86 (sextet, J = 7.4 Hz, 2 H), 0.66 (t, J = 7.1 Hz, 3 H) ppm; ^{13}C NMR ($CDCl_3$) δ 160.2 (d, J = 37.1 Hz), 148.1 (d, $^1J_{CF}$ = 254.7 Hz), 133.0, 131.1 (d, J = 3.0 Hz), 128.6 (d, J = 9.1 Hz), 128.4, 128l.1, 126.8 (d, J = 1.9 Hz), 126.1, 125.7, 124.7, 124.2, 118.5 (d, $^2J_{CF}$ = 23.9 Hz), 104.0, 65.1, 29.6, 18.4, 13.1 ppm; GC−MS, product isomerized on GC column, m/z (relative intensity) of one isomer 273 (M^+ + 1, 10), 272 (M^+, 61), 224 (2), 216 (5), 199 (16), 196 (78), 179 (43), 172 (21), 171 (39), 170 (100), 168 (18), 152 (28), 151 (51); the other isomer 272 (M^+ + 1, 9), 272 (M^+, 57), 216 (4), 199 (13), 196 (73), 179 (30), 171 (100), 170 (75), 168 (12), 152 (21), 151 (35); HRMS calcd 272.1213 for $C_{17}H_{17}FO_2$, obsd 272.1216.

General Procedures for the Preparation of (*Z*)-α-Fluoro-α,*β*-unsaturated Amides Z-8. An oven-dried 120 mL Hastelloy Parr pressure reactor equipped with a stirring bar was charged with 0.07 g (0.10 mmol) of $Cl_2Pd(PPh_3)_2$, 0.36 g (3.8 mmol) of freshly distilled aniline, and 4.0 mL of tri-n-butylamine. A 3.0 mmol portion of high E/Z ratio 1-bromo-1-fluoroalkene was added, and the pressure reactor was closed. (*Caution: All reactions should be carried out behind a safety shield in a well-ventilated hood.*) The pressure reactor was pressurized to 160 psi with carbon monoxide, and the pressure was released. This process was repeated four times to rid the system of air. Finally, this pressure reactor was pressurized to 160 psi and was allowed to stir at room temperature (for 1-bromo-1-fluoroalkenes, R= aryl) or in an oil bath at 50 °C (for 1-bromo-1-fluoroalkenes, R= alkyl). The consumption of carbon monoxide could be roughly determined by the reading on the gauge. When the reaction was completed, the reactor was allowed to cool to room temperature (if necessary) and the pressure was carefully released. The reaction mixture was transferred to a separatory funnel containing 100 mL of ethyl acetate. The organic layer was washed with aqueous 10% hydrochloric acid (3 × 15 mL), saturated sodium bicarbonate (2 × 15 mL), and brine (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation, and the crude product was further purified by silica gel column chromatography. Recrystallization from hexanes gave 100% pure (Z)-α-fluoro-α,β-unsaturated amides.

(*Z*)-2-Fluoro-3,*N*-diphenylacrylamide (Z-8a). Similarly, a mixture of 1-bromo-1-fluoro-2-phenylethylene (0.60 g, 3.0 mmol, E/Z = 85:15), aniline (0.36 g, 3.8 mmol), and $Cl_2Pd(PPh_3)_2$ (0.07 g, 0.10 mmol) in triethylamine (3.5 mL) was reacted with CO at room temperature for 90 h. ^{19}F NMR analysis of the mixture showed that the Z/E ratio of the crude product was 94:6. Silica gel column chromatography (ethyl acetate/hexanes = 15:85, R_f = 0.33) gave white crystals: mp 166−167 °C; 0.33 g, 46% yield (54% conversion based on the consumed (E)-1-bromo-1-fluoro-2-phenylethylene), Z/E = 100:0; ^{19}F NMR ($CDCl_3$) δ −129.9 (dd, $^3J_{FH}$ = 39.6 Hz, $J_{F\cdots HN}$ = 5.1 Hz) ppm; ^1H NMR ($CDCl_3$) δ 8.01 (broad s, 1 H), 7.63−7.68 (m, 4 H), 7.35−7.46 (m, 5 H), 7.18 (tt, J = 7.5 Hz, J = 1.0 Hz, 1 H), 7.08 (d, $^3J_{HF(trans)}$ = 39.5 Hz, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 158.2 (d, J = 26.1 Hz), 149.8 (d, $^1J_{CF}$ = 275.6 Hz), 136.8, 131.2 (d, J = 3.2 Hz), 130.2 (d, J = 8.2 Hz), 129.5 (d, J = 2.7 Hz), 129.2, 128.8, 125.1, 120.2, 114.6 (d, $^2J_{CF}$ = 4.9 Hz) ppm; GC−MS m/z (relative intensity) 241 (M^+, 73), 240 (31), 149 (100), 129(13), 121 (48), 120 (12), 101 (98), 93 (17), 77 (12), 75 (18), 65 (17), 51 (16); HRMS calcd 241.0903 for $C_{15}H_{12}FON$, obsd 241.0898.

General Procedure for the Preparation of (*E*)-α-Fluoro-α,*β*-unsaturated Amides E-8. An oven-dried 120 mL Hastelloy Parr pressure reactor equipped with a stirring bar was charged with 0.03 g (0.04 mmol) of $Cl_2Pd(PPh_3)_2$, 0.14 g (1.5 mmol) of freshly distilled aniline, and 4.0 mL of tri-n-butylamine. A mixture of (Z)-1-bromo-1-fluoroalkene (1.0 mmol) and the reduced products was added, and the pressure reactor was closed. (*Caution: All reactions should be carried out behind a safety shield in a well-ventilated hood.*) The pressure reactor was pressurized to 160 psi with carbon monoxide, and the pressure was released. This process was repeated four times to rid the system of air. Finally, the pressure reactor was pressurized to 160 psi and was allowed to stir in an oil bath at 70 °C. The consumption of carbon monoxide could be roughly determined by the reading on the gauge. When the reaction was completed, the reactor was allowed to cool to room temperature and the pressure was carefully released. The reaction mixture was transferred to a separatory funnel containing 100 mL of ethyl acetate. The organic layer was washed with aqueous 10% hydrochloric acid (3 × 15 mL), saturated sodium bicarbonate (2 × 15 mL), and brine (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation, and the crude product was further purified by silica gel column chromatography. Recrystallization from hexanes gave 100% pure (E)-α-fluoro-α,β-unsaturated amides.

(*E*)-2-Fluoro-3,*N*-diphenylacrylamide (E-8a). Similarly, a mixture of (*Z*)-1-bromo-1-fluoro-2-phenylethylene (contains (*Z*)-1-bromo-1-fluoro-2-phenylethylene 0.09 g, 0.4 mmol, *E*/*Z* = 0:100) and the reduced products, aniline (0.06 g, 0.6 mmol), and $Cl_2Pd(PPh_3)_2$ (0.01 g, 0.02 mmol) in tributylamine (4 mL) was reacted with CO at 70 °C for 182 h. Silica gel column chromatography (ethyl acetate/hexanes = 10:90, R_f = 0.31) followed by recrystallization from hexanes gave white crystals: mp 135−137 °C; 0.03 g, 25% yield, *Z*/*E* = 0:100; ^{19}F NMR ($CDCl_3$) δ −117.7 (dd, $^3J_{FH(cis)}$ = 26.7 Hz, $J_{F...HN}$ = 5.5 Hz, 1 F) ppm; ^{1}H NMR ($CDCl_3$) δ 7.88 (broad s, 1 H), 7.67 (dm, J = 7.3 Hz, 2 H), 7.53 (dm, J = 8.3 Hz, 2 H), 7.31−7.40 (m, 5 H), 7.15 (tt, J = 7.4 Hz, J = 1.1 Hz, 1 H)), 6.87 (d, $^3J_{HF(cis)}$ = 26.7 Hz, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 157.5 (d, J = 30.8 Hz), 148.7 (d, $^1J_{CF}$ = 259.2 Hz), 136.7, 130.6 (d, J = 11.6 Hz), 130.2 (d, J = 2.5 Hz), 129.1, 129.0, 128.2, 125.1, 120.3, 120.1 (d, $^2J_{CF}$ = 27.6 Hz) ppm; GC−MS *m*/*z* (relative intensity) 243 (M^+ + 2, 1), 242 (9), 241 (M^+, 58), 240 (35), 221 (15), 220 (9), 193 (5), 164 (13), 149 (76), 129 (23), 121 (41), 120 (18), 101 (100), 93 (20), 77 (25), 75 (35), 65 (46), 63 (17), 51 (38); HRMS calcd 241.0903 for $C_{15}H_{12}FON$, observed 241.0901.

Acknowledgment. We greatly acknowledge the National Science Foundation for their financial support of this work.

Supporting Information Available: Experimental procedures for the synthesis of **Z-6e**, **Z-6f**, **Z-8(b−g)**, **E-8b**, **E-8g**, and **E-8h** and their characterization by ^{19}F, ^{1}H, and ^{13}C NMR, GC−MS, and HRMS; copies of ^{1}H and ^{13}C NMR spectra of compounds **Z-6(a−g)**, **E-6a**, **E-6b**, **E-6c**, **E-6g**, **E-6h**, **Z-8(a−g)**, **E-8a**, **E-8b**, **E-8g**, and **E-8h**; NMR experiments on the existence of intramolecular F···HN coupling in (*Z*)- and (*E*)-α-fluoro-α,β-unsaturated amides. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050314A