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# Kinetic Separation Methodology for the Stereoselective Synthesis of (*E*)- and (*Z*)-α-Fluoro-α,*β*-unsaturated Esters via the Palladium-Catalyzed Carboalkoxylation of 1-Bromo-1-fluoroalkenes†

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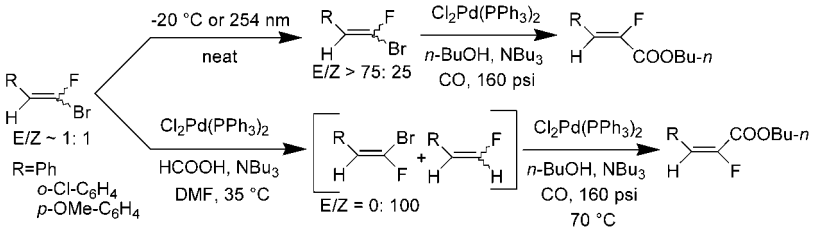
## ABSTRACT




**Methodology for the stereoselective preparation of both (*E*)- and (*Z*)-α-fluoro-α,*β*-unsaturated esters is described. 1-Bromo-1-fluoroalkenes (*E*/*Z* ≈ 1:1) can be isomerized to high *E*/*Z* ratio mixtures, which participate in palladium-catalyzed carboalkoxylation and lead to (*Z*)-α-fluoro-α,*β*-unsaturated esters in high stereoselectivity. The same starting material can also be kinetically reduced to get an *E*/*Z* ratio of 0:100; similar carboalkoxylation reaction at 70 °C affords (*E*)-α-fluoro-α,*β*-unsaturated esters stereospecifically.**

α-Fluoro-α,*β*-unsaturated esters have been widely employed as precursors in the preparation of monofluorinated retinoids,[1] fluorinated analogues of insect sex phermones,[2] and pyrethroids.[3] However, although a variety of methodologies have been explored and reported for their synthesis, there is no general and convenient method that permits preparation of **both** (*E*)- and (*Z*)-α-fluoro-α,*β*-unsaturated esters stereoselectively.

Methodologies for the stereoselective synthesis of (*Z*)-α-fluoro-α,*β*-unsaturated esters include Durst reaction from 3-hydroxy-2-fluoro-2-sulfinyl-esters,[4] condensation between 2-fluoro-3-oxo-succinnates and aldehydes,[5] thermal elimination from α-fluorosulfoxide,[6] multistep preparation from trifluorovinyl compounds,[7] one-pot reaction between aldehydes or ketones and diethyl chloromalonate in the "spray-dried" KF−sulfolane system,[8] dehydroxylation of α-fluoro-*β*-hydroxy esters,[9] reaction between α-azoesters and phenylselenenyl fluoride equivalent followed by oxidation by $H_2O_2$,[10] reaction between *β*,*β*′-dihydroxy carboxylic acid

† This paper is dedicated to Professor Herbert C. Brown, a pioneer in organometallic stereoselective synthesis, on the occasion of his 90th birthday.

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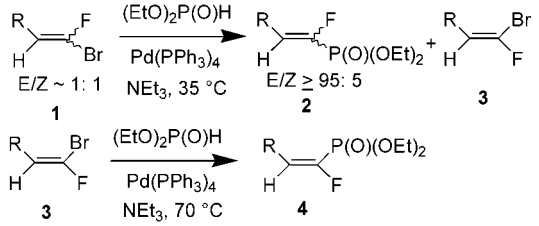
esters and vanadium(V) trichloride oxide,[11] Peterson olefination,[12] and reductive coupling−elimination reaction between methyl dichlorofluoroacetate and carbonyl compounds in the presence of zinc(0)-copper(I) chloride.[13]

The Wadsworth−Horner−Emmons reaction between fluorocarboalkoxy-substituted dialkylphosphonate anion and carbonyl compounds is the most popular method for the stereoselective preparation of (*E*)-α-fluoro-α,*β*-unsaturated esters.[14] Preparation from α-halo-*β*-mesyloxy sulfoxides has also been reported.[15]

Many of these methods provide a convenient route for the preparation of either (*E*)- or (*Z*)-α-fluoro-α,*β*-unsaturated esters stereoselectively. A general method that could offer a straightforward route to **both** (*E*)- and (*Z*)-isomers stereoselectively would be preferred. Herein, we describe the preparation of (*E*)- and (*Z*)-α-fluoro-α,*β*-unsaturated esters by palladium-catalyzed carboalkoxylation reaction of high *E*/*Z* and (*Z*)-1-bromo-1-fluoroalkenes, which are readily available from a common precursor.

1-Bromo-1-fluoroalkenes **1**, which are conveniently prepared from $CFBr_3$, $PPh_3$, and aldehydes,[16] could potentially serve as precursors for the preparation of both (*E*)- and (*Z*)-α-fluoro-α,*β*-unsaturated esters. The separation of the (*E*)- and (*Z*)-isomers of 1-bromo-1-fluoroalkenes continues to be a problem, however.[17,18] We have reported that the (*E*)-1-bromo-1-fluoroalkene in an isomeric mixture (*E*/*Z* ≈ 1:1) reacts faster than the corresponding (*Z*)-isomer at room temperature, as exemplified in the palladium-catalyzed preparation of (*E*)-α-fluorovinyl phosphonates **2** (Scheme 1).[18] Most of the (*Z*)-isomer in the mixture remains unreacted

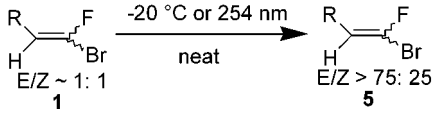
**Scheme 1.** Preparation of (*E*)- and (*Z*)-α-Fluorovinyl Phosphonates from **1**[18]




and could be recovered. Similar coupling of the recovered (*Z*)-1-bromo-1-fluoroalkene **3** at higher temperature gave pure (*Z*)-α-fluorovinyl phosphonates **4** in good yields. It was also demonstrated that the kinetic separation occurred in the oxidative addition step of the palladium catalytic cycle.[18]

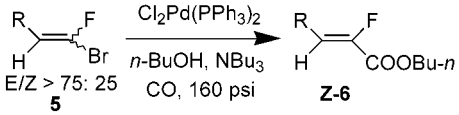
Recently we found that 1-bromo-1-fluoroalkenes (*E*/*Z* ≈ 1:1) **1** isomerize to 1-bromo-1-fluoroalkenes **5** with high *E*/*Z* ratios (normally *E*/*Z* > 75:25) when stored at −20 °C (Scheme 2) or by photochemical irradiation (254 nm) at room

**Scheme 2.** Isomerization of 1-Bromo-1-fluoroalkenes




temperature.[19] Since α,*β*-difluoro-α,*β*-unsaturated esters with defined stereochemistry have been successfully prepared in this group from 1,2-difluoro-1-iodoalkenes and α,*β*-difluoro-*β*-iodostyrenes via palladium-catalyzed stereospecific carboalkoxylation,[20] we examined similar palladium-catalyzed carboalkoxylation reaction of **5** at room temperature (Scheme 3). α-Fluoro-α,*β*-unsaturated esters **Z-6** with high *Z*/*E* ratios

**Scheme 3.** Palladium-Catalyzed Carboalkoxylation of High *E*/*Z* Ratio 1-Bromo-1-fluoroalkenes




were formed and successfully separated from the remaining (*Z*)-1-bromo-1-fluoroalkenes (Table 1, entries 1−4).

(*Z*)-1-Bromo-1-fluoroalkenes **3** were expected to undergo similar palladium-catalyzed carboalkoxylation at higher temperature to stereospecifically afford (*E*)-α-fluoro-α,*β*-unsaturated esters. To separate **3** from **1**, we decided to choose a reducing reagent that could selectively reduce the (*E*)-isomer in 1-bromo-1-fluoroalkene mixtures. It was found that the HCOOH/$NBu_3$/Pd(II)/DMF system gave the best results (Scheme 4). All of the (*E*)-isomer and a small amount of the (*Z*)-isomer were reduced to **7**; most of the (*Z*)-isomer **3** remained unreacted. Similar palladium-catalyzed reduction of vinyl halides by HCOOH/$NR_3$ has been reported.[21] *E*/*Z* ratios of the remaining 1-bromo-1-fluoroalkenes reached 0:100, and **3** could be isolated pure. As the isolation of **3** was time-consuming and the yields of **3** were lowered accordingly, we decided not to separate **3** from the reduced products **7** at this stage. This decision was based on the following reasons: the reduced products **7** generally do not


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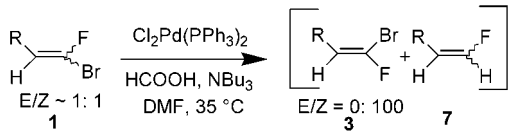
**Table 1.** Preparation of (*Z*)- and (*E*)-α-Fluoro-α,*β*-unsaturated Esters **6** from **5** and **3**

| entry | R | *E*/*Z* of **5** or **3** | temp (°C) | time (h) | *Z*/*E* of isolated product | *Z*/*E* in the reaction mixture[c] | isolated yield (conversion)[d] |
|---|---|---|---|---|---|---|---|
| 1 | Ph-**5a** | 88:12 | rt | 57 | 99:1 **Z-6a** | 99:1 | 72(82) |
| 2 | *o*-Cl-$C_6H_4$-**5b** | 82:18 | rt | 96 | 99:1 **Z-6b** | 99:1 | 78(95) |
| 3 | *p*-OMe-$C_6H_4$-**5c** | 81:19 | rt | 258 | 100:0 **Z-6c** | 98:2 | 73(91) |
| 4 | PhC($CH_3$)H-**5d** | 83:17 | 45 | 115 | 98:2 **Z-6d** | 98:2 | 56(67) |
| 5 | Ph-**3a** | 0:100[a] | 70 | 180 | 0:100 **E-6a** | 0:100 | 90 |
| 6 | *o*-Cl-$C_6H_4$-**3b** | 0:100[a] | 70 | 125 | 0:100 **E-6b** | 0:100 | 94 |
| 7 | *p*-OMe-$C_6H_4$-**3c** | 0:100[a] | 70 | 155 | 2:98[b] **E-6c** | 0:100 | 79 |
| 8 | PhC($CH_3$)H-**3d** | 0:100[a] | 70 | 161 | 0:100 **E-6d** | 0:100 | 92 |

[a] *E*/*Z* ratio of **3** in the mixture of **3** and **7**. [b] *Z*/*E* ratio was 100:0 when the reaction was completed; isomerization occurred in the process of separation. [c] *Z*/*E* ratio was determined by $^{19}$F NMR analysis of the reaction mixture when the reaction was completed. [d] Conversion was calculated on the basis of the amount of (*E*)-1-bromo-1-fluoroalkene in the starting (*E*,*Z*)-isomeric mixture (entries 1−4) or on the basis of the amount of (*Z*)-1-bromo-1-fluoroalkene **3** in the mixture of **3** and **7** (entries 5−8).

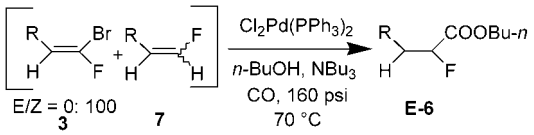
participate in further reactions (including carboalkoxylation); the desired products (e.g., (*E*)-α-fluoro-α,*β*-unsaturated esters) can be very easily separated from **7** by column chromatography; and the relative molar ratios of **3** and **7** in the mixture can be easily determined by $^{19}$F NMR analysis, which was utilized to calculate the weight percentage of **3** in a mixture of **3** and **7**. On the basis of this kinetic separation strategy several 1-bromo-1-fluoroalkenes (*E*/*Z* = 0:100) **3** and **7** were obtained (Scheme 4).

**Scheme 4.** Kinetic Separation Method to Prepare (Z) 1-bromo-1-fluoroalkenes




When the above mixture of **3** and **7** was reacted with *n*-BuOH, $NBu_3$, $Cl_2Pd(PPh_3)_2$ (4 mol %), and CO (160 psi) at 70 °C (Scheme 5), α-fluoro-α,*β*-unsaturated esters (*Z*/*E* = 0:100) were successfully formed, as detected by $^{19}$F NMR analysis of the reaction mixture (Table 1, entries 5−8). Pure (*E*)-α-fluoro-α,*β*-unsaturated esters **E-6** were isolated by silica gel column chromatography.

**Scheme 5.** Palladium-Catalyzed Carboalkoxylation of (*Z*)-1-Bromo-1-fluoroalkenes




In conclusion, we have described a general and convenient method to prepare **both** (*E*)- and (*Z*)-α-fluoro-α,*β*-unsaturated esters from common starting materials that are readily available. 1-Bromo-1-fluoroalkenes (*E*/*Z* ≈ 1:1) can be isomerized to high *E*/*Z* ratios, which undergo palladium-catalyzed carboalkoxylation to form (*Z*)-α-fluoro-α,*β*-unsaturated esters in high stereoselectivity. 1-Bromo-1-fluoroalkenes (*E*/*Z* ≈ 1:1) could also be kinetically reduced so that the remaining (*Z*)-1-bromo-1-fluoroalkenes reached an *E*/*Z* ratio of 0:100. A mixture of the (*Z*)-1-bromo-1-fluoroalkenes and the reduced products participate in a similar carboalkoxylation reaction at 70 °C to afford (*E*)-α-fluoro-α,*β*-unsaturated esters stereospecifically. Since this class of α,*β*-unsaturated esters has been shown to be converted into high ee 2-fluoroalkanoic acids via asymmetric hydrogenation,[22] this methodology should provide a useful entry to the precursors for asymmetric hydrogenation.

**Acknowledgment.** We gratefully acknowledge the National Science Foundation for their support of this work.

**Supporting Information Available:** Typical experimental procedures for the synthesis of **Z-6(a−d)**, **E-6(a−d)**, and their characterization by $^{19}$F, $^{1}$H, $^{13}$C NMR, GC−MS, and HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

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