JOC Article

Diethylzinc-Mediated One-Step Stereoselective Synthesis of α-Fluoroacrylates from Aldehydes and Ketones. Two Different Pathways Depending on the Carbonyl Partner

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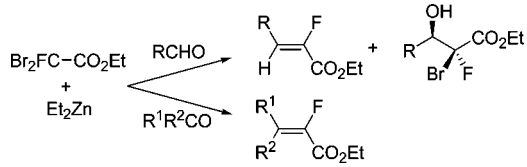

A efficient methodology allowing the one-pot stereoselective synthesis of α-fluoroacrylates, based on the addition of ethyl dibromofluoroacetate to a carbonyl derivative using diethylzinc as organometallic mediator, is described. Two different pathways have been identified depending on the involved carbonyl partner. In the case of aldehydes, an E2-type mechanism has been identified, whereas ketones go through an E1cb-type mechanism.

Introduction

Organofluorine compounds have received considerable interest in recent years due to their growing importance in life sciences, especially for drug development purposes and crop protection.[1] Modification of the physiological activity of bioactive compounds by specific introduction of a fluorine atom into molecules frequently led to the discovery of new and potent biochemical tools and medicinal agents. As a consequence, an important number of new pharmaceuticals incorporated one or more fluorine atoms.[2] One efficient access to organofluorine compounds is based on the rapid, stereoselective synthesis of fluorinated scaffolds from commercially available fluorinated precusors. α-Fluoro α,β-unsaturated esters, also known as α-fluoroacrylates, are broadly useful intermediates for the preparation of biologically active compounds.[3] Though other methods have been reported,[4] the main synthetic approaches for the preparation of such compounds are either the Wittig, thia-Wittig, Horner−Wadsworth−Emmons (HWE), Peterson, or fluoro Julia olefinations. Using the Wittig reaction, α-fluoroacrylates have been recently obtained, in a one-pot procedure, from alkoxycarbonylmethyl triphenylphosphonium bromides and Selectfluor (as fluorinating agent) in moderate yields.[5] Regarding the thia-Wittig version, a three-step stereoselective synthesis of (*Z*)-fluoroalkenoates, in moderate yields, was reported from methyl *tert*-butylsulfanylfluoroacetate.[6] Several efficient syntheses have been reported using the HWE reaction,[7] including a one-pot approach and a completely (*Z*)-stereoselective version, but these always require the use of the quite expensive ethyl 2-fluoro-2-diethylphosphonoacetate (or its carboxylic acid analogue). The Peterson olefination[8] tolerates only aromatic alde-

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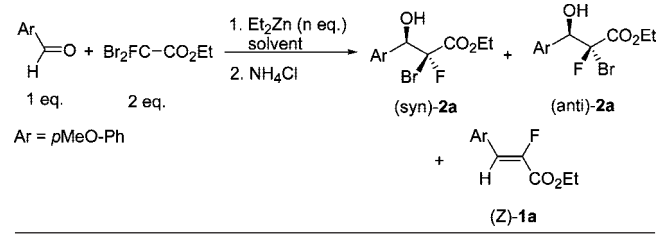
hydes. The fluoro Julia olefination[9] reaction has been applied to develop a stereoselective synthesis of α-fluoroacrylates from a fluorobenzothiazolyl sulfone (prepared in two steps) and an aldehyde or ketone. Depending on the base and the additive used to perform the reaction, (*Z*)- or (*E*)-α-fluoroacrylate could be obtained as the major isomer. Most of these procedures generally suffer from major drawbacks such as lack of selectivity, mutistep synthesis, expensive starting materials or the necessity to prepare the fluorinated precusor. To the best of our knowledge, there are only two examples of one-pot stereoselective synthesis of (Z)-α-fluoroacrylates. The first one reported by Kitazume,[10] involved a domino reaction between the sodium salt of dimethyl fluoromalonate and Michael acceptors. The second, developed by Mioskowski and Falck,[11] is based on the reaction of ethyl trifluoroacetate with aldehydes using a Cr(II)-mediated olefination sequence. Our group recently developed an efficient synthesis of α-fluoroacrylates via a diethylzinc-promoted Wittig reaction.[12] Our interest was to develop new approaches to stereoselective, atom-economical syntheses of such compounds. Thus, we report a one-pot stereoselective synthesis of α-fluoroacrylates from aldehydes and ketones using diethylzinc as an organometallic mediator.

Results and Discussion

When a THF solution of *p*-anisaldehyde (1 equiv) and ethyl dibromofluoroacetate (2 equiv) was treated at room temperature with 2 equiv of diethylzinc (Table 1, entry 1),[13] we first observed the formation of *syn*- and *anti*-α-bromo-α-fluoro-*β*-hydroxy esters **2a** (55/45 ratio) in nearly quantitative yield.

Next, when 4 equiv of diethylzinc (entry 2) were added to the initial solution, we observed the formation of α-fluoroacrylate (Z)-**1a** and esters **2a** (*syn*/*anti* ratio: 75/25) after 3 days of reaction. When the concentration of the reaction mixture was raised, no improvement was noticed (entry 3). In refluxing THF (entry 4), the addition of diethylzinc to the same mixture afforded only (*Z*)-**1a** but in moderate yield (40%). No trace of *syn*- and *anti*-α-bromo-α-fluoro-*β*-hydroxy esters **2a** was observed. This last observation could be explained by the degradation of **2a** which occurs under refluxing conditions.

TABLE 1. Optimization of (*Z*)-Olefination Process with *p*-Anisaldehyde



			ratio[i]		
entry[a]	solvent	yield[h] (%)	(*Z*)-**1a**/**2a**	*Z*/*E*-**1a**	*anti*/*syn*-**2a**
1[b]	THF[d]	96	0/100		45/55
2[c]	THF[e]	51	51/49	>99/1	24/76
3[c]	THF[e]	49	56/44	96/4	25/75
4[c]	THF[f]	40	100/0	>99/1	
5[c]	DCM[g,j]	84	63/37	>99/1	<1/99

[a] All the reactions were carried out with [*p*-MeOPhCHO] = 0.1 mol L^{-1} except entry 3: [*p*-MeOPhCHO] = 0.6 mol L^{-1}. [b] 2 equiv of Et_2Zn was used. [c] 4 equiv of Et_2Zn was used. [d] 2 h. [e] 3 days. [f] reflux (3 h). [g] rt, 3 h. [h] Global isolated yield. [i] Determined by ^{19}F NMR spectroscopy on the crude mixture. [j] When the same reaction was carried out in refluxing DCM, we observed the decomposition of *syn*-**2a**.

Changing the solvent from THF to DCM improved the yield to an excellent 84% (entry 5). Moreover, in that case, we obtained the expected α-fluoroacrylate **1a** in almost pure *Z* form (*Z*/*E* ratio >99/1) and the diastereoisomerically pure *syn*-α-bromo-α-fluoro-*β*-hydroxy ester **2a**.

To examine the scope of this one pot stereoselective synthesis of (*Z*)-α-fluoroacrylate **1** and *syn*-α-bromo-α-fluoro-*β*-hydroxy esters **2**, this methodology was applied to various aldehydes employing the above optimal conditions (Table 2).

Under these conditions, (*Z*)-α-fluoroacrylates **1** and *syn*-α-bromo-α-fluoro-*β*-hydroxy esters **2** were obtained in good to excellent overall yields. Even nonaromatic aldehydes could be converted efficiently into the expected products. With yields always between 43 and 96%, the reaction is general and tolerates various functional groups such as ester, nitrile, or protected alcohol. Moreover, in all cases, α-fluoroacrylate **1** is always obtained in *Z* pure form. Concerning α-bromo-α-fluoro-*β*-hydroxy esters **2**, the *syn* isomer was obtained selectively in most cases except for entries 5, 6, 10, and 12 (Table 2). For the mechanism of this conversion, we suggest the following sequence (Scheme 1) can be explained by a Zimmerman−Traxler transition-state model for aldol addition. Thus, enolization of ethyl dibromofluoroacetate by diethylzinc gives rise to a mixture of *E*- and *Z*-enolates. Each enolate adds to aldehyde through the intervention of a chairlike transition state resulting in the formation of zinc aldolate **B-1** and zinc aldolate **A** (Scheme 1). Aldolate **A** is prone to E2 elimination due to antiperiplanar arrangement of bromine atom and leaving group and as a consequence direct attack by diethylzinc affords fluoroacrylate (*Z*)-**1**. Zinc aldolate **B-1** is not properly placed for E2 elimination to occur as bromine atom and leaving group are not in antiperiplanar arrangement. So, for the E2 elimination to occur, a conformation change from conformation **B-1** to **B** must be developed. Conformation **B** could go into E2 elimination as bromine and leaving group are placed in antiperiplanar relationship and should afford (*E*)-**1**. However, this compound is not isolated because conformational movement from **B-1** to **B** is precluded by nonbonding destabilizing 1,3-diaxial interactions between R and OEt groups, so that zinc aldolate **B-1** remains

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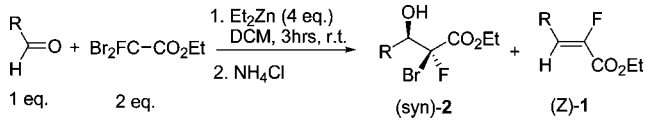
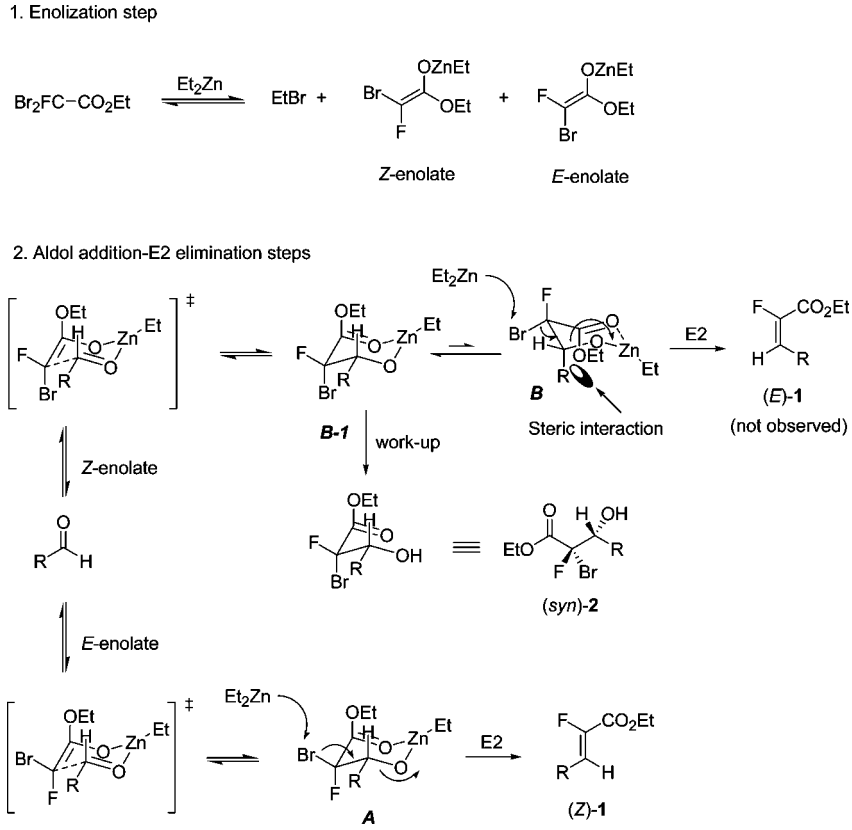
TABLE 2. Scope of the Olefination Process with Aldehydes



entry	R	yield[a] (%)	ratio[b] of (*Z*)-**1**/**2**	product	ratio[b] of *Z*/*E*-**1**	product	ratio[b] of *anti*/*syn*-**2**
1	4-$H_3COC_6H_4$	84	63/37	**1a**	>99/1	**2a**	<1/99
2	C_6H_5	80	35/75	**1b**	>99/1	**2b**	<1/99
3	4-FC_6H_4	90	59/41	**1c**	>99/1	**2c**	<1/99
4	4-BrC_6H_4	74	47/53	**1d**	>99/1	**2d**	<1/99
5	4-NCC_6H_4	62	56/44	**1e**	>99/1	**2e**	10/90
6	3,4,5-$(CH_3O)_3C_6H_4$	96	62/38	**1f**	>99/1	**2f**	20/80
7	4-$MeO_2CC_6H_4$	64	56/44	**1g**	>99/1	**2g**	<1/99
8	$C_6H_5CH{=}CH$	66	68/32	**1h**	>99/1	**2h**	<1/99
9	$C_6H_5(CH_2)_2$	67	58/42	**1i**	>99/1	**2i**	<1/99
10	H_7C_3-*i*-CH_2	43	59/41	**1j**	>99/1	**2j**[c]	25/75
11	$TBDPSO(CH_2)_2$	61	85/15	**1k**	>99/1	**2k**	<1/99
12	$H_3C(CH_2)_4-$	85	63/37	**1l**	>99/1	**2l**[d]	45/55[e]

[a] Isolated global yield. [b] Determined by ^{19}F NMR and by GC−MS spectroscopies on the crude mixture. [c] Decomposition of **2j** was observed during purification by flash column chromatography on silica gel, thus probably explaining the lower global isolated yield. [d] *anti*-**2l** and *syn*-**2l** could be separated during flash column chromatography on silica gel (see the Supporting Information). [e] This poor selectivity could be explained if we considered that the reaction has been stopped before completion.

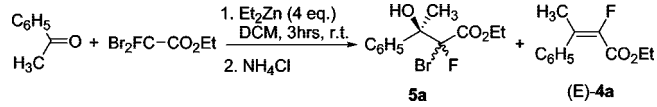
SCHEME 1. Proposed Mechanism



in the reaction mixture unchanged until workup converts it into *syn*-α-bromo-α-fluoro-*β*-hydroxy ester (*syn*)-**2**.

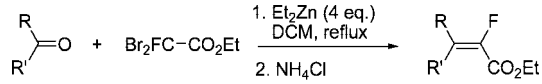
To extend the scope of the reaction, ketones were subjected to the olefination process under the conditions described above; acetophenone was chosen as a model substrate. In that experiment (Scheme 2), α-fluoroacrylate **4a** was obtained in pure *E* form but in moderate yield (52%). α-Bromo-α-fluoro-*β*-hydroxy esters **5a** were identified (20% yield) as byproducts, but in that case, the *anti*/*syn* ratio (95/5) was in favor of the *anti* isomer.

SCHEME 2. Olefination Process with Acetophenone as a Substrate



When the same reaction was carried out in refluxing dichloromethane, a very good (91%) yield in **4a** as an *E*/*Z* mixture (84/16 ratio) was obtained within 2 h. Under these conditions, no trace of *syn*- and *anti*-α-bromo-α-fluoro-*β*-hydroxy esters

TABLE 3. Scope of the Olefination Process with Ketones



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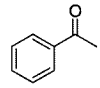
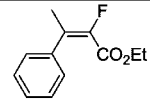
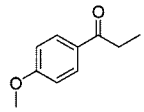
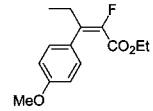
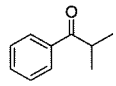
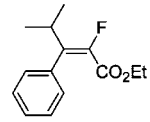
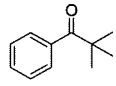
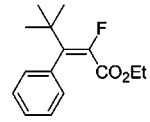
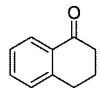
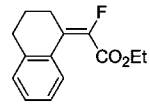
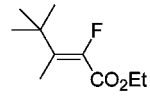
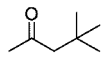
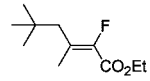
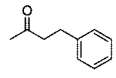
entry	ketone	time (h)	product	major or exclusive product	yield[a] (%)	ratio[b] Z/E **4**
1		2	**4a**		91	16/84[c]
2		2	**4b**		80	5/95[c]
3		2	**4c**		97	< 1/99[c]
4		1.5	**4d**		82	< 1/99
5		1	**4e**		62	14/86
6		1	**4f**		52	< 99/1
7		12	**4g**		97	70/30
8		3.5	**4h**	----------	91	52/48

[a] Isolated yield. [b] Determined by ^{19}F NMR and by GC−MS spectroscopies on the crude mixture. [c] Stereochemistry was confirmed by NOE NMR experiments (See Supporting Information).

5a was observed. With these optimized conditions in place, the scope and limitations of the method were explored. A range of different ketones were reacted under these conditions to afford the corresponding α-fluoroacrylates **4** in 52−97% yield (Table 3, entries 1−7).

When 4′-methoxypropiophenone (Table 3, entry 2), 2-methylpropiophenone (Table 3, entry 3), or 2,2-dimethylpropiophenone (Table 3, entry 4) was subjected to these reaction conditions, a nearly total stereoselectivity was observed. In these three cases, the (*E*) isomer was isolated in very good yield. Moreover, when an aliphatic ketone, possessing one hindered group, such as pinacolone (Table 3, entry 6), was subjected to these reaction conditions, α-fluoroacrylate **4f** was obtained in moderate yield but with a total reversal of stereoselectivity (because of inversion of priorities). Indeed, only *Z* isomer was isolated. When 4,4-dimethyl-2-pentanone was tested (Table 3, entry 7), we observed the formation of the expected α-fluoroacrylate **4g** in mostly quantitative yield but with a significant loss of stereoselectivity. No stereoselectivity was detected when benzylacetone (Table 3, entry 8) was engaged in this olefination process. Relative to these results, it seemed that an excellent stereoselectivity could only be obtained when disymmetrical

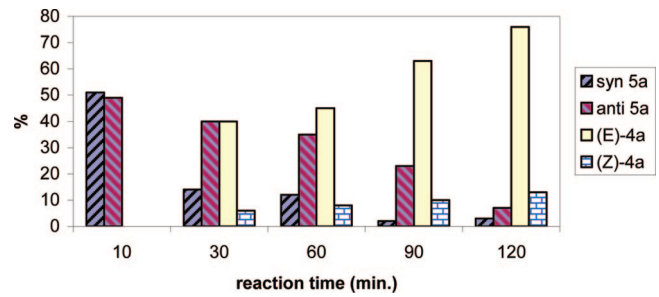


FIGURE 1. Olefination process with acetophenone.

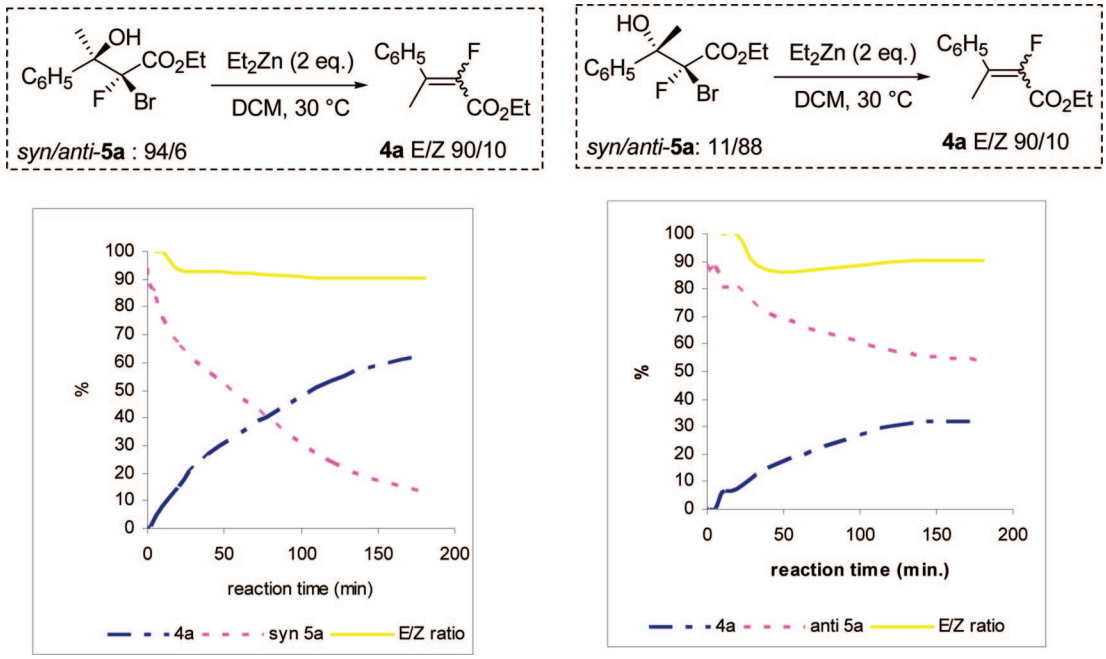


FIGURE 2. Application of the olefination process to the two diastereoisomeric *syn*- and *anti*-α-bromo-α-fluoro-*β*-hydroxy esters **5a**.

ketones possessing one hindered group were subjected to the olefination process. Indeed, when this process was applied to acetophenone (Table 3, entry 1) and α-tetralone (Table 3, entry 5) (for which the two substituents of the ketone moiety have a similar steric demands compared to pinacolone), incomplete *E* stereoselectivity was observed.

To rationalize all these results and elucidate the mechanism involved, the olefination process (with acetophenone as a substrate) was followed by ^{19}F NMR spectroscopy. Various species formed in the reaction as a function of time are shown in Figure 1. After 10 min of reaction, the two diastereoisomeric *syn*- and *anti*-α-bromo-α-fluoro-*β*-hydroxy esters **5a** were detected in almost equimolar quantities. Then, we observed the formation of the expected (*E*)- and (*Z*)-α-fluoroacrylates **4a**, with a nearly constant stereoisomeric ratio. The consumption of the two α-bromo-α-fluoro-*β*-hydroxy esters **5a** seemed to occur with very different kinetics. Indeed, *syn*-**5a** diseappeared more rapidly (Figure 1).

Two observations can be made considering this experiment: first, the two diastereoisomeric *syn*- and *anti*-α-bromo-α-fluoro-*β*-hydroxy esters **5a** led to the formation of the two (*Z*)- and (*E*)-α-fluoroacrylates **4a** with the same stereoisomeric ratio, meaning that a common intermediate was involved in the olefination process of ketones. Second, this common intermediate seemed to be formed more rapidly from the *syn* diastereoisomer of α-bromo-α-fluoro-*β*-hydroxy ester **5a**. To confirm these information, the *syn* and *anti* diastereoisomers of **5a** have been separated by chromatography on silica gel (only enriched fractions could be isolated) and treated with 2 equiv of diethylzinc. The two reactions were carried out at 30 °C in order to slow the rate of elimination, and the formation of fluoroacrylates was followed by ^{19}F NMR spectroscopy (Figure 2).

From Figure 2, it appears clearly that the formation of (*Z*)- and (*E*)-α-fluoroacrylates **4a** from *syn*-α-bromo-α-fluoro-*β*-hydroxy ester **5a** (left graph) occurs faster than that of the *anti* isomer (right graph). Moreover α-fluoroacrylates **4a** are obtained with the same *E*/*Z* ratio whether derived from *syn*-**5a** or *anti*-**5a**, suggesting that a common intermediate is involved in the conversion of both isomers.

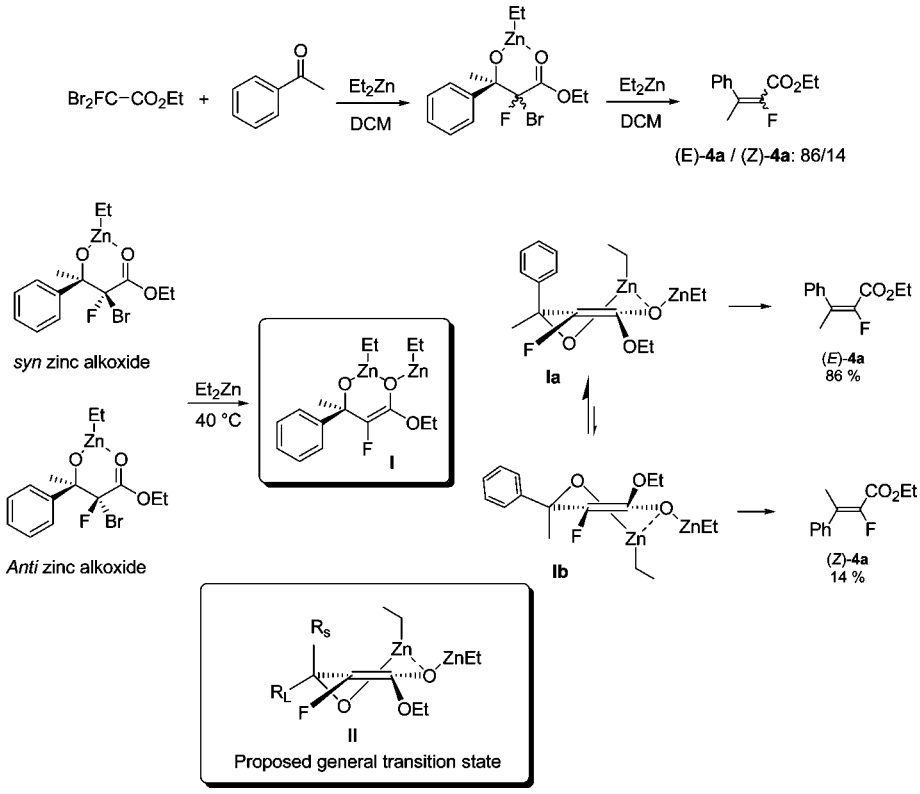
Therefore, in this olefination process involving ketones as carbonyl partner, we propose a mechanism similar to the one proposed by Concellon for the stereoselective synthesis of substituted acrylates.[14]

The observed stereoselectivity may be explained by assuming a chelation-control model (Scheme 3). Thus, metalation of the carbon−bromine bond, from either the *syn* or *anti* zinc alcoholate, generates the enolate intermediate **I**. This intermediate, stabilized by chelation of the Zn^{II} center with the oxygen atom of the alcohol moiety, involves a six-membered ring. This species can adopt two different half-chair conformations **Ia** and **Ib**. In the case of acetophenone, the most stabilized one is **Ia** in which the phenyl group adopts the axial position (the methyl group adopts the equatorial position), explaining therefore the observed incomplete *E* stereoselectivity.[15] The general intermediate **II** could be proposed (as described by Concellon) in which the larger group (R_L) adopts an equatorial position and the smaller group (R_S) an axial one. In the cases of pinacolone (R_L = *t*-Bu, R_S = CH_3) and 4,4-dimethyl-2-pentanone R_L = CH_2-*t*-Bu, R_S = CH_3), the most hindered alkyl group occupies the equatorial position leading exclusively or mainly to the *Z* isomer.

(14) (a) Concellon, J. M.; Pérez-Andrés, J. A.; Rodriguez-Solla, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2773. (b) Concellon, J. M.; Huerta, M. *Tetrahedron Lett.* **2003**, *44*, 1931. (c) Concellon, J. M.; Rodriguez-Solla, H.; Méjica, C. *Tetrahedron Lett.* **2004**, *45*, 2977. (d) Concellon, J. M.; Huerta, M.; Llovona, R. *Tetrahedron Lett.* **2004**, *45*, 4665. (e) Concellon, J. M.; Rodriguez-Solla, H.; Concellon, C.; Diaz, P. *Synlett* **2006**, 837. (f) Concellon, J. M.; Rodriguez-Solla, H.; Méjica, C. *Tetrahedron* **2006**, *62*, 3292.

(15) As pointed out by one of the reviewers, it is not clear why the half-chair conformer **Ia** with an axial phenyl group would be more stable than **Ib** with an equatorial phenyl group. Possibly, the sterochemical outcome of the elimination may be due to a higher reactivity of conformer **Ia** relative to **Ib**. This could be related to a stereoelectronic effect exerted by the axial phenyl group which might facilitate the cleavage of the benzylic C−O linkage and generation of the alkene bond. Such a stereoelectronic effect may be superimposed on the steric effect seen with the other aromatic ketones (Table 3, entries 2−4).

SCHEME 3. Proposed Mechanism



In the case of 4′-methoxypropiophenone (Table 3, entry 2), 2-methylpropiophenone (entry 3) or 2,2-dimethylpropiophenone (entry 4), the alkyl group ($R_L = CH_2CH_3$, $R_L = CH(CH_3)_2$, $R_L = t$-Bu, respectively) is in the equatorial position and the phenyl group in the axial one, leading to an enhanced or complete (*E*) stereoselectivity.

As depicted in Scheme 3, it appears that ketones go through an E1cb-type mechanism (whereas an E2 mechanism was operating during the stereospecific synthesis of (*Z*)-α-fluoroacrylates from aldehydes) leading to a stereoselective access of α-fluoroacrylates. Indeed, in the case of ketones, *syn*-**5a** or *anti*-**5a** underwent both (but with different kinetics) the metalation step followed by enolization and finally subsequent elimination.[16]

As previously mentioned (Figure 2), it appears that the consumption of *syn*-α-bromo-α-fluoro-*β*-hydroxy ester **5a** is more rapid than the *anti* isomer. In order to explain and rationalize this phenomenon, the modeling of the preferential conformations of the reaction intermediates was carried out. For that purpose, the difference of Gibbs free energies between the conformations of *syn*-**5a** (conformations **A** and **B**) and *anti*-**5a** (conformations **D** and **E**) have been calculated at the DFT-6-31G level of theory.[17] For each isomer, the more stable conformation corresponds to the more hindered group of the ketone moiety and the ester one in an *anti* relationship (Figure 3). By modeling, these two conformers (**B** and **E**) are obtained as a boat type model, **C** and **F**, respectively, where the phenyl group was in the equatorial position and the zinc atom was on the opposite side of the ethoxy group.

In order to rationalize the observed differences in the kinetics of metalation between the two α-bromo-α-fluoro-*β*-hydroxy esters **5a**, we proposed that the second equivalent of diethylzinc binds to the oxygen atom of the ethyl ester and to the zinc alcoholate from the less hindered face (conformations **C** and **F**), leading to the formation of the corresponding bicyclic intermediates **G** and **H** (Scheme 6).

Therefore, in the case of *syn* α-bromo-α-fluoro-*β*-hydroxy ester **5a**, the vicinity between diethylzinc and bromine (Scheme 4, conformation **G**) led to a more rapid halogen−metal exchange, explaining the more efficient formation of α-fluoroacrylate **4a** from *syn*-**5a**. On the other hand, in the conformation **H** of *anti*-α-bromo-α-fluoro-*β*-hydroxy ester **5a**, such a proximity effect cannot occur due to the equatorial position of the bromine substituent, thus resulting in slower metalation.

In summary, a new and efficient methodology allowing the one-pot stereoselective synthesis of α-fluoroacrylates was developed on the basis of the addition of ethyl dibromofluoroacetate to a carbonyl derivative using diethylzinc as organometallic mediator. Moreover, two different pathways have been identified, depending on the involved carbonyl partner (E2-type mechanism for aldehydes and E1cb in the case of ketones).

(16) The exact reasons for this change in mechanism are not clear. In the case of ketones, solvent and temperature had to be modified to complete the olefination process (compared to the experimental conditions used from aldehydes for which we observed a stereospecific reaction).

(17) Calculations were carried out with the DFT method implemented in the Gaussian03 program[18,19] with the three-parameter hybrid function of Becke based on the correlation function of Lee et al. (B3LYP).[20] The basis sets used were: 6-31G for C and H, 6-31G(d) for O, F, Br, and SVP[21] for Zn. Gibbs free energies have been determined after a frequency calculation in order to verify that the geometry corresponds to a stationary point and to perform the zero-point correction. Since Zn can usually accept four ligands, calculations were also carried out with a molecule of dimethyl ether as a mimic of THF. The computed Gibbs free energy differences were similar (0.90 kcal/mol between B and A and 3.0 kcal/mol between E and D).

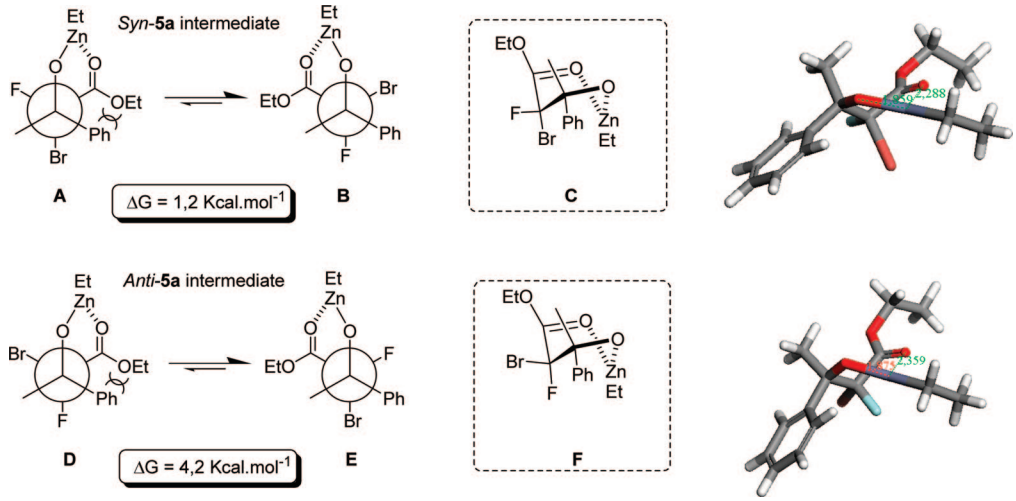
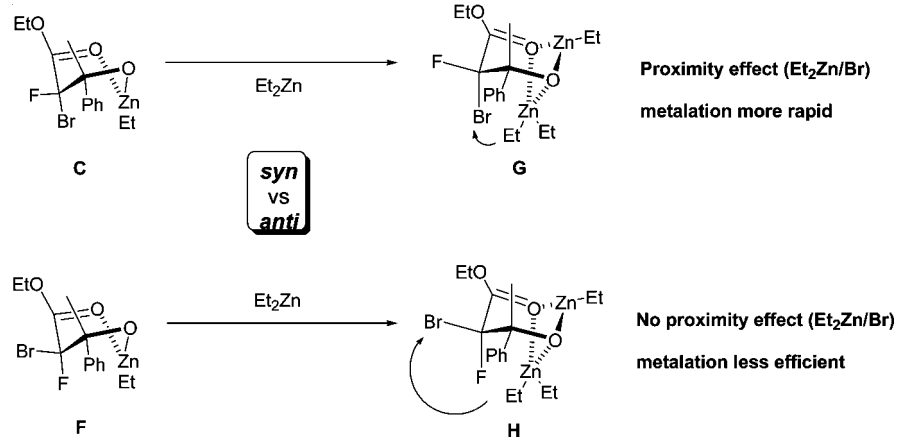


FIGURE 3. DFT calculation of *syn*-**5a** and *anti*-**5a** conformations.

SCHEME 4. Proposed Mechanism for the Metalation Step



Experimental Section

General Procedure for the Synthesis of (*Z*)-α-Fluoroacrylates and *syn*-α-Fluoro-α-bromo-*β*-hydroxy Esters from Aldehydes. To an anhydrous CH_2Cl_2 solution (10 mL) of the appropriate aldehyde (1 mmol, 1 equiv) and ethyl dibromofluoroacetate (2 mmol, 2 equiv) was added diethylzinc (1 M in hexane, 4 mmol, 4 equiv) dropwise under argon. The reaction mixture was stirred during 3 h at room temperature (until *anti* alcohol was not detected by ^{19}F NMR). The resulting solution was then poured into NH_4Cl satd (15 mL), CH_2Cl_2 was evaporated under vacuo, EtOAc was added, and the mixture was stirred for 15 min. The remaining zinc salts were filtered off through a Büchner funnel. The heterogeneous resulting solution was extracted twice with Et_2O (2 × 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by chromatography on silica gel (5% EtOAc in cyclohexane) afforded the expected (*Z*)-α-fluoroacrylate and *syn*-α-bromo-α-fluoro-*β*-hydroxy ester (global yield: 74%).

(*Z*)-Ethyl 2-fluoro-3-(4′-bromophenyl)acrylate (1d): ^1H NMR (300 MHz, $CDCl_3$) δ 7.47−7.54 (m, 4H), 6.85 (d, J_{HF} 33.9 Hz, 1H), 4.34 (q, J_{HH} 7.2 Hz, 2H), 1.37 (t, J_{HH} 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5 (d, J_{CF} 34 Hz), 147.7 (d, J_{CF} 269 Hz), 132.4 (2), 131.9 (d, J_{CF} 8 Hz), 130.3 (d, J_{CF} 5 Hz), 124.3 (d, J_{CF} 4 Hz), 116.6 (d, J_{CF} 5 Hz), 62.3, 14.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −124.4 (d, J_{HF} 34 Hz); IR 3452, 2924, 1813, 1747, 1488, 1371, 1271, 1144, 1075, 1034, 914, 769, 693, 623, 534 cm^{-1}; MS (EI) *m*/*z* 274 [$M^{+\bullet}$] (46), 226 (19), 200 (26), 180 (36), 148 (88), 120 (100). Anal. Calcd for $C_{11}H_{11}BrFO_2$: C, 48.38; H, 3.69. Found: C, 48.59; H, 3.78.

(*R*,*S*)- and (*S*,*R*)-ethyl 2-bromo-2-fluoro-3-hydroxy-3-(4′-bromophenyl) propanoate (2d): ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J_{HH} 8.3 Hz, 2H), 7.32 (d, J_{HH} 8.3 Hz, 2H), 5.18 (dd, J_{HH} 3.6 Hz, J_{HF} 16.1 Hz, 1H), 4.28 (q, J_{HH} 7.2 Hz, 2H), 3.30 (d, J_{HH} 3.6 Hz, 1H), 1.28 (t, J_{HH} 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8 (d, J_{CF} 25 Hz), 133.9, 131.8 (2), 130.2 (d, J_{CF} 1 Hz), 123.9, 100.1 (d, J_{CF} 276 Hz), 76.6 (d, J_{CF} 20 Hz), 64, 14.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −131.3 (d, J_{HF} 16 Hz); IR MS (EI) *m*/*z* 371

(18) *Gaussian 03, Revision C.02*: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, Mennucci, V.; B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Wallingford, CT, 2004.

(19) This package has been implemented on a power-575 IBM cluster. The jobs generally used four processors.

(20) For B3LYP, see: (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys Rev. B* **1988**, *37*, 785–789.

(21) For the SVP basis set, see: (a) Schaefer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571. (b) Schaefer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829.

[$M^{+\bullet}$] (1), 207 (13), 187 (86), 185 (100), 157 (15), 77 (19). Anal. Calcd for $C_{11}H_{11}Br_2FO_3$: C, 35.71; H, 3.00. Found: C, 35.61; H, 3.39.

General Procedure for the Synthesis of (*Z*)- and/or (*E*)-α-Fluoroacrylates from Ketones. To an anhydrous CH_2Cl_2 solution (10 mL) of the appropriate ketone (1 mmol, 1 equiv) and ethyl dibromofluoroacetate (2 mmol, 2 equiv) was added diethylzinc (1 M in hexane, 4 mmol, 4 equiv) dropwise under argon. The reaction mixture was stirred at reflux during several hours (until alcohol was totally consumed (followed by ^{19}F NMR)). The resulting solution was then poured into NH_4Cl satd (15 mL), CH_2Cl_2 was evaporated under vacuo, EtOAc was added, and the mixture was stirred for 15 min. If necessary, remaining zinc salts were filtered off. The resulting filtrate was extracted twice with Et_2O (2 × 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by chromatography on silica gel (5% EtOAc in cyclohexane) afforded the expected α-fluoroacrylate.

(*Z*)-2-Fluoro-3,4,4-trimethylpent-2-enoic acid ethyl ester (4f): yield 52%; ^1H NMR (300 MHz, $CDCl_3$) δ 4.2 (q, J_{HH} 7.2 Hz, 2H), 2.0 (d, J_{HF} 3.3 Hz, 3H), 1.2 (t, J_{HH} 7.2 Hz, 3H), 1.1 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (d, J_{CF} 25 Hz), 144.1 (d, J_{CF} 253 Hz), 139.7 (d, J_{CF} 8 Hz), 61.4, 33.4, 29.2 (2), 14.5 (4); ^{19}F NMR (282 MHz, $CDCl_3$) δ −119.8; IR (neat) 2975, 1724, 1292, 1250, 1062, 776 cm^{-1}. Anal. Calcd for $C_{10}H_{17}FO_2$: C, 63.81; H, 9.10. Found: C, 63.97; H, 8.90.

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Supporting Information Available: Experimental procedures for the preparation of compounds and spectroscopic data and Cartesian coordinates of intermediates species **A**−**E**. This material is available free of charge via the Internet at http://pubs.acs.org.

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