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Pathway for the Stereocontrolled *Z* and *E* Production of α,α-Difluorine-Substituted Phenyl Butenoates

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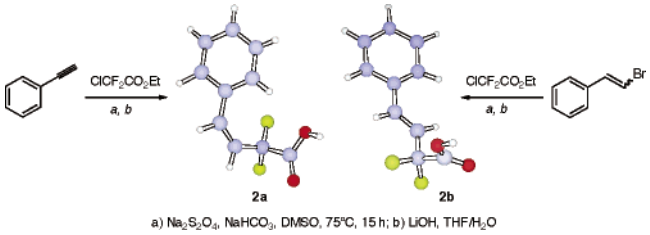

An efficient preparation of pure ethyl *Z*- and *E*-α,α-difluoro-4-phenyl-3-butenoate **1a** and **1b** together with the corresponding acids **2a** and **2b** is described. The procedures involve stereocontrolled additions of $^{\bullet}CF_2CO_2Et$ to phenylacetylene or *β*-bromostyrene. Compound **1a** is easily obtained by addition of $^{\bullet}CF_2CO_2Et$ to phenylacetylene via a mechanism where the stereochemistry is controlled by an electron-transfer process to produce predominantly the *Z* vinyl anion. The product **1b** is obtained by $^{\bullet}CF_2CO_2Et$ addition−elimination to *Z*- or *E*-*β*-bromostyrenes via a mechanism where the stereochemistry is controlled by steric factors in the conformational equilibration of the intermediates.

In the course of our study on the mechanism of the copper-containing monooxygenases D*β*M and PHM, the need for α,α-difluoro-4-phenyl-3(*E*)-butenoic acid **2b** as a PHM inhibitor became apparent.[1] In a recent paper, Long and Chen described the addition of perfluoroalkyl chlorides (R_FCl) to alkenes ($RCH{=}CH_2$) or alkynes ($RC{\equiv}CH$) in the presence of 1.5 equiv of $Na_2S_2O_4$ and $NaHCO_3$ in DMSO at 75−80 °C to give the corresponding adducts ($RCH_2CH_2R_F$ or $RCH{=}CHR_F$).[2] Based on inhibition experiments with radical scavengers, Long and Chen proposed that the perfluoralkyl radical ($R_F^{\bullet}$) is involved in the reaction mechanism. As one example, they reported the stereoselective synthesis of the ethyl α,α-difluoro-4-phenyl-3(*E*)-butenoate **1b** by addition of ethyl chlorodifluoroacetate to phenylacetylene. Under the reaction conditions (70 °C, 10 h), they obtained a 90:10 mixture of the isomers of ethyl α,α-difluoro-4-phenyl-3-butenoate in 64% yield. Attribution of the *E*-configuration to the main product was made by comparing the chemical shifts of the F-atoms in their respective ^{19}F NMR spectra, the downfield signal being assigned to the *Z*-isomer (**1a**) and the upfield shift to the *E*-isomer (**1b**). In the ^{19}F NMR spectra (in $(CD_3)_2CO$ as solvent and CF_3COOH as external standard), the major isomer exhibits a doublet (J_{H-F} = 13 Hz) at 11.5 ppm. The corresponding signal of the minor isomer was not provided in the article.

Our attempts to reproduce the reaction resulted in the formation of a 90:10 mixture of the isomers of ethyl α,α-difluoro-4-phenyl-3-butenoate. The main product shows the ^1H NMR features described by Long and Chen. However, after careful analysis of the latter, we arrived at the reverse conclusions; i.e., the main product is the *Z*-isomer (**1a**) and the minor product the *E*-isomer (**1b**). The new assignment was based on ^1H NMR spectroscopy. Our products **1a** and **1b** exhibit, respectively, two signals in the vinylic region corresponding to the H3 and H4 proton resonances (Figure 1a). For the H3 proton, the major isomer exhibits a doublet of triplet centered at 5.90 ppm with coupling constants of 13 Hz corresponding to the superimposition of the J_{H3-H4} and J_{H3-F} coupling constants. A doublet of triplet centered at 6.95 ppm (J_{H4-H3} = 13 Hz and J_{H4-F} = 1.6 Hz) is observed for the H4 proton. The minor isomer exhibits a doublet of triplet at 6.30 ppm (J_{H3-H4} = 16.2 Hz and J_{H3-F} = 11.4 Hz) for the H3 proton and a doublet of triplet centered at 7.08 ppm (J_{H3-H4} = 16.2 Hz and J_{H4-F} = 2.6 Hz) for the H4 proton. It is well-known that in 1,2-substituted ethylenic compounds the $^3J_{trans}$ constant is always larger than the $^3J_{cis}$ constant.[3] Since the major isomer exhibits a J_{H3-H4} constant lower than the minor isomer (13 Hz vs 16.2 Hz), we concluded that the main product is the *Z*-isomer (**1a**) and the minor product the *E*-isomer (**1b**).

To confirm unambiguously this attribution, we transformed the ester **1a** into the corresponding acid **2a** by hydrolysis with LiOH in THF/H_2O. Crystallization in toluene afforded suitable crystals for X-ray analysis. The structure confirmed the *Z* configuration for the product **2a** (see the Abstract graphic).

With *β*-bromostyrenes as substrate, two mechanisms are possible. Following the addition of the α,α-difluoroacetate radical, the benzyl radical can evolve to compounds **1a** and **1b** by (1) *β*-fragmentation of a Br atom or (2) reduction to yield the corresponding anion and subsequent Br^- elimination. The stereoconvergence of the addition−elimination process can be explained by a conformational equilibrium of anions **C** and **D** and/or radicals **C′** and **D′** via rotation around the single bond (Scheme 3). Due to steric hindrance between the CF_2CO_2Et and the phenyl groups, the conformers **D** and/or **D′** are favored compared to conformers **C** and/or **C′**, and the kinetic quenching resulting from the elimination of a Br^- and/or $Br^{\bullet}$ mainly leads to the stereoisomer **1b** independent of the stereochemistry of the *β*-bromostyrene.

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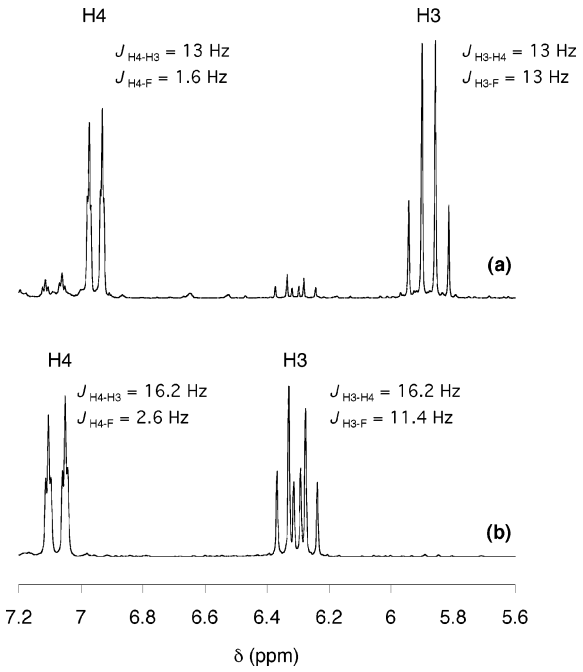

FIGURE 1. Vinylic region of the ^{1}H NMR spectra of ethyl α,α-difluoro-4-phenyl-3-butenoates resulting from addition of α,α-difluoroacetate radical to phenylacetylene (a) and *β*-bromostyrene (b).

In the mechanism proposed by Long and Chen, the formation of products **1a** and **1b** is explained by an H-atom abstraction from solvent (DMSO) by the vinyl radical **A** resulting from the addition of α,α-difluoroacetate radical to phenylacetylene. However, when we performed the reaction in DMSO-d_6, we did not observe any incorporation of D-atom into compounds **1a** and **1b**. We therefore pursued the identity of the H-donor. Since PhC≡CH is used in 1.5-fold excess with respect to ethyl chloro-α,α-difluoroacetate, and taking into account that the yield of **1a** and **1b** did not exceed 70%, another possibility would be PhC≡CH as the H4-atom donor. To test this possibility, we performed the reaction with PhC≡CD as the substrate. Again, we failed to observe any incorporation of D-atom into compounds **1a** and **1b**. Since the reaction is stopped by addition of a large excess of water after 15 h, water also was a viable candidate. However, with D_2O as quenching agent, no incorporation of D-atom into compounds **1a** and **1b** was detected. These experiments confirmed that neither DMSO, PhC≡CH, nor H_2O is the source of the H4-atom. The remaining possibility is that the H4-atom comes from $NaHCO_3$. Unfortunately, the difficulty in producing $NaDCO_3$ did not allow us to confirm this assumption. Nevertheless, we propose that $NaHCO_3$ is the source of the H4-atom. Since $NaHCO_3$ is a much better H^+ than a $H^\bullet$ donor and because the reaction is performed with an excess of reducing agent (1.5 equiv of $Na_2S_2O_4$ = 3 equiv of electron), we have modified the mechanism of Long and Chen. As shown in Scheme 1, the vinyl radical **A** undergoes rapid reduction to yield *Z* and *E* vinyl anions **B** and **C**. These species can, thus, be protonated by $NaHCO_3$ to generate the compounds **1a** and **1b**. A vinyl anion can be considered to be stereochemically stable since the inversion barrier is very high (>30 kcal mol^{-1}).[4] Consequently, subsequent protonation of the vinyl anion cannot be responsible for the high stereoselectivity of the reaction. On the contrary, the stereoselectivity can be explained

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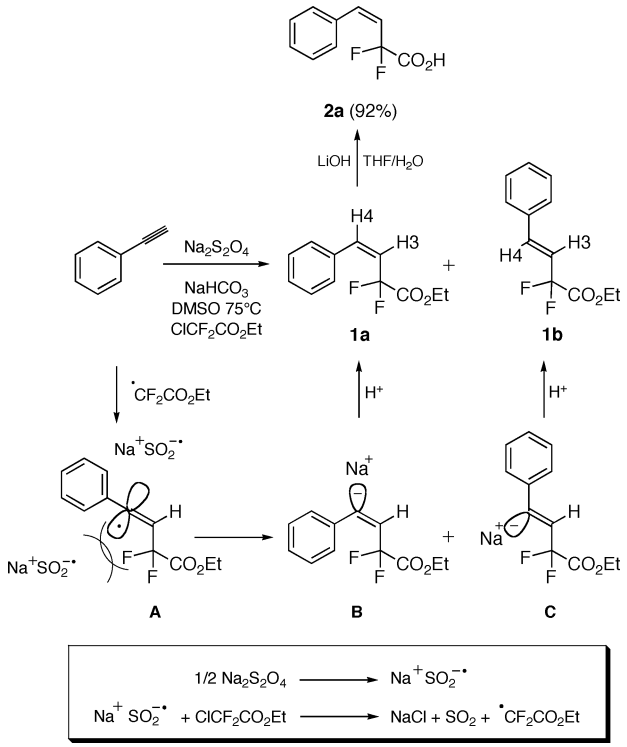
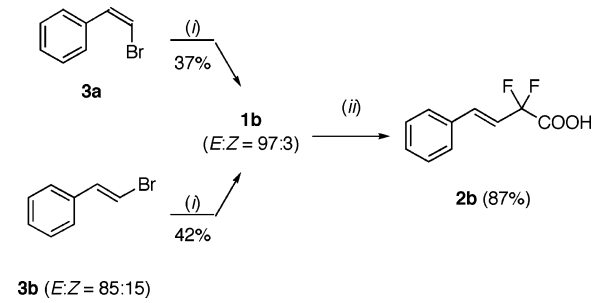
SCHEME 1. Addition of Ethyl Chlorodifluoroacetate to Phenylacetylene



SCHEME 2. Addition of Ethyl Chlorodifluoroacetate to *β*-Bromostyrenes 3a and 3b[a]



[a] Key: (i) $ClCF_2CO_2Et$, $Na_2S_2O_4$−$NaHCO_3$, DMSO, 70 °C, 10 h; (ii) LiOH, THF/H_2O, rt.

in terms of a single electron transfer to the vinyl radical **A**, leading to the formation of vinyl intermediates **B** and **C**.[5] A vinyl radical is known to have a low inversion barrier (6−9 kcalmol^{-1}), and *π*-conjugated substituents such as phenyl groups are usually thought to favor the linear form in order to ensure a better orbital overlap for resonance.[6] With such a linear vinyl radical, we can assume that the steric hindrance between the CF_2CO_2Et group and electron donor is unfavorable for formation of the *E*-isomer (**C**), leading to the *Z*-isomer (**B**).

To selectively obtain the *E*-isomer **1b**, we envisaged an addition−elimination sequence involving *β*-bromostyrene as the substrate, Scheme 2. Under Long and Chen's conditions, the commercially available mixture of *β*-bromostyrenes **3a** and **3b**

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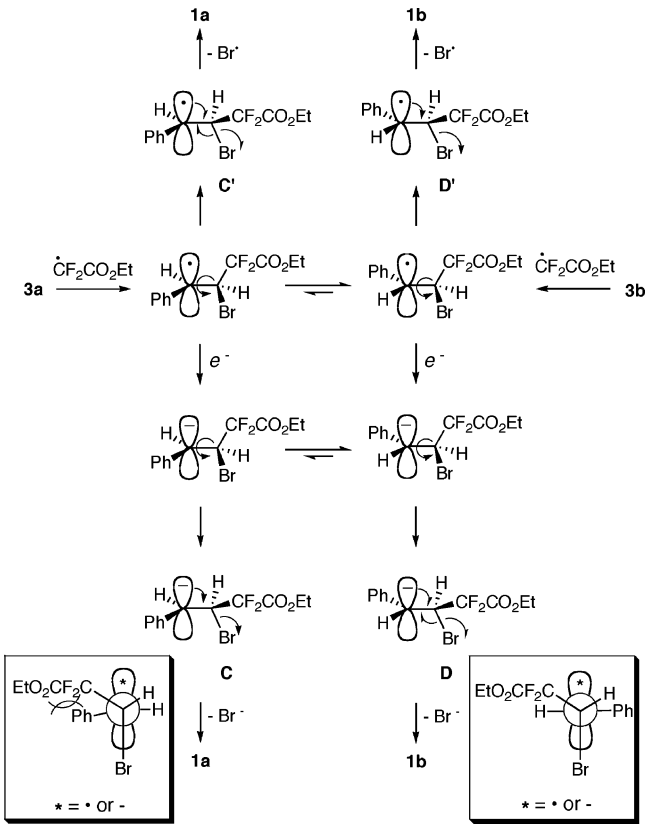
SCHEME 3. Possible Mechanism for the Formation of Products from the β-bromostyrene Reaction



(**3a**/**3b** = 15:85) leads to a mixture of adducts in which the *E*-isomer **1b** is the main product (Scheme 3). As revealed by ^{1}H NMR spectroscopy, less than 3% of *Z*-isomer **1a** is formed during the reaction (Figure 1b). In the same manner, pure *Z*-β-bromostyrene **3a**, prepared in one step by the Wittig reaction of benzaldehyde and chloromethyltrimethylphosphonium bromide,[7] afforded the *E*-isomer **1b** as the main adduct. Ester **1b** was then transformed into the corresponding acid **2b** by reaction with LiOH in THF/H_2O. Crystallization in toluene afforded suitable crystal for X-ray analysis. The structure confirmed the *E* configuration for the product **2b** (see the Abstract graphic).

In conclusion, in this report we first present results that correct unambiguously the wrong stereochemical structure attribution of ethyl *Z*-α,α-difluoro-4-phenyl-3-butenoate **1a** resulting from addition of the ethyl difluoroacetate radical to phenylacetylene. Second, inspired from the studies of Long and Chen,[2] we developed a novel and efficient method for the stereoselective preparation of pure ethyl *E*-α,α-difluoro-4-phenyl-3-butenoate **1b**.

Experimental Section

Reaction of Ethyl Chlorodifluoroacetate with Phenylacetylene. Under an argon atmosphere, phenylacetylene (0.765 g, 7.5 mmol), ethyl chlorodifluoroacetate (0.792 g, 5 mmol), $Na_2S_2O_4$ (0.630 g, 7.5 mmol), $NaHCO_3$ (1.38 g, 7.5 mmol), and DMSO (25 mL) were introduced into a 50 mL double-necked round-bottomed flask equipped with magnetic stirrer, thermometer, and condenser. The mixture was then heated to 75 °C for 15 h. After cooling, the mixture was poured into 30 mL of ice−water. The aqueous layer was extracted with diethyl ether (3 × 30 mL), and the combined extracts were washed with brine (3 × 20 mL) and dried over Na_2SO_4. After removal of diethyl ether under vacuum, the residue was chromatographed on silica gel (pentane/CH_2Cl_2 = 1:1) to give ethyl α,α-difluoro-4-phenyl-3-butenoates **1a** and **1b** (1.12 g, 66%) in an 88:12 ratio as determined by ^{1}H NMR spectroscopy.

Reaction of Ethyl Chlorodifluoroacetate with *Z*-β-Bromostyrene (3a). The same procedure applied to *Z*-β-bromostyrene **3a** (0.1 g, 0.55 mmol) in the presence of ethyl chlorodifluoroacetate (0.115 g, 0.81 mmol), $Na_2S_2O_4$ (0.069 g, 0.82 mmol), $NaHCO_3$ (0.143 g, 0.82 mmol), and DMSO (5 mL) afforded ethyl α,α-difluoro-4-phenyl-3-butenoate **1b** (68.4 mg, 55%).

Reaction of Ethyl Chlorodifluoroacetate with *E*-β-Bromostyrene (3b). The same procedure applied to β-bromostyrene **3b** (1 g, **3a**/**3b** = 15:85, 5.5 mmol) in the presence of ethyl chlorodifluoroacetate (1.15 g, 8.13 mmol), $Na_2S_2O_4$ (0.688 g, 8.19 mmol), $NaHCO_3$ (1.426 g, 8.19 mmol), and DMSO (25 mL) afforded ethyl α,α-difluoro-4-phenyl-3-butenoate **1b** (745 mg, 60%).

Ethyl 4-Phenyl-2,2-difluoro-3(*Z*)-butenoate (1a). Colorless oil. ^{1}H NMR: δ 1.07 (t, *J* = 7.2 Hz, 3H); 4.01 (q, *J* = 7.2 Hz, 2H); 5.90 (dt, J_{H-H} and J_{H-F} =13.0 Hz, 1H); 6.95 (dt, J_{H-H} = 13.0 Hz and J_{H-F} = 1.6 Hz, 1H); 7.35 (s, 5H). ^{13}C NMR: δ 163.8 (t, J_{C-F} 34 Hz); 139.1 (t, J_{C-F} 8.9 Hz); 134.7; 129.3 (t, J_{C-F} 2.7 Hz); 129.1; 128.6; 122.3 (t, J_{C-F} 27.9 Hz); 115.9; 112.7; 109.4; 63.3; 14.0. ^{19}F NMR: δ −94.38.

Ethyl 4-Phenyl-2,2-difluoro-3(*E*)-butenoate (1b). Colorless oil. ^{1}H NMR: δ 1.35 (t, *J* = 7.2 Hz, 3H); 4.33 (q, *J* = 7.2 Hz, 2H); 6.30 (dt, J_{H-H} = 16.2 Hz and J_{H-F} = 11.4 Hz, 1H); 7.08 (dt, J_{H-H} = 16.2 Hz and J_{H-F} = 2.6 Hz, 1H); 7.35 (m, 3H); 7.44 (m, 2H). ^{13}C NMR: δ 164.3 (t, J_{C-F} 35 Hz); 137.2 (t, J_{C-F} 9.4 Hz); 134.5; 130.0; 129.2; 127.8; 119.3 (t, J_{C-F} 24.5 Hz); 116.4; 113.1; 109.9; 63.5; 14.3. ^{19}F NMR: δ −103.68.

Typical Procedure for the Saponification of Ethyl 4-Phenyl-2,2-difluoro-3-butenoates (1a,b). Ethyl 4-phenyl-2,2-difluoro-3-butenoate **1a** or **1b** (0.55 g, 2.43 mmol) and LiOH−H_2O (0.857 g, 20.4 mmol) were stirred in a THF/H_2O (47:20) mixture for 4 h. The mixture was then acidified to pH 1 with a 35% HCl solution and extracted with diethyl ether (3 × 30 mL), and the organic layer was dried over Na_2SO_4. After diethyl ether was removed under vacuum, the crude product was crystallized in toluene.

4-Phenyl-2,2-difluoro-3(*Z*)-butenoic Acid (2a). Yield: 92%. Colorless crystals. ^{1}H NMR: δ 5.80 (t, J_{H-H} and J_{H-F} = 13.5 Hz, 1H); 7.00 (dt, J_{H-H} =13.5 Hz and J_{H-F} = 1.6 Hz, 1H); 7.33 (s, 5H). ^{19}F NMR: δ −95.68. Anal. Calcd for $C_{10}H_8F_2O_2$ (198.16): C, 60.61; H, 4.07. Found: C, 60.58; H, 4.05.

4-Phenyl-2,2-difluoro-3(*E*)-butenoic Acid (2b). Yield: 87%. Colorless crystals. ^{1}H NMR: δ 6.30 (dt, J_{H-H} = 16.1 Hz and J_{H-F} = 11.4 Hz, 1H); 7. 13 (dt, J_{H-H} = 16.2 Hz and J_{H-F} = 2.4 Hz, 1H); 7.38 (m, 3H); 7.468 (m, 2H). ^{19}F NMR: δ −104.48. Anal. Calcd for $C_{10}H_8F_2O_2$ (198.16): C, 60.61; H, 4.07. Found: C, 60.55; H, 4.09.

X-ray Structure Analysis. Crystal data for **2a** and **2b** together with details of the X-ray diffraction experiment are reported in the Supporting Information. Suitable colorless crystals of 0.5 × 0.5 × 0.1 mm^3 and 0.4 × 0.3 × 0.1 mm^3 for **2a** and **2b**, respectively, were mounted on a Bruker-Nonius KappaCCD diffractometer.[8] 180° φ scan measurements (through 2° steps of 60 s) were performed at room temperature using the Mo Kα wavelength. The cell parameters were refined and the data integrated using Denzo-Scalepack.[9]

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The structure solutions were determined with SIR92[10] and the refinements performed with SHELXL-97.[11] For **2a**, the H-atoms were introduced at idealized positions (except the H-atom of the acid group which was determined by a Fourier difference), included in the calculations but not refined. For **2b**, all H-atoms were determined experimentally, included in the calculations but not refined.

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Supporting Information Available: Copies of ^{1}H, ^{13}C, and ^{19}F NMR for compounds **1a** and **1b** and crystal data together with details of the X-ray diffraction experiments for compounds **2a** and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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