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Structural determination of a zinc reagent from ethyl 3-bromodifluoromethyl-3-benzyloxyacrylate and its reactions with aldehydes

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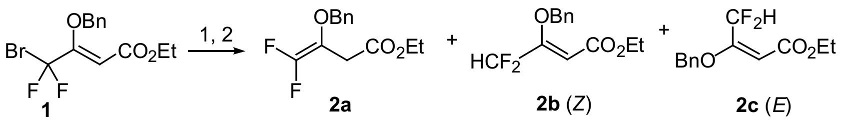
Abstract—The reactivity of ethyl 3-bromodifluoromethyl-3-benzyloxyacrylate as a novel *gem*-difluoromethylene synthon was investigated. ^{19}F NMR spectra of its zinc reagent in THF and DMF indicate unambiguously that the active species exists as the γ-carbon metallated form. Moreover, promoted by zinc or TDAE, a complete control of the addition reaction mode (α or γ) of this acrylate with aldehydes can be accomplished.

The difluoromethylene moiety (CF_2) is a key structural unit in many fluorinated compounds of biological and pharmaceutical significance.[1] It has been recognized as an isopolar-isosteric substitute for oxygen and is used as a strategy for modification of biologically active compounds.[2] Complementary to direct *gem*-difluorination[3] is the building-block approach. Halogeno-difluoromethylated compounds are widely used as building-blocks to introduce CF_2 into molecules. However, the reactions of β-halogenodifluoromethyl substituted acrylate derivatives have only been reported in two cases by Kitazume and by Hu to synthesize new *gem*-difluorinated compounds.[4] In connection with our studies of the synthetic applications of ethyl α-fluoroalkyl acetate,[5] we found that ethyl 3-bromodifluoromethyl-3-benzyloxyacrylate **1**, the benzyl vinyl ether derivative of ethyl α-(2-bromo-1,1,2,2-tetrafluoroethyl)-acetate, could be used as an excellent *gem*-difluoromethylene synthetic precursor. Herein, we report our preliminary results in this area.

The reactions of acrylate **1** with metals (such as Zn, In, Cu and Mg) or tetrakis(dimethylamino)ethylene (TDAE) in THF or DMF were first investigated. After complete conversion of acrylate **1** and conventional work-up followed by chromatographic separation, it was found that three reduction products (**2a**, **2b** or **2c**) could be formed (Scheme 1). Compound **2a** was produced from the reduction at the α-position of acrylate **1**, while **2b** and **2c** were derived from the reduction at the γ-position. Based on our previous results,[6] compounds **2b** and **2c** are geometric isomers. The total yields and ratios of the products as determined by ^{19}F NMR spectroscopy are summarized in Table 1.

Activated zinc reacted readily with acrylate **1** requiring only half an hour for complete reaction to afford the reduction product **2a** in nearly quantitative yield (Table 1, entries 1 and 2). The same acrylate reacted relatively slowly with indium and more so with copper (Table 1,



Scheme 1. Reagents and conditions: (1) metal or TDAE/solvent; (2) H$^+$.

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Table 1. Reaction results of acrylate **1** with metals or TDAE

Entry	Metal	Solvent	Temperature (°C)	Time (h)	Product	Yield (%) and ratio
1	Zn	DMF	0	0.5	**2a**	100
2	Zn	THF	60	0.5	**2a**	100
3	TDAE	DMF	−10	3	**2b**, **2c**	93 (7.8:1)
4	TDAE	DMF	−10	3	**2b**, **2c**	100 (1:9.4)[a]
5	In	DMF	60	4[b]	**2a**, **2b**, **2c**	100 (9:1:0.5)
6	In	THF	60	4[b]	**2a**	90
7	Cu	DMF	60	5	—[c]	—
8	Mg	THF	25	3	—[c]	—

[a] Compared with entry 3, the reaction was carried out in the presence of cyclopentanone or crotonaldehyde that might act as facile hydrogen donors to give the kinetic product **2c** as the major one but not **2b**.

[b] Acrylate **1** was not consumed completely.

[c] Complicated mixture.

entries 7 and 8). When acrylate **1** was treated with TDAE, the reduction products became to **2b** and **2c** predominantly. The corresponding reaction products from copper or magnesium were complex, which might be attributed to the highly nucleophilic Grignard or copper reagents formed in situ.

Reformatsky reagents have been widely used in the construction of carbon–carbon bonds. However, their structures remain unsettled in some cases. The structures of zinc reagents from normal α-haloesters have been extensively investigated by several groups,[7] and both carbon- and oxygen-metallated structures (Fig. 1, **Ia** and **Ib**) have been substantiated in various instances. On the other hand, few efforts have been made to investigate the structure of the so-called zinc dienolate that can be derived from different sources, although such knowledge may shed light to the understanding of the regio- and stereochemistry in its reactions with electrophiles. We were therefore interested in the structure of the zinc reagent from acrylate **1**. The double bond in acrylate **1** gives rise to three possible structures formulated as the γ-carbon metallated, α-carbon metallated and O-metallated (the so-called bromozinc dienolate) forms as depicted by **IIa**, **IIb** and **Iic** in Figure 1, respectively.

The zinc reagents from acrylate **1** prepared in THF and DMF were analyzed by ^{19}F NMR spectroscopy immediately to avoid degradation.[8] The two spectra obtained in THF and DMF are shown in Figure 2.

The two spectra indicate that the reduction products (**2a**, **2b** or **2c**) that are produced by protonation of the active zinc reagent species already exist in the two solvents. The corresponding signals of the three products are shown in Figure 2. Typically, **2a** exhibits two doublets at about −100.5 and −112.7 ppm ($J = 70$ Hz), while **2b** and **2c** appear as one doublet at −124.1 ppm ($J = 54$ Hz) and −119.4 ppm ($J = 54$ Hz), respectively.

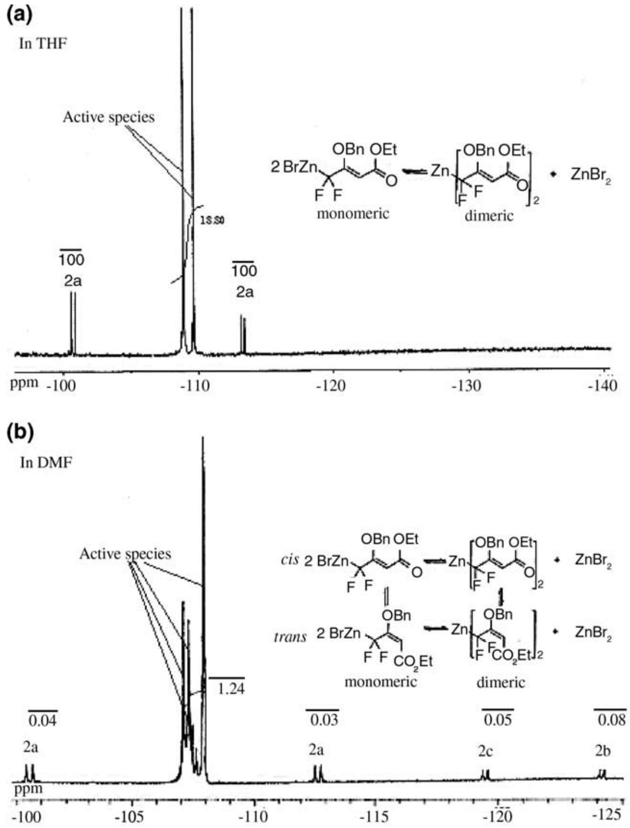


Figure 2. ^{19}F NMR spectra of the zinc reagent from acrylate **1** obtained in (a) THF and (b) DMF.

All the other singlet signals at around −107 ppm (108.7 and 109.4 ppm in THF, 107.1, 107.3, 107.5, 107.6 and 107.9 ppm in DMF) should be assigned to the active zinc reagent species, which is also shown in the two spectra. After the sample was quenched with a small amount of saturated NH$_4$Cl solution, the signals of the active

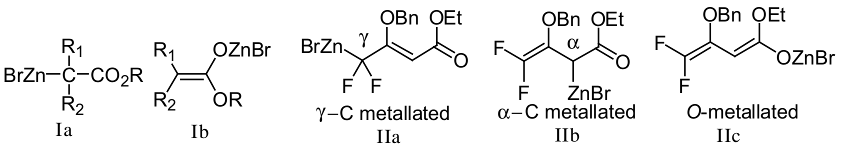


Figure 1.

species disappeared and only the signals of product **2a** increased significantly. This phenomenon indicated that all the active species was completely transformed into the reduction product **2a**. Ideally, if the active species exist as α-carbon metallated or O-metallated form, they are anticipated to appear in the ^{19}F NMR spectrometry as two doublets that resemble the signals of reduction product **2a**, and only if the active species exists as the γ-carbon metallated form, it would exhibit a singlet signal. From these anticipations and the patterns that the active species have displayed, we can come to the conclusion that the zinc reagent from acrylate **1** should unambiguously exist in the γ-carbon metallated form in either solution. According to the literature,[7a] the two singlets at −108.7 and −109.4 ppm in the spectra obtained in THF should correspond to the monomeric and dimeric association states of the zinc reagent that are in equilibrium in the solvent (Fig. 2a). The same monomeric and dimeric association equilibrium still exists in DMF (Fig. 2b). This phenomenon is not consistent with the literature in which Reformatsky reagent from *tert*-butyl bromoacetic acid ester existed as a monomer in very polar solvents such as DMSO.[7b] The reason why the spectra obtained in DMF exhibits more than two singlet signals in the same range might be attributed to double-bond isomerizaton (Fig. 2b) under this dynamically controlled condition (0.5 h at 0 °C). Further efforts to acquire additional evidence to support our above conclusions are in progress in our laboratory, all the experimental results about the structural determination of this zinc reagent active species (including ^{19}F NMR, ^{1}H NMR, IR, UV, MS, quantum calculation method and the others) will appear in a full article elsewhere.

The reaction of acrylate **1** with aldehydes mediated by zinc was performed in DMF at 0 °C for 0.5 h. The zinc reagent formed in situ could react with any aldehyde to give the α-mode addition product α-difluorovinyl substituted β-hydroxy esters **3** in high yields and in a highly regioselective manner (Table 2), and the reactions showed moderate stereoselectivity with the *anti* diastereomer as the major one,[9] which could be readily separated from the *syn* one by silica gel chromatography.

Table 2. Reaction results of ethyl 3-bromodifluoromethyl-3-benzyloxy acrylate **1** with aldehydes mediated by zinc or TDAE

Entry	RCHO	Mediator	Product (%)[a]	Ratio of diastereomers (*syn:anti*)[b]
1	R=Ph	Zinc	**3a** (95)	41:54
2	R=4-ClC$_6$H$_4$	Zinc	**3b** (78)	28:50
3	R=4-MeOC$_6$H$_4$	Zinc	**3c** (90)	42:48
4	R=furyl	Zinc	**3d** (70)	31:39
5	R=*trans*-PhCH=CH	Zinc	**3e** (92)	35:57
6	R=Ph(CH$_2$)$_2$	Zinc	**3f** (90)	28:62
7	R=Ph	TDAE	**4a** (48)	—
8	R=3,4-diMeOC$_6$H$_3$	TDAE	**4c** (49)	—
9	R=4-MeC$_6$H$_4$	TDAE	**4d** (48)	—
10	R=furyl	TDAE	**4e** (34)	—

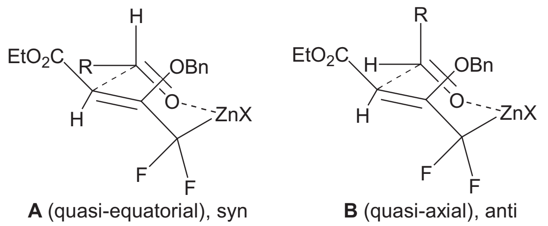
[a] Isolated yield.

[b] Based on isolated yield.

In the presence of zinc powder in THF at 60 °C, acrylate **1** reacted with benzaldehyde in γ addition mode to give the *gem*-difluorinated δ-hydroxy esters **4a**. Because the same reaction mode with aldehyde was observed before in the reaction of a similar fluorinated acrylate under the same reaction conditions,[4b] this reaction was not studied in detail. TDAE is an excellent electron donor whose reductive ability is equivalent to zinc.[10] TDAE-promoted reactions of halogeno-difluoromethylated substrates with some electrophiles were reported previously.[11] As acrylate **1** reacted with TDAE to afford the γ-position reduced product **2b** as the major product, it was anticipated that the TDAE-mediated reaction of acrylate **1** with aldehyde would also give the γ-mode addition product. Indeed, in the presence of TDAE, acrylate **1** reacted smoothly with either aromatic or heteroaromatic aldehydes to give the *gem*-difluorinated δ-hydroxy esters **4**[12] in a highly regioselective manner in moderate yields.[13]

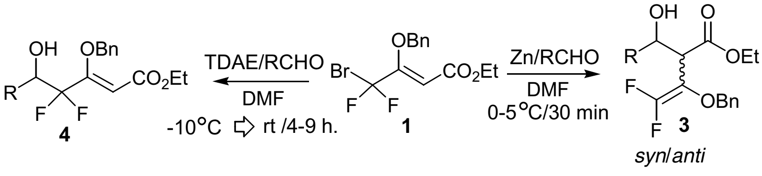
The effects of counterion, temperature, and substituents on α- and γ-coupling mode in the reactions of metal dienolates with aldehydes and imines were extensively investigated.[14] As indicated above, the active zinc reagent species exist in the γ-carbon metallated form (**IIa**). Under the kinetic control conditions (in DMF at 0 °C for 0.5 h), the active species reacted with aldehydes through the following two transition states (Fig. 3) to give the α-coupling mode products **3** that are kinetically more stable. And the diastereoselectivity is governed by the bulky effect of the aldehyde substituents to give the *anti*-isomer as major one through transition state **B** (quasi-axial). When the reaction was carried out in thermodynamical control conditions (in THF at 60 °C for 3 h), it is not difficult to understand that the thermodynamically more stable γ-coupled products **4** were formed. We are not sure about the reasons why TDAE-mediated reaction gave the thermodynamically more stable γ-coupled products **4** as predominant one under the kinetic control conditions (in DMF at −10 °C for 1 h). This might be attributed to the different counterion (TDAE^{2+} vs. Zn^{2+}) (Scheme 2).

In conclusion, the structure of the zinc reagent from acrylate **1** was investigated by ^{19}F NMR spectroscopy and it was found to exist in the γ-carbon metallated form but not the O-metallated and α-carbon metallated form. Up to now, this is the first case that studies the true structure of the so-called zinc dienolate. The reaction mode of acrylate **1** with aldehyde could be completely controlled by zinc and TDAE to give the α-mode



A (quasi-equatorial), syn **B** (quasi-axial), anti

Figure 3.



Scheme 2.

and γ-mode addition product, respectively. Synthetic applications of this acrylate for more complex fluorinated molecules are now in progress.

Acknowledgements

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12. All new compounds gave spectral and analytic data in accordance with the proposed structures. *syn*-**3a**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.16$ (3H, t, $J = 7.0$ Hz), 2.92 (1H, d, $J = 5.1$ Hz), 3.63 (1H, ddd, $J = 6.9$, 3.0, 1.8 Hz), 4.11 (2H, q, $J = 7.0$ Hz), 4.94 (2H, s), 5.32 (1H, dd, $J = 6.9$, 5.1 Hz), 7.27–7.42 (10H, m). ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -97.3$ (1F, d, $J = 66.3$ Hz), -111.2 (1F, d, $J = 66.3$ Hz). MS (EI, 70 eV): $m/z = 236$ (1, M^+−PhCO−HF−1), 197 (1), 179 (1), 140 (3), 115 (2), 105 (10), 92 (8), 91 (100), 77 (18), 65 (7), 51 (4). IR (KBr): $\nu = 3518$, 2983, 2882, 1800, 1750, 1736, 1497, 1455, 1389, 1370, 1280, 1244, 1175, 1095, 1075, 1026, 760, 738, 699 cm^{-1}. Anal. Calcd for $C_{20}H_{20}F_2O_4$: C, 66.29; H, 5.56. Found: C, 66.24; H, 5.62. *anti*-**3a**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.28$ (3H, t, $J = 7.2$ Hz), 3.51 (1H, d, $J = 3.3$ Hz), 3.54–3.59 (1H, m), 4.21–4.26 (2H, m), 4.68–4.71 (2H, m), 5.25 (1H, dd, $J = 9.6$, 3.3 Hz), 7.27–7.39 (10H, m). ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -99.5$ (1F, d, $J = 72.8$ Hz), -111.9 (1F, d, $J = 72.8$ Hz). MS (EI, 70 eV): $m/z = 324$ (20), 296 (21), 295 (100), 281 (1), 267 (7), 252 (1), 240 (2), 211 (1), 197 (4), 178 (2), 162 (4), 140 (2), 119 (11), 105 (89), 91 (57), 77 (27), 65 (8), 57 (7). IR (KBr): $\nu = 3491$, 2983, 1735, 1497, 1455, 1307, 1283, 1241, 1203, 1177, 1093, 1072, 1016, 770, 738, 699 cm^{-1}. Anal. Calcd for $C_{20}H_{20}F_2O_4$: C, 66.29; H, 5.56. Found: C, 66.15; H, 5.53. **4a**: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.28$ (3H, t, $J = 7.3$ Hz), 2.68 (1H, d, $J = 5.1$ Hz), 4.18 (2H, q, $J = 7.3$ Hz), 5.09 (1H, ddd, $J = 14.9$, 9.9, 5.1 Hz), 5.27 (2H, AB system, $J = 11.4$ Hz), 5.74 (1H, s), 7.25–7.42 (10H, m). ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -115.2$ (AB-d, $J = 251.3$, 14.9, 9.9 Hz). MS (EI, 70 eV): $m/z = 362$ (1, M^+), 361 (1), 346 (9), 345 (10), 296 (8), 295 (10), 272 (5), 249 (13), 205 (36), 181 (23), 159 (30), 135 (7), 115 (16), 91 (100), 77 (4), 65 (4). IR (KBr): $\nu = 3465$, 3034, 2983, 1715, 1657, 1497, 1455, 1343, 1233, 1197, 1066, 1028, 845, 738, 698, 612 cm^{-1}. Anal. Calcd for $C_{20}H_{20}F_2O_4$: C, 66.29; H, 5.56. Found: C, 66.21; H, 5.77.
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