Nucleophilic Addition of Ethyl 3-Bromodifluoromethyl-3-benzyloxyacrylate to Imines: An Effective Entry to Novel g*em*-Difluorinated Amino Esters and their Derivatives

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Abstract: Zinc- or tetrakis(dimethylamino)ethylene (TDAE)-mediated nucleophilic addition of ethyl 3-bromodifluoromethyl-3-benzyloxyacrylate to imines afforded *gem*-difluorovinyl substituted β-amino esters (α-addition product) and *gem*-difluorinated δ-amino esters (γ-addition product) or their cyclized derivatives, depending on the mediator and the nature of substituents on the imines.

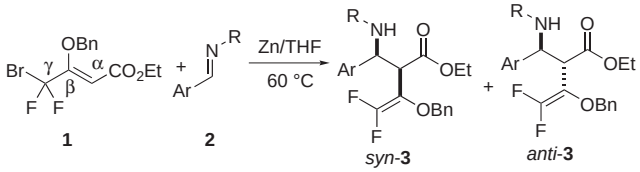
Key words: nucleophilic addition, amino esters, bromodifluoromethylated acrylate, imines, *gem*-difluorinated

The difluoromethylene moiety (CF_2) is a key subunit in many fluorinated compounds of biological and pharmaceutical significance.[2] It has been recognized as an isopolar-isosteric substitute for oxygen and has been used in the modification of some biologically active compounds.[3] Fluorinated amino acids and their derivatives are an important class of non-natural compounds and have received increasing interest from the fields of medicinal, agricultural, and material sciences.[4] Thus, in connection with our work on the synthesis and bioactivity of fluorine-containing compounds,[5] we were interested in the synthesis of *gem*-difluorinated amino acids as new potent bioactive compounds.

Halogenodifluormethylated compounds are widely employed as the starting point for the construction of some novel *gem*-difluorinated molecules.[6,7] However, up to now the reaction of β-halogenodifluoromethyl substituted acrylates have only been reported independently by Kitazume and Hu;[8] two fluorinated acrylates reacted with aldehydes in the presence of zinc to give the α-difluorovinyl substituted β-hydroxy ester and the *gem*-difluorinated δ-hydroxy esters. Although their reaction with imines afforded intriguing fluorinated amino esters, this was not further investigated by them, though it could be attributed to the reduced electrophilicity of the imine[9] compared with carbonyl compounds resulting in the acrylates failing to react with the imines.

Previously,[10] we found that ethyl 3-bromodifluoromethyl-3-benzyloxyacrylate (**1**) could serve as an excellent multifunctional building-block for the convenient synthesis of some CF_2-containing substrates; the benzyl vinyl ether moiety was a masked hydroxy or carbonyl group. The mode of addition (α or γ) could be completely controlled by the choice of mediator, zinc or TDAE, which produced α-difluorovinyl substituted β-hydroxy esters and *gem*-difluorinated δ-hydroxy esters, respectively. To extend the application of this building-block, the reaction of **1** with a wide variety of imines was investigated by us, it was found that the product distribution was dependent not only on the reaction mediators but also the substituent pattern on the imines.

Since it was believed that the low electrophilicity of the imines prepared from aromatic aldehydes and aromatic amines could detrimentally affect the reaction, our initial attempts were carried out with a sulfonimine, which is a stronger electrophile than normal imines due to the strong electron-withdrawing sulfonyl group.[11] Under classical Reformatsky reaction conditions, ethyl 3-bromodifluoromethyl-3-benzyloxyacrylate (**1**) smoothly reacted with sulfonimines **2a**–**c** in THF at 60 °C in the presence of zinc powder. After three hours, the α-addition products (Reformatsky reaction type product), α-difluorovinyl substituted β-amino esters **3a**–**c**, were isolated exclusively in good yield with the *syn*-diastereomer as the major product (Scheme 1, Table 1, entry 1–3);[12] no γ-addition product could be detected in the reaction mixture. The difluorovinyl unit of the resulting β-amino ester is the key structure of some fluoro-olefin derived enzyme inhibitors.[13]



Scheme 1

The stereochemical assignment was based on single-crystal X-ray diffraction analysis of the major product obtained from the reaction of acrylate **1** with imine **2b**. Although the *syn*/*anti* stereoselectivity was moderate, these two diastereomers could be readily separated by flash column chromatography. The reaction of acrylate **1** with imine **2d** [PhCH=NC_6F_4(4-Cl)] gave the same α-coupling product albeit in lower yield (Table 1, entry 4).

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Table 1 Reformatsky Reaction of Ethyl 3-Bromodifluoromethyl-3-benzyloxylacrylate **1** with Imines **2**

Entry	Imine (**2**)	Time (h)	Product (%)[a]	*syn*/*anti*[b]
1	**2a** Ar = Ph, R = Ts	3	**3a** (84)	61:23
2	**2b** Ar = 4-ClC_6H_4-, R = Ts	3.5	**3b** (76)	42:34
3	**2c** Ar = 4-$MeOC_6H_4$-, R = Ts	3.5	**3c** (78)	48:30
4	**2d** Ar = Ph, R = 4-ClC_6F_4-	2	**3d** (30)	7:23

[a] Isolated overall yield.
[b] Based on the isolated yield.

Table 2 Reaction of Ethyl 3-bromodifluoromethyl-3-benzyloxyacrylate **1** with Sulfonimines **2** Mediated by TDAE

Entry	Sulfonimine (**2**)	Time at r.t. (h)	Products[a] (%)
1	**2a** Ar = Ph	9	**4a** (51), **5a** (42)
2	**2b** Ar = 4-ClC_6H_4-	4	**4b** (49), **5b** (36)
3	**2b** Ar = 4-ClC_6H_4-	3.5[b]	**4b** (26), **5b** (24)
4	**2c** Ar = 4-$MeOC_6H_4$-	5	**4c** (51), **5c** (20)
5	**2e** Ar = 4-MeC_6H_4-	4	**4e** (57), **5e** (30)
6	**2f** Ar = Furyl	4	**4f** (54), **5f** (29)

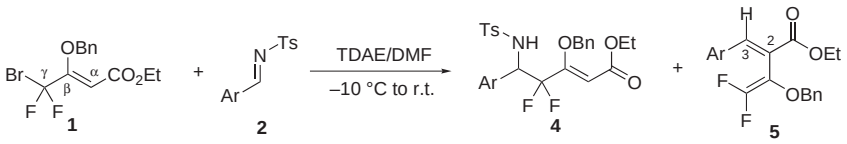
[a] Yield determined by ^{19}F NMR spectroscopy.
[b] THF as solvent instead of DMF.

Therefore, the 4-chlorotetrafluorophenyl has the same character as sulfonyl, whose strong electron-withdrawing power causes the corresponding imine to readily undergo nucleophilic attack.

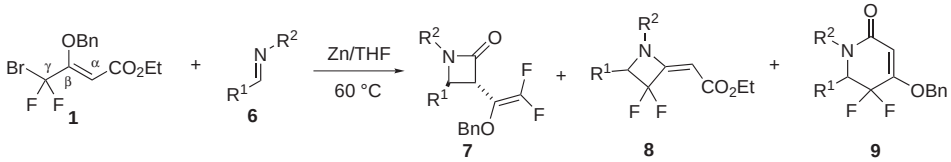
Tetrakis(dimethylamino)ethylene (TDAE) is an excellent electron donor, and it has the same reductive ability as zinc.[14] It was successfully utilized as a mediator instead of zinc to promote the reaction of arylate **1** with sulfonimine **2**. With a reaction time of one hour at –10 °C or four to eight hours at ambient temperature in DMF, the γ-additon product, *gem*-difluorinated δ-amino ester **4**, was favored over the α-addition product to predominantly give *gem*-difluorinated δ-amino esters **4** (Scheme 2).[15] Meanwhile, in situ formed β-amino esters **3** (α-addition product) lost one molecule of *p*-toluenesulfonamide to give the novel α-difluorovinyl substituted acrylate **5** as the minor product under basic reaction conditions. Traces of the stereoisomer of acrylate **5** were obtained in some cases (Table 2, entry 3–6); the olefinic proton signal appeared at higher field than that of **5** in the ^1H NMR spectrum. According to the literature,[16] when the olefinic proton was *cis* to the ethoxy carbonyl group in trisubstituted alkenes such as acrylate **5**, its chemical shift should appear at lower field than the *trans* configured olefin, thus, the 2,3-double bond (Scheme 2) in acrylate **5** was assigned as *trans*. The yield was dramatically diminished when the same reaction was performed in THF (Table 2, entry 3) due to the low solubility of the sulfonimine in THF.

Our earlier concern with respect to the low electrophilicity of imines prepared from aromatic aldehydes and primary amines was relieved by the observation that in the presence of zinc powder imines **6** reacted with acrylate **1** in THF at 60 °C. After five to six hours, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl, routine work-up followed by flash column chromatography, and then separation furnished three addition-cyclization products (**7**, **8**, and **9**) whose ratio was dependent on the substituent pattern on the imines (Scheme 3, Table 3).[17]

The reaction of imines **6a**–**c** prepared from aromatic aldehydes and aromatic amines (except *para*-methoxybenzaldehyde and *para*-methoxyaniline) underwent α-coupling and cyclization to produce *trans*-3-difluorovinyl substituted β-lactams **7a**–**c** exclusively in good yield (Table 3, entry 1–3). The *trans* configuration of lactam **7** was first confirmed by the 2–3 Hz vicinal coupling



Scheme 2



Scheme 3

Table 3 Reaction of Ethyl 3-Bromodifluoromethyl-3-benzyloxyacrylate **1** with Imines **6** Mediated by Zinc

Entry	Imine (**6**)	Products (%)[a]		
		β-Lactam	Azetidine	Pyridinone
1	**6a** R^1 = Ph, R^2 = Ph	**7a** (61)		
2	**6b** R^1 = 4-ClC_6H_4-, R^2 = Ph	**7b** (50)		
3	**6c** R^1 = Ph, R_2 = 4-ClC_6H_4-	**7c** (77)		
4	**6d** R^1 = 4-$MeOC_6H_4$-, R^2 = Ph	**7d** (33)		**9d** (22)[b]
5	**6e** R^1 = Ph, R^2 = 4-$MeOC_6H_4$-	**7e** (30)		**9e** (20)
6	**6f** R^1 = Ph, R^2 = Bn	**7f** (8)	**8f** (17)	**9f** (36)
7	**6g** R^1 = Furyl, R^2 = Bn		**8g** (17)	**9g** (66)
8	**6h** R^1 = *trans*-PhCH=CH-, R^2 = Ph		**8h** (10)	**9h** (37)
9	**6i** R^1 = 4-$MeOC_6H_4$-, R^2 = Bn		**8i** (19)	**9i** (34)[b]
10	**6j** R^1 = 4-ClC_6H_4-, R^2 = Bn		**8j** (19)	**9j** (34)
11	**6k** R^1 = Furyl, R^2 = Ph			**9k** (34)[b]

[a] Isolated yield.
[b] The non-cyclized γ-product was also obtained.

constants between the C-3 and C-4 proton on the cyclic lactam, which is attributed to a dihedral angle of almost 90° between C-3 and C-4. This was further confirmed by the single crystal X-ray diffraction analysis of lactam **7b**.

Previous studies revealed that the active zinc species from acrylate **1** in THF exists as the γ-carbon metallated form.[10] For the following reaction the energy level of transition state **B** is lower than transition state **A** due to the bulky effect of the imine substituents (Figure 1), the reaction followed the reaction pathway through transition state **B** to give the corresponding *anti*-α-difluorovinyl substituted β-amino ester, stereospecifically, which then underwent lactamization to afford *trans*-β-lactam **7**.

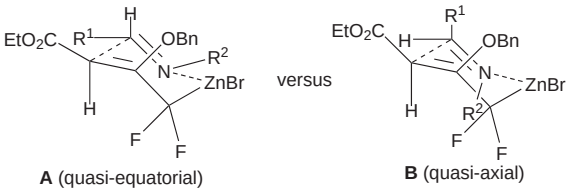


Figure 1

In addition to β-lactams **7d** and **7e**, the reactions of imines **6d** and **6e** with acrylate **1** also provided the *gem*-difluorinated 5,6-dihydropyridin-2-ones **9d** and **9e** in comparable yield (Table 3, entries 4, 5). Possibly due to the electron-donating methoxy group, these two reactions gave not only the β-amino esters but the δ-amino esters (γ-coupling) as intermediate products which also underwent lactamization to afford the 5,6-dihydropyridin-2-one compounds **9**.

Under the same reaction conditions, the reactions of imines **6f**–**j** substituted by a non-aromatic substituent almost completely underwent γ-coupling followed by cyclization. However, besides the *gem*-difluorinated pyridinone compound **9**, a novel *gem*-difluorinated azetidine compound **8** was also obtained. The presence of an olefinic proton signal at about 5.0 ppm in the ^{1}H NMR spectrum obviously indicates that this does not result from the α-coupling reaction of acrylate **1** with imine, but in fact is formed from the γ-coupling reaction. Compound **8** was further characterized as an azetidine because the ethoxy group proton signals were still visible while, the benzyloxy group proton signals are missing. The apparent ion peak and the scission pattern in the mass spectrum strongly support this structure. Due to the less demanding ring-strain in *aza*-four-membered rings, the amino group of the intermediate δ-amino esters could also undergo intramolecular Michael addition to the α,β-double bond, and then elimination of benzyl alcohol gave azetidine **8**. Based on the NOSEY spectra of azetidine **8f** which clearly exhibited the characteristic cross-peaks between the olefinic proton and the *N*-benzylic protons, the geometry of the exocyclic double bond was assigned to be *trans*.[18] These first reported novel fluorinated four-membered *aza*-heterocycles might represent a new class of β-amino acid derivatives.

In conclusion, the zinc- or TDAE-mediated reactions of β-bromodifluoromethyl substituted acrylate **1** with diversely substituted imines were investigated, and some novel *gem*-difluorinated amino esters and their derivatives were obtained. It was found that the products and the product distribution were governed by the mediator and the nature

of the substituents on the imines. A further study to explain the effect of mediator and substituent on the imine is in progress and will be reported in due course.

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References and Notes

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(12) **Zinc Powder Mediated Reaction of Acrylate 1 with Imines 2; General Procedure** To a suspension of activated zinc powder (100 mg, 1.5 mmol) and sulfonimine **2** (1 mmol) in THF (4 mL) was added acrylate **1** (335 mg, 1 mmol) dropwise over 5 minutes at 60 °C. The mixture was stirred continuously at 60 °C for the time specified in Table 1. The reaction was quenched by the addition of a sat. aq solution of NH_4Cl (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and the solvent was removed. The residue was purified by chromatography on silica gel (*n*-hexane–EtOAc, 3:1 or 5:1) to give α-difluorovinyl substituted β-amino esters **3** as two diasteromers. *syn*-**3b** White solid; mp 80–82 °C. IR (film): 3232, 3033, 2988, 1739, 1597, 1493, 1445, 1368, 1323, 1284, 1256, 1237, 1174, 1155, 1091, 1066, 1012, 961, 900, 813, 738, 724, 697, 673, 569, 542 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (3 H, t, *J* = 7.2 Hz), 2.33 (3 H, s), 3.53–3.56 (1 H, m), 4.07–4.12 (2 H, m), 4.96 (2 H, AB system, *J* = 10.2 Hz), 5.17 (1 H, dd, *J* = 8.7, 6.3 Hz), 5.82 (1 H, d, *J* = 8.7 Hz), 6.96–7.46 (13 H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –96.5 (1 F, d, *J* = 68.3 Hz), –110.9 (1 F, d, *J* = 68.3 Hz). MS: *m*/*z* (%) = 367 (1), 366 (1), 296 (5), 294 (14), 255 (1), 230 (1), 174 (2), 155 (14), 140 (1), 92 (8), 91 (100), 65(8), 51 (1). Anal. calcd for $C_{27}H_{26}ClF_2NO_5S$: C, 58.96; H, 4.76; N, 2.55. Found: C, 58.99; H, 4.88; N, 2.54.

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(15) **TDAE-Mediated Reaction of Acrylate 1 with Imines 2; General Procedure** To a solution of acrylate **1** (335 mg 1 mmol) and sulfonimine **2** (1 mmol) in anhyd DMF (4 mL) cooled in an ice-salt bath under argon was added TDAE (239 mg, 0.29 mL, 1.2 mmol) dropwise via syringe over 0.5 h. A red color developed immediately with the formation of a fine white precipitate. The mixture was stirred vigorously for 1 h under cooling and then warmed to r.t. When the reaction was complete the orange red turbid solution was filtered and quenched by the addition of a sat. aq solution of NH_4Cl (8 mL). The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo to give a residue, which was purified by flash chromatography (*n*-hexane–EtOAc, 20:1→3:1) to give the expected δ-amino ester **4** and the novel difluorovinyl substituted acrylate **5** as the by product. **4a** White solid; mp 138–139 °C. IR (film): 3406, 3257, 2986, 1720, 1662, 1600, 1498, 1458, 1447, 1409, 1369, 1334, 1320, 1246, 1203, 1161, 1115, 1095, 1064, 1028, 929, 852, 816, 751, 698, 564 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (3 H, t, *J* = 7.3 Hz), 2.31 (3 H, s), 4.13 (2 H, q, *J* = 7.3 Hz), 4.96 (1 H, ddd, *J* = 12.6, 12.6, 10.2 Hz), 5.21 (2 H, AB system, *J* = 11.7 Hz), 5.56 (1 H, s), 5.64 (1 H, d, *J* = 10.2 Hz), 7.03–7.48 (14 H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –110.2. MS: *m*/*z* (%) = 486 (1, M^+ – Et), 470 (1), 424 (2), 380 (9), 350 (7), 314 (2), 261 (5), 260 (32), 181 (3), 155 (16), 140 (2), 92 (8), 91 (100), 65 (6). Anal. calcd for $C_{27}H_{27}F_2NO_5S$: C, 62.90; H, 5.28; N, 2.72. Found: C, 62.97; H, 5.32; N, 2.81.

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(17) The general procedure for zinc powder mediated reactions was applied to imine **6**. **7f** Yellowish oil; R_f 0.2–0.3 (*n*-hexane–EtOAc, 10:1). IR (film): 3064, 3032, 2923, 1763, 1496, 1455, 1398, 1361, 1282, 1137, 1084, 743, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.75 (1 H, d, *J* = 15.3 Hz), 3.85–3.88 (1 H, m), 4.42 (1 H, d, *J* = 3.0 Hz), 4.84–4.94 (3 H, m), 7.02–7.43 (15 H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –95.7 (1 F, d, *J* = 65.7 Hz), –109.8 (1 F, d, *J* = 65.7 Hz). MS: *m*/*z* (%) = 405 (1), 380 (1), 350 (1), 333 (1), 315 (9), 314 (12), 273 (1), 253 (1), 194 (1), 181 (2), 162 (3), 140 (1), 131 (11), 106 (5), 91 (100), 77 (3), 65 (8), 51 (1). HRMS: *m*/*z* calcd for $C_{25}H_{21}F_2NO_2$ (M^+), 405.15404; found, 405.15897. **8f** Yellowish oil; R_f 0.3–0.4 (*n*-hexane–EtOAc, 5:1). IR (film): 3032, 2981, 2904, 1695, 1666, 1496, 1456, 1370, 1350, 1280, 1194, 1150, 1109, 1060, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (3 H, t *J* = 7.1 Hz), 4.10 (1 H, d, *J* = 15.0 Hz), 4.17 (2 H, q, *J* = 7.1 Hz), 4.42 (1 H, d, *J* = 15.0 Hz), 4.85 (1 H, s), 5.09 (1 H, dd, *J* = 9.6, 3.9 Hz), 7.13–7.43 (10 H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –103.8 (1 F, dd, *J* = 216.3, 9.6 Hz), –114.0 (1 F, dd, *J* = 216.3, 3.9 Hz). MS: *m*/*z* (%) = 343 (3), 314 (3), 298 (13), 271 (4), 250(72), 224 (2), 172 (2), 156 (2), 147 (3), 129 (7), 105 (6), 91 (100), 77 (3), 65 (11), 51 (2). Anal. calcd for $C_{20}H_{19}F_2NO_2$: C,

69.96; H, 5.58; N, 4.08. Found: C, 70.14; H, 5.75; N, 3.83.
9f Yellowish heavy oil; R_f 0.3–0.4 (*n*-hexane–EtOAc, 3:1). IR (film): 3461, 3064, 3032, 2922, 1711, 1665, 1632, 1496, 1452, 1431, 1396, 1365, 1238, 1199, 1138, 1096, 1063, 1029, 962, 849, 745, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.49 (1 H, d, *J* = 15.3 Hz), 4.67 (1 H, dd, *J* = 16.5, 2.1 Hz), 4.98 (2 H, AB system, *J* = 12.0 Hz), 5.54–5.60 (2 H, m), 7.17–7.40 (15 H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –89.1 (1 F, dd, *J* = 270.4, 16.5 Hz), –120.0 (1 F, dd, *J* = 270.4, 2.1 Hz). MS: *m*/*z* (%) = 405 (4), 386 (1), 314 (56), 288 (1), 250 (1), 226 (1), 196 (2), 174 (11), 140 (2), 118 (1), 106 (31), 92 (8), 91 (100), 79 (3), 77 (3), 65 (11), 51 (2). Anal. calcd for $C_{25}H_{21}F_2NO_2$: C, 74.06; H, 5.22; N, 3.45. Found: C, 73.84; H, 5.63; N, 3.21. HRMS: *m*/*z* calcd for $C_{25}H_{21}F_2NO_2$ (M^+): 405.15404; found: 405.15448

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