First highly stereoselective synthesis of *anti*-α-trifluoromethyl-β-amino acid derivatives

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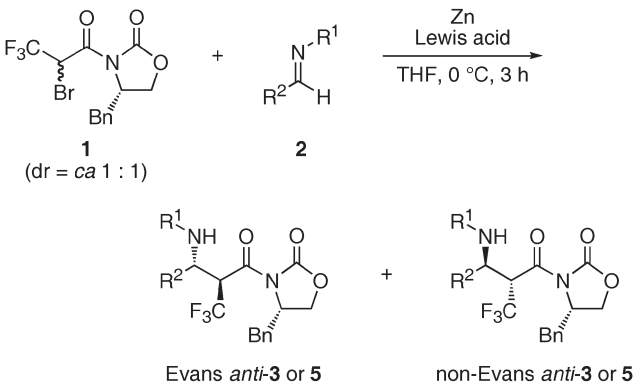
The Reformatsky-type reaction of 2-bromo-3,3,3-trifluoropropanoic imide with various types of imines, in the presence of $ZnBr_2$ as a Lewis acid in THF at 0 °C for 3 h, gave the corresponding α-trifluoromethyl-β-amino acid derivatives in a highly *anti*-selective manner.

Since the introduction of fluorine groups into bioorganic molecules very often exerts significant effects on their physical properties, physiological activities and metabolic profiles, efforts have continuously been made to synthesize fluorine-containing biologically active compounds.[1] Out of such molecules, α-trifluoromethyl (CF_3)-β-amino acids[2], possessing the unique properties of the CF_3 group, such as high electronegativity, electron density, steric hindrance and hydrophobic character, are attractive analogues of natural β-amino acids of biological interest.[3] However, the relative inaccessibility of most CF_3-containing β-amino acids in a non-racemic form, whose asymmetric synthesis often requires complex experimental protocols and difficult-to-handle starting materials, has obstructed systematic investigations of the biomedicinal and structural features of α-CF_3-β-amino acids and their peptidic derivatives. In this communication, we wish to disclose a convenient and easy route to optically active α-CF_3-β-amino acid derivatives *via* the highly stereoselective Reformatsky-type reactions of chiral 3-(2-bromo-3,3,3-trifluoropropanoyl)-4-benzyl-2-oxazolidinone (**1**)[4] with various types of imines (Scheme 1).

Initially, we started investigating Reformatsky-type reactions[5] using the diastereomeric mixture **1** (dr = *ca.* 1 : 1) and *N*-Boc benzaldehyde imine **2a**[6] (R^1 = Boc, R^2 = Ph) (Table 1). Thus, upon treating 1.0 equiv. of **1** with 1.5 equiv. of **2a** in the presence of activated zinc dust (1.2 equiv.) in THF (0.2 M) at 0 °C for 3 h, the corresponding adduct, **3a**, was afforded in only 18% yield, together with the reduction product **4** (Fig. 1) and unreacted α-bromo imide **1** in 49 and 30% yields, respectively (Table 1, entry 1). Interestingly, Evans *anti*-**3a** was obtained as a single isomer, and traces of other stereoisomers, such as non-Evans *anti*-**3a**, Evans *syn*-**3a** and non-Evans *syn*-**3a** (Fig. 1), were not detected. As shown in Table 1, entries 2 and 3, the addition of Lewis acid slightly increased the chemical yields without any loss of diastereoselectivity.



Scheme 1 Reformatsky-type reaction.

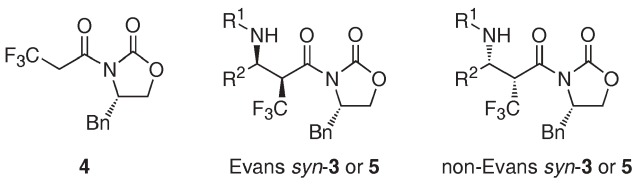


Fig. 1 Reduction product and *syn*-isomers.

Table 1 Investigation of the reaction conditions (R^1 = Boc, R^2 = Ph)

Entry[a]	Lewis acid	Yield of **3a** (%)[b]	*syn* (%)		*anti* (%) (Evans : non-Evans (%))	Yield of **4** (%)[b]	Recovery of **1** (%)[b]
1[c]	(none)	18	0	:	100 (>99 : 1)	49	30
2[c]	$ZnBr_2$	23	0	:	100 (>99 : 1)	49	23
3[c]	$EtAlCl_2$	33	1	:	99 (>99 : 1)	34	0
4	(none)	69	0	:	100 (>99 : 1)	27	0
5	Et_2AlCl	82	3	:	97 (>99 : 1)	10	0
6	$EtAlCl_2$	85	7	:	93 (>99 : 1)	10	0
7	$BF_3{\cdot}OEt_2$	82	7	:	93 (>99 : 1)	9	0
8	$ZnBr_2$	89	0	:	100 (>99 : 1)	10	0
9[d]	$ZnBr_2$	98 (92)	0	:	100 (>99 : 1)	1	0

[a] Unless otherwise noted, reactions were carried out at 0 °C for 3 h in 0.5 M THF solution using 1.2 equiv. of zinc dust and 1.5 equiv. of Lewis acid. [b] Determined by ^{19}F NMR. Value in parentheses is an isolated yield. [c] Carried out in 0.2M THF solution. [d] Molar ratio of **1** : **2a** : Lewis acid = 1.0 : 2.0 : 2.0.

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Table 2 Reformatsky-type reaction with various types of imines **2**

Entry[a]	Imine	R^{1b}	R^2	Product	Yield of **3** or **5** (%)[c]	*syn* (%)		*anti* (%) (Evans : non-Evans (%))
1	**2a**	Boc	Ph	**3a**	98 (92)	0	:	100 (>99 : 1)
2	**2b**	Boc	*p*-MeC_6H_4	**3b**	93 (85)	0	:	100 (>99 : 1)
3	**2c**	Boc	*p*-$MeOC_6H_4$	**3c**	84 (80)	0	:	100 (>99 : 1)
4	**2d**	Boc	*p*-ClC_6H_4	**3d**	92 (84)	0	:	100 (>99 : 1)
5	**2e**	Boc	*p*-$CF_3C_6H_4$	**3e**	93 (90)	0	:	100 (>99 : 1)
6	**2Aa**	Cbz	Ph	**5a**	88 (80)	0	:	100 (94 : 6)
7	**2Ab**	Cbz	*p*-MeC_6H_4	**5b**	94 (90)	0	:	100 (93 : 7)
8	**2Ac**	Cbz	*p*-$MeOC_6H_4$	**5c**	91 (88)	0	:	100 (96 : 4)
9	**2B**	PMP	Ph		0			
10	**2C**	Ts	Ph		0			

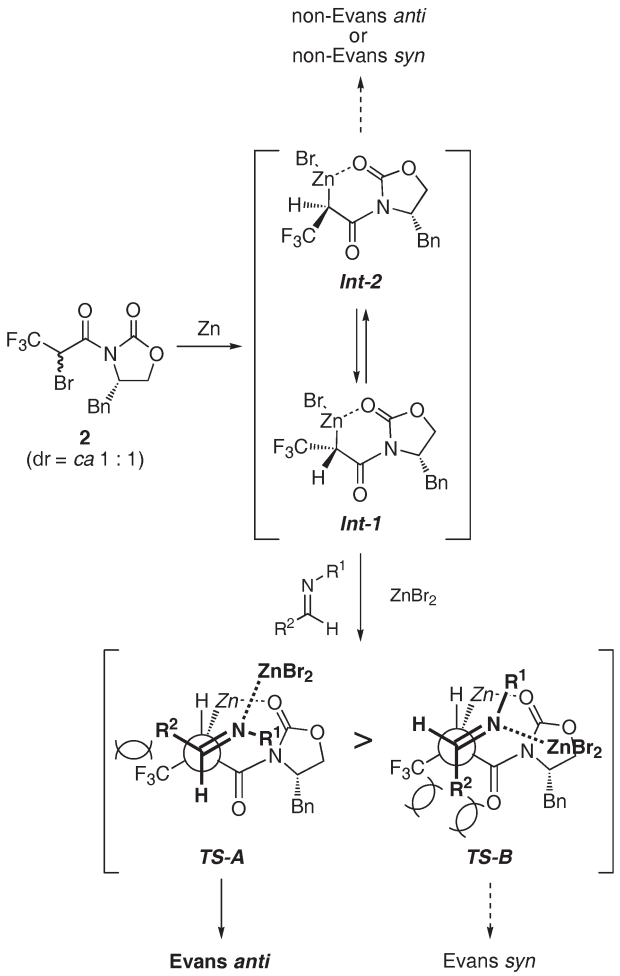
[a] Unless otherwise noted, reactions were carried out at 0 °C for 3 h in 0.5 M THF solution using 1.2 equiv. of zinc dust, and 2.0 equiv. each of **2** and $ZnBr_2$. [b] Boc = *tert*-Butoxycarbonyl, Cbz = Benzyloxycarbonyl, PMP = *para*-Methoxyphenyl, Ts = *para*-Toluenesulfonyl. [c] Determined by ^{19}F NMR. Values in parentheses are isolated yields.

Surprisingly, increasing the concentration of the reaction mixture from 0.2 to 0.5 M resulted in a significant improvement in yields, Evans *anti*-**3a** being afforded in 69% yield as the sole product, along with 27% of **4**. Next, we re-investigated the effect of Lewis acid on the reaction at 0.5 M concentration, as described in Table 1, entries 5–8. Et_2AlCl, $EtAlCl_2$, $BF_3{\cdot}OEt_2$ and $ZnBr_2$ were all effective, the desired product being obtained in 82–89% yield. Eventually, we found that the best yield was obtained when 2.0 equiv. each of **2a** and Lewis acid were employed. In this case, the desired β-amino acid derivative was furnished in 98% yield (Table 1, entry 9).

With the optimized reaction conditions, we next examined the Reformatsky-type reaction with various types of imines **2**. The results are summarized in Table 2.[7]

As shown in Table 2, entries 2–4, *N*-Boc imines possessing various substituents, such as Me, MeO (an electron-donating group), Cl or CF_3 (an electron-withdrawing group), on the benzene ring of R^2 could participate effectively in the coupling reaction to give the corresponding Evans *anti*-**3** in excellent yield with exclusive *anti*-selectivity. Changing the protecting group on a nitrogen atom from Boc to Cbz did not influence the chemical yield at all, though a slight decrease in diastereoselectivity was observed (Table 2, entries 6–8). However, the employment of a PMP or Ts group as R^1 resulted in the complete recovery of the reduction product **4** (Table 2, entries 9 and 10). Deprotection of **3a** under various conditions using $LiOH–H_2O_2$ did not give the desired carboxylic acid, but led to *N*-{(1*S*)-benzyl-2-hydroxyethyl}-3-(*tert*-butoxycarbonyl)amino-3-phenyl-2-trifluoromethylpropanamide without epimerization.[8]

The stereochemical assignment of **3** or **5** was made as follows: The single-crystal X-ray analyses of **3a**[9] and **5a**[10] could be carried out successfully, indicating that the stereochemistry of **3a** and **5a** was (2*S*,3*S*). The structures of the other products were determined by comparison of the ^{19}F NMR chemical shifts. These results allow us to draw the reaction mechanism described in Scheme 2.[11] Thus, $ZnBr_2$-activated imine approaches the reactive carbon of the Reformatsky reagents **Int-1** and **Int-2**, which are in equilibrium, from the side opposite to that occupied by the zinc atom. Due to a large steric repulsion between the imine and benzyl substituents of the oxazolidinone ring, the reaction of **Int-1** with imine proceeds preferentially *via* open-chain transition state **TS-A** or **TS-B**. In this case, **TS-A**, where the substituent R^2 occupies the antiperiplanar position to a bulky oxazolinylcarbonyl group, may be much more stable than **TS-B**, resulting in the highly diastereoselective formation of the Evans *anti*-coupling product.



Scheme 2 A proposed reaction mechanism.

In summary, we have accomplished the first convenient and effective synthesis of α-trifluoromethyl-β-amino acid derivatives *via* a highly stereoselective Reformatsky-type reaction, leading to the exclusive formation of Evans *anti*-isomers in excellent yields. Further studies to reveal the reaction mechanism and extend its synthetic utility are currently under way in our laboratory.

Notes and references

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7 A typical procedure for the Reformatsky-type reaction of **1** is as follows: To a suspension of zinc (0.039 g, 0.60 mmol), imine **2a** (0.205 g, 1.0 mmol) and $ZnBr_2$ (0.225 g, 1.0 mmol) in THF (2 mL) was added a solution of **1** (0.183 g, 0.50 mmol) in THF (1 mL) at 0 °C under argon. After stirring at that temperature for 3 h, the reaction was quenched with saturated aqueous NH_4Cl and a 1 M HCl solution. Extraction with AcOEt, drying over Na_2SO_4 and concentration *in vacuo*, followed by silica gel column chromatography (benzene : AcOEt = 49 : 1 to 19 : 1), afforded pure product **3a** (0.227 g, 0.46 mmol, 92%). **3a**: mp 125.0–127.0 °C; IR (KBr) 3032, 1771, 1697, 1508, 1396, 1256, 1159, 1124, 1053 and 997 cm^{-1}; ^1H NMR (500.13 MHz, $CDCl_3$) δ 1.46 (s, 9 H), 2.72 (dd, J = 9.5, 13.5 Hz, 1 H), 3.21 (d, J = 13.2 Hz, 1 H), 3.68–3.82 (m, 1 H), 4.04 (d, J = 8.4 Hz, 1 H), 4.41 (br s, 1 H), 5.51–5.62 (m, 2 H), 6.16–6.19 (br m, 1 H), 7.14–7.17 (m, 2 H) and 7.27–7.37 (m, 8 H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 28.3, 37.5, 49.9 (q, J = 26.5 Hz), 52.1, 55.4, 66.0, 80.1, 123.4 (q, J = 281.9 Hz), 126.0, 127.6, 128.1, 128.3, 128.7, 129.0, 129.3, 134.4, 138.4, 152.5, 154.8 and 166.2 (q, J = 2.8 Hz); HRMS (FAB^+) Found: m/z 491.1798. Calc. for ($M^+ - H$) ($C_{25}H_{26}F_3O_5N_2$) 491.1794.

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9 Crystal and molecular structural data for **3a**: Colorless needles, $C_{28}H_{30}F_3N_2O_5$, M = 531.55, monoclinic, space group $C2$ (no 5), a = 29.527 (5), b = 6.3638 (12), c = 14.506 (2) Å, β = 92.929 (13)° and V = 2722.1 (8) $Å^3$, Z = 4, μ(Cu-Kα) = 8.680 cm^{-1}, 4348 reflections measured, 3366 unique (R_{int} = 0.021) which were used in all calculations. $R(F)$ = 0.0400 ($I > 2\sigma(I)$), 0.0461 (all data), w$R(F^2)$ = 0.1155 (all data), GoF = 1.031. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. CCDC 611041. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b603882d.

10 Crystal and molecular structural data for **5a**: Colorless needles, $C_{28}H_{25}F_3N_2O_5$, M = 526.51, orthorhombic, space group $C2221$ (no 20), a = 11.039 (2), b = 24.551 (5), c = 18.700 (7) Å and V = 5067.9 (23) $Å^3$, Z = 8, μ(Cu-Kα) = 9.319 cm^{-1}, 4787 reflections measured, 3159 unique (R_{int} = 0.022) which were used in all calculations. $R(F)$ = 0.0420 ($I > 2\sigma(I)$), 0.0445 (all data), w$R(F^2)$ = 0.1063 (all data), GoF = 1.101. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. CCDC 611042. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b603882d.

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