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Highly Stereoselective $TiCl_4$-Catalyzed Evans–Aldol and Et_3Al-Mediated Reformatsky Reactions. Efficient Accesses to Optically Active *syn*- or *anti*-α-Trifluoromethyl-β-hydroxy Carboxylic Acid Derivatives

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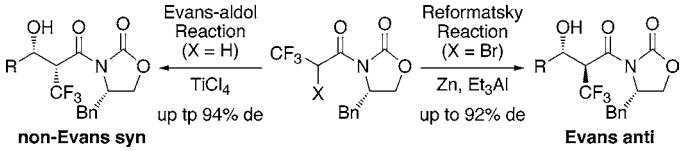
ABSTRACT



The $TiCl_4$-catalyzed Evans–aldol reaction of optically active 3,3,3-trifluoropropanoic imide gave the non-Evans syn product stereoselectively, whereas the Reformatsky reaction of 2-bromo-3,3,3-trifluoropropanoic imide in the presence of Et_3Al led to the Evans anti product. These new approaches enabled us to synthesize all stereoisomers of trifluoromethylated aldol products for the first time.

Growing interest in trifluoromethylated organic compounds in various fields such as medicine, pharmaceuticals, and fluoropolymers has led to a new focus on developing facile methods for the introduction of a trifluoromethyl group into useful intermediates or desired substrates.[1] Introduction of the trifluoromethyl group—with its high electronegativity, stability, and lipophilicity—often induces significant changes in their chemical, physical, and biological properties. However, synthetic methods for introducing this group into a specific position of organic compounds suffer from low applicability and selectivity. Consequently, the efficient synthesis of versatile intermediates having the trifluoromethyl group is an extremely attractive subject matter.[2] Out of the diversity of fluorinated intermediates, α-trifluoromethyl-β-hydroxy carboxylic acid derivatives **1** are recognized as one of the most valuable synthetic intermediates in view of the extensive studies on the nonfluorinated counterparts (Figure 1).

However, the aldol reaction of a fluorinated lithium enolate **2** (metal = Li), which would be the most straightforward

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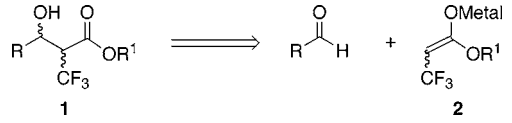
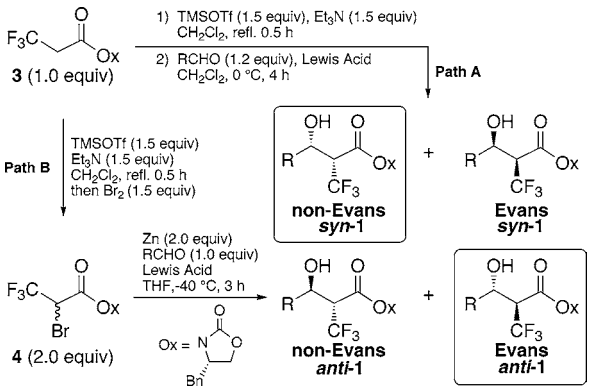


Figure 1. Retrosynthesis of α-trifluoromethyl-β-hydroxy carboxylic acid derivatives **1**.

approach to **1**, has been believed to be less attractive thus far because the enolate **2** is very labile due to susceptibility of β-elimination of fluoride ion[3] as well as lower nucleophilicity induced by the electron-withdrawing trifluoromethyl group. Herein, we wish to disclose the first enantioselective syntheses of **1** via highly syn-selective Evans−aldol reaction and highly anti-selective Reformatsky reaction.

First, we examined the Evans−aldol reaction[4,5] of chiral imide **3** which could easily be prepared from oxazolidinone and 3,3,3-trifluoropropanoic acid according to the literature method (Scheme 1, path A).[6] To a solution of 1.0 equiv of

Scheme 1



3 in CH_2Cl_2 was added 1.5 equiv each of TMSOTf and Et_3N in this order at −20 °C. After the reaction mixture was stirred at the reflux temperature for 0.5 h, ^{19}F NMR analysis revealed that the starting imide was completely consumed and the corresponding silyl ketene acetal was formed as a single stereoisomer. Without purification, the silyl ketene acetal was treated with 1.2 equiv each of $BF_3{\cdot}Et_2O$ and benzaldehyde at 0 °C for 4 h to afford α-trifluoromethyl-β-hydroxypropanoic imide **1** in 73% yield as a mixture of syn and anti isomers in a ratio of 73:27 (Table 1, entry 1).

Table 1. Evans−Aldol and Reformatsky Reactions

entry	substrate (equiv)	aldehyde (R)	Lewis acid (equiv)	yield[a,b] /%of **1**	ratio[a] *Syn* (non-Evans : Evans) : *Anti* (non-Evans : Evans)
1	**3** (1.0)	Ph	$BF_3{\cdot}Et_2O$ (1.2)	73	73 (96 : 4) : 27 (10 : 90)
2	**3** (1.0)	Ph	Et_2AlCl (1.2)	14	-[c] : -[c]
3	**3** (1.0)	Ph	$TiCl_4$ (1.2)	60 (59)	97 (99[d] : 1) : 3
4	**3** (1.0)	Ph	$TiCl_4$ (0.3)	71 (63)	95 (99 : 1) : 5
5	**3** (1.0)	Ph	$TiCl_4$ (0.1)	27	-[c] : -[c]
6	**3** (1.0)	*p*-MeC_6H_4	$TiCl_4$ (0.3)	65 (54)	84 (95 : 5) : 16
7	**3** (1.0)	*p*-$MeOC_6H_4$	$TiCl_4$ (0.3)	63 (60)	89 (96 : 4) : 11
8	**3** (1.0)	*p*-ClC_6H_4	$TiCl_4$ (0.3)	70 (59)	92 (99 : 1) : 8
9	**3** (1.0)	*p*-FC_6H_4	$TiCl_4$ (0.3)	68 (56)	89 (99 : 1) : 11
10	**3** (1.0)	*n*-Pr	$TiCl_4$ (0.3)	54 (38)	91 (99 : 1) : 9
11	**3** (1.0)	*i*-Pr	$TiCl_4$ (0.3)	15 (11)	90 (99 : 1) : 10
12	**3** (1.0)	MeCH=CH	$TiCl_4$ (0.3)	65 (56)	93 (99 : 1) : 7
13[e]	**4** (1.0)	Ph	none	0	- : -
14[e]	**4** (1.0)	Ph	$BF_3{\cdot}Et_2O$ (1.2)	0	- : -
15[e]	**4** (1.0)	Ph	Et_2AlCl (1.2)	50	40 (50 : 50) : 60 (2 : 98)
16[e]	**4** (1.0)	Ph	Et_3Al (1.2)	65	13 (39 : 69) : 87 (4 : 96)
17[e]	**4** (1.0)	Ph	$TiCl_4$ (1.2)	0	- : -
18[f]	**4** (2.0)	Ph	Et_3Al (1.0)	90	13 : 87 (7 : 93)
19	**4** (2.0)	Ph	Et_3Al (1.0)	90 (86)	4 : 96 (2 : 98)
20	**4** (2.0)	*p*-MeC_6H_4	Et_3Al (1.0)	99 (81)	7 : 93 (2 : 98)
21	**4** (2.0)	*p*-$MeOC_6H_4$	Et_3Al (1.0)	93 (85)	9 : 91 (3 : 97[d])
22	**4** (2.0)	*p*-ClC_6H_4	Et_3Al (1.0)	67 (65)	8 : 92 (3 : 97)
23	**4** (2.0)	*n*-Pr	Et_3Al (1.0)	91 (76)	25 (41 : 59) : 75 (27 : 73)
24	**4** (2.0)	*i*-Pr	Et_3Al (1.0)	94 (79)	26 (27 : 73) : 67 (34 : 66)
25	**4** (2.0)	MeCH=CH	Et_3Al (1.0)	85 (82)	14 : 86 (4 : 96)

[a] Determined by ^{19}F NMR. [b] Values in parentheses are of isolated yield. In entries 18−25, yields were based on the aldehydes. [c] Not determined. [d] The absolute configuration was determined on the basis of X-ray crystallographic analysis. [e] The reaction was carried out using 1.2 equiv of aldehyde at 0 °C for 3 h. [f] Carried out at 0 °C.

Switching a Lewis acid from $BF_3{\cdot}Et_2O$ to $TiCl_4$ led to a significant improvement of the diastereoselectivity, non-Evans syn product being obtained in good yield (entry 3). Et_2AlCl did not promote the reaction efficiently (entry 2). Eventually, the best yield was given when 0.3 equiv of $TiCl_4$ was employed (entry 4), and the use of 0.1 equiv of $TiCl_4$ caused a significant decrease of the yield (entry 5). As shown in entries 6−12, various types of aldehydes, such as *p*-tolaldehyde, *p*-anisaldehyde, *n*-butyraldehyde, crotonaldehyde, etc., could participate nicely in the aldol reaction to give the corresponding adducts **1** in good yields with high diastereoselectivity. However, the reaction with a bulky aldehyde, such as isobutyraldehyde, proceeded reluctantly to afford the desired product in only 15% yield, but high syn stereoselection was observed (entry 11).

We next investigated the Reformatsky reaction[7,8] of 2-bromo-3,3,3-trifluoropropanoic imide **4**, which could be prepared via bromination of the silyl ketene acetal derived

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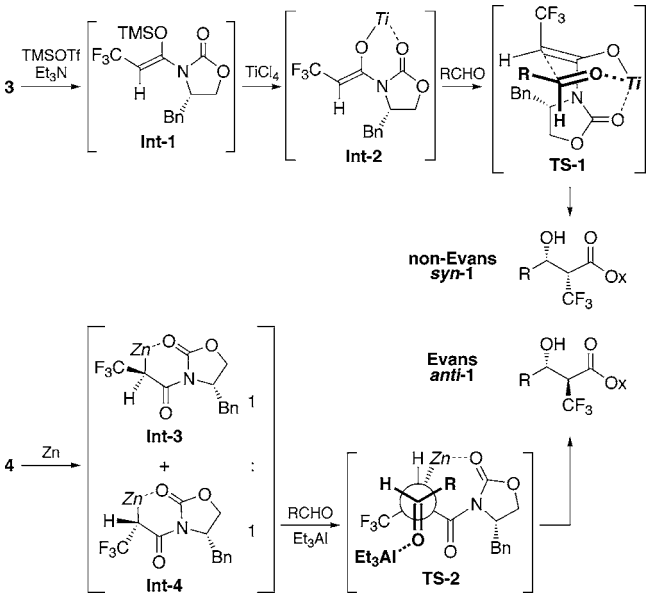
from **3** (Scheme 1, path B).[9] Thus, on treating **4** with 1.2 equiv each of zinc dust and benzaldehyde at 0 °C, no desired coupling product **1** was detected at all (Table 1, entry 13). The addition of BF_3·Et_2O as a Lewis acid did not improve the reaction, but the use of Et_2AlCl promoted the reaction to give the corresponding adduct **1** in 50% yield with low diastereoselectivity (entry 15). Interestingly, changing a Lewis acid from Et_2AlCl to Et_3Al brought about a significant improvement of the diastereoselectivity, Evans anti product being obtained preferentially (entry 16). $TiCl_4$ was found to be inactive in sharp contrast to the Evans−aldol reaction (entry 17). Additionally, the use of 2.0 equiv of **4** led to a dramatic increase of the chemical yield with high Evans anti selectivity (entry 18). Finally, the best diastereoselectivity was realized when the reaction was carried out at −40 °C (entry 19).

The optimized reaction conditions were applied for various types of aldehydes, as indicated in entries 20−25. Aromatic aldehydes, such as *p*-tolaldehyde, *p*-anisaldehyde, etc., could participate well in the coupling reaction to give the corresponding adducts **1** in high yields with high Evans anti stereoselection. However, the diastereoselectivity was somewhat eroded when *n*-butyraldehyde and isobutyraldehyde were employed.

The reaction mechanism may be considered as described in Scheme 2. In the Evans−aldol reaction, *Z*-enolate **Int-1**, which can be generated exclusively from **3**, undergoes the transmetalation with $TiCl_4$ to generate titanium enolate **Int-2**. An aldehyde would come to the titanium enolate from the less hindered *re* face, avoiding a benzyl substituent of the oxazolidinone ring. The subsequent coordination of titanium atom to the carbonyl oxygen of the aldehyde may lead to a six-membered chairlike transition state **TS-1**, where the substituent R occupies the equatorial position due to a 1,3-diaxial repulsion. Consequently, the non-Evans syn product is produced preferentially. In sharp contrast, Et_3Al-activated aldehyde would come to the reactive carbon of the Reformatsky reagent **Int-3** and **Int-4** from the side opposite to that occupied by zinc atom. Due to a large steric repulsion between an aldehyde and a benzyl substituent of the oxazolidinone ring, the reaction of **Int-4** with aldehyde

Scheme 2. Proposed Reaction Mechanism of Evans−Aldol and Reformatsky Reactions



proceeded preferentially via open-chain transition state **TS-2**, where the substituent R occupies the antiperiplanar position to a bulky CF_3 group, leading to the Evans anti coupling product.

In summary, we have developed new highly stereoselective approaches to α-trifluoromethyl-β-hydroxy-carboxylic acid derivatives, starting from optically active 3,3,3-trifluoropropanoic imide **3** or 2-bromo-3,3,3-trifluoropropanoic imide **4**. The $TiCl_4$-catalyzed Evans−aldol reaction of **3** was found to give the non-Evans syn isomers stereoselectively, whereas the Reformatsky reaction of **4** in the presence of Et_3Al led to the Evans anti products. Further study of the scope, mechanistic implications, and synthetic applications of the reactions are currently being investigated in our laboratory.

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Supporting Information Available: Detailed experimental procedure and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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