Tetrahedron Letters, Vol. 34, No. 50, pp. 8147-8150, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Reversal of Stereoselectivity in the Evans Aldol Reaction of α,α-Difluoro and α,α,α-Trifluoro Carbonyl Compounds

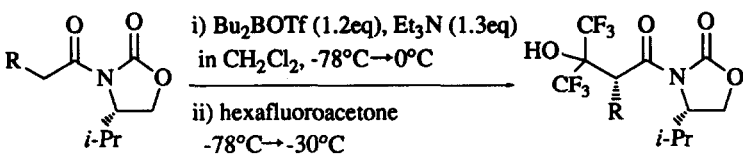
Katsuhiko Iseki,*,[a] Satoshi Oishi,[a] Takeo Taguchi[b] and Yoshiro Kobayashi*,[a]

[a]MEC Laboratory, Daikin Industries, Ltd., Miyukigaoka, Tsukuba, Ibaraki 305, Japan and
[b]Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

Abstract: The Evans aldol reaction of hexafluoroacetone and trifluoroacetaldehyde causes reversal of stereoselectivity. The boron enolate derived from oxazolidinone 1 reacts with trifluoroacetaldehyde to give anti and "non-Evans" syn aldols with stereoselectivities in the range, 7:3-17:3.

The synthesis of chiral trifluoromethylated molecules is an important aspect of organofluorine chemistry in relation to analytical and medicinal chemistry and opto-electric substances such as liquid crystals.[1] Optically active *N*-acyloxazolidinones have been applied to the stereocontrolled synthesis of chiral trifluoromethylated compounds.[2] This paper discusses the unexpected reversal of stereochemistry in the Evans aldol reaction of *N*-acyloxazolidinones with α,α-difluoro and α,α,α-trifluoro carbonyl compounds and applications of this finding to phenylglyoxal and ethyl glyoxylate.

Table1. Aldol Reactions of Imide **1** with Hexafluoroacetone



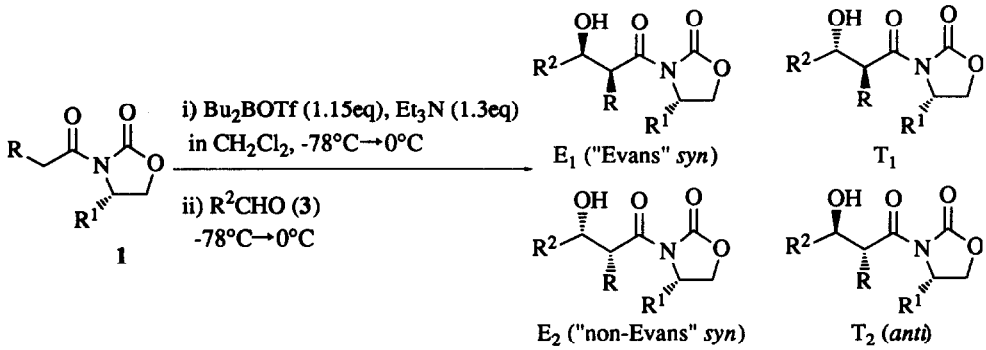
1 **2**

Entry	Imide **1** R		Product **2** % Yield[a]	% De[b]	
1	Me	(**1a**)	90	>99(*R*)[c]	(**2a**)
2	Bn	(**1b**)	86(94)	>99(*R*)[c]	(**2b**)
3	*n*-Bu	(**1c**)	88(96)	95(*R*)[c]	(**2c**)

a) All yields are those of isolated compounds. Values in parentheses are conversion yields; b) Des were determined by capillary GC; c) Configuration of a new asymmetric center. Relative stereochemical assignments were definitely established based on X-ray structure analysis.

The reversal of stereoselectivity in the Evans aldol reaction (boron enolate of the chiral *N*-acyloxazolidinone with aldehyde) has been shown to be achieved on adding an excess of dibutylboron triflate (Bu_2BOTf)[3] or Lewis acids.[4] As shown in Table 1, reactions of oxazolidinone **1** with hexafluoroacetone indicated normal Evans stereoselectivity to occur only to a limited extent even *in the absence of excess Bu_2BOTf or Lewis acids*.[5,6] Table 2, entries 1-4, show aldol reactions of **1** with trifluoroacetaldehyde to proceed with similar reverse stereoselectivity to provide anti aldols (T_2) selectively along with "non-Evans"

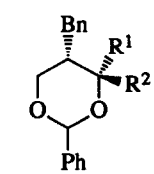
Table2. Aldol Reactions of Imide **1** with Aldehydes



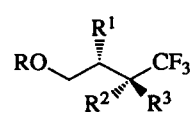
4

Entry	Imide **1**			Aldehyde **3**			Product **4**		
	R	R^1		R^2			% Yield[a]	$E_2 : T_2 : E_1 : T_1$[b]	
1	Me	*i*-Pr	(**1a**)	CF_3	(**3a**)		62(65)	15[e] : 85[e] : 0 : 0	(**4a**)
2	Bn	*i*-Pr	(**1b**)	CF_3	(**3a**)		64(75)	30[f] : 70[g] : 0 : 0	(**4b**)
3	*n*-Bu	*i*-Pr	(**1c**)	CF_3	(**3a**)		60(64)	19[h] : 81[i] : 0 : 0	(**4c**)
4	Me	Bn	(**1d**)	CF_3	(**3a**)		80	22[j] : 78[k] : 0 : 0	(**4d**)
5[c]	Me	*i*-Pr	(**1a**)	CF_3	(**3a**)		83(88)	54 : 46 : 0 : 0	(**4a**)
6[d]	Me	*i*-Pr	(**1a**)	$Ph(CH_2)_3CF_2$	(**3b**)		33(56)	12[l] : 82[m] : 6[n] : 0	(**4e**)
7[d]	Me	*i*-Pr	(**1a**)	PhCO	(**3c**)		55(65)	42[o] : 54[p] : 4[q] : 0	(**4f**)
8[d]	Me	*i*-Pr	(**1a**)	EtOCO		(**3d**)	50(55)	35[r] : 44[s] : 20[t] : 1[u]	(**4g**)

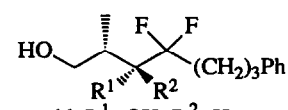
a) All yields are those of isolated compounds. Values in parentheses are conversion yields; b) Ratios were determined by capillary GC and isolated yields. Except for **4a**, relative and absolute stereochemical assignments were made based on conversion to stereochemically confirmed compounds; c) The reaction was carried out in the presence of $TiCl_4$;[7] d) The aldehyde was added at -5°C and the reaction mixture was stirred at the same temperature for 30min; e) Relative stereochemical assignments were confirmed based on X-ray structure analysis; f) Reduction with $LiBH_4$ and acetalization ($PhCH(OMe)_2$, TsOH) gave **5**;[9] g) **4b**(T_2) was coverted to acetal **6**.[9] See footnote f; h) Reduction with $LiBH_4$ in THF gave **7**;[10] i) Reduction with $LiBH_4$ gave **8**;[10] j) Reduction with $LiBH_4$ and benzoylation gave **9** which was prepared from **4a**(E_2) in the same manner. See footnote e; k) Reduction and benzoylation gave **10** which was prepared from **4a**(T_2). See footnote e and j; l) Reduction with $LiBH_4$ gave **11**;[11] m) Reduction with $LiBH_4$ gave **12**;[11] n) Reduction with $LiBH_4$ gave the enantiomer of **11**[11]. See footnote l; o) Reduction ($LiBH_4$ in THF), acetylation (Ac_2O, Py), hydrogenolysis (H_2, Pd-C) and deacetylation (K_2CO_3 in MeOH) gave **13**;[12] p) **4f**(T_2) was converted to diol **14**.[12] See footnote o; q) **4f**(E_1) was converted to the enantiomer of **13**.[12] See footnote o; r) Ethanolysis (NaH in EtOH, 0°C) gave diester **15**;[13] s) Ethanolysis gave **16**.[13] See footnote r; t) Ethanolysis gave the enantiomer of **15**.[13] See footnote r; u) Ethanolysis gave the enantiomer of **16**.[13] See footnote r.



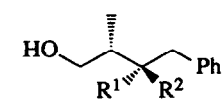
5 $R^1=CF_3$, $R^2=H$
6 $R^1=H$, $R^2=CF_3$



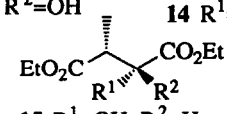
7 R=H, $R^1=n$-Bu, R^2=OH, R^3=H
8 R=H, $R^1=n$-Bu, R^2=H, R^3=OH
9 R=Bz, R^1=Me, R^2=OH, R^3=H
10 R=Bz, R^1=Me, R^2=H, R^3=OH



11 R^1=OH, R^2=H
12 R^1=H, R^2=OH



13 R^1=OH, R^2=H
14 R^1=H, R^2=OH



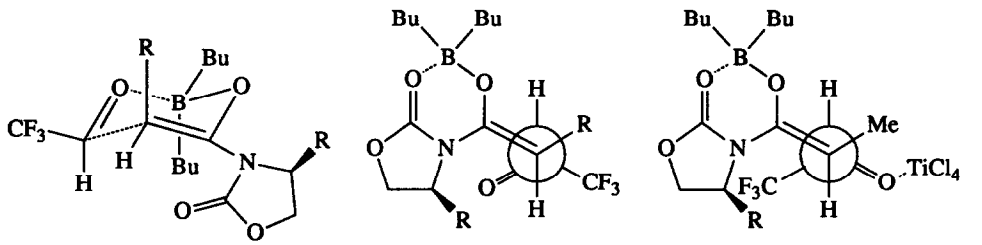
15 R^1=OH, R^2=H
16 R^1=H, R^2=OH

syn aldols (E_2).[5] Anti-syn ratios ranged from 7:3 to 17:3. The addition of $TiCl_4$ to the boron enolate prior to the aldehyde[7] resulted in loss of anti-syn selectivity (entry 5). With α,α-difluoroaldehyde **3b**, a small amount of the normal Evans syn aldol (E_1) was formed. However, the anti aldol (T_2) was the major product (entry 6).

The reversal of facial selectivity of the boron enolate with hexafluoroacetone, trifluoroacetaldehyde and α,α-difluoroaldehyde **3b** may possibly be related to the high electronegativity of fluorine atoms. Low Lewis basicity and high electrophilicity[8] of α, α-difluoro and α, α, α-trifluoro carbonyl compounds prevent carbonyls from coordinating the boron and promote reactions via open transition states. With trifluoroacetaldehyde, open transition state 1 may be favorable for giving the anti aldol (T_2) (Scheme 1). $TiCl_4$ may lead to competition between transion states 1 and 2 (Scheme 1).

The above considerations were extended to phenylglyoxal and ethyl glyoxylate. As shown in entry 7, with phenylglyoxal, the Evans syn product (E_1) was produced only to a slight degree. Reaction with ethyl glyoxylate gave an E_2:T_2:E_1:T_1 ratio of 35:44:20:1 (entry 8). In both cases, reversal of facial selectivity was predominant.

Scheme 1.



closed transition state *open transion state 1* *open transion state 2*

The following experiment is representative for the present study: To a solution of oxazolidinone **1a** (2mmol) in CH_2Cl_2 (4ml) at -78°C were added Bu_2BOTf (2.3mmol) and Et_3N (2.65mmol). The reaction mitxture was warmed to 0°C. After 45min at 0°C, the solution was recooled to -78°C, followed by adding gaseous trifluoroacetaldehyde (6mmol). After 30min at -78°C and warming to 0°C over 2h, the reaction was quenched with a mixture of phosphate buffer (pH 7), methanol and 30% H_2O_2. Flash chromatography gave the anti aldol (T_2) (52%), non-Evans syn aldol (E_2) (10%) and starting material **1a** (5%).

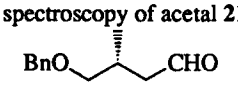
In conclusion, the present results indicate the Evans aldol reaction of α,α-difluoro and α,α,α-trifluoro carbonyl compounds to cause reversal of facial selectivity. This finding was extended to phenylglyoxal and ethyl glyoxylate. Some carbonyl compounds having an electron-withdrawing group at the α-position may also lead to reversal of stereoselectivity.

Acknowledgement: The authors thank Prof. M. Shibasaki of Tokyo University for his valuable comments, Dr. M. Shiro of Rigaku Corporation for conducting the X-ray structure analysis and Mr. D. Asada and Miss M. Takahashi for their technical assistance.

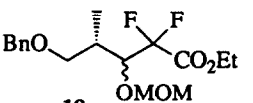
References and Notes

1. Bravo, P.; Resnati, G. *Tetrahedron: Asymmetry*, **1990**, *1*, 661.
2. a) Yamazaki, T.; Haga, J.; Kitazume, T. *Chem. Lett.* **1991**, 2175; b) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 2169.

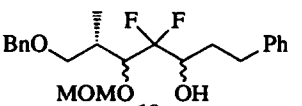
3. a) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173; b) Heathcock, C. H. *Aldrichimica Acta* **1990**, *23*, 99; c) Hayashi, K.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 7287.
4. a) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747; b) Heathcock, C. H. *Aldrichimica Acta* **1990**, *23*, 99; c) Chibale, K.; Warren, S. *Tetrahedron Lett.* **1992**, *33*, 4369.
5. Each reaction was carried out according to the procedure of Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83.
6. The enantiomer of **2a** was used to prepare a novel fluorinated vitamin D_2 analogue, 24-epi-26,26,26,27,27,27-hexafluoro-1α,25-dihydroxyvitamin D_2, with possible potential for treating bone diseases, osteoporosis. Preparation of the vitamin D_2 analogue and its biological properties will be reported in the future.
7. See general method A in ref. 4a.
8. Aldol reactions of the boron enolate derived from imide **1** with α,α,α-trifluoroacetone and acetone could not be successfully carried out.
9. Acetal **5** was prepared by the reduction of ethyl (2*R*,3*R*)-2-benzyl-4,4,4-trifluoro-3-hydroxybutanoate (Seebach, D.; Beck, A. K.; Renaud, P. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 98) with $LiAlH_4$ and acetalization of the resultant diol. In the same manner, the enatiomer of **6** was obtained from ethyl (2*S*,3*R*)-2-benzyl-4,4,4-trifluoro-3-hydroxybutanoate.
10. Diol **7** and the enantiomer of **8** were prepared as follows. Crotylation of ethyl (*R*)-3-hydroxy-4,4,4-trifluorobutanoate (Seebach, D.; Renaud, P.; Schweizer, W. B.; Züger, M. F.; Brienne, M.-J. *Helv. Chim. Acta* **1984**, *67*, 1843) gave ethyl (2*R*,3*R*)-2-crotyl-4,4,4-trifluoro-3-hydroxybutanoate and its (2*S*,3*R*)-isomer. The former was converted to **7** by hydrogenation (H_2, Pd-C) and reduction ($LiAlH_4$). In the same manner, the enantiomer of **8** was obtained from the latter.
11. Diols **11** and **12** were prepared starting from methyl (*S*)-3-hydroxy-2-methylpropionate as follows. The (*S*)-propionate was converted to aldehyde **17** by benzylation ($BnOC(=NH)CCl_3$,, TsOH), reduction ($LiAlH_4$) and Swern oxidation. Treatment of **17** with zinc and ethyl bromodifluoroacetate and methoxymethylation gave ester **18**. Grignard reaction of **18** (Mg, $Br(CH_2)_2Ph$) and reduction wth $LiAlH_4$ gave **19**. Treatment of **19** with thiocarbonyldiimidazole, reduction (n-Bu_3SnH in toluene, reflux) and demethoxymethylation afforded alcohol **20**. Finally, after the hydrogenolysis of **20** (H_2, Raney Ni), **11** and **12** were obtained. The relative stereochemistry of **12** was determined to be anti by ^1H NMR spectroscopy of acetal **21**.



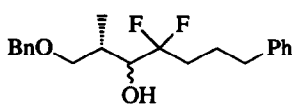
17



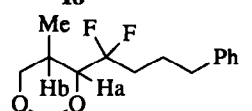
18



19



20



21 $J_{Ha\text{-}Hb}$ 10.0Hz (*anti*)

12. Tsukuda, T.; Kakisawa, H.; Painuly, P.; Shimizu, Y. *Tetrahedron Lett.* **1989**, *30*, 4245.
13. a) Mori, K.; Iwasawa, H. *Tetrahedron* **1980**, *36*, 87; b) Akita, H.; Matsukura, H.; Oishi, T. *Chem. Pharm. Bull.* **1986**, *34*, 2656.

(Received in Japan 27 August 1993)