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Reversal of Stereoselectivity in the Aldol Reaction of Boron Enolate Derived from Oppolzer's Sultam with α,α-Difluoro and α,α,α-Trifluoro Carbonyl Compounds

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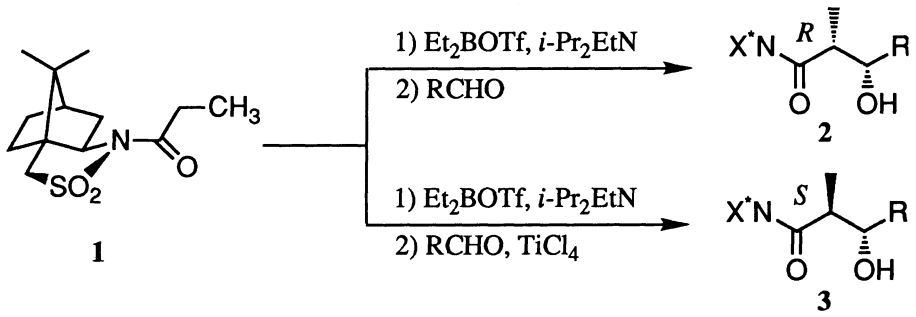
Hexafluoroacetone causes the complete reversal of stereochemistry in the aldol reaction of boron enolate derived from Oppolzer's sultam in the absence of Lewis acids such as $TiCl_4$. Trifluoroacetaldehyde and 2,2-difluoro-5-phenyl-1-pentanal cause partial reversal, giving a mixture of *syn*- and *anti*-aldols. This finding was extended to reactions of the boron enolate with phenylglyoxal and ethyl glyoxylate.

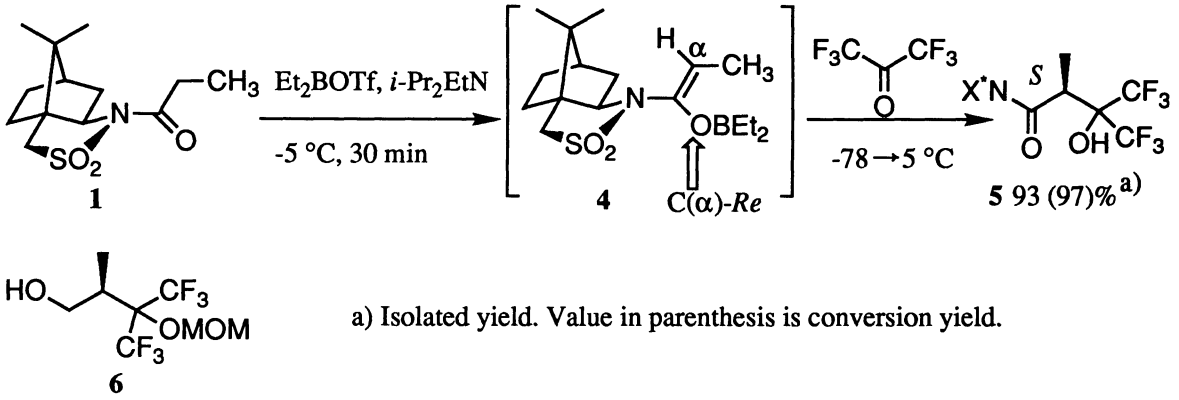
The synthesis of chiral fluoroorganic compounds is an important aspect of organofluorine chemistry in connection with analytical and medicinal chemistry and opto-electric substances such as liquid crystals.[1] The authors have directed their attention to the stereocontrolled synthesis of such chiral molecules for some years.[2-4] The unexpected reversal of stereochemistry was recently noted in the Evans aldol reaction of *N*-acyloxazolidinones with α,α-difluoro and α,α,α-trifluoro carbonyl compounds.[5]

Boron enolate **4** derived from *N*-propionylsultam **1** reacts with aldehydes stereoselectively to give *syn*-aldols **2**.[6] Oppolzer et al. reported the use of $TiCl_4$ reversed selectively the enolate faciality to give *anti*-aldols **3**.[7] In this study, examination was made of the reversal of stereochemistry in the aldol reaction of **4** with α,α-difluoro and α,α,α-trifluoro carbonyl compounds *in the absence of Lewis acids such as $TiCl_4$*. This finding was extended to reactions of **4** with phenylglyoxal and ethyl glyoxylate.

As shown in Scheme 2, hexafluoroacetone reacted on the *Re* face of **4** to give only aldol **5** stereoselectively in high yield, indicating normal stereoselectivity not to occur even *in the absence of $TiCl_4$*. Hexafluoroacetone caused the complete reversal of π-facial selectivity. The stereochemical assignment of **5** was clearly established by conversion to enantiomerically pure (*R*)-alcohol **6**. The methoxymethylation of **5**, followed by reduction of the resulting MOM ether with $LiAlH_4$ gave **6** ($[\alpha]_D^{24}$ -8.4° (c = 1.48, $CHCl_3$)).[8]



Scheme 1.



a) Isolated yield. Value in parenthesis is conversion yield.

Scheme 2.

Reactions of boron enolate **4** with aldehydes are summarized in Table 1. Entry 1 shows the aldol reaction of trifluoroacetaldehyde to proceed partially through *Re* face attack on **4** to provide *syn*-aldol (E_2) and *anti*-aldol (T_2). The major product was normal *syn*-aldol (E_1), formed through *Si* face attack on **4**. Trifluoroacetaldehyde caused the complete reversal of π-facial selectivity in the Evans aldol reaction of *N*-acyloxazolidinone.[5] With Oppolzer's sultam, the reversal was modest. The E_2:T_2:E_1:T_1 ratio was 19:7:73:1. The addition of $TiCl_4$ to boron enolate **4** prior to the aldehyde[7] brought about the complete reversal of facial selectivity and high *anti* selectivity (T_2) (entry 2). Reaction with α,α-difluoro aldehyde **7b** gave (E_2 and T_2):E_1 of 79:21, indicating reversal of facial selectivity to occur predominantly (entry 3).

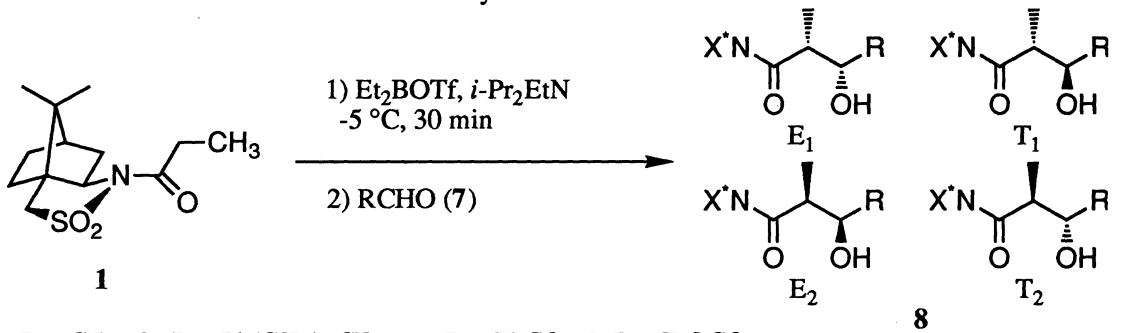
Oppolzer et al. proposed the reactions of boron enolate **4** with aldehydes (containing no fluorine atom) proceeded via closed transition state **C** to give *syn*-aldols **2** (E_1).[6] The partial or complete reversal of π-facial selectivity of boron enolate **4** with hexafluoroacetone, trifluoroacetaldehyde (entry 1) and α,α-difluoro aldehyde **7b** (entry 3) may possibly be related to the high electronegativity of fluorine atoms. The electron-withdrawing substituents (CF_3 or CF_2R) decrease the electron density on the carbonyl oxygen and cause LUMO lowering. The low Lewis basicity (the low electron density) and high electrophilicity (the LUMO lowering) of α,α-difluoro and α,α,α-trifluoro carbonyl compounds prevent carbonyls from coordinating the boron atom and promote reactions via open transition state **A** or **B** (Scheme 3). The reaction with hexafluoroacetone is assumed to proceed via the open transition state. Entries 1 and 3 suggest competition between open transition state **A** (**B**) and closed transition state **C**. $TiCl_4$ may lead to open transition state **D**.[7]

The above considerations were extended to reactions of **4** with phenylglyoxal and ethyl glyoxylate. As shown in entry 4, with phenylglyoxal, the normal *syn* product (E_1) was formed in only a small amount. Reaction with ethyl glyoxylate gave an E_2:T_2:E_1:T_1 ratio of 50:15:33:2 (entry 5). In both cases, reversal of π-facial selectivity was predominant.

The following experiment is representative for the present study: CF_3SO_3H (326 μl, 3.7 mmol) was added to a 1 M (1 M = 1 mol dm^{-3}) solution of Et_3B in hexanes (3.7 ml) at room temperature and the mixture was stirred at 40 °C until gas evolution ceased. The successive addition of a solution of *N*-propionylsultam **1** (501 mg, 1.85 mmol) in CH_2Cl_2 (7 ml) and one of *i*-Pr_2EtN (680 μl, 3.9 mmol) in CH_2Cl_2 (3.9 ml) at -10 °C and stirring at the same temperature for 30 min gave a solution of boron enolate **4**. The solution was cooled to -78 °C, followed by the addition of gaseous hexafluoroacetone (2 ml at -78 °C). After warming to 5 °C over 90 min and being left at this temperature for 30 min, the reaction was quenched by phosphate buffer (pH 7) and saturated aqueous NH_4Cl. Column chromatography gave **5** (93%) and starting material **1** (4%).

In conclusion, the present results indicate the aldol reaction of the boron enolate derived from Oppolzer's sultam with α,α-difluoro and α,α,α-trifluoro carbonyl compounds to bring about the reversal of π-facial selectivity even in the absence of Lewis acids. This finding was extended to reactions of **4** with phenylglyoxal and ethyl glyoxylate. Some carbonyl compounds having an electron-withdrawing group at the α-position may bring about the reversal of stereoselectivity.

Table. 1 Aldol Reactions of Sultam **1** with Aldehydes

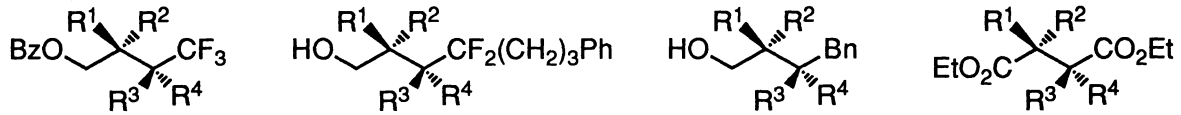


1 **8**

a: R = CF_3 **b**: R = $Ph(CH_2)_3CF_2$ **c**: R = PhCO **d**: R = EtOCO

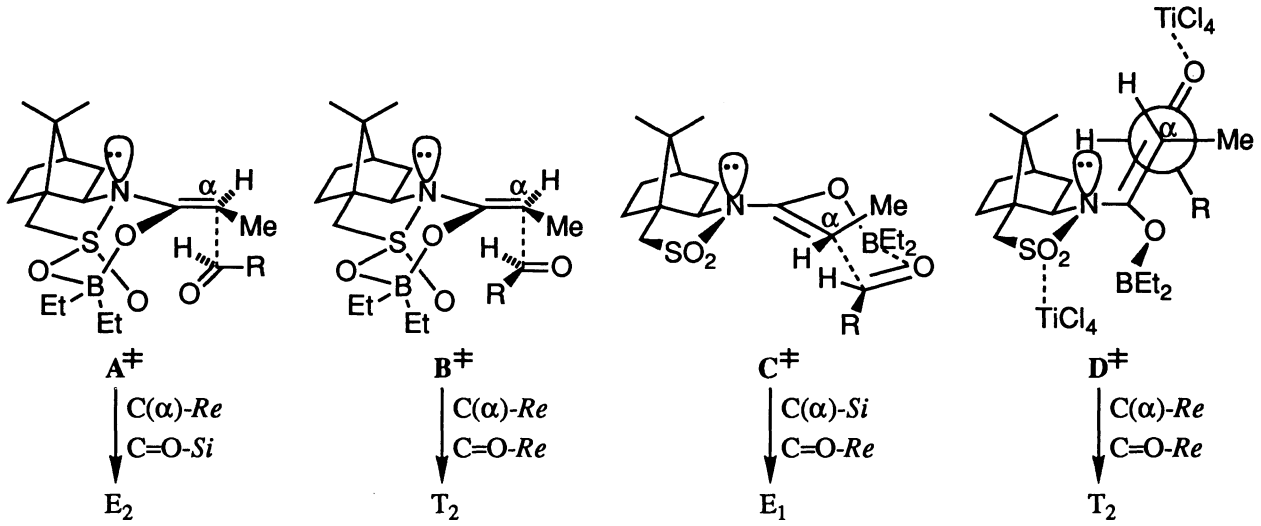
Entry	Aldehyde	Conditions Temp/°C (Time/min)	Yield/%[a]	Product **8** E_2 : T_2 : E_1 : T_1[b]	
1	**7a**	-78 - 5 (90), then 5 (30)	96 (100)	19[d] : 7[e] : 73[f] : 1	**(8a)**
2[c]	**7a**	-78 (90), then -78 - -30 (15)	89 (96)	1[d] : 99[e] : 0 : 0	**(8a)**
3	**7b**	-5 - 0 (120)	86 (99)	49[g] : 30[h] : 21[i] : 0	**(8b)**
4	**7c**	-5 (50)	78	25[j] : 58[k] : 17[l] : 0	**(8c)**
5	**7d**	-5 - 0 (180)	66 (100)	50[m] : 15[n] : 33[o] : 2	**(8d)**

a) All yields are those of isolated compounds. Values in parentheses are conversion yields; b) Ratios were determined by capillary GLC. 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) Reduction with $LiAlH_4$ and benzoylation gave **9a**;[9] e) Conversion to **9b** ($[\alpha]_D^{24}$ +18.4° (c = 0.47, $CHCl_3$)) was conducted in the same manner;[9] f) Conversion to **9c** ($[\alpha]_D^{23}$ +23.9° (c = 0.44, $CHCl_3$)) was conducted in the same manner;[9] g) Reduction with $LiAlH_4$ gave **10a**;[5] h) Reduction with $LiAlH_4$ gave **10b**;[5] i) Reduction with $LiAlH_4$ gave **10c**;[5] j) Reduction ($LiAlH_4$), acetylation (Ac_2O, Py), hydrogenolysis (H_2, Pd-C) and deacetylation (K_2CO_3 in MeOH) gave diol **11a**;[5] k) Conversion to **11b** was conducted in the same manner;[5] l) Conversion to **11c** was conducted in the same manner;[5] m) Ethanolysis (NaOEt in EtOH, 0 °C) gave diester **12a**;[5] n) Conversion to **12b** was conducted in the same manner;[5] o) Conversion to **12c** was conducted in the same manner.[5]



9 **10** **11** **12**

a: $R^1 = CH_3$, R^2 = H, R^3 =OH, R^4 = H, **b**: $R^1 = CH_3$, R^2 = H, R^3 = H, R^4 = OH,
c: R^1 = H, $R^2 = CH_3$, R^3 = H, R^4 = OH



Scheme 3.

References

1) P. Bravo and G. Resnati, *Tetrahedron: Asymmetry*, **1**, 661 (1990) and references cited therein.
2) K. Iseki, T. Nagai, and Y. Kobayashi, *Tetrahedron Lett.*, **34**, 2169 (1993).
3) K. Iseki, T. Nagai, and Y. Kobayashi, *Tetrahedron: Asymmetry*, in press.
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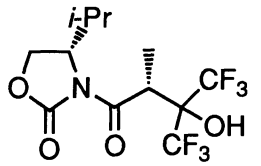
5) K. Iseki, S. Oishi, T. Taguchi, and Y. Kobayashi, *Tetrahedron Lett.*, **34**, 8147 (1993).
6) W. Oppolzer, C. Starkemann, I. Rodriguez, and G. Bernardinelli, *J. Am. Chem. Soc.*, **112**, 2767 (1990).
7) W. Oppolzer, and P. Lienard, *Tetrahedron Lett.*, **34**, 4321 (1993).
8) The enantiomer of **6** was prepared starting from stereochemically confirmed **13** by reduction ($LiBH_4$), *t*-butyldimethylsilylation (TBDMSCl, imidazole), methoxymethylation (MOMCl, *i*-Pr_2EtN) and desilylation (*n*-$Bu_4N^+F^-$): the enantiomer of **6** $[\alpha]_D^{24}$ +8.8° (c = 0.87, $CHCl_3$). See ref. 5
9) Benzoate **9a** ($[\alpha]_D^{25}$ -21.8° (c = 0.41, $CHCl_3$)) was prepared starting from stereochemically confirmed **14a** by reduction ($LiBH_4$) and benzoylation (BzCl, Py). In the same manner, **9b** ($[\alpha]_D^{26}$ +19.3° (c = 0.41, $CHCl_3$)) was prepared from stereochemically confirmed **14b**. Benzoate **9c** was the enantiomer of **9a**. See Ref. 5.



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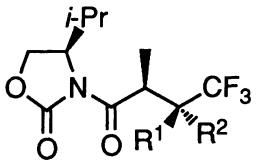

14a R^1 = OH, R^2 = H
14b R^1 =H, R^2 = OH

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