Tetrahedron Letters, Vol. 34, No. 27, pp. 4321-4324, 1993
Printed in Great Britain

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

Efficient Asymmetric Synthesis of Anti-Aldols from Bornanesultam Derived Boryl Enolates

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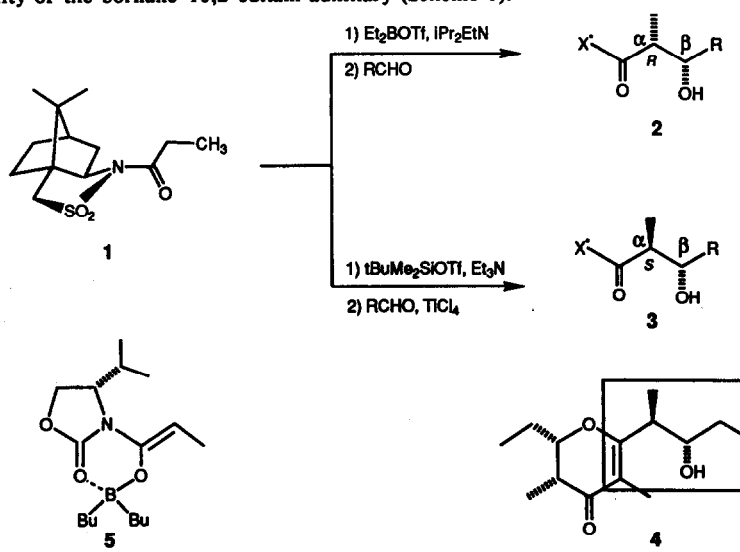
Abstract: *O*-Borylation of *N*-propionylsultam 1 provides *in situ* boryl enolate 6 which, at -78°C in the presence of $TiCl_4$, reacts with aliphatic, aromatic and α,β-unsaturated aldehydes giving mostly crystalline, diastereomerically pure *anti*-aldols 3.

The stereodivergent asymmetric synthesis of either *syn*-aldols 2 [1] or *anti*-aldols 3 [2] by aldolization of the same *N*-propionylsultam 1 with aromatic and aliphatic aldehydes highlights the exceptional chiral efficiency/versatility of the bornane-10,2-sultam auxiliary (Scheme 1).

Scheme 1



The configurations of aldols 2 and 3 differ at C(α) (enolate faciality), both being identical at C(β) (carbonyl faciality). *Anti*-products 3 are valuable building blocks as illustrated by the total synthesis of (-)-serricorole (4) [3].

Recently, it has been shown that the usually *syn*-selective aldolizations of oxazolidinone-derived boryl enolate 5 can be directed toward *anti*-products when carried out in the presence of Et_2AlCl (3 mol-equiv.) [4]. *Anti/syn* ratios (implying a reversed C(β)-topicity) range from 86:14 to 95:5 with aliphatic aldehydes but drop to 74:26 with benzaldehyde.

In this context it was interesting to explore the aldol condensation of sultam derived boryl enolate 6 in the presence of various Lewis acids. Boryl enolate 6 was obtained as usual *i.e.* by successive treatment of *N*-propionylsultam 1 with (*in situ* prepared) Et_2BOTf and iPr_2EtN [1] and the influence of various Lewis acids on the condensation of non-isolated 6 with propionaldehyde was tested (Scheme 2, Table 1).

Scheme 2

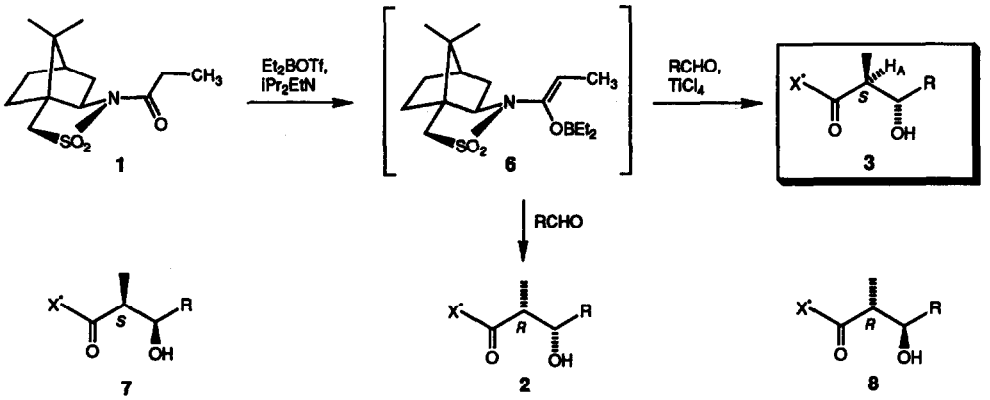


Table 1: Stereodirecting Effect of Various Lewis Acids on the Aldolization of Boryl Enolate 6 with Propanal in CH_2Cl_2 at -78°.

Entry	Lewis Acid	Mol-equiv. Lewis Acid/EtCHO	Product Ratio[a] 3 /2 /(7 + 8)
1	Et_2AlCl	2	27/37/36
2	Et_2BOTf	2	78/0 /22
3	$TiCl_4$	2	98/0 /2
4	$TiCl_4$	1	97/0 /3
5	$TiCl_4$	0.5	93/0 /7

[a]) HPLC of crude aldol mixture or GC of TBDMS derivatives.

No reaction was observed in the presence of $SnCl_4$ or $BF_3.OEt_2$ (2 mol-equiv.). Et_2AlCl and Et_2BOTf accelerated the aldolization of 6 but with disappointingly poor stereochemical control (entries 1,2). In delightful contrast, aldolization of 6 in the presence of $TiCl_4$ yielded *anti*- product 3, R = Et with excellent stereoselectivity which decreased slightly on lowering the amount of $TiCl_4$ (entries 3-5). The optimized procedure (entry 3) involves addition of a mixture of aldehyde (2 mol-equiv.)/$TiCl_4$ (4 mol-equiv.) in CH_2Cl_2 to a stirred solution of *in situ* prepared boryl enolate 6 at -78°, stirring at -78° for 0.5 to 4 h and aqueous workup. This protocol was applied to a series of aldehydes (Table 2) [5].

Analysis of the crude product mixtures revealed the predominant formation of *anti*-aldols 3. The major product 3 could be routinely (except 3d and 3e) isolated in >99% purity by crystallization. Condensation of 6 with aliphatic aldehydes proceeded smoothly at -78° with >96% stereoselectivity giving pure *anti*-aldols 3 in 73-77% yield. Only sterically hindered pivalaldehyde required a higher reaction temperature (-40°) to provide a 90:10 mixture of 3e/2e; flash chromatography furnished pure product 3e (oil) in 73% yield (entry 9).

Benzaldehyde condensed completely with 6 at -78°; the stereoselectivity increased from 92:8 to 99:1 when the $TiCl_4$/aldehyde ratio was lowered to 1:1 (entry 11). This lower $TiCl_4$/aldehyde ratio also proved suitable for the *anti*-aldolization of other aromatic aldehydes such as furfural and *p*-nitrobenzaldehyde (entries 12,13). However, a second mol-equiv. of $TiCl_4$ was again employed for the aldolization of 6 with *p*-methoxybenzaldehyde to accomodate coordination with the methoxy group (entry 14).

Table 2 : Asymmetric *Anti*-Selective Aldolizations of *N*-Propionylbornane-[10,2]-sultam 1 → 6 → 3.

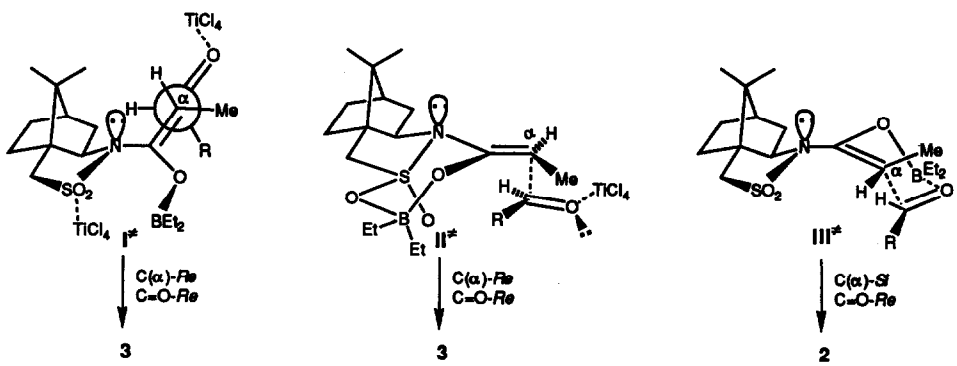
Entry	Series	R	Mol-equiv. $TiCl_4$/RCHO	Temp. [°C]	Time [h]	Product/Ratio 3 / 2 /(7 + 8)	Yield of 3 cryst. [%]	M.p. [°C]	Purity [%]
6	**a**	Me-	2	- 78	2	96.2/3.8/0[a)]	73	125-126	> 99
3	**b**	Et-	2	- 78	2	98 /2 /0[a)]	77	75-76	> 99
7	**c**	*i*Pr-	2	- 78	2	99.4/0.6/0[a)]	75	146-148	> 99
8	**d**	*i*Bu-	2	- 78	1	98.2/1.8/0[a,b)]	75	oil	96.7
9	**e**	*t*Bu-	2	- 40	15	90 /10 /0[b)]	73	oil	> 99
10	**f**	cycloC_6H_{11}-	2	- 78	1	97.7/2.3/0[b)]	73	128-129	> 99
11	**g**	Ph-	1	- 78	0.5	99 /1 /0[a)]	77	184-185	> 99
12	**h**	2-furyl-	1	- 78	0.5	93.7/5 /1.3[b)]	50	125-127	> 99
13	**i**	*p*$NO_2C_6H_4$-	1	- 78	4	96.4/1.8 /1.8[b)]	69	174-175	> 99
14	**j**	*p*$MeOC_6H_4$	2	- 78	1	89 /10 /1[b)]	62	134-135	> 99
15	**k**	(*E*)MeCH=CH-	1	- 78	1	94 /6 /0[b)]	60	94-96	> 99
16	**l**	CH_2=C(Me)-	1	- 78	1	98 /2 /0[b)]	60	115-120	> 99

a) Major products **3a**, **3b**, **3c**, **3d** and **3g** were identified by comparison (IR, ^{1}H-NMR, m.p., $[\alpha]_D$) with authentic samples. Comparison of crude reaction mixtures (HPLC of free aldols or GC of TBDMS derivatives) with authentic **2** and with mixtures **2/3/7/8** allowed the assignment of minor products **2a**, **2b**, **2c** and **2g** and to exclude the presence of isomers **7** and **8**. b) Major and minor products assigned by analogy to entries 3,6,7 and 11. Multiplicity of ^{1}H-NMR signal of H_A in major product is identical to that of **3a**, **3b**, **3c**, **3d** and **3g**.

The $TiCl_4$ stoichiometry had an even more critical impact on the reaction of **6** with crotonaldehyde. Whereas a $TiCl_4$/aldehyde ratio of 2:1 yielded a 82:18 mixture of 1,2- and 1,4-addition products, clean 1,2-addition was found in the presence of 1 mol-equiv. of $TiCl_4$/aldehyde. Crystallization afforded synthetically interesting allylic *anti*-aldol **3k** in 60% yield (entry 15) [6]. Analogous reaction of **6** with 2-methyl-2-propenal gave pure olefinic *anti*-aldol **3l** (60%, entry 16) [7].

Thus, $TiCl_4$ mediated aldolizations of aliphatic, aromatic and α,β-unsaturated aldehydes with boryl enolate **6** uniformly proceed with C(α)-*Re*/C=O-*Re* topicity as previously observed with the silyl enolate of **1**. An open transition state **I**≠, analogous to that postulated for *Mukaiyama* aldolizations 1 → 3 [2] (Scheme 1) may be proposed to rationalize this stereochemistry (Scheme 3).

Scheme 3



Chelation of the enolate and sulfone oxygen atoms with boron as depicted in open transition state II‡ should also lead to the same stereochemical preference. In the absence of $TiCl_4$, however, boryl enolate **6** reacts with aldehydes *via* C(α)-*Si*/C=O-*Re* attack consistent with the closed transition state III‡ [1].

The topological influence of Lewis acids on the aldolization of bornanesultam- and oxazolidinone derived boryl enolates **6** and **5** [4] is clearly quite different. Thus, $TiCl_4$ alters specifically the enolate topicity of **6** but inverts both, the enolate and carbonyl topicities in reactions of **5**. Et_2AlCl, on the other hand, effects loss of steric control in reactions of **6** but reverses selectively the carbonyl faciality in aldolizations of **5**.

Non-destructive removal of the auxiliary group by cleavage of aldols **3** with $LiOH/H_2O_2$ [2], propenol/$Ti(iPrO)_4$ [8] or with dilithiated methylphenylsulfone [9] provided enantiomerically pure *anti*-β-hydroxylcarbonyl derivatives.

In conclusion, starting from a single boryl enolate (**6**) enantiomerically pure *anti*- or *syn*-aldols can be readily obtained merely as function of the presence or absence of $TiCl_4$ in the aldolization process. The convenience, generality and efficiency of this stereodivergent protocol compares favorably with existing methodology [2, 4, 6].

Acknowledgements: Financial support of this work by the *Swiss National Science Foundation, Sandoz Pharma Ltd.*, Basel and *Givaudan-Roure AG*, Dübendorf, is gratefully acknowledged. We thank Mr. *J. P. Saulnier*, Mr. *A. Pinto* and Mrs. *C. Clément* for NMR and MS measurements.

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1) W. Oppolzer, J. Blagg, I. Rodriguez, E. Walther, *J. Am. Chem. Soc.* **1990**, *112*, 2767. The reaction 1 → 2 was routinely carried out using 2-3 mol-equiv. of aldehyde. Unfortunately due to a misunderstanding an error has crept into the literature, namely the claim that 5 mol-equiv. of aldehyde are required for complete conversion: D. A. Evans, D. L. Rieger, M. T. Bilodeau. F. Urpi. *J. Am. Chem. Soc.* **1991**, *113*, 1047.

2) W. Oppolzer, C. Starkemann, I. Rodriguez, G. Bernardinelli, *Tetrahedron Lett.* **1991**, *32*, 61.

3) W. Oppolzer, I. Rodriguez, *Helv. Chim. Acta* **1993**, *76*, 1275.

4) M. A. Walker, C. H. Heathcock, *J. Org. Chem.* **1991**, *56*, 5747.

5) All new compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and MS. The following procedure is representative: CF_3SO_3H (243 μl, 2.76 mmol) was added to a 1M soln. of Et_3B in hexane (2.76 ml) at r.t. and the mixture was stirred at 40°C (until gas evolution has ceased). Successive addition of a soln. of propionylsultam **1** (300 mg, 1.1 mmol) in CH_2Cl_2 (6 ml) and a 1M soln. of $(iPr)_2EtN$ in CH_2Cl_2 (2.97 ml) at -10°C and stirring at -10°C for 30 min. gave a soln. of boryl enolate **6** which was cooled to -78°C and cannulated into a soln. of propanal (160 μl, 2.2 mmol) and $TiCl_4$ (480 μl, 4.4 mmol) in CH_2Cl_2 (3 ml) at -78°C. Stirring the mixture at -78°C for 2 h, addition of sat. aq. NH_4Cl , extraction (CH_2Cl_2), flash chromatography (hexane/EtOAc 4:1) and crystallization (Et_2O/pentane) furnished aldol **3b** (280 mg, 77%), m.p. 75-76°C.

6) $TiCl_4$-mediated aldolization of the silyl enolate of **1** with crotonaldehyde gave aldol **3k** in 47% yield.

7) Acrolein condensed with **6** in the presence of $TiCl_4$ (1 mol-equiv./aldehyde) to give an inseparable 80:20 mixture of aldol/Michael addition products.

8) W. Oppolzer, P. Lienard, *Helv. Chim. Acta* **1992**, *75*, 2572.

9) W. Oppolzer, I. Rodriguez, *Helv. Chim. Acta* **1993**, *76*, 1282.

(Received in Germany 27 April 1993)