Pergamon

Tetrahedron Letters 40 (1999) 7421–7425

TETRAHEDRON
LETTERS

Boron azaenolates of chiral oxazolines: synthesis of optically active formyl oxiranes

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Received 30 June 1999; accepted 2 August 1999

Abstract

Boron azaenolates **2** and **8** from the optically active chloromethyloxazolines **1** and **7** have been found to couple with ketones in a highly diastereoselective fashion, which depends markedly upon the geometry (*Z*) of the azaenolates and the nature of the ligands which are present on the boron atom, in good accordance with semiempirical calculations (AM1). © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: boron azaenolates; chiral oxazolines; chiral chlorohydrins; oxiranyl oxazolines; formyl epoxides.

In comparison with boron enolates, which have proven to be extremely useful reactive intermediates for stereoselective aldol-type reactions,[1a–b,2a–c,3,4] boron azaenolates have received much less attention. Significant contributions to the understanding of the stereochemical features of the reactions of azaenolates have come from studies concerning achiral and chiral oxazolines.[5,6] In particular, Meyers had reported that the reaction of chiral oxazolines proceeds with exceptionally high and opposite diastereoselection moving from chiral oxazolines bearing the stereogenic centre(s) on the oxazolinyl ring and leading to *erythro* products, to achiral oxazolines having the stereogenic centre in the boron ligands and affording *threo* products.[6] In the present paper, we wish to report a highly diastereoselective aldol-type reaction carried out with differently substituted boron azaenolates of chiral oxazolines with ketones (Scheme 1).

Treatment of an ether solution of (4*S*,5*S*)-2-chloromethyl-4-methoxymethyl-5-phenyl-2-oxazoline **1** (prepared by chlorination[7a–c,8] of commercially available (4*S*,5*S*)-2-methyl-4-methoxymethyl-5-phenyl-2-oxazoline) with 9-BBNOTf/*i*Pr$_2$NEt at –40°C (1 h) afforded boron azaenolate **2a**. The reaction of **2a** with benzophenone gave a high yield of the chlorohydrin **3a** that was not isolated but straightforwardly converted into the oxazolinyl epoxide **4a**. The conversion of **2a** into **4a** was highly diastereoselective (dr *R*/*S*=93/7). Deprotection of **4a**, according to a known protocol,[9] furnished formyl epoxide **5a** (*R*, ee%=93). The configuration of **5a** was assigned by its comparison with the enantiomers obtained in the

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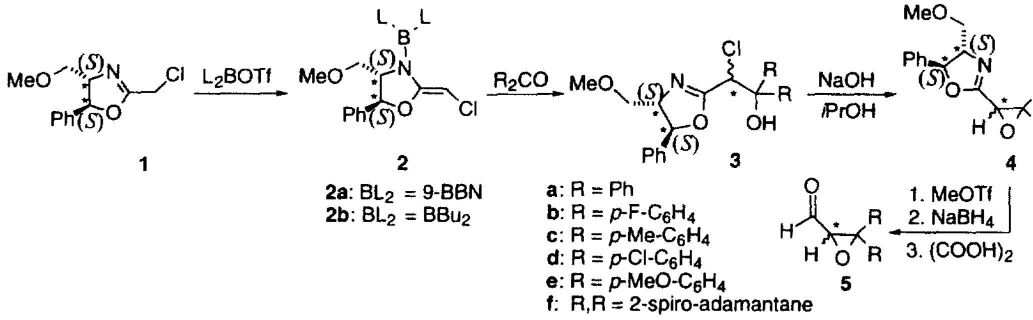
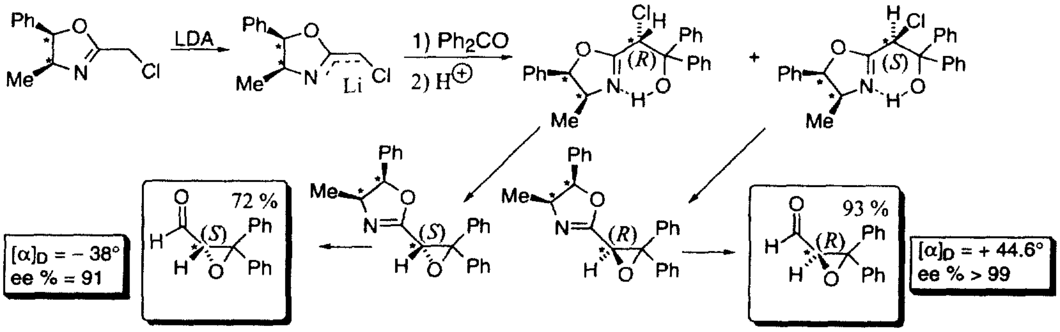
PII: S0040-4039(99)01480-X



Scheme 1.

lithiation–alkylation–deprotection sequence of (4*S*,5*R*)-2-chloromethyl-4-methyl-5-phenyl-2-oxazoline[8] (see below). In contrast, the lithiation–alkylation–deprotection sequence of (4*S*,5*R*)-2-chloromethyl-4-methyl-5-phenyl-2-oxazoline occurred with poor diastereoselectivity. However, the intermediate chlorohydrins could be separated and assigned the configuration at the α-carbon by X-ray analysis. The configurations to the related oxazolinyl and formyl oxiranes could be assigned consequently (Scheme 2).[10]



Scheme 2.

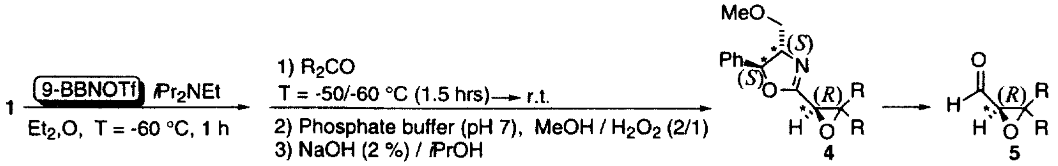
Equally, highly diastereoselective was the reaction of **2a** with *p*,*p*′-difluorobenzophenone that furnished oxazolinyl oxirane **4b** (dr=96/4) and then formyl oxirane **5b** (ee%=90). The reaction of **2a** with other aromatic ketones led to oxazolinyl epoxides **4c**, **4d** and **4e** with excellent diastereoselection (see Table 1).[11]

A much lower diastereoselection was observed in the reaction of **2a** with an aliphatic ketone such as 2-adamantanone. Oxazolinyl epoxide **4e** tended to isomerize to ketone **6** (Scheme 3).[11]

When boron azaenolate **2b** (Scheme 1) (prepared from 2-chloromethyloxazoline **1** and Bu_2BOTf/*i*Pr_2NEt in CH_2Cl_2, −78°C) was treated with benzophenone and then with NaOH in *i*PrOH the oxazolinyl oxirane **4a** was formed in good yield and high diastereoselection (dr *R*/*S*=15/85). It was interesting to observe that the diastereoselection of this reaction was opposite to that of the reaction of boron azaenolate **2a**. Even higher values of diastereoselection were observed in the reaction of **2b** with other ketones (Table 2).[11]

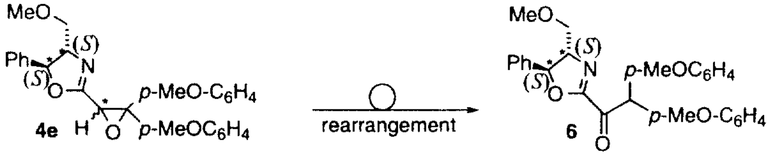
How can the opposite stereoselection observed in the reactions of **2a** and **2b** with ketones be explained? First of all, let us consider the geometry of **2a** and **2b**. In both cases, semiempirical calculations[12] indicate that the *Z* isomeric forms of **2a** and **2b** are more stable than the *E* ones by about 1.7–4.7 kcal/mol depending on the nature of ligands. If we assume that the *Z* isomer is the reactive species, the opposite diastereoselection observed in the reactions of **2a** and **2b** can be rationalized as follows, as computationally determined. In the case of **2a** (9-BBN) the ligands on boron allow coordination of boron to the methoxymethyl group. Therefore, the benzophenone attacks the reaction centre from the bottom,

Table 1



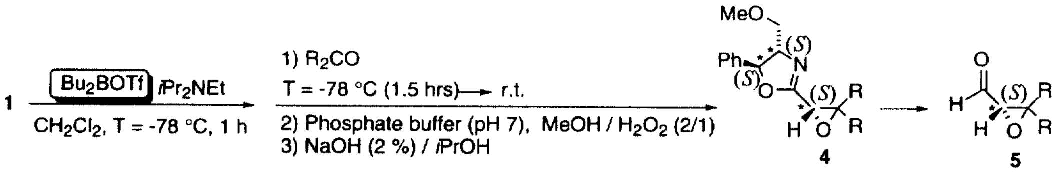
R_2CO	Oxazolinyl Epoxide (% yield)[a]	dr[b]	$[\alpha]_D$ (c 1, $CHCl_3$)[c]	Formyl Epoxide (% yield)[d]	ee (%)[e]	Configuration
Ph_2CO	85[a]	93/7	−31.2	80	93	R
(p-F-$C_6H_4)_2CO$	83	96/4	−25.4	50	90	R[f]
(p-Me-$C_6H_4)_2CO$	75	95/5	−30.6	-[g]	-	R[f]
(p-MeO-$C_6H_4)_2CO$	50 [h]	85/15	−34.2	-[g]	-	R[f]
(p-Cl-$C_6H_4)_2CO$	50	98/2	−55.4	-[g]	-	R[f]
2-Adamantanone	74	70/30	−37.0	50	40	R[f]

[a] Based on converted starting 2-chloromethyl-2-oxazoline which was quantitative in all cases except in the reaction with Ph_2CO (73 %). [b] Diastereomeric ratio determined by ^1H NMR (500 MHz) integrating the characteristic doublet exhibited by each of the two diastereomeric oxazolinyl ring hydrogens at C-5 in the range of 5.0-5.2 ppm. [c] Referred to oxazolinyl epoxides. [d] Isolated yields. [e] Determined by GC on a chiral stationary phase [f] Presumed configuration on the basis of ^1H NMR analysis of the corresponding oxazolinyl epoxides **4**. [g] The corresponding oxazolinyl epoxides were not deblocked to formyl epoxides. [h] In THF: the resulting chlorohydrins (not the epoxides) were isolated by chromatography on silica gel.



Scheme 3.

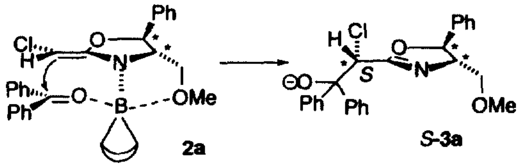
Table 2



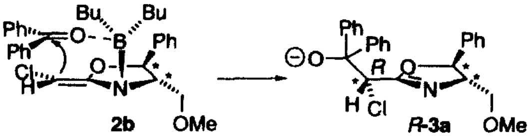
R_2CO	Oxazolinyl Epoxide (% yield)[a]	dr[b]	$[\alpha]_D$ (c 1, $CHCl_3$)[c]	Formyl Epoxide (% yield)[d]	ee (%)[e]	Configuration
Ph_2CO	63 [a]	85/15	−8.4	80	78	S
(p-F-$C_6H_4)_2CO$	63	90/10	−6.7	-[f]	-	S[g]
(p-Me-$C_6H_4)_2CO$	93	93/7	−4.9	-[f]	-	S[g]
(p-MeO-$C_6H_4)_2CO$	50 [h]	82/18	-	-[f]	-	S[g]
(p-Cl-$C_6H_4)_2CO$	50	94/6	−19.3	-[f]	-	S[g]
2-Adamantanone	74	90/10	−9.3	50	95	S[g]

[a] Based on converted starting 2-chloromethyl-2-oxazoline [b] Diastereomeric ratio determined by ^1H NMR (500 Mhz) [c] Referred to oxazolinyl epoxides. [d] Isolated yields. [e] Determined by GC on a chiral stationary phase. [f] The corresponding oxazolinyl epoxides were not deblocked to formyl epoxides. [g] Presumed configuration on the basis of ^1H NMR analysis of the corresponding oxazolinyl epoxides **4**. [h] Resulting chlorohydrins (not the epoxides) were isolated by chromatography on silica gel (petroleum ether/AcOEt 8/2).

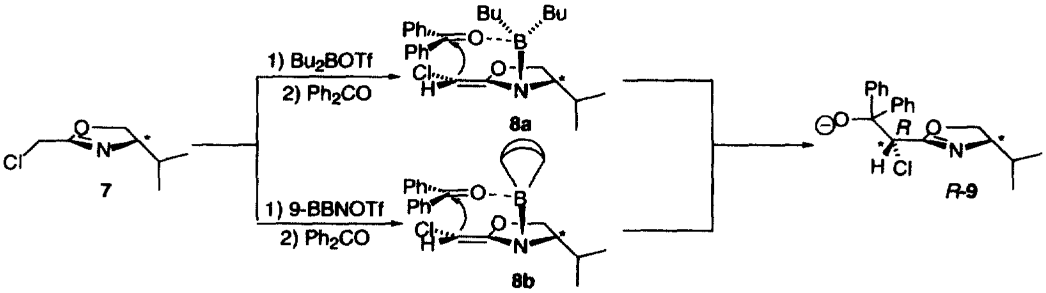
via a preliminary coordination of boron to the carbonyl, thus leading to the chlorohydrin adopting the *S* configuration at the α carbon (Scheme 4). In the case of **2b** (BBu_2), the two butyl groups on boron prevent the methoxymethyl group from coordinating the boron atom. Therefore, the carbonyl approaches the reaction centre from the top, once more via a preliminary coordination on boron, to give the chlorohydrin of *R* configuration at the α carbon (Scheme 5). Strong support for the influence of boron coordination by the methoxymethyl group in the establishment of the stereoselection of the reactions of **2a** and **2b** comes from the reaction of boron azaenolates of (4*S*)-4-isopropyl-2-chloromethyl-2-oxazoline **7**[8] with benzophenone (Scheme 6).



Scheme 4.



Scheme 5.



Scheme 6.

Indeed both the boron azaenolates derived from Bu_2BOTf **8a** and 9-BBNOTf **8b**, when treated with benzophenone, led to the chlorohydrin **9** of *R* configuration at the α carbon.

Semiempirical calculations[12] indicate that in the more stable arrangements of the boron azaenolates **8a** and **8b** the isopropyl group on the 4-position pushes the boron away so that the attack of the carbonyl, via a preliminary coordination of boron, occurs from the opposite side.

In conclusion, the stereochemistry of the aldol-type reaction of chiral azaenolates **2** and **8** is dictated by the substituents which are present either on the oxazoline ring and the boron atom.

Acknowledgements

Work carried out in the framework of the National Project 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni' supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome, and by the University of Bari. We also thank the Italian CNR for financial support.

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