Pergamon

Tetrahedron Letters 43 (2002) 4737–4740

TETRAHEDRON LETTERS

Stereoselective aldol condensation of boron enolates to *trans* α,β-epoxy aldehydes

Giuliana Righi,[a,*] Francesca Spirito[a] and Carlo Bonini[b]

[a]*Istituto di Chimica Biomolecolare-Sezione di Roma, c/o Dipartimento di Chimica, Università 'La Sapienza', P. le A. Moro 5, 00185 Roma, Italy*

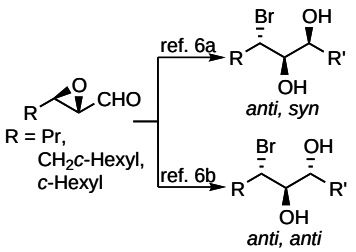
[b]*Dipartimento di Chimica, Università della Basilicata, Via N. Sauro 85, 85100 Potenza, Italy*

Received 8 May 2002; accepted 13 May 2002

Abstract—A study on the addition of boron enolates of methyl ketones to *trans* α,β-epoxy aldehydes is reported. The reaction proceeds with an excellent *anti* stereoselectivity, consistent with the Felkin–Ahn model, toward the synthesis of hydroxylated compounds with defined stereochemistry. © 2002 Published by Elsevier Science Ltd.

Optically active functionalised 1,2 or 1,3 polyhydroxylated fragments of defined stereochemistry are valuable synthetic intermediates for the preparation of many natural products such as polyene macrolide antibiotics.[1] Many synthetic methodologies leading to these structures have been developed, either starting from available natural compounds, either employing chiral precursors obtained by asymmetric chemical or by biocatalytic transformations.

Over the last few years we have extensively investigated both new biocatalytic[2] and chemical methodologies to this end. Regarding new chemical approaches, our attention was focused on two different routes: diastereoselective reduction of β-hydroxy ketones and hydroxy diketoesters[3] and, more recently, regio- and stereoselective opening and subsequent elaboration of 2-functionalised three-membered heterocycles, such as epoxides[4] and aziridines.[5]



Scheme 1.

In this context α,β-epoxy aldehydes, easily obtained in optically active form by the oxidation of the corresponding chiral epoxy alcohols, seem very useful substrates toward the synthesis of polyhydroxylated compounds. In fact their controlled ring opening and nucleophilic addition to the carbonyl group could allow the elongation of the chain with the formation of three stereogenic contiguous centers.

This hypothesis has been confirmed in our recent results on the study of the stereocontrolled Grignard addition to these substrates. In fact two different methodologies have been developed to prepare 3-bromo-1,2-diols with complementary stereochemistry in good yields with excellent stereoselectivity (Scheme 1).[6]

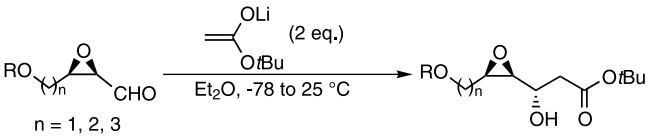
Prompted by these results, we decided to extend our studies on the diastereocontrolled aldol addition of ketones to *trans* α,β-epoxy aldehydes, obtainable in optically active form with a better enantiomeric excess than the corresponding *cis* ones.

This reaction has never been extensively exploited; one early study reported the diastereoselective addition of various lithium ester enolates to particular α,β-epoxy aldehydes with vicinal alkoxy groups.[7] Excellent diastereofacial preference in favour of the *anti* isomer was observed in the addition of *t*-butyl lithium acetate to *cis* 4-alkoxy-2,3-epoxy butanal, with a synergic effect of the temperature and enolate excess (*anti*:*syn* ~13:1) (Scheme 2), through a Felkin–Ahn T.S. model in order to explain this asymmetric induction.

Keywords: asymmetric synthesis; α,β-epoxy aldehydes; boron enolates; aldol condensation.

* Corresponding author. E-mail: giuliana.righi@uniroma1.it

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)00914-0



Scheme 2.

More recently, the same authors reported further results where the remote alkoxy group does not seem to sensibly influence the aldols ratio.[8]

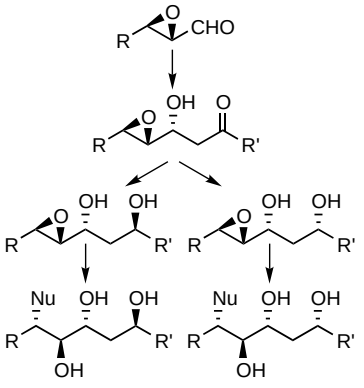
Instead, we have chosen to investigate the aldol addition of ketone enolates to alkyl substituted α,β-epoxy aldehydes, because in this case it would have been possible to easily obtain another stereogenic center by the known diastereoselective reduction of the formed β-hydroxy ketone to *anti*[9] or *syn*[10] 1,3-diol, as shown in the general strategy depicted in the Scheme 3.

Our preliminary studies were restricted, for convenience, to racemic compounds and we chose, as a standard test reaction, the addition of the pinacolon enolate to the *trans* α,β-epoxy hexanal.

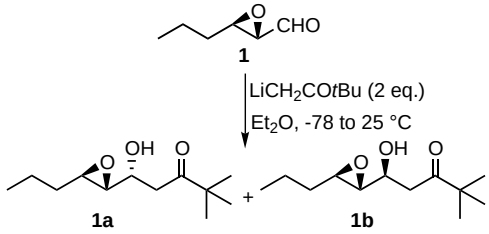
At first we employed the same reaction conditions shown in Scheme 2, but a 1:1 diastereomeric mixture of aldols was obtained (Scheme 4).

The stereochemical assignment for the obtained epoxy alcohols was based on their spectral characteristic. It is reported[11] that the general trend for these diastereoisomers is that C*H*OH of the *anti* isomer (corresponding to 3*R**,4*S**) absorbs at lower field than that of the corresponding *syn* isomer (corresponding to 3*R**,4*R**). This behaviour was also observed for the diastereomeric epoxy alcohols **1a** and **1b**, when the resonance of the C*H*OH of **1a** (4.06 δ) is shifted by 0.15 ppm downfield relative to the corresponding resonance of the C*H*OH of **1b** (3.91 δ). Consequently we attributed the *anti* configuration to **1a** and the *syn* configuration to **1b**.

In the light of this result we decided to change the means of generating enolates exploiting the behaviour of boron enolates, extensively employed in the stereoselective aldol additions.

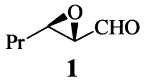


Scheme 3.



Scheme 4.

Table 1. Addition to aldehyde **1**



T (°C)	Yield (%)	*anti* **1a**/*syn* **1b**[a]
−78	58	70:30
−78 to rt	62	>95:5

[a] *t*-Butylboron enolate was added in a 1:1 ratio with aldehyde. Increasing the ratio (2:1) both chemical yield and diastereoselectivity did not significantly change.

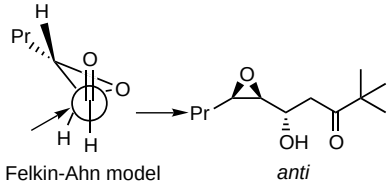


Figure 1.

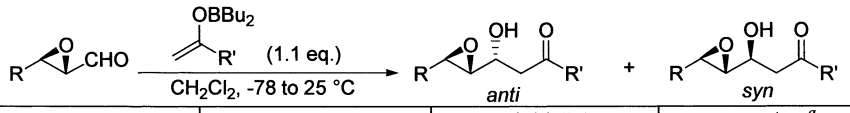
Thus, the dibutylboron enolate, formed by adding B_2BOTf and DPEA to pinacolon at 0°C for 30 min, was allowed to react with *trans* α,β-epoxyhexanal in the usual standard conditions[12] at the temperature reported in Table 1.

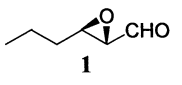
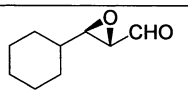
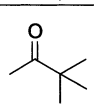
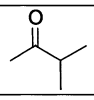
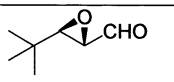
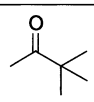
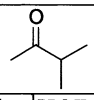
As reported, the reaction furnished predominantly one diastereoisomer (compound **1a**) when carried out at −78°C and only one detectable diastereoisomer when the reaction mixture was slowly allowed to warm up to room temperature.[13] This moderate dependence of the diastereomeric ratio from the temperature led us to speculate that both kinetic and thermodynamic control of the reaction were in favor of the *anti* isomer.[7b] A Felkin–Ahn model for the T.S. can be also invoked to explain the observed diastereoselectivity (see Fig. 1).

In the shown model we can assume that the incoming nucleophile attacks antiperiplanar to the oxygen of the epoxide ring, considered as the largest group of the molecule.

The general applicability of the methodology was extended to different *trans* substituted aldehydes such as the *trans* 3-cyclohexyl-2,3-epoxypropanal **2** and the *trans* 3-*t*butyl-2,3-epoxypropanal **3**, when a steric bulky substituent is present on the C-3 position (Table 2). The

Table 2. Addition of boron enolates to α,β-epoxy aldehydes **1**, **2** and **3**



α,β -Epoxy aldehyde	Ketone	Yield (%)	*anti/syn*[a]
 **1**		62	>95:5
		63	>95:5
 **2**		64	>95:5
		67	>95:5
 **3**		57	>95:5
		55	>95:5

[a] The ratio was determinated by ^{1}H-NMR analysis of the acetylated crude mixture. The *syn* isomer was never detected.

addition was also performed on *trans* 3-phenyl-2,3-epoxypropanal, but in this case a complex mixture of products was obtained, probably due to the high reactivity of the benzylic position.

Moreover, we performed the reaction with 3-methyl-2-butanone to further extend the addition also with ketones having two different enolizable sites (see Table 2). Generally, in these cases, the presence of tertiary amines, such as DPEA, allows the prevalence of the kinetically controlled regioisomer.

The observed results demonstrate that the stereoselectivity does not depend on the hindrance present at the oxirane ring and, consequently, the methodology can be considered of general applicability.

The studies carried out allow us to conclude that the aldol condensation of boron enolates with *trans* α,β-epoxy aldehydes, easily obtainable in optically active form from the corresponding *trans* allylic alcohols, proceeds with excellent stereoselectivity in favour of *anti* diastereoisomer, as predicted by T.S. Felkin–Ahn model. The possibility of utilizing this procedure in the synthesis of complex natural products is currently under investigation.

References

1. Omura, S.; Tanaka, H. In *Macrolide Antibiotics*: *Chemistry*, *Biology and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; pp. 351–552.
2. See for examples: (a) Bonini, C.; Giugliano, A.; Racioppi, R.; Righi, G. *Tetrahedron Lett.* **1996**, *37*, 2487–2490; (b) Bonini, C.; Chiummiento, L.; Funicello, M.; Marconi, L.; Righi, G. *Tetrahedron: Asymmetry* **1998**, *9*, 2559–2561 and references cited therein.
3. (a) Bianco, A.; Bonini, C.; Di Fabio, R.; Mecozzi, S.; Proposito, A.; Righi, G. *Gazz. Chim. Ital.* **1991**, *121*, 75–80; (b) Bonini, C.; Righi, G.; Rossi, L. *Tetrahedron* **1992**, *48*, 9801–9808.
4. (a) For reviews, see: Bonini, C.; Righi, G. *Synthesis* **1994**, 225–238; (b) Righi, G.; Bonini, C. *Target Heterocycl. Syst.* **2001**, *4*, 139–165; (c) Bonini, C.; Federici, C.; Righi, G.; Rossi, L. *J. Org. Chem.* **1995**, *60*, 4803–4812; (d) Bonini, C.; Righi, G.; Rumboldt, G. *Tetrahedron* **1995**, *48*, 13401–13408; (e) Bonini, C.; Righi, G.; Rumboldt, G. *J. Org. Chem.* **1996**, *61*, 3557–3560.
5. (a) Bonini, C.; Righi, G.; D'Achille, R. *Tetrahedron Lett.* **1996**, *37*, 6893–6896; (b) Bonini, C.; Righi, G.; Chionne, A.; D'Achille, R. *Tetrahedron: Asymmetry* **1997**, *8*, 903–908; (c) Righi, G.; Franchini, T.; Bonini, C. *Tetrahedron Lett.* **1998**, *39*, 2385–2388.
6. For *anti–syn* compounds, see: (a) Righi, G.; Chionne, A.; Bonini, C. *Eur. J. Org. Chem.* **2000**, 3127–3131. For *anti–anti* compounds, see: (b) Righi, G.; Ronconi, S.; Bonini, C. *Eur. J. Org. Chem.* **2002**, 1573–1577.
7. (a) Escudier, J. M.; Baltas, M.; Gorrichon, L. *Tetrahedron Lett.* **1991**, *32*, 5345–5348; (b) Escudier, J. M.; Baltas, M.; Gorrichon, L. *Tetrahedron* **1993**, *49*, 5253–5260; (c) Nacro, K.; Escudier, J. M.; Baltas, M.; Gorrichon, L. *Tetrahedron* **1996**, *52*, 9047–9056.
8. Nacro, K.; Baltas, M.; Gorrichon, L. *Tetrahedron* **1999**, *55*, 14013–14030.

9. Evans, D. A.; Chapman, K. T. *Tetrahedron Lett*. **1986**, *27*, 5939–5942.
10. Chen, K.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett*. **1987**, 1923–1926.
11. (a) Adam, W.; Nestler, B. *J. Am. Chem. Soc*. **1993**, *115*, 7226–7236; (b) Mihelich, E. D. *Tetrahedron Lett*. **1979**, *20*, 4729–4732.
12. (a) Inoue, T.; Mukaiama, T. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 174–178; (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc*. **1981**, *103*, 3099–3111.
13. General procedure: Di-*n*-butylboryl triflate (1 M in CH_2Cl_2, 1.1 mmol) was added dropwise to a stirred solution of ketone in 4 mL of CH_2Cl_2 at 0°C. After the mixture was stirred at 0°C for 10 min, diisopropylethylamine (1.2 mmol in 1 mL of CH_2Cl_2) was added dropwise. The reaction mixture was stirred at 0°C for 30 min and then recooled to −78°C. To the above enolate solution was added a solution of aldehyde (1 mmol) in 2 mL of CH_2Cl_2. After a few minutes the reaction was allowed to warm to room temperature and then quenched with a mixture of MeOH (6 mL), aqueous phosphate buffer (4 mL, pH 7) and H_2O_2 (4 mL of a 30% solution). The aqueous layer was extracted with two portions of AcOEt and the combined organic extracts were dried (Na_2SO_4) and concentrated. Generally TLC monitoring reveals about 30% of unreacted aldehyde also after a longer reaction time. The residue was purified on silica gel.