Pergamon

*Tetrahedron Letters*, Vol. 35, No. 26, pp. 4623-4626, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00841-8

# Reagent Control in the Aldol Addition Reaction of Chiral Boron Enolates with Chiral Aldehydes

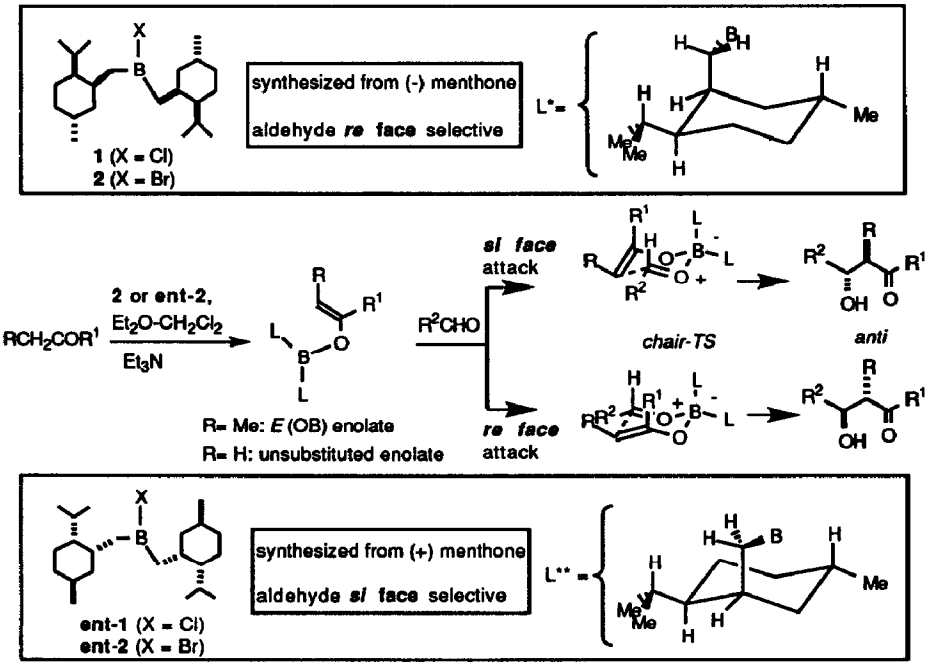
**Cesare Gennari,* Daniela Moresca, Anna Vulpetti, and Gilles Pain**

Dip. di Chimica Organica e Industriale, Universita' di Milano, Centro CNR (Sost.Org.Nat.), via Venezian 21, 20133 Milano, Italy

***Abstract***: Boron enolates bearing menthone-derived chiral ligands are capable of fair to excellent diastereocontrol in their reactions with chiral aldehydes. Thioester-derived (better than ketone derived) enolates are able to control aldol stereochemistry irrespective of the aldehyde preferences.

The boron aldol reaction has become a powerful method for the control of both relative and absolute stereochemistry in organic synthesis.[1] We have recently exploited transition state computer modelling to develop two new boron reagents (**1**, X = Cl; **2**, X = Br; **Scheme 1**) which allow the enantioselective synthesis of ketone-derived *anti* (74-88% ee; R = Me; $R^1$ = alkyl, aryl) and unsubstituted aldols (55-76% ee; R = H; $R^1$ = alkyl, aryl),[2a] and thioester-derived *anti* (≥98% ee; R = Me, $R^1$ = $SBu^t$) and unsubstituted aldols (87-97% ee; R = H, $R^1$ = $SBu^t$).[2b]

**Scheme 1**

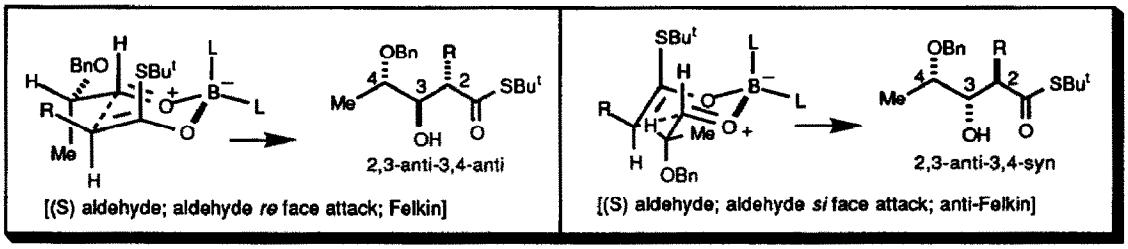


In the reaction of chiral enolates with chiral aldehydes the intrinsic diastereofacial selectivities of the two chiral components are either matched or mismatched.[1,3] If the aldehyde (substrate) intrinsic selectivity is moderate and the enolate (reagent) selectivity is very high, reagent control can be obtained.[1,3] Enolates bearing chiral metal ligands are often able to impart a high degree of reagent control, e.g. 2,5-*trans*-dimethylborolanyl enolates,[4a] 2,5-*trans*-diphenylborolanyl enolates,[4b,c] iron acyl enolates,[5] diisopinocampheylboron enolates,[6] chiral diamine complexed tin(II) enolates.[7]

Here we report that boron enolates derived from **2** or **ent-2** (X = Br) show a high degree of reagent control in reactions with chiral aldehydes, and that the efficiency of double asymmetric synthesis reflects the level of enantiomeric excess of the reactions with achiral aldehydes [thiopropionates (≥98% ee) ≥ thioacetates (87-97% ee) > ethylketones (74-88% ee)].

Protected lactic aldehyde shows a very modest inherent preference for the Felkin-type product (3,4-*anti*) in reactions with achiral thioester boron enolates (52:48 with thioacetate; 67:33 with thiopropionate).[8] The chiral boron enolates are able to impart complete reagent control with the propionates and very high selectivity with the acetates (**Scheme 2**).

**Scheme 2**



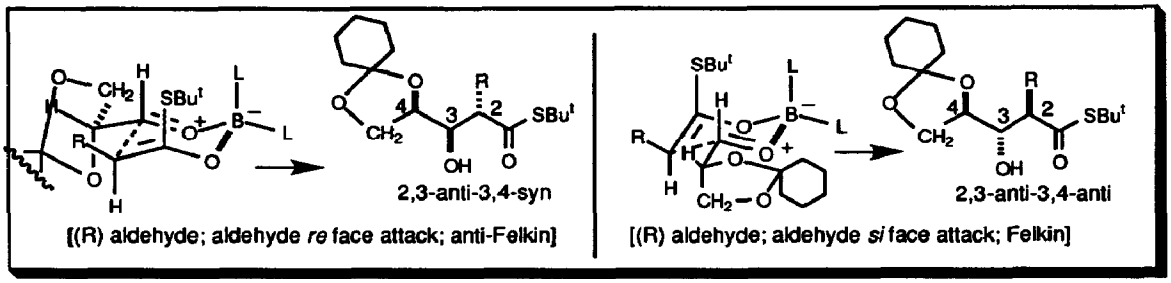

| Entry | R | L | Aldehyde Abs. conf. | Enolate *E* : *Z* [2,3-Anti: 2,3-Syn] | %E.E. (major diaster.) | 2,3-anti 3,4-anti (Felkin) | 2,3-anti 3,4-syn | 2,3-syn 3,4-anti (Felkin) | 2,3-syn 3,4-syn | Yield % |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Me | L* | S | >98:2 | 100 | ≥99 | ≤1 | Not detected | | 65 |
| 2 | Me | L** | S | >98:2 | 100 | ≤1 | ≥99 | Not detected | | 60 |
| 3 | H | L* | S | --- | 100 | 93 | 7 | --- | | 75 |
| 4 | H | L** | S | --- | 100 | 6 | 94 | --- | | 65 |

Protected glyceraldehyde shows a more pronounced inherent preference for the Felkin-type product (3,4-*anti*) in reactions with achiral thioester boron enolates (80:20 with thioacetate; 87.5:12.5 with thiopropionate).[8] The chiral boron enolates are again able to impart very high reagent controlled selectivity with both the propionates and the acetates (**Scheme 3**).

The situation is slightly more complicated with α-methyl-β-benzyloxypropionaldehyde. The aldol addition of the *Z* boron enolate derived from diethyl ketone was recently studied both computationally and experimentally and shown to be moderately 2,3-*syn*-3,4-*anti* (anti-Felkin) selective (65:35).[9a] The "normal" Felkin TS is destabilized by the presence of a (+/-) double gauche pentane interaction between the methyl of the *Z* enolate and that of the aldehyde.[9a,b] The usual Felkin selectivity should be restored with *E* enolates. The results (**Scheme 4**) are less clean than expected. Although it is possible that some aldehyde enolization and racemization is occurring during the aldol reaction [this would also explain some variability (± 3 %) of the product ratios in repeated reactions], there is no rationale at present for the different selectivity of the *E*-(OB)

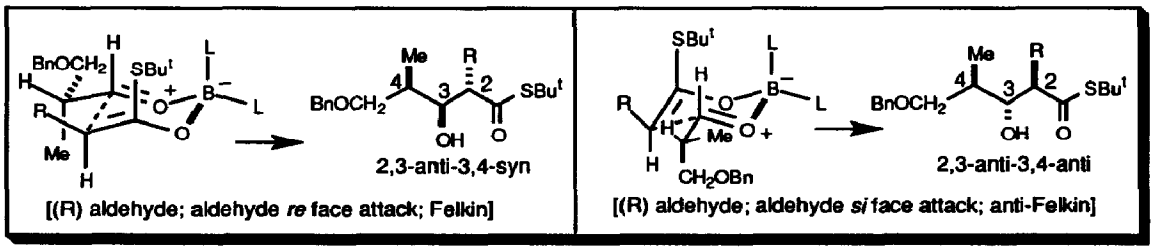
thiopropionate enolate [which is highly 3,4-*syn* (Felkin-type) selective] and of the thioacetate enolate [which is highly 3,4-*anti* (anti-Felkin-type) selective] (Scheme 4, *cf.* entries 2,3 with 5,6). Finally the aldol reactions of the *E* enolate derived from diethyl ketone were studied with α-methyl phenylacetaldehyde and α-methyl-β-benzyloxypropionaldehyde (**Scheme 5**). The results reflect the lower enantioinducing power of the ketone enolates compared to the thioester enolates. A computational study of these reactions using transition state computer modelling[2a,9a,10] gave results in qualitative agreement with the experiments (Scheme 5).

**Scheme 3**



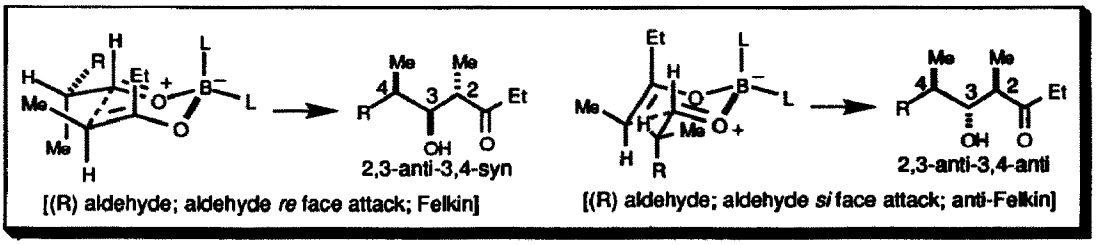

| Entry | R | L | Aldehyde Abs. conf. | Enolate *E* : *Z* [2,3-Anti: 2,3-Syn] | %E.E. (major diaster.) | 2,3-anti 3,4-anti (Felkin) | 2,3-anti 3,4-syn | 2,3-syn 3,4-anti (Felkin) | 2,3-syn 3,4-syn | Yield % |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Me | L* | R | >98:2 | 100 | 5 | **95** | Not detected | | 45 |
| 2 | Me | L** | R | >98:2 | 100 | **99** | 1 | Not detected | | 50 |
| 3 | H | L* | R | — | 100 | 3 | **97** | — | | 72 |
| 4 | H | L** | R | — | 100 | **96** | 4 | — | | 75 |

**Scheme 4**




| Entry | R | L | Aldehyde Abs. conf. | Enolate *E* : *Z* [2,3-Anti: 2,3-Syn] | %E.E. (major diaster.) | 2,3-anti 3,4-syn (Felkin) | 2,3-anti 3,4-anti | 2,3-syn 3,4-anti (Felkin) | 2,3-syn 3,4-syn | Yield % |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Me | L* | R/S | >98:2 | - | 51 | 49 | Not detected | | 81 |
| 2 | Me | L* | R | >98:2 | 100 | **95** | 5 | Not detected | | 60 |
| 3 | Me | L** | R | >98:2 | 100 | 35 | **65** | Not detected | | 60 |
| 4 | H | L* | R/S | — | - | 50 | 50 | — | | 70 |
| 5 | H | L* | R | — | 100 | **68** | 32 | — | | 70 |
| 6 | H | L** | R | — | 100 | 4 | **96** | — | | 60 |

**Scheme 5**




| Entry | R | L | Aldehyde Abs. conf. | Enolate *E* : *Z* [2,3-Anti: 2,3-Syn] | %E.E. (major diaster.) | 2,3-anti 3,4-syn (Felkin) | 2,3-anti 3,4-anti | 2,3-syn 3,4-syn (Felkin) | 2,3-syn 3,4-anti | Yield % |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Ph | c-$C_6H_{11}$ | R/S | 56:44 | 0 | 93 | 7 | 80 | 20 | 65 |
| 2 | Ph | L* | R/S | 90:10 | 25 | 96 | 4 | ≥90 | ≤10 | 75 |
| 3 | $CH_2OBn$ | c-$C_6H_{11}$ | R/S | 70:30 | 0 | 60 | 40 | 40 | 60 | 70 |
| 4 | $CH_2OBn$ | L* | R/S | 95:5 | - | 65 | 35 | 60 | 40 | 68 |
| 5 | $CH_2OBn$ | L* | R | 95:5 | 100 | 75 | 25 | 60 | 40 | 72 |
| 6 | $CH_2OBn$ | L** | R | 92:8 | 100 | 40 | 60 | 60 | 40 | 64 |
| 1 | Ph | c-$C_6H_{11}$ | R/S | only *E* | | 78 | 22 | | | |
| 2 | Ph | L* | R/S | only *E* | | 67 | 33 | | | |
| 3 | $CH_2OCH_2Pr^i$ | c-$C_6H_{11}$ | R/S | only *E* | | 86 | 14 | | | |
| 4 | $CH_2OCH_2Pr^i$ | L* | R/S | only *E* | | 43 | 57 | | | |
| 5 | $CH_2OCH_2Pr^i$ | L* | R | only *E* | | 62 | 38 | | | |
| 6 | $CH_2OCH_2Pr^i$ | L* | S | only *E* | | 26 | 74 | | | |

Computational studies

**Acknowledgements.** We thank the Commission of the European Union (HCM Network Grant: ERB CHR XCT 930141) for a research fellowship (to G.P.) and for financial support.

## References and Notes

1. "*Comprehensive Organic Synthesis*", ed. Trost, B.M. and Fleming, I., Pergamon Press, Oxford, **1991**, Vol.2 (Heathcock, C.H. editor): (a) Heathcock, C.H., chapter 1.5, page 133-179; chapter 1.6, page 181-238; (b) Kim, M.; Williams, S.F.; Masamune, S., chapter 1.7, page 239-275.
2. (a) Gennari, C.; Hewkin, C.T.; Molinari, F.; Bernardi, A.; Comotti, A.; Goodman, J.M.; Paterson, I. *J.Org.Chem.* **1992**, *57*, 5173. (b) Gennari, C.; Moresca, D.; Vieth, S.; Vulpetti, A. *Angew.Chem., Int.Ed.Engl.* **1993**, *32*, 1618.
3. Masamune, S.; Choy, W.; Peterson, J.S.; Sita, L.R. *Angew.Chem., Int.Ed.Engl.* **1985**, *24*, 1.
4. (a) Short, R.P.; Masamune, S. *Tetrahedron Letters* **1987**, *28*, 2841. (b) Reetz, M.T. *Pure and Appl. Chem.* **1988**, *60*, 1607. (c) Reetz, M.T.; Rivadeneira, E.; Niemeyer *Tetrahedron Letters* **1990**, *31*, 3863.
5. (a) Cooke, J.W.B.; Davies, S.G.; Naylor, A. *Tetrahedron* **1993**, *49*, 7955. (b) Beckett, R.P.; Davies, S.G.; Mortlock, A.A. *Tetrahedron* : Asymmetry **1992**, *3*, 123. (c) Bodwell, G.J.; Davies, S.G.; Mortlock, A.A. *Tetrahedron* **1991**, *47*, 10077.
6. Paterson, I.; Cumming, J.G.; Smith, J.D.; Ward, R.A. *Tetrahedron Letters* **1994**, *34*, 441, and references therein.
7. Kobayashi, S.; Ohtsubo, A.; Mukaiyama, T. *Chem. Lett.* **1991**, 831.
8. Gennari, C.; Bernardi, A.; Cardani, S.; Scolastico, C. *Tetrahedron* **1984**, *40*, 4059.
9. (a) Gennari, C.; Vieth, S.; Comotti, A.; Vulpetti, A.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992**, *48*, 4439. (b) Roush, W.R. *J.Org.Chem.* **1991**, *56*, 4151.
10. Bernardi, A.; Capelli, A. M.; Gennari, C.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3576.

(*Received in UK* 29 *March* 1994; *accepted* 29 *April* 1994)