Tetrahedron Letters, Vol. 33, No. 29, pp. 4233-4236, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

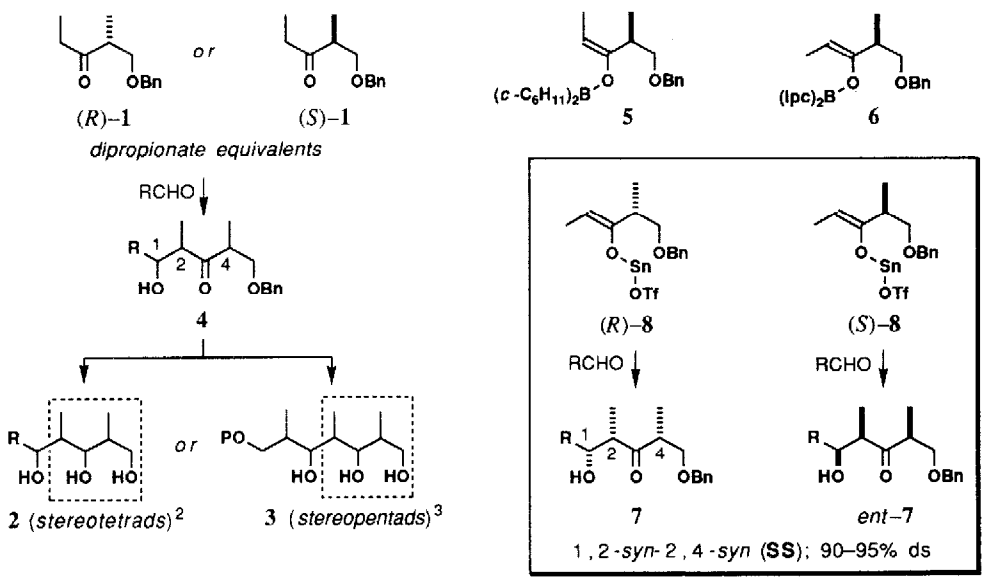
Studies in Polypropionate Synthesis: High π–Face Selectivity in *Syn* Aldol Reactions of Tin(II) Enolates from (*R*)- and (*S*)-1-Benzyloxy-2-methylpentan-3-one.

Ian Paterson* and Richard D. Tillyer

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

Abstract: Use of $Sn(OTf)_2$ / Et_3N in the aldol reactions of the α-chiral ethyl ketones (*R*)- or (*S*)-**1** with aldehydes leads to high stereoselectivity (90–95% ds, ≥97% ee) for the 1,2-*syn*-2,4-*syn* adduct **7** or *ent*-**7**. This substrate-based selectivity is rationalised by chelation of the Sn(II) enolate.

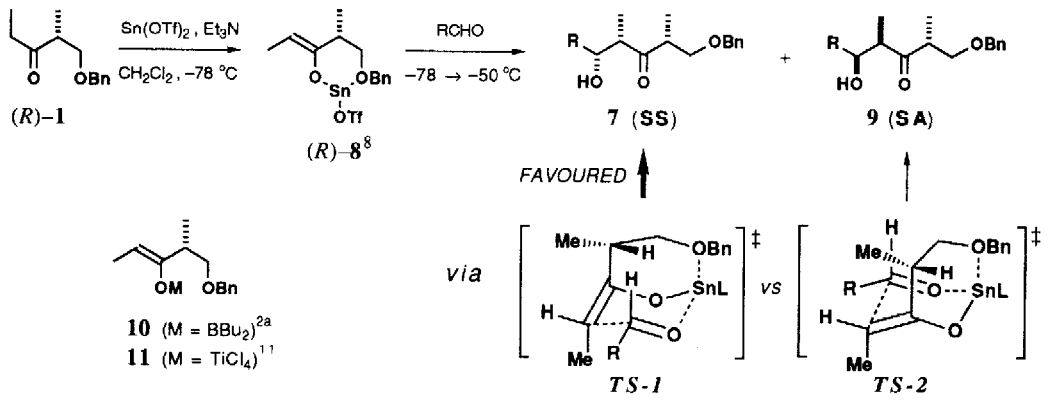
The development of effective, general methods for the stereocontrolled synthesis of polypropionate-derived natural products is of continuing importance.[1] Many methods rely on a biomimetic approach, involving the aldol addition or allylation of an aldehyde by a suitable propionate equivalent in an iterative fashion. We have introduced the α-chiral ethyl ketones (*R*)- and (*S*)-**1**[2,3] to serve as versatile *dipropionate* equivalents,[4] where stereocontrolled aldol additions to aldehydes allows a short, convergent synthesis of complex polypropionate segments, *e.g.* **2** and **3** in **Scheme 1**.[2c,3] Key features are (*i*) there is no chiral auxiliary[4] to be removed in the aldol adducts **4** and (*ii*) the subsequent ketone reduction proceeds with high diastereoselectivity to give the desired isomer of **2** or **3**, directly incorporating the six carbon atoms and stereocentre from **1**.



Scheme 1

We have already shown that efficient substrate control is possible in the *anti* aldol reaction of the *E* enol dicyclohexyl borinate **5** with aldehydes to give the 1,2-*anti*-2,4-*anti* isomer of **4** with ≥95% diastereoselectivity.[2b,3b,d] The analogous *syn* aldol reactions, however, have previously required reagent control from chiral ligands using the *Z* enol diisopinocampheyl borinates **6**.[2a,c,3c] We now report a more convenient, *substrate-controlled* aldol reaction giving the 1,2-*syn*-2,4-*syn* isomers **7** and *ent*-**7** with 90–95% diastereoselectivity and ≥97% ee, using the tin(II) enolates[5] (*R*)- and (*S*)-**8**, respectively.

Mukaiyama[5a] has introduced tin(II) enolates[4,5] for the *syn* selective aldol reactions of simple ethyl ketones, where *Z* enolates are formed using $Sn(OTf)_2$ and the hindered tertiary amine, *N*-ethylpiperidine. We found that enolisation of the ethyl ketone (*R*)-**1** was best performed under modified Mukaiyama conditions (**Scheme 2**), using $Sn(OTf)_2$ (1.3 equiv.) and Et_3N (1.6 equiv.) in CH_2Cl_2 at –78 °C for 2 h. The Sn(II) enolate so generated was then reacted with the aldehyde at –78 °C for 2 h, then at –50 °C for a further 1 h.[6] The crude mixtures of aldol adducts were subsequently analysed by HPLC and 400 MHz ^1H NMR.[7] Authentic samples of aldol isomers were available for comparison from our earlier work using boron enolates.[2a,b] The results for a range of achiral, saturated and α,β-unsaturated aldehydes are given in **Table 1**.



Scheme 2

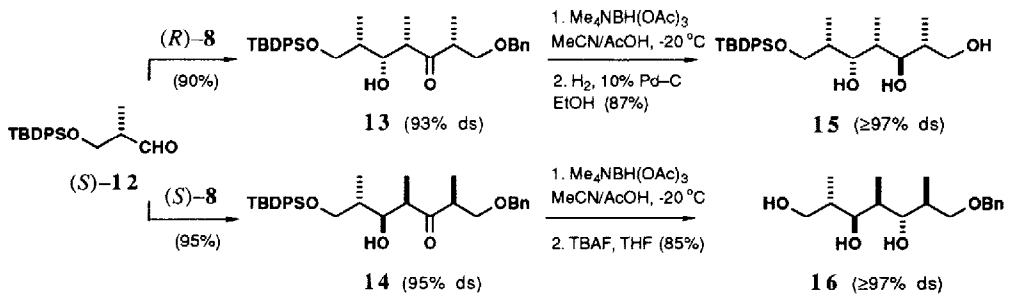
Table 1 Aldol reactions of ethyl ketone (*R*)-**1** using $Sn(OTf)_2$ / Et_3N in CH_2Cl_2.[a]

			product composition (%)[b]			
entry	R	% yield[c]	SS	SA	AA + AS	SS : SA
1	Et	93	92	7	≤1	13:1
2	$MPMOCH_2CH_2$	92	93	6	≤1	15:1
3	^{i}Pr	87	93	6	≤1	15:1
4[d]	^{i}Pr	88	86	4	10	21:1
5[e]	H_2C=CMe	92	92.5	6.5	≤1	14:1
6[e]	(*E*)-MeCH=CH	92	90.5	8.5	≤1	11:1

[a] Enolisation (–78 °C, 2 h), aldol addition (–78 °C, 2 h; –50 °C, 1 h), and workup conditions are standard unless otherwise stated. For typical experimental conditions, see note 6. [b] Isomer ratios from weighing isolated components after HPLC separation. [c] Isolated yield of aldol adducts after chromatography. [d] Reaction using (*R*)-**1**, where the benzyl group was replaced by a $^i Pr_3Si$ (TIPS) group. [e] See ref 2b and 3c for the corresponding $(Ipc)_2B$-mediated aldol reaction.

In all cases, high *syn* aldol selectivity was observed (1,2-*anti* adducts accounted for ≤1% of the product mixture), consistent with selective formation of the *Z* enolate (*R*)-**8**[8] and addition to the aldehyde *via* a chair transition state. Moreover, the **SS** (1,2-*syn*-2,4-*syn*) isomer **7** was formed preferentially, with the ratio of **SS** : **SA** (1,2-*syn*-2,4-*anti*) in the range 11–15 : 1. The major **SS** adduct[7] was isolated in 81–85% purified yield (≥97% ee[7]), which is generally superior to that previously achieved using the appropriate chiral boron triflate reagent, (–)-$(Ipc)_2BOTf$.[2b] In particular, the latter procedure[9] gives poor yields and stereoselectivities for α-branched saturated aldehydes, which now work well using the $Sn(OTf)_2$ method (*cf* entry 3 and **Scheme 3**).

These results indicate that the intermediate *Z* tin(II) enolate displays a useful level of π-face selectivity – now under substrate control. In contrast, both the analogous boron[2a] and titanium[10,11] enolates **10** and **11** show low π-face selectivity, giving only a small preference (*ca* 1.2:1 to 1.6:1) for the **SS** over the **SA** aldol adducts. All of the results for such boron[12] and titanium[10,11] *syn* aldol reactions can be best explained by a non-chelation chair transition state model, where the π-face selectivity is dependent on the relative steric demands of the substituents on the adjacent enolate stereocentre. The much higher diastereoface selectivity observed here for the tin(II) *syn* aldol reaction requires a more conformationally restricted enolate. If the benzyl ether oxygen is internally chelated to the Lewis-acidic divalent tin during the aldol addition of (*R*)-**8**,[8] this would be expected to favour ***TS-1*** over the more sterically congested ***TS-2***.[13,14] Replacement of the benzyl by a triisopropylsilyl (TIPS) ether in (*R*)-**1** also gave rise to high *Z* enolate π-face selectivity in favour of the **SS** aldol isomer (see entry 4, **SS** : **SA** = 21:1), but now 10% of a 1,2-*anti* isomer was also formed. This suggests that sterically-demanding siloxy groups may also be capable of chelation in $Sn(OTf)_2$ mediated aldol reactions of ketones.[15]



Scheme 3

We have also looked at the stereoselectivity of aldol additions of the Sn(II) enolates (*R*)- and (*S*)-**8** with the chiral aldehyde (*S*)-**12**,[16] as a novel route to stereopentad systems like **3**.[3a] Using our standard conditions,[6] the 1,2-*syn*-2,4-*syn* adducts **13** and **14** were obtained in high yield with 93% and 95% diastereoselectivity, respectively (**Scheme 3**). In each case, the major adduct stereochemistry was verified by reduction to the *anti* 1,3-diol with $Me_4NBH(OAc)_3$[17] and suitable deprotection to give the known stereopentads,[3a] *i.e.* **13** → **15** and **14** → **16**. This demonstrates that efficient aldol coupling between the ethyl ketones (*R*)- and (*S*)-**1** and α-chiral aldehydes can be carried out by the present procedure, where stereocontrol from the ketone component dominates.

In summary, we now recommend the use of the Sn(II) enolates derived from (*R*)- and (*S*)-**1** for the efficient, highly stereocontrolled synthesis of 1,2-*syn*-2,4-*syn* aldol adducts **7** and *epi*-**7** in enantiomerically-pure form. The diastereomeric 1,2-*syn*-2,4-*anti* adducts are best obtained using our existing reagent-controlled method based on the appropriate *Z* enol diisopinocampheyl borinate,[2a] while the 1,2-*anti*-2,4-*anti* isomers are easily obtained using the *E* enol dicyclohexyl borinate.[2b] Further applications[3] of these stereoregulated aldol reactions to polypropionate synthesis are underway. We are also investigating the role of chelation in the aldol reactions of other ketone-derived Sn(II) enolates[13,14] containing α- or β-heteroatom substituents.

Acknowledgement: We thank the SERC (Postdoctoral Award to RDT; GR/F43505) and EC (SCI*.0324.C) for support.

References and Notes

1. Reviews: (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569; (b) Masamune, S.; McCarthy, P. A. in *Macrolide Antibiotics. Chemistry, Biology, and Practice*, Omura, S., Ed., Academic Press, Orlando (1984); (c) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489. This last review highlights the need for "the elucidation of the principles by which the synthesis of molecules with long sequences of stereocentres can be approached."

2. (a) Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585; (b) Paterson, I.; Goodman, J. M; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121; (c) Paterson, I.; Lister, M. A.; Ryan, G. R. *Tetrahedron Lett.* **1991**, *32*, 1749.

3. (a) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797; (b) Paterson, I.; Perkins, M. V. *Tetrahedron Lett.* **1992**, *33*, 801; (c) Paterson, I.; Lister, M. A.; Norcross, R. D. *Tetrahedron Lett.* **1992**, *33*, 1767; (d) Paterson, I.; Cumming, J. G. *Tetrahedron Lett.* **1992**, *33*, 2847.

4. For an alternative class of chiral dipropionate equivalent, see: Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866.

5. For aldol reactions using Sn(II) enolates, see *inter alia*: (a) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381; (b) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391; (c) Evans, D. A.; DiMare M. *J. Am. Chem. Soc.* **1986**, *108*, 2476 and ref 4.

6. Et_3N (1.6 equiv.) was added to a stirred suspension of acid-free Sn(II) triflate (1.3 equiv.) in dry CH_2Cl_2 (*ca* 10 ml per mmol of reagent) under Ar. The mixture was immediately cooled to –78 °C and a solution of the ketone (*R*)- or (*S*)-**1** in CH_2Cl_2 (*ca* 3 ml per mmol of ketone) was added. After 2 h, a solution of the aldehyde (1.5–3 equiv.) was added slowly and the reaction mixture was maintained at –78 °C for 2 h, followed by 1 h at –50 °C. The reaction was then quenched by the addition of pH7 buffer and Et_2O. The layers were separated, the aqueous layer was extracted with Et_2O, and the combined organic fractions were washed with pH7 buffer and dried. After solvent removal, the residual oil was passed through a plug of flash silica gel, prior to HPLC analysis. For preparative scale runs, the major **SS** aldol isomer **7** (higher R_f) was easily separated from the minor **SA** isomer **9** by flash chromatography, eluting with 10% Et_2O in CH_2Cl_2.

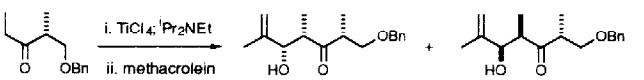
7. All new compounds gave spectroscopic data in agreement with the assigned structures. ^1H NMR analysis of the MTPA ester of the **SS** aldol adduct formed from (*R*)-**1** and methacrolein (entry 5, **Table 1**) indicated ≥97% ee. Thus no racemisation of the starting ketone was detected. $[\alpha]_D^{20}$ values in $CHCl_3$ were recorded as follows: **7**, R = Et, –17.5 (*c* 4.1); R = $MPMOCH_2CH_2$, +5.6 (*c* 5.2); R = ^{i}Pr, –26.1 (*c* 3.2); R = H_2C=CMe, –41.8 (*c* 3.9); R = (*E*)-MeCH=CH, +3.5 (*c* 4.5); **13**, +3.6 (*c* 2.2); **14**, +3.1 (*c* 2.6); **15**, –1.0 (*c* 2.3); **16**, +29.8 (*c* 1.3).

8. For simplicity, the structures of the intermediate tin(II) enolates (*R*)- and (*S*)-**8** are shown here as monomers, assuming that there is one triflate still attached to the metal centre. However, such tin(II) enolates may well be oligomeric, possibly with associated triethylamine.

9. Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.

10. Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.

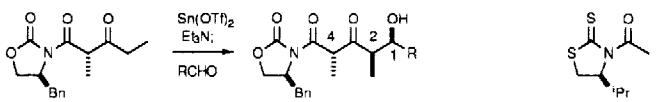
11. Low stereoselectivity was observed in the following titanium-mediated aldol reaction, based on the Evans[10] conditions. Paterson, I; Norcross, R. D., *unpublished results*.



(*R*)–**1** **7** (**SS**) 62 : 38 **9** (**SA**)

12. (a) Paterson, I.; McClure, C. K. *Tetrahedron Lett.* **1987**, *28*, 1229; (b) Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1991**, *47*, 3471.

13. In contrast to the 1,2-*syn*-2,4-*syn* aldol stereoselectivity observed for (*R*)-**8**, Evans *et al.*[4,5c] obtain the *opposite* sense of π-face selectivity using the Sn(II) enolate from **17**, giving the 1,2-*syn*-2,4-*anti* adduct **18** with 79–95% diastereoselectivity. The reasons for this apparent crossover are not clear at this time.



17 **18** **19**

14. Internal chelation accounts for the sense of π-face selectivity in the aldol reactions of the Sn(II) enolate derived from **19**.[5b]

15. Again the corresponding B and Ti aldol reactions for the TIPS (or TBS) protected analogues of (*R*)-**1** were much less selective in favour of the **SS** isomer, suggesting that the greater enolate π-face selectivity in the Sn(II) reaction originated from internal chelation. This contrasts with results for various organometallic addition and Mukaiyama-type aldol reactions to siloxy-substituted aldehydes and ketones, where the chelation outcome is not usually observed. However, this is probably due to attack at the carbonyl being faster than chelate formation in the latter reactions, whereas here the Sn(II) enolate undergoes internal chelation before the aldehyde is added to the reaction.

16. (*S*)-**12** was prepared from (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate (Aldrich).

17. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(Received in UK 18 May 1992)