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TOWARD THE DEVELOPMENT OF A GENERAL CHIRAL AUXILIARY 2. EVALUATION OF CAMPHOR LACTAM IMIDE AUXILIARIES FOR ASYMMETRIC ALDOL REACTIONS

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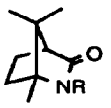
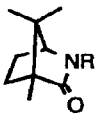
Summary: *Two camphor derived lactams 1 and 2 have been examined as to their utility as chiral auxiliaries for use in asymmetric aldol reactions. The results show good to excellent selectivities can be achieved with 2 in most cases employing diethyl boron enolates. These enolates proved less reactive than anticipated and exhibited a sensitivity to the steric size of the ligands on boron. A model which rationalizes the sense of diastereoselection is presented.*

The design of enantiomerically pure chiral molecules for use both as covalently bound adjuvants and as ligands in catalytic processes for the diastereofacially selective construction of carbon-carbon bonds is one of the important thrusts of synthetic organic chemistry.[1,2] As part of ongoing studies in this area in our laboratories, we have evaluated the use of the isomeric lactams **1** (distal) and **2** (proximal), both readily available in either antipode, to control diastereofacial selectivity in the aldol reaction.[3]





1 R = H
3 R = $CH_3CH_2C(O)$-
5 R = (Z)CH_3CH=C($OBEt_2$)-

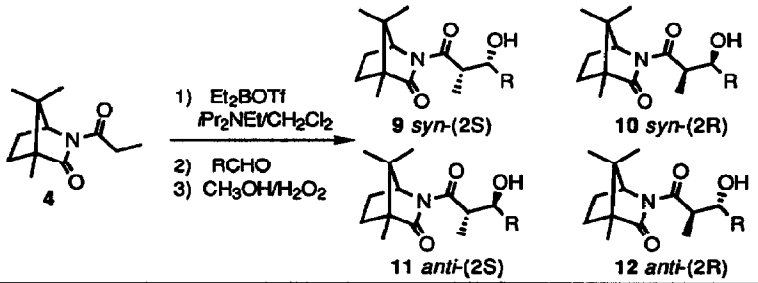
2 R = H
4 R = $CH_3CH_2C(O)$-
6 R = (Z)CH_3CH=C($OBEt_2$)-

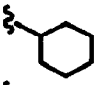
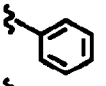
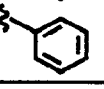
The required imides **3** (mp 50-51°C, $[\alpha]_D$ = -10.9° (c 5.31, $CHCl_3$)) and **4** (bp 51-51°C/0.2mm, $[\alpha]_D$ = +72.7° (c 4.95, $CHCl_3$)) are easily prepared from **1** and **2** by N-acylation of the corresponding lithium salt (n-butyllithium/ THF/ 0°C) with propionyl chloride at 0°C in 88% and 95% yields, respectively.[3]

Since the lithium enolates derived from **3** and **4** proved unsuitable owing both to their relatively high basicity and low diastereofacial selectivity, **3** and **4** were converted to the respective Z diethylboron enolates **5** and **6** by exposure to Et_2BOTf (1.0 equiv) and Hunigs' base (1.1 equiv) in CH_2Cl_2 at 0°C.[4,5] Addition of isobutyraldehyde (1.0 equiv) to diethylenolborinate **5** derived from **3** and stirring at 0°C for 4.5h was followed by an oxidative work-up (MeOH/ pH 7 phosphate buffer/30% aqueous H_2O_2). Isolation of the aldol products by column chromatography afforded a 2.2: 1 mixture of *syn*- diastereomers **7** and **8** in 35% yield (Scheme 1).[6] The minor isomer **8**, isolated as a crystalline solid, was found to possess the *syn*-(2R,3S) stereochemistry by single crystal x-ray analysis.[7] The proximal imide **4** was found to provide much higher selectivity. Under optimal conditions (Table 1), **4** afforded a 87% yield (75% conversion) of a 92:8 mixture of aldol products **9**-**10** (Entry 5, Table 1), with the crystalline *syn*-(2S,3R) diastereomer **9** being the major component of the mixture. These results clearly suggested imide **4** as the best candidate for further studies.

The reaction of the diethylenolborinate derived from **4** (1.0 equiv) with a representative series of aldehydes (2-3

Table 1



	Aldehyde[a]	*syn-/anti-*[b]	Diastereoselectivity[b]				Yield[c]
Entry	R	(9+10)/(11+12)	9	10	11	12	(%)
1		10.1/1	80	11	3	6	62
2		13.4/1	84	9	2	5	75(76)
3		16.5/1[d]	90	10	•	•	63(64)
4		>200/1[f]	96	4	•	•	92(50)
5		>200/1[g]	92	8	•	•	87(75)
6		13.2/1	80	13	•	•	82(78)
7		>30/1	86	14	•	•	43(43)
8		>200/1[g]	91	9	•	•	69(99)
9		>200/1[f]	93	7	•	•	64(50)
10		>200/1[g]	92	8	•	•	83

[a] Reactions conducted by slow addition of the aldehyde (1-3 equiv) to the boron enolate in CH_2Cl_2 at temperatures ranging from -78° to 0°C.

[b] Ratios determined by ^1H NMR. Absolute configuration of the major isomer determined by hydrolysis and comparison of $[\alpha]_D$ values of the resulting β-hydroxy acids or esters with literature values.

[c] Isolated yields of aldol products after flash chromatography corrected for conversion which is given in parentheses.

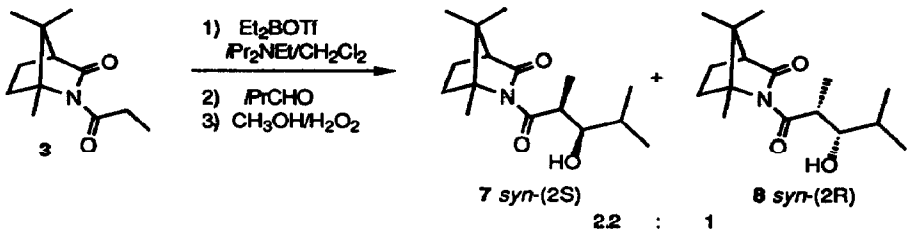
[d] Dimethyl boron bromide was utilized to form the dimethylenolborinate in this case.

[e] Below the detection limit of the NMR method (~2%).

[f] In this case, slow addition (0.5-2h) of 2.0 equiv of aldehyde was conducted at -45°C (case 9, -78°C) with a reaction period of 24-48 h, followed by quenching of the reaction mixture.

[g] In this case, slow addition (0.5-2h) of 3.0 equiv of aldehyde was conducted at -45°C with a reaction period of 24-48 h, followed by quenching of the reaction mixture.

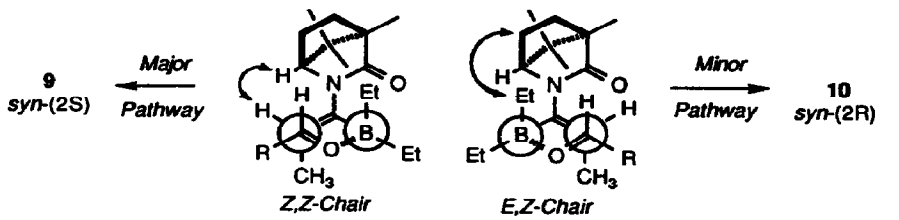
Scheme 1



equiv) in CH_2Cl_2 at -45°C for 24-48h is summarized in Table 1. The major product in each case was the *syn*-(2S,3R) diastereomer **9**. Since the chemical shift of the chiral auxiliary bridgehead methine proton was well-resolved for all diastereomers, the stereoselectivities were readily determined by ^1H NMR. After removal of the chiral auxiliary by treatment with tBuOOH/LiOH (superior to H_2O_2 in these cases), which afforded the desired β-hydroxy acids in 60-82% yields with >85% recovery of the chiral lactam **2**, the absolute stereochemistry of the resulting β-hydroxy acids or corresponding methyl esters was assigned by comparison of the observed optical rotations with values given in the literature.[8,9]

Under optimal reaction conditions, it was found that conversion with respect to the enolborinate **6** was improved by use of 2-3 equivalents of aldehyde as has been observed with the enol borinates derived from the Oppolzer camphor sultam auxiliary.[2d] Of course, use of excess **6** affords excellent conversions with respect to aldehyde as long as the presence of excess diethylboron triflate is avoided.[4,5] *Syn-Anti* ratios of up to 200:1 can be achieved under these optimized conditions (Table 1). Best results with respect to facial selectivity are obtained at low temperatures (-78°C), however, at the expense of lower reactivity. For many cases, an acceptable compromise between rate and selectivity can be reached by conducting the condensation at -45°C which affords synthetically useful facial selectivities, generally >12:1 (Table 1).

Figure 1



In an effort to understand the origin of the facial selectivity observed with this chiral enolate, a series of MNDO and molecular mechanics calculations was carried out. Comparison of relative energies for the possible transition states was not considered reliable, however the geometries were considered qualitatively valid. The resulting model of the transition state (Figure 1) suggests that the E,Z-chair transition state, leading to the minor product **10**, is less favorable due to the presence of a significant non-bonded interaction between an axial boron ligand and the proximal methylene group in the two carbon bridge of the lactam auxiliary. Our studies have shown that selectivity and reactivity decreases with increasing size of the ligands on boron (compare Table 1 cases 2 and 3). The alternative Z,Z transition state lacks this methylene-methylene interaction, but does possess a potentially destabilizing allylic interaction between the enolate double bond proton and the bridgehead methine proton in the auxiliary. Another contributing factor may be a

significant destabilization of the Z,Z transition state due to unfavorable dipole alignments.[2] These opposing effects may limit the ultimate level of diastereofacial selectivity attainable, and are in aggregate responsible for the lower reactivity of these boron enolates relative to those derived from oxazolidinone auxillaries.[2a] In most respects, the boron enolate derived from **4** more closely parallels the behavior of the boron enolates derived from the Oppolzer camphorsultam auxiliaries.[2d] We are currently testing this model by selective structural modification of the auxiliary.

The present studies clearly indicate that enolborinates derived from **4** afford synthetically useful *syn/anti* and facial selectivities, providing a useful alternative to the existing repertoire of auxiliaries for asymmetric aldol reactions particularly when modulated reactivity is required to achieve required regioselectivity or chemoselectivity.

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3. Boeckman, Jr, R. K.; Nelson, S. G.; Gaul, M. D. *J. Am Chem. Soc.* **1992**, *114*, 2258. The descriptors proximal and distal refer to the relationship of the lactam carbonyl to the bridgehead methyl group.

4. Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am Chem. Soc.* **1981**, *103*, 3099. A single boron enolate was observed (^{13}C NMR), geometry tentatively assigned Z, based upon literature precedent, NOE studies, and the observed *syn* diastereoselectivity of the aldol reactions. *Excess boron triflate, which catalyzes oligomerization of the aldehyde, must be avoided to achieve high conversions and prevent difficulties in purification of the aldol products.*

5. The sense of π-facial and *syn/anti* selectivity has been observed to reverse affording **12** and **10** (1:2-3 *syn/anti*; >10:1 (2(R)/2(S)) if impure dialkyl boron triflate is employed. The related monoalkyl boron ditriflate, which behaves as a chelating Lewis acid with **4**, has been identified as the probable catalyst. Preparation and use of authentic ethyl boron ditriflate afforded **12** and **10** (1:1.2 (*syn/anti*), 10.3:1 (2(R)/2(S)), a result in accord with the foregoing interpretation.

6. For the experimental protocol for boron aldol reactions, see: Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83.

7. The details of the single crystal X-ray analysis will be published subsequently as part of a full account of our studies.

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