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Toward the Development of a General Chiral Auxiliary. 3. Design and Evaluation of a Novel Chiral Bicyclic Lactam for Asymmetric Aldol Condensations: Evidence for the Importance of Dipole Alignment in the Transition State

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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 modern synthetic organic chemistry.[1] There has been a long-standing interest in the development of highly stereoregulated aldol condensations.[2] Numerous examples of metal-assisted condensations employing chiral enolates have been reported.[3,4] While the significance of dipole–dipole forces in determining the relative energies of transition structures in the aldol reaction has been postulated previously, we report experimental evidence that dipole alignment forces, in conjunction with nonbonded interactions, can play an important role in determining the relative energies of diastereomeric aldol transition state structures.[2e]

As part of our studies directed toward the development of novel chiral controller molecules, the camphor-derived lactam **1** has previously been evaluated as an auxiliary for the aldol condensation.[3a] The diethyl enol borinate derived from **2** proved less reactive and less selective than anticipated, providing aldol adducts in moderate yields and 70–90% de. Examination of the reactive conformations of the boron enolate derived from **2** suggested that optimal dipole alignment was not achieved in the aldol transition arising from the lowest energy conformer owing to opposing dipole and nonbonded interactions in the transition state structure derived from that enolate.[3a] The novel camphor-derived lactam **3** was then designed on the basis of consideration of the most probable chair-like transition state structures for the aldol condensation employing the reactive conformations of the (*Z*)-boron enolate derived from **4**. As depicted in Figure 1 for the case of the (*Z*)-enol borinate from **4**, optimal dipole alignment (*anti* relationship of ring carbonyl to enolate oxygen bond) is possible. Furthermore, the aldehyde can approach from the more sterically accessible face, *syn* to the one-carbon bridge, suggesting that enhanced diastereoselectivity and reactivity might be observed.

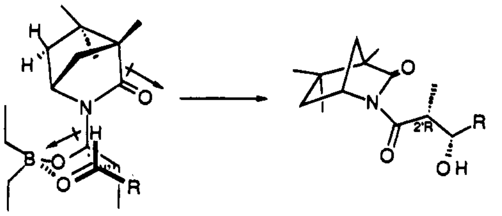
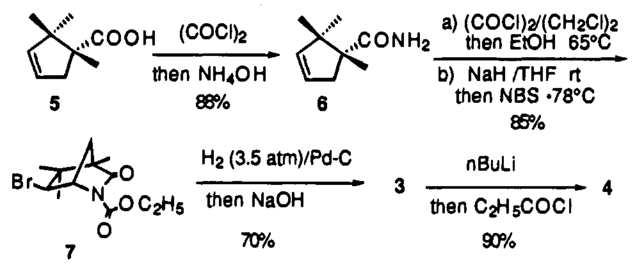
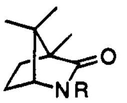


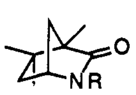
Figure 1.

Scheme 1





1 R = H
2 R = -C(O)C$_2$H$_5$



3 R = H
4 R = -C(O)C$_2$H$_5$

The highly crystalline auxiliary **3** (mp 192–194 °C, $[\alpha]^{23}_{D}$ +143° (*c* 0.008, CHCl$_3$) is easily prepared in three steps from the known acid **5**,[5] both antipodes of which are readily accessible from the corresponding camphoric acids (Scheme 1). Conversion of (1*R*)-**5** to the derived amide **6** *via* the acid chloride ((COCl)$_2$ and then NH$_4$OH) proceeds in 88% yield. In a single synthetic operation, amide **6** is first converted to the *N*-acyl carbamate *via* the acyl isocyanate, by treatment with (COCl)$_2$ in dichloroethane and trapping with ethanol at 65 °C,[6] then directly cyclized by treatment with NaH in THF (room temperature) followed by NBS at −78 °C, affording bromide **7** in 85% overall yield. Bromide **7** undergoes smooth hydrogenolysis (H$_2$ (3.5 atm)/10% Pd–C) followed by deacylation *in situ* upon exposure to NaOH to afford the desired lactam **3** in 70% yield. Acylation of **3** (*n*-BuLi, THF, C$_2$H$_5$COCl) proceeds uneventfully, providing the required imide **4** in 90% yield.

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[1] (a) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041. (b) Parmee, E. R.; Tempkin, O.; Masamune, S. *J. Am. Chem. Soc.* **1991**, *113*, 9365 and references cited therein.

[2] For reviews on the asymmetric aldol condensation, see: (a) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 32. (c) Heathcock, C. H. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, p 111. (d) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (e) Evans, D. A.; Nelson, T. R.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

[3] (a) Boeckman, R. K., Jr.; Johnson, A. T.; Musselman, R. A. *Tetrahedron Lett.* **1994**, *35*, 8521. (b) Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613. (c) Yan, T.-H.; Chu, V.-V.; Lin, T. C.; Tseng, W.-H.; Cheng, T.-W. *Tetrahedron Lett.* **1991**, *32*, 5563. (d) Bonner, M. P.; Thorton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299. (e) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767. (f) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Starkeman, C.; Walther, E. *Tetrahedron Lett.* **1990**, *31*, 5019. (g) Heathcock, C. H. *Aldrichimica Acta* **1990**, *23*, 99 and references cited therein. (h) Bold, G.; Duthaler, R. O.; Riediker, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 497. (i) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (j) Hsiao, C.-N.; Liu, L.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 2201. (k) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1987**, *28*, 6215. (l) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (m) Abdel-Magid, A.; Lendon, N. P.; Drake, S. E.; Ivan, L. *J. Am. Chem. Soc.* **1986**, *108*, 4595. (n) Heathcock, C. H.; Arseniyadis, S. *Tetrahedron Lett.* **1985**, *26*, 6009. (o) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556 and references cited therein. (p) Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderroth, B.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 989. (q) Evans, D. A.; Bartol, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

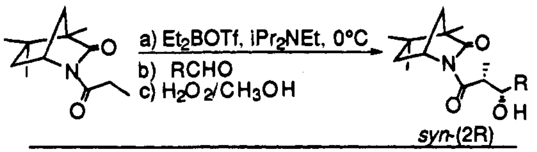
[4] For asymmetric "*anti*" aldol condensations, see: (a) Oppolzer, W.; Lienard, P. *Tetrahedron Lett.* **1993**, *34*, 4321. (b) Oppolzer, W.; Starkeman, C.; Rodriguez, I.; Bernardinelli, G. *Tetrahedron Lett.* **1991**, *32*, 61. (c) Corey, E. J.; Kim, S. S. *Tetrahedron Lett.* **1990**, *31*, 3715. (d) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976. (e) Danda, H.; Hansen, M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173. (f) Palazzi, C.; Colombo, L.; Gennari, C. *Tetrahedron Lett.* **1986**, *27*, 1735. (g) Gennari, C.; Molinari, F.; Cozzi, P.-G.; Oliva, A. *Tetrahedron Lett.* **1989**, *30*, 5163. (h) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (i) Oppolzer, W.; Marco-Contelles, J. *Helv. Chim. Acta* **1986**, *69*, 1699. (j) Helmchen, G.; Leikauf, U.; Taufer-Knöpfel, I. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 874. (k) Davies, S. G.; Dordor-Hedgecock, I. M.; Warner, P. *Tetrahedron Lett.* **1985**, *26*, 2125. (l) Meyers, A. I.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309.

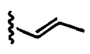
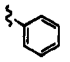
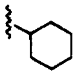
[5] Goldman, J.; Jacobsen, N.; Torssell, K. *Acta Chem. Scand. B* **1974**, *28*, 492.

[6] Speziale, A. J.; Smith, L. R.; Fedder, J. E. *J. Org. Chem.* **1965**, *30*, 4306.

0002-7863/95/1517-12368$09.00/0

Table 1



Aldehyde R	Diastereoselectivity *syn*-(2R):*syn*-(2S)	Yield[a] %
	>98:2	75(90)
	>98:2	80(95)
	>98:2	95(100)
	>98:2	80(80)
	>98:2	90(40)
	>98:2	74(90)

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

To test the above hypothesis, **4** was converted to the derived (*Z*)-diethyl enol borinate by treatment with Et$_2$BOTf (1 equiv) in CH$_2$Cl$_2$ at 0 °C followed by Hünig's base.[7] The resulting enolate was treated with a representative series of aldehydes (3 equiv) at −40 °C for 48 h (pivaldehyde −25 °C, benzaldehyde −78 °C (24 h)). The results are summarized in Table 1. To permit ready comparisons, individual cases were not further optimized. In each case, only one product was observed by 500 MHz ^{1}H NMR.[8] *The levels of diastereofacial selectivity observed in reactions of the boron enolate derived from **4** are equivalent to those obtained by employing the Evans and Oppolzer auxiliaries for comparable cases including the often problematic case of benzaldehyde.*[3efq,9] A single-crystal X-ray analysis of the adduct of **4** with benzaldehyde confirmed that the product obtained had the anticipated *syn*-(2*R*) absolute stereochemistry, consistent with the model for the transition state structure depicted in Figure 1.[10] In all cases, the absolute stereochemistry of the products was confirmed by removal of the auxiliary (LiOOtBu/THF/H$_2$O), affording the expected β-hydroxy acids (89−95% yield) along with recovery of the auxiliary **3** (85−90%), and comparison of the optical rotations of the β-hydroxy acids or the derived methyl esters with the values reported in the literature.[3d,e,q,9]

The dramatic improvement of both the diastereoselectivity and reactivity seen in the reactions utilizing **3**, when compared to those employing **1** as the chiral auxiliary, demonstrates the importance of evaluating both the dipole−dipole and steric interactions in estimating the relative energy of a set of diastereomeric aldol transition state structures. The use of the boron enolate bearing **3** results in an increase in the $\Delta\Delta G^\ddagger$ for the diastereomeric *syn* aldol transition state structures of 0.8−1.0 kcal/mol when compared to the $\Delta\Delta G^\ddagger$ for the equivalent transition state structures for the boron enolate bearing **1**. This substantial difference appears to be attributable in large part to the favorable dipole alignment. Thus, chiral enolate systems in which steric and dipole alignment factors are complementary rather than opposed would appear to have enhanced potential for providing very high levels of diastereofacial selectivity. Further extensions of our studies of enolate systems derived from **3** are currently under way in our laboratories.

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Supporting Information Available: Experimental procedures and characterization data for compounds **3**, **4**, **6**, **7**, and all new compounds in Table 1 (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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[7] A single boron enolate was observed (^{1}H NMR), whose geometry was tentatively assigned as *Z* based upon literature precedent and the observed *syn* diastereoselectivity of the aldol reactions.

[8] (a) The chemical shift of the auxiliary's C$_1$ bridgehead methine proton was shown to be well-resolved for all diastereomers, and the identity of the minor diastereomer was confirmed in the case of the adducts derived from isobutyraldehyde by comparison to authentic samples of the aldol adducts prepared from authentic samples of the β-hydroxy acids obtained using the Evans auxiliary.[3a] (b) The detection limit of the NMR method is ~2%. (c) Diastereomeric ratios were confirmed by capillary GLC to be 98.3:1.7−99:1. No *threo* diastereomers were detected.

[9] Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

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