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Diastereofacial Selectivity in the Aldol Reactions of Chiral α-Methyl Aldehydes: a Computer Modelling Approach.[1]

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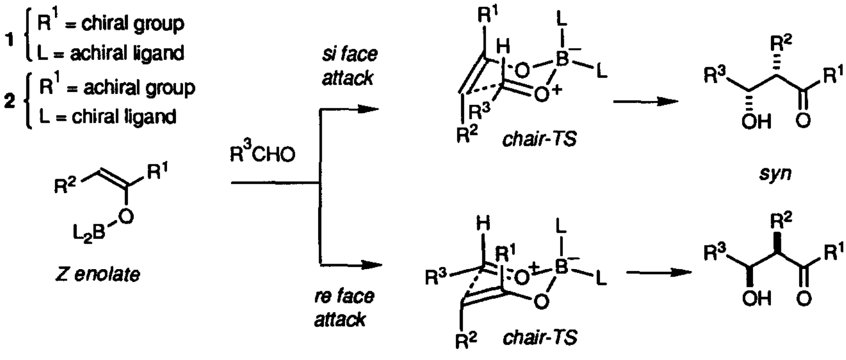
Abstract: *Transition state modelling of the aldol reaction of Z enol borinates with chiral α-methyl aldehydes (see **Schemes 4** and **6**) suggests that three transition structures (**F**, **AF**, **R**) play a dominant role in controlling π-facial selectivity. The "Felkin" structure (F) is characterized by Me-CH---C(O)-C* and CH---C(O)-C*-Me dihedral angles of about -60°/-65° and +100°. The "Roush" structure (R) has values of -60°/-65° and ±175°/180°, while the "Anti-Felkin" one (AF) has values of +60°/+65° and about +50°. Our analysis suggests that nonbonded interactions play the most important role in determining aldehyde diastereofacial selectivity in the reactions with Z enolates, and that stereoelectronic effects are possibly overridden by steric effects. Reactions with aldehydes bearing relatively small and "flat" substituents (Ph-, H_2C=CH-, Me_2C=CH-) are 3,4-syn selective ("Felkin" selective) while reactions with aldehydes bearing bulkier groups (various alkyls) are 3,4-anti selective ("Anti-Felkin" selective) (see **Tables 1** and **2**). This result is essentially due to destabilization of both (F) and (R) structures. In particular, in order to relieve strain-energy structure (F) opens the CH---C(O)-C*-Me dihedral angle from +60° to ca. +100°. In this way the bulky substituents (alkyls) are pushed towards the aldehyde hydrogen. In the (AF) structure the CH---C(O)-C*-Me dihedral angle is around +50° and the [aldehyde hydrogen - alkyl] interaction disappears. Enolate aggregation and chelation effects in the case of lithium enolates can possibly explain discrepancies observed between lithium and boron enolates and between the experimental ratios and the force field-predicted ratios.*

The aldol reaction has proven to be a very powerful method for the stereocontrolled synthesis of acyclic molecules. The relationship between enolate geometry and product stereochemistry (*i.e.* simple stereoselection) is well established, and several classes of highly enantioselective chiral enolates have been developed for use in asymmetric aldol reactions. As part of a theoretical study of aldol stereoselectivity using transition state modelling, we recently described the development of a force field model for the aldol reactions of ketone derived enol borinates with aldehydes.[2a,b] This force field is based on MM2, and on new parameters

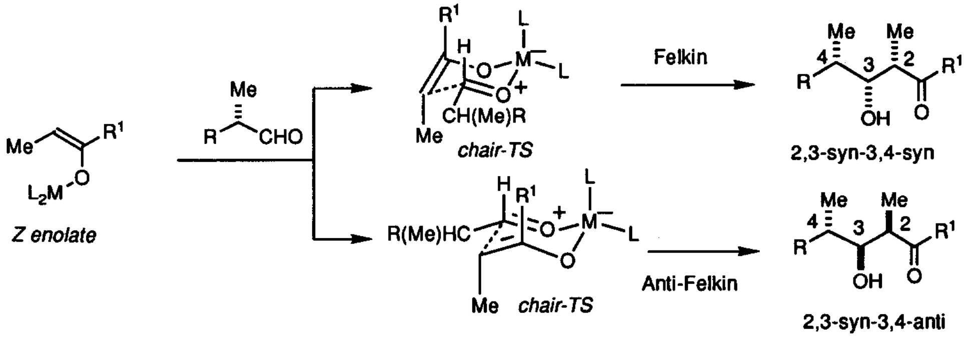
Scheme 1



developed from *ab initio* calculations on the cyclic transition structures (chair and boat) and from trial and error optimization.[2a] The model reproduces the simple stereoselection of the aldol reaction (*Z* enolates give *syn* aldols, *E* enolates give *anti* aldols with lower selectivity) and the aldehyde *si* : *re* selectivity for the *syn* selective aldol reactions of a range of chiral *Z* enol borinates **1** and **2** (**Scheme 1**). The use of this force field approach for rationalizing the observed stereoselectivity of various chiral Z enol borinates in synthetically useful aldol reactions has been discussed in detail.[2b]

In spite of the synthetic and theoretical attention devoted to this process, the factors that determine aldehyde diastereofacial selectivity in reactions of achiral enolates and chiral aldehydes are less well understood (**Scheme 2**). Diastereofacial selectivity is usually rationalized by invoking either the Felkin-Anh or the Cram chelate transition state models.[3] However, it has been noted that the Felkin-Anh model fails to properly rationalize the results of many aldol reactions involving Z enolates and chiral α-methyl aldehydes (**Scheme 2, Table 1**).[3,4] Mechanistically related reactions of (Z)-crotylboronates with chiral α-methyl aldehydes also experience the same failure. Evans,[3a] Hoffmann,[4] and Roush[5] have developed a qualitative transition state model for this situation, concluding that the anti-Felkin behaviour of the (Z)-crotylboronates is a consequence of destabilizing double gauche pentane interactions in the usually favoured Felkin-Anh transition structure.

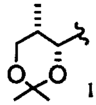
Scheme 2



The extension of this model to the aldol reaction of boron Z enolates was predicted by Evans in 1982, although experimental results were not available at that time.[3a] Recently, Rousn analyzed the diastereofacial selectivity of the aldol reactions of chiral α-methyl aldehydes with propionate and ethyl ketone derived lithium and boron enolates.[5e] While *E* enolates usually provide the diastereoisomer predicted by the Felkin-Anh model,[6] *Z* enolates preferentially provide the anti-Felkin one[3c,5f,7,8,9] (see also **Table 1**). Although chelation has often been invoked to explain these anomalous results,[3c,7b,8a,b] there are many cases where chelation is not applicable, *i.e.* the absence of a chelating group, the presence of a protecting group known to shield from chelation (such as TBDMS), use of a boron enolate which is incapable of further coordination after complexation with the aldehyde carbonyl group. Roush concludes that *"the dominant stereocontrol element that determines aldehyde diastereofacial selectivity is the minimization of gauche pentane interactions in the competing cyclic, chairlike transition states."*[5e] Transition structures **A**, **B**, and **C** were proposed for the aldol reaction on *Z* enolates and chiral α-methyl aldehydes (**Scheme 3**). According to Roush, transition structure **A** (the "normal" Felkin TS) is heavily destabilized by the presence of a (+/-) double gauche pentane interaction between the methyl of the enolate and that of the aldehyde, and should not be considered. When R is smaller than Me, transition structure **B** (the "Roush" TS) is favoured over **C** (the Anti-Felkin TS), and the reaction is 3,4-*syn* selective. When R is bigger than Me, transition structure **C** (which features a +60°, +60° [Me-Me] pentane interaction) is favoured over **B** (which features a -60°, -60° [Me-R] pentane interaction), and the reaction is 3,4-*anti* selective (**Scheme 3**).[5e] Consistent with this analysis, the 3,4-*anti* :*syn* ratio depends on the **C** : **B** ratio, and therefore on the steric requirements of R relative to Me.

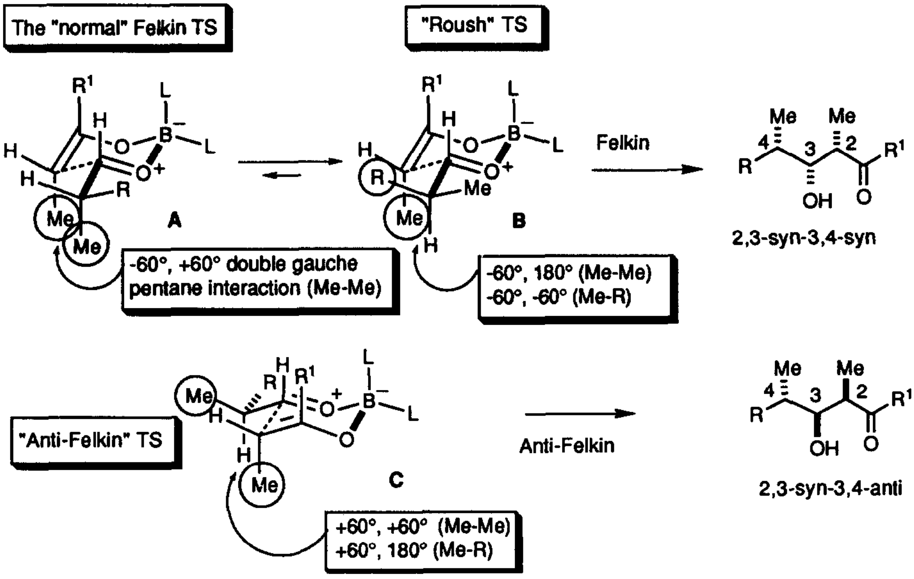
While this model accounts for many experimental results, it is not completely satisfactory. For example, TS **A** should have different ways to relax the (-60°, +60°) double gauche pentane interaction other than a 120° rotation around the O=C-C$_\alpha$ single bond to provide TS **B**. In this paper, we provide a quantitative analysis of the accessible transition structures using our force field approach. This suggests that competition among structures analogous to **A**, **B**, and **C** (and other less important ones) determines the aldehyde diastereofacial selectivity.

Table 1. Experimental results.[a]

		2,3-*syn*		2,3-*anti*-3,4-*syn*			
Aldehyde	R	3,4-*syn*	3,4-*anti*	%	M	R[1]	
Ref.							
3	Ph	**81**	19	-	Li	$C(Me_2)OSiMe_3$	b
	Ph	**89**	11	5	B[c]	SPh	d
	Ph	**86**	14	4	B[e]	Et	f
4	$CH_2=CH$	**75**	25	-	Li	$C(Me_2)OSiMe_3$	g
5	$Me_2C=CH$	**94**	6	-	Li	$C(Me_2)OSiMe_3$	h
6	$MeO_2CCH(Me)CH_2$[i]	45	**55**	-	B[j]	SPh	k
7	c-C_6H_{11}	27	**73**	-	Li	$C(Me_2)OSiMe_3$	k
	c-C_6H_{11}	14	**86**	9	B[e]	Et	f
8	$PhCH_2OCH_2$	33	**67**	-	Li	$C(Me_2)OSiMe_3$	h
	$PhCH_2OCH_2$	35	**65**	14	B[e]	Et	f
9	$AcOCH_2$	23	**77**	-	Li	$C(Me_2)OSiMe_3$	h
10	TBDMS-OCH_2	21	**79**	-	Li	$C(Me_2)OSiMe_3$	h
	TBDMS-OCH_2	46	**54**	7	B[e]	Et	f
11	 [l]	0	**100**	-	B[j]	SPh	m

[a] R; 3,4-*syn*; 3,4-*anti*; M; R[1] are referred to **Scheme 2**. [b] Ref. 7a. [c] $B(OCH_2)_2$ enolate. [d] Ref. 17. [e] $B(n\text{-}Bu)_2$ enolate. [f] This paper. [g] Ref. 7. [h] Ref. 7c. [i] Configuration of the two stereocentres: 2S, 4R. [j] 9-BBN enolate. [k] Ref. 8d. [l] Configuration of the three stereocentres: 2S, 3R, 4S. [m] Ref. 9b.

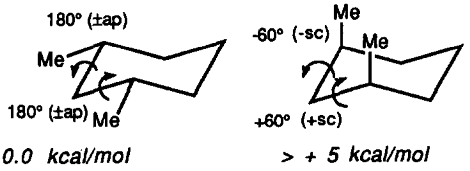
Scheme 3



Results and Discussion

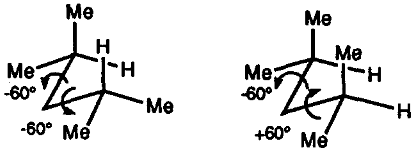
The destabilization known to arise in conformations in which two consecutive dihedral angles assume the values of -60° [-g (*-gauche*) or -sc, (- *syn-clinal*)] and +60° [+g (+ *gauche*) or +sc, (+ *syn-clinal*)] respectively, is more generally known as the *(+/-) double gauche pentane interaction.*[10] This interaction, for instance, occurs in the diaxial conformer of *cis*-1,3-dimethyl cyclohexane, and causes a destabilization of more than 5 kcal mol^{-1} compared to the diequatorial form (**Figure 1**).

Figure 1. *Cis*-1,3-dimethylcyclohexane



This high energy 1,3-dimethyl interaction is also possible in acyclic systems. Thus 2,4-dimethylpentane prefers conformation (**D**) by approximately 1.9 kcal/mol (according to MM2 force field) compared to (+/-) double gauche destabilized conformation (**E**) (**Figure 2**). The 1.9 kcal/mol penalty for the double gauche pentane interaction is substantially less than that associated with the similar interaction in *cis*-1,3-dimethylcyclohexane and results from the ability of the acyclic structure to relax in ways not accessible to the cyclic structure.

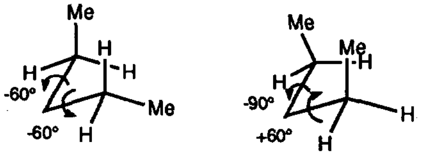
Figure 2. 2,4-Dimethylpentane



(D) *0.0 kcal/mol* (E)+ *1.9 kcal/mol*

Double gauche pentane itself appears even more capable of dissipating the steric interaction between the terminal methyls and opens one of the CH_2-CH_2-CH_2-CH_3 dihedral angles to approximately 90° to relieve strain.[11] In fact (+/-) double gauche pentane is only 0.9 kcal/mol less stable than (-60°, -60°) pentane by MM2 (**Figure 3**).

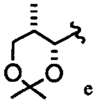
Figure 3. Double gauche pentane



0.0 kcal/mol *+0.9 kcal/mol*

It is conceivable that a transition structure like **A** (**Scheme 3**), possessing a rather long C-C forming bond would be able to relax in a similar way, *i.e.* by opening the C--C(=O)-C-Me dihedral angle to +90°/+100°.

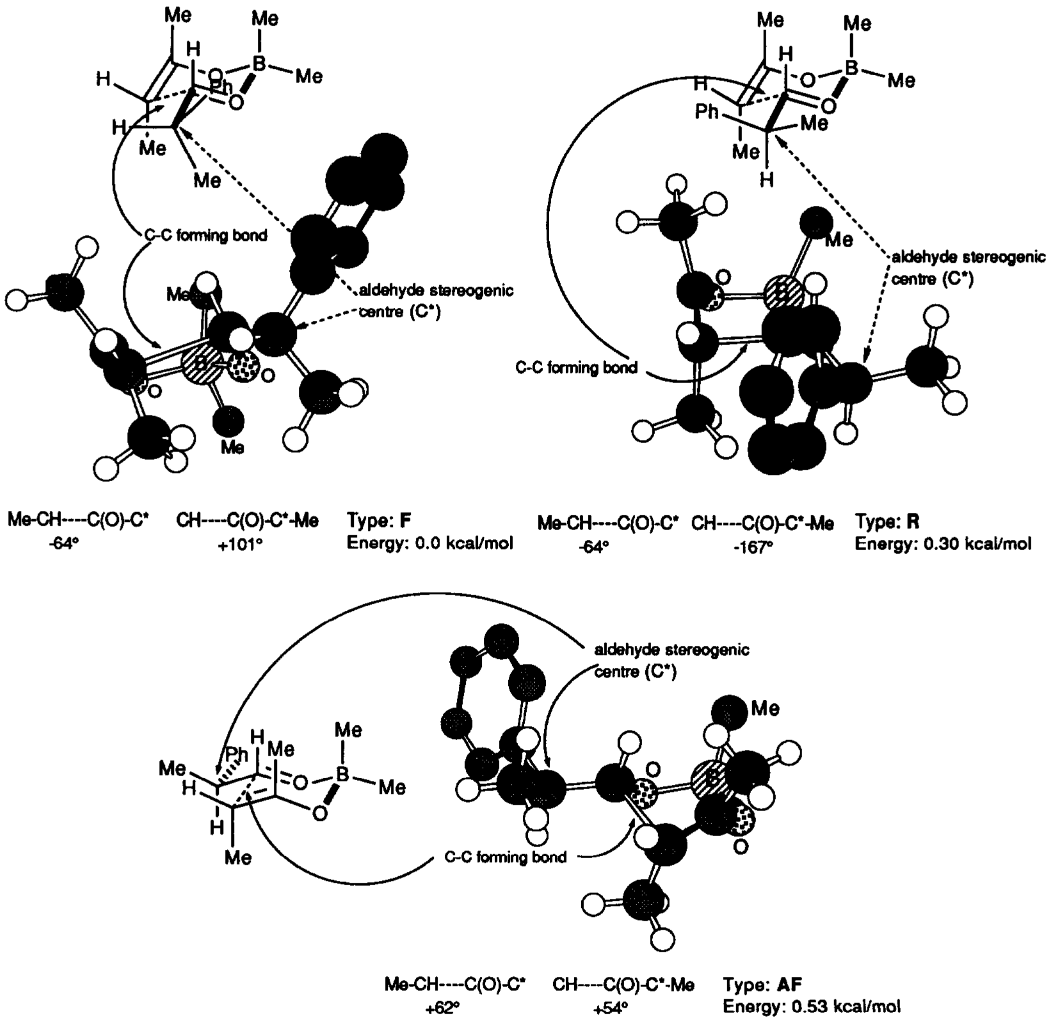
Table 2. Predictions based on computer modelling.[a]

Aldehyde	R	3,4-*syn*	3,4-*anti*	M	R^1
3	Ph	**84**	16	B^d	Me
4	CH_2=CH	**67**	33	B^d	Me
5	Me_2C=CH	**63**	37	B^d	Me
6	$MeO_2CCH(Me)CH_2$[b]	44	**56**	B^d	Me
7	*c*-C_6H_{11}	32	**68**	B^d	Me
8'	*i*-Pr-CH_2OCH_2[c]	36	**64**	B^d	Me
9	$AcOCH_2$	27	**73**	B^d	Me
10	TBDMS-OCH_2	44	**56**	B^d	Me
11	 [e]	22	**78**	B^d	Me

[a] R; 3,4-*syn*; 3,4-*anti*; M; R^1 are referred to **Scheme 2**. [b] Configuration of the two stereocentres: 2S, 4R. [c] *i*-Pr-CH_2OCH_2 was used instead of Ph-CH_2OCH_2. [d] Dimethyl boron enolate. [e] Configuration of the three stereocentres: 2S, 3R, 4S.

Using the parameters developed in our earlier work,[2a] and three new additional parameters which will be discussed in the following text, MacroModel[12] was used to generate accessible transition structures for the boron-enolate aldol reaction of interest (*vide infra* the Section on Computational Methods). A detailed transition structure analysis and prediction of the 3,4-*syn* : 3,4-*anti* ratios was obtained for all the aldehydes (3-11) reported in Table 1 (see **Table 2**). The good agreement between experimental and calculated ratios is self evident by comparing the results shown in **Table 1** and 2. Aldehyde 3 is a particularly simple and explanatory case which is discussed first. The lowest energy transition structures are shown in **Scheme 4**. The Felkin-type structure (F) is characterized by the opening of the CH---C(O)-C*-Me dihedral angle from +60° to 101°, and is the absolute minimum of the computer search. The second structure (+0.30 kcal/mol) is a Roush-type structure (R). Both these structure lead to the major 3,4-*syn* aldol. The third structure (+0.53 kcal/mol) is an Anti-Felkin-

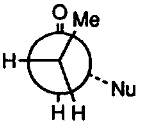
Scheme 4-Transition structures for aldehyde 3.



type structure (**AF**) and leads to the minor 3,4-*anti* product. Two other structures were found within the first 2.5 kcal/mol, but they are comparably higher in energy (+1.64, +1.69 kcal/mol) and less important in the Boltzmann distribution. The same kind of results were obtained for the vinyl substituted aldehydes **4** and **5** (for details see **Table 3** in the Computational Methods Section). Before discussing the meaning of these results we describe the new parameters which were introduced into the force field.

Additional force field parameters.

In addition to the parameters developed in our earlier work,[2a] the C=C-C-H and C=C-C-C torsional parameters developed by Houk, Hoffmann and Broeker[13] were implemented in the force field to treat the vinyl substituted aldehydes **4** and **5**. Therefore the C=C-C-H torsional parameters were assigned values of V_1= 0.00; V_2=0.00; V_3= -0.30 and the C=C-C-C values of V_1= -0.54; V_2=0.44; V_3= -0.60.[13] These new parameters improve the way MM2 reproduces the *ab initio* potential energy surfaces for rotation about the allylic bond of a series of alkenes.[13] The C----C(=O)-C*-C(sp^3) torsional parameters were assigned values of V_1=0.5; V_2=0.0; V_3=0.0. These parameters were set to reproduce the relative stability of the various diastereoisomeric transition structures for nucleophilic additions to propionaldehyde and isobutyraldehyde, derived from the *ab initio* calculations of Houk,[14a] Paddon-Row, and coworkers.[14b,c] According to these investigators the most stable conformer in the nucleophilic additions to propionaldehyde is the one with the methyl *inside* (*e.g.* **12** or **13**) and H *anti*. The preference for the *inside* alkyl rotamer is determined in our force-field by the original MM2 torsional parameters of the aldehyde (*e.g.* C[sp3]-C[sp3]-C=O),[14d] which were left unchanged. Houk's calculations also show that when the α-carbon is secondary (*e.g.* with isobutyraldehyde), the preferred transition-state geometry has one *anti* alkyl and one *inside* (as in **14**), because when alkyls are placed *inside* and *outside*, they cannot simultaneously achieve their preferred dihedral angles.[14a]



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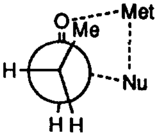

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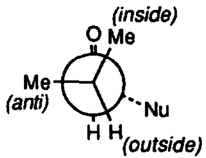

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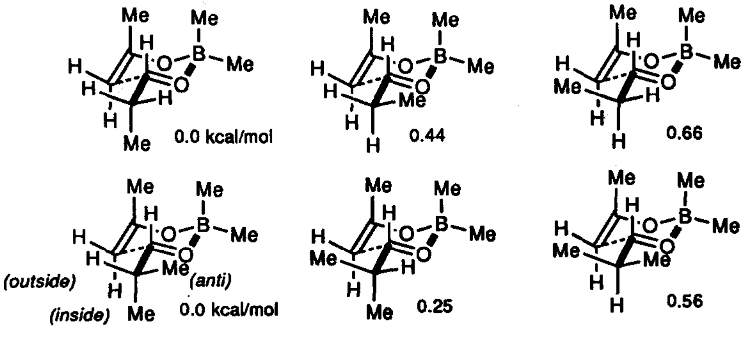
The C----C(=O)-C*-C(sp^3) torsional parameters were determined using as model-structures those reported in Scheme 5, which lack a Z methyl substituent on the enolate and therefore cannot generate (+/-) double gauche pentane interactions.

Scheme 5

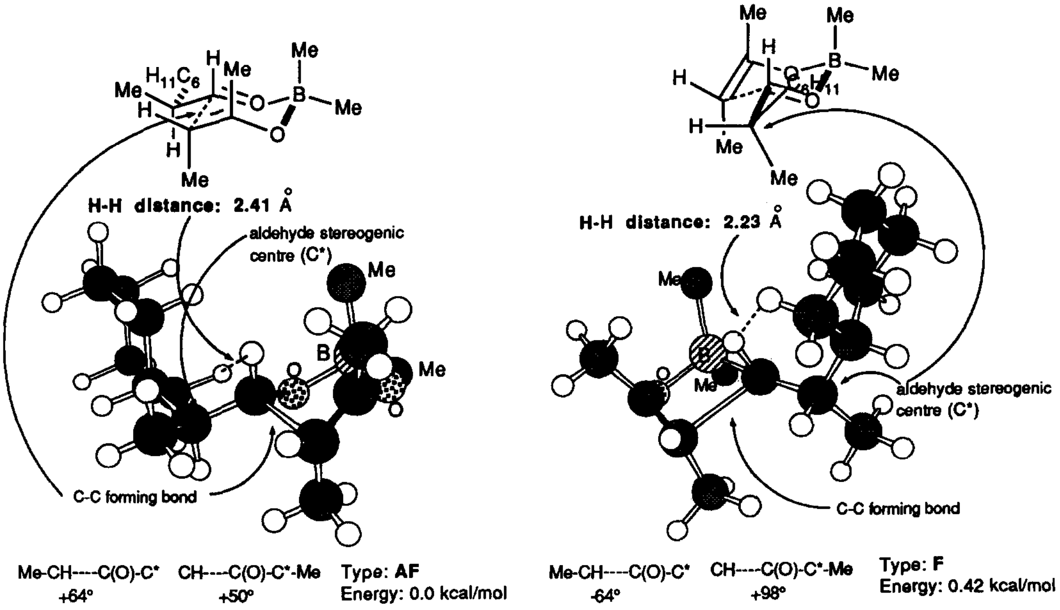


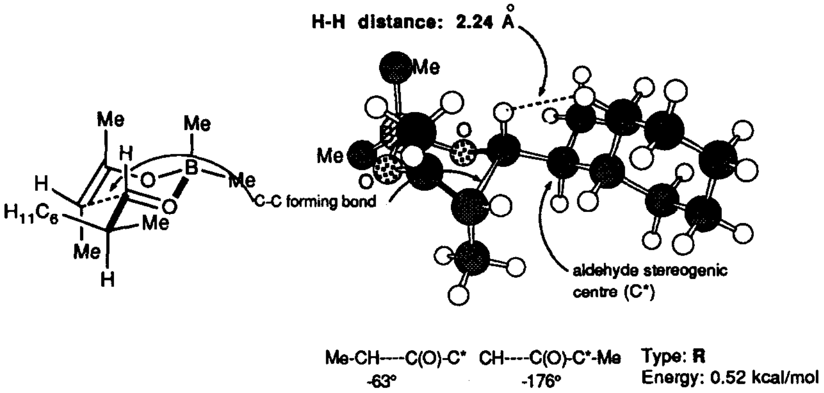
A torsional one-fold barrier of 0.5 (V_1=0.5) was found to be appropriate and gave rise to the energy distribution reported in **Scheme 5**. When these torsional parameters were set to zero (V_1=0.0; V_2=0.0; V_3=0.0) the structure with the two methyls in the *inside* and *outside* positions gave the lowest energy, while the *inside - anti* structure was 0.17 kcal/mol higher. It is worth noting that when the C----C(=O)-C*-C(sp^3) torsional parameters were set to 0.0, 0.0, 0.0, both the overall sense and the degree of selectivity did not substantially change in comparison with the values reported in **Table 2**. Note also that only the Felkin-type structure (F) has the proper *inside - anti* geometry (*i.e.* 14), while the Roush (R) and Anti-Felkin (AF) structures have the substituents *anti* and *outside*.

On the basis of the present results and discussion we agree with Roush that nonbonded interactions play the most important role in determining aldehyde diastereofacial selectivity in the reactions with *Z* enolates, and that stereoelectronic effects can be overridden by steric effects.[5e] We disagree that the Felkin transition structure (**F**) is ruled out by the (+/-) double gauche pentane interactions, because (**F**) can relax by opening the CH---C(O)-C*-Me dihedral angle from +60° to ca. +100°. It is interesting to observe that in the case of aldehyde **5**, the Roush structure (**R**) is destabilized by the -60°, -60° (Me - CH=CMe$_2$ -62°, -46°) interaction and is only third in energy (+0.26 kcal/mol) after the Anti-Felkin (**AF**) (+0.15 kcal/mol) and the Felkin (**F**) (0.0 kcal/mol). In this case, although the quantitative agreement is only moderate, the 3,4-*syn* selectivity of aldehyde **5** can be ascribed to the (**F**) structure.

Why does the selectivity reverse in changing from the relatively small and "flat" Ph-, H$_2$C=CH-, Me$_2$C=CH- (aldehydes **3-5**) to various alkyl groups (aldehydes **6-11**)[15] and the 3,4-*anti* product predominate? Let us examine the case of aldehyde **7** (R=*c*-C$_6$H$_{11}$, **Scheme 6**), where the (**AF**) structure is calculated to be lowest in energy (0.0 kcal/mol), with the (**F**) structure of higher energy (+0.42 kcal/mol).

Scheme 6-Transition structures for aldehyde 7.

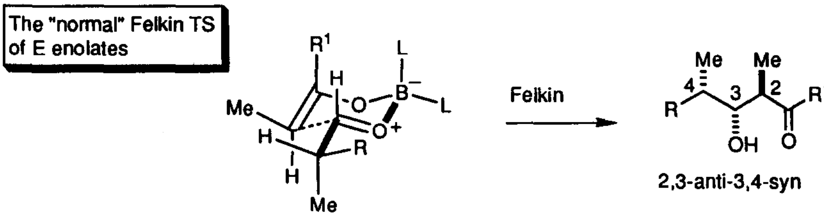




In order to relieve strain-energy the (**F**) structure opens the CH---C(O)-C*-Me dihedral angle from +60° to +98°. In this way the bulky cyclohexyl is pushed towards the aldehyde hydrogen. In the (**AF**) structure the CH---C(O)-C*-Me dihedral angle is around +50° and the [aldehyde hydrogen-*c*-C_6H_{11}] interaction disappears. It is obvious that the Roush structure (**R**) (+0.52 kcal/mol) is destabilized by the -60°, -60° (Me - *c*-C_6H_{11} -63°, -48°) interaction, which is now more important because of the greater size of the cyclohexyl group.

The results of **Table 1** clearly show that when the ketone derived *Z* boron enolates are 2,3-*syn*-3,4-*anti* selective there is a relatively large fraction of the reaction mixture which is represented by the 2,3-*anti*-3,4-*syn* diastereoisomer (up to 25% in the case of aldehyde **15**, Scheme 8). A possible explanation is that, as the transition structures accessible to the *Z* enolate (**AF**, **F**, **R**) are all destabilized to a certain extent for the above mentioned reasons, the *Z* enolate becomes less reactive than the *E* enolate which has access to the preferred Felkin transition structure without any (+/-) double gauche pentane interaction (**Scheme 7**). As a result, the *E* enolate originally present at -78°C (about 3%) plus the amount possibly formed due to enolate equilibration at a higher temperature during the reaction (-78/0°C), adds to the aldehyde at a good rate, while the *Z* enolate gives the condensation product at a lower rate and in a lower yield. Overall the reaction becomes quite sluggish, condensation yields are moderate (45-75%), and the different reactivity of the two enolates (*E* and *Z*) is thus probably responsible of the 2,3-*syn* : 2,3-*anti* ratios observed.

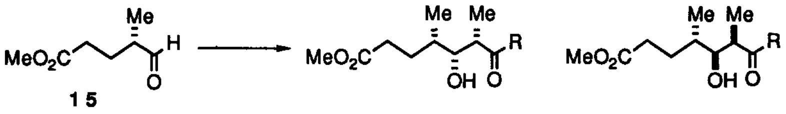
Scheme 7



Not all the reactions examined can be analyzed in such a straightforward way as discussed above. In many cases the balance between the various structures (**F**, **AF**, **R**) is very subtle and there is a large number of different conformations to be considered within the first 2.5 kcal/mol (see **Table 3** in the Computational Methods Section). Nonetheless, it is always clear that all three structures (**F**, **AF**, **R**) play an essential role for determining the reaction stereoselectivity. While our force-field approach correctly predicts the π-facial selectivity of various aldehydes (cf. **Table 1** and **2**), the quantitative prediction of the experimental 3,4-*syn* : 3,4-*anti* ratios is relatively inaccurate in some cases. This may be because some of the experimental results were obtained with lithium enolates, which are known to exist in solution as aggregates.[16] This important feature was not considered in our analysis. It is also possible that chelation effects, due to the presence of polar substituents in either the enolate or the aldehyde, could alter the stereochemical course of aldol reactions involving lithium enolates.

In the case of aldehyde **15** our analysis predicted the correct aldehyde π-facial selectivity when compared to the reaction with a boron enolate, and the incorrect π-facial selectivity when compared to the reaction with a lithium enolate. This is shown in **Scheme 8**.

Scheme 8

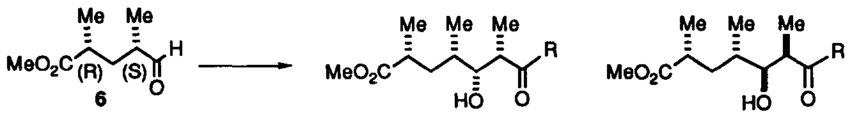


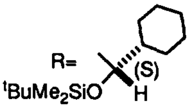
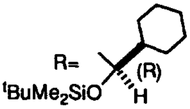
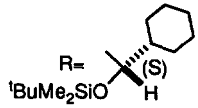
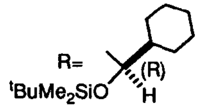
	2,3-*syn*-3,4-*syn*	2,3-*syn*-3,4-*anti*
Lithium enolate,[a] R=Bu^t	74	26
Boron enolate [-B(OCH$_2$)$_2$],[b] R=SPh	45	55
Boron enolate [-B(C$_4$H$_9$-*n*)$_2$],[c,d] R=Et	40	60
Predicted (Me$_2$B enolate),[c] R=Me	23	77

[a] Ref. 7a,b. [b] Ref. 17. [c] This paper. [d] 2,3-*Anti*-3,4-*syn* diastereoisomer is 25% of the mixture, see Experimental.

Another interesting case is shown in **Scheme 9**, an application of Masamune's "reagent control" through the use of a chiral enolate.[18] Aldehyde **6** has a modest intrinsic preference for the 3,4-*anti* diastereoisomer (1.2-1.3:1, see **Table 1** and **Table 2**). Using the chiral (S)-enolate, which is independently acting in favour of the 2(R),3(S) stereochemistry present in the 3,4-*anti* isomer, the selectivity is matched and the ratio is > 100:1. Using the chiral (R)-enolate, which is independently acting in favour of the 2(S),3(R) stereochemistry present in the 3,4-*syn* isomer, is correspondingly mismatched and the product ratio is reduced to 30:1. This complex example was modelled using our force field, and the results were in good agreement with the experiment (**Scheme 9**). This demonstrates that using this approach, we are able to predict both the sense and degree of stereochemical control in boron aldol reactions between chiral ketones and chiral aldehydes, identifying which of the two partners is dominant.[18]

Scheme 9



R		3,4-*syn*	3,4-*anti*
R= 	Expt. (^{n}Bu$_2$B enolate)	<1	>100
R= 	Expt. (^{n}Bu$_2$B enolate)	30	1
R= 	Predicted (Me$_2$B enolate)	1	30.0
R= 	Predicted (Me$_2$B enolate)	12.7	1

Conclusions

In summary, our force field approach suggests that three transition structures (**F**, **AF**, **R**) play a dominant role in controlling π-facial selectivity in *Z* enolate additions to chiral α-methyl aldehydes. The "Felkin" structure (**F**) is characterized by Me-CH---C(O)-C* and CH---C(O)-C*-Me dihedral angles of about -60°/-65° and +100°. The "Roush" structure (**R**) has values of -60°/-65° and ±175°/180°, while the "Anti-Felkin" one (**AF**) has values of +60°/+65° and about +50°. Our analysis suggests that nonbonded interactions play the most important role in determining aldehyde diastereofacial selectivity in the reactions with *Z* enolates, and that stereoelectronic effects are possibly overridden by steric effects. Reactions with aldehydes bearing relatively small and "flat" substituents (Ph-, H_2C=CH-, Me_2C=CH-) are 3,4-*syn* selective ("Felkin" selective) while reactions with aldehydes bearing bulkier groups (various alkyls) are 3,4-*anti* selective ("Anti-Felkin" selective).[15] This result is essentially due to destabilization of both (**F**) and (**R**) structures. In particular, in order to relieve strain-energy structure (**F**) opens the CH---C(O)-C*-Me dihedral angle from +60° to ca. +100°. In this way the bulky substituents (alkyls) are pushed towards the aldehyde hydrogen. In the (**AF**) structure the CH---C(O)-C*-Me dihedral angle is around +50° and the [aldehyde hydrogen - alkyl] interaction disappears. Enolate aggregation and chelation effects in the case of lithium enolates can possibly explain discrepances observed between lithium and boron enolates and between the experimental ratios with lithium enolates and the force field-predicted ratios. Using our approach we are able to predict the stereochemical outcome of reactions between chiral ketones and chiral aldehydes, and to indicate which of the two partners is controlling the stereoselectivity of the process.[18]

Computational Methods

Using the parameters developed in our earlier work,[2a] MacroModel[12] was used to generate accessible transition structures for the boron enolate aldol reaction of interest. The conformational space was searched with the Still-Chang-Guida usage-directed torsional Monte Carlo search[19] as implemented by the BATCHMIN program.[20] In selected cases, we tested for the presence of boat transition structures by including all rotatable bonds of the transition structure "core." Boats were found to be unimportant, because of their high energies relative to the chairs. Two separate Monte Carlo runs were necessary: one with attack at the aldehyde *si*-face (with chiral aldehydes with S absolute configuration this corresponds to the "Felkin" attack) and the other with attack at the *re*-face (with chiral aldehydes with S absolute configuration this corresponds to the "Anti-Felkin" attack). An alternative procedure made use of Multiconformer[21] using a 30° or 60° resolution for each dihedral angle. The two methods usually gave comparable results and were used in concert to make sure that our conformational analysis was not dependent on the search method used.[22] The transition structures found by these searches were analyzed by a Boltzmann distribution at -78 °C of the various conformers (within 2.5 kcal mol^{-1}) leading to each of the possible aldol stereoisomers (see **Table 3** for details). The force field calculations predicted essentially complete *syn* selectivity for *Z* enolates (*cf.* experimental *syn* : *anti* > 95:5), *i.e.* the chair pathway dominates over the boat. The predicted Felkin : Anti-Felkin (3,4-*syn* : 3,4-*anti*) ratios are shown in **Table 2, Scheme 8** and **Scheme 9.**

Table 3. Details of the most important TS found for each aldehyde.

Aldehyde 3 (5 Transition structures found within 2.5 kcal/mol).

3,4-*syn* selective-TS				**3,4-*anti* selective-TS**			
Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy		Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy	
-64°	+101°	F	0.00	+62°	+54°	AF	0.53
-64°	-167°	R	0.30	+68°	-99°	-	1.64
				+64°	+143°	-	1.69

Aldehyde 4 (16 Transition structures found within 2.5 kcal/mol; first 6 shown).

3,4-*syn* selective-TS				**3,4-*anti* selective-TS**			
Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy		Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy	
-63°	+101°	F	0.00	+62°	+52°	AF	0.20
-63°	-170°	R	0.15	+65°	-98°	-	0.77
-63°	+100°	F	0.62	+63°	+50°	AF	0.82

Aldehyde 5 (13 Transition structures found within 2.5 kcal/mol; first 6 shown).

3,4-*syn* selective-TS				**3,4-*anti* selective-TS**			
Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy		Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy	
-64°	+103°	F	0.00	+62°	+52°	AF	0.15
-62°	-168°	R	0.26	+67°	-98°	-	0.50
-63°	+101°	F	0.52	+62°	+52°	AF	0.73

Aldehyde 6 (50 Transition structures found within 2.0 kcal/mol; first 6 shown).

3,4-*syn* selective-TS				3,4-*anti* selective-TS			
Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy		Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy	
-62°	-178°	R	0.00	+64°	+46°	AF	0.25
-62°	-177°	R	0.07	+62°	+52°	AF	0.27
-64°	+97°	F	0.62	+64°	+46°	AF	0.33

Aldehyde 7 (15 Transition structures found within 2.5 kcal/mol; first 6 shown).

3,4-*syn* selective-TS				3,4-*anti* selective-TS			
Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy		Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy	
-64°	+98°	F	0.42	+64°	+50°	AF	0.00
-63°	-176°	R	0.52	+63°	+53°	AF	0.34
-64°	+98°	F	0.73	+64°	+43°	AF	0.83

Aldehyde 8' (47 Transition structures found within 1.65 kcal/mol; first 10 shown).

3,4-*syn* selective-TS				3,4-*anti* selective-TS			
Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy		Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy	
-63°	-172°	R	0.01	+64°	+48°	AF	0.00
-63°	-172°	R	0.07	+63°	+49°	AF	0.01
-63°	-180°	R	0.55	+63°	+53°	AF	0.01
-64°	-172°	R	0.57	+63°	+53°	AF	0.05
-63°	+98°	F	0.69	+63°	+49°	AF	0.14

Aldehyde 9 (46 Transition structures found within 2.5 kcal/mol; first 6 shown).

3,4-*syn* selective-TS				3,4-*anti* selective-TS			
Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy		Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy	
-65°	+178°	R	0.62	+63°	+49°	AF	0.00
-63°	+97°	F	0.68	+63°	+51°	AF	0.07
-63°	-178°	R	0.70	+63°	+50°	AF	0.26

Aldehyde 10 (50 Transition structures found within 2.05 kcal/mol; first 6 shown).

3,4-*syn* selective-TS				3,4-*anti* selective-TS			
Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy		Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy	
-65°	-172°	R	0.00	+63°	+55°	AF	0.09
-64°	-169°	R	0.52	+63°	+51°	AF	0.46
-64°	+96°	F	0.69	+61°	+56°	AF	0.56

Aldehyde 11 (14 Transition structures found within 2.5 kcal/mol; first 8 shown).

3,4-*syn* selective-TS				3,4-*anti* selective-TS			
Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy		Me-CH---C(O)-C*	CH---C(O)-C*-Me	Type/Energy	
-64°	+99°	F	0.68	+64°	+47°	AF	0.00
-65°	+103°	F	0.69	+67°	-89°	-	0.31
-68°	-40°	-	1.02	+64°	+48°	AF	0.81
-62°	-178°	R	1.13	+62°	+140°	-	1.16

Aldehyde 15 - Scheme 8 (50 Transition structures found within 1.87 kcal/mol; first 6 shown).

3,4-*syn* selective-TS			**3,4-*anti* selective-TS**		
Me-CH---C(O)-C*	CH---C(O)-C*-Me	**Type/Energy**	Me-CH---C(O)-C*	CH---C(O)-C*-Me	**Type/Energy**
-62°	-178°	**R** 0.96	+63°	+47°	**AF** 0.00
-62°	-177°	**R** 0.96	+64°	+46°	**AF** 0.63
-64°	+100°	**F** 1.00	+63°	+47°	**AF** 0.89

Aldehyde 6 - Scheme 9 - Reaction with S Enolate (33 Transition structures found within 1.89 kcal/mol; first 10 shown).

3,4-*syn* selective-TS			**3,4-*anti* selective-TS**		
Me-CH---C(O)-C*	CH---C(O)-C*-Me	**Type/Energy**	Me-CH---C(O)-C*	CH---C(O)-C*-Me	**Type/Energy**
-65°	+96°	**F** 1.08	+66°	-92°	- 0.00
-66°	+98°	**F** 1.26	+67°	-92°	- 0.02
-67°	+96°	**F** 1.74	+62°	+54°	**AF** 0.27
-66°	+99°	**F** 1.83	+64°	+56°	**AF** 0.47
-66°	-180°	**R** 1.89	+70°	-93°	- 0.54

Aldehyde 6 -Scheme 9 - Reaction with R Enolate (58 Transition structures found within 2.00 kcal/mol; first 10 shown).

3,4-*syn* selective-TS			**3,4-*anti* selective-TS**		
Me-CH---C(O)-C*	CH---C(O)-C*-Me	**Type/Energy**	Me-CH---C(O)-C*	CH---C(O)-C*-Me	**Type/Energy**
-65°	180°	**R** 0.00	+69°	-91°	- 0.88
-65°	-179°	**R** 0.10	+64°	+55°	**AF** 1.10
-65°	+97°	**F** 0.11	+69°	+35°	**AF** 1.10
-66°	+100°	**F** 0.12	+65°	+49°	**AF** 1.21
-67°	+178°	**R** 0.24	+64°	+55°	**AF** 1.40

Experimental Section

Diastereomeric mixtures relevant for the present study were synthesized by reaction of the *Z*-dibutylboron enolate of diethyl ketone (n-Bu_2OTf, i-Pr_2NEt, CH_2Cl_2, -78°C, Z:$E \geq 97$:3)[3] with various aldehydes [RCH(Me)CHO, CH_2Cl_2, -78°C to -10°C] shown in **Table 1** and in **Scheme 8**. All new compounds were fully characterized by ^1H- and ^{13}C-NMR spectroscopy (reported), IR, MS, and elemental analysis (not reported).

General Procedure for the Aldol Reaction. A dry flask, capped with a rubber septum and flushed with nitrogen was charged with dichloromethane (4.4 ml) and cooled to -78°C. Dibutyl boron triflate (1.0 M solution in dichloromethane, 2.36 ml, 2.36 mmol) was added dropwise under stirring. Diisopropylethylamine (0.82 ml, 4.72 mmol) and subsequently 3-pentanone (0.227 ml, 2.25 mmol) were slowly added. The resulting mixture was stirred at -78°C for 30 min, then the appropriate aldehyde (2.5 mmol) was added dropwise. The reaction mixture was stirred at -78°C for 30 min, then slowly warmed to -10°C and quenched pH 7 phosphate buffer (2 ml). Dichloromethane was evaporated under vacuum, the aqueous phase was extracted with Et_2O (3 x 5 ml), and the combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was dissolved in MeOH

(8.0 ml) and phosphate buffer (1 ml) at 0°C, and treated with 30% H_2O_2 (2 ml). After 2 h stirring at 0°C, methanol was evaporated under vacuum, the resulting mixture was diluted with pH 7 phosphate buffer (2 ml) and extracted with CH_2Cl_2 (3 x 5 ml). The organic phase was washed with saturated brine, dried (Na_2SO_4) and evaporated. The crude product was flash chromatographed to give the desired aldol compound.

Assignment of aldol product stereochemistry. 2,3-*Anti* : 2,3-*syn* and 3,4-*anti* : 3,4-*syn* ratios were determined by ^{1}H-NMR and ^{13}C-NMR spectroscopy (see ref. 3c, 17, and 23). In the case of aldehyde **8**, an authentic mixture of the 2,3-*syn*-3,4-*anti* and 2,3-*anti*-3,4-*anti* diastereoisomers (57:43) was synthesized using a method known to produce this mixture of diastereoisomers (see ref. 25). In the case of aldehydes **8** and **10**, the aldol products were converted to cyclic compounds (**16a-c**) which allowed for correct assignment of stereochemistry from ^{1}H-NMR coupling constants. In the case of aldehyde **15** the aldol products were treated with a catalytic amount of CF_3COOH: only the 3,4-*anti* diastereoisomers cyclized to di-equatorially substituted δ-lactones (**17**, see ref. 7b, 17, 24). Details are reported in the following paragraphs.

Aldol addition to aldehyde 3 (R=Ph). **^{1}H-NMR** ($CDCl_3$, δ), selected data: 3.63 (ddd, CHOH, $J_{CH\text{-}CH}$ = 4.9, 7.5 Hz; J_{CHOH} = 7.5 Hz; 2,3-*anti*-3,4-*syn*; 4% of the mixture); 4.05 (ddd, CHOH, $J_{CH\text{-}CH}$ = 9.4, 2.2 Hz; J_{CHOH} = 3.0 Hz; 2,3-*syn*-3,4-*syn*; 83% of the mixture); 4.22 (ddd, CHOH, $J_{CH\text{-}CH}$ = 8.9, 3.3 Hz; J_{CHOH} = 3.0 Hz; 2,3-*syn*-3,4-*anti*, 13% of the mixture).

^{13}C-NMR ($CDCl_3$, δ), selected data: 7.31 (CH_3; 2,3-*anti*-3,4-*syn*, minor), 7.47 (CH_3; 2,3-*syn*-3,4-*syn*, major), 9.19 (CH_3; 2,3-*syn*-3,4-*syn*, major), 9.70 (CH_3; 2,3-*syn*-3,4-*anti*, minor), 15.28 (CH_3; 2,3-*anti*-3,4-*syn*, minor), 16.88 (CH_3; 2,3-*anti*-3,4-*syn*, minor), 18.30 (CH_3; 2,3-*syn*-3,4-*anti*, minor), 18.93 (CH_3; 2,3-*syn*-3,4-*syn*, major);

34.42 (CH_2; 2,3-*syn*-3,4-*syn*, major), 36.02 (CH_2; 2,3-*anti*-3,4-*syn*, minor);

42.90 (CH; 2,3-*syn*-3,4-*syn* + 2,3-*syn*-3,4-*anti*, major), 44.20 (CH; 2,3-*anti*-3,4-*syn*, minor), 46.83 (CH; 2,3-*syn*-3,4-*syn* + 2,3-*anti*-3,4-*syn*, major), 47.90 (CH; 2,3-*syn*-3,4-*anti*, minor);

75.08 (CHOH; 2,3-*syn*-3,4-*syn*, major), 75.42 (CHOH; 2,3-*syn*-3,4-*anti*, minor), 79.32 (CHOH; 2,3-*anti*-3,4-*syn*, minor);

126.48 (CH=), 127.35 (2 CH=), 128.65 (2 CH=), 143.7 (C=; 2,3-*syn*-3,4-*anti*, minor), 144.11 (C=; 2,3-*syn*-3,4-*syn*, major), 144.68 (C=; 2,3-*anti*-3,4-*syn*, minor);

217.10 (C=O; 2,3-*syn*-3,4-*syn*, major), 217.92 (C=O; 2,3-*anti*-3,4-*syn*, minor).

In this way a 2,3-*syn*-3,4-*syn* : 2,3-*syn*-3,4-*anti* ratio 86:14 was determined.

Aldol addition to aldehyde 7 (R=*c*-C_6H_{11}). **^{1}H-NMR** ($CDCl_3$, δ), selected data: 3.88 (ddd, C$\underline{H}$OH, $J_{CH\text{-}CH}$ = 8.0, 2.6 Hz; J_{CHOH} = 5.7 Hz; 2,3-*anti*-3,4-*syn*; 9% of the mixture), 3.86 (dd, C$\underline{H}$OH, $J_{CH\text{-}CH}$ = 5.5, 4.4 Hz; 2,3-*syn*-3,4-*syn*; 13% of the mixture), 3.78 (ddd, C$\underline{H}$OH, $J_{CH\text{-}CH}$ = 10.0, 2.3 Hz; J_{CHOH} = 2.7 Hz; 2,3-*syn*-3,4-*anti*; 78% of the mixture); 2.78 (dq, COCH, J = 8.0, 7.0 Hz; 2,3-*anti*-3,4-*syn*), 2.76 (dq, COCH, J = 4.4, 7.1 Hz; 2,3-*syn*-3,4-*syn*), 2.66 (dq, COCH, J = 2.3, 7.1 Hz; 2,3-*syn*-3,4-*anti*); 1.15 (d, CH_3, J = 7.1 Hz; 2,3-*syn*-3,4-*syn*), 1.10 (d, CH_3, J = 7.1 Hz; 2,3-*syn*-3,4-*anti*), 1.10 (t, CH_3, J = 6.8 Hz; 2,3-*syn*-3,4-*syn*), 1.10 (t, CH_3, J = 7.0 Hz; 2,3-*anti*-3,4-*syn*), 1.07 (d, CH_3, J = 7.0 Hz; 2,3-*anti*-3,4-*syn*), 1.07 (t, CH_3, J = 7.0 Hz; 2,3-*syn*-3,4-*anti*), 0.94 (d, CH_3, J = 7.1 Hz; 2,3-*syn*-3,4-*syn*), 0.90 (d, CH_3, J = 7.0 Hz; 2,3-*anti*-3,4-*syn*), 0.70 (d, CH_3, J = 7.1 Hz; 2,3-*syn*-3,4-*anti*).

^{13}C-NMR (CDCl$_3$, δ), selected data: 7.43 (CH$_3$; 2,3-*anti*-3,4-*syn*), 7.50 (CH$_3$; 2,3-*syn*-3,4-*syn*), 7.56 (CH$_3$; 2,3-*syn*-3,4-*anti*, major), 8.27 (CH$_3$; 2,3-*syn*-3,4-*anti*, major), 9.72 (CH$_3$; 2,3-*anti*-3,4-*syn*), 10.52 (CH$_3$; 2,3-*syn*-3,4-*syn*), 10.58 (CH$_3$; 2,3-*syn*-3,4-*anti*, major), 10.78 (CH$_3$; 2,3-*syn*-3,4-*syn*), 14.03 (CH$_3$; 2,3-*anti*-3,4-*syn*);

25.97 (CH$_2$; 2,3-*syn*-3,4-*anti*, major), 26.52 (2 x CH$_2$; 2,3-*syn*-3,4-*syn*), 26.53 (CH$_2$; 2,3-*syn*-3,4-*anti*, major), 26.79 (CH$_2$; 2,3-*syn*-3,4-*syn*), 26.81 (CH$_2$; 2,3-*syn*-3,4-*anti*, major), 26.93 (CH$_2$; 2,3-*syn*-3,4-*anti*, major), 27.84 (CH$_2$; 2,3-*syn*-3,4-*syn*), 30.26 (CH$_2$; 2,3-*anti*-3,4-*syn*), 31.07 (CH$_2$; 2,3-*anti*-3,4-*syn*), 31.50 (CH$_2$; 2,3-*syn*-3,4-*syn*), 32.00 (CH$_2$; 2,3-*syn*-3,4-*anti*, major), 34.62 (CH$_2$; 2,3-*syn*-3,4-*anti*, major), 34.88 (CH$_2$; 2,3-*syn*-3,4-*syn*), 35.83 (CH$_2$; 2,3-*anti*-3,4-*syn*);

36.80 (CH; 2,3-*syn*-3,4-*anti*, major), 39.50 (CH; 2,3-*syn*-3,4-*syn*), 39.74 (CH; 2,3-*anti*-3,4-*syn*), 39.89 (CH; 2,3-*syn*-3,4-*anti*, major), 40.20 (CH; 2,3-*anti*-3,4-*syn*), 40.53 (CH; 2,3-*syn*-3,4-*syn*), 46.53 (CH; 2,3-*syn*-3,4-*anti*, 78%), 47.93 (CH; 2,3-*syn*-3,4-*syn*, 13%), 48.90 (CH; 2,3-*anti*-3,4-*syn*, 9%), 71.20 (CHOH; 2,3-*syn*-3,4-*anti*, 78%), 72.76 (CHOH; 2,3-*syn*-3,4-*syn*, 13%), 73.89 (CHOH; 2,3-*anti*-3,4-*syn*, 9%).

In this way a 2,3-*syn*-3,4-*anti* : 2,3-*syn*-3,4-*syn* ratio 86:14 was determined.

Aldol addition to aldehyde 8 (R=PhCH$_2$OCH$_2$). ^{1}H-NMR (CDCl$_3$, δ), selected data: 4.48 (s, OC$\underline{H}_2$Ph, 2,3-*syn*-3,4-*syn*; 30% of the mixture); 4.52 (s, OC$\underline{H}_2$Ph, 2,3-*syn*-3,4-*anti* + 2,3-*anti*-3,4-*syn*, 70% of the mixture); 3.84 (ddd, C$\underline{H}$OH, J$_{CH-CH}$ = 8.4, 3.25 Hz; J$_{CHOH}$ = 3.1 Hz; 2,3-*syn*-3,4-*anti*; 56% of the mixture); 3.90 (m, C$\underline{H}$OH; 2,3-*anti*-3,4-*syn*; 14% of the mixture); 3.91(dd, C$\underline{H}$OH, J$_{CH-CH}$ = 6.6, 4.6 Hz; 2,3-*syn*-3,4-*syn*; 30% of the mixture); 2.76 (dq, CHCO, J=6.6, 7.0; 2,3-*syn*-3,4-*syn*).

^{13}C-NMR (CDCl$_3$, δ), selected data: 7.35 (CH$_3$; 2,3-*anti*-3,4-*syn*, minor), 7.54 (CH$_3$; 2,3-*syn*-3,4-*syn*, major) 7.60 (CH$_3$; 2,3-*syn*-3,4-*anti*, major), 9.24 (CH$_3$; 2,3-*syn*-3,4-*anti*, major), 9.92 (CH$_3$; 2,3-*anti*-3,4-*syn*, minor), 11.80 (CH$_3$; 2,3-*syn*-3,4-*syn*, major), 12.47 (CH$_3$; 2,3-*syn*-3,4-*syn*, major), 13.84 (CH$_3$; 2,3-*syn*-3,4-*anti* + 2,3-*anti*-3,4-*syn*);

34.15 (CH$_2$; 2,3-*syn*-3,4-*anti*, major), 34.98 (CH$_2$; 2,3-*anti*-3,4-*syn*, minor), 34.99 (CH$_2$; 2,3-*syn*-3,4-*syn*, major);

35.86 (CH; 2,3-*syn*-3,4-*syn*, major), 35.89 (CH; 2,3-*anti*-3,4-*syn* + 2,3-*syn*-3,4-*anti*), 48.22 (CH; 2,3-*syn*-3,4-*anti*, major), 48.41 (CH; 2,3-*anti*-3,4-*syn*, minor), 48.70 (CH; 2,3-*syn*-3,4-*syn*, major);

73.19 (CH$_2$O; 2,3-*syn*-3,4-*syn*, major), 73.34 (CH$_2$O; 2,3-*anti*-3,4-*syn* + 2,3-*syn*-3,4-*anti*), 73.83 (CH$_2$O; 2,3-*syn*-3,4-*syn*, major), 74.26 (CH$_2$O; 2,3-*syn*-3,4-*anti*, major), 74.73 (CH$_2$O; 2,3-*anti*-3,4-*syn*, minor);

74.27 (CHOH; 2,3-*syn*-3,4-*syn*, major), 74.90 (CHOH; 2,3-*syn*-3,4-*anti*, major), 75.43 (CHOH; 2,3-*anti*-3,4-*syn*, minor);

127.57 (3 CH=), 128.30 (2 CH=), 137.83 (C=);

215.07 (C=O).

In this way a 2,3-*syn*-3,4-*anti* : 2,3-*syn*-3,4-*syn* ratio 65:35 was determined. An authentic mixture of the 2,3-*syn*-3,4-*anti* and 2,3-*anti*-3,4-*anti* diastereoisomers (57:43) was synthesized from aldehyde **8** **(R=PhCH$_2$OCH$_2$)** with TiCl$_4$ and the (Z) dimethyl-*t*-butyl silyl enol ether of diethylketone (-78°C, CH$_2$Cl$_2$).[25] **^{13}C-NMR** (CDCl$_3$, δ), 2,3-*anti*-3,4-*anti* , selected data: 7.36 (CH$_3$), 14.37 (CH$_3$), 15.21 (CH$_3$), 35.70 (CH$_2$), 35.86 (CH), 48.81 (CH), 72.53 (CH$_2$O), 73.35 (CH$_2$O), 77.50 (CHOH). **^{1}H-NMR** (CDCl$_3$, δ), selected data: 4.50 (s, OC$\underline{H}_2$Ph).

Aldol addition to aldehyde 10 (R=TBDMS-OCH$_2$). **^{1}H-NMR** (CDCl$_3$, δ), selected data: 3.86 (ddd, $C\underline{H}OH$, J_{CH-CH} = 8.2, 3.0 Hz; J_{CHOH} = 3.0 Hz; 2,3-*syn*-3,4-*anti*; 50% of the mixture); 3.92 (dd, $C\underline{H}OH$, J_{CH-CH} = 6.5, 5.5 Hz; 2,3-*syn*-3,4-*syn*; 43% of the mixture); 2.80 (dq, COCH, J= 6.5, 7.0 Hz, 2,3-*syn*-3,4-*syn*).

^{13}C-NMR (CDCl$_3$, δ), selected data: -3.74 (2 x CH$_3$Si; 2,3-*anti*-3,4-*syn*, minor), -3.40 (2 x CH$_3$Si; 2,3-*syn*-3,4-*anti*, major), -3.38 (CH$_3$Si; 2,3-*syn*-3,4-*syn*, major), -3.31 (CH$_3$Si; 2,3-*syn*-3,4-*syn*, major), 7.30 (CH$_3$; 2,3-*anti*-3,4-*syn*, minor), 7.48 (CH$_3$; 2,3-*syn*-3,4-*syn*, major) 7.58 (CH$_3$; 2,3-*syn*-3,4-*anti*, major), 9.09 (CH$_3$; 2,3-*anti*-3,4-*syn*, minor), 9.21 (CH$_3$; 2,3-*syn*-3,4-*anti*, major), 11.01 (CH$_3$; 2,3-*syn*-3,4-*syn*, major), 12.70 (CH$_3$; 2,3-*syn*-3,4-*syn*, major), 13.40 (CH$_3$; 2,3-*syn*-3,4-*anti*, major), 13.92 (CH$_3$; 2,3-*anti*-3,4-*syn*, minor);

25.51 [$(\underline{C}H_3)_3C$-Si; 2,3-*anti*-3,4-*syn*, minor), 25.67 [$(\underline{C}H_3)_3C$-Si; 2,3-*syn*-3,4-*syn*, major), 25.69 [$(\underline{C}H_3)_3C$-Si; 2,3-*syn*-3,4-*anti*, major);

33.99 (CH$_2$; 2,3-*syn*-3,4-*anti*, major), 35.01 (CH$_2$; 2,3-*syn*-3,4-*syn*, major), 35.75 (CH$_2$; 2,3-*anti*-3,4-*syn*, minor);

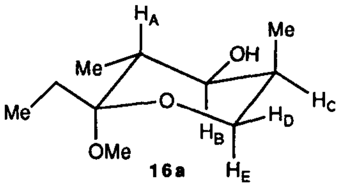
36.06 (CH; 2,3-*anti*-3,4-*syn*, minor), 36.88 (CH; 2,3-*syn*-3,4-*syn*, major), 37.23 (CH; 2,3-*syn*-3,4-*anti*, major), 48.66 (CH; 2,3-*syn*-3,4-*anti* + 2,3-*anti*-3,4-*syn*), 48.93 (CH; 2,3-*syn*-3,4-*syn*, major);

67.40 (CH$_2$O; 2,3-*syn*-3,4-*anti*, major), 67.89 (CH$_2$O; 2,3-*syn*-3,4-*syn*, major), 68.31 (CH$_2$O; 2,3-*anti*-3,4-*syn* , minor).

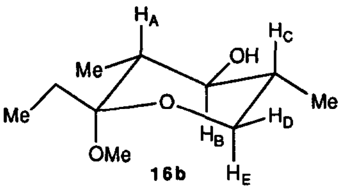
74.64 (CHOH; 2,3-*syn*-3,4-*syn*, major), 75.36 (CHOH; 2,3-*syn*-3,4-*anti*, major), 75.85 (CHOH; 2,3-*anti*-3,4-*syn*, minor).

In this way a 2,3-*syn*-3,4-*anti* : 2,3-*syn*-3,4-*syn* ratio 54:46 was determined.

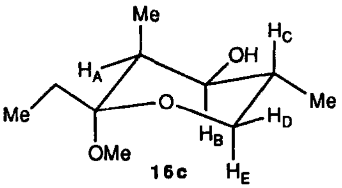
The 2,3-*syn*-3,4-*anti* compounds, originating from both aldehyde **8** (**R=PhCH$_2$OCH$_2$**) and aldehyde **10** (**R=TBDMS-OCH$_2$**) were converted into the cyclic compound shown below (**16a**) by simple transformations (**8**: H$_2$/Pd-C/MeOH; **10**: (a) n-Bu$_4$NF/THF; (b) MeOH/C$_5$H$_6$N$^+$TsO$^-$). Analogously, the 2,3-*syn*-3,4-*syn* compounds were converted into **16b**, and the 2,3-*anti*-3,4-*syn* compounds into **16c**.



16a



16b



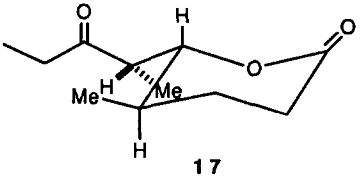
16c

Compound 16a. **^{1}H-NMR** (CDCl$_3$, δ), selected data: 3.87 (ddd, H$_B$, J_{HA-HB} = 10.6 Hz; J_{CHOH} = 5.3 Hz; J_{HB-HC} = 5.3 Hz), 3.76 (dd, H$_D$, J_{HD-HE} = 11.3 Hz, J_{HD-HC} = 2.3 Hz), 3.43 (dd, H$_E$, J_{HD-HE} = 11.3 Hz, J_{HE-HC} = 1.6 Hz). **^{13}C-NMR** (CDCl$_3$, δ): 8.21 (CH$_3$), 9.87 (CH$_3$), 11.06 (CH$_3$), 26.16 (CH$_2$), 34.89 (CH), 35.90 (CH), 46.79 (OCH$_3$), 64.34 (OCH$_2$), 71.41 (OCH), 103.66 (OCO).

Compound 16b. **^{1}H-NMR** (CDCl$_3$, δ), selected data: 3.52 (dd, H$_D$, J_{HD-HE} = 11.4 Hz, J_{HD-HC} = 5.1 Hz), 3.23 (t, H$_E$, J_{HD-HE} = 11.4 Hz, J_{HE-HC} = 11.4 Hz).

Compound 16c. **^{1}H-NMR** ($CDCl_3$, δ), selected data: 3.85 (ddd, H_B, $J_{HA\text{-}HB}$ = 4.7 Hz; J_{CHOH} = 4.7 Hz; $J_{HB\text{-}HC}$ = 10.9 Hz), 3.54 (dd, H_D, $J_{HD\text{-}HE}$ = 11.0 Hz, $J_{HD\text{-}HC}$ = 5.3 Hz), 3.16 (t, H_E, $J_{HD\text{-}HE}$ = 11.0 Hz, $J_{HE\text{-}HC}$ = 11.0 Hz).

Aldol addition to aldehyde 15 (R=$MeO_2C\text{-}CH_2CH_2\text{-}$). After the usual work-up, the crude condensation product was treated with a catalytic amount (5% mol) of CF_3COOH in dichloromethane. After 40 min at room temperature, the mixture was evaporated at reduced pressure and the crude product flash chromatographed (n-hexane-ethyl acetate 60:40) to give two diastereoisomeric δ-lactones. Major lactone (**17**)(42%), stereochemistry: 2,3-*syn*-3,4-*anti*, **^{1}H-NMR** ($CDCl_3$, δ), selected data: 4.45 (dd, C*H*OCO, $J_{CH\text{-}CH}$ = 3.4, 9.8 Hz). **^{13}C-NMR** ($CDCl_3$, δ): 7.42 (CH_3), 8.93 (CH_3), 16.87 (CH_3), 27.39 (CH_2), 29.20 (CH_2), 29.90 (CH_2), 33.63 (CH), 47.79 (CH), 85.09 (CH-O), 170.77 (COO), 211.23 (CO). Lactone methine H resonance in the ^{1}H-NMR spectrum of other similar compounds with 2,3-*syn*-3,4-*anti* stereochemistry: 4.43 (dd, C*H*OCO, $J_{CH\text{-}CH}$ = 3.8, 9.5 Hz),[24] 4.46 (dd, C*H*OCO, $J_{CH\text{-}CH}$ = 2.0, 10.0 Hz),[7b] 4.51 (dd, C*H*OCO, $J_{CH\text{-}CH}$ = 4.2, 8.9 Hz).[17] Minor lactone (5%), stereochemistry: 2,3-*anti*-3,4-*anti*, **^{1}H-NMR** ($CDCl_3$, δ), selected data: 4.43 (dd, C*H*OCO, $J_{CH\text{-}CH}$ = 2.2, 10.0 Hz). **^{13}C-NMR** ($CDCl_3$, δ): 7.52 (CH_3), 12.54 (CH_3), 15.14 (CH_3), 26.33 (2 CH_2), 27.04 (CH_2), 35.40 (CH), 47.67 (CH), 82.98 (CH-O), 171.92 (COO), 212.50 (CO). The 3,4-*syn* compounds, both the 2,3-*syn* (28%) and the 2,3-*anti* (25%) were transformed under these acidic conditions into the corresponding *n*-butyl esters (*n*-BuOH is present as side product of the *n*-Bu_2B-O-R oxidative cleavage). 2,3-*Anti*-3,4-*syn* : **^{13}C-NMR** ($CDCl_3$, δ), selected data: 7.47 (CH_3), 11.10 (CH_3), 13.49 (CH_3), 14.19 (CH_3), 18.95 (CH_2), 28.00 (CH_2), 30.50 (CH_2), 31.49 (CH_2), 34.82 (CH_2), 35.10 (CH), 47.71 (CH), 64.17 (OCH_2), 74.10 (CH-O), 173.82 (COO). 2,3-*Syn*-3,4-*syn* : **^{13}C-NMR** ($CDCl_3$, δ), selected data: 7.49 (CH_3), 9.15 (CH_3), 13.49 (CH_3), 15.39 (CH_3), 18.95 (CH_2), 27.67 (CH_2), 30.50 (CH_2), 31.62 (CH_2), 34.56 (CH_2), 34.98 (CH), 47.01 (CH), 64.03 (OCH_2), 74.49 (CH-O), 174.01 (COO).
In this way a 2,3-*syn*-3,4-*anti* : 2,3-*syn*-3,4-*syn* ratio 60:40 was determined.



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References and Notes

1. Presented in part as a lecture (C. Gennari) at the Seventh European Symposium on Organic Chemistry (7th ESOC, Namur, Belgium, July 15-19, 1991).

2. (a) Bernardi, A.; Capelli, A. M.; Gennari, C.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3576. (b) Bernardi, A.; Capelli, A.M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J.M.; Paterson, I. *Tetrahedron* **1991**, *47*, 3471.

3. Reviews: (a) Evans, D.A.; Nelson, J.V.; Taber, T.R. *Top.Stereochem.* **1982**, *13*, 1. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (c) Heathcock, C.H. In *Asymmetric Synthesis*; Morrison, J.D., Ed.; Academic Press: New York, **1984**; Vol. 3, p.111. (d) Hoffmann, R.W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489. (e) For recent calculations regarding the origin of π-facial diastereoselectivity in nucleophilic additions to chiral carbonyl compounds, see: Frenking, G.; Kœhler, K.F.; Reetz, M.T. *Tetrahedron* **1991**, *47*, 8991; *ibid.* 9005.

4. (a) Hoffmann, R.W.; Zeiss, H.-J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 218. (b) Hoffmann, R.W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3966. (c) Hoffmann, R.W.; Metternich, R.; Lanz, J.W. *Liebigs Ann. Chem.* **1987**, 881. (d) Hoffmann, R.W.; Brinkmann, H.; Frenking, G. *Chem. Ber.* **1990**, *123*, 2387. (e) Brinkmann, H.; Hoffmann, R.W. *Chem. Ber.* **1990**, *123*, 2395. (f) Hoffmann, R.W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555.

5. (a) Roush, W.R.; Adam, M.A.; Harris, D.J. *J. Org. Chem.* **1985**, *50*, 2000. (b) Roush, W.R.; Adam, M.A.; Walts, A.E.; Harris, D.J. *J. Am. Chem. Soc.* **1986**, *108*, 3422. (c) Roush, W.R.; Palkowitz, A.D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348. (d) Roush, W.R. In *Comprehensive Organic Synthesis*; Heathcock, C.H., Ed.; Pergamon Press: Oxford, **1991**; Vol. 2, Chapter 1.1, Pag. 1-53. (e) Roush, W.R. *J. Org. Chem.* **1991**, *56*, 4151. (f) Roush, W.R.; Palkowitz, A.D. *J. Org. Chem.* **1989**, *54*, 3009.

6. For example, see: (a) Heathcock, C.H.; Pirrung, M.C.; Montgomery, S.H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087. (b) Woodward, R.B.; et al. *J. Am. Chem. Soc.* **1981**, *103*, 3210. (c) Tschamber, T.; Waespe-Sarcevic, N.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 621.

7. (a) Buse, C.T.; Heathcock, C.H. *J. Am. Chem. Soc.* **1977**, *99*, 8109. (b) Heathcock, C.H.; Buse, C.T.; Kleschick, W.A.; Pirrung, M.C.; Sohn, J.E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. (c) Heathcock, C.H.; Young, S.D.; Hagen, J.P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095.

8. (a) Masamune, S.; Ellingboe, J.W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526. (b) Masamune, S. In *Organic Synthesis Today and Tomorrow*, Trost, B.M., Hutchinson, C.R., Eds.; Pergamon Press: New York, **1981**; p.199. (c) Masamune, S. *Aldrichimica Acta* **1978**, *11*,23. (d) Masamune, S.; Ali, Sk.A.; Snitman, D.L.; Garvey, D.S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557.

9. (a) Brooks, D.W.; Kellog, R.P. *Tetrahedron Lett.* **1982**, *23*, 4991. (b) Patel, D.V.; VanMiddlesworth, F.; Donaubauer, J.; Gannett, P.; Sih, C. *J. Am. Chem. Soc.* **1986**, *108*, 4603. The outcome of this aldol reaction (Anti-Felkin : Felkin > 99:1) was analyzed by the authors by comparing transition structures analogous to C (favoured) and A, which they note is destabilized by (+/-) double gauche pentane interactions between the two methyl group. (c) For a series of highly Anti-Felkin selective reactions of chiral boron Z enolates with chiral α-methyl aldehydes, see: Evans, D.A.; Polniaszeck, R.P.; DeVries, K.M.; Guinn, D.E.; Mathre, D.J. *J. Am. Chem. Soc.* **1991**, *113*, 7613.

10. (a) Klyne, W.; Prelog, V. *Experientia* **1960**, *16*, 521. (b) Allinger, N.L.; Miller, M.A. *J. Am. Chem. Soc.* **1961**, *83*, 2145. (c) Abe, A.; Jernigan, R.L.; Flory, P. *J. Am. Chem. Soc.* **1966**, *88*, 631. (d) Scott, R.A.; Scheraga, H.A. *J. Chem. Phys.* **1966**, *44*, 3054. (e) Sykora, S. *Collect. Czech. Chem. Commun.* **1968**, *33*, 3514. (f) For a list of interesting applications of the (+/-) double gauche pentane interactions to stereochemical control, see: Roush, W.R. *J. Org. Chem.* **1991**, *56*, 4151 and footnotes 27,28 in that paper.

11. (a) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150. (b) Still, W.C.; Cai, D.; Lee, D.; Hauck, P.; Bernardi, A.; Romero, A. *Lectures in Hetherocyclic Chemistry* **1987**, *9*, 33.

12. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M .; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440. We thank Professor Clark Still (Columbia University, New York) for providing copies of his programs and advice on their use.

13. Broeker, J.L.; Hoffmann, R.W.; Houk, K.N. *J. Am. Chem. Soc.* **1991,** *113*, 5006. For a related study, see: Pettersson, I.; Gundertofte, K. *J. Comp. Chem.* **1991,** *12*, 839.

14. (a) Wu, Y.-D.; Houk, K.N. *J. Am. Chem. Soc.* **1987,** *109*, 908. (b) Wong, S.S.; Paddon-Row, M.N. *J. Chem. Soc., Chem. Commun.* **1991**, 327. (c) Wong, S.S.; Paddon-Row, M.N. *J. Chem. Soc., Chem. Commun.* **1990**, 456. (d) Bowen, J.P.; Pathiaseril, A.; Profeta, S., Jr.; Allinger, N.L. *J. Org. Chem.* **1987,** *52*, 5162.

15. A phenyl group can be viewed as less sterically demanding than the smallest alkyl group (methyl). For example, conformational analyses have shown that the preferred conformation of 1-methyl-1-phenylcyclohexane is that in which the phenyl group mantains an axial orientation with an energy difference between the two conformers of about 0.30-0.34 kcal/mol. See: (a) Allinger, N.L.; Tribble, M.T. *Tetrahedron Lett.* **1971**, 3259. (b) De Beule, H.; Tavernier, D.; Anteunis, M. *Tetrahedron* **1974,** *30*, 3573.

16. For a review, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988,** *27*, 1624.

17. Gennari, C.; Bernardi, A.; Cardani, S.; Scolastico, C. *Tetrahedron* **1984,** *40*, 4059.

18. Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem., Int. Ed. Engl.* **1985,** *24*, 1, and references therein. Reactions of the chiral enolate shown in **Scheme 9** with achiral aldehydes have been modelled with good reproduction of the experimental results [e. g. reaction of the (S)-(9-BBN)-enolate with propionaldehyde: expt. *re-si* ratio ≥ 17:1, calcd. *re-si* ratio 16:1; see ref. 2b].

19. Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989,** *111*, 4379.

20. BATCHMIN is the non interactive modelling program connected to MacroModel. Version 3.1 was used on a Silicon Graphics Iris workstation.

21. Lipton, M.; Still, W. C. *J. Comp. Chem.* **1988,** *9*, 343.

22. Saunders, M.; Houk, K. N.; Wu, Y.-D.; Still, W. C.; Lipton, M.; Chang, G.; Guida, W. C. *J. Am. Chem. Soc.* **1990,** *112*, 1419.

23. Heathcock, C.H.; Pirrung, M.C.; Sohn, J.E. *J. Org. Chem.* **1979,** *44*, 4294.

24. Masamune,S.; Kim, C.U.; Wilson, K.E.; Spessard, G.O.; Georghiou, P.E.; Bates, G.S. *J. Am. Chem. Soc.* **1975,** *97*, 3512.

25. (a) Reetz, M.T. *Angew. Chem., Int. Ed. Engl.* **1984,** *23*, 556. (b) Gennari, C.; Beretta, M.G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986,** *42*, 893.