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Toward the development of a general chiral auxiliary. Part 6: Structural effects on diastereoselection using camphor derived lactams: evaluation of (1*R*,4*S*)-1,7,7-trimethyl-3-azabicyclo[2.2.1]hept-5-en-3-one as a chiral controller

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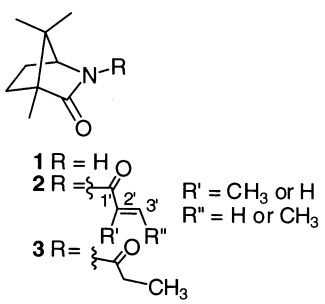
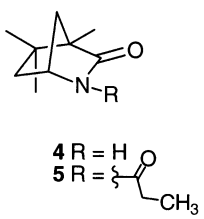
Abstract—A new camphor-derived chiral lactam was designed, prepared and evaluated as a chiral controller in asymmetric Diels–Alder and aldol reactions. The new lactam, bearing a C(5)–C(6) double bond, was anticipated to afford higher diastereofacial selection resulting from the removal of additional steric hindrance to reagent approach distal to the *geminal* dimethyl bridge by comparison with the previously studied saturated analogue (the favored mode approach in the saturated analogue). Surprisingly, a deterioration in the extent of diastereofacial selectivity was observed for both reaction types. These results are interpreted in terms of the geometric changes imposed upon the ring system as a whole by introduction of the unsaturation.

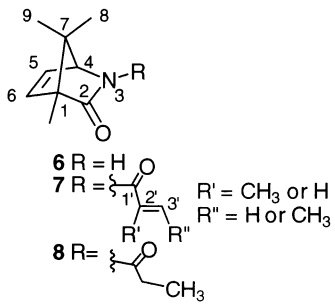
1. Introduction

Over the last 15 years, the use of chiral auxiliaries has been firmly established as an important general strategy to facilitate the preparation of enantiomerically pure compounds.[1–3] An increasingly large number of structurally diverse, naturally and non-naturally derived chiral substances have been shown to have value as auxiliaries in a diverse group of C–C bond forming and functional group transformations.[1,4–6] Camphor derivatives have occupied a central place among this group of compounds.[7–11] Although a number of rationally designed camphor derivatives have been introduced, including examples from our own laboratories,[12–14] few studies have sought to establish the relationship between auxiliary structure and the observed level of diastereoselection within a set of auxiliaries of the same structural class.[15]

Our early studies identified bicyclic lactams **1** and **4**, employed as the derived unsymmetrical imides **2**, **3**, and **5**, as effective chiral auxiliaries for controlling diastereofacial selectivity in Diels–Alder and aldol reactions, including those which create stereogenic centers (with d.e.s of 10–20:1).[12–14] We were interested in further enhancing the diastereofacial selectivity of this class of auxiliary. The following study was undertaken to examine the effect of structural changes in the auxiliary upon diastereofacial selectivity.







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To further probe which structural features of lactams **1** and **4** are the principle contributors to the observed selectivity, we modified the auxiliary by removal of the *endo*-hydrogens of the ethane bridge.[16] We anticipated that the reactive rotamer of imides **7** and **8**, derived from lactam **6**, would show enhanced diastereofacial selectivity resulting from a larger difference in steric interactions between the two carbon and *gem*-dimethyl bridges.

2. Results and discussion

2.1. Preparation of the lactam auxiliary 6

As shown in Scheme 1, the preparation of **6** was envisaged to proceed from the known cyclopentenecarboxylic acid **9**[17] via the highly functionalized dibromocyclopentanecarbonyl carbamate **10**. Attempts to directly generate the *N*-carboxyethyl carbamate **11** from acid **9** did not afford **11** efficiently. However, primary amide **12**, which was obtained from **9** in 76% yield using standard conditions, proved to be a suitable intermediate. Reaction of amide **12** with oxalyl chloride and quenching of the resulting acylisocyanate with ethanol then afforded the desired crystalline *N*-acylcarbamate **11** (mp 58–60°C) in 89% yield.[18] Bromination of the olefin **11** afforded a 3:1 mixture of diastereomeric dibromides **10** and **13**, from which **10** was easily isolated in 72% total yield by a combination of recrystallization of the crude solid product and flash chromatography of the mother liquors. Ring closure of dibromide **10** to lactam **6** was effected in two stages. Cyclization of **10** with sodium bistrimethylsilazide provided the crystalline monobromide **14** in 96% yield. Concomitant elimination of HBr and removal of the *N*-carboxyethyl group with potassium *tert*-butoxide gave the unsaturated lactam **6** as a white crystalline solid (in 87% yield after flash chromatography). The structure of **6** (and thus **10**) was confirmed by spectroscopic data and X-ray analysis of derivatives of **6**. As expected, similar treatment of diastereomeric dibromide **13** with NaHMDS afforded an isomeric bicyclic bromolactam.[14]

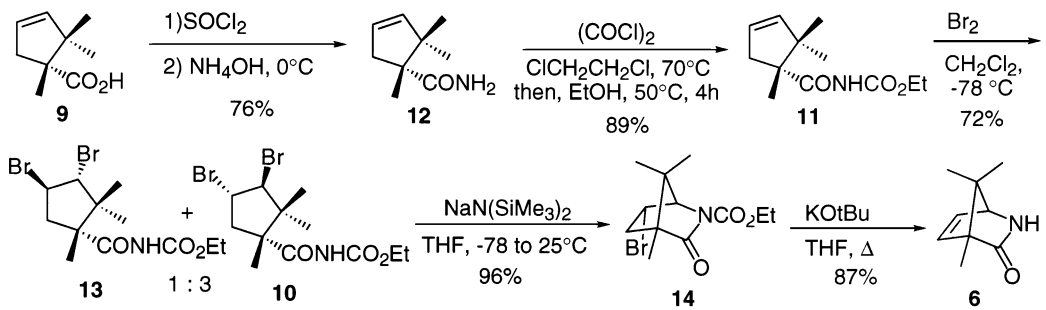
2.2. Asymmetric Diels–Alder reactions of imides derived from 6

The structural model for the sense of asymmetric induction in cycloaddition reactions for **2** (and **1**) is based upon rigidification of the reactive unit via chelation of the imide carbonyl groups which controls rotation about the N_{aux}–$C_{1'}$ bond, and differential allylic nonbonded interactions, between the auxiliary bridgehead C–H bond and either the $C_{3'}$ methylene or $C_{2'}$ methyl groups, which results in preferential reaction via the *s-trans*-rotamer. The diene then approaches the reactive rotamer in an *endo*-orientation from the less hindered face *syn* to the ethane bridge of the auxiliary.[12]

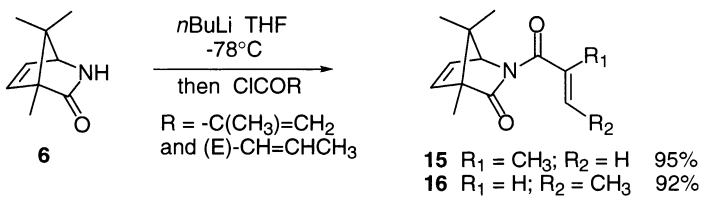
The required chiral dienophiles to test this model were obtained from **6** by acylation of the *N*-lithiated lactam, obtained by deprotonation of **6** with *n*-BuLi, with methacrolyl and crotonoyl chlorides affording the imides **15** and **16** in 95 and 92% yields, respectively (Scheme 2).

As shown in Table 1, when **15** and **16** were reacted with a variety of dienes in the presence of 1.5 equivalents of Lewis acid promoters such as methyl aluminum dichloride or titanium(IV) chloride under the conditions found to afford good d.e. levels with the first generation imides **2** (10 equiv. of diene, 10 mol% of $Al(CH_3)_3$, CH_2Cl_2 (0.25–0.5 M) at −78°C), good yields of adducts were obtained but surprisingly modest d.e. levels were observed.

The absolute stereochemistry of the major adducts **17**–**24** was determined in several ways; surprisingly, standard reductive and basic/nucleophilic cleavage methods

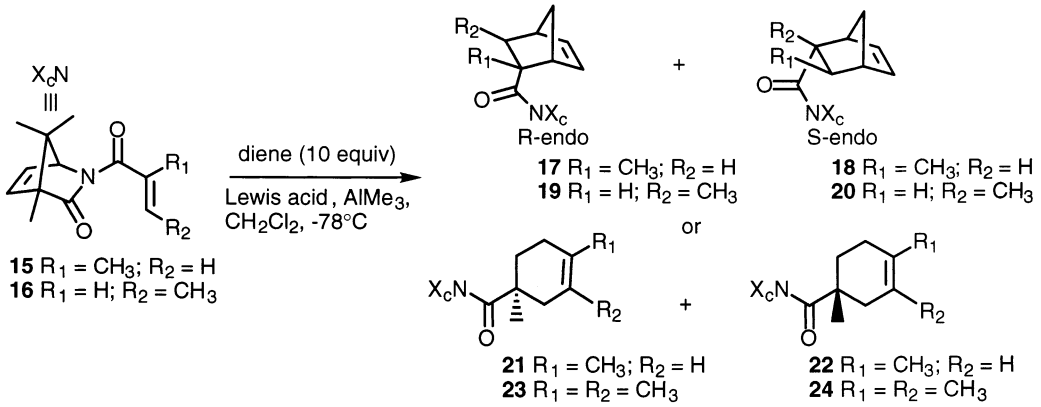


Scheme 1.



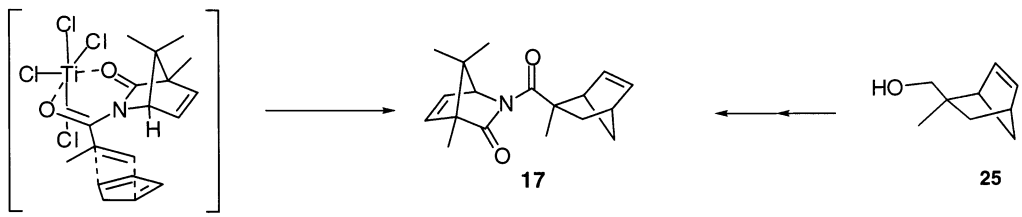
Scheme 2.

Table 1.



Diene	Dienophile	Adducts[a]	Lewis acid	Time (Temp)[b]	Yield (%)	*Endo*-/*Exo*-[c]	*R*/*S* (*R*/*S* from **2**)
	**15**	**17-18**	CH_3AlCl_2	48 h[d]	85	1.8 : 1	3.4 : 1 (91:9)
	**15**	**17-18**	$TiCl_4$	40 min	68	2.7 : 1	2.2 : 1
	**16**	**19-20**	CH_3AlCl_2	4 h	87	19: 1	1.5 : 1(95:5)
	**16**	**19-20**	$SnCl_4$	48 h[d]	52	19: 1	1.7 : 1
	**15**	**21-22**	CH_3AlCl_2	2.5h	70	-	1.7(*S*): 1(*R*)(9:1)
	**15**	**23-24**	$TiCl_4$	24h (-78°C)	51	-	2(*S*): 1(*R*)
	**15**	**23-24**	CH_3AlCl_2	24h (-60°C)	72	-	3.5 (*S*): 1(*R*)(95:5)

[a] Ratios determined by ^1H NMR and/or capillary GC; [b] all reactions conducted at –78 °C unless otherwise specified; [c] *exo*- adducts not pictured; [d] the reaction was held at –78 °C for 7 h. and then warmed to rt.

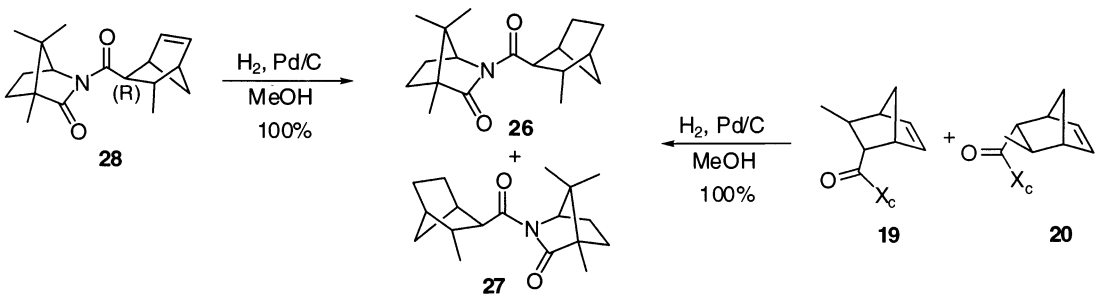


Scheme 3.

were not regioselective for **17–24** as they were for the related systems derived from **2**.[12,16] These results are another manifestation of the effects of introduction of $C_{5,6}$ unsaturation (vide infra). Thus, authentic samples of the adducts were prepared from enantiomerically enriched *endo*-(*R*)-(+) alcohol **25** (~80% e.e., derived from cycloaddition of **2**).[12] Oxidation of **22** with pyridinium dichromate (PDC) in DMF, conversion of the resulting acid to the acid chloride with $SOCl_2$, and treatment with the *N*-lithio derivative of **6** afforded **17** (mp 109–110°C) and **18** spectroscopically identical to the major and minor *endo*-adducts from the cycloaddition of **15** and cyclopentadiene including the sign of the optical rotation (Scheme 3). The *endo*-/*exo*-selectivity for adducts **19** and **20** derived from **16** was determined by comparison to authentic *exo*-compounds obtained from the known racemic *exo*-acid using ^1H NMR and GC analysis.[16,17]

The absolute configuration of the major *endo*-adduct **19** was verified to be (2*R*,3*R*) by catalytic reduction of **19** and **20** to their fully saturated analogues **26** and **27** and comparison to an authentic sample of **27** derived from catalytic reduction of authentic sample (86% d.e.) of the (2*R*,3*R*)-cycloadduct **28** (Scheme 4).[12]

The absolute configuration of the major adducts **21** and **23**, from **15** and isoprene and 2,3-dimethyl-1,3-butadiene, were also determined to possess (*R*)-configuration by catalytic reduction and comparison to authentic samples of known (2*R*)-configuration obtained by use of **1**.[12]



Scheme 4.

Thus, the stereochemical results for reaction of both **15** and **16** with cyclopentadiene, isoprene, and 2,3-dimethyl-1,3-butadiene are consistent with the expected transition state in which the cycloaddition proceeds through the *s-trans* conformer as the reactive rotamer principally from the face opposite the one carbon bridge (Scheme 5).[12] Surprisingly, however, the facial selectivity is uniformly lower than that observed for the related saturated analogues **2**.

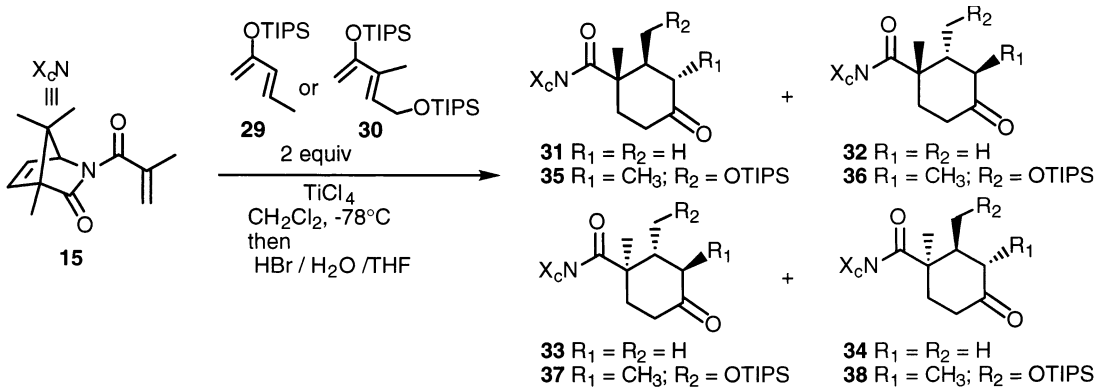
As shown in Table 2, we also evaluated the π-facial selectivity in the reaction of imide **15** with the oxygenated dienes **29** and **30**. For these oxygenated diene substrates, as we had observed previously,[12] optimal results were obtained by slow addition of $TiCl_4$ over 10 hours to a solution of diene **29** or **30** and the chiral dienophile **15** at –40°C and stirring the resulting mixture for a total of 48 hours at –40°C. Owing to the sensitivity of the silyl enol ether intermediates, the crude products were subjected to hydrolysis prior to determination of the enantiomeric composition of the adducts. The major products were established (see Table 2) to have (*S*)-configuration at the stereogenic center (opposite to that of adducts obtained from **2**), possibly arising from *exo*-addition to the *s-cis*-reactive rotamer, although the observed overall selectivity was modest (~2–3:1) both in π-facial and *exo*-/*endo*-selectivity.

For the first time in our experience using the camphor lactam class of auxiliaries, the major products were apparently observed to arise out of the *s-cis*-/*exo*-manifold. However, these results can also be rationalized by a stepwise cycloaddition pathway through the *s-trans*-reactive rotamer as shown in Scheme 5. In the absence of additional definitive data, we currently favor such a stepwise cycloaddition pathway.

2.3. Asymmetric aldol reactions of imides 8 derived from 6

Although a variety of auxiliaries and catalysts function very well in controlling asymmetric aldol reactions, as part of our ongoing studies we examined the utility of lactam **1** and its isomeric counterpart **4** in controlling boron-mediated aldol reactions. Our results indicated that the boron enolates derived from imides **3** and **5** performed comparably to existing imide auxiliaries, although their reactivity was lower.[13,14,19] The observed facial selectivity (Fig. 1) was impacted by two competing factors: firstly, steric interactions between the two carbon bridge of the bicyclic lactam and one of the

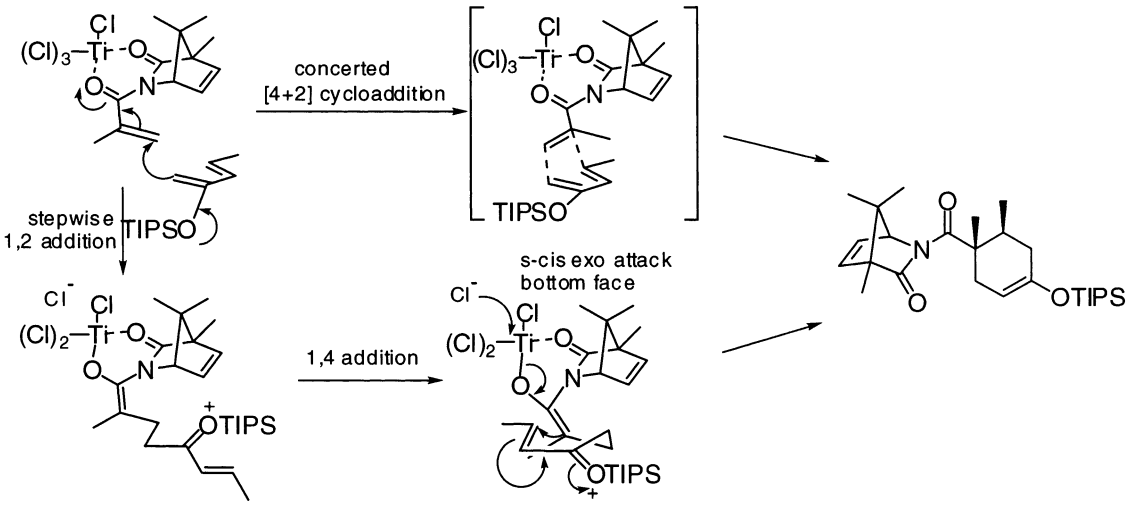
Table 2.



Diene	Dienophile	Adducts[a]	LA	Time (temp.)	Yield (%)	π-Facial (*exo*/*endo*)	**31** (**35**):**32** (**36**):**33** (**37**):**34** (**38**)[b]
29	**15**	**31**–**34**	$TiCl_4$	48 h (−40°C)	71	3:1 (3:1)	6.1:1.5:1.4:1.0
30	**15**	**35**–**38**	$TiCl_4$	48 h (−40°C)	87	6.3:3.7 (6.3:3.7)	5.0:2.5:1.25:1.25

[a] Ratios determined by ^1H NMR and/or capillary GC.

[b] The absolute stereochemistry of **31** was assigned by X-ray crystallography and **35** by comparison with authentic materials derived from **2**. The identity of minor products was tentatively assigned by comparison to authentic adducts obtained from **2** and **29** or **30**, or by analogy.



Scheme 5.

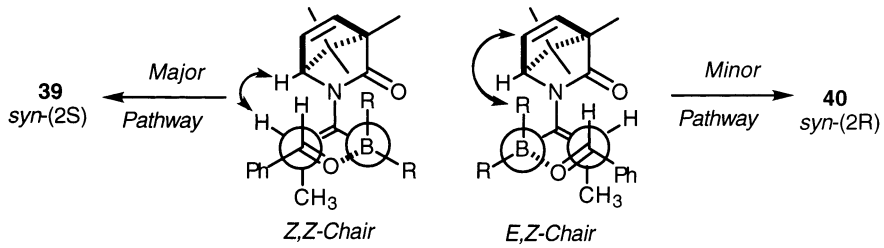
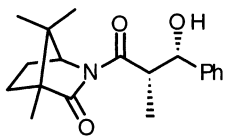


Figure 1. Non-bonded interactions leading to facial selectivity in the boron enolates derived from **8**.

alkyl groups on boron, and secondly, a combination of $A_{1,3}$ strain between the enolate vinyl proton and the auxiliary bridgehead hydrogen and unfavorable dipole–dipole interactions.[13,14]

In accord with this model, we observed the expected increase in facial selectivity upon increasing the size of the alkyl ligand on boron but accompanied by an unfortunate reduction in reactivity.[20] The role of bulky alkyl ligands on boron in controlling facial and 1,2-diastereoselectivity in boron enolate reactions has been documented previously.[19,21,22] Nevertheless, attempts to tailor the structure of the alkyl ligands in boron enolates to achieve high facial selectivity based upon transition state modeling have sometimes resulted in lower than expected selectivity.[23]

To further complement our prior studies and learn more about the origins of the diastereofacial selectivity in the boron-mediated aldol reactions of enolates derived from imides such as **3**, **5**, and **8**, we proceeded to examine the reactivity of the *Z*-boron enolate derived from **8** with benzaldehyde. The results in Table 3 clearly show that the facial selectivity observed for this boron enolate is uniformly lower than observed for the saturated counterpart (1–1.5:1 versus 11.5:1) when the alkyl groups on boron are small (Et).[13,14] The absolute stereochemistry was established by catalytic reduction of a mixture of **39** and **40** (H_2 (1 atm), Pd–C/EtOAc) and comparison to the reduction product of an authentic mixture of the adducts **41** and **42** derived from **3**.[13]



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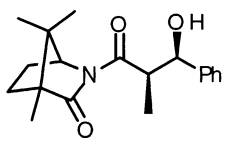


42

As seen from Fig. 1, removal of the *endo* hydrogens in the two carbon bridge would be expected to decrease the energy of the *E,Z*-chair relative to the *Z,Z*-chair transition state, resulting in a decrease in facial selectivity. However, the excellent 2,3 *syn*-diastereoselectivity observed argues for the same highly ordered chair-like transition state seen for most boron enolate aldol reactions.[13,14] It also seems reasonable to assume that the small structural modification in the lactam unit does not markedly affect the relative magnitude of dipole–dipole interactions in the two diastereomeric transition states. In accord with our model, use of the bulky cyclopentyl ligands on boron results in a significant increase of facial selectivity in the expected sense resulting from the increase of the energy of the *E,Z*-chair transition state owing to increased interaction between the axial cyclopentyl group on boron and the two carbon bridge.

Given the assumption that relative dipole–dipole interactions are constant pairwise (comparing the *Z,Z*-transition states (from **3** and **8**) and the *E,Z*-transition states (from **3** and **8**)) for the boron enolates, one can estimate the relative contribution of the diminished

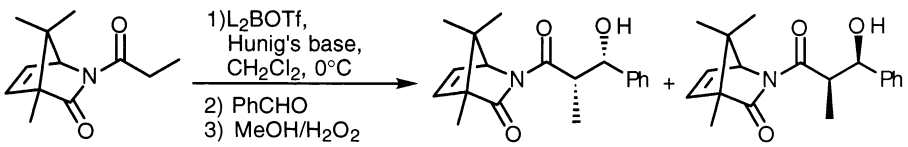
non-bonded interactions with the two carbon bridge compared with the contribution owing to allylic strain. For reaction with benzaldehyde at −78°C, the $\Delta\Delta G^{\ddagger}_{total}$ (enolates **3**–**8**) (R = Et) = −0.8 kcal/mol as determined from the product ratios.[16,24] The overall rates of product formation for R = Et for both enolates derived from **3** and **8** are approximately equal as judged from NMR monitoring. Thus, one can calculate the differential $A_{1,3}$ strain (for the boron enolates from **3** minus **8**) to be −0.17 kcal/mol, and the differential owing to diminished non-bonded interactions (for the boron enolates from **3** minus **8**) to be 0.63 kcal/mol.[16,20,24] While the major portion of the loss in selectivity does result from decreased non-bonded interactions in the transition state leading to **42**, the allylic strain component is ~1/4 the magnitude of the non-bonded interactions and unexpectedly destabilizes the transition state, leading to **41**, which further magnifies the loss in selectivity. It is a fact that magnitude of the increase in allylic strain interactions upon addition of the C(5)–C(6) unsaturation is larger than anticipated, coupled with the fact that the two effects are unexpectedly working in concert, which results in a larger than anticipated reduction in selectivity in the case of aldol reactions.

2.4. Analysis of the geometric changes resulting from introduction of C(5)–C(6) unsaturation

These results were most intriguing, as was the significant loss of diastereofacial selectivity seen for imides derived from unsaturated lactam **4** compared to the saturated analogue **1** in Diels–Alder reactions. Clearly, our initial premise that facial diastereoselection is principally controlled by the differential steric demands of the bridges in **1** seems questionable. During the initial design of **1**, molecular modeling of imides **2** identified an important non-bonded interaction between the bridgehead proton in **2** and the substituent in the α position of the unsaturated imide sidechain. This interaction leads to a modest thermodynamic preference for the *s-trans*-rotamer, and reaction through this rotamer correlates with the observed facial selectivity (although this may not have been so, as articulated by the Curtin–Hammett principle). Taken together, all these data suggested to us that perhaps the loss in diastereoselection arose in significant part from subtle changes in the geometry about the bridgehead carbon in **4** as a result of the geometric changes imparted to the bicyclic ring system as a whole by the introduction of the C(5)–C(6) unsaturation. Qualitatively, one would expect that introduction of the C(5)–C(6) double bond should result in an opening of the angles about the C(5)–C(6) bridge. This would require a closing of the N(3)–C(4)–C(5) and the C(5)–C(4)–C(7) angles, which would move the C(4) bridgehead carbon and its attached hydrogen outward. Thus, one might expect an increase in the non-bonded interaction between the bridgehead hydrogen and the unsaturated acyl sidechain which could result in a loss of the rotamer control essential for high diastereofacial selectivity. Similarly, such geometric changes in the boron enolates derived from **8** could result in an increase in $A_{1,3}$ strain in the boron aldol transition states, which raises the energy of the normally favored *Z*,*Z*-chair transition state, leading to a significant decrease in facial selectivity, since in this instance decreased non-bonded interactions with the bridge would also be expected to diminish selectivity.

Fortunately, we already had in hand data which would allow us to test this hypothesis. X-ray data for the structurally similar Diels–Alder adducts **31**[16] and **43**,[25] derived from **4** and **1**, respectively, were available.[26] Examination of the bond angles and dihedral angles of the bicyclic lactam moiety in these structures was quite revealing. In Table 4, the experimental values for relevant bond angles for **31** and **43** determined by X-ray crystallography are tabulated, along with values calculated via molecular mechanics.[27] Most notably, comparison of the C(6)–C(5)–C(4) angle shows the expected increase (4.0°) resulting from rehybridization at C(5)–C(6). Another significant change results from the expected decrease in the C(5)–C(4)–C(7) angle (2.5°),

Table 3.



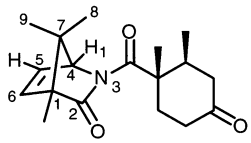
8 **39** **40**

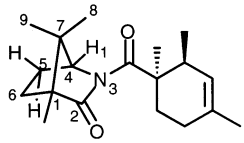
Entry	Boron triflate (equiv.)	Temperature (°C)	Reaction time (h)	% Yield (conversion)	**39**:**40**[a]
1	Et_2BOTf (1.1)	−78	48	85 (100)	1.5:1.0
2	Et_2BOTf (1.1)	−40	48	74 (100)	1.2:1.0
3	Et_2BOTf (1.0)	−45	24	80 (100)	1.0:1.0
4	*n*-Bu_2BOTf (1.0)	−60	36	NR	NR
5	*n*-Bu_2BOTf (1.1)	−40	30	10[b]	1.5:1.0
6	(*c*-$C_5H_9)_2BOTf$ (1.1)	−40	40	69 (83)	5.0:1.0
7	(Et)*tert*-BuBOTf (1.1)	−40	44	41 (50)	1.5:1.0

[a] The ratio was obtained by ^1H NMR after purification.

[b] The pure diastereomers were not isolated; the yield of products was determined by ^1H NMR of the product mixtures; the remainder of the material was unreacted imide.

Table 4.





C(5)–C(6) unsaturated lactam adduct **31**			C(5)–C(6) saturated lactam adduct **43**		
Angle designator	Experimental (°)	Calculated	Angle designator	Experimental (°)	Calculated
C(6)–C(5)–C(4)	105.9	106.8	C(6)–C(5)–C(4)	101.9	101.9
C(5)–C(4)–C(7)	101.5	100.3	C(5)–C(4)–C(7)	104.0	105.0
N(3)–C(4)–C(5)	105.7	102.6	N(3)–C(4)–C(5)	106.1	104.0
N(3)–C(4)–C(7)	100.3	98.8	N(3)–C(4)–C(7)	100.8	99.0
N(3)–C(4)–H(1)	112.6	120.9	N(3)–C(4)–H(1)	114.8	118.0
C(5)–C(4)–H(1)	116.2	117.0	C(5)–C(4)–H(1)	114.8	115.2
C(7)–C(4)–H(1)	118.7	114.0	C(7)–C(4)–H(1)	114.8	113.6

which moves the one carbon bridge back toward the two carbon bridge, presumably owing to removal of non-bonded interactions with the hydrogens attached to C(5) in **43** and the change in hybridization at C(5). The net result of these changes is the opening of the C(5)–C(4)–H(1) and C(7)–C(4)–H(1) bond angles and an increase in the pyramidal character at C(4), effectively moving the bridgehead hydrogen H(1) down and forward toward the N(3) substituent. This change results in apparent destabilization of the normally more reactive *s-trans*-rotamer in the unsaturated imides **7** and an increase in $A_{1,3}$ strain in the boron enolate derived from **8**, both of which result in decreased facial selectivity in reactions of these intermediates.

Importantly, these results suggest a strategy to further enhance the facial selectivity in structurally related chiral controller molecules. Functionalization of the C(8) methyl group with a bulky substituent should have two beneficial consequences. By increasing the C(8)–C(7)–C(9) bond angle, as the result of buttressing interactions with the C(8) methyl group, the C(1)–C(7)–C(4) angle should decrease and the N(3)–C(4)–C(7) angle open, effectively flattening the C(4) bridgehead carbon. These changes should result in significantly reduced interactions between the bridgehead hydrogen and the nitrogen substituent, as well as increased steric shielding of the face of the reactive rotamer of the nitrogen linked substituent *syn* to the one carbon bridge. Efforts to test this hypothesis and develop even more selective chiral controller molecules based on the bicyclic lactam template will be reported shortly.

3. Experimental

3.1. Introduction

All non-aqueous reactions were conducted in flame or oven-dried glassware under an argon atmosphere and were stirred magnetically unless otherwise noted. Air-sensitive reagents and solutions were transferred via syringe (unless noted otherwise) and were introduced to the reaction vessel through a rubber septum. Solids were introduced under a positive pressure of argon. Temperatures, other than room temperature, refer to bath temperatures unless otherwise indicated. The phrase 'concentrated in vacuo' refers to removal of solvents by means of a Buchi rotary-evaporator attached to a water aspirator (15–30 mmHg) followed by pumping to a constant weight (<1 mmHg).

Purification by flash chromatography was performed using the indicated solvent system on EM Reagents silica gel 60 (230–400) mesh. For acid sensitive compounds, silica gel was deactivated with 5% triethylamine in hexanes. Analytical thin-layer chromatography (TLC) was performed using EM silica gel 60 F-254 pre-coated glass plates (0.25 mm). Visualization was effected by short-wave UV illumination or by dipping into a solution of *p*-anisaldehyde (prepared by mixing 15 mL *p*-anisaldehyde, 3 mL glacial acetic acid, 10 mL concentrated H_2SO_4, and 260 mL of 95% ethanol) followed by heating on a hot plate. Purification by Prep 500 MPLC was accomplished using a Porasil column (particle size 37–55 mm, 125 Å). HPLC separation of diastereomers was performed on a 25×10 mm Prep Nova-Pak HR Silica column (particle size 6 mm, 60 Å).

Reagent-grade solvents were used without purification for all extractions and work-up procedures. Deionized water was used for all aqueous reactions, work-ups, and for the preparation of all aqueous solutions. Reaction solvents were dried and purified according to published literature procedures by distillation under argon or vacuum from an appropriate drying agent: stock solutions of *n*-butyllithium in hexanes were titrated using diphenylacetic acid. Cyclopentadiene was freshly cracked before use. Benzaldehyde was freshly distilled prior to use.

Proton and carbon NMR spectra were obtained on General Electric QE-300 (300 MHz), Bruker WH-400 (400 MHz), or Varian VXR-5000 (500 MHz) spectrom-

eters. Infrared (IR) spectra were recorded on a Perkin–Elmer 1610 FT-IR spectrophotometer. Low resolution mass spectra were obtained using a Hewlett–Packard 5970 mass selective detector coupled to an HP 5890 gas chromatograph, or measured by the national mass spectrometry facility at the University of California, Riverside. High resolution mass spectra were obtained at the University of California, Riverside. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. X-Ray structure determinations were performed using an Enraf–Nonius CAD4 diffractometer with calculations performed with the Molecular Structures Corporation TEXAN crystallographic software package.

3.2. (1*R*)-1,2,2-Trimethylcyclopent-3-ene carboxamide 12

To the neat carboxylic acid **9**[17] (20.1 g, 0.131 mol) was added thionyl chloride (11.0 mL, 18.0 g, 0.151 mol). The flask was equipped with a calcium sulfate drying tube and the reaction mixture was allowed to stir for 24 h. The solution was diluted with dry Et_2O (10 mL) and added dropwise over 30 min to a 30% ammonium hydroxide solution (58 mL) with stirring at 0°C. The reaction mixture was allowed to warm to rt over 1 h and stirred for an additional 2 h at rt. The solution was diluted with 200 mL of Et_2O and the phases were separated. The aqueous layer was extracted with Et_2O (3×50 mL) and the combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhyd. $MgSO_4$, filtered, and concentrated in vacuo to afford 17 g of crude material as a yellow oil. Flash chromatography of the crude product on silica gel eluting with 30% EtOAc/hexanes provided the amide **12** as a white solid (15.2 g, 76%), mp 149–152°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75–5.50 (m, 4H), 2.98 (d, J=16.3 Hz, 1H), 2.21 (d, J=16.3 Hz, 1H), 1.24 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.96, 141.05, 125.74, 54.27, 48.47, 42.39, 23.57, 23.01, 20.85; IR (KBr): 3450, 3169, 2963, 1641, 1460, 1398 cm^{-1}; $[\alpha]_D^{23}$ +105.5 (*c* 4.3, CH_2Cl_2). Anal. calcd for $C_9H_{15}NO$: C, 70.54; H, 9.87. Found: C, 70.67; H, 9.85%.

3.3. (1*R*)-1,2,2-Trimethylcyclopent-3-ene carboethoxycarboxamide 11

To a magnetically stirred solution of amide **12** (15.2 g, 99.0 mmol) in dry 1,2-dichloroethane (150 mL) was added a solution of freshly distilled oxalyl chloride (12.1 mL, 17.6 g, 139 mmol) in 1,2-dichloroethane (70 mL) dropwise via an addition funnel over 30 min. The solution solidified during the first 10 min of the addition of the oxalyl chloride but became homogeneous by the end of the addition. The reaction mixture was heated to 65–70°C for 20 h. The oil bath was then allowed to cool to 50°C and absolute ethanol (5.8 mL, 4.6 g, 99 mmol) was added. The solution was refluxed for 4 h before allowing the solution to cool to rt. The reaction mixture was washed with water (2×200 mL) and brine (200 mL), dried over anhyd. $MgSO_4$, filtered, and concentrated in vacuo to afford 21.5 g of crude material as a yellow solid. The crude product was purified by flash chromatography on silica gel eluting with 20% EtOAc/hexanes to provide *N*-acylcarbamate **74** as a white solid (19.9 g, 89%), mp 58–60°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (s, 1H), 5.77–5.74 (m, 1H), 5.66–5.64 (m, 1H), 4.25 (q, J=7.1 Hz, 2H), 2.95 (d, J=16.8 Hz, 1H), 2.32 (d, J=16.8 Hz, 1H), 1.33 (t, J=7.1 Hz, 3H), 1.27 (s, 3H) 1.09 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.63, 150.46, 142.18, 126.23, 61.64, 55.56, 48.91, 42.02, 23.78, 23.12, 19.59, 13.90; IR (film): 3302, 2977, 1763, 1702, 1508, 1191, 1038 cm^{-1}; $[\alpha]_D^{23}$ +21.7 (*c* 2.0, CH_2Cl_2).

3.4. (1*R*,3*R*,4*S*)-3-4-Dibromo-1,2,2-trimethylcyclopentane carboethoxycarboxamide 10

To a magnetically stirred solution of the *N*-acylcarbamate **11** (1.5 g, 51.0 mmol) in CH_2Cl_2 (250 mL) at −78°C was added a solution of bromine (2.6 mL, 8.1 g, 51 mmol) in CH_2Cl_2 (44 mL) dropwise via an addition funnel over 1.5 h. After the addition, the reaction mixture was allowed to stir for 1 h before quenching at −78°C with 5% aqueous $NaHCO_3$ solution (70 mL). The biphasic mixture was allowed to warm to rt. The phase was separated and the organic layer was washed with portions of water (2×100 mL) and brine (100 mL). The organic phase was dried over anhyd. $MgSO_4$, filtered, and concentrated in vacuo to afford 21.5 g of crude material as a yellow solid. The crude product was purified by recrystallization from 300 mL of 20% EtOAc/hexanes to obtain 12.2 g of a white solid. Flash chromatography of the mother liquor eluting with 20% EtOAc/hexanes provided an additional 1.9 g of a white solid to yield **10** (14.1 g, 72%), mp 139–141°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (s(br), 1H), 4.59 (d, J=9.4 Hz, 1H), 4.34–4.29 (m, 3H), 2.86 (dd, J=15.1, 6.1 Hz, 1H), 2.32 (dd, J=14.9, 10.7 Hz, 1H), 1.36–1.32 (m, 6H), 1.08 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.95, 150.36, 66.95, 62.49, 54.96, 51.28, 48.28, 44.69, 22.31, 20.98, 20.31, 14.19; IR (film): 3280, 2979, 1766, 1683, 1513, 1180, 1036 cm^{-1}; $[\alpha]_D^{23}$ +50.9 (*c* 2.2, CH_2Cl_2). Anal. calcd for $C_{12}H_{19}Br_2NO_3$: C, 37.42; H, 4.97. Found: C, 37.42; H, 5.07%.

3.5. (1*S*,4*R*,6*S*)-6-Bromo-4,7,7-trimethyl-2-azabicyclo[2.2.1]-5-hepten-3-one 14

To a magnetically stirred solution of dibromide **67** (7.06 g, 18.3 mmol) in THF (220 mL) at −78°C was added a 1.0 M solution of sodium hexamethyldisilazide in THF (18 mL, 18 mmol) dropwise over 30 min. After the addition was complete, the yellow solution was allowed to stir at −78°C for 2 h then at rt for an additional 3 h. The cloudy white reaction mixture was quenched with saturated aqueous NH_4Cl solution and diluted with Et_2O (200 mL). The phases were separated and the organic layer was washed with water (75 mL) and brine (75 mL), dried over anhyd. $MgSO_4$, filtered, and concentrated in vacuo to afford 6.02 g of crude material. The crude product was purified by flash chromatography on silica gel eluting with 30% EtOAc/hexanes to provide bromide **14** as a white solid (5.31 g, 96%), mp 95–96°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.61–4.56 (m,

1H), 4.38–4.28 (m, 3H), 2.49 (dd, $J=14.7$, 9.5 Hz, 1H), 1.89 (dd, $J=14.7$, 4.0 Hz, 1H), 1.38 (t, $J=7.1$ Hz, 3H), 1.07 (s, 3H), 1.05 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.90, 152.13, 69.72, 63.33, 57.15, 50.11, 47.26, 41.59, 19.76, 18.60, 14.79, 9.71; IR (film): 2970, 1791, 1760, 1723, 1293, 1027 cm^{-1}; $[\alpha]_D^{23}$ +50.4 (*c* 2.4, CH_2Cl_2).

3.6. (1*S*,4*R*)-4,7,7-Trimethyl-2-azabicyclo[2.2.1]-5-hepten-3-one 6

A stirred solution of potassium *tert*-butoxide (6.2 g, 55 mmol) in THF (150 mL) at reflux was treated dropwise with a solution of monobromide **14** (5.31 g, 17.7 mmol) in THF (140 mL) over 1.5 h. After the addition was complete, the solution was allowed to slowly cool to rt over 4 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (11.6 mL) and stirred for 30 min, the suspension was filtered and concentrated in vacuo to afford 3.45 g of crude material. Flash chromatography of the crude on silica gel eluting with 50% EtOAc/hexanes yielded the lactam **58** as a white solid (2.3 g, 87%), mp 160°C (subl.); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.60 (dd, $J=5.3$, 2.3 Hz, 1H), 6.52 (s(br) , 1H), 6.09 (dd, $J=5.3$, 1.4 Hz, 1H), 3.78 (s, 1H), 1.09 (s, 3H), 1.05 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.78, 141.58, 140.42, 84.86, 72.03, 66.47, 64.19, 20.49, 7.87; IR (KBr): 3214, 3068, 2989, 2962, 2928, 1699, 1676 cm^{-1}; $[\alpha]_D^{23}$ −284.3 (*c* 1.8, CH_2Cl_2). Anal. calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67. Found: C, 71.37; H, 8.87%.

3.7. (1*S*,4*R*)-2-(2-Methyl-2-propenoyl)-4,7,7-trimethyl-2-azabicyclo[2.2.1]-5-hepten-3-one 15

To a stirred solution of lactam **6** (0.61 g, 4.0 mmol) in THF (18 mL) at −78°C was added a 1.4 M solution of *n*-BuLi in hexanes (2.9 mL, 4.0 mmol) over 10 min. The reaction mixture was allowed to stir at −78°C for 15 min before removing the cold bath and allowing the solution to warm to rt over 30 min. The solution was cooled to −78°C prior to the dropwise addition of freshly distilled methacryloyl chloride (0.39 mL, 0.42 g, 4.0 mmol). The solution was then allowed to stir at −78°C for 1.5 h and then quenched with satd aq. NH_4Cl solution (5 mL). The cold bath was removed and the biphasic mixture was diluted with Et_2O (30 mL). The phases were separated and the organic phase was washed with water (2×20 mL) and brine (20 mL), dried over anhyd. $MgSO_4$, filtered, and concentrated in vacuo to afford a yellow oil. The crude product was purified by flash chromatography on silica gel eluting with 10% EtOAc/hexanes to provide imide **15** as a clear, viscous oil (0.84 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.80 (dd, $J=5.4$, 2.5 Hz, 1H), 6.10 (dd, $J=5.4$, 1.5 Hz, 1H), 5.43 (s, 1H), 4.68 (d, $J=1.7$ Hz, 1H), 1.99 (s, 3H), 1.18 (s, 3H), 1.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.46, 170.23, 140.00, 139.85, 138.44, 120.04, 67.45, 64.96, 64.75, 18.93, 18.52, 18.46, 7.27; IR (film): 2971, 1748, 1682, 1668, 1325, 1192 cm^{-1}; $[\alpha]_D^{23}$ −93.0 (*c* 2.3, CH_2Cl_2). Anal [HRMS (CI)]: *m*/*z* (MH^+) calcd for $C_{13}H_{18}NO_2$: 220.1338. Found: 220.1331.

3.8. (1*S*,4*R*)-2-(3-Methyl-2-propenoyl)-4,7,7-trimethyl-2-azabicyclo[2.2.1]-5-hepten-3-one 16

To a stirred solution of lactam **6** (0.23 g, 1.5 mmol) in THF (7 mL) at −78°C was added a 1.4 M solution of *n*-BuLi in hexanes (1.1 mL, 1.5 mmol) over 10 min. The reaction mixture was allowed to warm to −50°C over 1 h. The solution was then cooled to −78°C prior to the addition of freshly distilled crotonoyl chloride (0.14 mL, 0.16 g, 1.5 mmol) over 5 min. The solution was allowed to stir at −78°C for 2 h and was quenched with saturated aqueous NH_4Cl solution (3 mL). The cold bath was removed and the biphasic mixture was diluted with Et_2O (30 mL). The phases were separated and the organic phase was washed with water (2×10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 0.39 g of yellow oil. The crude material was purified by flash chromatography on silica gel eluting with 10% EtOAc/hexanes to provide **16** as a white solid (0.30 g, 92%), mp 69–70°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21–7.09 (m, 2H), 6.75 (dd, $J=5.2$, 2.5 Hz, 1H), 6.12 (dd, $J=5.2$, 1.6 Hz, 1H), 4.87 (s, 1H), 1.94 (d, $J=5.6$ Hz, 3H), 1.18 (s, 3H), 1.09 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.91, 165.52, 145.44, 141.19, 139.32, 123.74, 67.49, 66.20, 65.95, 19.63, 19.23, 18.73, 8.06; IR (film): 2971, 1745, 1679, 1639, 1344, 1197 cm^{-1}; $[\alpha]_D^{23}$ −1.4 (*c* 1.2, CH_2Cl_2). Anal. [HRMS (CI)]: *m*/*z* (MH^+) calcd for $C_{13}H_{18}NO_2$: 220.1338. Found: 220.1327.

3.9. General procedure for Diels–Alder reactions of imides 15 and 16 with alkyl dienes: (1*S*,4*R*)-2-[(3′*R*,4′*R*,6′*R*)-4′-methylbicyclo[2.2.1]heptene-4′-carbonyl]-4,7,7-trimethyl-2-azabicyclo[2.2.1]-5-hepten-3-one 17 and (1*S*,4*R*)-2-[(3′*S*,4′*S*,6′*S*)-4′-methylbicyclo[2.2.1]heptene-4′-carbonyl]-4,7,7-trimethyl-2-azabicyclo[2.2.1]-5-hepten-3-one 18 and *exo*-diastereoisomers

To a stirred solution of imide **15** (73 mg (0. 33 mmol) in CH_2Cl_2 (1.2 mL) at −78°C was added a 2.0 M solution of $Al(CH_3)_3$ in hexanes (17 μL, 0.033 mmol). The solution was allowed to stir for 10 min before the addition of a 1.0 M solution of CH_3AlCl_2 in hexanes (0.5 mL, 0 .50 mmol). After 15 min, cyclopentadiene (0.27 mL, 0.22 g, 3.3 mmol) was added dropwise down the side of the flask over 5 min (other dienes added dropwise via syringe pump over 2.5–3 h). The reaction mixture was allowed to stir for 40 min and was then quenched with aqueous 1 M HCl solution (0.5 mL). The reaction flask was removed from the cold bath and the biphasic mixture was allowed to warm to rt. The phases were separated and the organic layer was dried over anhyd. $MgSO_4$ and filtered. To the organic solution was added Celite (1 g) and EtOAc (5 mL). The suspension was allowed to stir for 15 min before filtration through a thin pad of Celite and concentrated in vacuo to provide a yellow solid. Purification of the cycloadduct by flash chromatography on silica gel eluting with 10% EtOAc/hexanes yielded a white solid (74 mg, 78%). ^{1}H NMR and GC analysis of the material indicated four products in a 5.2:1.3:2.5:1.0 ratio which

were assigned as (*R*)-*endo*-/(*S*)-*endo*-/*exo*-/*exo*-adducts, respectively: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.79–6.68 (m, 4H), 6.27–5.95 (m, 12H), 4.90 (s, 1H), 4.84 (s, 1H), 4.69 (s, 1H), 4.64 (s, 1H), 3.32 (s, 1H), 3.17 (s, 1H), 3.05 (s, 3H), 2.78–2.73 (m, 4H), 2.19 (dd, J=12.7, 3.9 Hz, 1H), 1.82–1.74 (m, 6H), 1.63–1.48 (m, 8H), 1.41 (s, 12H), 1.16 (s, 12H), 1.09–1.01 (m, 24H); IR (film): 2961, 1748, 1668, 1313, 1190 cm^{-1}. Anal. calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12. Found: C, 76.00; H, 8.27%.

The absolute stereochemistry of the *exo*-products was not determined. The major *endo*-products **17** and **18** were separated on a semi-preparative HPLC column eluting with 10% Et_2O/hexane and fully characterized. The (*R*)-*endo*-adduct **17** was obtained as a white solid (mp 109–110°C): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (dd, J=5.3, 2.5 Hz, 1H), 6.10–6.07 (m, 3H), 4.65 (s, 1H), 3.06 (s, 1H), 2.78 (s, 1H), 1.82 (s, 2H), 1.59 (s, 1H), 1.56 (s, 1H), 1.42 (s, 3H), 1.16 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.62, 177.57, 140.33, 138.75, 137.24, 136.95, 68.52, 65.54, 64.62, 52.79, 51.26, 45.85, 42.22, 40.31, 23.83, 19.22, 18.97, 7.78. The absolute stereochemistry of **17** was confirmed by single-crystal X-ray analysis.[16] (*S*)-*endo*-adduct **18**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (dd, J=5.3, 2.5 Hz, 1H), 6.14–6.04 (m, 3H), 4.85 (s, 1H), 3.18 (s, 1H), 2.73 (s, 1H), 1.80–1.74 (m, 1H), 1.64–1.59 (m, 3H), 1.51 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.65, 177.01, 140.59, 138.86, 137.17,136.95, 68.26, 65.68, 65.59, 52.63, 50.81, 46.15, 41.84, 40.00, 23.95, 19.10, 19.02, 7.78.

3.9.1. (1*S*,4*R*)–2-[(3′*R*,4′*R*,5′*S*,6′*R*)-5′-Methylbicyclo-[2.2.1]heptene-4′-carbonyl]-4,7,7-trimethyl-2-azabicyclo-[2.2.1]-5-hepten-3-one 19 and (1*S*,4*R*)-2-[(3′*S*,4′*S*,5′*R*,6′*S*)-5′-methylbicyclo[2.2.1]heptene-4′-carbonyl]-4,7,7-trimethyl-2-azabicyclo [2.2.1]-5-hepten-3-one 20. Using the above general procedure, imide **16** (56 mg, 0.25 mmol) upon reaction with cyclopentadiene afforded after chromatographic purification (SiO_2, 10% EtOAc/hexanes) an inseparable mixture of **19** and **20** as a colorless oil (65 mg (90%); this was a 1.5:1.0 mixture of (*R*)-*endo*/(*S*)-*endo*, >19.0:1.0 *endo*/*exo* by ^{1}H NMR and GC analysis). Adducts **19** and **20** were characterized as a mixture: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.75 (dd, J=5.4, 2.5 Hz, 1H), 6.71 (dd, J=5.4, 2.6 Hz, 1H), 6.38 (dd, J=5.6, 3.2 Hz, 1H), 6.34 (dd, J=5.6, 3.2 Hz, 1H), 6.18 (dd, J=5.3, 1.4 Hz, 1H), 6.13 (dd, J=5.3, 1.4 Hz, 1H), 5.77 (dd, J=5.6, 2.7 Hz, 1H), 5.71 (dd, J=5.6, 2.7 Hz, 1H), 4.83 (s, 1H), 4.71 (s, 1H), 3.46 (t, J=3.8 Hz, 1H), 3.34 (t, J=3.8 Hz, 1H), 3.02 (s, 1H), 2.51 (s, 2H), 2.15–2.04 (m, 2H), 1.72–1.62 (m, 2H), 1.46–1.35 (m, 3H), 1.20–1.06 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.48, 179.19, 174.20, 173.91, 141.11, 140.64, 139.70, 139.07, 138.87, 138.76, 131.38, 131.01, 67.39, 67.23, 67.13, 65.72, 65.58, 65.46, 52.73, 51.91, 49.66, 49.44, 47.17, 46.85, 46.79, 46.26, 36.60, 35.16, 20.52, 20.41, 19.22, 19.14, 18.85, 7.71, 7.63; IR (film): 2963, 1744, 1689, 1329, 1196 cm^{-1}. HRMS (CI): m/z (MH^+) calcd for $C_{18}H_24NO_2$: 286.1807. Found: 286.1813.

The absolute stereochemistry of the major adduct **19** was proven by GC comparison of **26** and **27**, the products of catalytic reduction (H_2 (1 atm)/Pd–C in EtOH) of the above mixture of **19** and **20**, with **26** obtained by catalytic reduction of **28**[12] under the same conditions.

3.9.2. (1*S*,4*R*)-2-[(4′*R*)-1′,4′-Dimethylcyclohexene-4′-carbonyl]-4,7,7-trimethyl-2-azabicyclo[2.2.1]-5-hepten-3-one 21 and (1*S*,4*R*)-2-[(4′*S*)-1′,4′-dimethylcyclohexene-4′-carbonyl]-4,7,7-trimethyl-2-azabicyclo[2.2.1]-5-hepten-3-one 22. Using the above general procedure, imide **15** (65 mg, 0.30 mmol) upon reaction with isoprene (added slowly via syringe pump) and quenching with saturated aqueous NH_4Cl solution (5 mL) afforded after chromatographic purification (SiO_2, 5% EtOAc/hexanes) (60 mg, 70%) an inseparable mixture (1.7:1, (4′*R*)-/(4′*S*)- by ^{1}H NMR and GC analysis) of **21** and **22** as a colorless oil which was characterized as a mixture: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77 (dd, J=5.3, 2.5 Hz, 2H), 6.11 (dd, J=5.3, 1.3 Hz, 2H), 5.33 (s, 2H), 4.81 (s, 1H), 4.74 (s, 1H), 2.70 (d, J=17.3 Hz, 1H), 2.51 (d, J=16.6 Hz, 1H), 2.34–2.26 (m, 1H), 2.18–1.86 (m, 8H), 1.80–1.63 (m, 4H), 1.29–1.27 (m, 9H), 1.18 (s, 6H), 1.07–1.05 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.25, 177.78, 177.74, 140.38, 140.33, 139.02, 138.92, 132.95, 132.57, 119.34, 119.30, 69.48, 69.39, 65.78, 65.72, 64.69, 64.54, 42.65, 42.58, 34.45, 33.96, 30.69, 29.70, 27.79, 27.69, 23.23, 23.21, 20.51, 19.87, 19.27, 19.10, 19.00, 7.94; IR (film): 2925, 1745, 1674, 1234 cm^{-1}; HRMS (CI): m/z (MH^+) calcd for $C_{18}H_{26}NO_2$: 288.1964. Found: 288.1961.

The structure and absolute stereochemistry of the major adduct **21** were proven by GC comparison of the products of catalytic reduction (H_2 (1 atm)/Pd–C in EtOH) of the above mixture of **21** and **22**, with the reduction product of the known (4′*R*)-adduct of **2** (R′=CH_3; R″=H) and isoprene.[12]

3.9.3. (1*S*,4*R*)-2-[(4′*R*)-1′,2′,4′-Trimethylcyclohexene-4′-carbonyl]-4,7,7-trimethyl-2-azabicyclo[2.2.1]-5-hepten-3-one 23 and (1*S*,4*R*)-2-[(4′*S*)-1′,2′,4′-trimethylcyclohexene-4′-carbonyl]-4,7,7-trimethyl-2-azabicyclo[2.2.1]-5-hepten-3-one 24

3.9.3.1. Procedure 1. Using the above general procedure, imide **15** (52 mg, 0.24 mmol) was treated with a 1.0 M solution of CH_3AlCl_2 in hexanes (0.36 mL, 0.36 mmol) then 2,3-dimethylbutadiene added slowly. After quenching, isolation, and chromatographic purification (SiO_2, 10% EtOAc/hexanes) an inseparable mixture of **23** and **24** was obtained as a colorless oil (52 mg, 72%) shown to be 3.5:1 (4′*R*)/(4′*S*) by ^{1}H NMR and GC analysis). Adducts **23** and **24** were characterized as a mixture: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (dd, J=5.1, 2.4 Hz, 2H), 6.11 (d, J=5.3 Hz, 2H), 4.80 (s, 1H), 4.75 (s, 1H), 2.62 (d, J=17.3 Hz, 1H), 2.42 (d, J=16.5 Hz, 1H), 2.36–2.27 (m, 1H), 2.15–2.09 (m, 1H), 2.02–1.95 (m, 6H), 1.82–1.66 (m, 2H), 1.62–1.59 (m, 12H), 1.28 (s, 3H), 1.24 (s, 3H), 1.18 (s, 6H), 1.07–1.04 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.20, 177.15, 177.75, 177.72, 140.36, 139.02, 138.97, 138.90, 124.25, 124.04, 123.90, 123.86, 69.53, 69.35, 65.77,

65.73, 64.57, 64.52, 43.62, 40.88, 40.64, 40.57, 40.41, 39.72, 31.14, 30.77, 30.10, 29.42, 23.71, 23.37, 20.74, 20.01, 19.29, 19.13, 19.00, 18.59, 16.55, 7.94; IR (film): 2930, 1744, 1674, 1310, 1234 cm^{-1}. HRMS (CI): m/z (MH^+) calcd for $C_{19}H_{28}NO_2$: 302.2120. Found: 302.2114.

The structure and absolute stereochemistry of the major adduct **23** were proven by GC comparison of the products of catalytic reduction (H_2 (1 atm)/Pd–C in EtOH) of the above mixture of **23** and **24**, with the reduction product of the known (4′*R*)-adduct of **2** (R′ = CH_3; R″ = H) and 2,3-dimethylbutadiene.[12]

3.9.3.2. Procedure 2. Using the above general procedure, imide **15** (52 mg, 0.24 mmol) was treated with a 1.0 M solution of $TiCl_4$ in hexanes (0.36 mL, 0.36 mmol) then 2,3-dimethylbutadiene was added slowly. After quenching with pyridine, isolation, and chromatographic purification (SiO_2, 10% EtOAc/hexanes) an inseparable mixture of **23** and **24** was obtained as a colorless oil (37 mg, 51%) shown to be 2:1, (4′*R*)/(4′*S*) by ^1H NMR and GC analysis.

3.10. General procedure for Diels–Alder reactions of imides 15 and 16 with oxygenated dienes: (1*S*,4*R*)-2-[(1′*S*,2′*S*)-1′,2′-dimethyl-4′-oxo-1′-cyclohexanecarbonyl]-4,7,7-trimethyl-2-azabicyclo[2.2.1]-5-hepten-3-one 31 and diastereomers 32–34

To a stirred mixture of imide **15** (50 mg, 0.23 mmol) and of (3*E*)-2-triisopropylsilyloxy-1,3-pentadiene (0.11 g, 0.45 mmol) in CH_2Cl_2 (0.6 mL) at −40°C was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (0.23 mL 0.23 mmol) over 10 h via syringe pump. The reaction mixture was allowed to stir for 48 h at −40°C and was quenched with pyridine (1.0 mL). The cloudy yellow solution was allowed to warm to rt before being filtered through a pad of Celite. The organic solution was concentrated in vacuo to obtain 0.15 g of a yellow oil. The crude product was dissolved in dry THF (7 mL) and the solution was cooled to 0°C, at which time acetyl bromide (28 μL, 47 mg, 0.38 mmol) was added followed by H_2O (7 μL). The cooling bath was removed after 1 h and the yellow solution was allowed to stir for 3 h at rt. The reaction mixture was quenched with aqueous 5% $NaHCO_3$ solution followed by dilution with H_2O (5 mL) and Et_2O (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (2×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhyd. $MgSO_4$, filtered, and concentrated in vacuo to provide a yellow oil. Flash chromatography purification on silica gel eluting with 30% EtOAc/hexanes yielded a colorless oil (49 mg, 71%). ^1H NMR analysis indicated a mixture of four diastereomers **31**–**34** in a 5.7:1.4:1.3:1.0 ratio. Isolation of the major cycloadduct **108** was achieved through separation on a semi-preparative HPLC column eluting with 15% Et_2O/hexane. Concentration in vacuo afforded a white solid which was recrystallized from *n*-heptane/Et_2O (mp 109–110°C): ^1H NMR (300 MHz, $CDCl_3$): δ 6.84 (dd, J = 5.2, 2.5 Hz, 1H), 6.12 (d, J = 5.2 Hz, 1H), 4.78 (s, 1H), 3.17–3.10 (m, 1H), 2.56–2.40 (m, 1H), 2.38–2.27 (m, 3H), 2.19–2.12 (m, 1H), 1.32 (s, 3H), 1.20 (s, 3H), 1.10 (s, 3H), 1.09 (s, 3H), 0.93 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.49, 178.39, 177.98, 140.74, 139.46, 70.39, 66.29, 64.71, 47.75, 46.43, 38.49, 34.94, 31.96, 19.76, 19.38, 17.28, 16.39, 8.41; IR (film): 2968, 1741, 1716, 1671, 1240, 1181 cm^{-1}. Anal. calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31. Found: C, 71.21; H, 8.43%.

The structure and absolute stereochemistry of **31** was unambiguously determined by single-crystal X-ray analysis.[16] The structures and stereochemistry of remaining minor diastereomers **32**–**34**, which were not further characterized, were assigned tentatively based upon analogy.

3.10.1. Diastereomers of (1*S*,4*R*)-2-[2′,4′-dimethyl-3′-triisopropylsilyloxymethyl cyclohexanecarbonyl]-4,7,7-trimethyl-2-azabicyclo[2.2.1]-5-hepten-3-one 35–38.

Using the above general procedure for oxygenated dienes, imide **65** (53 mg, 0.24 mmol) and (2*E*)-3-methyl-4-triisopropylsilyloxy-2,4-pentadien-1-ol (0.19 g, 0.45 mmol) afforded 0.15 g of crude cycloadducts as a colorless oil. The resulting product mixture was subjected to hydrolysis at 0°C–rt by exposure in THF to acetyl bromide (20 μL, 33 mg, 0.27 mmol) and H_2O (5 μL). After quenching with aqueous 5% $NaHCO_3$ solution, isolation, and chromatographic purification (SiO_2, 10% EtOAc/hexanes) a mixture of adducts **35**–**38** was obtained as a colorless oil (86 mg, 87%), shown to be a 4:2:1:1 mixture of adducts **35**–**38** by ^1H NMR analysis. This was characterized as a mixture: ^1H NMR (300 MHz, $CDCl_3$): δ 6.81 (dd, J = 5.1, 2.2 Hz, 2H), 6.76 (dd, J = 5.2, 2.5 Hz, 2H), 6.14–6.10 (m, 4H), 4.89 (s, 1H), 4.86 (s, 1H), 4.76 (s, 1H), 4.72 (s, 1H), 4.01–3.89 (m, 3H), 3.82–3.61 (m, 6H), 3.27–3.23 (m, 4H), 3.01–2.77 (m, 8H), 2.67 (q, J = 6.3 Hz, 4H), 2.43–2.23 (m, 8H), 1.86–1.81 (m, 3H), 1.72 (s, 3H), 1.65 (s, 6H), 1.56 (s, 3H), 1.51 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 1.35 (s, 3H),1.21–1.01 (m, 116H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.98, 213.19, 210.81, 210.55, 178.00, 177.77, 176.87, 176.21, 140.96, 140.80, 140.44, 139.97, 139.14, 139.06, 138.99, 138.82, 69.62, 69.52, 66.00, 65.21, 64.93, 62.37, 61.97, 55.00, 47.85, 46.07, 45.87, 44.74, 44.42, 40.55, 40.52, 37.19, 36.94, 34.89, 32.78, 32.46, 32.04, 31.64, 20.49, 19.44, 19.19, 19.01, 18.94, 17.95, 17.70, 14.44, 12.08, 11.87, 11.58, 7.88; IR (film): 2942, 2867, 1745, 1715, 1674, 1310, 1264, 1108 cm^{-1}. HRMS (DCI): m/z (MH^+). Calcd for $C_{28}H_{48}NO_4Si$: 490.3353. Found: 490.3353.

The structures and stereochemistry of adducts **35**–**38** were assigned by analogy with adducts **31**–**34**.

3.11. (1*S*,4*R*)-2-Propionoyl-4,7,7-trimethyl-2-azabicyclo[2.2.1]-5-hepten-3-one 8

To a stirred solution of lactam **6** (0.53 g, 3.5 mmol) in THF (20 mL) at −78°C was added a 1.4 M solution of *n*-BuLi in hexanes (2.5 mL, 3.5 mmol) over 5 min. The reaction mixture was allowed to stir at −78°C for 15 min then the cold bath was removed and the mixture was allowed to warm to room temperature over 20 min.

The solution was recooled to −78°C prior to the dropwise addition of freshly distilled propionyl chloride (0.31 mL, 0.33 g, 3.5 mmol). The solution was allowed to slowly warm to rt overnight (12 h) and was then quenched with saturated aqueous NH_4Cl solution (5 mL). The biphasic mixture was diluted with Et_2O (25 mL). The phases were separated and the aqueous phases was extracted further with Et_2O (2×10 mL). The combined ethereal extract was washed with brine (20 mL), dried over anhyd. $MgSO_4$, filtered, and concentrated in vacuo to provide a yellow oil. The crude product was purified by flash chromatography on silica gel eluting with 10% EtOAc/hexanes to afford imide **8** as a white solid (0.67 g, 93%), mp 73–74°C: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (dd, J=5.3, 2.5 Hz, 1H), 6.14 (d, J=5.1 Hz, 1H), 4.84 (s, 1H), 2.97–2.74 (m, 2H), 1.18 (s, 3H), 1.14 (t, J=7.4 Hz, 3H), 1.10 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.80, 174.30, 141.34, 139.22, 67.31, 66.51, 65.77, 29.92, 19.66, 19.29, 8.87, 8.05; IR (film): 2974, 1736, 1686, 1368, 1264 cm^{-1}; $[\alpha]_D^{23}$ −40.2 (*c* 2.2, CH_2Cl_2). Anal. calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27. Found: C, 69.72; H, 8.20%.

3.12. General procedure for aldol reactions of imide 8: (1*S*,4*R*)-2-[(2′*S*,3′*R*)-3′-hydroxy-3′-phenyl-2′-methylpropionyl)-4,7,7-trimethyl-2-azabicyclo[2.2.1]-5-hepten-3-one 39 and (1*S*,4*R*)-2-[(2′*R*,3′*S*)-3′-hydroxy-3′-phenyl-2′-methylpropionyl)-4,7,7-trimethyl-2-azabicyclo[2.2.1]-5-hepten-3-one 40

To a stirred solution of dicyclopentylboron triflate (87 mg (0.29 mmol) in CH_2Cl_2 (0.26 mL) at 0°C was added a solution of imide **8** (54 mg, 0.26 mmol) in CH_2Cl_2 (0.26 mL) followed by dropwise addition of diisopropylethylamine (54 μL, 40 mg, 0.31 mmol) over 5 min. The solution was allowed stir at 0°C for 30 min then cooled to −40°C. To the reaction mixture was added a solution of freshly distilled benzaldehyde (53 μL, 55 mg, 0.52 mmol) in CH_2Cl_2 (0.26 mL) dropwise over 1 h. After 40 h at −40°C, the solution was quenched with CH_3OH (0.39 mL), followed by pH 7 phosphate buffer (0.39 mL), and aqueous 30% hydrogen peroxide solution (0.39 mL). The biphasic mixture was allowed to warm to rt and stirred for 30 min before dilution with Et_2O (10 mL). The phases were separated and the organic layer was washed with H_2O (5 mL), aqueous 5% $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried over anhyd. $MgSO_4$, filtered, and concentrated in vacuo to provide a mixture of **39** and **40** as a yellow oil (90 mg), shown to be a 5:1 (2′*S*)-/(2′*R*)-mixture by ^{1}H NMR analysis. Purification by flash chromatography (SiO_2, 20% EtOAc/hexanes) afforded **39** and **40** as a colorless oil (48 mg, 69% yield, 83% overall conversion), shown to be a ratio of 5.0:1.0 (2′*S*)/(2′*R*) by ^{1}H NMR analysis. This was characterized as a mixture: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.23 (m, 10H), 6.74 (dd, J=5.4, 2.6 Hz, 1H), 6.70 (dd, J=5.4, 2.6 Hz, 1H), 6.14 (dd, J=5.4, 1.5 Hz, 1H), 6.11 (d, J=1.5 Hz, 1H), 5.13 (t, J=3.0 Hz, 1H), 5.05 (d, J=1.9 Hz, 1 H), 4.82 (s, 2H), 4.04–3.89 (m, 2H), 3.50 (d, J=2.1 Hz, 1H), 3.20 (d, J=2.6 Hz, 1H), 1.18 (s, 3H), 1.13 (s, 3H), 1.10–1.05 (m, 9H), 1.01 (d, J=6.9 Hz, 3H), 0.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.24, 176.99, 176.19, 141.61, 141.29, 140.88, 138.74, 128.16, 128.07, 127.30, 127.09, 126.15, 126.04, 73.81, 72.72, 67.01, 66.97, 65.74, 65.42, 44.88, 44.82, 44.61, 44.57, 19.16, 18.99, 18.95, 18.79, 18.03, 10.24, 9.94, 7.63; IR (film): 3486, 2970, 1745, 1679, 1382, 1313, 1194 cm^{-1}. HRMS (CI): m/z (MH^+). Calcd for $C_{19}H_24NO_3$: 314.1756. Found: 314.1767.

The major diastereomer **39** was separated on a semi-preparative HPLC column eluting with 12% EtOAc/hexane: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.25 (m, 5H), 6.74 (dd, J=5.4, 2.6 Hz, 1H), 6.14 (dd, J=5.4, 1.5 Hz, 1H), 5.14 (d, J=3.8 Hz, 1H), 4.82 (s, 1H), 4.02–3.99 (m, 1H), 3.18 (s, 1H), 1.18 (s, 3H), 1.08 (s, 3H), 1.01 (d, J=6.9 Hz, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.64, 176.65, 142.08, 141.35, 139.19, 128.60, 127.74, 126.60, 74.27, 67.50, 66.26, 66.18, 65.89, 45.33, 19.44, 19.25, 15.70, 10.38, 8.07.

The absolute stereochemistry of **39** and **40** was established by catalytic reduction (H_2 (1 atm)/10% Pd–C in EtOAc) of a 5:1 mixture of **39** and **40** and comparison of the reduction products with an authentic mixture of (2′*S*)- and (2′*R*)-diastereomers obtained from the aldol reaction of **3** with benzaldehyde.[12]

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24. Let k_1 and k_2 be the rate constants leading to the diastereomeric products (**41** and **42**) from the boron enolate derived from **3**, and k_3 and k_4 be the rate constants leading to the diastereomeric products (**39** and **40**) from the boron enolate derived from **8**. One can demonstrate that:

$\Delta\Delta G^{\ddagger}_{\text{total}}$ (ts **41**–**42**–ts **39**–**40**) $= -RT[\ln(k_1/k_3)+\ln(k_4/k_2)] = -RT[\ln\ \{1+(\mathbf{40}/\mathbf{39})/1+(\mathbf{42}/\mathbf{41})\}+\ln\{1+(\mathbf{41}/\mathbf{42})/1+(\mathbf{39}/\mathbf{40})\}]$, where **39**/**40** and **41**/**42** are the experimentally observed product ratios under kinetic control.

Also, it can be shown that: $\Delta\Delta G^{\ddagger}_{\text{total}} = \Delta\Delta G^{\ddagger}_{\text{A}_{1,3}}$ (ts **41**–ts **39**)$-\Delta\Delta G^{\ddagger}_{\text{NB}}$ (ts **42**–ts **40**), assuming that the dipole–dipole interactions for **41** versus **39** and **42** versus **40** cancel.

Thus, $\Delta\Delta G^{\ddagger}_{\text{A}_{1,3}} = \Delta\Delta G^{\ddagger}_{\text{total}} - \Delta\Delta G^{\ddagger}_{\text{NB}} = \Delta\Delta G^{\ddagger}_{\text{total}} + (-RT[\ln(k_2/k_4)])$, and $\Delta\Delta G^{\ddagger}_{\text{A}_{1,3}} = -RT\{[\ln\{1+(\mathbf{40}/\mathbf{39})/1+(\mathbf{42}/\mathbf{41})\}+\ln\{1+(\mathbf{41}/\mathbf{42})/1+(\mathbf{39}/\mathbf{40})\}]+[\ln\{1+(\mathbf{39}/\mathbf{40})/1+(\mathbf{41}/\mathbf{42})\}]\}$.

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