Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 61 (2005) 9495–9501
Tetrahedron

Salt, concentration, and temperature effects on an asparagine-based, aqueous Diels–Alder cycloaddition

Mathew P. D. Mahindaratne, Brian A. Quiñones, Antonio Recio, III, Eric A. Rodriguez, Frederick J. Lakner[†] and George R. Negrete*

Department of Chemistry, University of Texas at San Antonio, 6900 N. Loop 1604 West, San Antonio, TX 78249-0698, USA

Received 18 June 2005; revised 29 July 2005; accepted 1 August 2005

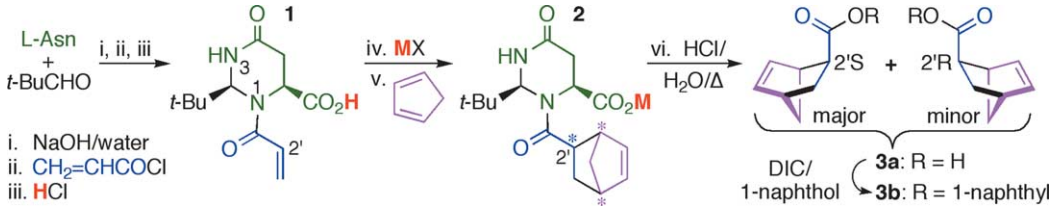
Abstract—Results are reported on the salt, concentration, and temperature effects in an aqueous, auxiliary-mediated asymmetric Diels–Alder cycloaddition. The auxiliaries were prepared under basic aqueous conditions from asparagine and trimethylacetaldehyde, and coupled to acryloyl chloride to generate dienophiles in one pot. Temperature and concentration modestly impacted cycloaddition stereochemistry. Experiments with a range of salts examined the speculation that complexation between the counterion of the auxiliary carboxylate and the dienophile carbonyl promotes the formation of the minor *endo* product, reducing cycloaddition diastereoselectivity for the *endo* products. The transformation was poorly selective for the carboxylic acid but gave moderate selectivities for several metallated carboxylates. The magnitude of the diastereoselectivity of the *endo* products was weakly dependent on carboxylate counterion and more strongly influenced by the basicity of the salt anion. Data presented suggest that Lewis acid catalysis reduces cycloaddition diastereoselectivity for the *endo* products.

1. Introduction

The Diels–Alder reaction is a powerful technique for assembling complex organic frameworks[2] and is a crucible for examining subtle electronic and steric effects.[3] Auxiliary-based methods for asymmetric Diels–Alder cycloadditions have received much attention but less has been disclosed on aqueous variants.[4,5] We recently reported preliminary results on such a reaction employing L-asparagine-derived pyrimidinones for chirality transmission (Scheme 1).[6] Among its notable features were the in situ auxiliary preparation using asparagine and aldehyde, the completion of the entire synthetic process in a two-pot sequence, and the compatibility of this system with ambient aqueous media. While experimentally simple and economical, this methodology suffered from moderate cycloaddition selectivity. We now report the results of salt, concentration, and temperature studies aimed at elucidating factors impacting cycloaddition stereochemistry.

2. Results and discussion

The present studies focused on investigating the possible participation of the metal counterion of the salt of **1** (generated by the addition of MX) in cycloaddition stereoselectivity.[7,8] Proton NMR and crystallography indicate that analogs of **1** maintain the carboxyl group at



Scheme 1. Aqueous, L-asparagine-based, auxiliary-mediated cycloaddition (*exo* products not shown).

Keywords: Diels–Alder; Cycloaddition; Aqueous; Salt effects; Auxiliary; Asymmetric.
* Corresponding author. Tel.: +1 210 458 5448; fax: +1 210 458 7428; e-mail: george.negrete@utsa.edu
† See Ref. 1.

0040–4020/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tet.2005.08.003

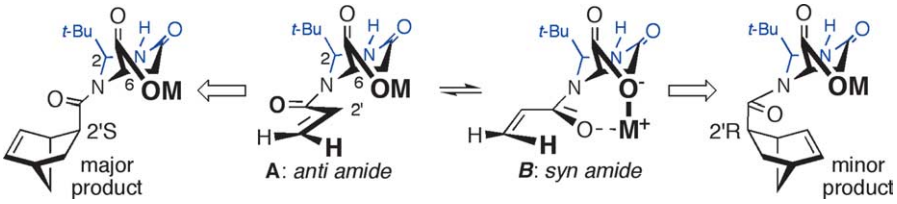


Figure 1. Dienophile conformations and their respective adducts with cyclopentadiene.

C6 and alkyl unit at C2 in pseudo-axial orientations[9] in order to minimize vicinal interactions with the amide unit.[10] Proton NMR of **1** in D_2O with 1.1 equiv $NaHCO_3$ at 25 °C indicated the presence of two major conformers in 4:1 ratio. We suspected these were the two *s-cis* amide rotomers (*anti*-amide **A** and *syn*-amide **B**; Fig. 1) since preliminary computational studies indicated that *s*-trans conformers are disfavored by congestion between the vinyl group and the pyrimidinone C2 and C6 substituents.[11] Assuming that the diene would react preferentially at the pi-face opposite to the sterically demanding pyrimidinone 2-*tert*-butyl and 6-carboxyl substituents, the observed major 2′*S*-*endo* cycloaddition product suggested that cycloadditions occurred primarily with *anti*-amide **A** conformer. We speculated that Lewis acid complexation between the carboxylate counterion (M) and the eneamide carbonyl of *syn*-amide **B** (a bidentate complexation as depicted below in Fig. 1) may electronically activate this dienophile conformer toward Diels–Alder cycloaddition. Catalysis of cycloadditions of the *syn*-amide **B** would increase the occurrence of the minor 2′*R*-*endo* cycloaddition product, thus leading to diminished *endo* selectivity for this transformation. Salt, concentration, and temperature studies were performed to examine this hypothesis and to survey for conditions that enhance cycloaddition stereoselectivity.

In these studies, acrylamide **1** was prepared, reacted with cyclopentadiene under specified conditions, and the resulting cycloadducts were analyzed as described below. Treatment of L-asparagine (10 g) with aqueous sodium hydroxide (2 M, 1 equiv) and trimethylacetaldehyde (1 equiv) at room temperature induced cyclocondensation. The resulting heterocycle was cooled to ice bath temperature and directly acylated upon treatment with solid sodium bicarbonate (1.5 equiv) and acryloyl chloride (1.3 equiv). Acrylamide **1** was precipitated upon acidification (10% HCl), filtered, washed with water, and evacuated overnight (0.1 mmHg) to yield a white amorphous solid in 55% yield. The individual cycloaddition stereoselectivity studies, which were conducted as specified below, resulted in 2-norbornene carboxylic acid cycloadducts **2**. The carboxylic acids (**3a**) were released from the pyrimidinone auxiliary upon aqueous acid exposure and heating (70 °C, 24 h), and were extractively isolated.[12] The dried CH_2Cl_2 solutions of **3a** were coupled to 1-naphthol (DIC/cat DMAP) to generate a mixture of UV active stereoisomeric esters (**3b**) for HPLC analysis. Individual isomer ratios of **3b** were determined by chiral stationary phase HPLC (Pirkle Type 1, 95% hexanes/isopropanol, 1 mL/min),[6] which exhibited baseline separated *endo* isomer signals (retention time = 16 and 18 min) that were widely separated from the *exo* isomer signals (retention time = 14 and 14.5 min; the *exo* isomers were only partially separated). The early eluting *endo* isomer (retention time = 16 min), which was the minor *endo* product in all preparations, was identified as the 2′*R*-enantiomer (Scheme 1; numbering is maintained for simplicity) based on coelution studies with the 1-naphthyl ester prepared from an authentic sample. In each case, integrated signals from the HPLC traces were used (uncorrected) to determine *endo* enantiomer ratios[13] and *endo*/*exo* diastereomer ratios. Minor experimental variations that were employed to examine salt, temperature, and concentration effects are described below.

2.1. Concentration effects on cycloaddition stereoselectivity

To begin these studies, concentration effects were examined to identify convenient and reproducible cycloaddition concentrations. The studies were conducted at 0.05, 0.10, 0.25, 0.50, 1.0 M acrylamide **1** (2.5 mmol scale) in satd $NaHCO_3$ solution and the results are presented in Table 1. These data indicate that concentrations at or below 0.25 M provide optimal selectivity. This may be due to species aggregation at higher concentrations of acrylamide, though this phenomenon was not investigated further. Based on these studies, succeeding reactions were conducted at 0.25 M acrylamide.

Table 1. Concentrations studies versus cycloaddition stereoselectivity

[Auxiliary] (M)	*endo* ee (%)[a]	*endo*/*exo*[a]
0.05	71.8 (±0.4)	24.9 (±1.3)
0.10	70.0 (±0.6)	23.7 (±0.7)
0.25	68.1 (±0.8)	27.2 (±2.3)
0.50	63.4 (±0.1)	20.9 (±0.3)
1.00	51.3 (±2.1)	20.4 (±0.4)

[a] Data are averages of triplicate experiments.

2.2. Temperature effects on cycloaddition stereoselectivity

For temperature studies, **1** (0.50 mmol) was added to satd $NaHCO_3$ solution (2 mL) at room temperature, cooled to the listed temperature (Table 2), and treated with

Table 2. Temperature effects (Scheme 1, Y = Na)

Entry	Temperature (°C)	Time (h)	*endo* ee (%)[a]	*endo*/*exo*[a]
1	−15[b]	148	59.2 (±0.6)	36.0 (±1.8)
2	0	72	71.3 (±0.7)	42.5 (±2.6)
3	7	48	71.8 (±0.6)	32.3 (±1.1)
4	14	36	69.7 (±0.2)	31.3 (±2.4)
5	23	24	68.3 (±0.1)	31.3 (±2.2)
6	35	12	66.6 (±0.2)	24.3 (±2.2)

[a] Data are averages of triplicate experiments.
[b] This sample congealed under these conditions.

cyclopentadiene. For preparations below room temperature, the diene was chilled upon contact with the cold interior surface of the reactor prior to exposure to **1**. After stirring for the time specified, the mixtures were processed to 1-naphthyl esters and analyzed by HPLC. The data from these preparations are presented in Table 2. It was found that lower temperatures gave greater selectivities as is normally found in DA reactions, except for entry 1, in which the cycloaddition was performed in a congealed mixture. There was concern that at the lower temperatures, the selectivity might be reduced due to aggregation effects, however, there was no significant reduction in selectivity for samples that remained dissolved at the tested temperatures.

2.3. Effect of sodium bicarbonate molar ratio on cycloaddition stereoselectivity

Next, we examined the selectivity as a function of molar equivalents of sodium bicarbonate (Table 3). These room temperature experiments were conducted as described above with varying amounts of sodium bicarbonate as listed. Because of the experimental consistency of the aforementioned trials and of these results, data presented below (except as indicated) were obtained from single preparations. The results of these experiments clearly indicate that the reaction requires a stoichiometric amount of bicarbonate, reaching the maximum diastereoselectivity for *endo* adducts at 1.0 equiv $NaHCO_3$. The correlation between the diastereoselectivity of the *endo* cycloadducts and bicarbonate molar proportion is highly linear up to 1 equiv (Fig. 2).

Table 3. Cycloaddition selectivity at various molar ratios of sodium bicarbonate (MX = $NaHCO_3$)

Entry	(MX/**1**) molar ratio	*endo* ee (%)	*endo*:*exo*
1	0.00	7.9	22:1
2	0.10	19.3	22:1
3	0.30	34.2	23.1
4	0.50	42.8	27:1
5	0.75	53.2	23:1
6	1.00	70.9	25:1
7	1.20	70.5	25:1
8	1.50	70.7	26:1
9	2.00	68.2	23:1
10	3.00	70.2	25:1

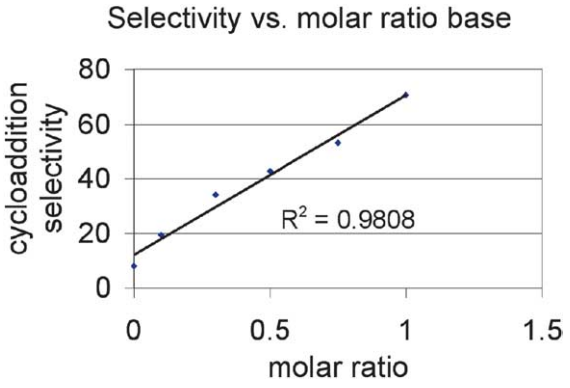


Figure 2. Cycloaddition *endo* selectivity versus sodium bicarbonate molar ratio.

Table 4. Salt influence on the Diels–Alder cycloaddition stereoselectivity (MX = salt in Scheme 1)

Entry	MX	*endo* ee (%)	*endo*:*exo*
1	None	7.9	22:1
2	NaCl	2.0	20:1
3	$BaCl_2$	4.7	20:1
4	LiOAc	62.8	23:1
5	NaOAc	64.5	24:1
6	CsOAc	61.9	23:1
7	$NaHCO_3$	70.7	26:1
8	Li_2CO_3	67.2	20.1
9	Na_2CO_3	67.0	19:1
10	K_2CO_3	67.4	31:1
11	Cs_2CO_3	67.9	30:1
12	$MgCO_3$	67.2	29:1
13	$CaCO_3$	64.9	34:1
14	LiOH	69.7	26:1
15	NaOH	67.5	23:1
16	KOH	66.5	24:1
17	$Ba(OH)_2$	60.2	28:1
18	NH_4OH	70.5	19:1
19	*n*-Bu_4NOH	64.9	26:1
20	MgO	66.5	24:1

2.4. Salt effects on cycloaddition stereoselectivity

Counterion experiments were conducted at room temperature in water using the alkali and alkaline earth salts listed in Table 4. In these studies acrylamide **1** was added to water containing the listed salt (1.5 equiv) and stirred for 1 h prior to the addition of cyclopentadiene. The mixtures were stirred overnight, processed, and analyzed routinely. Salts were selected to examine the impact of both cations and anions. As discussed above, cations that strongly complex to the carboxylate and eneamide carbonyl should exhibit decreased cycloaddition diastereoselectivity for *endo* isomers by enhancing the reactivity of the conformation that generates the minor product. Metal salts containing various anions with different basicities were employed to examine possible selectivity differences caused by metal association with the carboxylate, or carboxylic acid for salts with weakly basic anions, and the eneamide carbonyl. Thus, sodium was examined as the chloride, acetate, bicarbonate, carbonate, and hydroxide salts (Table 4, entries 2, 5, 7, 9, and 15, respectively). Selected other metal salts were also examined including transition metal salts that are presented in Table 5.

Several interesting trends emerged from these data. Poorly basic sodium and barium chloride (entries 2 and 3) exhibited

Table 5. Effect of the transition metal salts on the Diels–Alder cycloaddition reaction (Scheme 1, in water with salts listed)

Entry	MX	*endo* ee (%)	*endo*:*exo*
1	$NiCl_2$	2.7	21:1
2	$CoCl_2$	3.9	20:1
3	$BaCl_2$	4.7	20:1
4	$CuCl_2$	5.9	22:1
5	$ZnCl_2$	9.5	20:1
6	$Cu(OAc)_2$	40.4	30:1
7	$Zn(OAc)_2$	54.2	25:1
8	$Ni(OAc)_2$	56.5	25:1
9	$Mn(OAc)_2$	57.1	25:1
10	$Co(OAc)_2$	57.4	27:1
11	$Mn(OAc)_3$	36.4	29:1
12	$Ti(OAc)_4$	56.0	25:1

poor diastereoselectivities for *endo* isomer formation, while moderately basic lithium, sodium, and cesium acetates (entries 4–6) gave higher *endo* diastereoselectivities. Both of these salt series exhibited diastereoselectivities in narrow ranges of values. The alkali and alkaline earth carbonate entries 8–13 were also obtained in a small range of diastereoselectivities for *endo* adducts, which were slightly higher than the values obtained for the acetate salts. The alkali, alkaline earth, and ammonium hydroxides (entries 14–17, 18, and 19) exhibited a moderate range of selectivities (approximately 60–71% ee), which is suggestive of a modest cation effect. The calcium carbonate and barium hydroxide preparations (entries 13 and 17) exhibited the smallest selectivities in the carbonate and hydroxide series, respectively, which is supportive of a Lewis acid influence on these transformations (these trials were repeated to verify reproducibility). The tetrabutylammonium hydroxide salt (entry 19), which was expected to poorly activate the dienophile delivered lower *endo* diastereoselectivity, contrary to what was expected. Overall, these results suggest a modest impact of the salt cation on the cycloaddition *endo* diastereoselectivity.

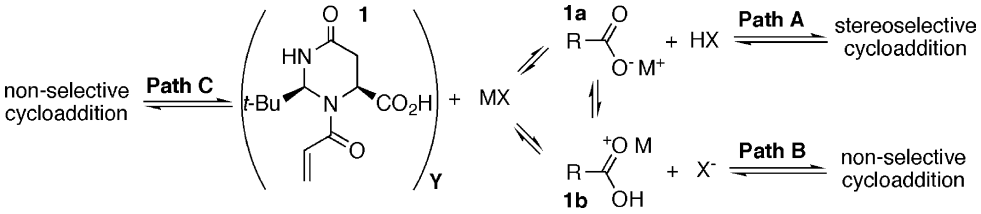
In contrast, anion effects appeared much stronger than cation effects. Thus, sodium salt entries 2, 5, 7, 9, and 15 (chloride, acetate, bicarbonate, carbonate, and hydroxide salts, respectively) were strongly affected by the anion. Generally, chloride salts gave poorly selective transformations while acetate salts gave much improved *endo* diastereoselectivities that varied little with cation (61.9–64.5%). Bicarbonate, carbonate, and hydroxide salts typically gave higher selectivities than acetate salts. The remainder of the salts tested exhibited similar behaviors relative to the magnitude of cation and anion impacts.

Several transition metal salts were also examined (Table 5). Weakly basic chloride salts (entries 1–5) exhibited comparable selectivities to their corresponding alkali and alkaline earth chlorides. Transition metal acetate salts (entries 6–12) exhibited a greater range of cycloaddition diastereoselectivities for *endo* products, and these were each smaller than the alkali acetate salts (entries 4–6 in Table 4). These results are consistent with the known propensities of these transition metals to chelate carbonyl groups and carboxylates in biomolecules such as peptides, hydroxamic acids, and siderophores.[14] Most striking is the smaller *endo* diastereoselectivity observed for the acetate salt of copper(II) (entry 6) relative to zinc(II), nickel(II), manganese(II), cobalt(II), manganese(III), and titanium(IV) (entries 7–12).

2.5. General discussion

Overall, these data indicate that salt cations influence the diastereoselectivity of the *endo* adducts only weakly compared to the effect of salt anions. Salts with weakly basic anions gave poor *endo* cycloaddition diastereoselectivities while salts with moderately to highly basic anions gave significantly enhanced *endo* cycloaddition diastereoselectivities. Cations derived from salts that generate dienophile carboxylates (bicarbonate, carbonate, and hydroxide) were associated with modest selectivity differences. Intermediately basic acetates gave *endo* diastereoselectivities between the extremes described above, though several showed a significant *endo* diastereoselectivity variance with different metals. Each of the transition metal acetate salts gave lower selectivities than the alkali and alkaline earth acetate salts, which is consistent with increased metal complexation with the eneamide carbonyl as suggested in the above model. This rationale for cycloaddition diastereoselectivity is further supported by the poor *endo* diastereoselectivities of oxophilic copper(II) and manganese(III) acetates, which are known to bind to carbonyls and complex strongly to carboxylate ions. It was somewhat surprising that titanium(IV) acetate, a metal that typically binds strongly to oxygen ligands, did not strongly influence the diastereoselectivity of *endo* adducts relative to other transition metal acetates. According to the data presented, the effectiveness of the metals in activating this Diels–Alder cycloaddition follows the order: $Mn^{+3} > Cu^{+2} > Zn^{+2} > Ti^{+4} \approx Ni^{+2} \approx Mn^{+2} \approx Co^{+2} >$ alkali metals-$\approx$alkaline earth metals, in good agreement with the empirical order given by Irvin and Williams ($Mn < Co < Ni < Cu > Zn$) for the bivalent ion complexation.[15a] Furthermore, the order of the activating ability of the transition metals reported here parallels the order of the binding strength of transition metals on a bidentate dienophile and Lewis acid dienophile activation reported by Otto and co-workers.[15b]

These results are consistent with a process in which the salt must form acrylamide carboxylate **1a** (Scheme 2, path A) for enhanced cycloaddition stereoselectivity. The weak influence of the alkali and alkaline earth metal cations in *endo* cycloaddition diastereoselectivity is likely due to strong water solvation about the metal, for which the eneamide carbonyl competes weakly.[5] The difficulty of overcoming metal ion hydration also extends to transition metals, though slightly less so, and is a significant problem associated with aqueous Lewis acid catalysis. Selectivity differences among salts with a common anion—particularly between alkali, alkaline earth, and transition metal acetate



Scheme 2. Cycloadditions from salt experiments (R=heterocycle acrylamide).

salts—are suggestive of differences in Lewis acid activation of the dienophile. Salts that do not form dienophile carboxylates undergo cycloadditions as weakly associated, metallated carboxylic acid **1b** (path B), or as free carboxylic acid **1**, which proceeds without significant Lewis acid dienophile activation (path C). The poor *endo* diastereoselectivity observed with weakly basic salts might be associated with cycloadditions with dienophile aggregates (Scheme 2, $Y>1$) that result from the poor solubility of the free carboxylic acid in water. Thus, the low selectivity of weakly basic salts may not correspond to the kinetic selectivities of monomeric acrylamide **1**. Intermediately basic acetate salts, which are expected to generate both metallated carboxylate **1a** and carboxylic acid **1**, gave intermediate selectivities, as anticipated for a product mixture generated from cycloadditions to both species.

These studies also examined for a correlation between *endo* diastereoselectivity and *endo*/*exo* ratios in the Diels–Alder cycloadditions.[16] According to the analysis, increased Lewis acid activation, which yields diminished *endo* diastereoselectivity, would lead to a concomitant increase in *endo*/*exo* ratios.[17] This correlation would not be expected to be dramatic since the *endo* selectivity data in Tables 4 and 5 suggest only a modest Lewis acid activation. Data from Table 4 do not indicate a strong correlation between the *endo* diastereoselectivity values and *endo*/*exo* ratios. Indeed, such a correlation, if present, is obscured by the variability of *endo*/*exo* ratios. However, the transition metal acetate salts in Table 5 routinely exhibited higher *endo*/*exo* selectivity ratios than the alkali or alkaline earth acetates (compare entries 4–6 in Table 4 with entries 6–12 in Table 5). Furthermore, the copper(II) and manganese(III) acetate salts (entries 6 and 11 in Table 5) each induced significantly less *endo* diastereoselectivity and higher *endo*/*exo* ratios than the other transition metal acetate salts tested (entries 7–10 and 12 in Table 5). Both of the aforementioned results are consistent with Lewis acid promotion of *endo*/*exo* ratios. Thus, while these results are subtle and additional studies are required to firmly establish trends, Lewis acid activation appears to be involved in this aqueous, auxiliary-mediated process, diminishing the *endo* diastereoselectivity in a salt-dependent manner, while simultaneously increasing the *endo*/*exo* selectivity in these preparations.[18]

3. Summary

Salt, concentration, and temperature influences on an aqueous, auxiliary-mediated Diels–Alder cycloaddition have been examined. The results of these studies suggest that the cycloaddition stereochemistry is reduced at higher concentration and temperature. These studies also indicate a strong correlation between cycloaddition stereoselectivity and salt anion basicity, and a modest impact associated with salt cation. The reported results suggest that the metals associated with the dienophile carboxylate are not strongly complexed with the eneamide carbonyl and thus, only weakly impart electronic activation to the dienophile eneamide. The limited impact of cation on the cycloaddition stereoselectivities reported here illustrates the challenges that remain to be addressed in exploiting Lewis acid catalysis in aqueous media. In this instance, Lewis acid activation appears to promote the formation of the minor *endo* diastereomer, thus leading to reduced *endo* diastereoselectivity and increased *endo*/*exo* ratios. Ongoing investigations on the origin of the selectivity of this process and approaches to enhance the cycloaddition stereoselectivity will be reported in due course.

4. Experimental

4.1. General methods

Proton and ^{13}C NMR spectra were recorded at 500 and 125 MHz (Varian Inova), respectively, in water-d_2 or $CDCl_3$ as indicated at 25 °C. Chemical shift values are reported in ppm with TMS as an internal reference. *J* values are given in Hz. Optical rotation was recorded on a Rudolph Autopol IV digital polarimeter at room temperature. Mass spectrometric data were recorded using Finnigan MAT95 mass spectrometer (CI+, 20 eV, reagent gas: CH_4). Kieselgel $60F_{254}$ silica gel TLC plates were used for monitoring reaction progress. Flash chromatography was performed using silica gel (Aldrich, 200–300 mesh) with ethyl acetate–hexanes gradients. Reactions were routinely effected in capped vials with magnetic stirring. Cyclopentadiene was fractionally distilled on the day of its use. All other chemicals were purchased from the Sigma-Aldrich Chemical Company (St. Louis, MO) and used without purification.

4.1.1. (2*S*,4*R*)-3-Acryloyl-2-*tert*-butyl-6-oxo-hexahydropyrimidine-4-carboxylic acid (1). Into a 100 mL flask was added (*S*)-asparagine monohydrate (7.51 g, 50 mmol) and aqueous NaOH (2.0 M, 1 equiv). The mixture was stirred 15 min and trimethylacetaldehyde (1 equiv) was added via syringe over 5 min. The mixture was stirred 4 h, treated with solid sodium bicarbonate (1.5 equiv), cooled in an ice bath, and acryloyl chloride (1.3 equiv) was added slowly (four portions over 1 h) to the vigorously stirred solution. Cooling and stirring were continued an additional 2 h, after which the mixture was treated with HCl (10%, 1.6 equiv) inducing precipitation of **1**. The product was filtered, washed with cold water, and dried overnight under high vacuum leaving behind **1** as an amorphous white power (55% yield). Mp=160 °C (dec); $[\alpha]_D^{25.6}$ −145.5° (c 0.015 g/cm^3, methanol); ^1H NMR (satd $NaHCO_3$ in D_2O): δ 0.98 (9H, s), 2.87 (dd, J=9.3, 18.1 Hz, 1H), 2.98 (dd, J=9.3, 3.9, 18.1 Hz, 1H), 4.75 (t, J=9.3 Hz, 1H), 5.69 (s, 1H), 5.82 (d, J=10.7 Hz, 1H), 6.23 (d, J=16.6 Hz, 1H), 6.55 (dd, J=10.7, 16.6 Hz, 1H); ^{13}C NMR (satd $NaHCO_3$ in D_2O): δ 25.7 (q), 31.5 (t), 39.2 (s), 55.5 (d), 69.5 (d), 128.2 (d), 130.1 (t), 170.2 (s), 172.9 (s), 176.9 (s); MS (*m*/*z*): 255 (16, $M^+ + 1$), 210 (16), 197 (90), 154 (38), 143 (88), 123 (36), 97 (44), 85 (45), 55 (100); IR (cm^{-1}): 2957, 1717, 1607, 1484, 1436, 1332, 1282, 1213, 1194, 1087, 1028, 975, 937. Anal. Calcd for $C_{12}H_{20}N_2O_5$ (monohydrate, as determined by a proton NMR integration study): C, 52.93; H, 7.40; N, 10.29. Found: C, 52.91; H, 7.16; N, 10.06.

4.1.2. General procedures for Diels–Alder cycloaddition (the synthesis of bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (3a) as a mixture of stereoisomers). Chiral acrylamide **1** (1 mmol) was dissolved in an aqueous salt

or Lewis acid solution (1.5 equiv) and treated with cyclopentadiene (3 equiv) under specified conditions. The mixture was stirred for 24 h at room temperature (unless otherwise specified) and the reaction was quenched by heterogeneous removal of unreacted cyclopentadiene with ethyl acetate (2×5 mL). The aqueous layer was then treated with HCl (10%, 1.5 equiv), extracted with ethyl acetate (2× 5 mL), and dried over anhydrous sodium sulfate. Removal of solvent in vacuo left behind a slightly yellow solid (**2**; M=H) that exhibited a forest of signals in ^{1}H NMR (satd $NaHCO_3$ in D_2O) and was not further characterized. The solid was suspended in water (5 mL) and heated to 70 °C for 24 h. The resulting clear solution was extractively (ethyl acetate) processed as described above to yield **3a** as a colorless oil (54%). For spectral observation, an aliquot was removed from ethyl acetate extract and the major *endo* isomer was enriched via silica gel chromatography, which exhibited proton and carbon NMR signals that were identical to reported values of **3a**.[19] ^{1}H NMR ($CDCl_3$): δ 1.28 (br d, J=8.3 Hz, 1H), 1.40 (ddd, J=2.4, 4.4, 11.72 Hz, 1H), 1.45 (ddt, J=2.4, 8.3, 2.0 Hz, 1H), 1.92 (ddd, J=3.4, 9.3, 11.7 Hz, 1H), 2.92 (br s, 1H), 3.00 (dt, J=9.3, 3.9 Hz, 1H), 3.23 (br s, 1H), 6.00 (dd, J=2.9, 5.4 Hz, 1H), 6.21 (dd, J=3.4, 5.9 Hz, 1H), 10–12 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 29.1 (t), 42.5 (d), 43.3 (d), 45.7 (d), 49.7 (t), 132.4 (d), 137.9 (d), 181.4 (s).

4.1.3. Naphthalen-1-yl bicyclo[2.2.1]hept-5-ene-2-carboxylate (3b, mixture of stereoisomers). The stereoisomeric mixture of carboxylic acid **3a** (34.5 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and treated with 1-naphthol (39.6 mg, 1.1 equiv), DMAP (7.6 mg, 25% mol) and DIC (34.7 mg, 1.1 equiv). After 6 h stirring, the mixture was washed with brine (2×1 mL), dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The crude residue was flash chromatographed in a 5×0.5 cm plug of silica gel (5% ethyl acetate in hexanes) prior to stereochemical analysis by chiral phase HPLC (Regis Pirkle Type 1, RR; 95:5 hexanes/isopropanol, 1.0 mL/min). For analytical purposes the *endo* product was enriched by gradient normal phase chromatography (hexanes to 20% ethyl acetate/hexanes) to yield **3b** as a light yellow solid. Mp=56–58 °C; ^{1}H NMR ($CDCl_3$): δ 1.39 (br d, J=8.3 Hz, 1H), 1.54 (ddt, J=2.4, 8.3, 2.0 Hz, 1H), 1.64 (ddd, J=2.9, 3.9, 11.7 Hz, 1H), 2.07 (ddd, J=3.4, 9.3, 11.7 Hz, 1H), 2.99 (br s, 1H), 3.37 (dt, J=9.3, 3.9 Hz, 1H), 3.50 (br s, 1H), 6.17 (dd, J=2.9, 5.9 Hz, 1H), 6.30 (dd, J=2.9, 5.9 Hz, 1H), 7.18 (d, J=7.3 Hz, 1H), 7.41 (t, J= 7.8 Hz, 1H), 7.47 (m, 2H), 7.68 (d, J=8.3 Hz, 1H), 7.82 (ddd, J=1.5, 2.5, 7.3 Hz, 1H), 7.87 (ddd, J=1.5, 2.4, 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 29.4 (t), 42.6 (d), 43.7 (d), 46.1 (d), 49.8 (t), 117.9 (d), 121.1 (d), 125.3 (d), 125.6 (d), 126.2 (d), 126.3 (d), 126.9 (s), 127.9 (d), 132.3 (d), 134.6 (s), 138.3 (d), 146.7 (s), 173.1 (s); HRMS (*m*/*z*): Calcd for $C_{18}H_{16}O_2$ 264.115030, found 264.115050; MS (*m*/*z*): 264 (40), 144 (100), 121 (44), 115 (22), 93 (24), 55 (38); IR (cm^{-1}): 3062, 2962, 2942, 2871, 1749, 1595, 1388, 1338, 1258, 1224, 1127, 1106, 1013.

Acknowledgements

This work was supported by grants from the NIGMS (S06 GM08194) and The Welch Foundation (#96-086). B.Q., A.R., and E.R. are indebted to the NIGMS MBRS-RISE (GM 60655) for partial support. NIGMS MBRS MARC-U*STAR support (GM 07717) for B.Q. is also gratefully acknowledged. We also appreciate discussions with Dr. Ghezai Musie on the interpretation of the transition metal results and Dr. Robert E. Lyle for helpful comments on this manuscript.

References and notes

1. Current address: Chemical Diversity, Inc., San Diego, CA, 92121.
2. (a) Nicolaou, K. C.; Snyder, S. A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11929–11936. (b) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650–1667. (c) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304–322.
3. (a) Singleton, D. A.; Merrigan, S. R.; Beno, B. R.; Houk, K. N. *Tetrahedron Lett.* **1999**, *40*, 5817–5821. (b) Morgan, K. M. *Annu. Rep. Prog. Chem. Sect. B: Org. Chem.* **2004**, *100*, 335–350.
4. For other examples of auxiliaries specifically developed for aqueous Diels–Alder transformations see: (a) Fringuelli, F.; Matteucci, M.; Piermatti, O.; Pizzo, F.; Burla, M. C. *J. Org. Chem.* **2001**, *66*, 4661–4666. (b) Waldmann, H. *Liebigs Ann. Chem.* **1989**, 231–238. (c) Waldmann, H.; Braun, M. *Gazz. Chim. Ital.* **1991**, *121*, 277–284. (d) Yu, L.; Li, J.; Ramirez, J.; Chen, D.; Wang, P. G. *J. Org. Chem.* **1997**, *62*, 903–907.
5. For a general discussion of aqueous Diels–Alder cycloadditions, see: Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, *72*, 1365–1372.
6. Lakner, F. J.; Negrete, G. R. *Synlett* **2002**, 643–645.
7. For a recent report on the effect of alkali cation on an aqueous aza-Diels–Alder cycloaddition see: Loncaric, C.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 574–575.
8. For a Diels–Alder cycloaddition study of the cations impact in organic solvents see: Jung, D. Y.; Park, D. H.; Kim, S. H.; Kim, Y. H. *J. Phys. Org. Chem.* **2004**, *17*, 1017–1022.
9. (a) Chu, K. S.; Negrete, G. R.; Konopelski, J. P.; Lakner, F. J.; Woo, N.-T.; Olmstead, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 1800–1812. (b) Seebach, D.; Lamatsch, B.; Amstutz, R.; Beck, A. K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradón, B.; Hidber, P. C.; Irwin, J. J.; Locher, R.; Maestro, M.; Maetzke, T.; Mouriño, A.; Pfammatter, E.; Plattner, D. A.; Schickli, C.; Schweizer, W. B.; Seiler, P.; Stucky, G.; Petter, W.; Escalante, J.; Juaristi, E.; Quintana, D.; Miravitlles, C.; Molins, E. *Helv. Chim. Acta* **1992**, *75*, 913–934. (c) Juaristi, E.; López-Ruiz, H.; Madrigal, D.; Ramírez-Quirós, Y.; Escalante, J. *J. Org. Chem.* **1998**, *63*, 4706–4710.
10. Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413.
11. MM2 calculations were performed using Chem3D Pro 5.0 on a Mac G3. Both *s*-trans structures exhibited significant out-of-plane distortions at the sigma bond connecting the vinyl and carbonyl groups.
12. This sequence was recently conducted in a single-pot synthesis: Mahindaratne, M. P. D.; Quiñones, B. A.; Recio III, A.; Rodriguez, E. A.; Lakner, F. J.; Negrete, G. R. ARKIVOC 2005 (vi), in press.
13. In this report, the term '*endo* diastereoselectivity' will be used to describe the cycloaddition diastereoselectivity values for

endo products **2**, which were derived from HPLC measurements of the *endo* enantiomers of the 1-naphthyl esters (**3b**).

14. For reviews on metal complexes of amino acids and peptides involving carboxylate complexation see: (a) Farkas, E.; Sòvágó, I. *Amino Acids, Peptides, and Proteins* **2002**, *33*, 295–364. (b) Bergs, R.; Beck, W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1634–1654. For studies on evidence for transition metal complexation with carbonyl oxygen of biological systems: (c) Myari, A.; Malandrinos, G.; Deligiannakis, Y.; Plakatouras, J. C.; Hadjiliadis, N.; Nagy, Z.; Sòvágó, I. *J. Inorg. Biochem.* **2001**, *85*, 253–261. (d) Liang, J. Y.; Lipscomb, W. N. *Biochemistry* **1989**, *28*, 9724–9733. For studies on the stability order of the bidentate metal complexes (both alkaline earth and transition metals) involving amide carbonyl oxygen of natural compounds see: (e) Enyedy, É.A.; Pócsi, I.; Farkas, E. *J. Inorg. Biochem.* **2004**, *98*, 1957–1966. (f) Farkas, E.; Enyedy, É.A.; Csóka, H. *Polyhedron* **1999**, *18*, 2391–2398.
15. (a) Irving, H. M.; Williams, R. J. P. *J. Chem. Soc., Chem. Commun.* **1953**, 3192–3210. (b) Otto, S.; Bertoncin, F.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1996**, *118*, 7702–7707.
16. (a) Kumar, A. *Chem. Rev.* **2001**, *101*, 1–19. (b) Schlachter, I.; Mattay, Y.; Suer, J.; Howeler, U.; Wurthwein, G.; Wurthwein, E. *Tetrahedron* **1997**, *53*, 119–126.
17. Otto and co-workers reported that Lewis acid complexation eliminated the increased *endo*/*exo* selectivity afforded by aqueous reactions. See Ref. 5.
18. To our knowledge, this is the first example of Lewis acid activation reducing cycloaddition diastereoselectivity for the *endo* products while simultaneously increasing *endo*/*exo* ratios. Enhanced *endo*/*exo* ratios in aqueous Diels–Alder reactions compared to that in organic solvents have, however, been reported: (a) Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1991**, *113*, 4241–4246. (b) Engberts, J. B. F. N. *Pure Appl. Chem.* **1995**, *67*, 823–828.
19. Montembault, V.; Desbrosses, J.; Campistron, I.; Reyx, D. *Macromol. Chem. Phys.* **2000**, *201*, 973–979.