JOC*Note*

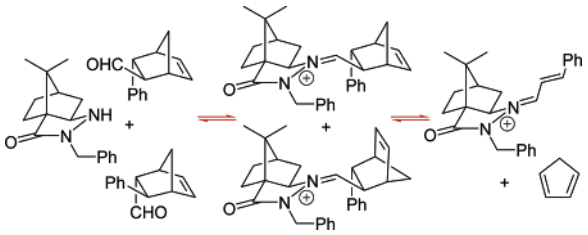
Mechanistic Studies of Hydrazide-Catalyzed Enantioselective Diels−Alder Reactions

Mathieu Lemay and William W. Ogilvie*

Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5

wogilvie@science.uottawa.ca

Received February 17, 2006

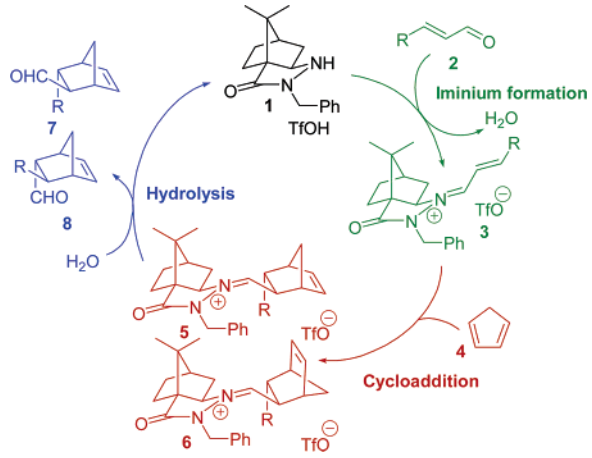


The mechanism of the enantioselective, hydrazide-catalyzed Diels−Alder cycloaddition was investigated in detail. Both the formation of the reactive iminium species and the hydrolysis of the product iminium intermediates were found to be extremely rapid, leaving the cycloaddition as the kinetically significant step. Mechanistic studies using NMR showed that a retro-Diels−Alder reaction occurred during the catalytic cycle, suggesting a thermodynamic component to the reaction.

Recent interest in asymmetric organocatalytic transformations has been intense, and considerable efforts have been directed toward developing new processes.[1,2] To date, considerably fewer reports have addressed the mechanistic aspects of organocatalytic transformations.[3] We recently described the design and development of new hydrazide-based organic catalysts functioning in water[4] that are capable of catalyzing [4+2] cycloadditions and other processes with high enantioselectivity. Thus, catalyst **1**, together with triflic acid as a cocatalyst, mediated asymmetric Diels−Alder reactions between aldehyde **2** and diene **4** producing *exo* and *endo* adducts (**7** and **8**) with enantiomeric excesses of up to 94%.

In this paper, we describe experiments that elucidate in detail the mechanism of the process. These results clearly showed that the cycloaddition is rate-limiting, and indicated that the hydrazide provides a very high concentration of active species. Evidence is also presented for thermodynamic contributions to enantioselectivity that suggest the potential development of desymmeterization catalysts.

SCHEME 1. Iminium Catalysis of Diels−Alder Cycloadditions by Hydrazides



The catalytic cycle for the process is depicted in Scheme 1. The cycle is initiated by the condensation of catalyst **1** with aldehyde **2** to produce the reactive iminium intermediate **3**. The electron-withdrawing ability of this charged iminium lowers the LUMO energy of **3**, thus accelerating the addition to diene **4**. This process produces two cycloadduct iminiums **5** and **6** corresponding to the *exo* and *endo* products, respectively.[5] After the cycloaddition has taken place, hydrolysis by water (present in the solvent or supplied by the formation of **3**) releases products **7** and **8** and regenerates the catalyst for the next cycle. To better understand the overall process, we studied each step of the catalytic cycle separately using NMR methods.

Iminium formation was studied by mixing equimolar quantities of **1** and **2** in CD_3NO_2[6] to observe the formation of **3** at fixed time intervals. As shown in Figure 1, the formation of **3** was rapid and essentially complete after 2 h at room temperature.[4] As previously reported, the structure of the major iminium species was found to be **3**.[4] This structure rationalizes the facial selectivity of our catalyst through bottom-face approach of the diene.

(1) Reviews: (a) List, B. *J. Chem. Soc., Chem. Commun.* **2006**, 819. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) List, B. *Adv. Synth. Catal.* **2004**, *346*, 1021. (d) Houk, K. N.; List, B. *Acc. Chem. Res.* **2004**, *37*, 487. (e) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (f) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (g) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, 2985.

(2) Cycloadditions: (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (c) Selkälä, S. A.; Tois, J.; Pihko, P. M.; Koskinen, A. M. P. *Adv. Synth. Catal.* **2002**, *344*, 941. (d) Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498. (e) Selkälä, S. A.; Koskinen, A. M. P. *Eur. J. Org. Chem.* **2005**, *8*, 1620. (f) Jurčik, V.; Wilhelm, R. *Org. Biomol. Chem.* **2005**, *3*, 239. (g) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504. (h) Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616.

(3) (a) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558. (b) Cheong, P. H.-Y.; Zhang, H.; Thayumanavan, R.; Tanaka, F.; Houk, K. N.; Barbas, C. F., III. *Org. Lett.* **2006**, *8*, 811. (c) Gordillo, R.; Houk, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 3543. (d) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770. (e) Iwamura, H.; Wells, D. H., Jr.; Mathew, S. P.; Klussmann, M.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 16312. (f) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16. (g) Dickerson, T. J.; Lovell, T.; Meijler, M. M.; Noodleman, L.; Janda, K. D. *J. Org. Chem.* **2004**, *69*, 6603. (h) Halland, N.; Lie, M. A.; Kjaersgaard, A.; Marigo, M.; Schiott, B.; Jorgensen, K. A. *Chem. Eur. J.* **2005**, *11*, 7083.

(4) Lemay, M.; Ogilvie, W. W. *Org. Lett.* **2005**, *7*, 4141.

(5) Only the major enantiomers are shown.

(6) The optimum solvent for the reaction (water) gave a yield of 89% and an *endo* enantiomeric excess of 88% for the condensation of cinnamaldehyde and cyclopentadiene. This presented technical difficulties for NMR work as the reaction was heterogeneous and the corresponding spectra of poor quality. Using CH_3NO_2 as solvent produced comparable yields (92%) and enantioselectivity (75% *endo* ee) to the fully aqueous process, and therefore, we carried out our mechanistic investigations in that solvent.

10.1021/jo060339p CCC: $33.50 © 2006 American Chemical Society
Published on Web 05/06/2006

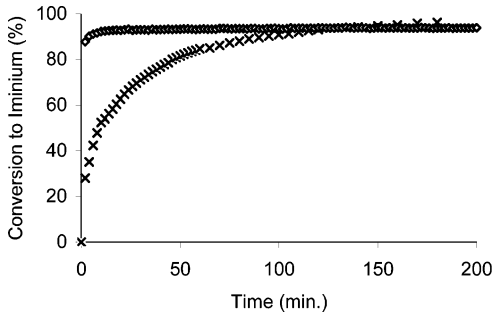


FIGURE 1. Rate of conversion of **1** to **3** in CD_3NO_2 (×) and in CD_3NO_2:D_2O 19:1 (◇). Performed using 1:1 mixtures of **1** and **2** (R = Ph) at 0.1 M.

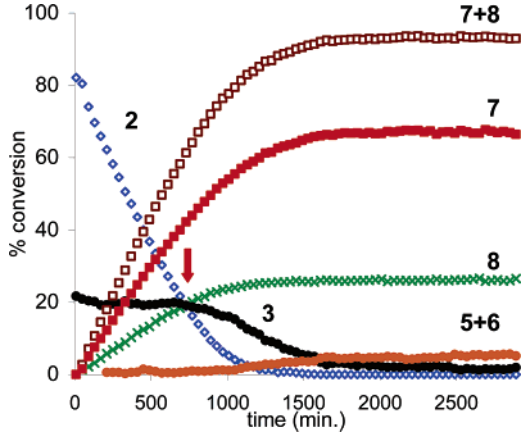


FIGURE 2. Rate of conversion of **1** to **7** and **8** in 0.1 M CD_3NO_2:D_2O 19:1. Species shown include **2** (◇, blue), **3** (●), **5** and **6** (●, orange), **7** (■, red), **8** (×, green). The combined amounts of products **7** and **8** are shown by (□, dark red).

Given that our catalyst performed well in water, and that many organocatalyzed reactions function best in wet solvents,[1,2] we investigated the effect of water on iminium generation. As shown in Figure 1, the addition of D_2O[7] to the sample dramatically increased the rate of iminium formation. In the presence of 5% D_2O, equilibrium was reached in less than 6 min. Presumably, this effect was due to an increase in H^+ supply allowing for faster proton transfers. More importantly, this result suggests that iminium formation was not rate-limiting for the aqueous process.

After observing the formation of **3**, our attention was directed toward the formation of intermediate cycloadducts **5** and **6** from iminium **3** in the presence of cyclopentadiene. Water played a key role in this transformation, limiting polymerization and degradation of the sample. Consequently, cycloadditions run in 1.0 M CD_3NO_2:D_2O (19:1) were very well-behaved and resulted in smooth conversion to cycloadducts that could be monitored by NMR (Figure 2).[8] The experiment was conducted using 0.2 equiv of catalyst **1** in 5% D_2O/CD_3NO_2. Spectra were collected at fixed intervals and the amounts of the various species determined as the reaction proceeded.[9] Distinct resonances were apparent for all species present.[10]

The formation of **3** was essentially complete as limited by the amount of original catalyst **1** (0.2 equiv). This species displayed steady-state behavior throughout the reaction until the amount of residual aldehyde **2** fell below 20% (arrow on graph), as there was no longer sufficient **2** available to maintain a full concentration of **3**. The concentration of **3** then fell smoothly as the amount of aldehyde **2** declined. This result could only

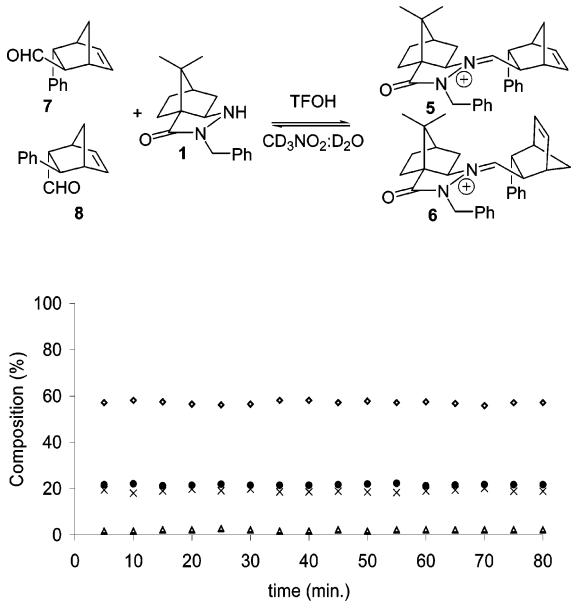


FIGURE 3. Rate of conversion of **7** and **8** to **5** and **6** in the presence of **1** in 1.0 M CD_3NO_2:D_2O (19:1). Species shown include **5** and **6** (×), **3** (△), **7** (◇), **8** (●).

be possible if the equilibrium between **1** and **3** was extremely rapid relative to the overall process. Concurrently, the concentration of product iminiums **5** and **6**[10] began to increase as the supply of **2** fell below that of **1**. This implied that the hydrolysis of iminiums **5** and **6**, to products **7** and **8**, was extremely rapid.[2a] Had this not been the case, the concentrations of these intermediates (**5** and **6**) would have been higher throughout the reaction. The fact that the amounts of these iminiums were negligible initially and became significant only after the supply of **2** was exhausted is consistent with this hypothesis. This experiment clearly showed that the cycloaddition was kinetically significant as both processes of iminium formation were extremely rapid relative to the cycloaddition event.[2a]

The hydrolysis phase of the reaction was further studied by a series of experiments which examined the formation of **5** and **6**, from **7** and **8**, respectively. This was done to alleviate the technical difficulties associated with observing the forward process. Mixing products **7** and **8** with 0.2 equiv of catalyst **1** immediately produced ~20% of iminiums **5** and **6** before our first time point could be taken (Figure 3), and this concentration remained constant through duration of the experiment.[11] These results corroborated our earlier hypothesis regarding the hydrolysis of iminiums **5** and **6** to products that suggested the rate of the final hydrolysis phase was extremely rapid relative to the overall process.

We noted in our initial communication that the nature of the cocatalyst counterion had a significant effect on the outcome of the reaction, both in terms of yield and enantioselectivity.[4]

(7) The addition of 5% and 10% D_2O was investigated. These experiments gave essentially the same results; however, spectral resolution was better with 5% D_2O. Performing the reaction at 0.01 M gave low conversion to **3** (65%, equilibration was still rapid). Increasing the concentration to 0.1 or 1.0 M resulted in rapid and complete conversion to **3**.

(8) At the conclusion of this experiment, the products were isolated in 88% yield and 83% ee (*exo*) and 81% ee (*endo*).

(9) Control spectra for **3**and **5**−**8** were independently collected.

(10) Spectral overlap precluded the direct measurement of the concentration of **6** in the mixture. The amounts of this compound were obtained by subtraction and used to normalize the values in Figure 2.

(11) After 16 h the amounts of all species were unchanged.

TABLE 1. Effect of Acid Cocatalyst on the Enantioselective Diels−Alder Reactions of Cyclopentadiene and Cinnamaldehyde Catalyzed by 1[a]

entry	acid	pK_a	yield[b] (%)	*exo*:*endo* (**7**:**8**)	*endo* ee[c] (%)
1	$HSbF_6$		59	1.8:1	81
2	HBF_4		98	1.7:1	85
3	CF_3SO_3H	−14	89	1.9:1	88
4	$HClO_4$	−10	82	1.7:1	85
5	HI	−10	13	1.2:1	31
6	HBr	−9	40	1.7:1	65
7	HCl	−8	11	1.3:1	27
8	CSA	−3	17	1.6:1	57
9	CH_3SO_3H	−2.6	8	1.2:1	15
10	$C_6H_5SO_3H$	−6.5	7	1.2:1	24
11	4-CH_3-$C_6H_4SO_3H$	−2.8	15	1.5:1	41
12	CF_3CO_2H	−0.3	13	1.7:1	30
13	CH_3CO_2H	4.8	7	1:1	2
14	H_2SO_4	−10	11	1.1:1	17

[a] 1 M in water using 20 mol % of **1** and indicated acid. [b] Combined isolated yield. [c] Enantiomeric excess determined by chiral GLC.

Initially this appeared to be correlated with the acid strength of the cocatalyst used. To better understand this effect, we carried out an expanded study of acids looking for patterns that could suggest improved reaction conditions.

Strong acids such as $HClO_4$ and CF_3SO_3H (Table 1, entries 3 and 4) were extremely efficient in the process whereas weaker acids such as CH_3SO_3H, CF_3CO_2H, or CH_3CO_2H were much less efficient (entries 9, 12, and 13). Several other acids were investigated in order to gain insight into this counterion effect, and it was quickly apparent that catalytic efficiency did not strictly correlate with acid strength. $HClO_4$, H_2SO_4, HI, and HBr are of comparable acidity, yet produced dramatically different turnovers and inductions (entries 4−6 and 14). All of the halogen acids in fact were rather inefficient cocatalysts (entries 5−7). The use of sulfonic acids also did not show any clear trends. Changing the steric bulk of the counterion (entries 3 and 8−10) did not give any discernible pattern other than acid strength. Acid strength did not correlate when steric bulk was controlled as exemplified by the results in the phenylsulfonyl series (entries 10−11). Interestingly, two very strong acids, HBF_4 and $HSbF_4$, proved to be very effective but did not offer any advantages in terms of efficiency, selectivity, or practicality (entries 1−2) over CF_3SO_3H.

The nucleophilic ability of certain conjugate bases could possibly deter overall reaction conversion and selectivity through the formation of aminals rather than iminium intermediates. However, no signs of such a species could be detected by ^1H or ^{13}C NMR using CF_3SO_3H, CH_3SO_3H, or HI.

Careful examination of the spectra obtained in the hydrolysis experiment (Figure 3) showed trace quantities of an unexpected species that was produced initially and remained at a concentration ~2% throughout the experiment. A typical spectrum from this experiment is shown in Figure 4a. All of the resonances could be accounted for by comparisons with sample spectra of the various species present (**5**−**8**) with the exception of a small resonance at 8.25 ppm. The chemical shift of this signal was consistent with a resonance of iminium **3**. Comparison with spectra of **3**, prepared separately in the same solvent, showed excellent overlap (Figure 4b). To isolate the spin system of **3** from the reaction spectrum, a 1D-TOCSY experiment was performed (Figure 4c). Irradiation of the signal at 8.25 ppm produced enhancements at 7.79 and 7.11 ppm, consistent with the resonances in the spin system of iminium **3** (Figure 4b).

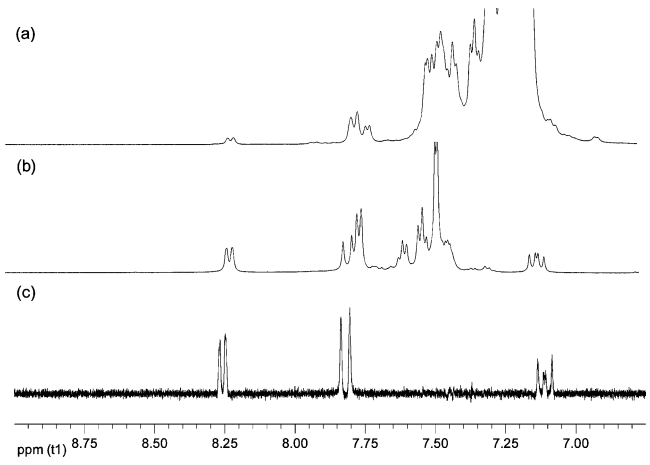
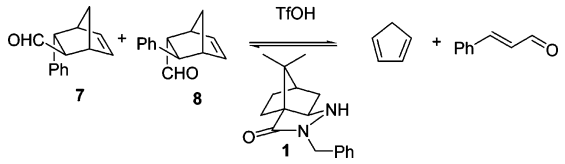


FIGURE 4. (a) Expansion of a spectrum of the conversion of **7** and **8** to **5** and **6** in the presence of **1** in 1.0 M CD_3NO_2:D_2O (19:1) after 80 min. (b) Expansion of a portion of the ^1H spectrum of **3**. (c) Expansion of the 1D-TOCSY spectrum of the sample in part a, irradiating the resonance at 8.25 ppm.

TABLE 2. Deracemization of Cycloadducts 7 and 8 in 19:1 CH_3NO_2:H_2O[a]



entry	equiv	equiv TfOH	*exo* ee[c] (%)	*endo* ee[c] (%)
1	0.2	0.2	13	8
2	1.0	1.0	32	16
3	0.2	0.18	6	5
4	0.2	1.0	11	28
5[b]	0.2	1.0	18	26

[a] Reactions performed at 1.0 M and 23 °C for 24−48 h. [b] Reaction performed at 4 °C. [c] Enantiomeric excess determined by chiral GLC.

Compound **3** could arise only through a catalyzed retro-Diels−Alder process. To test this, a racemic sample of **7** and **8** (1.7:1 *exo*:*endo*) was subjected to the standard reaction conditions (0.2% **1** in 19:1 CH_3NO_2:H_2O) to verify the presence of the reverse process.[12] After 48 h at room temperature, a small increase in enantiomeric excess was observed for both **7** and **8** confirming that retro-Diels−Alder reactions had in fact taken place (Table 2, entry 1). In water the effect was less dramatic as enantiomeric excesses of 8% and 3% (*endo*; *exo*) were observed using 20 mol % catalyst. Attempts to improve the selectivity by performing the reaction at 4 °C were unsuccessful (entry 5). However, by using 1 equiv of catalyst and acid we found that the extent of deracemization increased slightly (entry 2).[13] This observation prompted us to investigate the effects of varying the ratios of acid and hydrazide on the extent of chiral amplification. Using a slight excess of catalyst relative to acid resulted in a smaller enantioselectivity change (entry 3) whereas the presence of excess acid produced a modest enantioselectivity increase (entry 4). This suggested that the incidence of retro-Diels−Alder was dependent on free acid.[14]

When 20 mol % of TfOH was added to a mixture of **7** and **8** in 19:1 CD_3NO_2:D_2O, the NMR spectra of this mixture clearly

(12) To simulate the normal forward process, 2 equiv of cyclopentadiene was added.

(13) When a stoichiometric amount of catalyst was used, changes in the ratio of diastereomers were more pronounced (from 1.7:1 to 1:1 *endo*:*exo*).

showed the presence of small amounts of cinnamaldehyde arising from a retro-Diels−Alder process. Conversely, triflic acid alone was a poor catalyst of the forward reaction giving only 7% yield of **7** and **8** after a 48 h reaction with **2** and **4**.[4,15] Taken together, these results imply that triflic acid can catalyze a small amount of retro-Diels−Alder directly from **7** and **8**, but the cinnamaldehyde produced would then afford imminium **3** that reacts in a kinetically controlled process to give nonracemic adducts.[16]

Our investigations showed that the cycloaddition step was rate-limiting in the hydrazide catalyzed Diels−Alder reaction. The equilibrium between iminium **3** and free catalyst **1** was extremely rapid and heavily favored iminium **3**, thus maximizing the effective concentration of the reactive dienophile. Final hydrolysis of intermediate iminiums **5** and **6** to products was very rapid, and so this step did not significantly affect the rate of the overall process.

The key cycloaddition step was in fact a reversible process. The extent of the reverse reaction was slight and did not significantly impact the enantioselectivity of the overall reaction.[4] This retrocyclization component could be used to amplify the enantiomeric ratio of racemic Diels−Alder products by carefully limiting the amount of acid cocatalyst present. As such, it has significant implications for the design of subsequent catalysts and can potentially be exploited to design deracemization reactions. There are currently very few methods available to perform this type of chiral amplification, and such a process would have practical significance. We are currently investigating this possibility with catalysts related to **1**.

Experimental Section

^{1}H and ^{13}C NMR were recorded at 500 and 125 MHz, respectively, in CD_3NO_2 or in a mixture of CD_3NO_2/D_2O. Chemical shifts are reported in ppm relative to CH_3NO_2 ($\delta = 4.33$ ppm) for ^{1}H NMR and relative to the central CD_3NO_2 resonance at 62.8 ppm for ^{13}C NMR. Cyclopentadiene and cinnamaldehyde were freshly distilled before use. Unless noted, all compounds were reported in the literature or were commercially available.

NMR Study of Iminium Ion (3) Formation (Figure 1). To a solution of (*E*)-cinnamaldehyde (12.2 mg, 0.092 mmol) and **1** (25.0 mg, 0.092 mmol) in 19:1 CD_3NO_2:D_2O (1.0 mL) was added trifluoromethanesulfonic acid (8.2 μL, 0.092 mmol). The reaction was monitored at 23 °C by ^{1}H NMR using an automated experiment that acquired spectra at 4 min intervals until equilibrium was reached. ^{1}H NMR (300 MHz, CD_3NO_2) δ 8.22 (dd, $J = 10.2$, 2.1 Hz, 1H), 7.81 (d, $J = 15.3$ Hz, 1H), 7.77−7.40 (m, 2H), 7.59−7.42 (m, 8H), 7.12 (dd, $J = 15.3$, 10.5 Hz, 1H), 5.31 (d, $J = 17.0$ Hz, 1H), 5.27 (d, $J = 17.0$ Hz, 1H), 5.04−4.99 (m, 1H), 2.84−2.73 (m, 1H), 2.66 (dd, $J = 13.5$, 8.4 Hz, 1H), 2.42 (ddd, $J = 11.9$, 11.9, 5.4 Hz, 1H), 2.23−2.19 (m, 2H), 1.84−1.76 (m, 1H), 1.66−1.57 (m, 1H), 1.22 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (75 MHz, CD_3NO_2) δ 170.1, 158.6, 146.4, 135.3, 133.2, 131.1, 130.8, 130.7, 130.3, 129.0, 115.7, 74.2, 58.6, 55.1, 48.6, 47.8, 38.5, 27.8, 27.1, 20.6, 20.0.

NMR Study of Cycloaddition To Form 7 and 8 (Figure 2). To a suspension of (*E*)-cinnamaldehyde (12.2 mg, 0.092 mmol) in 19:1 CD_3NO_2:D_2O (1 mL) was added **1** (5 mg, 0.018 mmol) followed by trifluoromethanesulfonic acid (1.6 μL, 0.018 mmol). After stirring for 1−2 min, cyclopentadiene (18.3 mg, 0.277 mmol) was added, and the resulting mixture was monitored at 23 °C by ^{1}H NMR using an automated experiment that acquired spectra at 40 min intervals for 48 h. The reaction mixture was then extracted twice with ether, and the combined organic extracts were washed successively with water and brine and then dried over Na_2SO_4. Purification by silica gel chromatography (5% EtOAc in hexanes) provided the desired material as a 2.4:1 mixture of *exo* and *endo* isomers **7** and **8** (colorless oil, 16 mg, 88%), *exo* ee 83%, *endo* ee 81%. Enantiomeric ratios were determined using chiral GLC analysis (Agilent/J&W CycloSil-B, 100 °C hold 3 min then 2 °C/ min gradient, flow = 3.0 mL/min), *exo* isomers $t_R = 42.7$ min, 43.8 min, *endo* isomers $t_R = 43.4$ min, 44.3 min.

TOCSY NMR Experiment on Racemic 3-Phenylbicyclo[2.2.1]-hept-5-ene-2-carboxaldehydes (7 and 8) (Figures 2 and 4). Compound **1** (22.6 mg, 0.083 mmol) was dissolved in 19:1 CD_3NO_2:D_2O (0.45 mL) followed by the addition of trifluoromethanesulfonic acid (7.4 μL, 0.083 mmol). To this solution was then added racemic **7** and **8** (83 mg, 0.419 mmol), and the reaction was monitored at 23 °C by ^{1}H NMR recording spectra at 5 min intervals for 80 min (Figure 2). At this time, a TOCSY experiment was performed by irradiation of the doublet at 8.25 ppm at 60, 120, 150, and 200 ms mixing times. Resonances at 7.79 and 7.11 ppm were most significant at 60 ms and were consistent with the resonances of spin system **3**.

General Procedure for Hydrazide-Catalyzed Diels−Alder Reactions (Table 1, Entry 2). To a suspension of (*E*)-cinnamaldehyde (100 mg, 0.756 mmol) in distilled water (0.75 mL) was added compound **1** (41 mg, 0.151 mmol) followed by 48% tetrafluoroboric acid (13.5 μL, 0.151 mmol). After the mixture stirred for 1−2 min, cyclopentadiene (150 mg, 2.27 mmol) was slowly added, and the resulting mixture was stirred at 23 °C until the reaction was judged complete by TLC analysis (24 h). The reaction mixture was extracted twice with ether, and the combined organic extracts were washed successively with water and brine and then dried over Na_2SO_4. Purification by silica gel chromatography (5% EtOAc in hexanes) provided the desired material as a 1.7:1 mixture of *exo* and *endo* isomers (colorless oil, 147 mg, 98%), *exo* ee 89%, *endo* ee 85%.

General Procedure for Deracemization of Racemic Cycloadducts 7 and 8 (Table 2 entry 4). A solution of compound **1** (68.1 mg, 0.252 mmol) in 0.25 mL of 19:1 CH_3NO_2:H_2O was treated with trifluoromethanesulfonic acid (22.3 μL, 0.252 mmol). To this solution was added a 1.7:1 *exo*:*endo* racemic mixture of **7** and **8** (50 mg, 0.252 mmol). Freshly distilled cyclopentadiene (33 mg, 0.504 mmol) was slowly added, and the reaction stirred for 24 h at 23 °C. The reaction mixture was extracted twice with ether, and the combined organic extracts were washed successively with water and brine and then dried over Na_2SO_4. Purification by silica gel chromatography (5% EtOAc in hexanes) provided the desired material as a 1:1 mixture of *exo* and *endo* isomers (colorless oil, 23.5 mg, 47%), *exo* ee 11%, *endo* ee 28%.

Acknowledgment. M.L. is grateful for graduate scholarships from NSERC, OGSST, and the University of Ottawa. We thank Dr. Glenn Facey for technical assistance. This research has been supported by NSERC, the Canadian Foundation for Innovation, and the University of Ottawa.

Supporting Information Available: Copies of Figures 1−4. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060339P

(14) Similar contributions could be occurring in other organocatalyzed cycloadditions. Only small amounts of retrocycloaddition were observed when racemic **7** and **8** were mixed with Macmillan's imidazolidinone catalyst[2a] in 9:1 MeOH:H_2O for 24 h.

(15) (a) Cavill, J. L.; Peters, J.-U.; Tomkinson, N. C. O. *J. Chem. Soc., Chem. Commun.* **2003**, 728−729. (b) Cavill, J. L.; Elliot, R. L.; Evans, G.; Jones, I. L.; Platts, J. A.; Ruda, A. M.; Tomkinson, N. C. O. *Tetrahedron* **2006**, *62*, 410.

(16) This is supported by the observation that the enantioselectivities for the entire process were not dependent on the relative amounts of catalyst and acid. See ref 4.