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Aqueous Enantioselective Organocatalytic Diels–Alder Reactions Employing Hydrazide Catalysts. A New Scaffold for Organic Acceleration

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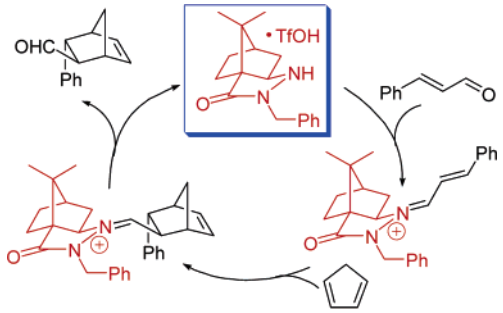
ABSTRACT



Cyclic hydrazides function as asymmetric organocatalysts in aqueous Diels–Alder reactions. The hydrazide is employed as the catalytic machinery in a compact camphor-derived framework that imparts facial selectivity to the cycloadditions. Kinetic evidence suggests the reaction involves rapid iminium formation.

Recent interest in asymmetric organocatalytic transformations has been intense.[1] Many reactions have been enantioselectively accelerated by organic compounds. Among these, aldols, alkylations, and Mannich reactions have generally received the most attention.[1] The use of organocatalysis in cycloaddition reactions has been less extensively explored.[2−5] The most general mode of enantioselective organocatalysis in cycloadditions is the generation of active iminium ions.[3] These species act to lower the energy of the dienophile LUMO, producing acceleration analogous to that of Lewis acids.[3] In this paper, we disclose the design and synthesis of a new structural class of organic catalysts functioning in water. A hydrazide is employed as the catalytic machinery in a compact camphor-derived framework that imparts facial

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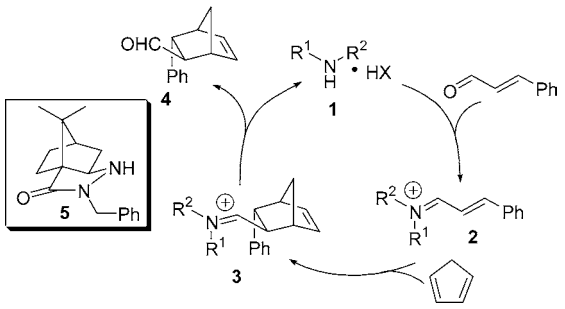
selectivity to Diels−Alder reactions. Evidence of a novel mechanism of action, involving rapid iminium formation, is also presented.

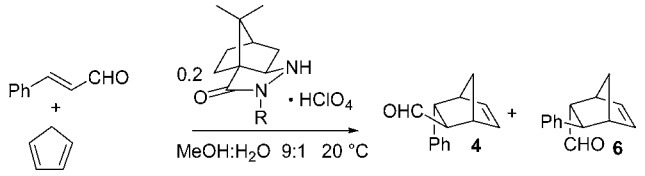
Scheme 1. Iminium Catalysis in Diels−Alder Cycloadditions



The design of our organocatalysts was driven by the goal of increasing catalyst turnover. Catalysis in iminium-based processes involves three phases: formation of an iminium, such as **2** from catalyst **1** and aldehyde, cycloaddition to form **3**, and finally hydrolysis to release products and regenerate catalyst **1**. It has been suggested[6] that the overall efficiency in iminium-catalyzed reactions is dictated by the rate of iminium generation. To address this issue, we decided to enhance the nucleophilicity of our catalyst by means of the α-heteroatom effect.[7] Such a modification would presumably increase the rate of formation of **2**, while maintaining a high rate of conversion to **3**. This hypothesis has led to the development of a new catalyst system based on cyclic hydrazides.[8] Our catalyst design sought to incorporate a hydrazide moiety into a chiral framework featuring a five-membered ring. The hydrazide would provide the necessary α-heteroatom for nucleophilic acceleration together with an electron-withdrawing moiety to improve the rate of iminium hydrolysis (**3** → **1**). Such architecture would require geminal substitution α to the carbonyl in order to suppress *β*-elimination. A readily available scaffold, which provides such features, is found in hydrazides such as **5** that are readily synthesized in four steps from camphorsulfonic acid.

The efficiency of this system was first evaluated using hydrazide **7**[9] in a Diels−Alder reaction between cinnamaldehyde and cyclopentadiene. This strategy proved successful as the use of **7** resulted in catalysis of the cycloaddition with modest enantioselectivity[10] and low yield (Table 1, entry 1).[11] Changes to the indicated side chain proved crucial for

Table 1. Hydrazide-Catalyzed Asymmetric Diels−Alder Reactions



entry	catalyst	R	yield (%)[a]	*exo*:*endo* (**4**:**6**)	*endo* ee (**6**)[11] (%)
1	**7**	Ph	25	1.1:1	60
2	**8**	H	25	0.9:1	3
3	**9**	Me	18	1.2:1	58
4	**5**	Bn	90	2.1:1	82
5	**10**	CH_2-1-naphthyl	82	1.7:1	74

[a] Combined isolated yield.

reactivity and enantioselectivity. Removal of the side chain was deleterious to catalyst activity[12] and resulted in almost no enantioselectivity (entry 2). Small aliphatic groups at this position gave yields and facial selectivity similar to that of **7** (entry 3). Catalyst **5**, however, gave efficient conversion to product with an enantioselectivity of 82% (entry 4). The reaction displayed selectivity for *exo* isomer **4**, and both the *exo* and *endo* isomers showed similar enantioselectivities. Increasing the size of the aromatic function relative to a benzyl group did not improve enantioselectivity (entry 5).

The use of catalyst **5** in a variety of aqueous solvent mixtures (9:1 solvent:H_2O) was explored. We found that aqueous mixtures of MeOH (yield 90%, *endo* ee 82%) and CH_3NO_2 (yield 92%, *endo* ee 75%) gave efficient and enantioselective conversion to products, whereas the use of CH_3CN (yield 49%, *endo* ee 73%), THF (yield 23%, *endo* ee 83%), or CH_2Cl_2 (yield 64%, *endo* ee 75%) resulted in only moderate yields. Enantioselectivity was less sensitive to the nature of the solvent. Optimal catalyst performance was noted in water, in which an enantioselectivity of 85% and a chemical yield of 82% were achieved. Reactions in water were biphasic, and enantioselectivity was maintained with substrate concentrations up to 2 M.

Tuning the acid co-catalyst led to a further performance enhancement for catalyst **5**. A striking correlation was apparent between the strength of the acid used and the efficiency of the reaction (Table 2). Steady erosion in both yield and enantioselectivity was observed as the acidity of the co-catalyst was decreased. We obtained the best results using CF_3SO_3H, which gave not only the best yield and selectivity but also the cleanest and fastest reactions. To our knowledge, such a correlation has not been previously observed in organically catalyzed asymmetric reactions.[5a]

Such strong acids could have been capable of catalyzing the Diels−Alder process, resulting in lowered enantioselectivity through a competing achiral process.[13] The potential impact of this background reaction was tested using 0.2 equiv

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(11) Enantiomer ratios were determined on the aldehydes by chiral GLC and by ^{1}H 500 MHz NMR of the corresponding (+)-(*R*,*R*)-hydrobenzoin acetals. The absolute configurations of major products **4** and **6** were established by comparison to the NMR spectra of the (+)-(*R*,*R*)-hydrobenzoin acetals of (*S*)-**4** and (*S*)-**6** prepared independently (refs 3 and 10).

(12) In contrast, acyclic hydrazides lacking substitution at this position are effective in an achiral sense. See ref 8.

Table 2. Effect of Acid Co-catalyst on the Asymmetric Diels−Alder Reactions of Cyclopentadiene and Cinnamaldehyde Catalyzed by **5**[a]

entry	acid	pK_a	yield (%)[b]	*exo*:*endo* (**4**:**6**)	*endo* ee (%)[11]
1	CF_3SO_3H	−14	89	1.9:1	88
2	$HClO_4$	−10	82	1.7:1	85
3	CSA	−3	17	1.6:1	57
4	CH_3SO_3H	−2.6	8	1.2:1	15
5	CF_3CO_2H	−0.3	13	1.7:1	30
6	CH_3CO_2H	4.8	7	1:1	2

[a] With 1 M in water using 20 mol % of **5** and indicated acid. [b] Combined isolated yield.

of catalyst **5** with varying amounts of CF_3SO_3H (0.1, 0.2, and 0.4 equiv). In all cases, the enantioselectivities were identical, indicating that strong acid was not detrimental to selectivity.

Experiments that outline the scope of the present process are given in Table 3. Substituted cinnamaldehyde dienophiles

Table 3. Asymmetric Diels−Alder Reactions between Cyclopentadiene and Various Dienophiles Catalyzed by **5**[a]

entry	diene	dienophile	yield (%)[c]	*exo*:*endo*	*exo* ee (%)[11,14]
1	CP[b]	(*E*)-PhCH=CHCHO	96	1.9:1	90
2	CP	(*E*)−4-NO_2−PhCH=CHCHO	93	2.2:1	92
3	CP	(*E*)−4-Cl−PhCH=CHCHO	92	2:1	90[d]
4	CP	(*E*)−4-^{i}Pr −PhCH=CHCHO	84	1.7:1	90[d]
5	PBD	(*E*)−4-NO_2−PhCH=CHCHO	86	-	85
6	MPD	(*E*)−4-NO_2−PhCH=CHCHO	71	1.9:1	69[d]
7	CP	(*E*)−2-NO_2−PhCH=CHCHO	90	1.2:1	87
8	CP	(*E*)−3-NO_2−PhCH=CHCHO	88	2.1:1	94[d]
9	CP	(*E*)-PrCH=CHCHO	83	1.6:1	81
10	CP	(*E*)-^{i}Pr CH=CHCHO	84	2.6:1	85

[a] Conditions: 3 equiv of diene, 1 equiv of dienophile, 0.2 equiv of **5**, 0.2 equiv of CF_3SO_3H, H_2O, 20 °C. [b] CP: cyclopentadiene; PBD: 2-phenylbutadiene; PMD: 2-methyl-1,3-pentadiene. [c] Combined isolated yield. [d] The *endo* isomer.

produced excellent selectivity and yields (entries 1−4).[15] A variety of substitutions on the aryl ring, including electron-withdrawing and -donating groups, were tested and gave excellent enantioselectivities. Ortho or meta substitution was tolerated and gave high facial selectivity (entries 7 and 8). Aliphatic substitution was also possible with increased bulk of the substituent, producing slight advantages in terms of facial selectivity (entries 9 and 10).[16] Substituted dienes, such as 2-phenylbutadiene, gave high enantioselectivity when the addition was catalyzed by **5**, as did the use of doubly substituted dienes (entries 5 and 6).

(13) An uncatalyzed reaction did not produce any detectable product after 24 h at 23 °C. A reaction catalyzed by 0.2 equiv of acid gave a trace of product (<5%) after 24 h at 23 °C, showing a slight preference for the *endo* product (1.3:1).

(14) Enantiomeric excesses for *endo* isomers are given in Supporting Information.

(15) The absolute configurations of products were established by correlation of the chemical shifts of the (+)-(*R*,*R*)-hydrobenzoin acetals with those of the corresponding acetals derived from **4** and **6**.[3,10]

We examined the structure of the iminiums formed in our reactions using semiempirical calculations (PM3 in Spartan Pro). These calculations indicated that the iminium illustrated below (Figure 1) was the lowest energy conformer. This

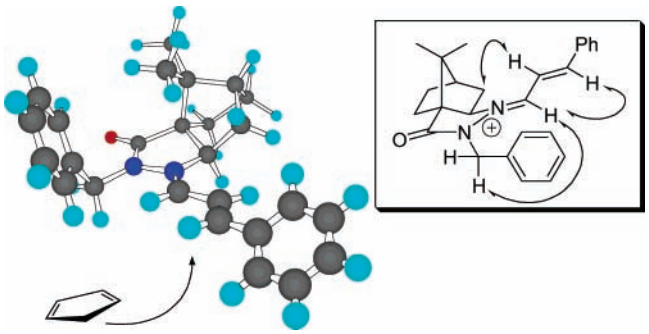

Figure 1. Minimum energy iminium ion formed from cinnamaldehyde and **5**.

geometry was confirmed by spectral analysis of the iminium formed between **5** and cinnamaldehyde. A NOESY spectrum of this species showed strong correlations between the hydrogens, consistent with the calculated structure. Approach of the diene to the bottom face of this favored iminium as indicated leads to the major stereoisomers in all cases.

Using ^{1}H NMR, we monitored the rate of iminium formation and discovered that the process was extremely rapid, in agreement with our initial hypothesis. This is in contrast to the case of imidazolidinone catalyst **11**,[3a] which forms an iminium species considerably more slowly and is not fully implicated as the reactive form, even after several hours (Figure 2). This suggests that the rate-limiting step

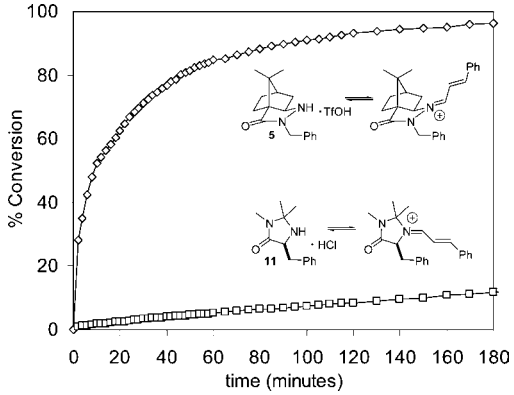

Figure 2. Extent of iminium formation over time.

for the present reaction is not iminium formation, as has been proposed for the case of catalysis by compounds, such as

(16) The absolute configurations of the major products of entries 9 and 10 were established by GLC comparison to authentic samples.[3]

11,[6] but is another transformation in the overall process. Investigations into the mechanism of the current process are ongoing.

We have developed a new class of catalysts for asymmetric organocatalyzed Diels−Alder reactions. The catalysts function best in water, providing an environmentally benign reaction that gives excellent yields and enantioselectivities. The reactions produce a preference for the *exo* isomer, and enantioselectivities for both the *exo* and *endo* products were excellent. Acid co-catalyst strength was important, with strong acids producing the best selectivity. Preliminary mechanistic studies indicate that iminium formation is extremely rapid, suggesting a catalytic process distinct from other organocatalytic cycloadditions. Further studies to address the scope and mechanism of this transformation as well as investigations of other chiral transformations using hydrazides derived from **5** will be described shortly.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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