Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 3033

www.rsc.org/obc

PAPER

A novel hydrazide type organocatalyst for enantioselective Diels–Alder reactions†

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Received 8th December 2010, Accepted 1st February 2011
DOI: 10.1039/c0ob01138j

The development of a new class of hydrazide type organocatalyst, (4*R*,5*R*)-1,3-bis(isopropylamino)-4,5-dihenylimidazolidin-2-one **2a**, for enantioselective Diels–Alder reactions between cyclopentadiene and α,β-unsaturated aldehydes are presented. The new organocatalyst **2a** promoted the reaction, affording Diels–Alder adducts in good yields with good levels of enantioselectivity.

Introduction

Diels–Alder reaction is one of the most useful synthetic methods for constructing six-membered carbocyclic and heterocyclic frameworks, and enantioselective versions of this reaction have attracted much attention due to their applicability to enantioselective synthesis of natural products and biologically active compounds.[1,2] While the use of chiral auxiliaries and the employment of chiral Lewis acid catalysts have been recognized as conventional and reliable methods in enantioselective reactions, organocatalysts have recently emerged as powerful tools for many enantioselective reactions including Diels–Alder reactions.[3,4] Among the recently reported organocatalytic transformations, the use of chiral secondary amines, such as proline, prolinol, imidazolidine and their derivatives, has been a mainstream; however, long reaction time and/or loading 10 mol% or more of catalysts have often been required to complete the reactions. These catalysts have a highly nucleophilic pyrrolidine or imidazoline framework as a catalysis core; therefore, it seems to be difficult to dramatically improve the inherent reactivity of these catalysts by structural modifications. To overcome these difficulties, Tomkinson first introduced an acyl hydrazine as an organocatalyst in Diels–Alder reactions and showed that the hydrazide was a catalyst superior to usual aminocatalysts.[5] After this report, Ogilvie[6] reported the first example of acyl hydrazide-type chiral organocatalysts for enantioselective Diels–Alder reactions in aqueous media, and Lee[7] and Langlois[8] reported that chiral sulfonylhydrazides also catalyzed Diels–Alder reactions effectively, and more recently, Smith[9] reported pyrazolidinone-mediated enantioselective Diels–Alder reactions. While hydrazines, hydrazides and their derivatives are fascinating as a catalysis core due to their enhanced nucleophilicity caused by an α-heteroatom effect as mentioned above, they have attracted much less attention, and reported successful examples of chiral catalysts are limited to camphor-based cyclic hydrazides. We thought that this situation was probably caused by the lack of chiral sources that were easily available for preparing chiral hydrazinocatalysts, and we therefore decided to explore effective chiral catalyst-platforms with structural diversity. For this purpose, we screened several hydrazines and hydrazides for their catalytic efficiency in Diels–Alder reactions. We were delighted to find that 1-aminooxazolidinone **1a–1c** and 1,3-diaminoimidazolidinone **2a–2b** showed higher catalytic activity than did the other catalysts tested because these results indicated that we could utilize the existing chiral oxazolidinones and imidazolidinones for our catalyst design. In this paper, we report that chiral 1-aminooxazolidinones **1a–1c** and 1,3-diaminoimidazolidines **2a–2b** effectively catalyzed Diels–Alder reactions of cyclopentadiene and α,β-unsaturated aldehydes with moderately to good enantioselectivity (Fig. 1.)

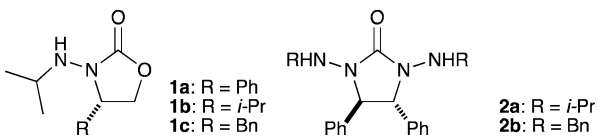

Fig. 1 Catalysts in this study.

Results and Discussions

The new hydrazide-type catalysts **1** and **2** were readily prepared from commercially available materials as shown in Scheme 1.

Commercially available chiral oxazolidinones were treated with NaH and $DPPONH_2$ in 1,4-dioxane at 60 °C followed by a reductive amination process giving catalysts **1a–1c**.[10] Catalysts **2a** and **2b** were also prepared by a procedure similar to that employed for preparing **1a–1c**. We first examined Diels–Alder reactions between cinnamaldehyde and cyclopentadiene in the presence of catalysts **1a–1c** or catalysts **2a** and **2b** in MeOH or IPA, and the results are summarized in Table 1.

All of the catalysts efficiently catalyzed Diels–Alder reactions to give adducts in good yields within a few hours, though diastereoselectivity was not observed. As for the reaction rate, **1a**

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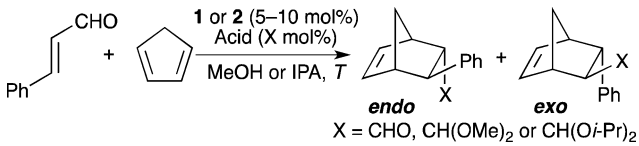
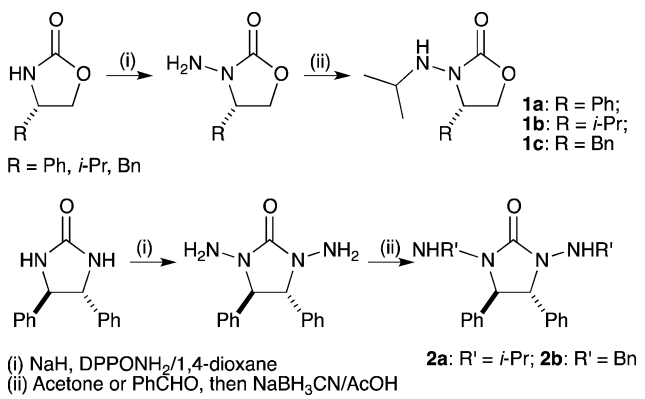
† Electronic supplementary information (ESI) available: See DOI: 10.1039/c0ob01138j

Table 1 Diels–Alder reactions between cinnamaldehyde and cyclopentadiene in MeOH in the presence of **1a–1c**, **2a** and **2b**[a]



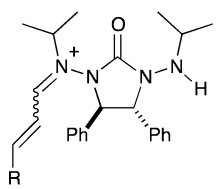
Entry	Cat.	acid (X)[f]	T/°C	t/h	Yield/%[b]	*endo* : *exo*[c]	*endo* ee/%[d]
1	**1a**	HCl (10)	rt	0.3	91	44 : 56	–14 (–15)
2	**1b**	HCl (10)	rt	2.5	86	44 : 56	–53 (–42)
3	**1c**	HCl (10)	rt	1.5	83	45 : 55	–56 (–39)
4	**2a**	HCl (10)	rt	0.9	86	49 : 51	61 (53)
5	**2a**	HCl (10)	–22	3.0	73	54 : 46	80 (72)
6	**2a**	TFA (10)	–22	17	60	44 : 56	40 (47)
7	**2a**	MsOH (10)	–22	6.0	75	52 : 48	74 (66)
8	**2a**	H_2SO_4 (5)	–22	24	79	47 : 53	52 (55)
9	**2a**	TfOH (10)	–22	3.0	68	44 : 56	62 (61)
10	**2a**	HCl (30)	rt	0.5	83	51 : 49	78 (72)
11	**2a**	HCl (30)	–22	1.0	77	57 : 43	85 (76)
12[e]	**2a**	HCl (30)	rt	0.7	80	50 : 50	83 (76)
13[e]	**2a**	HCl (30)	–22	2.5	80	51 : 49	89 (70)
14[e]	**2b**	HCl (30)	–22	0.9	69	39 : 61	63 (58)

[a] Cinnamaldehyde (1.0 mmol) was dissolved in MeOH (3 M) and to this solution were added 10 mol% of **1a–1c** (5 mol% for **2a** and **2b**), 10 mol% of acid cocatalyst and cyclopentadiene (3.0 mmol) in this sequence. [b] Products were obtained as a mixture of an aldehyde and an acetal and yields were determined after hydrolysis of the acetal to the aldehyde. [c] Determined by ^{1}H–NMR. [d] Determined by chiral HPLC and the values in parentheses indicate ee of *exo* isomer. [e] The reactions were carried out in IPA (3 M solution). [f] 1,4-Dioxane solution of HCl (4 M) was used.

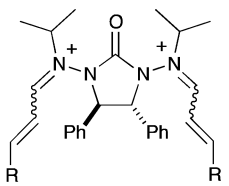


Scheme 1 Preparation of catalysts.

was most effective and the reaction was completed within 20 min, but the enantioselectivity of both *endo* and *exo* isomers was very low (14% ee for the *endo* isomer, entry 1). When **1b**, **1c** and **2a** were employed as catalysts, the reaction proceeded smoothly to give adducts with moderate enantioselectivity (53–61% ee for the *endo* isomer) (entries 2–4). When the reaction using **2a** was conducted at –22 °C, enantioselectivity was improved to 80% ee for the *endo* isomer, though the reaction time was prolonged to 3.0 h (entry 5). In the reactions using catalyst **2a**, the absolute configurations of major enantiomers of both *endo* and *exo* isomers were assigned *2S* by comparison with reported data.[4f] It is noteworthy that twin-core type catalyst **2a** gave results superior to those given by single-core type **1a** as for enantioselectivity, although the chiral environment around each catalysis core of **2a** is similar to that of single-core **1a** except for absolute configuration (entries 1 *vs.* 4). Other acid cocatalysts, such as TFA, MsOH, H_2SO_4 and TfOH, proved to be less effective, and lower enantioselectivity was observed than that observed in the reaction using HCl as a cocatalyst (entries 6–9). Since the catalyzed reaction involves three processes, namely, hydrazonium ion formation, Diels–Alder reaction and hydrolysis and/or solvolysis of the resulting adducts, it is difficult to quantitatively explain the effects of acid cocatalysts on the reaction efficiency including asymmetric induction.[11] However, based on the assumption that the rate-determining step is hydrazonium ion formation,[5b] as for the reaction rate, we can provide some reasonable explanations. Acid cocatalysts promote the dehydration reaction in the hydrazonium ion formation process, but the addition of a catalyst to an aldehyde was retarded at the same time due to a decrease of a nucleophilic unprotonated catalysis-core in the presence of acids. For example, TfOH can more effectively facilitate the dehydration reaction than can HCl. However, compared to HCl, TfOH must more extensively protonate a catalysis-core, and the amount of a free catalysis-core should be decreased, leading to net efficiency similar to that of HCl. At present, we consider HCl to be an optimal acid, its acidity beeing sufficiently high to facilitate the dehydration reaction but not so high as to completely protonate the catalysis-core even in the presence of excess HCl. Acid cocatalysts also affected efficiency of asymmetric induction. In the catalyzed-reactions using **2a**, two hydrazonium ions **I** and **II** are involved as possible reactive intermediates.



I



II

We now assume that a reactive intermediate is altered by the acid cocatalyst used and that **II** worked as a reactive intermediate

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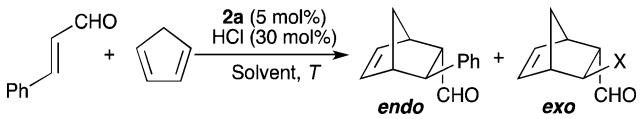
Table 2 Optimization of reaction solvents[a]



Entry	Solvent	T/°C	t/h	Yield/%	*endo* : *exo*[b]	*endo* ee/%[c]
1	Toluene	rt	8	89	50 : 50	76 (72)
2	DCM	rt	2.5	95	54 : 46	78 (72)
3	AcOEt	rt	4.0	90	54 : 44	79 (73)
4	1,4-dioxane	rt	3.5	71	53 : 47	79 (73)
5	CH_3CN	rt	0.7	89	58 : 42	77 (69)
6	CH_3NO_2	rt	0.7	77	59 : 41	77 (68)
7	DMF	rt	0.8	88	54 : 46	85 (73)
8	DMF	0	4.0	80	55 : 45	88 (78)
9	Water	rt	12	92	46 : 54	40 (44)
10	Sat. brine	rt	8.5	90	48 : 52	63 (54)

[a] Cinnamaldehyde (1.0 mmol) was dissolved in an indicated solvent (5 M) and to this solution were added 5 mol% of **2a**, 30 mol% of HCl (4 M soln. in 1,4-dioxane) and cyclopentadiene (3.0 mmol) in this sequence. [b] Determined by ^{1}H-NMR. [c] Determined by chiral HPLC and the values in parentheses indicate ee of *exo* isomer.

in the presence of HCl, giving good enantioselectivity. These mechanistic aspects are discussed together with the unexpectedly low enantioselectivity observed in the reaction using **1a** in a later section. When the reaction was carried out in the presence of 30 mol% of HCl at rt and –22 °C, the enantioselectivity was improved to 78% ee and 85% ee for the *endo* isomer, respectively (entries 10 and 11). In addition, when IPA was used as a solvent, enantioselectivity was slightly improved, though longer reaction time was needed compared to MeOH (entries 12 and 13). We also examined the use of **2b** as a catalyst. Catalyst **2b** exhibited higher efficiency than did **2a** and the reaction was completed within 1 h even at –22 °C; however, enantioselectivity of both *endo* and *exo* isomers was not high, 63% ee and 58% ee, respectively (entry 14). Although **2a** worked well as a catalyst for the reaction of cinnamaldehyde and cyclopentadiene in MeOH and IPA, the reactions had to be carried out at –22 °C to obtain a satisfactory result. In addition, the reaction using 3-(4-methoxypheny)propenal as a dienophile was not completed even after 48 h, and 3-(4-nitrophenyl)propenal did not react at all at –22 °C probably due to their poor solubility in MeOH and IPA at this temperature. We therefore screened reaction solvents for their applicability to the catalyzed-reactions, and the results are summarized in Table 2.

In organic solvents, enantioselectivity was less sensitive to the nature of the solvents, whereas the reaction rate was considerably dependent on the solvent. In non- or less-polar solvents, such as toluene, DCM, AcOEt and 1,4-dioxane, the reaction also proceeded with good enantioselectivity (70–80% ee), but longer reaction time than that in MeOH was needed. In these reactions, a precipitate was formed immediately after addition of HCl, and the reaction became inhomogeneous (entries 1–4). Since the reactions proceeded as the precipitate decreased, the precipitate was thought to be an intermediary hydrazonium ion. On the other hand, in polar solvents, such as acetonitrile, nitromethane and DMF, the reactions became homogeneous and were completed within 1 h at rt giving adducts with good enantioselectivity (68–85% ee, entries 6–7). In particular, DMF was shown to be a better solvent than the others, and the reaction was completed within 4 h with good yield and enantioselectivity (88% ee for the *endo* isomer) at 0 °C. We also examined the use of water and saturated brine as solvents (entries 9 and 10). In these aqueous conditions, catalyst **2a** did not work well, leading to considerable decrease of enantioselectivity, whereas Ogilvie's pyrazolidinone-based catalyst and Lee's sulfonylhydrazide could work efficiently in aqueous media.[6a,7] We further investigated the effects of acid cocatalysts and amount of catalyst **2a** in DMF, and the results are shown in Table 3.

When TFA and TfOH were used, enantioselectivity was lowered to 42% ee and 60% ee for the *endo* isomer, respectively. TsOH gave better results than did the former two acids but was slightly less effective than HCl (entries 1–3). The amount of HCl did not affect the enantioselectivity but affected reaction time in DMF, whereas both enantioselectivity and reaction rate were improved in MeOH as the amount of HCl was increased (entries 4 and 5). When the amount of catalyst **2a** was decreased to 1 mol%, the reaction was also completed to give Diels–Alder adducts with good enantioselectivity, but reaction time was considerably prolonged to 72 h (entry 6).

On the other hand, interestingly, using 30 mol% of catalyst **2a** did not improve the reaction rate, and the efficiency was rather decreased compared with that in the case of using 5 mol% of catalyst **2a**, whereas enantioselectivity was not affected by the amount of **2a** (entry 7). These results implied that not only the amount of catalyst **2a** but also the ratio of catalyst **2a** to acid cocatalyst is crucial to obtain satisfactory reaction efficiency. We further carried out a series of Diels–Alder reactions using various aldehydes, and the results are summarized in Table 4.

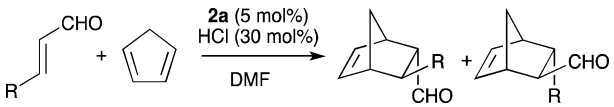
While (*E*)-3-(4-nitrophenyl)propenal reacted very smoothly at 0 °C to afford Diels–Alder adducts in 97% yield with good enantioselectivity, (*E*)-3-(4-isopropylphenyl)propenal and (*E*)-3-(4-methoxyphenyl)propenal reacted very slowly at 0 °C, and the reaction had to be conducted at rt to obtain satisfactory results (entries 1–4). When (*E*)-3-(2-nitrophenyl)propenal was used as a dienophile, enantioselectivity of *endo* and *exo* isomers reached 96% ee and 92% ee, respectively. In this reaction, interestingly, the *endo* isomer was formed in preference to the *exo* isomer, and the dr

Table 3 Optimization of reaction conditions in DMF[a]

Entry	Acid (X)	**2a** (Y)	T/°C	t/h	Yield/%	*endo* : *exo*[b]	*endo* ee/%[c]
1	TFA (30)	5	rt	6.0	88	54 : 46	42 (44)
2	TsOH (30)	5	rt	1.3	91	55 : 45	79 (68)
3	TfOH (30)	5	rt	1.0	89	44 : 56	60 (57)
4	HCl (10)	5	0	24	85	53 : 47	86 (74)
5	HCl (50)	5	0	2.5	82	56 : 44	87 (76)
6	HCl (30)	1	0	72	82	55 : 45	87 (74)
7	HCl (30)	30	0	7	84	54 : 46	84 (70)

[a] Cinnamaldehyde (1.0 mmol) was dissolved in DMF (5 M) and to this solution were added 5 mol% of **2a**, 30 mol% of HCl (4 M Soln. in 1,4-dioxane) and cyclopentadiene (3.0 mmol) in this sequence. [b] Determined by ^{1}H-NMR. [c] Determined by chiral HPLC and the values in parentheses indicate ee of *exo* isomer.

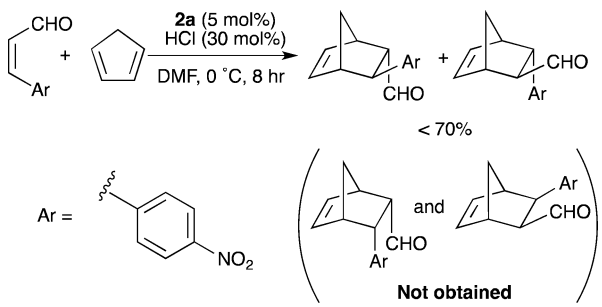
Table 4 Diels–Alder cycloaddition reactions using various aldehydes in the presence of **2a**[a]



Entry	*R*	T/°C	t/h	Yield/%	*endo* : *exo*[b]	*endo* ee/%[c]
1	4-*i*-Pr-Ph	0	24	27	49 : 51	—
2	4-*i*-Pr-Ph	rt	1.5	73	51 : 49	80 (68)
3	4-MeO-Ph	rt	9.0	86	44 : 56	81 (73)
4	4-NO_2-Ph	0	2.0	97	59 : 41	90 (80)
5	2-NO2-Ph	0	2.5	90	80 : 20	96 (92)[d]
6	4-Br-Ph	0	2.6	92	55 : 45	86 (78)
7	Me	0	2.0	77	63 : 37	78[d]
8	*n*-Pr	0	4.5	85	59 : 41	80 (74)

[a] An α,β-unsaturated aldehyde (1.0 mmol) was dissolved in DMF (5 M) and to this solution were added 5 mol% of **2a**, 30 mol% of HCl (1,4-dioxane soln.) and cyclopentadiene (3.0 mmol) in this sequence. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC and the values in parentheses indicate ee of *exo* isomer. [d] Ee of *endo* isomer was obtained by acetalization with (+)-(*R*,*R*)-hydrobenzoin and ^{1}H NMR analysis

reached 80 : 20, unlike in the reactions using other unsaturated aldehydes. Aliphatic aldehydes, such as crotonaldehyde and 2-hexenal, also reacted efficiently affording adducts in 77% and 85% yields, respectively, and with enantioselectivity of 76% ee and 80% ee for *endo* isomers, respectively. We also examined the reaction of cyclopentadiene with (*Z*)-3-(4-nitrophenyl)propenal.[12] This reaction proceeded sluggishly giving Diels–Alder adducts that were the same products as those obtained in the reaction of (*E*)-3-(4-nitrophenyl)propenal along with considerable amounts of polymeric materials. This result indicated that *E*/*Z* isomerization of the aldehyde or the intermediary hydrazonium ion occurred in the reaction (Scheme 2).



Scheme 2 Diels–Alder reaction using (*Z*)-3-(4-nitrophenyl)propenal.

To obtain a mechanistic insight into asymmetric induction, we performed NMR studies for the intermediary hydrazonium ions. The catalyzed-reaction proceeded in CH_3CN similarly to that in DMF, though enantioselectivity was slightly decreased. In the NMR experiments, we then used more convenient CD_3CN as a solvent. We first examined the reactions using DCl (12 M, D_2O soln.) as an acid cocatalyst, but the formation of hydrazonium ions was considerably suppressed, probably due to the addition of D_2O. In addition, when HCl (4 M, 1,4-dioxane soln.) was used, hydrazonium ions were rapidly formed; however, gradual decomposition of hydrazonium ions occurred, and we could not obtain reliable data. We therefore decide to use TFA as an acid cocatalyst. Hydrazide **2a** was treated with 1.0–15.0 equivalents of aldehyde **3** in the presence of 1, 3 and 6 equivalents of TFA-d in CD_3CN at rt, and the reaction was monitored by ^{1}H-NMR. In all measurements, the reactions reached equilibria within 3 min regardless of the amounts of TFA-d and aldehyde **3**; therefore, we could not obtain a reactivity profile of catalyst **2a** in detail. The equilibrated mixtures contained hydrazonium ions **I**, **II** and aldehyde **3**, and the amount of **2a**, the ratios **I**/(**2a**+**I**+**II**) and **II**/(**2a**+**I**+**II**) of each measurements are summarized in Fig. 2-**A**, **B** and **C**.

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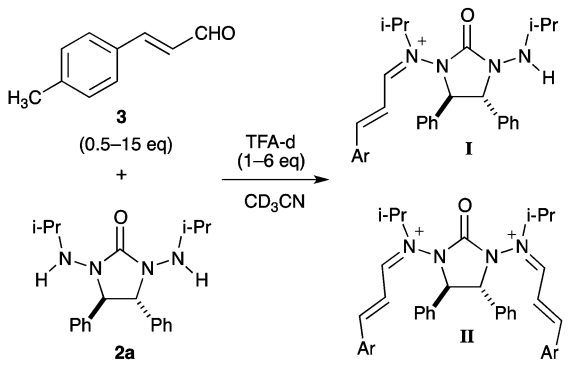
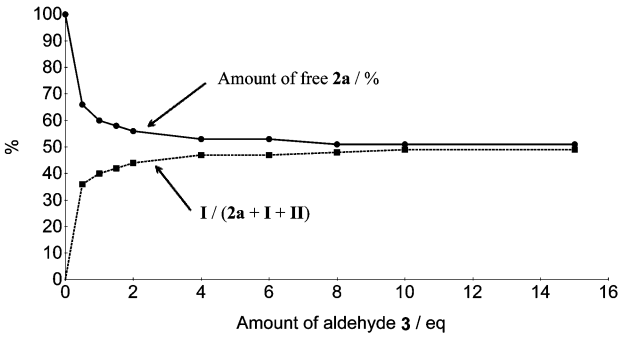
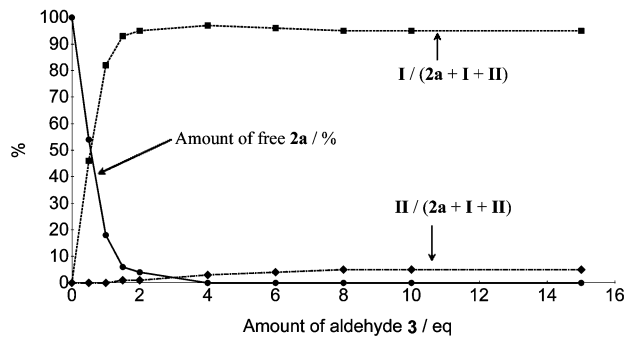


A: Hydrazonium ion formation using TFA-d (1 eq)



B: Hydrazonium ion formation using TFA-d (3 eq)



C: Hydrazonium ion formation using TFA-d (6 eq)

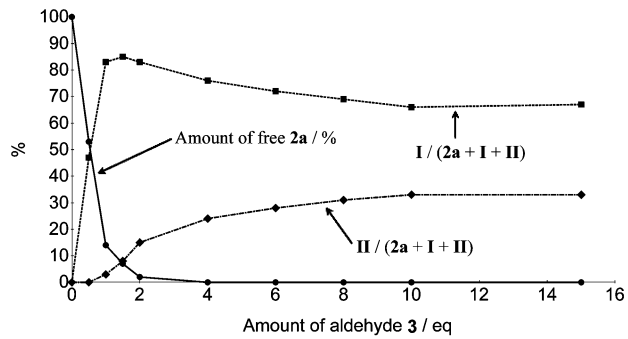


Fig. 2 ^{1}H-NMR study of hydrazonium ion formation.

In the presence of 1 equivalent of TFA-d, the reaction almost reached an equilibrium at the addition of 8 equivalents of aldehyde **3**, and only **I** was formed with 50% conversion of **2a** (Fig. 2-**A**). In this case, since TFA-d was consumed in the formation of **I**, it is reasonable that 50% of **2a** remained unchanged. When the amount of TFA-d was increased to 3 equivalents, the reaction was equilibrated at the addition of 8 equivalents of aldehyde **3**, and hydrazide **2a** was completely converted to hydrazonium ions **I** along with the small amount of **II** (**II/I** = 5 : 95) (Fig. 2-**B**). In addition, when the reaction was carried out in the presence of 6 equivalents of TFA-d, **2a** disappeared at the addition of 4 equivalents of **3**, and the ratio **II/I** finally reached 33 : 67 (Fig. 2-**C**). These results indicate that hydrazide **2a** is highly reactive and was able to react with aldehyde **3** to give **I** even with only 1 equivalent of TFA-d. On the other hand, hydrazonium ion **I** showed considerably reduced reactivity in comparison with **2a**, and excess amount of TFA was required to give hydrazonium ion **II**. The stereochemistries of **II** and **I** were determined by NOESY analysis as shown in Fig. 3.

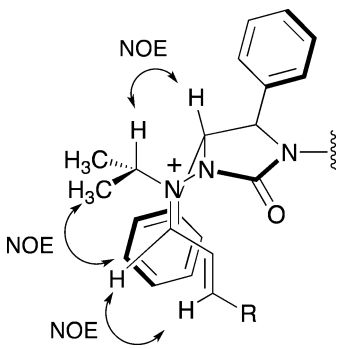


Fig. 3 NOESY analysis of the hydrazonium ion **I** and **II**.

Since a crosspeak in the NOESY spectrum between the methyl proton of the isopropyl group and the hydrazonium proton on the carbon-nitrogen double bond was observed for both **I** and **II**, the geometry of the carbon-nitrogen double bond was determined to be a *Z*–configuration. In addition, the iminium ion moiety of **II** and **I** is considered to be positioned perpendicular to the imidazolidinone ring. This arrangement is supported by a crosspeak in the NOESY spectrum between the methine proton of the isopropyl group and the proton on the imidazolidinone ring. The observed preference of the *Z* isomer over the *E* isomer can be rationalized by considering the steric repulsion around the carbon–nitrogen double bond (Fig. 4, **A** *vs.* **B**). Additionally, conformer **A** is considered more favorable than **C** due to steric repulsion between the phenyl group and the isopropyl group. In major conformers **I**(*Z*) and **II**(*Z*, *Z*), the phenyl group on the imidazolidinone ring blocked one side of the carbon-carbon double bond of the hydrazonium ion; therefore, cyclopentadiene is thought to approach the less-hindered side of the dienophile giving an adduct having a *2S* configuration (Fig. 4, **D**).

However, these schemes could not fully explain the catalytic behavoir of our catalysts in asymmetric induction. For example, unexpectedly low enantioselectivity in the reaction using **1a**, which has an asymmetric environment similar to that of **2a**, cannot be rationalized by these schemes. We thought that enantioselectivity of the catalyzed-reactions was greatly affected by the participation

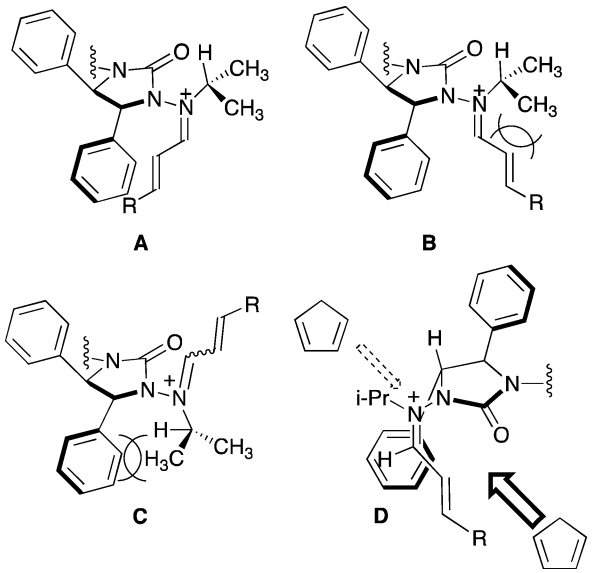


Fig. 4 Conformations of the hydrazonium ion.

of conformers, such as **C** in Fig. 4, in the reactions. We therefore performed conformational analysis of hydrazonium ions using *ab initio* calculations. Conformational searches of hydrazonium ions were performed by the Monte Carlo method using AM1 level of the theory, and the obtained geometries were first optimizaed by RHF/3-21G level of the theory. After removing duplicate conformers, the remaining conformers were reoptimized by using the theory of B3LYP/6-31G*[13–15] We first calculated the energy of an intermediary hydrazonium ion derived from **1a**, and the results are shown in Fig. 5.

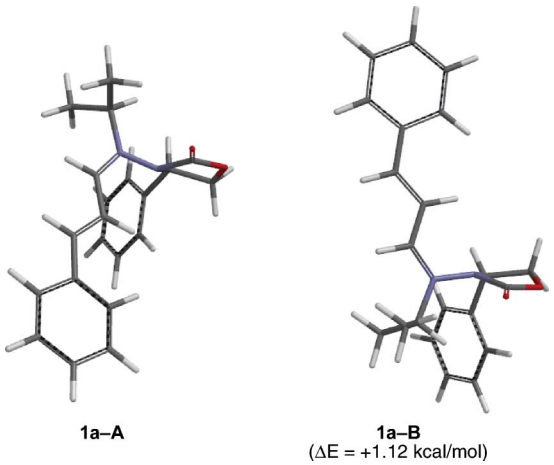


Fig. 5

In the conformational analysis, conformers **1a**–**A** and **1a**–**B**, which correspond to **A** and **C** in Fig. 4, appeared as the most stable conformer and the second conformer, respectively, as expected. However, the energy difference between these conformers was unexpectedly small, 1.12 kcal mol^{-1}, which was not so large as to exclude the participation of **1a**–**B**. In addition, considering that **1a**–**B** should be more reactive than **1a**–**A** due to the lesser steric hindrance around a reaction site, the participation of **1a**–**B** must be further increased, leading to the observed low enantioselectivity in the reaction. We next discuss asymmetric induction of the reactions using **2a**. In these reactions, each hydrazonium ion **I** or **II** can act as a reactive intermediate. We then investigated the conformational distribution in **I** and **II**. For hydrazonium ion **I**, the energy difference between **I–A** and **I–B** was also small, 1.38 kcal mol^{-1}, which is similar to that between **1a**–**A** and **1a**–**B** (Fig. 6).

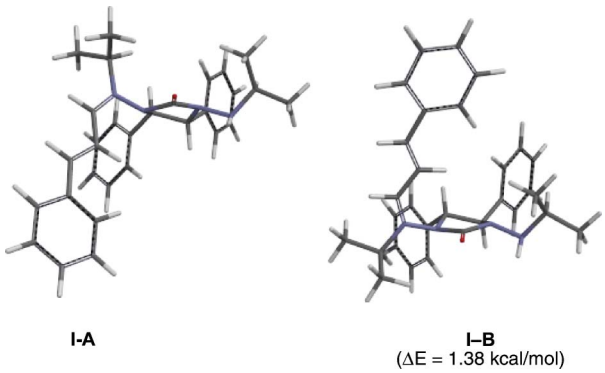


Fig. 6

Therefore, if hydrazonium ion **I** participates in the reactions, high levels of enantioselectivity cannot be expected. On the other hand, in the conformational analysis of **II**, we found that **II–A** was the most stable conformer and was more stable than **II–B** and **II–C** by 3.36 kcal mol^{-1} and 3.63 kcal mol^{-1}, respectively (Fig. 7).

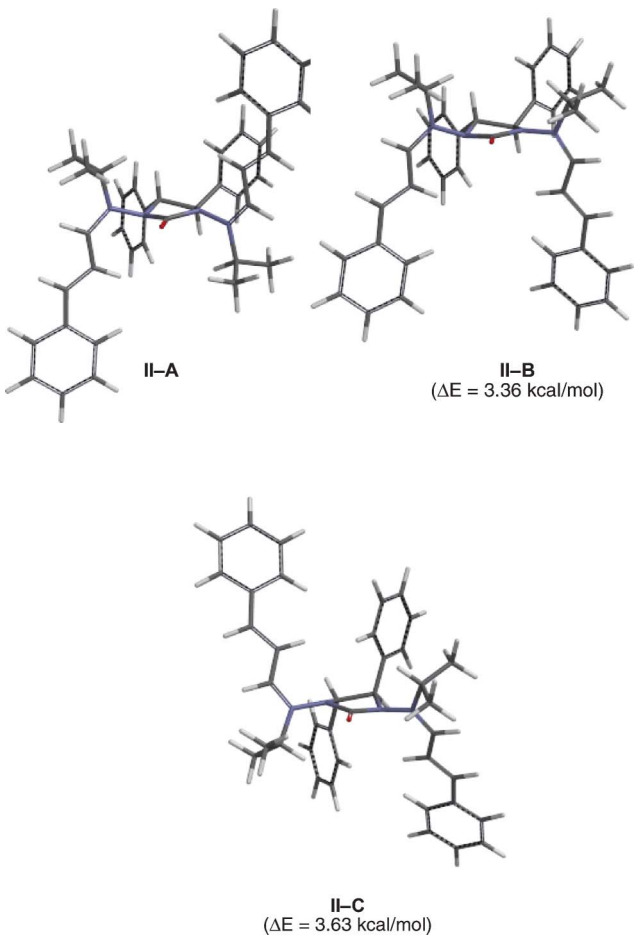


Fig. 7

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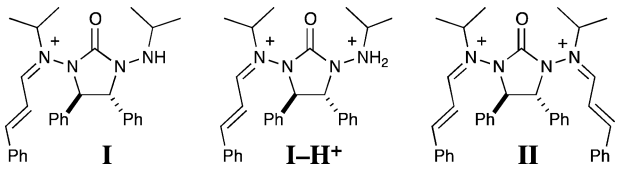
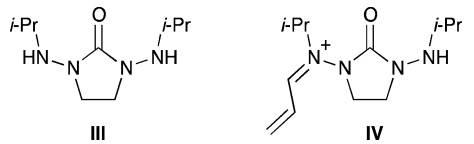
Table 5 LUMO energy levels of hydrazonium ion[a]



Entry	Iminium ion[b]	LUMO[c]/eV
1	**I**	−6.20
2	**I–H$^+$**	−8.58
3	**II**	−8.21

[a] All of the calculations were carried out using Spartan '08 (ver. 1.2.1). [b] Geometries were optimized using B3LYP/6-31G* level of the theory. [c] Calculated using B3LYP/6-311++G** level of the theory.

Table 6 Proton affinities of **III** and **IV**[a]



Compound	E[b]/a.u.	ZPE[c]/a.u.	PA[d]/kJ mol^{-1}
III	−649.390434	0.303960763	928
III–H$^+$	−649.757862	0.317960473	—
IV	−765.281143	0.354302202	642
IV–H$^+$	−765.540476	0.369219408	

[a] All of the calculations were carried out using Spartan'08 (ver. 1.2.1). [b] Geometries were optimized by B3LYP/6-31G and energies were calculated using B3LYP/6-311++G** level of the theory. [c] Calculated by B3LYP/6-31G*. [d] Corrected with zero-point energy (scaled by 0.9806).

These values are so large that we can neglect the participation of **II–B** and **II–C**, and **II–A** has the most suitable arrangement in asymmetric induction. In other words, to obtain good enantioselectivity, not **I** but **II** must become a reactive intermediate. We next investigated which hydrazonium ion, namely **I** or **II**, was a reactive intermediate. Since the reactions were carried out under acidic conditions, hydrazonium ion **I** may be in an equilibrium with **I-H$^+$**, and therefore, we should compare the reactivity of **I**, **I-H$^+$** and **II** to elucidate the reactive intermediate. We then calculated their energy levels of LUMO by *ab initio* calculations. Structures of hydrazonium ions were optimized by the level of the theory B3LYP/6-31G*, and their energy levels of LUMO were obtained using B3LYP/6-311++G** level calculations.[15] The results are summarized in Table 5.[16]

The LUMO levels of **I**, **I–H$^+$** and **II** are sufficiently low, and therefore each hydrazonium ion can work as reactive intermediates.[17] Since the LUMO level of **I–H$^+$** is further lowered than that of **I**, if **I–H$^+$** is formed, **I–H$^+$** become a reactive intermediate. We next mention whether **I–H$^+$** was formed or not. In the ^{1}H-NMR study mentioned above, a signal corresponding to isopropyl methine proton H_C of **II** appeared at 4.72 ppm. On the other hand, signals corresponding to methine protons H_A and H_B of **I** appeared at 4.47 ppm and 3.04 ppm, respectively. Considering a signal of H_D of **2a** appeared at 3.06 ppm in the absence of TFA-d (Fig. 8), it may be reasonable to assume that the equilibrium between **I** and **I-H$^+$** is not largely shifted to **I-H$^+$**.

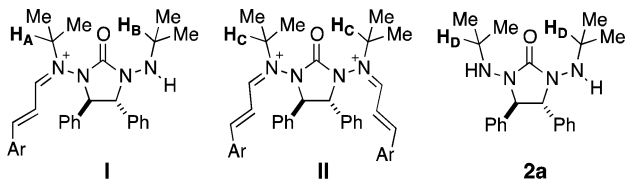


Fig. 8 Chemical shift of H_A–H_D in CD_3CN at rt.

However, since methine protons H_A–H_D might shift upfield or downfield by the shielding effects of neighboring phenyl groups, we could not determine whether **I** was protonated or not only by ^{1}H-NMR studies.[18] To clarify this point, we calculated proton affinities of model compounds **III** and **IV** at B3LYP/6-31++G** level of the theory, and the results are shown in Table 6.[16]

Geometries and proton affinities of **III**, **III-H$^+$**, **IV** and **IV+H$^+$** were calculated using B3LYP level density functional theory. The basis set 6-31G* was used for the geometrical optimization and frequency calculations, and 6-311++G** for single-point energy calculations. PA values were corrected with zero-point energy that was obtained by the level of B3LYP/6-31G* and was scaled by 0.9804.[19] Hydrazide **III** showed a typical value of PA (928 kJ mol^{-1}).[5b,5c] In contrast to **III**, **IV** showed a considerably low PA (642 kJ mol^{-1}), which was lower than that of CH_3CN (788 kJ mol^{-1}).[20] These results indicate that protonation of **I** scarcely proceed in CH_3CN, because CH_3CN is more basic than **IV**.

In our catalyzed-Diels–Alder reactions, DMF was used as a solvent. Considering that DMF is more basic than CH_3CN, the possibility of formation of **I–H$^+$** should become still lower in DMF than in CH_3CN. When TFA was used as a cocatalyst, hydrazonium ion **I** must be formed mainly accompanied by the formation of **II** in DMF as in the reaction in CH_3CN.[21] In this case, not only **II** but also **I** worked as a reactive intermediate, leading to low enantioselectivity. On the other hand, the formation of **II** should be further facilitated, in the presence of HCl, and not **I** but **II** worked as the main reactive intermediate, giving good enantioselectivity. For the reactions using TfOH, if TfOH worked in a manner similar to that of HCl, TfOH should give a result comparable to that of the reaction using HCl as for asymmetric induction. We now assume that TfOH protonates **I** unlike HCl even in DMF, giving **I–H$^+$** that worked as a reactive intermediate in a manner similar to **I**, resulting in low enantioselectivity. These considerations are based on the assumption that only acid strength of a cocatalyst governs the reaction pathway and counter anions do not participate in the reactions; however, the formation of **I–H$^+$** might be affected by counter anions, resulting in a change in the equilibrium point between **I**, **II** and **I–H$^+$**. In addition, we cannot exclude the possibility that conformational preference and reactivity of hydrazonium ions might be influenced by counter anions. At present, we do not have sufficient data to fully clarify the effects of counter anions on the reaction course; however, we consider that elucidation of these points to be essential for improving the catalysis design and, therefore, to be an important subject of further studies.

Conclusion

In conclusion, a novel hydrazide-type organocatalyst **2a** has been developed for enantioselective Diels–Alder reactions of α,β-unsaturated aldehydes. The reaction was completed in a very short reaction time to afford cycloadducts in good yields with good enantioselectivity. To access into mechanistic insight, we also performed the conformational analysis of the intermediary hydrazonium ions by ^{1}H-NMR including NOESY measurements, and the geometry of the carbon-nitrogen double bond was determined to be a *Z*-configuration for both hydrazonium ion **I** and **II**. We further investigated the reactive intermediate, and revealed that the hydrazonium ion **II** was a reactive intermediate in our catalyzed Diels–Alder reactions by using *ab initio* calculations. Further studies to clarify the scope and limitations of this organocatalyst and for further improvements in the efficiency of asymmetric induction are now in progress.

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17 Hydrazide **1a–1c** could efficiently worked as catalysts. Intermediary hydrazonium ions in these reactions are thought to show LUMO levels similar to that of **I**.

18 We also performed titration experiments of **2a** using TFA-d in CD_3CN and found that H_D shifted downfieldshift by only 0.07 ppm, whereas two signals corresponding to isopropyl methyl groups shifted downfield by 0.15 and 0.28 ppm, respectively.

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21 We also calculated a PA value of DMF using the same methods, and an obtained PA value is 874 kJ mol^{-1}.

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