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DEVELOPMENT OF CYCLIC HYDRAZINE AND HYDRAZIDE TYPE ORGANOCATALYST—MECHANISTIC ASPECTS OF CYCLIC HYDRAZINE/HYDRAZIDE –CATALYZED DIELS-ALDER REACTIONS

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Abstract – Some hydrazines and hydrazides were prepared and screened for their catalytic efficiencies in Diels-Alder reactions. ^{1}H-NMR studies and *ab initio* calculations revealed that catalytic efficiencies of these catalysts are greatly dependent on the release of the catalysts from the Diels-Alder adducts.

INTRODUCTION

In the early 1970s, two industrial research groups reported the first examples of (*S*)-proline-catalyzed enantioselective intramolecular aldol reactions. These reactions, so-called Hajos–Parrish–Eder–Sauer–Wiechert reactions, attracted little attention for about 30 years despite their potential values.[1] In the early 2000s, List and coworkers reported (*S*)-proline-catalyzed intermolecular asymmetric aldol reactions.[2] Thereafter, as well as proline, related five-membered cyclic secondary amine derivatives have also been applied to many reactions that proceed through enamine or iminium ion intermediates.[3] It is well established that a nitrogen atom that is directly bonded to an atom with one or more lone pairs, such as H_2N-NH_2 and H_2N-OH, tends to be a stronger nucleophile than would otherwise be expected. The nucleophic enhancement is called "α-heteroatom effect",[4] and such α-nucleophiles seem to be more advantageous as nitrogen-based heterocyclic organocatalysts than simple secondary amine catalysts, but there are not many reported examples. This type of organocatalyst was first reported to promote Diels-Alder reactions efficiently via iminium ions in 2003,[5] and camphor-based chiral hydrazide catalysts were also reported.[6] Recently, we have investigated Biginelli reaction catalyzed by cyclic hydrazine-type organocatalysts as shown in Figure 1, and we have reported that pyrazolidine dihydrochloride **1a** could catalyze Biginelli reactions very efficiently under mild conditions.[7] These results promoted us to screen several cyclic hydrazines and hydrazides for their catalytic activities

in other reactions, including Diels-Alder reactions; however, during these studies, we became aware of ambiguities in the catalytic activities of the hydrazine-type organocatalysts.

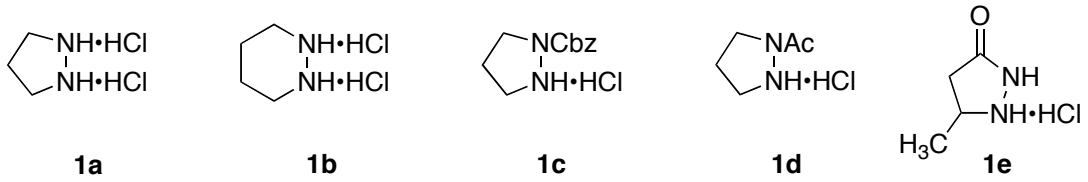
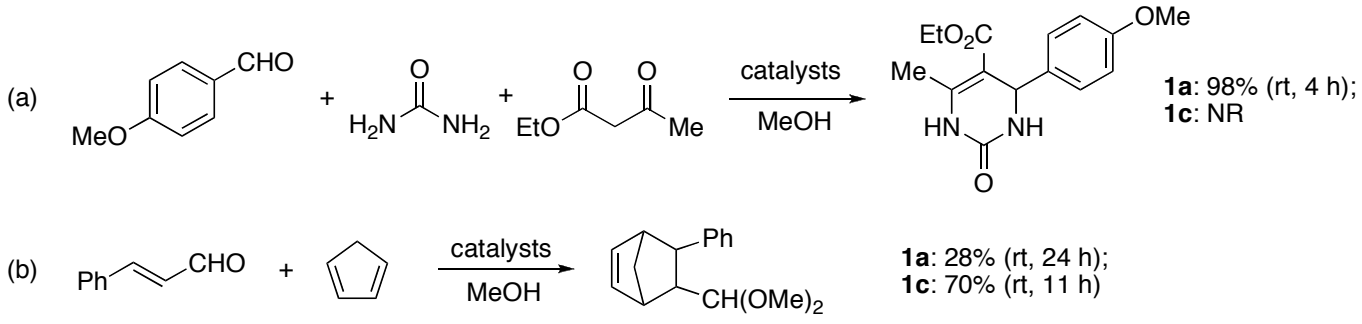


Figure 1. List of hydrazines and hydrazides employed in this study.

For example, *N*-Cbz pyrazolidine hydrochloride **1c** accelerated Diels-Alder reactions more efficiently than did catalyst **1a**, which showed a significantly higher level of catalytic activity than did **1c** in Biginelli reactions as shown in Scheme 1.

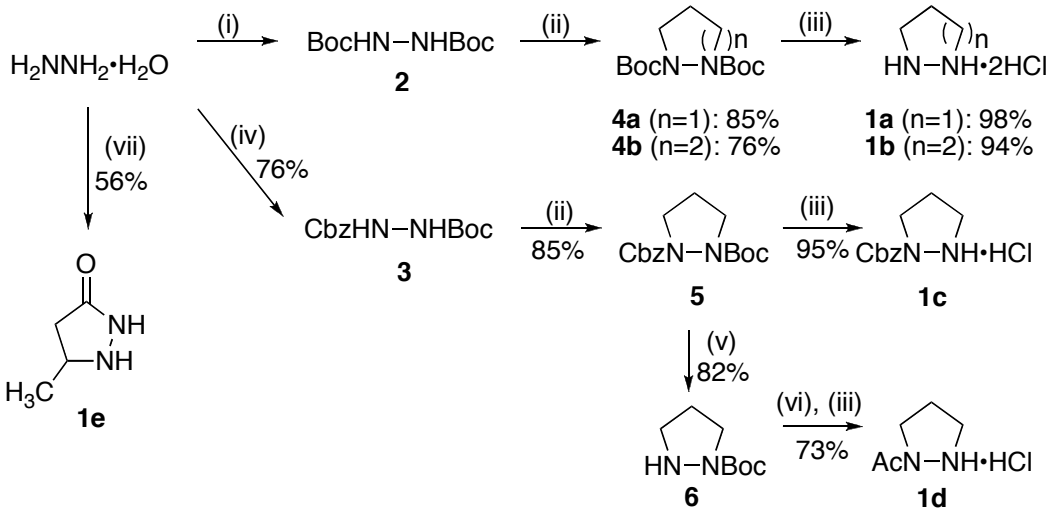


Scheme 1. Biginelli reactions (a) and Diels-Alder reactions (b) catalyzed by **1a** and **1c**.

In order to develop chiral hydrazine-type organocatalysts superior to conventional pyrrolidine-based organocatalysts, it is important to elucidate these ambiguities, and we have therefore carried out the mechanistic studies on hydrazine/hydrazide-catalyzed Biginelli and Diels-Alder reactions. In this paper, we present the results of experiments and *ab initio* calculations on hydrazine- and hydrazide-catalyzed Diels-Alder reactions. These results showed that not the formation of reactive hydrazonium ions but the regeneration of hydrazine/hydrazide catalysts was more important in the catalyzed Diels-Alder reactions.

RESULTS AND DISCUSSION

All hydrazines **1a**, **1b** and hydrazides **1c** – **1e** were prepared by methods reported in the literature[8-11] as depicted in Scheme 2. For catalysts **1a** and **1b**, we first tried to isolate them in acid-free forms, but all attempts failed because they are prone to immediately suffer from air oxidation under neutral or basic conditions to give only polymeric materials. In contrast to **1a** and **1b**, hydrazides **1c** – **1e** were relatively stable in acid-free forms when stocked in a refrigerator for a few weeks.

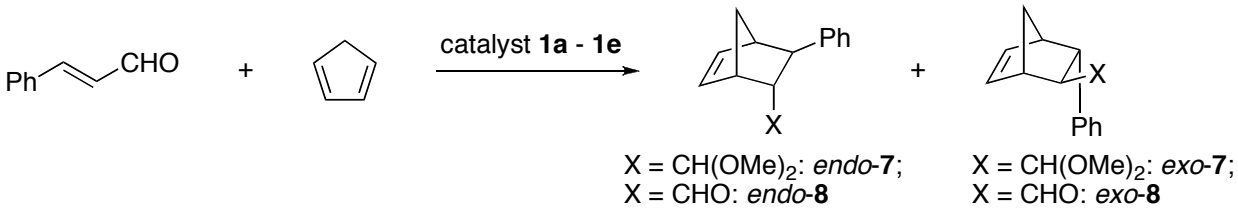


Reagents and conditions: (i) $(Boc)_2O$ (2.1 equiv.)/MeOH, rt; (ii) NaH (2.2 equiv.), $Br(CH_2)_3Br$ (1.2 equiv.) for **4a** and **5**, $Br(CH_2)_4Br$ (1.2 equiv.) for **4b**; (iii) 4M HCl/1,4-dioxane, rt; (iv) $(Boc)_2O$ (0.2 equiv.)/IPA, rt, then CbzCl (1.2 equiv.), 4-Methylmorpholine (1.5 equiv.)/THF, 0 °C to rt; (v) H_2 baloon, 10% Pd-C/MeOH; (vi)AcCl (1.2 equiv.), Et_3N (1.5 equiv.)/DCM, 0 °C to rt; (vii) crotonic acid (1.2 equiv.), Al_2O_3/*n*-BuOH-toluene.

Scheme 2. Preparation of hydrazine and hydrazide catalysts **1a** – **1e**.

Diels-Alder reactions of cinnamaldehyde and cyclopentadiene were performed in the presence of 10 mol% of catalysts **1a** – **1e** at room temperature, and the results are summarized in Table 1. When the reaction was carried out in the presence of **1a**, the reaction was very sluggish, affording an inseparable mixture of *endo*/*exo* isomers of dimethylacetals (*endo*/*exo*)-**7**[12] in 25% yield after 24 h (entry 1). The yield was slightly improved when the reaction time was extended to 48 h (entry 2). Catalyst **1b** showed a level of catalytic activity similar to that of catalyst **1a** (entries 3 and 4). On the other hand, *N*-Cbz pyrazolidine hydrochloride **1c** showed a higher level of catalytic activity and the reaction was completed within 11 h, giving acetals (*endo*/*exo*)-**7** in 70% yield with 6% aldehydes (*endo*/*exo*)-**8**[13] (entry 5). The reaction proceeded in an *endo* selective manner in the presence of catalyst **1c**, though catalysts **1a** and **1b** accelerated the reactions *exo*-selectively. These reactions were constituted by three reversible processes: (1) hydrazonium ion formation, (2) Diels-Alder reaction, and (3) solvolysis of Diels-Alder adducts. This mechanistic complexity make it difficult to clearly explain the obtained *endo*/*exo* ratios by simple kinetic and/or thermodynamic reasons. Interestingly, *N*-acetyl pyrazolidine hydrochloride **1d** is much less effective than **1c**, and the reaction did not complete even after 46 h, with acetals **7** and aldehydes **8** being obtained in 63% and 6% yields, respectively accompanied by 29% recovery of cinnamaldehyde (entry 6). Hydrazides **1e** could also catalyze the reaction, but the catalytic efficiency of **1e** was unexpectedly low, giving Diels-Alder adducts in a total 32% yield even after 48 h (entries 7 and 8).

Table 1. Diels-Alder reactions in the presence of cataltsts **1a** – **1e**.

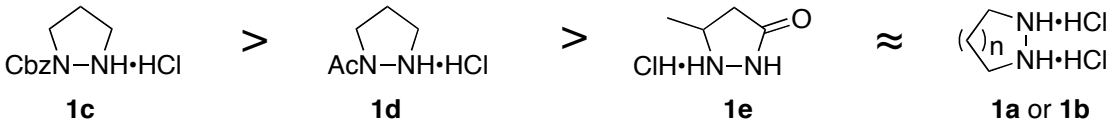


entry	catalyst	solvent	time (h)	yield (%)		*endo*:*exo*	recovery (%)
				7	**8**		
1	**1a**	MeOH	24	25	trace	81:19[a]	66
2	**1a**	MeOH	48	30	2	78:22[a]	56
3	**1b**	MeOH	24	28	trace	79:21[a]	63
4	**1b**	MeOH	48	30	2	77:23[a]	64
5	**1c**	MeOH	11	70	6	33:67[a]	-
6	**1d**	MeOH	46	63	6	40:60[a]	29
7	**1e**	MeOH	28	30	2	63:37[a]	52
8	**1e**	MeOH	47	36	2	57:43[a]	35
9	**1a**	MeOH-H_2O (9:1)	48	14	trace	70:30[a]	47
10	**1c**	MeOH-H_2O (9:1)	9	35	5	29:71[a]	36
11	**1c**	MeOH-H_2O (9:1)	49	60	6	34:66[a]	15
12	**1d**	MeOH-H_2O (9:1)	48	28	2	41:59[a]	55
13	**1a**	H_2O	45	-	18	52:48[b]	44
14	**1c**	H_2O	48	-	73	34:66[b]	-
15	**1d**	H_2O	63	-	12	52:48[b]	63
16	**none**	MeOH	24	6	-	63:37[a]	64
17	**none**	MeOH-H_2O (9:1)	24	7	-	66:34[a]	62
18	**none**	H_2O	24	-	2	55:45[b]	68

a) Ratios were determined for adduct **7** by ^{1}H-NMR. b) Ratios were determined for adduct **8** by ^{1}H-NMR.

Since aqueous MeOH and water were employed for the reaction solvent in reported examples,[5,6] we also examined the reactions in these solvents. When the reactions were carried out in MeOH containing 10 v/v% of water, the reactions became inhomogeneous and very sluggish and acetals **7** were also obtained (entries 9 – 12). For instance, after 49 h, the starting aldehyde did not disappear even in the reaction

using the most effective catalyst **1c** (entry 11). Furthermore, when water was used as a reaction solvent, catalysts worked less efficiently as in MeOH, giving miserable results except for **1c** (entries 13 – 15).
In addition, Diels-Alder reactions of cinnamaldehyde and cyclopentadiene in MeOH, MeOH-H_2O (9:1) and water were carried out in the absence of catalyst. In these reactions, Diels-Alder adducts were obtained in only low yields (entries 16 – 18). From these results, it became clear that catalytic efficiency of **1a** - **1e** is in the following order in MeOH;



These catalysts would be in equilibria with acid-free forms in solutions and the catalysts should work as acid-free forms. In considering catalytic activities of these catalysts, it is reasonable to assume that pyrazolidine is more nucleophilic than *N*-acylpyrazolidines and pyrazolidinones and catalyst **1c** therefore shows a higher level of catalytic activities than do other catalysts; however, the experimentally obtained order did not reflect this expected order.[14] Then, we investigated the reasons why more nucleophilic pyrazolidine showed only limited catalytic activity in Diels-Alder reactions by using *ab initio* calculations and ^{1}H-NMR techniques.
Diels-Alder reaction is thought to include three processes as shown in Figure 2: (1) hydrazonium ion formation from a catalyst hydrazine and an aldehyde, (2) cycloaddition of diene to the hydrazonium ion, and (3) hydrolysis of the resulting hydrazonium ion to release hydrazine.

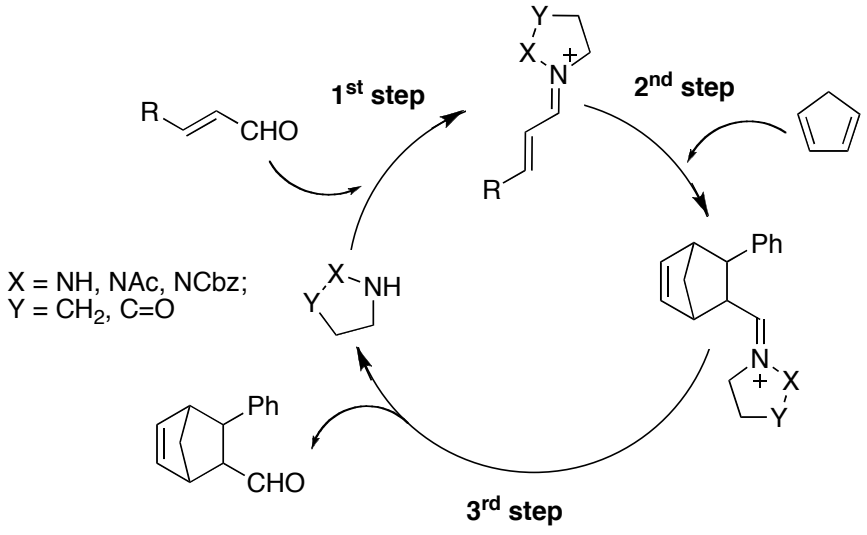
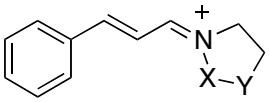
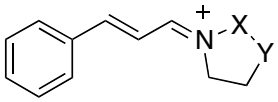


Figure 2. Catalytic cycle of hydrazine/hydrazide-catalyzed Diels-Alder reactions.

In a cycloadditon step, the second step, Diels-Alder reaction is generally considered to be an orbital-controlled reaction, and therefore the facility of the reaction must be dependent on LUMO levels of the hydrazonium ions. We therefore calculated LUMO levels of cinnamaldehyde, iminium ion **9**, and hydrazonium ions **10a** – **10e**.[15] To avoid conformational ambiguity, we employed **10c** and **10e** as computational models. For hydrazonium ions **10a** – **10e**, both *E* and *Z* isomers were calculated. All geometries were optimized at the B3LYP/6-31+G(d) level of theory, followed by calculations of LUMO levels and energies at the B3LYP/6-311+G(d, p) level[16], and the results are shown in Table 2.

Table 2. *Ab initio* calculations of LUMO levels by B3LYP/6-311+G(d, p)//B3LYP/6-31+G(d).





9 X = Y = CH_2
(*Z*)-**10a** X = NH•HCl, Y = CH_2
(*Z*)-**10b** X = NH•HCl, Y =$(CH_2)_2$
(*Z*)-**10c** X = NCO_2Me, Y = CH_2
(*Z*)-**10d** X = NAc, Y = CH_2
(*Z*)-**10e** X = NH, Y = C=O

9 X = Y = CH_2
(*E*)-**10a** X = NH•HCl, Y = CH_2
(*E*)-**10b** X = NH•HCl, Y =$(CH_2)_2$
(*E*)-**10c** X = NCO_2Me, Y = CH_2
(*E*)-**10d** X = NAc, Y = CH_2
(*E*)-**10e** X = NH, Y = C=O

entry	Dienophile	Energy (Hartrees)	LUMO (eV)
1	cinnamaldehyde	-423.0925709	-2.55
2	iminium ion **9**	-559.687863	-6.55
3	(*E*)-**10a**	-575.697198	-6.55
4	(*Z*)-**10a**	-575.698419 (-0.77)[a]	-6.48
5	(*E*)-**10b**	-615.025357	-6.53
6	(*Z*)-**10b**	-615.02777 (-1.5)[a]	-6.49
7	(*E*)-**10c**	-803.643674	-6.39
8	(*Z*)-**10c**	-803.641975 (+1.1)[a]	-6.40
9	(*E*)-**10d**	-728.394822	-6.39
10	(*Z*)-**10d**	-728.392926 (+1.2)[a]	-6.42
11	(*E*)-**10e**	-649.737450	-6.80
12	(*Z*)-**10e**	-649.739326 (-1.2)[a]	-6.81

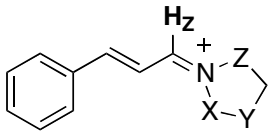
a) Values in parentheses indicate the ΔE values ($E_{Z\text{-isomer}} - E_{E\text{-isomer}}$) in kcal/mol

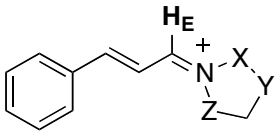
For hydrazonium ions **10a**, **10b** and **10e**, *Z* isomers were more stable than *E* isomers by 0.77 kcal/mol, 1.5 kcal/mol and 1.2 kcal/mol, respectively (entries 3 – 6, 11 and 12). On the other hand, for **10c** and **10d**, *E* isomers were more stable than *Z* isomers by 1.1 kcal/mol and 1.2 kcal/mol, respectively (entries 7 – 10). Since LUMO energy levels of *E* and *Z* isomers for **10a** – **10e** were essentially the same,[17] the preference

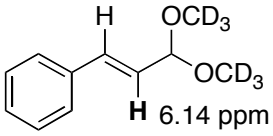
for *E* or *Z* isomer should not affect the net reactivity of each type of hydrazonium ions. The LUMO level of cinnamaldehyde was -2.55 eV and the levels of iminium ion **9** and hydrazonium ions **10a** – **10e** were in the range of -6.81 to -6.39 eV. These results indicate that hydrazonium ions **10a** – **10e** are more active for Diels-Alder reactions than is the parent aldehyde, as well as iminium ion **9**; however, we could not find out any remarkable differences in LUMO energy levels that are consistent with catalytic activities of **10a** – **10e**.

Since we could not rationalize the tendency of the reactivity of catalysts **1a** – **1e** only by LUMO levels of intermediate hydrazonium ions, we next investigated the formation of hydrazonium ions (the first step in Figure 2). Cinnamaldehyde was treated with 1 equivalent of catalyst **1a** – **1e** in CD_3OD, and the reactions were monitored by ^{1}H-NMR, and the results are summarized in Table 3. All reactions proceeded to give hydrazonium ions **10a** – **10e** and/or acetal **11** without any by-products.

Table 3. ^{1}H-NMR study for firmation of hydrazonium ions **10a** – **10e**.







11

(*Z*)-**10a** X = NH•HCl, Y = CH_2, Z = CH_2
(*Z*)-**10b** X = NH•HCl, Y =$(CH_2)_2$, Z = CH_2
(*Z*)-**10c** X = NCO_2Bn, Y = CH_2, Z = CH_2
(*Z*)-**10d** X = NAc, Y = CH_2, Z = CH_2
(*Z*)-**10e** X = NH, Y = C=O, Z = $CHCH_3$

(*E*)-**10a** X = NH•HCl, Y = CH_2, Z = CH_2
(*E*)-**10b** X = NH•HCl, Y =$(CH_2)_2$, Z = CH_2
(*E*)-**10c** X = NCO_2Bn, Y = CH_2, Z = CH_2
(*E*)-**10d** X = NAc, Y = CH_2, Z = CH_2
(*E*)-**10e** X = NH, Y = C=O, Z = $CHCH_3$

entry	Hydrazonium ion	H_Z/H_E (ppm)	ratio[a] (%)		
			10 (*E*/*Z*)[b]	**11**	Cinnamaldehyde
1	**10a**	8.22/8.36	100 (24:76)	0	-
2	**10b**	8.47/8.50	73 (15:85)	23	4
3	**10c**	8.97/9.13	59 (67:33)	33	8
4	**10d**	8.90/9.18	21 (71:29)	68	11
5	**10e**	8.58/9.44	61 (31:69)	35	4

a) ratios were determined by ^{1}H-NMR. b) Stereochemistry of hydrazonium ions were assigned on the basis of *ab initio* calculations.

When catalyst **1a** was reacted with cinnamaldehyde, exclusive formation of hydrazonium ion **10a** was observed within 10 min at 25 °C, giving a mixture of *E*- and *Z*-isomers (24:76). On the other hand, the reaction of catalyst **1b** and **1c** with cinnamaldehyde gave equilibrium mixtures containing hydrazonium ion **10b** (73%), **10c** (59%) and acetal **11** within 10 min. Additionally, in the reaction of catalyst **1d** and

the aldehyde, hydrazonium ions **10d** and acetal **11** were formed similarly; however, the equilibrium between hydrazonium ions and the acetal was shifted to the acetal formation and the yield of hydrazonium ions **10d** was reduced to 21% with increasing the formation of acetal **11** to 68% yield. While we could not observe noticeable differences in the rates of hydrazonium ion formations in our ^{1}H-NMR experiments, it is noteworthy that the ratios of hydrazonium ions to the acetal **11** changed from 64:36 (for **10c**) to 24:76 (for **10d**). These results can rationalize the observed catalytic activities of catalysts **10c** and **10d**. In the catalyzed reactions, the formation of hydrazonium ions, which are reactive intermediates, is essential, and catalyst **1c** yielded much more hydrazonium ion **10c** than did **1d**, being reflected in the higher level of catalytic activity of **1c** than that of **1d**. On the other hand, although the reaction of cinnamaldehyde and catalyst **1a** afforded reactive intermediary hydrazonium ions **10a** exclusively, **1a** catalyzed the Diels-Alder reactions less efficiently than did catalyst **1c**. This result implies that the formation of hydrazonium ions is not necessarily a rate-determining step. In this case, we must additionally consider release of a catalyst **1a** from Diels-Alder adducts (Figure 2, the third step). In this step, hydrazine/hydrazide moieties work as leaving groups, and hence *p*Ka values of their conjugate acids should be taken into account.[14, 18] Since acyl hydrazines, such as catalyst **1c**, are considered to be less basic than hydrazines **1a** and **1b** by 4~5 pka units, it is reasonable that catalysts **1c** worked as a leaving group more efficiently than did **1a** and **1b**, leading to enhanced net catalytic efficiency. Although catalyst **1e** gave hydrazonium ion **10e** and acetal **11** in a ratio similar to that of **10c** and their acidities are considered to be almost same, catalytic efficiency of **1e** was considerably inferior to catalyst **1c**. It is plausible that the steric repulsion between the alkene part and the acyl moiety in hydrazonium ion **10c** might be more severe than the steric repulsion in hydrazonium ion **10e** as shown in Figure 3. This severe steric repulsion would facilitate the hydrolytic release of **1c** from hydrazonium ion **10c**.

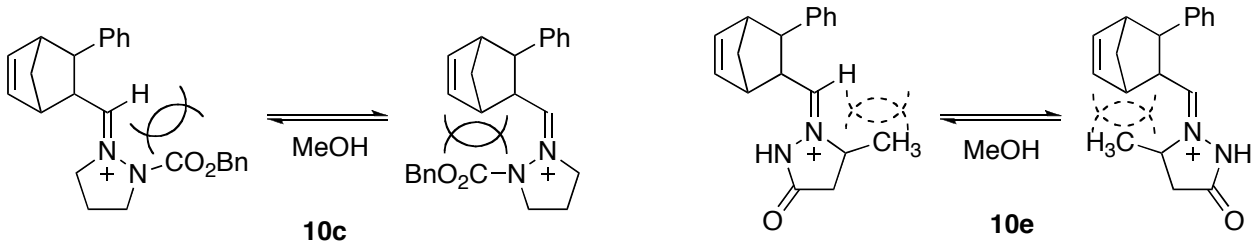


Figure 3. Steric repulsion between substituents in hydrazonium ion **10c** and **10e**.

In conclusion, we investigated the mechanistic features of hydrazine/hydrazide-catalyzed Diels-Alder reactions. ^{1}H-NMR studies and *ab initio* calculations revealed that catalytic efficiencies of these catalysts are greatly dependent on the release of the catalysts from the Diels-Alder adducts.

EXPERIMENTAL

General Remarks

^{1}H-NMR spectra were measured in $CDCl_3$, DMSO-d_6 or CD_3OD solutions and referenced to $CHCl_3$ (7.26 ppm), DMSO-d_6 (2.54 ppm) and CD_3OD (3.30 ppm) using JEOL Delta-500 (500 MHz) spectrometer. ^{13}C-NMR spectra were measured in $CDCl_3$, DMSO-d_6 or CD_3OD solutions and referenced to $CDCl_3$ (77.0 ppm), DMSO-d_6 (39.7 ppm) and CD_3OD (49.0 ppm) using JEOL Delta-500 (125 MHz) spectrometers. Column chromatography was performed on silicagel, KANTO KAGAKU N-60. Thin-layer chromatography was performed on precoated plates (0.25 mm, silicagel Merck Kieselgel 60 F254). All solvents were distilled prior to use. All reactions were performed in oven-dried glassware under positive pressure of nitrogen, unless otherwise noted.

Pyrazolidine dihydrochloride (**1a**).[8]

^{1}H-NMR (500 MHz, DMSO-d_6) δ 3.06 (4H, t, J = 7.4 Hz), 1.98 (2H, quint, J = 7.4 Hz); ^{13}C-NMR (125 MHz, DMSO-d_6) δ 46.5, 26.1.

1,2-Piperazine dihydrochloride (**1b**).[9]

^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.99 (4H, m), 1.67 (4H, m); ^{13}C-NMR (125 MHz, DMSO-d_6) δ 45.2, 21.7.

Benzyl pyrazolidine-1-carboxylate hydrochloride (**1c**).[10]

^{1}H-NMR (500 MHz, CD_3OD) δ 7.50-7.30 (5H, m), 5.28 (2H, s), 3.76 (2H, t, J = 6.9 Hz), 3.59 (2H, t, J = 6.9 Hz), 2.36 (2H, quint, J = 6.9 Hz); ^{13}C-NMR (125 MHz, CD_3OD) δ 153.6, 135.6 and 135.2, 128.5, 128.4, 128.3, 128.2, 68.9 and 68.0, 46.4 and 46.2, 24.3.

N-Acetyl Pyrazolidine hydrochloride (**1d**).[10]

^{1}H-NMR (500 MHz, CD_3OD) δ 3.90 (2H, t, J = 6.5 Hz), 3.57 (2H, t, J = 6.5 Hz), 2.50-2.40 (2H, m); 2.19 (3H, s); ^{13}C-NMR (125 MHz, CD_3OD) δ 168.6, 46.6 and 46.3, 45.4, 25.6 and 25.0, 19.9.

5-Methylpyrazolidin-3-one (**1e**).[11]

^{1}H-NMR (500 MHz, DMSO-d_6) δ 4.11 (1H, ddd, J = 6.9, 8.0 and 8.7 Hz), 3.59 (2H, brs), 2.70 (1H, dd, J = 8.0 and 16.7 Hz), 2.34 (1H, dd, J = 8.7 and 16.7 Hz), 1.38 (3H, d, J = 6.9 Hz); ^{13}C-NMR (125 MHz, CD_3OD) δ 173.8, 55.3, 35.3, 15.6.

General procedure for catalyzed Diels-Alder reaction

To a solution of (*E*)-cinnamaldehyde (126 μL, 1.0 mmol) and cyclopentadiene (247 μL, 3.0 mmol), which was distilled by cracking dicyclopentadiene at 180 ˚C prior to use, in distilled MeOH (333 μL) was added *N*-Cbz pyrazolidine hydrochloride **1c** (24 mg, 0.1 mmol), and the resulting mixture was stirred at rt until the reaction was judged to be completed by TLC analysis. The reaction was quenched with 1N HCl and the mixture was extracted twice with Et_2O. The combined organic layers were washed successively with saturated aqueous solution of $NaHCO_3$ and brine, and dried over $MgSO_4$. After evaporation, the residue was purified with silica gel chromatography (5% AcOEt in hexane was used as an eluent) to give the desired adducts as a mixture of acetals **7** (colorless oil, 171 mg, 70%, *endo*/*exo* = 33:67) and aldehydes **8** (colorless oil, 12 mg, 6%).

5-(Dimethoxymethyl)-6-phenylbicyclo[2.2.1]hept-2-ene (*endo*-**7**).[12]

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.37-7.12 (5H, m), 6.34 (1H, m), 6.15 (1H, dd, *J* = 2.8 and 5.7 Hz), 3.93 (1H, d, *J* = 9.2 Hz), 3.37 (3H, s), 3.13 (3H, s), 2.96 (1H, brs), 2.87 (1H, brs), 2.54 (1H, m), 2.40 (1H, dd, *J* = 1.5 and 4.8 Hz), 1.77 (1H, d, *J* = 8.7 Hz), 1.55 (1H, m); ^{13}C-NMR (125 MHZ, $CDCl_3$) δ 145.1, 138.5, 135.1, 128.3, 127.9, 125.7, 108.3, 52.7, 52.4, 49.4, 46.7, 47.3, 44.5.

5-(Dimethoxymethyl)-6-phenylbicyclo[2.2.1]hept-2-ene (*exo*-**7**).[12]

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.37-7.12 (5H, m), 6.35 (1H, m), 5.94 (1H, dd, *J* = 2.8 and 5.7 Hz), 4.36 (1H, d, *J* = 8.3 Hz), 3.38 (3H, s), 3.12 (1H, dd, *J* = 3.4 and 5.1 Hz), 3.07 (3H, s), 3.00 (1H, brs), 2.90 (1H, dd, *J* = 1.4 and 4.9 Hz), 2.03 (1H, ddd, *J* = 1.6, 5.1 and 8.2 Hz), 1.68 (1H, d, *J* = 8.6 Hz), 1.49 (1H, m); ^{13}C-NMR (125 MHZ, $CDCl_3$) δ 144.3, 137.4, 135.3, 128.1, 127.9, 125.9, 108.0, 53.5, 52.4, 49.4, 49.1, 47.6, 45.3.

3-Phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (*endo*-**8**).[13]

^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.60 (1H, d, *J* = 2.3 Hz), 7.13–7.34 (5H, m), 6.35 (1H, dd, *J* = 3.2 and 5.5 Hz), 6.10 (1H, dd, *J* = 3.2 and 5.8 Hz), 3.26 (1H, brs), 3.06 (1H, brs), 3.02 (1H, dd, *J* = 1.6 and 4.9 Hz), 2.91 (1H, ddd, *J* = 2.3, 3.5 and 4.9 Hz), 1.74 (1H, m), 1.62 (1H, m); ^{13}C-NMR (125 MHZ, $CDCl_3$) δ 203.6, 143.7, 139.3, 133.9, 128.7, 127.5, 126.3, 60.9, 48.5, 47.2, 45.8, 45.3.

3-Phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (*exo*-**8**).[13]

^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.85 (1H, d, *J* = 2.1 Hz), 7.13–7.34 (5H, m), 6.27 (1H, dd, *J* = 3.5 and 5.8 Hz), 6.00 (1H, dd, *J* = 3.5 and 5.8 Hz), 3.65 (1H, dd, *J* = 3.5 and 4.9 Hz), 3.15 (2H, m), 2.52 (1H, ddd, *J* = 2.3, 3.5 and 4.9 Hz), 1.53–1.59 (2H, m); ^{13}C-NMR (125 MHZ, $CDCl_3$) δ 202.9, 143.7, 136.6, 136.4, 128.2, 128.0, 126.4, 59.5, 48.5, 47.7, 45.59, 45.56.

General procedure for ^{1}H-NMR experiments

A solution of cinnamaldehyde (15 μL, 0.12 mmol) in CD_3OD (0.4 mL) was mixed with pyrazolidine dihydrochloride **1a** (17 mg, 0.12 mmol) in an NMR tube at rt. The reaction was monitor by ^{1}H-NMR .

Hydrazonium ion **10a**.

Major isomer: ^{1}H-NMR (500 MHz, CD_3OD) δ 8.22 (1H, d, *J* = 10.3 Hz), 7.80-7.70 (2H, m), 7.65 (1H, d, *J* = 15.6 Hz), 7.50-7.40 (3H, m), 7.37 (1H, dd, *J* = 10.3 and 15.6 Hz), 4.38 (2H, m), 3.60 (2H, m), 2.50-2.30 (2H, m); **minor isomer**: ^{1}H-NMR (500 MHz, CD_3OD) δ 8.36 (1H, d, *J* = 10.6 Hz), 7.80-7.70 (2H, m), 7.60 (1H, d, *J* = 15.4 Hz), 7.50-7.40 (3H, m), 7.24 (1H, dd, *J* = 10.6 and 15.4 Hz), 4.38 (2H, m), 3.51 (2H, m), 2.50-2.30 (2H, m).

Hydrazonium ion **10b**.

Major isomer: ^{1}H-NMR (500 MHz, CD_3OD) δ 8.47 (1H, d, *J* = 10.1 Hz), 8.00-7.20 (7H, m), 4.12 (2H, m), 3.29 (2H, m), 2.05 (2H, m), 1.91 (2H, m); **minor isomer**: ^{1}H-NMR (500 MHz, CD_3OD) δ 8.50 (1H, d, *J* = 10.8 Hz), 8.00-7.20 (7H, m), 4.26 (2H, m), 3.15 (2H, m), 1.80 (4H, m).

Hydrazonium ion **10c**.

Major isomer: ^{1}H-NMR (500 MHz, CD_3OD) δ 9.13 (1H, d, *J* = 10.3 Hz), 8.00-7.20 (6H, m), 7.24 (1H, dd, *J* = 10.3 and 17.9 Hz), 5.24 (2H, s), 4.53 (2H, m), 4.07 (2H, m), 2.70-2.50 (2H, m); **minor isomer**: ^{1}H-NMR (500 MHz, CD_3OD) δ 8.97 (1H, d, *J* = 10.8 Hz), 8.40-7.20 (7H, m), 7.08 (1H, dd, *J* = 10.8 Hz, and 17.9 Hz), 5.30 (2H, s), 4.39 (2H, m), 4.07 (2H, m), 2.70-2.50 (2H, m).

Hydrazonium ion **10d**.

Major isomer: ^{1}H-NMR (500 MHz, CD_3OD) δ 9.18 (1H, d, *J* = 10.8 Hz), 8.40-7.20 (7H, m), 4.51 (2H, m), 4.18 (2H, m), 2.60-2.30 (2H, m), 2.34 (3H, s); **minor isomer**: ^{1}H-NMR (500 MHz, CD_3OD) δ 8.90 (1H, d, *J* = 10.3 Hz), 8.40-7.20 (7H, m), 4.37 (2H, m), 4.33 (2H, m), 2.60-2.30 (2H, m), 2.37 (3H, s).

Hydrazonium ion **10e**.

Major isomer: ^{1}H-NMR (500 MHz, CD_3OD) δ 9.44 (1H, d, J = 10.1 Hz), 7.90-7.20 (7H, m), 5.00 (1H, ddd, *J* = 5.0, 6.9 and 9.0 Hz), 3.43 (1H, dd, *J* = 9.0 and 17.5 Hz), 2.89 (1H, dd, *J* = 5.0 and 17.5 Hz), 1.69 (3H, d, *J* = 6.9 Hz); **minor isomer**: ^{1}H-NMR (500 MHz, CD_3OD) δ 8.58 (1H, d, *J* = 11.0 Hz), 7.90-7.20 (7H, m), 5.38 (1H, ddd, *J* = 2.1, 6.7 and 9.0 Hz), 3.53 (1H, dd, *J* = 9.0 and 17.2 Hz), 2.84 (1H, dd, *J* = 2.1 and 17.2 Hz), 1.61 (3H, d, *J* = 6.7 Hz)

Cinnamaldehyde dimethylacetal-d_6 (**11**).

^{1}H-NMR (500 MHz, CD_3OD) δ 7.60-7.20 (5H, m), 6.71 (1H, d, J = 16.1 Hz), 6.14 (1H, dd, J = 5.1 and 16.1 Hz), 4.92 (1H, d, J = 5.1 Hz).

REFERENCES AND NOTES

1. E. Eder, G. Sauer, and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 496; Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1615.
2. B. List, R. A. Lerner, and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2000, **122**, 2395; W. Notz and B. List, *J. Am. Chem. Soc.*, 2000, **122**, 7386; B. List, P. Pojarliev, and C. Castello, *Org. Lett.*, 2001, **3**, 573.
3. A. Dondoni and A. Massi, *Angew. Chem. Int. Ed.*, 2008, **47**, 4638; B. List, *Chem. Commun.*, 2006, 819; K. A. Ahrendt, C. J. Borths, and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2000, **122**, 4243; .
4. N. J. Fina and J. O. Edwards, *Int. J. Chem. Kinet.*, 1973, **5**, 1; A. P. Grekov and V. Y. Veselov, *Russ. Chem. Rev.*, 1978, **47**, 631; S. Hoz and E. Buncel, *Israel J. Chem.,* 1985, **26**, 313.
5. J. L. Cavill, J.–U. Peters, and N. C. O. Tomkinson, *Chem. Commun.*, 2003, 728.
6. M. Lemay and W. W. Ogilvie, *Org. Lett.,* 2005, **7**, 4141; M. Lemay and W. W. Ogilvie, *J. Org. Chem.*, 2006, **71**, 4664; H. He, B.–J. Pei, H.–H. Chou, T. Tian, W.–H. Chan, and A. W. M. Lee, *Org. Lett.*, 2008, **10**, 2421.
7. I. Suzuki, Y. Iwata, and K. Takeda, *Tetrahedron Lett.*, 2008, **49**, 3238.
8. E. E. Boros, F. Bouvier, S. Randhawa, and M. H. Rabinowitz, *J. Heterocycl. Chem.*, 2001, **38**, 613.
9. D. E. Wilkinson, B. E. Thomas, D. C. Limburg, A. Holmes, H. Sauer, D. T. Ross, R. Soni, Y. Chen, H. Guo, P. Howorth, H. Valentine, D. Spicer, M. Fuller, J. P. Steiner, G. S. Hamilton, and Y.–Q. Wu, *Bioorg. Med. Chem.*, 2003, **11**, 4815.
10. J. H. Ahn, J. A. Kim, H.–M. Kim, H.–M. Kwon, S.–C. Huh, S. D. Rhee, K. R. Kim, S.–D. Yang, S.–D. Park, J. M. Lee, S. S. Kim, and H. G. Cheon, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1337; W.–J. Zhang, A. Berglund, J. L.–F. Kao, J.–P. Couty, M. G. Gershengorn, and G. R. Marshall, *J. Am. Chem. Soc.*, 2003, **125**, 1221; R. E. Melendez and W. D. Lubell, *J. Am. Chem. Soc.*, 2004, **126**, 6759.
11. S. T. Perri, S. C. Slater, S. G. Toske, and J. D. White, *J. Org. Chem.*, 1990, **55**, 6037.
12. B. F. Bonini, E. Capitò, M. Comes-Franchini, M. Fochi, A. Ricci, and B. Zwanenburg, *Tetrahedron: Asymmetry*, 2006, **17**, 3135.
13. K. Ishihara, H. Kurihara, M. Matsumoto, and H. Yamamoto, *J. Am. Chem. Soc.*, 1998, **120**, 6920.
14. C. K. M. Heo and J. W. Bunting, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2279.
15. All calculations were performed using Spartan '04 Macintosh, ver 1.03.

16. C. Lee, W. Yang, and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785; A. D. Becke, *Phys. Rev. A*, 1988, **38**, 3098; A. D. Becke, *J. Chem. Phys.*, 1992, **96**, 2155; A. D. Becke, *J. Chem. Phys.*, 1992, **97**, 9173; A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.
17. From calculations of the geometries of hydrazonium ions **10c** and **10d**, it was suggested that nitrogen atom that connected to an acyl group is considerably pyramidalized to avoid the steric repulsion between the alkene and the acyl group. By this structural feature, an *N*-acyl group would not work well as an electron-withdrawing group.
18. R. L. Hinman, *J. Org. Chem.*, 1958, **23**, 1587; C. R. Lindegren and C. Niemann, *J. Am. Chem. Soc.*, 1949, **71**, 1504.