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Organocatalysis using protonated 1,2-diamino-1,2-diphenylethane for asymmetric Diels–Alder reaction

Kyoung Hoon Kim, Seil Lee, Dae-Woong Lee, Dong-Hyun Ko and Deok-Chan Ha*

Department of Chemistry, Korea University, Seoul 136-701, Korea

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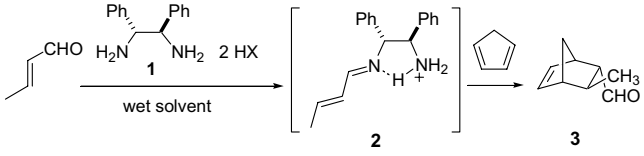
Abstract—Bisammonium salts of mono-*N*-alkylated chiral 1,2-diamino-1,2-diphenylethane (DPEN) were employed in the catalytic and asymmetric Diels–Alder reaction between cyclopentadiene and crotonaldehyde. The *N*-3-pentyl diamine·2HCl catalyst shows high *endo*/*exo* selectivity and *endo*-enantioselectivity for the cycloaddition, and this organocatalysis is the first example of the use of a chiral 1,2-diamine to generate an imine intermediate which is activated by an internal ammonium Brønsted acid for the cycloaddition in a wet solvent.

Enantioselective catalysis has made an enormous advance in synthetic chemistry during the last few decades.[1] Recently, methods based on metal-free organic catalysts have been attracted great attention, due to the advantages associated with the use of small organic molecules as chiral catalysts.[2] These organic catalysts are mostly inexpensive, stable under aerobic wet conditions, and do not cause metal contamination of the reaction products.

As one of the most powerful methods for constructing enantiomerically enriched molecules, chiral Lewis acid promoted Diels–Alder reactions have been studied with great success to achieve, in many cases, almost complete enantioselection.[3] Processes activating the chiral Lewis acids by Brønsted acids[4,5] and activating the dienophiles with chiral Brønsted acids for Diels–Alder reactions[6] are attracting significant attention. Another notable example is the use of chiral imidazolidinones and strong Brønsted acids for the activation of α,β-enals by reversibly forming iminium ion intermediates as reactive dienophiles for cycloadditions in wet solvents.[7]

Based on these advances in organic catalysis, we became interested in the question as to whether the ammonium salts of the (*R*,*R*)-1,2-diamino-1,2-diphenylethane (DPEN, **1**) and its derivatives would be able to directly catalyze the enantioselective Diels–Alder reaction of α,β-enals through the formation of imine intermediate **2** in which the imine is activated by an internal hydrogen bonding with the ammonium proton (Eq. 1). Herein, we disclose that the bisammonium salts of *N*-monoalkylated DPEN are good catalysts for the direct asymmetric Diels–Alder reaction between crotonaldehyde and cyclopentadiene.



(1)

In an initial screen of the reaction conditions, we found that the cycloaddition actually proceeded smoothly for 24 h at room temperature in wet solvents. The reaction was optimized with the use of 5 mol % of **1** in dioxane–water (95:5 by volume) in the presence of hydrochloric acid acting as a Brønsted acid (Table 1, entry 4). Solvents having more than 10% (by volume) of water showed decreased *endo*/*exo* selectivity and *endo*-enantioselectivity. With the use of less than 2 equiv of HCl for 1 equiv of diamine **1**, the *endo*/*exo* selectivity and the enantioselectivity of the *endo*-**3** were also deteriorated (Table 1, entry 5). The low conversion yield with 1 equiv of HCl for **1** may be due to the formation of a tight internal hydrogen bonding of mono-protonated

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* Corresponding author. Tel.: +82 02 3290 3131; fax: +82 02 3290 3121; e-mail: dechha@korea.ac.kr

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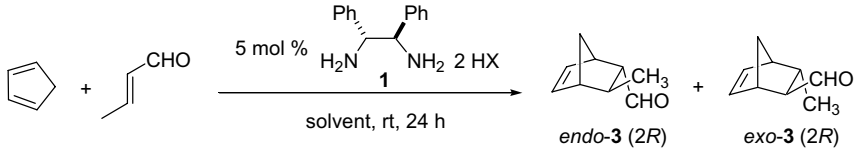
Table 1. Enantioselective Diels–Alder cycloaddition between cyclopentadiene and (*E*)-crotonaldehyde catalyzed by bisammonium salts of (*R*,*R*)-1,2-diamino-1,2-diphenylethane

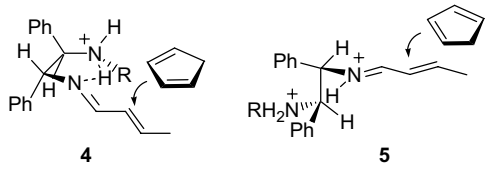


Entry	HX	Solvent	Yield (%)[a,b]	*endo*:*exo*[c]	% ee, *endo* (*exo*)[c]
1	HCl	MeOH–H_2O (95:5)	97	2.4:1	56 (46)
2	HCl	THF–H_2O (95:5)	92	3.8:1	72 (26)
3	HCl	DME–H_2O (95:5)	98	2.4:1	62 (25)
4	HCl	Dioxane–H_2O (95:5)	96	4.8:1	79 (31)
5	HCl[d]	Dioxane–H_2O (95:5)	96	2.3:1	75 (23)
6	HCl[e]	Dioxane–H_2O (95:5)	46	2.2:1	65 (15)
7	HBr	Dioxane–H_2O (95:5)	98	4.3:1	77 (30)
8	$HClO_4$	Dioxane–H_2O (95:5)	96	3.4:1	54 (22)
9	*p*-TsOH	Dioxane–H_2O (95:5)	61	1.2:1	47 (30)
10	CF_3CO_2H	Dioxane–H_2O (95:5)	76	1.1:1	31 (28)
11	$CH_3(CH_2)_{11}C_6H_4SO_3H$	H_2O	98	3.3:1	77 (34)

[a] GC conversion yields.
[b] 0.5 M aldehyde concentration.
[c] Determined by chiral GC (Chiraldex Γ-TA column).
[d] 7.5 mol % HCl used.
[e] 5 mol % HCl used.

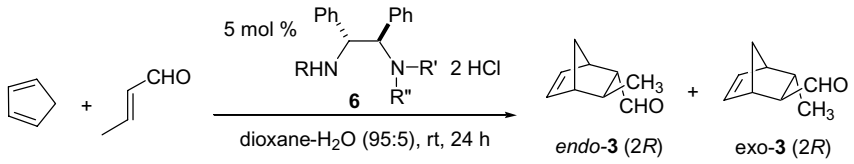
diamine **1** as a result of which the catalytic cycle of the formation and hydrolysis of the imine intermediate is slowed down (entry 6).[8] Several other strong Brønsted acids were also tested and a gradual decrease in stereoselectivity was observed as the size of the acid increased (entries 7–9). Closely interacting ion pairs of the ammonium salts, which are not completely dissociated in this wet solvent, are supposed to affect the stereocontrol in this cycloaddition. We also tested the capacity of *p*-dodecylbenzenesulfonic acid (DBSA) to act both as a Brønsted acid and a surfactant for this asymmetric Diels–Alder reaction.[9] This **1** $(DBSA)_2$ salt, poorly soluble in wet dioxane, was found to be a good catalyst for the cycloaddition in water, although the resultant stereocontrol was less effective than that observed in the case where HCl was used as a Brønsted acid in wet dioxane (entry 11).

With these results in hand, we tried structural modifications of **1**, by attaching an alkyl substituent to one of the two amino nitrogens. We expected that imine **4**, which is generated in situ from the mono-*N*-alkylated diamine and crotonaldehyde, would adapt its (*E*)-geometry to avoid the non-bonding interaction between the substrate olefin and the geminal phenyl group. We also anticipated that the neighboring phenyl group would force the alkyl group, which is attached to the ammonium nitrogen of **4**, to occupy the opposite face of the hydrogen bonded five-membered ring to which it is attached. With this steric arrangement, improved stereocontrol was expected, since the *re*-face of dienophile **4** would be effectively shielded by both the phenyl and *N*-alkyl groups, leaving the *si*-face more favorable for the cycloaddition to give *endo*-**3** (2*R*) as a major product. Cycloaddition through another possible intermediate, diprotonated amino-imine **5**, is unlikely since the most stable conformation of **5** would provide the enantiomeric *endo*-**3** (2*S*) product.



The experiments on the steric contribution of the *N*-alkyl group of the diamine to the diastereomeric and enantiomeric control in the Diels–Alder reaction are summarized in Table 2.[10] Increasing the size of the *N*-substituted secondary alkyl group from isopropyl (**6a**) to 3-pentyl (**6c**)[11] gradually improved the regio- and enantioselectivity, and maximum stereoselectivity (*endo*/*exo*, 7.8:1; *endo* 91% ee) was observed with **6c** (Table 2, entries 1–3).[12] With longer and more branched *N*-alkyl groups, a slight loss of stereocontrol was observed (entries 4 and 5). Much lower stereoselectivity and yield resulted from the use of a primary alkyl (**6f** and **6g**) or phenyl (**6h**) *N*-substituent. The *N*,*N*-dialkylated diamine, **6i** having a pyrrolidine ring, showed a level of stereocontrol almost comparable to that of diamines having only one secondary alkyl substituent. One methylene group bonded to the nitrogen in the pyrrolidine ring of **6i** seems to assume a *pseudo*-equatorial position with respect to the hydrogen bonded five-membered ring **4**, thereby causing the *si*-face to be subjected to less steric constraint than expected. The *N*,*N*′-dialkylated derivatives **6j** and **6k** showed poor reactivity and stereoselectivity. These results, together with that observed for **6f**, obviously indicate that this cycloaddition takes place through imine intermediates, rather than through

Table 2. Enantioselective Diels–Alder cycloaddition catalyzed by bis-ammonium salts of *N*-alkylated (*R*,*R*)-1,2-diamino-1,2-diphenylethane



Entry	R	R′,R″	Yield (%)[a,b]	*endo*:*exo*[c]	% ee, *endo* (*exo*)[c]
1	H	*i*-Pr, H (**6a**)	97	6.3:1	86 (43)
2	H	Cyclohexyl, H (**6b**)	96	6.5:1	85 (39)
3	H	3-Pentyl, H (**6c**)	97	7.8:1	91 (38)
4	H	5-Nonyl, H (**6d**)	94	7.1:1	87 (49)
5	H	2,4-Dimethyl-3-pentyl, H (**6e**)	98	6.5:1	81 (32)
6	H	1-Decyl, H (**6f**)	65	3.0:1	26 (37)
7	H	CH_2Ph, H (**6g**)	75	2.2:1	50 (18)
8	H	Ph, H (**6h**)	68	1.3:1	30 (15)
9	H	$-(CH_2)_4-$ (**6i**)	98	7.0:1	84 (22)
10	*i*-Pr	*i*-Pr, H (**6j**)	77	2.0:1	19 (9)
11	Cyclohexyl	Cyclohexyl, H (**6k**)	70	2.1:1	22 (10)
12[d]	H	3-Pentyl, H (**6c**)	94	4.3:1	78 (37)

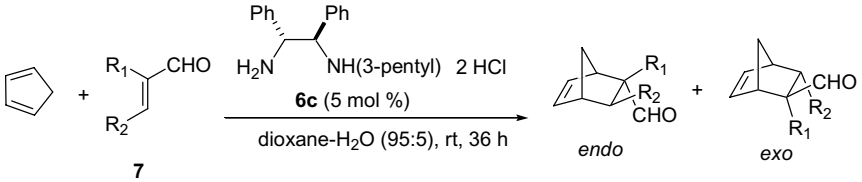
[a] Isolated yield.
[b] 0.5 M aldehyde concentration.
[c] Determined by chiral GC (Chiraldex Γ-TA column).
[d] $CH_3(CH_2)_{11}C_6H_4SO_3H$ (10 mol %) was used in pure water.

the iminium ions formed with the participation of the secondary amines. This primary amine catalyzed asymmetric cycloaddition was also tested with **6c**·$(DBSA)_2$ in pure water. However, in this case, the stereocontrol was found to be less effective than that observed with the use of **6c**·$(HCl)_2$ in wet dioxane (entry 12).

The scope of the unsaturated aldehyde as the dienophile for this cycloaddition was briefly probed and the results are summarized in Table 3. Slight losses of stereocontrol and reaction yield were observed as the increased size and the electron-donating ability of the β-substituent of the dienophile were increased (Table 3, entries 1–3). Methacrolein, an α-substituted α,β-enal, showed *exo*-selective cycloaddition with low enantioselectivity, and cyclohexene-1-carboxaldehyde was not reactive under the reaction conditions used in this study (entries 4 and 5).

In summary, we showed that the bisammonium salt of mono-*N*-alkylated chiral 1,2-diamino-1,2-diphenylethane is an efficient organocatalyst for the asymmetric Diels–Alder reaction between cyclopentadiene and crotonaldehyde with high *endo*/*exo* selectivity and *endo*-enantioselectivity. Although the successful application of this reaction is restricted to the use of β-substituted α,β-enals as the dienophile, this organocatalysis is the first example of the use of a chiral 1,2-diamine to generate an imine intermediate which is activated for the cycloaddition by an internal ammonium Brønsted acid in wet solvent.

Table 3. Diels–Alder cycloaddition catalyzed by bisammonium chloride of **6c**



Entry	R_1	R_2	Yield (%)[a]	*endo*:*exo*[b]	% ee[b]	
					endo	*exo*
1	H	*n*-Pr (**7a**)	90	4.7:1	85 (2*R*)	18 (2*R*)
2	H	Ph (**7b**)	75	9.0:1	78 (2*S*)	17 (2*S*)
3	H	2-Furyl (**7c**)	67	8.0:1	85 (2*S*)	29 (2*S*)
4	CH_3	H (**7d**)	65	1:4.3	34 (2*R*)[c]	30 (2*R*)
5	$-(CH_2CH_2CH_2CH_2)-$ (**7f**)		Trace	—	—	

[a] Isolated yields.
[b] Determined by chiral GC (Chiraldex Γ-TA column).
[c] Absolute configuration and enantiomeric excess determined by comparison with the known optical rotation after separation of the *endo*/*exo* mixture by silica gel chromatography.[13]

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.025.

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11. Preparation of **6c**: A mixture of **1** (1.0 mmol), 3-pentanone (1.0 mmol) and 800 mg of 4 Å powdered molecular sieves in 50 mL of toluene was heated at reflux for 48 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo to give the diaminoacetal. This diaminoacetal, without further purification, was dissolved in 50 mL of ethanol, and $NaBH_3CN$ (1.5 mmol) and 1 N HCl (1.0 mL) were added at 0 °C. The mixture was stirred for 48 h at 0 °C, quenched by adding 1 N NaOH (100 mL) and extracted twice with 100-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by silica gel chromatography to give **6c** in 72% overall yield.
12. In a representative procedure, crotonaldehyde (1.0 mmol) and cyclopentadiene (3.0 mmol) were sequentially added to a solution of diamine **5c** (0.05 mmol, 5 mol %) and 1 N HCl (0.1 mL, 10 mol %) in 2 mL of dioxane at ambient temperature. The resulting solution was stirred for 24 h at room temperature, diluted with ether and washed with water and brine. The organic layer was dried (Na_2SO_4), concentrated, and then purified by silica gel chromatography (5% Et_2O/hexanes). GLC (Chiraldex Γ-TA column, 50 °C to 100 °C, 1 °C/min gradient, N_2 23 psi, injection temp. 220 °C, detection temp. FID 250 °C): *exo* (2*S*) isomer $t_R = 37.90$ min, *exo* (2*R*) isomer $t_R = 39.06$ min, *endo* (2*S*) isomer $t_R = 42.55$ min, *endo* (2*R*) isomer $t_R = 42.90$ min.
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