Synthetic Methods

DOI: 10.1002/ange.200801408

Asymmetric Diels–Alder Reactions of α,β-Unsaturated Aldehydes Catalyzed by a Diarylprolinol Silyl Ether Salt in the Presence of Water**

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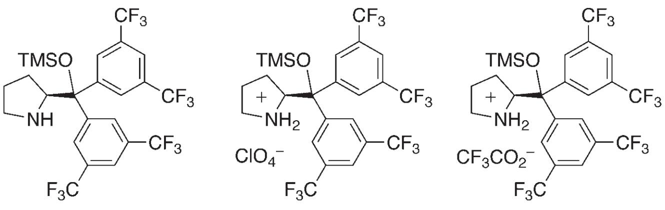
The Diels–Alder reaction is a powerful synthetic method for the construction of regio- and stereochemically defined cyclohexane frameworks. There are several catalytic enantioselective methods,[1] and MacMillan and co-workers developed the first Diels–Alder reaction involving an organocatalyst, which proceeds by a LUMO-lowering activation mechanism.[2] Since then several asymmetric Diels–Alder reactions involving organocatalysts have been reported.[3,4] Our group[5] and that of Jørgensen[6] developed a diarylprolinol silyl ether as an effective organocatalyst in 2005, and this type of catalyst has since been employed widely in several asymmetric reactions.[7] Recently, we found that diarylprolinol silyl ether **1** combined with CF_3CO_2H is an effective Diels–Alder catalyst in toluene.[8]

In contrast, water has attracted a lot of interest as a reaction medium in current organic chemistry because of its unique properties.[9] In the Diels–Alder reaction, for instance, the reaction is accelerated "in water" (homogeneous dilute conditions)[10] and "on water" (biphasic conditions).[11] We reported the positive effect of water on diastereo- and enantioselectivities for the asymmetric aldol reaction in the presence of water.[12] Palomo et al.[13] and Ma and co-workers[14] reported the enantioselective Michael reaction catalyzed by dialkyl- and diphenylprolinol silyl ethers, respectively in the presence of water. Some organocatalyzed reactions are known to be affected by dissolved water,[15] and on the basis of our interest in reactions in the presence of water,[16] we have examined the enantioselective Diels–Alder reaction by using diarylprolinol silyl ether as an organocatalyst. Although Northrup and MacMillan[2b] and Ogilvie and co-workers[3c,g,h] reported the asymmetric Diels–Alder reaction in the presence of water, we developed a green and practical procedure that does not require an organic solvent, even for the purification step. We also observed an interesting phenomenon, namely the positive effect of water on the rate and enantioselectivity of the reaction, which is different from that of the "on water" reaction and will be described herein.

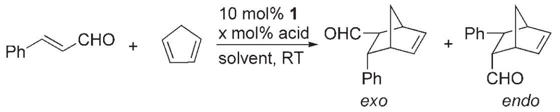
First, we chose the model reaction between cinnamaldehyde and cyclopentadiene, which we had found to be promoted by a combination of **1** (Figure 1) and CF_3CO_2H in toluene within 20 hours (Table 1, entry 1).[8] When we used water as a solvent, a biphasic system formed and the reaction proceeded slowly, affording the product in lower yield with moderate enantioselectivity (Table 1, entry 2). Acid was found to have an important effect on the yield of the reaction (Table 1). The reaction was slower in the presence of a weaker acid such as CCl_3CO_2H (Table 1, entry 3), whereas the enantioselectivity increased in the presence of fluorinated



1 **2** **3**

Figure 1. The organocatalysts examined in this study.

Table 1: The effect of additives on the Diels–Alder reaction.[a]



Entry	Amount of Acid [equiv]	Solvent	*t* [h]	Yield [%][b]	*exo*/*endo*[c]	*ee* [%][d]	
						exo	*endo*
1	CF_3CO_2H (20)	toluene	20	86	84:16	95	83
2	CF_3CO_2H (20)	H_2O	20	54	76:24	58	41
3	CCl_3CO_2H (20)	H_2O	20	39	76:24	56	33
4	$CF_3(CF_2)_3SO_3H$ (10)	H_2O	20	66	79:21	86	58
5	$CF_3(CF_2)_7SO_3H$ (10)	H_2O	20	16	41:59	n.d.	n.d.
6	TsOH (10)	H_2O	20	63	82:18	92	76
7	$HClO_4$ (10)	H_2O	4	100	80:20	95	90

[a] Unless otherwise shown, the reaction was conducted by using catalyst **1** (0.07 mmol), acid (0.14 or 0.07 mmol), cinnamaldehyde (0.7 mmol), and cyclopentadiene (2.1 mmol) at room temperature in toluene (1.4 mL) or in water (1.4 mL). [b] Yields of isolated products as a mixture of *exo* and *endo* isomers. [c] Determined by ^1H NMR (400 MHz) spectroscopy. [d] The *ee* value was determined by HPLC on a chiral stationary phase or GC analysis. n.d. = not determined, Ts = *para*-toluenesulfonyl.

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[**] This work was partially supported by the Toray Science Foundation, and a Grant-in-Aid for Scientific Research from MEXT. S.S. is grateful to the Japan Society for the Promotion of Science (JSPS) for a postdoctoral fellowship.

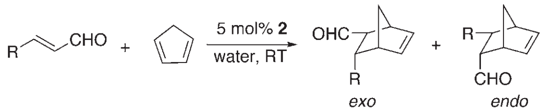
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200801408.

sulfonic acid (Table 1, entry 4). Fluorinated sulfonic acid with long alkyl chains formed an emulsion and increased the interface area between the organic and aqueous phases, but the yield remained low (Table 1, entry 5). When we employed $HClO_4$, the reaction was complete within 4 hours and afforded the Diels–Alder product quantitatively with excellent enantioselectivity (Table 1, entry 7). Notably, the reaction with **1** and $HClO_4$ run in the presence of water was much faster (4 h) than the reaction run with **1** and CF_3CO_2H in toluene (20 h).

As **1** and $HClO_4$ were found to be a suitable combination for the reaction in the presence of water, the isolation of this key salt was examined. Salt **2** was precipitated as a white powder, when aqueous $HClO_4$ was slowly added to an ether solution of **1** at 0 °C. By using 5 mol % of this salt as a catalyst the reaction proceeds with the same efficiency.

The scope of the reaction was investigated and the results are shown in Table 2. Phenyl-substituted, as well as *p*-bromophenyl- and *p*-nitrophenyl-substituted acrolein derivatives gave good yields with excellent enantioselectivities. Aromatic and heteroaromatic groups, such as furyl groups, are suitable substituents for the reaction (Table 2, entry 4), and reactions of alkyl-substituted acrolein derivatives resulted in nearly perfect enantioselectivity (Table 2, entries 5–7). Although catalyst **2** did not afford good results in the reaction of reactive acrolein with cyclopentadiene, trifluoroacetic acid salt **3** was found to be a suitable catalyst in this particular reaction[17] and provided the Diels–Alder adduct at low temperature (−60 °C) with excellent enantioselectivities in both the *exo* and *endo* isomers (Table 2, entry 8).

Table 2: Enantioselective Diels–Alder reaction between cyclopentadiene and an α,β-unsaturated aldehyde catalyzed by the $HClO_4$ salt of a diarylprolinol silyl ether (**2**).[a]

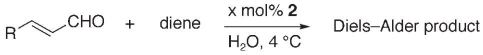


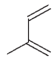
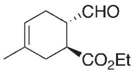
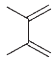
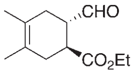
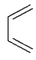
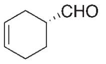
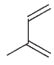
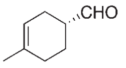
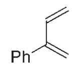
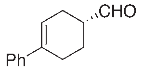
Entry	R	*t* [h]	Yield [%][b]	*exo*/*endo*[c]	*ee* [%][d]	
					exo	*endo*
1	Ph	7	93	80:20	97 (2*S*)[e]	92 (2*S*)[e]
2[f]	*p*-BrPh	7	89	84:16	96	86
3[f]	*p*-NO_2Ph	5	94	84:16	95	86
4[f,g]	2-furyl	40	76	76:24	92 (2*S*)[e]	84 (2*S*)[e]
5	Me	4	73	72:28	99	99
6	*n*Bu	2	95	80:20	98	92
7	Cy	7	91	85:15	98	98
8[h]	H	24	85	62:38	98	97

[a] Unless otherwise shown, the reaction was conducted by using catalyst **2** (0.025 mmol), cinnamaldehyde (0.5 mmol), and cyclopentadiene (1.5 mmol) at room temperature and in the presence of water (252 μL). [b] Yields of isolated products as a mixture of *exo* and *endo* isomers. [c] Determined by ^1H NMR (400 MHz) methods. [d] The *ee* value was determined by chiral HPLC or GC analysis. [e] Absolute configuration, see reference [2a]. [f] Cyclopentadiene (2 mmol) was employed. [g] Catalyst (10 mol%) was used. [h] The reaction was conducted by using trifluoroacetic acid salt **3** (0.05 mmol), acrolein (1.0 mmol), and cyclopentadiene (3.0 mmol) at −60 °C in the presence of water (54 μL). Cy = cyclohexyl.

Various dienes were investigated and the results are shown in Table 3. Isoprene and 2,3-dimethylbutadiene both worked well for the reaction (Table 3, entries 1, 2, and 4).

Table 3: Enantioselective Diels–Alder reaction between acrolein or its derivatives and dienes, catalyzed by diarylprolinol silyl ether salt **2**.[a]



Entry	R	Diene	Product	X [mol %]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	EtO_2C			5	11	93	94
2	EtO_2C			5	11	89	85
3[d]	H			10	48	41	87 (*R*)[f]
4[d]	H			10	36	72	90 (*R*)[f]
5[e]	H			10	28	71	88

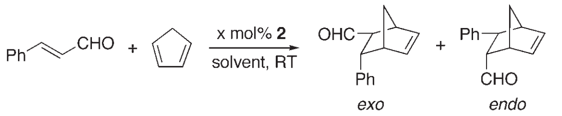
[a] Unless otherwise shown, the reaction was conducted by using α,β-enal (0.5 mmol), diene (1.5 mmol), water (252 μL), and catalyst **2** at 4 °C. [b] Yields of isolated product. [c] The *ee* values were determined by chiral HPLC or GC analysis. [d] Water (126 μL) was employed. [e] Acrolein (1.0 mmol), diene (0.25 mmol), water (126 μL) and catalyst **2** (0.025 mmol) at 4 °C. [f] Absolute configuration; see the Supporting Information.

Although butadiene is a useful diene component in the Diels–Alder reaction, its reaction is rather limited as a result of its low reactivity.[18] The first successful Diels–Alder reaction of butadiene and acrolein proceeded to provide the adduct with high enantioselectivity (Table 3, entry 3).

The large-scale preparation of the Diels–Alder adduct of cinnamaldehyde and cyclopentadiene under our conditions was investigated. After stirring a reaction mixture containing cinnamaldehyde (20 mmol, 2.64 g), cyclopentadiene (4.7 mL), and water (10 mL) in the presence of catalyst **2** (1.0 mmol, 700 mg) at room temperature for 8 hours, the water phase was removed by decantation. A ^1H NMR analysis of the crude mixture indicated that there was quantitative conversion of the dienophile. Direct distillation of the crude mixture gave the Diels–Alder product in 81 % yield with excellent optical purity (*exo*/*endo* = 82:18, *exo* 97 % *ee*, *endo* 92 % *ee*). Notably, no organic solvent is needed for any step, including the purification.

The effect of water on the reaction was examined for the reaction of cinnamaldehyde and cyclopentadiene (Table 4). Contrary to the excellent results in the presence of water, immediate polymerization of cyclopentadiene occurred when run neat, in toluene, or in CH_2Cl_2 (Table 4, entries 1–3). The reaction is slow in MeOH and provides the Diels–Alder adduct with moderate enantioselectivity in low yield along recovered starting material (Table 4, entry 4). Thus, water has

Table 4: The effect of solvent on the Diels–Alder reaction.[a]



Entry	Solvent (µL)	Cat. [mol %]	t [h]	Yield [%][b]	*exo*/*endo*[c]	*ee* [%][d] *exo*	*ee* [%][d] *endo*
1	neat (0)	10	0.1	0			
2	toluene (250)	10	0.1	0			
3	CH_2Cl_2 (250)	10	0.1	0			
4	MeOH (252)	10	5	37	67:38	86	58
5	H_2O (252)	10	3	91	80:20	97	95
6	H_2O (36)	5	7	59	77:23	92	80
7	H_2O (90)	5	7	70	80:20	95	88
8	H_2O (126)	5	7	92	80:20	97	92
9	H_2O (252)	5	7	93	80:20	97	92
10[e]	H_2O (252)	5	7	100	80:20	97	92
11	H_2O (900)	5	7	90	81:19	97	92
12	brine (126)	5	7	44	84:16	94	82

[a] Unless otherwise shown, the reaction was conducted by using catalyst **2** (0.025 mmol), cinnamaldehyde (0.5 mmol), and cyclopentadiene (1.5 mmol) at room temperature in the indicated solvent. [b] Yields of the isolated product as a mixture of *exo* and *endo* isomers. [c] Determined by ^{1}H NMR (400 MHz) methods. [d] The *ee* values were determined by chiral HPLC analysis. [e] The reaction was stirred for only the first minute.

a positive effect on the rate and enantioselectivity of the reaction. The amount of water was also found to be important. In the presence of a small amount of water (Table 4, entries 6 and 7), the reaction was slow and the enantioselectivity decreased, whereas in the presence of more than 126 µL of water led to excellent results that were consistently obtained. The reaction even proceeds efficiently in the presence of a large amount of water (Table 4, entry 11) for the reaction of hydrophobic cinnamaldehyde, in which two phases were formed. In contrast, too much water decreased the reactivity for the reaction of acrolein, which dissolves in water (Table 2, entry 8). This evidence suggests that the reaction proceeds in organic phase. Moreover, stirring is not essential; for a reaction in which there was initial stirring for one minute, the reaction efficiency was unchanged without additional stirring (Table 4, entry 10). When brine was used instead of water, the reaction was slow and the enantioselectivity decreased, indicating a salting out effect that reduces the reactivity. These results indicate that 1) the reaction proceeds in the organic phase and does not proceed at the interface between the water and organic phases and 2) a small amount of water dissolved in the organic phase accelerates the reaction and affects the transition state, resulting in increased enantioselectivity. This water effect is completely different from that observed by Rideout and Breslow, in which all the reagents dissolved homogeneously "in water",[10] and it is also different from the effect of the "on water reaction" reported by Sharpless and co-workers, in which vigorous stirring was essential for the reaction to proceed at the interface of two phases.[11a]

In summary, the enantioselective Diels–Alder reaction catalyzed by a diarylprolinol silyl ether salt in the presence of water was developed and provides the Diels–Alder adducts with high *exo* selectivities and excellent enantioselectivities. There are several noteworthy features in the present reaction: 1) completely organic solvent-free procedures, including the purification step, have been established and provide an ideal method for the preparation of chiral Diels–Alder products, 2) the *exo* isomer is predominantly obtained, in contrast with the existing chiral Lewis acid mediated method, 3) some of the combinations of diene and dienophile are the first successful examples of those enantioselective Diels–Alder reactions, 4) water accelerates the reaction and increases the enantioselectivity, and 5) the role of water in the present reaction is different from that of Breslow's well-known homogeneous reaction "in water" and that of Sharpless' "on water" reaction.

Experimental Section

Typical experimental procedure (Table 2, entry 1): Cyclopentadiene (1.5 mmol, 117 µL) was added to a stirred heterogeneous mixture containing catalyst **2** (17.5 mg, 5 mol %), *trans*-cinnamaldehyde (66 mg, 63 µL, 0.5 mmol), and water (14 mmol, 252 µL) at room temperature. After completion of the reaction (monitored by TLC), the reaction was quenched with a saturated $NaHCO_3$ solution, the organic materials were extracted by using ethyl acetate and then the organic solution was dried over Na_2SO_4. After filtration, low boiling compounds were removed under reduced pressure to leave the crude product, which was purified by column chromatography on silica gel to furnish the pure product (92 mg, 93 % yield). The *endo*/*exo* ratio was determined from the ^{1}H NMR spectrum of the crude material. The product was converted into the corresponding alcohol by using $NaBH_4$ and the enantioselectivity was determined by HPLC methods by using a Chiralcel OJ-H column.

Received: March 24, 2008
Revised: May 28, 2008

Keywords: asymmetric synthesis · cycloaddition · enantioselectivity · organocatalysis · water chemistry

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