



# Preparation of optically active *cis*-4-methylcyclohex-4-ene-1,2-dicarboximides by a combination of Diels–Alder reaction and complexation with optically active hosts and enantioselective Diels–Alder reaction in inclusion crystals in a water suspension medium

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Optically active Diels–Alder adducts were prepared using a one-pot preparative method and enantioselective Diels–Alder reaction with optically active hosts in a water suspension medium.

## Introduction

Optically active enantiomers of the *cis*-4-methylcyclohex-4-ene-1,2-dicarboximides, important as key starting materials for the synthesis of various bioactive compounds, have been prepared by biological synthesis. These, however, are neither always simple nor efficient. The Diels–Alder reaction is a simple and efficient tool to form the key step in the preparation of six-membered rings. Many procedures have been developed to increase the yields and selectivities of Diels–Alder reactions.<sup>1</sup> Recently, organic reactions in aqueous media, particularly in water, have received much attention, because water is economical and harmless to the environment.<sup>2</sup>

Optically active *cis*-4-methylcyclohex-4-ene-1,2-dicarboximides were prepared by Diels–Alder reaction using optically active hosts and enantioselective Diels–Alder reactions in inclusion crystals in a water suspension medium.

## Results and discussion

We report a one-pot preparative method<sup>3</sup> to prepare optically active compounds by a combination solid state Diels–Alder reaction in a water suspension medium and an enantioselective inclusion complexation of the product with an optically active host compound in the same aqueous medium. Heating *in vacuo* of the inclusion complex crystal isolated from the aqueous medium by filtration gave optically active product by distillation. Since no solvent is necessary throughout the reaction, inclusion complexation and isolation of the optically active product from the inclusion complex, this is genuinely sustainable and green chemistry. For example, when a mixture of *N*-ethylmaleimide **2b** (0.2 g, 1.60 mmol), 2-methyl-1,3-butadiene **1** (0.400 g, 5.87 mmol), and water (2 mL) was stirred at room temperature for 12 h, *rac*-**3b** was produced. To a water suspension medium of *rac*-**3b** was added the optically active compound **4c**<sup>4</sup> (0.405 g, 0.80 mmol) and the mixture was stirred for 12 h to give a 1:1 inclusion complex of **4c** with (+)-**3b**. Heating the filtered inclusion complex *in vacuo* gave (+)-**3b** with 94% ee (0.043 g, 31% yield). From the filtrate left after separation of the inclusion crystals, (–)-**3b** with 37% ee (0.043 g, 28% yield) was obtained by extraction with ethyl acetate. By the same procedure, optically active **3a** was prepared (Table 1). In the case of (+)-**3b**, the efficiency of enantiomeric resolution

is very high. Optical resolution of **3a** using **4b** gave only the (–)-product. To clarify the results, we attempted to characterize the inclusion complex of **3a** with **4b** by X-ray analysis but unfortunately suitable single crystals could not be grown. Inclusion complexes of **3a** with **4c**, **3b** with **4a**, and **3c** with **4a–c** were not obtained (Table 1). Furthermore, optical resolution of *rac*-**3c** with **4c** by recrystallization was successful giving (+)-**3c** with 85% ee in 47% yield. Since the optically active host remained after separation of the optically active guest from its inclusion complex by distillation it can be used repeatedly. This one-pot method in water is thus both ecological and economical.

We also report enantioselective Diels–Alder reaction in inclusion crystals in a water suspension medium. A suspension of the powdered 2:1 inclusion compound of **4b** with **2c** (2.00 g, 3.1 mmol) and **1** (1.00 g, 14.70 mmol) in water (15 mL) containing hexadecyltrimethylammonium bromide (0.04 g) as a surfactant to aid dispersion was stirred for 12 h. The solid reaction product was filtered off and the product dried. The filtered crystals included the product as shown by IR spectroscopy. The product in comparison with the starting material **2c** has a greater affinity towards the optically active host **4b**. Heating of the filtered crystals *in vacuo* gave (+)-**3c** with 11% ee in 81% yield. Since the optically active product was obtained the reaction occurred in the inclusion crystals. Optically active **3a** and **3b** were prepared by the same procedure (Table 2). **4b** did not form inclusion complexes with **3b** and **3c** after recrystallization.

## Green Context

Diels–Alder reactions are perfectly atom economic. They also have the potential for being enantioselective and forming complex multifunctional products from relatively simple raw materials. This paper shows that such procedures can take place readily in aqueous environments with good enantiomeric purity. This is achieved through the formation of inclusion complexes in chiral hosts suspended in water. Heating the filtered solid allowed the Diels–Alder reaction to proceed to give the chiral product in good yield. No organic solvents are used in this sequence, although extraction was carried out with ethyl acetate. *DJM*

A suspension of the powdered 3 : 1 inclusion compound of **4b** with **1** (1.5 g, 5.5 mmol) and **2c** (0.168 g, 0.99 mmol) in water (15 mL) containing hexadecyltrimethylammonium bromide (0.04 g) as a surfactant to aid dispersion was stirred for 12 h. The solid reaction product was filtered off and dried. The filtered crystals included the product as shown by IR spectroscopy. The product in comparison with the starting material **1** has a greater affinity towards the optically active host **4b**. Heating of the filtered crystals *in vacuo* gave (+)-**3c** with 77% ee in 13% yield. Since the optically active product was obtained the reaction occurred in the inclusion crystals. By the same procedure, optically active **3a** and **3b** were prepared (Table 3). In the case of (+)-**3c**, using the inclusion complex of **4b** with **1**, the efficiency of the enantiomeric resolution is high. We found enantioselective Diels–Alder reaction in inclusion crystals in a water suspension medium gave optically active *cis*-4-methylcyclohex-4-ene-1,2-dicarboximides.

## Conclusion

In conclusion, optically active Diels–Alder adducts were prepared by a one-pot preparative method and enantioselective

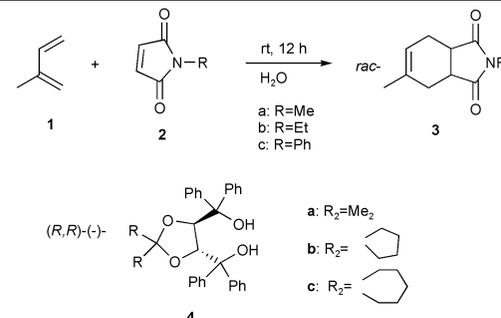
Diels–Alder reaction using optically active hosts in a water suspension medium.

## Experimental

### General procedure for one-pot preparation of optically active Diels–Alder adducts by a combination of synthesis and enantiomeric resolution with optically active hosts in a water suspension medium

To a suspension of 2-methyl-1,3-butadiene **1** (0.40 g, 5.87 mmol) in 2 mL water was added *N*-ethylmaleimide **2b** (0.20 g, 1.60 mmol), and the mixture was stirred at room temperature for 12 h to give *rac*-**3b** in 90% yield. To the water suspension medium of *rac*-**3b** was added powdered optically active host **4c** (0.405 g, 0.80 mmol), and the suspension stirred at room temperature for 12 h, the product filtered off, and dried to give the 1:1 inclusion complex of **4c** with (+)-**3b** as a colorless powder (0.51 g, 75% yield, mp 127–130 °C). IR (Nujol):  $\nu_{\max}$  3409, 3305, 1684  $\text{cm}^{-1}$ . Anal. Calc. for  $\text{C}_{45}\text{H}_{49}\text{NO}_6$ : C, 77.23; H, 7.06; N, 2.00. Found: C, 76.93; H, 7.12; N, 1.82%. Heating of the filtered inclusion crystals *in vacuo* (190 °C/22 mmHg)

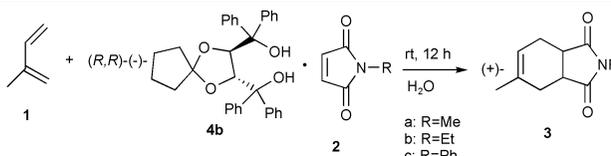
**Table 1** Results of the one-pot preparative method of optically active cyclohex-4-ene-1,2-dicarboximides by a combination of Diels–Alder reaction and enantiomeric resolution in a water suspension medium



Dienophile	Host (% ee)	Inclusion complex <sup>a</sup>		From complex			From filtrate		
		Host:Guest	Mp/°C	Product	Yield (%)	Enantiomeric purity <sup>b</sup> (% ee)	Product	Yield (%)	Enantiomeric purity <sup>b</sup> (% ee)
<b>2a</b>	<b>4a</b> (100)	1 : 1	118–120	(+)- <b>3a</b>	35	29	(-)- <b>3a</b>	40	59
<b>2a</b>	<b>4b</b> (100)	2 : 1	132–135	(-)- <b>3a</b>	48	71	(+)- <b>3a</b>	40	63
<b>2a</b>	<b>4c</b> (100)						<i>rac</i> - <b>3a</b>	74	0
<b>2b</b>	<b>4a</b>						<i>rac</i> - <b>3b</b>	69	0
<b>2b</b>	<b>4b</b>	2 : 1	123–125	(+)- <b>3b</b>	76	78	(-)- <b>3b</b>	48	50
<b>2b</b>	<b>4c</b>	1 : 1	127–130	(+)- <b>3b</b>	31	94	(-)- <b>3b</b>	28	37
<b>2c</b>	<b>4a</b>						<i>rac</i> - <b>3c</b>	78	0
<b>2c</b>	<b>4b</b>						<i>rac</i> - <b>3c</b>	80	0
<b>2c</b>	<b>4c</b>						<i>rac</i> - <b>3c</b>	80	0

<sup>a</sup> All crystals are colorless powders. <sup>b</sup> Enantiomeric purities were determined by HPLC.

**Table 2** Enantioselective Diels–Alder reactions using the 2 : 1 inclusion complex 2(**4b**)-**2** and **1** in a water suspension medium



Dienophile	Inclusion complex <sup>a</sup>		Product	Yield (%)	Enantiomeric purity <sup>b</sup> (% ee)
	Host:Guest	Mp/°C			
<b>2a</b>	2 : 1	146–150	(+)- <b>3a</b>	30	18
<b>2b</b>	2 : 1	125–130	(+)- <b>3b</b>	46	11
<b>2c</b>	2 : 1	120–123	(+)- <b>3c</b>	81	11

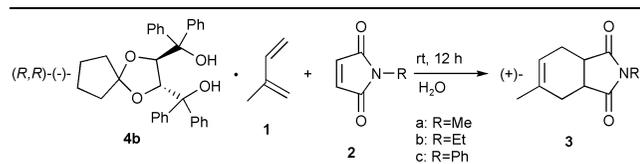
<sup>a</sup> All crystals are colorless powders. <sup>b</sup> Enantiomeric purities were determined by HPLC.

gave (+)-**3b** with 94% ee (0.047 g, 31% yield,  $[\alpha]_D +48$  (c 0.13, MeOH)). The filtrate remaining after separation of the inclusion crystals was extracted twice with 10 mL ethyl acetate. The ethyl acetate solution was dried over  $MgSO_4$ , and evaporated to give (-)-**3b** with 37% ee (0.043 g, 28% yield,  $[\alpha]_D -19$  (c 0.11, MeOH)).

#### General procedure for enantioselective Diels–Alder reaction using the 2:1 inclusion compound 2(4b)·2 and 1 in a water suspension medium

When a solution of **4b** (2.10 g, 4.26 mmol) and **2c** (0.37 g, 2.14 mmol) in diethyl ether (10 mL) was allowed to stand at room temperature for 12 h, a 2:1 inclusion compound of **4b** and **2c** was obtained as a colorless powder (2.0 g, 81% yield, mp 120–123 °C), IR (Nujol):  $\nu_{max}$  3421, 3233  $cm^{-1}$ . Anal. Calc. for

**Table 3** Enantioselective Diels–Alder reactions using the 3:1 inclusion complex<sup>a</sup> 3(4b)·1 and 2 in a water suspension medium



Dienophile	Product	Yield (%)	Enantiomeric purity <sup>b</sup> (% ee)
<b>2a</b>	(+)- <b>3a</b>	18	56
<b>2b</b>	(+)- <b>3b</b>	10	45
<b>2c</b>	(+)- <b>3c</b>	13	77

<sup>a</sup> All crystals are colorless powders. <sup>b</sup> Enantiomeric purities were determined by HPLC.

$C_{76}H_{71}NO_{10}$ : C, 78.80; H, 6.18; N, 1.21. Found: C, 78.86; H, 6.37; N, 1.25%. A suspension of powdered 2(4b)·2c (2.00 g, 3.1 mmol) and **1** (1.00 g, 14.70 mmol) in water (15 mL) containing hexadecyltrimethylammonium bromide (0.04 g) as a surfactant was stirred for 12 h. The solid reaction product was filtered off and dried. Heating of the filtered crystals *in vacuo* gave (+)-**3c** with 11% ee (0.34 g, 81% yield,  $[\alpha]_D +7$  (c 0.30, MeOH)).

#### General procedure for enantioselective Diels–Alder reaction using the 3:1 inclusion compound 3(4b)·1 and 2 in a water suspension medium

When a solution of **4b** (2.60 g, 5.28 mmol) and **1** (0.68 g, 10 mmol) in diethyl ether (10 mL) was allowed to stand at room temperature for 20 h, a 3:1 inclusion compound of **4b** and **1** was obtained as a colorless powder (1.5 g, 55% yield, mp was not clear). IR (Nujol)  $\nu_{max}$  3435, 3228  $cm^{-1}$ . A suspension of powdered 3(4b)·1 (1.5 g, 5.5 mmol) and **2c** (0.168 g, 0.99 mmol) in water (15 mL) containing hexadecyltrimethylammonium bromide (0.04 g) as a surfactant was stirred for 12 h. The solid reaction product was filtered off and dried. Heating of the filtered crystals *in vacuo* gave (+)-**3a** with 77% ee (0.30 mg, 13% yield,  $[\alpha]_D +48$  (c 0.13, MeOH)).

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