

Article

# ADMET Polymerization of Dimeric Cinchona Squaramides for the Preparation of a Highly Enantioselective Polymeric Organocatalyst

Mohammad Shahid Ullah, Sadia Afrin Chhanda and Shinichi Itsuno \* 

Department of Applied Chemistry and Life Science, Toyohashi University of Technology, Toyohashi 441-8580, Japan; shahid\_chem\_du@yahoo.com (M.S.U.); afrinchanda@gmail.com (S.A.C.)

\* Correspondence: itsuno@chem.tut.ac.jp

Received: 30 April 2020; Accepted: 22 May 2020; Published: 25 May 2020



**Abstract:** Under the acyclic diene metathesis (ADMET) reaction condition, the C3-vinyl groups of cinchona alkaloids readily react with each other to form a C-C bond. A novel type of cinchona alkaloid polymers was synthesized from dimeric cinchona squaramides using the Hoveyda-Grubbs' second-generation catalysts ( $\text{HG}_2$ ) by means of ADMET reaction. The chiral polymers, containing cinchona squaramide moieties in their main chains, were subsequently employed as catalysts for the enantioselective Michael reaction to give the corresponding chiral adducts in high yields with excellent enantioselectivity and diastereoselectivity. Both enantiomers from the asymmetric Michael reaction were distinctively prepared while using the polymeric catalysts, possessing pseudoenantiomeric structures. The catalysts were readily recovered from the reaction mixture and recycled several times due to the insolubility of the cinchona-based squaramide polymers.

**Keywords:** ADMET; cinchona alkaloid; squaramide; polymeric organocatalyst; Michael addition; pseudoenantiomer

## 1. Introduction

Polymeric catalysts have been widely used in organic syntheses. Their easy recoverability, applicability to continuous flow systems, and simple modification and control of their microenvironment have attracted significant attention [1,2]. Chiral catalysts, for asymmetric syntheses, require the precise control of the reaction microenvironment to optimize the catalyst performance. Cinchona alkaloid and its derivatives have demonstrated their splendid catalytic activity in many kinds of enantioselective reactions. The polymeric version of the cinchona alkaloid compounds, as catalysts, has been highly desired. We prepared various chiral polymeric catalysts, possessing cinchona alkaloid moieties in their main chains, by various kinds of polymerization techniques, such as etherification [3], ion-exchange [4,5], and neutralization [6,7]. These optically active polymeric catalysts have been employed in enantioselective reactions, including C-C bond forming reactions. The utilization of the chiral main-chain polymeric catalysts confirmed their splendid catalytic activity in enantioselective reactions. In several cases, superior ability in stereoselections was achieved with the optically active main-chain polymeric catalysts. From these results, the catalytic moiety should have reasonable conformation in the optically active polymer main-chain. These results also facilitated the development of novel optically active polymeric catalyst. We recently initiated the application of Mizoroki-Heck (MH) coupling reaction to polymer synthesis of cinchona alkaloid derivatives [8–10]. The preparation of optically active polymeric catalysts requires the chiral functionalities to act as a catalytic active site, which must be maintained during and after the polymer synthesis. A chiral monomer requires extra functionalities for a polymerization that is not associated with catalytically active functionalities.

The polymerization reaction conditions must be tolerant to these active functional groups. Moreover, the MH reaction fulfills these requirements. The copolymerization of the dimers [11] of cinchona alkaloid derivatives and aromatic diiodide in the presence of a Pd catalyst produced chiral polymers in good yield. This polymerization effectively utilized the C3-vinyl group of the cinchona alkaloid compounds.

The acyclic diene metathesis (ADMET) polymerization is another possible polymerization that utilizes the C3-vinyl group of cinchona alkaloid. Dimers of cinchona squaramide derivatives [8,10] possess vinyl groups in both cinchona moieties and they are considered to be optically active diene. ADMET polymerization does not require other monomers, such as 1,4-diiodobenzene, which are required in MH polymerization. Since the dimers of cinchona alkaloid always contain two vinyl groups, they can be polymerized directly under the condition of ADMET reaction. The concept of ADMET has been discussed in scientific literature since the 1970s [12–14]. The first successful ADMET polymerization was reported by Wagner's group in 1987. ADMET polymerization is highly tolerant to various functionalities and it proceeds under mild polymerization conditions [3]. In 1991, Wagner et al. reported the reaction mechanism of the ADMET polymerization [15]. This polymerization method can be used to give a different kinds of polymers and polymer architectures that cannot be accomplished with other polymerization methods. Different kinds of polymers, such as unsaturated poly[carbo(dimethyl)silanes] [16], unsaturated polyethers [17–19], hydrocarbons [20], unsaturated polycarbonates [21], unsaturated polyamines [22], unsaturated polyacetals [23], organoboronates [24], carbosilane-/carbosiloxane-based homopolymers/copolymers [25], and unsaturated polyesters [26] were prepared by the Wagener group. Most of the polymers, which were synthesized using ADMET polymerization, were optically inactive polymers. One exception is the chiral polymers synthesized from  $\alpha$ -amino acid derivatives [27]. The ADMET polymerization technique has not been adopted in the synthesis of optically active polymers derived from cinchona alkaloid until our recent publication of preliminary results of the polymerization [28]. Cinchona alkaloids and their derivatives are widely employed for the preparation of different types of catalysts, and their most important application is as chiral organocatalysts in asymmetric reactions [29–33]. Since cinchona alkaloids exhibit various functionalities, such as a quinuclidine tertiary  $N_2$ , secondary alcohol, a quinoline ring, and a vinylic unit, it was feasible to modify their functionalities for the design of novel polymeric catalysts [34–36]. Rawal et al. successfully introduced cinchona squaramide derivatives as important organocatalysts by their pioneering work [37], and exhibited outstanding catalytic performance for enantioselective C-C bond forming reaction, such as the Michael-type reactions [38,39]. The cinchona-based squaramides contain an acidic NH that can be a hydrogen bond donor, and the quinuclidine tertiary nitrogen could also be a hydrogen bond acceptor and a base in enantioselective Michael reactions. A number of modifications of the catalyst have been reported after Rawal's group initiated the excellent work on cinchona alkaloid squaramide organocatalysts. Various catalysts containing cinchona alkaloid squaramide have been developed and used for different types of asymmetric reactions [40–48].

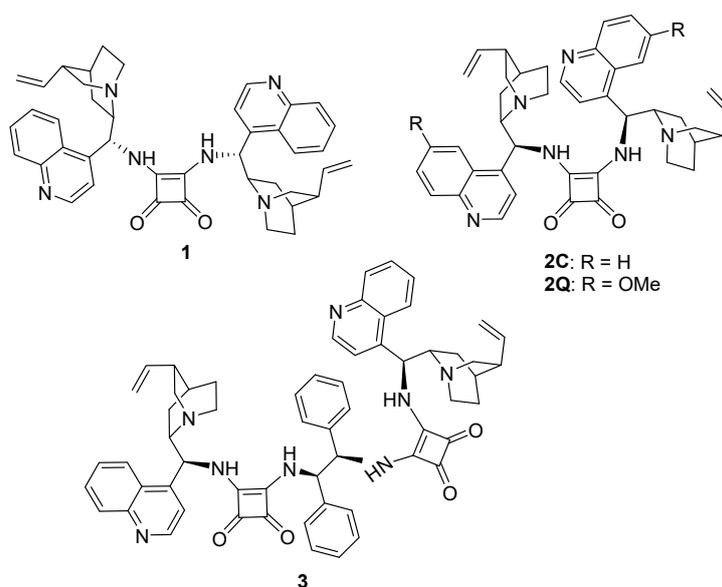
In this paper, we describe the ADMET polymerization of cinchona squaramide dimers using the Hoveyda–Grubbs second-generation catalysts to prepare novel optically active polymeric catalysts. We applied these optically active polymeric catalysts for the enantioselective Michael type reactions to examine the catalytic performance and stereoselectivity. The enantioselective Michael reaction is one of the most important C-C bond forming reactions for the construction of chiral building blocks. Because the resulting ADMET polymeric organocatalysts were insoluble in some generally utilized organic solvents, we also examined their recyclability.

## 2. Results and Discussion

### *Synthesis of Dimeric Cinchona Squaramides and Their Corresponding Polymers by ADMET Polymerization*

Cinchona-based squaramide dimers (1–3) (Figure 1) were prepared from dimethylsquarate and the C9-amino substituted cinchona alkaloids according to the literature procedures [8]. The C9-amino derivatives were synthesized by the Mitsunobu-type azide formation, followed by the Staudinger

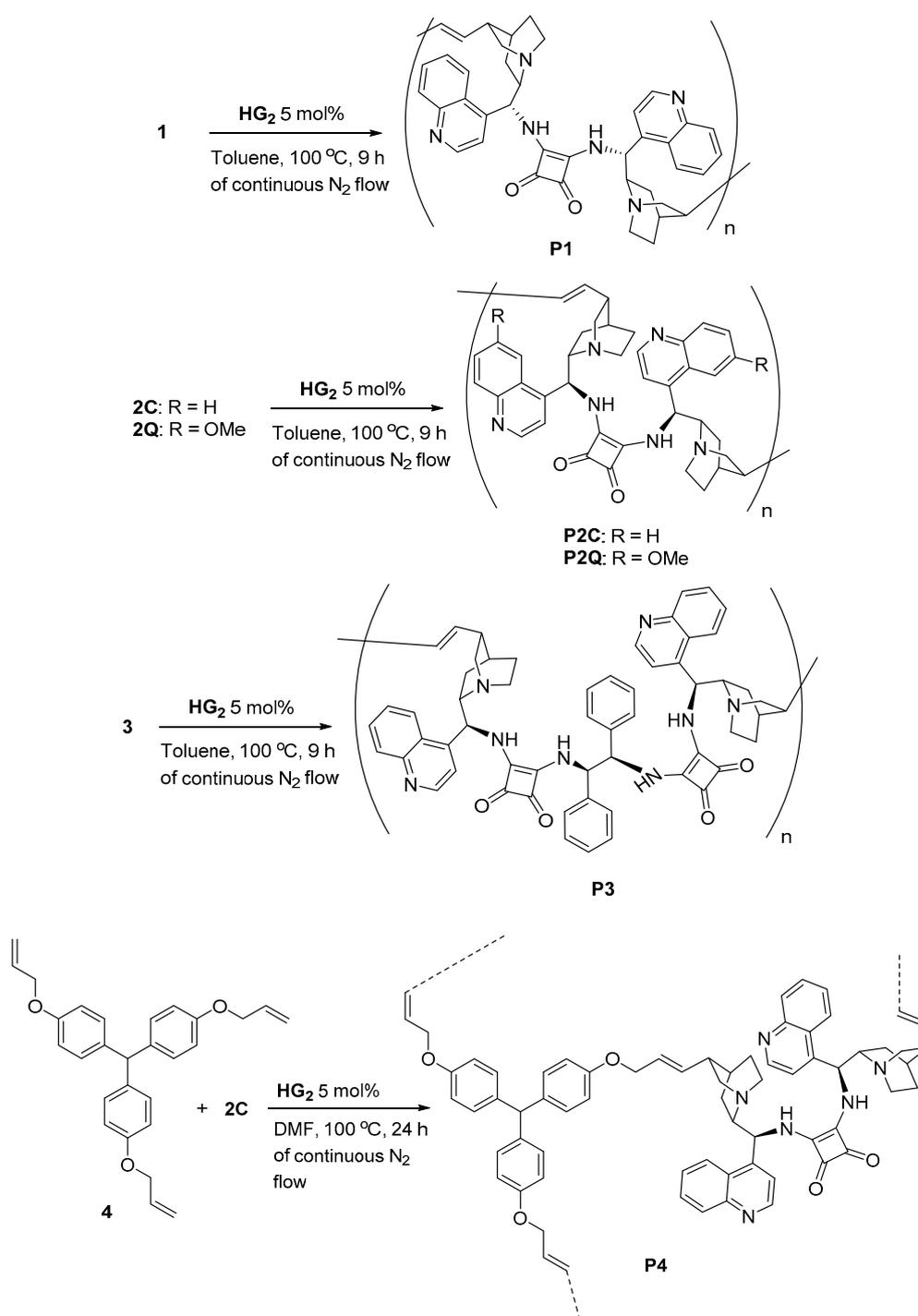
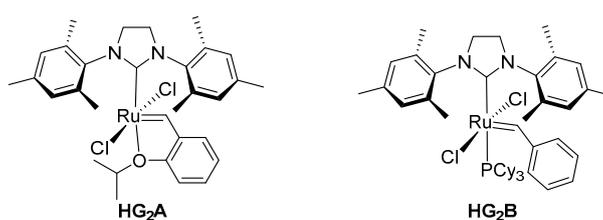
reaction according to the previously reported procedure [37,45]. Dimers **1** (a cinchonine-derived catalyst), **2C** (a cinchonidine-derived catalyst), and **2Q** (a quinine-derived catalyst) were successfully prepared. Another dimeric cinchona squaramide (**3**), which contained a chiral diamine moiety between two squaramides, was also synthesized [10]. The treatment of the two equivalents of dimethylsquarate with (1*R*,2*R*)-1,2-diamino-1,2-diphenylethane afforded the bisquaramide. Subsequently, the C9-aminated quinine could react with the chiral bisquaramide to afford **3** in good yield.



**Figure 1.** Dimeric cinchona squaramides 1–3.

The dimeric cinchona squaramides that are shown in Figure 1 possess two olefinic double bonds in their structures. These squaramides are chiral dienes and they are amenable to ADMET polymerization. A variety of diene compounds has been polymerized under the ADMET reaction condition to afford the polymers [15–22]. We synthesized the chiral polymers by repetitive ADMET reactions of 1–3. The ADMET polymerization of 1–3 with catalyst **HG<sub>2</sub>A** readily proceeded in dry DMF, affording chiral polymers **P1–3**, respectively, which contained cinchona squaramides in repeated units, in their main chains (Scheme 1). Further, the copolymerization of **2C** and achiral triallyl ether (**4**) was also performed to prepare a hyperbranched polymer (**P4**). After the copolymerization, the reaction mixture was poured into ether to precipitate the product polymer. **P1–3** were soluble in dichloromethane (DCM), methanol (MeOH), CDCl<sub>3</sub>, as well as in highly polar solvents, such as DMF and DMSO. **P4** was slightly soluble in these solvents. All of the polymers were insoluble in generally employed organic solvents, including ether, tetrahydrofuran (THF), hexane, toluene, acetonitrile, and EtOAc.

Table 1 summarizes the results of the ADMET polymerizations of different cinchona squaramides with **HG<sub>2</sub>**. First, we examined the condition for the polymerization of the dimeric cinchona squaramides. Different reaction conditions were examined while using **2Q**, as shown in Table 1. In DMF, **2Q** was polymerized using catalyst **HG<sub>2</sub>A** (5 mol%) to give the quinine-derived polymer (**P2Q**) with 81% yield (entry 1). It was also observed that a low concentration of **2Q** afforded a low yield of **P2Q** (entry 2). Moreover, **HG<sub>2</sub>A** achieved better results than **HG<sub>2</sub>B** (Figure 2). We observed that the ADMET polymerization of **2Q** proceeded readily in toluene at 100 °C. After 9 h stirring at the same temperature, **P2Q** was generated with a 92% isolated yield (entry 6). Polymerization at 85 °C caused a lowering of the yield in prolonged reaction time (entry 7). Other dimeric cinchona squaramides were also polymerized to afford their corresponding chiral ADMET polymers under the optimized condition for the polymerization of **2Q** (entries 8–11). All of the polymers obtained by ADMET polymerization possessed  $M_n > 40,000$ , except for **P3**.

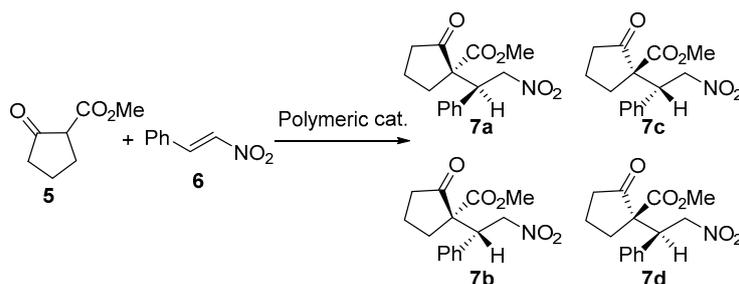
Scheme 1. Synthesis of P1–P4 from 1–4, using HG<sub>2</sub>.Figure 2. Hoveyda-Grubbs 2nd generation catalysts (HG<sub>2</sub>).

**Table 1.** Synthesis of **P1–P4** by acyclic diene metathesis (ADMET) polymerization <sup>a</sup>.

Entry	Polymer	Diene	Solvent	Time (h)	Yield (%)	$M_n^b$	$M_w^b$	$M_w/M_n^b$
1 <sup>d</sup>	<b>P2Q</b>	<b>2Q</b>	DMF	24	81	49,000	58,000	1.18
2 <sup>c,d</sup>	<b>P2Q</b>	<b>2Q</b>	DMF	24	70	44,000	52,000	1.18
3 <sup>c,d,e</sup>	<b>P2Q</b>	<b>2Q</b>	DMF	24	58	46,000	53,000	1.15
4 <sup>d,f</sup>	<b>P2Q</b>	<b>2Q</b>	DMF	24	74	41,000	47,000	1.14
5	<b>P2Q</b>	<b>2Q</b>	<i>o</i> -Dichloro benzene	24	77	56,000	74,000	1.32
6	<b>P2Q</b>	<b>2Q</b>	Toluene	9	92	42,000	46,000	1.10
7 <sup>g</sup>	<b>P2Q</b>	<b>2Q</b>	Toluene	25	52	49,000	56,000	1.14
8	<b>P1</b>	<b>1</b>	Toluene	9	77	47,000	49,000	1.04
9	<b>P2C</b>	<b>2C</b>	Toluene	9	93	54,000	55,000	1.02
10	<b>P3</b>	<b>3</b>	Toluene	9	86	74,000	75,000	1.01
11	<b>P4</b>	<b>2C + 4</b>	DMF	24	70	9000	19,000	2.19

<sup>a</sup> Polymerization was performed in 0.5 mL of solvent at 100 °C using 0.2 mmol of **1–3** in the presence of **HG<sub>2</sub>A** (5 mol%). <sup>b</sup> Determined by SEC, using DMF (0.5 wt%, LiCl) as an eluent at a flow rate of 1.0 mL/min at 40 °C (the calibration curve was made the use of polystyrene standards). <sup>c</sup> 1.0 mL of DMF was utilized. <sup>d</sup> See ref. [21]. <sup>e</sup> 2.5 mol% catalyst was employed. <sup>f</sup> **HG<sub>2</sub>B** was employed as a catalyst. <sup>g</sup> Polymerization was performed at 85 °C.

The enantioselective Michael addition reactions between **5** and **6** (Scheme 2) were investigated to evaluate the catalytic activity of the resulting cinchona squaramide polymers. Table 2 illustrates the results of the enantioselective reaction. The reaction between **5** and **6** smoothly occurred with the low-molecular-weight catalyst (**1**) in MeOH to afford the product (**7**) with 91% yield and 93% enantiomeric excess (*ee*) of the major diastereomers (**7a** and **c**) (Table 2, entry 1). The corresponding **P1** successfully catalyzed the reaction in the same solvent to yield **6** in good yield and high stereoselectivities (entry 2). The solvent effect on the catalytic performance of **P1** was also investigated. MeOH, acetonitrile, THF, EtOAc, hexane, dichloromethane, ether, hexane, and toluene were employed, because they are generally used organic solvents. Among these solvents, **P1** was partially soluble in MeOH, DCM, and CDCl<sub>3</sub>. **P1** was insoluble in the other solvents utilized and the reaction proceeded in heterogeneous condition. However, **P1** was swollen well in these solvents. Highly catalytic activity was obtained, even in heterogeneous condition. In DCM, its diastereoselectivity improved and higher enantioselectivity (97% *ee*) for the major diastereomer was achieved using (entry 3). Under a heterogeneous condition, in THF, the asymmetric reaction readily proceeded to afford the chiral product with high enantioselectivity (entry 4). Relatively prolonged reaction times were required for the reaction in EtOAc, ether, toluene, and hexane. However, high *ees* were obtained in all cases (entries 5–8). Toluene afforded poor isolated yield and decreased in diastereoselectivity with **P1** (entry 7). When CH<sub>3</sub>CN was used as a solvent for the enantioselective reaction, the reaction was completed in 9 h at room temperature (entry 9). Very high diastereoselectivity (1:>100) was achieved with **P1** in acetonitrile. In this case, the *ee* of the major diastereomers was 95%. The temperature effect on the catalyst performance in acetonitrile was also investigated. The reaction was performed in the range of –10 to 80 °C (entries 9–12) to see the temperature effect on the stereoselectivity. The diastereoselectivity decreased with increasing temperature. Interestingly, the high *ee* of 95% was still achieved at 80 °C.

**Scheme 2.** Asymmetric Michael addition of **5** and **6** to yield **7a–d**.

**Table 2.** Asymmetric Michael addition of **5** and **6** using the ADMET polymeric catalyst <sup>a</sup>.

Entry	Catalyst	Solvent	Temp (°C)	Reaction Time (h)	Yield (%) <sup>b</sup>	<i>dr</i> <sup>c</sup>	% <i>ee</i> <sup>c</sup>
1	<b>1</b>	MeOH	25	6	91	1:14	93
2	<b>P1</b>	MeOH	25	6	77	1:12	87
3	<b>P1</b>	DCM	25	30	52	1:81	97
4	<b>P1</b>	THF	25	7	89	1:80	99
5	<b>P1</b>	EtOAc	25	27	34	1:62	92
6	<b>P1</b>	ether	25	20	87	1:45	97
7	<b>P1</b>	Toluene	25	24	29	1:3	90
8	<b>P1</b>	Hexane	25	24	84	1:38	96
9	<b>P1</b>	Acetonitrile	25	9	97	1:>100	95
10	<b>P1</b>	Acetonitrile	0	24	92	1:>100	96
11	<b>P1</b>	Acetonitrile	−10	24	99	1:89	99
12	<b>P1</b>	Acetonitrile	80	6	78	1:16	95
13 <sup>e</sup>	<b>2C</b>	DCM	25	4	95	>100:1	98
14	<b>P2C</b>	Acetonitrile	25	9	75	68:1	91
15 <sup>d</sup>	<b>2Q</b>	DCM	25	2	95	79:1	91
16 <sup>d</sup>	<b>P2Q</b>	DCM	25	48	45	59:1	96
17	<b>P3</b>	acetonitrile	25	9	67	95:1	97
18	<b>P4</b>	acetonitrile	25	20	85	24:1	99

<sup>a</sup> Reactions were performed with **5** (0.50 mmol), **6** (0.55 mmol), and a polymeric catalyst (5 mol%) in solvent (2.5 mL).

<sup>b</sup> Isolated yield of the product after purification by column chromatography. <sup>c</sup> The diastereomeric ratio (*dr*) and *ee* were determined by chiral HPLC (Chiralcel OD-H, Supplementary Materials). <sup>d</sup> See ref. [21]. <sup>e</sup> See ref. [48].

Cinchonine and cinchonidine are pseudoenantiomers. When **2C** was employed, the major products of the asymmetric Michael addition were **7b** and **7d** (entry 13). The corresponding polymeric catalyst **P2C** also afforded the same isomers (entry 14). Quinine possesses the same configuration as cinchonidine. **2Q** and its corresponding polymeric catalyst (**P2Q**) catalyzed the reaction in the same direction of stereo selection (entries 15 and 16). We introduced a chiral diamine moiety (C9-aminated quinine) between cinchonidine squaramide (chiral bisquaramide) to afford **3**, which was thereafter polymerized under an ADMET condition to produce **P3**. The same asymmetric reaction was observed with **P3** as a catalyst. When compared to **P2C**, somewhat higher diastereoselectivity was achieved with **P3** (entry 17). Another chiral polymer (**P4**) was prepared by the copolymerization of **3** and **4**. Although the diastereoselectivity decreased, an excellent *ee* was achieved with **P4** (entry 18).

The asymmetric reactions proceeded in a heterogeneous system since the chiral ADMET polymers were insoluble in most of the generally utilized organic solvents. The utilization of **P1** facilitated the easy separation of the catalyst from the reaction mixture by filtration. The recyclability test was, therefore, performed with **P1** in acetonitrile at room temperature. At the end of the reaction, the polymer was readily separated from the reaction mixture and washed with ether three times. The recovered polymer was employed in subsequent reactions. Although the third and fourth reuse cycles exhibited lower *ee* (Table 3, entries 3 and 4) than the first and second, the catalytic performance of **P1** was maintained for several cycles.

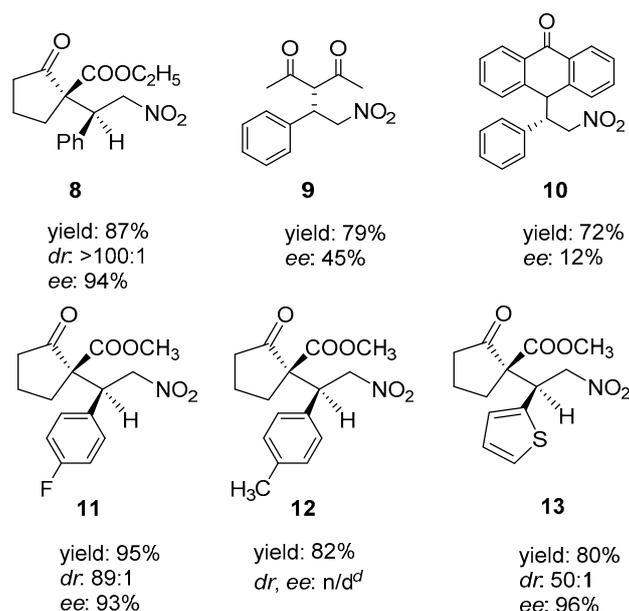
**Table 3.** Recycling of **P1** <sup>a</sup>.

Cycle	Yield (%) <sup>b</sup>	<i>dr</i> <sup>c</sup>	% <i>ee</i> <sup>c</sup>
original	97	1:>100	95
1	73	1:54	97
2	93	1:59	97
3	90	1:39	94
4	82	1:46	93
5	72	1:51	95

<sup>a</sup> Reactions were performed with **5** (0.50 mmol), **6** (0.55 mmol), and **P1** (5 mol%) in CH<sub>3</sub>CN (2.5 mL) at 25 °C.

<sup>b</sup> Isolated yield of the product **7** after purification by column chromatography. <sup>c</sup> *dr* and *ee* were determined by chiral HPLC (Chiralcel OD-H).

Finally, we applied **P1** as a polymeric organocatalyst in the asymmetric Michael addition of various kinds of substrates. The reaction between ethyl 2-oxocyclopentanecarboxylate and **6** proceeded readily in acetonitrile to afford the corresponding asymmetric product **8** in good yield and excellent diastereoselectivity of >100:1, *dr*, and high *ee* (Scheme 3). Further, **6** was allowed to react with two other Michael donors, including pentane-2,4-dione and anthrone. In the case of anthrone, product **10** was obtained with low enantiopurity. The Michael donor (**5**) readily reacted with 4-fluoro-*trans*- $\beta$ -nitrostyrene, 4-methyl-*trans*- $\beta$ -nitrostyrene, and (2-nitrovinyl)thiophene in the presence of **P1** to afford the Michael adducts (**11**, **12**, and **13**) with good yields and high *ees*. The stereoselectivity of the chiral product that was obtained from methyl-*trans*- $\beta$ -nitrostyrene was not determined due to the incomplete separation of the products by chiral HPLC analysis.



**Scheme 3.** Asymmetric Michael addition reaction involving different combinations of the Michael donors and acceptors, using **P1**. Reactions were conducted with the Michael donor (0.50 mmol), Michael acceptor (0.55 mmol), and **P1** (5 mol%) in acetonitrile (2.5 mL) at 25 °C. Isolated yield of the product after purification by column chromatography. *dr* and *ee* were determined by chiral HPLC (Chiralcel OD-H) for compounds **8**, **11**–**13**; Chiralcel AD-H for compound **9** and Chiralcel AS-H for compound **10**. <sup>d</sup> *dr* and *ee* were not determined due to the incomplete separation of the products by chiral HPLC.

### 3. Materials and Methods

#### 3.1. Materials and General Considerations

All of the solvents and reagents were purchased from Sigma Aldrich (St. Luis, MO, USA), Wako Pure Chemical Industries, Ltd. (Tokyo, Japan), or Tokyo Chemical Industry (TCI) Co., Ltd. (Tokyo, Japan). in the highest available purity and they were utilized as received. The reactions were monitored by thin-layer chromatography (TLC) using precoated silica gel plates (Merck 5554, 60F254). Column chromatography was performed using a silica gel column (Wakogel C-200, 100–200 mesh). The NMR spectra were recorded on JEOL JNM-ECS400 spectrometers in deuterated chloroform (CDCl<sub>3</sub>) or deuterated dimethyl sulfoxide (DMSO-*d*<sub>6</sub>) solvent at room temperature operating at 400 (<sup>1</sup>H) and 100 MHz (<sup>13</sup>C{<sup>1</sup>H}). Tetramethylsilane (TMS) and CDCl<sub>3</sub> were used as the internal standards for <sup>1</sup>H and <sup>13</sup>C NMR, respectively. The chemical shifts are reported in parts per million (ppm) while using TMS as a reference, and the *J* values are reported in hertz (Hz). The infrared (IR) spectra were recorded on a JEOL JIR-7000 Fourier-transform (FT)–IR (FT–IR) spectrometer and they were reported in reciprocal centimeters (cm<sup>−1</sup>). High-performance liquid chromatography (HPLC) was

performed on a Jasco HPLC system consisting of a DG-980-50 three-line degasser, PU-980 HPLC pump, and CO-965 column oven and equipped with a chiral column (Chiralpak OD-H, AD-H Daicel), using hexane/2-propanol as the eluent. A Jasco UV-975 UV detector was employed for peak detection. Size-exclusion chromatography (SEC) was performed using a Tosoh HLC 8020 instrument with UV (254 nm) for refractive index detection. Dimethylformamide (DMF) with 0.5 wt% LiCl/LiBr was used as the carrier solvent at a flow rate of 1.0 mL min<sup>-1</sup> at 40 °C. Two polystyrene gel columns with 10 µm beads were utilized. A calibration curve was generated for determining the number average molecular weight ( $M_n$ ) and molecular weight distribution ( $M_w/M_n$ ), using polystyrene standards. The optical rotation was recorded on a JASCO DIP-149 digital polarimeter using a 10 cm thermostated microcell.

### 3.2. Synthesis of Cinchona-Based Squaramide Containing the Chiral ADMET Polymer

#### 3.2.1. Polymer P1

Squaramide **1** (133.0 mg, 0.200 mmol), **HG<sub>2</sub>A** (6.26 mg, 0.010 mmol), and toluene (0.5 mL) were collected in a dried Schlenk tube, after which they were set in an oil bath with a condenser. The Schlenk tube was connected to continuous N<sub>2</sub> gas flow. The reaction mixture was stirred for 9 h after setting the desired reaction temperature (100 °C). Thereafter, the reaction mixture was cooled to room temperature and then poured into diethyl ether (50 mL). Next, the solid polymer product was purified by reprecipitation in diethyl ether (70–80 mL) three times. The precipitate was filtered out and vacuum-dried at 40 °C for 3 h to afford the desired polymer (**P1** with 77% yield as a brownish solid), which is an ADMET polymeric organocatalyst.  $[\alpha]_D^{25} = +90.99$  (*c* 0.175 g/dL in DMF at 26.0 °C). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 25 °C); δ 8.37, 8.43, 8.84, 8.98 (1H), 7.48–8.26 (aromatic H), 5.71–6.08 (vinylic H), 5.43 (2H), 5.02–5.15 (m, 2H), 3.05, 2.89, 2.72, 2.67, 2.34, 2.10, 1.55, 1.45, 1.26, 1.09, 0.93, 0.76, and 0.65 (quinuclidine H) ppm. IR (KBr): ν = 3380, 3208, 2936, 2863, 1793, 1672, 1360, 1258, 1239, 1085, 1030, 975, 848, 692, and 624 cm<sup>-1</sup>.  $M_n$  (SEC) =  $4.7 \times 10^4$ ,  $M_w/M_n = 1.04$ .

Other optically active polymers were prepared from different cinchona-based squaramides (**1–3**) with **HG<sub>2</sub>A** while using the same process. Table 1 summarizes the relevant results.

#### 3.2.2. Representative Procedure for the Asymmetric Michael Reaction between β-Ketoesters and Trans-β-Nitrostyrene to Yield Nitroolefins Using P1

Methyl 2-oxocyclopentanecarboxylate (**5**) (63 µL, 0.50 mmol) and *trans*-β-nitrostyrene (**6**) (82.05 mg, 0.55 mmol) were placed in a vessel with 2.5 mL of a solvent. Subsequently, **P1** (5 mol%) was added to the mixture. The reaction mixture was then stirred at 25 °C for a specified time. The solvent was evaporated with a rotary evaporator after the complete consumption of **5**, which was monitored by TLC. The residue was washed with ether, which was subsequently separated by decantation. Unused **P1** was recovered for reuse. The collected ether solution was concentrated in vacuo, and the crude product was purified by silica gel column chromatography (100–200 mesh) with hexane/ethyl acetate (EtOAc), 6.0/1.0, as the eluent to afford **7** as a colorless oil. <sup>1</sup>H NMR (400 MHz, 25 °C, CDCl<sub>3</sub>); δ = 7.29–7.23 (m, 5H), 5.14 (dd, *J* = 13.8 Hz, 3.8 Hz, 1H), 5.00 (dd, *J* = 13.8 Hz, 10.7 Hz, 1H), 4.08 (dd, *J* = 10.8 Hz, 3.8 Hz, 1H), 3.74 (s, 3H), 2.38–2.33 (m, 2H), and 2.04–1.84.

Additional asymmetric Michael additions were similarly performed and the results are summarized in Tables 2 and 3, as well as in Scheme 3.

## 4. Conclusions

In summary, we successfully synthesized chiral cinchona squaramide polymers **P1–P3** by ADMET polymerization. The vinyl group in cinchona alkaloid exhibited good reactivity in ADMET polymerization when **HG<sub>2</sub>** was employed to afford the optically active polymers in high yields. The copolymerization with triallyl ether also readily proceeded to afford **P4**. Asymmetric Michael reaction of **5** with **6** was efficiently catalyzed by the cinchona squaramide polymers to afford the Michael adducts with high stereoselectivity and isolated yields. **P1a** afforded **7a** and **c** as major

diastereomers, while **P2C**, **P2Q**, **P3**, and **P4** afforded **7b** and **d**. Both pseudoenantiomeric polymeric catalysts exhibited excellent performance in the same asymmetric reaction with high stereoselectivity. Different stereoisomers can be obtained by the proper selection of the catalytic structure of the cinchonidine and cinchonine derivatives. The recovery of the catalysts from the reaction mixture was dramatically improved by using the insoluble polymeric organocatalysts. These catalysts can be reused several times in the same asymmetric reaction without any significant loss in their catalytic activity.

**Supplementary Materials:** The following are available online at <http://www.mdpi.com/2073-4344/10/5/591/s1>, details and data supplemental to the main text is shown here.

**Author Contributions:** Conceptualization, methodology, S.I.; supervision, S.I., formal analysis and data curation, M.S.U.; S.A.C. writing—original draft preparation, M.S.U.; writing—review and editing, S.I. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Acknowledgments:** The authors would like to thank Naoki Haraguchi of the Toyohashi University of Technology, for useful discussions.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Itsuno, S.; Haraguchi, N. *Catalyst Immobilization, Methods and Applications, Chapter 2*; Benaglia, M., Puglisi, A., Eds.; Wiley: Hoboken, NJ, USA, 2020; pp. 23–75.
2. Itsuno, S.; Ullah, M.S. *Flow Chemistry in Organic Synthesis, Science of Synthesis*; Jamison, T.F., Koch, G., Eds.; Thieme: New York, NY, USA, 2018; pp. 347–380.
3. Itsuno, S.; Paul, D.K.; Ishimoto, M.; Haraguchi, N. Designing Chiral Quaternary Ammonium Polymers: Novel Type of Polymeric Catalyst for Asymmetric Alkylation Reaction. *Chem. Lett.* **2010**, *39*, 86–87. [[CrossRef](#)]
4. Itsuno, S.; Paul, D.K.; Salam, M.A.; Haraguchi, N. Main-Chain Ionic Chiral Polymers: Synthesis of Optically Active Quaternary Ammonium Sulfonate Polymers and Their Application in Asymmetric Catalysis. *J. Am. Chem. Soc.* **2010**, *132*, 2864–2865. [[CrossRef](#)]
5. Parvez, M.M.; Haraguchi, N.; Itsuno, S. Molecular design of chiral quaternary ammonium polymers for asymmetric catalysis applications. *Org. Biomol. Chem.* **2012**, *10*, 2870–2877. [[CrossRef](#)] [[PubMed](#)]
6. Haraguchi, N.; Kiyono, H.; Takemura, Y.; Itsuno, S. Design of main-chain polymers of chiral imidazolidinone for asymmetric organocatalysis application. *Chem. Commun.* **2012**, *48*, 4011–4013. [[CrossRef](#)] [[PubMed](#)]
7. Haraguchi, N.; Takenaka, N.; Najwa, A.; Takahara, Y.; Mun, M.K.; Itsuno, S. Synthesis of Main-Chain Ionic Polymers of Chiral Imidazolidinone Organocatalysts and Their Application to Asymmetric Diels–Alder Reactions. *Adv. Synth. Catal.* **2018**, *360*, 112–123. [[CrossRef](#)]
8. Ullah, M.S.; Itsuno, S. Synthesis of cinchona alkaloid squaramide polymers as bifunctional chiral organocatalysts for the enantioselective Michael addition of  $\beta$ -ketoesters to nitroolefins. *Mol. Catal.* **2017**, *438*, 239–244. [[CrossRef](#)]
9. Parvez, M.M.; Haraguchi, N.; Itsuno, S. Synthesis of Cinchona Alkaloid-Derived Chiral Polymers by Mizoroki–Heck Polymerization and Their Application to Asymmetric Catalysis. *Macromolecules* **2014**, *47*, 1922–1928. [[CrossRef](#)]
10. Ullah, M.S.; Itsuno, S. Cinchona Squaramide-Based Chiral Polymers as Highly Efficient Catalysts in Asymmetric Michael Addition Reaction. *ACS Omega* **2018**, 4573–4582. [[CrossRef](#)]
11. Boratynski, P.J. Dimeric Cinchona alkaloids. *Mol. Divers.* **2015**, *19*, 385–422. [[CrossRef](#)]
12. Lindmarkhamberg, M.; Wagener, K.B. Acyclic metathesis polymerization: The olefin metathesis reaction of 1,5-hexadiene and 1,9-decadiene. *Macromolecules* **1987**, *20*, 2949–2951. [[CrossRef](#)]
13. Wagener, K.B.; Boncella, J.M.; Nel, J.G.; Duttweiler, R.P.; Hillmyer, M.A. The key to successful acyclic diene metathesis polymerization chemistry. *Macromol. Chem.* **1990**, *191*, 365–374. [[CrossRef](#)]
14. Wagener, K.B.; Nel, J.G.; Konzelman, J.; Boncella, J.M. Acyclic diene metathesis copolymerization of 1,5-hexadiene and 1,9-decadiene. *Macromolecules* **1990**, *23*, 5155–5157. [[CrossRef](#)]
15. Wagener, K.B.; Boncella, J.M.; Nel, J.G. Acyclic diene metathesis copolymerization of 1,5-hexadiene and 1,9-decadiene. *Macromolecules* **1991**, *24*, 2649–2657. [[CrossRef](#)]
16. Wagener, K.B.; Smith, D.W. Acyclic diene metathesis polymerization: Synthesis and characterization of unsaturated poly[carbo(dimethyl)silanes]. *Macromolecules* **1991**, *24*, 6073–6078. [[CrossRef](#)]

17. Wagener, K.B.; Brzezinska, K. Acyclic diene metathesis (ADMET) polymerization: Synthesis of unsaturated polyethers. *Macromolecules* **1991**, *24*, 5273–5277. [[CrossRef](#)]
18. Wagener, K.B.; Patton, J.T. Acyclic diene metathesis (ADMET) polymerization. Synthesis of unsaturated polycarbonates. *Macromolecules* **1993**, *26*, 249–253. [[CrossRef](#)]
19. Portmess, J.D.; Wagener, K.B. Acyclic diene metathesis (ADMET) polymerization: The synthesis of unsaturated polyamines. *J. Polym. Sci. Pol. Chem.* **1996**, *34*, 1353–1357. [[CrossRef](#)]
20. Wolfe, P.S.; Wagener, K.B. An ADMET route to unsaturated polyacetals. *Macromol. Rapid Commun.* **1998**, *19*, 305–308. [[CrossRef](#)]
21. Wolfe, P.S.; Wagener, K.B. Investigation of Organoboronates in Metathesis Polymerization. *Macromolecules* **1999**, *32*, 7961–7967. [[CrossRef](#)]
22. Brzezinska, K.R.; Schitter, R.; Wagener, K.B. Carbosilane/carbosiloxane-based ADMET homopolymers and copolymers possessing latent reactivity. *J. Polym. Sci. Pol. Chem.* **2000**, *38*, 1544–1550. [[CrossRef](#)]
23. Cummings, S.K.; Smith, D.W.; Wagener, K.B. Environmental degradation of biodegradable polyesters 1. Poly( $\epsilon$ -caprolactone), poly[(R)-3-hydroxybutyrate], and poly(L-lactide) films in controlled static seawater. *Macromol. Rapid Commun.* **1995**, *16*, 347–355. [[CrossRef](#)]
24. Patton, J.T.; Boncella, J.M.; Wagener, K.B. Acyclic diene metathesis (ADMET) polymerization: The synthesis of unsaturated polyesters. *Macromolecules* **1992**, *25*, 3862–3867. [[CrossRef](#)]
25. Hopkins, T.E.; Pawlow, J.H.; Koren, D.L.; Deters, K.S.; Solivan, S.M.; Davis, J.A.; Gomez, F.J.; Wagener, K.B. Chiral Polyolefins Bearing Amino Acids. *Macromology* **2001**, *34*, 7920–7922. [[CrossRef](#)]
26. Ullah, M.S.; Itsuno, S. Synthesis of Cinchona Alkaloid Derived Chiral Squaramide Polymers by ADMET Polymerization and Their Application to Asymmetric Catalysis. *Chem. Lett.* **2018**, *47*, 1220–1223. [[CrossRef](#)]
27. Song, C.E. *Cinchona Alkaloids in Synthesis and Catalysis*; Wiley: Weinheim, Germany, 2009.
28. Jianga, L.; Chen, Y.C. Recent advances in asymmetric catalysis with cinchona alkaloid-based primary amines. *Catal. Sci. Technol.* **2011**, *1*, 354–365. [[CrossRef](#)]
29. Yeboah, E.M.O.; Yeboah, S.O.; Singh, G.S. Recent applications of Cinchona alkaloids and their derivatives as catalysts in metal-free asymmetric synthesis. *Tetrahedron* **2011**, *67*, 1725–1762. [[CrossRef](#)]
30. Marcelli, T. Organocatalysis: Cinchona catalysts. *WIREs Comput. Mol. Sci.* **2011**, *1*, 142–152. [[CrossRef](#)]
31. Ingemann, S.; Hiemstra, H. *Comprehensive Enantioselective Organocatalysis*; Dalko, P.I., Ed.; Wiley: Weinheim, Germany, 2013; pp. 119–160.
32. Itsuno, S.; Parvez, M.M.; Haraguchi, N. Polymeric chiral organocatalysts. *Polym. Chem.* **2011**, *2*, 1942–1949. [[CrossRef](#)]
33. Itsuno, S.; Hassan, M.M. Polymer-immobilized chiral catalysts. *RSC Adv.* **2014**, *4*, 52023–52043. [[CrossRef](#)]
34. Haraguchi, N.; Itsuno, S. *Polymeric Chiral Catalyst Design and Chiral Polymer Synthesis*; Itsuno, S., Ed.; Wiley: Hoboken, NJ, USA, 2011; Volume 2, pp. 17–61.
35. Malerich, J.P.; Hagihara, K.; Rawal, V.H. Chiral Squaramide Derivatives are Excellent Hydrogen Bond Donor Catalysts. *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417. [[CrossRef](#)]
36. Tsakos, M.; Kokotos, C.G. Primary and secondary amine-(thio)ureas and squaramides and their applications in asymmetric organocatalysis. *Tetrahedron* **2013**, *69*, 10199–10222. [[CrossRef](#)]
37. Zhao, B.L.; Du, D.M. Chiral Squaramide-Catalyzed Michael/Alkylation Cascade Reaction for the Asymmetric Synthesis of Nitro-Spirocyclopropanes. *Eur. J. Org. Chem.* **2015**, *2015*, 5350–5359. [[CrossRef](#)]
38. Lee, J.W.; Ryu, T.H.; Oh, J.S.; Bae, H.Y.; Jang, H.B.; Song, C.E. Self-association-free dimeric cinchona alkaloid organocatalysts: Unprecedented catalytic activity, enantioselectivity and catalyst recyclability in dynamic kinetic resolution of racemic azlactones. *Chem. Commun.* **2009**, *46*, 7224–7226. [[CrossRef](#)]
39. Rao, K.S.; Ramesh, P.; Chowhan, L.R.; Trivedi, R. Asymmetric Mannich reaction: Highly enantioselective synthesis of 3-amino-oxindoles via chiral squaramide based H-bond donor catalysis. *RSC Adv.* **2016**, *6*, 84242–84247. [[CrossRef](#)]
40. Yang, W.; Du, D.M. Chiral Squaramide-Catalyzed Highly Enantioselective Michael Addition of 2-Hydroxy-1,4-naphthoquinones to Nitroalkene. *Adv. Synth. Catal.* **2011**, *353*, 1241–1246. [[CrossRef](#)]
41. Konishi, H.; Lam, T.Y.; Malerich, J.P.; Rawal, V.H. Enantioselective  $\alpha$ -Amination of 1,3-Dicarbonyl Compounds Using Squaramide Derivatives as Hydrogen Bonding Catalysts. *Org. Lett.* **2012**, *12*, 2028–2031. [[CrossRef](#)]
42. Yang, W.; Jia, Y.; Du, D.M. Squaramide-catalyzed enantioselective Michael addition of malononitrile to chalcones. *Org. Biomol. Chem.* **2012**, *10*, 332–338. [[CrossRef](#)]

43. Yang, W.; Du, D.M. Highly Enantioselective Michael Addition of Nitroalkanes to Chalcones Using Chiral Squaramides as Hydrogen Bonding Organocatalysts. *Org. Lett.* **2010**, *12*, 5450–5453. [[CrossRef](#)]
44. Yang, W.; Du, D.M. Cinchona-based squaramide-catalysed cascade aza-Michael–Michael addition: Enantioselective construction of functionalized spirooxindole tetrahydroquinolines. *Chem. Commun.* **2013**, *49*, 8842–8844. [[CrossRef](#)]
45. Yang, W.; Du, D.M. Chiral squaramide-catalyzed highly diastereo- and enantioselective direct Michael addition of nitroalkanes to nitroalkenes. *Chem. Commun.* **2011**, *47*, 12706–12708. [[CrossRef](#)]
46. Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. Highly Enantioselective Conjugate Addition of Nitromethane to Chalcones Using Bifunctional Cinchona Organocatalysts. *Org. Lett.* **2005**, *7*, 1967–1969. [[CrossRef](#)]
47. Tripathi, C.B.; Kayal, S.; Mukherjee, S. Catalytic Asymmetric Synthesis of  $\alpha,\beta$ -Disubstituted  $\alpha,\gamma$ -Diaminophosphonic Acid Precursors by Michael Addition of  $\alpha$ -Substituted Nitrophosphonates to Nitroolefins. *Org. Lett.* **2012**, *14*, 3296–3299. [[CrossRef](#)]
48. Chhanda, S.A.; Itsuno, S. Design and synthesis of chiral hyperbranched polymers containing cinchona squaramide moieties and their catalytic activity in the asymmetric Michael addition reaction. *J. Catal.* **2019**, *377*, 543–549. [[CrossRef](#)]



© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).