RSC Advances

This article can be cited before page numbers have been issued, to do this please use: S. Takata, Y. Endo, M. S. Ullah and S. Itsuno, *RSC Adv.*, 2016, DOI: 10.1039/C6RA14535C.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

View Article Online
DOI: 10.1039/C6RA14535C

RSC Advances

ARTICLE

Synthesis of Cinchona Alkaloid Sulfonamide Polymers as Sustainable Catalysts for the Enantioselective Desymmetrization of Cyclic Anhydrides

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

S. Takata,[a] Y. Endo,[a] S. Ullah[a] and S. Itsuno*[a]

The Mizoroki-Heck polymerization of cinchona-based sulfonamide dimers and aromatic diiodides was investigated in the presence of a palladium catalyst, to obtain chiral polymers in high yields. An iodobenzenesulfonamide derivative of a cinchona alkaloid was also polymerized *via* self-polycondensation under the same reaction conditions. The catalytic activities of these chiral polymers were examined by using them as catalysts in the enantioselective desymmetrization of cyclic anhydrides.

Introduction

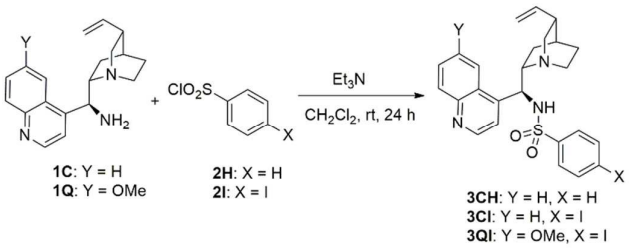
Cinchona alkaloids are extracted from the bark of the *Cinchona ledgeriana*, which is an important medicinal plant of tropical and sub-tropical regions.[1] In addition to their medicinal use in as antimalarial and antiarrhythmic compounds, cinchona alkaloids have also been employed as chiral organocatalysts in asymmetric synthesis.[2] Various efficient asymmetric catalysts have been designed based on cinchona alkaloids, an important class of which are their sulfonamide derivatives. Cinchona alkaloids have various functionalities, including a quinuclidine group, a secondary alcohol, a quinoline ring, and a vinylic unit. The secondary alcohol can be easily converted into an amine, which may be further modified to incorporate a sulfonamide group. The acidic NH of a sulfonamide can act as a H-bond donor, whereas the tertiary nitrogen of quinuclidine in cinchona alkaloids may act as both a H-bond acceptor and a base. By incorporating both acidic and basic sites into the cinchona alkaloid sulfonamide derivatives, the combination of acidic and basic sites allows the cinchona alkaloid sulfonamide derivatives to hold substrates in a particular orientation, therefore leading to a chiral environment. Several examples of cinchona-based sulfonamide catalysts have been developed for asymmetric reactions. For example, Chin *et al*. reported that a sulfonamide derived from quinine showed excellent catalytic activity in the enantioselective desymmetrization of cyclic anhydrides.[3] When cinchona-based sulfonamide derivatives are incorporated into polymers, the microenvironment of the catalyst site is precisely modified and controlled by polymerization.

Various kinds of polymer-immobilized cinchona alkaloid catalysts have been synthesized *via* attachment onto the side chain of synthetic polymers like crosslinked polystyrene.[4] Silica-supported cinchona alkaloids have also been prepared and used as catalysts in asymmetric reactions.[5-7] Interestingly however, chiral polymers containing a cinchona-based catalyst as the repeating unit have rarely been synthesized. We have developed several syntheses of polymeric cinchona-based quaternary ammonium salts, with polymerization methods involving a Menshutkin reaction,[8] ether formation,[9] a Mizoroki-Heck coupling reaction,[10] and an ion exchange reaction.[11,12] In this paper, we present a new synthesis of chiral polymers containing repeating cinchona-based sulfonamides in their main chain structure. The well-established Mizoroki-Heck reaction was chosen for the synthesis of the chiral sulfonamide polymers, which usually provides the coupling product in high yield. The chiral polymers were subsequently investigated as catalysts for the asymmetric desymmetrization of cyclic anhydrides.

Results and discussion

Synthesis of chiral polymers of cinchona sulfonamide

9-Amino derivatives of cinchonidine[13] and quinine[14] (**1C**, **1Q**) were prepared by Mitsunobu-type azide formation, followed by Staudinger reduction. Sulfonamides **3** were easily



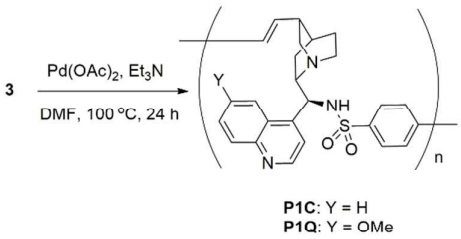
[a] *Department of Environmental and Life Sciences, Toyohashi University of Technology, Toyohashi, 441 Japan. E-mail: itsuno@ens.tut.ac.jp; Fax +81-(0)532-48-5833; Tel: +81-532-44-6813*

†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C6RA14535C

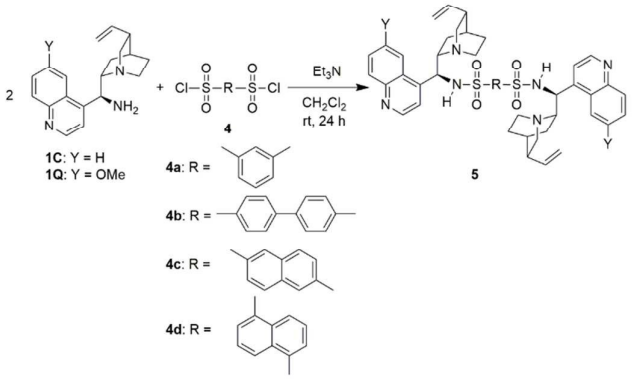
formed by the

Scheme 1 Preparation of cinchona alkaloid monomers **3**.



Scheme 2 Synthesis of cinchona alkaloid polymers by Mizoroki-Heck polymerization.

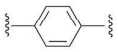
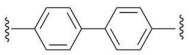
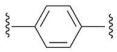
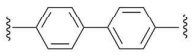
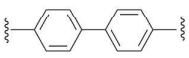
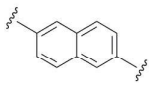
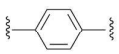
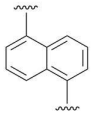
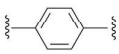
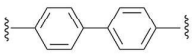
reaction of **1** and sulfonyl chloride **2** (Scheme 1). Sulfonamides **3Cl** and **3Ql** possess both aromatic iodide and vinyl groups. Since Mizoroki-Heck (MH) coupling reactions occur between aromatic iodides and olefins, repetitive MH reactions may occur with these sulfonamides to give rise to polymers. Indeed, under MH reaction conditions, both **3Cl** and **3Ql** readily react intermolecularly to form chiral polymers **P1C** and **P1Q** (Scheme 2). The polymers **P1** were only soluble in high polar solvents



Scheme 3 Preparation of cinchona alkaloid dimers **5**.

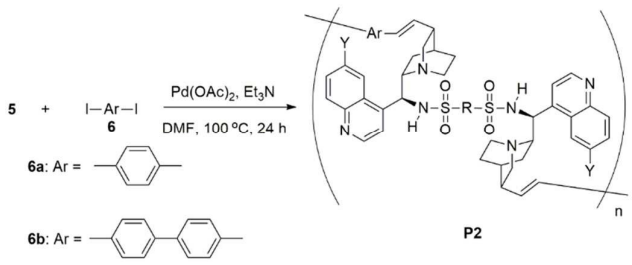
such as DMF and DMSO. This efficient method of one component, self-polycondensation of a chiral monomer represents the first example of polymer synthesis using cinchona alkaloid-derived sulfonamides. The polymerization results are summarized in Table 1.

Table 1 Synthesis of chiral sulfonamide polymers **P1**, **P2** using Mizoroki-Heck polymerization

Entry	Chiral sulfonamide polymer	Y	R	Ar	Yield %	M_n	M_w	M_w/M_n
1	**P1C**	H	-	-	99	8500	11000	1.4
2	**P1Q**	OMe	-	-	95	5800	9400	1.6
3	**P2Caa**	H			99	9500	29000	3.1
4	**P2Cba**	H			99	3800	4100	1.1
5	**P2Cbb**	H			97	11000	18000	1.7
6	**P2Cca**	H			99	3100	4400	1.4
7	**P2Cda**	H			98	6200	21000	3.5
9	**P2Qba**	OMe			99	7400	12000	1.6

[a]Polymerized in DMF at 100 °C for 24 h. [b]Determined by SEC (polystyrene standards) using DMF as an eluent at a flow rate of 1.0 mL·min^{-1} at 40 °C.

View Article Online
DOI: 10.1039/C6RA14535C

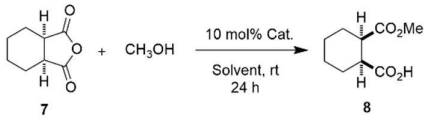


Scheme 4 Synthesis of cinchona alkaloid polymers **P2** by two component polycondensation.

The successful synthesis of chiral polymers **P1** by repetitive MH polymerization prompted us to apply the same method to a two-component polycondensation system. Two equivalents of 9-amino cinchona alkaloid **1** were allowed to react with disulfonyl dichloride **4** to afford sulfonamide dimers **5**, as shown in Scheme 3. Polycondensation between the dimer **5** and aromatic diiodide **6** under the previously identified MH conditions gave the chiral polymer **P2**. In the case of the two-component polycondensation system, changing the structure of the disulfonyl dichloride **4** and aromatic diiodide **6** allowed the synthesis of various polymeric structures according to Scheme 4. The results of the two-component polycondensation are summarized in Table 1.

Enantioselective desymmetrization reaction with chiral polymer catalysts derived from cinchona alkaloid sulfonamide

Cinchona alkaloid sulfonamides are efficient catalysts in various asymmetric reactions.[15-25] These asymmetric transformations have been applied to the synthesis of biologically active compounds and chiral building blocks for pharmaceutical targets.[26,27] In order to confirm the catalytic activity of the newly explored chiral polymers **P1** and **P2**, we chose to investigate the enantioselective desymmetrization of a cyclic anhydride. In the presence of the polymeric catalyst, which is insoluble in the organic solvent used, methanol reacted with cyclic anhydride **7** to give the hemiester **8** (Scheme 5). To identify the optimum reaction conditions, the influence of solvent upon the **P1C**-catalyzed enantioselective desymmetrization of **7** was studied (Table 2).



Scheme 5 Enantioselective desymmetrization of cyclic anhydride **7**.

Table 2 Solvent effect in enantioselective desymmetrization of cyclic anhydride **7** with polymeric catalyst **P1C**[a]

Entry	Catalyst	Solvent	Temperature °C	Yield[b] %	% ee[c]
1	**P1C**	hexane	25	99	10
2	**P1C**	CH_2Cl_2	25	91	49
3	**P1C**	EtOAc	25	39	51
4	**P1C**	Et_2O	25	93	37
5	**P1C**	Cyclopentyl methyl ether	25	89	34
6	**P1C**	MTBE	25	23	20
7	**P1C**	Dioxane	25	81	79
8	**P1C**	THF	25	86	94
9	**P1C**	THF	0	40	94
10	**P1C**	THF	-20	6	95
11	**P1Q**	THF	25	97	95
12	**3CH**	THF	25	99	93
13	**3CI**	THF	25	99	93

[a]Unless otherwise indicated, reactions were carried out with **7** (0.1 mmol), methanol (10 equiv, 1.0 mmol), and the polymeric catalyst (10 mol%). [b]Isolated yield. [c]Determined by chiral HPLC (Chiralcel AD-H) after derivatization to 4-bromophenyl ester of **8**.

We found that the choice of solvent had a dramatic effect on both the catalytic activity and enantioselectivity of the desymmetrization of **7**. In hexane, the reaction occurred smoothly to give **8** in an almost quantitative yield. However, the ee was only 10% (entry 1). Dichloromethane and ethyl acetate gave higher enantioselectivities under the same reaction conditions (entries 2, 3), whereas ethers led to relatively lower enantioselectivity (entries 4-6). However, interestingly, cyclic ethers such as dioxane and THF showed both high reactivity and increased enantioselectivity (entries 7, 8). In the reaction conducted in THF, the polymeric catalyst **P1C** showed a slightly higher ee of 94% (entry 8) when compared to the corresponding low-molecular-weight model catalyst **3CH** (entry 12). The structurally similar polymer **P1Q** also showed excellent activity under the same reaction conditions, with an ee of 95% observed in THF (entry 11). The effect of temperature on the reaction with polymeric catalyst **P1C** was also surveyed (entries 9, 10). Although no significant effect on the enantioselectivity was observed, the reaction rate decreased considerably at lower reaction temperatures.

View Article Online
DOI: 10.1039/C6RA14535C

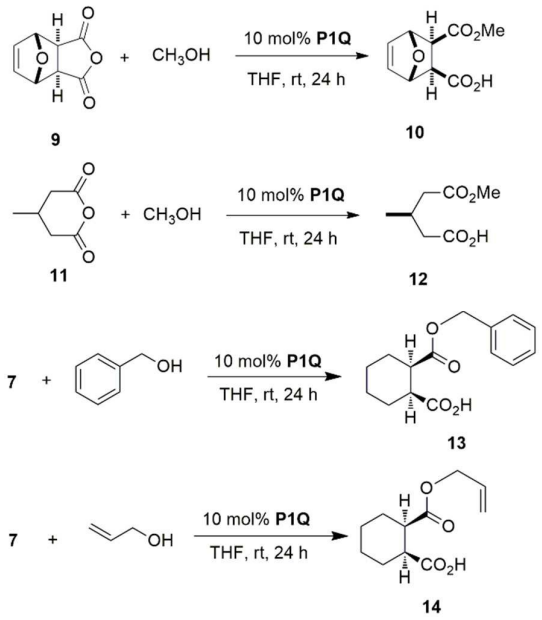
We then used another chiral polymeric catalysts **P2,** prepared as previously by a two component MH polymerization from **5** and aromatic diiodides. With THF identified as the best solvent for the asymmetric reaction with the polymeric catalyst **P1**, the same solvent was used in the asymmetric reaction with **P2**. As shown in Table 3, the reaction with **P2** in THF occurred smoothly at room temperature. We also found that the polymer structure of **P2** considerably affected both the catalytic activity and enantioselectivity of the reaction. A disulfonamide linker with a biphenyl structure gave a relatively higher yield and enantioselectivity for **8** (entries 2–4) when compared to naphthalene-based disulfonamides (entries 5, 6). Since the polymeric catalyst forms an insoluble suspension in THF, the catalyst could be easily separated from the reaction mixture by simple filtration. The recovered polymer powder could then be reused in subsequent reactions, without any loss of catalytic activity or enantioselectivity. The polymeric catalyst **P2Cba** can be reused at least 4 times (entries 2-5).

Table 3 Enantioselective desymmetrization of cyclic anhydride **7** with polymeric catalyst in THF[a]

Entry	Catalyst	Temperature °C	Yield[b] %	ee[c] %
1	**P2Caa**	25	93	90
2	**P2Cba**	25	98	91
3[d]	**P2Cba**	25	99	92
4[e]	**P2Cba**	25	99	93
5[f]	**P2Cba**	25	99	95
6	**P2Cbb**	25	99	93
7[g]	**P2Cbb**	25	99	93
8	**P2Cca**	25	42	84
9	**P2Cda**	25	32	65
10	**P2Qba**	25	99	88
11	**5Ca**	25	99	96
12	**5Cb**	25	99	93

[a]Unless otherwise indicated, reactions were carried out with **7** (0.1 mmol), methanol (10 equiv, 1.0 mmol), and the polymeric catalyst (10 mol%). [b]Isolated yield. [c]Determined by chiral HPLC (Chiralcel AD-H) after derivatization to 4-bromophenyl ester of **8**. [d]The recovered polymer catalyst **P2Cba** used in entry 2 was used. [e]The recovered polymer catalyst **P2Cba** used in entry 3 was used. [f]The recovered polymer catalyst **P2Cba** used in entry 4 was used. [g]The recovered polymer catalyst **P2Cbb** used in entry 6 was used

In order to further demonstrate the usefulness of chiral polymeric organocatalysts, **P1Q** was used in the enantioselective desymmetrization of cyclic anhydrides **9** and **11** (Scheme 6). The reaction occurred smoothly to give the corresponding hemiesters **10** and **12**, as summarized in Table 4. In addition to methanol, benzyl alcohol and allyl alcohol were also examined in the desymmetrization reaction of cyclic anhydride **7**, and gave rise to the corresponding chiral hemiesters **13** and **14** (entries 4, 5). The results obtained from one of the most efficient catalyst **3QF**[3] in the same asymmetric reaction were shown in Table 4. In case of the reactions of **7**, the catalytic activity of the polymer catalyst was equivalent to that of **3QF**.



Scheme 6 Enantioselective desymmetrization of cyclic anhydrides with polymeric catalyst **PQ1**.

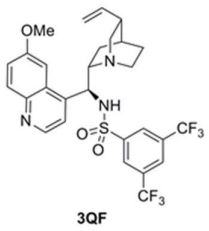


Figure 1 Quinine derived sulfonamide **3QF**

Table 4 Enantioselective desymmetrization of cyclic anhydride with polymeric catalyst **P1Q** in THF[a]

Entry	Cyclic anhydride	Catalyst	Alcohol	Product	Yield[b] %	ee[c] %
1	**7**	**P1Q**	CH_3OH	**8**	97	95
2[d]	**7**	**3QF**	CH_3OH	**8**	92	95
3	**7**	**P1Q**	$PhCH_2OH$	**13**	99	71
4	**7**	**P1Q**	$CH_2=CHCH_2OH$	**14**	80	95
5	**9**	**P1Q**	CH_3OH	**10**	88	73
6[d]	**9**	**3QF**	CH_3OH	**10**	90	94
7	**11**	**P1Q**	CH_3OH	**12**	41	78
8[d]	**11**	**3QF**	CH_3OH	**12**	95	91

View Article Online
DOI: 10.1039/C6RA14535C

[a]Unless otherwise indicated, reactions were carried out with cyclic anhydride (0.1 mmol), alcohol (10 equiv, 1.0 mmol), and the polymeric catalyst (10 mol%). [b]Isolated yield. [c]Determined by chiral HPLC (Chiralcel AD-H) after derivatization to 4-bromophenyl ester of hemiester. [d]See Ref. 3.

Conclusions

In conclusion, chiral polymers containing a cinchona-based sulfonamide structure in their main chain were successfully synthesized by Mizoroki-Heck polymerization. This is the first synthesis of a chiral, polymeric catalyst containing both acidic and basic functionality by means of a repeated MH reaction. The chiral polymers showed catalytic activity in the enantioselective desymmetrization reactions of cyclic anhydrides, with high levels of enantioselectivity observed. The polymeric catalysts were easily separated from the reaction mixture and reused several times without loss of either catalytic activity or enantioselectivity. Since the cinchona-based sulfonamides are known to be excellent catalysts in various asymmetric reactions, the polymers developed in this study will find further application as catalysts in alternative asymmetric transformations. For instance, the use of the chiral polymers in asymmetric Michael-type reactions is now under investigation.

Experimental

General methods

All solvents and reagents were purchased from Sigma-Aldrich, Wako Pure Chemical Industries, Ltd., or Tokyo Chemical Industry (TCI) Co., Ltd. at the highest available purity and were used as received, unless otherwise mentioned. Reactions were monitored by thin-layer chromatography using pre-coated silica gel plates (Merck 5554, 60F254). Column chromatography was performed using a silica gel column (Wakogel C-200, 100-200 mesh). Melting points were recorded using a Yanaco micro melting apparatus and the values were not corrected. NMR spectra were recorded on JEOL JNM-ECS400 spectrometers in $CDCl_3$ or DMSO-d_6 at room temperature operating at 400 MHz (^{1}H) and 100 MHz (^{13}C{^{1}H}). Tetramethylsilane (TMS) was used as an internal standard for ^{1}H NMR, and $CDCl_3$ for ^{13}C NMR. Chemical shifts are reported in ppm using TMS as a reference, and the *J* values were recorded in Hertz. The IR spectra, recorded on a JEOL JIR-7000 FTIR spectrometer, are reported in cm^{-1}. Elemental analyses (carbon, hydrogen, nitrogen) were performed on a Yanaco-CHN coder MT-6 analyzer. HRMS (ESI) spectra were recorded on a microTOF-Q II HRMS/MS instrument (Bruker). High-performance liquid chromatography (HPLC) was performed with a Jasco HPLC system composed of a DG-980-50 three-line degasser, a PU 980 HPLC pump, and a CO-965 column oven equipped with a chiral column (Chiralpak AD-H, Daicel) with hexane/2-propanol as an eluent. A Jasco UV-975 UV detector was used for peak detection. Size-exclusion chromatography (SEC) was performed using a Tosoh instrument with HLC 8020 UV (254 nm) or refractive index detection. DMF was used as the carrier solvent at a flow rate of 1.0 mL min^{-1} at 40 °C. Two polystyrene gel columns of bead size 10 μm were used. A calibration curve was obtained to determine the number-average molecular weight (M_n) and molecular weight distribution (M_w/M_n) values with polystyrene standards. Optical rotation was recorded using a JASCO DIP-149 digital polarimeter, using a 10-cm thermostated microcell.

Synthesis of sulfonamide 3CH. To a stirred mixture of **1C** (0.90 g, 3.1 mmol) in CH_2Cl_2 (5 mL) and NEt_3 (0.31 g, 3.1 mmol), a solution of benzenesulfonyl chloride (0.53 g, 3.0 mmol) in CH_2Cl_2 (5 mL) was slowly added under a nitrogen atmosphere, and the reaction mixture was stirred at room temperature for 24 h. After the addition of water (5 mL), the mixture was extracted with CH_2Cl_2 (10 mL × 3) and the organic extracts were dried over anhydrous Na_2SO_4. After filtration, the solvent was removed by evaporation and the residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH = 9/1, v/v) to afford **3CH** (1.04 g, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δH 8.74 (d, 0.25H, *J* = 3.97 Hz), 8.64 (d, 0.75H, *J* = 4.58 Hz), 8.36 (d, 0.25H, *J* = 8.85 Hz), 8.14 (d, 0.75H, *J* = 8.24 Hz), 8.08 (d, 0.75H, *J* = 8.24 Hz), 7.95 (d, 0.25H, *J* = 8.24 Hz), 7.74 (t, 0.75H, *J* = 7.93 Hz), 7.65-7.56 (m, 1H), 7.48-7.30 (m, 4H), 7.22 (d, 0.25H, *J* = 3.97 Hz), 7.11 (t, 1.5H, *J* = 7.63 Hz), 6.95 (t, 0.5H, *J* = 7.93 Hz), 5.69-5.54 (m, 1H), 5.10 (d, 0.75H, *J* = 10.4 Hz), 5.00-4.84 (m, 2H), 4.33 (d, 0.25H, *J* = 10.7 Hz), 3.37-3.22 (m, 1.25H), 3.05-2.94 (m, 1.5H), 2.85-2.63 (m, 2.25H), 2.33 (br s, 1H), 1.68-1.56 (m, 3H), 1.31-1.27 (m, 1H), 0.93-0.86 (m, 1H). IR (KBr) ν_{max} 3446, 3197, 3064, 2943, 2866, 1636, 1591, 1568, 1509, 1447, 1324, 1239, 1159, 1092, 1059, 1033, 988, 955, 922, 878, 817, 754 cm^{-1}. HRMS (ESI): m/z calc'd for $[C_{25}H_{28}N_3O_2S]$+: 434.1897, found: 434.1898.

Synthesis of sulfonamide dimers 5Ca. A typical procedure for the synthesis of 5 is described. To a stirred mixture of **1C** (0.90 g, 3.1 mmol) in CH_2Cl_2 (5.0 mL) and NEt_3 (0.31 g, 3.1 mmol), a solution of *m*-benzenedisulfonyl dichloride (0.42 g, 1.5 mmol) in CH_2Cl_2 (5 mL) was slowly added under a nitrogen atmosphere, and the reaction mixture was stirred at room temperature for 24 h. After the addition of water (5 mL), the mixture was extracted with CH_2Cl_2 (10 mL × 3) and the organic extracts were dried over anhydrous Na_2SO_4. After filtration, the solvent was removed by evaporation and the residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH = 9/1, v/v) to afford **5Ca** (727 mg, 60% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.73 (d, *J* = 4.27 Hz), 8.70 (d, *J* = 4.27 Hz), 8.64 (d, *J* = 4.58 Hz), 8.12-8.04 (m), 7.97 (s), 7.89-7.83 (m), 7.75-7.49 (m), 7.30 (d, 1.3H, *J* = 4.58 Hz), 7.21-7.19 (m), 7.09 (d, *J* = 7.93 Hz), 6.94 (d, *J* = 7.93 Hz), 6.79 (q, *J* = 16.17, 8.24 Hz), 6.54 (t, *J* = 7.93 Hz), 6.31 (t, *J* = 7.63 Hz), 5.67-5.51 (m), 5.03-4.82 (m), 4.32 (d, *J* = 10.7 Hz), 4.19 (d, *J* = 10.99 Hz), 3.35-3.07 (m), 2.96-2.45 (m), 2.28 (br s), 1.67-1.39 (m), 1.27-1.17 (m), 0.89-0.74 (m). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 150.0, 149.3, 148.7, 148.1, 144.0, 143.7, 141.0, 140.6, 140.3, 139.7, 139.1, 130.4, 130.2,

View Article Online
DOI: 10.1039/C6RA14535C

130.1, 130.0, 129.6, 129.5, 129.4, 129.2, 128.7, 127.6, 127.5, 127.3, 126.8, 126.7, 126.3, 126.2, 125.4, 124.1, 123.9, 123.8, 122.1, 120.2, 120.1, 115.2, 115.1, 114.9, 62.7, 61.1, 61.0, 56.6, 55.6, 55.3, 52.5, 52.4, 45.8, 40.3, 39.9, 39.6, 39.1, 27.6, 27.3, 27.2, 26.1, 24.8, 8.7. IR (KBr) ν_{max} 3609, 3421, 3209, 3073, 2942, 2866, 2604, 2495, 1922, 1716, 1636, 1591, 1569, 1510, 1457, 1413, 1326, 1240, 1175, 1154, 1082, 1059, 1032, 988, 956, 912, 879, 814, 795, 759, 684, 580, 517, 418 cm^{-1}. HRMS (ESI): m/z calc'd for $C_{44}H_{47}N_6O_4S_2$ ($[M-H]^-$) 787.3106, found 787.3106.

Synthesis of cinchona alkaloid polymers by self polycondensation

Synthesis of P1C. A mixture of sulfonamide **3CI** (0.21 g, 0.38 mmol) in the presence of 3 mol% Pd $(OAc)_2$ (2.5 mg, 11.3 μmol) and Et_3N (38 mg, 0.38 mmol) was stirred in 3 mL anhydrous DMF at 100 °C for 24 h. After completion of the reaction, the reaction mixture was cooled to room temperature. The reaction mixture was then added dropwise into ether (40 mL) with stirring. The solid precipitate was filtered, then sequentially washed with diethyl ether, ethyl acetate, CH_3OH, and hexane to afford 176 mg (99% yield) of the product **P1C**. IR (KBr) ν_{max} 3435, 3061, 2931, 2866, 1656, 1592, 1568, 1510, 1466, 1386, 1327, 1243, 1160, 1089, 1055, 1003, 928, 876, 815, 763, 729, 698 cm^{-1}. $[\alpha]^{25}_D$ = -134.7 (*c* 1.0, DMSO). M_n (SEC) = 8.5 x 10^3; M_w/M_n = 1.4.

Synthesis of P1Q. A mixture of sulfonamide **3QI** (224 mg, 0.38 mmol) in the presence of 3 mol% $Pd(OAc)_2$ (2.5 mg, 11.3 μmol) and NEt_3 (38 mg, 0.38 mmol) was stirred in 3 mL anhydrous DMF at 100 °C for 24 h. After completion of the reaction, the reaction mixture was cooled to room temperature. The reaction mixture was then added dropwise into diethyl ether (40 mL) with stirring. The solid precipitate was filtered, then sequentially washed with ether, ethyl acetate, CH_3OH, and hexane to afford 174 mg (99% yield) of the product **P1Q**. IR (KBr) ν_{max} 3435, 3061, 2931, 2866, 1656, 1592, 1568, 1510, 1466, 1386, 1327, 1243, 1160, 1089, 1055, 1003, 928, 876, 815, 763, 729, 698 cm^{-1}. $[\alpha]^{25}_D$ = -154.7 (*c* 1.0, DMSO). M_n (SEC) = 5.8 x 10^3; M_w/M_n = 1.6.

Representative procedure for the Synthesis of P2C by two component polycondensation.

A typical procedure for the synthesis of **P2Caa** is described. A mixture of sulfonamide dimer **5Ca** (0.30 g, 0.38 mmol) and 4,4'-diiodobenzene (0.13 mg, 0.38 mmol) in the presence of 3 mol% Pd $(OAc)_2$ (2.6 mg, 0.011 mmol) and NEt_3 (77 mg, 0.76 mmol) was stirred in 3 mL anhydrous DMF at 100 °C for 24 h. After completion of the reaction, the reaction mixture was cooled to room temperature. The reaction mixture was then added dropwise into ether (40 mL) with stirring. The solid precipitate was filtered, then sequentially washed with ether, ethyl acetate, CH_3OH, and hexane to afford 313 mg (99% yield) of the product **P2Caa**. ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 170.4, 149.6, 147.3, 137.8, 137.1, 129.4, 129.0, 128.3, 127.4, 126.3, 125.9, 124.1, 122.7, 119.9, 59.8, 59.4, 51.1, 45.7, 41.4, 26.6, 20.8, 14.1, 11.1, 8.6. IR (KBr) ν_{max} 3421, 3057, 2939, 2864, 1730, 1654, 1591, 1569, 1510, 1465, 1337, 1242, 1154, 1080, 1058, 1003, 967, 908, 878, 795, 762, 683, 580, 521 cm^{-1}. $[\alpha]^{25}_D$ = -134.7 (*c* 1.0, DMSO). M_n (SEC) = 9.5 x 10^3; M_w/M_n = 3.1.

Representative procedure for asymmetric desymmetrization of prochiral cyclic anhydride with methanol

Methanol (40.5 μL, 1.00 mmol) was added dropwise to a solution of **7** (15.4 mg, 0.10 mmol) and **P1C** (4.3 mg, 0.01 mmol) in THF (2 mL) at room temperature with stirring, and the mixture was stirred at room temperature for 24 h. The reaction mixture was directly subjected to column chromatography (SiO_2, Et_2O) to give the hemiester product **8** (16 mg, 86%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.68 (s, 3H), 2.85 (br s, 2H), 2.10–1.94 (m, 2H), 1.82–1.73 (m, 2H), 1.61–1.38 (m, 4H).

To determine the enantiomeric excess (ee), **8** was converted to the corresponding 4-bromophenyl ester according to a literature procedure.[28] To a solution of **8** (18.6 mg, 0.10 mmol) and 4-bromophenol (34.6 mg, 0.200 mmol) in CH_2Cl_2 (2 mL) at 0 °C, *N*,*N*'-dicyclohexylcarbodiimide (41.3 mg, 0.20 mmol) and 4-dimethylaminopyridine (DMAP, 6.10 mg, 0.05 mmol) were added. The mixture was allowed to warm to room temperature and stirred overnight. The white solid was filtered off and the solvent was removed in *vacuo*. The residue was then purified *via* column chromatography (SiO_2, EtOAc/*n*-hexane=1/5, v/v) to afford the 4-bromophenyl ester (28.8 mg, 98% based on **8**) as a colourless oil. The ee of the 4-bromophenyl ester was determined to be 94% by chiral HPLC analysis (Chiralpak AD-H column, 2-propanol/n-hexane=1/9 v/v, 1.0 mL/min). $t_{(1S,2R)}$=7.8 min, $t_{(1R,2S)}$=8.3 min. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.47 (d, *J*=8.9 Hz, 2H), 6.97 (d, *J*=8.9 Hz, 2H), 3.70 (s, 3H), 3.06–2.98 (m, 2H), 2.16–2.03 (m, 2H), 1.96–1.89 (m, 2H), 1.82–1.61 (m, 2H), 1.58–1.41 (m, 2H).

In the same way, other polymers and monomers were also employed as catalysts for the enantioselective desymmetrization reaction. These results are summarized in Table 2.

Acknowledgements

The authors would like to thank Dr. Naoki Haraguchi at Toyohashi University of Technology for fruitful discussions. This work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (Japan).

Notes and references

1 E. M. O. Yeboah, S. O. Yeboah and G. S. Singh, *Tetrahedron*, 2011, **67**, 1725-1762.
2 *Cinchona Alkaloids in Synthesis & Catalysis*, Ed. C. E. Song, 2009, Wiley-VCH, Weinheim.
3 S. H. Oh, H. S. Rho, J. W. Lee, J. E. Lee, S. H. Youk, J. Chin and C. E. Song, *Angew. Chem. Int. Ed.* 2008, **47**, 7872-7875.
4 S. Itsuno and M. M. Hassan, *RSC Adv.* 2014, **4**, 52023-52043.
5 P. Yu, J. He and C. Guo, *Chem. Commun.* 2008, 2355-2357.
6 W. Zhao, Y. Zhang, C. Qu, L. Zhang, J. Wang and Y. Cui, *Catal. Lett.* 2014, **144**, 1681-1688.
7 C. E. Song, J. W. Yang and H. J. Ha, *Tetrahedron: Asymmetry* 1997, **8**, 841-844.

View Article Online
DOI: 10.1039/C6RA14535C

8 P. Ahamed, M. A. Haque, M. Ishimoto, M. M. Parvez, N. Haraguchi and S. Itsuno, *Tetrahedron* 2013, **69**, 3978-3983.
9 S. Itsuno, D. K. Paul, M. Ishimoto and N. Haraguchi, *Chem. Lett.* 2010, **39**, 86-87.
10 M. M. Parvez, N. Haraguchi and S. Itsuno, *Macromolecules* 2014, **47**, 1922-1928.
11 S. Itsuno, D. K. Paul, M. A. Salam and N. Haraguchi, *J. Am. Chem. Soc.* 2010, **132**, 2864-2865.
12 M. M. Parvez, N. Haraguchi and S. Itsuno, *Org. Biomol. Chem.* 2012, **10**, 2870-2877.
13 C. B. Tripathi, S. Kayal, S and Mukherjee, *Org. Lett.* 2012, **14**, 3296-3299.
14 B. Vakulya, S. Varga, A. Csámpai and T. Soós, *Org. Lett.* 2005, **7**, 1967-1969.
15 S. E. Park, E. H. Nam, H. B. Jang, J. S. Oh, S. Some, Y. S. Lee and C. E. Songa, *Adv. Synth. Catal.* 2010, **352**, 2211-2217.
16 Y. Zhang, H. Xing, W. Xie, X. Wan, Y. Lai and D. Mab, *Adv. Synth. Catal.* 2013, **355**, 68-72.
17 N. Hara, S. Nakamura, M. Sano, R. Tamura, Y. Funahashi and N. Shibata, *Chem. Eur. J.* 2012, **18**, 9276-9280.
18 H. Y. Bae, J. H. Sim, J.-W. Lee, B. List and C. E. Song, *Angew. Chem. Int. Ed.* 2013, **52**, 12143-12147.
19 H. Brunner and M. A. Baur, *Eur. J. Org. Chem.* 2003, 2854-2862.
20 P. Jakubec, D. M. Cockfield, P. S. Hynes, E. Cleator and D. J. Dixon, *Tetrahedron: Asymmetry* 2011, **22**, 1147-1155.
21 S. Nakamura, S. Takahashi, D. Nakane and H. Masuda, *Org. Lett.* 2015, **17**, 106-109.
22 J. Luo, L.-W. Xu, R. A. S. Hay and Y. Lu, *Org. Lett.* 2009, **11**, 437-440.
23 K. M. Johnson, M. S. Rattley, F. Sladojevich, D. M. Barber, M. G. Nu˜nez, A. M. Goldys and D. J. Dixon, *Org. Lett.* 2012, **14**, 2492-2495.
24 M. A. Baur, A. Riahi, F. He´nin and J. Muzart, *Tetrahedron: Asymmetry* 2003, **14**, 2755-2761.
25 M. Ding, F. Zhou, Y.-L. Liu, C.-H. Wang, X.-L. Zhao and J. Zhou, *Chem. Sci.* 2011, **2**, 2035-2039.
26 S. Nakamura and S. Takahashi, *Org. Lett.* 2015, **17**, 2590-2593.
27 F. Xiong, X.-X. Chen and F.-E. Chen, *Tetrahedron: Asymmetry* 2010, **21**, 665-669.
28 R. Manzano, J. M. Andres, M. -D. Muruzabal and R. J. Pedrosa, *J. Org. Chem.*, 2010, **75**, 5417-5420.

View Article Online
DOI: 10.1039/C6RA14535C

Table of contents:

Synthesis of Cinchona Alkaloid Sulfonamide Polymers as Sustainable Catalysts for the Enantioselective Desymmetrization of Cyclic Anhydrides

S. Takata, Y. Endo, S. Ullah and S. Itsuno*

Department of Environmental & Life Sciences, Toyohashi University of Technology, Toyohashi 441-8580, Japan

Mizoroki-Heck polymerization of cinchona sulfonamide gave the chiral polymers, which are active catalysts for enantioselective desymmetrization of cyclic anhydrides to give chiral hemiesters in high yield with high enantioselectivities.