Synthesis and structural features of chiral cyclic squaramides and their application in asymmetric catalytic reaction

Xiaoqing Jin, Qiaoqiao Min, Yangfan Zheng, Pengcheng Wang, Jun Zhu, and Hai-Bing Zhou*

State Key Laboratory of Virology, College of Pharmacy, Wuhan University, Wuhan 430071 China

E-mail: zhouhb@whu.edu.cn

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Abstract

We report the synthesis and structural elucidation of two series of chiral cyclic squaramides, i.e. six- and twelve-membered ring squaramides **4** and **6**, based on the cyclobutenedione structure, containing enantiomerically pure (1*R*,2*R*)-1,2-diphenylethylenediamine as the chiral element. Compounds **4a-d** obtained from alkylation of **3**, crystallize in space groups of monoclinic $P2_1$, monoclinic $P2_1$, monoclinic chiral $P2_12_12_1$, and the orthorhombic $C222_1$, respectively. For the first time the crystal structures of six-membered ring chiral cyclic squaramides are reported. These novel ligands have been tested in the enantioselective addition of diethylzinc to aryl aldehydes to give the corresponding alcohols in moderate yields, albeit with low enantioselectivity.

Keywords: Chiral cyclic squaramides, crystal structure, asymmetric catalysis, squaric acid

Introduction

Squaric acid is an aromatic four-membered ring cyclic compound with unique properties and applications. The squaric acid system possesses a rigid skeleton, two oxygen atoms with a pronounced Lewis base character, particularly as proton acceptor sites, and two reactive hydroxyl groups that can be submitted to a variety of substitution processes either in a simultaneous or a sequential manner, providing the potential for the preparation of a large number of compounds by substituent variation. This unique reactivity enables the employment of squarate molecules in multiple research areas such as advanced materials,[1] chemosensors,[2] enzyme inhibition, pharmaceutically active compounds,[3-6] and as a useful diene synthon in

organic synthesis.[7] We and others have used chiral derivatives of squaric acid as ligands for asymmetric catalytic reactions.[8-12]

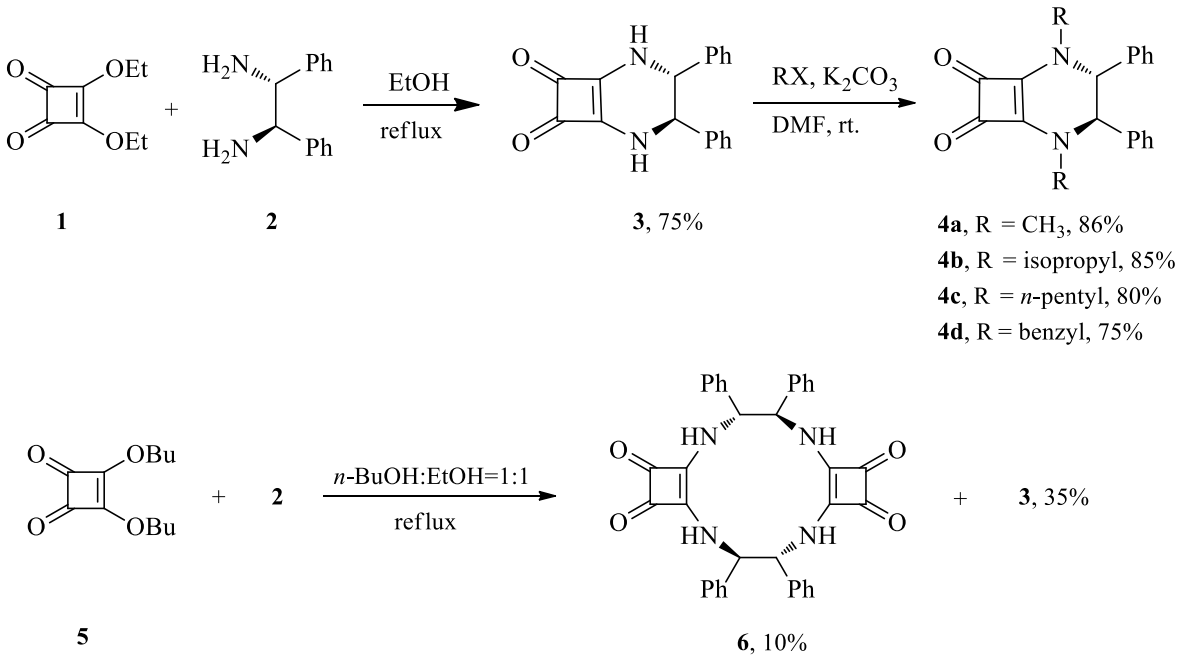
It is well known that these molecules also exhibit a dual donor–acceptor hydrogen bonding ability. In particular, the diamido-derivatives (also known as squaramides) have been studied in the conttext of molecular recognition,[13] supramolecular assemblies,[14,15] and as improved chiral organocatalysts. These properties have been applied to enhance the biological activity of several drugs and to functionalize organic molecules. For example, very recently, a number of chiral squaramides were designed as chiral organocatalysts in a manner where the squaramido groups were used as hydrogen bond donors, with distinctly different structural parameters than the corresponding thioureas.[16-19] Several crystal structures of squaramides have also been examined for a crystal engineering study using hydrogen bonding as a non-covalent force, in which secondary aromatic interactions such as CH–π can also be observed.[20]

However, to the best of our knowledge, there is no report on the synthesis and structural features of chiral cyclic squaramides and their use as catalysts in asymmetric reactions. In continuation of our interest in developing new squaramides that are of potential in asymmetric catalysis and crystal engineering sectors, we report herein the design, synthesis, and structural elucidation of six-membered and twelve-membered ring chiral cyclic squaramides based on the cyclobutenedione structure and containing an enantiomerically pure diamine as the chiral element, as well as their application in asymmetric catalytic addition of diethylzinc to aldehydes.

Results and Discussion

Synthesis

Chiral cyclic squaramide (3*R*,4*R*)-3,4-diphenyl-2,5-diaza-bicyclo[4.2.0]oct-1(6)-ene-7,8-dione **3** was prepared by the reaction of diethyl squarate **1** with one equivalent of (1*R*,2*R*)-1,2-diphenylethylenediamine **2** in refluxing ethanol. Alkylation of **3** with haloalkyl reagents in the presence of potassium carbonate in DMF at ambient temperature afforded the alkyl substituted cyclic squaramides **4**. Chiral twelve-membered cyclic squaramide **6** was prepared by the reaction of di-*n*-butyl squarate **5** with one equivalent of **2** in *n*-butanol/ethanol (1:1) at reflux in 10% yield, accompanied by 35% of **3** (Scheme 1). Identifying features in the ^{1}H NMR spectra of **3** and **6** include singlets for the methine protons at 4.32 and 4.76 ppm, respectively. The ^{13}C NMR spectra displayed seven signals for both compounds, indicating that the molecules are symmetric. The structures of ligands **4a-d** were unambiguously established by X-ray determination.[21] Unfortunately, attempts to obtain a single crystal of **3** or **6** failed.



Scheme 1. Synthetic route for compounds **4** and **6**.

X-Ray structural analysis

Compounds **4a-d** were recrystallized from EtOAc/CH_2Cl_2 at room temperature. The crystal data and structural refinements for **4a-d** are given in Table S1 in Supplementary Materials. Perspective views of **4a-d** are depicted in Figures 1-9. It should be noted that in all the structures reported here, the adjacent phenyl groups of diphenylethylenediamine moiety show electron-rich and stereo-hindrance effect, thus distinct differences of spatial position of the two phenyl groups were observed. The C atoms of the plane of the 1,4−diaza six-membered ring is tilted towards that of the total planarity of squaric acid ring at a distance of 0.269Å for **4a** (C13), 0.558Å for **4b** (C8 and C32), 0.531Å for **4c** (C6) and 0.341Å for **4d** (C7 and C26), respectively. In additional, the increasing dihedral angle of both side benzyl ring and squaric acid ring are 77.4º and 72.2º for **4a,** 79.16º and 83.88º for **4b,** 83.9º and 89.15º for **4c** and 83.96º and 78.04º for **4d**.

Compound **4a** crystallizes in the monoclinic space group $P2_1$. An ORTEP diagram is given in Figure 1. In **4a**, the two oxygen atoms of the squaric acid fragment provide proton acceptor sites leading three kinds of C–H···O hydrogen bonding rings ($R_2^2(10)$, $R_2^2(9)$ and $R_1^2(7)$), namely $R_2^2(10)$: −C1−C13−C14−H14···O2−C17−C18−O1···H2−C2−, O1···H2−C2: 3.466 Å, 146.10° and O2···H14−C14 3.276 Å, 134.56°; $R_2^2(9)$: −C17−C18−O1···H20B−C20−N1−C13−H13···O2−, O1···H20B−C20: 3.1946 Å, 131.59° and O2···H13−C13 3.518 Å, 140.44; $R_1^2(7)$: −C14−C7−C12−H12···O2···H13−C13−, O2···H12−C12: 3.481 Å, 162.62° and O2···H13−C13 3.518 Å, 140.44°. Through these hydrogen bonding rings, molecules of **4a** were extended to a 1D chain (Figure 2).

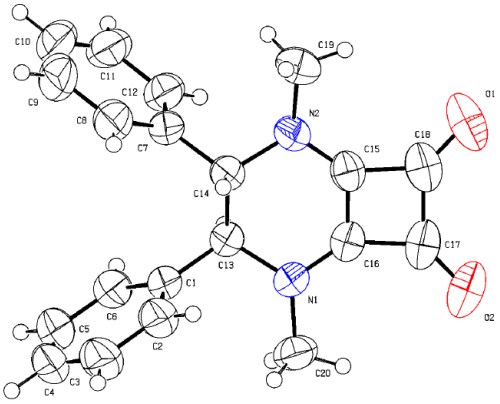


Figure 1. ORTEP diagram of **4a**. Displacement ellipsoids are drawn at the 50% probability level; hydrogen atoms are drawn at arbitrary size.

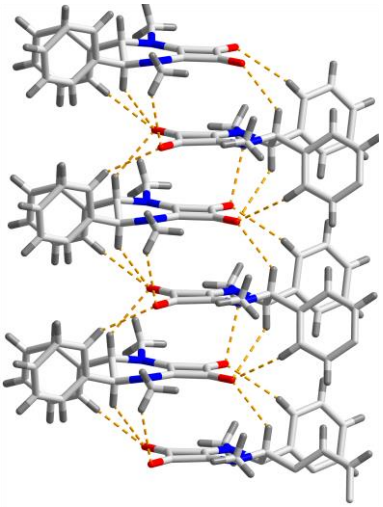


Figure 2. Linkage of the molecules of **4a.** The hydrogen bonds are represented by dashed lines.

Compound **4b** also crystallizes in the monoclinic space group $P2_1$ (Figure 3). Similar to **4a,** in the crystal structure of **4b**, there exist also three hydrogen-bonding rings despite the different substituent component. The hydrogen-bonding cyclic [$R_1^2(6)$, $R_1^2(7)$, $R_2^2(10)$] geometries are as follows: $R_1^2(6)$: −C6−C5−H5···O3···H7−C7−, O3···H5−C5: 3.3271 Å, 142.58° and O3···H7−C7 3.327 Å, 153.76°; $R_1^2(7)$: −N3−C46−C47−H47A···O2···H32−C32−, O2···H32−C32: 3.343 Å, 151.45° and O2···H47A−C47 3.560 Å, 159.42°; $R_2^2(10)$: −C20−C21−O2···H32−C32−C31−C30−C25−H25···O1−, C25−H25···O1: 3.507 Å, 157.99° and O2···H32−C32 3.343 Å, 151.45°. Based on this connectivity, the 1-D chain was assembled (Figure 4). Furthermore, each of the water molecules serve as μ_2-linker to connect the 1-D chains into 2-D supramolecular network (Figure 5). The hydrogen bond separations of the adjacent water molecule and chains are 2.884 Å (angle: 129.73º) and 2.968 Å (angle: 155.47º), respectively. Apparently, intense steric hindrance occurs in compound **4b** due to the presence of the isopropyl group.

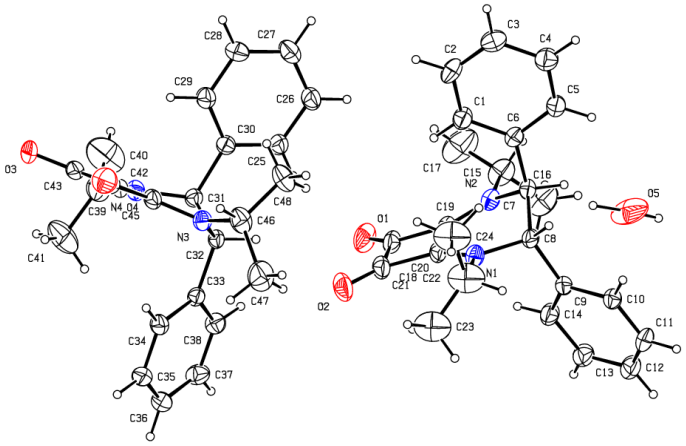


Figure 3. ORTEP diagram of **4b**. Displacement ellipsoids are drawn at the 50% probability level; hydrogen atoms are drawn at arbitrary size.

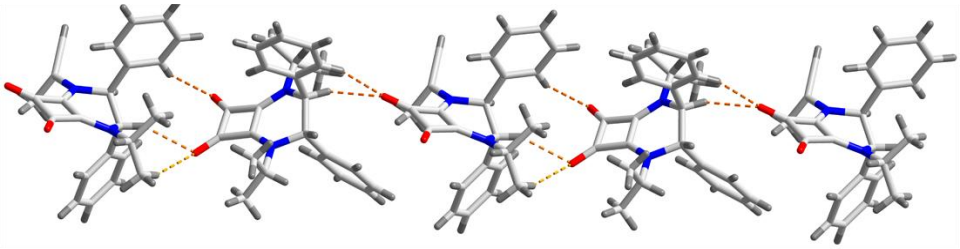


Figure 4. Hydrogen-bonding 1D chain pattern in the structure of **4b**. Hydrogen bonds are represented by dashed lines.

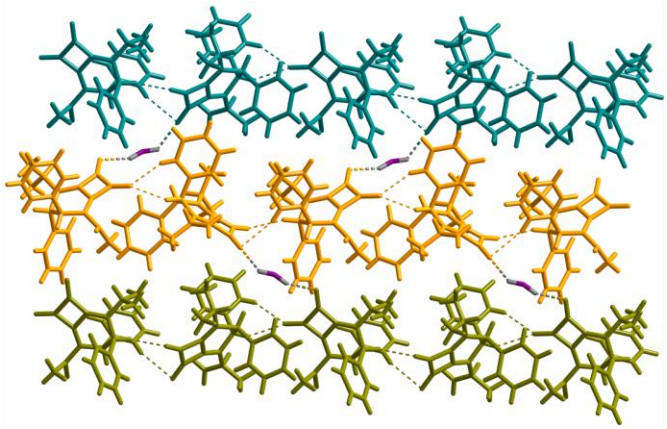


Figure 5. Hydrogen-bonding 2D network linked through the water molecule. Hydrogen bonds are represented by dashed lines.

Interestingly, **4c** was crystallized in the monoclinic chiral space group $P2_12_12_1$, the asymmetric unit is depicted in Figure 6. The zig-zag helix chains along *a* axis (Figure 7**)** were formed by hydrogen-bonding cyclic $R_1^2(6)$ [$R_1^2(6)$: −C13−C6−H6···O2···H14−C14−, O2···H14−C14: 3.413 Å, 152.58° and O2···H6−C6 3.449 Å, 96.19°], which arise from **an** oxygen atom of the squaric acid fragment (O2) and a hydrogen from different molecule.

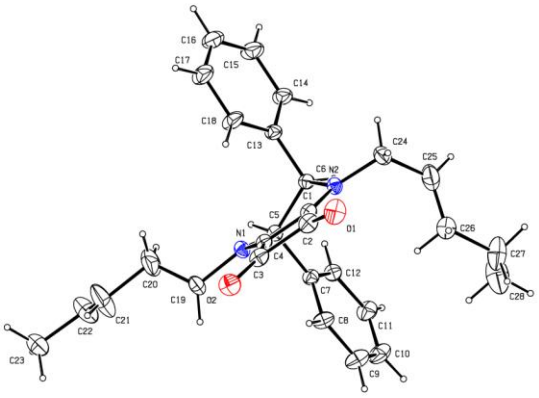


Figure 6. ORTEP diagram of **4c**. Displacement ellipsoids are drawn at the 50% probability level; hydrogen atoms are drawn at arbitrary size.

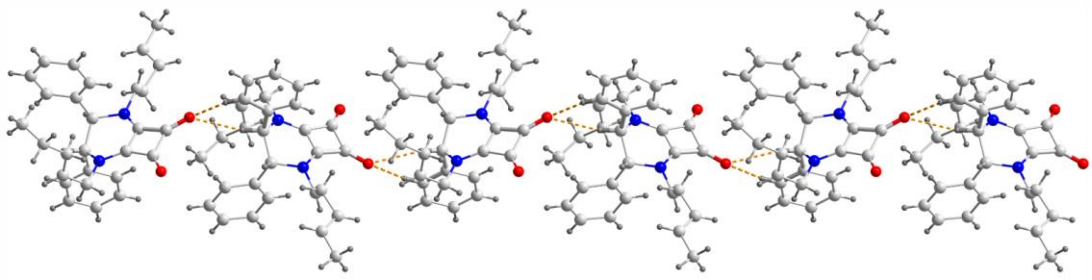


Figure 7. Supramolecular zig-zag and helix structure in **4c.** The hydrogen bonds are represented by dashed lines.

Compound **4d** crystallizes in the orthorhombic space group $C222_1$. An ORTEP diagram is given in Figure 8. An unusual conformation of the benzyl moiety was observed, in which four phenyl groups are alternately arrayed above or below the 1,4−diaza six-membered ring. The conformation of the benzyl group at N1 is very close to the benzyl ring below (CH···C_{phenyl} = 2.683 Å) enabling it to form the CH···π interaction. These geometries are consistent with the corresponding theoretical values (φ = 68−93º; CH···π = 2.6−2.8 Å) in a series of benzyl ethers reported previously.[22] Thus, the corresponding H···C distance of 2.683 Å in **4d**, indicating a strong CH···π interaction, and the formation of helix chains through this interaction are observed (Figure 9).

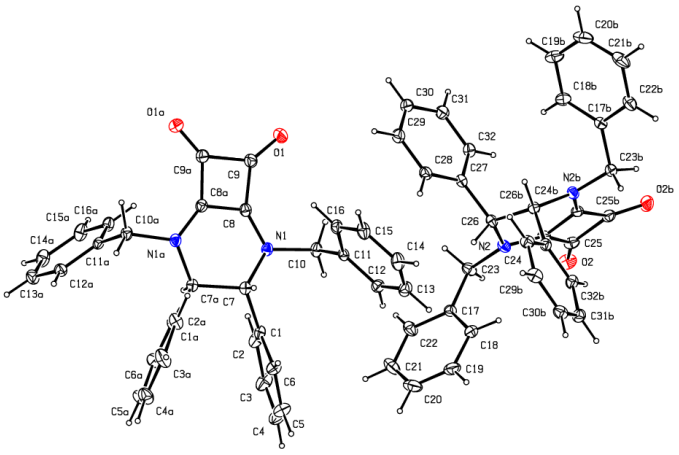


Figure 8. ORTEP diagram of **4d**. Displacement ellipsoids are drawn at the 50% probability level; hydrogen atoms are drawn at arbitrary size. Symmetry related atoms are labeled with "a".

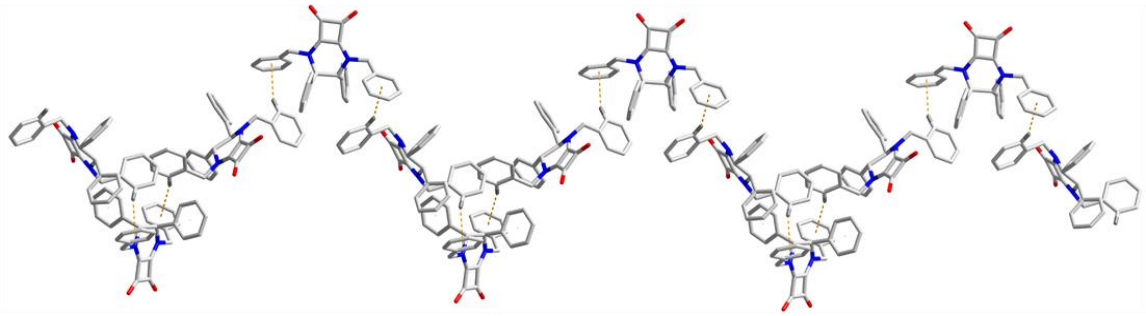


Figure 9. Infinite 1D helix chains conneted by C–H···π (orange dashed line)

Chiral cyclic squaramides 3, 4 and 6 in catalyzed organic reactions.

In the literature,[23] chiral macrocyclic tetra- and hexamine macrocycles derived from *trans*-1,2-diaminocyclohexane (DACH) in complexes with diethylzinc efficiently catalyze the asymmetric hydrosilylation of aryl alkyl ketones with enantiomeric excesses up to 89%. A copper(II) complex of C_2-symmetric cyclic diamine has also been proved to be an efficient catalyst for the enantioselective Henry reaction between nitroalkanes and various aldehydes.[24] In view of these results, showing that chiral cyclic amines are useful catalysts for a number of organic transformations, and in continuation of our interest in developing new ligands for asymmetric catalytic reactions, we were intrigued with the possibility of developing chiral cyclic squaramides containing an inexpensive enantiomerically pure diamine. Indeed, our primary study showed that some of squaramides derived chiral diamine skeleton catalyzed the addition of diethylzinc to aldehyde with modest enantioselectivity.[25]

Here we present the reactivities of chiral cyclic squaramides **3**, **4** and **6** in the asymmetric addition of diethylzinc to aldehydes. In order to find suitable conditions for using these ligands,

we briefly optimized their use by changing the solvent and temperature, as well as the catalyst loading (Table 1), and found that in the addition of diethylzinc to aldehyde with 10 mol% **3**, the use of 4 equivalents of diethylzinc in dicloromethane at –78 to r.t. provided a good yield and modest selectivity (Table 1, entry 6). Only enatioselectivity (40% ee), comparable to our previous result (Table 1, entry 4)[25] was obtained at lower temperature.

The optimized conditions were then used to assess the effectiveness of several related chiral squaramides. However, it was found that the chiral squaramides **4a-d**, derived from the alkylation of **3**, afforded the product in low yield, provided no enantioselectivity (Table 1, entries 12-15), which implied that the hydrogen bond might play a key role in the asymmetric addition. Furthermore, catalyst **6** having the twelve-membered ring core structure was examined, and was found to provide an inferior result compared to the six-membered cyclic squaramide **3** (entry 16).

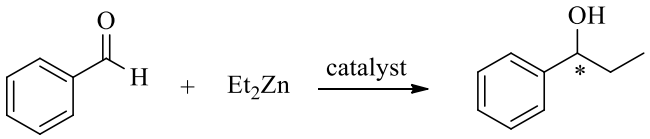


Table 1. Asymmetric addition of diethylzinc to benzaldehyde catalyzed by **3**, **4a-d** and **6**

Entry	Solvent	Ligand (%)	Et_2Zn	T (ºC)	Time (h)	Yield (%)[a]	Ee (%)[b]	Config.[c]
1	CH_2Cl_2	**3** (10)	3 eq	0~r.t	24	46	22	(*R*)
2	CH_2Cl_2	**3** (10)	3 eq	-20~ r.t	24	33	23	(*R*)
3	CH_2Cl_2	**3** (10)	3 eq	r.t	24	58	18	(*R*)
4	CH_2Cl_2	**3** (10)	2 eq	-78~ -20	24	12	40	(*R*)
5	CH_2Cl_2	**3** (10)	2 eq	-78~ r.t	24	16	16	(*R*)
6	**CH_2Cl_2**	**3 (10)**	**4 eq**	**-78~ r.t**	**24**	**43**	**27**	**(*R*)**
7	Toluene	**3** (10)	4 eq	-78~ r.t	24	46	24	(*R*)
8	THF	**3** (10)	4 eq	-78~ r.t	24	25	17	(*R*)
9	CH_2Cl_2	**3** (20)	4 eq	-78~ r.t	24	34	23	(*R*)
10	CH_2Cl_2	**3** (30)	4 eq	-78~ r.t	24	33	21	(*R*)
11	CH_2Cl_2	**3** (10)	4 eq[d]	-78~ -20	24	77	6	(*R*)
12	CH_2Cl_2	**4a** (10)	4 eq	-78~ r.t	24	13	-	-
13	CH_2Cl_2	**4b** (10)	4 eq	-78~ r.t	24	16	-	-
14	CH_2Cl_2	**4c** (10)	4 eq	-78~ r.t	24	17	-	-
15	CH_2Cl_2	**4d** (10)	4 eq	-78~ r.t	24	19	-	-
16	CH_2Cl_2	**6** (10)	4 eq	-78~ r.t	24	35	14	(*R*)

[a]Determined by HPLC using OD-H column. [b]Isolated products. [c]Determined by measurement of the specific rotation and comparison with an authentic sample. [d]One equivalent of $Ti(O\text{-}i\text{-}Pr)_4$ was added.

To demonstrate the influence of electronic and steric effects of the substrate in this asymmetric addition, a series of different aryl aldehydes were evaluated for ligand **3** and the results are summarized in Table 2. There was no apparent trend observed for the influence of substituent in the aryl aldehydes. The substrate with an electron-withdrawing groups afforded enantioselectivity at lower rate (entries 1 and 2). The aryl aldehyde with an electron-donating group (methoxy group) in the *para*-position of phenyl ring afforded no enantioselectivity (entry 5), but in the *meta*-positions gave the product in 8% ee (entry 3).

Table 2. Asymmetric addition of diethylzinc to substituted aldehydes catalyzed by **3**[a]

Entry	Aldehyde	Yield (%)[b]	Ee (%)[c]	ConFigure[d]
1	*p*-Florobenzaldehyde	33	16	(*R*)
2	*p*-Bromobenzaldehyde	26	9	(*R*)
3	*o*-Methoxybenzaldehyde	45	8	(*R*)
4	*o*-Bromobenzaldehyde	58	0	(*R*)
5	*p*-Methoxybenzaldehyde	46	0	(*R*)

[a]Unless otherwise specified, the reaction was carried out with 1 mmol of aldehyde and 4 mmol of diethylzinc, 0.1 mmol of **3** in 3 mL dicloromethane at -78~ r.t for 12 h. [b]Isolated products. [c]Determined by HPLC using OD-H column. [d]Determined by measurement of the specific rotation and comparison with an authentic sample.

Conclusions

In summary, we report the synthesis and structural analysis of two series of chiral cyclic squaramides, a six-membered squaramide **4** and a twelve-membered squaramide **6**, based on the cyclobutenedione structure, and containing an (1*R*,2*R*)-1,2-diphenylethylenediamine as the chiral element. For the first time the crystal structure of six-membered ring chiral cyclic squaramides is reported. Although there is no active proton, i.e. proton of an amide, in ligands **4a-d**, supramolecular helix chains are obtained in all cases, formed by C–H···O moderate intermolecular hydrogen bonding or relatively strong CH···π interaction, suggesting that the H-bonding acceptor or CH···π interaction ability of tertiary squaramides can be used as a synthon in crystal engineering in the future. As a first example of their application, these novel ligands were tested in the enantioselective addition of diethylzinc to aldehyde. Although the control of enantioselection of the reaction was modest, future modifications of the system based on this scaffold are now on course in our laboratories and will be reported in the future. These results may open a new way for the design and synthesis of novel chiral cyclic ligands derived from squaric acid for asymmetric reactions and also open new applications for crystal engineering.

Experimental Section

General. Tetrahydrofuran, diethyl ether and toluene were dried over Na/benzophenone, dichloromethane was dried over CaH_2 and distilled prior to use. Glassware was oven-dried, assembled while hot, and cooled under an inert atmosphere. Unless otherwise noted, all reactions were conducted in an inert atmosphere. Reaction progress was monitored using analytical thin-layer chromatography (TLC) on 0.25 mm Merck F-254 silica gel glass plates. Visualization was achieved by either UV light (254 nm). Flash chromatography was performed with silica gel (Merck, 230-400 mesh). Unless otherwise specified, all NMR spectra were recorded using $CDCl_3$ as the solvent with reference to residual $CHCl_3$ (^1H at 7.24 ppm and ^{13}C at 77.0 ppm). Optical rotations were measured at room temperature on a Perkin–Elmer 241MC automatic polarimeter (concentration in g/100 mL). Melting points were obtained on a micro-melting apparatus and the data were uncorrected. Elemental analyses (C, H, N) were carried out on a VarioEL III (German) instrument. Determination of % ee was achieved using a chiral HPLC equipped with a chiralpak OD-H column with 99:1 *n*-hexane: 2-propanol as the mobile phase at a flow rate of 1 mL/min.

(3*R*,4*R*)-3,4-Diphenyl-2,5-diazabicyclo[4.2.0]oct-1(6)-ene-7,8-dione (3). To a solution of diethyl squarate **2** (170 mg, 1 mmol) in 10 mL ethanol was added dropwise a solution of (1*R*,2*R*)-1,2-diphenylethylenediamine **2** (212 mg, 1 mmol) in 10 mL ethanol over 3 h by refluxing, and the reaction was heated at reflux for a total of 24 h. After the reaction was complete, the reaction mixture was poured into water (15 mL) and extracted with EtOAc (2 × 25 mL). The organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the concentrated filtrate by flash column chromatography on silica gel (40% EtOAc/hexane) gave product as a light-yellow needle in 75% yield; further purification was effected by recrystallization. mp 314-316 °C, $[\alpha]_D^{20} = 46.7°$ (*c* 0.5, EtOH), IR (ν_{max}, cm^{-1}): 3143 (NH), 3004 (ArH), 2883 (CH) and 1795 (C=O). ^1H NMR（400 MHz, $CDCl_3$), δ_H 4.32 (s, 2 H, 2 × C*H*), 6.33 (s, 2 H, 2 × N*H*), 6.94-7.30 (m, 10 H, 2 × Ar*H*) ppm. ^{13}C NMR (100 MHz, acetone-d_6), δ_C 61.97, 127.92, 128.29, 128.42, 137.93, 170.12, 180.90 ppm. MS (*m/z*): 290 (M^+, 60%). Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65%. Found: C, 74.50; H, 4.89; N, 9.59%.

General procedure for the synthesis of (4a-d)

To a solution of (3*R*,4*R*)-3,4-diphenyl-2,5-diaza-bicyclo[4.2.0]oct-1(6)-ene-7,8-dione **3** (290 mg, 1 mmol) in anhydrous DMF (5 mL) was added potassium carbonate (431 mg, 3 mmol) followed by the haloalkyl reagent (3 mmol), and the reaction was stirred for 24 h at room temperature. The reaction mixture was poured into water (5 mL) and extracted with EtOAc (2 × 20 mL). The organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the concentrated filtrate by flash column chromatography

on silica gel (40% EtOAc/hexane) gave product; further purification was effected by recrystallization.

(3*R*,4*R*)-2,5-Dimethyl-3,4-diphenyl-2,5-diazabicyclo[4.2.0]oct-1(6)-ene-7,8-dione (4a). Obtained by the reaction of **3** with methyl iodide. Colorless flakes. 83% yield, mp 260-262 °C, $[\alpha]_D^{20}$ = 93° (*c* 0.3, CH_2Cl_2), IR (ν_{max}, cm^{-1}): 3034 (ArH), 2911 (CH) and 1788 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 3.01 (s, 6H, 2 × C*H*$_3$), 4.27 (s, 2H, 2 × C*H*), 7.02-7.32 (m, 10H, 2 × Ar*H*) ppm. ^{13}C NMR (100Hz, $CDCl_3$), δ_C 36.48, 68.89, 126.76, 129.04, 129.43, 137.27, 167.87, 180.13 ppm. MS (*m/z*): 340.9.

(3*R*,4*R*)-2,5-Diisopropyl-3,4-diphenyl-2,5-diazabicyclo[4.2.0]oct-1(6)-ene-7,8-dione (4b). Obtained by the reaction of **3** with isopropyl bromide. Pale yellow flakes. 61% yield, mp 232-234 °C, $[\alpha]_D^{20}$ = 67° (*c* 0.3, CH_2Cl_2), IR (ν_{max}, cm^{-1}): 3061 (ArH), 2976 (CH) and 1791 (C=O). ^{1}H NMR（400 MHz, $CDCl_3$), δ_H 1.07-1.10（dd, *J* = 4.0, 8.0 Hz, 12H, 4 × C*H*$_3$), 3.66-3.72 (m, 2H, 2 × C*H*), 4.58 (s, 2H, 2 × C*H*), 7.18-7.43 (m, 10H, 2 × Ar*H*) ppm. ^{13}C NMR (100Hz $CDCl_3$), δ_C 22.22, 54.12, 67.78, 126.00, 128.63, 129.25, 140.14, 167.15, 179.07 ppm. MS (*m/z*): 396.8.

(3*R*,4*R*)-2,5-Di-*n*-pentyl-3,4-diphenyl-2,5-diazabicyclo[4.2.0]oct-1(6)-ene-7,8-dione (4c). Obtained by the reaction of **3** with *n*-pentyl bromide. Yellow flakes. 83% yield, mp 109-111 °C, $[\alpha]_D^{20}$ = 54° (*c* 0.3, CH_2Cl_2), IR (ν_{max}, cm^{-1}): 3054 (ArH), 2929 (CH) and 1793 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 0.61-0.64 (t, *J* = 7.12 Hz, 6H, 2 × C*H*$_3$), 0.82-1.56 (m, 12H, 6 × C*H*$_2$), 2.97-3.65 (m, 4H, 2 × C*H*$_2$), 4.47 (s, 2H, 2 × C*H*), 7.10-7.35 (m, 10H, 2-Ar*H*) ppm. ^{13}C NMR (100Hz, $CDCl_3$), δ_C 13.77, 22.10, 27.65, 28.19, 49.65, 67.35, 126.20, 128.83, 129.34, 138.14, 167.85, 179.65 ppm. MS (*m/z*): 452.8. HRMS (ESI): Calcd for $C_{28}H_{34}N_2O_2$ $[M+Na]^+$ = 453.2518. Found: 453.25122.

(3*R*,4*R*)-2,5-Dib*e*nzyl-3,4-diphenyl-2,5-diazabicyclo[4.2.0]oct-1(6)-ene-7,8-dione (4d). Obtained by the reaction of **3** with benzyl bromide. Yellow flakes. 89% yield, mp 146-148 °C, $[\alpha]_D^{20}$ = 62° (*c* 0.3, CH_2Cl_2), IR (ν_{max}, cm^{-1}): 3022 (ArH), 2923 (CH) and 1791 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 4.0 (s, 4H, 2 × C*H*$_2$), 4.97 (s, 2H, 2 × C*H*), 6.73-7.29 (m, 20H, 4 × Ar*H*) ppm. ^{13}C NMR (100Hz, $CDCl_3$), δ_C 52.64, 65.67, 126.72, 128.28, 128.68, 129.18, 133.98, 136.38, 168.10, 180.11 ppm. MS (*m/z*): 493.0. HRMS (ESI): Calcd for $C_{32}H_{26}N_2O_2$ $[M+Na]^+$ = 493.1892. Found: 493.18859.

(3*R*,4*R*,11*R*,12*R*)-3,4,11,12-Tetraphenyl-2,5,10,13-tetraazatricyclo[12.2.0.0^{6,9}]hexadeca-1(14),6(9)-diene-7,8,15,16-tetraone (6). To a solution of di-*n*-butyl squarate **5** (226 mg, 1 mmol) in 50 mL *n*-butanol was added dropwise a solution of (1*R*,2*R*)-1,2-diphenylethylenediamine **2** in 50 mL ethanol over 3 h by refluxing, and the reaction was then heated at reflux for a total of 24 h. After the reaction was complete, the reaction mixture was poured into water (15 mL) and extracted with EtOAc (2 × 25 mL). The organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the concentrated filtrate by flash column chromatography on silica gel (40% EtOAc/hexane) gave product as a light-yellow solid; further purification was effected by recrystallization. 10% yield. mp 117-119 °C, $[\alpha]_D^{20}$ = 15° (*c* 1, CH_2Cl_2), IR (ν_{max}, cm^{-1}): 3055 (ArH), 2919 (CH) and 1791 (C=O). ^{1}H NMR（400 MHz, $CDCl_3$), δ_H 4.76 (s, 4 H, 4 × C*H*), 4.97

(s, 4 H, 4 × N*H*), 7.19-7.23 (m, 20 H, 4 × Ar*H*) ppm. ^{13}C NMR (100Hz, $CDCl_3$), δ_C 62.69, 127.30, 128.85, 129.06, 136.01, 158.58, 196.44 ppm. MS (*m/z*): 580 (M^+, 10%). Anal. Calcd for $C_{36}H_{28}N_4O_4$: C, 74.47; H, 4.86; N, 9.65%. Found: C, 74.46; H, 4.88; N, 9.60%.

Typical procedure for the asymmetric addition of Et_2Zn to aldehydes

Diethylzinc (4 mmol, 4 mL, 1 M solution in hexanes) was added to a solution of chiral ligand (10 mol%) in dry dichloromethane (3 mL) at the appropriate temperature under an atmosphere of argon. After 30 min, to the reaction mixture was added aldehyde (1 mmol). The mixture was warmed to room temperature and stirred for the appropriate time (Tables 1 and 2). The reaction was quenched with a saturated solution of ammonium chloride (5 mL). The reaction mixture was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by the column chromatography using appropriate eluents (hexane/ethyl acetate). The ees were determined with HPLC using OD-H Chiralcel column.

Single-crystal structure determination

Single-crystal X-ray diffraction intensities for complexes **4a-d** were measured on a Bruker Smart APEX CCD-based diffractometer equipped with a graphite crystal monochromator for data collection at 292(2) K. The determinations of unit cell parameters and data collections were performed with Mo-Ka radiation (λ = 0.71073 Å), and unit cell dimensions were obtained with least-squares refinements. The program Bruke SAINT7 was used for reduction date. All structures were solved by direct methods using SHELXS-97 (Sheldrick, 1990) and refined with SHELXL-97 (Sheldrick, 1997);[26] non-hydrogen atoms were located in successive difference Fourier syntheses. The final refinement was performed by full matrix least-squares methods with anisotropic thermal parameters for non-hydrogen atoms on F^2. The hydrogen atoms were treated by a mixture of independent and constrained refinement. Relevant crystallographic structure data and refinement details are presented in Table S1 in supplementary section.

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21. Crystallographic data (excluding structure factors) for compounds **4a-d** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 783602-783605, respectively. Copies of the data can be

obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (44) 01223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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