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Design, synthesis and structure of new chiral squaric acid monoaminoalcohols and diaminoalcohols and their use as catalysts in asymmetric reduction of ketones and diketones[☆]

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Abstract—Many chiral squaric acid aminoalcohols and C_2-symmetric diaminoalcohols have been synthesized and their in situ formed chiral boron heterocycles have been used as catalysts for the enantioselective reduction of prochiral ketones and diketones by borane to give alcohols with up to 99% enantiomeric excess and 99% yield. The effects of solvent, catalyst–substrate ratio and temperature were also investigated. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The reduction of ketones to enantiomerically enriched alcohols remains a fundamental asymmetric transformation.[2] Many asymmetric catalysts have been developed for the reduction of ketones by borane, and the most significant catalyst, oxazaborolidines, have been extensively reviewed.[3] However, in this regard, most of the ligands are derived from natural compounds such as amino acids,[4] camphor[5] etc. and in many cases these ligands are usually based on the basic amino alcohol skeleton and are inconvenient to modify for a practical purpose. From a practical point of view, it is important to develop effective and versatile chiral ligands that are easy to modify so that highly enantioselective catalysts can be screened. Recently, some chiral aminoalcohols containing electron-withdrawing groups such as phosphosphinamidoalcohols[6] and sulfonamidoalcohols[7] were developed and successfully used as bifunctional catalysts[8] in the enantioselective reduction of ketones using borane. However, the reactive intermediate(s) involved in these catalytic reactions remain poorly understood and in most cases enantioselectivity needs a further improvement. In order to find highly effective and stereoselective catalysts, we initiated a study to develop new bifunctional ligands.

Squaric acid has long been known as an aromatic compound with unique character and wide applications.[9] Based on the cyclobutenedione structure, the acidic hydroxyl groups can be replaced by various functional groups so that versatile chiral ligands can be conveniently prepared. However, to the best of our knowledge, previous synthesis of chiral derivatives of squaric acid was rare.[10] Herein, we wish to report our work on the synthesis of two types of versatile new chiral ligands, monoaminoalcohols and C_2-symmetric diaminoalcohols of squaric acid, and a procedure for their use as improved catalysts in asymmetric carbonyl reduction. The advantages of the structures are that the rigid ring of squaric acid can be attached to either one or two chiral amino alcohols and, at the same time, the rigid ring moiety provides an efficient chiral environment for coordination of the substrate as well as the reagent in the reaction. The squaric acid monoaminoalcohols can serve as prototypical examples of bifunctional catalysts, since the C-3 position of the squaric acid ring can be conveniently modified by introducing a second functional group, which can preferentially coordinate with the borane. Furthermore, the intramolecular delivery of hydride to the carbonyl group may proceed in a highly selective manner by changing the size of the C-3 substituent. The C_2-symmetric squaric acid diaminoalcohols have two catalytic centers, which may serve as bifunctional catalysts for the reduction of prochiral ketones, especially diketones.

[☆] See Ref. 1.

Keywords: asymmetric synthesis; enantioselective reduction; squaric aminoalcohol and diaminoalcohols; prochiral ketones and diketones.

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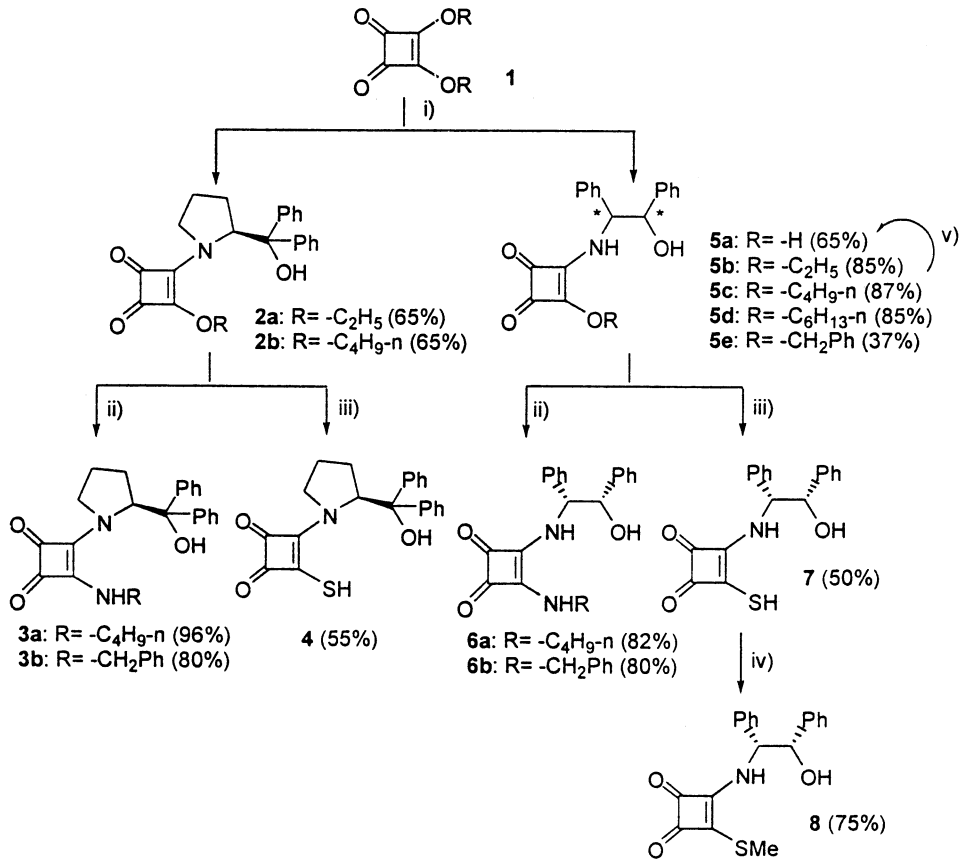


Scheme 1. *Reaction conditions*: (i) diester squarate/β-amino alcohols/Et_3N=1.1:1:1, EtOH. (ii) RNH_2, EtOH. (iii) NaHS, HCl, EtOH. (iv) K_2CO_3, CH_3I, CH_3COCH_3. (v) 2N HCl, EtOH, reflux.

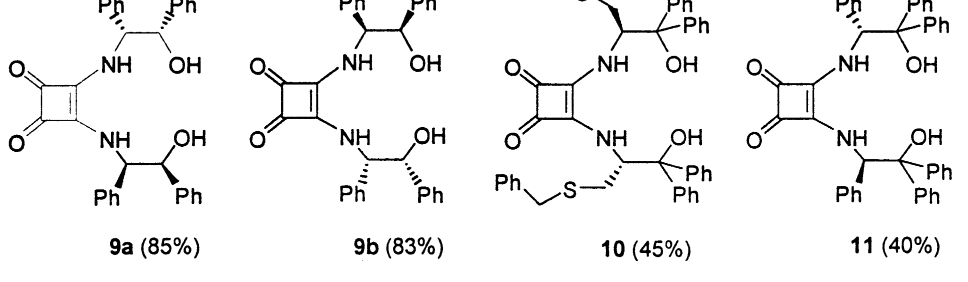
2. Results and discussion

2.1. Synthesis and characterization of ligands

Two types of chiral squaric acid aminoalcohols were derived from squaric acid diester **1** and β-amino alcohols as shown in Scheme 1. Squaric acid aminoalcohols **2** and **5** were prepared by the reaction of chiral aminoalcohols with a slight excess of squaric acid diesters in the presence of triethylamine in ethanol or ether at ambient temperature. Aminoalcohol **5a** was obtained when the ester group of **5c** was hydrolyzed. In order to investigate the effect of the substituent at C-3 of squaric acid on the reduction, we introduced other heteroatoms such as nitrogen or sulfur to this site. The amino substituted squaric acid aminoalcohols **3** and **6** can be prepared from the ammonolysis of **2b** and **5c**, respectively. Unlike the ligands **3** and **6**, the alkylthio squaric acid aminoalcohol **8** could not be prepared directly by reacting alkylthioalcohols with squaric acid aminoalcohol esters, which only led to a complex result.[11] An alternative method was used, reactions of thio-sqauric acid **7** with methyl iodide in the presence of K_2CO_3 gave the aminoalcohol **8**. The squaric acids **4** and **7** were prepared by the reactions of **2b** and **5c** with aqueous sodium thiolate followed by the treatment with hydrochloric acid.

C_2-symmetric squaric acid diaminoalcohols **9**–**11** can be conveniently prepared by the reaction of 2 equiv. of β-amino alcohols with squaric acid diester **1** (Scheme 2).

All of the new ligands were characterized by IR, ^1H NMR, MS and elemental analysis, the results conformed well with



Scheme 2.

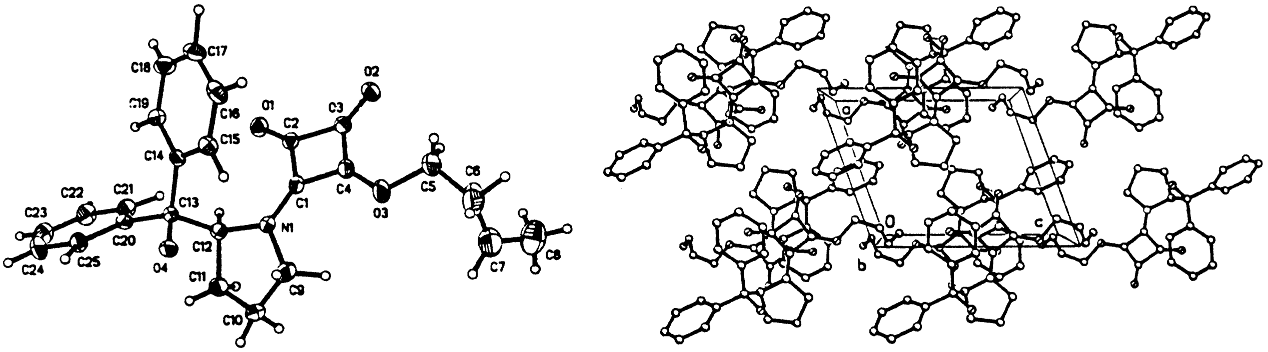


Figure 1. ORTEP drawing scheme and cell stacking for ligand **2b**.

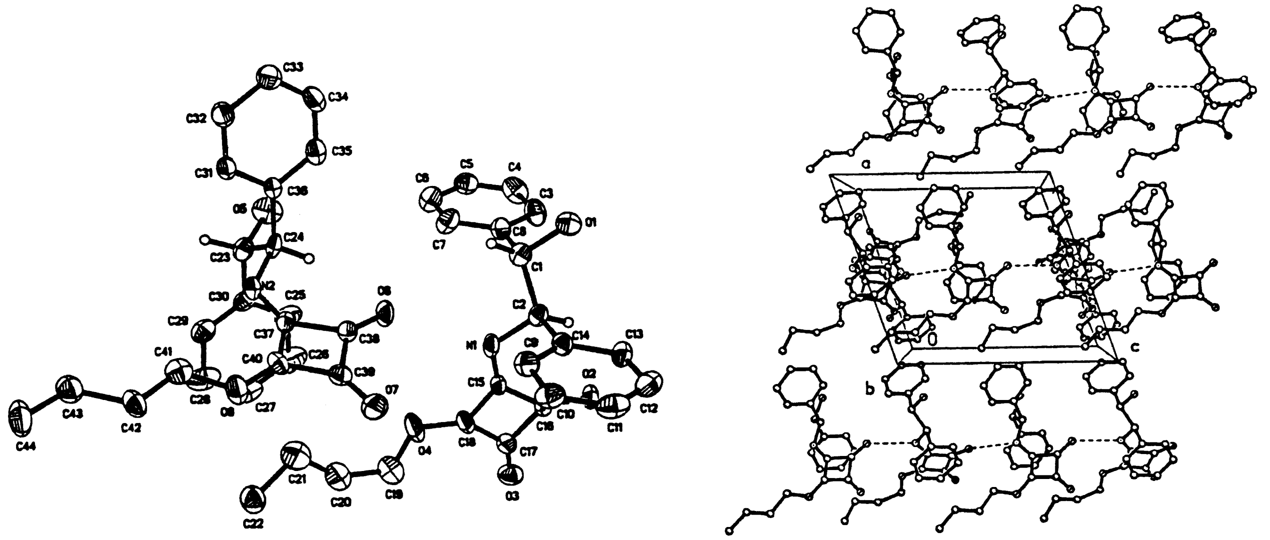


Figure 2. Crystal structure and cell packing of ligand (1′*R*,2′*S*)-**5c**.

the expected structures, in which the structures of ligands **2b**, (1′*R*,2′*S*)-**5b**,[12] (1′*R*,2′*S*)-**5c** and (1′*S*,2′*R*)-**5e** were also confirmed by X-ray analysis.

The main feature of the crystal packing in **2b** is that every two molecules are linked by O–H···O hydrogen bonds (Fig. 1). Similar to the crystal structure of the ligands (1′*R*,2′*S*)-**5b**, the structure determination (Fig. 2) of (1′*R*,2′*S*)-**5c** reveals that the unit cell contains two molecules with slightly different conformation. The molecules are linked by O–H···O and N–H···O hydrogen bonds to form a two-dimensional network. While for

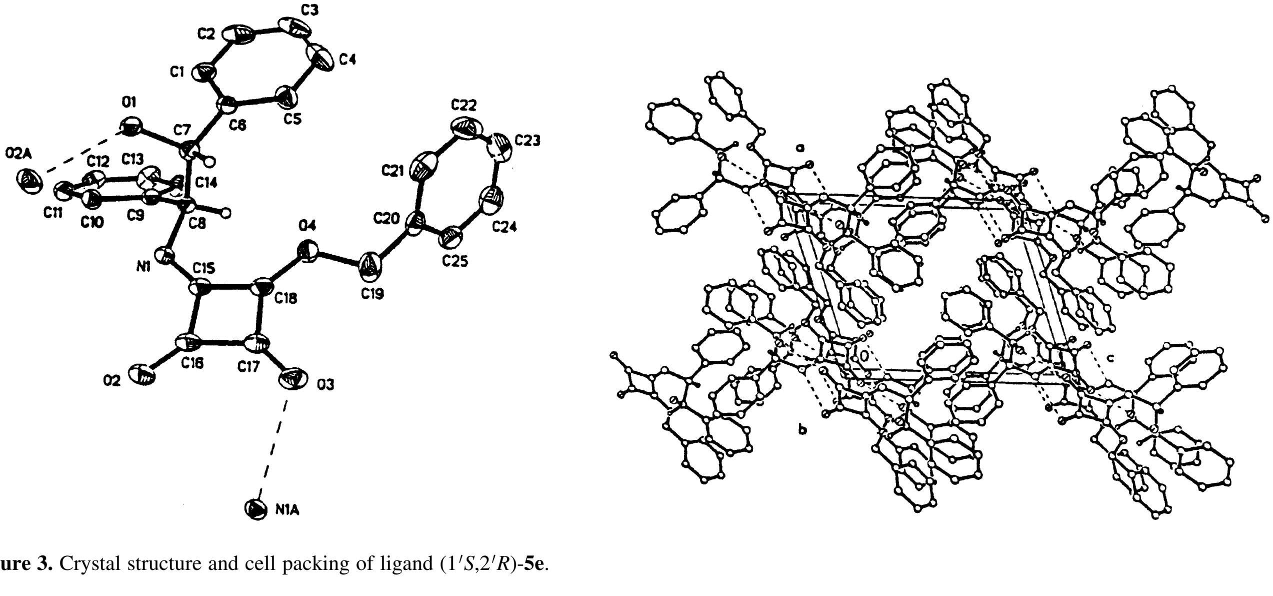


Figure 3. Crystal structure and cell packing of ligand (1′*S*,2′*R*)-**5e**.

compound **5e**, in which the amino alcohol moiety has opposite configuration and has a steric benzyl group at C-3 of squaric acid, the crystal structure has a large difference. The main feature of this crystal stacking is that both layers were hold together through π–π stacking effect of phenyls and squaric acid moieties. Every four molecules were linked by O–HO and N–HO hydrogen bonds within a layer and form a supramolecular system (Fig. 3).

Table 1. The enantioselective catalytic reduction of prochiral ketones with $BH_3 \cdot Me_2S$ by using 10 mol% of ligands **5–8**

Entry	Ligand	Solvent	Ketone	ee %[a]	Configuration[b]
1	(1′*R*,2′*S*)-**5a**	Toluene	$PhCOCH_2Br$	58	*R*
2	(1′*R*,2′*S*)-**5b**	Toluene	$PhCOCH_2Br$	61	*R*
3	(1′*R*,2′*S*)-**5c**	Toluene	$PhCOCH_2Br$	75	*R*
4	(1′*S*,2′*R*)-**5c**	Toluene	$PhCOCH_2Br$	75	*S*
5	(1′*R*,2′*S*)-**5d**	Toluene	$PhCOCH_2Br$	82	*R*
6	(1′*S*,2′*R*)-**5d**	Toluene	$PhCOCH_2Br$	82	*S*
7	(1′*R*,2′*S*)-**5e**	Toluene	$PhCOCH_2Br$	52	*R*
8	(1′*S*,2′*R*)-**5e**	Toluene	$PhCOCH_2Br$	52	*S*
9	**6a**	Toluene	$PhCOCH_2Br$	62	*R*
10	**6b**	Toluene	$PhCOCH_2Br$	62	*R*
11	**7**	Toluene	$PhCOCH_2Br$	76	*R*
12	**8**	THF	$PhCOCH_2Br$	57	*R*
13	**8**	CH_2Cl_2	$PhCOCH_2Br$	25	*R*
14	**8**	Toluene	$PhCOCH_2Br$	69	*R*
15	(1′*R*,2′*S*)-**5b**	Toluene	PhCOMe	52	*S*
16	(1′*R*,2′*S*)-**5c**	THF	PhCOMe	49	*S*
17	(1′*R*,2′*S*)-**5c**	CH_2Cl_2	PhCOMe	22	*S*
18	(1′*R*,2′*S*)-**5c**	Toluene	PhCOMe	61	*S*
19	(1′*R*,2′*S*)-**5d**	Toluene	PhCOMe	40	*S*
20	**6a**	Toluene	PhCOMe	52	*S*
21	**7**	Toluene	PhCOMe	63	*S*
22	**8**	Toluene	PhCOMe	52	*S*

Unless otherwise noted, all experiments were conducted at 50°C and the chemical yields were 85–100%.

[a] The ee values were determined by capillary GC analysis with a CP-cyclodex (0.25 mm×25 m) column.

[b] The product configuration was determined by comparison with an authentic sample.

2.1.1. Effect of the solvent.

On observing the effect of solvent on the reduction, it was found that toluene is the best solvent for the reduction. Lower ees were obtained when using dichloromethane or THF as solvent (Table 1, entries 12–14 and 16–18).

2.1.2. Effect of the temperature.

We carried out the reduction of ketones at various temperatures and the results are summarized in Table 2. The results indicate that the temperature has a critical effect on the reduction. The optimum reaction temperature was found to be about 50°C (entries 2 and 5). Either raising or lowering the temperature might lead to a decrease of the ee.

2.1.3. Effect of the catalyst–substrate ratio.

The molar ratio of the ligand to the substrate was also an important factor influencing the enantioselectivity of the resulting alcohol (Table 3), the optimum ligand-to-substrate ratio was about 10 mol% for monoaminoalcohols (entries 3, 5 and 8) and 5 mol% for diaminoalcohols (entry 11). Further increasing the amount of ligand led to a decrease of the ee. The reasons for these phenomena are the possibility of

Table 2. Effect of temperature on the enantioselective reduction of acetophenone

Entry	Ligand	Temperature (°C)	Solvent	Ketone	ee %[a]	Configuration[b]
1	(1′*R*,2′*S*)-**5b** (0.1)	30	Toluene	PhCOMe	43	*S*
2	(1′*R*,2′*S*)-**5b** (0.1)	50	Toluene	PhCOMe	52	*S*
3	(1′*R*,2′*S*)-**5b** (0.1)	70	Toluene	PhCOMe	42	*S*
4	(1′*R*,2′*S*)-**5c** (0.1)	30	Toluene	PhCOMe	45	*S*
5	(1′*R*,2′*S*)-**5c** (0.1)	50	Toluene	PhCOMe	61	*S*
6	(1′*R*,2′*S*)-**5c** (0.1)	70	Toluene	PhCOMe	47	*S*

The chemical yields were 85–100%.

[a] The ee values were determined by capillary GC analysis with a CP-cyclodex (0.25 mm×25 m) column.

[b] The product configuration was determined by comparison with an authentic sample.

Table 3. Effect of catalyst–substrate ratio on the enantioselective reduction of prochiral ketones

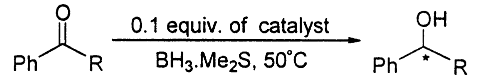
Entry	Ligand (equiv.)	Solvent	Ketone	ee %[a]	Configuration[b]
1	**2a** (0.025)	Toluene	$PhCOCH_2Br$	92	*S*
2	**2a** (0.05)	Toluene	$PhCOCH_2Br$	97	*S*
3	**2a** (0.1)	Toluene	$PhCOCH_2Br$	99	*S*
4	(1′*R*,2′*S*)-**5c** (0.05)	Toluene	PhCOMe	47	*S*
5	(1′*R*,2′*S*)-**5c** (0.1)	Toluene	PhCOMe	61	*S*
6	(1′*R*,2′*S*)-**5c** (0.15)	Toluene	PhCOMe	45	*S*
7	(1′*R*,2′*S*)-**5d** (0.05)	Toluene	$PhCOCH_2Br$	72	*R*
8	(1′*R*,2′*S*)-**5d** (0.1)	Toluene	$PhCOCH_2Br$	82	*R*
9	(1′*R*,2′*S*)-**5d** (0.15)	Toluene	$PhCOCH_2Br$	72	*R*
10	**9a** (0.025)	Toluene	$PhCOCH_2Br$	84	*R*
11	**9a** (0.05)	Toluene	$PhCOCH_2Br$	92	*R*
12	**9a** (0.1)	Toluene	$PhCOCH_2Br$	84	*R*

Unless otherwise noted, all experiments were conducted at 50°C and the chemical yields were 85–100%.

[a] The ee values were determined by capillary GC analysis with a CP-cyclodex (0.25 mm×25 m) column.

[b] The product configuration was determined by comparison with an authentic sample.

Table 4. The enantioselective catalytic reduction of prochiral ketones with $BH_3{\cdot}Me_2S$ by using 10 mol% of ligands **2**–**4** at 50°C in toluene



Entry	Ligand	Ketone	ee %[a]	Configuration[b]
1	**2a**	$PhCOCH_2Br$	99	*S*
2	**2b**	$PhCOCH_2Br$	98	*S*
3	**3a**	$PhCOCH_2Br$	94	*S*
4	**3b**	$PhCOCH_2Br$	96	*S*
5	**4**	$PhCOCH_2Br$	99	*S*
6	**2a**	PhCOMe	97	*R*
7	**3b**	PhCOMe	94	*R*
8	**4**	PhCOMe	95	*R*

The chemical yields were 85–100%.

[a] The ee values were determined by capillary GC analysis with a CP-cyclodex (0.25 mm×25 m) column.

[b] The product configuration was determined by comparison with an authentic sample.[14]

forming multinuclear aggregates of achiral catalysis in the reaction system.[13]

2.2. Effect of the structure of ligands on the enantioselectivity of the asymmetric reduction

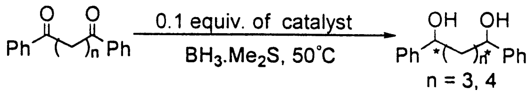
In order to examine the effect of the structure of the catalysts on the reaction, enantioselective reduction of prochiral ketones by borane were conducted at 50°C in the presence of a catalytic amount (10 mol%) of various squaric acid aminoalcohols. Almost all catalysts afforded product alcohols in over 90% synthetic yields. The results indicated that the ligand structure is critical for enantioselectivity in the reduction. Catalysts **2**–**4** which possess a rigid pyrrolidinylmethanol moiety always gave high enantioselectivities, up to 99% yield and 99% ee were obtained in the reduction of ω-bromo-acetophenone with ligands **2a**, **2b** and **4** (Table 4, entries 1, 2 and 5). The ligands **3** gave a slightly lower ee, in the reduction of ω-bromo-acetophenone, up to 94 and 96% ee were obtained by using **3a** and **3b**, respectively (entries 3 and 4).

Ligands **5**–**8** which possess flexible chiral 2-amino-1,2-diphenylethanol moiety exhibited moderate to good enantioselectivity in the reduction, and the substituents at C-3 of squaric acid have an effect on the ee of the resulting alcohols. In ligands **5a**–**d**, the ee values increase with the chain length of the alkoxy group (Table 1, entries 1–6). The lower ee by ligand **5e** might be due to the steric repulsion between the phenyl ring of ligand and the aryl ketone, which obstructs the latter from getting in close proximity to the catalytic center (entries 7 and 8). The use of butylamino squaric acid aminoalcohols **6** led to a decrease in ee (entries 9 and 10). The thiohydroxy squaric acid **7** gave an ee value comparable to **8**, in which a methylthio group is on the C-3 position (entry 11 and 14).

As expected, using the opposite enantiomers of the ligands gave alcohols with opposite configurations and essentially identical ees (Table 1, entries 3–8). The reduction of ω-bromo-acetophenone consistently gave higher ees as compared to the reduction of the acetophenone.

The enantioselective reduction of prochiral ketones and diketones catalyzed by bisoxazaborolidines is relatively rare.[15,16] Herein we report the results of our study of the use of C_2-symmetric squaric acid diaminoalcohols **9**–**11** in this enantioselective reaction (Table 5). The diaminoalcohols which have two catalytic centers seem particularly favorable in the enantioselective reduction of prochiral diketones: ees of up to 99% were obtained in the reduction of 1,6-diphenyl-1,6-hexanedione with 10 mol% of ligands **9** and **11** (entries 8, 9 and 13). In the reduction of ω-bromo-acetophenone, up to 92% ee was obtained with only 5 mol% of ligands **9a** and **9b** (entries 1 and 2). It is probably due to the co-operative effect of a bifunctional catalyst with the substrate or the enhanced rigid effect.

Table 5. The enantioselective reduction of prochiral ketones and diketones with $BH_3{\cdot}Me_2S$ catalyzed by diaminoalcohols of squaric acid



Entry	Ligand (equiv.)	Ketone	$[\alpha]_D^{20}$ (*c*, MeOH)	Meso/(*R*,*R*+*S*,*S*)	ee %[a]	Configuration[b]
1	**9a** (0.05)	$PhCOCH_2Br$			92[a]	*R*
2	**9b** (0.05)	$PhCOCH_2Br$			92[a]	*S*
3	**9a** (0.05)	PhCOMe			81[a]	*S*
4	**9a** (0.1)	$PhCOCH_2Br$			84[a]	*R*
5	**9b** (0.05)	PhCOMe			81[a]	*R*
6	**10** (0.1)	$PhCOCH_2Br$			35	*S*
7	**11** (0.1)	$PhCOCH_2Br$			82	*R*
8	**9a** (0.1)	$PhCO(CH_2)_4COPh$	−13.87 (1.5)	3/97	99[c]	(*S*,*S*)
9	**9b** (0.1)	$PhCO(CH_2)_4COPh$	+13.57 (1.5)	3/97	99[c]	(*R*,*R*)
10	**9a** (0.1)	$PhCO(CH_2)_3COPh$	−13.57 (1.5)	8/92	86[c]	(*S*,*S*)
11	**9b** (0.1)	$PhCO(CH_2)_3COPh$	+13.87 (1.5)	8/92	86[c]	(*R*,*R*)
12	**10** (0.1)	$PhCO(CH_2)_4COPh$	+7.87 (1.5)	18/82	61[d]	(*R*,*R*)
13	**11** (0.1)	$PhCO(CH_2)_4COPh$	−13.87 (1.5)	3/97	99[d]	(*S*,*S*)

Unless otherwise noted, all experiments were conducted at 50°C and the chemical yields were 85–100%.

[a] The ee values were determined by capillary GC analysis with a CP-cyclodex (0.25 mm×25 m) column.

[b] The product configuration was determined by comparison with an authentic sample.

[c] The ee% and *meso*% of chiral diols were determined by HPLC with Chiralpak AS column.

[d] The ee% and *meso*% of chiral diol were determined by HPLC with Whelk-01 column.

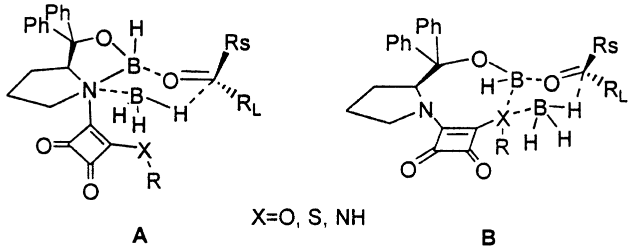


Figure 4. Postulated reactive complexes.

2.3. Possible mechanisms

One reactive intermediate proposed by Corey[14a] could be a clue to explain the mechanism of borane reduction catalyzed by squaric aminoalcohols **5**–**8**. The second BH_3 molecule coordinates with the nitrogen atom on the oxazaborolidine cycle to form the oxazaborolidine·BH_3 complex. We postulate the reactive complexes as the transition state model of the borane reduction catalyzed by squaric prolinols **2**–**4** shown in Fig. 4. Two possibilities such as **A** (Corey's mechanism[14a]) and **B** can be considered and further studies are underway. In **B**, because there is no hydrogen on the N atom of the prolinol and owing to the steric block of the squaric ring, it is likely that the borane molecule may combine with the heteroatom (such as nitrogen, oxygen or sulfur atom) at the C-3 position of the ligands to form an eight-membered boron heterocycle complex with both donor and acceptor groups which may interact with a molecule of BH_3 and ketone. Then the carbonyl compound will orient itself *anti* to the prolinol portion for steric reasons, the attack of hydride occurs through a six-membered cycle on the *si* face of the complexed ketone within a most reactive distance. So the absolute configuration of the product alcohol may be estimated in advance.

3. Experimental

Melting points were taken on a micro-melting apparatus and the data were uncorrected. Optical rotations were measured on a WZZ-1 polarimeter. IR spectra were measured on FT-IR 16PC infrared spectrophotometer with KBr disc. ^1H NMR spectra were recorded at Bruker DPX-400 MHz, Bruker DPX-300 MHz and Bruker AC-E 200 MHz and chemical shifts in ppm are reported relative to internal Me_4Si. Mass spectral data were recorded on a Finnigan MAT 4510 spectrometer. Elemental analyses were performed with Carlo Erba 1106 instrument. Column chromatography using SiO_2 (230–400 mesh). Dichloromethane, tetrahydrofuran and toluene were purified according to the standard methods. All other chemicals and reagents were obtained commercially and used without further purification.

3.1. General procedure for the synthesis of diesters of squaric acid 1

Squaric acid (1.1 mmol) was added to the alcohols (10 mL) and the mixture was refluxed for 3 h. Alcohol was removed to about 5 mL under vacuum and further alcohol (10 mL) were added and refluxed for 0.5 h. This procedure was repeated three times. Finally the alcohol was removed under reduced pressure as dry as possible. The resulting diesters were purified by flash chromatography (petroleum ether/ethyl acetate, 6:1) or directly used in the following procedure without purification.

3.2. General procedure for the synthesis of ligands 2 and 5b–5e

To a solution of squaric acid diester **1** (1.1 mmol) in dry ethanol or ether (10 mL) was added slowly a solution of β-amino alcohols (1.0 mmol) in ethanol or ether (10 mL) over 2–3 h at room temperature in the presence of triethylamine (1.0 mmol). The reaction was monitored by TLC and after completion (~24 h), the solvent was removed under reduced pressure. Further purification was achieved by either crystallization from ethanol (**5b**) or column chromatography (petroleum ether/ethyl acetate, 1:1).

3.2.1. 3-Ethoxy-4-[(2′*S*)-2′-(diphenylhydroxymethyl) pyrrolidino]-3-cyclobutene-1,2-dione 2a. Colorless flake. 65% yield. Mp 106–107°C. $[\alpha]_D^{20}=-175.3$ (*c* 0.8, CH_2Cl_2). IR ν: 3403, 3032, 2966, 2885, 1799, 1707, 1608, 1585 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 1.33 (t, J=7.2 Hz, 3H, CH_3), 2.04 (m, 2H, CH_2), 2.76 (m, 3H, CH_2), 3.33 (m, 2H, CH_2), 4.69 (q, J=7.2 Hz, 2H, CH_2O), 5.18 (s, 1H, CH), 7.24–7.54 (m, 10H, 2ArH). MS (EI) *m/z* 378 (M^++1, 30), 360, 195 (100). Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.18, H, 6.15, N, 3.71. Found: C, 73.01, H, 6.11, N, 3.66.

3.2.2. 3-Butoxy-4-[(2′*S*)-2′-(diphenylhydroxymethyl) pyrrolidino]-3-cyclobutene-1,2-dione 2b. Colorless flake. 65% yield. Mp 162–163°C. $[\alpha]_D^{20}=-184.0$ (*c* 0.5, CH_2Cl_2): IR ν: 3351, 3012, 2951, 2887, 1800, 1702, 1589 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.10 (m, 3H, CH_3), 1.56 (m, 2H, CH_2), 1.71–1.90 (m, 4H, $2CH_2$), 2.17–2.36 (m, 2H, CH_2), 3.34 (br, 1H, OH), 3.61–3.80 (m, 2H, CH_2), 4.85 (m, 2H, CH_2O), 5.31 (m, 1H, CH), 7.38–7.48 (m, 10H, 2ArH). MS (EI) *m/z*: 406 (M^++1, 30), 332, 223, 166 (100). Anal. Calcd for $C_{25}H_{27}NO_4$: C, 74.04, H, 6.72, N, 3.46. Found: C, 73.98, H, 6.68, N, 3.45.

3.2.3. 3-Ethoxy-4-[(1′*R*,2′*S*)-(2′-hydroxy-1′,2′-diphenylethyl)amino]-3-cyclobutene-1,2-dione 5b. Colorless flake. 75% yield. Mp 213–215°C. $[\alpha]_D^{20}=-76.8$ (*c* 1.0, THF). IR ν: 3392, 3262, 3012, 2963, 1807, 1694, 1605 cm^{-1}. δ_H (200 MHz, DMSO-d_6): 1.31 (q, J=7.5 Hz, 3H CH_3), 3.44 (m, 1H, OH), 4.51–4.67 (m, 2H, CH_2O), 4.84 (d, J=10.4 Hz, 1H, CH), 5.23–5.61 (m, 1H, CH), 7.28–7.41 (m, 10H, 2ArH), 9.10 (2d, J=9.7 Hz, 1H, NH). MS (EI) *m/z*: 406 (M^++1, 30), 332, 223, 166, 110. Anal. Calcd for $C_{20}H_{19}NO_4$: C, 83.05, H, 5.68, N, 4.15. Found: C, 82.78, H, 5.50, N, 3,97.

3.2.4. 3-Butoxy-4-[(1′*R*,2′*S*)-(2′-hydroxy-1′,2′-diphenylethyl)amino]-3-cyclobutene-1,2-dione 5c. Colorless flake. 85% yield. Mp 104–105°C. $[\alpha]_D^{20}=-100.0$ (*c* 1.0, EtOH). IR ν: 3437, 3232, 3018, 2963, 1804, 1691, 1610 cm^{-1}. δ_H (400 MHz, $CDCl_3$): 0.92 (s, 3H, CH_3), 1.33 (m, 2H, CH_2), 1.67 (m, 2H, CH_2), 3.31 (s, 1H, OH), 4.75 (m, 2H, CH_2O), 4.93 (m, 1H, CH), 5.24 (d, J=4.6 Hz, 1H, CH), 7.09–7.28 (m, 10H, 2ArH), 9.39–9.80 (m, 1H, NH). MS (EI) *m/z*: 365 (M^+, 15). Anal. Calcd for

$C_{22}H_{23}NO_4$: C, 72.29, H, 6.35, N, 3.84. Found: C, 72.54, H, 6.48, N, 3.69.

3.2.5. 3-Butoxy-4-[(1′*S*,2′*R*)-(2′-hydroxy-1′,2′-diphenylethyl)amino]-3-cyclobutene-1,2-dione 5c. Colorless flake. 87% yield. Mp 104–105°C. $[\alpha]_D^{20}=+102.0$ (*c* 1.0, EtOH). IR ν: 3390, 3268, 3010, 2962, 1806, 1698, 1600 cm^{-1}. δ_H (400 MHz, $CDCl_3$): 0.92 (s, 3H, CH_3), 1.30 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 3.27 (s, 1H, OH), 4.73 (m, 2H, CH_2O), 4.93 (m, 1H, CH), 5.23 (d, J=4.6 Hz, 1H, CH), 7.08–7.28 (m, 10H, 2ArH), 9.36–9.81 (m, 1H, NH). MS (EI) *m/z*: 365 (M^+, 20). Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.29, H, 6.35, N, 3.84. Found: C, 72.12, H, 6.21, N, 3.47.

3.2.6. 3-Hexyloxy-4-[(1′*R*,2′*S*)-(2′-hydroxy-1′,2′-diphenylethyl)amino]-3-cyclobutene-1,2-dione 5d. Pale yellow oil. 85% yield. $[\alpha]_D^{20}=-2.4$ (*c* 2.5, CH_2Cl_2). IR ν: 3402, 3265, 2931, 1805, 1704, 1600 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 0.86–0.96 (m, 3H, CH_3), 1.22–1.28 (br, 6H, $3CH_2$), 1.68 (m, 2H, CH_2), 2.51 (br, 1H, OH), 4.57–4.67 (m, 2H, CH_2O), 4.90 (m, 1H, CH), 5.25 (d, J=4.8 Hz, 1H, CH), 7.10–7.30 (m, 10H, 2ArH), 7.68 (m, 1H, NH). MS (EI) *m/z*: 394 (M^++1, 60). Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.24, H, 6.92, N, 3.56. Found: C, 73.16, H, 6.56, N, 3.78.

3.2.7. 3-Hexyloxy-4-[(1′*S*,2′*R*)-(2′-hydroxy-1′,2′-diphenylethyl)amino]-3-cyclobutene-1,2-dione 5d. Pale yellow oil. 85% yield. $[\alpha]_D^{20}=+2.4$ (*c* 2.5, CH_2Cl_2). IR ν: 3402, 3265, 2931, 1805, 1704, 1600 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 0.86–0.96 (m, 3H, CH_3), 1.22–1.28 (m, 6H, $3CH_2$), 1.68 (m, 2H, CH_2), 2.51 (br, 1H, OH), 4.57–4.67 (m, 2H, CH_2), 4.90 (m, 1H, CH), 5.25 (d, J=4.8 Hz, 1H, CH), 7.10–7.30 (m, 10H, 2ArH), 7.68 (br, 1H, NH). MS (EI) *m/z*: 394 (M^++1, 60). Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.24, H, 6.92, N, 3.56. Found: C, 73.16, H, 6.56, N, 3.78.

3.2.8. 3-Benzyloxy-4-[(1′*R*,2′*S*)-(2′-hydroxy-1′,2′-diphenylethyl)amino]-3-cyclobutene-1,2-dione 5e. Colorless prism. 32% yield. Mp 177–179°C. $[\alpha]_D^{20}=-94.3$ (*c* 0.5, EtOH). IR ν: 3441, 3169, 3002, 1805, 1706, 1598 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 2.93 (br, 1H, OH), 4.89 (s, 2H, CH_2), 5.17 (d, J=4.5 Hz, 1H, CH), 5.62 (s, 1H, CH), 6.99–7.30 (m, 15H, 3ArH), 7.36 (m, 1H, NH). MS (EI) *m/z*: 400 (M^++1, 5). Anal. Calcd for $C_{25}H_{21}NO_4$: C, 75.16, H, 5.30, N, 3.51. Found: C, 74.97, H, 5.15, N, 3.26.

3.2.9. 3-Benzyloxy-4-[(1′*S*,2′*R*)-(2′-hydroxy-1′,2′-diphenylethyl)amino]-3-cyclobutene-1,2-dione 5e. Colorless prism. 37% yield. Mp 177–179°C. $[\alpha]_D^{20}=+93.4$ (*c* 0.7, EtOH). IR ν: 3441, 3173, 3002, 1804, 1706, 1598 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 2.92 (br, 1H, OH), 4.88 (s, 2H, CH_2), 5.16 (d, J=4.5 Hz, 1H, CH), 5.60 (s, 1H, CH), 6.89–7.26 (m, 15H, 3ArH), 7.34 (m, 1H, NH). MS (EI) *m/z*: 401 (M^++2, 5). Anal. Calcd for $C_{25}H_{21}NO_4$: C, 75.16, H, 5.30, N, 3.51. Found: C, 75.01, H, 5.01, N, 3.46.

3.3. General procedure for the synthesis of ligands 3 and 6

To a solution of **2b** or **5c** (1.0 mmol) in ethanol (10 mL) was added amine (1.1 mmol) at room temperature for 24 h. Further purification of **3** was achieved by flash chromatography (petroleum ether/ethyl acetate, 1:4) and **7** was obtained by recrystallization from a mixture of ethanol and dichloromethane.

3.3.1. 3-Butylamino-4-[(2′*S*)-2′-(diphenylhydroxymethyl) pyrrolidino]-3-cyclobutene-1,2-dione 3a. Colorless flake. 96% yield. Mp 62–64°C. $[\alpha]_D^{20}=-159.7$ (*c* 0.72, AcOEt). IR ν: 3279, 3075, 1791, 1662, 1566, 1512 cm^{-1}. ^1H NMR ($CDCl_3$) δ_H: 0.93 (t, J=7.3 Hz, 3H, CH_3), 1.52–1.64 (m, 6H, $-CH_2-$), 3.68 (qd, J=6.7, 2.0 Hz, 2H, $-CH_2N-$), 3.77 (t, J=9.9 Hz, 2H, $-CH_2N-$), 5.10 (d, J=7.1 Hz, 1H, $-CHN-$), 5.86 (s, 1H, OH), 7.26–7.39 (m, 10H, ArH), 7.81 (d, J=7.1 Hz, 1H, NH). MS (EI) *m/z*: 405 (M^++1, 95). Anal. Calcd for $C_{25}H_{28}N_2O_3$: C, 74.23, H, 6.98, N, 6.93. Found: C, 74.67, H, 6.87, N, 6.89.

3.3.2. 3-Benzylamino-4-[(2′*S*)-2′-(diphenylhydroxymethyl) pyrrolidino]-3-cyclobutene-1,2-dione 3b. Flake. 80% yield. Mp 172–174°C. $[\alpha]_D^{20}=-210$ (*c* 1.15, CH_2Cl_2). IR ν: 3275, 1790, 1666, 1565, 1509 cm^{-1}. ^1H NMR (DMSO-d_6) δ_H: 0.93 (d, J=6.7 Hz, 2H, $-CH_2-$), 1.73–1.76 (m, 2H, $-CH_2-$), 1.89–2.14 (m, 2H, $-CH_2N-$), 3.67 (br, 2H, $-CH_2N-$), 4.69 (t, J=7.6 Hz, 1H, $-CHN-$), 5.92 (s, 1H, OH), 7.12–7.49 (m, 15H, ArH), 7.71 (d, J=9.8 Hz, 1H, NH). MS (EI) *m/z*: 440 (M^++2, 20). Anal. Calcd for $C_{28}H_{26}N_2O_3$: C, 76.69, H, 5.98, N, 6.39. Found: C, 76.47, H, 5.91, N, 6.29.

3.3.3. 3-Butylamino-4-[(1′*R*,2′*S*)-(2′-hydroxy-1′,2′-diphenylethyl)amino]-3-cyclobutene-1,2-dione 6a. White solid. 82% yield. Mp 262–264°C. $[\alpha]_D^{20}=+5.0$ (*c* 0.5, DMSO). IR ν: 3410, 3185, 2941, 1800, 1646, 1558 cm^{-1}. δ_H (200 MHz, DMSO-d_6): 0.91 (tr, J=7.5 Hz, 3H, $-CH_3$), 1.25–1.60 (m, 3H, 2-CH_2–), 3.40 (m, 3H, $-CH_2-$, OH), 5.03 (m, 1H, CH), 5.25 (m, 1H, CH), 7.12–7.28 (m, 10H, –ArH), 7.40 (s, H, –NH–), 7.80 (d, J=8.4 Hz, 1H, –NH–). MS (EI) *m/z*: 365 (M^++1, 30). Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50, H, 6.64, N, 7.69. Found: C, 72.61, H, 6.73, N, 7.54.

3.3.4. 3-Benzylamino-4-[(1′*R*,2′*S*)-(2′-hydroxy-1′,2′-diphenylethyl)amino]-3-cyclobutene-1,2-dione 6b. White solid. 80% yield. Mp 284–286°C. $[\alpha]_D^{20}=+17.0$ (*c* 0.5, DMSO). IR ν: 3412, 3182, 3052, 2936, 1794, 1638, 1569 cm^{-1}. δ_H (200 MHz, DMSO-d_6): 2.48 (m, 1H, OH), 4.71 (d, J=6.0 Hz, 2H, CH_2), 5.08 (m, 1H, CH), 5.34 (m, 1H, CH), 7.22–7.33 (m, 15H, 3ArH), 7.88–8.00 (m, 2H, 2NH). MS (EI) *m/z*: 395 (M^++1, 100). Anal. Calcd for $C_{25}H_{22}N_2O_3S$: C, 75.36, H, 5.57, N, 7.03. Found: C, 75.48, H, 5.52, N, 7.08.

3.4. General procedure for the synthesis of ligands 4 and 7

To a solution of **2b** or **5c** (1.0 mmol) in ethanol (10 mL) was added aqueous sodium hydrosulfide (1.1 mmol) dropwise at room temperature, the yellow solution was stirred for 3 h then treated with hydrochloric acid. The precipitate was filtered off and recrystallized from dichloromethane to afford **4** or **7** as pale yellow flakes.

3.4.1. 3-Mercapto-4-[(2′*S*)-2′-(diphenylhydroxymethyl) pyrrolidino]-3-cyclobutene-1,2-dione 4. Pale yellow flake. 55% yield. Mp 163–165°C. $[\alpha]_D^{20}=-82.0$ (*c* 0.7, EtOH). IR ν: 3446, 3064, 1774, 1662, 1563 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ_H: 1.98 (m, 2H, –CH$_2$–), 2.19 (m, 2H, –CH$_2$–), 3.86 (s, 2H, –CH$_2$N–), 4.00 (m, 1H, SH), 5.27 (br, 1H, –CHN–), 6.15 (s, 1H, OH), 7.18–7.50 (m, 10H, ArH). MS (EI) *m*/*z*: 366 (M^{+}+1, 37). Anal. Calcd for $C_{21}H_{19}NO_3S$: C, 69.04, H, 5.21, N, 3.84. Found: C, 68.87, H, 5.28, N, 3.90.

3.4.2. 3-Mercapto-4-[(1′*R*,2′*S*)-(2′-hydroxy-1′,2′-diphenylethyl)amino]-3-cyclobutene-1,2-dione 7. Pale yellow flake. 50% yield. Mp 182–183°C. $[\alpha]_D^{20}=+82.0$ (*c* 0.7, EtOH). IR ν: 3445, 3324, 3018, 1770, 1690, 1578 cm^{-1}. δ_H (200 MHz, C_3D_6O): 4.30 (s, 1H, SH), 4.94 (s, 1H, OH), 5.37 (s, 1H, CH), 5.59 (s, 1H, CH), 7.42–7.17 (m, 10H, 2ArH), 7.80 (s, 1H, NH). MS (EI) *m*/*z*: 326 (M^{+}+1, 45), 219 (M−106, 75). Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.45, H, 4.65, N, 4.31. Found: C, 66.36, H, 4.57, N, 4.29.

3.5. Procedure for the synthesis of ligand 8

To a dry one-necked, round-bottomed flask with **7** (1.0 mmol) was added acetone (10 mL), K_2CO_3 (0.5 mmol), the mixture was stirred at 40°C until the K_2CO_3 disappeared, then CH_3I (1.1 mmol) was added and the solution was stirred overnight at 40°C. After filtration to remove KI, the filtrate was evaporated under reduced pressure and the resulted residue was subjected to flash chromatography (petroleum ether/ethyl acetate, 2:1) to afford **8** as pale yellow flakes.

3.5.1. 3-Methylthio-4-[(1′*R*,2′*S*)-(2′-hydroxy-1′,2′-diphenylethyl)amino]-3-cyclobutene-1,2-dione 8. Pale yellow flake. 75% yield. Mp 211–212°C. $[\alpha]_D^{20}=-18.0$ (*c* 0.7, EtOH). IR ν: 3388, 3041, 2929, 1771, 1686, 1576 cm^{-1}. δ_H (200 MHz, DMSO-d_6): 2.32 (s, 3H, CH$_3$), 4.94 (s, 1H, OH), 5.34 (s, 1H, CH), 5.54 (s, 1H, CH), 7.09–7.18 (m, 10H, 2ArH), 7.75 (s, 1H, NH). MS (EI) *m*/*z*: 340 (M^{+}+1, 100). Anal. Calcd for $C_{19}H_{17}NO_3S$: C, 67.24, H, 5.05, N, 4.13. Found: C, 67.47, H, 5.01, N, 4.19.

3.6. Procedure for the synthesis of ligand 5a

5c (1 mmol) in the mixture of ethanol (10 mL) and 2N HCl (5 mL) was heated to reflux and the reaction was monitored by TLC. After completion (~10 h), the solvent was removed and the precipitate was recrystallized from a mixture of ethanol and dichloromethane (1:1) to afford fine colorless crystals.

3.6.1. 3-Hydroxy-4-[(1′*S*,2′*R*)-(2′-hydroxy-1′,2′-diphenylethyl)amino]-3-cyclobutene-1,2-dione 5a. 65% yield. Mp 208–210°C. $[\alpha]_D^{20}=+108.4$ (*c* 0.75, EtOH). IR ν: 3360, 3221, 3086, 1808, 1671, 1593 cm^{-1}. δ_H(200 MHz, DMSO-d_6): 4.40 (br, 1H, OH), 4.87 (d, *J*=8.5 Hz, 1H, CH), 5.03 (t, *J*=8.5 Hz, 1H, CH), 7.21–7.41 (m, 10H, 2ArH), 8,74 (d, *J*=9.7 Hz, 1H, NH), 10.17 (s, 1H, OH). MS (EI) *m*/*z*: 310 (M^{+}+1, 5). Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.88, H, 4.89, N, 4.53. Found: C, 69.79, H, 4.98, N, 4.77.

3.7. General procedure for the synthesis of ligands 9–11

To a solution of dibutyl squarate **1** (1.0 mmol) in dry ethanol (10 mL) was added β-amino alcohols (2.1 mmol) in the presence of triethylamine (2.0 mmol) at room temperature with stirring, and the stirring was continued until the reaction was completed (24 h TLC, silica gel, petroleum ether/ethanol, 2:1). The precipitate was filtrated and recrystallized from a mixture of ethanol and THF (1:1) to afford product as colorless needles.

3.7.1. 3,4-Bis[(1′*R*,2′*S*)-(2′-hydroxy-1′,2′-diphenylethyl)-amino]-3-cyclobutene-1,2-dione 9a. 85% yield. Mp 288–289°C (dec.). $[\alpha]_D^{20}=+43.3$ (*c* 0.6, DMSO). IR ν: 3424, 3156, 3042, 1800, 1642, 1572 cm^{-1}. δ_H (400 MHz, DMSO-d_6): 5.03 (t, *J*=4.6 Hz, 2H, 2OH), 5.26 (t, *J*=4.4 Hz, 2H, 2CH), 5.83 (d, *J*=4.4 Hz, 2H, 2CH), 7.07–7.26 (m, 20H, 4ArH), 8.18 (t, *J*=4.8 Hz, 2H, NH). MS (EI) *m*/*z*: 505 (M^{+}+1, 15). Anal. Calcd for $C_{32}H_{28}N_2O_4$: C, 76.16, H, 5.56, N, 2.78. Found: C, 76.45, H, 5.47, N, 2.99.

3.7.2. 3,4-Bis[(1′*S*,2′*R*)-(2′-hydroxy-1′,2′-diphenylethyl)-amino]-3-cyclobutene-1,2-dione 9b. 83% yield. Mp 286–287°C (dec.). $[\alpha]_D^{20}=-42.5$ (*c* 0.6, DMSO-d_6). IR ν: 3446, 3213, 3065, 1802, 1640, 1570 cm^{-1}. δ_H (400 MHz, DMSO-d_6): 5.02 (d, *J*=3.8 Hz, 2H, 2OH), 5.22 (t, *J*=4.6 Hz, 2H, 2CH), 5.83 (d, *J*=3.8 Hz, 2H, 2CH), 7.08–7.33 (m, 20H, 4ArH), 8.17 (d, *J*=9.3 Hz, 2H, NH). MS (EI) *m*/*z*: 505 (M^{+}+1, 15). Anal. Calcd for $C_{32}H_{28}N_2O_4$: C, 76.16, H, 5.56, N, 2.78. Found: C, 75.98, H, 5.29, N, 2.61.

3.7.3. 3,4-Bis[(1′*R*)-(2′-hydroxy-1′-benzylthiomethyl-1′,2′-diphenylethyl)amino]-3-cyclobutene-1,2-dione 10. 45% yield. Mp 250°C (dec.). $[\alpha]_D^{20}=-307$ (*c* 0.4, DMSO). IR ν: 3420, 3151, 3026, 1800, 1573 cm^{-1}. δ_H (400 MHz, DMSO-d_6): 3.27 (br, 2H, 2OH), 3.65 (m, 4H, 2CH$_2$), 3.77 (m, 4H, 2CH$_2$), 5.77 (m, 2H, 2CH), 7.03–7.65 (m, 30H, 6ArH), 8.60 (m, 2H, 2NH). MS (EI) *m*/*z*: 778 (M^{+}+2, 35). Anal. Calcd for $C_{48}H_{44}N_2O_4S_2$: C, 74.20, H, 5.71, N, 3.61. Found: C, 74.97, H, 5.59, N, 3.67.

3.7.4. 3,4-Bis-[(1′*R*)-(2′-hydroxy-1′,2′2′-triphenylethyl)-amino]-3-cyclobutene-1,2-dione 11. 40% yield. Mp 250°C (dec.). $[\alpha]_D^{20}=+180$ (*c* 0.5, DMSO). IR ν: 3466, 3206, 3209, 2962, 1804, 1644, 1571, 1543 cm^{-1}. δ_H (400 MHz, DMSO-d_6): 2.15 (br, 2H, 2OH), 4.75 (m, 2H, 2CH), 5.13 (s, 1H, CH), 7.60 (m, 30H, 6ArH), 8.12 (m, 2H, 2–NH–). MS (EI) *m*/*z*: 657 (M^{+}+1, 20). Anal. Calcd for $C_{44}H_{36}N_2O_4$: C, 80.45, H, 5.53, N, 4.27. Found: C, 79.98, H, 5.49, N, 4.61.

3.8. A general procedure for the catalytic reduction of prochiral ketones

Under an argon atmosphere, to a solution of chiral ligand in toluene was added $BH_3{\cdot}Me_2S$ at 0°C. The reaction mixture was stirred for 3 h at ambient temperature to form an oxazaborolidine catalyst and then was warmed to specified temperature and stirred for another 1 h. The ketone was added slowly over a period of 1.5 h and stirred for another 1 h. The reaction mixture was cooled to 0°C and quenched with 5 mL of 2N HCl solution. The organic layer was extracted with ethyl acetate (10 mL×3) and washed with saturated brine solution. The organic layer was then concentrated in vacuum and passed through a short silica gel column eluted with petroleum ether and ethyl acetate (6:1) before being subjected to GC analysis.

Crystallographic data (excluding structure factors) for compound (1′*R*,2′*S*)-**5c**, (1′*S*,2′*R*)-**5e** and **2b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 161175–161177, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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