Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1907–1912

TETRAHEDRON:
ASYMMETRY

Chiral squaric prolinols: a new type of ligand for the asymmetric reduction of prochiral ketones by borane

Ji Zhang,[a] Hai-Bing Zhou,[a] Shou-Mao Lü,[a] Mei-Ming Luo,[a] Ru-Gang Xie,[a,*] Michael C. K. Choi,[b] Zhong-Yuan Zhou,[b] Albert S. C. Chan[b] and Teng-Kuei Yang[c]

[a] *Department of Chemistry, Sichuan University, Chengdu 610064, PR China*
[b] *Open Laboratory of Chirotechnology and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, PR China*
[c] *Department of Chemistry, National Chung-Hsing University, Taichung, Taiwan*

Received 2 July 2001; accepted 25 July 2001

Abstract—A series of chiral bifunctional squaric prolinol ligands, having *N*, *S* substituents at C(3) of the squaric ring were synthesized and applied to the asymmetric borane reduction of prochiral ketones via an in situ formed chiral boron heterocycle, affording secondary alcohols with high yields and excellent enantiomeric excesses (up to 99%). The crystal structure of **5a** was obtained and the mechanism of the catalytic asymmetric reduction is also discussed. © 2001 Elsevier Science Ltd. All rights reserved.

---

1. Introduction

The asymmetric reduction of prochiral ketones which lead to almost enantiomerically pure secondary alcohols has been a hot field in organic chemistry.[1] Chiral oxazaborolidines, derived from β-amino alcohols by Itsuno[2] and Corey,[3] have been widely used in the asymmetric reduction of ketones. This method has been recognized as one of the most efficient ways for the preparation of homochiral alcohols and a number of reports have appeared in recent years.[4] It is clear that obtaining versatile ligands that are easily prepared and modified is very important work.

Some *N*-electron-withdrawing group substituted ligands such as sulfonamidoalcohols[5] and phosphinamidoalcohols[6] were reported as efficient catalysts for the asymmetric borane reduction of prochiral ketones, but the details of the mechanism and reactive intermediates involved in these reactions were poorly understood. Furthermore, these ligands were difficult to modify for better enantioselectivity. Squaric acid (3,4-dihydroxy-3-cyclobutene-1,2-dione) has a unique four-membered ring structure, its C(3) and C(4) hydroxy groups can be easily substituted by several nucleophiles.[7] However, to date there have been no reports of asymmetric catalysis using chiral squaric acid derivatives. We have synthesized and utilized several homochiral squaric aminoalcohol derivatives as ligands in the asymmetric reduction of prochiral ketones and found that the squaric prolinols showed superior stereoinduction.[8] The ligands based on the cyclobutenedione structure containing a prolinol residue could still be modified easily with various substituents. Thus, a series of new chiral ligands with different electronic charge distributing and stereo structures were conveniently prepared. We studied the asymmetric catalytic abilities of chiral squaric prolinol ligands systematically. Herein, we report several homochiral squaric prolinol ligands having different substituents such as alkoxy, amino and alkylthio groups on C(3) of the squaric ring. These ligands have provided better stereoinduction than other electron-withdrawing group containing ligands.

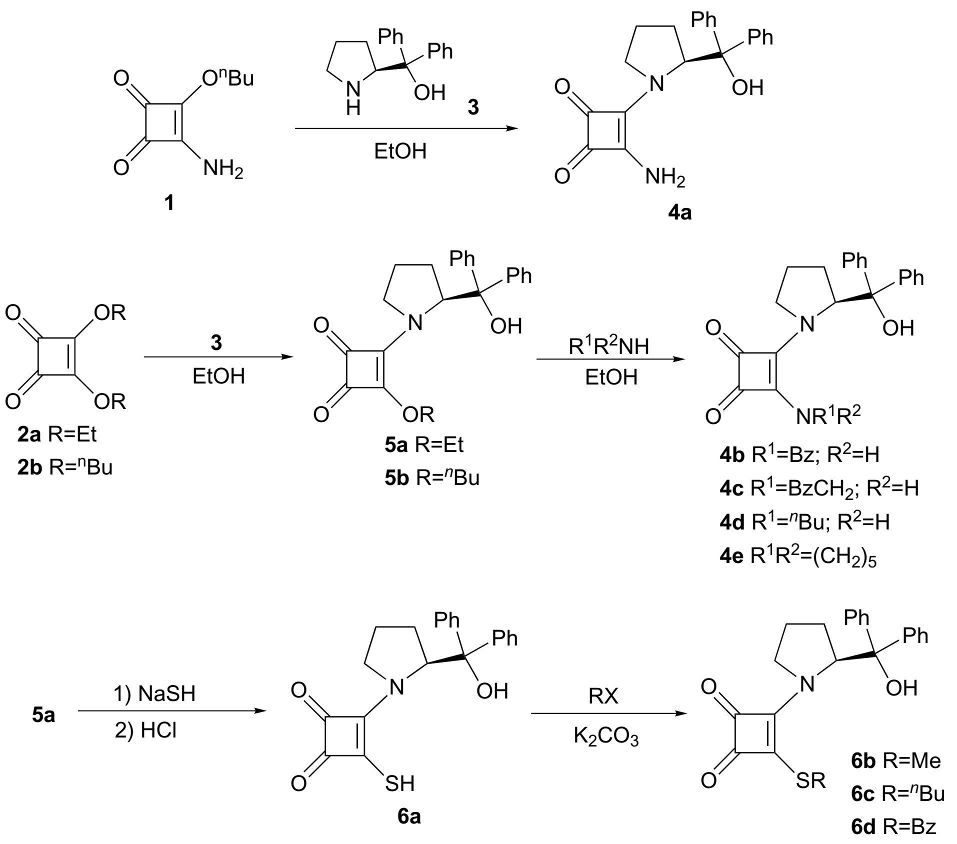
2. Results and discussion

The synthesis of chiral squaric prolinol ligands is shown in Scheme 1. Reaction of 3-amino-4-butoxy-3-cyclobutene-1,2-dione **1** with prolinol **3** afforded 3-amino squaric prolinol **4a**. We also prepared 3-alkoxy squaric prolinols **5** by dropping an ethanolic solution of diphenylprolinol **3** into the squaric acid diesters.[9] The

---

* Corresponding author. Tel./fax: +86-28-5412285; e-mail: schemorg@mail.sc.cninfo.net

PII: S0957-4166(01)00333-0



Scheme 1.

other amines **4b**–**4e** were obtained by the reaction between **5a** and a slight excess of the corresponding amines in ethanol for 1 day. The prolinol **6a** was obtained by treatment of **5a** with aqueous NaSH and then a 1N aqueous HCl solution. Further reaction of **6a** with the corresponding alkyl halides using anhydrous K_2CO_3 as base led to the alkylthiosquaric acid prolinols **6b**–**6d**. All new ligands were characterized by IR, ^{1}H NMR, MS and elemental analysis.

As a proven excellent squaric acid-derivative ligand and a useful synthetic intermediate for several asymmetric reactions,[10] the crystal of 3-ethoxy-squaric prolinol **5a** was obtained by slow volatilization in petroleum ether and ethyl acetate. The structure is shown in Fig. 1. Selected bond length and angles are listed in Table 1.

The asymmetric reductions were carried out under the optimized conditions we studied previously.[9,10] The catalysts were formed in situ by mixing the ligands (0.1 equiv.) and $BH_3{\cdot}Me_2S$ (1.2 equiv.) at 0°C, and the subsequent reduction of prochiral ketones was carried out at 50°C in toluene. We applied the ligands in the asymmetric reduction of ω-bromoacetophenone giving the alcohol product with e.e. of up to 99% (Table 2). All the listed ligands have good to excellent asymmetric inductivity. In the asymmetric reduction, ligand **5** in general gave higher e.e.s than that of ligands **4** and **6** (entries 6 and 7). However, when the C(3) substituent contained an acidic hydrogen (viz NH_2, NHR or SH), the proton would leave more easily to form the nitrogen or sulfur anion, which might be prone to coordinate with borane. The ligands having substituents with high acidity on C(3) gave higher e.e.s (entries 1 and 8). On the contrary, lower e.e.s were obtained when the C(3) substituent lacked an acidic proton (entries 5, 9 and 10). For ligands **4** and **6**, with an *N*- or *S*-benzyl substituent, the prochiral ketone directs itself to the boron-heterocycle catalyst with higher selectivity due to the bulky benzyl group and high e.e.s were obtained (entries 2 and 11). However, when using phenylethylamino substituted ligand **4c**, an e.e. of only 82% was obtained (entry 3), this phenomenon may due to the lower rigidity of the ligand.

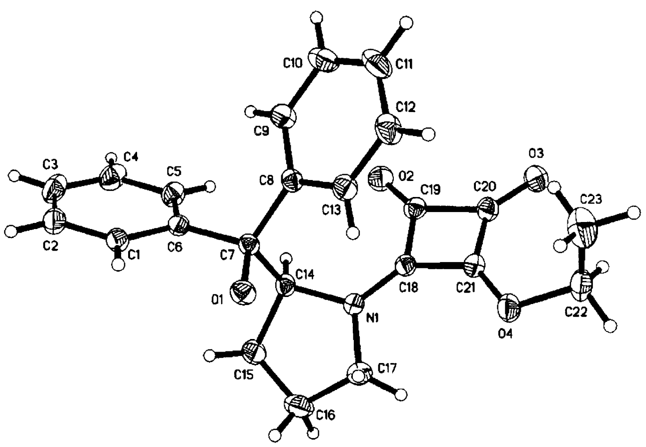


Figure 1. Crystal structure of **5a**.

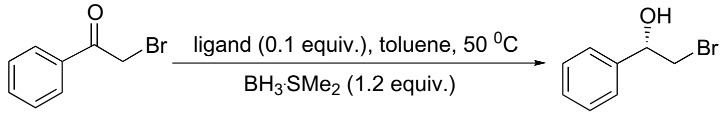
Table 1. Selected bond lengths (Å) and angles (°) for crystal **5a**

C(18)–C(19)	1.4780(15)	C(19)–C(20)	1.5201(15)
C(20)–C(21)	1.4546(16)	C(18)–C(21)	1.3947(14)
O(2)–C(19)	1.2123(13)	O(3)–C(20)	1.2177(14)
N(1)–C(18)	1.3263(13)	O(4)–C(21)	1.3262(13)
C(18)–C(19)–C(20)	88.15	C(18)–C(21)–C(20)	94.09
C(19)–C(18)–C(21)	90.83	C(19)–C(20)–C(21)	86.93
O(2)–C(19)–C(20)	137.41	O(2)–C(19)–C(18)	134.42
O(3)–C(20)–C(19)	136.03	O(3)–C(20)–C(21)	137.03
O(4)–C(21)–C(18)	128.04	O(4)–C(21)–C(20)	137.84
N(1)–C(18)–C(19)	135.02	N(1)–C(18)–C(21)	134.11

The excellent asymmetric induction led us to choose ligand **6a** to catalyze the borane reduction of several aromatic ketones. High enantiomeric excesses were achieved. For α,β-unsaturated ketones such as benzalacetone, moderate e.e. was obtained. The results are summarized in Table 3.

The asymmetric borane reduction catalyzed by squaric prolinol ligands such as **6a** may be rationalized through two proposed mechanisms. Owing to the blocking effect of the squaric ring on the nitrogen of prolinol, it is likely that two borane molecules cannot complex with the nitrogen atom simultaneously to form a transition state like Corey's.[1c] Thus we proposed **A**–**D** as the possible mechanisms for facial attack of hydride to the carbonyl group. The first borane molecule could combine to nitrogen or sulfur atoms to form Corey's oxazaborolidine **A** or an eight-membered boron heterocycle **B**, respectively. In the case of **A**, the second borane

Table 2. Asymmetric reduction of ω-bromo-acetophenone using chiral squaric prolinols

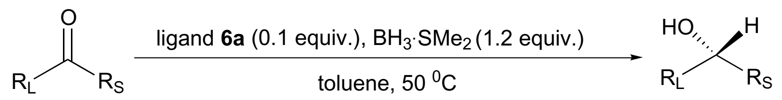


Entry	Ligands	Yield (%)[a]	E.e. (%)[b]
1	**4a**	83	90
2	**4b**	99	96
3	**4c**	90	82
4	**4d**	82	94
5	**4e**	88	77
6	**5a**	91	99
7	**5b**	93	98
8	**6a**	92	99
9	**6b**	85	82
10	**6c**	95	87
11	**6d**	94	95

[a] Isolated yield.

[b] Determined by HPLC analysis, the configuration of all products is (*S*).

Table 3. Asymmetric reduction of prochiral ketones using **6a**

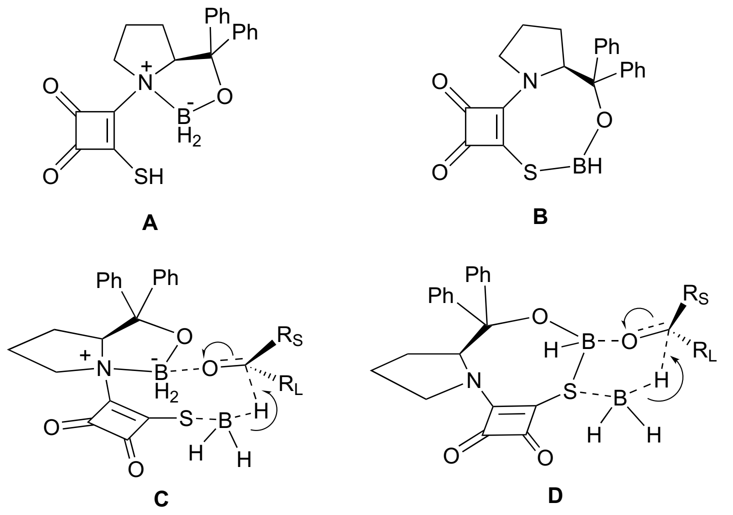


Entry	Ketone	Yield (%)[a]	E.e. (%)[b]	Config.[c]
1	Acetophenone	95	95	*R*
2	ω-Bromoacetophenone	92	99	*S*
3	Propiophenone	89	85	*R*
4	*p*-Chloroacetophenone	90	93	*R*
5	β-Acetonaphthalone	92	91	*R*
6	Benzalacetone	87	76	*R*
7	Tetralone	85	87	*R*

[a] Isolated yield.

[b] Determined by HPLC analysis.

[c] Determined by specific rotations.



Scheme 2.

molecule will be difficult to connect nitrogen for steric and electric reasons. So it can only combine to sulfur as another Lewis base atom. As a result the facial attack of hydride to ketone substrate occurs through a nine-membered cycle shown as **C**. In another proposed transition state, the first borane reacts with the hydroxyl group and 3-heteroatom of the ligand to form **B**. This bifunctional boron heterocycle also contains both a Lewis acid and Lewis base site, which can interact with a molecule of borane and ketone. Hydride will attack the ketone through the more stable six-membered-cyclic transition state **D** (Scheme 2). In contrast with transition state **C**, the transition state **D** has a 'free' nitrogen atom. However, it may also interact with a boron atom and some enantiofacial differentiation may result in the hydride-attack step. Obviously a more in-depth study is needed to elucidate the mechanism of the asymmetric borane reduction.

3. Conclusion

In summary, we have synthesized a series of chiral squaric prolinol ligands with different substituents at C(3) of the squaric ring. The boron heterocycle catalysts were formed in situ to catalyze the asymmetric borane reduction of aromatic ketones with good to excellent e.e.s. A possible mechanism was discussed.

4. Experimental

4.1. Instruments and materials

Melting points were taken on a micro-melting apparatus and the data were not corrected. Optical rotations were measured on a WZZ-1 polarimeter. IR spectra were measured on a FT-IR 16PC infrared spectrophotometer with KBr disc. ^{1}H NMR spectra were recorded at Bruker DPX-400 MHz and Bruker AC-E 200 MHz with chemical shift in ppm and tetramethylsilicon as internal standard. Mass spectra data were obtained on a Finnigan MAT 4510 spectrometer. Flash chromatography was carried out using SiO_2 (230–400 mesh). Elemental analyses were performed with a Carlo Erba 1106 elemental analyzer. HPLC analyses were carried out through Chiracel OD column. Prolinol **3** and 3-alkoxy-squaric prolinol **5** were prepared according to Refs. 11 and 9, respectively. $BH_3{\cdot}Me_2S$ (2 M) was purchased from Aldrich. The solvent (toluene) and all prochiral ketones were purified before use. Other chemicals were obtained and used without any further purification.

4.2. Preparation of squaric prolinol amides 4

Method 1. To a solution of 3-amino-4-butoxy-3-cyclobutene-1,2-dione **1** (1 mmol) in ethanol (10 mL) was added diphenyl prolinol **3** (1 mmol) and the mixture was stirred at room temperature for 1 day. The mixture was filtered, and the filter cake dried, and recrystallized from absolute ethanol and THF to afford a colorless flaky solid of 3-amino-4-[(2′*S*)-2′-(diphenylhydroxymethyl)pyrrolidino]-3-cyclobutene-1,2-dione **4a**: 79% yield. Mp 146–148°C. $[\alpha]_D^{20}$ −95.4 (*c* 0.5, CH_2Cl_2). IR ν: 3296, 1801, 1664, 1566, 1507 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 1.58–1.75 (m, 2H, -CH$_2$-), 1.99–2.18 (m, 2H, -CH$_2$N-), 3.57–3.69 (m, 2H, -CH$_2$N-), 5.20 (s, 1H, OH), 5.76 (br, 1H, -CHN-), 7.14–7.39 (m, 10H, ArH), 7.47 (d, J=7.4 Hz, 2H, NH). MS (m/z): 349 (M$^+$+1, 100). Anal. calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.54; H, 5.63; N, 7.96%.

Method 2. To a solution of **5a** (1.0 mmol) in ethanol (10 mL) was added amine (1.1 mmol) and the mixture was stirred at room temperature for 1 day. The reaction was monitored by TLC until completion. Column chromatography (dichloromethane:ethyl acetate, 5/1, v/v) gave the pure products as colorless flaky solids.

4.2.1. 3-Benzylamino-4-[(2′*S*)-2′-(diphenylhydroxymethyl)-pyrrolidino]-3-cyclobutene-1,2-dione 4b. 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}. ^{1}H NMR (DMSO-d_6) δ:

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 (*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, 77.47; H, 5.91; N, 6.29%.

4.2.2. 3-Phenylethylamino-4-[(2′*S*)-2′-(diphenylhydroxymethyl)pyrrolidino]-3-cyclobutene-1,2-dione 4c. 95% yield. Mp 222–224°C. $[\alpha]_D^{20}$ −229 (*c* 0.35, CH_2Cl_2). IR ν: 3267, 1792, 1667, 1561, 1510 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.92 (t, J=6.0 Hz, 2H, -CH_2N-), 3.95 (q, J=6.5 Hz, 2H, -CH_2N-), 4.89 (d, J=8.5 Hz, 1H, -CHN-), 5.93 (s, 1H, OH), 7.17–7.60 (m, 15H, ArH), 7.81 (d, J=7.1 Hz, 1H, NH). MS (*m*/*z*): 269 (M^+–Ph_2COH, 34). Anal. calcd for $C_{29}H_{28}N_2O_3$: C, 76.97; H, 6.24; N, 6.19. Found: C, 77.12; H, 6.18; N, 6.01%.

4.2.3. 3-Butylamino-4-[(2′*S*)-2′-(diphenylhydroxymethyl)pyrrolidino]-3-cyclobutene-1,2-dione 4d. 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: 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 (*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%.

4.2.4. 3-Pyperidinyl-4-[(2′*S*)-2′-(diphenylhydroxymethyl)pyrrolidino]-3-cyclobutene-1,2-dione 4e. 98% yield. Mp 241–243°C. $[\alpha]_D^{20}$ +44.0 (*c* 0.96, $CHCl_3$). IR ν: 2967, 1794, 1663, 1569, 1507 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.23–1.78 (m, 10H, -CH_2-), 2.72 (q, J=8.5 Hz, 2H, -CH_2N-), 3.24 (td, J=9.0, 3.2 Hz, 1H, -CHN-), 3.49–3.54 (m, 2H, -CH_2N-), 3.69–3.72 (m, 2H, -CH_2N-), 5.80 (dd, J=3.6, 5.2 Hz, 1H, OH), 7.25–7.32 (m, 10H, ArH). MS (*m*/*z*): 417 (M^++1, 75). Anal. calcd for $C_{26}H_{28}N_2O_3$: C, 74.98; H, 6.78; N, 6.73. Found: C, 74.76; H, 6.74; N, 6.59%.

4.3. Preparation of squaric prolinol mercaptan 6a

To a solution of **5a** (377 mg, 1 mmol) in ethanol (10 mL) was added aqueous sodium hydrosulfide (62 mg, 1.1 mmol) dropwise at room temperature. The reaction was complete soon after the end of the addition. The yellow solution was treated with diluted hydrochloride acid and yellow precipitates appeared. The solid was filtered off and recrystallized from water and acetone to afford 3-mercapto-4-[(2′*S*)-2′-(diphenylhydroxymethyl)-pyrrolidino]-3-cyclobutene-1,2-dione **6a** (330 mg, 91%) as a yellow flaky solid. Mp 163–165°C. $[\alpha]_D^{20}$ −82.0 (*c* 0.7, EtOH). IR ν: 3446, 3064, 1774, 1662, 1563 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.98 (m, 2H, -CH_2-), 2.19 (m, 2H, -CH_2-), 3.86 (s, 2H, -CH_2N-), 4.00 (m, 1H, SH), 5.27 (br, 1H, -CHN-), 6.15 (s, 1H, OH), 7.18–7.50 (m, 10H, ArH). MS (*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%.

4.4. Preparation of 3-alkylthio squaric prolinol 6b–6d

To a solution of **6a** (1 mmol) in acetone (10 mL) was added anhydrous K_2CO_3 (69 mg, 0.5 mmol). The mixture was stirred at 40°C until K_2CO_3 disappeared. Then a catalytic amount of KI and corresponding alkyl halide (1.1 mmol) was added into the reaction mixture.[12] Stirring was continued overnight at 40°C, the insoluble solid was filtered and the filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography (petroleum ether:ethyl acetate, 2/1, v/v) to give **6b–6d** as pale yellow flakes.

4.4.1. 3-Methylthio-4-[(2′*S*)-2′-(diphenylhydroxymethyl)-pyrrolidino]-3-cyclobutene-1,2-dione 6b. 55% yield. Mp 183–185°C. $[\alpha]_D^{20}$ −148.8 (*c* 0.42, CH_2Cl_2). IR ν: 3315, 1772, 1649, 1562 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.90–2.15 (m, 4H, -CH_2-), 2.74 (s, 3H, CH_3), 3.72–3.89 (m, 2H, -CH_2N-), 5.27 (d, J=7.7 Hz, 1H, -CHN-), 6.05 (s, 1H, OH), 7.12–7.50 (m, 10H, ArH). MS (*m*/*z*): 380 (M^++1, 24). Anal. calcd for $C_{22}H_{21}NO_3S$: C, 69.63; H, 5.58; N, 3.69. Found: C, 69.92; H, 5.51; N, 3.64%.

4.4.2. 3-*n*-Butylthio-4-[(2′*S*)-2′-(diphenylhydroxymethyl)-pyrrolidino]-3-cyclobutene-1,2-dione 6c. 88% yield. Mp 159–160°C. $[\alpha]_D^{20}$ −108.8 (*c* 0.74, CH_2Cl_2). IR ν: 3320, 1774, 1650, 1561 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 0.91 (t, J=7.2 Hz, 3H, CH_3), 2.11–2.27 (m, 2H, -CH_2S-), 3.75–3.92 (m, 2H, -CH_2N-), 5.28 (d, J=7.5 Hz, 1H, -CHN-), 6.06 (s, 1H, OH), 7.12–7.51 (m, 10H, ArH). MS (*m*/*z*): 422 (M^++1, 100). Anal. calcd for $C_{25}H_{27}NO_3S$: C, 71.23; H, 6.46; N, 3.32. Found: C, 71.08; H, 6.59; N, 3.36%.

4.4.3. 3-Benzylthio-4-[(2′*S*)-2′-(diphenylhydroxymethyl)-pyrrolidino]-3-cyclobutene-1,2-dione 6d. 70% yield. Mp 203–204°C. $[\alpha]_D^{20}$ −74.4 (*c* 0.45, CH_2Cl_2). IR ν: 3307, 1769, 1646, 1559 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.17–1.24 (m, 2H, -CH_2-), 1.85–1.94 (m, 2H, -CH_2-), 2.09 (t, J=7.3 Hz, 2H, -CH_2S-), 3.65–3.87 (m, 2H, -CH_2N-), 4.56 (t, J=14.5 Hz, 1H, -CHN-), 6.04 (s, 1H, OH), 6.96–7.49 (m, 15H, ArH). MS (*m*/*z*): 456 (M^++1, 68). Anal. calcd for $C_{28}H_{25}NO_3S$: C, 73.82; H, 5.53; N, 3.07. Found: C, 73.57; H, 5.56; N, 3.10%.

4.5. General procedure for the catalytic reduction of prochiral ketones

To a 25 mL round-bottom flask was added 0.05 mmol (0.1 equiv.) of chiral ligand. Under an argon atmosphere and at 0°C, $BH_3{\cdot}Me_2S$ (0.6 mmol, 1.2 equiv.) was added. The mixture was stirred at ambient temperature for 2 h and warmed to 50°C for a further hour. The ketone (0.5 mmol) was added slowly over a period of 1.5 h under the same temperature and stirred for a further hour. The reaction mixture was cooled to 0°C and quenched with a 1N aqueous HCl solution (8 mL), then extracted with ethyl acetate (3×10 mL). The combined ethyl acetate solution was washed twice with brine and dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The residue was passed through a short silica column to afford the pure product.

Crystallographic data (excluding structure factors) for compound **5a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 161178. 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].

Acknowledgements

The financial support of The Hong Kong Polytechnic University ASD Fund is gratefully acknowledged.

References

1. For reviews, see: (a) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763; (b) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475; (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986 and references cited therein.
2. (a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Org. Chem.* **1984**, *49*, 555; (b) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039.
3. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
4. (a) Santhi, V.; Rao, J. M. *Tetrahedron: Asymmetry* **2000**, *11*, 3553; (b) Molvinger, K.; Lopez, M.; Court, J. *Tetrahedron: Asymmetry* **2000**, *11*, 2263; (c) Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902; (d) Li, X. S.; Yeung, C. H.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron: Asymmetry* **1999**, *10*, 759; (e) Li, X. S.; Xie, R. G. *Tetrahedron: Asymmetry* **1996**, *7*, 2779; (f) Li, X. S.; Xie, R. G. *Tetrahedron: Asymmetry* **1997**, *8*, 2283.
5. (a) Hu, J.-B.; Zhao, G.; Yang, G.-S.; Ding, Z.-D. *J. Org. Chem.* **2001**, *66*, 303; (b) Hu, J.-B.; Zhao, G.; Ding, Z.-D. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1109; (c) Yang, G.-S.; Hu, J.-B.; Zhao, G.; Ding, Y.; Tang, M.-H. *Tetrahedron: Asymmetry* **1999**, *10*, 4307; (d) Altava, B.; Burguete, M. I.; Collado, M.; García-Verdugo, E.; Luis, S. V.; Salvador, R. V.; Vicent, M. J. *Tetrahedron Lett.* **2001**, *42*, 1673; (e) Sibi, M. P.; Cook, G. R.; Liu, P. R. *Tetrahedron: Asymmetry* **1999**, *10*, 2477; (f) Inoue, T.; Sato, D.; Komure, K.; Itsuno, S. *Tetrahedron Lett.* **1999**, *40*, 5379.
6. (a) Gamble, M. P.; Studley, J. R.; Wills, M. *Tetrahedron Lett.* **1996**, *37*, 2853; (b) Burns, B.; King, N. P.; Tye, H.; Studley, J. R.; Gamble, M.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1027; (c) Gamble, M. P.; Smith, A. R. C.; Wills, M. *J. Org. Chem.* **1998**, *63*, 6068.
7. (a) West, R. *Oxocarbons*; Academic Press: New York, 1980; (b) Schmidt, A. H. *Synthesis* **1980**, 961; (c) Prohens, R.; Tomàs, S.; Morey, J.; Deyà, P. M.; Ballester, P.; Costa, A. *Tetrahedron Lett.* **1998**, *39*, 1063; (d) Yuan, D.-Q.; Chen, Y.-Z.; Li, J.-C.; Zhao, H.-M. *Youji Huaxue (Chin. J. Org. Chem.)* **1992**, *12*, 312.
8. Zhou, H.-B.; Lü, S.-M.; Xie, R.-G.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron Lett.* **2001**, *42*, 1107.
9. Zhou, H.-B.; Zhang, J.; Lü, S.-M.; Xie, R.-G.; Zhou, Z.-Y.; Choi, M. C. K.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron*, submitted.
10. Zhou, H.-B. Ph.D. Thesis, Sichuan University, 2000.
11. Kapfhammer, J.; Matthes, A. *Hoppe-Seylers Zeit. Physiol. Chem.* **1933**, *223*, 43.
12. The preparation of **6b** does not need KI because of the high reactivity of CH_3I. The alkyl halides used in the preparation of **6b**–**6d** are methyl iodide, *n*-butyl bromide and benzyl bromide (or chloride), respectively.