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Chiral monoaminoalcohols and diaminoalcohols of squaric acid: new catalysts for the asymmetric reduction of ketones by borane†

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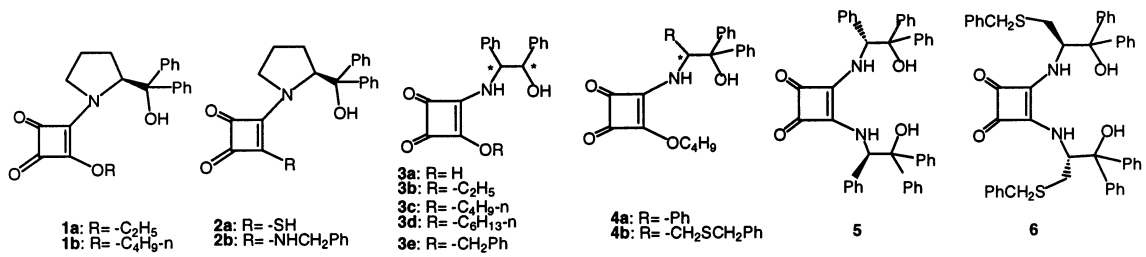
Abstract—Two series of new chiral ligands, squaric acid aminoalcohols and C_2-symmetric squaric acid diaminoalcohols have been synthesized. The chiral oxazaborolidines formed in situ from these ligands have been used in the enantioselective borane reduction of prochiral ketones and diketones to afford alcohol products with up to 99% enantiomeric excesses. The structures of the ligands have an obvious effect on the ee of the resulting alcohols. © 2001 Elsevier Science Ltd. All rights reserved.

Enantioselective reduction of prochiral ketones by oxazaborolidines derived from chiral amino alcohols has been recognized as one of the most efficient methods for the preparation of optically active secondary alcohols. A large number of β-amino alcohols have been synthesized and evaluated using this method.[1] However, *N*-substituted amino alcohols were not widely used and low enantioselectivities were usually obtained when these ligands were used. From a practical point of view, it is important to develop versatile chiral ligands which are easy to prepare so that highly enantioselective catalysts can be screened by simple modifications. Recently some chiral electron-withdrawing group containing ligands such as phosphinamidoalcohols[2] and sulfonamidoalcohols[3] were reported as efficient catalysts for the enantioselective reduction of ketones using borane. However, the reactive intermediate(s) involved in these catalytic reactions remain poorly understood and in most cases the enantioselectivity of these ligands needs further improvement.

Squaric acid is an aromatic four-membered cyclic compound which has unique characteristics and wide applications[4] based on the cyclobutenedione structure with acidic hydroxyl groups which can be replaced by various functional groups so that versatile chiral ligands can be conveniently prepared. However, to the best of our knowledge, the synthesis of chiral deriva-



Scheme 1.

Keywords: Enantioselective reduction; aminoalcohol and diaminoalcohol derivatives of squaric acid; oxazaborolidines; ketones.
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† Dedicated to Professor Huang Shu on the occasion of his 80th birthday.

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tives of squaric acid is rare[5] and their application to asymmetric synthesis has never been reported. Herein, we report our work on the synthesis of two types of optimized versatile chiral ligands, aminoalcohols and C_2-symmetric diaminoalcohols of squaric acid, and a procedure for their use as improved catalysts in asymmetric carbonyl reduction using borane. 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 for coordination of the substrate as well as the reagent in reaction. The monoaminoalcohols of squaric acid can serve as prototypical examples of bifunctional catalysts (Scheme 1, ligands **1**–**4**), since their substitutents at C-3 of the squaric acid ring can be conveniently modified by introducing a second functional group, which can preferentially coordinate with the borane thus leading to intramolecular delivery of hydride to the carbonyl group in a highly selective manner. The diaminoalcohols of squaric acid can serve as prototypical examples of bimetallic catalysts (Scheme 1, ligands **5** and **6**) since they have good symmetry and two catalytic centers, which may serve as a bimetallic catalyst for the reduction of prochiral ketones, especially diketones. These ligands have proved to be effective in the enantioselective reduction of prochiral aryl ketones and diketones.

Squaric acid aminoalcohols **1**, **3b**–**3e** and **4** were prepared by the reaction of chiral aminoalcohols with a slight excess of squaric acid diesters in the presence of triethylamine in ethanol at ambient temperature. Thiosquaric acid aminoalcohol **2a** was formed by reaction of **1a** with aqueous sodium hydrosulfide then treatment with hydrochloric acid. The aminosquaric acid aminoalcohol **2b** can be prepared from ammonolysis of **1a**. Aminoalcohol **3a** was obtained when the ester group of **3b** was hydrolyzed. When 2 equivalents of aminoalcohols were used, the symmetric squaric acid diaminoalcohols **5** and **6** were formed (Scheme 1).[6] All of the new ligands were characterized by IR, ^{1}H NMR, MS and elemental analysis, and crystal structures of the ligands **1b**, **3b**, **3c** were confirmed by X-ray analysis.[7]

In order to find suitable conditions for using these ligands, we briefly optimized their use by changing the solvent and temperature, as well as reducing reagents and found that in the reduction of ω-bromo-acetophenone with 10 mol% **1a**, the use of $BH_3{\cdot}Me_2S$ in toluene at 50°C provided the best selectivity.[8] The optimum ligand-to-substrate ratio was about 10 mol%; for example, in the reduction of ω-bromo-acetophenone. When 5 mol% **3c** was used, a 72% ee was obtained, 82% ee was obtained using 10 mol% (Table 1, entry 11, 12) and when the amount was increased to 15 mol%, the ee decreased to 75%.[9]

The effect of the structure of the catalysts was examined by using different aminoalcohols and by changing the substituent at C-3 of the squaric acid. For all the ketones investigated, catalysts **1** and **2** which possess a pyrrolidinylmethanol moiety always gave higher enantioselectivities, up to 99% yield and 99% ee being

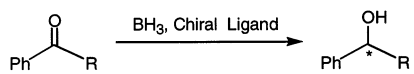
Table 1. The enantioselective catalytic reduction of prochiral ketones with $BH_3{\cdot}Me_2S$ using chiral ligands[a]

Entry	Ligand (equiv.)	Ketone	Ee%[b]	Config.[c]
1	**1a** (0.1)	$PhCOCH_2Br$	99	S
2	**1a** (0.1)	PhCOMe	97	R
3	**1b** (0.1)	$PhCOCH_2Br$	98	S
4	**2a** (0.1)	$PhCOCH_2Br$	99	S
5	**2a** (0.1)	PhCOMe	96	R
6	**2b** (0.1)	$PhCOCH_2Br$	96	S
7	**2b** (0.1)	PhCOMe	94	R
8	(1′*S*,2′*R*)-**3a** (0.1)	$PhCOCH_2Br$	58	S
9	(1′*R*,2′*S*)-**3b** (0.1)	$PhCOCH_2Br$	61	R
10	(1′*R*,2′*S*)-**3c** (0.1)	$PhCOCH_2Br$	75	R
11	(1′*R*,2′*S*)-**3d** (0.1)	$PhCOCH_2Br$	82	R
12	(1′*S*,2′*R*)-**3d** (0.1)	$PhCOCH_2Br$	82	S
13	(1′*R*,2′*S*)-**3e** (0.1)	$PhCOCH_2Br$	52	R
14	(1′*R*)-**4a** (0.1)	$PhCOCH_2Br$	55	R
15	(1′*R*)-**4b** (0.1)	$PhCOCH_2Br$	35	S

[a] The chemical yields of isolated products were 85–99%.
[b] The ee values were determined by capillary GC analysis with a CP-cyclodex 236 m (0.25 mm×25 m) column.
[c] The product configuration was determined by comparison with an authentic sample.

obtained, respectively, in the reduction of ω-bromo-acetophenone. For ligands which contained an oxygen or sulfur atom at C-3 higher ee's were obtained when compared to the nitrogen containing ligand (Table 1, entries 1, 4 and 6). For ligands **3a**–**3d**, the ee values increased along with the length of the alkoxy group (Table 1, entry 8–12). The ligands **3e** and **4** give lower ee's probably due to the steric repulsion between the phenyl rings of the ligand and the aryl ketone, which obstructs the latter from getting in close proximity to the catalytic center. Our proposed rational is that the heteroatoms at C-3 in ligands **1**, **2** and **3** can effectively coordinate with BH_3 and direct the hydride to approach specifically one of the prochiral faces of the carbonyl group in the substrate ketone. The alcohol products obtained by using the opposite enantiomers of the ligands have opposite configurations and essentially identical ee's (Table 1, entry 11, 12). It should be emphasized that the ligands can be recovered in 90% yield and reused for the same reaction without loss of enantioselectivity (Scheme 2).

The enantioselective reduction of prochiral ketones and diketones catalyzed by bisoxazaborolidines is rare.[10] We investigated the diaminoalcohols of squaric acid **5** and **6** in this enantioselective reaction (Table 2). The diaminoalcohol **5** which has two catalytic centers gave higher ee values compared to the corresponding monoaminoalcohols of squaric acid in the reduction of ω-bromo-acetophenone, up to 91% ee being obtained with 5 mol% of **5**. This ligand seems especially suitable for the enantioselective reduction of prochiral diketones giving 99% ee and only 3% of the meso isomer in the



Scheme 2.

Table 2. The enantioselective reduction of prochiral ketones and diketones with $BH_3{\cdot}Me_2S$ catalyzed by diaminoalcohols of squaric acid **5** and **6**

Entry	Ligand (equiv.)	Ketone	$[\alpha]_D^{20}$ (*c*, MeOH)	*meso*/*R*,*R*+*S*,*S*	Ee%	Config.
1	(1′*R*)-**5** (0.025)	$PhCOCH_2Br$			84	R
2	(1′*R*)-**5** (0.05)	$PhCOCH_2Br$			91	R
3	(1′*R*)-**5** (0.05)	PhCOMe			80	S
4	(1′*R*)-**5** (0.1)	$PhCOCH_2Br$			82	R
5	(1′*R*)-**6** (0.05)	$PhCOCH_2Br$			35	S
6	(1′*R*)-**5** 0.05)	$PhCO(CH_2)_4COPh$	−13.44 (1.5)	4/96	95[a]	(*S*,*S*)
7	(1′*R*)-**5** (0.1)	$PhCO(CH_2)_4COPh$	−13.87 (1.5)	3/97	99[a]	(*S*,*S*)
8	(1′*R*)-**5** (0.15)	$PhCO(CH_2)_4COPh$	−13.57 (1.5)	3/97	97[a]	(*S*,*S*)
9	(1′*R*)-**6** (0.1)	$PhCO(CH_2)_4COPh$	+7.87 (1.5)	18/82	61[a]	(*R*,*R*)
10	(1′*R*)-**5** (0.1)	$PhCO(CH_2)_3COPh$	−20.21 (1.0)	5/95	89[b]	(*S*,*S*)

see footnotes a–c of Table 1.

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

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

reduction of 1,6-diphenyl-1,6-hexanedione with 10 mol% of ligand **5**; while for ligand **6**, only moderate ee values were obtained. This is probably due to the remote flexible phenyl group which may obstruct the substrate ketones from getting in close proximity to the catalytic center or the enantioselective transfer of the hydride. Obviously more in-depth study is needed to elucidate this interesting phenomenon and to apply these novel chiral ligands to the other catalytic asymmetric reactions.

In summary, two series of new chiral ligands, aminoalcohols and C_2-symmetric diaminoalcohols of squaric acid were prepared by convenient synthetic routes and were applied successfully to the enantioselective reduction of prochiral ketones and diketones, giving chiral alcohols and diols in good to excellent ee's. This paper discloses, for the first time, that chiral derivatives of squaric acid can be successfully used in asymmetric catalytic reactions. These results will open a new way for the design and synthesis of novel chiral ligands derived from squaric acid for asymmetric reactions and also open new applications for chiral derivatives of squaric acid.

Acknowledgements

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6. Sample procedure, synthesis of 3-ethoxyl-4-[(2′*S*)-2′-(diphenylhydroxymethyl)pyrrolidino]-3-cyclobutene-1,2-dione **1a**: To a solution of squaric acid diethyl ester (1.1 mmol) and triethylamine (1.0 mmol) in dry ethanol (10 mL) was added slowly a solution of (*S*)-(−)-2-(diphenylhydroxymethyl)pyrrolidine (1.0 mmol) in ethanol (10 mL) at room temperature. The reaction was monitored by TLC and after completion of the reaction (~24 h), the solvent was removed under reduced pressure. Further purification was achieved by chromatography (petroleum ether (60–90°C): ethyl acetate, 1:1). Data for **1a**: Colorless flake. 65% yield; mp 107–109°C; $[\alpha]_D^{20}$ = --175.3 (*c* 0.8, CH_2Cl_2). IR (KBr): 3403, 3032, 2966, 2885, 1799, 1707, 1608, 1585 cm^{-1}. δ_H (200 MHz, $CDCl_3$): 1.33 (t, *J*=7.2 Hz, 3H, -C*H*$_3$), 2.04 (m, 2H, -C*H*$_2$-), 2.76–3.33 (m, 5H, -C*H*$_2$-, -C*H*-), 4.69 (q, *J*=7.2 Hz, 2H, -C*H*$_2$O-), 5.18 (s, 1H, -O*H*), 7.24–7.54 (m, 10H, 2-Ar*H*) ppm. MS(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.
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9. Typical procedure for catalytic reduction of prochiral ketones: To a solution of chiral ligand **1a** (0.1 mmol) in toluene (5 mL) was added $BH_3 \cdot Me_2S$ (1.1 mmol) at 0°C under an argon atmosphere. The reaction mixture was stirred for 3 h (12 h for diaminoalcohols of squaric acid) at ambient temperature to form an oxazaborolidine catalyst and then was warmed to 50°C and the stirring was continued for another 1 h. The ω-bromoacetophenone (1 mmol in 2 mL toluene) was added slowly over a period of 2 h and stirred for additional 0.5 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 concentrated in vacuum and purified through a silica column to afford 185 mg (*R*)-2-bromo-1-phenylethanol; the enantiomeric excess was determined by GC analysis.
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