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A novel C_3-symmetric prolinol-squaramide catalyst for the asymmetric reduction of ketones by borane

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ABSTRACT

A novel C_3-symmetric prolinol-squaramide has been developed for the asymmetric reduction of ketones by borane. By using only 5 mol % catalyst **1a** for the reaction, high yields and excellent enantioselectivities (up to 95% yield, 93% ee) were obtained. Moreover, **1a** can be easily recovered by simple precipitation and re-used for four cycles without losing the selectivity.

1. Introduction

The reduction of ketones to enantiomerically enriched alcohols is a pivotal transformation in synthetic organic chemistry.[1] Over the past decades, many asymmetric catalyst systems, pioneered by CBS catalysts[2] such as hydroxyl-amides,[3] sulfonamides,[4] and phosphinamides[5] have been developed as efficient catalysts for the asymmetric reduction of ketones. Meanwhile, chiral squaramides were first used in the reduction of ketones in 2001 and recently were used as organocatalysts for asymmetric reactions.[6,7] Despite important progress in this area, there is still room for improvement regarding this type of asymmetric reduction reaction, for example, the cultivation of catalytic enantioselective variants of this reaction is still in high demand. Furthermore, due to the difficulty in catalyst recycling, the application of these catalytic systems in pharmaceutical production has been limited. Therefore, new strategies to design efficient, recyclable chiral catalysts for asymmetric reduction reactions are highly desirable.

Recently, C_3-symmetric chiral molecules have gained much attention in the area of supramolecular coordination chemistry[8] and molecular recognition.[9] In particular, much progress has been made with C_3-symmetric catalysts for asymmetric transformations.[10] For example, Du reported the C_3-symmetric phosphoramide promoted borane reduction of ketones.[11] Liang et al. developed the C_3-symmetric sulfonamide for the asymmetric reduction of prochiral ketones.[12] Meanwhile, due to its diverse structural features, well-defined coordination geometry and unique chiral environments, C_3-symmetric chiral molecules have great potential in asymmetric catalysis. We anticipated that the synthesis of C_3-symmetric catalysts with a squaric acid moiety, would not only provide a unique chiral environment in asymmetric transformations, but also open a new way for the design and synthesis of novel catalysts. As part of our continuous efforts to design and synthesize novel C_3-symmetric chiral squaramides and their applications in asymmetric transformations,[13] we decided to explore the application of C_3-symmetric squaramides in enantioselective borane reduction. To the best of our knowledge, there has been no report on C_3-symmetric chiral squaramides for the asymmetric borane reduction of a ketone. Chiral C_3-squaramide organocatalyst pioneered by our group have been demonstrated to be a new family of efficient and versatile recyclable organocatalysts for the asymmetric additions of 1,3-dicarbonyl compounds to nitrostyrenes with high enantioselectivity.[13a] We envisioned that the combination of a prolinol framework and a squaric acid skeleton would enhance the enantioselectivity. Moreover, the poor solubility of the C_3-squaramide in organic solvents enabled its easy recovery by a simple precipitation method, allowing its recycling. Herein we report the first C_3-symmetric prolinol-squaramide as a new robust, highly efficient, recyclable catalyst for the enantioselective reduction of ketones by borane.

Based on the above consideration, C_3-symmetrical catalysts **1a**–**e** were synthesized, in which the three chiral subunits were connected with each other via a triamine core. As illustrated in Scheme 1, squaramides **1a**–**c** can be readily prepared in two steps from commercial available squaric acid and proline in 86% yield under mild conditions. In addition, C_3-symmetrical catalysts **1d** and **1e**, possessing the indanol or 2-amino-1,2-diphenylethanol moiety, and the monosquaramide (C_1) **1f** were also prepared for comparison.

2. Results and discussion

With these C_3-symmetric squaramides in hand, their efficiency and activity were examined in detail with α-bromo-acetophenone as a substrate (Table 1). Initially the reaction was conducted in the presence of 5 mol % **1a** in toluene at 0 °C and afforded the (*S*)-product in 83% ee (entry 1).[11] When other solvents such as THF and

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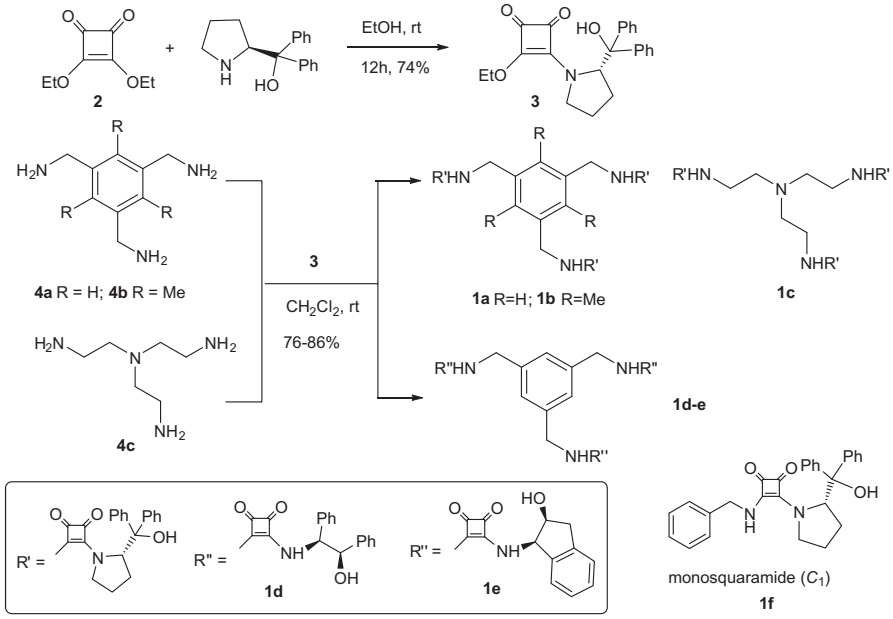
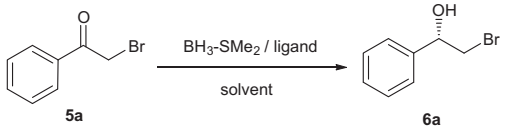


Scheme 1. Preparation of C_3-symmetric squaramides **1a**–**f**.

Table 1
Optimization and catalyst screening for the borane reduction of ketone **5a**[a]



Entry[a]	Catalyst (mol %)	Solvent	Temp (°C)	Yield[b] (%)	ee[c,d] (%)
1	**1a** (5.0)	Toluene	0	89	83
2	**1a** (5.0)	THF	0	90	67
3	**1a** (5.0)	DCM	0	83	78
4	**1a** (5.0)	Toluene	50	93	87
5	**1a** (1.0)	Toluene	50	84	56
6	**1a** (10)	Toluene	50	96	82
7	**1a** (5.0)	Toluene	30	94	93
8	**1b** (5.0)	Toluene	30	86	75
9	**1c** (5.0)	Toluene	30	89	84
10	**1d** (5.0)	Toluene	30	91	7
11	**1e** (5.0)	Toluene	30	84	8
12	**1f** (5.0)	Toluene	30	86	78
13	**1f** (15.0)	Toluene	30	67	80
14	**3** (15.0)	Toluene	30	58	86

[a] Reaction was carried out on a 1.0 mmol scale in 2 mL of solvent, molar of $PhCOCH_2Br$, BH_3–SMe_2 = 1.0:1.1.
[b] (*S*)-product was isolated by column chromatography.
[c] Determined by HPLC analysis using a Daicel Chiralcel column.
[d] An (*S*)-configuration was assigned on the basis of the sign of the specific rotation with that reported in the literature.

dichloromethane were used, the ee decreased (entries 2 and 3). Varying the catalyst loading had an obvious effect on the ee values (entries 5 and 6). Increasing the reaction temperature to 50 °C, resulted in better yield and ee. We were encouraged to observe that 93% ee was obtained in the presence of 5 mol % **1a** at 30 °C (entry 7), as Xu reported the catalytic reduction became faster at 30 °C, then the enantioselectivity improved.[3d,e] The enantioselectivity decreased significantly when changing catalyst **1a** to **1b** (entry 8), which may be due to the existence of the methyl group reducing the steric differentiation between *Si*- and *Re*-face of the transition states. As expected, the more flexible **1c** gave inferior ee to **1a** (entry 9). The C_3-symmetric catalyst based on chiral indanol **1d** or 2-amino-1, 2-diphenylethanol **1e** gave worse enantioselecitvity (entries 10 and 11). It can be inferred that the existence of two N–H groups in the squaramide moiety would disorder the desired transition states. Under the same reaction conditions, in comparison with **1a**, monosquaramide **1f** gave moderate enantioselectivity (entries 12 and 13). When compound **3** was used, the reaction of **5a** with borane formed the desired product in 58% yield and 86% ee (entry 14).

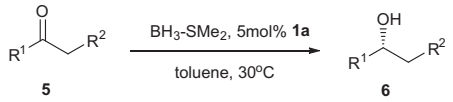
With the optimized conditions in hand, we next investigated the scope of the reduction with respect to the ketone. As summarized in Table 2, a variety of ketones were smoothly reduced to alcohols with good yields and enantioselectivities. Importantly, the presence of substituents on the phenyl ring of α-bromo-acetophenone substrate had no obvious effect on the enantioselectivity (entries 1–11). For example, ketones **5c** and **5g** were reduced to their corresponding alcohols in 90% ee (entries 3 and 7), while, *p*-methyl functionalized α-bromo-acetophenone **5e** gave 85% ee (entry 5). Phenyl alkyl ketones **5j** and **5k**, as well as cyclic 1-tetralone **5l** furnished corresponding alcohols in modest ee values (entries 10–12). Compared with the CBS catalyst, the slight decrease of ee and relatively lower efficiency of our C_3-catalyst might be attributed to the poorer solubility of the C_3-catalyst in the solvent.

The poor solubility of the C_3-squaramide in organic solvents enabled its easy recovery by a simple precipitation method, allowing it to be recycled. We decided to test the recyclability of our reagents. To determine the recycling ability of the catalyst, **1a** was recovered after the catalytic process by precipitation from the reaction mixture with the addition of ethyl ether, and after simple filtration through a silica pad, reused in the reduction of **5a** by borane under the optimized reaction (Table 3). We were pleased to observe that the recovered catalyst retained its high activity and enantioselectivity and can be reused four times without a loss of reactivity or enantioselectivity.

3. Conclusions

New C_3-symmetric prolinol-squaramides have been successfully prepared in two steps from commercially available squaric acid and proline with excellent yields. We have demonstrated that

Table 2
Reaction scope for the reduction of ketones by borane

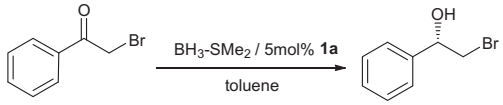


5 6

Entry[a]	R^1	R^2	Yield[b] (%)	ee[c] (%)
1	Phenyl **5a**	Br	94	93 (*S*)
2	3-Bromophenyl **5b**	Br	93	90 (−)[d]
3	4-Fluorophenyl **5c**	Br	95	90 (−)[d]
4	4-Bromophenyl **5d**	Br	91	88 (*S*)
5	4-Methylphenyl **5e**	Br	90	85 (*S*)
6	4-Nitrophenyl **5f**	Br	81	50 (*S*)
7	4-Fluorophenyl **5g**	Cl	95	90 (*S*)
8	4-Bromophenyl **5h**	Cl	91	84 (*S*)
9	Phenyl **5i**	H	92	68 (*R*)
10	Phenyl **5j**	Me	92	68 (*R*)
11	Phenyl **5k**	Et	92	70 (*R*)
12	1-Tetral **5l**	H	83	70 (*R*)

[a] Reaction was carried out on a 0.5 mmol scale in 1 mL toluene, the molarity of $PhCOCH_2Br$, BH_3–SMe_2 = 1.0:1.1.
[b] Isolated yield by column chromatography.
[c] Determined by HPLC analysis using a Daicel Chiralcel column, the absolute configuration of the product was assigned by the sign of the specific rotation with that reported in the literature.[3e,14–16]
[d] Not determined.

Table 3
Recycling experiments of **1a** in the reduction of **5a**



5a 6a

Cycle[a]	1	2	3	4
Recovery (%)	88	85	86	85
Yield[b] (%)	90	92	90	91
ee[c] (%)	92	90	90	89

[a] Reaction was carried out on a 1.0 mmol scale in 2 mL toluene, molar of $PhCOCH_2Br$, BH_3–SMe_2 = 1.0:1.1.
[b] Isolated yield by column chromatography.
[c] Determined by HPLC analysis using a Daicel Chiralcel column.

catalyst **1a** is a readily available, efficient, and recoverable reagent for the asymmetric reduction of ketones by borane. Further applications of the newly constructed C_3-symmetric squaramides to other asymmetric transformations are underway.

4. Experimental

4.1. Materials and methods

Unless otherwise noted, reagents and materials were obtained from commercial suppliers and used without further purification. All solvents were purified according to the reported procedures. Reactions were monitored by thin layer chromatography (TLC) and column chromatography purifications were performed using 230–400 mesh silica gel. Melting points were uncorrected and measured on an SGW X-4 apparatus. ^1H and ^{13}C NMR spectra were obtained on a Bruker DPX400 apparatus in $CDCl_3$ or DMSO-d_6 with TMS as an internal standard. High resolution MS data were determined by IonSpec 4.7 Tesla FTMS instrument. Enantiomeric excesses (ee value) were determined by HPLC analysis

4.2. Representative procedure for the synthesis of C_3-symmetric squaramides 1a–e

To a solution of **2** (382 mg, 1.01 mmol) in CH_2Cl_2 (10 mL) was added a solution of amine **3** (53.8 mg, 0.33 mmol) in MeOH (2 mL) under a N_2 atmosphere. After 48 h, the reaction was completed (monitored by TLC) and the reaction mixture was concentrated and purified by column chromatography to give product **1a** as a yellowish solid 328 mg (86% yield). Mp 228–230 °C, $[\alpha]_D^{23} = +78.6$ (*c* 3, DMSO), ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 3H), 7.35 (br, 30H), 4.93 (s, 3H), 4.77 (s, 3H), 4.37 (s, 3H), 3.88 (br, 6H), 2.62 (s, 3H), 2.20 (s, 3H), 2.14–1.62 (m, 6H), 1.45 (s, 3H), 0.91–0.42 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.64, 182.10, 168.28, 167.34, 137.77, 135.74, 127.57, 127.42, 127.14, 127.12, 126.98, 126.61, 78.23, 66.86, 48.84, 45.27, 28.76, 21.53. HRMS (ESI) calcd for $C_{72}H_{66}N_6O_9Na$ $[M+Na]^+$ 1181.4751; found 1181.4783.

Compound **1b**: Mp 234–238 °C; $[\alpha]_D^{23} = +82.7$ (*c* 3, DMSO), ^1H NMR (400 MHz, DMSO-d_6) δ 7.79–7.63 (m, 3H), 7.49 (d, *J* = 7.6 Hz, 6H), 7.37 (t, *J* = 7.6 Hz, 6H), 7.26 (dd, 15H), 4.99 (s, 3H), 4.03 (dd, *J* = 14.2, 7.1 Hz, 3H), 3.74 (s, 6H), 3.70–3.33 (m, 6H), 2.35 (d, 6H), 2.11–2.00 (m, 3H), 1.86 (s, 3H), 1.74 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.61, 182.56, 170.34, 167.26, 144.84, 137.48, 136.95, 132.69, 132.32, 129.59, 128.56, 127.75, 127.38, 127.34, 127.23, 127.10, 126.95, 126.81, 80.88, 59.75, 49.90, 45.39, 30.80, 27.10, 23.17. HRMS (ESI) calcd for $C_{75}H_{72}N_6O_9Na$ $[M+Na]^+$ 1223.5238; found 1223.5253.

Compound **1c**: Mp: 208–212 °C; $[\alpha]_D^{23} = +33.6$ (*c* 3, DMSO), ^1H NMR (400 MHz, DMSO-d_6) δ 7.54 (s, 6H), 7.37 (t, *J* = 7.5 Hz, 6H), 7.29 (d, *J* = 3.4 Hz, 9H), 7.17 (d, *J* = 7.5 Hz, 9H), 5.49–4.84 (m, 3H), 4.06–3.87 (m, 3H), 3.73 (s, 9H), 3.42–3.27 (m, 9H), 2.11 (t, *J* = 12.5 Hz, 3H), 1.91 (d, *J* = 6.3 Hz, 3H), 1.79 (t, *J* = 13.9 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.51, 182.03, 170.35, 167.31, 144.80, 127.73, 127.34, 127.14, 126.92, 126.82, 59.75, 53.34, 49.90, 45.46, 27.23, 23.05. HRMS (ESI) calcd for $C_{69}H_{69}N_7O_9Na$ $[M+Na]^+$ 1162.5060; found 1162.5049.

Compound **1d**: Mp: 235–240 °C; $[\alpha]_D^{23} = -25.3$ (*c* 3, DMSO), ^1H NMR (400 MHz, DMSO-d_6) δ 8.40–7.73 (m, 6H), 7.27 (s, 33H), 5.90 (s, 3H), 5.36 (s, 3H), 5.12 (s, 3H), 4.81 (d, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.55, 182.40, 167.27, 166.95, 142.00, 139.75, 138.75, 138.68, 128.02, 127.68, 127.60, 127.14, 127.05, 126.56, 126.51, 126.21, 84.81, 75.21, 62.62, 46.79, 46.50. HRMS (ESI) calcd for for $C_{63}H_{54}N_6O_9Na$ $[M+Na]^+$ 1061.3877; found 1061.3844.

Compound **1e**: Mp: 233–238 °C; $[\alpha]_D^{23} = +14.1$ (*c* 1.7, DMSO), ^1H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 3H), 7.89 (d, *J* = 8.6 Hz, 3H), 7.38 7.24 (m, 15H), 5.51 (s, 6H), 4.84 (d, *J* = 5.9 Hz, 6H), 4.58 (s, 3H), 3.14 (dd, *J* = 16.1, 4.5 Hz, 3H), 2.89 (d, *J* = 16.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.67, 182.60, 167.73, 167.41, 141.77, 140.46, 139.87, 127.84, 126.64, 126.11, 125.05, 124.22, 72.37, 60.79, 56.03, 46.70. HRMS (ESI) calcd $C_{48}H_{42}N_6O_9Na$ $[M+Na]^+$ 869.2941; found 869.2905.

4.3. Standard procedure for the asymmetric reduction of ketones

Under an argon atmosphere, $BH_3{\cdot}SMe_2$ (1.1 mmol) was added to a suspension of C_3-catalyst **1a** (0.05 mmol) in toluene (2 mL) at 0 °C. The mixture was stirred for 3 h at room temperature and heated at 30 °C for 1 h. Then the ketone (1.0 mmol) was added over a period of 1.5 h and the mixture was stirred for another 1 h. The reaction mixture was quenched by the addition of water (2 mL) and extracted with CH_2Cl_2 three times. The combined organic extracts were washed with brine and dried over $MgSO_4$. After evaporating the solvent under reduced pressure, the product was isolated by flash

column chromatography on silica gel. The ee value was determined by HPLC with Chiralcel AJ-H or Chiralcel OD-H columns.

Compound **6a**: Chiralcel OD column (250 mm × 4.6 mm), 2% *i*PrOH/hexane, 1.0 mL/min, 220 nm. Rt_{minor} = 26.973 min; Rt_{major} = 23.797 min. $[\alpha]_D^{23} = +48.3$ (*c* 1, $CHCl_3$), Lit.[15] $[\alpha]_D^{20} = +52.3$ (*c* 1, $CHCl_3$).

Compound **6b**: Chiralcel OJ-H column (250 mm × 4.6 mm), 2% *i*PrOH/hexane, 1 mL/min, 220 nm. Rt_{major} = 51.413 min; Rt_{minor} = 38.492 min. $[\alpha]_D^{20} = +22.3$ (*c* 0.95, $CHCl_3$).

Compound **6c**: Chiralcel OJ-H column (250 mm × 4.6 mm), 2% *i*PrOH/hexane, 1 mL/min, 220 nm. Rt_{major} = 42.975 min; Rt_{minor} = 41.128 min. $[\alpha]_D^{20} = +30.6$ (*c* 0.64, $CHCl_3$).

Compound **6d**: Chiralcel OJ-H column (250 mm × 4.6 mm), 2% *i*PrOH/hexane, 1 mL/min, 220 nm. Rt_{minor} = 42.897 min; Rt_{major} = 48.630 min. $[\alpha]_D^{20} = +27.6$ (*c* 0.41, $CHCl_3$). Lit.[16] $[\alpha]_D^{23} = +42.7$ (*c* 1, $CHCl_3$).

Compound **6e**: Chiralcel OD column (250 mm × 4.6 mm), 2% *i*PrOH/hexane, 1.0 mL/min, 220 nm. Rt_{minor} = 22.632 min; Rt_{major} = 19.827 min. $[\alpha]_D^{20} = +34.7$ (*c* 0.63, $CHCl_3$). Lit.[15] $[\alpha]_D^{23} = +41.8$ (*c* 1, $CHCl_3$).

Compound **6f**: Chiralcel OD column (250 mm × 4.6 mm), 2% *i*PrOH/hexane, 1.0 mL/min, 220 nm. Rt_{major} = 30.458 min; Rt_{minor} = 25.225 min. $[\alpha]_D^{20} = +34.5$ (*c* 0.27, $CHCl_3$), Lit.[16] $[\alpha]_D^{23} = +60.8$ (*c* 0.4, $CHCl_3$).

Compound **6g**: Chiralcel OJ-H column (250 mm × 4.6 mm), 2% *i*PrOH/hexane, 1 mL/min, 220 nm. Rt_{major} = 43.297 min; Rt_{minor} = 41.187 min. $[\alpha]_D^{20} = +47.0$ (*c* 0.21, $CHCl_3$), Lit.[16] $[\alpha]_D^{23} = +51.1$ (*c* 1, $CHCl_3$).

Compound **6h**: Chiralcel OJ-H column (250 mm × 4.6 mm), 2% *i*PrOH/hexane, 1 mL/min, 220 nm. Rt_{major} = 41.832 min; Rt_{minor} = 36.842 min. $[\alpha]_D^{20} = +27.5$ (*c* 0.2, $CHCl_3$), Lit.[15] $[\alpha]_D^{23} = +35.9$ (*c* 1.1, $CHCl_3$).

Compound **6i**: Chiralcel OD column (250 mm × 4.6 mm), 2% *i*PrOH/hexane, 1.0 mL/min, 220 nm. Rt_{major} = 15.988 min; Rt_{minor} = 20.677 min. Lit.[16] $[\alpha]_D^{23} = +51.2$ (*c* 1.1, $CHCl_3$).

Compound **6j**: Chiralcel OD column (250 mm × 4.6 mm), 2% *i*PrOH/hexane, 1.0 mL/min, 220 nm. Rt_{minor} = 17.722 min; Rt_{major} = 19.183 min. Lit.[16] $[\alpha]_D^{23} = +37.1$ (*c* 0.9, $CHCl_3$).

Compound **6k**: Chiralcel OD column (250 mm × 4.6 mm), 2% *i*PrOH/hexane, 1.0 mL/min, 220 nm. Rt_{minor} = 16.367 min; Rt_{major} = 17.645 min. $[\alpha]_D^{20} = +30.5$ (*c* 0.2, $CHCl_3$), Lit.[15] $[\alpha]_D^{23} = +47.6$ (*c* 0.5, $CHCl_3$).

Compound **6l**: Chiralcel OD column (250 mm × 4.6 mm), 2% *i*PrOH/hexane, 1.0 mL/min, 220 nm. Rt_{major} = 23.035 min; Rt_{minor} = 18.758 min. $[\alpha]_D^{20} = -20.8$ (*c* 0.25, $CHCl_3$), Lit.[16] $[\alpha]_D^{23} = -32.5$ (*c* 1.0, $CHCl_3$).

Acknowledgments

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