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Synthesis of Bis-*N*-squaramidoacids and their Applications to Asymmetric Reduction of Prochiral Ketone and Diketones

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Abstract: A series of novel bis-squaramidoacid ligands were prepared. Prochiral ketone and diketones were direct reduced by borane in the presence of these ligands giving secondary alcohol products with enantiomeric excesses up to 64.2% for ω-bromoacetophenone and 90.0% for 1, 6-diphenyl-1, 6-hexanedione.

Keywords: Bis-squaramidoacid, asymmetric reduction, ketone.

Asymmetric reduction of prochiral ketones with borane catalyzed by various chiral aminoalcohols ligands has been deeply researched in recent years[1, 2]. In these studies, excellent results including chemical yields and enantiomeric excesses were achieved and the mechanism of the reaction was studied. Among these chiral aminoalcohols, chiral mono-squaramidoalcohols have been proven to be efficient chiral ligands for enantioselective reduction of prochiral ketones[3-8]. Some C^2-symmetric bis- squaramidoalcohols with bicatalytic center were applied in asymmetric reduction of diketones[3,6,7]. They showed good to excellent enantioselectivities due to the bicatalytic center, which is able to match with the diketone.

As a cheap and commercially available chiral source, amino acids can also be used in asymmetric reduction of prochiral ketones without being reduced to amino alcohols previously[9]. In our lab, we replaced the aminoalcohol groups to amino acids and got a series of novel mono-*N*-squaramidoacid ligands, which are more convenient to prepare[10]. These ligands were applied to asymmetric reduction of prochiral aromatic ketones, it was found that some of them afforded secondary alcohols with good yields and high enantiomeric excesses. In this paper, we synthesized a series of bis-squaramidoacid ligands, which is utilized in the asymmetric reduction of prochiral ketone and diketones. Some good results were obtained.

We designed two routes to synthesize these bis-squaramidoacid ligands. We synthesized bis-squaryl proline by method I and II as shown in **Scheme 1**. In method I, we prepared mono-*N*-squaryl proline from squaryl diester **1**, which was obtained through esterification of squaric acid. Subsequent reaction between **1** and (R,R)-1,2- diphenyl-ethylene-diamine gave bis-squaryl proline **4a**.

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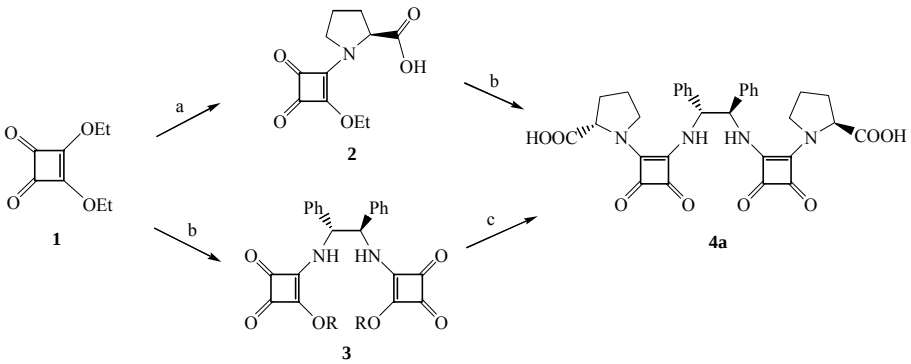
Scheme 1 Synthesis of bis-squaramidoacid

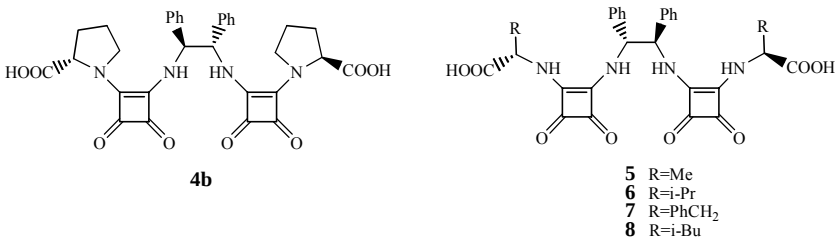


Method I: (a) L-proline, Et_3N, DMAP, EtOH. (b) (R, R)-1, 2- diphenylethylenediamine, EtOH, Et_3N.

Method II: (b) (R, R)-1, 2- diphenylethylenediamine, EtOH, Et_3N. (c) L-proline, Et_3N, DMAP, EtOH or $CHCl_3$ as solvent.

We also prepared the same product by another method in which **1** were bridged with (R,R)-1,2-diphenylethylenediamine previously[11] and then reacted with L-proline. We found that method II is more efficient for ligand **4** when chloroform was used as solvent in step c (64% yield for **4a**). However, for other amino acids such as L-alanine, L-valine, *etc*. reaction in ethanol could give higher chemical yields (70% yield for **5**). Bis-squaramidoacids **4b**, **5**~**8** were synthesized in the same way, and their structures are shown in **Scheme 2**. All the ligands are new compounds and their structures were confirmed by several analytic methods.

Scheme 2 Bis-squaramidoacid ligands **4b**, **5**~**8**

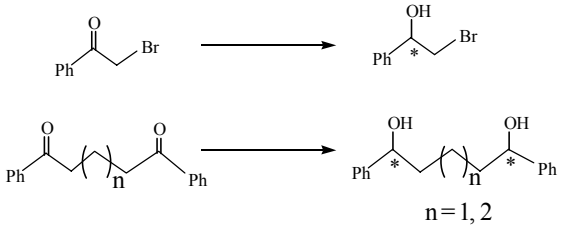


Then we applied these bis-squaramidoacids as chrial ligands to asymmetric borane reduction of ω-bromoacetophenone and diketones as shown in **Scheme 3**.

In a typical procedure, the chiral ligand was dissolved in 3 mL of toluene under argon atmosphere. Then BH_3/Me_2S (0.6 mmol, 1.2 equiv.) was added, cooling in ice bath. The mixture was stirred for 30 minutes at 0°C and then 2 hours at room temperature. The solution of ketone (0.5 mmol) in 2 mL toluene was added slowly over 1 hour and stirred for additional 2 hours. The reaction was quenched by 8 mL of 1mol/L HCl at 0°C and the water layer was extracted with ethyl acetate (3×15 mL). The

combined organic layer was dried with anhydrous $MgSO_4$. Then removed the solvent under reduced pressure. The residue was purified through silica gel column (10:1 petro ether : AcOEt as eluent).

Scheme 3 Asymmetric borane reduction of ω-bromoacetophenone and diketones



The results are summarized in **Table 1**. In the asymmetric reduction of ω-bromoacetophenone, only bis-squaryl proline shows good catalytic activity. Others bis-squaramidoacid ligands only gave the alcohol product with poor ee values. The configuration of the diamine backbone did not seem to affect the configuration of the alcohol product, for both bis-squaryl prolines bridged by (R, R) and (S, S)-1, 2-diphenylethylenediamine afforded the alcohol product with S configuration (Entries 1and 5). It demonstrates that the catalytic center is not at the diamine but at the amino acid positions.

Table 1 Asymmetric reduction of prochiral ketones using bis-squaramidoacids as chiral ligands[a]

Entry	Ligands (equiv.)	Ketone	Temp. (°C)	ee (%)[b]	Config.
1	**4a** (0.05)	$PhCOCH_2Br$	40	0	-
2	**4a** (0.05)	$PhCOCH_2Br$	70	64.2	S
3	**4b** (0.05)	$PhCOCH_2Br$	70	54.3	S
4	**4a** (0.05)	$PhCOCH_2Br$	90	56.0	S
5	**4a** (0.05)	$PhCOCH_2Br$	105	63.0	S
6	**5** (0.05)	$PhCOCH_2Br$	70	11.0	S
7	**7** (0.05)	$PhCOCH_2Br$	70	39.0	S
8	**4a** (0.1)	$PhCO(CH_2)_3COPh$	70	75.2	R, R
9	**4a** (0.1)	$PhCO(CH_2)_4$ COPh	70	90.0	R, R
10	**5** (0.1)	$PhCO(CH_2)_3$ COPh	70	10.8	R, R
11	**6** (0.1)	$PhCO(CH_2)_3$ COPh	70	24.4	R, R
12	**7** (0.1)	$PhCO(CH_2)_3$ COPh	70	10.1	R, R
13	**8** (0.1)	$PhCO(CH_2)_3$ COPh	70	28.2	R, R

a. All of the chemical yield were >80% (isolated yield).

b. ee values were determined by comparing the optical rotation to optical pure alcohol. Maximum rotations: $[\alpha]_D$ -22.86 (c 1, MeOH) for (S, S)-1, 5-diphenyl-1, 5-dihydroxyl pentane 99% ee with 2% of meso isomer[12]; $[\alpha]_D$ -12.6 (c 1, MeOH) for (S, S)-1, 6-diphenyl-1, 5-dihydroxyl pentane 99% ee with 1% of meso isomer[12].

We also applied these ligands to the asymmetric borane reduction of diketones. Good enantiomeric excesses were achieved when the bis-squaryl proline was used.

Better ee values were obtained in the reduction of 1, 6-diphenyl-1, 6-hexanedione (ee 90%, entry 9) than 1, 5-diphenyl-1, 5-pentenedione (ee 75%, entry 8). It is proposed that the bis-catalytic center matched better with the former than with the latter.

Acknowlegments

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References

1. L. Deloux, M. Srebnik, *Chem. Rev.,* **1993**, *93* (2), 763.
2. E. J. Corey, C. J. Helal, *Angew. Chem.*, *Int. Ed. Engl*., **1998**, *37* (15), 1986.
3. H. B. Zhou, S. M. Lü, R. G. Xie, Z. Y. Zhou, A. S. C. Chan, T. K. Yang, *Tetrahedron Lett.,* **2001**, *42* (6), 1107.
4. J. Zhang, H. B. Zhou, S. M. Lü, M. M. Luo, R. G. Xie, M. C. K. Choi, Z. Y. Zhou, A. S. C. Chan, T. K. Yang, *Tetrahedron: Asymmetry*, **2001**, *12* (13), 1907.
5. H. B. Zhou, J. Zhang, S. M. Lü, R. G. Xie, Z. Y. Zhou, M. C. K. Choi, A. S. C. Chan, T. K. Yang, *Tetrahedron,* **2001**, *57* (45), 9325.
6. S. M. Lü; H. B. Zhou, R. G. Xie, Z. Y. Zhou, A. S. C. Chan, T. K. Yang, *Huaxue Xuebao* (*Acta Chimica Sinica, Chinese*), **2001**, *59* (4), 587.
7. S. M. Lü, H. B. Zhou, J. Zhang, R. G. Xie, Z. Y. Zhou, A. S. C. Chan, T. K. Yang, *Gaodeng Xuexiao Huaxue Xuebao* (*Chem. J. Chin. Univ., in Chinese*), **2001**, *22* (11), 1847.
8. S. M. Lü, H. B. Zhou, R. G. Xie, X. X. Sun, *Sichuan Daxue Xuebao, Ziran Kexueban* (*J. Sichuan Univ., Nat. Sci. Ed., in chinese*), **2000**, *37* (5), 736.
9. S. Huang, B. Wang, Z. Shan, D. Zhao, *Synth. Commun*., **2000**, *30* (13), 2423.
10. J. Zhang, L. L. Li, J. J. Chen, K. B. Yu, R. G. Xie, *Tetrahedron: Asymmetry*, submitted.
11. H. B. Zhou, *Ph. D. Thesis*, Sichuan University, **2000**.
12. G. J. Quallich, K. N. Keavey, T. M. Woodall, *Tetrahedron Lett*., **1995**, *36* (26), 4729.
13. The analytical data of 4, 5, 6, 7, 8 were submitted to editorial office of CCL.

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