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Design and Synthesis of Novel C_2-Symmetric Chiral Piperazines and an Application to Asymmetric Acylation of σ-Symmetric 1,2-Diols

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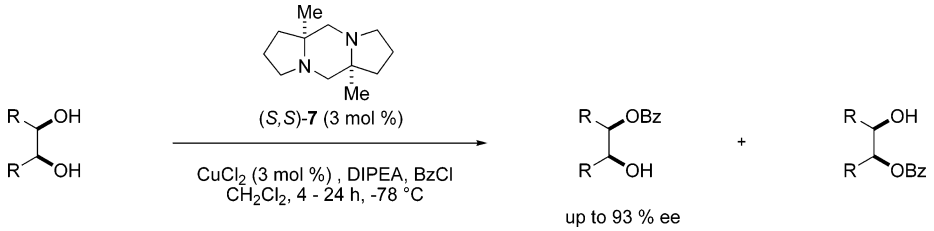
ABSTRACT



A novel alicyclic chiral C_2-symmetric piperazine, (*S*,*S*)-7, is designed and synthesized from L-proline. Benzoylation of a series of cyclic and acyclic *meso*-1,2-diols with a catalytic amount of (*S*,*S*)-7 and $CuCl_2$ provided optically active monobenzoates with high enantioselectivity.

Designing of new chiral ligands to improve enantioselectivity of organic reactions has become an important issue. Chiral tertially diamines (**1**−**5**) have been used as efficient chiral inductors, particularly (−)-sparteine (**1**) and bisoxazoline (**3**) have been found to be effective in many asymmetric transformations.[1] Our project has focused on the development of a new class of C_2-symmetric alicyclic chiral diamines. In this article, we describe the design and the synthesis of a novel C_2-symmetric chiral alicyclic tertiary diamine, (5a*S*,10a*S*)-5a,10a-dimethyldecahydrodipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine ((*S*,*S*)-**7**, DMPP), and its application to asymmetric desymmetrization of *meso*-1,2-diols by enantioselective monoacylation.

Prior to the synthesis of (*S*,*S*)-**7**, we reinvestigated the synthesis of (5a*S*,10a*S*)-decahydrodipyrrolo[1,2-*a*:1′,2′-*d*]-pyrazine ((*S*,*S*)-**6**, DHPP), which was reported by Breitmeier and co-worker,[2] by intramolecular aminolysis of L-proline methyl ester at high temperature followed by $LiAlH_4$ reduction. Unfortunately, their experimental procedure was not reproducible and the product was obtained in low yield and contained inseparable unidentified impurity. In addition, their reported ^{13}C NMR spectra indicates ten ^{13}C-signals for the structure of (*S*,*S*)-**6** even though it has C_2-symmetry,

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(1) (a) Nozaki, H.; Aratani, T.; Toraya, T. *Tetrahedron Lett.* **1968**, 4097. (b) Mukaiyama, T.; Asami, S. *Top. Curr. Chem.* **1985**, *127*, 133. (c) Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213. (d) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708. (e) Park, Y. S.; Boys, M.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757. (f) Hodgson, D. M.; Lee, G. P. *Chem. Commun.* **1996**, 1015. (g) Bennan, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161. (h) Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574. (i) Hoppe, D. M.; Hense, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2282 and references sited therein. (j) Lucet, D.; LeGall, T.; Mioskwski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (k) Li, X.; Schenkel, L. B.; Kozlowski, M. C. *Org. Lett.* **2000**, *2*, 875. (l) Ganguly, B.; Freed, D. A.; Kozlowski, M. C. *J. Org. Chem.* **2001**, *66*, 1103. (m) Xu, Z.; Kozlowski, M. C. *J. Org. Chem.* **2002**, *67*, 3072. (n) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 1870. (o) Kozlowski, M. C.; Li, X.; Carroll, P. J.; Xu, Z. *Organometallics* **2002**, *21*, 4513. (p) Phuan, P.-W.; Ianni, J. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 15473.
(2) Zadel, G.; Breitmaier, E. *Chem. Ber.* **1994**, *127*, 1323.

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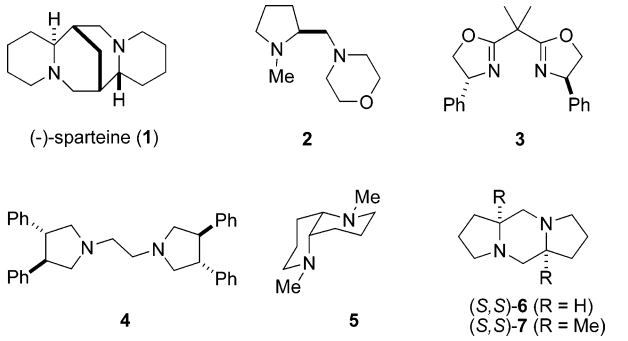
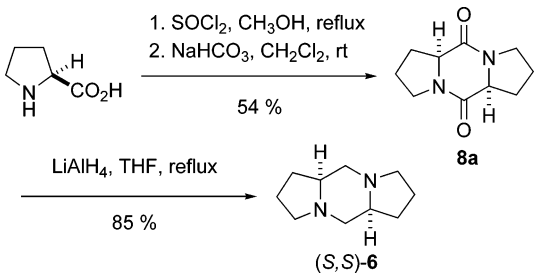


Figure 1. Chiral tertially diamines.

which should give five ^{13}C-signals. It is implied that the product obtained by Breitmeier's procedure may not be chemically and/or optically pure. Therefore, we modified the procedure of the multigram scale preparation of (*S*,*S*)-**6** as follows (Scheme 1). L-Proline methyl ester hydrochloride,

Scheme 1. Modified Synthesis of (*S*,*S*)-**6**



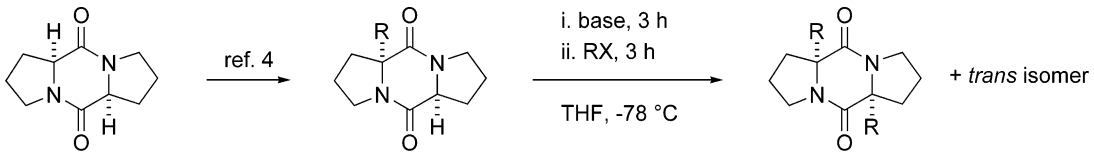
obtained by thionyl chloride in methanol, was neutralized with sodium bicarbonate (powder) in dichloromethane and the resulting precipitate was filtered and the filtrate was concentrated in vacuo. Then, the neat residue was stirred at room temperature for several days. The resulting diketopiperazine **8a**[3] was purified by silica gel column chromatography and recrystallization. Reduction of **8a** with $LiAlH_4$ and bulb-to-bulb distillation gave pure (*S*,*S*)-**6**, with only five ^{13}C NMR signals as expected, in high yield.

With the chiral diamine (*S*,*S*)-**6** in hand, synthesis of a variety of subsutituted chiral diamines, which may have enhanced potential as the chiral ligand for asymmetric catalyst, was investigated here. Diastereoselective alkylation of **8a** via potassium enolate with Romo's method[4] gave the monoalkylated products **8b**−**d** in good yield. Then, an introduction of the same alkyl group on another bridgehead carbon center was attempted to obtain C_2-symmetric *cis*-dialkylated products. However, obtaining C-methylation of monomethyl diketopiperazine **8b** by conventional methods with LDA or KHMDS as the hindered base and iodomethane in THF was unsuccessful. It was assumed that the methyl group on the bridgehead interfered with the approach of the amide base, therefore we employed lithium diethylamide (LDEA), a more accessible base than the hindered LDA, to give the desired chiral *cis*-dimethyl isomer **9b** in good yield as sole diastereomer (Table 1). Unfortunately, synthesis of *cis*-diallyl (**9c**) and *cis*-dibenzyl (**9d**) analogues was unsuccessful to give undesired achiral *trans*-isomers predominantly, presumably due to severe steric hindrance between the first alkyl group on the bridgehead center and the electrophile.

Finally, reduction of **8b** with $LiAlH_4$ gave the chiral diamine (*S*,*S*)-**7**, which was purified as dipicrate and regenerated by neutralization in 67% yield from **8b** (Scheme 2).

Acylation of alcohol is one of the most essential reactions in organic synthesis and many asymmetric acylations have been developed for preparation of small chiral compounds well suited for further manipulation of the optically active molecules. Enzymatic acylation of racemic alcohols by kinetic optical resolution and desymmtetrization of prochiral diols have been extensively studied[5] and almost established as potential methods for the preparation of certain chiral alcohol variants. Recently, catalytic asymmetric acylation of alcohols with achiral acylating agents has emerged in

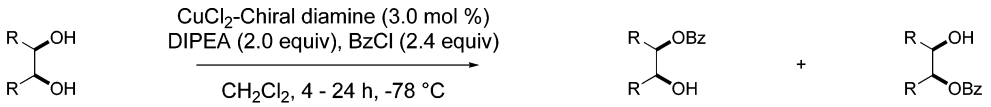
Table 1. Diastereoselective Alkylation of Diketopiperazine

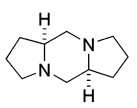


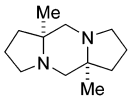
entry	diketopiperazine	base	RX	yield (%)[a]	cis:trans[b]
1	**8b** (R = Me)	KHMDS	MeI	N.R.	
2	**8b**	LDA	MeI	N.R.	
3	**8b**	LDA + HMPA	MeI	N.R.	
4	**8b**	LDEA	MeI	75	1:0
5	**8c** (R = allyl)	LDEA	AllylBr	65	1:8[c]
6	**8d** (R = Bn)	LDEA	BnBr	78	0:1

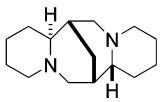
[a] Yield of dialkylated product (cis and/or trans) from **8b**−**d**. [b] Ratio was obtained by ^{1}H NMR of the crude mixture. [c] Inseparable mixture of epimers.

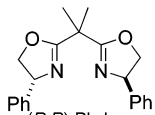
Table 2. Asymmetric Benzoylation of *meso*-1,2-Diols Catalyzed by $CuCl_2$-Chiral Diamines

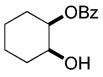
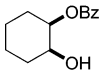
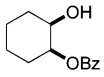
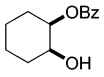
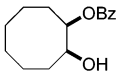
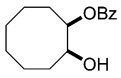
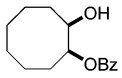
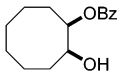
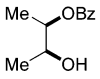
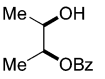
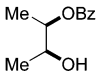
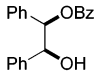
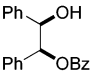
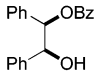



(*S*,*S*)-**6**


(*S*,*S*)-**7**


(-)-sparteine


(*R*,*R*)-Ph_2box

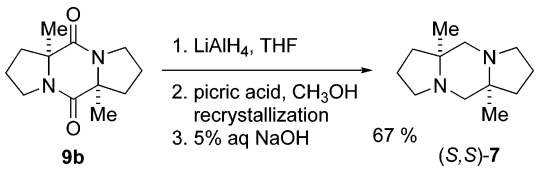
major enantiomer	%	% ee[a]	major enantiomer	%	% ee[a]	major enantiomer	%	% ee[a]	major enantiomer	%	% ee[a]
	56	18		73	79		61	66		20	12
	80	91		100	93		80	94		32	56
	82	31		82	70		98	77		98	39
	58	3		77	92		55	94		51	78
	66	70		73	86		98	97		86	59

[a] Optical purity was determined by chiral HPLC.

succession.[6] Matsumura and co-workers reported excellent asymmetric acylation catalyzed by the complex of $CuCl_2$ and chiral bisoxazoline. Here, we applied chiral piperazine (*S*,*S*)-**7** (DMPP) as the ligand to the above-noted asymmetric acylation.

Benzoylation of *meso*-1,2-diols with 3 mol % of $CuCl_2$-chiral diamines, such as (*S*,*S*)-**6**, (*S*,*S*)-**7**, (−)-sparteine, and bisoxazoline, for comparison, provided optically active monobenzoates in moderate to excellent enantioselectivity (Table 2). Desymmetrization of all the *meso*-diols investigated was achieved in high enantioselectivity with $CuCl_2$−(*S*,*S*)-**7** complex, while use of $CuCl_2$−bisoxazoline and $CuCl_2$−(*S*,*S*)-**6** exhibited relatively low optical yield. It was demonstrated that an introduction of two methyl groups on bridgehead centers of (*S*,*S*)-**6** greatly enhanced the enantioselectivity. Interestingly, $CuCl_2$−(−)-sparteine complex showed high enantioselectivity giving the antipodes of mono-

Scheme 2. Reduction of Dimethyldiketopiperazine



9b (*S*,*S*)-**7**

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benzoates obtained by use of the $CuCl_2$−(*S*,*S*)-**7** complex. Although the availability of D-proline is severely limited, (−)-sparteine could serve as the pseudoenantiomer of (*S*,*S*)-**7**.

In conclusion, the synthesis of the novel class of alicyclic chiral piperazine ligand (*S*,*S*)-**7** has been developed. It was also demonstrated that (*S*,*S*)-**7** is an effective ligand for copper-catalyzed asymmetric acylation of *meso*-1,2-diols. Mechanistic studies of asymmetric acylation and further application of other asymmetric transformations with (*S*,*S*)-**7** are currently under investigation.

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Supporting Information Available: Synthetic procedure, spectral and analytical data for (*S*,*S*)-**6**, (*S*,*S*)-**7**, and asymmetric acylation of *meso*-1,2-diols. This material is available free of charge via the Internet at http://pubs.acs.org.

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