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Lithium diisopinocampheylamide: a new and highly effective chiral catalyst in the enantioselective deprotonation of *meso*-epoxides

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Dedicated to Professor Herbert C. Brown on his 90th birthday

Abstract—α-Pinene based novel chiral lithium amides have been used for the catalytic enantioselective deprotonation of cyclohexene oxide. An enantiomeric excess of up to 95% for (*R*)-2-scyclohexen-1-ol was achieved with lithium (−)-*N*,*N*-diisopinocampheylamide. A systematic study shows that the isopinocampheyl moiety plays an important role in achieving high enantioselectivity.

1. Introduction

Asymmetric synthesis using chiral lithium amides is emerging as a useful method for the preparation of non-racemic compounds.[1–6] These chiral bases have been exploited in a variety of efficient enantioselective reactions such as deprotonation of prochiral cyclic ketones,[7] kinetic resolution of racemic ketones,[8] enantioselective dehydohalogenation,[9] alkylation of achiral ketones,[10] deracemization of chiral ketones by protonation,[11] etc. These methodologies offer the advantage that the chiral auxiliaries can be easily recycled, thereby making the process both effective and cost efficient. Rearrangement of *meso*-epoxides into optically active allylic alcohol using chiral lithium amide is of great interest and has received much attention as a useful method for the preparation of chiral products.[1–6] This transformation has been applied in the synthesis of biologically important compounds such as lasiol,[12] prostagladin precursors,[13] carbovir,[14] faranal,[15] and leukotrienes.[16] In most cases, however, the procedure requires more than a stoichiometric amount of the chiral base. Therefore, development of an effective, readily available and cost efficient catalytic system using a chiral lithium amide is currently a significant challenge in this growing area of chemistry.

There are only a few reports where good enantioselectivities have been seen when less than a stoichiometric amount of chiral base has been used.[17–23] In these cases high ee is reported with the use of an additive or a co-solvent in the reaction medium. The current study reports the application of new chiral secondary amines based on α-pinene, in the catalytic enantioselective deprotonation of cyclohexene oxide **1**, to the product 2-cyclohexen-1-ol, **2** (Eq. (1)). These amines were employed in catalytic amounts in combination with an excess of achiral lithium amide to achieve the deprotonation of prochiral epoxide **1** to obtain the corresponding optically active allylic alcohol **2**. The reactions were carried out in THF in the absence of any additive or co-solvent.

2. Results and discussion

Remarkable success has been achieved with a large number of pinane-based reagents, for various organic transformations resulting in the formation of optically active compounds.[24] However, almost all the pinene based reagents are effective in the stoichiometric amount. Since both the (+)- and (−)-isomers of α-pinene are readily available commercially, an enantioselective catalyst with this moiety be highly useful in providing the product with desired absolute configura-

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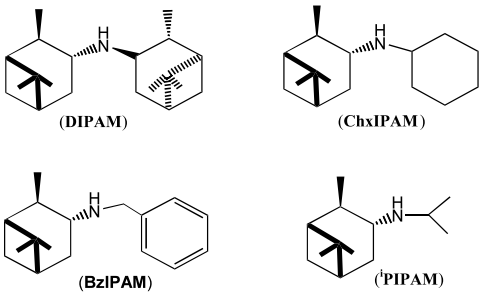
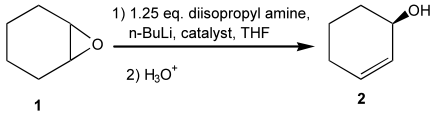
tion. With this rationale in mind, a study to investigate the possibility of developing a catalytic process with lithium salts of α-pinene-based chiral ligands was initiated.[25]



Initially, C_2-symmetric (−)-*N*,*N*-diisopinocampheylamine **DIPAM**, prepared from (+)-α-pinene was used for catalytic deprotonation of cyclohexene oxide.[26] Also, in order to study the effect of the ispinocampheyl (α-pinene) moiety in creating chiral pocket for deprotonation, other chiral auxiliaries namely *N*-cyclohexyl-*N*-isopinocampheylamine **ChxIPAM**, *N*-benzyl-*N*-isopinocampheylamine **BzIPAM** and *N*-isopropyl-*N*-isopinocampheylamine **^{i}PIPAM** with one isopinocampheyl moiety in DIPAM replaced by other groups were prepared,[27] and studied for this reaction. The results are summarized in Table 1.



(1)

At the outset, a number of achiral lithium amides formed from bases such as diethylamine, diisopropylamine and pyrrolidine were tested to evaluate their reactivity with cyclohexene oxide, in comparison with the lithium salt of **DIPAM**. It was found that this chiral lithium amide was more reactive towards epoxide than achiral lithium amides, indicating that it would be possible to regenerate **DIPAM** and other chiral amines in the reaction mixture with the help of an appropriate achiral lithium amide via the cycle shown in Scheme 1. The most satisfactory results were obtained with lithium diisopropyl amide (LDA), therefore, it was used in the entire study for the regeneration of chiral amines.

Deprotonation of cyclohexene oxide was studied both at room temperature (rt) and at 0°C, with varying amounts of **DIPAM**. As entries 1–5 in Table 1 show, better results were obtained at 0°C. Therefore, a study with other chiral amines was carried out at 0°C. The best results with each catalyst were obtained when the chiral auxiliary was used at a level of 0.2 molar equivalent. A maximum ee of 95% for the product was obtained with the lithium salt of **DIPAM**. However, on substituting one isopinocampheyl group in **DIPAM** with a cyclohexyl group, the ee of the product **2** dropped to 78% (entry 9). On replacing the isopinocampheyl group with a benzyl (entries 10–13) or isopropyl moiety (entries 14–17) the ee dropped even further. This clearly indicates that the isopinocampheyl moiety plays an important role in orienting the epoxide and the lithium salt in such a way that the enantioselective deprotonation takes place giving very high ee. In other words, when two isopinocampheyl groups are present 97.5% of the deprotonation occurs from one face, resulting in the product allylic alcohol **2** with 95% ee. In all cases the product with *R* configuration was obtained.

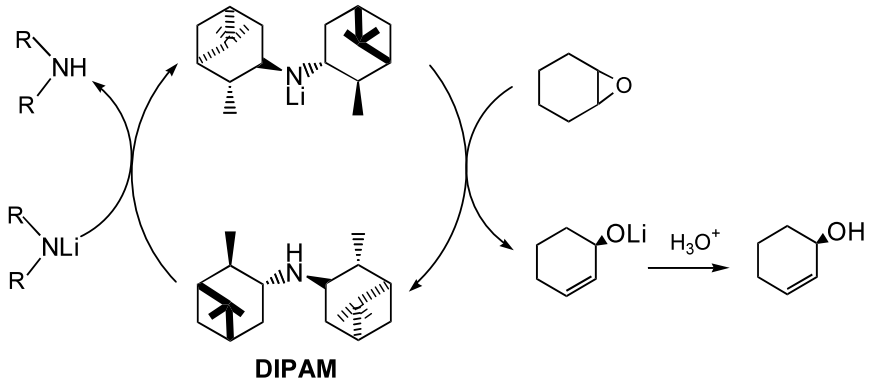
3. Conclusion

This study has introduced new α-pinene-based chiral ligands for the catalytic deprotonation of *meso*-epox-

Table 1. Catalytic enantioselective deprotonation of cyclohexene oxide **1**

Entry	Amine	Mol (%)	Temp. (°C)	Yield (%)[a]	Ee (%)[b]	Config.[c]
1	DIPAM	5	0 (rt)	59 (62)	80 (77)	*R*
2	DIPAM	10	0 (rt)	66 (68)	81 (74)	*R*
3	DIPAM	15	0 (rt)	69 (73)	83 (79)	*R*
4	DIPAM	20	0 (rt)	77 (82)	95 (87)	*R*
5	DIPAM	25	0 (rt)	78 (79)	89 (83)	*R*
6	ChxIPAM	5	0	55	65	*R*
7	ChxIPAM	10	0	57	74	*R*
8	ChxIPAM	15	0	66	76	*R*
9	ChxIPAM	20	0	70	78	*R*
10	BzIPAM	5	0	51	34	*R*
11	BzIPAM	10	0	53	39	*R*
12	BzIPAM	15	0	58	46	*R*
13	BzIPAM	20	0	57	48	*R*
14	^{i}PIPAM	5	0	50	43	*R*
15	^{i}PIPAM	10	0	51	47	*R*
16	^{i}PIPAM	15	0	55	51	*R*
17	^{i}PIPAM	20	0	58	52	*R*

[a] Isolated yield.
[b] Ee of the (*R*)-MTPA ester derivative (Refs. 21 and 23).
[c] Assignment based on the sign of the specific rotation.



Scheme 1.

ides. The highest recorded ee for the conversion of cyclohexene oxide **1** to 2-cyclohexen-1-ol **2** using a catalytic system has been achieved with lithium **DIPAM**. These results certainly promise the catalytic application of **DIPAM** and similar pinene-based ligands in the complex synthesis of natural products and biologically important compounds.

Acknowledgements

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26. **Representative procedure for asymmetric deprotonation**: *n*-Butyllithium (0.093 g; 1.45 mmol) was added slowly to a mixture of (–)-*N*,*N*-diisopinocampheylamine (DIPAM, 0.058 g, 0.2 mmol) and diisopropylamine (0.126 g, 1.25 mmol) in dry THF (8 ml) at 0°C under a nitrogen atmosphere. The mixture was stirred for 30 min and cyclohexene oxide (0.098 g, 1.0 mmol) was added slowly via a syringe. The reaction mixture was then stirred for 15 h. The solution was acidified with dil. aqueous HCl (3N, 8 ml) and allowed to warm to rt. The organic layer was separated, washed with water and dried over anhydrous $MgSO_4$. Column chromatography (silica, pentane/Et_2O, 90/10) and removal of solvents gave the product 2-cyclohexen-1-ol (0.087 g, 89%). The spectroscopic properties of this product were identical to those reported in the literature.[28] The MTPA (Mosher) ester of the product alcohol was prepared[29] and analyzed using a gas chromatograph fitted with SPB-5 capillary column to establish the ee.
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