Pergamon

Tetrahedron 58 (2002) 4665–4668

TETRAHEDRON

Asymmetric base-promoted epoxide rearrangement: achiral lithium amides revisited

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Received 16 October 2001; accepted 28 January 2002

Abstract—The use of achiral bases other than lithium diisopropylamide (LDA) was investigated for the asymmetric (1*S*,3*R*,4*R*)-3-(pyrrolidinyl)methyl-2-azabicyclo[2.2.1]heptane catalyzed rearrangement of cyclohexene oxide to (1*R*)-cyclohex-2-en-1-ol. No significant improvement of the reaction protocol was achieved although some interesting trends were observed. The enantioselectivity in the cyclohexene oxide rearrangement was however markedly improved by slow addition of the achiral base. © 2002 Published by Elsevier Science Ltd.

1. Introduction

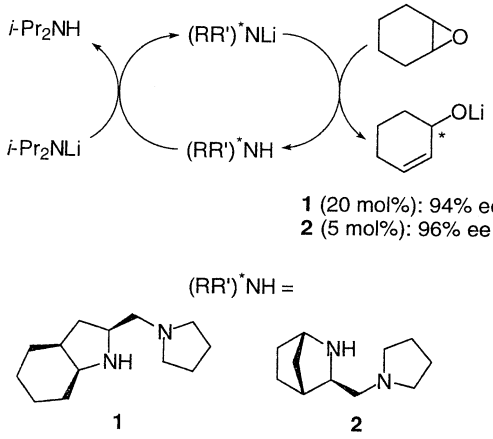
Enantioenriched allylic alcohols can be prepared from epoxides via a stereo- and regiocontrolled base-mediated rearrangement.[1,2] A variety of optically active lithium amide bases[3–6] have been applied to the reaction.[7] However, most systems suffer from low substrate generality and the need for a superstoichiometric amount of the chiral base in order to induce acceptable enantioselectivity. To obtain a successful protocol using substoichiometric non-racemic lithium amide, a catalyst has to be found that reacts much faster with the epoxide compared to the stoichiometric achiral base. The first truly catalytic version of the reaction was presented in 1997 by Asami et al., who used diamine **1** together with LDA in the isomerization of cyclohexene oxide (Scheme 1).[8]

Our contribution to the field involves the development of the lithium salt of diamine **2** as a catalytic base for the rearrangement reaction (Scheme 1).[9] At catalyst loadings as low as 5 mol%, a number of *meso*-epoxides can be isomerized with enantioselectivities of up to 97% ee. This makes lithiated **2** the most potent and general catalyst for the title reaction at present. During our work with the catalytic reaction, the importance of the small, yet significant competition from the background reaction, i.e. the reaction mediated by the achiral, stoichiometric base (LDA) became evident.[9,10] Although the rate of the LDA-mediated isomerization was much lower than that of the catalyst,[11] it could be clearly recognized that the background reaction was more pronounced in the initial stages of the reaction when the concentration of LDA was high. Consequently, in a typical reaction of cyclohexene oxide using 5 mol% of catalyst and 1.5 equiv. of LDA, the enantiomeric purity of the product increased from ca. 92% ee at <10% conversion, to a final 96% ee at full epoxide consumption.

The objective of the present study was to investigate if the reaction protocol could be improved by maintaining a low LDA concentration throughout the reaction. The role of the achiral base was further studied by evaluating a number of achiral bases other than LDA for the rearrangement.

2. Results and discussion

A variety of achiral bases was evaluated in the cyclohexene oxide isomerization to (1*R*)-cyclohex-2-en-1-ol in the search for an achiral lithium amide with less tendency to



Scheme 1. Catalytic asymmetric rearrangement of cyclohexene oxide to (1*R*)- or (1*S*)-cyclohex-2-en-1-ol.

Keywords: lithium amide; epoxide rearrangement; allylic alcohol; desymmetrization; asymmetric synthesis.

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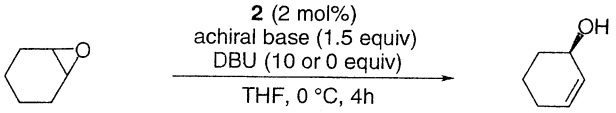
PII: S0040-4020(02)00372-1



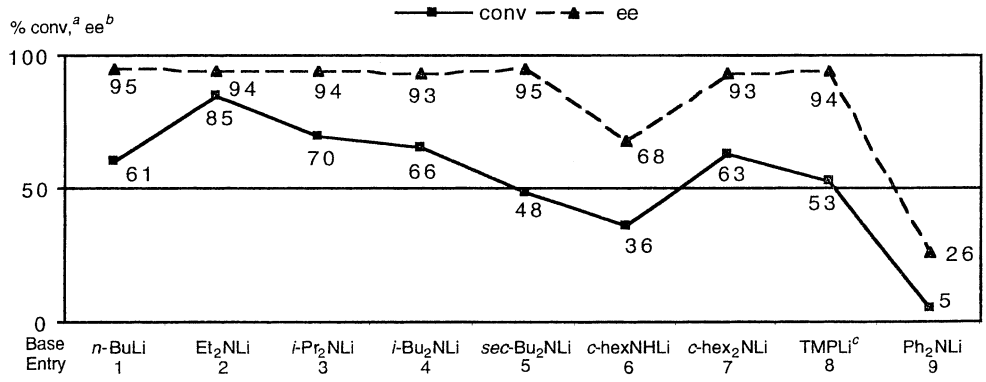
Scheme 2. Evaluation of achiral bases in the rearrangement of cyclohexene oxide catalyzed by **2**.

deprotonate the epoxide substrate.[12] A catalyst loading of 2 mol% of **2** was used together with 1.5 equiv. of the stoichiometric base in THF at 0°C (Scheme 2). Due to the well known influence of co-solvents,[13] the achiral bases were evaluated both in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) (10 equiv., Fig. 1) and in the absence of this additive (Fig. 2).

In the presence of co-solvent, none of the studied bases offered significant advantages over the commonly used LDA (Fig. 1). However, some interesting features could be observed. For example, *n*-BuLi could be employed with very good results in the reaction (cf. entry 1, Fig. 1).[14] Furthermore, the expected correlation between rapid conversions and poor enantioselectivity was not observed. Instead, with few exceptions, the highest conversions were recorded for reactions that also exhibited high levels of asymmetric induction. Decreasing the steric bulk of the achiral amide resulted in an acceleration of the β-elimination reaction rate without any loss of enantioselectivity (cf. entries 2 and 3, Fig. 1). On the other hand, an increased steric hindrance generally resulted in a lowered reaction rate (cf. entries 3–5, and 7 and 8, Fig. 1). The asymmetric induction was however practically unchanged. The results obtained with lithium cyclohexylamide, the only primary amide in the study, were unexpected and indicate an unusual acidity of the chiral amine. However, lithium diphenylamide reacts sluggishly showing the insufficient basicity of this reagent.

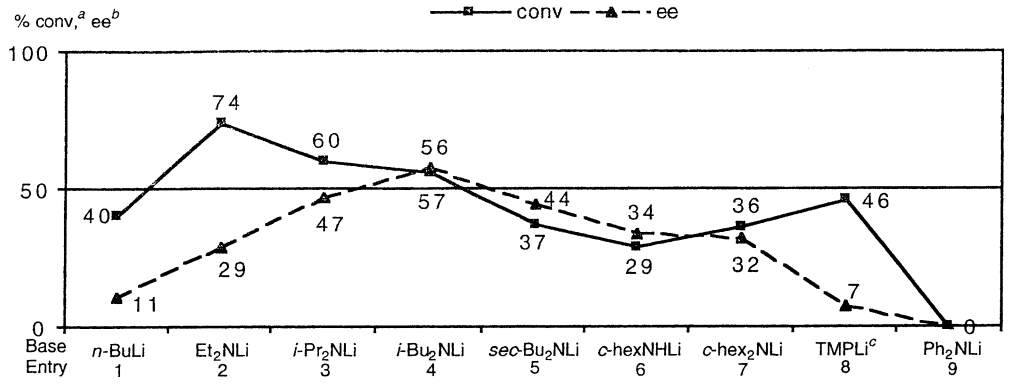
The great influence of the achiral amide on the reaction outcome could indicate a dual role of the base in the rearrangement reaction.

LDA is also in absence of a co-solvent one of the most successful achiral bases in the asymmetric rearrangement reaction (Fig. 2). In contrast to the reactions with DBU, *n*-BuLi was an unsuitable base (entry 1, Fig. 2) giving rise to a reaction with low asymmetric induction. In this case, the rearrangement was also accompanied by nucleophilic addition. A decrease in steric bulk compared to LDA resulted in a slightly accelerated but less enantioselective reaction (entry 2, Fig. 2). Similar to the investigation using co-solvent, an increased steric hindrance resulted in a



[a] Determined after 4h by GC from epoxide consumption relative to an internal standard.
[b] Determined by chiral GC (Chirasil Dex-CB column). [c] Lithium 2,2,6,6-tetramethylpiperidide.

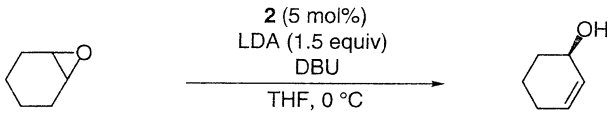
Figure 1. Catalytic rearrangement of cyclohexene oxide using different achiral bases in the presence of 10 equiv. of DBU.



[a] Determined after 4h by GC from epoxide consumption relative to an internal standard.
[b] Determined by chiral GC (Chirasil Dex-CB column). [c] Lithium 2,2,6,6-tetramethylpiperidide.

Figure 2. Catalytic rearrangement of cyclohexene oxide using different achiral bases in the absence of DBU.

Table 1. Slow addition of LDA



Entry	Equiv. of DBU	LDA addition time (5 min)		LDA addition time (5 h)	
		% Conv.[a]	% ee[b]	% Conv.[a]	% ee[b]
1	0	53	70	53	86
2	10	98	95	95	98

[a] Determined after 16 h by GC.
[b] Determined by chiral GC (Chirasil Dex-CB column).

lowered reaction rate (cf. entries 3–5, and 7 and 8, Fig. 2). However, in contrast to the DBU-assisted reaction, a decrease in enantioselectivity was also observed.

An ideal stoichiometric base in the rearrangement reaction would be lithium hydride, a cheap reagent with the potency to provide a clean reaction. However, probably due to low basicity and/or low solubility, LiH did not react under the conditions depicted in Scheme 1. Further, no reaction was observed when the reaction was performed at elevated temperature or when ultrasound was used.

The P_1-base *N‴-tert*-butyl-*N*,*N*,*N′*,*N′*,*N″*,*N″*-hexamethyl-phosphorimidic triamide was also included in the study to show the presumed need for a lithium counter ion in the reaction. Indeed, the P_1-base failed to react in the rearrangement reaction both in the presence and in the absence of DBU.

Due to the difficulties in finding a good replacement for LDA in the catalytic rearrangement reaction, a series of reactions were carried out to investigate whether or not the enantioselectivity could instead be improved by slow addition of the achiral base. Cyclohexene oxide was used as a model substrate. The results are presented in Table 1.

It was found that the levels of enantioselectivity could indeed be significantly raised by means of slow LDA addition (Table 1). A further optimization of the mode of base addition may allow the use of even lower catalyst loadings without loss of enantioselectivity, and perhaps diminish the required concentration of DBU. These issues will be further investigated, and progress reported in due course.

3. Conclusion

The achiral base had great influence on the reaction outcome of the catalytic asymmetric lithium amide-mediated rearrangement of epoxides. No clear correlation between enantioselectivity and conversion could be detected, which might indicate that the achiral base has an additional role in the reaction.[12b,15] Of the bases investigated, LDA remains superior. However, in the presence of DBU, *n*-BuLi reacts with similar efficiency. By keeping the concentration of achiral base low during the reaction, the enantioselectivity can be significantly improved.

4. Experimental

4.1. General

All reactions were conducted under nitrogen or argon using oven-dried glassware (140°C for at least 6 h) and magnetic stirring. THF was freshly distilled from a deep-blue solution of sodium-benzophenone ketyl under nitrogen. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and amines were heated with powdered CaH_2 and distilled at reduced pressure prior to use. Enantiomeric determination was accomplished by analytical GC using a Chirasil Dex-CB column (25 m/0.25 mm I.D.), N_2 (12 psi) as the carrier gas, and a FID detector.

4.2. (1*S*,3*R*,4*R*)-3-(*N*-Pyrrolidinyl)methyl-2-azabicyclo-[2.2.1]heptane (2)

The title compound was prepared from (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid methyl ester according to a published procedure.[9]

4.3. Achiral base-study

The following procedure was used in the evaluation of different achiral bases in the rearrangement of cyclohexene oxide: *n*-BuLi (0.47 mmol, 1.6 M in hexane) was added dropwise over 5 min to a solution of diamine **2** (6 μmol, 0.02 equiv.), achiral amine (0.46 mmol), and DBU [either 10 equiv. (3.1 mmol) or 0 equiv.] in THF at 0°C. The resulting solution was stirred at 0°C for 30 min, and cyclohexene oxide (0.31 mmol) in THF containing *n*-dodecane (ca. 10 mg, as internal standard for GC analysis) was then added dropwise over a period of 5 min. The reaction mixture volume was 2.8 mL, adding either a total of 2.0 mL (when using 10 equiv. DBU) or 2.5 mL (0 equiv. DBU) of THF. The reaction mixture was stirred at 0°C for 4 h and then diluted with Et_2O (15 mL) and washed with 10% aqueous citric acid (2×5 mL), water (5 mL), and brine (5 mL) and dried ($MgSO_4$). Conversion and enantiomeric excess were determined by chiral GC (Chirasil Dex-CB column). The spectroscopic properties of the isolated (1*R*)-cyclohex-2-en-1-ol were identical to those reported.[16]

4.4. (1*R*)-Cyclohex-2-en-1-ol

GC (100°C isotherm): $t_R(S)$= 11.50 min, $t_R(R)$=11.98 min.

4.5. Slow addition of achiral base

The diamine **2** (16 μmol, 0.05 equiv.), DBU [either 10 equiv. (3.1 mmol) or 0 equiv.], and cyclohexene oxide (0.31 mmol) was dissolved in THF (containing ca. 10 mg *n*-dodecane as internal standard for GC analysis). The amount of THF was either 2.0 mL (when using 10 equiv. DBU) or 2.5 mL (0 equiv. DBU). LDA (0.47 mmol) was then added to the reaction mixture at 0°C either during 5 min or 5 h (syringe pump). After stirring at 0°C for a total of 16 h, the reaction mixture was diluted with Et_2O (15 mL) and washed with 10% aqueous citric acid (2×5 mL), water (5 mL), and brine (5 mL) and dried ($MgSO_4$). Conversion and enantiomeric excess were determined by chiral GC (Chirasil Dex-CB column).

Acknowledgements

This work was supported by the Swedish Natural Research Council (NFR), the Swedish Research Council for Engineering Sciences (T. F. R.), and the Swedish Council for Strategic Research (S. S. F.). We are grateful to Dr Mikael J. Södergren for valuable help with the manuscript preparation.

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