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Kinetic resolution of racemic epoxides using a chiral diamine catalyst

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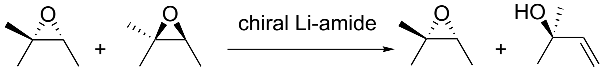
Abstract—The kinetic resolution of a variety of racemic epoxides has been performed using a chiral bicyclic diamine ligand. Using 5 mol % of catalyst very high selectivity could be achieved; both epoxide and the corresponding allylic alcohol could be obtained in up to 99% ee.

The use of enzymes for the kinetic resolution of racemic substrates, to afford enantiopure compounds in high ee and good yields has long been a popular strategy in synthesis.[1] It is only recently that the widespread application of non-enzymatic chiral catalysts for kinetic resolution[2] (or dynamic kinetic resolution[3]) has gained popularity within the synthetic community.[4] In a typical kinetic resolution, the two enantiomers of a racemic substrate react at different rates allowing partial separation. Depending on whether one is interested in recovering the unreacted starting material in high enantiomeric excess or the product (if chiral), the reaction must be stopped shortly after or before 50% conversion is reached.

The first kinetic resolution method applied to the resolution of a racemic epoxide was described by Asami et al.[5] Using a chiral lithium amide they performed the kinetic resolution of *cis*-3-alkylcyclohexene oxides. However, a stoichiometric amount of the chiral base was necessary in order to obtain both the alcohol and the unreacted epoxide in good enantiomeric excess (Scheme 1).



Scheme 1. Lithium amide mediated kinetic resolution of racemic epoxides.

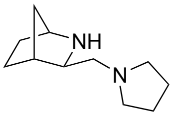


Figure 1. Chiral diamine **1**.

Our group recently showed that the diamine **1** (Fig. 1) could be used as a very efficient ligand for the kinetic resolution of racemic epoxides.[6] Using **1**, the chiral non-racemic epoxide and the corresponding allylic alcohol were both isolated in up to 99% ee. A limitation of this ligand was a low substrate tolerance, as only α-substituted and β-disubstituted epoxides could be successfully resolved. Epoxides having other substitution patterns, either did not react or led to racemic mixtures.

The bicyclic diamine **2**[7] featuring a dimethylpyrrolidine has proven to be superior to **1**[8,9] having a simple pyrrolidine ring, in the rearrangement of *meso*-epoxides, both in terms of activity and selectivity. Therefore, diamine **2** was tested in the kinetic resolution of a racemic epoxide in order to increase the scope of the reaction (Fig. 2).

The reactions were performed as previously described[6] using 5 mol % of the chiral diamine and LDA as stoichiometric base. The result are summarised in Table 1.

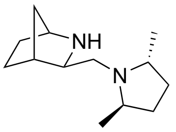


Figure 2. Chiral diamine **2**.

Keywords: Kinetic resolution; Epoxide rearrangement; Allylic alcohol; Chiral diamine.

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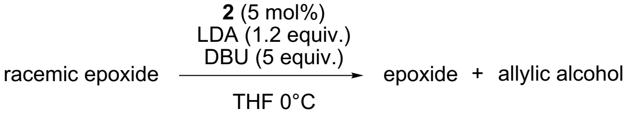
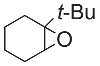
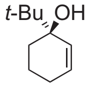
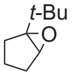
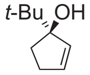
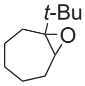
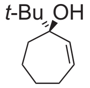
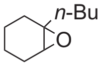
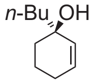
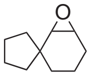
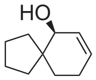
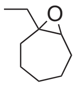
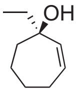
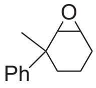
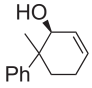
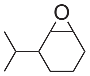
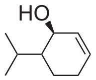
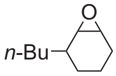
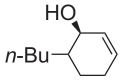
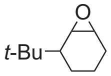
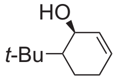
Table 1. Kinetic resolution of racemic epoxides



Entry	Epoxide[a]		Conv. (%)[b]	ee (%)[c] epoxide	Alcohol[d]	ee (%)[c] alcohol
1[6]			46	72		99
2[6]			32	nd		96
3[6]			34	nd		96
4			41	42		94
5[6]			56	96		85
6			49	51		95
7		*cis*	62	99		55
8		*trans*	70	99		40
9		*cis*	60	99		90
10		*trans*	65	21		20
11		*cis*	80	99		64
12		*trans*	30	5		16
13		*trans*	32	nd[e]		94

[a] *cis* and *trans* refers to the relative stereochemistry between the epoxide and the substituent.

[b] Determined by GC. Based on epoxide consumption relative to an internal standard.

[c] Determined by chiral GC.

[d] Absolute configuration tentatively assigned on the basis of the selectivity model published earlier.[9]

[e] Not determined. The enantiomers could not be successfully separated by chiral GC.

Diamine **2** displays an equal or higher selectivity than its non-substituted equivalent **1** for a large range of substrates (Table 1). Using this chiral base, racemic cyclic α-*tert*-butyl epoxides can be converted to the corresponding allylic alcohols in up to 99% ee when the reaction is stopped before 50% conversion (entries 1–3). Decreasing the size of the α-substituent did not affect the selectivity, with 1-ethylcyclohept-2-en-1-ol being produced in 95% ee from the corresponding epoxide after 49% conversion (entry 6). A β-spiro epoxide was also resolved with high stereoselectivity, the starting material and the alcohol were obtained in 96 and 85% ee's, respectively, after 56% conversion.

More interesting, are the cases of cyclohexene oxides having two different substituents at the β-position. In the case of β-disubstituted cyclohexene oxides both the *cis*- and *trans*-epoxides could be successfully subjected to kinetic resolutions (entries 7 and 8). Diamine **2** was also able to resolve β-monosubstituted cyclic epoxides, but in this case the size of the substituent and its relative position to the epoxide had a tremendous effect on the selectivity. *cis*-Epoxides proved to be excellent candidates for kinetic resolution irrespective of the size of the β-substituents (entries 9 and 11), while only *trans*-epoxides having a very large β-substituent can be successfully resolved. *trans*-β-*tert*-Butyl cyclohexene oxide produced the corresponding allylic alcohol in 94% ee after 32% conversion. Replacement of the *tert*-butyl group by an isopropyl group resulted in a dramatic loss of selectivity, with the epoxide and the alcohol obtained in 21% and 20% ee, respectively, after 65% conversion (entry 10).

Further reduction in the size of the β-substituent resulted in very poor selectivity; the use of an *n*-butyl substituent produced the epoxide in 5% ee and the allylic alcohol in 16% ee after 30% conversion (entry 12).

It is also worth noting that α-hydrogen abstraction in the *exo*-cyclic position observed using the diamine **1** has been greatly diminished using the second generation amine **2**. This is probably due to better selectivity and a shorter reaction time.

In conclusion we have demonstrated that the dimethylpyrrolidine diamine **2** in combination with LDA as a stoichiometric base is a very selective catalyst for the kinetic resolution of racemic epoxides. Using 5 mol % of catalyst, both epoxide and allylic alcohol can be obtained in up to 99% ee when the reaction is stopped shortly before or after 50% conversion is reached. Using **2** we were able to increase the scope of the reaction to β-mono-substituted cyclohexene oxides, which so far have proven to be problematic substrates.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.05.017.

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