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Synthetic Approaches to (*R*)-cyclohex-2-enol

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ABSTRACT

(R)-Cyclohexenol is a valuable building block in organic synthesis. This mini-review provides methods for synthesis of *(R)*-cyclohexenol from commercially available reactants. Only reactions with yields in excess of 80% are discussed (*ee's* range from 99% to 26%). The asymmetric synthesis methods include enantioselecive deprotonation of cyclohexene oxide by chiral lithium amides, asymmetric hydrosilylation of 2-cyclohexen-1-one with chiral catalyst followed by hydrolysis, and enantioselective hydroboration of 1,3-cyclohexadiene with chiral dialkylboranes.

Key words: (*R*)-cyclohexenol, asymmetric synthesis, chiral Li-amides**.**

INTRODUCTION

Asymmetric synthesis starting from achiral reactants to produce synthetically useful chiral compounds is an attractive and established branch of synthetic organic chemistry. (*R*)-cyclohexenol 1 serves as a versatile chiral precursor for synthesis of natural products and complex medicinally active compounds like (+) Daphmandin E 2,(1) and antiarrhythmic aminohydroisoquinocarbazole RS-2135 3 (2) respectively (Figure 1).

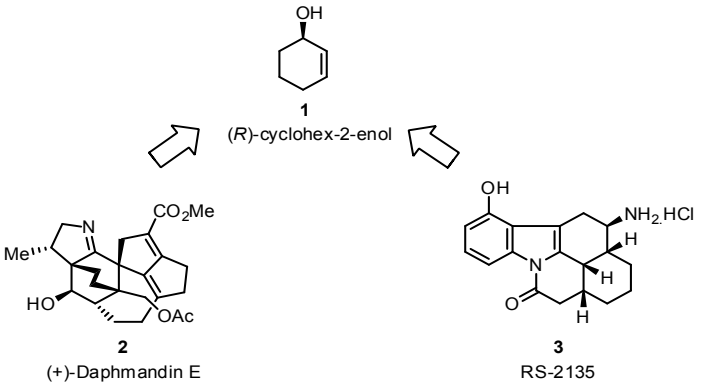


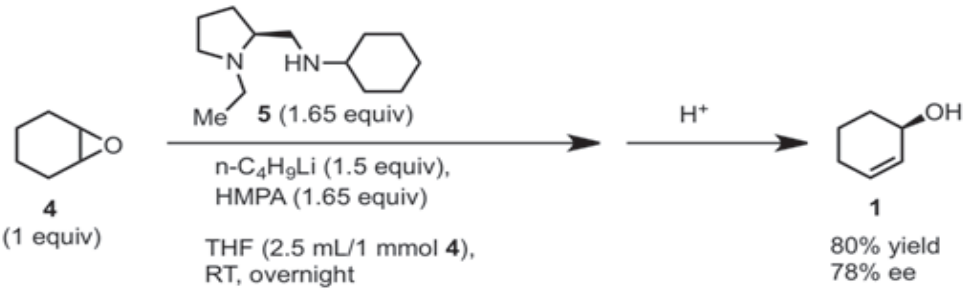
Fig. 1: (*R*)-Cyclohexenol is a valuable building block in organic synthesis

A scifinder scholar® search of methods to synthesize (*R*)-cyclohexenol in February 2014 resulted in 129 hits. This mini-review discusses methods from these 129 results wherein the isolated yield for the target from commercially available reactants was in excess of 80% and the *ee* ranged from 99% to 26%. This mini-review is intended to present synthetic chemists with a guide for synthesis of (*R*)-cyclohexenol and its derivatives.

Synthetic strategies to (*r*)-cyclohexenol

From cyclohexene oxide

Asami *et al.*(3) report conversion of cyclohexene oxide 4 to 1 (80% yield, 78% ee) using chiral catalyst – cyclohexyl[(*S*)-1-ethylpyrrolidin-2-yl] methylamine 5 from (Scheme 1). The mechanism involves enantioselective deprotonation of symmetrical epoxide 4 using the chiral lithium amide prepared from *n*-butyl lithium and 5. HMPA is used



Scheme 1: Asymmetric transformation of cyclohexene oxide by catalyst 5

as an additive. It has been suggested that additives inhibit the formation of reactive but unselective aggregates of chiral Li-amides[4-7].

As lithium amide induced transformation of epoxides to allylic alcohols I supposed to proceed in a cyclic concerted manner[8] Asami *et al.*,[3] presume the transition states' (TSs') as shown in figure 2 to account for the stereoselectivity of the reaction. As indicated in transition state T1, epoxide approaches the lithium amide from the less hindered side in such a way that the steric repulsion can be avoided. Thus T1 is favored over T2, and the alcohol with *R*-configuration is obtained.

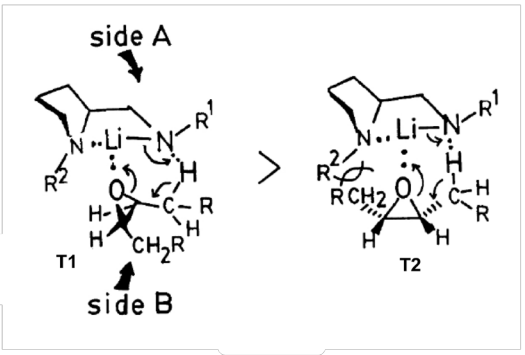
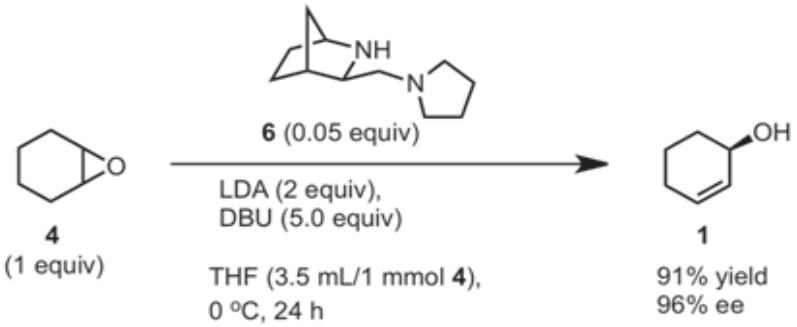
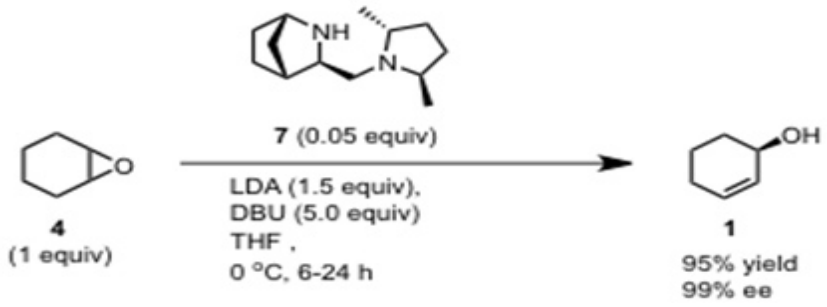


Fig. 2: Transtion state model for enantioselective deprotonation by 5



Scheme 2: Asymmetric transformation of cyclohexene oxide by catalyst 6

Sodergren *et al.*,[9] report conversion of cyclohexene oxide 4 to 1 (91% yield, 96% ee) using chiral catalyst – 3-aminomethyl-2-azabicyclo [2.2.1] heptane 6 (Scheme 2). DBU is used as an additive. The authors reasoned that Li-amide with a more rigid back bone would adopt a more well-ordered TS in the deprotonation reaction to afford higher asymmetric induction as the result of more strict discrimination between the enantiotopic protons in 4.



Scheme 3: Asymmetric transformation of cyclohexene oxide by catalyst 7

Bertilsson *et al.*[10] report conversion of cyclohexene oxide 4 to 1 (95% yield, 99% ee) using chiral catalyst – (1*R*,3*R*,4*S*)-3-(((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)methyl)-2-azabicyclo[2.2.1] hept-5-ene 7 (Scheme 3).

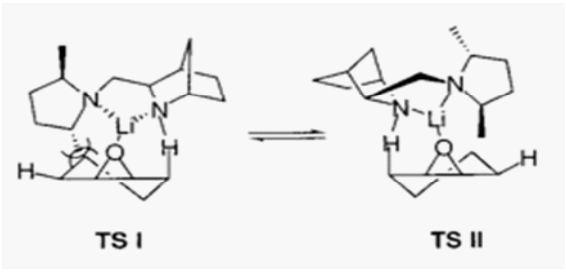
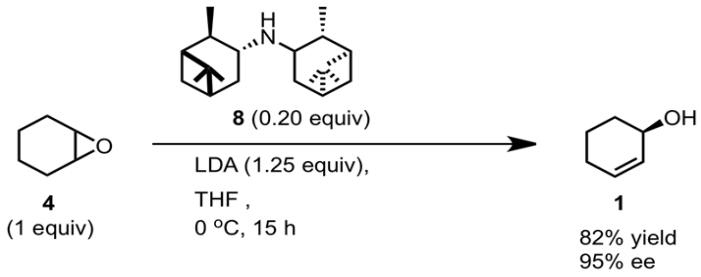


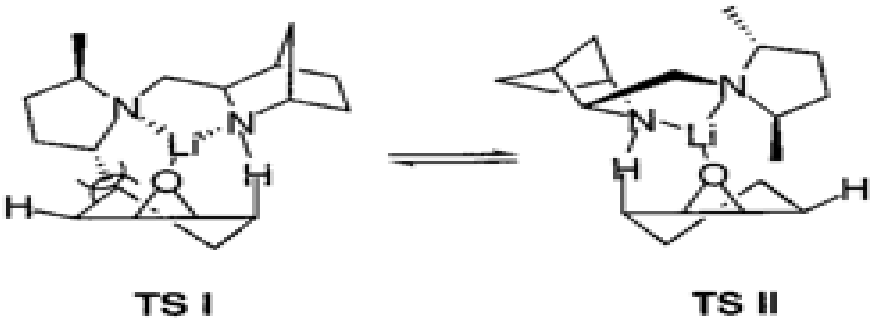
Fig. 3: Transtion state model for enantioselective deprotonation by 7



Scheme 4. Asymmetric transformation of cyclohexene oxide by catalyst 8

As indicated in the TS model (Figure 3), the (2*R*,5*R*)-dimethyl groups do not interfere with the favored TS II, whereas the unfavored pathway is effectively blocked by the steric repulsion between the (2*R*)-methyl group and the cis-*g* -proton of the epoxide.

Malhotra[11] reports conversion of cyclohexene oxide 4 to 1 (82% yield, 95% ee) using chiral catalyst – C2-symmetric (“)-N,N-diisopinocampheyl- amine (DIPAM) 8 (Scheme 4). No additive was used in the reaction.



Scheme 5: Asymmetric transformation of 2-cyclohexene-1-one by $ZnEt_2$/pybox system

From 2-cyclohexen-1-one

Junge *et al.,*[12] report conversion of 2-cyclohexen-1-one 9 to 1 (88% yield, 26% ee) by asymmetric hydrosilylation with a combination of $ZnEt_2$, chiral 2,6-bis((*R*)-4-phenyl-4,5-dihydrooxazol -2-yl)-pyridine (pybox) catalyst 10, and polymethylhydrosiloxane (PMHS), followed by hydrolysis to the alcohol (Scheme 5).

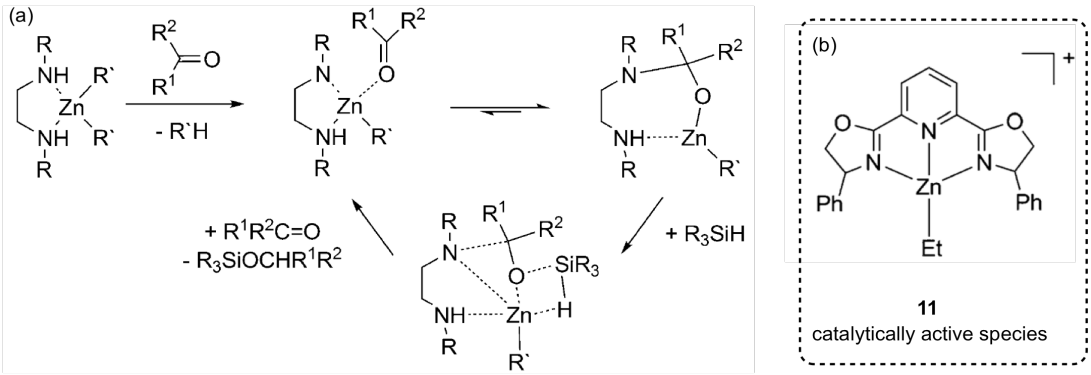
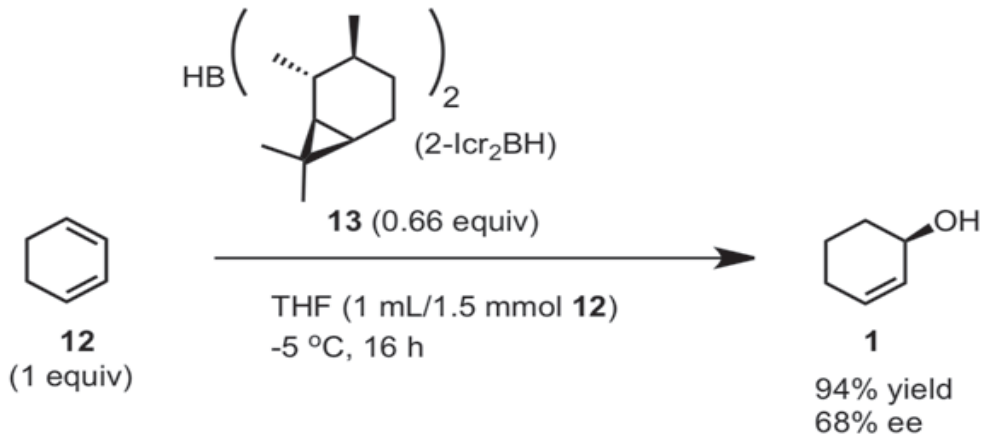


Fig. 4(a): Mechanism of asymmetric hydrosilylation by $ZnEt_2$/pybox system. (b) Catalytically active species 11 as confirmed by ESI-MS



Scheme 6: Asymmetric transformation of cyclohexene oxide by catalyst 8

The proposed mechanism of the asymmetric hydrosilylation process (Figure 4a) by Mimoun *et al*.[13,14] was confirmed by Junge *et al*.,[12] by confirming the presence of 11 (Figure 4b) by ESI-MS studies.

From 1,3-cyclohexadiene

Zaidlewicz et al.(15) report conversion of 1,3-cyclohexadiene 12 to 1 (94% yield, 68% ee) using chiral catalyst – di-(2-isocaranyl)borane (2-Icr_2-BH) 13 (Scheme 6). Mechanism involves the enantioselective hydroboration of 12 in presence of bulky dialkylboranes.

CONCLUSION

In conclusion, we present here enantioselective approaches to (*R*)-cyclohexanol using commercially available reactants such as cyclohexene oxide, 1,2-cyclohexenone, and 1,3-cyclohexadiene. Reactions enantioselecive deprotonation of cyclohexene oxide by chiral lithium amides, asymmetric hydrosilylation of 2-cyclohexen-1-one with chiral catalyst followed by hydrolysis, and enantioselective hydroboration of 1,3-cyclohexadiene with chiral dialkylboranes. The yields of the aforementioned methods range from 95 to 80% and the ee's range from 99 to 26%.

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