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Synthesis of Chiral Cyclic Alcohols from Chiral Epoxides by H or N Substitution with Frontside Displacement

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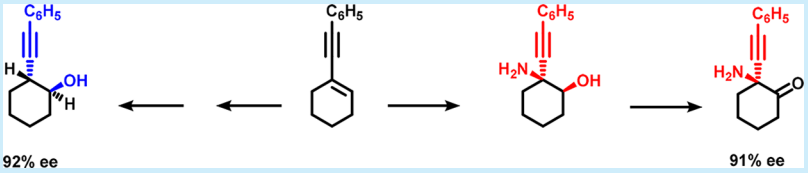
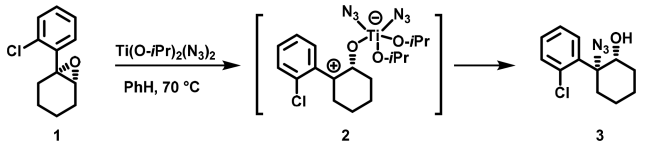
Supporting Information



ABSTRACT: Diverse examples are provided of enantioselective sequences for the transformation of cycloalkenes to either chiral *trans*-β-substituted cycloalkanols or chiral α-amino ketones.

We have recently reported an unusual example of epoxide ring-opening displacement with retention of configuration.[1] This process was discovered in connection with work on the enantioselective synthesis of the potentially important antidepressant (2*R*,6*R*)-hydroxynorketamine. Specifically, it was found that the reaction of epoxide **1** with the reagent $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$[2] in benzene gave the azido alcohol **3**, presumably via the intermediate carbocation **2** with a *cis*-internal transfer of an azido unit from titanium to carbon (Scheme 1).

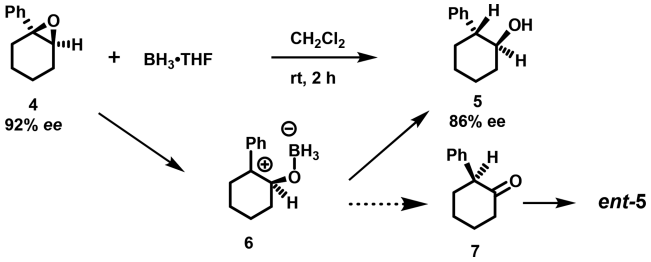
Scheme 1. Epoxide Ring Opening with Retention



In this paper, we report further studies in this area, including the extension to reductive cleavage with internal delivery of hydrogen to carbon and the demonstration of internal delivery of N_3 as a useful general process for the synthesis of chiral cyclic α-amino ketones as well as cyclic *cis*-vicinal amino alcohols.

(*S*,*S*)-1-Phenylcyclohexene oxide (**4**)[3] was selected for initial studies of reductive epoxide cleavage. Reaction of **4** (92% ee) with 1.5 equiv of BH_3·THF in CH_2Cl_2 at rt for 2 h led to complete reaction and clean formation of *trans*-(1*S*,2*R*)-2-phenylcyclohexanol **5** of 86% ee in 85% yield. None of the *cis*-diastereomer could be detected by TLC analysis. It seems likely that this reaction proceeds via the carbocationic intermediate **6** shown in Scheme 2, with internal *cis*-transfer of hydrogen from boron to carbon. It is also likely that the small loss of enantiopurity in the reduction of **4** to **5** is due to a minor side reaction involving 1,2-hydrogen migration in **6** to form the ketone **7**, which then undergoes reduction to give *ent*-**5** (vide infra). *ent*-**5** was readily prepared from (*R*,*R*)-1-

Scheme 2. Diastereoselective Reduction of a Chiral Epoxide with Retention of Configuration



phenylcyclohexene oxide (*ent*-**4**) and BH_3·THF in CH_2Cl_2 at 23 °C in 85% yield and 86% ee.

Using the same method, the chiral *trans*-2-substituted cycloalkanols shown in Scheme 3 were prepared in the indicated yield and enantiopurity. The ee values of the starting epoxides are shown in parentheses.

The epoxides precursors of **5**, **8**, **9**, **10**, and **11** were prepared by modified Jacobsen epoxidation[1,3] of the corresponding olefins. The epoxide precursor of **12** was synthesized by epoxidation using Shi's chiral dioxirane.[4]

The reaction of epoxide **1** with BH_3·THF in CH_2Cl_2 requires additional discussion. Starting with epoxide of 90% ee, the product was a 99:1 mixture of the expected *trans* alcohol **13** (77% ee) and *cis* alcohol **14** (Scheme 4). We believe that the reduced ee observed for the major product is due to the competing pathway outlined in Scheme 5, in which the racemic ketone **16 is** generated from intermediate **15** by proton loss. This interpretation finds support from the fact that the reaction of (±)-**16** with BH_3·THF affords (±)-**13** and (±)-**14** in a ratio of 90:10 as shown in Scheme 5.

The above explanation for the diminished enantioselection in the BH_3·THF reduction of epoxide **1** to the *trans* alcohol **13**

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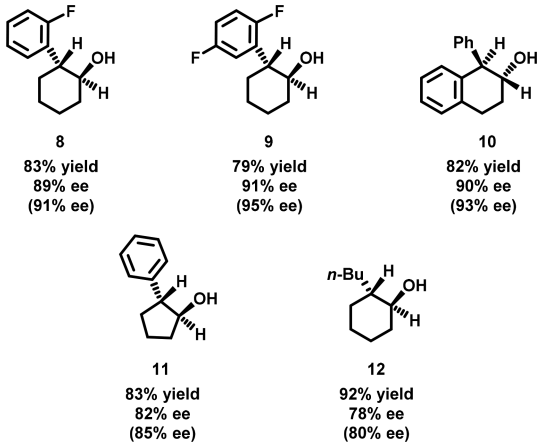
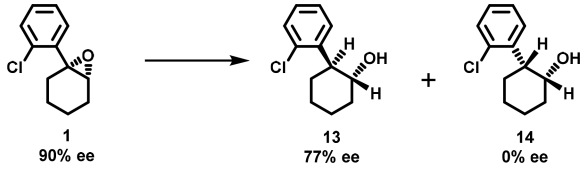
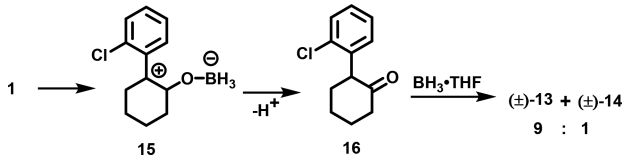
Scheme 3. Reductive Cleavage of Epoxides with Frontside Displacement



Scheme 4. Competing Racemization

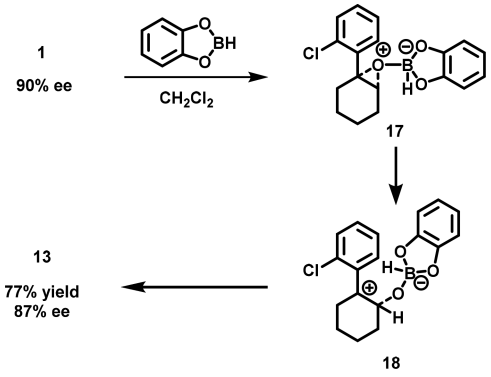


Scheme 5. Possible Pathway for Racemization in the Transformation of 1 to 13



suggested that the use of catechol borane in place of BH_3 for this reduction might result in higher enantioselectivity by the pathway shown in Scheme 6. It was anticipated that the

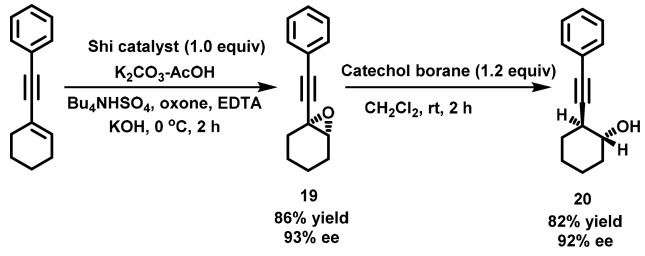
Scheme 6. Improvement in the Enantioselectivity of Reduction of 1 Using Catechol Borane



hydride transfer from boron to the cationic carbon of **18** would be accelerated relative to ketone formation by 1,2 hydrogen migration in **18**. The fact that the *trans* alcohol **13** was produced from **1** with much improved enantioselectivity relative to the reaction using BH_3·THF supports our conjecture that the three oxygens attached to boron in **17** substantially increase the rate of B → C hydride transfer.

The use of catechol borane for epoxide cleavage clearly is advantageous for the other substrates which contain functional groups that are reactive toward BH_3·THF. For example, the acetylenic epoxide **19** affords the *trans* alcohol **20** in only 10% yield due to competing addition of BH_3·THF to C≡C. However, the reaction of epoxide **19** with catechol borane produces the *trans* alcohol **20** in 82% yield and with high position and enantioselectivity as shown in Scheme 7.

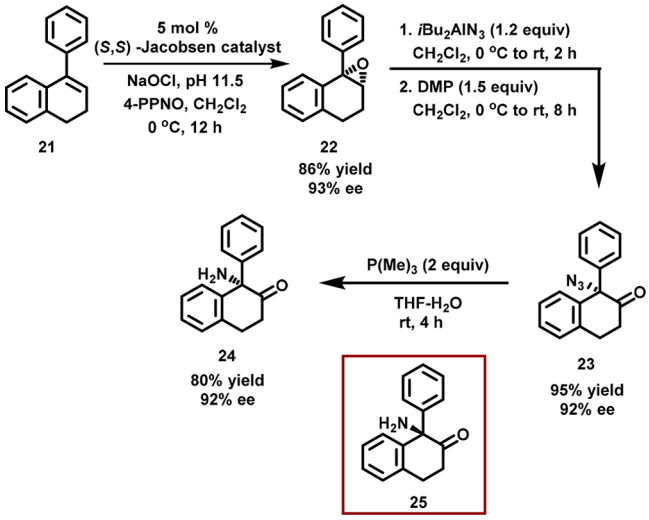
Scheme 7. Selective Reduction of Acetylenic Epoxide Using Catechol Borane



We have also explored the synthesis of chiral *cis*-*β*-azido alcohol from chiral epoxides as exemplified by the initial findings summarized in Scheme 1 above. This type of process could be very useful as a route to chiral cyclic *cis*-*β*-amino alcohols and chiral *α*-amino ketones.

One example is the enantioselective synthesis of the potential antidepressant benzo-(*S*)-norketamine (**24**), which has been synthesized as outlined in Scheme 8. Structural relatives of ketamine are currently of great interest for application to treatment resistant depression and ketamine itself has just been submitted for FDA approval.

Scheme 8. Simple Enantioselective Synthesis of Benzo-(*S*)-norketamine



The epoxide **22** underwent clean conversion as shown in Scheme 8 to the chiral *α*-azido ketone **23** which by reduction gave benzo-(*S*)-norketamine **24**. The same sequence was employed for the synthesis of the enantiomer of **24**, benzo-(*R*)- norketamine (**25**). The recent discovery that the relief of depression by ketamines linked to the blocking of firing by neurons in the lateral habenula has provided increased incentive for the study of *α*-amino cyclic ketones such as **24**

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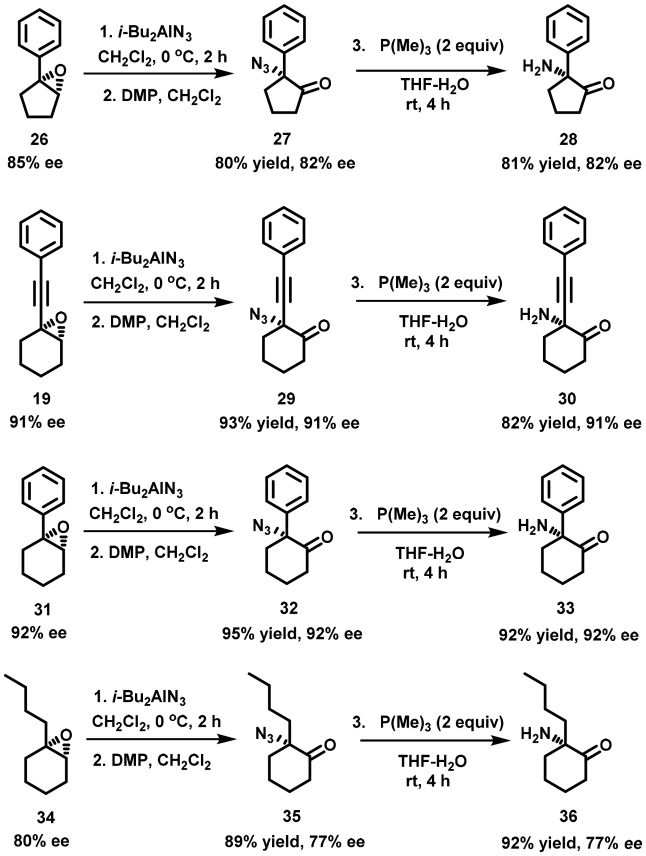
and **25**[5] because there is now a straightforward in vivo method for screening to find superior antidepressants.

Three additional examples of the application of the stereoretention O → N displacement route to chiral azido or amino ketones are shown in Scheme 9, and the ketamine analogues **24**, **25**, **28**, **30**, **33**, and **36** are now available for neuroscience research.

Scheme 9. Synthesis of Other Chiral Cyclic α-Amino Ketones



It should be mentioned that there are previous reports of the use of alkyl aluminum azides for the epoxide → azido alcohol conversion.[6]

Representative procedures for the diastereoselective epoxide cleavages leading to chiral *trans*-2-substituted cycloalkanols or chiral α-amino ketones are provided below for the convenience of the reader.[7,8]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02822.

Experimental procedures and characterization data for novel reactions and products including copies of ^{1}H- and ^{13}C NMR spectra and chiral HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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(7) To a rapidly stirred solution of **4** (100.0 mg, 0.57 mmol) in CH_2Cl_2 (10 mL) at 0 °C was slowly added 1 M of BH_3 in THF (0.9 mL, 0.86 mmol). The reaction mixture was warmed to rt and vigorously stirred for 2 h, and after completion of the reaction as judged by TLC, the reaction mixture was treated with a solution of sodium potassium tartrate. The phases were separated, and the aqueous phase was further extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extract was washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate 8:2) to afford the compound **5** (83 mg, 83% yield, 86% ee) as a white solid, mp 65−67 °C, $[\alpha]_D^{23}$ = +22.2 (*c* = 0.98, $CHCl_3$), HPLC (Chiralcel OD-H, 0.46 cm × 25 cm, hexane/iPrOH 99:1, 0.5 mL/min, 220 nm): minor: 3.14 min; major: 3.40 min. Harada, S.; Kuwano, S.; Yamaoka, Y.; Yamada, K.-I.; Takasu, K. *Angew. Chem.* **2013**, *125*, 10417−10420.
(8) To a suspension of NaN_3 (500 mg, 7.78 mmol) in 15 mL of CH_2Cl_2 was added *i*-Bu_2AlCl (0.72 mL, 3.89 mmol) at 0 °C. The resulting mixture was warmed to 25 °C and stirred for 12 h, after which a 50 mL CH_2Cl_2 solution of **31** (400 mg, 2.59 mmol) was added at 0 °C. After the substrate was consumed as judged by TLC, saturated aqueous $NaHCO_3$ (2 mL) was added, and the mixture was filtered through a Celite pad which was washed with CH_2Cl_2 (2 × 50 mL). The filtrate was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give the *cis* azido alcohol (372 mg, 93% yield). A solution of the above azido alcohol in CH_2Cl_2 was treated with $NaHCO_3$ (230 mg, 2.59 mmol) and Dess−Martin periodinane (1.10 g, 2.59 mmol). After the substrate was consumed as judged by TLC, saturated aqueous Na_2SO_3 (10 mL) was added, and the mixture was separated. Then the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, hexanes/dichloromethane 4:1) afforded the azido ketone **32** (218 mg, 95% yield) as a colorless oil. To a solution of the azido ketone **32** (100 mg, 0.46 mmol) in 15 mL of THF−H_2O (4:1) was added a 1 M solution of Me_3P in THF (0.46 mL, 0.46 mmol) at 0 °C. The resulting mixture was warmed to rt and

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stirred for 4 h. The mixture was washed with water, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic phase was washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, hexanes/ethyl acetate 9:1) afforded the α-amino ketone **33** (92 mg, 92% yield, 92% ee) as a colorless oil, $[\alpha]_D^{23} = -56.2$ (c = 0.98, $CHCl_3$), HPLC (Chiralcel OD-H, 0.46 cm × 25 cm, hexane/iPrOH 99:1, 0.5 mL/min, 220 nm): minor: 5.61 min; major: 8.01 min, (ref 1).

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