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Synthesis and Enantioselective Rearrangement of 4-Amino-substituted Cyclopentene Oxides

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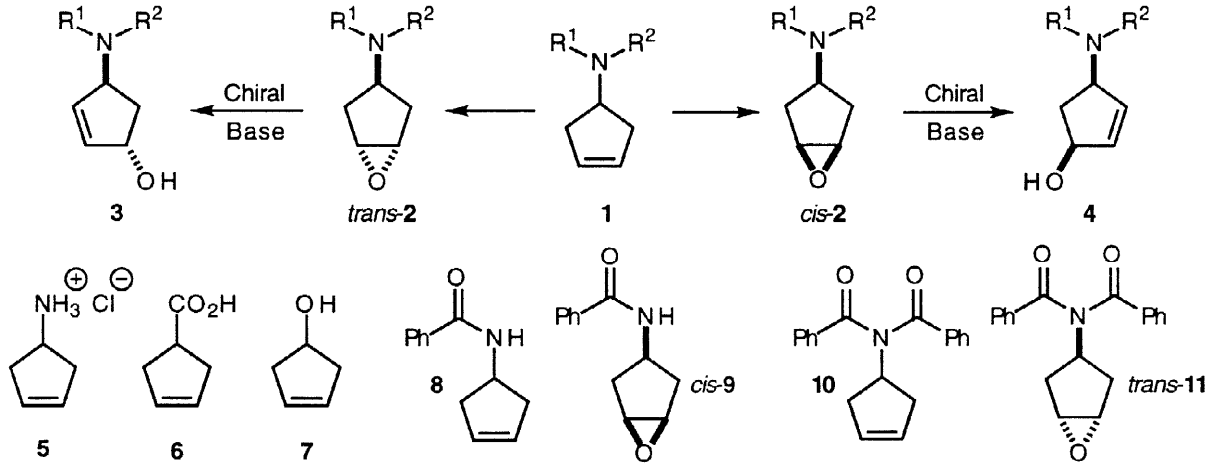
Abstract: Several *N*-mono- and diprotected alkenes have been prepared and the stereoselectivity of their epoxidation has been investigated: *N*-monoprotected alkenes give *cis* epoxides preferentially (due to hydrogen bonding directed epoxidations) whereas *N*-diprotected alkenes produce *trans* epoxides exclusively (due to steric effects). Chiral lithium amide base-mediated rearrangement of a *cis*-monoprotected epoxide generated the corresponding amino-cyclopentenol in good yield and with an enantiomeric excess of 60%.

Keywords: epoxidation; diastereoselection; rearrangements; enantioselection

The conversion of *meso* 4-substituted cyclopentene oxides into enantiomerically enriched allylic alcohols using chiral lithium amide bases has received considerable attention over the last few years.[1-3] Despite this, the enantioselective rearrangement of 4-amino-substituted epoxides *trans*- and *cis*-**2** has not been reported. Amino alcohols **3** and **4**, the products of such reactions, are useful intermediates for the synthesis of antiviral carbocyclic nucleoside analogues[4] and 4-aminocyclopent-2-ene-1-one.[5] Thus, we decided to investigate the stereoselective synthesis of each of the epoxides *trans*- and *cis*-**2** and to attempt their chiral base-mediated rearrangement. Our results in both of these areas are described in this paper.



Amine hydrochloride salt **5** is a known compound that has been synthesised using (i) Curtius rearrangement of acid **6**[6,7] or (ii) Mitsunobu displacement (HN_3) of alcohol **7** with concomitant azide reduction[8,9] or (iii) hydroboration-amination of cyclopentadiene.[10] Each of these routes is unsatisfactory – either the route is many steps or low yielding or both. There are only a few reported examples of epoxides **2**.[8,11-14] Of these, epoxide *cis*-**9**[8,11] was prepared by a highly stereoselective amide-directed[15,16] epoxidation of alkene **8** and epoxide *trans*-**11** was synthesised by epoxidation of alkene **10** (*via* a sterically controlled

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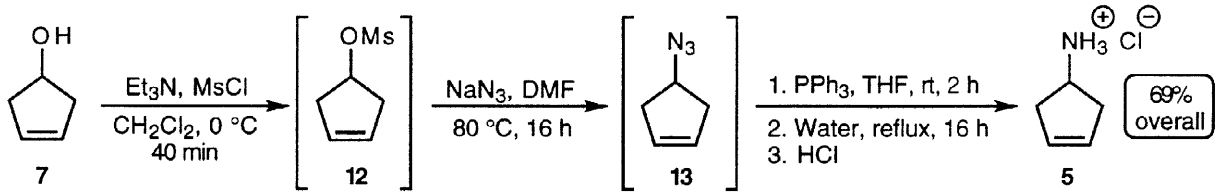
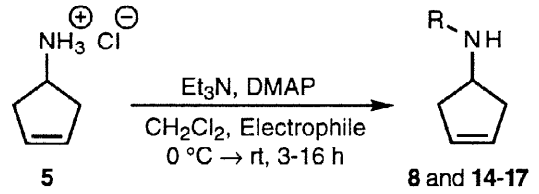
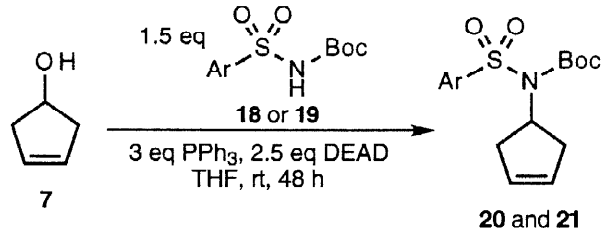
process). We envisaged making use of directed epoxidations on *N*-monoprotected amines **1** (R^2 = H) as a route to a range of epoxides *cis*-**2** and, in order to further probe the effect of *N*-protecting groups on the stereoselectivity of epoxidation, we also wanted to prepare some *N*-diprotected amines **1**.[17]

As a starting point, we developed a new approach to amine hydrochloride **5** which is as good if not better than previously published routes.[6-10] Thus, as shown below, known[18] alcohol **7** was converted into hydrochloride salt **5** (*via* mesylate **12** and volatile azide **13**) in 69% yield over the three steps; for the first two steps, the reactions were worked-up but **12** and **13** were not purified. Standard *N*-monoprotection generated benzamide **8**,[11] sulfonamides **14** and **15** and carbamates **16**[14] and **17**[7] in good yields.[19]





R	Bz	Ms	Ts	Cbz	Boc
Product	**8**	**14**	**15**	**16**	**17**
Yield (%)	83	100	94	78	77



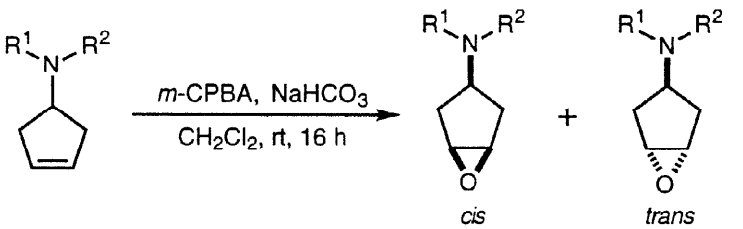
Ar	4-MeC_6H_4–	2-$NO_2C_6H_4$–
Starting material	**18**	**19**
Product	**20**	**21**
Yield (%)	76	64

In order to prepare representative *N*-diprotected alkenes, we decided to use a Mitsunobu approach with alcohol **7**. Of the known methods for Mitsunobu reactions with nitrogen,[20-22] we selected Weinreb's TsNHBoc reagent (**18**)[20,23] as it generally gives high yielding Mitsunobu reactions. We also developed the novel Weinreb-Fukuyama hybrid reagent (**19**)[20,21,23] as this would produce an alkene with orthogonal and easily removed *N*-protecting groups.[24] It was satisfying that combination of alcohol **7** with each of **18** and **19** under normal Mitsunobu conditions furnished good yields of *N*-diprotected alkenes **20** and **21**.

With a range of *N*-mono- and diprotected alkenes in hand, we were ready to study the stereoselectivity of their epoxidation. All of the epoxidations were carried out under standard conditions (*m*-CPBA, $NaHCO_3$, CH_2Cl_2, room temperature, overnight) and the crude products were analysed by ^1H NMR spectroscopy to determine the stereoselectivity (Table). The major products of epoxidation of the *N*-monoprotected alkenes (Entries 1-5) were assigned as having *cis* stereochemistry by comparison with the known[8,11] epoxidation of alkene **8**; our assignments are also consistent with a ^1H NMR spectroscopy correlation method.[25] In contrast, epoxidation of the *N*-diprotected alkenes (Entries 6 and 7) was completely *trans* selective. The *trans* selectivity was expected;[13] it was established by synthesising *N*-diprotected epoxide *cis*-**26** by Boc-protection (Et_3N, DMAP, Boc_2O, CH_2Cl_2) of the 84:16 mixture of *N*-monoprotected epoxides *cis*- and *trans*-**23** and comparison of ^1H NMR spectra. Presumably, with *N*-diprotected alkenes, steric factors result in *trans*

selectivity. However, with *N*-monoprotected alkenes, hydrogen bonding to *m*-CPBA leads to *cis* selectivity; amides and sterically small sulfonamides (R^1 = Ms) and carbamates (R^1 = Cbz) give the largest proportions of *cis* epoxides. Notably, the use of an epoxidation system that *cannot* participate in hydrogen bonding [*in situ* generated methyl(trifluoromethyl)dioxirane[26]] with *N*-monoprotected alkene **15** gave a 60:40 mixture of epoxides *trans*- and *cis*-**23**. To summarise the epoxidation results, we have found *N*-protecting groups that allow preparation of a *cis* epoxide (*eg cis*-**9**, 79% isolated yield) or a *trans* epoxide (*eg trans*-**26**, 88% isolated yield) in diastereomerically pure form.

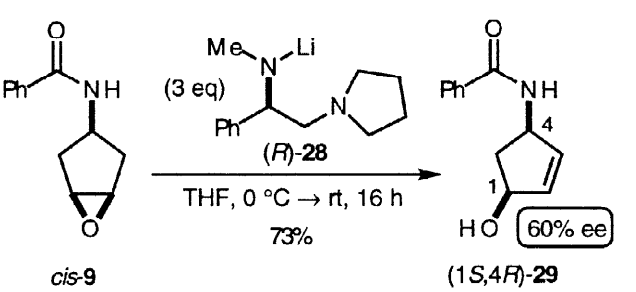
Table: *Stereoselective Epoxidation of N-Mono- and Diprotected 4-Amino-substituted Cyclopentenes*



Entry	Alkene	R^1	R^2	Epoxide	*cis* : *trans*[a]
1	**8**	Bz	H	**9**	97 : 3[b]
2	**14**	Ms	H	**22**	98 : 2[c]
3	**15**	Ts	H	**23**	84 : 16
4	**16**	Cbz	H	**24**	82: 18
5	**17**	Boc	H	**25**	75 : 25
6	**20**	Ts	Boc	**26**	2 : 98[c,d]
7	**21**	Ns[e]	Boc	**27**	2 : 98[c,f]

[a] The ratio of *cis* and *trans* epoxides was determined from the ^{1}H NMR spectrum of the crude product mixtures; [b] Epoxides *cis*-**9** (79%) and *trans*-**9** (3%) were isolated after chromatography; [c] Only one diastereosiomer was visible in the ^{1}H NMR spectrum of the crude product mixture; [d] Epoxide *trans*-**26** (88%) was isolated after chromatography; [e] Ns = 2-$NO_2C_6H_4SO_2$–; [f] Epoxide *trans*-**27** (84%) was isolated after chromatography.

Based on our[27] experience with chiral base-mediated epoxide rearrangement reactions, we tried to rearrange *N*-diprotected epoxides *trans*-**26** and *trans*-**27** with two equivalents of Singh's[28] chiral lithium amide base *rac*-**28**. Unfortunately, no allylic alcohol could be detcted in the ^{1}H NMR spectrum of the crude product mixture and in the case of *trans*-**27**, a 65% yield of recovered starting epoxide was isolated. We had more success with the rearrangement of epoxide *cis*-**9**. In this case, three equivalents of Singh's chiral base (*R*)-**28** were used (because of the presence of an acidic amide NH) and smooth rearrangement occurred to generate allylic alcohol (1*S*,4*R*)-**29** in 73% yield and with 60% ee (as shown by chiral HPLC). The absolute stereochemistry was established by formation of the Mosher's esters and analysis of the resulting ^{1}H NMR spectrum (Kakisawa's method).[27,29] Thus, the sense of induction was the same as we had observed previously using chiral base (*R*)-**28** with *meso*-cyclohexene oxides[27] and as Singh had observed using similar chiral bases with *meso*-cyclopentene oxides.[28]



In summary, we have described methods for the stereoselective synthesis of the previously scarse epoxides *trans*- and *cis*-**2** and have reported the first ever enantioselective rearrangement of a 4-amino-substituted cyclopentene oxide. Our preliminary conclusion on the chiral base reaction is that a deprotonated amide *cis* to the epoxide is important for facilitating the rearrangement process.

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24. Deprotection of either protecting group in *N*-diprotected alkene **21** was easy. Boc deprotection using TFA or sulfonamide deprotection using mercaptoacetic acid (according to Fukuyama's procedure reported in reference 18) gave the *N*-monoprotected alkenes (each in quantitative yield).
25. Previous studies on epoxide **9** (and a related compound) indicated that, in the ^{1}H NMR spectra, the δ_H (CHO) signal for *cis* epoxides was more downfield than that for *trans* epoxides. We have used this correlation to support our assignments of epoxide stereochemistry for *N*-monoprotected epoxides – δ_H (CHO) values: 3.57 for *cis*-**9**, 3.54 for *trans*-**9**; 3.49 for *cis*-**23**, 3.40 for *trans*-**23**; 3.47 for *cis*-**24**, 3.40 for *trans*-**24**; 3.58 for *cis*-**25**, 3.54 for *trans*-**25**. However, this correlation did not apply to *N*-diprotected epoxides – δ_H (CHO) values: 3.47 for *cis*-**26**, 3.57 for *trans*-**26**.
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