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# *cis*- and *trans*-Stereoselective Epoxidation of N-Protected 2-Cyclohexen-1-ylamines

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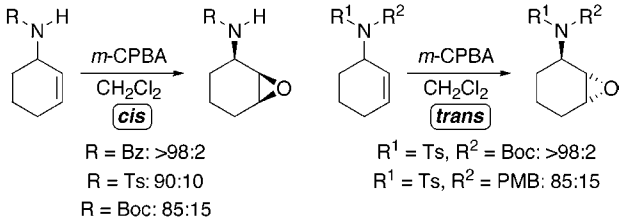
## ABSTRACT

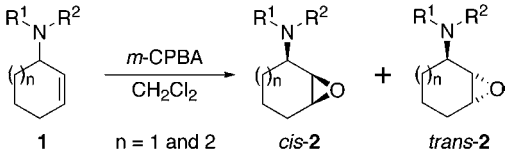



**The first systematic study of the cis and trans stereoselectivity in the *m*-CPBA epoxidation of N-protected cyclic allylic amines has been completed. Mono-N-protected systems gave epoxides with cis stereochemistry (amides are better cis directors than sulfonamides or carbamates) whereas di-N-protected systems gave *trans*-epoxides (TsNBoc protection gave complete trans stereoselectivity).**

The success of strategies for total synthesis continues to depend on high levels of stereoselectivity being observed in substrate-controlled diastereoselective reactions.[1] In this context, one of the more widely used processes is alkene epoxidation, and although much has been reported on the diastereoselectivity of epoxidation of cyclic alkenes with an *O*-allylic directing group (following Henbest's pioneering contribution[2]), it turns out that there have been only a few reports on the epoxidation of N-protected cyclic allylic amines.[3,4]

For example, epoxidation of mono-N-protected alkenes (carbamate,[3c,3d] amide,[3a−c] sulfonamide[5] protecting group) with peracids gives an unquantified degree of cis selectivity (presumably via a "Henbest-like" hydrogen-bonding interaction). More recent work by Murray et al. has established that a benzamide-protected allylic amine can be preferentially converted into a *cis*-epoxide using DMDO.[3e] Asensio and co-workers have also shown that alkenes containing an allylic trialkylammonium substituent undergo cis-stereoselective epoxidations with *m*-CPBA or dioxiranes.[3f] By way of contrast, we have found only one example of the epoxidation of a cyclic N-diprotected allylic amine, and this showed trans selectivity, presumably due to steric factors.[5] In this paper, we now report on the first systematic study of the *m*-CPBA epoxidation of a wide range of mono- and di-N-protected cyclic allylic amines **1** (Scheme 1). We also report on the

**Scheme 1**

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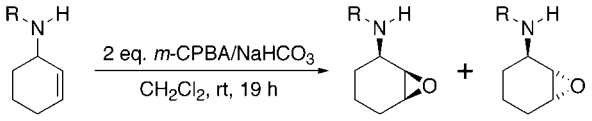
optimal protecting groups for the synthesis of epoxides *cis*-**2** or *trans*-**2**.

Initially, a wide range of mono-N-protected cyclic allylic amines **3a**−**j** were prepared using standard methods. The key synthetic intermediates were trichloroacetamide **3h** (prepared by Overman rearrangement[6]) and 2-cyclohexen-1-ylamine (formed by hydrolysis[7] of **3h** and isolated as the hydrochloride salt[8]). N-Protection of 2-cyclohexen-1-ylamine gave sulfonamides **3a**−**d**, carbamates **3e**−**g**, and amides **3i**,**j** (see the Supporting Information). The epoxidation of alkenes **3a**−**j** was carried out under standard conditions (0.5 mmol scale): 2 equiv of *m*-CPBA/$NaHCO_3$, $CH_2Cl_2$, rt, 19 h followed by workup with aq $Na_2SO_3$ (Table 1). In each case, quantitative crude yields of mixtures of epoxides *cis*- and *trans*-**4a**−**j** were obtained, and the ratio of epoxides was determined from the $^1$H NMR spectrum of the crude product mixture. The major products were identified as epoxides *cis*-**4a**−**j** by analogy with the known stereochemistry of *cis*-**4b**,[5] *cis*-**4f**,[3d] and *cis*-**4i**.[3e]

**Table 1.** Stereoselective Epoxidation of Mono-N-protected Alkenes **3a**−**j**




**3a-j** *cis*-**4a-j** *trans*-**4a-j**

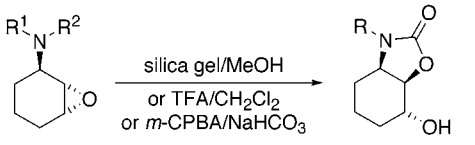
| entry | R | alkene | epoxide[a] | cis/trans[b] |
|---|---|---|---|---|
| 1 | Ms | **3a** | **4a** | 90:10 |
| 2 | Ts | **3b** | **4b** | 90:10 |
| 3 | *o*-Ns[c] | **3c** | **4c** | 90:10 |
| 4 | *p*-Ns[d] | **3d** | **4d** | >95:5 |
| 5 | $CO_2$Me | **3e** | **4e** | 90:10 |
| 6 | $CO_2$Bn | **3f** | **4f** | 90:10 |
| 7 | $CO_2{}^t$Bu | **3g** | **4g** | 85:15 |
| 8 | $Cl_3$CC(O) | **3h** | **4h** | 95:5 |
| 9 | PhC(O) | **3i** | **4i** | >98:2 |
| 10 | $^t$BuC(O) | **3j** | **4j** | >98:2 |

[a] Epoxidation conditions: *m*-CPBA, $NaHCO_3$, $CH_2Cl_2$, rt, 19 h. [b] Ratio determined by $^1$H NMR spectroscopy on the crude product mixture. [c] *o*-$NO_2C_6H_4SO_2$−. [d] *p*-$NO_2C_6H_4SO_2$−.

All these epoxidations were cis selective but our results show that amides are the best cis directors for the *m*-CPBA-mediated epoxidation of mono-N-protected cyclohexene-derived allylic amines (Table 1, entries 8−10). Notably, a Boc group gave the worst cis selectivity (Table 1, entry 7) (and should be avoided in synthesis), and of the sulfonamides investigated, a *p*-$NO_2C_6H_4SO_2$ gave the highest cis selectivity (Table 1, entry 4). The best compromise of high *cis*-selectivity and ease of protecting group introduction/removal involved the use of either a *p*-$NO_2C_6H_4SO_2$ or trichloroactamide N-protecting group for the epoxidation of cyclohexene-derived allylic amines.

Next, we prepared five di-N-protected cyclic allylic amines **5a**−**e**. Alkenes **5a**, **5b**, and **5e** were prepared by protection of *N*-(cyclohex-2-enyl)-4-methoxybenzylamine,[9] whereas a Mitsunobu approach was used for the synthesis of alkenes **5c** and **5d** (see the Supporting Information).[10] The epoxidation results with **5a**−**e** are shown in Table 2. With di-N-protected allylic amines, *trans*-epoxides were obtained as the major products and this was established as follows. Reaction of the 90:10 mixture of epoxides *cis*- and *trans*-**4b** (of known relative stereochemistry[5]) with *p*-methoxybenzyl chloride ($K_2CO_3$, MeCN, reflux) gave a major product which, by comparison of $^1$H NMR spectra, was clearly the minor product (epoxide *cis*-**6a**) from the epoxidation of alkene **5a**. Epoxide **6b** was assigned in the same way. In addition, separate Boc-protection of the 90:10 mixtures of *cis*- and *trans*-**4b** and -**4c** identified *trans*-**6c** and -**6d**, respectively. Proof of stereochemistry in epoxides *trans*-**6c**−**e** was provided by their rearrangement to oxazolidinones **7a**−**c** (via participation of the Boc carbonyl group and subsequent loss of the *tert*-butyl group[3e,4]) under acidic conditions (e.g., silica gel/MeOH, TFA/$CH_2Cl_2$) or even under the epoxidation conditions for *trans*-**6c** or *trans*-**6e** (Scheme 2). Indeed, a reduced epoxidation time for alkene **5c** was required to prevent any rearrangement occurring during the reaction. In contrast, we could not stop rearrangement with epoxide *trans*-**6e**, and oxazolidinone **7c** was isolated as the only product (93% yield) after chromatography.

**Scheme 2**




*trans*-**6c-e**

**7a** (R = Ts)
**7b** (R = *o*-Ns)
**7c** (R = PMB)

The results in Table 2 indicate that very high levels of trans stereoselectivity are obtained from the epoxidation of di-N-protected cyclic allylic amines containing a Boc group and either a sulfonamide or *p*-methoxybenzyl group (Table 2, entries 3−5). The stereoselectivity is governed by steric factors. If the epoxide product is required from *N*-Boc-protected allylic amines **5c**−**e**, the reaction time of the

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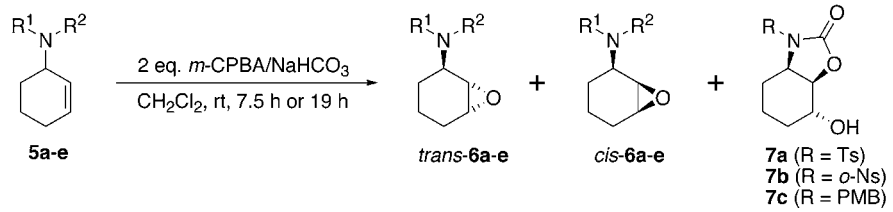
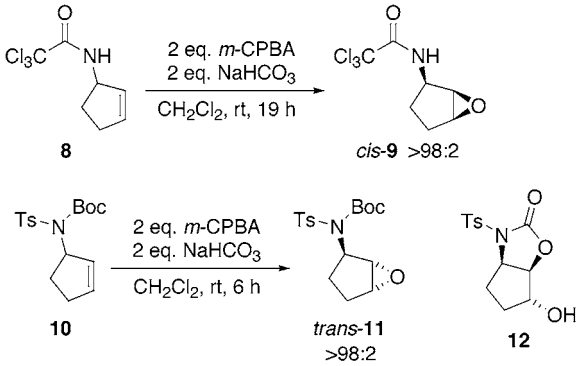
**Table 2.** Stereoselective Epoxidation of Di-N-protected Alkenes **5a**−**e**




| entry | $R^1$ | $R^2$ | time (h) | alkene | epoxide[a] | trans/cis[b] |
|---|---|---|---|---|---|---|
| 1 | Ts | $p$-$MeOC_6H_4CH_2$ | 19 | **5a** | **6a** | 85:15 |
| 2 | $o$-Ns[c] | $p$-$MeOC_6H_4CH_2$ | 19 | **5b** | **6b** | 90:10 |
| 3 | $p$-Ns[d] | $CO_2{}^tBu$ | 7.5[e] | **5c** | **6c** | >98:2 |
| 4 | $o$-Ns[c] | $CO_2{}^tBu$ | 19 | **5d** | **6d** | >98:2 |
| 5 | $p$-$MeOC_6H_4CH_2$ | $CO_2{}^tBu$ | 7.5 | **5e** | **6e**[f] | >98:2 |

[a] Epoxidation conditions: *m*-CPBA, $NaHCO_3$, $CH_2Cl_2$, rt. [b] Ratio determined by $^1H$ NMR spectroscopy on the crude product mixture. [c] $o$-$NO_2C_6H_4SO_2$−. [d] $p$-$NO_2C_6H_4SO_2$−. [e] If the epoxidation was left for 19 h, some rearrangement to oxazolidinone **7a** was observed. [f] Epoxide *trans*-**6e** not isolated: the only product of this reaction was the rearranged oxazolidinone **7c** (see Scheme 2).

**Scheme 3**




epoxidation must be carefully monitored; otherwise, rearrangement to the oxazolidinones **7a**−**c** occurs.

We have also carried out a preliminary study on epoxidation of five-membered ring N-protected allylic amines (Scheme 3). Epoxidation of trichloroacetamide-protected alkene **8** furnished a single diastereomeric epoxide, assigned as *cis*-**9**. This result is consistent with our previous report of the cis directing effect of an allylic NHBoc group in the epoxidation of a substituted cyclopentene system (during the development of a route to the agelastatins).[11] In contrast, epoxidation of TsNBoc-diprotected alkene **10** with *m*-CPBA for 6 h gave epoxide *trans*-**11** (>98:2 trans/cis). With an extended reaction time (19 h), there was evidence for the formation of some oxazolidinone **12**.

In summary, complementary routes to *cis*- and *trans*-epoxides from protected cyclic allylic amines have been established. With mono-N-protected alkenes, it has been demonstrated that amides and a $p$-$NO_2C_6H_4SO_2$ group are the best cis directors of epoxidation (≥95:5 cis/trans). The presence of an NBoc substituent is crucial for high stereoselectivity (>98:2 trans/cis) in the epoxidation of di-N-protected alkenes. These results are consistent with our results with 4-amino-substituted cyclopentenes.[12] Finally, rearrangement of epoxides *trans*-**6c**−**e** (diprotected, possessing a NBoc group) either in situ (**6e**) or after treatment with acid (**6c**,**d**) generates oxazolidinones **7a**−**c**, which appear to be very useful, stereodefined synthetic building blocks.

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**Supporting Information Available:** Outline details of the routes used to synthesize compounds **3a**,**b** and **5a**−**e**, general epoxidation procedure, key $^1H$ NMR spectroscopy data for all epoxides **4a**−**j** and **6a**−**d**, characterization data for oxazolidinones **7a**−**c**, and copies of $^1H$ NMR spectra of all epoxides and oxazolidinones. This material is available free of charge via the Internet at http://pubs.acs.org.

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