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Synthetic applications of the amino-Cope rearrangement: enantioselective synthesis of some tetrahydropyrans

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Abstract—We report a novel and enantioselective approach to 2,4-disubstituted tetrahydropyrans that utilises the asymmetric amino-Cope rearrangement as a key synthetic step.

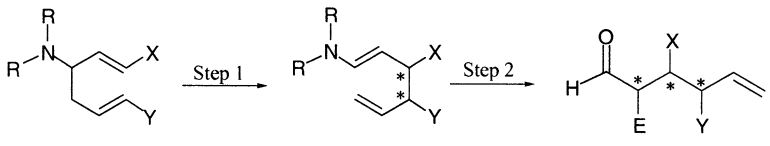
Asymmetric synthetic routes to tetrahydropyran subunits are of considerable interest since these heterocyclic components are found in many biologically active molecules and natural products. In this communication we wish to present the first demonstration of the synthetic utility of the asymmetric anionic amino-Cope rearrangement, and highlight its potential for future application in natural product synthesis. The novel route described in this paper delivers functionalised 2,4-disubstituted tetrahydropyrans in high enantiomeric excesses from readily available precursors. The key step in our synthetic protocol is the introduction of asymmetry via our recently developed asymmetric anionic amino-Cope rearrangement methodology.

There is growing interest in asymmetric variants of sigmatropic rearrangements,[1] and we are continuing to develop the amino-Cope rearrangement as a new synthetic protocol. Scheme 1 summarises our ultimate goal: the one-pot asymmetric synthesis of acyclic targets containing (up to) three contiguous chiral centres via amino-Cope rearrangement (Step 1) and subsequent (tandem) enamine derivatization and hydrolysis (Step 2).

Our group has demonstrated the key steps of this protocol, including a successful tandem amino-Cope rearrangement/enamine derivatisation reaction.[2] More recently we have established that an anionic variant of the amino-Cope rearrangement is possible, and that asymmetric induction can be achieved at an asymmetric centre created during the rearrangement of a diastereoisomerically pure substrate.[3]

Although the precise mechanism of the amino-Cope rearrangement remains a matter for debate,[4] we have demonstrated that the asymmetric amino-Cope rearrangement can have significant advantages over the analogous oxy-Cope rearrangement in terms of asymmetric induction.[5] For example, the axial/equatorial preference of an oxy-anion substituent in the proposed chair-like transition state of the oxy-Cope rearrangement can be low, leading to a rearrangement product with a correspondingly low e.e.[6]

The preparation of the 3-amino-1,5-diene substrate required for the asymmetric amino-Cope rearrangement has been detailed elsewhere.[5] Substrate **1** was readily isolated in diastereoisomerically pure form by column chromatography on silica gel, and the relative stereochemistry has been confirmed by single-crystal X-ray analysis. Amino-Cope rearrangement of **1** was carried out by treating the substrate with 2.5 equiv. of *n*-BuLi at −78°C in THF, the reaction mixture was then



Scheme 1. Synthetic potential of the amino-Cope rearrangement.

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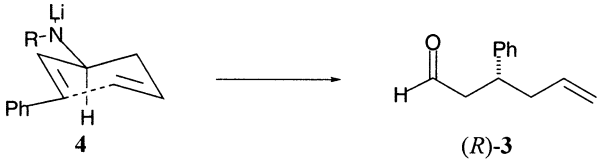
allowed to reach room temperature, and heated under reflux for 2 h before dilute acid work-up (Scheme 2). The target aldehyde **3** was not observed in the crude product mixture by ^{1}H NMR, but rather the oxazolidine **2** resulting presumably from ring-closure of the intermediate enamine on acidic work-up. Liberation and purification of aldehyde **3** was effected simply by column chromatography of the crude oxazolidine on silica gel.

The enantiomeric excess and absolute configuration of aldehyde **3** was determined by conversion to the corresponding diastereoisomeric oxazolidine derived from 1*R*,2*S*-(−)-ephedrine, as described by Agami.[7] The absolute stereochemistry induced on rearrangement of the 3-amino-1,5-diene substrates used in all of our studies to date has been rationalised by invoking a chair-like transition state model, **4**, having the amine component occupying a pseudo-equatorial orientation, although a model such as this is surely an over-simplification. Indeed, as mentioned above, there is currently some debate over the mechanism of the rearrangement, with certain 4-substituted 3-amino-1,5-dienes having been shown[4] to rearrange by a stepwise mechanism. Nevertheless, model **4** provides a useful 'rule of thumb'.



4 (*R*)-**3**

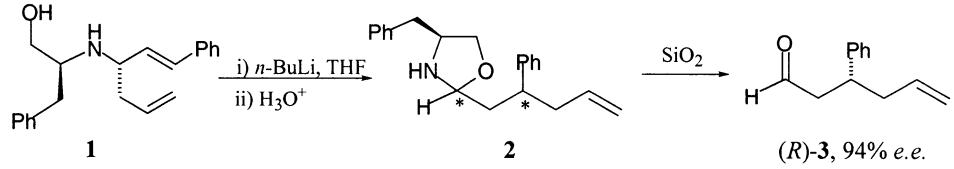
One useful method for the formation of oxygen heterocycles involves the electrophile-induced cyclisation of an unsaturated alcohol precursor.[8] We were able to access the corresponding alcohol **5** from aldehyde **3** in 99% yield by sodium borohydride reduction. Analysis of **5** by chiral HPLC[9] showed essentially the same level of e.e. for the alcohol product (92%) as was observed for the aldehyde precursor by NMR determination.

With **5** in hand we performed an iodine-induced cyclisation at room temperature (I_2, $NaHCO_3$, MeCN) and achieved an almost quantitative conversion to the target iodo-THP **6**. ^{1}H NMR analysis of the crude reaction mixture revealed that the cyclisation had proceeded with a diastereoselectivity of 4:1 in favour of the *cis*-diastereoisomer **6a**.[10]

The major diastereoisomer **6a** was isolated by column chromatography in 60% yield and further analysis by chiral HPLC[11] showed this compound to have an e.e. of 92%, confirming no loss of stereochemical integrity during cyclisation (Scheme 3).

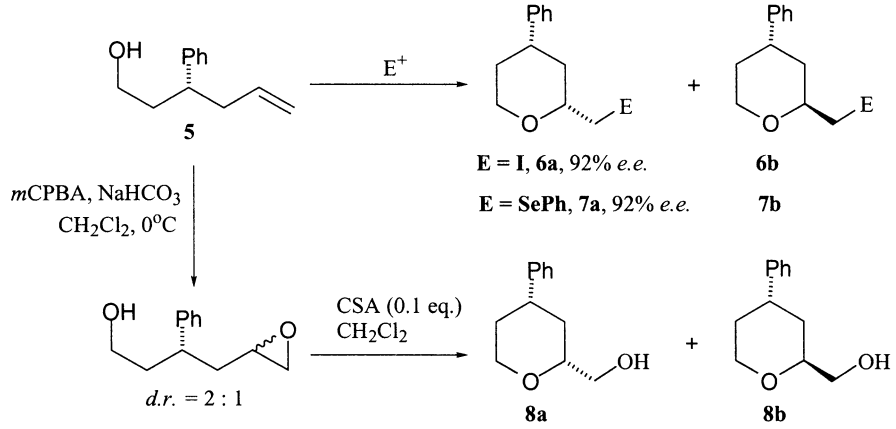
After our success with iodine as the electrophile we chose to investigate a variant of this cyclisation methodology. The phenylselenyl group is a useful handle that can allow further molecular elaboration, and by applying a suitable selenium electrophile, *N*-(phenylseleno)phthalimide (NPSP, 1.7 equiv.), in the presence of pyridinium *p*-toluenesulfonate (PPTS, 0.3 equiv.) in CH_2Cl_2 at −78°C we were able to achieve cyclisation to the corresponding tetrahydropyran products. In this case however, a 1:1 diastereoisomeric ratio was observed by ^{1}H NMR analysis of the crude reaction mixture. We were able to separate each component by column chromatography to yield 39% of **7a** and 36% of **7b**.

A significant reduction in the level of product diastereoselectivity is observed on moving from the I^+



1 **2** (*R*)-**3**, 94% *e.e.*

Scheme 2. Asymmetric amino-Cope rearrangement.



Scheme 3. Electrophile mediated cyclisations.

to the $PhSe^+$ electrophile, and this has been noted previously by Greeves for similar substrates.[8c] It is likely that this results from a reduced preference by the $PhSe^+$ electrophile to adopt the same equatorial orientation during cyclisation via a chair-like transition state that is clearly favoured by I^+. Indeed, the work of Greeves shows that $PhSe^+$ favours an axial orientation during cyclisation.[8c]

Analysis of the separated diastereoisomers by chiral HPLC[11] showed that THP **7a** had an e.e. of 92%, again in good agreement with the e.e. of the starting alcohol **5**. The chromatogram of THP **7b** was not fully resolved, although the HPLC trace clearly showed that the compound was highly enantiomerically enriched.

One final class of tetrahydropyran was prepared through epoxidation of the double bond followed by treatment with catalytic CSA. The intermediate epoxides (a 2:1 mixture of diastereoisomers) were not separated, but directly treated with CSA in CH_2Cl_2 at 0°C to yield the target THP **8** as a 2:1 mixture of diastereoisomers. We were able to separate the diastereoisomers to yield 28% of the major diastereoisomer **8a** and 12% of **8b**, and confirm the relative stereochemistries by comparison with the ^1H NMR spectra of the iodotetrahydropyrans.[10] In this case we were unable to determine the e.e. of either diastereoisomer by NMR or HPLC techniques.

In summary we have demonstrated the preparation of various substituted tetrahydropyran targets in high enantiomeric excess, representing the first synthetic application of the asymmetric amino-Cope rearrangement. Further applications are underway in our group, and these will be reported in due course.

Acknowledgements

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9. Chiral HPLC study carried out using a Chiralcel-OD column eluting with a 95 hexanes–5% propan-2-ol solvent mixture at 0.6 ml/min. A racemic sample of the target under study was prepared and investigated prior to the enantiomerically enriched product. Retention times: major enantiomer = 18.9 min, minor = 22.2 min.
10. In all cases, the major (*cis*-) diastereoisomers display a large diaxial coupling of ca. 12 Hz between the C-2 proton at the chiral centre created on electrophile-induced cyclisation and the axial C-3 proton. For the minor (*trans*-) diastereoisomers, the now equatorial C-2 proton displays a much weaker axial–equatorial coupling (ca. 4 Hz) to the same C-3 proton.
11. Chiral HPLC study carried out using a Chiralcel-OD column eluting with a 99.5 hexanes–0.5% propan-2-ol solvent mixture at 0.25 ml/min. A racemic sample of the target under study was prepared and investigated prior to the enantiomerically enriched product. Retention times: **6a**: major enantiomer = 46.9 min, minor = 42.5 min; **7a**: major enantiomer = 51.2 min, minor = 60.1 min.