[Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), www.mdpi.org/ecsoc-4.htm, September 1-30, 2000]

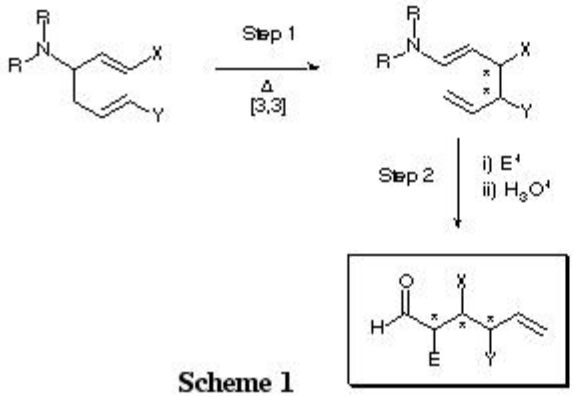
[A0017]

Loughborough University

Synthetic Applications of the Asymmetric Amino-Cope Rearrangement

Rob D. Baird, Martin A.C. Button and Steven M. Allin *

Department of Chemistry, Loughborough University, Loughborough, LE11 3TU.



Scheme 1

Introduction

There is growing interest in asymmetric variants of sigmatropic rearrangements [1]. We have recently initiated a programme aimed at developing the amino-Cope rearrangement as a novel synthetic protocol.

Scheme 1 summarizes our ultimate goal, the one-pot synthesis of acyclic products containing (up to) three contiguous asymmetric centres *via* sigmatropic rearrangement (Step 1) and subsequent enamine derivatization (Step 2). Our group is the first to have demonstrated key steps of this protocol, including a tandem amino-Cope rearrangement/enamine derivatization 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 a chiral centre created during the rearrangement of a diastereoisomerically pure substrate [3].

Asymmetric Anionic Amino-Cope Rearrangement

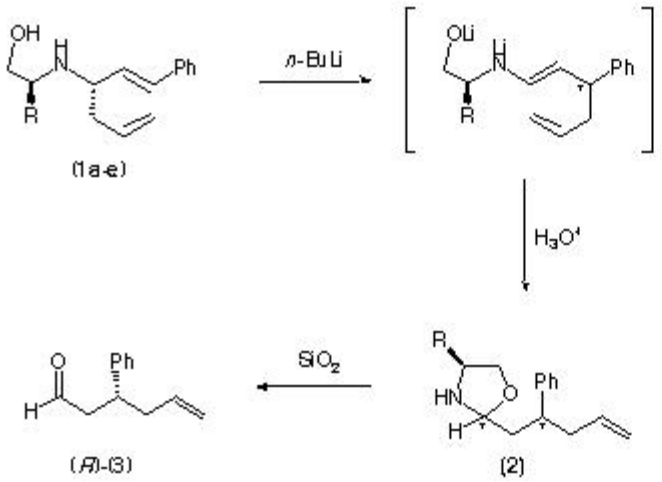
Following our preliminary work we reasoned that an increase in the steric bulk of the amine component would result in a corresponding increase in product enantioselectivity during the amino-Cope rearrangement. To investigate the effect of variation of the amine component on product enantioselectivity we chose to employ a range of enantiomerically pure **β**-

	R	(*R*)-3, (%)	*e.e.* (%)
(a)	*i*-Pr	60	84
(b)	*t*-Bu	53	88
(c)	*i*-Bu	57	71
(d)	Ph	61	83
(e)	$PhCH_2$	65	94

Table 1

The required 3-amino-1,5-diene products were synthesized in good yield using a

aminoalcohols.



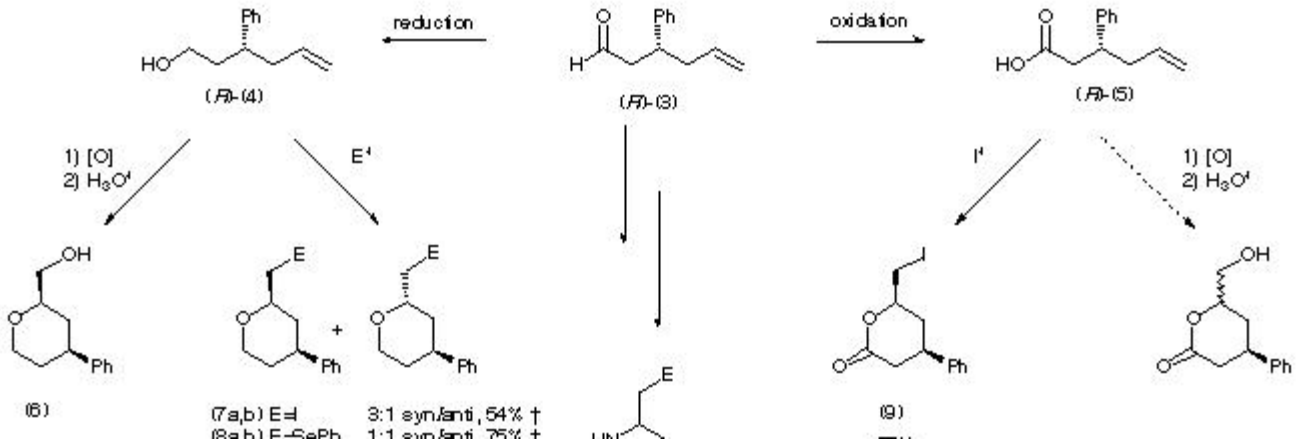
Scheme 2

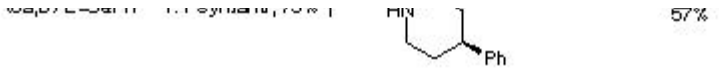
protocol previously described by our group[4] and the major diastereoisomer was easily accessible by column chromatography or recrystallisation. Amino-Cope rearrangement of the major epimer of substrates (**1a-e**) was carried out (Scheme 2, Table 1) by treating the substrate with 2.5 equivalents of *n*BuLi at –78°C in THF, the reaction mixture was allowed to warm to room temperature, and refluxed for 2 hours before work-up. Interestingly the crude product was observed not as the expected aldehyde, but as the oxazolidine (**2**) resulting from ring-closure of the intermediate enamine on acidic work-up. Liberation and purification of (**3**) was effected by flash column chromatography of the crude oxazolidine on silica gel.

Heterocycle Synthesis

Tetrahydropyrans, lactones and piperidines are commonly found as sub-units in a wide range of natural products. Using the amino-Cope rearrangement we are able to access the aldehyde (**3**) with a high level of enantiomeric excess using phenylalaninol as our chosen amino-alcohol auxiliary. Simple reduction of the aldehyde affords alcohol (**4**) with no loss of *e.e.* (92% measured by chiral HPLC, ChiralCel OD) and cyclisation is achieved by treatment of the alcohol with an electrophile (I^+ or $PhSe^+$) in acetonitrile to yield two separable diastereoisomers (**7/8a** and **7/8b**, ratio 3:1 where E=I). If alcohol (**4**) is treated with *m*CPBA followed by catalytic CSA in dichloromethane the hydroxytetrahydropyran (**6**) can be synthesised *via* intramolecular cyclisation onto the intermediate epoxide.

Oxidation of the aldehyde with sodium chlorite[5] yields the carboxylic acid (**5**) which can also undergo cyclisation with a number of electrophiles. Treatment with iodine in acetonitrile gives predominantly the *syn* diastereoisomer, with both large groups being equatorial. It is note-worthy that the spectroscopic data suggest the heterocycle prefers to sit in a boat-like conformation [6].





via reductive amination and electrophilic cyclisation

Scheme 3

Conclusion

We have demonstrated the first synthetic application of the asymmetric anionic amino-Cope rearrangement to synthesize novel chiral building blocks without loss of *e.e.* Current work is underway to expand the scope of the rearrangement and its use in natural product synthesis.

References

1 For a recent review see: Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, 7, 1847

2 Allin, S. M.; Button, M. A. C.; Shuttleworth, S. J. *Synlett* **1997**, 725

3 Allin, S. M.; Button, M. A. C. *Tetrahedron Lett.* **1998**, 39, 3345

4 Allin, S. M.; Button, M. A. C.; Baird, R. D. *Synlett* **1998**, 1117

5 Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.*, **1973**, 27, 888

6 Greeves, N.; Lee W.; Barkley J. *Tetrahedron Lett*, **1997**, 38, 6453

E-mail: s.m.allin@lboro.ac.uk
