

# High Asymmetric Induction in Anionic Amino-Cope Rearrangements Controlled by $\beta$ -Aminoalcohol Auxiliaries

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

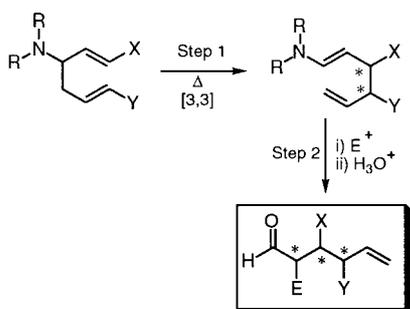
Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, England.

Fax: 44 (0)1509 223925; email: S.M.Allin@lboro.ac.uk

Received 3 June 1998

**Abstract:** Novel 3-amino-1,5-dienes were prepared with high diastereoselectivity by unprecedented 1,2-addition of allyl Grignard to  $\alpha,\beta$ -unsaturated imines containing  $\beta$ -aminoalcohol auxiliaries. Asymmetric anionic amino-Cope rearrangement of the diastereoisomerically pure 3-amino-1,5-diene substrates proceeded to yield the target 3-substituted aldehyde in good yield and with high levels of asymmetric induction (up to 94% *e.e.*).

There is growing interest in asymmetric variants of sigmatropic rearrangements.<sup>1</sup> We have recently initiated a programme aimed at developing the amino-Cope rearrangement as a novel synthetic cascade. 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).



Synthetic Potential of the amino-Cope Rearrangement

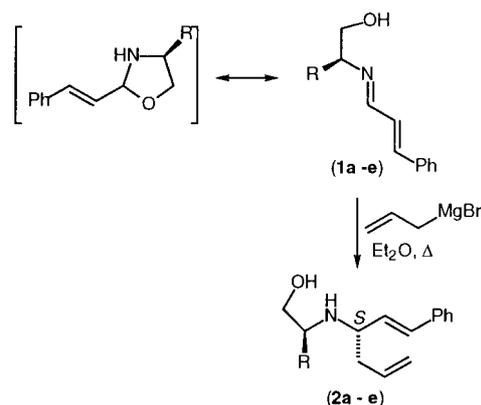
## Scheme 1

Our group is the first to have demonstrated key steps of this protocol, including a successful tandem amino-Cope rearrangement/enamine derivatization reaction.<sup>2</sup> 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.<sup>3</sup> We believe that the asymmetric amino-Cope rearrangement has significant advantages over the analogous oxy-Cope rearrangement in terms of asymmetric induction. The reported axial/equatorial preference for an oxy-anion substituent in the proposed chair-like transition state of the oxy-Cope rearrangement can be low, leading to a product with a correspondingly low enantioselectivity.<sup>4</sup> For example, the asymmetric oxy-Cope and amino-Cope rearrangements can yield the same aldehyde product, but whereas the amino-Cope rearrangement has yielded the product with 75% *e.e.*,<sup>3</sup> the oxy-Cope is known to lead to only 30% *e.e.*<sup>4</sup> Our initial study into the asymmetric amino-Cope rearrangement suffered from drawbacks including low diastereoselectivity (1.3 : 1) in the preparation of the required 3-amino-1,5-diene substrates, and a maximum *e.e.* of only 75% in the amino-Cope rearrangement.<sup>3</sup> The diastereoselectivity obtained during preparation of the 3-amino-1,5-diene substrates is of key importance to our work, since each diastereoisomer is known to lead to opposite enantiomers of the

rearrangement product,<sup>3</sup> hence separation of the substrate diastereoisomers is an additional problem if one aims to achieve high enantioselectivity in the sigmatropic rearrangement. The results outlined in this current paper describe the synthesis of the required 3-amino-1,5-diene substrates with much improved levels of diastereoselectivity using  $\beta$ -aminoalcohol chiral auxiliaries, and a significant increase in product *e.e.* during the amino-Cope rearrangement of these novel substrates.

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. This postulate was based on our proposed transition state models that involve a favoured chair-like conformation of the substrate with the amine component occupying a pseudo-equatorial orientation.<sup>3</sup> This transition state model has, so far, allowed us to predict the absolute configuration of the product resulting from rearrangement of a given substrate diastereoisomer. We believed that an increase in amine "bulk" would disfavour the competing chair transition state leading to the opposite product enantiomer due to an increased possibility of unfavourable 1,3-diaxial interactions with the axial amine substituent. To investigate the effect of variation of the amine component on product enantioselectivity we chose to employ a range of enantiomerically pure  $\beta$ -aminoalcohols. These auxiliaries are known to control a range of asymmetric transformations, and are capable of forming a 5-membered chelate in the presence of a metal counter-ion<sup>5</sup> - a property we aimed to exploit in order to increase the effective steric bulk of the 3-amino substituent.

The 3-amino-1,5-diene substrates required for this current study were prepared in only two synthetic steps. Condensation of the corresponding  $\beta$ -aminoalcohol with an equimolar quantity of cinnamaldehyde gave the desired imines (**1a - e**) in good yield (Scheme 2, Table 1).<sup>6</sup>



## Scheme 2

Interestingly, similar imino-alcohols have been observed by others to exist in chloroform solution as a mixture of the imine/oxazolidine tautomers (Scheme 2).<sup>7</sup> However, in our study, products (**1a - e**) were observed exclusively as the imine by 250MHz <sup>1</sup>H-NMR spectroscopy in CDCl<sub>3</sub> solvent.

**Table 1. Preparation of 3-amino-1,5-dienes.**

	<b>R</b>	<b>1 (%)</b>	<b>2 (%)</b>	<b>d.e. (%)<sup>a</sup></b>
(a)	<i>i</i> -Pr	99	78	97
(b)	<i>t</i> -Bu	99	77	94
(c)	<i>i</i> -Bu	86	60	92
(d)	Ph	99	64	96
(e)	PhCH <sub>2</sub>	99	67	82

a) - determined by 250MHz <sup>1</sup>H-NMR spectroscopy

The 3-amino-1,5-diene products (**2a - e**) were synthesized in good yield by addition of allyl magnesium bromide to the imines (Scheme 2, Table 1). The organometallic addition reaction proceeded in all cases with an extremely high level of diastereoselectivity (Table 1).<sup>8</sup> This reaction is of interest for several reasons; the addition of organometallic species to imines derived from non-racemic β-aminoalcohols and their derivatives is known to be highly diastereoselective and has been proposed to proceed through a chelated transition state. The "sense" of stereochemical induction during imine addition is then controlled by the absolute stereochemistry inherent in the chiral auxiliary, allowing accurate predictions to be made about the relative configuration of the amine product.<sup>9</sup> However, in the case of α,β-unsaturated imine substrates, the possibility of 1,2 *v/s* 1,4-addition arises. Other research groups have addressed this question, and the following generalizations have been made for α,β-unsaturated imine substrates containing a β-aminoalcohol auxiliary:<sup>10</sup>

- organolithium, cerium and cuprate reagents undergo 1,2-addition;
- Grignard reagents add exclusively in a 1,4-fashion.

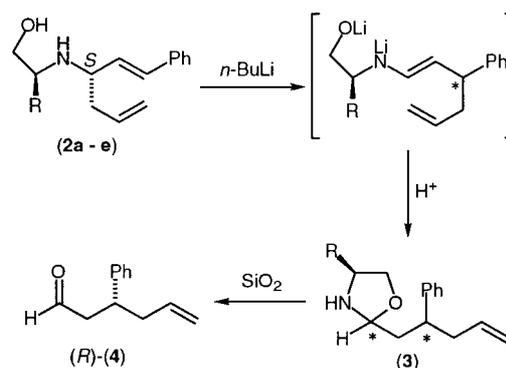
It is clear from our own results (Scheme 2, Table 1) that allyl Grignard reagents represent an anomaly to this generalization, since we have observed **no** 1,4-addition products. Our current understanding is that this observation has not been noted previously, and is currently under further study by us.

Amino-Cope rearrangement of the major diastereoisomer of substrates (**2a - e**) was carried out (Scheme 3, Table 2) 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 (**3**) resulting from ring-closure of the intermediate enamine on acidic work-up. Liberation and purification of (**4**)<sup>11</sup> was effected by flash column chromatography of the crude oxazolidine on silica gel.

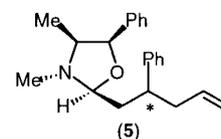
The enantiomeric excess (Table 2) and absolute configuration of the product aldehyde was confirmed by conversion to the corresponding diastereoisomeric oxazolidine (**5**) derived from 1*R*, 2*S*(-)-ephedrine, as described by Agami.<sup>12</sup> The absolute stereochemistry induced on rearrangement of these novel substrates can be rationalized by invoking the chair-like transition state model (**6**), with the amine component occupying a pseudo-equatorial orientation.

In a recent report<sup>3</sup> we proposed that the stereochemistry at C-3 of the 3-amino-1,5-diene substrate was the controlling factor in determining the absolute stereochemistry of the rearranged product [*S* stereochemistry at C-3 leads to the (*R*)-aldehyde, and *vice-versa*]. The predictive capacity of this model was further verified in an experiment using a substrate derived from the (*R*)-enantiomer of valinol (i.e. the enantiomer of entry a, Table 2). In this case the (*S*)-enantiomer of aldehyde (**4**) was obtained, as expected, with a comparable *e.e.* (84%).

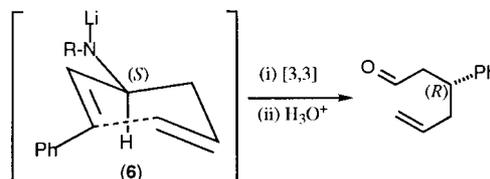
Although a transition state model such as (**6**) is surely an oversimplification, combined with our current results it does suggest that an increase in steric bulk, possibly provided by intramolecular chelation in the amine component, leads to an increased preference for an equatorial amine substituent in our proposed transition state. This in turn leads to

**Scheme 3****Table 2. Asymmetric amino-Cope Rearrangement**

	<b>R</b>	<b>(R)-4, (%)</b>	<b>e.e. (%)</b>
(a)	<i>i</i> -Pr	60	84
(b)	<i>t</i> -Bu	53	88
(c)	<i>i</i> -Bu	57	71
(d)	Ph	61	83
(e)	PhCH <sub>2</sub>	65	94



an enhanced level of enantioselectivity in the asymmetric amino-Cope rearrangement.



**Acknowledgements:** Universities of Loughborough and Huddersfield for facilities and financial support, and Dr Tim Smith (Loughborough) for assistance with NMR spectroscopy. We also thank Dr. David Ager (NSC Technologies) for a generous donation of the phenylglycinol used in this study.

#### References and Notes:

- (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) Lee, E.; Lee, Y. R.; Moon, B.; Kwon, O.; Shim, M. S.; Yun, J. S. *J. Org. Chem.* **1994**, 59, 1444.
- (5) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, 96, 835.
- (6) General procedure for the synthesis of imines (**1a - e**): Cinnamaldehyde (1.13g 8.53mmol) was added dropwise to a stirred solution of (*S*)-*tert*-leucinol (1g, 8.53mmol) in diethyl ether (10ml) at 0°C. The reaction mixture was allowed to stir at room

temperature for 80 minutes before adding anhydrous magnesium sulphate (1g) and stirring for a further 10 minutes. The solution was filtered and the solvent removed under reduced pressure to give imine (**1b**) as a pale yellow oil. The imine was used without further purification.

$\nu_{\max}$  (neat) 3261, 2956, 2868, 1636, 1618, 1478, 1051, 980, 958, 749, 734,  $691\text{cm}^{-1}$ ,  $\delta\text{H}$  (250 MHz,  $\text{CDCl}_3$ ) 0.94 (9H, s), 2.69 (1H, br.s), 2.81-2.87 (1H, dd,  $J$  8.1, 5Hz), 3.83-3.93 (2H, m), 6.86-6.90 (2H, m), 7.26-7.39 (5H, m), 7.94 (1H, d,  $J$  7.8Hz);  $\delta\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) 26.2, 27.0 (3C), 33.4, 62.2, 82.2, 127.2, 127.5, 128.7 (2C), 129.1, 137.0, 142.3, 164.7;  $m/z$  (EI) found 231.1624 [ $\text{M}^+$  + H],  $\text{C}_{15}\text{H}_{21}\text{NO}$  requires 231.1623.

- (7) Scaldione, M. A.; Meyers, A. I. *Tetrahedron Lett.* **1994**, 35, 7533; Pridgen, L. N.; Mokhallalati, M. K.; Wu, M. J. *J. Org. Chem.* **1992**, 57, 1237.

- (8) General procedure for the synthesis of amines (**2a – e**): Allylmagnesium bromide was prepared by the dropwise addition of allyl bromide (1.62ml, 18.80mmol) to magnesium turnings (0.45g, 18.80mmol) in dry diethyl ether (10ml) containing a crystal of iodine. Imine (**1b**) was added to the Grignard reagent at  $0^\circ\text{C}$  in a dropwise fashion over a 45 minute period. The reaction mixture was then heated at reflux for 2 hours before being poured onto ice water (20ml). Extraction into diethyl ether was followed by subsequent washing with 2N NaOH (2 x 20ml), and brine (2 x 20ml). The organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to yield the target amine (**2b**) as a pale yellow oil. The major diastereoisomer was isolated by crystallisation from petroleum ether/diethyl ether (10:1).

$\nu_{\max}$  (neat) 3396, 2954, 1636, 1618, 1477, 991, 1051, 984, 915,  $750\text{cm}^{-1}$ ,  $\delta\text{H}$  (250 MHz,  $\text{CDCl}_3$ ) 0.85 (9H, s), 2.39-2.43 (3H, m), 3.27-3.33 (1H, m), 3.46-3.64 (2H, m), 5.07-5.16 (2H, m), 5.82-5.91 (1H, m), 5.91-6.01 (1H, dd,  $J$  15, 7.5Hz), 6.43 (1H, d,  $J$  15Hz), 7.26-7.35 (5H, m), [OH, NH not visible];  $\delta\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) 27.3 (3C), 33.8, 40.9, 59.2, 59.5, 63.1, 117.5, 126.2 (2C),

127.5, 128.5 (2C), 131.4, 131.9, 134.8, 137.0;  $m/z$  (EI) found 274.2172 [ $\text{M}^+$  + H],  $\text{C}_{18}\text{H}_{27}\text{NO}$  requires 274.2173.

- (9) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, 96, 835; Bocoum, A.; Savoia, D.; Umami-Ronchi, A. *Tetrahedron Lett.* **1991**, 32, 1367; Basile, T.; Bocoum, A.; Savoia, D.; Umami-Ronchi, A. *J. Org. Chem.* **1994**, 59, 7766; Alvaro, G.; Martelli, G.; Savoia, D. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 775.
- (10) Pridgen, L. N.; Mokhallalati, M. K.; Wu, M. J. *J. Org. Chem.* **1992**, 57, 1237; Hashimoto, S.; Yamada, S.; Koga, K. *J. Am. Chem. Soc.* **1976**, 98, 7450.
- (11) General method for the amino-Cope rearrangement of amines (**2a – e**): The amine in dry THF was cooled to  $-78^\circ\text{C}$  under an inert atmosphere and 2.5 equivalents of *n*-butyllithium was added dropwise. After 10 minutes the reaction flask was allowed to warm to room temperature and then heated to reflux for 2 hours. The reaction was quenched by dropwise addition of a solution of sodium acetate/acetic acid/water (1:1:2) and refluxed for a further 4 hours. The solution was allowed to cool to room temperature, before addition of further 15ml of diethyl ether and washing with sodium bicarbonate solution (2 x 10ml) and brine (2 x 10ml). The organic phase was dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel using an eluent mixture of light petroleum ether/diethyl ether/acetone (10:2:1). Aldehyde (**4**) was isolated as a pale yellow oil.
- $\nu_{\max}$  (neat) 1724, 1640, 1602, 1494, 1453, 995, 916, 762, 701;  $\delta\text{H}$  (250 MHz,  $\text{CDCl}_3$ ) 2.36-2.44 (2H, m), 2.73-2.78 (2H, m), 3.27-3.33 (1H, m), 4.98-5.05 (2H, m), 5.64-5.67 (1H, m), 7.18-7.34 (5H, m), 9.67 (1H, t,  $J$  1.91Hz);  $\delta\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) 39.6, 40.9, 49.3, 117.1, 126.6, 127.4 (2C), 128.6 (2C), 135.7, 143.0, 201.6;  $m/z$  (EI) found 174.1044 [ $\text{M}^+$ ],  $\text{C}_{12}\text{H}_{14}\text{O}$  requires 174.1045.
- (12) Agami, C.; Meynier, F.; Berlan, J.; Besace, Y.; Brochard, L. *J. Org. Chem.* **1986**, 51, 73.