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The First Example of Asymmetric Induction in an Anionic Amino-Cope Rearrangement

Steven M. Allin* and Martin A. C. Button

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

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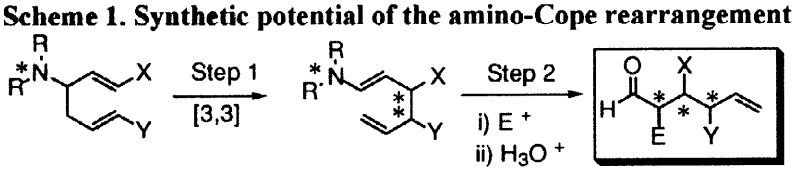
Abstract: The anionic amino-Cope rearrangement of suitably functionalized acyclic 3-amino-1,5-diene substrates has been achieved and we report the first example of an asymmetric anionic amino-Cope rearrangement to yield an enantiomerically enriched product (75% e.e.). The absolute stereochemistry of the products has been verified and transition state models are proposed to rationalize the stereochemical outcome.

Few examples highlighting the synthetic application of the amino-Cope rearrangement are known. Indeed, much of the work that has previously been reported has concentrated on the effect of the amine substituent on reaction rate [1], although Macdonald has reported an example of the amino-Cope rearrangement leading to cyclic products [2]. Our group has recognized that the amino-Cope rearrangement of suitably functionalized 3-amino-1,5-diene substrates could potentially constitute a powerful tool for the stereoselective synthesis of highly functionalized product systems in a cascade-like sequence.

Scheme 1. Synthetic potential of the amino-Cope rearrangement



1 **2**

As highlighted in Scheme 1, successful sigmatropic rearrangement of a 3-amino-1,5-diene substrate such as **1** would lead to formation of enamine product **2**. Substitution at the 1- or 6-position of the diene moiety in **1** would allow, during Step 1, creation of new asymmetric centres in product **2**. Indeed, high stereoselectivities are known to be induced at the chiral centres which are created in related [3,3]-sigmatropic rearrangements [3]. If this synthetic step could be further associated with typical enamine derivatization, as outlined in Step 2, up to 3 new asymmetric centres could be introduced in a one-pot reaction. An asymmetric centre within the amine component could essentially act as a chiral multiplier: producing (and controlling) the stereochemical induction at the three newly created asymmetric centres. We have recently reported one key step of the sequence outlined above: a successful tandem amino-Cope rearrangement/enamine derivatization reaction [4]. We now describe our initial investigations into the anionic variant of the amino-Cope rearrangement, and report the first example of an asymmetric anionic amino-Cope rearrangement.

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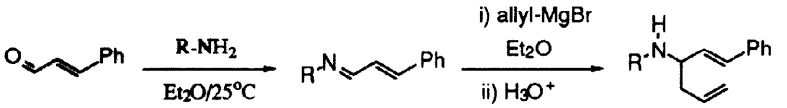
In order to study the anionic amino-Cope rearrangement we were required to prepare suitably substituted secondary amine substrates. This was achieved as highlighted in Scheme 2 by addition of allyl magnesium bromide to the corresponding imines derived from *trans*-cinnamaldehyde to yield the desired amines **4a-d** in good yield (Table 1).



3a-d **4a-d**

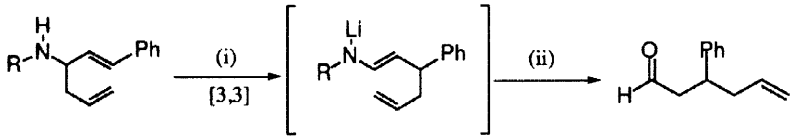
Scheme 2

Table 1. Preparation of 3-amino-1,5-diene substrates

R	Yield 3a-d, %	Yield 4a-d, %
(a) $PhCH_2$-	94	95
(b) cyclohexyl-	87	72
(c) (±)-α-methylbenzyl-	89	82
(d) (*R*)-α-methylbenzyl-	93	85[a]

(a) - as a 1.3:1 mixture of separable diastereoisomers

We were pleased to find that the anionic amino-Cope rearrangement proceeded as expected with the racemic substrates **4a-c** on employing *n*-butyllithium as base. The reaction was complete in under 3 hours. The intermediate lithiated enamines were directly hydrolysed to yield the desired racemic aldehyde **5** in good yield in all cases (Scheme 3, Table 2). Interestingly no reaction was observed using potassium hydride as base, or with a range of non-nucleophilic bases (LDA, LHMDS, KHMDS, NHMDS) in THF.



4a-c (±)-**5**

(i) *n*-BuLi (1.5 eq.), THF, 25 °C, 3 hr; (ii) NaOAc/HOAc/H_2O (1/1/2), Δ, 2 hr

Scheme 3.

Table 2. Anionic amino-Cope rearrangement of substrates 4a-c

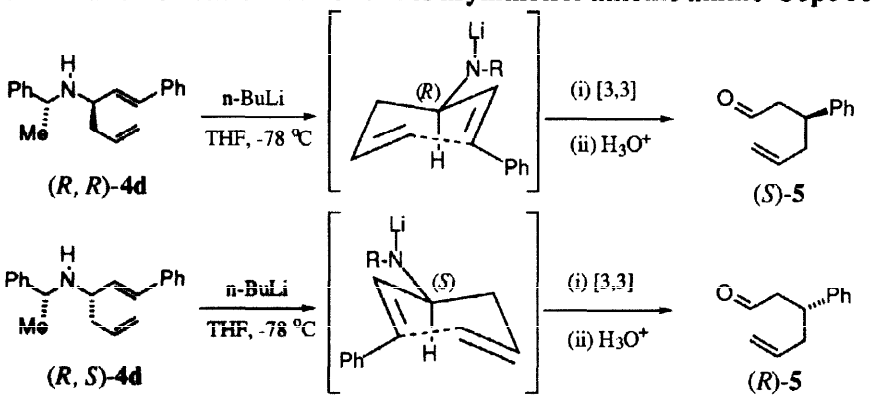
Substrate	Yield 5, %
4a	81
4b	64
4c	78

To further develop the scope of the anionic amino-Cope rearrangement, we have investigated the effect of incorporating an enantiomerically pure amine substituent into a typical substrate for anionic amino-Cope rearrangement. We believed that the amino-Cope rearrangement of a diastereoisomerically pure, non-racemic substrate would lead to formation of an enantiomerically enriched β-substituted aldehyde product.

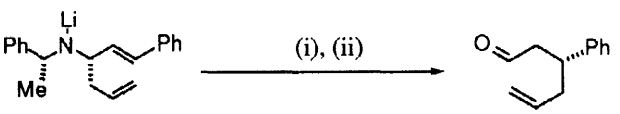
Simple transition state models (Figure 1) suggest that each substrate diastereoisomer should undergo concerted rearrangement through a highly ordered transition state, presumed at this stage to be a chair-like conformation as preferred in related rearrangements [3] to yield a product of defined chirality. The amine substituent is believed to prefer an equatorial orientation [4].

Such models, if accurate, would allow us to predict the stereochemical outcome of the rearrangement. From these models we predicted that anionic amino-Cope rearrangement of substrate (*R*, *R*)-**4d** would yield the (*S*)-aldehyde, whereas (*R*, *S*)-**4d** would generate the (*R*)-enantiomer of **5**.

Figure 1. Proposed transition state models for the asymmetric anionic amino-Cope rearrangement



Following the protocol outlined in Scheme 2 we prepared substrate **4d** from commercially available (*R*)-α-methylbenzylamine, as a 1.3 : 1 mixture of diastereoisomers. Separation of the diastereoisomers of **4d** was achieved by column chromatography. The minor diastereoisomer (*R*, *S*)-**4d** was subjected to the anionic amino-Cope rearrangement, as described above, to yield the target aldehyde **5** (Scheme 4).



(*R*, *S*)-**4d** (*R*)-**5**, 75% e.e.

(i) *n*-BuLi (1.5 eq.), THF, -78 °C to 25 °C, 3 hr; (ii) NaOAc/HOAc/H_2O (1/1/2), Δ, 2 hr

Scheme 4.

The enantioselectivity of the reaction was determined by derivatization of **5** with (1*R*, 2*S*)-ephedrine to form a diastereoisomeric oxazolidine product for ^{1}H-NMR analysis as described by Agami [5]. This revealed an e.e. of 75% for the aldehyde and also confirmed the absolute stereochemistry at the β-position to be as expected from the proposed transition state models highlighted in Figure 1. To our knowledge, this reaction represents the first example of asymmetric induction in an amino-Cope rearrangement (thermal or anionic) of a 3-amino-1,5-diene substrate.

The corresponding asymmetric rearrangement of the major diastereoisomer (*R*, *R*)-**4d** gave the expected product (*S*)-**5**, but with a lower level of enantioselectivity. A summary of our results is presented in Table 2. Interestingly, a type of matched/mis-matched diastereoisomer effect appears to be involved. This would, however, be of no consequence to the outcome of our synthetic strategy since we would be able to prepare both

enantiomers of product **5** with the same high level of enantioselectivity by application of the diastereoisomeric substrate derived from the opposite enantiomer of α-methylbenzylamine [i.e. (*S*, *R*)-**4** would yield (*S*)-**5**]. The interesting variation in product enantioselectivity with substrate structure is currently under investigation in our laboratory, and our results will be presented in due course.

Table 3. Asymmetric anionic amino-Cope rearrangement

Substrate	Yield 5, %	e.e. %[a]	Major enantiomer[a]
(*R*, *R*)-**4d**	73	41	(*S*)
(*R*, *S*)-**4d**	66	75	(*R*)

(a) - determined by 250 MHz ^{1}H NMR spectroscopy (see text) [5]

In summary, the anionic amino-Cope rearrangement of a series of 3-amino-1,5-diene substrates was found to proceed at low temperature in good yield on using *n*-butyllithium to generate the lithium anion. We have also presented the first example of asymmetric induction in an anionic amino-Cope rearrangement reaction. The absolute stereochemistry of the major product can be predicted from simple transition state models, the major enantiomer resulting from a chair-like conformation of the substrate with the amine component occupying a pseudo-equatorial orientation.

The fact that we have been successful not only in demonstrating the anionic amino-Cope rearrangement of several acyclic substrates, but in achieving a moderate to good level of enantioselectivity in the reaction, is of significance since our results are in stark contrast to a recent report by Houk and Meyers [6]. This group was unable to demonstrate the anionic amino-Cope rearrangement of four 3-amino-1,5-diene substrates, and rationalised their results on the basis of *ab initio* calculations, concluding that an anionic amino-Cope rearrangement of acyclic 3-amino-1,5-diene substrates was in fact a disfavoured process. The preferred reaction pathway was proposed to involve deallylation of the substrate *via* an allyl anion-imine intermediate. Our results show that the anionic amino-Cope rearrangement can indeed be achieved with acylic 3-amino-1,5-diene substrates. Whether the reaction proceeds in a concerted or dissociative fashion is still a matter for debate. Further results in this area will be reported in due course.

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