Quaternary centres bearing nitrogen (α-tertiary amines) as products of molecular rearrangements

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Received 4th January 2011, Accepted 1st February 2011
DOI: 10.1039/c1cc00049g

Quaternary centres bearing a nitrogen substituent (α-tertiary amines and their derivatives) are found in a variety of bioactive molecules but pose a major challenge in synthesis, particularly when enantiomeric purity is required. Approaches comparable to those used for tertiary alcohols are typically hampered by the poor electrophilicity of imines, requiring powerful nucleophiles that may also act as bases. A set of powerful alternative approaches make use of the rearrangement of readily available precursors, often (but not always) with formation of a new tertiary carbon to nitrogen bond. In this Feature Article we review the scope, limitations and specificities of some of these rearrangements in order to illuminate their synthetic potential.

1. Introduction

Among the simple structural classes which form the building blocks of organic chemistry, α-tertiary amines1 pose a surprisingly difficult synthetic challenge—especially when the quaternary carbon centre has to be synthesised in an enantioselective way. Nonetheless, their wide occurrence in naturally occurring and synthetic bioactive molecules1 (Fig. 1) has provided an impetus for the development of a number of synthetic strategies over the last 50 years. The most common approach has been the addition of a nucleophile to a ketimine,2 but the lack of reactivity of these species coupled...
with the difficulty of achieving good stereoselectivity has encouraged the exploration of alternative ways of constructing the quaternary centre. Of these, rearrangement of readily available substrates appears to be one of the most promising, and has already allowed the development of powerful tools for the synthesis of compounds that would be far more challenging to obtain efficiently by other methods. An important feature of many of these rearrangements is a well-defined cyclic transition state, allowing a high degree of stereospecificity and/or stereoselectivity. By their nature, rearrangements are atom-economic processes, consistent with the requirements of modern efficient synthetic methods.

In this article we review the scope, limitations and specificities of some of these rearrangements, illustrating our discussion with selected examples from the literature. Most of the major synthetic advances in this field have been made over the last fifteen years. For this reason the review focusses principally on the period 1995–2010. Our own interest in the use of rearrangements to synthesise hindered amines was spurred by our discovery, in 2006, of a new rearrangement of lithiated ureas, and the article concludes with an analysis of these urea rearrangements as a new means of making \( \text{\textalpha}-\text{tertiary amines} \).

### 2. Curtius rearrangement

In 1890, Curtius observed the decomposition of acyl azide \( \text{2} \) with loss of nitrogen (3) to generate aniline after hydrolysis of the intermediate isocyanate 4 (Scheme 1). The Curtius rearrangement now provides a valuable and commonly used way to synthesize amines from the corresponding acid (Scheme 1).

In 2005, Lebel and coworkers published a one-pot method for the synthesis of Boc-protected amines from carboxylic acids using the Curtius rearrangement. In this example, the treatment of the acid 6 with a mixture of Boc\(_2\)O and sodium azide in the presence of a phase-transfer catalyst, at room temperature, produced the acyl azide. The desired carbamate 7 was generated by increasing the temperature to 80 °C (Scheme 2).

When the reaction was carried out at 40 °C, only traces of 7 were observed. This problem was solved using zinc triflate as an additive (3.3 mol%), which resulted in complete conversion. Malonate derivatives 8 were also used as substrates for the rearrangement, with the corresponding amino acid derivatives 9 being obtained in good yields (Scheme 3).

The Curtius rearrangement can also be performed on strained substrates such as cyclopropenes or cyclobutane derivatives. Sunami and coworkers have reported an efficient method for solid phase synthesis of amines. The carboxylic acid 13 was converted to the corresponding isocyanate 14 which can be trapped with Wang resin to generate the carbamate 15.

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**Fig. 1** Bioactive molecules bearing an \( \text{\textalpha}-\text{tertiary amines} \).

**Scheme 1** Curtius rearrangement.

**Scheme 2** Synthesis of Boc-protected amines using Curtius rearrangement.

**Scheme 3** Curtius rearrangement in the presence of zinc-triflate.

**Scheme 4** Synthesis of dihydroisoquinolines.

**Scheme 5** Curtius rearrangement and reaction with Wang resin.
Cleavage of the resin using TFA led to the desired amine 16 (Scheme 5).

3. **[3,3]-Sigmatropic rearrangements**

[3,3]-Sigmatropic rearrangements have long been used in organic chemistry, due to the fact that they allow regio and stereoselective carbon–carbon or carbon–heteroatom bond formation with relative ease.

3.1 **Allylic cyanate to isocyanate rearrangement**

3.1.1 Thiocyanate to thioisocyanate (the Billerter–Gerlich rearrangement). The first [3,3]-sigmatropic rearrangement to be described—the transposition of allyl thiocyanate to allyl isothiocyanate (mustard oil)—was discovered independently in 1875 by Otto Billerter and Gustav Gerlich. This reaction has received detailed investigation over the last century and it is now well established that it proceeds via a suprafacial mechanism. Surprisingly few studies involving the construction of a quaternary centre have been reported: in those few cases the reaction takes place efficiently. An interesting example was reported by Gonda et al. during investigation into the diastereoselective synthesis of 3-(S)-isothiocyanato-3-deoxy-3-C-vinyl glucose, a compound which can be easily converted to an advanced precursor of (+)-myriocin (Scheme 6). In the course of these studies Gonda demonstrated that the [3,3]-sigmatropic rearrangement of both geometrical isomers of the substrate allylic hexofuranosides (Scheme 6) provides the same diastereoisomerically pure product. The results, supported by DFT calculations, allowed the authors to attribute the stereoselectivity of the reaction to the steric interactions of the 1,2-O-isopropylidene group in the transition state (Scheme 7). In addition, optimisation of this thermal rearrangement (usually performed at 90 °C in o-xylene for 4 h) showed that the time of reaction can be halved with identical results (i.e. 88% yield, 1 diastereoisomer) by using microwave irradiation.

3.1.2 Cyanate to isocyanate. The first rearrangement of this type involving a cyanate instead of a thiocyanate was reported by Holms et al. in 1970. In spite of the fairly mild conditions, the difficulties encountered in generating the allyl cyanate discouraged chemists from using this approach until Ichikawa’s domino dehydration–[3,3]-sigmatropic rearrangement of carbanions.

desired product 23 in good yields. In addition to its practical advantages, this modification allowed for the first time the efficient synthesis (yield ≥ 90%) of a quaternary carbon atom bearing a nitrogen substituent using this transformation (Scheme 8). It is interesting to notice that under normal conditions a 3-substituted cyclohexenyl group gave rise to a [1,3]-sigmatropic (16%) in addition to the desired allylic rearrangement (38%). However, the addition of methoxytributyltin and methanol allowed this competitive pathway to be avoided by directly converting the [3,3]-sigmatropic product into its corresponding methyl carbanate in good overall yield (70%).

This reaction proceeds with a complete 1,3-transfer of stereochemistry. This stereospecificity can be explained by the lower energy transition state 25-A which leads to the isocyanate with a E-double bond. By contrast, the Z-isomer is never observed, undoubtedly due to the A1,3 strain incurred in the alternative transition state 25-B (Fig. 2). In 2001, the first direct observation, by NMR, of the [3,3]-sigmatropic cyanate to isocyanate rearrangement was made by Banert et al., allowing measurement of its activation parameters. The large negative activation entropy (ΔS° = −100 J mol⁻¹ K⁻¹) is characteristic of a cyclic transition state. During this study it was furthermore demonstrated that this transposition is much more rapid than the analogous rearrangement of a propargylic cyanate to an allenyl isocyanate.

Since this reaction proceeds under mild conditions with complete stereospecificity, it has been used as a key tool for
the construction of quaternary centres bearing nitrogen in several total syntheses. Recent examples feature in the syntheses of (−)-adaline and (−)-euphococcine reported by Spino et al.,22 the synthesis of prostaglandin derivatives described by Florent et al.23 and the (S)-ketamine synthesis by Kiyooka et al.24 Common to all these studies is the fact that the [3,3]-sigmatropic rearrangement provides a crucial step for the efficient and stereoselective syntheses of compounds that were previously challenging to obtain.

3.2 Allylic imidate rearrangement (the Overman rearrangement)

The aza-Claisen rearrangement is a [3,3]-sigmatropic rearrangement involving an iminium C—N bond acting as a π component, and much interest has been invested in the development of this reaction and its variants. Some of the advances in this area have been discussed in recent reviews.25

3.2.1 Thermal rearrangement. In 1974, Overman first reported the conversion of a trichloroacetimidate into a trichloroacetamide either by heating or by metal (M = Hg, Pd or Co) catalysis. More recent work has greatly expanded this field. This rearrangement offers an elegant route to allylic amines from their counterpart allylic alcohols. Treating the allylic alcohol with trichloroacetonitrile in the presence of base (DBU) gives rise to the allylic trichloroacetimidate esters 29.26 Heating 29 leads to a [3,3]-sigmatropic rearrangement, and subsequent removal of the trichloroacetamide group under basic conditions gives the free allylic amine (Scheme 9). Chirality is retained in the sigmatropic rearrangement by suprafacial migration through the chair-like transition state shown for the rearrangement of 31 (Scheme 10).27

More recently Ramachandran et al. have exploited as starting materials for this reaction the addition products of unsaturated aldehydes and the α-pinene based allylating reagents 35. The resulting homoallylic allylic alcohols, formed in moderate to good yields with high ees, were subjected to the Overman rearrangement to give the trichloroacetamides 36 in good yields and retention of configuration (Scheme 11).28 Further chemical transformations allow access to the α,α-disubstituted amino acid derivatives 38 (Scheme 12).

The thermal [3,3]-sigmatropic rearrangement of imidates has been utilised in a number of total syntheses, such as the synthesis of sphingofungins E, F and lactacystin.29 In Isobe’s synthesis of tetrodotoxin, the potent toxin found in the puffer fish,30 the acetimidate 39 undergoes rearrangement to acetamide 40 (Scheme 13). The steric constraints of the ring system favour conformer 41, which in turn dictates the stereochemistry...
of the rearrangement. Further chemical transformations yield tetrodotoxin.

### 3.2.2 Metal-catalysed rearrangement

The aza-Claisen rearrangement can be catalysed by transition metals, allowing the reaction to take place at a lower temperature. Catalysts tend to be soft metal salts such as those of palladium(II) and mercury(II). It is presumed that this reaction occurs via a cyclic intermediate (as shown in Scheme 14 for a Pd(II) catalyst), and chiral catalysts have been developed to allow this reaction to take place enantioselectively.

Overman and coworkers reported the use of cobalt based palladacycles in 2003. These catalysts allow the aza-Claisen rearrangement of trifluoroacetimidates to take place with high enantioselectivities (Scheme 15).

The COP catalysts were an improvement on the previously reported ferrocene analogue FOP (Scheme 16): they avoid the need for activation by silver salts and are easier to prepare. The use of the COP catalysts allows prochiral imidates to be converted to the chiral allylic acetamides. By careful selection of amine protecting group, the corresponding enantiomerically enriched amine can also be obtained.

Application of these catalysts to the synthesis of quaternary stereocentres has not been straightforward, due to the steric bulk of C3-disubstituted allylic alcohols. These catalyst systems struggle to rearrange trifluoroacetimidates (requiring Pd loadings of >10%), which are more desirable substrates as a result of the ease of hydrolysis of the trifluoroacetamide group.

In 2006 Berkowitz et al. reported the synthesis of racemic amines bearing a quaternary centre using a palladium-catalysed aza-Claisen reaction of PMP protected trifluoroacetimidates. Optimal catalysts were found to be Cl2Pd(MeCN)2 or Cl2Pd(PhCN)2. The amines synthesised contain a protected hydroxyl group which can be further manipulated in order to access vinyl-substituted carbon centres. A series of ferrocenylimidazoline palladacycles were an improvement on the previously reported ferrocene analogue FOP (Scheme 16: they avoid the need for activation by silver salts and are easier to prepare. The use of the COP catalysts allows prochiral imidates to be converted to the chiral allylic acetamides. By careful selection of amine protecting group, the corresponding enantiomerically enriched amine can also be obtained.

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Not long after this racemic reaction was reported, the Peters group reported the development of a group of catalysts that are effective for the enantioselective generation of quaternary carbon centres. A series of ferrocenylimidazoline palladacycles were developed to allow the synthesis of highly enantioenriched N-aryl/alkyl amidates to be synthesised, but the catalyst was further improved by creating a hybrid between COP and COP (Scheme 17). After optimisation of rearrangement condition, the palladacycle allowed the synthesis of allylic amines bearing quaternary stereocentres (Table 1).

More hindered substrates are problematic, as the catalyst begins to struggle when both substituents are bigger than methyl groups: higher catalyst loadings are required and a drop off in yield is also observed.

The enantioselectivity of the rearrangement, induced by the planar chirality of the palladium complex, is independent of the steric difference between the R and R' substituents of the olefin. The reaction is stereospecific, with E and Z olefins giving opposite enantiomers. The enantiodetermining step is thought to be the face-selective coordination of the olefin to the active palladium complex. The olefin is expected to coordinate trans to the imidazoline nitrogen, allowing the imidate nitrogen to attack the face of the olefin trans to Pd. The less sterically demanding olefin coordinates near the ferrocene core reducing unfavourable interactions, whereas the bulkier imidate is kept away from the ferrocene (see Scheme 18 for a pictorial representation). The protected amide products can undergo further transformations to provide for example synthetically useful α- and β-amino acids (Scheme 19).

It is important to note that the choice of activating agent plays a crucial role in the catalytic activity of these systems. With AgO2CCF3 the hybrid catalyst performs worse than FIP, but with AgNO3 excellent catalytic activity is restored.
Despite these developments, access to these highly substituted amines via the aza-Claisen rearrangement is still challenging.

### 3.3 Phosphorimidate rearrangements

In 2004 Mapp et al. described for the first time a one-pot phosphorimidate to phosphoramidate [3,3]-sigmatropic rearrangement.\(^{37}\) The allylic phosphorimidate 62, being the reactive intermediate in this transposition, is produced *in situ* by a three-component combination of an allylic alcohol, a chlorophosphite and an organic azide. Crossover experiments confirm that the rearrangement is intramolecular and that, as usual, the stereochemistry of the starting material is efficiently transferred to the transposed product. However, even though the reaction gives quaternary carbon atoms efficiently (yield up to 70%) (Scheme 20), the reaction was explored only with achiral starting materials.\(^{38}\) Nonetheless, this reaction remains particularly interesting when it is considered that one of the protecting groups on the nitrogen of the fully protected allylic amine product 63 is a phosphoramidate.\(^{39}\) Phosphoramidates are stable under a wide range of reaction conditions but can nonetheless be easily removed by either treatment with TMSI or nucleophilic attack by a thiol followed by HCl/MeOH.\(^{40}\)

It is interesting to notice as well that the second protecting group, derived from the azide, can be very easily varied—the three-component process is particularly tolerant of such variations. Activation of the allylic system either by incorporation of electron-deficient functional groups or by using a transition metal catalyst significantly facilitates the reaction.

### 4. Steglich–Höfle rearrangement (O to C acyl transfer)

An interesting and powerful way to make quaternary oxazolones (precursors of α-alkylated α-aminomalonic acids) is the organo-catalysed rearrangement of 5-acyloxyoxazoles 64 into the corresponding C-4 acylated oxazolone 65. First discovered by Steglich and Höfle in 1970\(^{41}\) as a racemic transposition promoted by 4-(dimethylamino)pyridine (DMAP) or 4-(pyrrolidino)pyridine (PPY), this reaction advanced in utility in 1998 when Fu et al. developed the first enantioselective version, introducing new planar-chiral derivatives of the catalysts\(^{42}\) and (Scheme 21). This study demonstrated that the best enantiodiscrimination is obtained with O-benzylcarbamate substrates and that high yields (93–95%) and ee’s (88–92%) can be reached with a wide range of C4-substituents R\(^2\) (Scheme 21).

Interestingly, Fu’s studies indicated that under typical reaction conditions the rearrangement is zero-order in substrate
and independent of concentration. This observation supports a mechanism with the tight ion pair 66 as the resting state of the system (Scheme 21). Fu designed additional experiments which suggested that reaction of the O-acylated azlactone with PPY* (Scheme 21, step A) is reversible. The configurational stability of the product 65 under the reaction conditions demonstrates without ambiguity that step B is irreversible.43 Subsequently Vedejs et al. described another chiral derivative of DMAP ((S)-TADMAP 69) which gave similar results to those reported by Fu (Scheme 21) but with best enantioselectivities obtained with an O-phenylcarbamate as the migrating group. In 2009, Groger et al. reported the synthesis of all the stereoisomers of α-methylthreonine 45 using the Steglich-Höfle rearrangement catalysed by Birman-type catalyst 70 as a key step. During this investigation the asymmetric transfer of acyl groups (er up to 93:7) to yield a ketone instead of the usual ester was achieved (Scheme 21). An interesting extension of this transposition has been the development by Smith et al. of an N-heterocyclic carbene-promoted tandem

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5. [2,3]-Sigmatropic rearrangements

Few [2,3]-sigmatropic rearrangements have been applied to the synthesis of α-tertiary amines, and stereoselective examples are rare. This section discusses the scope of these reactions, and also points out where lack of information concerning stereoselective versions of the reactions points to future potential for new methods for constructing a quaternary nitrogen-bearing centre.

5.1 [2,3]-Sigmatropic aza-Wittig rearrangement

Despite a few earlier reports,47 the aza-Wittig variant of [2,3]-Wittig rearrangement (Scheme 23)48 was first studied thoroughly by Eisch and Kovacs in 1971.49 Since then the reaction has been shown to be generally slower and less selective than its oxygen based counterpart.

Relief of steric strain in cyclic systems such as azetidinone 77 and in vinyl aziridine 7951 promotes the [2,3]-aza-Wittig rearrangement, forming azepinones and tetrahydropyridines in high yields and stereoselectivities (Scheme 24).

Prior to 1995 there were few reported examples of this reaction working well with acyclic compounds, limiting its potential use in the synthesis of amines bearing quaternary stereocentres. In 1995 Anderson et al. reported the [2,3]-aza-Wittig rearrangement of crotyl derived amines (Scheme 25).52 Here the amine had been specifically designed to favour rearrangement (with an electron withdrawing group on the nitrogen to stabilise the nitrogen-centred anion formed in the reaction). The reaction worked well, allowing access to the rearranged product 82 in good yield but with poor diastereoselectivity.

This work has been further developed to allow the diastereoselective synthesis of protected amines and amino acids bearing a α,α-disubstituted centre using a silylated olefin to direct the selectivity (Scheme 26).53 The selectivity of the

Scheme 23 [2,3]-Aza-Wittig rearrangement.
The rearrangement is thought to arise from the transition state shown (Scheme 27) in which steric interactions between the R groups and the bulky silyl group lead to the observed diastereoselectivity (the largest of the R groups having an anti relationship with the methyl group of the cis olefin in the favoured diastereomer).

The methyl esters were subsequently studied as well and also show good stereoselectivities for some of the more hindered substrates (Scheme 28).

Some work has been carried out on an enantioselective version of this reaction, starting from enantioenriched amines. However so far the results reported are ambiguous. The use of chiral bases (i.e. alkyllithium–sparteine complexes) has also been studied by Anderson, so far without success (due to the rate of epimerisation of the chiral lithiated intermediate being faster than that of the [2,3]-rearrangement). Instead, asymmetric induction with chiral auxiliaries and chiral Lewis acids is being investigated, but these have so far not been applied to the generation of quaternary stereocentres.

Recently the methodology has also been applied to the diastereoselective synthesis of substituted prolines in which the [2,3]-sigmatropic rearrangement is followed by a rare 5-endo-trig cyclisation.

5.2 Tandem imidation-rearrangement of sulfides or selenides

5.2.1 Sulfide rearrangement. Among the four different [2,3]-sigmatropic rearrangements involving the transposition of an allylic sulfur derivative to give an amine as a product, only one of those allows the efficient enantioselective synthesis of a quaternary centre bearing a nitrogen substituent: the conversion of an S-allylsulfimine 91 (X = S) to an N-allylsulfenamide 93 (X = Se) (Scheme 29). This transposition was reported in 1951 by Challenger et al., who found that diallyl-sulfide was converted under the action of chloramine T (sodium N-chlorotoluenesulfonamide salt) to the corresponding N-allylsulfenamide. Evidence for a [2,3]-sigmatropic rearrangement emerged when Challenger showed that the migration of a cinnamyl group involves an allylic inversion. After these studies, this reaction remained unexploited for two decades until the development of new imidation reagents that were more efficient and easier to handle than chloramine T. The reaction can be promoted with PhI = NTs in the presence of a Cu(I)-salt, with O-mesitylenesulfonylhydroxylamine (MSH), with N-aminophthalimide/Pb(OAc)₄, with...
ethyl \(N\)-[(trifluoromethanesulfonyl)oxy]carbamate \(^{63}\) and with \(\text{BocN}_2/\text{FeCl}_2\). Many of these transpositions allowed the synthesis of quaternary carbon atoms, but invariably without stereoselectivity. Everything changed in 2006 when Armstrong et al. reported that the use of their previously developed oxaziridine-based amination reagent \(^{95}\) allows the stereoselective rearrangement of chiral \(\alpha\)-branched allyl sulfoxides \(^{94}\) to \(\alpha\)-tertiary amines with an \(\text{er}\) up to 97:3 (Scheme 30).\(^{66}\) Armstrong also demonstrated that the transposition using these imidation conditions could be performed, for the first time, on sulfur-containing \(\alpha,\beta\)-unsaturated esters \(^{94}\) to give \(\alpha\)-amino acids (Scheme 30).

While pushing this investigation further, Armstrong demonstrated that it is possible to obtain selectively either enantiomer of the desired amine while keeping the absolute configuration at the sulfur-bearing stereocentre, providing the geometry of the carbon–carbon double bond is inverted instead. The product nonetheless always contains a double bond of \(E\) stereochemistry. By assuming that the rearrangement is suprafacial and concerted, the authors rationalised the stereoselectivity by comparing the transition states \(^{98-A}\) and \(^{98-B}\) (Scheme 31). It appears that \(^{98-A}\) is significantly lower in energy than \(^{98-B}\), probably because of a destabilizing allylic interaction between \(R^1\) and \(R^3\) in \(^{98-B}\). Exchange of \(R^2\) and \(R^3\) by inverting the geometry of \(R^2\) clearly leads to the enantiomer of the product (Scheme 31). Even though the stereogenic centre generated on the sulfur atom during the sulfinimidation is not controlled, yields are excellent and \(E\)-selectivity in the final product is complete, suggesting that the sulfinimide configuration does not significantly affect the stereochemical outcome of the rearrangement.

### 5.2.2 Selenide rearrangement

In 1975, inspired by the previously reported and widely used allylic selenoxide to allylic alcohol transformation, Sharpless et al.\(^{67}\) described the \([2,3]\)-sigmatropic rearrangement of allylic selenides \(^{91}\) (X = Se) to the corresponding allylic amines \(^{93}\) (X = Se) (Scheme 29). This transposition was promoted by imidation of the selenide with anhydrous chloramine T and gave the desired rearranged product in 44\% yield. This encouraging but moderate results stimulated Hopkins et al.\(^{68}\) to investigate this reaction further, developing alternative imidation methods in order to avoid the use of chloramine T (essentially because of the difficulty of removing the \(p\)-tolylsulfonyl protecting group from the final product) and by optimising the overall yield of the two step sequence. First of all, a new imidation method was developed to allow the use of an \(N\)-chlorocarbamate or, even more simply, a pair of reagents consisting of a carbamate and an oxidant such as \(N\)-chlorosuccinimide. Indeed, it appears that the first step of this imidation is the chlorination of selenium which can then be attacked by the nucleophilic carbamate (Scheme 32). Using this new imidation, Hopkins increased the rearrangement yield to up to 95\% and demonstrated the synthesis of \(\alpha\)-tertiary amines. Although the stereoselectivity of this reaction has been investigated,\(^{69}\) this approach has thus far only been applied to symmetrical dialkylalkenes from which the rearrangement generates only an achiral quaternary carbon atom.

### 5.3 N–O [2,3]-sigmatropic rearrangement

In 1998, while investigating lithium amide chemistry, Davies’s group discovered that \(N\)-benzyl-O-allylhydroxylamine \(^{105}\) can give \(N\)-allyl-N-benzylhydroxylamine \(^{106}\) when treated with \(n\)-BuLi.\(^{70}\) This transformation was attributed to a [2,3]-sigmatropic rearrangement analogous to the Wittig transformation described above and its intramolecular was confirmed by crossover experiments.\(^{71}\) After rearrangement, a trisubstituted alkene returned an \(\alpha\)-tertiary amine in moderate yield (60\%) (Scheme 33). Interestingly, it appeared that for this particular transposition the reaction mixture had to be heated, probably due to the more hindered substrate. So far, only achiral \(\alpha\)-tertiary amines have been synthesised using this methodology, and no information is yet available on the stereospecificity of the rearrangement.\(^{72}\)
6. Ammonium salt rearrangements

6.1 Stevens rearrangement

In 1928, Stevens and co-workers observed a 1,2-shift of ammonium ylides during work on quaternary ammonium salts as protecting groups for amines. Treatment of 107 with a solution of sodium hydroxide led to the rearranged compound 108 in excellent yield. In his early studies, Stevens demonstrated the intramolecular character of this reaction and proposed an ionic mechanism involving the formation of a zwitterionic intermediate 109 which rapidly dissociates to form the amine 108. In 1932, Stevens and Thomson hypothesised an alternative mechanism involving a radical pathway, evidence for which was found later. The mechanism proceeds via homolytic cleavage of the C–N bond (Scheme 34) to generate the most stable radical. Rapid recombination forms the rearranged product. In the same study, Stevens presented the first example of rearrangement involving an allyl group, which later came to be referred to as the Stevens [2,3]-shift.

In 1952, Stevens provided the first synthesis of an α-tertiary amine using fluorenly derivatives (Scheme 35). In all previous examples, the treatment of the quaternary ammonium salt with a strong base was necessary to form the ylides that undergo rearrangement. Unfortunately, side reactions, such as Hofmann degradation, could be observed during these reactions. In 1952 Stevens presented an alternative method, generating ylides from carbenes (Scheme 35).

West and co-workers investigated chirality transfer from nitrogen to carbon in the Stevens rearrangement using cyclic ammonium salts (Scheme 36). This method uses a temporary chiral nitrogen atom to transfer selectively only one of the N-substituents in a suprafacial migration. Ammonium salt 115 was treated with potassium tert-butoxide to generate the desired ylides which underwent [1,2]- or [2,3]-shift depending on the R group. The resulting α-tertiary amines were obtained with good diastereoselectivity. The relative stereochemistry of the final product was confirmed by X-ray crystallography.

This method can be extended to oxazolidines (Scheme 37). In this case the compound 121 can be obtained using Me₂OBF₄.

Coldham et al. developed a simple method for the synthesis of glycine derivatives based on a [2,3]-Stevens rearrangement (Scheme 38). Glycine methyl ester was treated with allyl bromide to form a quaternary ammonium ylid 124 which rearranged directly to the corresponding α-tertiary amine 125. Deprotection with palladium(0) gave the amino acid derivative. Substituted simple α-amino esters were also investigated.

Based on the work reported by West, this method has also been used for the synthesis of proline derivatives (Scheme 39). In 2002, Clark showed that α-substituted and α,α-disubstituted amino acids could be made using the rearrangement of ammonium ylides. In this work, the ylides were generated from the metal carbenes (Scheme 40) using copper or rhodium catalysts (Table 2).

The [2,3]-Stevens rearrangement of spiro ylids (Scheme 41) is also successful. Compound 133 was treated with Cu(acac)₂ in toluene to generate the intermediate ylid 134 which rearranged to form the desired amine 135 in 54% yield (with a cis:trans selectivity of 57:43).

Rearrangement of a proline-derived ammonium salt is highly enantioselective. In order to perform the Stevens rearrangement with high stereospecificity, different biphasic conditions were investigated (Scheme 42). Treatment of
t-butyl ester 136 with solid CsOH in dichloroethane formed the desired amine 137 in 73% yield and 92% ee. Variation of the aromatic group of the ammonium salt increased the selectivity up to 99% ee.

An enantioselective [1,2]-Stevens rearrangement was reported in 2008 by Tomooka and co-workers,81 with sugar-derived alkoxides as chiral promoters. The treatment of the ammonium salt 138 in the presence of a chiral alkoxide led to the formation of the enantiomerically enriched α-tertiary amine (4–61% ee) (Scheme 43).

Metal-containing ammonium ylids undergo tandem [1,2]-Stevens-1,2 alkyl migration of (Scheme 44).82 In the presence of a metal, the alkyne π-complex 144 is generated and the corresponding metal-containing ammonium ylid 146 is formed. 146 undergoes a [1,2]-Stevens rearrangement followed by alkyl migration to generate the N-fused tricyclic indole 148. Different metallic complexes were also investigated with only W(CO)6 providing the desired product. Photoirradiation was crucial for the generation of the unsaturated tungsten species. The carbene intermediate was trapped using 10% Et3SiH, allowing the α-tertiary amine 149 to be recovered in 7% yield (Scheme 44).

Lewis-acids can be used to promote [1,2]-Stevens rearrangement of proline derivatives,83 with complete C to N to C chirality transfer (Scheme 45). The desired free amine was obtained in moderate to good yields via a mechanism involving the formation of 151 with a high degree of stereospecificity. Addition of triethylamine promotes the formation of 152 which can recombine after homolysis to form the desired amine 154 (after hydrolysis) (Scheme 45).

6.2 Sommelet–Hauser rearrangement

In 1937, M. Sommelet observed that the decomposition of the quaternary ammonium salt 155 led to the formation of the rearranged amine 156 (Scheme 46).84 In 1957, C. Hauser investigated the rearrangement of the benzyltrimethylammonium ion.85

Chem. Commun., 2011, 47, 4624–4639
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Published on 07 March 2011 on http://pubs.rsc.org | doi:10.1039/C1CC00049G
Hauser also proposed a possible mechanism for this rearrangement involving the deprotonation of the quaternary ammonium salt 157 followed by [2,3]-sigmatropic rearrangement (Scheme 46).86

Following their work on the Stevens rearrangement, Tayama and coworkers reported a unique example of Sommelet–Hauser rearrangement in which no [1,2]-Stevens rearrangement was detected (Scheme 47).80 The treatment of the ammonium iodide 161 with solid CsOH in DCE at −10 °C led to the formation of the rearranged amine 162 (product of [1,2]-Stevens rearrangement). The treatment of the same amine with t-BuOK at −40 °C in THF led to the Sommelet–Hauser product 163.

Tayama also reported an asymmetric version of Sommelet–Hauser rearrangement (Scheme 48).87 Ammonium salts 164 were treated with t-BuOK to generate the α-tertiary amine 165 with excellent diastereoselectivity. Meta and ortho substituted compounds also gave α-tertiary amines in good yields.

7. N to C Migration of α-lithiated ureas and carbamates

7.1 Nitrogen to carbon aryl migration

Although amides and amide-like functional groups (carbamate, oxazolines etc.) have long been recognised as powerful directors of lithiation,88 the use of ureas as lithiation directors had until recently received little attention,89 despite growing interest in ureas as a structural class in catalytic, foldamer and supramolecular chemistry.90 As part of a study of the conformation of aromatic ureas,91 we had cause to investigate the lithiation of benzylic ureas such as 166. Remarkably, the expected
deprotonation of the urea in the benzylic position was followed rapidly by an unexpected migration of the second aryl ring from nitrogen to carbon, yielding rearranged diarylurea 167.92 Noting the potential of this rearrangement for the synthesis of z-tertiary amines, we repeated the reaction on the enantiomerically pure z-methylbenzyl ureas 168. Rearrangement was slower, but could be accelerated by addition of DMPU as a cosolvent, returning high yields of ureas 169 with essentially complete retention of configuration (Scheme 49).93

The reaction was surprisingly tolerant of the electronic or steric nature of the substituents borne by the migrating ring—even 2,6-dimethyl and 3,4-dimethoxyphenyl rings migrate successfully. Alkylithium bases are frequently incompatible with electron-deficient arenes, but during a screen of bases suitable for the rearrangement of pyridyl ureas we discovered that LDA in a mixture of THF and DMPU likewise promotes lithiation and stereospecific rearrangement of 168.94 Removal of the carbamoyl group from the rather acid sensitive products to reveal the z-tertiary amine 170 was initially achieved by reduction with DIBAL or by hydrolysis of their N-nitroso derivatives. However, in later work we discovered that simple solvolysis of 169 on reflux in ethanol, or for faster reaction, n-butanol (if necessary buffered with sodium carbonate) provides 170 cleanly and efficiently. This new reactivity of lithiated ureas, featuring an anionic heteroatom-to-carbon aryl migration reminiscent of the Truce-Smiles rearrangement,95 has opened up numerous new possibilities for the synthesis of enantiomerically enriched z-tertiary amines by stereospecific arylation of their secondary homologues. In particular, it allows for the first time the synthesis of enantipure nitrogen-bearing quaternary centres carrying two similar aryl rings.

The stereospecificity of the reaction is presumably a consequence of the configurational stability of the intermediate dipole-stabilised organolithium 171.96 We gained further insight into the mechanism of the transposition when we discovered that, in the case of a naphthyl migrating ring, oxidative conditions return a dearomatised spirocycle 172—evidence that rearrangement proceeds through a dearomatised intermediate 172 (Scheme 49). X-ray crystallography confirmed the absolute stereochemistry of 172 and proved the rearrangement to be stereochemically retentive, rather than invertive.97

The related rearrangement of various cyclic substrates took place in good yield (up to 89%) but even with enantiomerically enriched starting material, the rearranged products turned out to be racemic Presumably racemisation of the intermediate organolithium competes with slower rearrangement in the constrained cyclic system.98

Recently, we found that the rearrangement takes place not only with N-benzyl ureas 166 and 168 but also with their N-allyl or N-vinyl analogues 174 or 176. Both can be deprotonated, respectively z or y to nitrogen, to generate an allyllithium intermediate susceptible to rearrangement. The most effective conditions made use of lithium amides as bases and DMPU or LiCl as promoters of rearrangement. We also found that the protecting group on the nitrogen atom adjacent to the anionic centre influences dramatically the efficiency of the rearrangement. A PMP (p-methoxyphenyl) group promotes a clear increase in the rate of aryl migration in comparison with the customary methyl group. Given that the simple unsubstituted allylurea 174 can be deprotonated and rearranged, an alternative approach to vinylureas 176 is possible: the rearranged product 175 can be coupled, using palladium chemistry, to a second aryl ring to give a product that can be rearranged a second time (Scheme 50).99

Because the vinyl urea 176 is achiral, this sequence offers the opportunity to carry out an asymmetric synthesis of z-tertiary amines by a stereoselective (rather than a stereospecific, as in Scheme 49) process. Replacing LDA with a chiral lithium amide 177 allows the synthesis of enantioenriched rearrangement products in good yields and er’s (yield up to 91%, er up to 94:6) (Scheme 50). Interestingly, the reaction seems to be sensitive to the geometry of the vinyl group of 176: the Z isomer...
gives better results in terms of yield and er, while the E
isomer reacts poorly to give the desired product in a racemic
mixture.

Attempts to rearrange more hindered analogues of benzyl
substrates 166 give poor yields of the desired product. Alter-
native ways of generating the required benzyl organolithium
were investigated with the aim of circumventing this problem.
The solution emerged during work on the deprotonation
of N-vinyl ureas. While investigating deprotonation with bases
more nucleophilic than LDA and lithium amide derivatives,
we discovered that the attack of an alkyl lithium on vinyl urea
179 gave not the expected alkyl lithium by deprotonation
but instead a carbolithiated intermediate 180 by nucleophilic
attack on the vinyl group. Addition of DMPU to promote
rearrangement gives the α-tertiary amine derivative 181 in
very good yields (up to 86%) (Scheme 51).100 The carbolithia-
ation is remarkable for its “umpolung” character, with attack
occurring on the more nucleophilic carbon of the enamine
derivative 179. The carbolithiation is also diastereospecific:
substrates 179 with E or Z C C double bonds101 give
different diastereoisomers of the product 180. X-ray structures
of the products 181 allowed us to conclude (assuming a retentive rearrangement93) that the carbolithiation is a syn
addition. A wide range of alkylamines and aromatic urea
substituents are tolerated, making this approach particularly
versatile for the synthesis of derivatives of branched α-tertiary
amines (Scheme 51). Encouraging preliminary results on an
enantioselective version of this tandem reaction are currently
in progress.

7.2 Nitrogen to carbon carboxyl migration

In 2007, Coudert et al. reported a tandem carbolithiation
and N-to-C acyl migration of vinyl carbamates 182 to give
α-quaternary α-amin esters 184 (Scheme 52).102 The general
behaviour of the carbolithiation step is similar to the one
observed with vinyl ureas (section 7.1).100 However the carbamate
carbolithiation seems more tolerant to different substrates
and was extended to a wider range of organolithium reagents.
Even lithium amides and lithium phosphides added to the
C=C double bond in satisfactory to excellent yields
(up to 95%)102,103 (Scheme 52) allowing the synthesis of unusual
α-amin acid precursors. No details are reported of an
enantioselective version of this reaction.

8. Conclusions

The range of reactivity embodied in rearrangement reactions
means that many classes of α-tertiary amines may be made
using rearrangement strategies. New reactions, such as the
rearrangement of aryl ureas, and those based on carbolithiation
chemistry, are still emerging, and many of the rearrangements
described in this review still do not exist in asymmetric form.
Concepts explored in this field will also be of value in the
synthesis of other challenging targets—quaternary centres adjacent
to sulfur for example.104

Acknowledgements

We are grateful to the EPSRC for research grants, and to
AstraZeneca for support.

Notes and references

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