Cyclisations of Organolithiums onto Aromatic Rings

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Abstract: The synthesis of bicyclic and other polycyclic structures by intramolecular nucleophilic attack of organolithiums on aromatic rings is reviewed. This review begins with some early observations of cyclisation-rearomatisation reactions that suggested the possibility of using aromatic rings to trap organolithiums. More recent results have shown that anion-stabilising groups, particularly sulfur- or amide-containing functional groups, are able to retard the rearomatisation step and may lead to dearomatised products. Recent optimisation of such reactions, particularly those employing aromatic amides, has allowed them to be used as key steps in a number of syntheses of natural products and their analogues.

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Key words: organolithium, anionic cyclisation, dearomatisation

1 Organolithium Cyclisations

The cyclisation of unsaturated organolithiums, particularly of hex-5-enyllithium 1a (Scheme 1) and its derivatives and analogues, is now an established method for the synthesis of 5-membered rings,1,2 though to date it has not shown the versatility of comparable radical cyclisation methods.3

There are, in addition, a number of reports of cyclisations of unsaturated organolithiums in which the π-system trapping the organolithium is an aromatic ring. Cyclisation of an organolithium such as 1b may be possible if the gain in stability in the organolithium 2b outweighs the energy forfeited by loss of aromaticity in the ring. This may be true particularly if the aromatic ring carries electron-withdrawing substituents, although the formation of a pentadienyllithium 2b from a primary alkyllithium 1b may also provide sufficient driving force.

In a very early account of such a reaction, aryllithium 4, produced by directed metallation of 3, added into an adjacent phenyl ring, eliminating LiOMe (Scheme 2). A second deprotonation yielded the phenylfluorenyl anion 6.
2 Dearomatising Organolithium Cyclisations

In the 1990’s there appeared several isolated reports of organolithium cyclisations onto activated aromatic rings. An electron- withdrawing group conjugated with the ring stabilises the intermediate cyclised organolithium and slows rearomatisation, making possible the isolation of potentially synthetically versatile dearomatised products.

When attempting ring-opening reactions of an N-tosyl aziridine 17a with allylic silyl anions, Schaumann et al. in 1991 observed side-products arising from dearomatising cyclisation (Scheme 5). They found that sulfonamide 17a was deprotonated by sec-butyllithium/TMEDA to give the organolithium 18 which cyclised onto the aromatic ring, giving the stabilised anion 19. Protonation gave a single diastereoisomer of dearomatised tricyclic product 20a in 44% yield. The same reaction of silylated analogue 17b to give the dearomatised product 20b was observed by Aggarwal.

A dearomatising cyclisation promoted by a sulfonyl substituent was reported by Crandall. Iodine-lithium exchange of 21 gave an alkyllithium 22 which rearranged by a 1,3-sulfonyl shift to the allenyllithium 23 (Scheme 6). Intramolecular attack on the phenyl sulfone, via the terminus of the allenyl anion, gave a dearomatised sulfonyl anion 24 which was protonated to yield around 50% of the bicyclic sulfone 25.

A second cyclisation onto a phenylsulfone was reported by Padwa et al. (Scheme 7) who, in attempting to aromatisate a pyrazole ring succeeded in dearomatising a phenyl ring! Deprotonation of 26 led to a conjugated anion 27 which cyclised to the sulfonyl-stabilised anion 28. Upon
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protonation of 28, tricyclic product 29 was isolated as a stereoisomeric mixture in remarkably high yield. Overall, aromaticity had transferred from phenyl to pyrazole.

Our own interest in the dearomatising cyclisation of organolithiums began with an attempted ortholithiation of the chiral amide 30. The conditions we chose gave 20% yield of a 1:1 mixture of the expected atropisomers 32a and 32b; the major product from the reaction was the remarkable tricyclic lactam 31 (Scheme 8).\textsuperscript{12}

Despite its high stereoselectivity and the way that it constructs an almost completely substituted pyrrolidinone ring carrying two quaternary centres, this reaction might have remained an isolated curiosity were it not for an almost simultaneous observation by a graduate student in another research group in the Department of Chemistry at Manchester, who had been aiming to develop a [2,3]-aza-Wittig rearrangement. Attempted rearrangement of the lithiated amide 34 to 35 by treating amide 33 with \textit{t}-BuLi in the presence of HMPA at \(-78^\circ\text{C}\) gave, in 23% yield, a by-product which had clearly lost aromaticity one of the phenyl rings and which turned out to be 36 (Scheme 9).\textsuperscript{13}

It was clear that the reactions in Schemes 8 and 9 were the same transformation in different guises, the naphthamide giving a better yield, but the benzamide remarkably yielding a fully dearomatised ring. Despite the long association of organolithiums with amides,\textsuperscript{14–25} these were apparently the first observations of dearomatising cyclisations of lithiated amides. The development of this reaction into a useful synthetic method is described below.

More recently, other related nitrogen-containing functional groups have been shown to promote dearomatising reactions. For example, the \textit{N}-benzyl phosphinamides 37\textsuperscript{26,27} and 40\textsuperscript{28} cyclise in a way comparable with the amides 33 and 30, yielding dearomatised products 39 and 42 (Scheme 10). Poor regioselectivity was obtained on quenching the intermediate 38 (though not 41) with electrophiles. These cyclisations have been used to synthesise unusual aminophosphinic acids.\textsuperscript{27}
The triazines 43 are lithiated α to nitrogen by n-BuLi and the resulting organolithium 44 undergoes cyclisation with dearomatisation to give 45 which can be isolated as its Boc derivative 46 (Scheme 11). Without the two ortho methyl groups, 45 decomposes: this cyclisation is unusual in that the ring is attacked at a substituted position.

A superficially comparable reaction occurs when the iminium ion 47 is deprotonated. A stable carbene, with an alternative tautomer 48, is formed and slowly undergoes dearomatising cyclisation to yield 49 in moderate yield (Scheme 12). This cyclisation is evidently an electrocyclic process, and it seems likely that several of the other dearomatising cyclisations presented in this section also result from a pericyclic mechanism. Stereochemical evidence for a pericyclic mechanism in the cyclisation of a lithiated amide will be presented later.

3 Dearomatising Cyclisations of Amides

3.1 Nitrogen Substituents

Building on the results shown in Schemes 8 and 9, in 1996 we began a programme of research into the synthetic potential of the dearomatising organolithium cyclisations of aromatic tertiary amides. We quickly established that the cyclisation is a general reaction of N-benzyl amides, along with some allyl-substituted amides. Naphthamides such as 50 cyclised more readily than benzamides such as 52, simply requiring lithiation with s-BuLi at –78 °C with subsequent addition of DMPU increasing the cyclisation rate and improving the yields. With benzamides such as 52, the t-BuLi–HMPA conditions chanced upon in the reaction in Scheme 9 gave among the best yields possible (Scheme 13), though we were unable to avoid formation of regioisomeric mixtures upon protonation or electrophilic quench of the benzamide cyclisations.

Early work concentrated principally on the naphthamide cyclisations, partly because they gave single regioisomers of the dearomised products, and also because it turned out that they could be carried out without HMPA. We discovered a few key features of compounds which gave good results, some of which we could link to mechanistic features of the cyclisation. One of the first things we noted was that consistently good yields and stereoselectivities could be obtained only when one of the groups carried by the nitrogen atom was bulky. For example, although N,N-dibenzyllbenzamide 52 could be cyclised in acceptable yield in the presence of HMPA, N,N-

Scheme 10

Scheme 11

Scheme 12  Ad = adamantyl
dibenzynaphthamide 54 was lithiated α to nitrogen to give 55 (and could be alkylated to give 56) but failed to cyclise (Scheme 14). Dibenzyl amides are typically lithiated syn to oxygen,2,18,36 where the lithium atom benefits from O–Li coordination. However, for the benzyllithium 55 to adopt a conformation 58 in which the anion can attack the ring, an unfavourable loss of O–Li complexation has to occur. By contrast, N-tert-butylnaphthamides such as 50 adopt a conformation which places the single benzyl group permanently in proximity to the ring, and the benzylic organolithium 58 is able to cyclise without the need for further bond rotations.

Using deuterium labelling, we found that we could follow the detailed choreography of the deprotonation (Scheme 14).37 While some of the amide 50 was clearly deprotonated directly in the α (benzylic) position to give 58, a significant amount was ortholithiated first, to give 57 and the anion thus formed subsequently ‘translocated’ to the benzylic position of the amide. Trapping experiments (Mel gave a 1:2 mixture of ortho-functionalised 59 and α-functionalised 60) suggested that 57 and 58 are in rapid equilibrium, and that DMPU or HMPA biases the equilibrium in favour of 58.

3.2 Alternatives to N-Benzyl Groups

Cyclisation of amides with a benzyl N-substituent yields 5-phenyl pyrrolidinone derivatives, which we later converted to members of the kainoid family by Ru-catalysed oxidation of Ph to CO₂H.38 The common requirement in synthetic targets for a 5-CO₂H substituent led us to examine other potential cyclisable nitrogen substituents. Few were successful: the requirement that the substituent should be sufficiently acidic to be deprotonated, but also that the resulting anion still be sufficiently unstable for there to remain a driving force for dearomatisation, is a stringent one. In the end, we achieved some success with N-allyl naphthamides 61 (though not benzamides), which gave principally the 7-membered ring products 62 (Scheme 15), and more significantly with the N-benzoyl oxazolidines 63,31 which cyclise to give the tricyclic products 67 (Scheme 16).
3.3 Cyclisation of N-Benzoyl Oxazolidines

Deuterium labelling again allowed the detailed mechanism of this cyclisation to be established, as shown in Scheme 16. However, the most interesting aspect of this cyclisation, apart from its potential synthetic use, is the stereochemistry of the tricyclic products 67. The cis-tricyclic arrangement is clearly less thermodynamically stable than the corresponding trans arrangement, since aqueous acid promotes the epimerisation of 67 to 68. The fact that the cis stereochemistry is the sole kinetic product of the reaction may be indicative of the mechanism of the cyclisation, which we propose may be pericyclic. Representing 65 as 65a (Scheme 17) makes this more apparent: the 6π-electron thermal electrocyclic ring closure must be disrotatory and hence yield the observed stereochemistry of 67. While the stereochemical outcome of this reaction is consistent with a pericyclic mechanism, it, of course, does not prove that the cyclisation is pericyclic, nor does it give any definitive information about the cyclisation of N-benzylbenzamides. Further chemistry of 67 and 68 remains to be exploited.

3.4 Cumyl as a Protecting Group

The t-butyl group provided us with some useful ‘workhorses’ for developing the scope of the cyclisation, since

N-tert-butylbenzylamine is cheap and readily available. However, we found it was almost impossible to remove from the products, even on extended treatment with acid. Replacing one of the methyl groups of the t-butyl with a phenyl group stabilised the positive charge formed during E1 elimination and allowed us to deprotect the products to yield N-unsubstituted pyrrolidinones (Scheme 18).

Thus, cyclisation of 69 gives 70 and hence 71. This ‘cumyl’ protecting group, more or less simultaneously published by Snieckus, is not a true protecting group in the sense that it has to be introduced at the start of the sequence by using cumylamine (72) as a starting material. (Cumylamine 72 is rather expensive commercially, but is reportedly simple to make.)

The use of carbonyl-based protecting groups such as Boc led to rearrangement reactions rather than cyclisation.

3.5 Functionalised Benzamides: Enones as Products

The final step of the cyclisation mechanism also posed problems for application in synthesis. The initial product of the cyclisation reaction is an extended enolate, 73, from the naphthamide 50 (Scheme 19) and 77 from the benzamide 75 (Scheme 20). Enolate 73 can be alkylated or protonated both regio- and stereoselectively, giving a 6,5-cis-fused product and avoiding dearomatising the second aromatic ring of the naphthalene system. On the other hand, 77 was generally alkylated or protonated non-regioselectively, and indeed alkylation was also non-stereoselective, forming difficult-to-separate mixtures of dienes. We had some limited success in controlling the regioselectivity of the protonation, but we realised that if the dienes were functionalised with methoxy groups, they would both be enol ethers 81 and therefore hydrolysable to give enones, with the regiochemistry of the double bonds in the hydrolysed products being under thermodynamic control. Indeed, cyclisation of 75 (R = OMe) gave the enone 82 in 71–73% overall yield, even without isolation of the intermediate enol ethers 81 (Scheme 20).
3.6 Avoiding HMPA: LDA as a Cyclisation Promoter

There remained two obstacles to the general application of the cyclisation in synthesis: the fact that the cyclisation gives racemic products, and the requirement for the use of pyrophoric t-BuLi and carcinogenic HMPA in order to obtain good yields. In the end, we managed to overcome both of these problems by building on a single observation. Our first attempts to develop an asymmetric cyclisation made use of (−)-sparteine in place of the HMPA, but with little success, partly due to the insolubility of the starting amide in solvents which typically give good enantioselectivities with (−)-sparteine- t-BuLi complexes.45 The other group of broadly successful chiral bases are the chiral lithium amides, such as 83 or 84 (Scheme 21), though in almost all of the cases in which these compounds react selectively, they are used to deprotonate at one of two enantiotopic reaction sites rather than to remove one of two enantiotopic protons from a single carbon atom.46

In preparation for an attempted asymmetric cyclisation using 83 or 84, we managed to establish that LDA was (just) sufficiently basic to deprotonate the benzylic position of an N-benzylbenzamide, but only at temperatures above about –30 °C. Raising the temperature still further – to around 0 °C – promoted the cyclisation (Scheme 22), and temperature control turned out to be an effective alternative to the use of HMPA in the cyclisation reaction.40 Avoiding t-BuLi afforded not only the practical benefits of not having to use such a pyrophoric reagent, but also allowed greater versatility of starting material, since LDA promoted the cyclisation of even halogenated benzamides and 2-naphthamides, both of which gave extensive side reactions with t-BuLi. The only compounds which did not cyclise under these conditions were those carrying a methoxy substituent para to the position to be attacked.

Table 1 shows the range of amides we cyclised under these conditions.40 In only one case, the cyclisation of a cyano-substituted benzamide, was rearomatisation of the intermediate enolate a significant side reaction. However, given that rearomatised products may nonetheless be interesting targets themselves, we demonstrated that an electrophilic quench with certain oxidising agents was able to give isoidolones.47
3.7 Asymmetric Cyclisation with Chiral Lithium Amides

The LDA-promoted cyclisation was transformed into an asymmetric cyclisation simply by replacing LDA with 83 or 84 (Scheme 21). Base 84 is more basic than LDA and deprotonation and cyclisation at as low a temperature as possible gave cyclised product in 75% ee (Scheme 21). Initially yields were low, because we had problems separating the amine (84H) from the product. However, changing the base to the even simpler 83 solved this problem, because the hydrochloride salt of 83 seems much less soluble in organic solvents than that of 84. Base 83 gave a maximum of 88% yield and 81% ee in the cyclisation (Scheme 21).

There are two limiting possibilities for the source of the asymmetry in the reaction. Either the cyclisation step itself is stereoselective, with the stereochemistry induced by the presence of the chiral amine 83H, perhaps acting as a chiral ligand for the organolithium during the cyclisation, or the lithiation step is stereoselective and the stereochemistry of 86 is a consequence of stereospecific cyclisation of an intermediate chiral organolithium which has configurational stability on the timescale of its cyclisation. Although similar considerations have informed the investigation of the stereochemistry of (–)-sparteine-promoted reactions of benzyllithiums, neither possibility has any direct precedent, because rarely have chiral lithium amides been used to remove enantioselectively one of two enantiotopic protons at a prochiral methylene group, nor have they been used as chiral ligands for organolithiums less basic than LDA.

We investigated the possibility that 83H acts as a ligand, introducing enantioselectivity in the cyclisation step of the sequence, by making the intermediate 76 as a racemate and cyclising it in the presence of 83H (Scheme 23). Racemic product was formed, indicating that enantioselectivity is introduced in the first, lithiation step. This implies that the intermediate organolithium is configurationally stable, at least on the timescale of its cyclisation. Configurational stability is known in similar N-Boc benzylamines, so this hypothesis did not seem unreasonable. A second experiment confirmed that the stereochemistry of the organolithium intermediate is responsible for the stereochemistry of the final cyclisation product: cyclisation of the racemic deuterated compound 75D, even using the chiral base 83, gave racemic but deuterated material 82D:

Table 1

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
</tr>
</tbody>
</table>

Synthesis 2004, No. 11, 1721–1736 © Thieme Stuttgart · New York
the kinetic isotope effect has overridden the enantioselectivity of the base, generating a racemic intermediate organolithium 76D and therefore racemic product.

3.8 Stereospecific Cyclisation of Chiral Benzamides

Lithiated tertiary N-Boc- benzylamines are considerably more configurationally stable than their secondary analogues, so we proposed that lithiating and cyclising tertiary amides such as 89 might preserve stereochemistry of the starting material through into the product. We expected tertiary centres to cyclise without difficulty because the first cyclisation we had ever observed was of 1-naphthamide 30 bearing chiral substituents. Unlike N,N-dibenzyl naphthamides, N,N-bis-(α-methylbenzyl)-naphthamides generally cyclise successfully even without an additive (DMPU or HMPA). We verified first of all that the cyclisations of 87a and 87b were stereospecific: each starting diastereoisomer gave a different diastereoisomer of the product 88 (Scheme 24), so both lithiation and cyclisation must be stereospecific, proceeding via a configurationally stable tertiary benzyllithium intermediate.

When we cyclised 89, and a series of related examples, the product 90 was formed in high ee: the product stereochemistry depends solely on the absolute stereochemistry of the centre in the starting amide 89. These results account for the stereoselectivity evident in the cyclisation of 30, though it also became evident that stereospecificity in the naphthamide cyclisations was complicated by the presence of a sterogenic Ar–CO axis at low temperature.

3.9 Cyclisation onto Pyrroles

Given that benzamides containing either electron-poor or electron-rich benzenoid aromatic rings undergo the dearomatising cyclisation, it seemed reasonable to suppose that dearomatising cyclisations onto either electron-rich or electron-poor heteroaromatic rings should be possible. At the time of writing (May 2004) such work is ongoing, but, for example, it has become evident that the N-allylpyrrolecarboxamides 91 undergo cyclisation to yield 92 (Scheme 25).

The corresponding N-benzyl compounds 93 cyclised less successfully because the intermediate 5,5-fused ring systems were too strained, yielding ring opened products 94. As with the benzamides, chiral and enantiomerically pure starting materials 95 were transformed stereospecifically into enantiomerically pure products 96 (Scheme 26).
3.10 Applications of the Dearomatising Cyclisation to the Synthesis of Kainoids

The kainoids, principal examples of which are shown in Figure 1, are all pyrrolidinedicarboxylic acids with the general structure 100 (Scheme 27), many of them exhibiting potent activity at neurotransmitter receptors.55 The parent member of the family is kainic acid 97, and biologically active kainoids all share the features highlighted in Scheme 27. The kainoids have a number of structural features which made them appealing targets for synthesis from products of the cyclisation of lithiated amides, and the application of dearomatising cyclisation to their synthesis has recently been reviewed.56 Scheme 27 summarises the strategy employed in these syntheses, and Scheme 28 shows the targets – an aryl pyroglutamate 104, an acromelic acid analogue 98, (−)-59 [and (±)-]60 kainic acid 97, and an α-methylated kainic acid analogue 111 – which have been made thus far using dearomatising cyclisation.

One of most important features of the biologically active kainoids, and one which has made them more of a synthetic challenge than they would otherwise have been, is the cis relative stereochemistry of the two substituents at the C3 and C4 positions (the epimeric allo-kainoids are, by and large, biologically inactive). The cyclisation products 101, when mapped onto the kainoids, also exhibit cis stereochemistry at these positions because of their 6,5-fused bicyclic structure, and indeed several previous syntheses of kainoids incorporate this cis stereochemistry by tying the two groups into a ring during the synthesis.56 Synthetic routes from 101 to molecules of type 100 require some functional group transformations, including the challenging oxidation of the aryl ring at C2 to a carboxylate substituent,58,61–64 and an appropriate late-stage ring cleavage reaction of the six-membered ring joining the C3 and C4 substituents. Further work in this area, particularly with regard to the synthesis of the domoic acid family, is ongoing.

Scheme 27
vent it rearomatising. In most examples using amides, sulfonamides, triazines, etc., these two functions are performed by the same group (section 2). We wondered whether decoupling the organolithium from the activating group, and forming it by halogen-lithium or tin-lithium exchange, would allow a new range of dearomatising cyclisations to be developed.

Nucleophilic addition of organolithiums to naphthalene rings with rearomatisation has been known for some time, and Stoyanovich,65 Meyers66,67 and others68–71 have shown how to use electron-withdrawing groups to stabilise the addition products and hence give dihydronaphthalenes, many of them of synthetic use. We aimed to develop an intramolecular version of this reaction, allowing annelation of a five membered ring, for example, to a naphthalene system.

Preliminary experiments with 112 showed that cyclisation onto the 2-position of an unactivated naphthalene ring is possible but yields rearomatised products.72 Iodine-lithium exchange of 112 in various solvents gave the organolithium 113. Stirring at various temperatures, with and without additives, in order to promote cyclisation (Scheme 29), gave two major compounds (114 and 115), the ratios of which are shown in Table 2. Good yields of cyclisation product 114 required the presence of TMEDA and temperatures above 0 °C.

### 4.1 Oxazoline Activation

With Meyers’ success66,67 using oxazolines to promote dearomatising additions to naphthalenes in mind, the starting material 116 was made. Iodine-lithium exchange of 116 was performed using tert-butyllithium in THF at −78 °C (Scheme 30). The organolithium 117 was stirred at −78 °C for one hour, and cyclised to give the aza-enoate 118; this reacted with electrophiles to give dearomatising products.
tised cyclised products 119a and 119b in good yield (Table 3).

The ammonium chloride quench (entry 3) gave the single
diastereoisomer 119b, placing the oxazoline on the exo
face of the bicyclic system, while the alkylating agents
MeI (entry 1) and BnBr (entry 2) gave the single diaste-
reoisomer 119a (E = Me, Bn), presumably by attack on
the less hindered exo face. All the cyclisation products
were acid sensitive, and attempts to hydrolyse (using 2 M
HCl, in THF) the enol ether 119b (E = H) led to decom-
position. However, it was possible to transform the oxazo-
lone-containing product 119a to the ketone 122 by the

Table 2 Cyclisation of Unactivated Naphthalene Derivative 112

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time</th>
<th>Additive</th>
<th>114:115</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pentane–ether</td>
<td>−78 to r.t.</td>
<td>1 h</td>
<td>–</td>
<td>0:100</td>
</tr>
<tr>
<td>2</td>
<td>pentane–ether</td>
<td>−78 to reflux</td>
<td>2 h</td>
<td>–</td>
<td>25:75</td>
</tr>
<tr>
<td>3</td>
<td>pentane–ether</td>
<td>−78 to r.t.</td>
<td>3 h</td>
<td>TMEDA</td>
<td>78:25 (60% 114 isolated)</td>
</tr>
<tr>
<td>4</td>
<td>pentane–ether</td>
<td>−78</td>
<td>2 h</td>
<td>TMEDA</td>
<td>0:100</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>−78 to r.t.</td>
<td>3 h</td>
<td>TMEDA</td>
<td>0:100</td>
</tr>
<tr>
<td>6</td>
<td>pentane–ether</td>
<td>−78 to 0</td>
<td>3 h</td>
<td>TMEDA</td>
<td>58:42</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>−78 to −40</td>
<td>16 h</td>
<td>HMPA</td>
<td>0:100</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>−78 to r.t.</td>
<td>3 h</td>
<td>HMPA</td>
<td>0:100</td>
</tr>
</tbody>
</table>
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method shown in Scheme 31. The stereochemistry of 122b was confirmed by X-ray crystallography.

By introducing an oxygen atom into the tether linking the organolithium to the ring, THF-fused dihydronaphthalenes could be made. Tin-lithium exchange of stannane 123, using methyllithium and TMEDA in THF at −78 °C, gave the organolithium 124. This cyclised to aza-enolate 125 over one hour at −78 °C, which reacted with electrophiles to give dearomatised cyclised products 126a and 126b (Scheme 32, Table 4). Interestingly, stereoelectron-ic effects in the intermediate 125 mean that it was both alkylated and protonated principally on the endo face.

A nitrogen tether was also studied. Tin-lithium exchange of stannane 127 with methyltholithium and TMEDA in THF at −40 °C gave the organolithium 128, which cyclised to aza-enolate 129 over one hour at −40 °C (Scheme 33). The electrophiles shown in Table 5 gave dearomatised products 130.

4.2 Sulfone Activation

Other activating groups were also examined. Little success was obtained with activation by an amide group,
probably due to competing ortholithiation. However, tin-
lithium exchange of stannane \( \text{SnBu}_3 \) gave the \(-\)oxy organolithium \( \text{LiO}^+ \), which cyclised over one hour at \(-78^\circ\text{C}\). The cyclisation product, sulfone-stabilised anion \( \text{S}^+ \), was treated with alkylating agents (Scheme 34, Table 6). The initial alkylated methyl enol ether products were hydrolysed (2 M HCl) before purification. These cyclisations were clean reactions, delivering good yields of the alkylated ketone products \( \text{K} \). All quenches gave single diasteroisomers, the stereochemistries of which were assigned by crystal structure.

Scheme 34

Cyclisation of a chiral analogue \( \text{C} \) of organolithium \( \text{D} \) was diasteroselective, giving \( \text{E} \) after alkylation (Scheme 35, Table 7).

Table 5 Electrophilic Trapping of Aza-enolate \( \text{F} \)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Yield of ( \text{G} )</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>MeI</td>
<td>71%</td>
</tr>
<tr>
<td>2</td>
<td>NH(_4)Cl</td>
<td>73%</td>
</tr>
<tr>
<td>3</td>
<td>PhCHO</td>
<td>80%(^b)</td>
</tr>
<tr>
<td>4</td>
<td>AllylBr</td>
<td>57%</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield.
\(^b\) Yield of 3:2 epimeric mix at alcohol centre.

Table 6 Alkylation of Sulfone-Stabilised Anion \( \text{H} \)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Yield of ( \text{I} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BnBr(^a)</td>
<td>71%</td>
</tr>
<tr>
<td>2</td>
<td>MeI(^b)</td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td>AllylBr</td>
<td>71%</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield.
\(^b\) Product stereochemistry proved by X-ray crystallography.

4.3 Synthetic Application of the Dearomatising Cyclisation of Lithiated Naphthylsulfones

The similarity between the cyclisation products \( \text{J} \) and the lignan natural product podophyllotoxin \( \text{K} \) suggests the potential application of this chemistry to the synthesis of this class of compounds. Quenching the cyclisation product \( \text{L} \) derived from \( \text{M} \) with ammonium chloride, followed by hydrolysis, gave a single diasteroisomer of the ketone \( \text{N} \), which was used to synthesise the podophyllotoxin analogue \( \text{O} \) (Scheme 36).

5 Summary

Isolated reports of dearomatising cyclisation reactions during the 1990’s led to the development of two major synthetically useful methods, one based on the cyclisation of lithiated amides to yield unsaturated isoindolones, the other employing lithioalkylnaphthalene derivatives to give 6,6,5-fused tricyclic compounds. Further developments in the area are continuing, particularly with regard to cyclisation onto heteroaromatic systems.
References


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(49) Clayden, J.; Knowles, F. E.; Menet, C. J. Synlett 2003, 1701.