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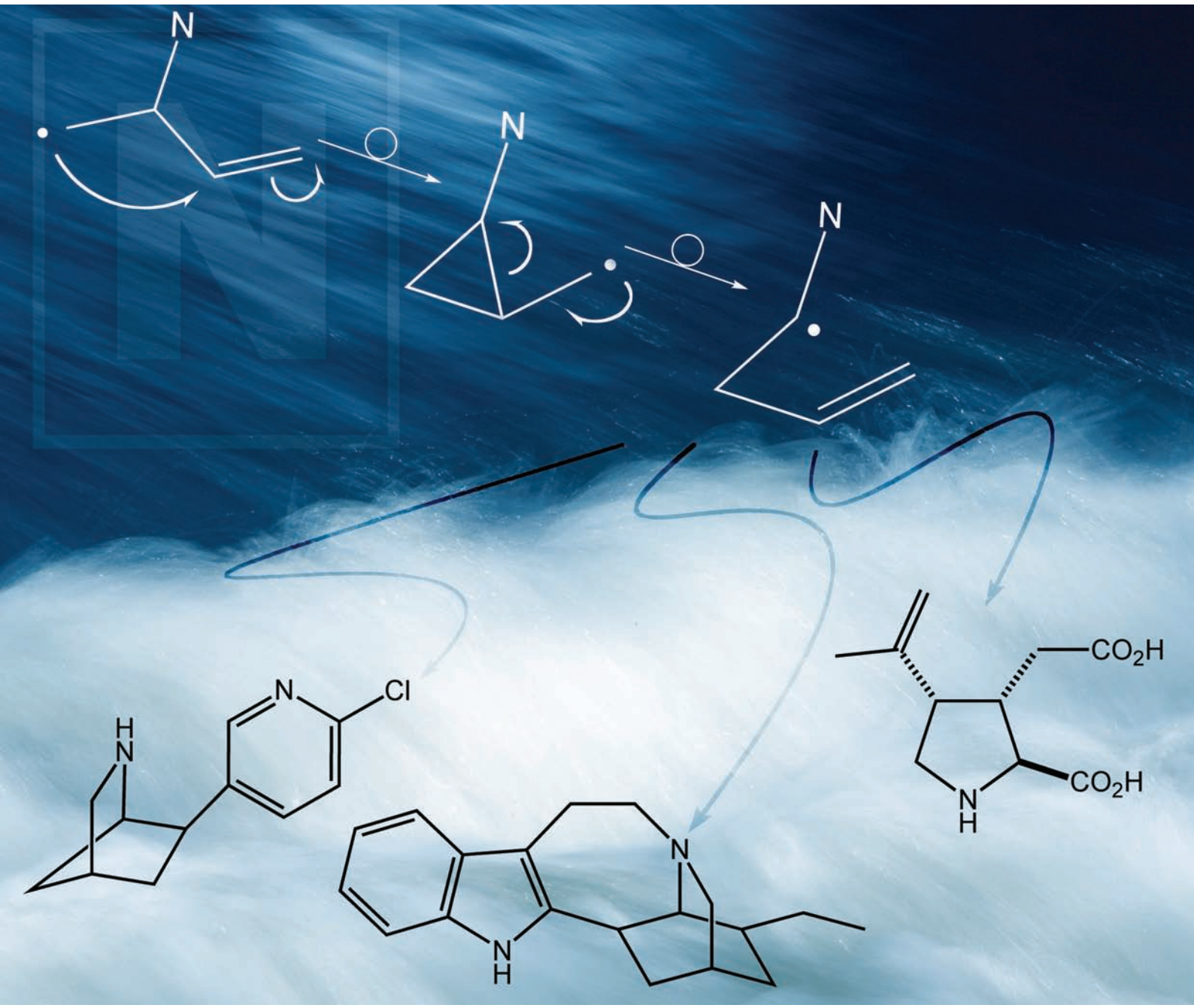

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Synthesis of azabicyclic systems using nitrogen-directed radical rearrangements

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Radical rearrangements are important transformations in organic synthesis. The stabilisation of α-nitrogen radicals is shown to be a useful effect for the control of radical rearrangements and is applied to the synthesis of a variety of azabicyclic frameworks. The utility of this method is illustrated in the synthesis of bioactive targets.

1. Introduction

Carbon-centred radicals are important intermediates in organic chemistry: they can demonstrate a high degree of selectivity in their reactions and their applications in synthesis have become widespread.[1–6] Methods involving radicals can exhibit significant advantages over those proceeding *via* ionic pathways.[7] Radicals are highly reactive intermediates with fast reaction kinetics, yet can be generated under mild conditions without the need for strongly acidic or basic conditions. They are also widely tolerant of functional groups (*e.g.* amines and alcohols usually do not require protection), and radicals are generally much less sensitive to steric effects since the counter-ions or aggregation spheres associated with charged intermediates are not involved. Furthermore, the understanding of radical chain reactions has enabled radical-based methods to be applied to the synthesis of complex targets,[7,8] and routes using radical intermediates can readily be considered during retrosynthetic planning.[9]

For the successful execution of any radical chain reaction it is necessary to be able to generate the initial radical on a substrate in a site specific manner and for each radical generated within the propagation steps to persist with sufficient lifetime to undergo the desired subsequent reactions.[7] The utility of radical-based methodologies is further enhanced by the potential for effecting cascade reactions, where the careful design of a substrate will allow several radical reactions to proceed in sequence, often with a considerable enhancement of molecular complexity,[10] *e.g.* in the synthesis of steroid rings.[11] An elegant example is found in Feldman's approach to the brefeldins (Scheme 1).[12]

One interesting radical intermediate is the cyclopropylmethyl radical **1**, which is known to ring open to give homoallyl radical **2** (Scheme 2).[13] The rate of such a process can be very fast: ring-opening of the cyclopropylmethyl radical is known to proceed with a rate of 1.2×10^8 s^{-1} at 37 °C.[14] More substituted cyclopropylmethyl–homoallylic radical systems can be found embedded in a range of more complex substrates, *e.g.* in the brefeldin study above. These systems have also found significant

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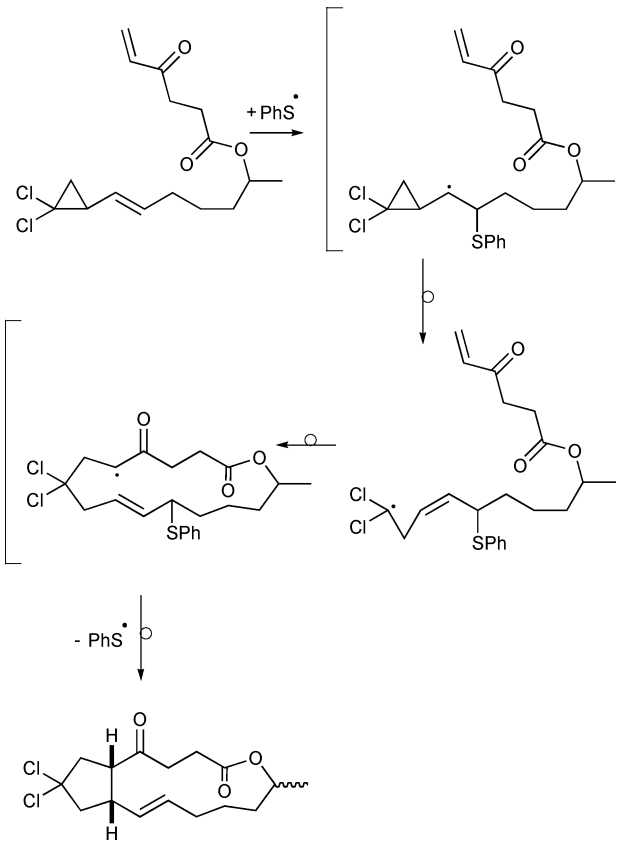
David Hodgson obtained a PhD at Southampton University (with P. J. Parsons) and was appointed in 1990 to a lectureship at Reading University. In 1995 he moved to the Chemistry Department at Oxford University, where he is now a Professor of Chemistry. He was recipient of a GlaxoWellcome Award For Innovative Organic Chemistry in 1999, the 2000 Pfizer Academic Award, the 2000 AstraZeneca Research Award in Organic Chemistry, and the 2006 Royal Society of Chemistry Bader Prize for eminence in organic chemistry. His research interests are broadly in the development and application of synthetic methods.

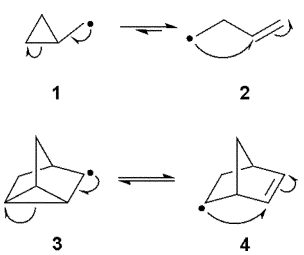
Leonard H. Winning

Leonard Winning obtained an M.Chem. at St. John's College, Oxford which included a Part II under the supervision of Prof. Hodgson in 2003. His D.Phil. research in Prof. Hodgson's group has involved nitrogen-directed radical rearrangements for which he was awarded a Lilly Scholarship from the Oxford Organic Chemistry Sub-Department, in recognition of outstanding graduate work in his first year.



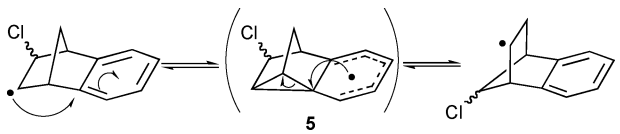
Scheme 1 An approach to the brefeldins using a radical cascade.[12]

application as so-called 'radical clock reactions',[15] in kinetic competition experiments for the determination of the rates of other radical reactions. One such group of structures is that based upon the bicyclo[2.2.1]heptene (norbornenyl) framework, where a nortricyclyl radical **3** undergoes ring-opening to a norbornenyl radical **4** (Scheme 2). Starting from nortricyclyl or norbornenyl bromide, treatment with Bu_3SnH and AIBN is known to lead to the same (approximately equal) mixture of nortricyclane and norbornene.



Scheme 2 Cyclopropylmethyl–homoallyl and nortricyclyl–norbornenyl radical systems.

Both the ionic[16] and radical[17] intermediates that may be generated on the norbornenyl framework have been the subject of considerable interest; norbornenyl radicals have been shown not to exhibit the 'non-classical' behaviour that is seen in the corresponding cation, and studies have shown that the norbornenyl and nortricyclyl radicals are discrete intermediates.[18,19] In the structurally similar system created by the formal fusion of the norbornenyl skeleton with an aromatic ring, the 'nortricyclyl' radical **5** (Scheme 3) is delocalised in the originally aromatic π-system. Ring-opening of this 'nortricyclyl' radical species can lead to an overall 1,2-aryl (neophyl) migration.[20] Related aryl migrations are widely known.[21]



Scheme 3 Neophyl rearrangement.

As indicated in the above Schemes, homoallyl–cyclopropylmethyl interconversions can be readily reversible, and the final product distribution is found to be heavily dependent upon reactant concentrations as well as substrate structure.[17] In order to make these reactions useful in synthesis, it is helpful to have substrate structural directing effect(s) that will favour the radical leading to the desired product.[22] In the brefeldin studies (Scheme 1), this was achieved by the incorporation of *gem*-dichloro functionality on the cyclopropane ring, which biased ring-opening [to give a tertiary (doubly datively stabilised) radical] and aided macrocyclisation. Our research has focussed on using the potential dative stabilising effect of an α-nitrogen in the product producing radical to direct homoallyl radical rearrangements for use in azacycle synthesis.

2. Nitrogen-directed homoallylic radical rearrangements using azanortricyclanols: synthesis of an epibatidine analogue

Our interest in nitrogen-directed radical rearrangements began with the synthesis of *endo*-6-(6-chloropyridin-3-yl)-2-azabicyclo[2.2.1]heptane (**6**), an isomer of epibatidine (**7**) (Fig. 1).[23,24] The latter alkaloid, isolated from the skin of the Ecuadorian frog *Epipedobates tricolor*, is a potent non-opioid analgesic, and acts as a nictotinic acetylcholine receptor (nAChR) agonist.[25–27] We considered that azabicycle **6** represented an interesting analogue of epibatidine, since it translocates the secondary amine from the 7-position to the 2-position of the rigid bicyclo[2.2.1]heptyl framework, but retains the same basic framework connectivity and maintains a similar orientation of the amine group with respect to the chloropyridyl substituent. It was hoped that such an analogue might provide useful SAR information in the search for less toxic epibatidine analogues.[28,29]

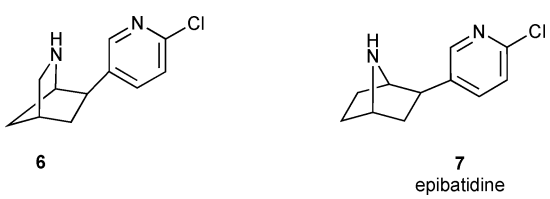
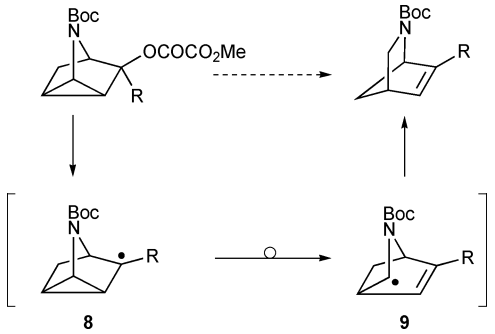


Fig. 1 An isomeric analogue **6** of epibatidine (**7**).

We anticipated using the radical rearrangement of 7-azanortricyclyl radical **8** to 2-azanorbornyl radical **9** as a key step in our synthesis of azabicycle **6** (Scheme 4),[30] a related rearrangement in a [3.2.1] system having been reported by Rigby (see Section 6).[31]



Scheme 4 Proposed radical rearrangement as a key step in the synthesis of epibatidine analogue **6**.

The synthesis of the radical progenitor to azanortricyclic radical **8** used Boc-protected 7-azanorbornene **11**, which was most concisely prepared *via* [4+2] cycloaddition of *N*-Boc pyrrole and tosyl acetylene to give diene **10**, followed by hydrogenation and sodium amalgam induced desulfonylation.[32–33] We also envisaged that this route would have the potential for an asymmetric synthesis, by using enantioselective deprotonation to desymmetrise the derived (achiral) epoxide **12**.[34] This strategy was successfully developed to furnish the epibatidine analogue **6** in 10 steps from cycloadduct **10** (Scheme 5), as well as related 6-substituted-2-azabicyclo[2.2.1]hept-5-enes.[33] Biological studies showed that analogue **6** had a high binding affinity with nAChR, showing analgesic activity equivalent to that of epibatidine.

Since the radical rearrangement (**8** → **9**, Scheme 4) proceeds even if a potentially radical-stabilising alkyl or aryl group is present at the site of initial radical generation (Scheme 4, R = alkyl, aryl), it suggests that a driving force for this rearrangement might be due to the dative stabilisation conferred upon the product producing radical **9** by the presence of the α-nitrogen. The latter can be argued from a consideration of the interaction of the nitrogen lone-pair and the radical SOMO: the overlap of these orbitals is expected to result in an overall lowering of free energy (Fig. 2).[1,35,36] This interaction also results in the radical SOMO being raised in energy, enhancing the nucleophilic character of the radical—a feature we have subsequently exploited in selective functionalisation of the azabicyclo[2.2.1] framework (see Section 5).

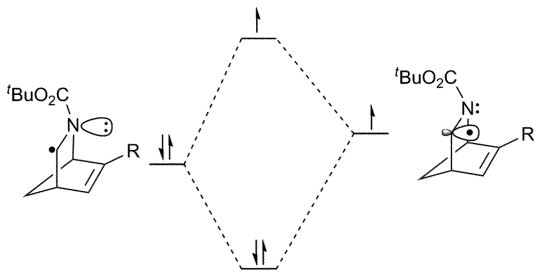
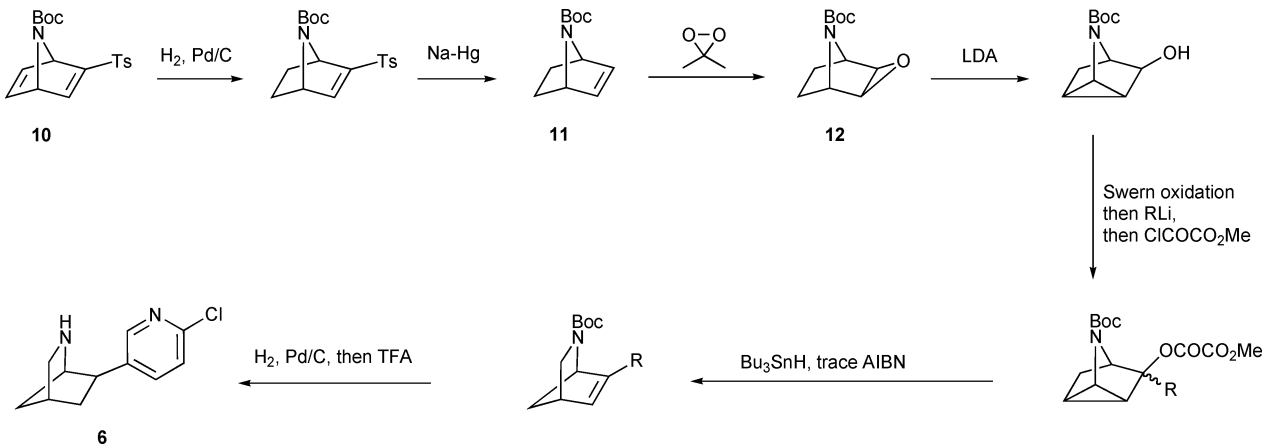


Fig. 2 Radical SOMO–α-nitrogen lone-pair interaction.

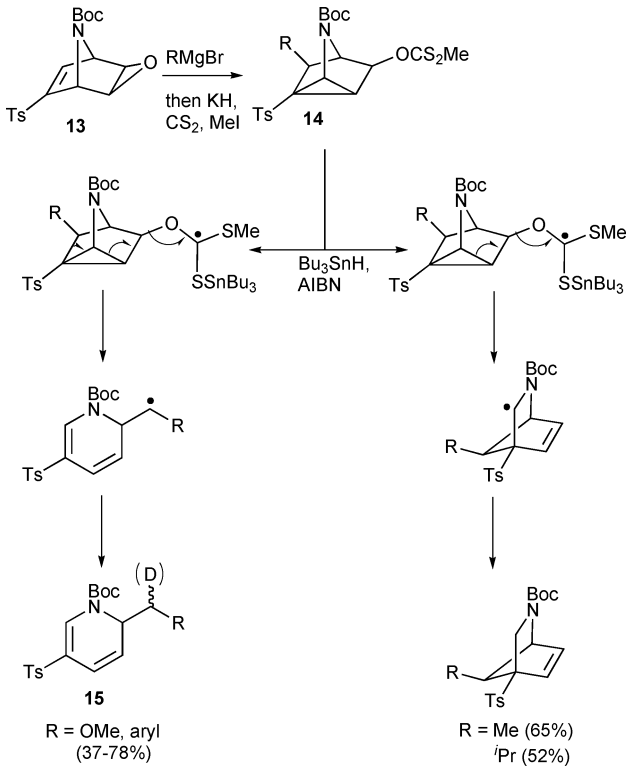
The above observations led us conclude that the 'nitrogen-directed' radical rearrangement had the potential to be more widely applied and we began to consider ways to broaden its scope. These investigations commenced with the synthesis of various 5-substituted 7-azanortricyclanols by the addition of Grignard reagents to epoxide **13** (Scheme 6, available by epoxidation of cycloadduct **10**).[37] These alcohols were obtained in good yields (72–96%) and were subsequently converted to the corresponding methyl xanthates **14** for radical deoxygenation–rearrangement. For alkyl substituents (**14**, R = Me, ^{i}Pr) the anticipated deoxygenation–rearrangement proceeded in 65% and 52% yields, respectively (Scheme 6). However, in the case of the methoxy, phenyl, 6-chloropyridin-3-yl, 4-methoxyphenyl and 6-methoxypyridin-3-yl substituents (several of which were of interest for the synthesis of further epibatidine analogues), the deoxygenation reaction proceeded cleanly to furnish 1,2-dihydropyridines **15** in 37–78% yield.[38] A suggested pathway for the divergence to dihydropyridine formation is shown in Scheme 6, and this was supported by the observation that use of Bu_3SnD resulted in deuterium incorporation at the side chain methylene group of the dihydropyridine.

3. Nitrogen-directed homoallylic radical rearrangements initiated by thiol addition

During studies on the preparation of alkene **11** (Scheme 5) it was found that desulfonylation of sulfone **16** gave rearranged alkene **20** as a by-product, in 18% yield (Scheme 7).[33] It was reasoned that alkene **20** could be derived by homolysis of the likely intermediate radical anion initially generated in the desulfonylation, followed



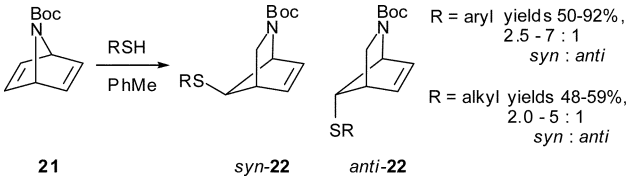
Scheme 5 Synthesis of epibatidine analogue **6**.



Scheme 6 Radical deoxygenation of azanortricyclanols to 7-substituted 2-azanorborn-5-enes and 1,2-dihydropyridines.

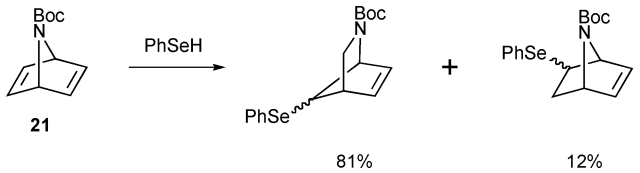
by radical cyclisation from azabicyclic radical **17** to azanortricyclyl radical **18** and subsequent ring-opening to nitrogen-stabilised radical **19**.

Given the above observations, we sought to develop a convenient route to azabicyclic radical **17** in order to investigate the synthetic utility of this process, which would avoid the synthesis of a tricyclic starting material. An attractive and experimentally straightforward method of generating alkyl radicals is by addition of thiols to alkenes (*cf.* Scheme 1), and such additions to norbornadiene have been well-studied, though the nortricyclanes are reported to be the major products.[39] In contrast, we found that aromatic and aliphatic thiols reacted with *N*-Boc 7-azanorbornadiene **21** to give only the corresponding rearranged azabicyclic sulfides **22** (Scheme 8).[40a,c]



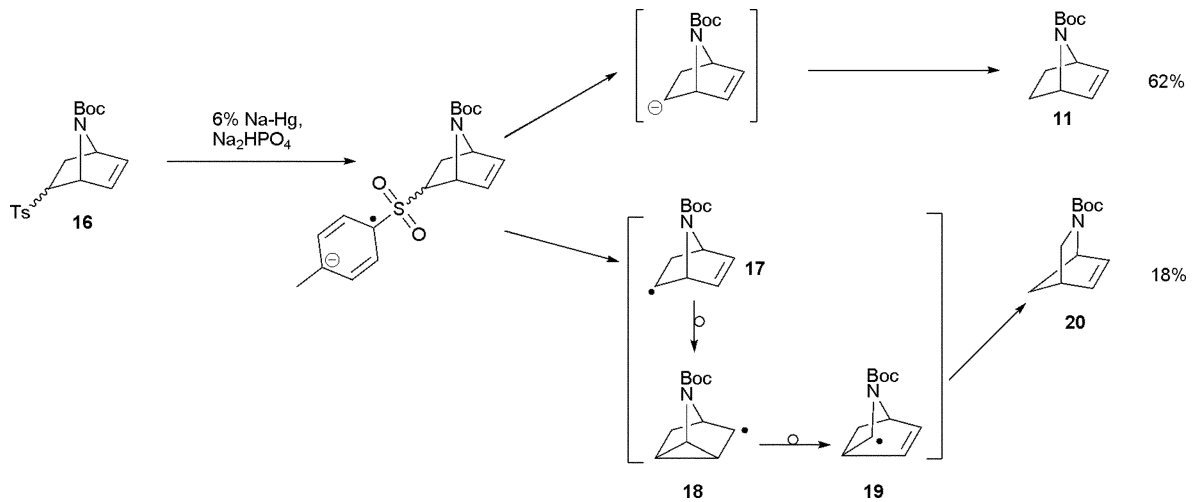
Scheme 8 Radical addition of thiols to *N*-Boc 7-azanorbornadiene **21**.

Benzeneselenol behaved in a similar fashion to the thiols, though the greater hydrogen atom-donating ability of the benzeneselenol[41] was reflected in the isolation of mixtures of diastereomers of both the rearranged and unrearranged products (Scheme 9).



Scheme 9 Phenylselenol radical addition to *N*-Boc 7-azanorbornadiene **21**.

The combined results of the thiol and selenol radical addition experiments allowed an estimation of the rate of the radical rearrangement. The absence of unrearranged products in the addition of the aromatic thiols suggests that the rate of rearrangement is at least an order of magnitude faster than hydrogen atom transfer from the thiol, which is known to be of the order of 10^8 dm^3 mol^{-1} s^{-1}.[41] Conversely, the formation of small amounts of the unrearranged adduct in the reaction with benzeneselenol suggests that the rate of rearrangement cannot be more than an order of magnitude greater than that of hydrogen atom transfer from the selenol, known to be of the order of 10^9 dm^3 mol^{-1} s^{-1}.[41] Thus, the rate of the rearrangement lies within the range of 10^8–10^9 s^{-1}. Another noteworthy feature of this reaction is that no products from hydrogen-atom-transfer to the azanortricyclyl



Scheme 7 Desulfonylation of alkene **16**.

intermediates (*cf.* **18**) are isolated, suggesting the lifetime of this intermediate is very brief, presumably due to the stabilising interaction between the new radical SOMO and the α-nitrogen lone pair developing in the transition state (*cf.* Fig. 2).

4. Nitrogen-directed homoallylic radical rearrangements by tin-mediated reductions and application in the synthesis of kainoids

Having developed methodology for the formation of 7-substituted-2-azanorbornenes, we considered its potential as a key step in the synthesis of kainoids, a family of 2,3,4-trisubstituted pyrrolidine-based non-proteinogenic amino acids.[42] Such compounds exhibit potent neuroexcitory effects, and are potentially applicable in the treatment of Alzheimer's and other neurodegenerative diseases. They likely function biologically as conformationally-restricted forms of glutamic acid; some kainoids are shown in Fig. 3.

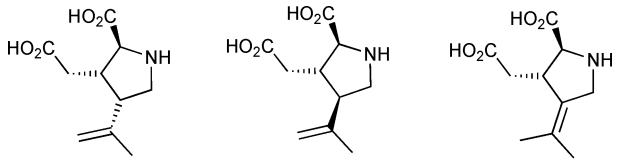
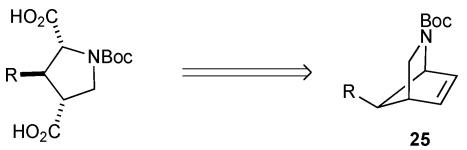


Fig. 3 Example kainoids.[42]

We considered that oxidative cleavage of a 7-substituted 2-azanorbornene **25** would give a pyrrolidine with the characteristic kainoid substitution pattern (Scheme 10).

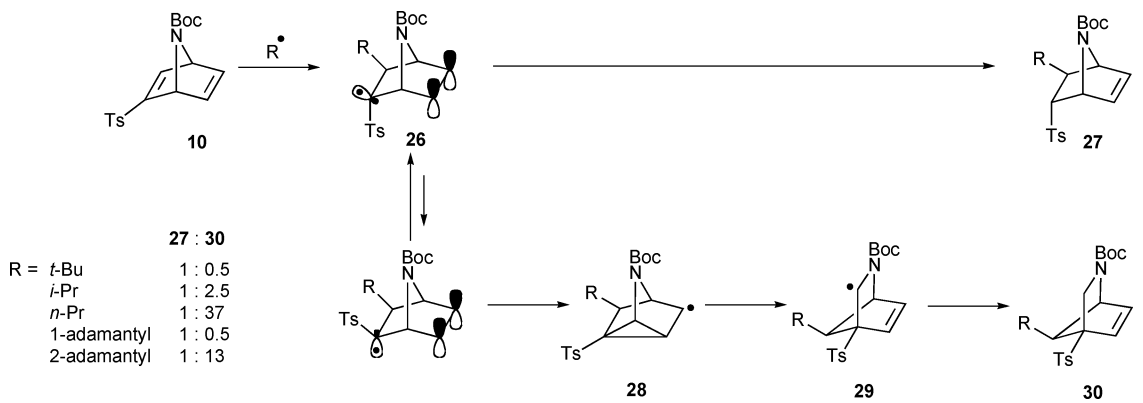


Scheme 10 2-Azanorbornenes as potential kainoid precursors.

Before commencing specifically-targeted kainoid syntheses, a series of model studies were undertaken to prove the viability of the proposed key step and to probe the scope of the reaction. Dienyl sulfone **10** was chosen as a substrate for these investigations because of its convenient (1 step) preparation and because resolution of the enantiomers has been demonstrated.[43] Unlike symmetrical 7-azanorbornadiene **21**, dienyl sulfone **10** has four different potential sites for radical addition, with the further possibility of *exo* or *endo* attack at each of these sites. There was also the possibility of the formation of direct addition or addition–rearrangement products: it was clear that a high degree of selectivity would need to be achieved in order for this reaction to be applied successfully in kainoid synthesis.

Initial attempts to add electrophilic radicals to **10** were disappointing, leading to complex mixtures in all cases. In contrast, nucleophilic radicals discriminated between the alkenes, favouring reaction at the more electron-deficient sulfonyl-substituted alkene. Reaction with *t*-butyl iodide led to a 2 : 1 mixture of unrearranged (**27**) and rearranged (**30**) adducts respectively, in an encouraging 83% combined yield (Scheme 11);[44] the product distribution presumably reflecting the stabilisation conferred upon the initially-formed radical by the presence of the α-tosyl group. Screening of other iodides with various steric demands showed radical addition to be efficient in all cases, with addition occurring exclusively to the *exo* face, however the ratio of unrearranged to rearranged products was found to be markedly dependent upon both the nature of the radical undergoing the addition. Tertiary radicals gave predominantly unrearranged products, secondary radicals gave mixtures whereas primary radicals gave almost exclusively the rearranged products.

Intrigued by the above trend in reactivity an azanortricyclic xanthate was synthesised[37,38,44] and deoxygenated with Bu_3SnH–AIBN to generate the putative intermediate azanortricyclyl radical **28** (Scheme 11 R = ^{t}Bu). Only 2-azanorbornene **30** (R = ^{t}Bu) was obtained from this reaction, suggesting that once the intermediate tricyclic radical is formed, the reaction proceeds only forwards to the 'rearranged' 2-azanorbornenyl radical and that the 'unrearranged' and 'rearranged' radicals are not in equilibrium. It follows, therefore, that the product ratio in additions to diene **10** is determined by the rate of formation of the tricyclic intermediate from the initially-formed adduct radical **26** (Scheme 11). Interestingly, the same product ratio was obtained from addition of the *t*-butyl radical and the 1-adamantyl radical. These species are sterically similar, but differ in their electronic nature because the 1-adamantyl group is unable to participate in hyperconjugative radical stabilisation.[45,46] From these latter observations it may be



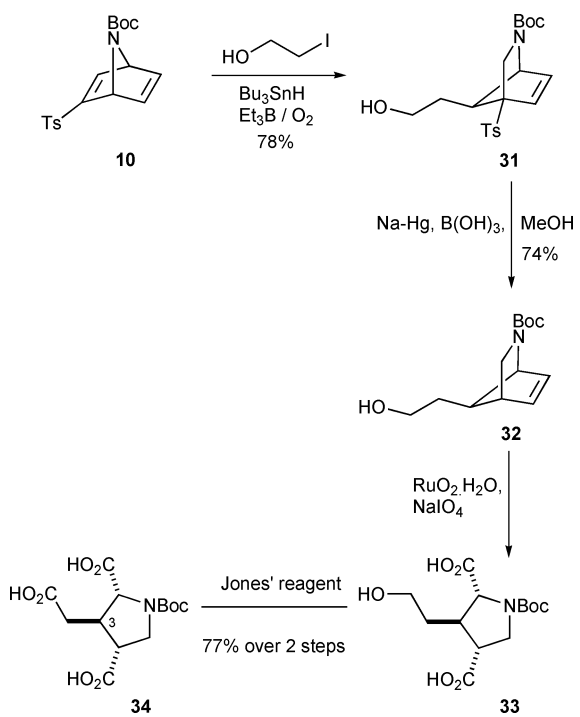
Scheme 11 Alkyl radical addition to cycloadduct **10**.

inferred that the origin of the selectivity is mainly due to the steric demand of the adding radical alkyl group.

Electronic effects are also likely to be important in determining the product distribution when the rigidity of the bicyclo[2.2.1] framework is taken into consideration. The initially formed radical **26** is likely to be of mainly sp^3 character, because the 120° bond angle required for sp^2 hybridisation cannot be accommodated.[47] The radical must therefore adopt either an *exo* or an *endo* conformation, as shown in Scheme 11. The *exo* radical is likely to be preferred, since steric interactions between the alkyl group and the sulfone are minimised, but this conformation does not permit orbital overlap with the alkene π-orbitals and prevents the formation of the tricyclic intermediate. Only when the radical is in the *endo* conformation can the overlap necessary for bond formation occur. Thus, a bulky tertiary alkyl group will make the formation of the tricyclic intermediate less favourable, whilst a less sterically demanding primary alkyl group will allow the intermediate to adopt the required conformation, giving access to **28** and then desired rearranged product **30**.

Having established that the desired alkyl-substituted rearranged products could be formed, attention turned to the synthesis of the kainoids. Our strategy was to introduce the carboxymethylene group at C-3 *via* reductive radical addition of 2-iodoethanol, followed by oxidation. Optimisation of the addition of 2-iodoethanol led to the conclusion that the reaction was most effectively performed at room temperature.

A first target was triacid **34** (Scheme 12), itself known to exhibit strong neuroexcitatory activity.[48] The rearrangement proceeded without difficulty when Bu_3SnH was employed as the radical reductant. The addition of a hydroxyethyl radical was found to occur exclusively at the *exo* face giving alcohol **31** (*cf.* the epimeric mixtures obtained by the addition of thiols and selenides) and only trace amounts of the adduct arising from simple addition across the sulfone-bearing double bond were recovered, implying that the putative α-radical from the initial addition is not significantly stabilised by the presence of the sulfone. Desulfonylation to **32** was effected by the use of 6% sodium amalgam with boric acid in refluxing methanol.[49] It was noted that when the latter was carried out on a mixture of rearranged and unrearranged sulfones (1 : 0.33) the quantity of 2-azabicycle produced from desulfonylation exceeded the quantity of 2-azabicyclic sulfone initially present. This fortuitous enhancement in yield presumably derives from the possibility of a radical generated during desulfonylation, as described in Section 3 (Scheme 7). Oxidative cleavage and a separate Jones′ oxidation of the primary alcohol **33** furnished the desired triacid **34**.[43,49]



Scheme 12 Synthesis of triacid **34**.

With this result in hand, a synthesis of α-kainic acid **23** was then developed, in 13 steps from rearranged azabicyclic alcohol **31** (Scheme 13).[44,50] Key features of the synthesis included Swern oxidation of the equilibrating mixture of lactols (**35** and **36**) following ozonolysis of azabicyclic alcohol **31**, which proceeded selectively *via* lactol **36**. Also, subsequent lactone methanolysis and carbonate formation provided fused bicyclic sulfone **37**, which underwent desulfonylation to generate the *cis* 3,4-disubstitution required for kainic acid **23** (Scheme 13).

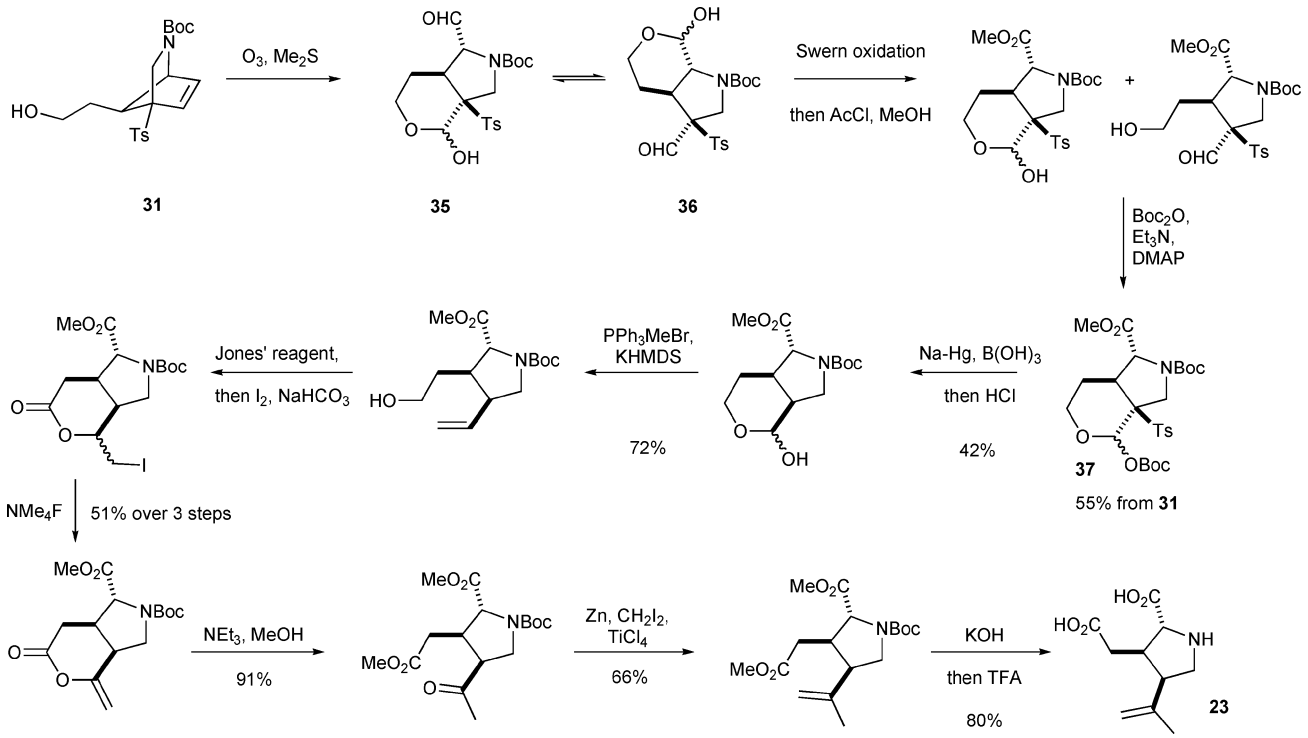
A modified form of intermediate **31** was then developed as a starting point for the synthesis of racemic α-isokainic acid **24** and α-dihydroallokainic acid **39** (Scheme 14).[44,51] The use of a sulfone bearing a $CClMe_2$ group, rather than the *p*Me-C_6H_4 group, provided the functionality required for a subsequent cascade oxidation–decarboxylative Ramberg–Bäcklund process, allowing direct introduction of the isopropylidene unit at C-4.

5. Nitrogen-directed homoallylic radical rearrangements by silane-mediated xanthate deoxygenation in 7-azabenzonorbornenes

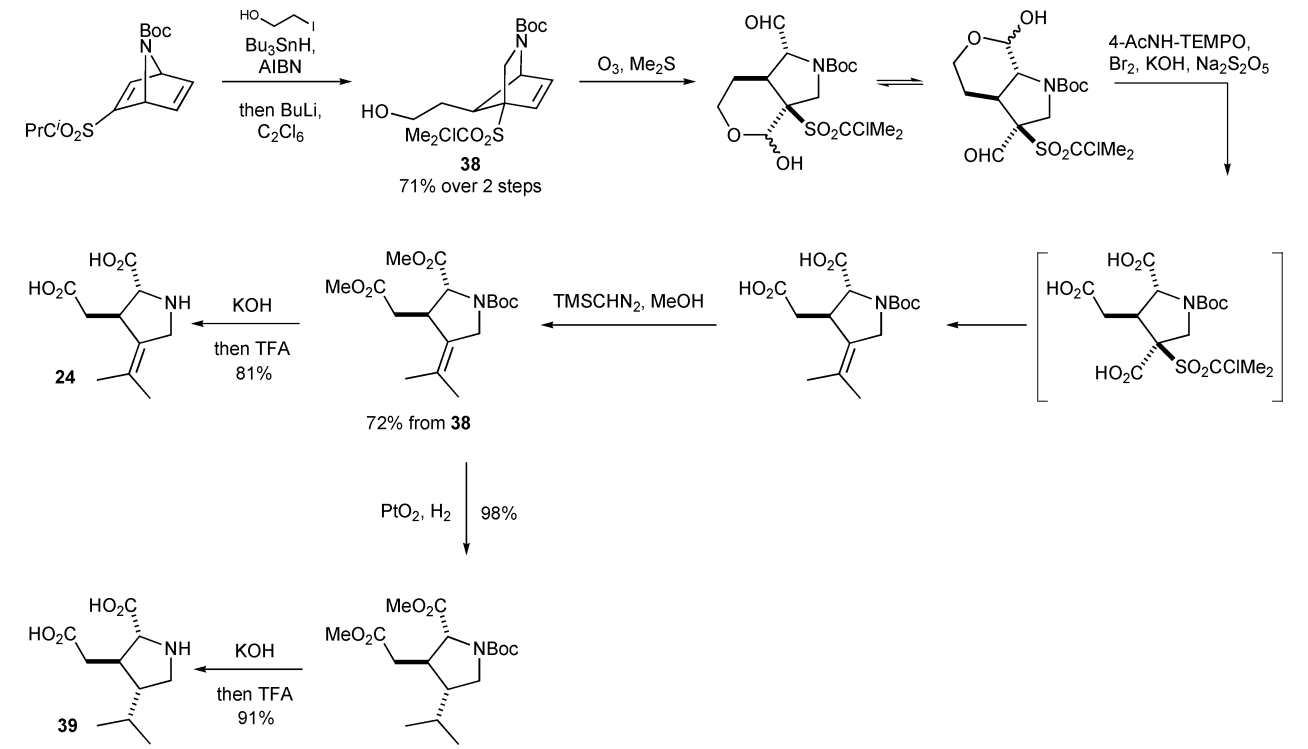
While radical rearrangements in norbornenes are well-documented, there are fewer reported rearrangements in benzonorbornadienes (*cf.* Scheme 3), presumably due to the energetic barrier to the disruption of aromaticity. However, 2-azabenzonorbornenes **41** are attractive synthetic targets *e.g.* as conformationally defined adrenergic agents,[52] and are synthetically challenging when approached from conventional routes. We considered that the radical rearrangement that we had developed in the norbornene system could be extended to the benzo-fused analogue, allowing access from the conveniently available[53,54] 7-azabenzonorbornadienes **40** (Scheme 15).

However, our first attempts to effect rearrangement by the addition of thiocresol to cycloadduct **40** were disappointing, resulting only in direct addition to the alkene. Hydroboration–oxidation, followed by Barton–McCombie deoxygenation[55] was considered to be an attractive alternative strategy, since hydroboration is known to proceed with high facial and regioselectivity in substituted alkenes,[56] and this method also offered the potential for desymmetrising the achiral 7-azabenzonorbornane system *via* asymmetric hydroboration–oxidation (*vide infra*).

Xanthate **42** was first prepared in 2 steps from cycloadduct **40**. Barton–McCombie deoxygenation mediated by Bu_3SnH (0.04 M

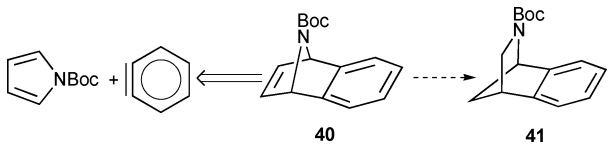


Scheme 13 Synthesis of kainic acid **23**.

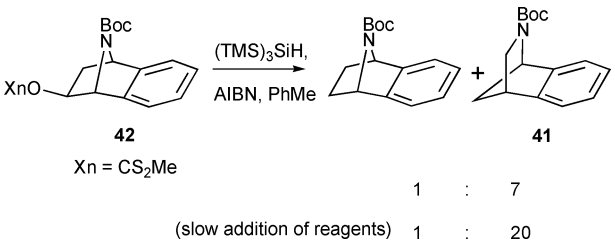


Scheme 14 Syntheses of α-isokainic acid **24** and α-dihydroallokainic acid **39**.

in xanthate **42**) gave a 3 : 1 mixture of rearranged and unrearranged azacycles and also chromatographic removal of tin residues was problematic. We reasoned that the formation of the putative cyclopropyl intermediate (*cf.* Scheme 3) would be a relatively slow process, and that extending the lifetime of the precursor radical should favour the rearrangement. To this end the reaction was repeated, but using the slower H-atom donor (and non-toxic) $(TMS)_3SiH$[57–59] which gave an improved 7 : 1 mixture of rearranged and unrearranged azacycles (Scheme 16). Further optimisation using a slow (syringe pump) addition of the silane and the initiator



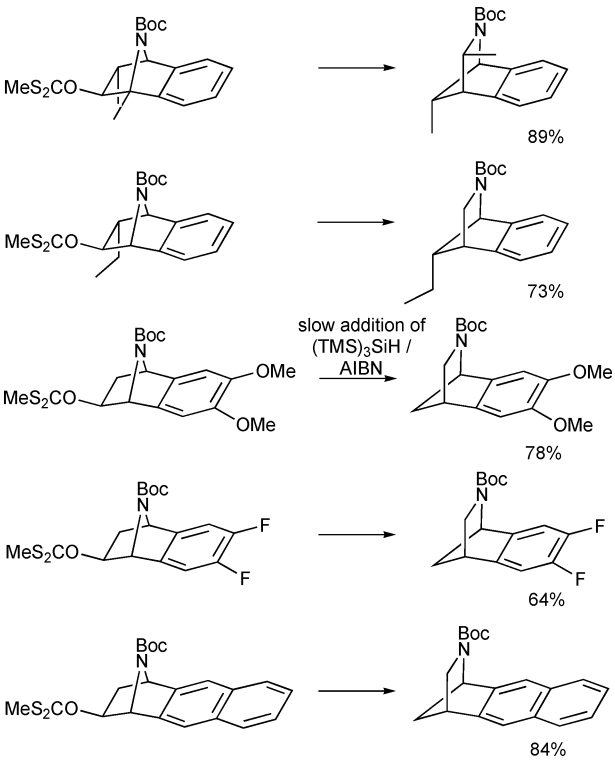
Scheme 15 2-Azabenzonorbornenes from 7-azabenzonorbornenes.



Scheme 16 Tandem deoxygenation–rearrangement–reduction of benzo–fused azacyclic xanthate **42**.

led to a 90% isolated yield of rearranged–reduced azacycle **41**, with only ~5% of the unrearranged product.

With these results in hand, we were interested in the effects of substitution at both the azabicyclo[2.2.1] framework and at the aromatic ring. More substituted xanthates were prepared and deoxygenation was performed with slow addition as before (Scheme 17). NOESY NMR experiments demonstrated that H-atom transfer from $(TMS)_3SiH$ to the rearranged intermediate occurred exclusively from the *exo* face, leading to a single product diastereomer, and that the 7-alkyl substituents are *anti* with respect to the nitrogen atom in the rearranged product.[40c]



Scheme 17 Deoxygenation–rearrangement–reduction of more substituted 7-azabenzonorbornenyl xanthates.

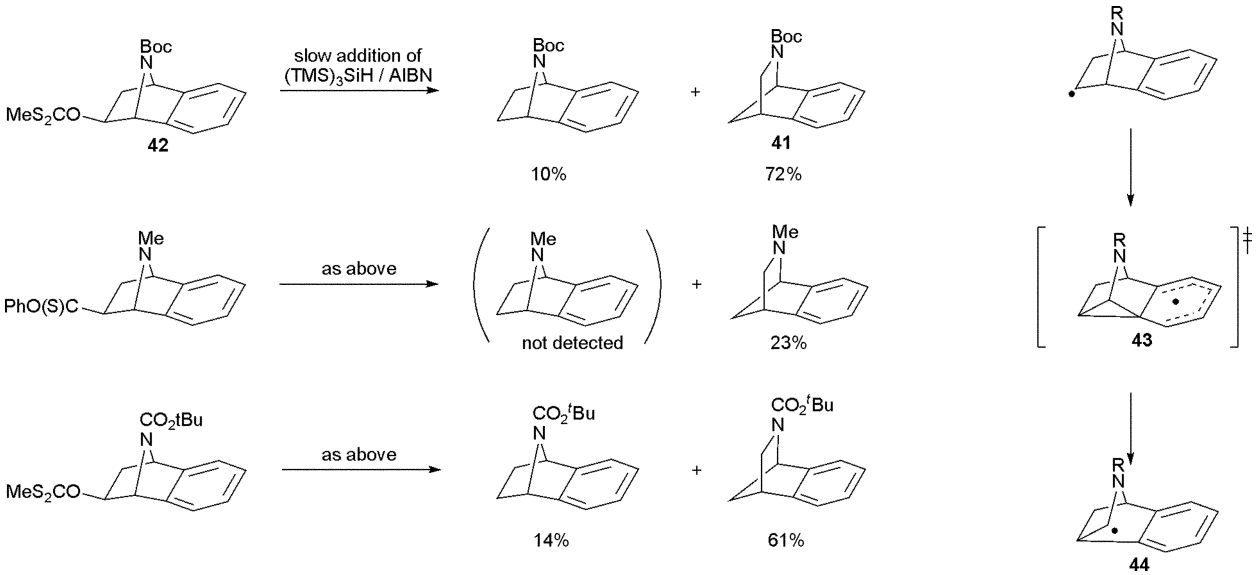
Having demonstrated a wider reaction scope, we wanted to try to understand more of the mechanistic detail: in particular we wished to investigate the driving force for the reaction. Variation of the exocyclic *N*-substituent gave the results shown in Scheme 18.

These results suggest that in systems where the nitrogen lone pair is less available due to amide resonance, there is a lesser driving force for rearrangement, supporting the previous suggestion that interaction between the *N*-lone-pair and the radical SOMO is the key effect. The observation that variation of the exocyclic *N*-substituent affects the rate of the rearrangement also has implications for understanding the nature of the intermediates in the reaction and the detail of the reaction profile. The fact that the electronic structure of the final radical **44** has an effect upon the rate of reaction, coupled with the postulate that ring-opening of a benzonortricyclyl radical is unlikely to be rate-limiting,[60] suggests that **43** is a transition state, rather than a discrete intermediate (Scheme 18). With this in mind, it is possible to estimate the rate of the rearrangement based upon the rate of hydrogen atom transfer from $(TMS)_3SiH$ to a secondary alkyl radical, for which the Arrhenius function has been derived by Chatgilialoglu *et al*.[61] For reaction in refluxing toluene, the second order rate constant is calculated to be approximately 7×10^5 dm^3 mol^{-1} s^{-1}. Reduction of xanthate **42** using $(TMS)_3SiH$ at an initial concentration of 0.12 M gave approximately equal amounts of rearranged and directly reduced products, suggesting that the rate of rearrangement is, within an order of magnitude, equal to the rate of hydrogen atom transfer—*i.e.* the rate of rearrangement is approximately 10^5 s^{-1}.

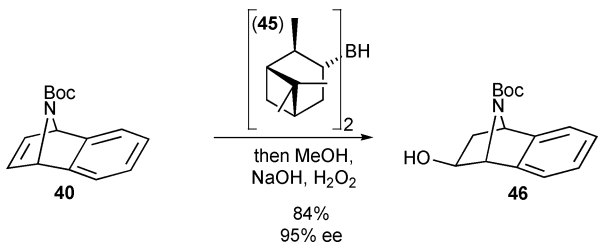
Having developed the deoxygenation–rearrangement method for the preparation of 2-azabenzonorbornanes, our attention turned to developing an asymmetric access. Initial efforts to perform rhodium-catalysed asymmetric hydroboration–oxidation[62] did not give ees at a synthetically useful level,[63] however stoichiometric hydroboration–oxidation with (−)-diisopinocampheylborane [(−)-Ipc_2BH], **45** followed by oxidative workup gave alcohol **46** in 84% yield and 95% ee (Scheme 19).[64] This method was found to be applicable to representative members of the other more substituted 7-azabenzonorbornadienes, with good yields and excellent ees. The absolute sense of asymmetric induction was confirmed in the case of 2-azabenzonorbornadiene **41** by chemical correlation[64] and the others were assigned by analogy.

Having developed an asymmetric entry into the 2-azabenzonorbornenes, we investigated whether the more nucleophilic character of the rearranged radical (*cf.* Fig. 2) could be exploited in electrophile trapping in tandem with the deoxygenation–rearrangement. The optimised conditions for deoxygenation–rearrangement [slow addition of $(TMS)_3SiH$ and AIBN to a solution of xanthate in refluxing toluene] closely matched those developed for deoxygenation–direct electrophile trapping by Chatgilialoglu *et al.*,[57] and we were pleased to find that by including an electrophile, the rearranged-trapped products **47** could be isolated in good yields for a range of electron-deficient alkenes (Scheme 20).

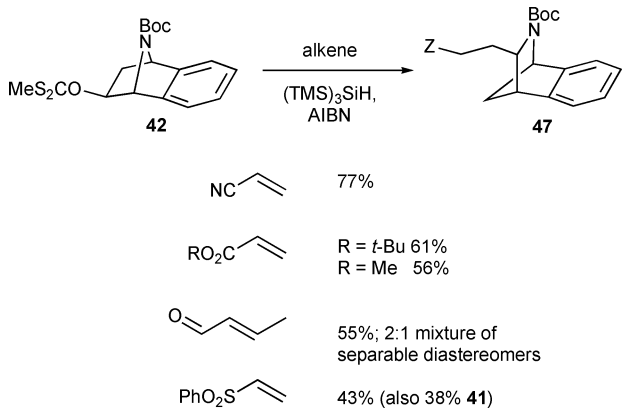
With phenyl vinyl sulfone, a roughly 1 : 1 mixture of reduced and trapped rearranged azacycles was obtained, suggesting that for this electrophile the rate of addition to radical **44** (R = Boc) is approximately equal to that of hydrogen atom transfer from $(TMS)_3SiH$. Less electron-deficient alkenes, such as *N*,*N*-dimethyl acrylamide and acrolein diethyl acetal returned only rearranged reduced azacycle **41**.



Scheme 18 Effect of varying the exocyclic *N*-substituent.



Scheme 19 Asymmetric hydroboration–oxidation of **40** by (−)-Ipc$_2$BH.



Scheme 20 Preparation of 3-substituted 2-azabenzonorbornenes by rearrangement–electrophile trapping.

When the deoxygenation–rearrangement–electrophile trapping reaction was investigated with the xanthates derived from the more substituted alcohols, we found that the desired reactions occurred, but were followed by isomerisation to pharmaceutically relevant[65] aminomethyl indenes, presumably *via* trace acid-catalysed ring-opening (Scheme 21).

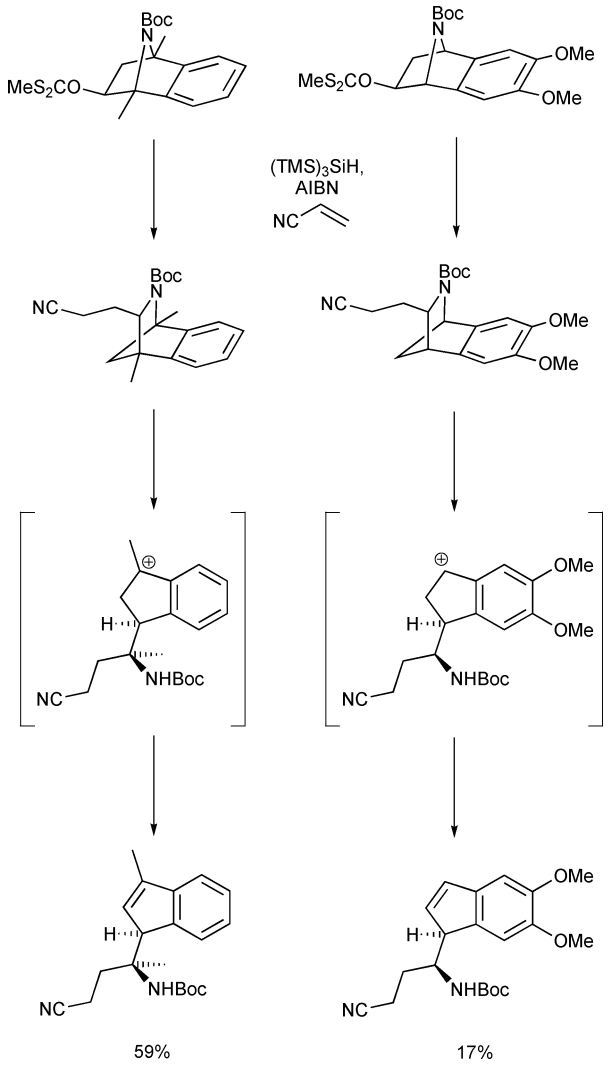
6. Nitrogen-directed homoallylic radical rearrangements in the 8-azabicyclo[3.2.1]octane system

Prior to commencing our studies with azabicyclo[2.2.1] systems (Section 2), we had noted that a related homoallylic radical rearrangement had been reported by Rigby and Pigge in an 8-azabicyclo[3.2.1]octane system, where a 6-azabicyclo[3.2.1]octane was detected as a minor byproduct of a radical decarboxylation reaction.[31] In this latter chemistry, photochemically-induced decomposition of a pyridine-2-thione-*N*-oxycarbonyl (PTOC) ester **48** generates radical **50**, which is postulated to undergo transannular cyclisation to **51**, followed by ring-opening to radical **52** (Scheme 22). Optimisation studies allowed isolation of rearranged product **49**, in 42% yield.

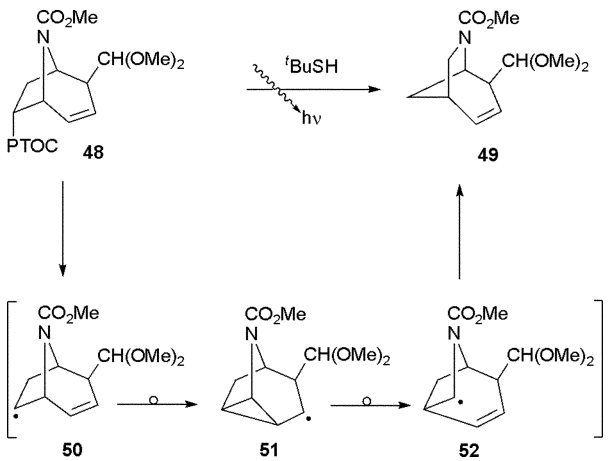
Furthermore, it has been demonstrated that the capto effect of carbonyl groups can direct homoallylic radical rearrangements in bicyclo[2.2.2] systems. Markó and co-workers have shown that radical-mediated skeletal rearrangements can occur in bicyclo[2.2.2]octenone **53**[66,67] and applied this to the synthesis of Corey's lactone, by subsequent acid-catalysed rearrangement of bicyclic lactone **54** (Scheme 23). This system has also found application in the synthesis of oxatriquinanes.[68]

This precedent, in combination with the understanding we had accrued from our own studies in bicyclo[2.2.1] systems, led us to consider the application of nitrogen-directed homoallylic radical rearrangement to the synthesis of isoquinuclidine-containing alkaloids. The isoquinuclidines (2-azabicyclo[2.2.2]octanes) are found in several bioactive natural products, such as (+)-ibogamine (**55**, Scheme 24).[69,70] Furthermore, the isoquinuclidine framework is employed in medicinal chemistry as a rigid azabicyclic scaffold.[71]

We reasoned that a nitrogen-directed homoallylic radical rearrangement reaction could be used as a key step in the preparation of (+)-ibogamine (**55**),[72] with enantioselective desymmetrisation[73] of the readily-available tropenone **56** allowing an asymmetric access (Scheme 24).

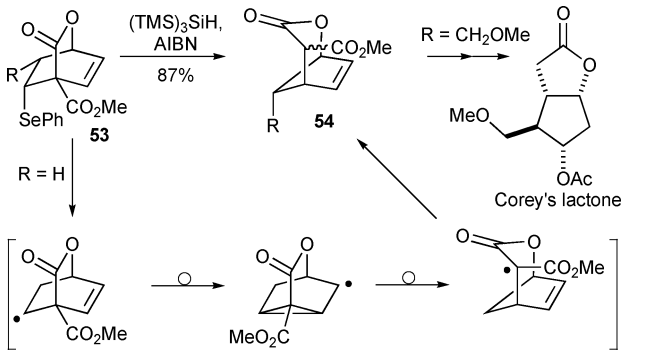


Scheme 21 Tandem deoxygenation–rearrangement–electrophile trapping followed by trace acid-catalysed ring-opening to aminomethylindenes.

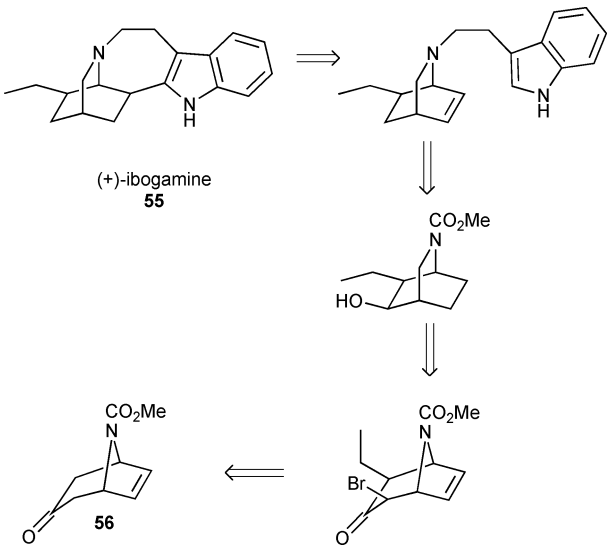


Scheme 22 Radical decarboxylation–rearrangement–reduction in an 8-azabicyclo[3.2.1]system.[30]

Achiral tropinone precursor **56** was made *via* cycloaddition of commercially available *N*-(carbomethoxy)pyrrole and 1,1,3,3-tetrabromoacetone (Scheme 25).[74] Desymmetrisation was



Scheme 23 Homoallylic radical rearrangement in a bicyclo[2.2.2]-octenone.[67]

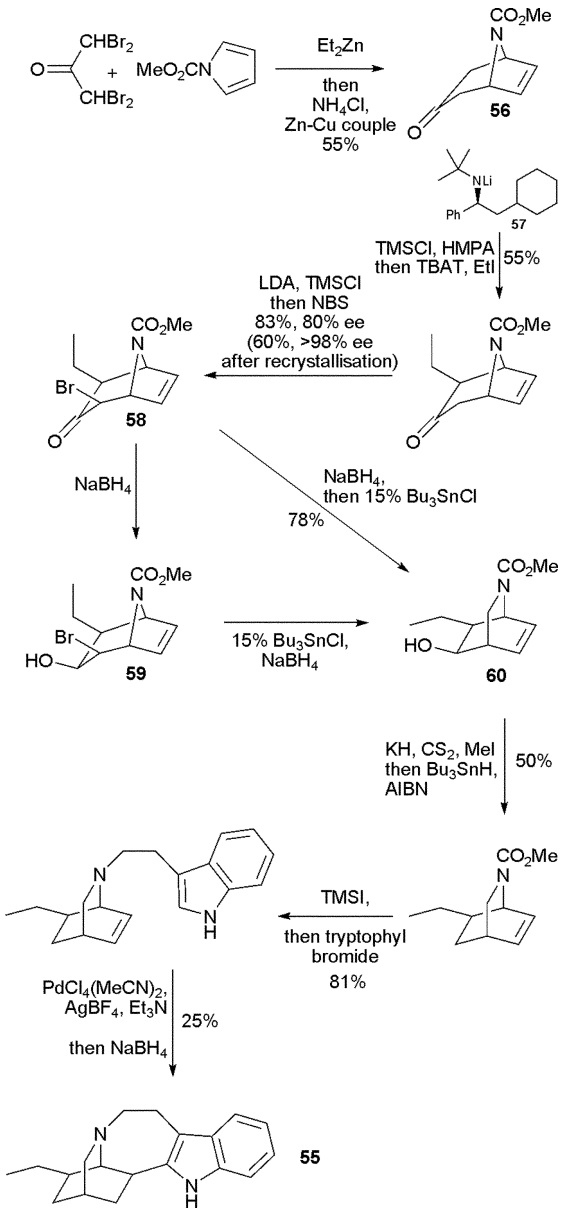


Scheme 24 Homoallylic radical rearrangement strategy for the synthesis of (+)-ibogamine **55**.

achieved in 80% yield and 80% ee using chiral lithium amide **57** and, after incorporation of bromo and ethyl substituents, the resulting radical precursor **58** was subjected to our previously developed radical rearrangement conditions.[40,44] Disappointingly, these conditions did not effect the desired rearrangement. We postulated that the radical initially formed by abstraction of the bromine atom might be stabilised with respect to rearrangement by the capto effect of the α-carbonyl group. Both deoxygenation and acetal protection of the carbonyl proved to be unsuccessful, but careful reduction to bromohydrin **59**, followed by treatment with $NaBH_4$, 15% Bu_3SnCl and AIBN as an initiator in ethanol at reflux gave the desired rearranged alcohol **60**. Furthermore, we were pleased to discover that these reactions could be combined in a one pot procedure to give rearranged alcohol **60** directly. Subsequent Barton deoxygenation[55] of the alcohol, followed by deprotection, coupling with tryptophyl bromide and cyclisation under Trost's conditions[75] gave (+)-ibogamine **55** (Scheme 25).

Conclusions

Radical induced skeletal reorganisation by homoallylic rearrangement in readily assembled bridged azabicyclic systems has been demonstrated to be a synthetically useful protocol for accessing



Scheme 25 Synthesis of (+)-ibogamine **55**.

2-azabicyclo[2.2.1]hept-5-enes, 2-azabenzonorbornanes and 2-azabicyclo[2.2.2]oct-5-enes, containing substitution patterns not otherwise easily attainable. Especially noteworthy, because of the convergency and associated rapid generation of molecular complexity, are the processes developed involving tandem intermolecular radical addition followed by homoallylic rearrangement, and homoallylic rearrangement followed by intermolecular radical trapping. A guiding principle in the rearrangement chemistry is the likely stability engendered by placement of the final, product forming radical adjacent to nitrogen. The strategy has been exemplified in the synthesis of a variety of bioactive unnatural and natural products.

In this research area, progress can be envisioned in: demonstrations of the principle with other azacyclic systems, the use of other guiding heteroatoms, the development of strategically different (and more benign) ways of radical generation prior to rearrangement and radical manipulation post rearrangement, and further applications towards targets of specific interest.

Acknowledgements

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