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Development of two processes for the synthesis of bridged azabicyclic systems: intermolecular radical addition–homoallylic rearrangements leading to 2-azanorborn-5-enes and neophyl-type radical rearrangements to 2-azabenzonorbornanes† ‡

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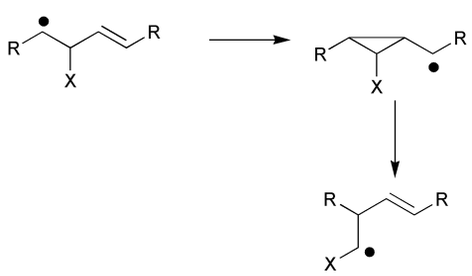
Radical thiol additions to 7-azanorbornadienes give 7-thio-substituted 2-azanorbornenes and Barton deoxygenations of 7-azabenzonorbornanols give 2-azabenzonorbornanes. The processes both involve novel nitrogen-directed radical rearrangements. The kinetics and mechanisms of the reactions are also discussed.

Introduction

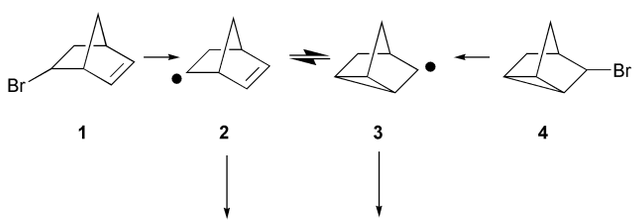
Azabicyclic systems are ubiquitous in natural products and pharmaceutical agents.[1] New processes for their construction are therefore of continuing synthetic interest. Radical cyclisations and rearrangements are potentially among the most powerful methods for the synthesis of such polycycles.[2–4] Homoallylic radical rearrangements, such as in the cyclopropylmethyl-homoallyl system (Scheme 1) have been the subject of considerable mechanistic study,[5] but their application to synthesis has yet to be widely exploited.[6]



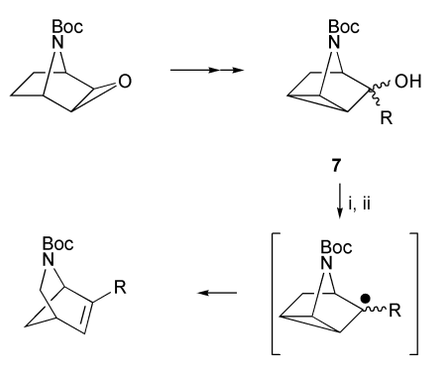
Scheme 1

Following reports that these processes could be directed by substitution α to the radical centre (*e.g.* group X, Scheme 1),[7–9] we decided to investigate the possibility that a nitrogen atom could be used in this way,[7] allowing access to otherwise synthetically challenging azacycles. Radical reduction of norbornenyl bromide **1** or nortricyclyl bromide **4** is known to produce the same (~60 : 40) mixture of norbornene **5** and nortricyclene **6** (Scheme 2).[10,11] However, during the development of novel analgesics related to epibatidine by a strategy involving indirect skeletal interconversion of 7-aza- to 2-azabicyclo[2.2.1]heptyl ring systems, we reported that radical deoxygenation of azanortricyclanol **7** delivers a single product **8**, even when R is potentially radical stabilising (*e.g.* Ar, Scheme 3).[12,13]

Given this demonstration of 'nitrogen-directed' radical rearrangement, we considered that a synthetically attractive



Scheme 2



Scheme 3 *Reagents and conditions*: i, $ClCOCO_2Me$, DMAP, MeCN, 25 °C, 30 min; ii, Bu_3SnH, AIBN, toluene, 100 °C, 45 min.

direct skeletal interconversion might be possible by intermolecular radical addition–homoallylic radical rearrangement (Scheme 4). This would provide convergent access to synthetically important 2-azabicyclo[2.2.1]heptyl ring systems containing substitution not easily available by other methods.[1] We also considered that the rearrangement could be applicable to the synthesis of a variety of other azabicyclic ring systems. Herein we report a full account of our results concerning the development of nitrogen-directed free radical rearrangements.[14,15]

Results and discussion

Radical additions to norbornadiene **12** and its derivatives, using thiols for example, have been well-studied and usually result in substituted nortricyclanes as the major products.[16] Consistent

† This is one of a number of contributions from the current members of the Dyson Perrins Laboratory to mark the end of almost 90 years of organic chemistry research in that building, as all its current academic staff move across South Parks Road to a new purpose-built laboratory.

‡ Electronic supplementary information (ESI) available: the preparation and characterisation of compounds **20b–i**, **28c–g**, **30b–g**, **30i**, **32e–g**, **32i**, **33b–g**. See http//www.rsc.org/suppdata/ob/b3/b306717n/

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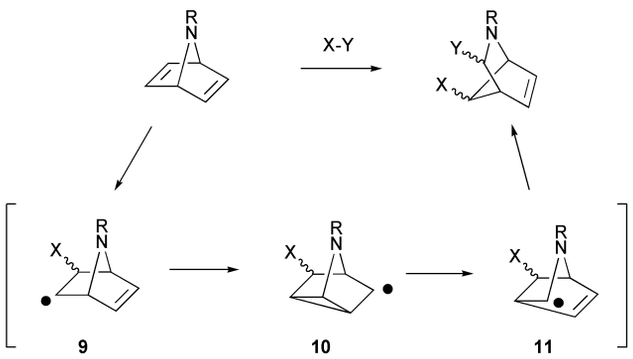
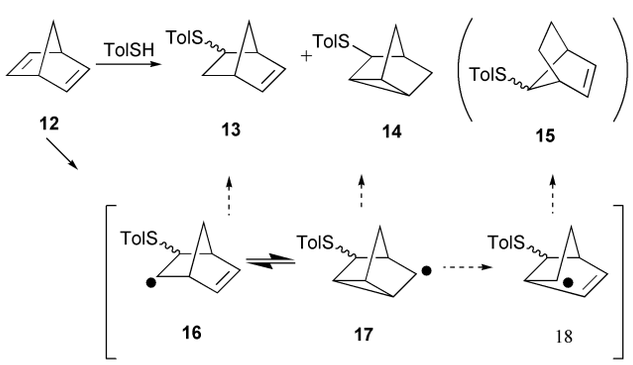
Table 1 Relative proportions of **13** and **14** formed from addition of *p*-thiocresol to norbornadiene **12** at varying concentrations[a]

$[Thiol]_{initial}$/mol dm^{-3}	^{1}H NMR ratio[b] **13**[c] : **14**
5.0 (neat)	40 : 60
2.0	26 : 74
1.0	17 : 83
0.1	14 : 86

[a] The appropriate concentration of *p*-thiocresol was added to a solution of **12** in toluene in one portion at 25 °C. [b] Average of two runs. [c] *exo* : *endo* ratio of sulfides **13** was 5 : 1.



Scheme 4



Scheme 5

with these earlier studies, we found that addition of *p*-thiocresol to norbornadiene **12** at 25 °C led to a mixture of nortricyclyl sulfide **14** and bicyclic sulfide **13**[17,18] (Scheme 5, Table 1).

Further experiments at increasing dilution indicated that the product ratio reached a constant level (within experimental error, **13** : **14**, ~ 1 : 6), once the concentration of each reactant was <0.1 mol dm^{-3}. These latter results indicate attainment of equilibrium between the substituted norbornenyl and nortricyclyl radicals **16** and **17**.

The ratio of norbornenes : nortricyclane products in this case differs significantly from that obtained from generation of the unsubstituted radicals, where a 60 : 40 ratio in favour of norbornene is obtained at various concentrations.[10,11] This difference in behaviour requires an explanation. Given that no 7-substituted norbornenes **15** derived from radical **18** are produced in the thiol additions, then, one possibility is that ring-opening of nortricyclyl radical **17** produces only norbornenyl radical **16**. Wong and Griller, however, were able to detect 7-substituted radicals in EPR studies on the addition of *tert*-butoxyl to norbornadiene,[19] which suggests that ring opening of nortricyclyl radicals such as **17** to 7-substituted norbornenyl radicals is not prevented stereoelectronically. An alternative explanation is that the ring opening of **17** leading to **16** is promoted by a radical stabilising effect of the sulfur substituent *β* to the radical centre. A sulfur-bridged intermediate is thought to be unlikely in similar bicyclic systems,[20] but it is possible that

Table 2 Thiol additions to 7-azabicyclo[2.2.1]heptadiene **19a**

Entry	R	*T*f/°C	*t*/h	Yield (%)	*syn*-**20** : *anti*-**20**
a	Tol[a]	20	24	92	3 : 1
b	Ph	20	24	92	4 : 1
c	2,6-$DiMeC_6H_3$	20	24	90	4 : 1
d	4-$NO_2C_6H_4$	20	72	50	7 : 1
e	4-$MeOC_6H_4$	20	24	59	2.5 : 1
f	Bu^n	80	6	59	2 : 1
g	Bu^t	80	24	48	5 : 1
h	$HO(CH_2)_3$	80	14	56	4 : 1

[a] TolSH with **19b** (PG = CO_2Me) at 20 °C for 4 h gave **20i** (R = Tol, PG = CO_2Me) in 66% yield (*syn* : *anti*, 4 : 1).

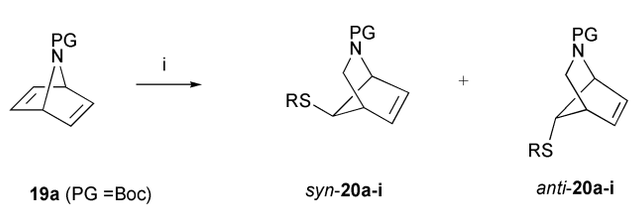
an interaction between the SOMO and the adjacent C–S *σ* or *σ** orbitals confers stability on radical **16**, which drives the cyclopropane ring opening leading to its formation. Such an interaction would clearly not be possible in radical **18**, and furthermore *exo*-approach of the H-atom donor would be hindered by the presence of the 7-tolylthio group which would lie predominantly *syn* to the radical centre.

If the rates of H-atom transfer to **16** and **17** were assumed to be equal, the product ratio would be a direct reflection of the **16**–**17** equilibrium position, but there does not seem to be any evidence to support this assumption. Indeed, it has been argued that norbornenyl radicals react more rapidly with certain H-atom donors than do nortricyclyl radicals, and that the radical equilibrium **2**–**3** favours **3**, even though more product from the reduction of **2** is actually isolated.[21] Our results suggest a difference in the rate of H-atom transfer from *p*-thiocresol to **16** and **17**. If radical **16** is stabilised, as we have suggested above, and the rates of H-atom transfer to **16** and **17** were equal, the ratio of products **13** : **14** would be greater than the ratio **5** : **6**, since radical **2** cannot be subject to the same stabilising interaction as **16**. However, this analysis contradicts the experimental results. Attack of the thiyl radical on norbornadiene is known to occur predominantly from the *exo* face,[22] and given the results of Davies *et al.*,[23] approach of the H-atom donor (another molecule of *p*-thiocresol) would be expected to occur from the same face. For this reason, the rate of H-atom transfer to radical **16** could conceivably be slower than that to **17**, as the approach of the thiol would be subject to steric interactions with the *β*-thio substituent. It is therefore likely that proportionately more of **17** would be trapped than **16**, so that the ratio **13** : **14** does not reflect the **16**–**17** equilibrium position.

This analysis thus provides a plausible explanation for both the absence of sulfide **15** in the addition of *p*-thiocresol to norbornadiene *and* the differing ratios of bicyclic and tricyclic products obtained from equilibria of substituted and unsubstituted norbornenyl and nortricyclyl radicals.

By comparison to the reactions of norbornadiene with thiols, the corresponding 7-aza systems such as **19a** and **19b** (available in two steps from alkoxycarbonyl-protected pyrrole and tosylethyne)[24] behave in dramatically different fashion (Scheme 6, Table 2), but in accord with the earlier analysis (Scheme 4).

Pleasingly, both aromatic and aliphatic thiols were found to react cleanly with only a slight excess (1.1 equiv.) of azadiene **19a** or **19b** in benzene or toluene (0.1 mol dm^{-3}) to give

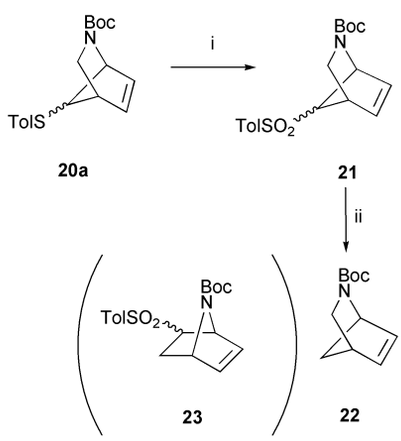


19a (PG =Boc)
19b (PG = CO_2Me)
syn-**20a-i**
anti-**20a-i**

Scheme 6 *Reagents and conditions*: i, RSH (0.9 equiv.), benzene or toluene, 20 °C (R = aryl) or 80 °C (R = alkyl), 6–72 h.

rearranged sulfides **20a**–**i** in 6–72 h, depending on the reactivity of the thiol. In the case of the less reactive aliphatic thiols, heat was required for completion of the reaction in a satisfactory time. Aliphatic thiols are considerably poorer H-atom transfer agents than their aromatic counterparts.[25] This may explain the lower yields in these cases, as polymerisation could compete with atom transfer. The major diastereoisomer of **20a** in the reaction with *p*-thiocresol was shown by NOE analysis to be the *syn*-isomer arising from initial *exo*-attack of the thiyl radical on azadiene **19a**, and the predominant isomer obtained with the other thiols is assigned as *syn* by analogy. Selectivity for *exo*-attack was modest, which is consistent with formation of a long C–S bond *via* a transition state whose energy is not greatly affected by the steric bulk of the reacting partners. However, a more hindered thiol, such as *tert*-butylthiol, shows higher selectivity than the straight chain examples (entries **f**–**h**). This suggests *exo*-attack is indeed less hindered, but the highest selectivity was observed in the case of *p*-nitrothiophenol. The *p*-nitrophenylthiyl radical is subject to greater delocalisation than the other aromatic thiyl radicals, thereby increasing its relative stability. This suggests that the *p*-nitrophenylthiyl radical addition to **19a** is less exothermic than in the other examples, resulting in a later transition state and greater selectivity for the comparatively less hindered *exo* attack.

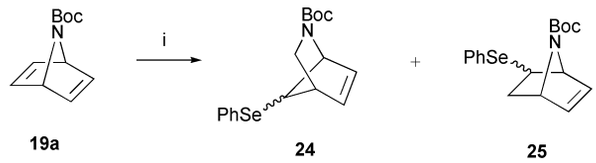
Evidence that the product sulfides **20** possess the rearranged 2-azabicyclo[2.2.1]hept-5-ene framework is that oxidation of **20a** (R = Tol) using buffered peracetic acid gave in 91% yield the epimeric sulfones **21** (Scheme 7) with spectral data distinctly different from the sulfones **23**[26] that would be obtained from oxidation of the product of simple thiol addition across one double bond in azadiene **19a**. Subsequent desulfonylation of sulfones **21** with 6% sodium-amalgam gave the known 2-azabicyclic alkene **22**[12,13,27] in 33% yield as the only identifiable product (Scheme 7).



Scheme 7 *Reagents and conditions*: i, CH_3CO_3H, NaOAc, CH_2Cl_2, 0 °C, 6 h, then 20 °C, 14 h; ii, Na–Hg, NaH_2PO_4, Na_2HPO_4, MeOH, 25 °C, 12 h.

Benzeneselenol shows similar behaviour with unsaturated systems to aromatic thiols, but is an order of magnitude superior as an H-atom transfer agent.[25] Under otherwise identical conditions to the earlier reactions of aromatic thiols (Table 2), it was found that the reaction of benzeneselenol with azadiene **19a** gives a small proportion (12%) of the selenide **25** arising from simple addition across one double bond, as well as the expected rearranged selenide **24** (81%, Scheme 8).

Interestingly, the epimeric ratio of selenides **25** (*exo* : *endo* 1 : 6) was found to be different from the epimeric ratio of rearranged selenides **24** (*syn* : *anti* 3 : 1), as determined by a NOESY experiment. This could be explained if the rate of H-atom transfer to *endo*-phenylselenyl radical **27** is faster than that to *exo*-phenylselenyl radical **26** for steric reasons (Fig. 1). From the yields and epimeric ratios of products **24** and **25** we



Scheme 8 *Reagents and conditions*: i, PhSeH (0.9 equiv.), benzene, 25 °C. 24 h.

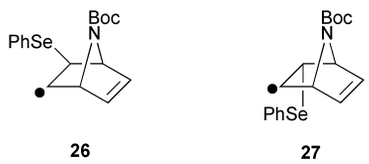


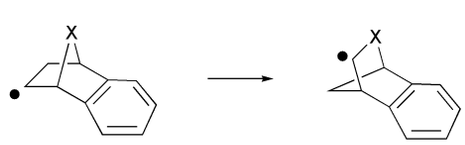
Fig. 1

can estimate that the true ratio of *exo*/*endo* attack is approximately 2 : 1, [28] lower than for the addition of thiophenol. This may reflect greater d-orbital interactions between the selenium atom and the π-orbital lobes which converge on the *endo* face of the diene and therefore increase the propensity for *endo*-attack compared to the thiols.[16]

The combined results of the thiol and selenol additions to **19a** allow an estimation of the rate constant for the rearrangement **9** ⟶ **11** (Scheme 4). No products other than the 2-azabicyclic epimers **20** are observed in the addition of aromatic thiols. This suggests that the rate constant for the rearrangement is at least one order of magnitude faster than the initial rate of H-atom transfer from such thiols. Therefore an initial thiol concentration of 0.1 mol dm^{-3} (typical in our studies) and an approximate second order rate constant for H-atom transfer of 10^8 dm^3 mol^{-1} s^{-1},[25] indicate a rate constant of at least 10^8 s^{-1} for the rearrangement at 25 °C. The isolation of small amounts of unrearranged selenides **25** in the selenol addition suggests that the rate of rearrangement cannot be more than one order of magnitude faster than H-atom transfer from benzeneselenol. A second order H-atom transfer rate constant of 10^9 dm^3 mol^{-1} s^{-1},[25] and a selenol concentration of 0.1 mol dm^{-3} indicate an upper limit for the rate constant of 10^9 s^{-1} at 25 °C.

The absence of tricyclic products in any of the reactions with azadienes **19** suggests that the lifetime of the azatricyclic intermediate **10** is much shorter than that for either of the bicyclic intermediates **9** and **11** (Scheme 4). In kinetic studies of the nortricyclyl–norbornenyl radical rearrangement [**2** and **3**, Scheme 2], the rates of ring opening and ring closure have been shown to be similar: ~10^7 s^{-1} at 25 °C.[19] In the azabicyclic system, however, it seems probable that the ring opening step (**10** ⟶ **11**) is significantly faster, with the transition state being lowered in energy by the stabilisation of the developing radical α to nitrogen.[29,30] Rate constants for the ring opening of cyclopropylmethyl radicals to but-3-enyl radicals are known to be strongly influenced by substitution.[5]

Having demonstrated that nitrogen-directed homoallylic radical rearrangement was a viable method for the synthesis of azacycles, we next considered extending its application to a related process—radical aryl migration. Compared with radical rearrangements in norbornenyl systems, neophyl-type rearrangements (1,2-shift of an aryl group, Scheme 9, X = CH_2) in the corresponding benzofused systems are much rarer.[31] This applies both to free radical additions to benzonorbornadiene and to H-atom abstraction from benzonorbornane.[32–34] Indeed, many additions to benzonorbornadiene were found to proceed

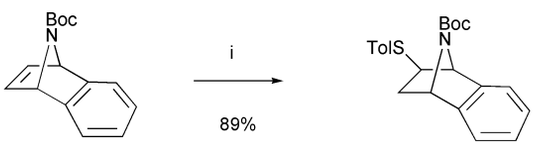


Scheme 9

without any rearrangement. This is presumably due to the comparatively unfavourable disruption of aromaticity.[35]

These early observations, together with our more recent studies (*vide supra*), suggested that extending the 'aza homo-allylic rearrangement' process to 7-azabenzonorbornyl systems (Scheme 9, X = NR) would be challenging, but could provide an attractive entry to 2-azabenzonorbornanes.[36] The latter systems are of interest, for example as conformationally defined adrenergic agents.[37]

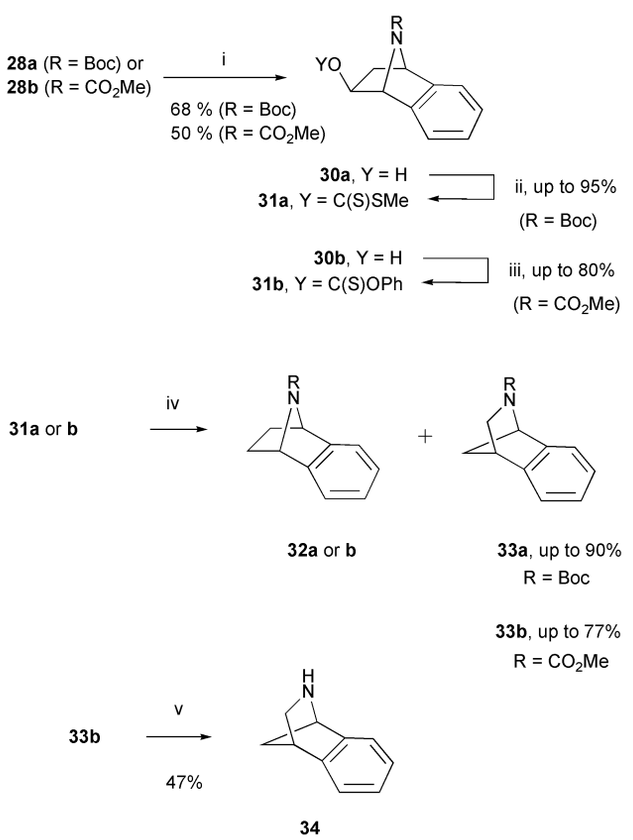
7-Azabenzonorbornadienes (*e.g.* **28a**, Scheme 10) were considered to be excellent substrates to examine the chemistry in Scheme 9 (X = NR), since they are readily available *via* aryne cycloadditions[38] to pyrroles.[39] However, radical addition of *p*-thiocresol to **28a**[40] gave only simple addition to the double bond, without any rearrangement, to give **29** (Scheme 10), solely as the *exo*-isomer.



28a **29**

Scheme 10 *Reagents and conditions*: i, TolSH, toluene, 25 °C, 24 h.

Therefore, hydroboration of **28a** followed by oxidation to the alcohol and then Barton deoxygenation was thought an attractive alternative method for radical generation, since hydroboration is known to proceed with good facial and regio-selectivity in substituted alkenes,[41] and the rate of H-atom transfer would be slowed relative to a thiol.[25] Hydroboration–oxidation of **28a** gave alcohol **30a** as a single isomer (Scheme 11) in satisfactory yield (68%), assigned as the *exo*-product in accordance with previous work.[42] Formation of xanthate



Scheme 11 *Reagents and conditions*: i, 9-BBN, THF, 25 °C, 24 h; ii, KH, CS_2, MeI, THF, 0–25 °C, 90 min; iii, PhOC(S)Cl, DMAP, CH_2Cl_2, 25 °C, 18 h; iv, TTMSS, AIBN, toluene, reflux, 2 h; v, KOH, ethylene glycol–water, reflux, 14 h.

31a then proceeded smoothly in excellent yield (95%). We were pleased to find that treatment of xanthate **31a** with tris-(trimethylsilyl)silane (TTMSS) (1.5 equiv., 0.12 mol dm^{-3} initial concentration) in boiling toluene with AIBN as initiator for 2 h gave a 1 : 1 mixture of **32a**,[43] the product of direct reduction, and **33a**, which was identified as the desired rearranged product by NMR studies and by comparison with known alkene **20** (Scheme 7).[27]

The skeletal structure of the rearranged product was confirmed by hydrolysis of the *N*-methoxycarbonyl-protected rearranged product **33b** (prepared in analogous fashion to **33a**) to give the known amine **34**.[37] We supposed that increasing the lifetime of the first-formed radical would lead to a higher proportion of the rearranged product **33a**. By increasing the dilution by a factor of 3, and adding a mixture of TTMSS and AIBN to a pre-heated solution of xanthate **31a** over 100 minutes, the ratio increased to ~20 : 1, and gave a 90% isolated yield of **33a**.

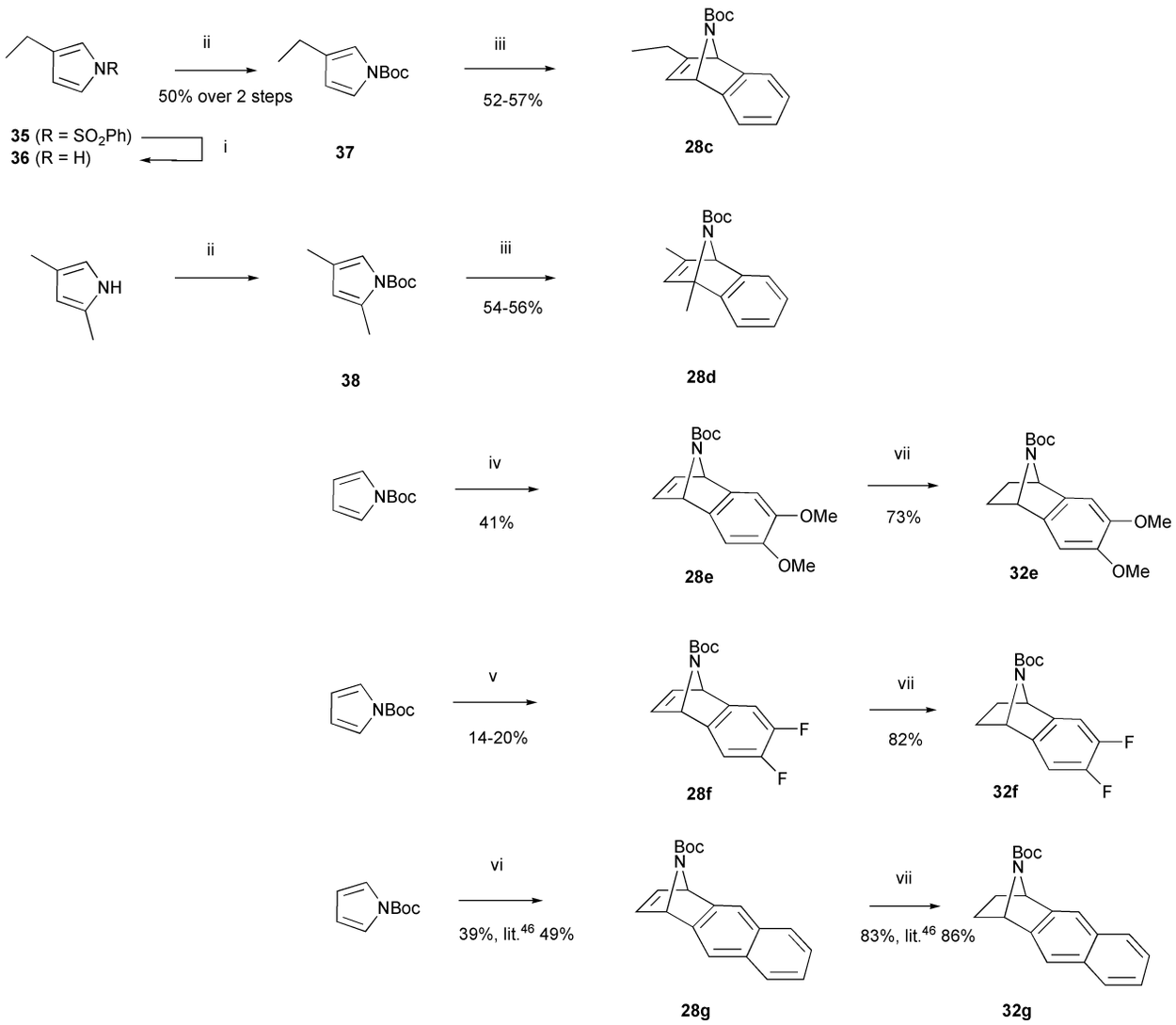
Encouraged by these results, we undertook a more detailed study of the effect on the rearrangement of bicyclic core substitution and also of variation of electronics in the aromatic ring. 3-Ethylpyrrole **36**[44] was prepared by hydrolysis of the known 1-phenylsulfonyl-3-ethylpyrrole **35**.[45] Both 3-ethylpyrrole and commercially available 2,4-dimethylpyrrole were Boc-protected to give substituted Boc-pyrroles **37** and **38** which were used in benzyne cycloadditions (Scheme 12)[40] to give adducts **28c** and **28d**. Hydroboration then occurred with complete facial and regioselectivity to produce alcohols **30c** and **30d** as single diastereomers (Scheme 13).

Radical deoxygenation of the xanthates **31c** and **31d** in the manner previously described for **31a** gave good yields of the rearranged products (Scheme 13). Only traces of directly-reduced products were observed in the crude ^{1}H NMR spectra [by comparison with the ^{1}H NMR data of **32a** (*vide supra*)]. Noteworthy is that NOESY experiments revealed that H-atom transfer to form **33d** occurs exclusively from the *exo* face, leading to a single diastereomer. These studies also showed that the 7-alkyl substituent in **33c** and **33d** resides *anti* to nitrogen, confirming that the earlier hydroborations were completely *exo*-selective.

To determine the effect of arene ring electronics on the neophyl-like migration, we prepared adducts **28e**–**g** (Scheme 12) by diazotization of the appropriate aromatic amino acid derivatives in the presence of *N*-Boc-pyrrole.[46] Hydrogenation[43] of these adducts was conducted to give reference samples of the products of direct reduction **32e**–**g**, as substitution of the aromatic ring was expected to affect the ratio of directly-reduced : rearranged products.

Hydroboration–oxidation and then deoxygenation of the derived xanthates **31e**–**g** gave the expected products **33e**–**g** in good yields (Scheme 13). Dimethoxy-substitution in **31e** was found to have a retarding effect on the rearrangement, as shown by a 6 : 1 ratio of rearranged : directly-reduced products—13% of **32e** was isolated in addition to **33e**. This is consistent with the initial formation of a nucleophilic secondary alkyl radical and a slower cyclisation onto the more electron-rich aromatic ring than in the unsubstituted system. This ratio in the reaction of the difluorinated xanthate **31f** did not appear to differ greatly from that of **33a** : **32a**, which suggests only a mild overall electron-withdrawing effect due to the fluorine substituents. None of the directly-reduced product was detected in the reaction of **31g**, which is in agreement with rate-enhancements observed (compared to phenyl) in studies of other naphthyl group radical migrations.[31]

At this point, we chose to investigate the possible driving force(s) for the nitrogen-directed rearrangements we had observed. It was considered that there are potentially two explanations for the selectivity of the rearrangements: first, that interaction of the nitrogen lone pair with the adjacent radical centre gives rise to a stabilising interaction (Fig. 2) in the



Scheme 12 *Reagents and conditions*: i, NaOH, MeOH, reflux, 2.5 h; ii, Boc_2O, DMAP, MeCN, 25 °C, 16–24 h; iii, *o*-bromofluorobenzene, Mg, THF, reflux, 2 h; iv, 3,4-dimethoxyanthranilic acid, isoamyl nitrite, MeCN, 25 °C, 30 min, then reflux, 2 h; v, 3,4-difluoroanthranilic acid, isoamyl nitrite, THF, reflux, 90 min; vi, 3-amino-2-naphthoic acid, isoamyl nitrite, dioxan, reflux, 4 h; vii, H_2 (1 atm), 5% Pd/C, MeOH, 25 °C, 10 min.

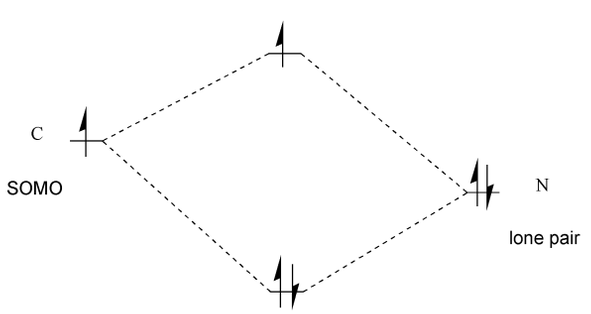


Fig. 2

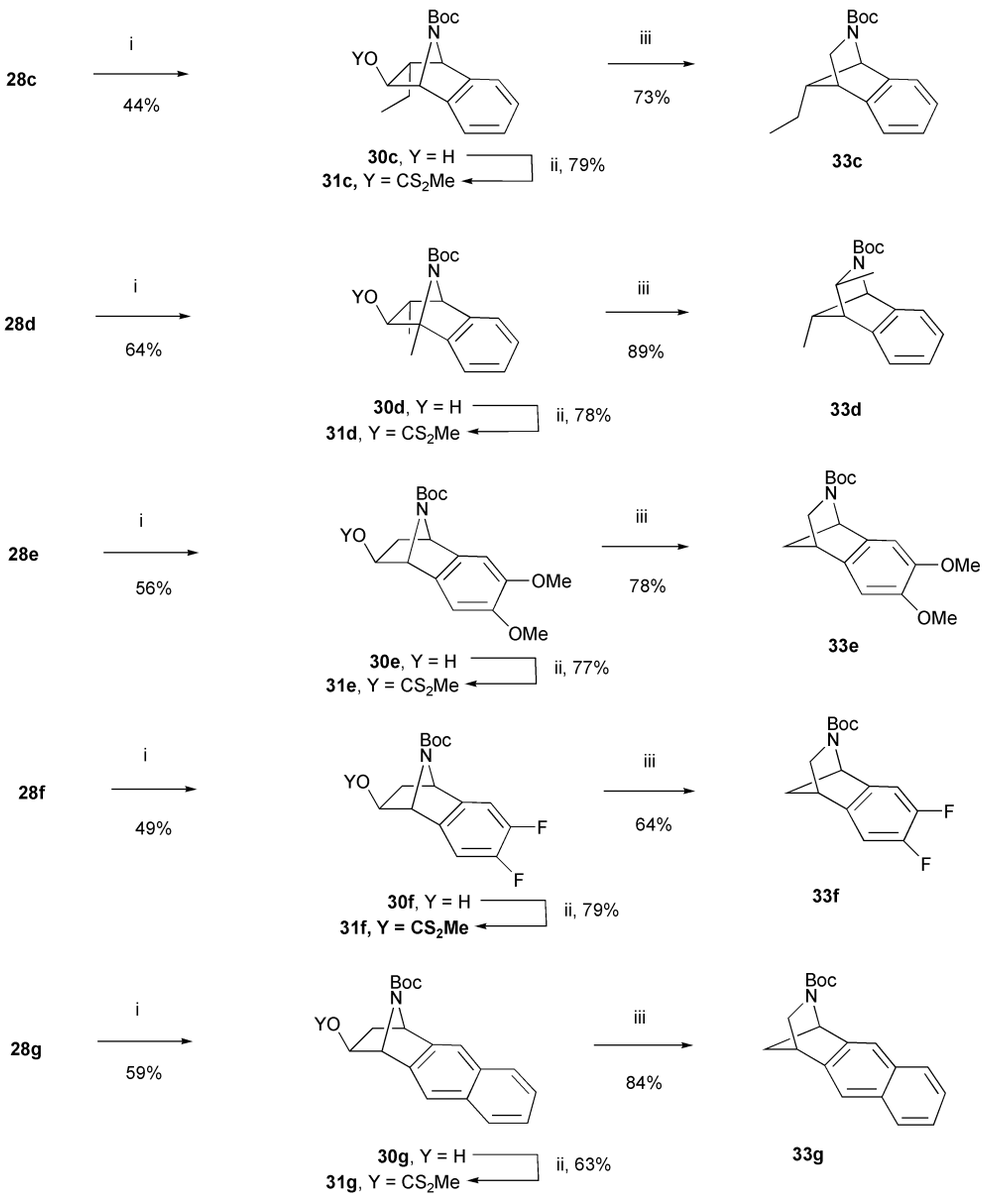
rearranged radical (*e.g.* Scheme 9, X = NR) that is not available to the first formed radical. Second, that the C–N–C bond angle is larger for the rearranged than for the first formed radical, which could allow more significant and stabilising amide-type resonance in the rearranged radical when R = Boc.

In order to distinguish between these two possibilities, the protecting group on nitrogen was altered. The *N*-methyl precursor **31h** was available from reduction of alcohol **30a** (Scheme 14). Deoxygenation of **31h** using TTMSS–AIBN added as one portion gave the rearranged amine **33h** as a single product, albeit in low yield (23%), with no **32h** detected (Scheme 15, Table 3). A sample of **32h**[47] prepared independently from **32a** was subjected to the original deoxygenation conditions and was found to be stable—the amine was fully recovered.

Table 3 Effect of the nitrogen protecting group R on rearrangement product profile

R	Y	Yield **32** (%)	Yield **33** (%)
Boc	CS_2Me	10	72
Me	C(S)OPh	0	23
C(O)^{t}Bu	CS_2Me	14	61

Using the original *N*-Boc protected system, the ratio of the directly-reduced : rearranged products was 1 : 7 when the silane was added as one portion at the same concentration ($[silane]_{initial}$ = 0.04 mol dm^{-3}) which suggests that the change to *N*-methyl had accelerated the rearrangement. This result confirmed that a change in the amide-type resonance was not essential for the rearrangement to occur, but given the low isolated yield of **33h**, we felt that it was not possible to confirm that resonance was not a contributing factor in this chemistry. For this reason, we elected to prepare a substrate with nitrogen protected as an amide. In this case the lone pair is less available for interaction with a radical centre, but resonance is more significant than for the original carbamate. 1-*tert*-Butylcarbonylpyrrole **39**[48] was readily available from pyrrole and pivaloyl chloride in the presence of DMAP and Et_3N. Benzyne cycloaddition and hydroboration led to the alcohol **30i** (Scheme 14). Reaction of the derived xanthate **31i** then gave the rearranged product **33i** and the directly reduced **32i** (Scheme 15, Table 3).



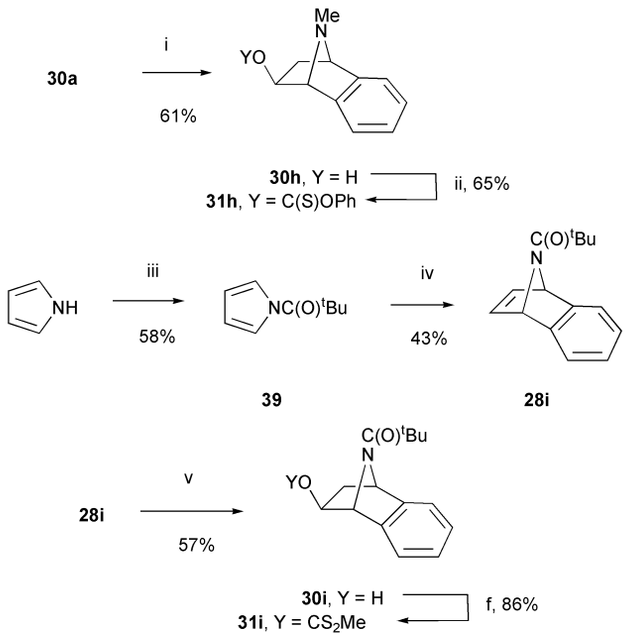
Scheme 13 *Reagents and conditions*: i, 9-BBN, THF, 25 °C, 24 h; ii, KH, CS_2, MeI, THF, 0–25 °C, 90 min; iii, TTMSS, AIBN, toluene, reflux, 2 h.

Significantly, the fraction of rearranged product was less than in the *N*-Boc case. These three results suggest that SOMO-lone pair interactions are responsible for the rearrangements. The closer in energy the orbitals are, the greater the stabilising interaction (Fig. 2). There is considerable precedent for such an interaction, as it is thought to be responsible for the low α-C–H bond dissociation enthalpies of amines.[30,49] In accordance with this analysis, in the current chemistry the *N*-methyl substrate showed the highest propensity for rearrangement, and the *N*-*tert*-butylcarbonyl the lowest. The idea that changes in the amide-type resonance were responsible for the rearrangements can therefore be discounted.

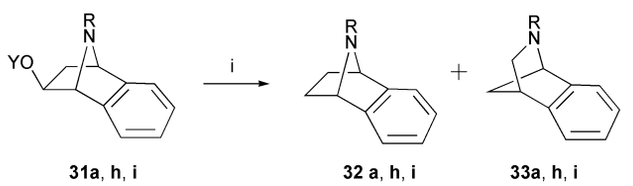
The fact that the rate of the neophyl-like rearrangement appears to depend on the substitution at nitrogen has implications for the mechanism of the rearrangement. Any rate-determining step must be affected by the proposed orbital interaction, in the absence of significant structural variation in the bicyclic core with *N*-substitution. There has been much debate over whether a species of type **41** (Scheme 16) is a discrete intermediate or a transition state in the original neophyl rearrangement.[31] Ingold[50] was able to generate radical **43** by H-atom abstraction and measure its decay spectroscopically to **44**, a process which occurred on the nanosecond timescale.

An estimation of the rate constant for H-atom transfer from TTMSS to a secondary alkyl radical can be obtained from the Arrhenius function derived by Chatgilialoglou and co-workers.[51] Using $T = 384$ K (the boiling point of toluene) gives a second order rate constant of $\sim 7 \times 10^5$ dm^3 mol^{-1} s^{-1}. This in turn allows an estimate of the rate constant for rearrangement: reduction of xanthate **31a** using TTMSS at an initial concentration of 0.12 M gave approximately equal amounts of rearranged and directly reduced products. This suggests that the rate of rearrangement is, within an order of magnitude, equal to the average rate of H-atom transfer to give the directly reduced product. The first-order rate constant for the rearrangement is thus approximately 10^5 s^{-1}.

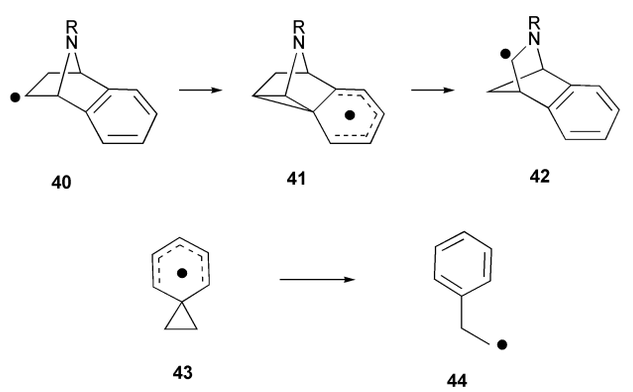
It seems most unlikely that ring opening of **41** to give **42** could be rate-determining, as it would occur too quickly to be the slowest step of this reaction.[50] Instead, formation of **41**, with the accompanying disruption of aromaticity, is more likely to be rate-determining. Under these circumstances it is difficult to see how the product profile would show such a marked dependence upon substitution at nitrogen, since the orbital interaction that drives the rearrangement could not affect the reaction until the radical began to develop α to nitrogen. However, the product profile can be explained if **41** is a transition state, and the rearrangement of **40** to **42** occurs in one step. The energy of the transition state would then be lowered by stabilisation of the radical developing α to nitrogen and depend directly on the *N*-protecting group.



Scheme 14 *Reagents and conditions*: i, $LiAlH_4$, Et_2O, reflux, 16 h; ii, PhOC(S)Cl, DMAP, CH_2Cl_2, 25 °C, 16 h; iii, Bu^tCOCl, DMAP, Et_3N, CH_2Cl_2, 25 °C, 24 h; iv, anthranilic acid, isoamyl nitrite, THF, reflux, 3.5 h; v, *rac*-BINAP, $[Rh(COD)Cl]_2$, catecholborane, THF, 25 °C, 3 h, then NaOH, H_2O_2, 0–25 °C, 16 h.



Scheme 15 *Reagents and conditions*: i, TTMSS, AIBN, toluene, reflux, 2 h.



Scheme 16

In summary, we present our work so far in the field of nitrogen-directed radical rearrangements. Two synthetically useful and conceptually interesting radical rearrangement processes have been established, leading to azabicycles that are not readily accessible by other means. The nature of the orbital interaction that drives the rearrangement has been confirmed. Extensions of the processes to provide enantio-enriched products, as well as manipulation of the products to targets of biological interest are under investigation.

Experimental

All reactions requiring anhydrous conditions were conducted in flame dried apparatus under an atmosphere of argon. Syringes and needles for the transfer of reagents were oven dried and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from benzophenone ketyl, hydrocarbons from CaH_2, and alcohols from their magnesium alkoxides. All reactions were monitored by TLC using commercially available (Merck or Camlab) plates, pre-coated with a 0.25 mm layer of silica containing a fluorescent indicator. Visualisation of reaction components was achieved with 254 nm light, and with vanillin or $KMnO_4$ dips. Organic layers were dried using $MgSO_4$, evaporated on a Buchi rotary evaporator, followed by drying on a high vacuum oil pump (~1 mmHg). Column chromatography was carried out on Kieselgel 60 (40–63 μm). Melting points were determined using a Gallenkamp hot stage apparatus and are uncorrected. Elemental analysis was performed by Elemental Microanalysis Limited, Okehampton, Devon, UK. IR spectra were recorded as either KBr discs or thin films, using a Perkin-Elmer 1750 FTIR spectrometer. Peak intensities are specified as strong (s), medium (m) or weak (w). Only selected absorbancies are reported. ^{1}H NMR spectra of compounds were recorded in $CDCl_3$ unless otherwise stated, using a Varian Gemini 200 (200 MHz), Bruker DPX400 (400 MHz) or AMX500 spectrometer (500 MHz). Chemical shifts (δ) are reported relative to $CHCl_3$ (δ 7.27). Coupling constants (J) are given in Hz, multiplicities are given as multiplet (m), doublet (d), triplet (t) and quartet (q). ^{13}C NMR spectra were recorded on the Bruker DPX400 (100 MHz) or AMX500 (125 MHz) spectrometer. Chemical shifts are reported relative to $CDCl_3$ (central line of triplet δ 77.0) unless stated otherwise. ^{19}F NMR spectra were recorded on a Bruker AMX 500 (235 MHz) spectrometer and chemical shifts are reported relative to $CFCl_3$ (δ = 0.0). Mass spectra were obtained from the EPSRC Mass Spectrometry Service Centre, Swansea with a Micromass, ZAB-E instrument or 900 XLT high resolution double focusing mass spectrometer with tandem ion trap. Alternatively they were recorded in-house using a VG mass Lab. TRIO1 (GCMS) or Micromass platform APCI spectrometer. All organolithiums were titrated against 2,2,2′-trimethylpropionanilide before use. A known amount of the amide was dissolved in THF (2 cm^3) and the organolithium was then added to this stirring solution until a colour change was observed (clear colourless to bright orange).'Petroleum ether' refers to the fraction boiling in the range 30–40 °C.

7-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]hepta-2,5-diene 19a[52]

2-*p*-Toluenesulfonyl-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]hepta-2,5-diene[26] (5.20 g, 14.9 mmol) was added to a 250 cm^3 beaker containing a stirrer bar, methanol (80 cm^3), Na_2HPO_4 (8.0 g, 56 mmol) and 6% Na–Hg (5.0 g) at −10 °C. The mixture was stirred at 0 °C for 6 h. Water (100 cm^3) was then added and the mixture filtered. The filtrate was extracted with CH_2Cl_2 (3 × 100 cm^3), washed with brine (100 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Column chromatography (SiO_2, 20% Et_2O : petroleum ether) gave **19a** (690 mg, 23%) as a colourless oil: R_f (25% Et_2O : petroleum ether) 0.33; ν_{max}(thin film)/cm^{-1} 2978m, 1708s, 1480w, 1458w, 1345s, 1172s; δ_H(200 MHz) 6.99 (4 H, d, J 7.0, 4 × HC=C), 5.19 (2 H, s, C(1)H and C(4)H), 1.41 (9 H, s, Bu^t); δ_C(100 MHz) 154.6 (C=O), 144.5 (C=C), 143.5 (C=C), 80.3 (*C*Me$_3$), 66.7 (CH), 66.1 (CH), 28.0 and 28.2 (CMe$_3$); *m*/*z* (CI$^+$, NH$_3$) 194 (M + H$^+$, 82%), 110 (10), 94 (M − Boc, 100) (Found: M + H$^+$, 194.1181. $C_{11}H_{15}NO_2$ requires 194.1181).

7-(Methoxycarbonyl)-7-azabicyclo[2.2.1]hepta-2,5-diene 19b[24]

Trifluoroacetic acid (1.5 cm^3, 19.5 mmol) was added to a solution of diene **19a** (186 mg, 0.96 mmol) in CH_2Cl_2 (15 cm^3) and stirred at room temperature for 1 h. The crude TFA salt was azeotroped with toluene (3 × 40 cm^3) and the resulting brown solid (310 mg, >100%) used without further purification. Methoxycarbonylation was achieved using the procedure of Corey *et al.*[53] as follows. To a solution of the TFA salt prepared

in the previous step in acetone (5 cm^3) was added K_2CO_3 (830 mg, 6.0 mmol), and methyl chloroformate (310 μL, 4.0 mmol) and the mixture heated to reflux for 18 h. Water (10 cm^3) was added and the aqueous layer was extracted with Et_2O (3 × 5 cm^3) and the combined extracts washed with 1 M NaOH (10 cm^3), brine (10 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, 50% Et_2O : petroleum ether) gave the carbamate **19b** as a yellow oil (92 mg, 63% from **18a**): R_f (50% Et_2O : petroleum ether) 0.35; δ_H (200 MHz) 7.02 and 7.00 (4 H, 2 × s, 4 × HC=C, split by carbamate rotamers), 5.25 (2 H, s, C(1)H and C(4)H), 3.62 (3 H, s, Me).

General procedure for thiol/selenol additions

The thiol or benzeneselenol (0.9 equiv.) was added as one portion to a solution of diene **19a** or diene **19b** (~0.1 mol dm^{-3}) in benzene or toluene and stirred under argon for the specified time at the specified temperature. The solvent was then removed at reduced pressure. In all cases the products were obtained as an inseparable mixture of epimers. 1D NOE experiments established that the relative stereochemistry of the major epimer was with the thio group *syn* to nitrogen for **20a**: irradiation of the proton at C7 showed enhancement of the olefinic protons. The stereochemistries of the other products were assigned by analogy.

2-(*tert*-Butoxycarbonyl)-7-*syn*/*anti*-(*p*-tolylthio)-2-azabicyclo-[2.2.1]hept-5-ene 20a

Reaction of diene **19a** (100 mg, 0.52 mmol) and *p*-thiocresol (56 mg, 0.45 mmol) as described above for 24 h at 20 °C gave a yellow oil after removal of solvent. Column chromatography (SiO_2, 15% Et_2O : petroleum ether) gave **20a** as a colourless oil (132 mg, 92%): R_f (25% Et_2O : petroleum ether) 0.24; ν_{max}(thin film)/cm^{-1} 2975m, 2929s, 2889m, 1699s, 1493s, 1394s, 1363s, 1250s, 1177m, 1168s, 1100s; δ_H (500 MHz, 90 °C, DMSO-d_6, *syn* : *anti*, 3 : 1), (*syn*-epimer) 7.31 (2 H, d, *J* 8.0, 2 × CH of aromatic), 7.16 (2 H, d, *J* 8.0, 2 × CH of aromatic), 6.43 (2 H, m, HC=CH), 4.45 (1 H, s, C(1)H), 3.54 (1 H, dd, *J* 9.5 and 3.0, C(3)H *exo*), 3.25 (1 H, s, C(7)H), 3.06 (1 H, s, C(4)H), 2.59 (1 H, d, *J* 9.5, C(3)H *endo*), 2.30 (3 H, s, Me), 1.42 (9 H, s, Bu^t), (*anti*-epimer) 7.26 (2 H, d, *J* 8.0, 2 × CH of aromatic), 7.15 (2 H, d, *J* 8.0, 2 × CH of aromatic), 6.33 (2 H, m, HC=CH), 4.56 (1 H, s, C(1)H), 3.50 (1 H, s, C(7)H), 3.41 (1 H, dd, *J* 9.5 and 3.0, C(3)H *exo*), 3.25 (1 H, s, C(4)H), 2.57 (1 H, d, *J* 9.5, C(3)H *endo*), 2.30 (3 H, s, Me), 1.40 (9 H, s, Bu^t); δ_C (125 MHz, 90 °C, DMSO-d_6) (both epimers) 155.8, 155.4 (both C=O), 138.8, 137.4, 137.2, 136.0, 135.2, 132.9, 132.8, 131.9, 131.4, 130.6, 130.4 (all C=C or C–Ar), 79.7, 79.5 (both *C*Me_3), 65.9 (C7), 64.9, 63.8 (Both C1), 63.6 (C7), 49.2, 47.8 (Both C4), 47.2, 44.2 (Both C3), 29.0 (C*Me*$_3$), 21.3 (Me–Ar); *m*/*z* (CI^+, NH_3) 318 (M + H^+, 29%), 279 (33), 262 (100), 218 (48), 201 (23), 189 (23), 157 (14), 140 (13), 124 (14), 94 (78) (Found: M + H^+, 318.1531. $C_{18}H_{24}NO_2S$ requires 318.1528).

The experimental procedures and characterisation data for thiol addition products **20b**–**i** are included in the accompanying electronic supplementary information. ‡

2-(*tert*-Butoxycarbonyl)-7-*syn*/*anti*-(*p*-tolylsulfonyl)-2-aza-bicyclo[2.2.1]hept-5-ene 21

Peracetic acid (1.77 cm^3 of 36–40% solution in water, 9.5 mmol) was added to a mixture of sulfide **20a** (500 mg, 1.57 mmol), NaOAc (290 mg, 3.53 mmol) and Na_2HPO_4 (4.5 g, 31 mmol) in CH_2Cl_2 (50 cm^3) at 0 °C. The reaction was stirred at 0 °C for 6 h and then at 20 °C for 14 h. Water (50 cm^3) was added and the aqueous layer extracted with CH_2Cl_2 (3 × 50 cm^3). The combined organic extracts were washed with sodium bisulfite solution (50 cm^3), brine (50 cm^3), dried ($MgSO_4$) and the solvent was removed at reduced pressure to give a white solid. Column chromatography (SiO_2, Et_2O) gave **21** as a white solid (500 mg, 91%): R_f (50% Et_2O : petroleum ether) 0.28; mp (from Et_2O) 110–112 °C (Found: C, 61.7; H, 6.7; N, 4.0. $C_{18}H_{23}NO_4S$ requires C, 61.7; H, 6.6; N, 4.0%); ν_{max}(KBr)/cm^{-1} 2963s, 2892m, 1688s, 1597s, 1408s, 1364s, 1260s, 1120s, 1068s; δ_H (500 MHz, 90 °C, DMSO-d_6, *syn* : *anti*, 3 : 1) (*syn*-epimer) 7.77 (2 H, d, *J* 8.0, 2 × CH of aromatic), 7.47 (2 H, d, *J* 8.0, 2 × CH of aromatic), 6.50–6.47 (1 H, m, 1 × HC=C), 6.41–6.38 (1 H, m, 1 × HC=C), 4.66 (1 H, br s, C(1)H), 3.72 (1 H, dd, *J* 9.0 and 3.0, C(3)H *exo*), 3.39 (1 H, s, C(4)H), 3.31 (1 H, s, C(7)H), 2.52 (1 H, d, *J* 9.0, C(3)H *endo*), 2.45 (3 H, s, Me), 1.42 (9 H, s, Bu^t), (*anti*-epimer) 7.69 (2 H, d, *J* 8.0, 2 × CH of aromatic), 7.46 (2 H, d, *J* 8.0, 2 × CH of aromatic), 6.20–6.17 (2 H, m, HC=CH), 4.67 (1 H, s, C(1)H), 3.79 (1 H, s, C(7)H), 3.39 (1 H, s, C(4)H), 3.37 (1 H, dd, *J* 9.5 and 3.0, C(3)H *exo*), 2.52 (1 H, d, *J* 9.0, C(3)H *endo*), 2.44 (3 H, s, Me), 1.38 (9 H, s, Bu^t); δ_C (125 MHz, 90 °C, DMSO-d_6) (both isomers) 155.8 (C=O), 145.4, 145.2, 139.2, 138.3, 137.3, 134.9, 134.4, 130.9, 130.7, 128.8, 128.7 (all C=C or C of aromatic), 80.6 (C7), 80.1, 79.7 (both *C*Me_3), 75.4 (C7), 62.2, 60.8 (both C1), 47.7 (C3), 45.9, 45.1 (both C4), 44.1 (C3), 29.1, 29.0 (both C*Me*$_3$), 21.8 (Me–Ar); *m*/*z* (CI^+, NH_3) 367 (M + NH_4^+, 18%), 350 (M + H^+, 7), 311 (100), 250 (10), 201 (23), 189 (23), 157 (14), 96 (17) (Found: M + H^+, 350.1429. $C_{18}H_{24}NO_4S$ requires 350.1426).

2-(*tert*-Butoxycarbonyl)-2-azabicyclo[2.2.1]hept-5-ene 22[27] by desulfonylation

Freshly prepared 6% Na–Hg (3.76 g, 9.8 mmol Na), and Na_2HPO_4 (1.5 g, 10.5 mmol) were added to a stirred solution of sulfones **21** (376 mg, 1.07 mmol) in anhydrous methanol (10 cm^3) under argon at −10 °C. The reaction was warmed to 25 °C over 3 h and left for a further 9 h at 25 °C. Water (10 cm^3) was added and the mixture filtered. The filtrate was extracted with CH_2Cl_2 (3 × 20 cm^3), the combined extracts dried ($MgSO_4$) and the solvent removed at reduced pressure to give an oil. Chromatography (SiO_2, 15% Et_2O : cyclohexane) gave the carbamate **22** as a clear colourless oil (73 mg, 33%): R_f (50% Et_2O: petroleum ether) 0.63; δ_H (400 MHz) (3 : 2 mixture of rotamers) 6.35 and 6.27 (2H, 2 × s, 2 × HC=C), 4.71 and 4.57 (1 H, 2 s, C(1)H), 3.30 (1 H, dd, *J* 9.0 and 3.0, C(3)H *exo*), 3.16 (1 H, s, C(4)H), 2.68–2.48 (1 H, m, C(3)H *endo*), 1.68–1.50 (2 H, m, CH_2), 1.44 (9 H, s, Bu^t); δ_C (125 MHz, mixture of rotamers) 155.8, 155.6 (C=O), 136.5 (C5), 134.4, 133.7 (C6), 78.9 (*C*Me_3), 61.1, 59.9 (C1), 48.0 (C7), 46.2, 45.8 (C7), 43.4, 42.9 (C4), 28.4 (C*Me*$_3$).

2-(*tert*-Butoxycarbonyl)-7-*syn*/*anti*-(phenylselenyl)-2-aza-bicyclo[2.2.1]hept-5-ene 24 and 7-(*tert*-butoxycarbonyl)-2-*exo*/*endo*-(phenylselenyl)-7-azabicyclo[2.2.1]hept-5-ene 25

Benzeneselenol (71 mg, 0.45 mmol) was added to a solution of diene **19a** (99 mg, 0.51 mmol) in toluene under argon and the reaction was stirred at 20 °C for 24 h. Removal of solvent at reduced pressure gave a yellow oil. Column chromatography (SiO_2, 15% Et_2O : 85% petroleum ether) first gave selenide **25** as a colourless oil which crystallised on standing to a white solid (19 mg, 12 %): R_f (30% Et_2O : 70% petroleum ether) 0.40; mp (from light petroleum) 70–72 °C; ν_{max}(thin film)/cm^{-1} 3045w, 2792s, 2926s, 1688s, 1578m, 1477m, 1436m, 1368s, 1285m, 1233w, 1169m, 1097m, 846m, 737m; δ_H (400 MHz, *exo* : *endo*, 1 : 6: NOESY analysis suggested that the major isomer had the selenyl substituent on the *endo* face: NOE enhancement was observed between the olefinic protons and the C3 *endo* proton *trans* to the proton attached to C2), (*endo*-epimer) 7.55–7.51 (2 H, m, 2 × H of Ph), 7.31–7.23 (3 H, m, 3 × H of Ph), 6.40 (2 H, br s, 2 × HC=C), 4.81–4.60 (2 H, m, C(1)H and C(4)H), 3.64 (1 H, br s, C(2)H), 2.49 (1 H, br s, C(3)H *exo*), 1.44 (9 H, s, Bu^t), 1.10 (1 H, dd, *J* 12.0 and 4.0, C(3)H *endo*), (*exo*-epimer) 7.55–7.51 (2 H, m, 2 × H of Ph), 7.31–7.23 (3 H, m, 3 × H of Ph), 6.22 (2 H, br s, 2 × HC=C), 4.81–4.60 (2 H, m, C(1)H and

C(4)H), 3.48 and 3.40 (1 H, 2 × br s, C(2)H), 1.82 (1 H, br s, C(3)H *exo*), 1.44 (9 H, s, Bu^t), 1.10 (1 H, dd, *J* 12.0 and 4.0, C(3)H *endo*); δ_C (100 MHz) (*endo*-epimer observed only—*exo* too weak to appear in ^{13}C spectrum) 154.5 (C=O), 135.8, 133.9, 132.8, 130.1, 129.2, 127.1 (all C=C or C of Ph), 80.3 (*C*Me$_3$), 62.2, 60.5 (C1 and C4), 38.0 (C2), 34.5 (C3), 29.0 (Bu^t); *m*/*z* (FAB$^+$, NOBA Matrix) 374 (M + Na$^+$, 30%), 352 (M + H$^+$, 65%), 296 (100), 194 (62), 167 (68), 149 (77), 121 (56), 105 (75) (Found: M + H$^+$, 352.0817. $C_{17}H_{22}NO_2Se$ requires 352.0815).

Second to elute was **24** as a colourless oil which crystallised on standing to a white solid (128 mg, 81%): R_f (30% Et$_2$O : petroleum ether) 0.27; mp (from petroleum ether) 58–59 °C (Found: C, 57.9; H, 6.1; N, 4.0. $C_{17}H_{21}NO_3Se$ requires C, 58.3; H, 6.0; N, 4.0%); ν_{max}(thin film)/cm^{-1} 3064m, 2975m, 2937m, 1700s, 1578m, 1487s, 1392m, 1293s, 1253s, 1153s, 1096m; δ_H (500 MHz, 90 °C, DMSO-d$_6$, *syn* : *anti*, 3 : 1) (*syn*-epimer) 7.57–7.49 (2 H, m, 2 × CH of Ph), 7.35–7.28 (3 H, m, 3 × CH of Ph), 6.48–6.40 (2 H, m, HC=CH), 4.52 (1 H, s, C(1)H), 3.57 (1 H, dd, *J* 9.5 and 3.0, C(3) *exo*), 3.40 (1 H, s, C(7)H), 3.14 (1 H, s, C(4)H), 2.63 (1 H, d, *J* 9.5, C(3)H *endo*), 1.43 (9 H, s, Bu^t), (*anti*-epimer) 7.57–7.49 (2 H, m, 2 × CH of Ph), 7.35–7.28 (3 H, m, 3 × CH of Ph), 6.40–6.33 (2 H, m, HC=CH), 4.68 (1 H, s, C(1)H), 3.43 (1 H, s, C(7)H), 3.40 (1 H, dd, *J* 9.5 and 3.0, C(3)H *exo*), 3.35 (1 H, s, C(4)H), 2.57 (1 H, d, *J* 9.0, C(3)H *endo*), 1.41 (9 H, s, Bu^t); δ_C (125 MHz, 90 °C, DMSO-d$_6$) (both isomers) 155.8, 155.3 (C=O), 139.0, 137.4, 136.9, 135.5, 134.0, 133.9, 133.7, 133.6, 130.1, 129.9, 128.1, 127.9 (all C=C or C of Ph), 80.1, 79.6 (*C*Me$_3$), 65.6, 64.8 (C1), 61.2, 59.3 (C7), 50.2, 48.4 (C4), 47.2, 44.8 (C3), 29.0, 28.9 (C*Me$_3$*); *m*/*z* (EI$^+$) 351 (M$^+$, 2%), 184 (10), 157 (18), 138 (69), 120 (10), 94 (83), 84 (27), 77 (33), 65 (28), 57 (100), 49 (24), 41(41) (Found: M$^+$, 351.0736. $C_{17}H_{21}NO_3Se$ requires 351.0737).

N-(*tert*-Butoxycarbonyl)-1,4-dihydro-1,4-iminonaphthalene 28a[40]

Prepared according to the method of Carpino *et al.* from *o*-bromofluorobenzene and *N*-Boc-pyrrole in the presence of magnesium in 58% yield (lit.[40] 58%): mp 71–72 °C (lit.[40] 72–73 °C); R_f 0.30 (30% Et$_2$O : petroleum ether); δ_H (200 MHz) 7.30–7.21 (2 H, m, 2 × CH of aromatic), 7.02–6.92 (4 H, m, 2 × CH of aromatic and HC=CH), 5.50 (2 H, s, C(1)H and C(4)H), 1.40 (9 H, s, Bu^t). Compounds **28c** and **28d** were prepared analogously from pyrroles **37** and **38** respectively (*vide infra*). Experimental details and characterisation data can be found in the electronic supplementary information. ‡

N-Methoxycarbonyl-1,4-dihydro-1,4-iminonaphthalene 28b[54]

Prepared according to the method of Cragg *et al.* from anthranilic acid and commercially available *N*-methoxycarbonylpyrrole: R_f 0.23 (20% Et$_2$O : petroleum ether); δ_H (200 MHz) 7.33–7.20 (2 H, m, 2 × CH of aromatic), 7.05–6.90 (4 H, m, 2 × CH of aromatic and HC=CH), 5.58 (2 H, s, C(1)H and C(4)H), 3.62 (3 H, s, MeO). Compound **28e** was prepared by adaptation of the procedure of Cragg *et al.*[54] who used 3,6-dimethoxyanthranilic acid. Compound **28f** was prepared by adaptation of the procedure of Vernon *et al.*[55] who used anthranilic acid in a benzyne cycloaddition with 1-Boc-2,5-dimethylpyrrole. Compound **28g** was prepared according to the procedure of Remy and Bornstein and their co-workers.[46] Details can be found in the electronic supplementary information. ‡

N-(*tert*-Butylcarbonyl)-1,4-dihydro-1,4-iminonaphthalene 28i

Isoamyl nitrite (3.10 g, 26.5 mmol) in THF (10 cm^3) and anthranilic acid (3.63 g, 26.5 mmol) in THF (10 cm^3) were added simultaneously to a solution of pyrrole **39** (4.0 g, 26.5 mmol) in THF (40 cm^3) at reflux over 2 h. The reaction was left at reflux for a further 1.5 h, then allowed to cool. Water (50 cm^3) was added and the mixture extracted with Et$_2$O (3 × 100 cm^3). The combined organic extracts were washed with saturated NaHCO$_3$ (100 cm^3), water (100 cm^3) and dried (MgSO$_4$). The solvent was then removed at reduced pressure to give an oil. Chromatography (SiO$_2$, 20% Et$_2$O : petroleum ether) gave the amide **28i** as a white solid (2.6 g, 43%): R_f (30% Et$_2$O : petroleum ether) 0.36; mp (from EtOAc–petroleum ether) 133–134 °C (Found: C, 79.3; H, 7.6; N, 6.2. $C_{15}H_{17}NO$ requires C, 79.3; H, 7.5; N, 6.2%); ν_{max}(KBr)/cm^{-1} 3042m, 2985s, 2970m, 1622s, 1474m, 1447m, 1403m, 1366s, 1292m, 1196m, 759s; δ_H (400 MHz) 7.26 (2 H, s, 2 × CH of aromatic), 7.02 (2 H, br s, HC=CH), 6.96–6.92 (2 H, m, 2 × CH of aromatic), 5.89 (2 H, s, C(1)H and C(4)H), 1.18 (9 H, s, Bu^t); δ_C (100 MHz) 173.7 (C=O), 148.2 (2 × C(quat) of aromatic), 144.8 and 142.0 (2 × C=C), 125.0 (2 × C of aromatic), 121.4 and 120.2 (2 × C of aromatic), 66.3 and 64.8 (C1 and C4), 38.4 (*C*Me$_3$), 27.3 (C*Me$_3$*); *m*/*z* (EI$^+$) 227 (M$^+$, 5%), 170 (14), 142 (41), 128 (38), 115 (52), 89 (16), 57 (100), 41 (52) (Found: M + H$^+$, 228.1381. $C_{15}H_{18}NO$ requires 228.1388).

N-(*tert*-Butoxycarbonyl)-*exo*-2-(*p*-tolylthio)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 29

To a solution of **28a** (100 mg, 0.41 mmol) in toluene (5 cm^3) was added *p*-thiocresol (77 mg, 0.62 mmol). The mixture was stirred at 25 °C for 24 h, after which time the solvent was removed at reduced pressure. Chromatography (10% Et$_2$O : petroleum ether) gave the sulfide **29** as a white solid (135 mg, 89%): R_f (10% Et$_2$O : 90% petroleum ether) 0.25; mp (from petroleum ether) 88–89 °C; ν_{max}(KBr)/cm^{-1} 3020s, 2977s, 2931s, 1698s, 1493s, 1460s, 1366s, 1279s, 1256s, 1169s, 1090s, 1017m, 973m, 908s, 812s, 753s; δ_H (400 MHz) 7.43–7.34 (2 H, m, 2 × CH of aromatic), 7.30–7.05 (6 H, 6 × CH of aromatic), 5.25 (1 H, br s, C(1)H), 5.05 (1 H, br s, C(4)H), 3.21 (1 H, s, C(2)H), 2.36 (3 H, s, Me), 2.02–1.95 (1 H, m, H of CH$_2$), 1.93–1.86 (1 H, m, H of CH$_2$), 1.44 (9 H, s, Bu^t); δ_C (100 MHz) 154.6 (C=O), 145.1 (C(quat) of aromatic), 143.6 (C(quat) of aromatic), 137.0 (C(quat) of aromatic), 132.2 (C(quat) of aromatic) 131.3, 129.8, 126.9, 126.6, 120.3, 119.8 (all C of aromatic), 80.2 (*C*Me$_3$), 65.2 (C4), 60.3 (C1), 48.4 (C2), 35.1 (C3), 28.3 (C*Me$_3$*), 21.1 (Me); *m*/*z* (EI$^+$) 367 (M$^+$, 1%), 217 (35), 161 (93), 117 (100), 91 (62), 84 (55), 57 (95) (Found: M + H$^+$, 368.1678. $C_{22}H_{26}NO_2S$ requires 368.1684).

General procedure for alkene hydroboration: *N*-(*tert*-butoxycarbonyl)-*exo*-1,2,3,4-tetrahydro-1,4-iminonaphthalen-2-ol 30a

9-BBN (0.5 M in THF, 2.40 cm^3, 1.20 mmol) was added dropwise to a stirred solution of **28a** (250 mg, 1.02 mmol) in THF (3 cm^3) at 25 °C. The reaction was left to stir for 24 h. The flask was then cooled to 0 °C and H_2O_2 (1.25 cm^3 of a 30% aq. solution) was added, followed by NaOH (1.7 cm^3 of a 2 M aq. solution). The reaction vessel was removed from the ice bath and the reaction mixture was then stirred at 25 °C for 5 h. The mixture was washed with saturated K_2CO_3 (10 cm^3) and extracted with Et$_2$O (3 × 20 cm^3). The combined extracts were dried (MgSO$_4$) and the solvent removed at reduced pressure to give an oil. Column chromatography (50% Et$_2$O : petroleum ether) gave the alcohol **30a** as an oil which crystallised on standing to a white solid (180 mg, 68%): R_f (50% Et$_2$O : petroleum ether) 0.23; mp (from Et$_2$O) 90–91 °C; ν_{max}(thin film)/cm^{-1} 3254br s, 3024m, 2978s, 2928m, 2893s, 1704s, 1690s, 1456s, 1366s, 1348s, 1294m, 1251s, 1158s, 1141m, 1102s, 1088s, 1057s, 903m, 746s; δ_H (400 MHz) 7.27–7.23 (1 H, m, CH of aromatic), 7.19–7.17 (1 H, m, CH of aromatic), 7.14–7.06 (2 H, m, 2 × H of aromatic), 5.11 (1 H, br s, C(1)H), 5.01 (1 H, br s, C(4)H), 4.04–4.00 (1 H, m, C*H*–OH), 3.20 (1 H, br. s, OH), 1.87–1.84 (2 H, m, CH$_2$), 1.38 (9 H, s, Bu^t); δ_C (100 MHz) 156.5 (C=O), 146.2, 141.5, (both C(quat) of aromatic) 127.0, 126.4, 121.3, 119.6 (all C of aromatic), 80.4 (*C*Me$_3$), 72.0 (CH–O), 68.4 (C1), 60.8 (C4), 39.4 (C3), 28.2 (Bu^t); *m*/*z* (CI$^+$, NH$_3$), 279

(M + NH_4^+, 5%), 262 (M + H^+, 70), 162 (100), 118 (25) (Found: M + H^+, 262.1440. $C_{15}H_{20}NO_3$ requires 262.1443).

Details of the preparation and characterisation of alcohols **30b**–**g** and **30i** are to be found in the electronic supplementary information. ‡

N-(Methyl)-*exo*-1,2,3,4-tetrahydro-1,4-iminonaphthalen-2-ol 30h

A solution of $LiAlH_4$ (1.5 cm^3 of a 1.0 M solution in Et_2O, 1.5 mmol) was added to a stirred solution of alcohol **30a** (100 mg, 0.38 mmol) in Et_2O (3.5 cm^3) at 25 °C and the mixture heated to reflux overnight. The mixture was then allowed to cool and aqueous NaOH (2.5 cm^3 of a 2 M aq. solution) was added, followed by water (10 cm^3) and the aqueous layer was extracted with Et_2O (3 × 20 cm^3). The solvent was removed at reduced pressure. Chromatography (EtOAc containing 2% Et_3N) gave alcohol **30h** as a white solid (43 mg, 61%): R_f (EtOAc containing 2% Et_3N) 0.13; mp 123–124 °C; ν_{max}(thin film)/cm^{-1} 3352s, 3249s, 2974s, 2946s, 2860m, 1446s, 1415s, 1337m, 1294m, 1167s, 1105s, 1066s, 1003m, 748s; δ_H (400 MHz) 7.30–7.27 (1 H, m, CH of aromatic), 7.21–7.12 (3 H, m, 3 × CH of aromatic), 4.06 (1 H, s, C(1)H), 3.98 (1 H, s, C(4)H), 3.86–3.83 (1 H, m, C*H*-O), 3.47 (1 H, br s, OH), 2.13 (3 H, s, Me), 1.89–1.84 (2 H, m, CH_2); δ_C (100 MHz), 145.8, 140.6 (both C(quat)), 127.0, 126.5, 123.5, 122.0 (4 × C of aromatic), 75.4, 72.6 (C1 and C4), 66.7 (C2), 40.6 (C3), 35.2 (Me); *m*/*z* (CI^+, NH_3) 176 (M + H^+, 100%), 143 (29) (Found: M + H^+, 176.1072. $C_{11}H_{14}NO$ requires 176.1075).

General procedure for xanthate preparation: *N*-(*tert*-butoxycarbonyl)-*exo*-2-(methylsulfanylthiocarbonyloxy)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 31a

Alcohol **30a** (200 mg, 0.76 mmol) was added to KH (400 mg of a 30% suspension, 3 mmol) in THF (10 cm^3) at 0 °C and the mixture was then stirred at room temperature for 20 min. The mixture was cooled to 0 °C and CS_2 (228 mg, 3 mmol) was added and the mixture stirred for 10 min at 0 °C. Finally MeI (425 mg, 3 mmol) was added and the solution was stirred at room temperature for 20 min. The reaction was quenched with dropwise addition of water until effervescence had ceased and the aqueous layer extracted with Et_2O (2 × 10 cm^3), the combined extracts dried ($MgSO_4$), and the solvent removed at reduced pressure. Column chromatography (SiO_2, 20% Et_2O : petroleum ether) gave **31a** as a yellow solid (220 mg, 83%): R_f (50% Et_2O : petroleum ether) 0.59; ν_{max}(KBr)/cm^{-1} 3019m, 2975s, 2924s, 1696s, 1372s, 1294s, 1269s, 1222s, 1160s, 1092s, 1060s, 1002m, 771s; δ_H (400 MHz) 7.37 (1 H, s, CH of aromatic), 7.30–7.15 (3 H, m, 3 × CH of aromatic), 5.42 (2 H, s, C(1)H and C(4)H), 5.21 (1 H, s, CH-O), 2.59 (3 H, s, SMe), 2.23–2.15 (1 H, m, H of CH_2), 2.09–1.99 (1 H, m, H of CH_2), 1.43 (9 H, s, Bu^t); *m*/*z* (CI^+, NH_3) 369 (M + NH_4^+, 2%), 352 (M + H^+, 15), 262 (43), 252 (50), 218 (16), 207 (38), 189 (10), 162 (69), 146 (100), 118 (62), 90 (19) (Found: M + H^+, 352.1041. $C_{17}H_{21}NO_3S_2$ requires 352.1041).

The other xanthates were not fully characterised, but were identified by the appearance of a 3 H singlet at ~2.6 ppm and a shift of the CH–O proton from ~4.0 ppm to ~5.3 ppm. Preparation of the other radical precursors is included with the subsequent reduction–rearrangements.

General procedure for hydrogenation of bicyclic alkenes: *N*-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 32a [43]

Alkene **28a** (100 mg, 0.41 mmol) was dissolved in MeOH (3 cm^3), and 10% Pd/C (42 mg, 0.04 mmol Pd) was added. The mixture was placed under 1 atm of hydrogen for 10 min at 25 °C using a balloon. The flask was then opened to the atmosphere and the mixture filtered through a Celite pad. The solvent was removed at reduced pressure to give an oil. Chromatography (SiO_2, 15% Et_2O : petroleum ether) gave compound **32a** as a white solid (95 mg, 94%, lit.[43] 86%); mp 40–41 °C (lit. 41–42 °C); δ_H (400 MHz) 7.26–7.18 (2 H, m, 2 × CH of aromatic), 7.14–7.09 (2 H, m, 2 × CH of aromatic), 5.12 (2 H, s, C(1)H and C(4)H), 2.11 (2 H, d, *J* 8.0, 2 × CH *exo*), 1.41 (9 H, s, Bu^t), 1.29 (2 H, d, *J* 8.0, 2 × CH *endo*); δ_C (100 MHz), 155.2 (C=O), 144.8 (2 × C(quat) of aromatic), 126.3 (2 × C of aromatic), 119.4 (2 × C of aromatic), 79.9 (CMe_3), 61.0 (C1 and C4), 26.7 (C2 and C3), 28.2 (CMe_3).

Experimental details and characterisation data for reduced compounds **32e**–**g** and **32i** are to be found in the electronic supplementary information. ‡

N-Methyl-1,2,3,4-tetrahydro-1,4-iminonaphthalene 32h [47]

A solution of $LiAlH_4$ (1.0 M in Et_2O, 1.0 cm^3, 1.0 mmol) was added to a stirred solution of carbamate **32a** (100 mg, 0.41 mmol) in Et_2O (4 cm^3) at 25 °C and the mixture heated to reflux overnight. The mixture was then allowed to cool and NaOH (2.5 cm^3 of a 2 M aq. solution) was added, followed by water (10 cm^3) and the aqueous layer was extracted with Et_2O (3 × 20 cm^3). The solvent was removed at reduced pressure. Column chromatography (EtOAc containing 2% Et_3N) gave amine **32h** as a white solid (35 mg, 54%): R_f (EtOAc containing 2% Et_3N) 0.20; δ_H (400 MHz) 7.22–7.17 (2 H, m, 2 × CH of aromatic), 7.13–7.07 (2 H, m, 2 × CH of aromatic), 4.06 (2 H, s, C(1)H and C(4)H), 2.11 (2 H, d, *J* 8.0, 2 × CH *exo*), 2.03 (3 H, s, Me), 1.20 (2 H, dd, *J* 8.0 and 2.0, 2 × CH *endo*); δ_C (100 MHz) 144.3 (2 × C (quat) of aromatic), 126.2 (2 × C of aromatic), 121.7 (2 × C of aromatic), 67.3 (C1 and C4), 35.4 (Me), 27.1 (C2 and C3).

General procedure for neophyl-type rearrangement: *N*-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydro-1,4-methanoisoquinoline 33a

A mixture of AIBN (60 mg, 0.37 mmol) and TTMSS (266 mg, 1.07 mmol), in toluene (2 cm^3), was added over 100 min to a preheated solution of xanthate **31a** (250 mg, 0.71 mmol) in toluene (21 cm^3). The reaction was left at reflux for a further 30 min after completion of the addition, allowed to cool, and the solvent removed at reduced pressure. Column chromatography (SiO_2, 10% Et_2O : petroleum ether) gave **33a** as a colourless oil that crystallised on standing to a white solid (158 mg, 90%); R_f (50 Et_2O : petroleum ether) 0.54; mp (from petroleum ether) 65–66 °C; ν_{max}(thin film)/cm^{-1} 2977s, 2889m, 1698s, 1462m, 1392s, 1251m, 1181m, 1152s, 1093s, 838m, 755m; δ_H (500 MHz, DMSO-d_6, 90 °C) 7.34 (1 H, d, *J* 7.0, CH of aromatic), 7.24 (1 H, d, *J* 7.0, CH of aromatic), 7.21–7.11 (2 H, m, 2 × CH of aromatic), 4.94 (1 H, br s, C(1)H), 3.66 (1 H, s, C(4)H), 3.48 (1 H, dd, *J* 9.0 and 3.0, C(3)H *exo*), 2.64 (1 H, dd, *J* 9.0 and 2.0, C(3)H *endo*), 1.96 (1 H, d, *J* 9.0, C(9)H), 1.79 (1 H, d, *J* 9.0, C(9)H), 1.37 (9 H, s, Bu^t); δ_C (125 MHz, DMSO-d_6, 90 °C) 155.4 (C=O), 146.4, 145.1 (2 × C(quat) of aromatic), 127.8, 126.7, 122.2, 121.0 (4 × CH of aromatic), 79.4 (CMe_3), 62.2 (C1), 49.5 (C3), 49.1 (C9), 44.5 (C4), 28.2 (Bu^t); *m*/*z* (CI^+, NH_3) 263 (M + NH_4^+, 21%), 246 (M + H^+, 25), 207 (100), 146 (M + H − Boc^+, 96) (Found: M + H^+, 246.1494. $C_{15}H_{20}NO_2$ requires 246.1494).

Experimental procedures and characterisation data for rearranged products **33b**–**g** are to be found in the electronic supplementary information. ‡

N-Methyl-1,2,3,4-tetrahydro-1,4-methanoisoquinoline 33h

a) From radical deoxygenation. To a solution of alcohol **30h** (122 mg, 0.70 mmol) in CH_2Cl_2 (5 cm^3) was added DMAP (342 mg, 2.8 mmol) and phenylchlorothionocarbonate (144 mg, 0.83 mmol). The reaction was stirred for 16 h and the solvent was then removed at reduced pressure. Column chromatography (SiO_2, 20% Et_2O : petroleum ether containing 2% Et_3N) gave thiocarboxylate **31h** as a yellow oil (140 mg, 65%): R_f (EtOAc containing 2% Et_3N) 0.55. The product was not fully characterised but instead was identified by a change in chemical

shift of the CH–O proton from 3.8 in the starting alcohol to 5.1 ppm in the product and an increase in the aromatic proton integral from 4 H to 9 H. AIBN (18 mg, 0.10 mmol) and TTMSS (166 mg, 0.67 mmol) were added to a solution of thiocarboxylate **31h** (140 mg, 0.44 mmol) in toluene (17.5 cm^3) and the flask was then lowered into an oil bath preheated to 125 °C. The mixture was stirred at reflux for 2 h and then allowed to cool. The solvent was removed at reduced pressure. Column chromatography (SiO_2, EtOAc containing 2% Et_3N) gave amine **33h** as a yellow oil (16 mg, 23%): R_f (EtOAc containing 2% Et_3N) 0.17; ν_{max}(thin film)/cm^{-1} 3045m, 2974s, 2855s, 2780s, 1459m, 1275m, 1194m, 1174m, 1151m, 1128m, 1091m, 1032m, 1013m, 954w, 909w, 754m; δ_H (400 MHz) 7.29–7.23 (1 H, m, CH of aromatic), 7.21–7.13 (3 H, m, 3 × CH of aromatic), 4.08 (1 H, s, C(1)H), 3.45 (1 H, dd, *J* 8.0 and 2.0, C(3)H *exo*), 3.41 (1 H, s, C(4)H), 2.04 (1 H, dd, *J* 9.5 and 3.0, C(9)H), 1.95 (3 H, s, Me), 1.82 (1 H, dd, *J* 9.5 and 3.0, C(9)H), 1.44 (1 H, dd, *J* 8.0 and 2.0, C(3)H *endo*); δ_C (100 MHz), 146.5, 140.8 (both C(quat)), 126.7, 125.2, 122.7, 120.5 (4 × CH of aromatic), 67.3 (C1), 56.0 (C3), 49.1 (C9), 45.0 (C4), 40.8 (Me); *m*/*z* (TOF ES^+) 160 (M + H^+, 100%) (Found: M + H^+, 160.1129. C_{11} $H_{14}N$ requires 160.1126).

b) From hydride reduction. $LiAlH_4$ (1.0 M in THF, 0.92 cm^3, 0.92 mmol) was added to a solution of amine **33a** (150 mg, 0.61 mmol) in THF (4 cm^3) and the mixture heated at reflux for 2 h. The mixture was then allowed to cool and aqueous NaOH (1.5 $cm^3$of a 2 M aq. solution) was added, followed by water (6 cm^3). The aqueous layer was extracted with Et_2O (3 × 5 cm^3), the combined organic extracts dried ($MgSO_4$), and the solvent removed at reduced pressure. Column chromatography (SiO_2, EtOAc containing 2% Et_3N) gave amine **33h** as a yellow oil (44 mg, 45%): R_f (EtOAc containing 2% Et_3N) 0.17. Other data as above.

N-(*tert*-Butylcarbonyl)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 32i and *N*-(*tert*-butylcarbonyl)-1,2,3,4-tetrahydro-1,4-methanoisoquinoline 33i

Reaction of alcohol **30i** (150 mg, 0.61 mmol) according to the general procedure gave an oil. Chromatography (SiO_2, 10% Et_2O : petroleum ether to 30% Et_2O : petroleum ether, gradient elution) gave xanthate **31i** (176 mg, 86%) as an oil: R_f (15% Et_2O : petroleum ether) 0.14. AIBN (21 mg, 0.13 mmol) and TTMSS (197 mg, 0.79 mmol) were added to a solution of xanthate **31i** (176 mg, 0.52 mmol) in toluene (21 cm^3). The mixture was brought to reflux and left for 2 h. The mixture was then allowed to cool, and the solvent removed at reduced pressure. Column chromatography (SiO_2, 30% Et_2O : petroleum ether) first gave **32i** as a colourless oil that crystallised on standing to a white solid (17 mg, 14%); data as in the electronic supplementary information. ‡

Second to elute was **33i** as a white solid (73 mg, 61%): R_f (30% Et_2O : petroleum ether) 0.19; mp (from petroleum ether) 102–103 °C; ν_{max}(KBr)/cm^{-1} 2974s, 2882m, 1602s, 1475m, 1416s, 1386m, 1364m, 1309m, 1262m, 1212m, 1113m, 1003s, 764s; δ_H (500 MHz, toluene-d_8, 90 °C) 7.15 (1 H, d, *J* 6.5, CH of aromatic), 7.02–6.85 (3 H, m, 3 × CH of aromatic), 5.33 (1 H, br s, C(1)H), 3.45 (1 H, dd, *J* 9.5 and 4.0, C(3)H *exo*), 3.14 (1 H, s, C(4)H), 2.77 (1 H, d, *J* 9.5, C(3)H *endo*), 1.57–1.49 (2 H, m, 2 × C(9)H), 1.07 (9 H, s, Bu^t); δ_C (125 MHz, toluene-d_8, 90 °C) 175.4 (C=O), 146.0, 144.8 (2 × C(quat) of aromatic), 127.1, 126.4, 121.2, 121.0 (4 × CH of aromatic), 62.4 (C1), 50.5 (C3), 47.8 (C9), 44.7 (C4), 38.9 (*C*Me_3), 27.8 (C*Me*$_3$); *m*/*z* (EI^+) 229 (M^+, 21%), 144 (11), 129 (82), 116 (63), 84 (15), 57 (100) (Found: M + H^+, 230.1547. $C_{15}H_{20}NO$ requires 230.1545).

1,2,3,4-Tetrahydro-1,4-methanoisoquinoline 34[37]

To a solution of carbamate **33b** (150 mg, 0.74 mmol) in ethylene glycol (8 cm^3) was added 10% aq. KOH (8 cm^3). The mixture was brought to reflux and left for 14 h. The mixture was allowed to cool, extracted with Et_2O (5 × 100 cm^3), the organic extracts washed with water (2 × 100 cm^3), dried (K_2CO_3) and the solvent removed at reduced pressure. Chromatography (Et_2O, 1% MeOH, 2% Et_3N) gave the known amine **34** (50 mg, 47%): R_f (Et_2O, 2% Et_3N) 0.12; ν_{max}(thin film)/cm^{-1} 3327br m, 3239br m, 3044m, 2977s, 2871m, 1698s, 1460s, 1374w, 1256w, 1167w, 1049w, 966w, 754s; δ_H (400 MHz) 7.30–7.05 (4 H, m, 4 × CH of aromatic), 4.38 (1 H, s, C(1)H), 3.56 (1 H, s, C(4)H), 3.18 (1 H, dd, *J* 9.0 and 3.0, C(3)H *exo*), 2.27 (1 H, dd, *J* 9.0 and 1.0, C(3)H *endo*), 1.95–1.65 (1 H, br s, NH), 1.86 (1 H, d, *J* 7.0, C(9)H), 1.76 (1 H, d, *J* 7.0, C(9)H); δ_C (100 MHz) 146.5, 145.2 (both C(quat) of aromatic), 144.0 and 143.9 (2 × C(quat) of aromatic), 126.4, 125.9, 121.0, 119.1 (4 × CH of aromatic), 60.8 (C1), 48.3 (C9), 46.6 (C3), 44.4(C1).

3-Ethylpyrrole 36[44]

A solution of 3-ethyl-1-phenylsulfonylpyrrole **35**[45] (1.60 g, 6.8 mmol) in methanol (26 cm^3) was added to NaOH (13 cm^3 of a 5 M aq. solution) and the mixture heated to reflux for 2.5 h under argon. The mixture was allowed to cool and extracted with EtOAc (3 × 50 cm^3). The combined organic extracts were washed with brine (100 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure to give spectroscopically pure **36** (520 mg, 80%): δ_H (200 MHz) 8.20–7.80 (1 H, br s, NH), 6.79–6.77 (1 H, m, C(5)H), 6.65 (1 H, s, C(2)H), 6.20 (1 H, s, C(4)H), 2.61 (2 H, q, *J* 8.0, CH_2), 1.31 (3 H, t, *J* 8.0, Me). The material was Boc-protected[56] immediately.

1-(*tert*-Butoxycarbonyl)-3-ethylpyrrole 37

DMAP (256 mg, 2.1 mmol) was added to a stirred solution of Boc_2O (5.45 g, 25 mmol) and 3-ethylpyrrole **36** (1.98 g, 21 mmol) in acetonitrile (20 cm^3) and the reaction left to stir for 24 h under argon at 25 °C. Imidazole (3.0 g, 44 mmol) was added and the solution stirred for 15 min according to the procedure of Basel and Hassner[57] for removal of Boc_2O. CH_2Cl_2 (25 cm^3) was added and the solution washed with 0. % aq. HCl (3 × 50 cm^3). The organic layer was separated, dried ($MgSO_4$) and the solvent was removed at reduced pressure. Column chromatography (SiO_2, 3% Et_2O : petroleum ether) gave the pyrrole **37** as a yellow oil (2.58 g, 54%): R_f (10% Et_2O : petroleum ether) 0.67. An analytical sample was prepared by Kugelrohr distillation (bp 80 °C at 10 mmHg). ν_{max}(thin film)/cm^{-1} 3148m, 3101m, 2969s, 2934s, 2874s, 1741s 1561m, 1489s, 1461s, 1404s, 1371s, 1313s, 1243s, 1162s, 1122s, 1071s, 1050m, 971s, 933m, 854s, 829m, 772s; δ_H (400 MHz) 7.17 (1 H, s, C(5)H), 7.00 (1 H, s, C(2)H), 6.18 (1 H, s, C(4)H), 2.47 (2 H, q, *J* 7.5, CH_2), 1.60 (9 H, s, Bu^t), 1.20 (3 H, t, *J* 7.5, Me); δ_C (100 MHz) 149.0 (C=O), 129.6, 120.0, 115.9, 112.6 (all pyrrole C), 83.1 (*C*Me_3), 28.0 (C*Me*$_3$), 20.0 (CH_2), 14.5 (Me); *m*/*z* (CI^+, NH_3) 196 (M + H^+, 100%), 152 (13), 149 (19), 96 (M − Boc^+, 100) (Found: M + H^+, 196.1329. $C_{11}H_{18}NO_2$ requires 196.1338).

1-(*tert*-Butoxycarbonyl)-2,4-dimethylpyrrole 38

DMAP (180 mg, 1.5 mmol) was added to a stirred solution of Boc_2O (650 mg, 3.00 mmol) and 2,4-dimethylpyrrole (500 mg, 5.25 mmol) in MeCN (5 cm^3) and the reaction stirred under argon at 25 °C for 24 h. The solvent was then removed at reduced pressure. Column chromatography (SiO_2, 3% Et_2O : petroleum ether) gave the pyrrole **38** as a colourless oil (325 mg, 55%): R_f (10% Et_2O : petroleum ether) 0.70; ν_{max}(thin film)/cm^{-1} 3153m, 3123m, 3089m, 2978s, 2929s, 2750m,1736s, 1607m, 1535s, 1479s, 1456s, 1432s, 1391s, 1340s, 1257s, 1169s, 1095s, 1039m, 1005m, 989m, 968m, 859s, 848s, 802s; δ_H (400 MHz) 6.93 (1 H, s, C(5)H), 5.79 (1 H, s, C(3)H), 2.40 (3 H, s, Me–C(2)), 2.01 (3 H, s, Me–C(4)), 1.59 (9 H, s, Bu^t); δ_C (100 MHz, $CDCl_3$), 149.6 (C=O), 131.6, 120.4, 117.5, 114.2 (all pyrrole C), 82.7 (*C*Me_3), 28.0 (C*Me*$_3$), 15.4 (H_3C–C(2)), 11.7 (H_3C–C(4));

m/z (CI^+, NH_3) 196 ($M + H^+$, 52%), 149 (17), 96 ($M - Boc^+$, 52) (Found: $M + H^+$, 196.1328. $C_{11}H_{18}NO_2$ requires 196.1338).

1-(*tert*-Butylcarbonyl)pyrrole 39[48]

Et_3N (5.66 g, 56 mmol) was added dropwise to a solution of trimethylacetyl chloride (6.75 g, 56 mmol) and pyrrole (5.0 g, 76 mmol) in dry CH_2Cl_2 (30 cm^3) at 25 °C. DMAP (0.68 g, 5.6 mmol) was then added as one portion and the mixture stirred for 24 h at 25 °C. The solution was then diluted with Et_2O (30 cm^3), washed with saturated $KHSO_4$ (20 cm^3), saturated $NaHCO_3$ (20 cm^3) and water (40 cm^3). The organic layer was dried ($MgSO_4$) and the solvent removed at reduced pressure to give an oil. Column chromatography (SiO_2, 3% Et_2O : petroleum ether) gave **39** as a colourless oil (4.9 g, 58%): R_f (10% Et_2O : petroleum ether) 0.80; ν_{max}(thin film)/cm^{-1} 2978s, 2935m, 2908w, 2877w, 1705s, 1460s, 1406m, 1371m, 1296s, 1223s, 1101s, 1078m, 1052m, 903s, 714s; δ_H (200 MHz), 7.48–7.40 (2 H, m, C(2)H and C(5)H), 6.28–6.22 (2 H, m, C(3)H and C(4)H), 1.45 (9 H, s, Bu^t); δ_C (100 MHz) 175.8 (C=O), 120.5 (C2 and C5), 111.9 (C3 and C4), 40.6 (CMe_3), 28.5 (CMe_3); *m/z* (TOF CI^+, NH_3) 152 ($M + H^+$, 100%), 131 (63), 87 (24), 70 (29) (Found: $M + H^+$, 152.078. $C_9H_{13}NO$ requires 152.075).

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