Highly Enantioenriched 2-Azabenzonorbornenes from 7-Azabenzonorbornadienes by Asymmetric Hydroboration–Oxidation and Tandem Deoxygenation–Rearrangement–Electrophile Trapping

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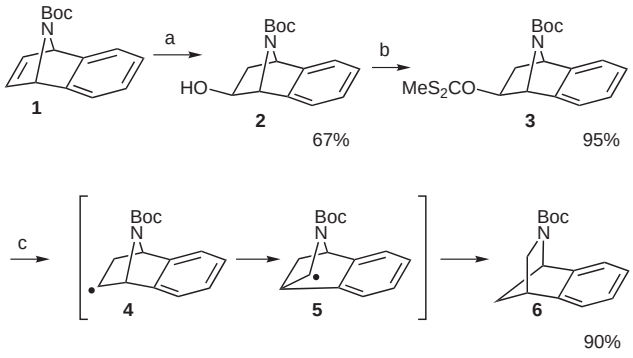
Abstract: 3-*exo*-Substituted 2-azabenzonorbornenes are accessible from 7-azabenzonorbornadienes in good yields and high enantiomeric excess via asymmetric hydroboration–oxidation, followed by tandem deoxygenation–rearrangement–electrophile trapping and also provide access to substituted aminomethylindenes.

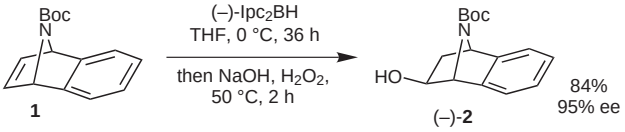
Key words: asymmetric synthesis, radicals, tandem reactions, deoxygenation, rearrangements

Radical cascade processes constitute a powerful methodology for the fast assembly of complex molecular frameworks.[1] We previously demonstrated the synthetic utility of nitrogen-directed radical rearrangements,[2] and recently applied this concept in a neophyl-type rearrangement process (**4** → **5**) to obtain racemic 2-azabenzonorbornenes, e.g. **6**, using xanthates **3** of 7-azabenzonorbornenols **2** (Scheme 1).[3] To build on this latter methodology we sought firstly to develop an asymmetric entry and secondly to trap the rearranged radical **5** with an electrophile in tandem with the deoxygenation–rearrangement.



Scheme 1 *Reagents and conditions*: (a) 9-BBN, THF, 20 °C, 24 h, then NaOH, H_2O_2, 0 °C → 20 °C, 90 min; (b) KH, THF, then CS_2, then MeI; (c) $(Me_3Si)_3SiH$, AIBN (slow addition), PhMe, reflux, 2 h.

To examine the first objective, initial studies were undertaken screening ligands in rhodium-catalysed asymmetric hydroboration–oxidation[4] for desymmetrisation of 7-azabenzonorbornadiene **1**. However, yields and ees for alcohol **2** could not be optimised to synthetically useful levels.[5] Alkene hydroboration–oxidation using organoboranes derived from α-pinene has been shown to be useful for the preparation of alcohols in high ee,[6] and (–)-diisopinocampheylborane [(–)-Ipc_2BH] has recently been successfully applied to the structurally related tropenone framework.[7] We envisaged that, by analogy, asymmetric hydroboration–oxidation of readily available benzyne/*N*-Boc-pyrrole cycloadduct **1**[8] might generate alcohol **2** in good ee. We were pleased to discover that hydroboration–oxidation with 1.5 equivalents (–)-Ipc_2BH, [prepared from commercial (+)-α-pinene of 92% ee according to the method of Brown][9] furnished alcohol (–)-**2** in 84% yield and 95% ee (Equation 1).[10]



Equation 1

In order to determine the absolute stereochemistry of (–)-**2**, rearranged–reduced azacycle (+)-**6** was prepared from (–)-**2** (Scheme 2) and subsequently converted to pyrrolidine diester (+)-**7** by oxidation using RuO_4 generated in situ,[11] followed by esterification using Me_3SiCHN_2.[12] Commercially available lactam (1*R*)-(–)-**8** was also transformed to (+)-**7**, following a procedure for the racemate via azabicycle (+)-**9**.[13,14] These results imply that the absolute stereochemistry of azacycle (–)-**2** and its derivatives is as shown. The sense of asymmetric induction on hydroboration with (–)-Ipc_2BH is consistent with that observed with tropenone derivatives.[7]

Attention then turned to exploring the second objective, and deoxygenation of methyl xanthate (+)-**3** was attempted in the presence of methyl acrylate. It was noted that the optimised conditions for deoxygenation–reduction [slow addition of $(Me_3Si)_3SiH$ to refluxing xanthate **3** in toluene][3] were very similar to those previously reported for silane-mediated xanthate deoxygenation–electrophile trapping.[15] It was found that addition over 100 minutes of a solution of $(Me_3Si)_3SiH$ (1.5 equiv), methyl acrylate (1.5 equiv) and AIBN (0.5 equiv) in toluene to a refluxing solution of xanthate (+)-**3** in toluene (0.035 M) gave a good yield of rearranged trapped azacycle (+)-**10** (Equation 2).[16]

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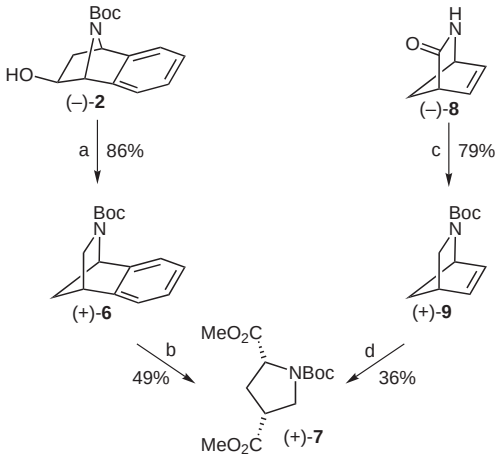
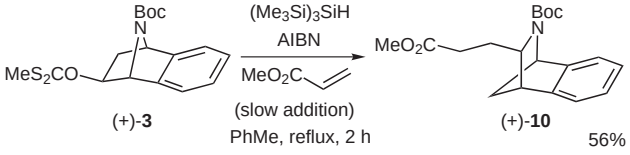


Scheme 2 *Reagents and conditions*: (a) as Scheme 1; (b) $RuCl_3·H_2O$, (12 mol%), $NaIO_4$ (17 equiv), H_2O–EtOAc–MeCN (2:1:1), 20 °C, 4 h, then Me_3SiCHN_2 (2.1 equiv), MeOH–PhMe (3:10), 20 °C, 45 min; (c) $LiAlH_4$ (5 equiv), THF–Et_2O (5:1); (d) $RuCl_3·H_2O$ (15 mol%), $NaIO_4$ (16 equiv), H_2O–EtOAc, (4:11), 0 °C, 8 h, then Me_3SiCHN_2 (2.1 equiv), MeOH–PhMe (3:10), 20 °C, 45 min.



Equation 2

Previous NOE studies on a related skeleton, **11** (Figure 1) showed enhancement at H_a upon irradiation at H_b.[3b] However, in trapped azacycle **10** no enhancement was seen between H_a and H_c, but rather between H_a and H_d, indicating exclusively *exo* trapping of radical **5**.

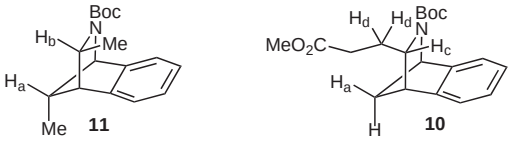
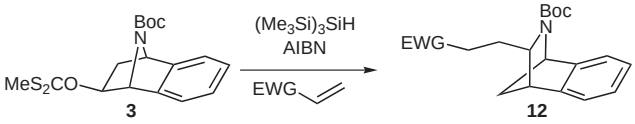


Figure 1

Encouraged by the above trapping result, other representative electron-deficient alkenes were examined and the corresponding rearranged–trapped azabicyclic adducts **12** (Equation 3) were obtained in 43–77% yields (Table 1, entries 2–4).[16]

The more electron-deficient alkenes (entries 1, 2 and 4) gave good yields of the trapped azacycles **12**. Phenylvinylsulfone (entry 3) gave an approximately 1:1 mixture



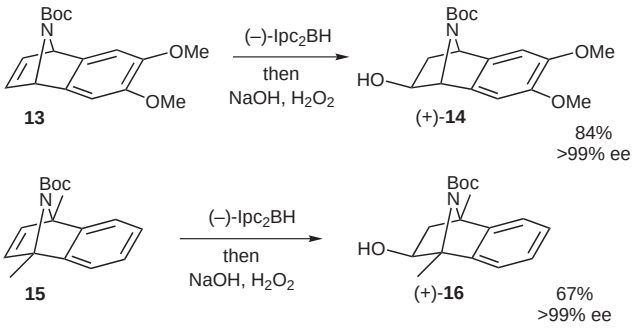
Equation 3

Table 1 Yields of Rearranged–Trapped Azabicyclic Adducts **12**

Entry	Alkene	Yield of adduct **12** (%)	Yield of **6** (%)
1	CO_2Me	56	0
2	$CO_2{}^tBu$	61	0
3	SO_2Ph	43	38
4	CN	77	0
5	CO_2NMe_2	0	37
6	$CH(OEt)_2$	0	81
7	CHO	55	0

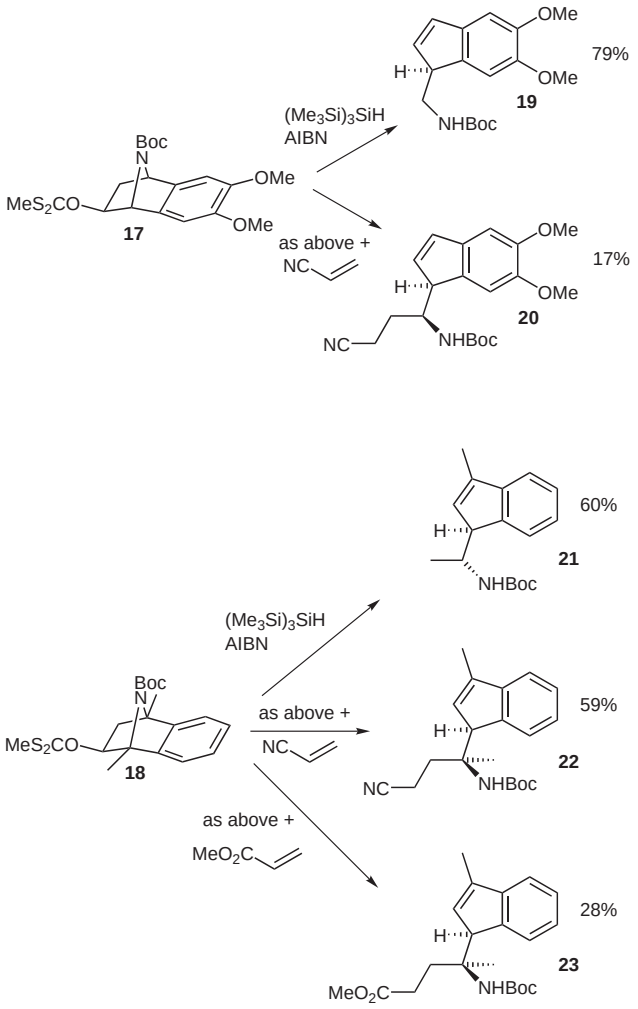
of trapped and reduced azacycles, suggesting that the rate of addition of rearranged radical **5** to phenylvinylsulfone is approximately equal to that of hydrogen-atom transfer from $(Me_3Si)_3SiH$. In contrast, the less electron-deficient alkenes such as diethyl acetal (entry 6) gave only rearranged–reduced material **6**, and the alkene appeared to have no reactivity with respect to the deoxygenated xanthate under these conditions. In contrast, *N*,*N*-dimethyl acrylamide gave only a poor yield of reduced material but a small amount of hydrosilylated alkene was also recovered and hydrosilylation of the alkene may be a significant competing process in these reactions.[17,18] In all cases, none of the directly reduced or trapped azacycles from the unrearranged radical **4** were observed. Substitution at the β-carbon of the alkene was tolerated: crotonaldehyde (entry 7) gave a good yield of trapped product, as a 2:1 mixture of diastereomers.

It was considered important to establish if the above chemistry could be extended to other azacycles previously shown to undergo deoxygenation–rearrangement.[3] We were pleased to find that the asymmetric hydroboration–oxidation chemistry could also be applied to the more electron-rich cycloadduct **13**, furnishing alcohol (+)-**14** in 84% yield and >99% ee.[19] Similarly, the more substituted framework of cycloadduct **15**[20] also proved amenable to these conditions, giving alcohol (+)-**16** in 67% yield and >99% ee (Scheme 3).[21] These representative results suggest that other azacyclic frameworks could be suitable substrates for this desymmetrisation process.



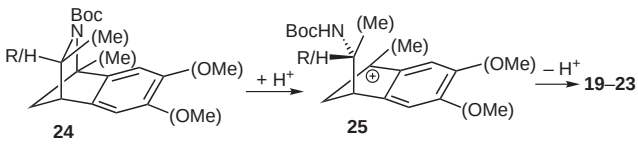
Scheme 3

For these latter alcohols, dexoxygenation–rearrangement–trapping of the corresponding xanthates **17** and **18**, was followed by isomerisation to give substituted aminomethylindenes **19**–**23** (Scheme 4).



Scheme 4

Isomerisations of the intermediate 2-azabenzonorbornenes **24** are likely to be catalysed by traces of acid and probably occur in these cases due to increased stability of the putative intermediate cation **25** (Scheme 5).



Scheme 5

In conclusion, we have developed an asymmetric access to 3-*exo*-substituted 2-azabenzonorbornenes in good yields by a novel tandem deoxygenation–rearrangement–electrophile trapping methodology and demonstrated routes to substituted pharmaceutically significant[22] aminomethylindenes. Whilst stannane-mediated dehalogenations and silane-mediated xanthate deoxygenations have been reported in tandem with electrophile trapping,[1,15,23] to the best of our knowledge, the current results constitute the first examples of tandem xanthate deoxygenation–rearrangement–electrophile trapping cascades. We are continuing to investigate the scope and synthetic applications of these reactions.

Acknowledgment

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(16) **Typical Procedure for Tandem Deoxygenation–Rearrangement–Electrophile Trapping**: Xanthate (+)-**3** (250 mg, 0.71 mmol) was dissolved in toluene (20 mL) and then heated to reflux. $(Me_3Si)_3SiH$ (256 mg, 1.1 mmol), AIBN (58 mg, 0.36 mmol) and methyl acrylate (9.6 μL, 1.1 mmol) were dissolved in toluene (4 mL) and were added to the refluxing solution via syringe pump over 100 min. The reaction mixture was allowed to reflux for a further 30 min before being cooled to r.t. and evaporated under reduced pressure. Column chromatography [SiO_2; gradient elution 5% → 20% Et_2O in PE (bp 30−40 °C)] of the residue gave ester (+)-**10** as a colourless oil (131 mg, 56%); R_f (Et_2O−PE, 1:4) 0.07; $[\alpha]_D^{25}$ 81.0 (*c* = 1.00, $CHCl_3$). IR (neat): 2977 (m), 1739 (s), 1695 (s), 1462 (m), 1366 (s), 1260 (m), 1170 (s), 1121 (m), 1100 (m), 1074 (m), 1000 (w), 910 (w), 839 (w), 757 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.05−7.39 (m, 4 H, aromatic CH), 4.86, 4.98 (0.25 H, 0.75 H, rotamers, CH), 3.67 (s, 3 H, OCH_3), 2.92−3.04, 2.79−2.92 (m, 0.75 H, 0.25 H, rotamers CH), 2.59−2.44 (m, 2 H, CH_2), 2.08−2.30 (overlapping m, 2 H, 2 × CH), 1.79−1.98 (m, 1 H, CH_2), 1.71−1.79 (m, 1 H, CH_2), 1.35−1.42, 1.26−1.35 [m, 10 H, $C(CH_3)_3$, CH]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174 (CO), 157 (CO), 146 (quat. aromatic), 144 (quat. aromatic), 127 (aromatic CH), 126 (aromatic CH), 122, 121 (rotamers, aromatic CH), 120 (aromatic CH), 79.5 [$C(CH_3)_3$], 62.7, 61.7 (rotamers, CH), 59.8 (CH), 51.8, 51.5 (rotamers, CH_3), 48.2, 47.8 (rotamers, CH), 45.3, 44.8 (rotamers, CH_2), 32.5, 31.9 (rotamers, CH_2), 30.5, 30.3 (rotamers, CH_2), 28.5, 28.3 [rotamers, $C(CH_3)_3$]. MS (CI+): *m*/*z* (%) = 332 (100) $[M + H]^+$, 276 (43), 232 (77), 214 (12), 200(5), 183 (4), 172 (10), 158 (15), 144 (17), 130 (11), 116 (26). HRMS: *m*/*z* calcd for $C_{19}H_{26}NO_4$: 332.1865; found: 332.1866.

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