Searching for intermediates in Prins cyclisations: the 2-oxa-5-adamantyl carbocation†

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The 2-oxa-5-adamantyl carbocation **4** is shown to be a viable intermediate in several S_N1 substitution reactions. However, attempts to observe the formation of **4** from various precursors by NMR methods (which succeed for the 1-adamantyl cation **5**) failed, suggesting that **4** does not survive on longer timescales. DFT calculations suggest that the retro-Prins process (β-cleavage, Grob fragmentation) to give enantiomeric (1*R*,5*R*)- and (1*S*,5*S*)-7-methylene-2-oxoniabicyclo[3.3.1]non-2-ene cations **22** is the only realistic unimolecular escape route for **4**. With the 6-31G(d) basis set, B3LYP calculation predicts that **4** is only 11 kJ mol⁻¹ more stable than **22**, and the barrier separating **4** and **22** is calculated to be only 15 kJ mol⁻¹, so rapid equilibration of these species is likely on the laboratory time scale. The implications of this study for the mechanism of the Prins cyclisation are discussed.

Introduction

Substituted tetrahydropyrans are common structural features of many natural products and biologically active compounds. A valuable approach for the synthesis of these heterocycles is the acid-promoted Prins-type cyclisation of an oxycarbenium ion generated *in situ*, for example, from reaction of a homoallylic alcohol with an aldehyde or from a homoallylic acetal, enol ether or α-acetoxy ether.[1–4] These stereoselective reactions have been used to good effect in the synthesis of a number of natural products.[5–8] However, the mechanism of Prins cyclisations is not simple and there is good evidence for oxonia-Cope rearrangements and allyl transfer processes occurring under certain conditions.[9–12] An in-depth understanding of the mechanisms involved is important to assist in the design of efficient strategies to complex targets. In 2002, Alder and co-workers proposed on the basis of DFT calculations[13] that these reactions proceeded *via* a discrete carbocation intermediate **1** (Scheme 1).
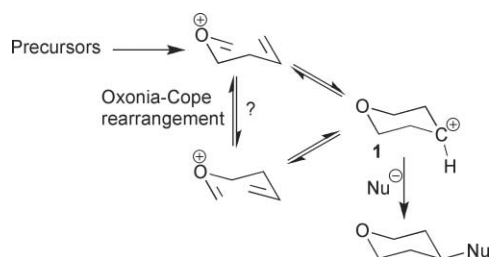
Scheme 1 Proposed mechanism for Prins cyclisations and oxonia-Cope rearrangements *via* the tetrahydro-2*H*-pyran-4-ylium cation **1**.

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These proposals have since received significant support from experimental work,[14,15] but we hoped to obtain direct evidence for the existence of an intermediate related to **1**, particularly because the DFT calculations predicted that **1** would show evidence of cyclic delocalisation (aromaticity), and unusual bond lengths. Carbocation **1** could also be an intermediate in the oxonia-Cope rearrangements, which can accompany Prins cyclisations. Intermediates in pericyclic reactions are rare[16] so such species clearly deserve experimental study. This paper describes our studies to probe for a suitably-substituted tetrahydro-2*H*-pyran-4-ylium cation.

Results and discussion

The parent tetrahydro-2*H*-pyran-4-ylium carbocation **1** is not expected to possess unusual thermodynamic stability in spite of its delocalised nature, since potential aromaticity is only gained at the expense of the CH_2–CH_2 bond strength. The electron-withdrawing inductive (dipole) effect of the oxygen works against the conjugative effect and will also destabilise **1**. B3LYP/6-311G(d) calculation of the formal equilibrium shown in eqn (1) predicts that this will lie marginally on the right-hand side (ΔE −3 kJ mol⁻¹ in the gas phase).


$$\qquad (1)$$
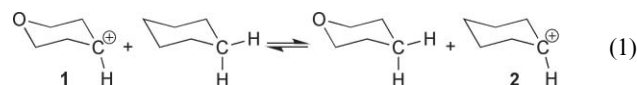
Tarbell and Hazen[17] reported that the rate of solvolysis for 4-tetrahydropyranyl tosylate in acetic acid at 85 °C is only 0.027 that of cyclohexyl tosylate (they did not report on the products of solvolysis). While this is in qualitative agreement with the calculations for eqn (1), it is likely that the ability of the oxygen atom in 4-tetrahydropyranyl tosylate to donate electron density towards the developing carbocation centre is diminished by hydrogen bonding from the acetic acid solvent.

$$\qquad (2)$$
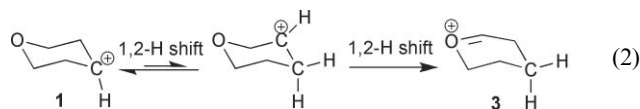
The cyclohexyl carbocation **2** has never been observed under stable ion conditions, because it rearranges too rapidly to the 1-methylcyclopentyl cation.[18] In the case of cation **1**, we may expect that, in the absence of trapping nucleophiles, hydride shifts will lead rapidly to the tetrahydro-2*H*-pyran-2-ylium carbocation **3**, eqn (2). Carbocation **3** is 112 kJ mol^{-1} more stable than **1** at the B3LYP/6-311G(d) level. Any substituted version of **1** where hydride shifts are possible is also likely to suffer the same fate.

These considerations led us to the adamantane skeleton, where hydride shifts are expected to have high barriers due to poor orbital overlap (see below) and our target cation became the 2-oxa-5-adamantyl carbocation **4**. B3LYP/6-311G(d) calculation of the position of the intermolecular hydride transfer reaction in eqn (3) shows that equilibrium lies just on the side of adamantane plus **4** (ΔE +1 kJ mol^{-1}), emphasising again that no special stability is associated with ions like **4**. Nevertheless, carbocation **5** is readily generated under stable ion conditions,[19,20] in spite of its bridgehead character, and one would expect that carbocation **4** might be generated under similar conditions.
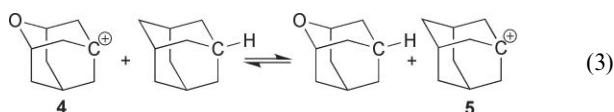

The oxaadamantane system possesses several other advantages for our study:

1. Preparation of 5-bromo-2-oxaadamantane **7** has been reported.[21]

2. The 2-oxa-1-adamantyl carbocation **6** (the counterpart of ion **3**) is not stabilised by oxonium resonance (bridgehead π-bond) and is calculated to be less stable that ion **4** (ΔE +9 kJ mol^{-1}) at the B3LYP/6-311G(d) level. Thus, even if **6** could be reached, *e.g. via* intermolecular hydride transfers, it should not predominate at equilibrium.

3. Since backside attack on **7** is impossible, *any* substitution reaction of **7** that results in a 5-substituted 2-oxaadamantane product must have proceeded by an $S_N 1$ mechanism with **4** as the intermediate.
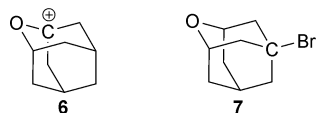

The substrate 5-bromo-2-oxaadamantane **7** was prepared using the four-step procedure shown in Scheme 2. Commercially available 2-adamantanone **8** was treated with methylmagnesium bromide to give 2-methyl-2-adamantanol **9**.[22,23] Krasutsky and co-workers have reported two methods for the fascinating conversion of tertiary alcohol **9** to 2-oxaadamantane **11**.[24,25] In our hands, the two-step procedure proved to be the more efficient. Thus, alcohol **9** was first treated with TFAA–H$_2$O$_2$ at −25 °C to give, after work-up, acetate **10** in 86% yield. On reaction with sulfuric acid, hydroxy acetate **10** readily cyclised to the required 2-oxaadamantane skeleton. The final step was a phase-transfer catalysed bromination of **11**[21] to give **7**. We found that using a minimum amount of 50% NaOH solution was crucial to the success of this reaction otherwise the corresponding 5-hydroxy-2-oxaadamantane **13** was isolated as the major product.
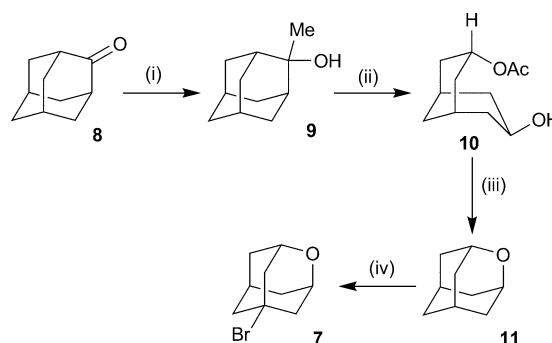
Scheme 2 Synthesis of 5-bromo-2-oxaadamantane **7**. (i) MeMgBr, Et$_2$O, 96%; (ii) TFAA, H$_2$O$_2$, -25 °C, 86%; (iii) 98% H$_2$SO$_4$, 98%; (iv) 50% NaOH, CBr$_4$, BTEAC, CH$_2$Cl$_2$, 40 °C, 39%.
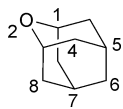
Reactions of 5-bromo-2-oxaadamantane

Initially, our aim was to gain evidence for the existence of an intermediate carbocation by conversion of 5-bromo-2-oxaadamantane **7** to other 5-substituted-2-oxaadamantanes *via* $S_N 1$ reactions. Thus, bromide **7** was treated with TMSN$_3$ and SnCl$_4$ in dichloromethane at room temperature and the analogous azide **12** was isolated in 93% yield (Scheme 3). Furthermore, hydrolysis of 5-bromo-2-oxaadamantane under a variety of conditions produced 2-oxaadamantan-5-ol **13**;[26,27] no other products could be detected. These products were characterised by spectroscopic methods and their ^{13}C NMR data compared with calculated chemical shift values (Table 1). Thus, it is immediately clear that the 2-oxa-5-adamantyl carbocation **4** is a real intermediate and is stable to ring opening and rearrangement on the time scale for displacement by azide or water.
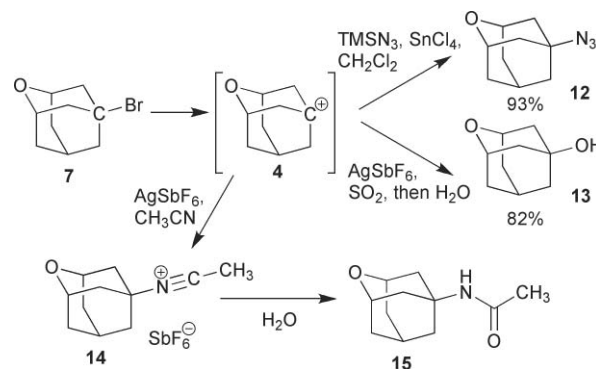
Scheme 3 Reactions involving the 2-oxa-5-adamantyl carbocation **4**.

Next, in an attempt to observe cation **4** by ^{13}C NMR spectroscopy, 5-bromo-2-oxaadamantane **7** was reacted with AgSbF$_6$ in dry acetonitrile under argon. This resulted in the clean production of nitrilium salt **14**, which could be isolated as a white solid that was stable in the absence of moisture. The ^{13}C NMR spectrum of **14** revealed a downfield signal at δ_C 176.5 assigned to the quaternary carbon, RN$^+$≡CMe. As a guide for identifying possible ions and products in this and other reactions, we calculated NMR shifts for a number of species using the GIAO procedure at the B3LYP/6-31G(d) level in Spartan. In Table 1, calculated shifts are shown in italics, observed shifts

Table 1 Observed and calculated[a] ^{13}C NMR shifts for 2-oxaadamantane derivatives

| Group at position 2	Group at position 5	C-1	C-4	C-5	C-6	C-7	C-8
O	H–C	69.4	36.2	26.9	35.9	26.9	36.2
		67.6	*36.7*	*29.8*	*36.7*	*29.8*	*36.7*
HO$^+$	H–C	90.7	34.2	24.4	33.2	24.4	34.2
		100.0	*34.6*	*26.8*	*33.4*	*26.4*	*36.0*
O	Br–C	71.7	47.8	62	47.5	30.2	34.2
		70.1	*52.5*	*68.7*	*51.4*	*37.6*	*39.0*
HO$^+$	Br–C	*108.8*	*48.4*	*67.1*	*48.1*	*33.5*	*39.1*
O	Cl–C	69.0	47.5	71.9	47.6	32.6	36.4
HO$^+$	Cl–C	*86.6*	*45.5*	*56.8*	*44.4*	*28.9*	*34.9*
O	HO–C	70.4	44.2	67.0	43.6	28.5	34.6
		70.0	*45.8*	*65.8*	*45.8*	*30.6*	*35.7*
HO$^+$	H$_2$$^+$O–C	90.4	38.8	88.8	37.9	27.5	32.3
		86.3	*38.9*	*87.6*	*40.5*	*30.3*	*34.1*
O	CH$_3$–C≡N$^+$–C	68.6	38.7	57.2	37.9	27.2	34.0
		67.1	*40.6*	*65.7*	*40.2*	*29.4*	*33.4*
O	C$^+$	*123.4*	*73.3*	*250.5*	*60.1*	*74.7*	*34.0*
H$_2$O$^+$–H···O	C$^+$	*117.8*	*65.7*	*282.4*	*72.7*	*90.4*	*34.3*
HO$^+$	C$^+$	*129.9*	*58.9*	*290.4*	*83.1*	*98.7*	*35.2*

[a] Calculated NMR shifts from the GIAO procedure at the B3LYP/6-31G(d) level in Spartan. Calculated shifts are shown in italics, observed shifts (where known) are in plain text.

(where known) are in plain text. For nitrilium salt **14**, there is good agreement between observed and calculated shift for the ring carbon atoms. However the calculated shift for the sp carbon in the nitrilium ion is 101.6, but the observed shift is 176.5 ppm. A similarly large discrepancy was found between observed (160) and calculated (103.4) shifts for the CH$_3$–C≡N$^+$–CH$_3$ nitrilium ion. We have no simple explanation, but note that the calculated B3LYP/6-31G(d) GIAO shift for the sp carbon atom in acetonitrile (102.7) is also significantly lower than the observed shift (117.7 ppm); for methyl isocyanide, the calculated (162.4) and observed shifts (157.5) are in better agreement. Agreement between calculated and observed shifts for these carbons might be improved by the inclusion of diffuse functions in the basis set used and the use triple zeta functions for the valence electrons, but we did not examine this. The nitrilium salt **14** was readily hydrolysed in quantitative yield to 5-acetamido-2-oxaadamantane **15** (Scheme 3). Again it is clear that cation **4** survives for long enough to react with the relatively weak nucleophile acetonitrile, admittedly present as the solvent.

While no sign of peaks which might be attributed to **4** were present in the NMR spectrum of nitrilium ion **14**, we hoped that it might be in equilibrium with low concentrations of **4**. The salt **14** was therefore treated with excess AgSbF$_6$ in dichloromethane in the knowledge that silver ions complex strongly with nitriles and so might remove any acetonitrile formed, but no changes could be detected. Salt **14** was also treated with CH$_3$OTf, which is known to react with free acetonitrile to form MeC≡N–CH$_3$$^+$,[28] but again no changes could be observed. Finally **14** was dissolved in CD$_3$C≡N, and the NMR monitored for a week, but no exchange of CH$_3$C≡N and CD$_3$C≡N groups was observed.

## Attempts to observe the 2-oxa-5-adamantyl carbocation 4 by NMR

Although it is clear that the 2-oxa-5-adamantyl carbocation **4** is behaving as a true intermediate in several reactions, observing it under stable ion conditions has proved elusive. Prior to embarking on these studies, we deemed it prudent to confirm our experimental techniques by ensuring that we could indeed generate and observe the known 1-adamantyl carbocation **5**.[19,20] We experienced no difficulties in observing clean generation of **5** (δ_C 302) by either reaction of commercially available 1-adamantanol with magic acid (4 : 1 HSO$_3$F : SbF$_5$), or from 1-bromoadamantane through reaction with SbF$_5$ in liquid SO$_2$ (Scheme 4).
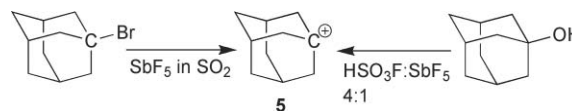
Scheme 4 Generation of the 1-adamantyl carbocation **5**.

Similar transformations on the 2-oxa-5-adamantyl analogues were then investigated. First, reaction of 2-oxaadamantan-5-ol **13** with excess magic acid (4 : 1) at –80 °C produced a clean ^{13}C NMR spectrum of a species which was clearly not a carbocation (no resonance below δ 100 ppm). We assign the spectrum to the diprotonated species **16** (Scheme 5) although SbF$_5$ adducts in place of protons cannot be ruled out. In particular the resonances at 90.4 and 88.8 ppm are in satisfactory agreement with those predicted at 86.3 and 87.6 in the calculated spectrum (Table 1). Unfortunately, careful warming of the solution did not lead to the formation of **4**; the ^{13}C NMR which resulted indicated that a complex mixture of products was formed.
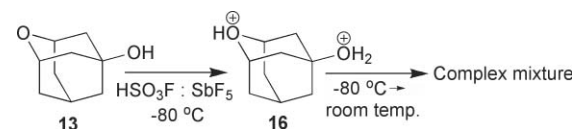
**Scheme 5** Protonation of 2-oxaadamantan-5-ol **13**.

Reaction of 5-bromo-2-oxaadamantane **7** with SbF$_5$ in liquid SO$_2$ also did not lead to the formation of **4**; a complex ^{13}C NMR spectrum resulted at –80 °C. We had anticipated difficulties with reaction of bromide **7** with Lewis acids, since the oxygen atom provides an alternative basic site, and once this is complexed, there is expected to be less opportunity for ionisation of the bromide.

We had hoped that silver ion would discriminate in favour of bromide removal, but reaction of **7** with AgSbF$_6$ in liquid SO$_2$ only resulted in the formation of the hydrolysis product 2-oxaadamantan-5-ol **13**, in spite of extensive efforts to ensure that the reactants and solvent were dry. It is worth noting that, in these experiments, no protic or Lewis acid is present to convert any adventitious water to non-nucleophilic H$_3$O$^+$.

In addition to AgSbF$_6$, silver carboranes were investigated as potential halide abstraction reagents because the exceptional inertness of carborane anions makes them especially useful in stabilising tertiary carbocations. The t-butyl cation is stable at room temperature as a carborane salt and amenable to X-ray crystallographic characterisation.[29] Compared to SbF$_6$$^-$ and related oxy- and fluoroanions, icosahedral carborane anions of the type CHB$_{11}$R$_5$X$_6$$^-$ (R = H, Me, X; X = halide) have lower

nucleophilicity and this can lead to different outcomes in halide metathesis reactions.[30] Counterintuitively, the electrophilicity of Ag^{+} is diminished as a carborane salt because the halide metathesis reaction is arrested at a halide-bridged intermediate stage. Intermediates of the type substrate-X-Ag(carborane) can frequently be observed.[31] This appears to be the case with 5-bromo-2-oxaadamantane as substrate because treatment of **7** with Ag(CHB$_{11}$H$_6$Br$_6$) in dichloromethane produces a white precipitate whose IR spectrum as a KBr pellet is consistent with 1:1 adduct formation and a supernatant whose ^{13}C NMR in CD$_2$Cl$_2$ indicates a mildly perturbed substrate (67.1, 62.9, 38.8, 38.4, 32.5, 25.9 ppm) alongside peaks from the starting material (70.7, 63.4, 47.1, 46.5, 33.3 and 29.6 ppm). The presence of acetonitrile, expected to give the nitrilium cation **14** if the desired cation **4** is accessible, had no effect on the outcome of this reaction confirming that the metathesis reaction was indeed stalled. Thus, a stronger halide abstracting reagent than Ag^{+} is required if we are to take advantage of carboranes as inert counterions.

We therefore turned our attention to trialkylsilylium carborane reagents, R$_3$Si(carborane), which are much superior as halide abstractors compared to silver.[32] Treatment of 5-bromo-2-oxaadamantane **7** with 1 equiv. of Et$_3$Si(CHB$_{11}$H$_5$Br$_6$) in *o*-dichlorobenzene-*d$_4$* gave a new product whose ^{1}H NMR spectrum is consistent not with halide abstraction, but with silylation at the ether O atom, forming the oxonium ion **17** (Scheme 6). Consistent with cationic character, nearly all of the ^{1}H resonances of the product (4.97, 2.55–1.83 ppm) are downfield of the starting material (4.16, 2.63–1.61 ppm). In particular, the downfield resonance ascribed to the C1 proton adjacent to the oxonium centre (4.16 ppm in **7**) experiences the largest downfield shift. Addition of a second equivalent of R$_3$Si(CHB$_{11}$H$_5$Br$_6$) to this product had no detectable effect in the ^{1}H NMR spectrum, suggesting that the positive charge on **17** inhibits reaction of the silyl electrophile at Br, preventing the desired bromide abstraction.
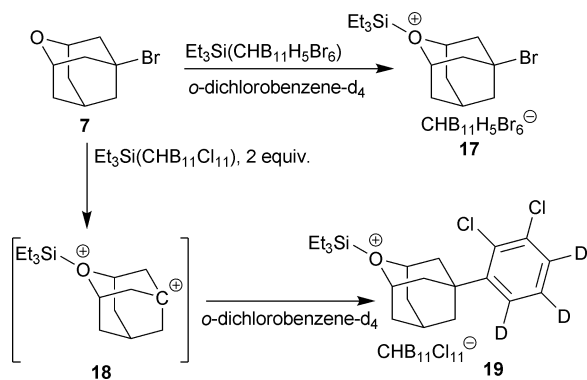
Scheme 6 Reactions of 5-bromo-2-oxaadamantane with trialkylsilylium carborane reagents.

However, when the electrophilicity of the silylium carborane reagent was increased by using the less nucleophilic CHB$_{11}$Cl$_{11}$[−] anion in place of CHB$_{11}$H$_5$Br$_6$[−], reaction of **7** with two equivalents of Et$_3$Si(CHB$_{11}$Cl$_{11}$) in *o*-dichlorobenzene-*d$_4$* did occur. As expected, ^{1}H NMR indicated that the first equivalent silylated **7** at O to form cation **17**. The second silylium equivalent produced further changes in the aliphatic region of the ^{1}H NMR spectrum but without obvious interpretation. Fortunately, crystals of the

product suitable for X-ray analysis were obtained (CCDC 752133) and shown to have the 5-bromo group of cation **17** replaced by an *o*-dichlorophenyl group (Fig. 1). This result can be understood in terms of silyl abstraction of Br from **17** to form dication **18** followed by electrophilic attack on the *o*-dichlorobenzene solvent to form **19** (Scheme 6). Due to its overall dipositive charge, dication **18** is expected to be more reactive than the desired carbocation **4** so reaction of this intermediate with solvent is not surprising.
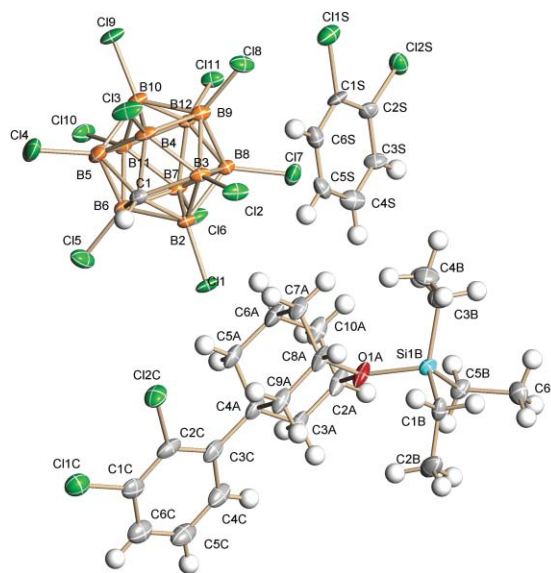
Fig. 1 X-Ray structure of **19**.

Further evidence for the formation of a reactive dication **18** comes from the observation that when the same reaction is performed in the presence of hexane, crystals of the 2-methylpentyl carbocation salt were isolated and characterised by single crystal X-ray analysis. This cation has been previously isolated and characterised by X-ray analysis by reacting hexanes with the highly electrophilic CH$_3$(carborane) derivatives.[29] Hydride abstraction from n-hexane is presumed to occur forming the primary hexyl carbocation which rapidly rearranges *via* 1,2 Meerwein shifts to the more stable tertiary 2-methylpentyl cation.[29] Evidently, a highly reactive carbocation must be formed in the reaction of 2 equiv. of Et$_3$Si(CHB$_{11}$Cl$_{11}$) with **7** and it is reasonable to assign this role to dication **18**, a more electrophilically activated analogue of the desired cation **4**.
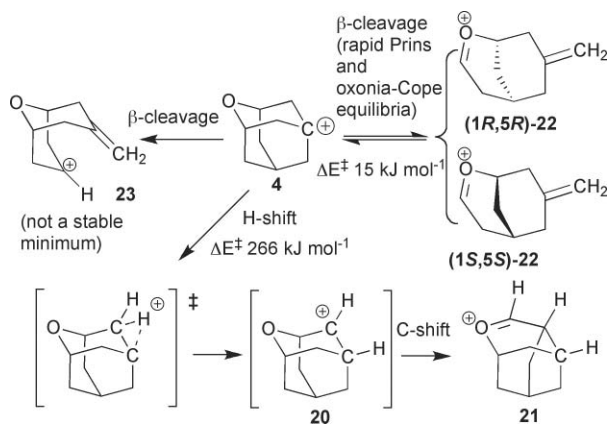
In summary, various reasonable ways to generate cation **4** failed to produce NMR spectroscopic evidence for its existence on an extended time scale, and in the next section we explore possible reasons for this.

Potential fates for the 2-oxa-5-adamantyl carbocation

In principle, cation **4** (C$_2$ symmetry) can undergo six unimolecular rearrangements: two 1,2-hydrogen shifts, two 1,2-carbon shifts, and two β-cleavages. As mentioned in the introduction, 1,2-hydrogen shifts in the adamantane system are expected to have high barriers due to poor orbital overlap. We located the transition state for the rearrangement pathway leading to ion **20** (see Scheme 7). This lies 266 kJ mol^{−1} above **4** at the B3LYP/6-31G(d) level; the enormous barrier certainly rules out this intramolecular

1554 | *Org. Biomol. Chem.*, 2010, **8**, 1551–1559

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Table 2 B3LYP/6-31G(d) energies relative to 2-oxa-5-adamantyl carbocation **4** (kJ mol^{-1})

	ΔE, kJ mol^{-1}
6	10.1
Prins cyclisation TS	15.2
22	11.3
22	−25.6
TS for H-shift to give	265.7
20	

MP2.[34–36] Finally the G3(MP2) procedure, normally considered to be reliable to 10 kJ mol^{-1}, favours the closed ion **4** by 14 kJ mol^{-1}.

In spite of these uncertainties, the general conclusion must be that **4** and **22** are likely to be in equilibrium on any but the very shortest timescales. The observation of clean S$_N$1 reactions *via* **4** under neutral or weakly acidic conditions may be due to either:

1. Reactions occuring on a shorter timescale than required to establish the **4/22** equilibrium.

2. The **4/22** equilibrium lying sufficiently far on the side of **4**, that products from **22** are not detected (a ΔE of 10 kJ mol^{-1} corresponds to 1–2% of products from **22** being formed.

Our present evidence does not allow a decision between these possibilities and it is unlikely that further computational studies will provide a satisfactory answer. Under sufficiently gentle ionising conditions, the **4/22** equilibrium might be observable, and we are still seeking to achieve this. However the bicyclic cation **22** is undoubtedly capable of reacting further in various ways under strongly acidic conditions (Scheme 8).

Scheme 7 Potential fates of the 2-oxa-5-adamantyl carbocation **4**. At the B3LYP/6-31G(d) level, **21** is 26 kJ mol^{-1} more stable than **4**, **22** is 11 kJ mol^{-1} less stable, and **23** is about 100 kJ mol^{-1} less stable, but is not a minimum.

hydrogen shift, and this is surely also true for the alternative shift. Actually ion **20** itself does not appear to exist but rearranges without a further barrier to give oxonium ion **21**, containing the tricyclo[4.3.1.0^{3,8}]decane (protoadamantane) skeleton, which the calculations indicate is the most stable ion in the whole system (Table 2).

The 1,2-carbon shifts lead to primary carbocations that would be expected to undergo rapid β-cleavage to give the same ions as derived from **4** itself by β-cleavages. Thus, the two possible β-cleavages shown in Scheme 7 are the only likely unimolecular reaction pathways. The retro-Prins process to give enantiomeric (1*R*,5*R*)- and (1*S*,5*S*)-7-methylene-2-oxonia-bicyclo[3.3.1]non-2-ene cations **22** is discussed in more detail below. Surprisingly, the alternative β-cleavage does not lead to a stable minimum at the B3LYP/6-31G(d) level. The classical structure corresponding to **23** (Scheme 6) lies about 100 kJ mol^{-1} above that for **4**, but the energy continues to rise as the alkene and the carbocation centre are driven further apart.

Computational estimates for the retro-Prins **4/22** equilibrium and reaction barrier vary somewhat with computational method and basis set, but all the indications are that this offers a very easy escape route for **4**. B3LYP/6-31G(d) calculations clearly favour the closed ion **4**, ΔE 11 kJ mol^{-1} with an activation energy for ring opening of 15 kJ mol^{-1} (see Table 2). With the larger 6-311G(d) basis set, ΔE is reduced to 3 kJ mol^{-1} and $\Delta E^{\ddagger}$ comes down to 12 kJ mol^{-1}. The mPW1K functional,[33] often recommended for transition states fails to find the ions **22** to be stable minima (*i.e.* the situation is similar to that for **23**), and this is also the situation predicted by Grimme's spin-component-scaled modification of
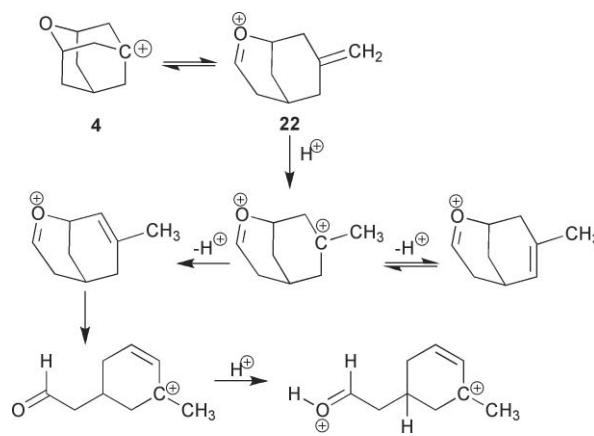

Scheme 8 Potential protonation and ring opening reactions of **22**.

Conclusions and implications for the mechanism of Prins cyclisations

We have shown that the 2-oxa-5-adamantyl carbocation **4** is a viable intermediate in several S$_N$1 substitution reactions. However, all attempts to date to observe it directly by NMR have failed. Although this is disappointing, we believe that the present evidence concerning **4** lends support to the proposal that 4-oxacyclohexyl carbocations related to **1** are intermediates in Prins cyclisation reactions and oxonia-Cope rearrangements.

Experimental

General procedures and solvent purification

^{1}H and ^{13}C NMR spectra were recorded using a Jeol Delta/GX 270 MHz, Jeol Delta/GX 400 MHz, Jeol Eclipse 300 MHz, Jeol Eclipse 400 MHz and Alpha 500 MHz spectrometers in deuterated chloroform unless otherwise stated using tetramethylsilane (TMS) as internal reference. Chemical shifts are reported in parts per million (ppm), and coupling constants (J) are in Hertz (Hz). NMR tubes fitted with PTFE valves manufactured by J. Young (Scientific

Glassware) Ltd. were used for experiments using sulfur dioxide and were stored at r.t. under argon.

Infrared spectra were recorded on either a Perkin Elmer 881 spectrometer or Perkin Elmer Spectrum One FT-IR spectrometer as neat solution, solids or films on sodium chloride plates.

Mass spectra, both high (HR) and low resolution (LR), were recorded on VG Micromass 3DS/2RS MS9 double focusing mass spectrometer and were obtained using electron ionisation (EI), chemical ionisation (CI) or electrospray (ESI) techniques.

Melting points (m.p.) were measured in open capillary tubes, unless otherwise stated, using a Gallenkamp melting point apparatus and are uncorrected.

Thin layer chromatography (TLC) was carried out on Merck silica gel 60 F254 aluminium backed plates. Visualisation was achieved with UV light at 254 nm or by dipping into a 0.5% aqueous potassium permanganate solution, by Hanessian's stain solution and heating with a hot air gun or by exposure to iodine.

Flash column chromatography was carried out using silica gel (obtained from Fluorochem Ltd.) as the adsorbent according to the procedure of Still et al.[37] The crude product was introduced into the column as a solution in the same elution solvent system, as a powder obtained by mixing the crude product with the same weight of silica gel in acetone and solvent was removed in vacuo at room temperature or dissolved into the minimum amount of dichloromethane (DCM).

All moisture or air sensitive reactions were carried out in oven-dried glassware under a positive pressure of nitrogen or argon using standard syringe/septa techniques.

Dry tetrahydrofuran (THF), DCM, toluene, diethyl ether and acetonitrile were obtained by passing through a modified Grubbs system of alumina columns, manufactured by Anhydrous Engineering. Hexanes were purified by distillation from 4 Å molecular sieves under reduced pressure. KSF clay and K-10 montmorillonite clay were activated by storing in oven at 120 °C overnight.

Sulfur dioxide was purchased from Aldrich Chemical Co. and used after passing through sulfuric acid traps combined with phosphorus pentoxide columns. Alternatively, it was distilled from phosphorus pentoxide at −12 °C under normal pressure. All the inert gases used (nitrogen or argon) were passed through phosphorus pentoxide in jacket columns.

Magnesium for Grignard reactions was crushed in a mortar before use, washed with diethyl ether, dried in an oven at 120 °C for 24 h and then stored under vacuo at r.t.

Silver hexafluoroantimonate, silver tetrafluoroborate, 1-bromo-adamantane, 5-bromo-2-oxaadamantane, 1-azidoadamantane and 5-azido-2-oxaadamantane were stored under nitrogen or argon before use. Ag(CHB$_{11}$H$_6$Br$_6$),[38] Et$_3$Si(CHB$_{11}$H$_6$Br$_6$)[38] and Et$_3$Si(CHB$_{11}$Cl$_{11}$)[32] were prepared as previously described and handled in a Vacuum Atmospheres Corp. glovebox with H$_2$O, O$_2$ <1 ppm. Commercial o-dichlorobenzene-d$_6$ was dried over 4 Å molecular sieves.

All other solvents and chemicals were used as supplied from Aldrich Chemical Co., Acros, Fisher, Alfa Aesar or Lancaster Synthesis.

2-Hydroxy-2-methyl-adamantane 9

Adamantan-2-one **8** (6.0 g, 1.0 eq) in dry diethyl ether (70 ml) was added dropwise to a fresh prepared solution of methyl magnesium iodide in dry diethyl ether. The mixture was stirred at r.t. for 1.5 h under a nitrogen atmosphere and then quenched with a saturated aqueous ammonium chloride solution (70 ml). The mixture was extracted with diethyl ether (3 × 30 ml) and the combined organic layers washed with a saturated aqueous sodium hydrogen carbonate solution (3 × 30 ml), dried over magnesium sulfate, filtered and concentrated in vacuo to give a white solid compound that was purified by silica gel column chromatography eluting with 25% ethyl acetate in n-hexane to give **9** as a crystalline solid m.p. 207 °C (lit[22] 207.8–209.0 °C) (6.38 g, 96% yield). δ_H (400 MHz, CDCl$_3$) 1.33-2.20 (17H, m); δ_C (100 MHz, CDCl$_3$) 27.4, 27.5 (CH$_3$), 29.3, 33.0, 35.1, 38.3, 39.1 and 73.7.

Double Criegee rearrangement on 2-hydroxy-2-methyl adamantane 9[24]

A solution of trifluoroacetic anhydride (108.8 g, 43.5 eq) and 50% aqueous hydrogen peroxide (11.8 g, 15.0 eq) was prepared at −25 °C and the solution stirred for 30 min at the same temperature. Then 2-hydroxy-2-methyl adamantane **9** (2.0 g, 1.0 eq) was added in 4 portions and the reaction stirred at −20 °C for 2.5 h. The reaction was quenched by slow addition of water (100 ml) keeping the temperature below −30 °C and then stirred for 10 min at r.t. The solution was extracted with dichloromethane (3 × 30 ml) and the combined organic layers washed with water (3 × 20 ml), saturated aqueous solution of sodium sulfite (3 × 30 ml) and water (3 × 30 ml). A small amount of the above solution (0.2 ml) was tested for peroxides and then, if test is negative, the mother solution was dried over magnesium sulfate, filtered and solvent evaporated in vacuo to give a white solid compound that was crystallised from n-hexane to afford 7-hydroxybicyclo[3.3.1]nonan-3-yl acetate **10** (1.70 g, 86% yield) δ_H (400 MHz, CDCl$_3$) 1.34 (1H, m), 1.54 (1H, m) 1.72-2.24 (14H, m), 4.04 (1H, tt, J 7.4, 6.5), 5.13 (1H, q, J 5.3); δ_C (100 MHz, CDCl$_3$) 21.6 (CH$_3$), 24.5, 27.7, 36.2, 36.7, 65.9, 69.6 and 170.2 (C=O).

Synthesis of 2-oxaadamantane 11

Concentrated sulfuric acid (50 ml) was cooled at −10 °C then hydroxyacetate **10** (1.0 g) was added all at once and the mixture was vigorously stirred at the same temperature for 1 h. The reaction was poured into ice and extracted with dichloromethane (3 × 15 ml). The combined organic layers were washed with 5% aqueous solution of sodium hydrogen carbonate (3 × 20 ml), dried over magnesium sulfate, filtered and evaporation of solvent in vacuo gave a white solid compound which was purified by sublimation (bath temperature 80 °C, 10 mm Hg) to afford 2-oxaadamantane **11** as a crystalline solid product (0.68 g, 98% yield) m.p. 224 °C (sealed tube), lit[39] m.p. 226-229 °C; δ_H (400 MHz, CDCl$_3$) 1.66 (4H, d, J 9.0), 1.90 (2H, s) 2.06-2.09 (6H, m), 4.01 (2H, m); δ_C (100 MHz, CDCl$_3$) 26.6, 35.8, 36.3 and 68.1.

Double Criegee rearrangement on 2-hydroxy-2-methyladamantane 9 and cyclisation (one-pot reaction)

A solution of trifluoroacetic anhydride (108.8 g, 43.5 eq) and 50% aqueous hydrogen peroxide (11.8 g, 15.0 eq) was prepared at −25 °C and the solution stirred for 30 min at the same temperature. Then 2-hydroxy-2-methyladamantane **9** (2.0 g, 1.0 eq) was added in 4 portions and the reaction stirred at −15–20 °C for 2.5 h. The

reaction was quenched by slow addition of water (100 ml) keeping the temperature below −30 °C and then it was stirred for 24 h at r.t. The solution was extracted with dichloromethane (3 × 50 ml) and the combined organic layers washed with water (3 × 30 ml), saturated aqueous solution of sodium sulfite (3 × 30 ml), water (3 × 30 ml). A small amount of the above solution (0.2 ml) was tested for peroxides and if the test was negative the mother solution was dried over magnesium sulfate, filtered and evaporated to dryness to give a white solid compound which was purified by sublimation (bath temperature 80 °C, 10 mm Hg) to afford 2-oxaadamantane **11** as a crystalline solid product (0.91 g, 55%).

5-Bromo-2-oxaadamantane 7

A solution of 50% sodium hydroxide in water (0.5 ml) was added to a solution of 2-oxaadamantane **11** (1.35 g. 1.0 eq), benzyltrimethylammonium chloride (0.13 g, 20 mol%) and carbon tetrabromide (1.05 g, 1.1 eq) in dichloromethane (38 ml). The mixture was vigorously stirred at 40 °C for 90 h. The reaction was cooled at r.t., diluted with water (100 ml), filtered thought Celite® and extracted with dichloromethane (7 × 30 ml). The combined organic layers were dried over magnesium sulfate, filtered and solvent removed *in vacuo* to give a waxy solid product that was purified by sublimation *in vacuo* (bath temperature 80 °C, 10 mm Hg) to remove starting material and the residue obtained by silica gel column chromatography eluting with 70% dichloromethane in n-hexane to afford 5-bromo-2-oxaadamantane **7** as a white solid: m.p. 47–48 °C; δ_H (400 MHz, CDCl$_3$) 1.63 (2H, d, J 12.4), 2.06 (2H, d, J 12.4), 2.32 (3H, d, J 11.9), 2.50 (2H, s), 2.63 (2H, d, J 11.9), 4.16 (2H, s); δ_C (100 MHz, CDCl$_3$) 30.3, 34.4, 47.6, 48.0, 61.7 and 71.3.

5-Azido-2-oxaadamantane 12

Tin(IV) chloride (0.22 g, 1.8 equiv.) was added to a stirring solution of azidotrimethylsilane (0.07 g, 1.2 equiv.) and 5-bromo-2-oxaadamantane **7** (0.10 g, in dry DCM (5 ml) under a nitrogen atmosphere at 0 °C. The reaction was stirred at r.t. for 4 h and then quenched with ice-cold water (10 ml). Extraction with DCM (3 × 5 ml) and the combined organic layers were dried over magnesium sulfate, filtered and evaporation of the solvent *in vacuo* gave a white solid which was purified by sublimation *in vacuo* (bath temperature 30 °C, 10 mm Hg) to afford *5-azido-2-oxaadamantane* **12** (0.07 g, 93% yield) as a pale yellow oil, silica gel TLC R_f 0.23 (ethyl acetate–n-hexane 70%); v_{max} (Neat) cm^{-1}, 2933 (C–H), 2855 (C–H), 2086 (N$_3$); δ_H (400 MHz, CDCl$_3$) 1.53-2.65 (11H, m), 4.25 (2H, s, 1-H, 3-H); δ_C (100 MHz, CDCl$_3$) 27.7, 34.5, 40.0, 40.3, 59.7 and 69.3; m/z (EI) 179 ([M]$^+$, 7%), 137 (100), 93 (100). Found (EI): 179.1055 [M]$^+$ (C$_9$H$_{13}$NO$_3$ requires 179.1059).

2-Oxaadamantan-5-ol 13

5-Bromo-2-oxaadamantane **7** (0.08 g, 1.0 eq) was added to silver hexafluoroantimonate (0.15 g, 1.2 eq) in liquid sulfur dioxide (1 ml) at −60 °C and the reaction was stirred at the same temperature under an argon atmosphere until a change of colour was noticed (usually after 3–5 min). The mixture was then stirred at r.t. until evaporation of sulfur dioxide ceased and was extracted with DCM (3 × 15 ml). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 2-oxaadamantan-5-ol **13**[26,27] (0.04 g, 70% yield) as a white solid,

which did not require further purification; m.p. 212–214 °C; δ_H (400 MHz, CDCl$_3$) 1.52 (2H, d, J 11.7, 7-H$_{ax}$, 10-H$_{ax}$), 1.71 (2H, J 11.5, 4-H$_{ax}$, 6-H$_{ax}$), 1.88 (2H, s, 9-H$_2$), 1.97 (4H, m, 7-H$_{eq}$, 10-H$_{eq}$, 4-H$_{eq}$, 6-H$_{eq}$), 2.34 (1H, s, 8H); 4.26 (2H, s, 1-H, 3-H); δ_C (100 MHz, CDCl$_3$) 28.5, 34.6, 43.6, 44.2, 67.0 and 70.4.

5-Acetonitrilium-2-oxaadamantane hexafluoroantimonate 14

5-Bromo-2-oxaadamantane **7** (0.10 g, 1.0 eq) and silver hexafluoroantimonate (0.18 g, 1.1 eq) were introduced into a dry NMR tube under a stream of dried argon. The NMR tube was sealed with a rubber septum, and the solids kept *in vacuo* for 10 min and flushed with argon; this procedure was repeated 5–8 times. Dry acetonitrile (*ca.* 0.5 ml) was added through a dry cannula, and the NMR tube was sealed and sonicated at r.t. until the formation of a yellow precipitate of AgBr had ceased (usually 15 min). The mixture was centrifuged to settle all the precipitate on the bottom of the tube and then the upper clear solution was transferred through a dry cannula to another dry NMR tube. The solution was centrifuged again to remove remaining residues of AgBr and transferred again to a dry NMR tube. Solvent was removed *in vacuo* overnight and then the white solid obtained was suspended in dry dichloromethane and sonicated twice. Finally, elimination of solvent *in vacuo* for 4–12 h afforded *5-acetonitrilium-2-oxaadamantane hexafluoroantimonate* **14** (0.12 g, 95% yield) as a white solid: δ_H (400 MHz, CD$_3$CN) 1.68-1.74 (9H, m, CH$_3$), 2.10 (6H, s), 2.28 (3H, s); δ_C (100 MHz, CD$_3$CN) 21.3, 29.7, 35.8, 40.2, 59.3 and 176.0.

5-*N*-(Acetyl)-2-oxaadamantane 15

Acetonitrilium-2-oxaadamantane hexafluoroantimonate **14** (0.11 g), was added to water and the solvent removed *in vacuo* to give a white solid residue that was purified by silica gel column chromatography eluting with 70% DCM in n-hexane and then 100% ethyl acetate affording *5-N-(acetyl)-2-oxaadamantane* **15** (0.05 g, 92% yield) as a light-brown solid: m.p 119–121 °C; silica gel TLC R_f 0.40 (ethyl acetate 100%); v_{max} (Neat) cm^{-1}, 3276 (N–H), 3077, 2928 (C–H), 1636 (C=O), 1555; δ_H (400 MHz, CDCl$_3$) 1.61 (2H, dd, J 12.7, 3.2, 4-H$_{ax}$, 6-H$_{ax}$), 1.93 (3H, s, CH$_3$), 1.99 (2H, d, J 12.7, 4-H$_{eq}$, 6-H$_{eq}$), 2.07 (4H, s, 7-H$_2$, 10-H$_2$), 2.21 (2H, s, 9-H$_2$), 2.23 (1H, s, 8-H), 4.18 (2H, s, 1-H, 3-H), 5.33 (1H, brs, N–H); δ_C (100 MHz, CDCl$_3$) 24.5 (CH$_3$), 27.2 (C-8), 34.9 (C^{-4}, C-6), 39.5 (C-9), 40.6 (C^{-7}, C-10), 50.5 (C-5), 69.1 (C^{-1}, C-3) and 169.5 (C=O); m/z (EI) 195 ([M]$^+$ 63), 138 (100), 136 (42) and 92 (42); Found (EI): 195.1261 [M]$^+$ (C$_{11}$H$_{17}$NO$_2$ requires 195.1259). Scans of the ^{1}H and ^{13}C NMR spectra for this compound are in the ESI.†

X-Ray structure determination

A colorless prism fragment (0.23 × 0.17 × 0.04 mm^3) was used for the single crystal X-ray diffraction study of [C$_6$H$_3$Cl$_2$C$_9$H$_{13}$OSiC(C$_2$H$_5$)$_3$][CHB$_{11}$Cl$_{11}$].0.5[C$_6$H$_4$Cl$_2$] (*ID cr283_0m*). The crystal was coated with paratone oil and mounted on to a cryo-loop glass fiber. X-Ray intensity data were collected at 100(2) K on a Bruker APEX2 platform-CCD X-ray diffractometer system (Mo-radiation, $\lambda = 0.71073$ Å, 50 kV/40 mA power). The CCD detector was placed at a distance of 5.0280 cm from the crystal.

A total of 2400 frames were collected for a hemisphere of reflections (with scan width of 0.3° in ω, starting ω and 2θ angles at −30°, and ϕ angles of 0, 90, 180 and 270° for every 600 frames, 30 s/frame exposure time). The frames were integrated using the Bruker SAINT software package and using a narrow-frame integration algorithm. Based on a monoclinic crystal system, the integrated frames yielded a total of 49 229 reflections at a maximum 2θ angle of 52.74° (0.80 Å resolution), of which 8499 were independent reflections ($R_{int} = 0.0745$, $R_{sig} = 0.0517$, redundancy = 5.8, completeness = 100%) and 5893 (69.3%) reflections were greater than $2\sigma(I)$. The unit cell parameters were, $a = 15.1970(5)$ Å, $b = 14.7033(5)$ Å, $c = 19.8581(7)$ Å, $\beta = 110.4569(6)°$, $V = 4157.4(2)$ Å^3, $Z = 4$, calculated density $D_c = 1.588$ g cm^{-3}. Absorption corrections were applied (absorption coefficient $\mu = 0.983$ mm^{-1}; max/min transmission = 0.9617/0.8048) to the raw intensity data using the SADABS program.

The Bruker SHELXTL software package (2008) was used for phase determination and structure refinement. The distribution of intensities (E2-1 = 0.958) and systematic absent reflections indicated one possible space group, $P2_1/c$. The space group $P2_1/c$ (#14) was later determined to be correct. Direct methods of phase determination followed by two Fourier cycles of refinement led to an electron density map from which most of the non-hydrogen atoms were identified in the asymmetry unit of the unit cell. With subsequent isotropic refinement, all of the non-hydrogen atoms were identified. There was one cation of $[C_9H_{13}OC_6H_3Cl_2Si[C_2H_5]_3]^+$, one anion of $[CHB_{11}Cl_{11}]^-$, and half a molecule of $C_6H_4Cl_2$ present in the asymmetry unit of the unit cell. The $C_6H_4Cl_2$ solvent was located at the inversion center and modeled as 50%/50% disordered molecule.

Atomic coordinates, and isotropic and anisotropic displacement parameters of all the non-hydrogen atoms were refined by means of a full matrix least-squares procedure on F2. The H-atoms were included in the refinement in calculated positions riding on the atoms to which they were attached, except the carborane CH-group (restrained C–H distance using DFIX to 0.96 Å). The refinement converged at $R_1 = 0.0430$, w$R_2 = 0.0947$, with intensity $I > 2\sigma(I)$. The largest peak/hole in the final difference map was 0.983/−0.466 e/Å^3.

Calculational methods

All initial DFT calculations were initially performed using Becke's three–parameter exchange functional[40] with the correlation functional of Lee, Yang and Parr (B3LYP).[41] All species were characterised by full geometry optimization with the standard 6-31G(d) basis set. Final energies were computed at the mPW1k/6-311G(d)//B3LYP/6-31G(d) level. Spin-component-scaled (SCS) MP2 energies were computed as described by Grimme[34,35] at B3LYP/6-31G(d) geometries. Calculations were performed with the Gaussian 03,[42] Jaguar[43] or Spartan[44] program packages. G3MP2 calculations[45] were carried out with Gaussian 03. Minima and transition states were characterised by analytical frequency calculations.

Acknowledgements

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Org. Biomol. Chem., 2010, **8**, 1551–1559 | 1559