Bu_3SnH mediated oxidative radical cyclisations: synthesis of 6*H*-benzo[*c*]chromen-6-ones †

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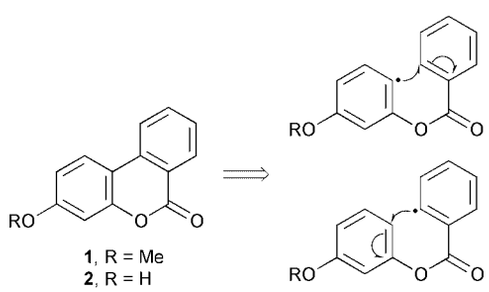
Attempts to synthesise 6*H*-benzo[*c*]chromen-6-ones by Bu_3SnH mediated cyclisation of *o*-(benzoyl)aryl radicals failed because of the preferred *trans* conformation of the ester. This problem was overcome by using cyclisation of *o*-(benzyloxy)aryl and *o*-[(aryloxy)methyl]aryl radicals to yield 6*H*-benzo[*c*]chromenes followed by oxidation to the 6*H*-benzo[*c*]chromen-6-ones. 3-Methoxy-6*H*-benzo[*c*]chromen-6-one **1**, one of the main biologically active constituents of *shilajit*, a herbal medicine used in countries surrounding the Himalayan mountains, was synthesised using Bu_3SnH mediated cyclisation of 1-benzyloxy-2,4-dibromo-5-methoxybenzene **31** to yield 3-methoxy-6*H*-benzo[*c*]chromene **25** followed by PCC oxidation of the 6-position. In order to avoid the problems of rearrangement, the aryl radical cyclisation must be designed such that whichever way the spirodienyl intermediate rearranges, the same product is obtained. For instance, the Bu_3SnH mediated cyclisation of 1-iodo- and 1-bromo-2-(3-methoxyphenyloxymethyl)benzenes **22** and **23** respectively gave both the isomers, 1-methoxy-6*H*-benzo[*c*]chromenes **24** and 3-methoxy-6*H*-benzo[*c*]chromenes **25** *via* rearrangement of the intermediate spirodienyl radical. The synthesised 6*H*-benzo[*c*]chromenes were oxidised in high yield to the corresponding 6*H*-benzo[*c*]chromen-6-ones. The mechanism of the 'oxidative' Bu_3SnH mediated cyclisation is discussed.

Synthesis of heterocycles using radical cyclisation is an important part of modern synthetic organic chemistry.[1] The most common reagent of choice for generating free radicals in these cyclisations is tri-*n*-butyltin hydride (Bu_3SnH). The mechanisms of these protocols using Bu_3SnH are reductive and well understood, *i.e.* in the radical chain the tri-*n*-butyltin radical ($Bu_3Sn^{\cdot}$) abstracts a suitable leaving group to generate an initial radical intermediate which undergoes cyclisation onto an unsaturated bond to form a cyclised intermediate radical, which in turn is reduced by hydrogen abstraction from Bu_3SnH to give the cyclised product. However, in a large number of these Bu_3SnH mediated cyclisations, the intermediate cyclised radical undergoes oxidation by loss of hydrogen rather than reduction by hydrogen abstraction from Bu_3SnH, *i.e.* an oxidative process.[2–20] Most of the intermediate cyclised radicals are aromatic π-radicals which undergo rearomatisation by loss of hydrogen. The mechanism has been the subject of debate in the literature.[2,3,6,8,9,11,18–20]

In our continuing studies[8,9] of the mechanism of Bu_3SnH mediated oxidative cyclisation and the application to the synthesis of heterocycles we investigated the preparation of 6*H*-benzo[*c*]chromen-6-ones. These synthetic and mechanistic studies are reported in this paper. 3-Methoxy-6*H*-benzo[*c*]-chromen-6-one **1** and 3-hydroxy-6*H*-benzo[*c*]chromen-6-one **2** (see Scheme 1) are key bioactive constituents of *shilajit*, a herbal medicine used in countries surrounding the Himalayan mountains. *Shilajit* is a black exudate of plant origin found in rocks at altitudes between 1000 and 5000 m in India, Pakistan, Nepal, Afghanistan, Tibet and Bhutan.[21] *Shilajit* is made up of a large number of natural products which differs between the regions in which it is found. A large number of medicinal properties are claimed for *shilajit* which include cures for asthma, diabetes, rheumatism and ulcers.[21] The 6*H*-benzo[*c*]chromen-6-ones are thought to be anti-oxidants and amongst the more important of the *shilajit* bioactive constituents.[21]

We planned to use the oxidative Bu_3SnH protocol for the synthesis of the 6*H*-benzo[*c*]chromen-6-ones **1** and **2**. An obvious homolytic retrosynthetic analysis is shown in Scheme 1



Scheme 1 Retrosynthesis of *shilajit* constituents.

which indicates two possible radical intermediates which could be generated for carrying out the synthesis. At the time this study was carried out this proposed oxidative Bu_3SnH mediated cyclisation had not been reported in the literature. A closely related attempted synthesis and mechanistic study has since been reported.[6] Other recent syntheses for the formation of the biphenyl moiety of heterocycles using oxidative Bu_3SnH mediated cyclisation of aryl radicals onto arenes have been reported for an increasing number of natural product molecules.[2–6] Recent related heterocyclic syntheses involving oxidative cyclisation which include radical cyclisation onto naphthalenes,[7] pyrroles,[8,10,11] imidazoles and benzimidazoles,[8] indoles,[12] indolines,[13] pyridinium salts,[14] acridines,[15] pyridones[16] and pyridines[17] have also been reported.

Radical cyclisation of esters

Initially, we studied the simplest system and attempted the radical cyclisation 2-bromo-4-methylphenyl benzoate **3**. Bu_3SnH

† Further details regarding the synthesis of radical precursors and the alkylation of phenols are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b002539i/

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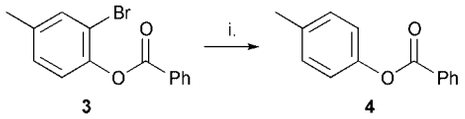
was added slowly using a syringe pump in order to facilitate cyclisation. Only the uncyclised reduced product, 4-methylphenyl benzoate **4** was isolated in low yield (22%) (Scheme 2).

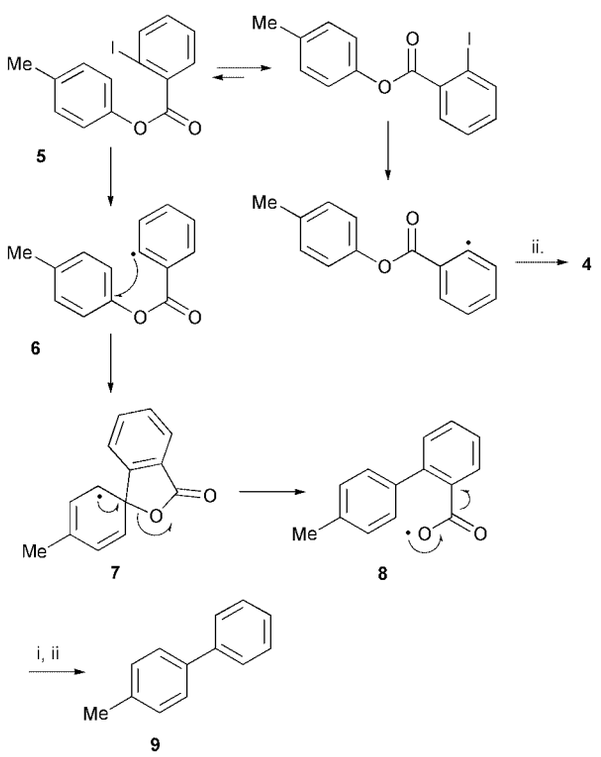


3 4

Scheme 2 *Reagents and conditions*: i. Bu_3SnH, AIBN, toluene, reflux, 22 and 77%.

The problems of separating tributyltin residues from products led to the low yield. In order to determine whether any of the required cyclised product, 2-methyl-6*H*-benzo[*c*]chromen-6-one had been formed and lost in isolation, the reaction was repeated and the crude product mixture was analysed by GC-MS. Only 4-methylphenyl benzoate was formed in 77% yield with no observable traces of 2-methyl-6*H*-benzo[*c*]chromen-6-one, *i.e*. no cyclisation had taken place.

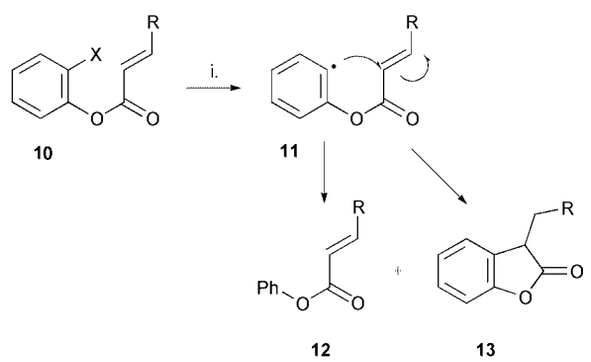
In order to determine whether there was any difference in reaction depending on which ring the radical was generated on, we also reacted 4-methylphenyl 2-iodobenzoate **5** under similar conditions (Scheme 3). Again, no cyclised material could be



Scheme 3 *Reagents and conditions*: Bu_3SnH, AIBN, toluene (**4**, 45%) and *p*-xylene (**4**, 36%), reflux. i. – CO_2, ii. Bu_3SnH.

detected by ^{1}H NMR spectroscopy or GC-MS and the main product was the uncyclised 4-methylphenyl benzoate **4** (45%). A small amount of 4-methylbiphenyl was also isolated. The reaction was repeated with a higher boiling solvent to encourage isomerisation of the ester bond but without success. The lack of cyclisation is explained by the *cis–trans* isomerisation of the ester bond in **5** which strongly favours the more stable *trans* conformation.[22] The *trans* radical intermediate is reduced without cyclisation to yield **4**. A small amount of the *cis* radical intermediate **6** undergoes 5-*exo* cyclisation to a spiro intermediate **7** which undergoes rearrangement to carboxyl radical **8**. Rapid loss of carbon dioxide from **8** yields a biphenyl radical which is reduced by Bu_3SnH to 4-methylbiphenyl **9**. Crich and Hwang[6] have proposed the same mechanism to explain the lack of cyclisation and also the formation of biphenyl from 2-iodophenyl benzoate under Bu_3SnH reaction conditions. In their study the spiro intermediate is trapped with phenylselenol (PhSeH) which is a very fast hydrogen donor and the rate of hydrogen abstraction is faster than rearrangement. Their trapping experiments clearly show that 5-*exo* cyclisation is favoured over 6-*endo* cyclisation. The mechanism and rates are fully discussed in the Crich and Hwang paper. They suggest that even if the *cis* conformation was more favourable, the angle of attack of the aryl radical on the other arene ring is not favourable. With the failure of these cyclisations, studies using the methoxy derivatives for the synthesis of the *shilajit* components **1** and **2** were therefore not attempted.

We were surprised by the total lack of cyclisation of the benzoates **3** and **5** because there are a number of reports in the literature of successful 5-*exo* cyclisation of radicals α to the carbonyl or alcohol moiety in esters.[23] Therefore, we also studied the potential cyclisation of aryl radicals onto alkenes instead of arenes with the precursors **10a**–**10d** (Scheme 4).



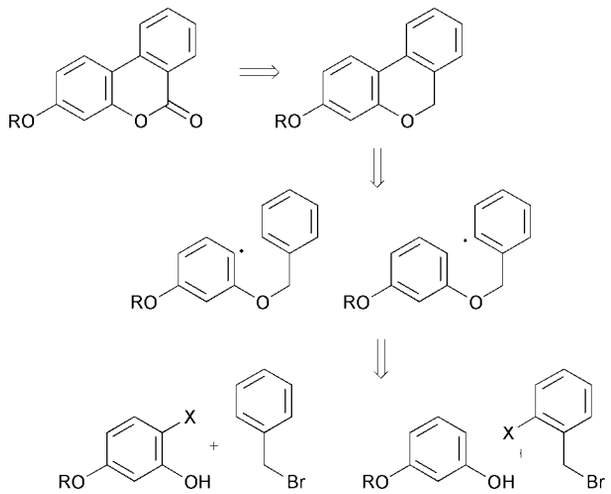
Scheme 4 *Reagents and conditions*: Bu_3SnH, AIBN, toluene, reflux; **10a**, R = Ph, X = Br (**12a**, R = Ph, 79%); **10b**, R = Ph, X = I (**12a**, R = Ph, 69%); **10c**, R = Me, X = Br (**12b**, R = Me, 52%); **10d**, R = Me, X = I (**12b**, R = Me, 53%).

Intramolecular addition of aryl radicals should be considerably more favoured for alkenes than for arenes. The same conditions that were used for the aryl benzoates were used for **10a** but again only the uncyclised reduced product, phenyl cinnamate **12a**, was isolated. Bu_3SnH was not added by syringe pump for the other three compounds **10b**–**d** and the uncyclised reduced phenyl esters with only traces of cyclised products as observed by ^{1}H NMR spectroscopy and GC-MS. Our results indicate that the precursor is in the *trans* conformation and that the intermediate aryl radical **11** is also *trans* and is therefore not lined up for cyclisation to yield the cyclic esters **13**.

Radical cyclisation of benzyl ethers

With the failure of radical cyclisation of aryl benzoates, we sought to carry out the synthesis of the 6*H*-benzo[*c*]chromen-6-ones **1** and **2** *via* cyclisation of the corresponding aryl benzyl ethers, followed by oxidation to yield the required 6*H*-benzo[*c*]-chromen-6-ones (Scheme 5). Precedent for the radical cyclisations of aryl benzyl ethers had already been reported[4] and therefore provided an obvious synthetic protocol.

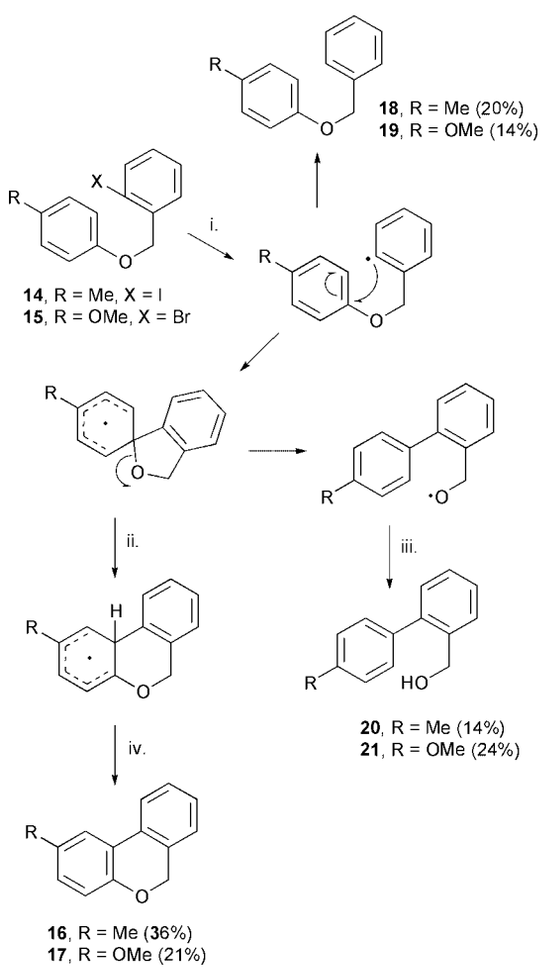
The required radical precursors were synthesised by substitution reactions between *o*-halogenobenzyl bromides and substituted phenolate anions or benzyl bromide and the *o*-halogenophenolate anions in yields ranging from 36–100% (NaH, THF, reflux, 4 h). The yields were not optimised. The *o*-halogenophenols were purchased or prepared by monobromination of the substituted phenol. Initially we attempted to mono-brominate 3-methoxyphenol without success and a complex mixture of brominated isomers was obtained. However, in these studies 4,6-dibromo-3-methoxyphenol crystallised out of the crude product and was used in place of the required mono-bromo derivative as the 'extra' bromine would be



Scheme 5 Retrosynthetic scheme for the synthesis of *shilajit* components.

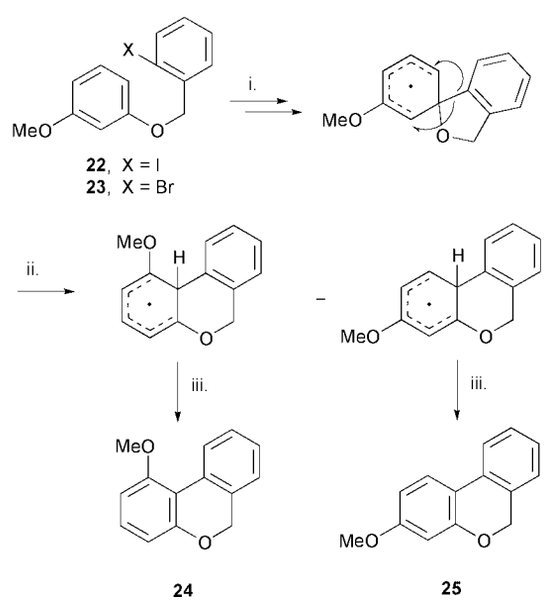
removed during the radical reaction. The order of removal of the bromines in the radical reaction is not important.

Initially we investigated the simplest route with *p*-substituted phenyl ethers **14** and **15** because any possible neophyl rearrangements would not lead to different regioisomers. The radical reactions, using Bu_3SnH added by syringe pump to encourage cyclisation, gave a mixture of the expected cyclised 6*H*-benzo[*c*]chromenes **16** (36%) and **17** (21%), uncyclised reduced ethers **18** (20%) and **19** (14%) and the ring-opened benzyl alcohols **20** (14%) and **21** (24%) respectively (Scheme 6). The similar amounts of cyclised and uncyclised reduced products indicate that for the intermediate aryl radicals the rate of cyclisation and rate of reduction by Bu_3SnH are competitive and that even the use of syringe pump addition of Bu_3SnH does not eliminate reduction. This balance of reactivity is common in reported[2–6] reactions of the synthesis of tricyclic biphenyl compounds by radical cyclisation of aryl radicals. The formation of the ring-opened benzyl alcohols **20** and **21** indicates either that competition between rearrangement of the spirodienyl radical intermediates to the ring-opened benzyl alcohols and 'neophyl' rearrangement to the 6-*endo* cyclised radical intermediates or that cyclisation of the intermediate aryl σ-radicals proceeds by 5-*exo* (followed by neophyl rearrangement) in competition with 6-*endo* cyclisation. The PhSeH trapping results of Crich and Hwang[6] suggest that the former competition is prevalent but does not rule out the latter. This rearrangement has been previously reported.[4]



Scheme 6 *Reagents and conditions*: i. $Bu_3Sn^{\bullet}$; ii. neophyl rearrangement; iii. Bu_3SnH; iv. $(-H^{\bullet})$ or $-H^{+}$, $-e^{-}$.

In order to synthesise the *shilajit* component **1** the 1-iodo- and 1-bromo-2-(3-methoxyphenyloxymethyl)benzenes **22** and **23** respectively were reacted with Bu_3SnH. As expected, the intermediate spirodienyl intermediate rearranged to give both the isomers, 1-methoxy-6*H*-benzo[*c*]chromenes **24** and 3-methoxy-6*H*-benzo[*c*]chromenes **25** in approximately equal amounts (Scheme 7). The iodo starting material **22** gave a mixture of the two isomers in an inseparable mixture with uncyclised reduced 1-benzyloxy-3-methoxybenzene (69%) and the ring-opened 2-(3-methoxyphenyl)benzyl alcohol (25%), whereas the bromo derivative **23** gave a lower yield of the two isomers (26%) and uncyclised reduced 1-benzyloxy-3-methoxybenzene (50%) but no ring-opened benzyl alcohol product.



Scheme 7 *Reagents and conditions*: i. $Bu_3Sn^{\bullet}$; ii. neophyl rearrangement; iii. $(-H^{\bullet})$ or $-H^{+}$, $-e^{-}$.

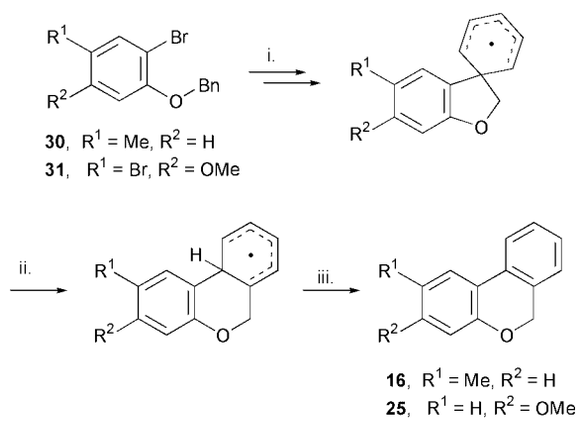
Attempts to synthesise 3-hydroxy-6*H*-benzo[*c*]chromen-6-one **2**, one of the other main constituents of *shilajit*, by conversion of the methoxy group in 3-methoxy-6*H*-benzo[*c*]-chromen-6-one **1** to the phenol failed. Such attempts included the use of boron tribromide in DCM, hydrobromic acid in acetic acid, trimethylsilyl iodide in DCM, and all gave unaltered starting material. The methoxy group appears to be particularly stable. Similarly, attempts to the convert the methoxy group on 1-methoxy-6*H*-benzo[*c*]chromen-6-one to the phenol on 1-hydroxy-6*H*-benzo[*c*]chromen-6-one failed.

Therefore, we planned the synthesis using a benzyl protected phenol to yield the 3-benzyloxy-6*H*-benzo[*c*]chromen-6-one. The benzyl protective group should be easy to remove and would yield the required 3-hydroxy-6*H*-benzo[*c*]chromen-6-one. To this end 1-bromo-2-(3-benzyloxyphenyloxymethyl)-

benzene **26** was reacted with Bu_3SnH (see Scheme 7 with methoxy replaced by benzyloxy, and X = Br). However, the required 3-benzyloxy derivative, 3-benzyloxy-6*H*-benzo[*c*]chromene **27** (**25** with methoxy replaced by benzyloxy) was a very minor product from the cyclisation and surprisingly the 1-benzyloxy analogue, 1-benzyloxy-6*H*-benzo[*c*]chromene **28**, was predominant. Small amounts of the reduced uncyclised 1-benzyloxy-3-methoxybenzene **29** (**22** with methoxy replaced by benzyloxy, and X = H) were observed but no rearranged benzyl alcohol was detected. In a repeat experiment the isomers were formed in a ratio of 7:3 for 1-benzyloxy:3-benzyloxy derivatives. This regioselective arrangement of the intermediate spirodienyl radical is not obvious. No further attempts were made to repeat the synthesis using radical precursors to ensure the correct product.

Rearrangement of the spirodienyl radical intermediates to two isomers for both the 3-methoxy and 3-benzyloxy radical precursors, as well as ring-opening to benzyl alcohols, precludes good synthetic application of this protocol to the *shilajit* components **1** and **2**. This route was not further investigated. The inseparable mixtures were carried on to the oxidation synthetic step.

In order to avoid the problems of rearrangement, the aryl radical cyclisation must be designed such that whichever way the spirodienyl intermediate rearranges the same product is obtained, *i.e.* to generate the aryl radical on the substituted ring and cyclise onto an unsubstituted ring. Scheme 8 shows the

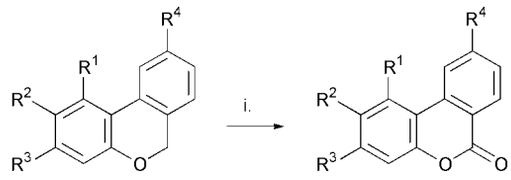


Scheme 8 *Reagents and conditions*: i. $Bu_3Sn^{\bullet}$; ii. neophyl rearrangement; iii. $(-H^{\bullet})$ or $-H^{+}$, $-e^{-}$.

synthesis of 2-methyl- and 3-methoxy-6*H*-benzo[*c*]chromene, **16** (42%) and **25** (40%) respectively from the benzyl ethers **30** and **31**. The reaction of **30** also gave unreacted starting material (35%) and uncyclised reduced 1-benzyloxy-4-methylbenzene (10%). The yield of **25** was raised to 54% by the use of DABCO (1,4-diaza-bicyclo[2.2.2]octane).

Oxidation of 6*H*-benzo[*c*]chromene to 6*H*-benzo[*c*]chromen-6-ones

The 6*H*-benzo[*c*]chromenes were oxidised in high yield to the corresponding 6*H*-benzo[*c*]chromen-6-ones, **1** and **34**–**38**, using PCC (pyridinium chlorochromate) (Scheme 9). The benzylic methylene in the 6*H*-benzo[*c*]chromenes was selectively oxidised over the benzylic methylene in uncyclised benzyl ethers allowing easy separation when the oxidation was carried out on mixtures of inseparable compounds. Several of the 6*H*-benzo[*c*]chromenes were characterised by derivatisation to the corresponding 6*H*-benzo[*c*]chromen-6-ones. The oxidation of 3-methoxy-6*H*-benzo[*c*]chromene **25** to 3-methoxy-6*H*-benzo[*c*]chromen-6-one **1** gives the third step in the synthesis of the bioactive component of *shilajit*. All the 6*H*-benzo[*c*]-chromen-6-ones are unpleasantly pungent smelling, which explains the Indian nickname for *shilajit* as 'cow's urine'. The reactions of the chromenes with methyl substituents also



16→**34** (28%), $R^1 = R^3 = R^4 = H$, $R^2 = Me$
17→**35** (100%), $R^1 = R^3 = R^4 = H$, $R^2 = OMe$
25→**1** (100%), $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
28→**36** (63%), $R^1 = OBn$, $R^2 = R^3 = R^4 = H$
32→**37** (68%), $R^1 = R^3 = R^4 = H$, $R^2 = Cl$
33→**38** (24%), $R^1 = R^3 = H$, $R^2 = Me$, $R^4 = Cl$

Scheme 9 *Reagents and conditions*: i. PCC, DCM, 24 h, reflux.

yielded some oxidation of the methyl groups to carboxylic acids.

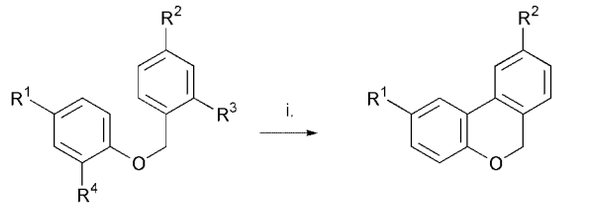
Mechanism

We were concerned about the low yields and sluggish reactions which suggested that inhibition was taking place. The reactions were all carefully deoxygenated thereby making inhibition by oxygen unlikely. In a personal communication of kinetic studies,[24] reactive aryl radicals in slow reactions add to the benzene or toluene solvent yielding σ-radical intermediates which undergo disproportionation with further aryl radical intermediates. Such disproportionation would inhibit chain reactions. Products of this disproportionation are unlikely to be observed because of the small amounts required for inhibition. Disproportionation could also take place between the cyclised π-radical intermediate and the intermediate aryl σ-radical. Large amounts of AIBN were required (>one equivalent) indicating that AIBN or a breakdown product thereof could be abstracting a hydrogen from the cyclised π-radical intermediate to yield the cyclised and 'oxidised' product.

In order to avoid this problem we used cyclohexane in place of toluene. Cyclohexane has a similar boiling point to benzene and has proved very suitable in many radical reactions as a substitute for benzene or toluene. However, due to the lower polarity of the solvent many substrates are not soluble. AIBN is not soluble even at reflux which is a major disadvantage. Towards the end of our study we found that the use of AMBN [*azobis*methyliso*butyro*nitrile, or by IUPAC nomenclature, 2-(1-cyano-1-methylpropylazo)-2-methylbutyronitrile] largely overcame this problem. AMBN is partly soluble in refluxing cyclohexane and acts as an initiator. Accurate comparisons of yields of reactions, carried out in toluene and cyclohexane, were not made and therefore it was not clear whether inhibitory disproportionation by addition to toluene was a problem in these reactions.

The mechanism of these oxidative Bu_3SnH mediated reactions remains unclear. We have proposed a chain mechanism involving single electron transfer and radical anion intermediates.[2,8,9] A similar mechanism has been proposed by Russell and co-workers[25] for additions to arenes with electron withdrawing groups. In order to gain evidence for this mechanism and for the intermediacy of radical anions, we sought to apply a diagnostic test developed by Bunnett and Rossi in their studies on the $S_{RN}1$ reaction.[26] In this diagnostic test for intermediate radical anions, chlorobromo- or chloroiodo-arenes are used. Chloroarenes do not undergo $S_{RN}1$ substitution but when chloroarene radical anions, $(ArCl)^{-\bullet}$, are generated as radical anion intermediates, chloride is readily lost to yield aryl σ-radicals, [*i.e.*$(ArCl)^{-\bullet} \rightarrow Ar^{\bullet} + Cl^{-}$].

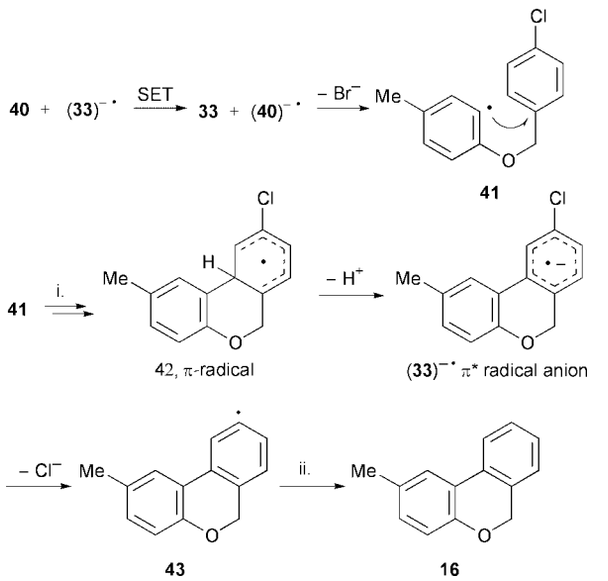
We therefore studied the cyclisation of two chlorobromo radical precursors **39** and **40** to determine whether chloride loss could be observed as evidence for radical anion intermediates (Scheme 10). The putative chain mechanism proceeding *via* radical anions is illustrated for **40** in Scheme 11. The initial



39, R^1 = Cl, R^2 = R^4 = H, R^3 = Br
40, R^1 = Me, R^2 = Cl, R^3 = H, R^4 = Br

32, R^1 = Cl, R^2 = H
33, R^1 = Me, R^2 = Cl

Scheme 10 Radical cyclisation of chlorobromo radical precursors. *Reagents and conditions*: i. Bu_3SnH; **39**: toluene, AIBN; **40**: cyclohexane, AMBN.



Scheme 11 SET and radical anion mechanism for **40**. i. cyclisation and neophyl rearrangement, ii. Bu_3SnH.

σ-radical **41** undergoes cyclisation as expected to yield a cyclised π-radical **42** which loses a proton to yield radical anion $(\mathbf{33})^{-\bullet}$. Single electron transfer (SET) between $(\mathbf{33})^{-\bullet}$ and starting material **40** yields a new radical anion $(\mathbf{40})^{-\bullet}$ which dissociates with loss of bromide to yield to σ-radical **41** again, thereby completing the chain reaction. Loss of chloride would be predicted from the intermediate radical anion $(\mathbf{33})^{-\bullet}$ to yield a new σ-radical **42** which would be reduced by Bu_3SnH to yield a cyclised product **16** which has lost chlorine.

Using the standard Bu_3SnH conditions **39** yielded the corresponding 6*H*-benzo[*c*]chromenes (12%) and uncyclised 1-benzyloxy-4-chlorobenzene (12%) with a large amount of unreacted starting material. A repeat reaction using Bu_3SnCl and sodium borohydride to generate Bu_3SnH *in situ* gave an improved yield of **32** (42%). The reaction of **40** also gave only 12% of **33**. When DABCO was added the yield increased to 37%. Although the yields of cyclised products were poor, there were no traces of chloride loss even in very minor products as determined by GC-MS. A blank reaction under the normal Bu_3SnH conditions with 1-benzyloxy-4-chlorobenzene gave a quantitative recovery of unaltered starting material indicating that the chlorine group would not be reduced off by a 'normal' chain Bu_3SnH mediated reaction *via* the aryl radical. Therefore, if the chlorine was lost in the Bu_3SnH reaction with (2-bromophenyl)methyl (4-chlorophenyl) ether the mechanism was proceeding *via* a radical anion intermediate.

The results do not provide evidence for radical anion intermediates but are negative results and could be explained by a number of factors, *e.g.* SET prior to proton loss rather than proton loss followed by SET. Russell and co-workers[25] have shown that DABCO deprotonates the intermediate π-radicals to yield radical anions to facilitate the SET mechanism. We studied the use of DABCO and obtained mixed results of improved yields, *i.e.* not clear cut one way or another. We also determined that the reactions required at least one equivalent of AIBN or AMBN, *i.e.* two equivalents of the 2-cyanopropan-2-yl radical. If the chain SET mechanism were operative, considerably less than one equivalent of both Bu_3SnH and AIBN/AMBN would be required. These observations together militate against the earlier proposed SET chain mechanism.

Therefore the alternative mechanism involving H-abstraction from the intermediate π-radicals (*e.g.* as shown in Schemes 6, 7, 8 and 11) by some radical species appears more likely. There is a strong thermodynamic driving force for rearomatisation and H-abstraction will proceed readily. Disproportionation between the intermediate π-radical and aromatic σ-radical in a non-chain mechanism is possible and in some reactions both reduced uncyclised aryl benzyl ethers, as well as cyclised product, are observed. However, in many of the reactions reported herein this is not the case and many of the reactions reported in the literature proceed in high if not quantitative yields.[2–20] A number of possibilities can be considered for the H-abstraction. $Bu_3Sn^{\bullet}$ radicals could abstract hydrogen to yield Bu_3SnH but would mean that Bu_3SnH is catalytic and this is not the case. There is no evidence, to our knowledge, for abstraction of hydrogen by $Bu_3Sn^{\bullet}$ radicals. Curran and Liu[19] have shown that Bu_3SnH and AIBN cannot be used in catalytic amounts and also concluded that no tributyltin species acts as the oxidant in these reactions.

The large amounts of AIBN/AMBN required can be explained by a very short chain length requiring continual initiation to regenerate $Bu_3Sn^{\bullet}$ radicals from Bu_3SnH. Alternatively as suggested by Curran,[18,19,27] the AIBN/AMBN, or a breakdown product thereof, may act as the oxidant. Dialkyldiazenes (R–N=N–R) have been shown to abstract hydrogen from benzhydryl radicals to yield the corresponding hydrazines[28] indicating that possibly AIBN/AMBN may have a similar role. Abstraction by 2-cyanopropan-2-yl radicals is also a possibility but literature evidence[3] reporting similar studies militates against this explanation, but it cannot be ruled out. Both $Bu_3Sn^{\bullet}$ radicals[29] and 2-cyanopropan-2-yl radicals[30] rapidly quench any traces of oxygen present yielding the corresponding peroxides, $Bu_3SnOO^{\bullet}$ and $Me_2C(CN)OO^{\bullet}$ which would act as excellent H-abstractors. Although all the reactions were thoroughly deoxygenated using nitrogen gas, studies[30] have shown that trace amounts of oxygen do remain unless very special conditions are used and that the peroxides can be significant in the course of radical reactions. Our conclusion is that these reactions are largely non-chain radical reactions in which H-abstraction from the intermediate π-radicals is responsible for the 'oxidative' step. A variety of radical species in each reaction is probably responsible for the thermodynamically favourable H-abstraction which has made it difficult to determine exactly which species is involved.

In conclusion, our studies indicate the synthetic utility of 'oxidative' Bu_3SnH mediated cyclisation in synthesis. However, the reaction conditions need to be considerably improved to facilitate higher yields. Further studies are underway to determine the mechanism of 'oxidative' Bu_3SnH mediated reactions.

Experimental

Commercial dry solvents were used in all reactions except for light petroleum and ethyl acetate which were distilled from $CaCl_2$ and dichloromethane was distilled over phosphorus pentaoxide. Light petroleum refers to the bp 40–60 °C fraction. Sodium hydride was obtained as 60% dispersion in oil and was washed with light petroleum. Mps were determined on an Electrothermal 9100 melting point apparatus and are uncorrected. Elemental analyses were determined on a Perkin-Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin-Elmer AD-4 Autobalance. IR spectra were recorded on a

Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. ^{1}H (250 MHz) and ^{13}C (62.5 MHz) NMR spectra were recorded on a Bruker AC-250 spectrometer as solutions of $CDCl_3$ with tetramethylsilane (TMS) as the internal standard for ^{1}H NMR spectra and deuteriochloroform the standard for ^{13}C NMR spectra unless otherwise specified. Chemical shifts are given in parts per million (ppm) and *J* values in hertz (Hz). Mass spectra were recorded on a JEOL SX102 mass spectrometer or carried out by the EPSRC Mass Spectrometry Service at University of Wales, Swansea. GC-MS was carried out on Fisons 8000 series GC-MS using a 15 m × 0.25 mm DB-5 column and an electron impact low resolution mass spectrometer. TLC using silica gel as absorbent was carried out with aluminium backed plates coated with silica gel (Merck Kieselgel 60 F254). Silica gel (Merck Kieselgel 60 H silica) was used for column chromatography unless otherwise specified.

Synthesis of radical precursors

4-Methylphenyl 2-iodobenzoate 5. General Schotten–Baumann procedure for the synthesis of benzoates. *p*-Cresol (2.18 g, 18 mmol) was added to 2-iodobenzoyl chloride (4.93 g, 20.00 mmol) in aqueous sodium hydroxide solution (4 M) and shaken vigorously for 10 min. 4-Methylphenyl 2-iodobenzoate **5** was obtained as a pale yellow solid (5.71 g, 84%), mp 38–40 °C (Found: M^+, 337.9809. $C_{14}H_{11}IO_2$ requires 337.9805) (Found: C, 49.52; H, 3.22. $C_{14}H_{11}IO_2$ requires C, 49.73; H, 3.28%); ν_{max}(Nujol)/cm^{-1} 1459, 1377, 797 and 736; δ_H 2.36 (3 H, s, CH_3), 7.11–7.24 (5 H, m, 1′-, 2′-, 4′-, 5′- and 4-H), 7.46 (1 H, t, *J* 7.6, 5-H) and 7.99–8.06 (2 H, m, 3- and 6-H); δ_C 20.90 (CH_3), 94.55 (CH_3), 121.28, 128.02, 130.00, 131.42, 133.10, 134.36, 135.77, 141.56, 148.53 and 165.11; *m*/*z* (EI) 338 (M^+, 100%), 294 (15), 232 (65), 211 (35), 203 (55), 181 (25), 168 (50), 152 (40), 128 (25), 108 (60), 104 (40) and 91 (20).

2-Bromo-4-methylphenyl benzoate, 4-methylphenyl benzoate, 2-iodophenyl cinnamate and 2-bromophenyl but-2-enoate were also synthesised using the general procedure. Their characterisation data are provided as supplementary data.

2-Bromophenyl cinnamate 10a

Cinnamoyl chloride (1.46 g, 8.81 mmol) was added dropwise to 2-bromophenol (1.53 g, 8.80 mmol) in toluene (15 cm^3) with stirring over 30 min. Triethylamine (1.50 cm^3) was added dropwise with stirring for 30 min and stirred for a further 60 min. The reaction mixture was poured into water, separated, washed with aqueous sodium hydrogen carbonate solution, dried and evaporated to dryness. Recrystallisation from ethanol–light petroleum afforded 2-bromophenyl cinnamate **10a** as yellow crystals (2.43, 91%), mp 79–80 °C (Found: M^+, 301.9940. $C_{15}H_{11}O_2{}^{79}Br$ requires 301.9943); ν_{max}(Nujol)/cm^{-1} 3074, 1743, 1633, 1466, 1307, 1207, 1128, 1043, 765 and 737; δ_H 6.68 (1 H, d, *J* 16.1, 2-H), 7.05–7.66 (9 H, m, Ph-H) and 7.92 (1 H, d, *J* 16.1, 3-H); δ_C 116.28 (4′- C), 116.50 (4-C), 123.42 (5-C), 123.85 (3-C), 127.84 (6-C), 128.37 (3′-, 5′-C), 129.38 (2′-, 6′-C), 133.40 (1′-C), 133.97 (alkene 2-C), 133.99 (2-C), 147.31 (alkene 3-H), 148.31 (3-C) and 164.31 (C=O); *m*/*z* 304 (M^+, ^{81}Br, 3%), 302 (M^+, ^{79}Br, 3), 174 (11), 172 (11), 147 (5), 131 (100), 103 (48), 93 (98), 91 (100), 77 (26) and 65 (21).

1-Iodo-2-[(4-methylphenoxy)methyl]benzene 14. General procedure for the alkylation of phenols

p-Cresol (1.46 g, 13.47 mmol) was added to sodium hydride (0.67 g, 28.06 mmol) in THF under reflux and stirred for 30 min. 2-Iodobenzyl bromide (2.05 g, 6.74 mmol) was added and the mixture stirred under reflux for a further 4 h. After cooling to room temperature and evaporating to dryness, the mixture was purified by column chromatography using light petroleum–DCM as eluent to yield a white solid which was recrystallised to give 1-iodo-2-[(4-methylphenoxy)methyl]benzene **14** as a colourless crystalline solid (0.89 g, 40%), mp 40–45 °C (from hot light petroleum) (Found: M^+, 324.0008. $C_{14}H_{13}IO$ requires 324.0012) (Found: C, 51.73; H, 4.02. $C_{14}H_{13}IO$ requires C, 51.87; H, 4.04%); ν_{max}(DCM)/cm^{-1} 2922, 2853, 1462 and 744; δ_H 2.29 (3 H, s, CH_3), 5.01 (2 H, s, CH_2O), 6.86–6.89 (2 H, m, phenyl 3- and 5-H), 6.98–7.05 (1 H, m, 4-H), 7.08–7.12 (2 H, m, phenyl 2- and 6-H), 7.36 (1 H, ddd, *J* 7.4, 7.4, 1.2, 5-H), 7.49 (1 H, ddd, *J* 8.6, 1.9, 0.8, 3-H) and 7.87 (1 H, dd, *J* 7.9, 1.3, 6-H); δ_C(100 MHz) 20.50 (Me), 74.05 (CH_2O), 97.10 (*C*-Me), 114.80, 128.36, 128.63, 129.38, 129.98, 130.47, 139.22, 139.40 and 156.34 (*C*–O); *m*/*z* (EI) 324 (M^+, 26%), 217 (100), 197 (5), 169 (8), 127 (3), 107 (5), 90 (50), 73 (15) and 63 (14).

1-Iodo-2-(3-methoxyphenyloxymethyl)benzene 22. Light yellow oil (43%) (Found: M^+, 339.9962. $C_{14}H_{13}IO_2$ requires 339.9960); ν_{max}(neat)/cm^{-1} 2924, 1594, 834 and 747; δ_H 3.77 (3 H, s, MeO), 5.01 (2 H, s, CH_2O), 6.50–6.59 (3 H, m, 2′-, 4′- and 6′-H), 6.95–7.03 (1 H, m, 5′-H), 7.18 (1 H, dd, *J* 8.0, 0.6, 5-H), 7.34 (1 H, ddd, *J* 7.5, 7.5, 1.3, 4-H), 7.47–7.51 (1 H, m, 6-H) and 7.82 (1 H, dd, *J* 7.9, 1.2, 3-H); δ_C 29.66 (CH_2O), 55.23 (MeO), 97.11 (2-C), 101.43 (5′-C), 106.71 (5-C), 106.98 4-C), 128.32 (6′-C), 128.59 (4′-C), 129.40 (6-C), 129.90 (3-C), 139.19 (2′-C), 160.00 (1′-C) and 161.00 (3′-C); *m*/*z* 340 (M^+, 15%), 217 (100), 111 (6), 97 (10), 90 (43) and 69 (26).

1-Benzyloxy-2,4-dibromo-5-methoxybenzene 31

2,4-Dibromo-5-methoxyphenol. 3-Methoxyphenol (3.00 g, 2.41 mmol) was added to a solution of potassium carbonate (1.67 g, 1.20 mmol) in DCM (50 cm^3) at 0 °C with stirring. Bromine (1.93 g, 1.21 mmol) was added dropwise, and the solution stirred for a further 2.5 h. The solution was filtered over Celite and concentrated under reduced pressure to yield a brown liquid and crystals. Purification of the crystals by column chromatography afforded 2,4-dibromo-5-methoxyphenol as a pale yellow solid (1.00 g, 15%), mp 67–70 °C (Found: M^+, 281.8715. $C_7H_6Br_2O_2$ requires 281.8708); ν_{max}(DCM)/cm^{-1} 3498, 2968, 2941, 1316, 874, 827 and 668; δ_H 3.85 (3 H, s, MeO), 5.50 (1 H, s, OH), 6.61 (1 H, s, 2-H) and 7.57 (1 H, s , 5-H); δ_C 56.38 (MeO), 100.23 (5-C), 100.00 (6-C), 102.50 (4-C), 134.38 (2-C), 153.00 (1-C) and 157.00 (3-C); *m*/*z* 282 (M^+, 100%), 267 (18), 239 (30), 204 (29), 172 (4), 161 (9), 131 (7), 119 (12), 79 (6) and 69 (49).

1-Benzyloxy-2,4-dibromo-5-methoxybenzene 31. Light yellow crystals (81%), mp 60–64 °C (Found: M^+, 371.9186. $C_{14}H_{12}Br_2O_2$ requires 371.9185); ν_{max}(DCM)/cm^{-1} 2935, 2851, 809 and 735; δ_H 3.79 (3 H, s, MeO), 5.14 (2 H, s, CH_2O), 6.49 (1 H, s, 2-H), 7.14–7.32 (5 H, m, phenyl-H) and 7.66 (1 H, s, 5-H); δ_C 56.39 (MeO), 71.38 (CH_2O), 99.61 (5-C), 102.97 (6-C), 103.34 (1-C), 126.95, 127.04, 128.34, 128.51, 128.62, 133.00 (1′-C) 135.87 (2-C), 155.15 (4-C) and 156.00 (4-C); *m*/*z* 372 (M^+, 26%), 291 (23), 253 (5), 181 (10), 157 (5), 129 (4) and 91 (100).

1-Bromo-2-(4-methoxyphenyloxymethyl)benzene, 1-bromo-2-(3-methoxyphenyloxymethyl)benzene, 1-bromo-2-(3-benzyloxyphenyloxymethyl)benzene, 1-benzyloxy-2-bromo-4-methylbenzene, 1-bromo-2-(4-chlorophenyloxymethyl)benzene, 2-bromo-4-methylphenyl[(4-chlorophenyl)methyl]ether, 1-benzyloxy-4-methylbenzene, 1-benzyloxy-3-methoxybenzene, 1-methoxy-4-benzyloxybenzene and 4-chlorophenyl benzyl ether were also synthesised using the general procedure. Their characterisation data are provided as supplementary data.

General procedure for radical cyclisation using tributyltin hydride

Radical cyclisation of 2-bromo-4-methylphenyl benzoate 3. A solution of Bu_3SnH (1.00 g, 3.43 mmol) and AIBN (0.14 g, 0.58 mmol) in toluene (50 cm^3) was added to 2-bromo-4-methylphenyl benzoate **3** (0.15 g, 1.71 mmol) in toluene (500 cm^3) at reflux under an atmosphere of nitrogen over 8 h using a syringe pump. AIBN was added portion-wise or by syringe pump over

the period of the reaction. After cooling to room temperature, the mixture was evaporated to dryness to afford a yellow oil, which was re-dissolved in ethyl acetate (30 cm^3). Saturated aqueous potassium fluoride solution (50 cm^3) was added and the mixture shaken vigorously for 15 min. The resultant solution was filtered and extracted with diethyl ether. The organic fractions were dried and evaporated to dryness to yield a crude yellow oil. The oil was purified by column chromatography using light petroleum–DCM as eluent to yield 4-methylphenyl benzoate **4** (87 mg, 22%). The reaction was repeated under identical conditions and the reaction mixture directly analysed by GC-MS to afford 4-methylphenyl benzoate **4** (77%) as the sole product. No 2-methyl-6*H*-benzo[*c*]chromen-6-one was observed when the reaction mixture was analysed by GC-MS.

Radical cyclisation of 4-methylphenyl 2-iodobenzoate 5. The above procedure for the attempted radical cyclisation of 2-bromo-4-methylphenyl benzoate was carried out with 4-methylphenyl 2-iodobenzoate **5** (0.76 g, 1.48 mmol), Bu_3SnH (0.64 g, 2.22 mmol), and AIBN (0.12 g, 0.74 mmol) in toluene (500 cm^3). The reaction yielded 4-methylphenyl benzoate **4** (0.16 g, 45%) and 4-methylbiphenyl **9** as a semi-solid (12 mg, 3%). The 4-methylphenyl benzoate and 4-methylbiphenyl **9** had identical spectra and TLC to authentic commercial material. A repeat reaction at higher temperature using *p*-xylene in place of toluene gave only 4-methylphenyl benzoate (36%).

Attempted radical cyclisation of 2-bromophenyl cinnamate 10a. The general procedure for radical cyclisation was used to yield only phenyl cinnamate **12a** (79%) (Found: M^+, 224.0843. $C_{15}H_{12}O_2$ requires 224.0843); ν_{max}(neat)/cm^{-1} 3062, 2929, 2583, 1731, 1637, 1493, 1450, 1308, 1196, 1162, 1140, 911, 766, 735, 703 and 698; δ_H 6.64 (1 H, d, *J* 16.1, 3-H), 7.13–7.44 (10 H, aromatic-H), 7.57–7.61 (3 H, aromatic-H) and 7.87 (1 H, d, *J* 15.9, 2-H); δ_C 117.36 (4′-C), 121.64 (2′- and 6′-C), 125.77 (4-C), 128.30 (3- and 5-C), 129.08 (3′- and 5′-C), 129.43 (2- and 6-C), 130.69 (alkene 2-C), 134.21 (1′-C), 146.55 (alkene 3-C), 150.84 (1-C) and 165.37 (C=O); *m*/*z* 224 (M^+, 5%), 131 (100), 103 (32) and 77 (19).

2-Iodophenyl cinnamate **10b**, 2-iodophenyl but-2-enoate **10d** and 2-bromophenyl but-2-enoate **10c** were each reacted using the general procedure with the exception that Bu_3SnH and AIBN were added in one portion at the beginning and the crude products were analysed by GC against authentic phenyl cinnamate **12a** and phenyl but-2-enoate **12b**.

2-Methyl-6*H*-benzo[*c*]chromene 16

Radical cyclisation of 1-iodo-2-(4-methylphenyloxymethyl)-benzene 14. The general procedure for radical cyclisation was used with 1-iodo-2-(4-methylphenyloxymethyl)benzene **14** (0.51 g, 3.08 mmol), Bu_3SnH (0.99 g, 3.43 mmol) and AIBN (0.12 g, 0.84 mmol) to yield a crude yellow oil (0.19 g). Purification using column chromatography with light petroleum–DCM as eluent yielded unaltered 1-iodo-(4-methylphenyloxymethyl)-benzene **14** (22 mg, 7%), 1-benzyloxy-4-methylbenzene **18** (63 mg, 20%) (spectra and TLC were identical with authentic material) and 2-methyl-6*H*-benzo[*c*]chromene **16** (0.11 g, 34%) (Found: M^+, 196.0892. $C_{14}H_{12}O$ requires 196.0888); ν_{max}(DCM)/cm^{-1} 3029, 2960, 2920, 2841, 1497, 1246, 815 and 770; δ_H 2.35 (3 H, s, Me), 5.07 (2 H, s, CH_2O), 6.86 (1 H, d, *J* 8.2, 4-H), 7.04 (1 H, ddd, *J* 7.4, 2.1, 0.7, 7-H), 7.13 (1 H, ddd, *J* 7.4, 2.1, 0.7, 8-H), 7.25 (1 H, ddd, *J* 7.4, 7.4, 1.3, 8-H), 7.35 (1 H, ddd, *J* 7.6, 7.6, 1.5, 9-H), 7.52 (1 H, d, *J* 1.6, 1-H) and 7.69 (1 H, dd, *J* 8.2, 1.6, 3-H); δ_C 20.88 (Me), 68.46 (CH_2O), 115.00 (2-C), 117.01 (1-C), 121.88 (3-C), 123.61 (4-C), 124.60 (9-C), 127.46 (10^b-C), 127.81 (10–C), 128.31 (10^a-C), 129.86 (8-C), 130.19 (7-C), 131.52 (6^a-C) and 152.50 (4^a-C); *m*/*z* 198 (M^+, 12%), 195 (100), 183 (3), 165 (12), 152 (13), 139 (2), 115 (5), 97 (13), 84 (29) and 47 (3). 2-(*p*-Methylphenyl)benzyl alcohol[31] **20** was also afforded as a yellow oil (0.07 g, 24%) (Found: M^+, 198.1043. $C_{14}H_{14}O$ requires 198.1044); ν_{max}(neat)/cm^{-1} 3347, 2922, 822 and 760; δ_H 2.40 (3 H, s, Me), 4.62 (2 H, s, CH_2O), 7.21–7.29 (5 H, m, tolyl-H and 3-H), 7.31–7.38 (2 H, m, 4- and 5-H) and 7.52–7.55 (1 H, m, 6-H); δ_C 21.17 (Me), 63.27 (CH_2), 127.53, 127.66, 128.39, 128.88, 130.14, 136.97 (4′-C), 137.69 (1′-C), 138.08 (1-C) and 141.29 (2-C); *m*/*z* 198 (M^+, 100%), 180 (49), 165 (76), 152 (20), 115 (11) and 91 (24).

2-Methoxy-6*H*-benzo[*c*]chromene 17

Radical cyclisation of 1-bromo-2-(4-methoxyphenyloxy-methyl)benzene 15. The general procedure for radical cyclisation was used with 1-bromo-2-(4-methoxyphenyloxymethyl)-benzene **15** (0.38 g, 1.02 mmol), Bu_3SnH (0.74 g, 2.56 mmol) and AIBN (1.1 equiv.). Purification using column chromatography with light petroleum–DCM gave three fractions. The first fraction yielded 1-benzyloxy-4-methoxybenzene **19** as a yellow oil (38 mg, 14%) which was characterised by comparison with authentic material. The second fraction yielded 2-(4-methoxyphenyl)benzyl alcohol[32] **21** as a yellow oil (67 mg, 24%) which was not fully characterised; δ_H 3.85 (3 H, s, MeO) and 4.62 (2 H, s, CH_2O). The third fraction yielded 2-methoxy-6*H*-benzo[*c*]chromene **17** as a yellow oil (57 mg, 21%) (Found: M^+, 212.0837. $C_{14}H_{12}O_2$ requires 212.0837); δ_H 3.80 (3 H, s, Me), 5.06 (2 H, s, CH_2O), 6.78–6.95 (3 H, m, 1-, 3- and 4-H), 7.24–7.43 (3 H, m, 8-, 9- and 10-H) and 7.64 (1 H, dd, *J* 7.6, 1.2, phenyl 7-H); δ_C 55.75 (MeO), 68.50 (CH_2O), 101.00 (10^a-C), 108.26 (8- and 9-C), 114.96 (7-C), 117.89 (10-C), 118.00 (6^a-C), 122.00 (3-C), 124.62 (4-C), 127.26 (4^a-C), 127.75 (1-C), 130.14 (10^a-C) and 131.00 (2-C); *m*/*z* 212 (M^+, 20%), 197 (4), 159 (7), 141 (6), 115 (8), 106 (4), 91 (100), 77 (6) and 69 (12).

3-Methoxy-6*H*-benzo[*c*]chromene 25[33]

Radical cyclisation of 1-iodo-2-(3-methoxyphenyloxy-methyl)benzene 22. 1-Iodo-2-(3-methoxyphenyloxymethyl)-benzene **22** (0.46 g, 1.47 mmol), was dissolved in toluene (500 cm^3) and stirred under reflux. A solution of Bu_3SnH (1.07 g, 3.67 mmol) in toluene (50 cm^3) was added by a syringe pump over 6 h. AIBN (1.1 equiv.) was added independently every 45 min. After cooling to room temperature the usual potassium fluoride work-up was employed, to yield a crude yellow liquid (0.20 g), which was purified by column chromatography to yield a mixture of 1-methoxy-6*H*-benzo[*c*]chromene **24** and 3-methoxy-6*H*-benzo[*c*]chromene **25** and 1-benzyloxy-3-methoxybenzene (69%, *ca*. 1:1) and 2-(3-methoxyphenyl)benzyl alcohol (25%). The yields were calculated by GC-MS. The purified mixture was used without further characterisation and characterised by derivatisation.

Radical cyclisation of 1-bromo-2-(3-methoxyphenyloxy-methyl)benzene 23. The general procedure for radical cyclisation was used with 1-bromo-2-(3-methoxyphenyloxymethyl)-benzene **23** (0.51 g, 1.71 mmol), Bu_3SnH (0.99 cm^3, 3.75 mmol) and AIBN (0.14 g, 0.85 mmol) with the exception that 50 cm^3 solutions of the Bu_3SnH and AIBN were added separately by syringe pump over 16 h. Normal work-up gave a yellow oil (0.28 g). Analysis using GC-MS showed a mixture of 1-methoxy-6*H*-benzo[*c*]chromene **24** (10%) and 3-methoxy-6*H*-benzo[*c*]chromene (16%) **25** and 1-benzyloxy-3-methoxybenzene (50%), but no 2-(3-methoxyphenyl)benzyl alcohol. The purified mixture was used without further characterisation and characterised by derivatisation.

1-Benzyloxy-6*H*-benzo[*c*]chromene 28

Radical cyclisation of 1-bromo-2-(3-benzyloxyphenyloxy-methyl)benzene 26. The general procedure for radical cyclisation was used with 1-bromo-2-(3-benzyloxyphenyloxymethyl)-benzene **26** (0.57 g, 1.35 mmol), Bu_3SnH (0.79 cm^3, 2.98 mmol)

and AIBN (1.1 equiv.). Normal work-up and column chromatography yielded 1-benzyloxy-6*H*-benzo[*c*]chromene **28** as a colourless oil (0.17 g, 48%) (Found: M^+, 288.1152. $C_{20}H_{16}O_2$ requires 288.1150); ν_{max}(neat)/cm^{-1} 3064, 3031, 2927, 2868, 834 and 750; δ_H(400 MHz) 5.03 (2 H, s, 6-CH_2), 5.10 (2 H, s, PhCH_2), 6.58–6.71 (3 H, m, 2-, 3- and 4-H), 7.12–7.23 (1 H, m, 8-H), 7.31–7.44 (6 H, m, 9- and Ph-H), 7.52 (1 H, ddd, *J* 8.0, 1.0, 0.7, 10-H) and 7.58 (1 H, dd, *J* 0.8, 5.0, 7-H); δ_C(100 MHz) 69.37 (PhCH_2), 69.97 (6-CH_2O), 102.22 (9-C), 107.50 (8-C), 127.53 (10-C), 127.73 (benzyl 3- and 5-C), 127.97 (benzyl 4-C), 128.84 (7-C), 129.18 (3-C), 129.89 (2-C), 132.56 (4-C), 136.22 (10^a-C), 136.84 (10^b-C), 160.00 (1-C) and 160.03 (4^a-C); *m*/*z* 291 (M^+, 9%), 290 (42), 289 (11), 288 (17), 219 (8), 197 (8), 181 (21), 171 (92), 149 (7), 119 (8) and 91 (100). Only traces of the 3-benzyloxy analogue **27** were observed by analysis of the crude product by ^{1}H NMR spectroscopy and GC-MS. In a second experiment, the ratio of 3-:1-benzyloxy analogues was 7:3 as measured by ^{1}H NMR spectroscopy.

2-Methyl-6*H*-benzo[*c*]chromene 16

Radical cyclisation of 1-benzyloxy-2-bromo-4-methylbenzene 30. The general procedure for radical cyclisation was used with 1-benzyloxy-2-bromo-4-methylbenzene **30** (0.48 g, 1.80 mmol), Bu_3SnH (1.31 g, 4.51 mmol) and AMBN (0.17 g, 0.90 mmol) with cyclohexane (500 cm^3) in place of toluene as the solvent to yield unaltered 1-benzyloxy-2-bromo-4-methylbenzene **30** (0.12 g, 35%), 1-benzyloxy-4-methylbenzene (35 mg, 10%) and 2-methyl-6*H*-benzo[*c*]chromene **16** (0.15 g, 42%). The compounds were identified by comparison with authentic material.

3-Methoxy-6*H*-benzo[*c*]chromene 25

Radical cyclisation of 1-benzyloxy-2,4-dibromo-5-methoxybenzene 31. The general procedure for radical cyclisation was used with 1-benzyloxy-2,4-dibromo-5-methoxybenzene **31** (0.43 g, 1.08 mmol), Bu_3SnH (1.25 cm^3, 4.73 mmol) and AMBN (1.1 equiv.) but with cyclohexane in place of toluene. Normal work-up and chromatography afforded a clean mixture of 3-methoxy-6*H*-benzo[*c*]chromene **25** and 1-benzyloxy-3-methoxybenzene as a pale yellow liquid (0.13 g). Analysis using ^{1}H NMR spectroscopy with an internal standard showed 1-benzyloxy-3-methoxybenzene (11%) and 3-methoxy-6*H*-benzo[*c*]chromene **25** (40%); δ_H 3.81 (3 H, s, MeO), 5.10 (2 H, s, CH_2O), 6.55 (2 H, d, *J* 2.5, 4-H), 6.62 (1 H, dd, *J* 8.6, 2.6, 2-H), 7.12–7.24 (1 H, m, 1-H), 7.30–7.37 (3 H, m, phenyl 8-, 9- and 10-H) and 7.61 (1 H, d, *J* 8.5, phenyl 7-H). The purified mixture was used without further characterisation and characterised by derivatisation.

The general procedure for radical cyclisation was repeated with 1-benzyloxy-2,4-dibromo-5-methoxybenzene **31** (92.7 mg, 0.54 mmol), DABCO (0.24 g, 2.15 mmol) and Bu_3SnH (0.63 cm^3, 2.36 mmol). The solution of the Bu_3SnH in toluene (50 cm^3) was added *via* a syringe pump over 6 h. AIBN was added independently every 45 min. After cooling to room temperature, the solvent was evaporated to dryness and the yellow residue extracted between aqueous hydrochloric acid (1 M) and ethyl acetate. Normal work-up and column chromatography afforded pure 3-methoxy-6*H*-benzo[*c*]chromene **25** as a colourless oil (28.7 mg, 54%) which was characterised by derivatisation to the chromenone.

Radical reaction of (2-bromophenyl)methyl 4-chlorophenyl ether 39

The general procedure for radical cyclisation was used with (2-bromophenyl)methyl 4-chlorophenyl ether **39** (0.53 g, 1.68 mmol), Bu_3SnH (0.98 cm^3, 3.70 mmol) and AIBN (1.1 equiv.). Analysis of the crude reaction mixture using GC-MS analysis showed 4-chlorophenyl benzyl ether (12%), 2-chloro-6*H*-benzo[*c*]chromene **32** (12%) and unreacted (2-bromophenyl)methyl 4-chlorophenyl ether **39** (66%). No 6*H*-benzo[*c*]chromene was detected by GC-MS.

A repeat reaction with (2-bromophenyl)methyl 4-chlorophenyl ether **39** (0.46 g, 1.68 mmol), Bu_3SnCl (0.046 cm^3, 0.17 mmol) and sodium borohydride (0.12 g, 3.36 mmol) in dry *tert*-butyl alcohol (150 cm^3) and stirred under reflux under an atmosphere of nitrogen. A solution of AIBN (0.14 g, 0.84 mmol) in toluene (50 cm^3) was added dropwise *via* a syringe pump over 6 h. Normal work-up afforded a yellow oil (0.32 g). GC-MS analysis showed that the products were benzyl 4-chlorophenyl ether (22%), 2-chloro-6*H*-benzo[*c*]chromene **32** (42%) and (2-bromophenyl)methyl 4-chlorophenyl ether **39** (33%). The purified mixture was oxidised without further characterisation and characterised by derivatisation.

Radical cyclisation of 2-bromo-4-methylphenyl (4-chlorophenyl)-methyl ether 40

The general procedure for radical cyclisation was used with 2-bromo-4-methylphenyl (4-chlorophenyl)methyl ether **40** (0.39 g, 1.28 mmol) and Bu_3SnH (0.70 cm^3, 2.83 mmol) with the exception that DABCO (0.72 g, 6.42 mmol) was added and AMBN (1.1 equiv.) and cyclohexane were used in place of AIBN and toluene respectively. GC-MS analysis of the crude product showed the products as 9-chloro-2-methyl-6*H*-benzo-[*c*]chromene **33** (12%) and 4-methylphenyl (4-chlorophenyl)-methyl ether (12%). The reaction was repeated without DABCO and the crude product was analysed by GC-MS to show 9-chloro-2-methyl-6*H*-benzo[*c*]chromene **33** (37%), 4-methylphenyl (4-chlorophenyl)methyl ether (21%) and 2-bromo-4-methylphenyl (4-chlorophenyl)methyl ether **40** (9%). Neither reaction showed any traces of 2-methyl-6*H*-benzo[*c*]-chromene **16**. The purified mixture was oxidised without further characterisation and characterised by derivatisation.

2-Methyl-6*H*-benzo[*c*]chromen-6-one 34. General procedure for PCC oxidations

2-Methyl-6*H*-benzo[*c*]chromene **16** (0.11 g, 0.54 mmol) in a clean mixture with unseparated 4-methylphenyl benzoate and 4-methylphenyl 2-iodobenzoate was dissolved in DCM (25 cm^3). PCC (0.12 g, 0.54 mmol) was added and the mixture stirred under reflux for 1 h. PCC (0.23 g, 1.09 mmol) was added and the mixture stirred under reflux for a further 24 h. After cooling to room temperature, water and diethyl ether were added and the resultant precipitate filtered through a Celite plug. The solution was extracted with brine, dried, filtered and evaporated to dryness. Column chromatography using light petroleum–DCM as the eluent afforded 2-methyl-6*H*-benzo[*c*]-chromen-6-one **34** as a colourless solid (29.9 mg, 28%), mp 126–128 °C (Found: M^+, 210.0678. $C_{14}H_{10}O_2$ requires 210.0681); ν_{max}(neat)/cm^{-1} 3057, 2923, 1728, 814 and 770; δ_H 2.44 (3 H, s, Me), 7.19–7.27 (2 H, m, 3- and 4-H), 7.22 (1 H, s, 1-H), 7.51-7.57 (1 H, m, 9-H), 7.75–7.82 (1 H, m, 8-H), 8.05 (1 H, d, *J* 8.1, 10-H) and 8.35 (1 H, dd, *J* 7.0, 0.8, 7-H); δ_C 66.06 (Me), 117.32 (1-C), 121.11 (2-C), 121.49 (3-C), 122.63 (4-C), 128.58 (9-C), 128.72 (10^a-C), 130.41 (8-C), 130.63 (10^b-C), 131.23 (10-C), 134.00 (6^a-C), 134.62 (7-C), 144.00 (4^a-C) and 161.00 (6-C); *m*/*z* 211 (M^+, 16%), 210 (100), 209 (10), 182 (10), 167 (5), 152 (10), 127 (8), 104 (3) and 76 (13).

2-Methoxy-6*H*-benzo[*c*]chromen-6-one 35

The general procedure for PCC oxidations with a mixture of 2-methoxy-6*H*-benzo[*c*]chromene **17** (70 mg, 0.33 mmol) gave 2-methoxy-6*H*-benzo[*c*]chromen-6-one **35** as a strong smelling, pale yellow solid (75 mg, 100%), mp 113–115 °C (Found: M^+, 226.0631. $C_{14}H_{10}O_3$ requires 226.0630); ν_{max}(Nujol)/cm^{-1} 1719; δ_H 3.88 (3 H, s, MeO), 6.91 (1 H, d, *J* 9.2, 4-H), 7.04 (1 H, dd, *J* 9.0, 2.9, 3-H), 7.47 (1 H, d, *J* 2.8, 1-H), 7.57 (1 H, dd, *J* 7.7, 7.7, 9-H), 7.83 (1 H, ddd, *J* 7.7, 7.7, 1.3, 8-H), 8.06 (1 H, d,

J 8.1, 10-H) and 8.41 (1 H, dd, *J* 8.0, 7-H); δ_C 55.78 (MeO), 106.24 (9-C), 117.02 (8-C), 118.63 (10-C), 121.53 (10^a-C), 121.64 (7-C), 128.91 (4-C), 130.59 (3-C), 134.50 (6^a-C) and 134.69 (1-C); *m*/*z* 226 (M^+, 100%), 211 (63), 183 (48), 155 (22), 127 (50) and 101 (20).

3-Methoxy-6*H*-benzo[*c*]chromen-6-one 1

The general procedure for PCC oxidations with 3-methoxy-6*H*-benzo[*c*]chromene **25** (0.13 g, 0.59 mmol) yielded 3-methoxy-6*H*-benzo[*c*]chromen-6-one **1** as a pungent smelling, brilliant white powder (0.13 g, 100%), mp 123–129 °C (lit.[34] mp 143 °C) (Found: M^+, 226.0634. $C_{14}H_{10}O_3$ requires 226.0630); ν_{max}(Nujol)/cm^{-1} 2924, 2854, 1735, 835 and 761; δ_H 3.88 (3 H, s, MeO), 6.88–6.95 (2 H, m, 2- and 4-H), 7.50 (1 H, dd, *J* 7.6, 7.6, 9-H), 7.78 (1 H, dd, *J* 7.6, 7.6, 8-H), 7.96 (1 H, d, *J* 8.7, 1-H), 8.33 (1 H, d, *J* 7.6, 10-H) and 8.33 (1 H, d, *J* 7.6, 7-H); δ_C 55.62 (MeO), 101.53 (9-C), 112.37 (8-C), 123.70 (7-C), 127.65 (4^a-C), 127.72 (1-C), 130.47 (2-C), 134.80 (4-C), 135.01 (6^a-C), 152.52 (C=O) and 161.51 (3-C); *m*/*z* 226 (M^+, 63%), 211 (9), 184 (8), 183 (68), 155 (38), 139 (30), 127 (100), 126 (45), 133 (19) and 101 (31).

1-Benzyloxy-6*H*-benzo[*c*]chromen-6-one 36

The general procedure for PCC oxidations with a clean mixture (0.29 g) of 1- and 3-benzyloxy-6*H*-benzo[*c*]chromene **28** afforded 1-benzyloxy-6*H*-benzo[*c*]chromen-6-one **36** as a colourless solid (17.80 mg, 63%) (Found M^+, 302.0943. $C_{20}H_{14}O_3$ requires 302.0943); ν_{max}(neat)/cm^{-1} 3065, 3032, 2921, 1604, 790 and 718; δ_H(400 MHz) 5.31 (2 H, s, CH_2O), 6.94 (1 H, dd, *J* 8.3, 1.1, 2- or 4-H), 7.05 (1 H, dd, *J* 8.3, 1.1, 2- or 4-H), 7.36–7.46 (5 H, m, Ph-H), 7.38 (1 H, t, *J* 8.3, 3-H), 7.50–7.53 (1 H, m, 9-H), 7.69 (1 H, ddd, *J* 8.4, 7.3, 1.6, 8-H), 8.43 (1 H, ddd, *J* 8.4, 1.0, 0.5, 10-H) and 9.05 (1 H, ddd, *J* 8.4, 1.0, 0.5, 7-H); δ_C(100 MHz) 71.83 (CH_2O), 108.64 (2- or 4-C), 111.10 (2- or 4-C), 121.50 (6^a-C), 127.95 (7-C), 128.17 (9-C), 128.44 (phenyl-CH), 128.73 (phenyl-CH), 129.15 (3-C), 130.26 (phenyl-CH), 130.57 (10-C), 130.97 (Ph*C*H_2O), 134.93 (10^a-C), 135.17 (8-C), 136.40 (10^b-C), 153.06 (4^a-C), 157.85 (1-C) and 161.81 (C=O); *m*/*z* 302 (M^+, 80%), 212 (7), 183 (9), 167 (10), 139 (8), 127 (29), 113 (4), 101 (10), 91 (100), 84 (17), 71 (7) and 65 (36). 3-Benzyloxy-6*H*-benzo[*c*]chromen-6-one was also afforded (7.63 mg, 27%); δ_H(400 MHz) 5.14 (2 H, s, CH_2O), 6.99 (1 H, dd, *J* 8.8, 2.6, 2-H), 7.78 (1 H, ddd, *J* 15.36, 8.7, 1.4, 9-H), 7.96 (1 H, d, *J* 8.8, 1-C), 7.90 (1 H, d, *J* 8.4, 10-H) and 8.35 (1 H, ddd, *J* 8.0, 1.4, 0.5, 7-H). The 3-benzyloxy analogue was not fully chracterised.

2-Chloro-6*H*-benzo[*c*]chromen-6-one and 9-chloro-2-methyl-6*H*-benzo[*c*]chromen-6-one were also synthesised by PCC oxidation and their characterisation data are provided as supplementary data.

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