ARENE TRANSITION METAL COMPLEXES IN SYNTHESIS

A thesis submitted in partial fulfilment

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Doctor of Philosophy

by

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Arene Transition Metal Complexes In Synthesis

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Abstract

This thesis deals with the applications of organopalladium and organochromium chemistry to the functionalisation of the benzopyran ring system, at a variety of oxidation levels.

Section I demonstrates the functionalisation of 3-, 6-, and 8-bromochromones *via* palladium (0) insertion into the C-Br bond. The resultant arylpalladium species are shown to undergo addition to the least substituted end of a variety of olefins including methyl acrylate, acrylonitrile and styrene. Subsequent palladium-hydride elimination leads to overall palladium catalysed vinylation of the chromone and the synthesis of a number of novel compounds. Vinylation occurs regiospecifically at the site of chromone bromination and is shown to allow clean substituent introduction into each of the three sites. The palladium catalysed reaction of 3,6-dibromochromone with methyl acrylate leads to vinylation at both the C3 and C6 positions. Carbonylation of the 6-bromochromone in ethanol or butanol leads to the 6-ethyl or 6-butyl esters respectively. The palladium catalysed vinylation of the 6-bromochromone with ethyl vinyl ether leads to a mixture of products from addition of the chromone to either end of the olefin. With *p*-bromophenol or *p*-bromo-*N*,*N*-dimethylaniline the reaction gives exclusively the acetylated product arising from addition to the more substituted end of the olefin. This change in orientation is rationalised by considering the polarisation of the olefin and the arylpalladium species.

Section II demonstrates the functionalisation of chroman and 4-chromanol *via* coordination to the $Cr(CO)_3$ moiety. (η^6-Chroman)$Cr(CO)_3$ is synthesised and is shown to undergo regiospecific ring deprotonation at C8 under kinetic conditions or regiospecific benzylic deprotonation at C4 under thermodynamic conditions. The resultant anions are quenched with alkyl halides, aldehydes, Eschenmoser's salt and methyl disulphide resulting in selective functionalisation of either site. No mixed products are observed. The uncomplexed arene is shown to be totally unreactive under identical conditions. (η^6-4-Chromanol)$Cr(CO)_3$ is synthesised and is shown to undergo regiospecific C8 ring deprotonation by comparison with authentic samples of the C5 and C8 methylated alcohols. Protection of the hydroxyl group as its methyl, *t*-butyldimethylsilyl or methoxymethyl ethers is found not to alter the regiochemistry of deprotonation. The 4-chromanol *t*-butyldimethylsilyl and tri-*i*-propylsilyl ethers are synthesised and coordinated to the metal unit. Cleavage of the silyl ethers is shown to proceed with loss of stereochemistry, indicating C-O bond cleavage.

Acknowledgements

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Finally my thanks go to Amanda who has been very understanding over the last few months.

Contents

Abbreviations

DIBAL	Di*iso*butylaluminium hydride
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
*m*CPBA	*meta*-Chloroperbenzoic acid
MoOPH	Oxodiperoxymolybdenum(pyridine)hexaphosphoramide
THF	Tetrahydrofuran
Ac	CH_3CO
Ar	Aryl
B^-	Base
E^+	Electrophile
[H]	Reducing agent
L	Two electron ligand
M	Metal
MOM	Methoxymethyl
Nu	Nucleophile
[O]	Oxidation
Ph	Phenyl
TBDMS	*t*-Butyldimethylsilyl
TIPS	Tri*iso*propylsilyl
X^-	Halide
Y	Leaving group
t.l.c.	Thin layer chromatography

n.m.r. spectroscopy

s	singlet	sx	sextet
d	doublet	dd	doublet of doublets
t	triplet	dt	doublet of triplets
q	quartet	m	multiplet
qu	quintet	n.O.e	Nuclear Overhauser Effect

infrared spectroscopy

(v)w	(very) weak	s	strong
m	medium	br	broad

mass spectroscopy

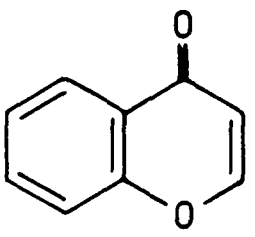
EI	Electron Impact
IBEI	In Beam Electron Impact
CI	Chemical Ionisation

Foreword

There are many examples of natural products containing an oxygen heterocycle and with the attention paid to natural product chemistry over the last century, the synthetic organic chemistry relating to these sytems is, by and large, well understood.

In recent years organometallic chemistry has begun to extend the scope of the methods available to the synthetic organic chemist[1] and this thesis explores the potential of two areas of organometallic chemistry with respect to the benzopyran system.

The benzopyrans are the class of compounds containing a benzene ring fused to a six-membered oxygen heterocycle. A variety of compound types exist, many of which occur naturally in plants and several of which exhibit interesting pharmacological properties. Benzopyrans of three structural types will be considered; the 4H-1-benzopyran-4-ones, the 3,4-dihydro-2H-1-benzopyrans and the 3,4-dihydro-2H-1-benzopyran-4-ols for which the parent structures are 1 - 3 respectively.



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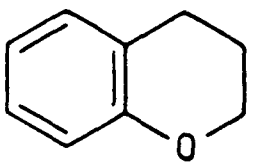

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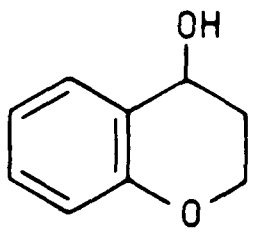
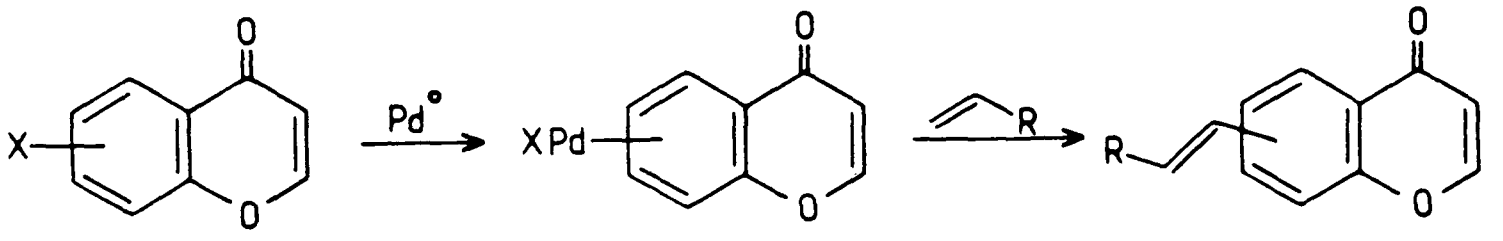


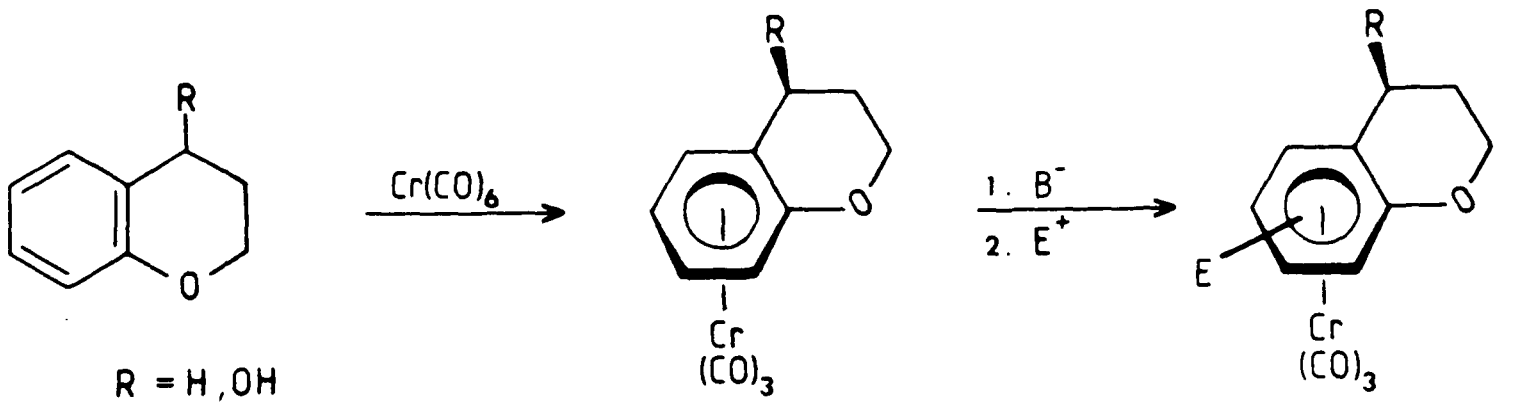
3

Henceforth these will be referred to by their trivial and more common names; chromones (1), chromans (2) and 4-chromanols (3). The dihydroderivative of chromone 1, 4-chromanone 4, will also be mentioned in connection with the latter compounds.

Section I is concerned with the activation of bromochromones through the use of a palladium catalyst by insertion into the C-X bond. The resultant aryl-palladium species are known to undergo a number of reactions, *e.g.* coupling to olefins, leading to overall halogen substitution.



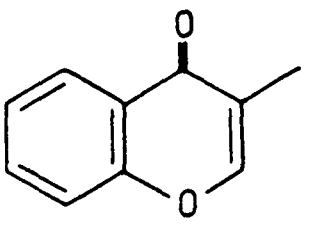
Section II is concerned with the synthesis and subsequent reactions of the (η^6-arene) chromium tricarbonyl complexes of the chromans and 4-chromanols. Coordination of the chromium tricarbonyl moiety to the arene unit results in a significant change in arene reactivity which is utilised for novel synthetic transformations.



Benzopyrans-Biological importance and pharmacological activity

For each of the three benzopyran systems under study, the naturally occurring compounds are dominated by their 2- and 3- aryl derivatives which form part of the flavanoid family.[2] This class of compound occurs almost exclusively in plants. They are frequently highly coloured and therefore play an important ecological role in making the fruit and flowers attractive to birds and insects.

Other naturally occurring chromones are much less common, only about fifty compounds being known.[3a] The interest in chromones however, stems from the pharmacological activity of some of the derivatives. Amongst the alkyl chromones, the 3-methyl derivative 5 has been thoroughly studied with respect to its therapeutic use. Pharmacological studies have shown it to possess muscle relaxant properties and particularly a vasodilatory effect on coronary blood vessels.[4] Its spasmolytic action was found to be comparable to that of khellin 6, a naturally occurring antispasmodic.



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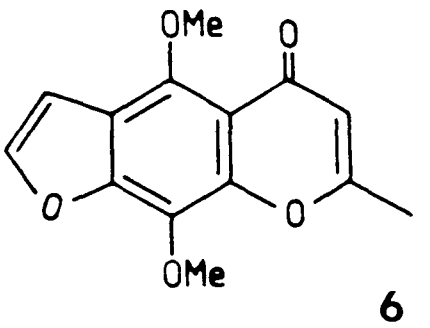

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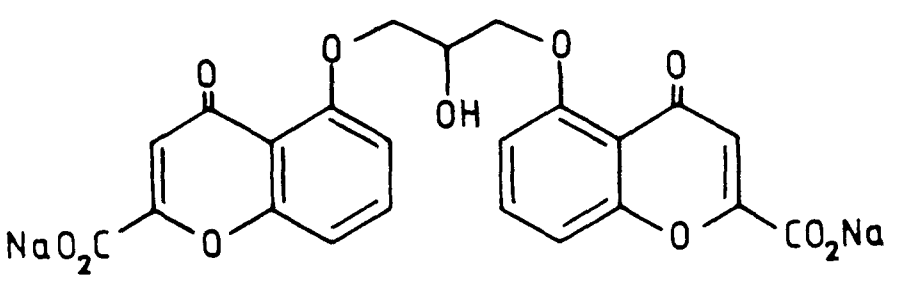
This latter compound is found in the fruits and seeds of the eastern Mediterranean plant, *Ammi visnaga*[5] and extracts of this plant have been used medicinally. Khellin 6 induces muscular relaxation and it has therefore been used to relieve the symptoms of bronchial asthma. Following its structure determination,[5] attempts to synthesise synthetic analogues, to increase the potency and reduce the side effects, showed that the 4-pyrone ring was essential for activity.[6] During these studies, it was found that if the substituent in the 2-position of the chromone ring was

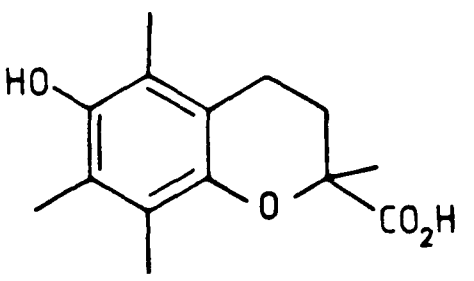
replaced by a carboxylic acid functionality a new type of biological activity emerged. Though such compounds had no antispasmodic effects, they could act prophylactically in preventing the onset of the symptoms of asthma.[7] One of these derivatives, disodium cromoglycate 7 (Intal R, Fisons Pharmaceuticals) is now widely prescribed for the prevention of bronchial asthma.



7

Unfortunately, this compound is inactive orally and there has therefore been a considerable effort (by more than fifty pharmaceutical companies) to find orally active analogues. Much of the work in the chromone field has been targetted towards this. Chromone carboxylic acid derivatives have also been reported to reduce serum lipid levels[8] and to possess sedative and hypnotic activity.[9]

The chromans (2) also form part of an important class of biological compounds, the tocopherols or vitamins E.[10a] These compounds are generally found in plants, with vegetable oils, particularly wheat germ oil being a rich source. The tocopherols behave as antioxidants, protecting plant lipids from excessive oxidation. Various synthetic chromans (*e.g.* 8)[11] have been found to mimic this behaviour and act as efficient antioxidants for various vegetable oils.



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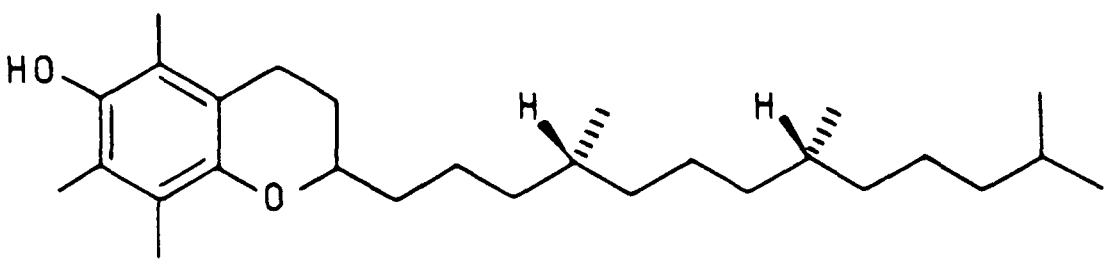

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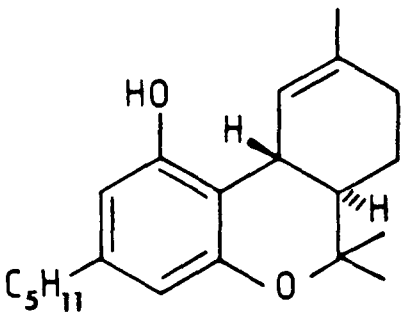
Vitamin E, α-tocopherol, 9 is required to prevent mammilian sterility and has been reported to protect mice against the cardiotoxic effects of the anticancer drug adriamycin.[12] Many chroman derivatives have been prepared in attempts to find compounds that possess activity similar to Vitamin E.

Another well known chroman derivative is Δ-3,4-*trans*-tetrahydrocannabinol 10, the physiologically active component of marihuana.[13]



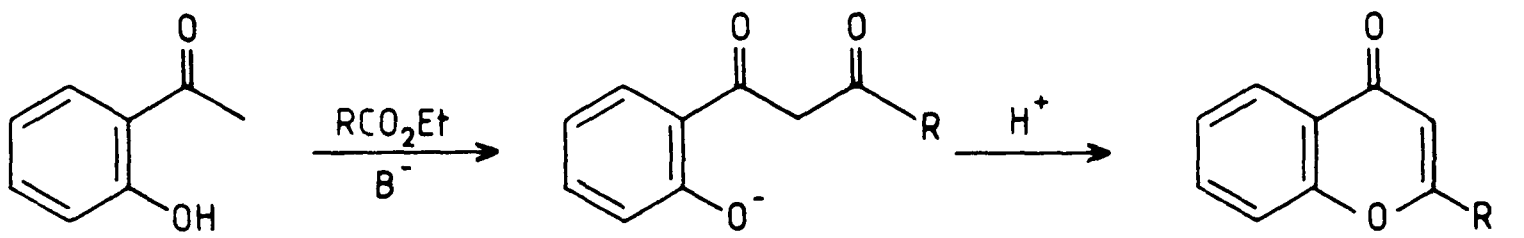
10

With the exception of members of the flavanoid family, naturally occurring 4-chromanols (3) and 4-chromanones (4) are comparatively rare. Synthetic derivatives of the 4-chromanols that have been tested for pharmacological activity appear to possess mild analgesic activity while the Mannich bases of the 4-chromanones have a wide spectrum of activity including antimicrobial, antidepressant and vasodilatory effects.[3b]

Synthesis[3c]

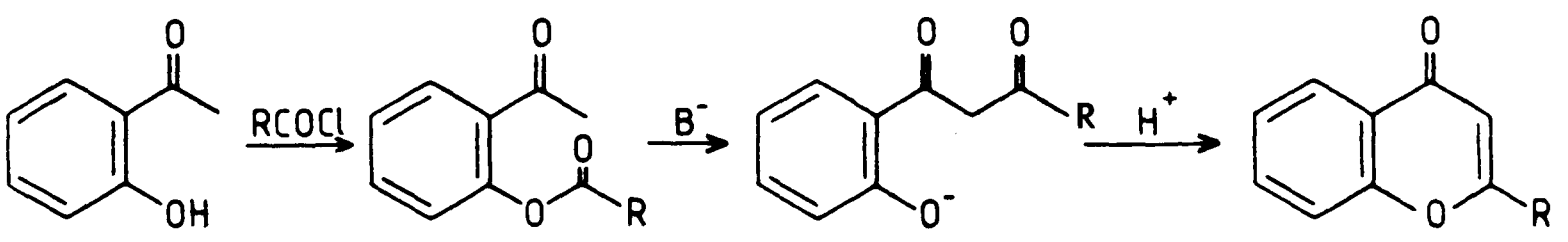
Synthesis of the ring systems can be divided into two broad categories, either ring formation *via* a cyclisation or manipulation of the oxidation level of the preformed pyran ring.

The two most common precursors for chromone formation, *via* a cyclisation, are *o*-hydroxyacetophenones and phenols. The Claisen condensation of the former with a carboxylic ester in the presence of a strong base produces a 1,3 diketone 11. While this intermediate may be isolated, as its sodium salt, cyclisation to the chromone 12 occurs readily on acidification.



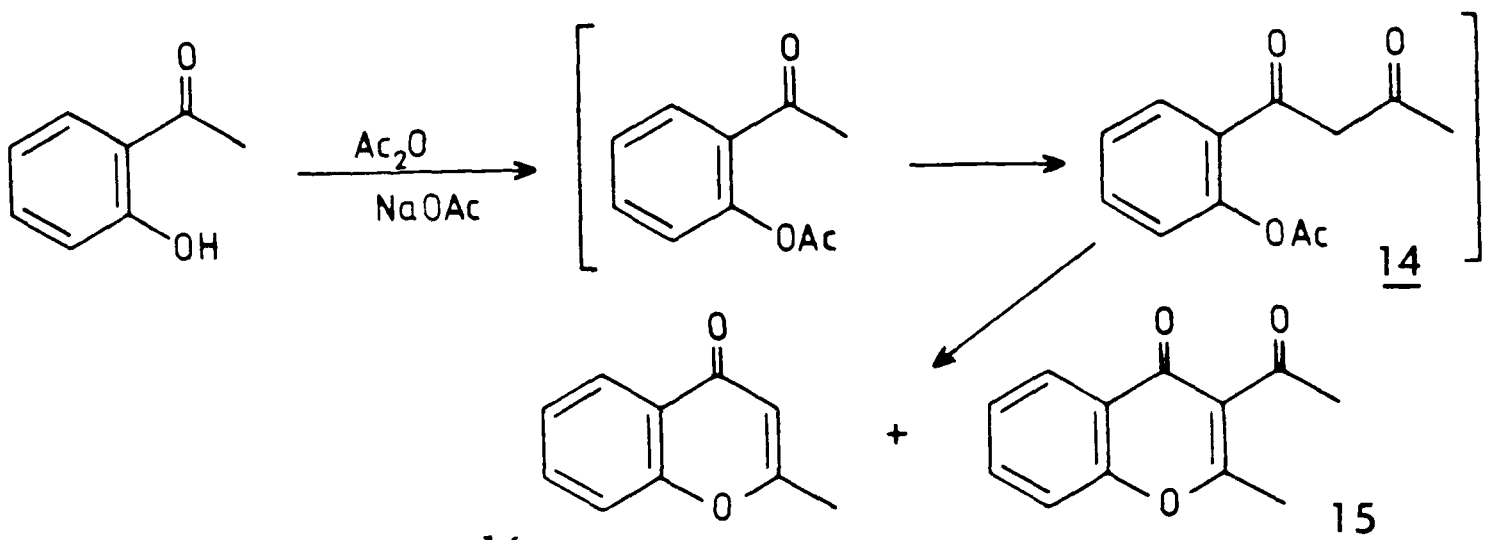
11 12

The use of diethyl oxalate as the ester component (R = CO_2Et) allows the synthesis of a variety of chromone 2-carboxylic esters *via* transesterification with an alcohol during the acidic work up. An alternative source of the 1,3 diketone intermediate 11 formed in the Claisen condensation, is from *O*-acyloxyacylbenzenes 13, readily prepared by *O*-acylation of *o*-hydroxy-acetophenones. Treating these compounds with base results in an overall intramolecular transfer of the acyl moiety from oxygen to carbon - the Baker-Venkataraman rearrangement. The reaction proceeds by attack of the enolate on the ester and does not involve acylium ion transfer.

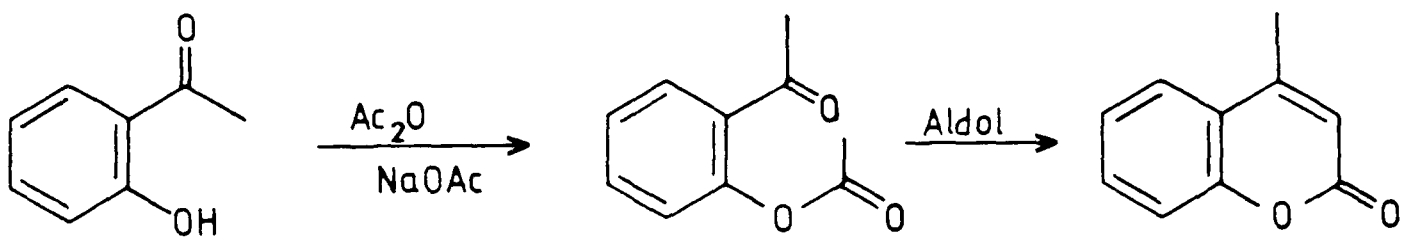


13 11

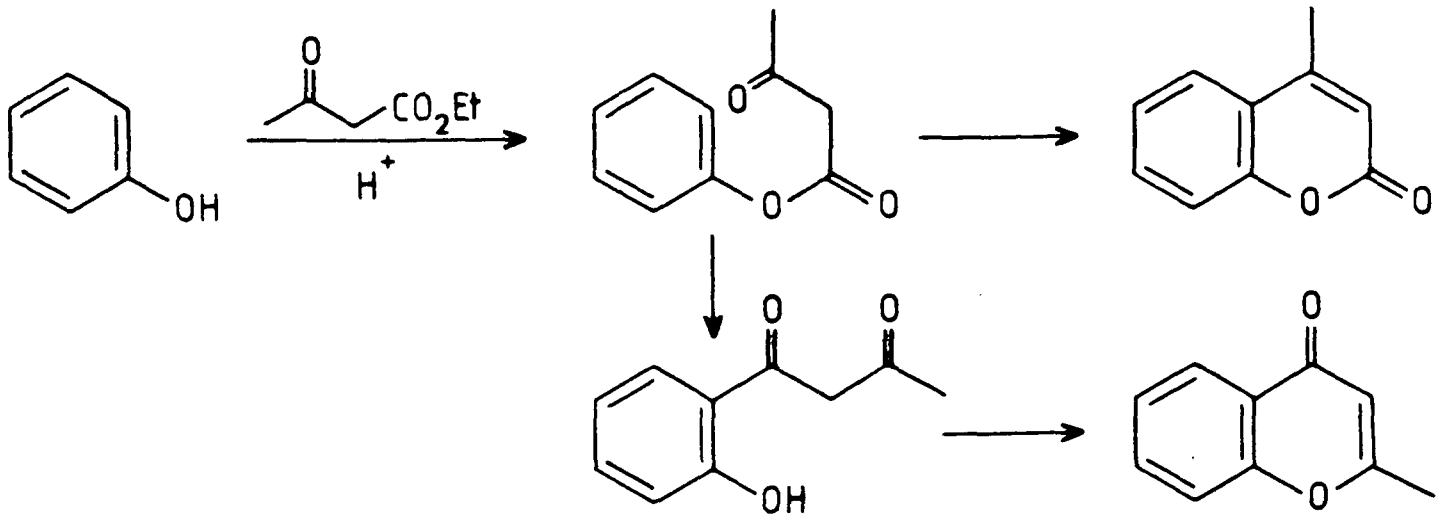
The other common chromone synthesis from *o*-hydroxyacetophenones is the Kostanecki-Robinson reaction. This involves heating the acetophenone with the anhydride and sodium salt of an aliphatic acid (*e.g.* sodium acetate and acetic anhydride). The reaction proceeds *via O*-acylation followed by a Baker-Venkataraman rearrangement to give the 1,3 diketone 14. The initial cyclisation product is the 3-acylchromone 15 which is frequently cleaved to the chromone 16 during product isolation.



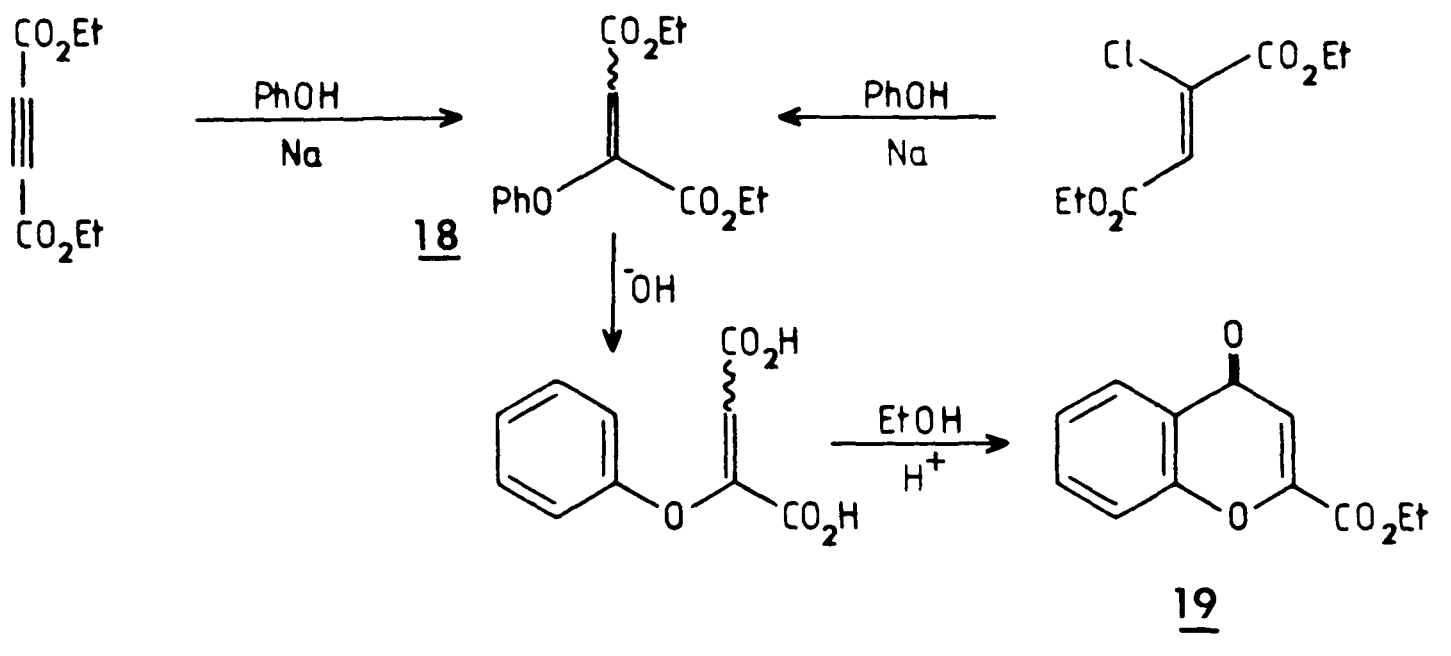
This method has the disadvantage that a number of isomeric products may arise, including the isomeric coumarin 17, formed by an intramolecular aldol condensation and loss of water.



The reaction of phenols and β-ketoesters with a condensing agent (*e.g.* phosphorus pentoxide), leads directly to chromones. In addition to indifferent yields, this synthesis also suffers from frequently producing the isomeric coumarin as the sole product, or a mixture of the two heterocycles. There appears to be no reliable correlation between the choice of condensing agent and the final product.



An alternative synthesis from phenols involves the reaction with acetylenedicarboxylic esters or with a chlorofumaric ester to form a phenoxyfumaric ester 18. While these esters may be cyclised directly to the chromone 19, hydrolysis to the corresponding carboxylic acid followed by cyclisation is the more common route. This type of synthesis suffers from the inherant formation of both the maleate and fumarate derivatives as intermediates, only the latter cyclising to the chromone.



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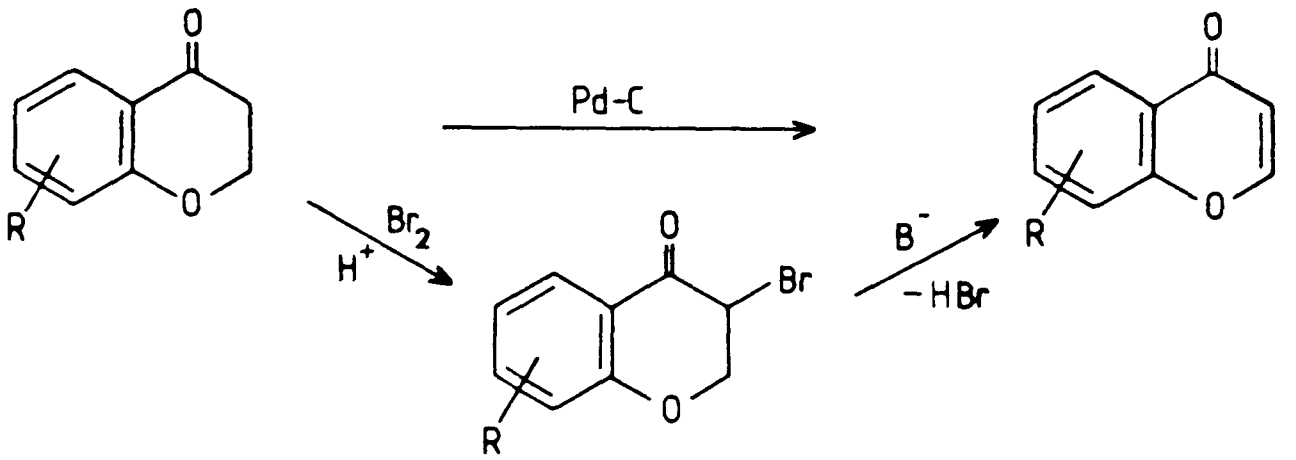
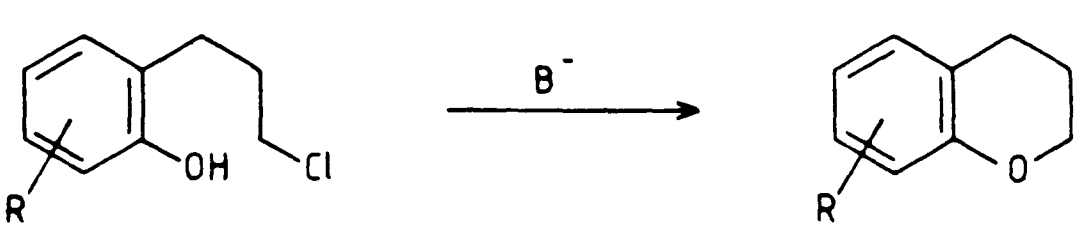
19

Chromones are generally resistant to electrophilic attack and the pyrone ring is susceptible to attack and cleavage by a variety of nucleophiles. Substituents are therefore usually introduced into the acetophenone or ester component prior to condensation and cyclisation.

Chromone synthesis from a preformed pyran ring system is limited to the oxidation of 4-chromanones 4. Direct dehydrogenation may be effected by palladium on charcoal but the reaction appears to be somewhat unreliable and fails completely for the 2-carboxylic acid derivatives. Alternatively, the chromanones may be brominated at the 3-position and subsequently dehydrobrominated, although care must be taken to avoid opening the pyrone ring.

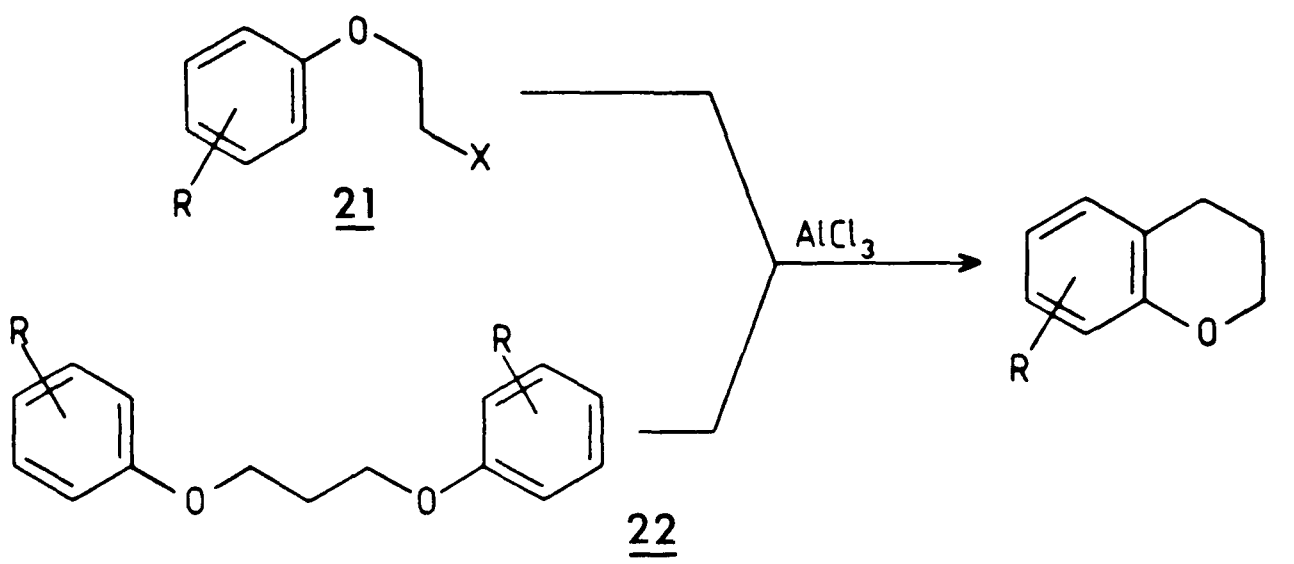


A number of cyclisations are available for the synthesis of chromans (2), all of which involve the formation of the tetrahydropyran ring.[10b] An established route which was used for the first preparation of chroman 2 (R = H),[14] involves the cyclisation of 2-(3-chloropropyl)phenols 20 with aqueous base.

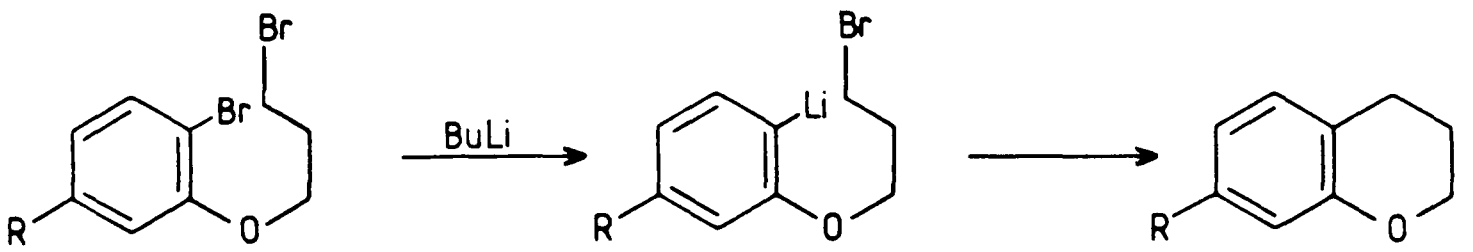


20 2

The use of Friedel-Crafts conditions allows the cyclisation of phenylpropyl ethers 21 or the 1,3-diaryloxypropanes 22.



Both these methods are largely unaffected by substituents on the aromatic ring, providing they are compatible with the reaction conditions. For *o*- and *p*- substituted arenes the regiospecificity of cyclisation is fixed and unequivocal, respectively. The use of *m*-substituted arenes, however, leads to mixtures of the 5- and 7- isomeric chromans. The only method that controls the regiospecificity of cyclisation, proceeds through an aryllithium species 23 which is formed *via* halogen-lithium exchange.[15]



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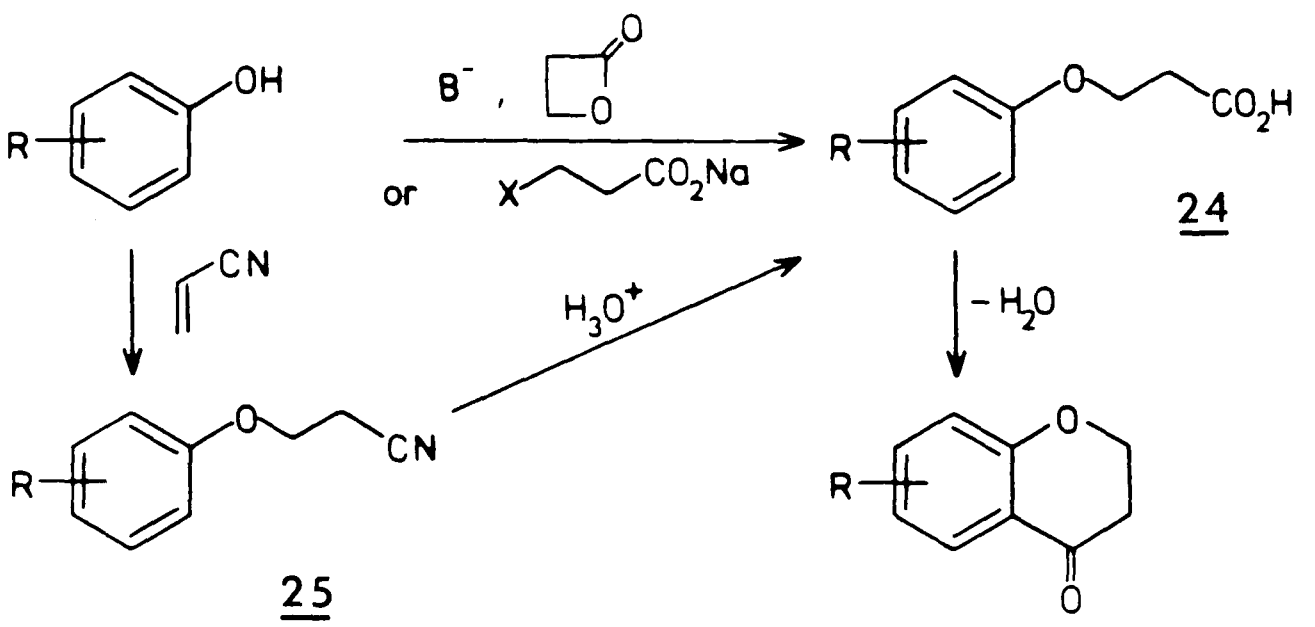
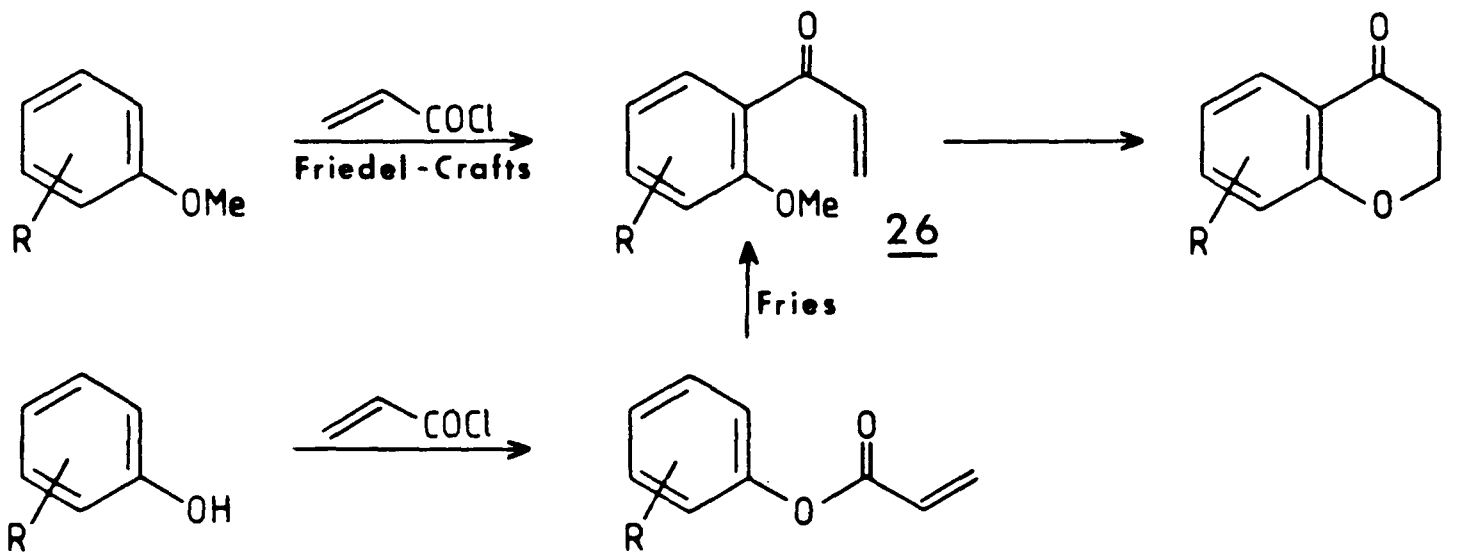
The cyclisation of phenoxypropionic acids 24 or their corresponding nitriles 25, normally prepared from phenols, using a variety of dehydrating agents gives rise to 4-chromanones.[3b]



As with the chroman cyclisation, Friedel-Crafts conditions can be used to prepare 4-chromanones. The substrates most commonly used are a substituted anisole and the acyl chloride of an unsaturated acid. A closely related synthesis involves the formation of the acrylophenone 26 *via* a Fries rearrangement from an acylated phenol. Rearrangement of the acyl moiety to both *ortho*- and *para*- positions can occur and consequently the yields of the 4-chromanone are somewhat lower.



There are few direct syntheses of 4-chromanols by cyclisations; they are more usually prepared by reduction of the 4-chromanones with any of the standard reducing agents. Although the chromone ring is rather resistant to hydrogenation, the use of Raney-nickel catalysts allows reductions to the 4-chromanones to be achieved. Over reduction to the 4-chromanol or the chroman is a problem and can lead to mixtures of products.

Section I

CHROMONE ELABORATION *VIA* σ-PALLADIUM COMPLEXES

1. Introduction to Palladium chemistry

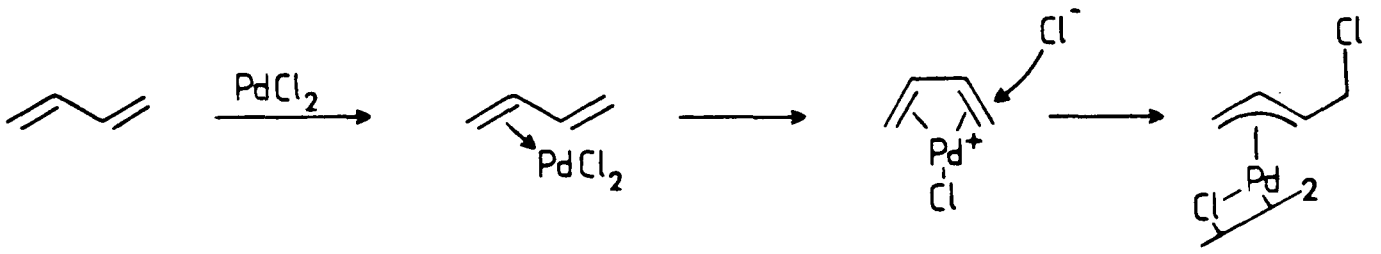
The development of organopalladium chemistry was originally stimulated by the industrial Wacker process (1958) in which ethylene is oxidised to acetaldehyde using palladium chloride and copper II chloride as catalysts. Since then extensive research has shown that many unique transformations can be achieved using palladium compounds - either as stoicheiometric reagents or as catalysts.[16] Due to the high cost of palladium, the latter is the more attractive route for synthesis, although with a stoicheiometric process it is usually feasible to recover and recycle the metal.

The chemistry of palladium is governed by its two most common oxidation states 0 and +2; palladium (0) acts as a nucleophile, while palladium (II) is an electrophile. The reactions of palladium compounds can be divided into two main groups: (i) oxidative reactions with palladium (II) compounds, and (ii) catalytic reactions. The first type of reaction consumes an equivalent of palladium (II) which is reduced to palladium (0) on completion of the reaction. Reoxidation of the 'noble' metal, palladium (0) to palladium (II) is not always easy, but with the appropriate choice of conditions this can sometimes be achieved *in situ* to regenerate palladium (II) and render the whole oxidative process catalytic. Reactions of the second type are carried out either with palladium (0) or palladium (II) compounds and the reactions proceed catalytically without reoxidation. An alternative approach is to divide organopalladium chemistry according to the two main types of intermediate involved, either: (i) π-allyl species, or (ii) σ-palladium species. These two intermediates can result from either of the two common palladium reactions mentioned above. The work in this section involves the use of σ-palladium species and therefore only a brief summary will be given of the many syntheses and reactions of the π-allyl species.

The most common source of palladium (II) is its commercially available chloride. This, however has a low solubility in most non-complexing organic solvents and its use usually requires the formation of the more soluble complex salts M_2PdCl_4 (M = Li, Na, K).[16a] Other more soluble species include the *bis*triphenylphosphine complex $[Pd(PPh_3)_2Cl_2]$ and the acetate $[Pd(OAc)_2]$ which is also commercially available. For catalytic reactions palladium (0) species are required. Whilst preformed complexes, such as *tetrakis*(triphenylphosphine)palladium $[Pd(PPh_3)_4]$ may be used they are air-sensitive and tend to lose their catalytic activity on storage. *In situ* preparation from palladium (II) is therefore preferable.

(i) π-Allyl species

The first π-allyl complex was prepared by the stoicheiometric reaction of palladium chloride with butadiene,[17] and isolated as the bridged chloride dimer - a common structure for these complexes. The reaction proceeds *via* nucleophilic attack of the chloride ion on an initial π-olefin palladium complex 27.



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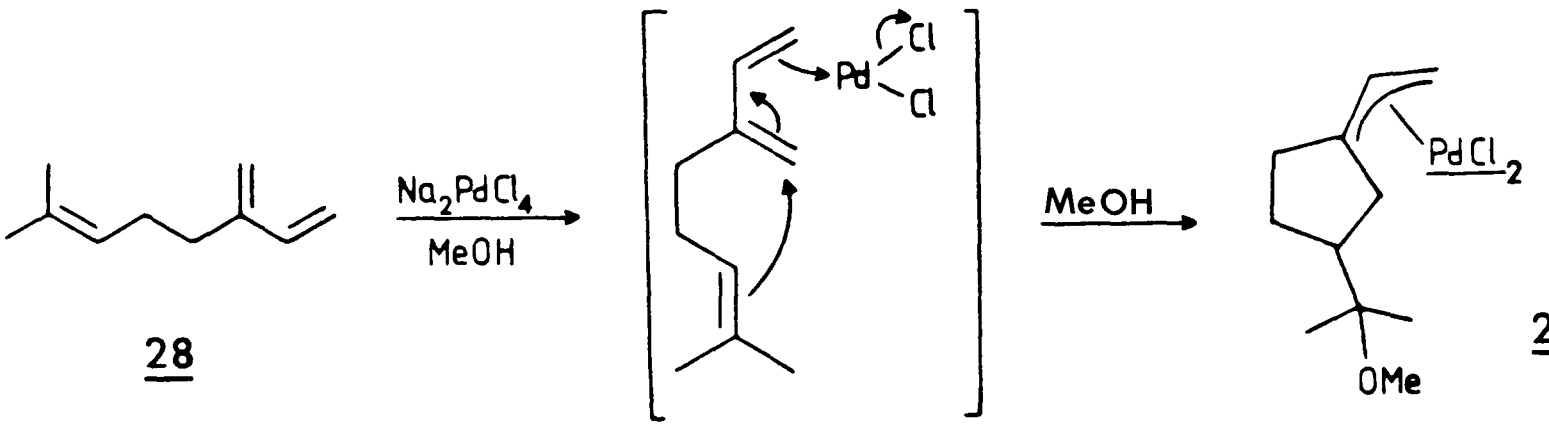
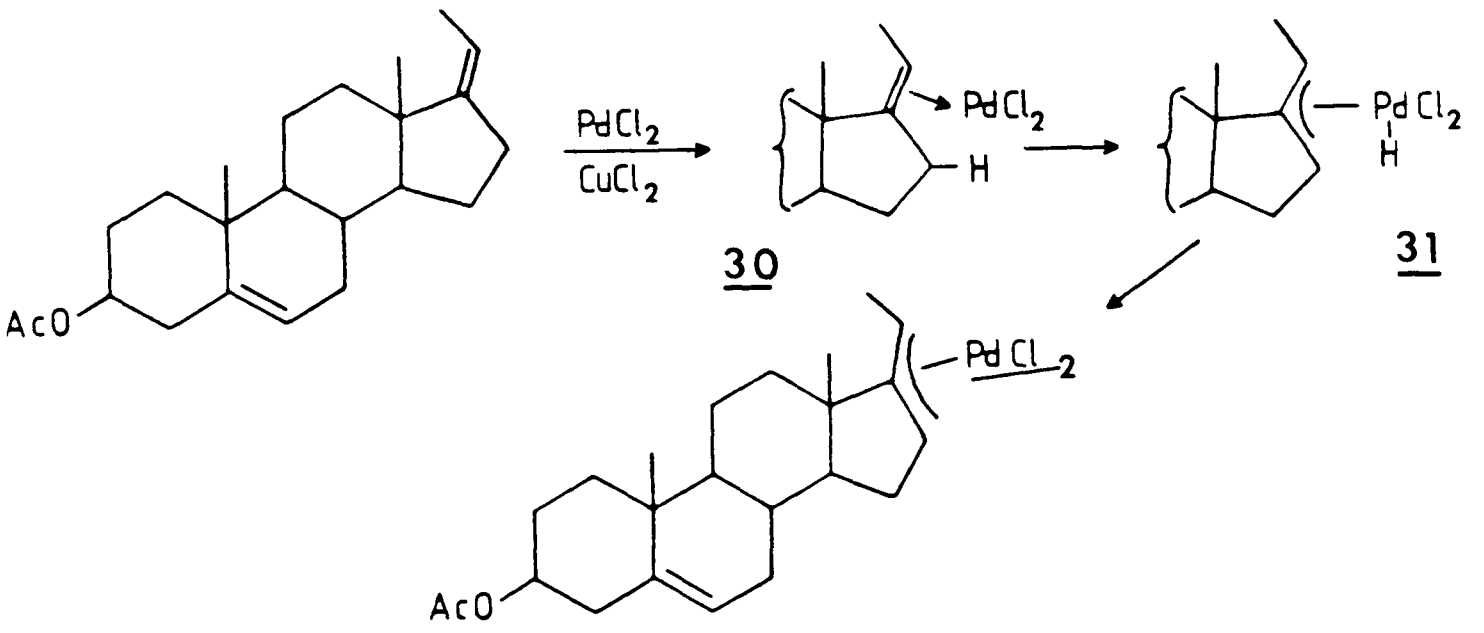
These reactions usually use the chloride or an alcohol as the nucleophile, however with some compounds a neighbouring double bond can compete. Thus myrcene 28 undergoes cyclisation during the process of forming the π-allyl species 29.[18]



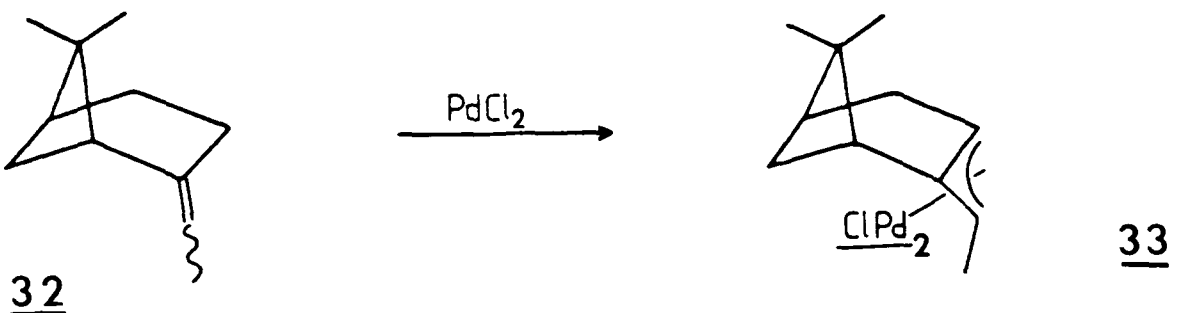
28 29

Direct conversion of alkenes to π-allyl palladium species is possible by treatment with a palladium (II) salt. The reaction is presumed to proceed through a similar π-olefin complex 30 followed by a palladium hydride species 31. A more reliable approach is to include a weak base in the reaction mixture[19] or to add cupric chloride[20] which promotes rapid conversion of the palladium hydride species 31 to the dimer. The reaction is affected by the steric environment of the olefin and good regioselectivity is usually observed with the hydrogen abstracted being allylic to the more substituted end of the olefin.



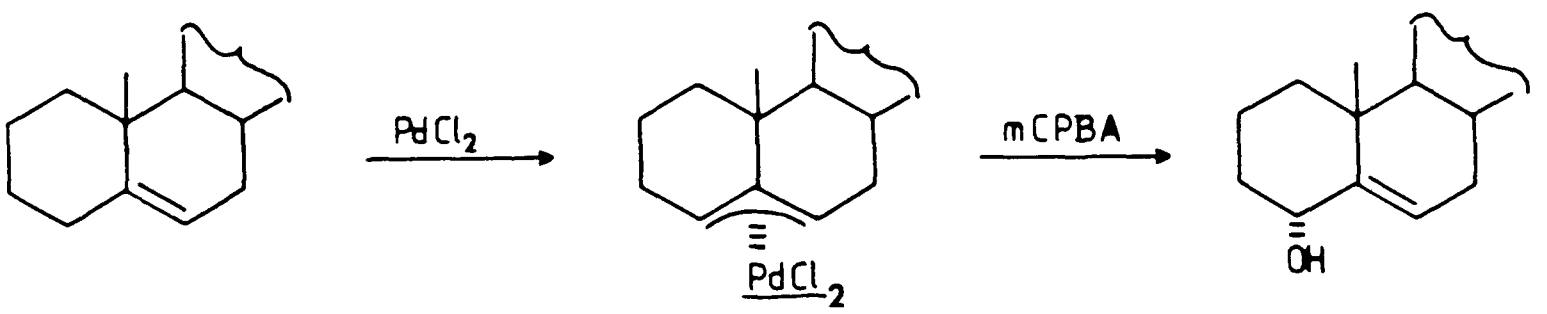
30 31

The stereochemistry of the π-allyl palladium complex reflects the thermodynamic stability of the complex and is independent of the stereochemistry of the olefin. The bulky metal and associated ligands usually lie on the less hindered face of the π-allyl unit. A mixture of geometric isomers of 2-ethylidenenorpinane 32 therefore gave a single complex 33 with the palladium *anti* to the *gem* dimethyl bridge.[21]



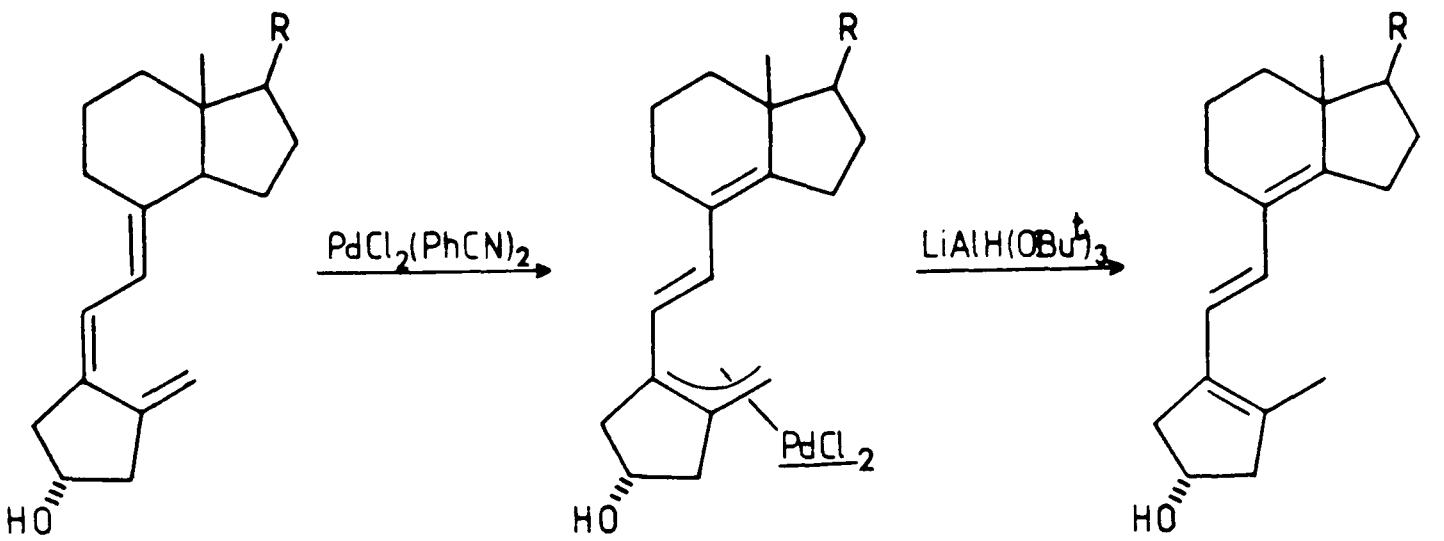
32 33

These stoicheiometrically prepared π-allyl palladium complexes undergo a number of addition reactions. If the complex originates from an alkene an overall allylic functionalisation results. For example, oxidation of steroidal complexes (*e.g.* 34) with *m*CPBA effects a stereospecific allylic oxidation with retention of configuration.[22]



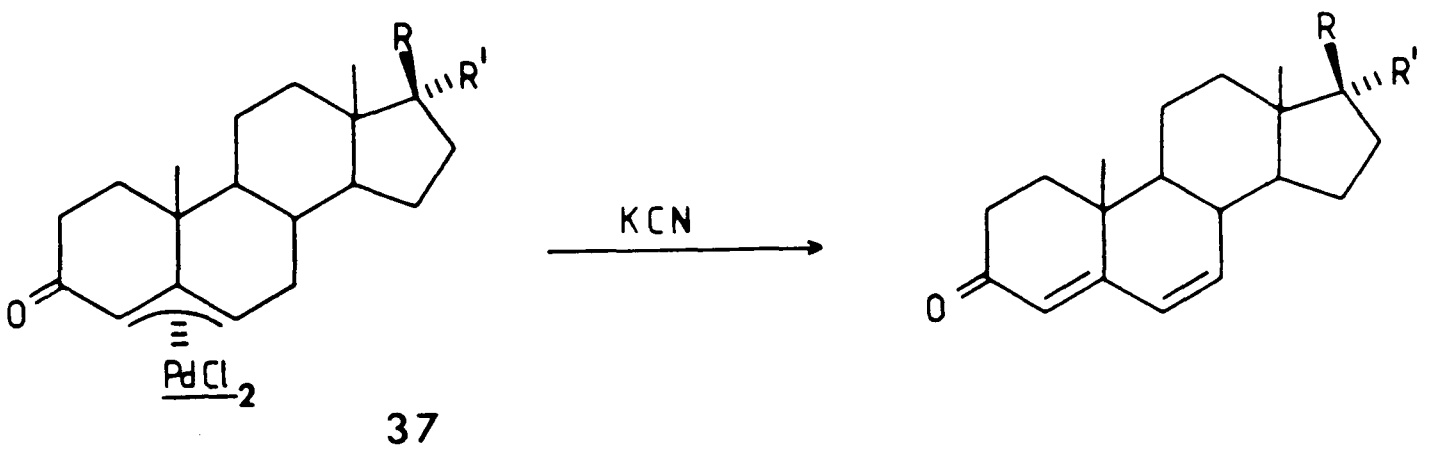
34

Reduction of the allyl complex to an olefin can be effected by various metal hydrides. In cases where the π-allyl complex is not stereochemically identical to the initial olefin, this has been used to effect regiospecific olefin isomerisations. (*e.g.*[23] 35 to 36).



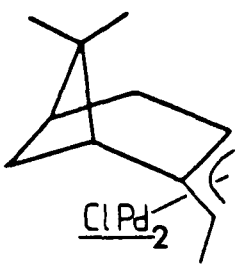
35 36

Although the π-allyl complexes are much less susceptible to β-hydride elimination than the σ-bonded species (*vide infra*) this can be achieved thermally - resulting in a net dehydrogenation from the olefin.[24] For complex 37 which is particularly prone to decomposition this can also be effected by nucleophiles.[25]

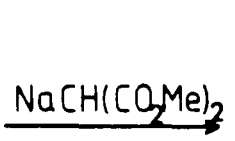


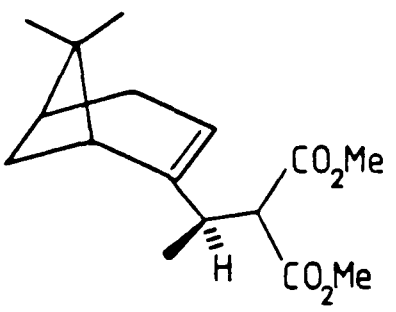
37

One of the major uses of these complexes is for carbon-carbon bond formation. Activation of the complexes by cleavage of the halide bridged dimers with phosphine ligands allows the addition of stabilised carbanions. The reactions show high stereochemical control with the nucleophile usually approaching from the face opposite to the metal. Addition is normally observed at the sterically less hindered end of the π-allyl unit. Thus complex 33 is alkylated to give 38.[21]



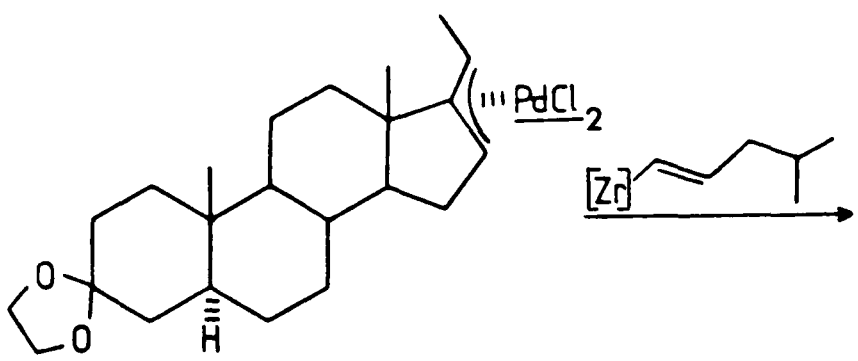
33

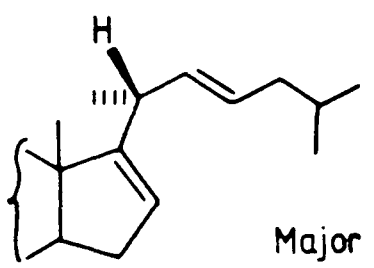




38

Attempts to extend this to hard nucleophiles have generally been unsuccessful. The π-allyl complexes are ambident electrophiles and attack then occurs at the metal. Secondary reactions such as β-hydride elimination then compete with transfer of this nucleophile from palladium to carbon. When such side reactions are structurally precluded then alkylation can occur. The stereoselective introduction of a steroid side chain has been achieved in complex 39 by the use of an alkenylzirconium species.[26] The stereochemistry obtained is the opposite to that achieved with soft nucleophiles.

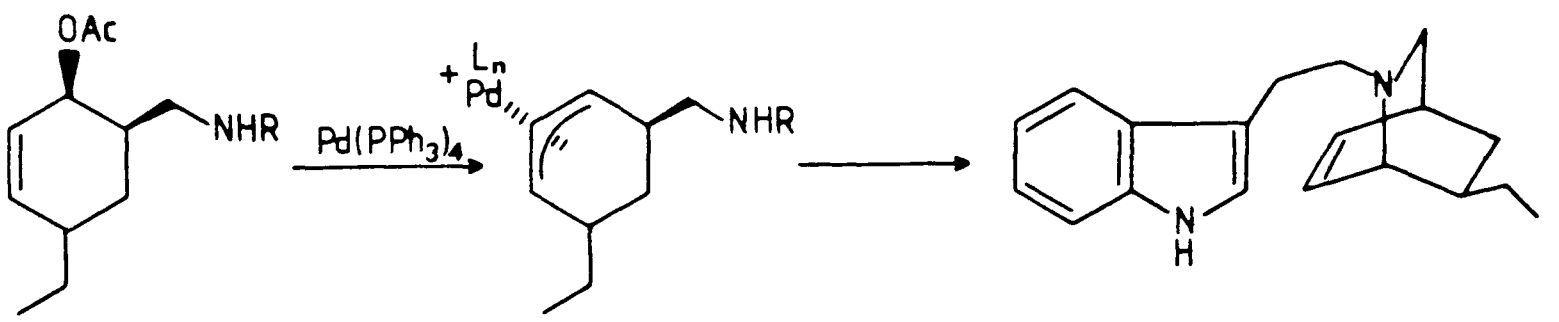




39

This activation of olefins *via* their π-allyl palladium complexes can only be synthetically useful on a small scale since the reaction requires stoicheiometric quantities of Pd(II) and to date no catalytic process has been developed. Of greater synthetic use is the formation of the π-allyl species from allylically oxidised compounds with palladium (0) catalysts. The complex is formed by prior coordination of the metal to the

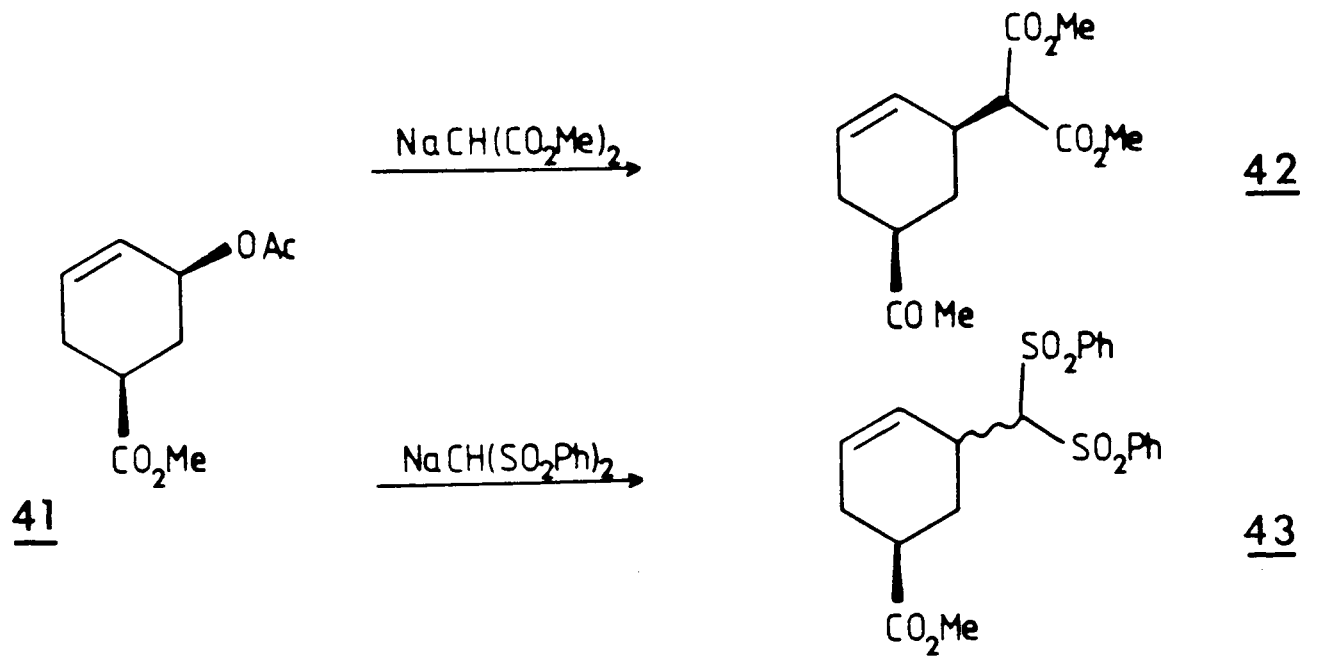
olefin on the face opposite to that of the leaving group. Loss of this allylic group then generates the π-allyl cation. The resultant complexes undergo a similar range of reactions to the stoicheiometrically prepared complexes. The use of heteroatom nucleophiles leads to an overall allylic exchange, with retention of configuration resulting from two S_N2 displacements. The positional identity of the original allylic substituent is however frequently lost during the substitution. These features are observed in the intramolecular amino additions employed in the synthesis of isoquinuclidines 40.[27]



40

The addition of carbon nucleophiles again constitutes a versatile method of C-C bond formation. Retention of configuration is observed providing the nucleophile is sufficiently reactive to trap the kinetically formed π-allyl complex (*e.g.* 41 to 42).[28] With less reactive nucleophiles isomerisation of the π-allyl complex can sometimes occur in competition with addition and low stereospecificity is observed (*e.g.* 41 to 43).[29]

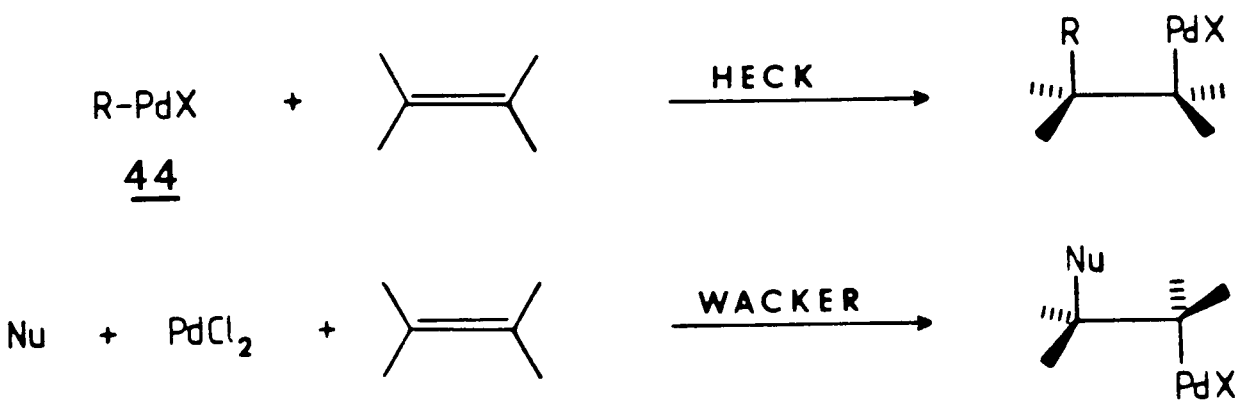
Such stereoscrambling problems are rare and the catalytic π-allyl systems have been used to create a wide range of acyclic units with predictable stereochemistry.



41

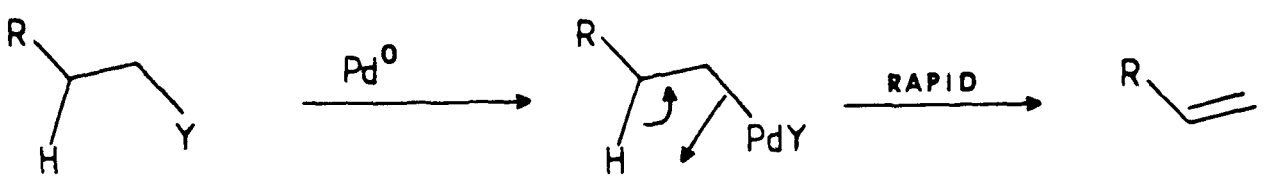
(ii) σ-Palladium species

An alternative method for olefin functionalisation is *via* σ-palladium derivatives. Two main methods exist for the formation of these species either (i) by the *cis* addition of a preformed σ-palladium species 44 across the olefin (the Heck reaction), or (ii) by a palladium initiated nucleophilic *trans* attack on the olefin (the Wacker process).



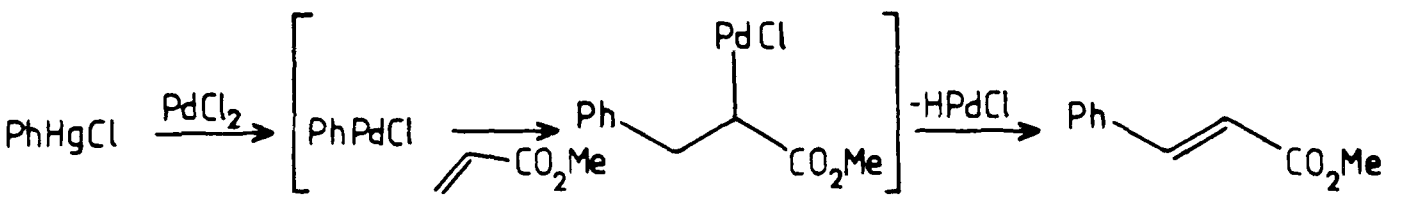
σ-Palladium species undergo rapid β-hydride elimination to olefins so the final products from these two reactions are usually the result of overall vinyl substitution - a process not readily achieved by any other

method. For the Heck reaction this facile β-hydride elimination renders intermediates such as 45 unstable and substrates are therefore limited to groups such as aryl, vinyl and benzyl.

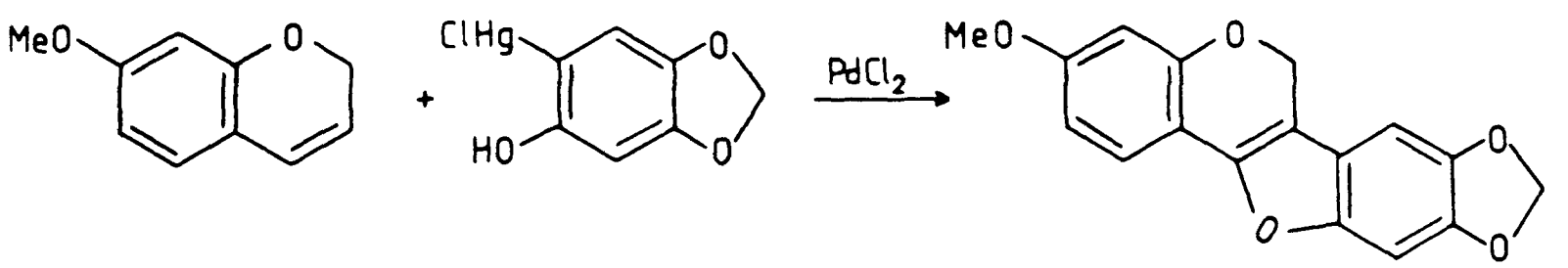


45

There are three main approaches to the intermediates for the Heck reaction:transmetallation, direct palladation of aromatic compounds and insertion into the C-X bond of organic halides. The most common transmetallation approach is *via* an organomercury compound. Treatment of this with a stoicheiometric quantity of a palladium (II) salt generates *in situ* the σ-palladium species which readily adds to olefins, β-hydride elimination can then occur to give an olefin and a palladium (0) species.[30]

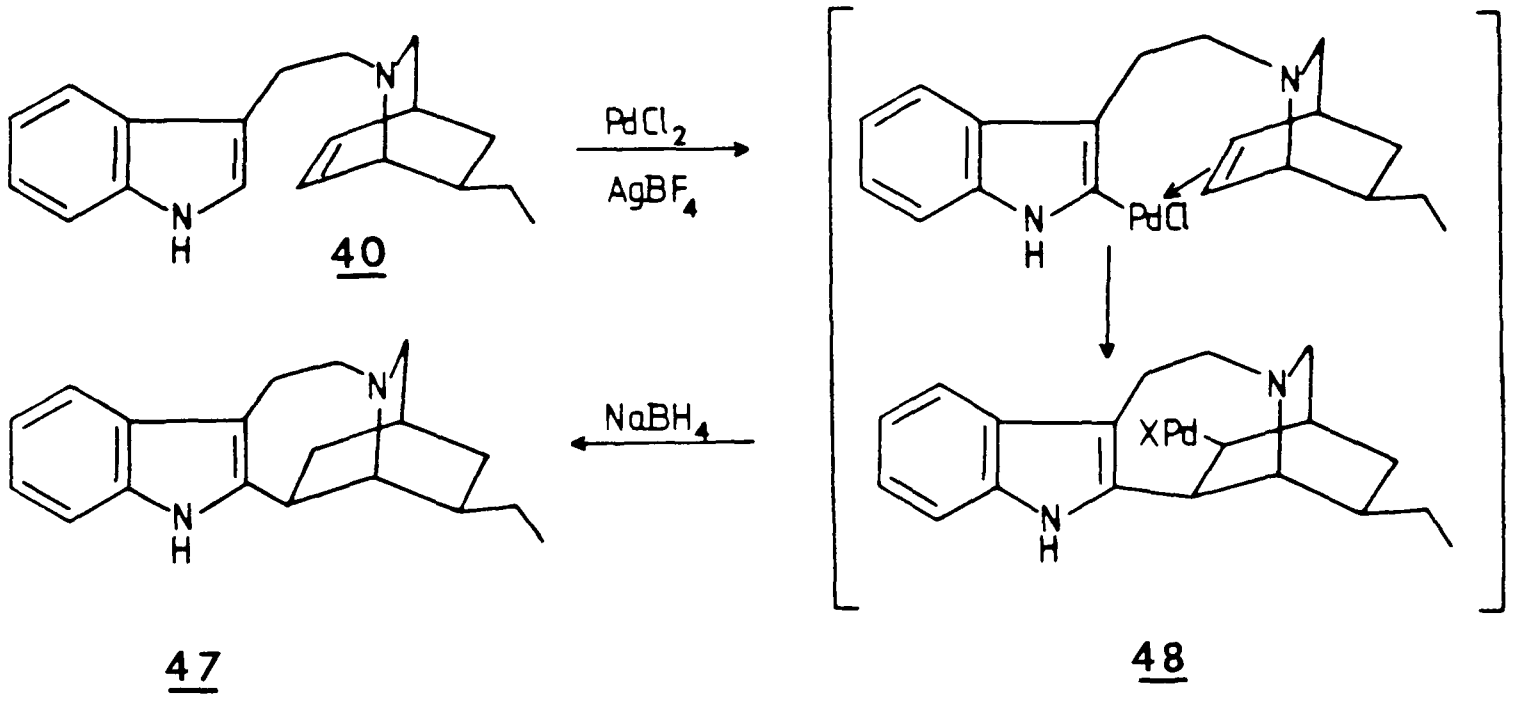


Alternatively if β-hydride elimination is slow, the σ-palladium species can be trapped by nucleophiles. A simple synthesis of pterocarpin 46 has been achieved by this route.[31]



46

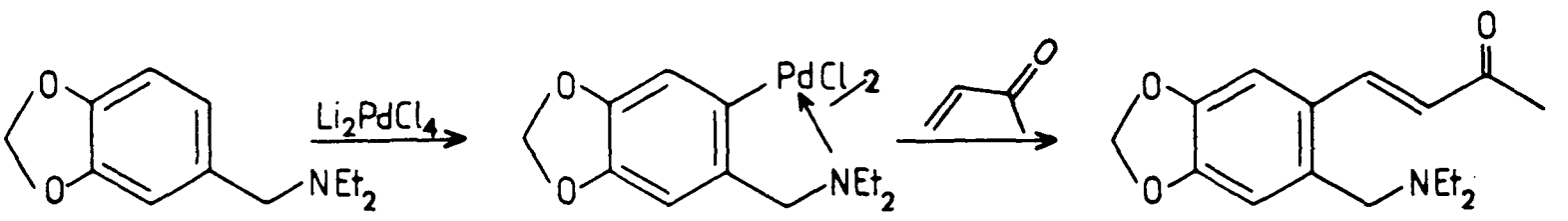
Attempts to produce a catalytic process by the oxidation of the Pd(0) back to a Pd(II) salt have met with little success. Direct stoicheiometric palladation of aromatic compounds can be achieved with palladium acetate in acetic acid.[32] The reaction is an electrophilic substitution and the usual substituent directing effects are observed. The aryl palladium species thus formed can be vinylated by olefins in the usual Heck manner. An intramolecular version of this served as one of the key steps in a synthesis of ibogamine 47,[27] the isoquinuclidine precursor having been prepared using a π-allyl palladium species (*vide supra*).



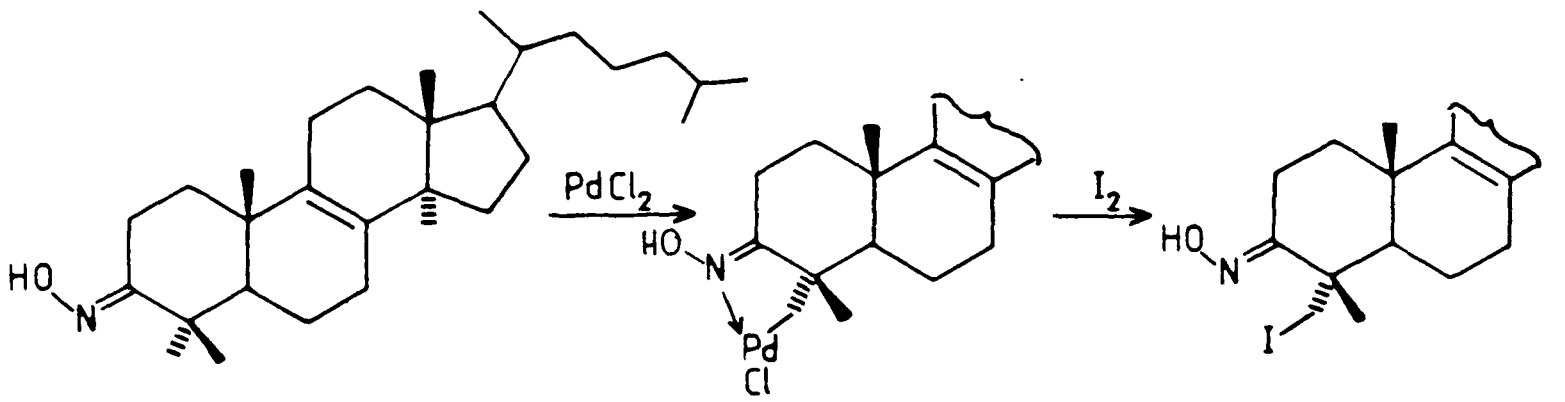
40 48 47

The σ-bonded palladium intermediate 48 can be isolated since the ring structure precluded a *syn* palladium-hydride elimination to the olefin. The direct palladation of aromatic species tends to give lower overall yields in the Heck reaction than the transmetallation approach - mainly due to poor yields of the initial palladation step. Coordinating substituents which stabilise the σ-bonded palladium intermediate dramatically improve this reaction.[33] Palladation then occurs *ortho* to the chelating substituent - the most common being nitrogen, although examples with phosphorus, sulphur and

oxygen are known. These complexes usually react well under the Heck conditions. An example is the palladation of piperonyldiethylamine 49 followed by its reaction with methyl vinyl ketone, leading to the vinylated product. The literature contains many examples, such as the reaction of the steroid derivative 50.[35]



49

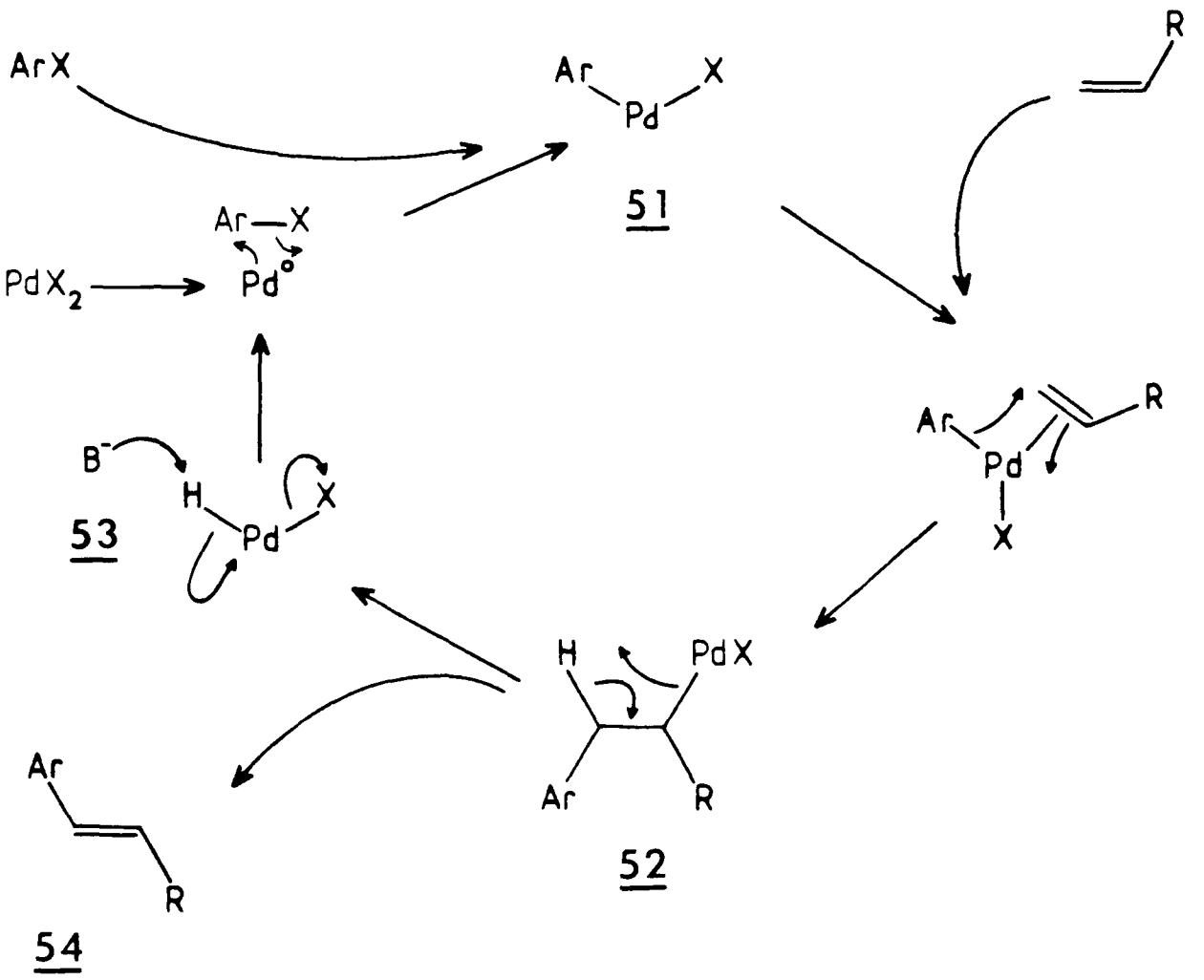


50

The two approaches to the σ-palladium species for the Heck reaction mentioned so far have involved the stoicheiometric use of a palladium (II) salt. The most useful approach, however, is with an aryl halide and a catalytic quantity of a palladium (0) complex.[36] Aryl halides are usually rather unreactive; the Heck reaction therefore provides a useful method of carbon-carbon bond formation by vinylation of the aromatic system.

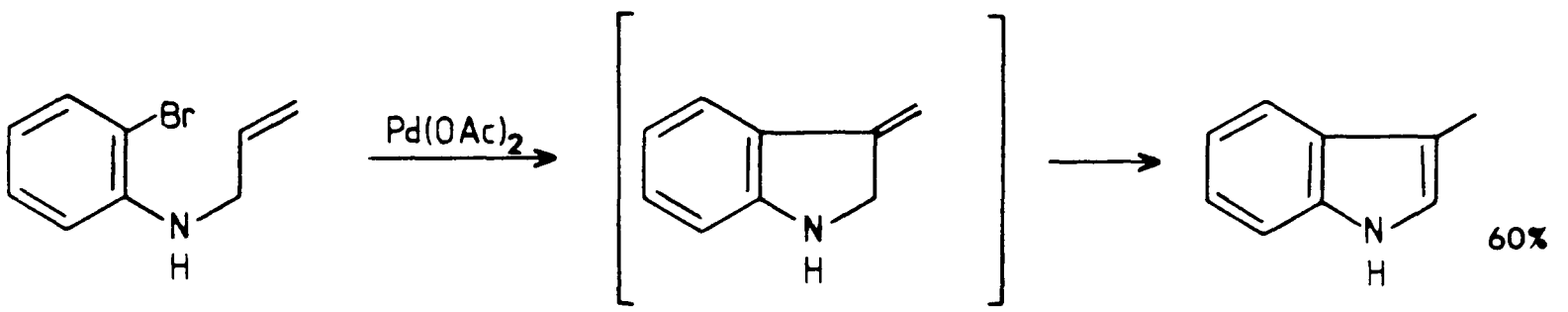
The mechanism for the reaction is generally believed to proceed as follows. The first step is the pericyclic addition of the organic halide to the metal to give the aryl palladium complex 51. Addition of this complex 51 to an olefin to give the σ-complex 52 is followed by rapid pericyclic elimination of a palladium-hydride species 53 to give the

coupled product 54. Treatment of this palladium hydride species 53 with a tertiary amine base results in the regeneration of palladium (0) thus rendering the cycle catalytic with respect to the metal.



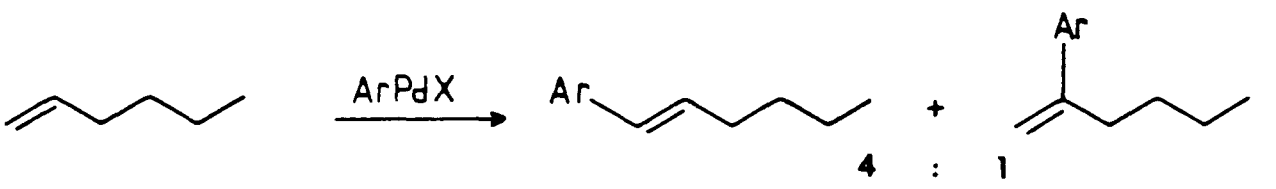
The catalyst, which is usually stabilised by triaryl phosphine ligands can be added in a variety of forms. Whilst preformed palladium (0) species have been used, for convenience *in situ* generation of the catalytic species from a palladium (II) salt has more commonly been employed. Palladium acetate is more commonly used than palladium chloride due to its greater solubility. The initial *in situ* reduction of the palladium (II) salt has been proposed to occur *via* a Wacker oxidation of the excess olefin (*vide infra*). Recent work, however, suggests that this reduction may be achieved by triethylamine, one of the co-reactants.[37]

The reactivity of the aryl halides is in the order I > Br >> Cl; the reaction only being practical with the iodides and bromides. Most functional groups appear to be compatible with the reaction conditions. Both inter and intramolecular vinylations have been achieved, an example of the latter being the formation of the indole 55 from the aryl bromide 56.[38]



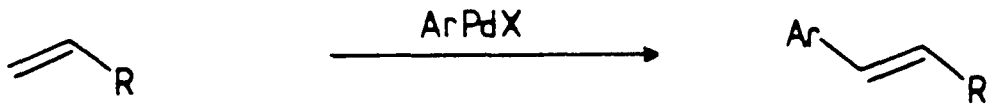
56 55

While the range of functional groups on the aromatic system appears to be unrestricted, there is less scope with the olefin. Steric hindrance plays a dominant role in olefin reactivity. Ethylene is the most reactive olefin[39] and rates of reaction and product yields generally decrease with the increase in the number of substituents around the double bond. Most monosubstituted olefins, however, appear to react normally. The regiochemistry of addition of the organopalladium species to the olefin exhibits both electronic and steric effects with carbon-carbon bond formation occurring predominantly at the less substituted olefin carbon.[36] Thus 1-hexene gives a 4:1 mixture of the 1- and 2- arylated adducts 57 and 58 respectively.



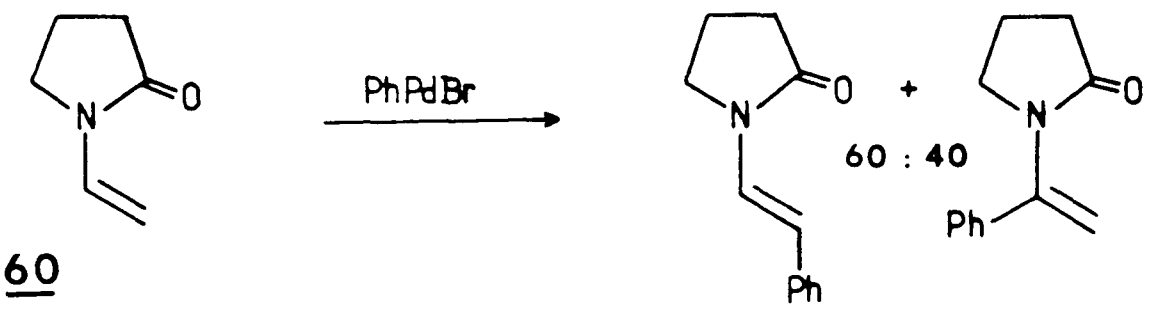
57 58

Olefins with electron withdrawing groups such as methyl acrylate (59, R = CO_2Me) and acrylonitrile (59, R = CN) undergo exclusive addition to the less substituted end of the olefin.



59

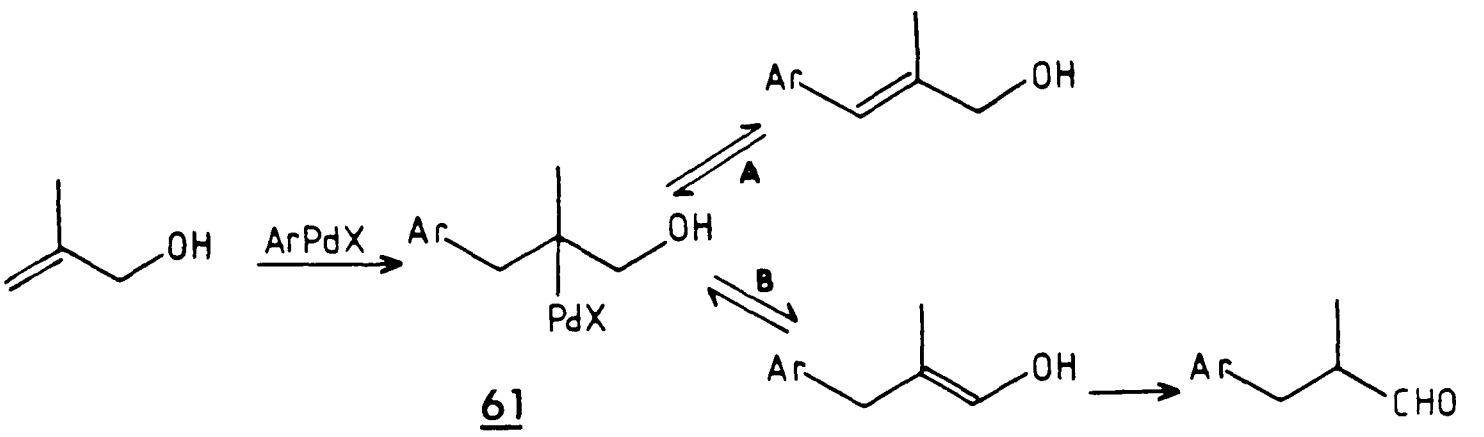
Electron donating substituents tend to reduce the preference for terminal addition. Thus *N*-vinylpyrrolidone 60 gives a 60:40 mixture of terminal and internally phenylated products with bromobenzene.[40]



60

These two features suggest some form of electronic control superimposed on the largely dominant steric effect. The observed orientation of additions correlates with the polarisation of the aryl-palladium bond, adding the aryl group to the most electron deficient and the palladium to the most electron rich centre.

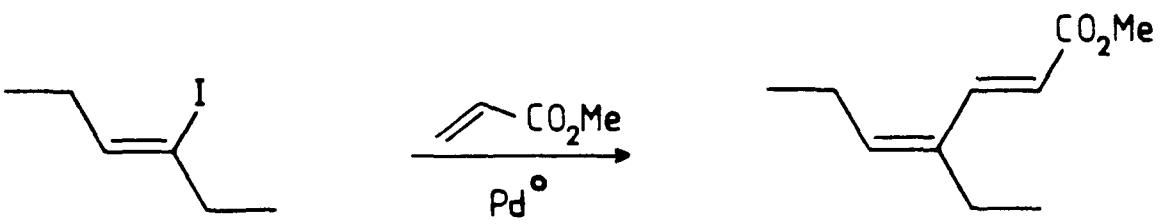
The use of allyl alcohols as substrates in the reaction leads to the formation of carbonyl compounds.[36] Addition of the aryl-palladium species in the usual manner to the olefin produces the intermediate σ-palladium species 61. There are now two potential β-hydride eliminations, to give either an allyl alcohol or an enol as the product. Formation of the two organic products from the σ-palladium species 61 is reversible and it is the irreversible formation of the aldehyde 62 from its enol which drives the reaction along path B, to give predominantly the aldehyde.



61

62

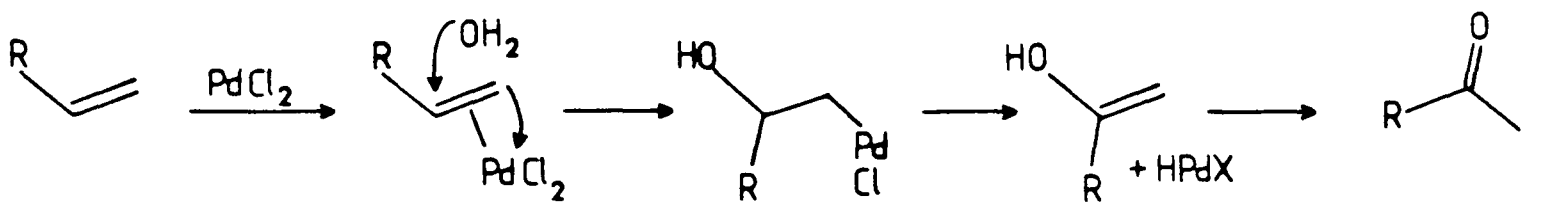
The Heck reaction with organic halides is only limited by the requirement that the substrate should not possess a β-hydrogen. The reaction therefore is applicable to vinyl halides, the products being dienes. Predominent retention of olefin stereochemistry is observed during the reaction, thus *Z*-3-iodo-3-hexene 63 on reaction with methyl acrylate gave methyl *E,Z* - 4-ethyl-2,4-heptadienoate 64.[36]



63

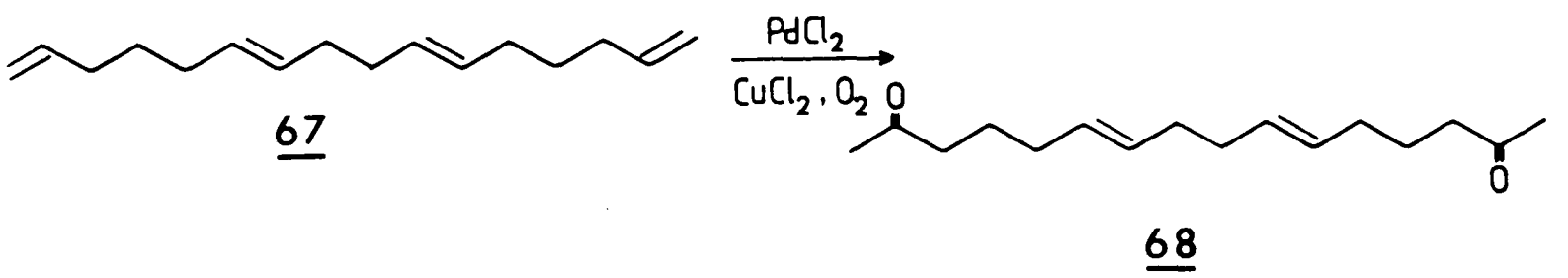
64

The Wacker oxidation forms the basis of the alternative method for forming σ-palladium species by a direct palladium initiated nucleophilic attack on an olefin. The reaction is used as an industrial process for the conversion of ethylene to acetaldehyde.[16] An initial π-complex 65 is formed between the olefin and a palladium (II) salt. Attack by a heteroatom nucleophile generates the σ-palladium species 66 which undergoes rapid β-hydride elimination. With water as the nucleophile the final product is a methyl ketone.



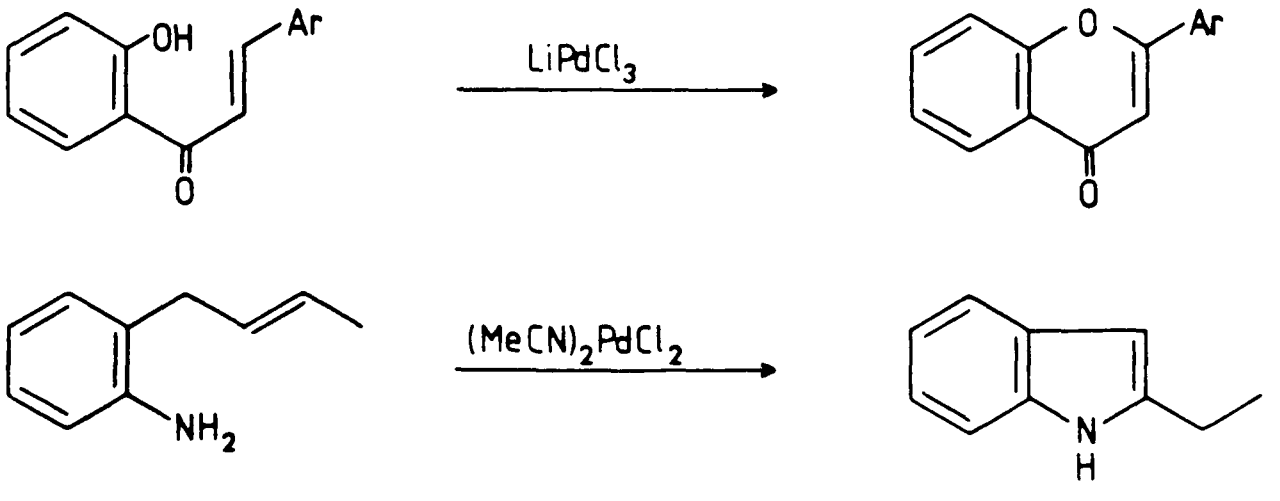
65 66

The overall reduction of palladium (II) to palladium (0) requires an oxidant to render the reaction catalytic. Copper II chloride is the most common oxidant, and when run in an oxygen atmosphere even this salt may be used catalytically. The reaction shows outstanding chemoselectivity with terminal alkenes reacting selectively in the presence of internal olefins; thus 67 gave the diketone 68.[41]



67 68

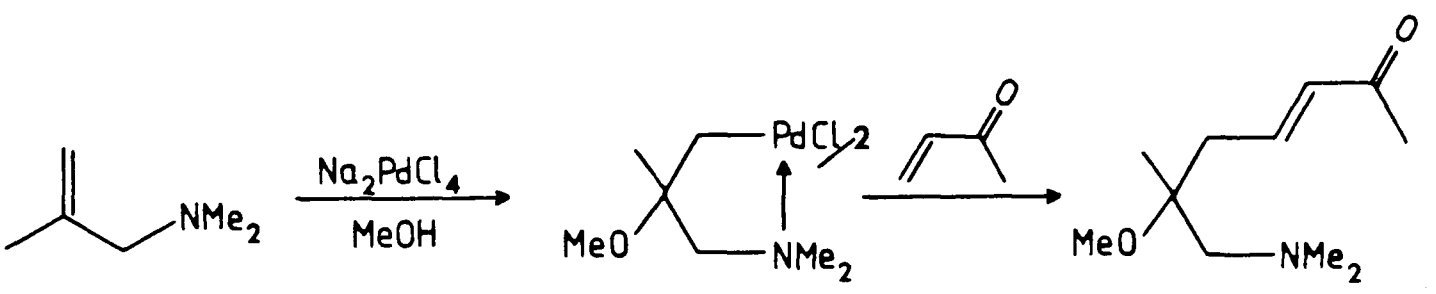
Whilst oxygen nucleophiles have predominantly been used, the reaction works well with amines. Intramolecular versions lead to the synthesis of heterocycles such as the flavanoid 69[42] and the indole 70.[43]



69

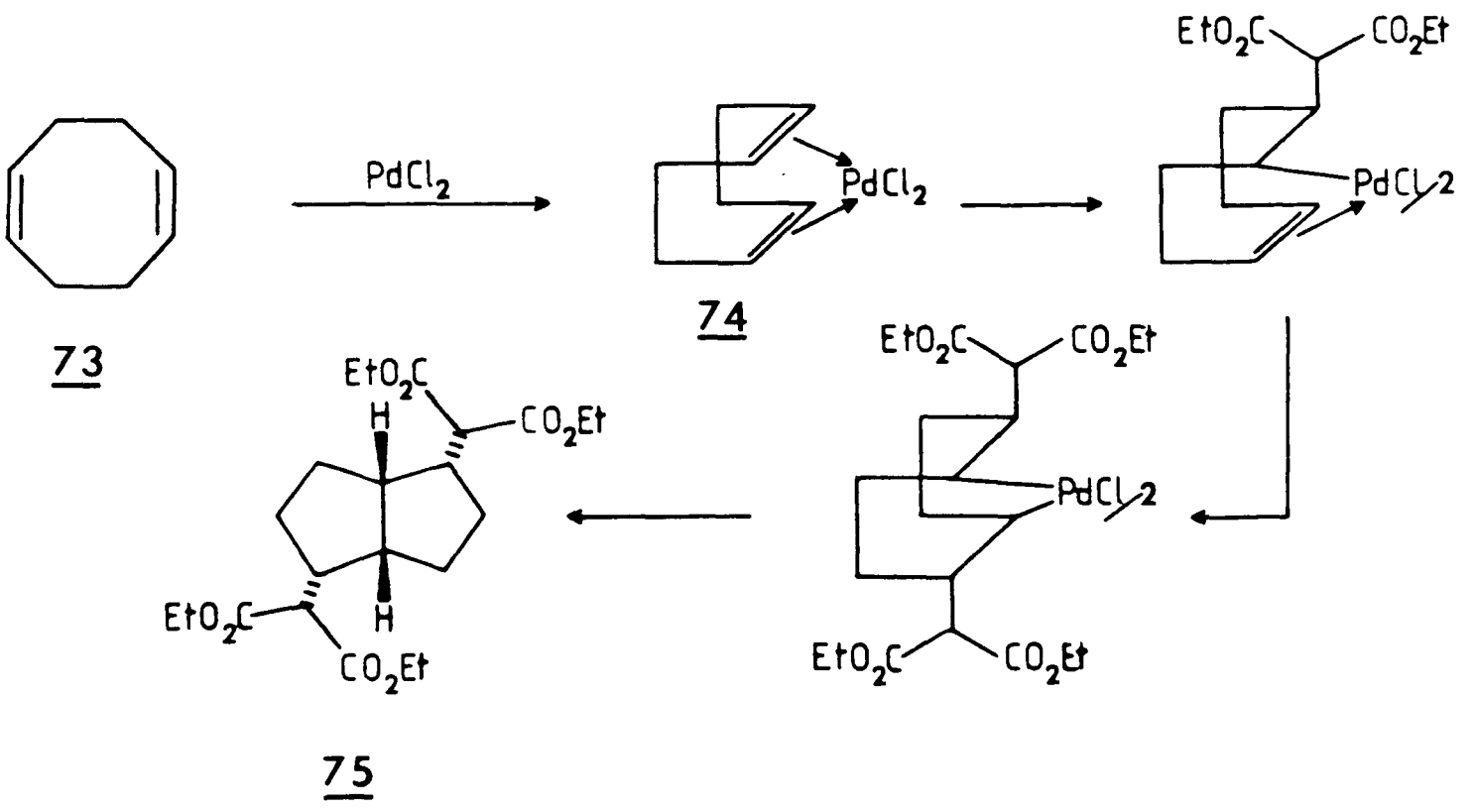
70

The σ-palladium intermediate 66 does not always undergo β-hydride elimination - particularly if a chelating group is present. The σ-intermediate 72 from 2-*N*,*N*-trimethylallyl amine 71 was trapped by methyl vinyl ketone to give an addition product.[44]



71 72

The formation of carbon-carbon bonds by nucleophilic addition to an olefin has been limited to nonconjugated dienes, such as 1,5-cyclo-octadiene 73, that can act as bidentate ligands to palladium. The carbon nucleophile then approaches *trans* to the metal, as with the π-allyl systems, in a manner analogous to an S_N2 displacement. The addition of the diethyl malonate anion to the diene complex 74 results in the formation of a [3,3,0] bicyclo system 75 from a reductive elimination of palladium (0) as the final step (*vide infra*).[45]

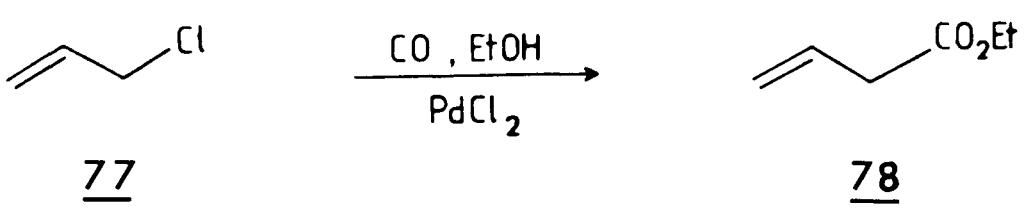


73 74 75

A feature all these palladium species have in common is that if the reaction is run under a carbon monoxide atmosphere, insertion of carbon monoxide into the carbon-palladium bond occurs. The resulting acyl-palladium species 76 is then usually trapped by nucleophiles to give carbonyl products.

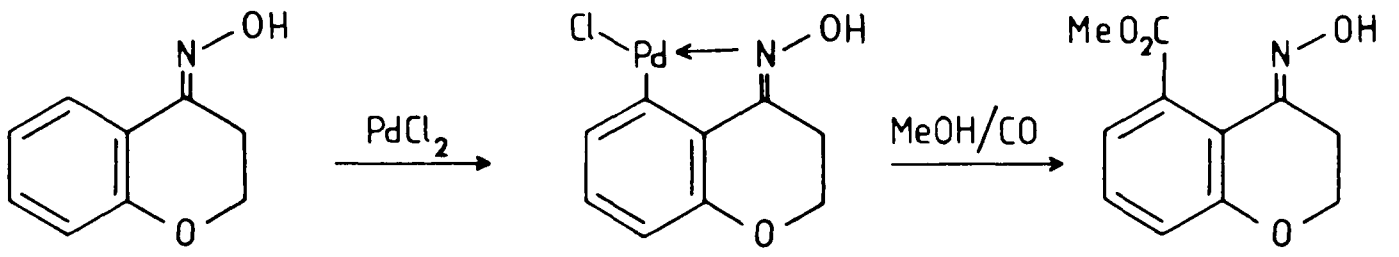
76

Allylic halides are carbonylated to give β,γ-unsaturated esters in alcoholic solvents *via* their π-allyl complexes. For example, ethyl 3-butenoate 78 is formed from allyl chloride 77.[46]



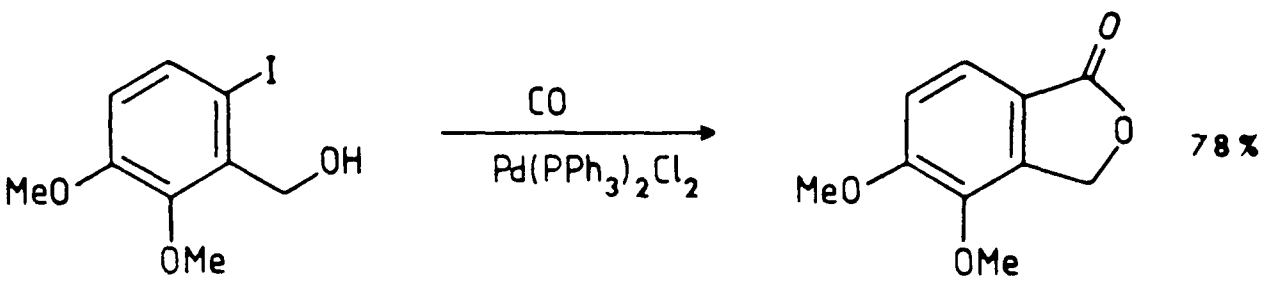
77 78

Direct palladation of the oxime of 4-chromanone 79 followed by carbonylation with methanol as the solvent led to regiospecific carboxymethylation.[47]



79

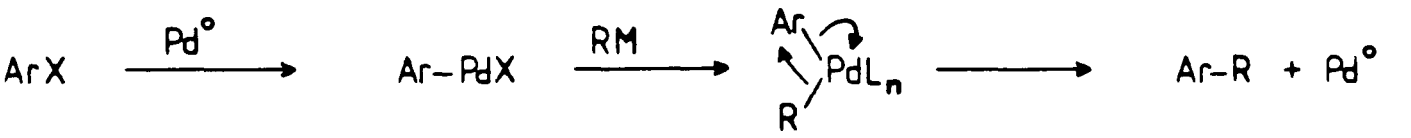
Aryl halides are the most common source of these aryl palladium intermediates. The use of the haloalcohol 80 led to intramolecular trapping of the acyl-palladium intermediate to form the lactone 81, in high yield.[48]



80 81

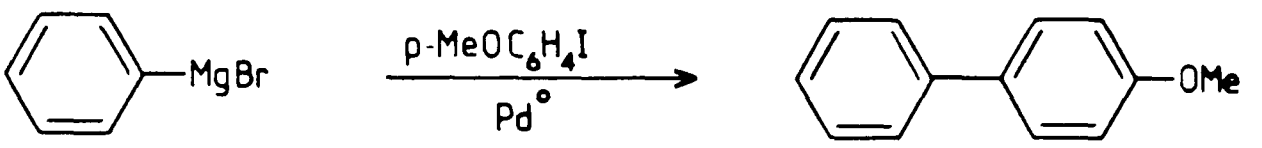
Saturated esters are formed by the carbonylation of olefins in alcohols. High pressures and temperatures are normally required and the reaction gives poor regioselectivity. This can be enhanced with terminal alkenes to give predominantly the terminal esters by the use of tin (II) chloride.[49]

The final class of reactions of the σ-palladium species are their coupling reactions. Disubstituted σ-palladium species 82 are unstable and their formation results in a rapid pericyclic elimination to give a coupled product. The most common approach to these intermediates has been from an organometallic reagent and an organic halide.[50]

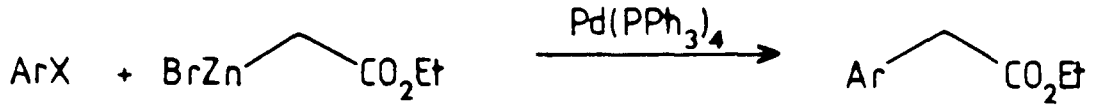


82

Grignard or alkyl zinc reagents are common organometallic intermediates. Biaryl coupling has been achieved using aryl-magnesium compounds (*e.g.* phenylmagnesium bromide 83)[51] while the Reformatsky reagent 84 was similarly coupled with aryl halides using a palladium (0) catalyst.[52]

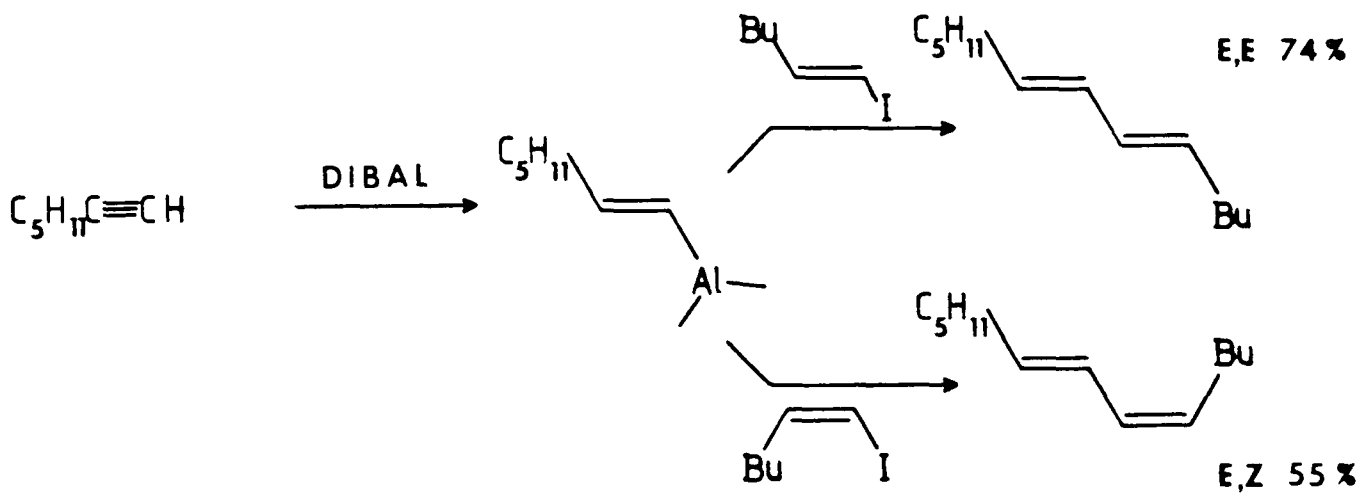


83



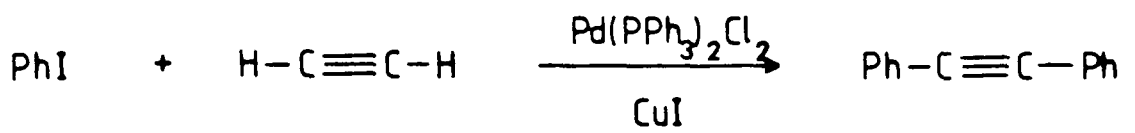
84

Vinyl halides undergo analogous reactions in a stereospecific fashion. The availability of stereodefined vinyl organometallic derivatives has allowed this to be used for the stereospecific synthesis of 1,3 dienes, *e.g.* 85, with either *E,E*- or *E,Z*- geometry.[53]



85

Terminal alkynes undergo facile cross couplings with aryl and vinyl halides to give substituted acetylenes, the latter again with retention of stereochemistry. The use of acetylene with iodobenzene led to the formation of diphenylacetylene 86.[54]



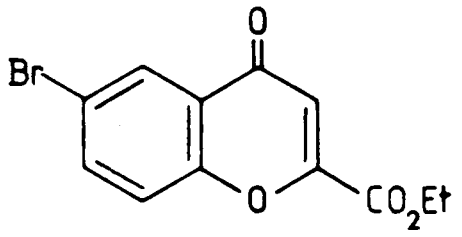
86

Palladium therefore offers considerable scope for the functionalisation of a number of organic species and for effecting transformations not readily achieved by any other method.

2. Elaboration of 6- and 8-bromochromones

There has been considerable work in the general field of organopalladium chemistry both with stoicheiometric and catalytic reagents (*cf.* introduction). In the area of aryl halide functionalisation *via* palladium (0) insertion into the carbon-halogen bond, work has usually concentrated on simple aryl bromides or iodides with limited functionalisation - although a wide range of functional groups are known to be compatible with the reaction conditions.[36]

With the interest in pharmacologically active benzopyrans containing the chromone system, we decided to ascertain whether organopalladium chemistry might provide a general route to aryl functionalised chromones, *via* the readily available bromides. The two compounds chosen for study were the 6- and 8-bromo-2-carboethoxychromones, 87 and 88 respectively.



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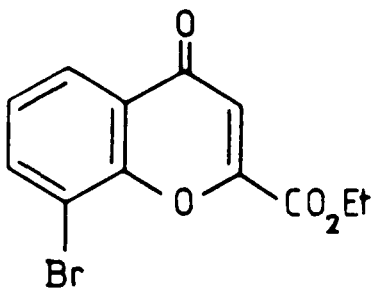
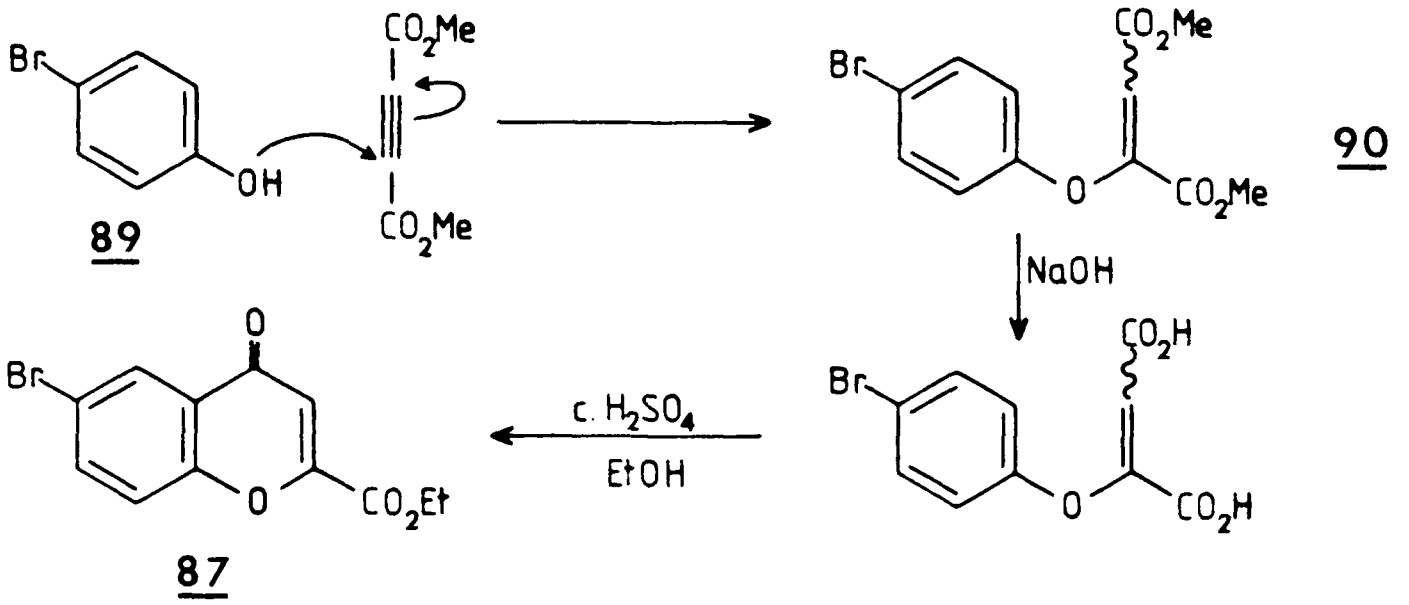


88

2(i) Bromochromone synthesis

The early halochromone vinylation studies utilised a small sample of 6-bromo-2-carboethoxychromone 87 provided by Fisons Pharmaceuticals and after a short period further material was required. The synthesis[55] involved heating an ethanol solution of *p*-bromophenol 89 with dimethylacetylene dicarboxylate in the presence of a catalytic quantity of benzyltrimethylammonium hydroxide solution. On cooling, white crystals of the Michael adduct 90 (as a mixture of the phenoxy maleic and fumaric esters) crystallised from the reaction mixture. These esters were then hydrolysed and the mixture

of acids treated with concentrated sulphuric acid in ethanol. The fumaric acid cyclised to the chromone and its ethyl ester 87 crystallised from the reaction mixture leaving the more soluble maleic ester in solution.

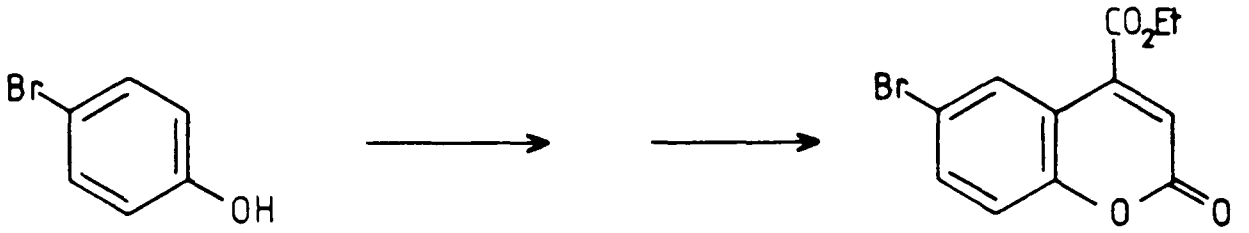


Attempts to repeat this synthesis gave results at variance with the recommended procedure, the first stage of the preparation yielding a viscous purple oil. Continuation of the synthesis, however, ultimately produced one product 91 as pale cream needles m.p. 122-5°C (87 lit.,[56] 144-5°C). The overall yield (21%) of this product 91 was comparable to that reported for 87 (35%). This product, although exhibiting very similar spectroscopic features, was found to be different from the desired chromone 87.

The 6-bromochromone 87 has a distinctive ^{1}H n.m.r. spectrum in which all the protons are well resolved and can easily be assigned. In addition to the ethyl ester resonances (t, δ1.44; q, δ4.48) the spectrum contains a singlet (δ7.13), a doublet (δ8.33) and an AB system (δ7.53 and 7.83) - the low field signals being further split into doublets. The first two resonances are assignable to the C3 and C5 protons respectively, the C5 proton occurring as a doublet due to a small *meta* aromatic coupling. The C7 and C8 protons give rise to the AB system; the C7 proton being assigned as the low field signals from the additional small *meta* coupling to the C5 proton.

Two molecular ions, m/z = 296 (^{79}Br) and 298 (^{81}Br) of equal intensity are observed in the mass spectrum.

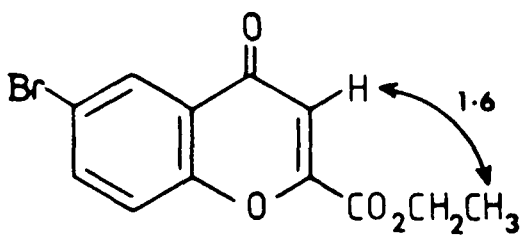
The product 91 isolated from the attempted synthesis of the 6-bromochromone 87 had a ^{1}H n.m.r. spectrum containing an identical number of signals with the same splittings. All the aromatic resonances, however, were shifted by around 0.2 ppm from the expected values, when compared to a spectrum of the 6-bromochromone 87. The infrared spectrum contained two ester carbonyl absorptions (1740 and 1720 cm^{-1}) and lacked the lower frequency absorption of the pyrone carbonyl group (1655 cm^{-1} for the 6-bromochromone 87). This data, together with two molecular ions m/z = 296 (^{79}Br) and 298 (^{81}Br) of equal intensity in the mass spectrum, indicated the product 91 to be isomeric with the desired 6-bromochromone 87 and it was assigned as 6-bromo-4-carboethoxycoumarin 91.



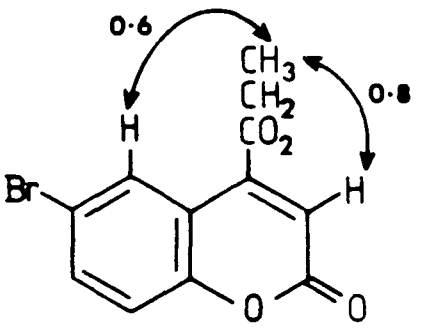
89 91

Confirmation of this structural assignment was obtained from two n.O.e. studies. Irradiation of the methyl group of the ethyl ester in the bromocoumarin 91 produced 0.6 and 0.8% intensity enhancements of the C5 and C3 protons respectively. Any enhancements observed are the result of through-space, as opposed to through-bond, relaxation effects and indicate some degree of proximity between the site of irradiation and the sites of enhancement.[57] This indicates that the ester group must be adjacent to both the C3 and C5 protons, *i.e.* attached to C4. A similar n.O.e. study performed on the 6-bromochromone 87 with irradiation of the corresponding methyl group produced a 1.6% intensity enhancement to the C3 proton only; no enhancement was observed to the C5 proton.

Confirmation of the product as the novel bromocoumarin 91 was further achieved by elemental analysis.



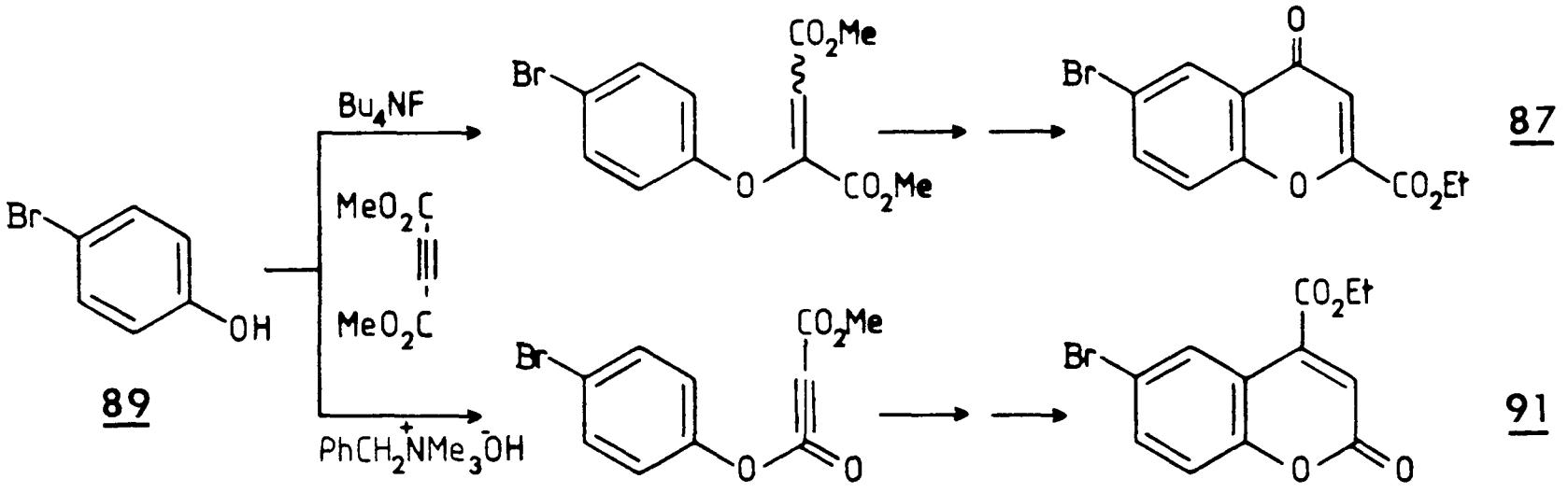
87



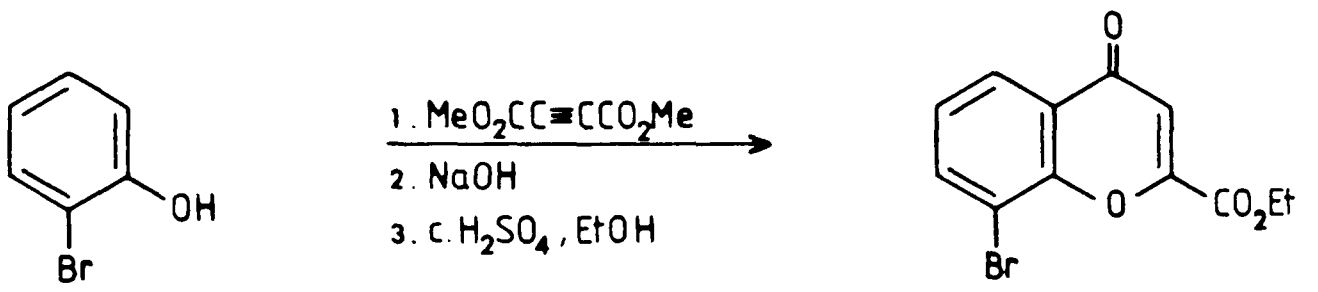
91

n.O.e. enhancements (%) on irradiation

The unexpected formation of the bromocoumarin 91 possibly occurs as a result of the bromophenol 89 undergoing trans-esterification with the dimethylacetylene dicarboxylate, rather than the required Michael addition (only one similar reaction has been reported[58]). Subsequent cyclisation would then give the coumarin 91 rather than the chromone 87.



The required bromochromone 87 was eventually synthesised by a modification of the recommended procedure. Thus heating an *iso*propanol solution of *p*-bromophenol 89 with dimethylacetylenedicarboxylate and a catalytic quantity of tetrabutylammonium fluoride gave the Michael adduct 90 in good yield. This was converted to the bromochromone 87 by the standard method in 44% overall yield, an improvement on the 'literature' method. The novel 8-bromo-2-carboethoxychromone 88 was prepared analogously from *o*-bromophenol 92 in 56% overall yield.



92 88

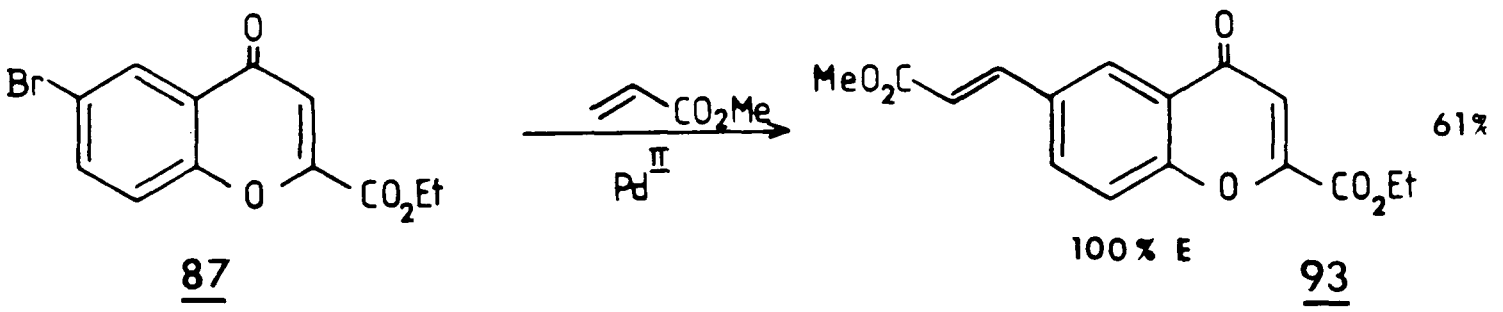
The ^1H n.m.r. spectrum again contains a well resolved aromatic region in addition to the high field ethyl ester absorptions. A singlet (δ7.13) due to the C3 proton and a triplet (δ7.31) which must arise from the C6 proton are readily assigned. The remaining aromatic signals are two doublets of doublets (δ8.12 and 7.95) arising from the C5 and C7 protons, which exhibit a small *meta* coupling to each other as well as a larger *ortho* coupling to the C6 proton. By analogy with the 6-bromo isomer 87, the lower field signal was assigned to the C5 proton. The infrared spectrum contained the expected ester and pyrone carbonyl absorptions (1735 and 1655 cm^{-1}), and the mass spectrum contained two molecular ions m/z = 296 (^{79}Br) and m/z = 298 (^{81}Br) of equal intensity.

2(ii) Vinylation

With the synthesis of the desired bromo chromones 87 and 88 the feasibility of chromone functionalisation *via* a palladium catalysed vinylation was studied. Initially studies were limited to mono-substituted olefins.

6-Bromo-2-carboethoxychromone, 87 was heated with methyl acrylate, triethylamine and a catalytic quantity of *bis*(triphenylphosphine)palladium chloride in DMF under a nitrogen atmosphere. With the relatively high

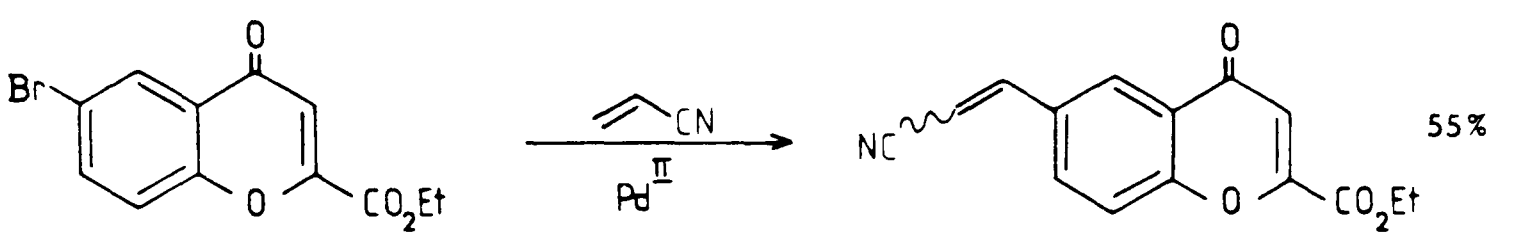
temperature required (120°C) a closed system must be used to prevent loss of the volatile reagents. After precipitation from water, t.l.c. indicated the formation of a single product and this was isolated by chromatography on silica gel. In addition to the ester resonances, the ^{1}H n.m.r. spectrum contained the four well resolved aromatic signals with the same couplings as were observed in the starting material - indicating an unchanged substitution pattern in the chromone ring system. The new features were a three proton singlet (δ3.83) and two, one proton doublets (δ7.75, 6.53 J = 16 Hz). These latter features were consistent with a 3-substituted methyl propenoate group and indicated the product to be methyl 3-[6-(2-carboethoxychromone)]propenoate 93. The infrared spectrum contained an additional band at 1700 cm^{-1} indicative of an α,β-unsaturated ester, and the structure of the product was confirmed by a molecular ion (m/z = 302) in the mass spectrum and by elemental analysis. Of the two possible product isomers (olefin in the *E*- or *Z*-conformation) only one was observed, the coupling constant of 16 Hz between the two olefinic protons clearly showing that it was the *E*-isomer.



87 93

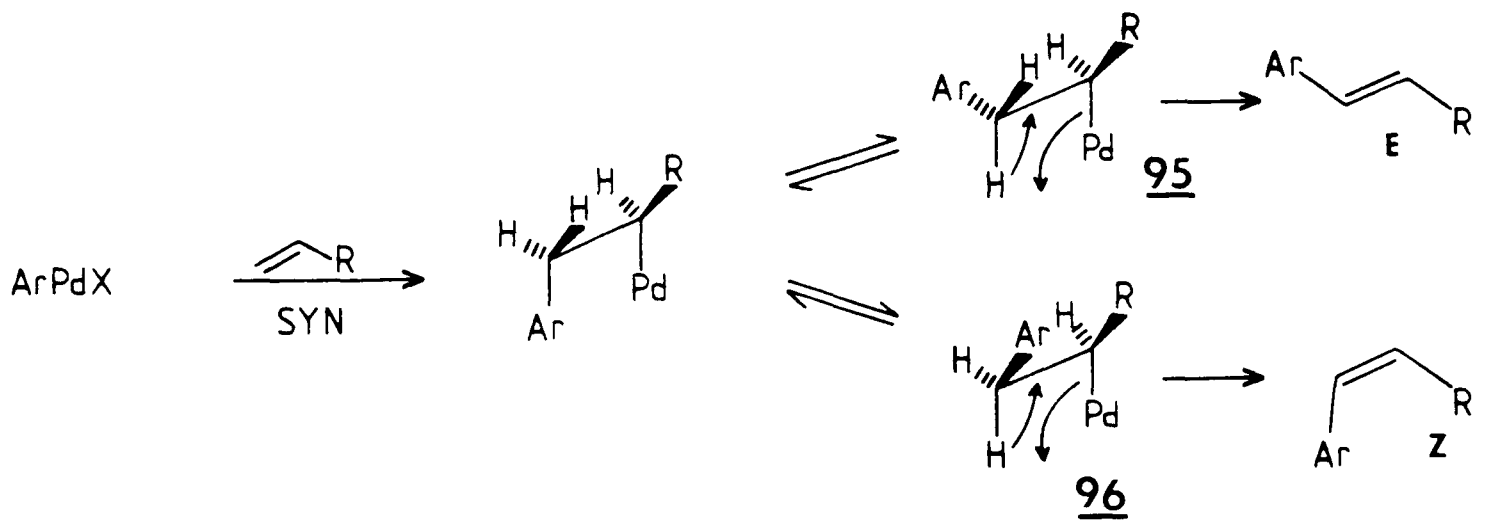
Reaction of the 6-bromochromone 87 under the same reaction conditions with acrylonitrile after work-up gave a product containing a nitrile absorption (2215 cm^{-1}) in the infrared spectrum indicating the coupled product. The ^{1}H n.m.r. spectrum, however, contained two AB systems in the olefinic region (δ7.48, 6.02 J = 16 Hz and δ7.72, 5.63 J = 11 Hz) in the ratio 3:1 in addition to the expected chromone ester resonances. With no additional signals it was clear that these corresponded to the two possible

olefin isomers and from the signal intensities the *E*-isomer clearly predominated over the *Z*-isomer. The two isomers could be separated by gas chromatography, and were shown to have identical mass spectra with molecular ions *m/z* = 269. The structure of the product as 3-[6-(2-carboethoxychromone)]propenenitrile 94 was further confirmed by elemental analysis.



87 94

The accepted mechanism for this vinylation reaction[59] involves a *syn* pericyclic addition of an aryl-palladium species to the olefin, followed by a *syn* pericyclic elimination of a palladium hydride species to give the coupled product. The two olefin isomers originate from the two possible conformations 95 and 96 available to the adduct in which a *syn* elimination can occur.



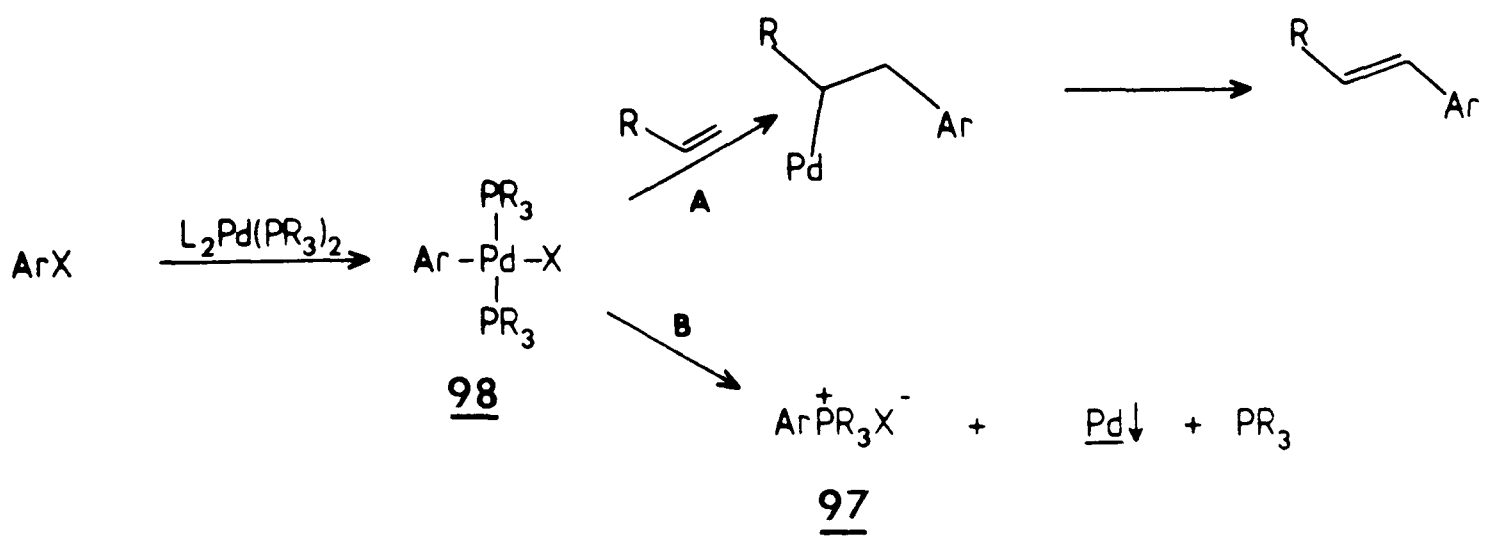
After the aryl-palladium species has undergone addition to the olefin, a 120° rotation about the central carbon-carbon bond is required before a *syn* elimination of a palladium hydride species can occur. The ratios of the *E*:*Z* products will depend upon the relative energies of the two conformations 95 and 96. Conformation 96, leading to the *Z*-product will be of considerably higher energy due to the steric interaction between the aryl group and the substituent R. Since the two conformations are in equilibrium, conformation 95

will predominate and the observed elimination will therefore occur to give the *E*-isomer as the major product.

The formation of only the *E*-isomer for R = CO_2Me 93 whereas both were observed for R = CN 94, indicates a considerably greater steric bulk for the methyl ester substituent when compared to the linear nitrile.

These initial reactions were performed in a glass-walled pressure apparatus, but subsequent reactions were attempted in a stainless-steel bomb. Without exception these failed to proceed to completion, and attempts to repeat the two initial vinylations also failed. The failure of these reactions was assumed to be caused by inactivation of the palladium catalyst by some degree of binding to the metal surface of the reactor. A return to the original glass-walled apparatus solved this problem.

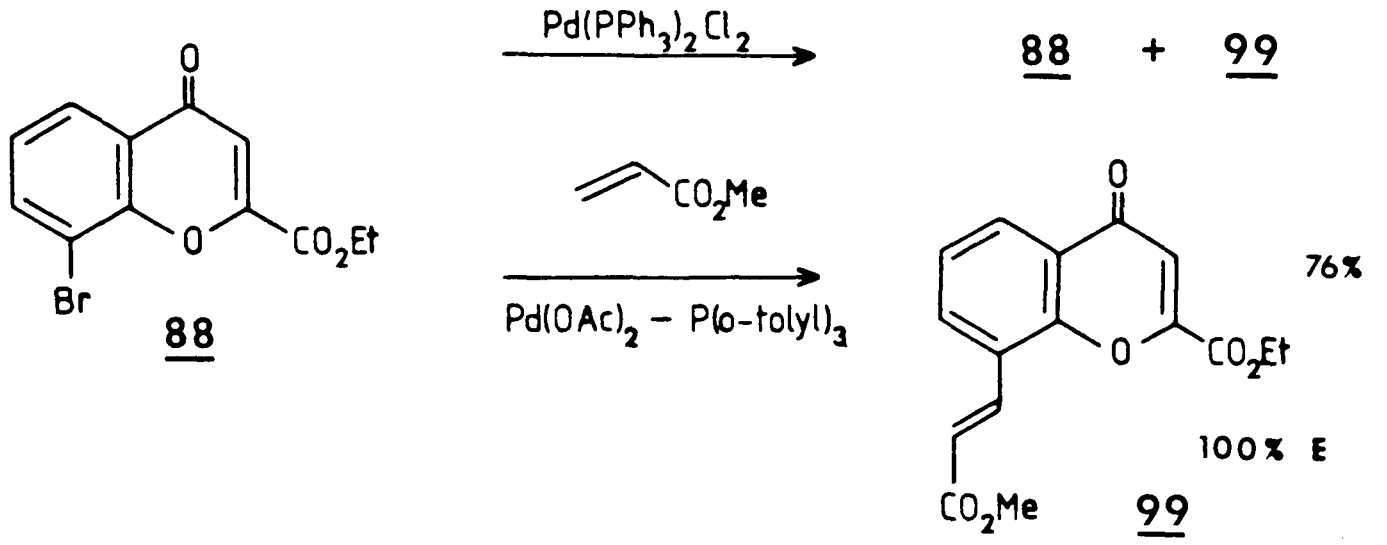
Early attempts to achieve the vinylation of the 8-bromochromone 88 with methyl acrylate in the glass-walled apparatus also resulted in incomplete reaction. This was probably caused by another potential problem with these reactions. There exists, in addition to the vinylation, a competing side reaction that removes the triphenylphosphine required to stabilise the catalyst.[36] With the consumption of the phosphine the palladium precipitates from solution, and so with the catalyst inactive the reaction stops. This side reaction is the formation of a phosphonium salt 97 with the aryl halide, by a pericyclic elimination from the initial organopalladium complex 98.



This side reaction (path B) competes with the addition of the complex to the olefin (path A) and is likely to predominate either if the olefin is relatively unreactive or if the formation of the phosphonium salt 97 is unusually facile. The suppression of this side reaction requires a phosphine that is slow to quaternise but still functions efficiently as a ligand for the palladium catalyst. A study of a variety of phosphines has revealed that *o*-alkylated triarylphosphines are significantly less reactive regarding quaternisation but still performed as well as triphenylphosphine as ligands for palladium.[60] These phosphines are therefore the ligands of choice and the addition of a slight excess further improves the chemical yields, probably by replacing the small amounts that do undergo quaternisation.

It was this problem of phosphine quaternisation that was assumed to be responsible for the incomplete reaction of the 8-bromochromone 88 with methyl acrylate. Heating the chromone under the usual conditions with *bis*(triphenylphosphine)palladium chloride as catalyst, for varying lengths of time, led after work-up to a mixture of one product and some starting material being isolated. The use of a mixture of palladium acetate and tri-*o*-tolylphosphine under identical conditions led to a single product in 76% yield with no starting material present.

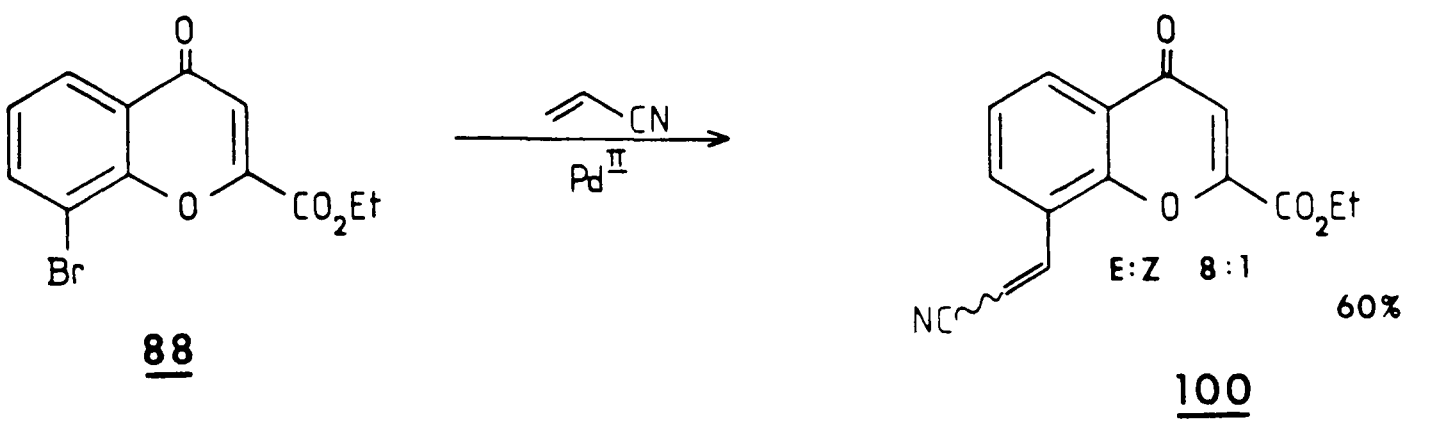
The infrared spectrum indicated a vinylated product with an α,β-unsaturated ester absorption at 1720 cm^{-1} in addition to the chromone ester at 1730 cm^{-1}. The ^1H n.m.r. spectrum contained a three proton singlet and two one proton doublets in addition to the expected chromone signals. A molecular ion m/z = 302 in the mass spectrum and elemental analysis confirmed this product to be methyl 3-[8-(2-carboethoxychromone)]propenoate 99. The distinctive 16 Hz coupling constant between the two olefinic protons confirmed the expected *E*-stereochemistry.



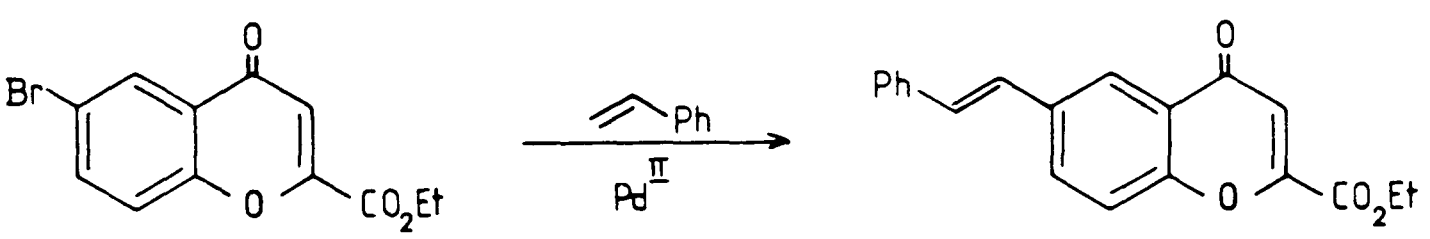
Following the success of the palladium acetate - tri-*o*-tolylphosphine catalyst mixture it was adopted as the standard catalyst for all subsequent reactions.

Heating a DMF solution of the 8-bromochromone 88 with this catalyst mixture in the presence of acrylonitrile under the standard conditions again led to the formation of a single product (by t.l.c.). The infrared spectrum indicated the vinylated product from the nitrile absorption at 2215 cm^{-1} and the ^{1}H n.m.r. spectrum contained two sets of olefin doublets with coupling constants of 11 and 16 Hz. These two sets of signals must arise, as with the 6-chromone isomer 94, from the two isomeric olefins.

The isomer ratio was 8:1, by integration, with the *E*-isomer predominating as expected. Both isomers could be separated by gas chromatography and gave identical mass spectra with molecular ions m/z = 269, confirming the product to be 3-[8-(2-carboethoxychromone)]propenenitrile 100.



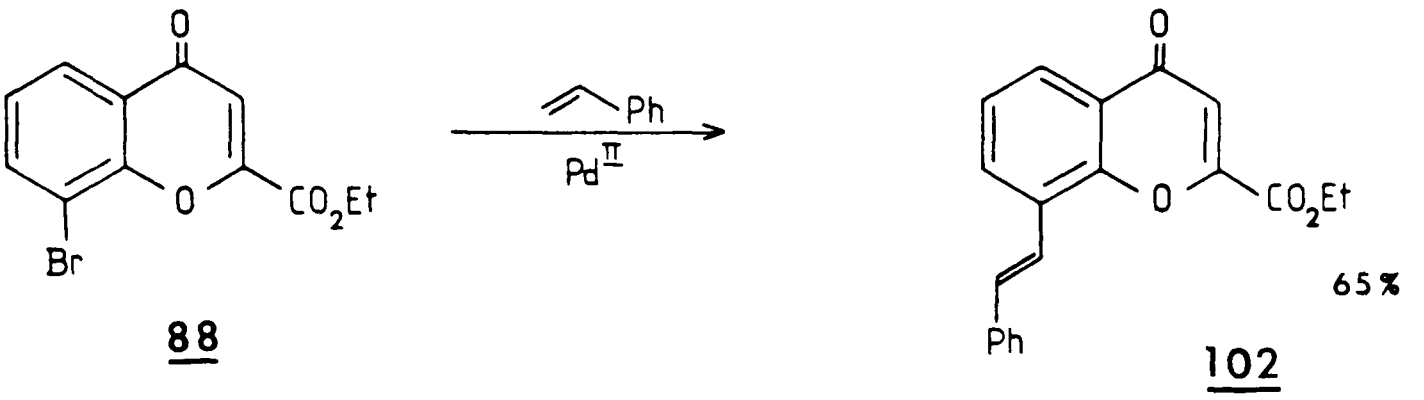
Styrene was found to react readily with the two bromochromones to give the desired coupled products. Thus heating styrene with the 6-bromochromone 87 under the usual conditions gave, after work-up, a single product as pale yellow needles. A molecular ion m/z = 320 in the mass spectrum indicated the coupled product but this could not be immediately confirmed from the ^{1}H n.m.r. spectrum as even at 300 MHz the vinylic protons were not resolved from the phenyl and chromone ring proton resonances. The ^{13}C n.m.r. spectrum contained eighteen carbon signals and from the off-resonance spectrum, seven of these were quaternary and nine were tertiary carbons. This is consistent with the product being 6-(2-carboethoxychromone)-β-styrene 101 and was confirmed by elemental analysis.



87 — 67% → 101

Only eighteen, rather than the initially expected twenty, signals are observed in the ^{13}C n.m.r. spectrum due to the equivalence of the *ortho* and *meta* phenyl carbons. A considerable expansion of the aromatic region of the ^{1}H n.m.r. spectrum allowed the identification of the olefinic protons and the observed coupling constant of 16 Hz confirmed the anticipated *E*-stereochemistry.

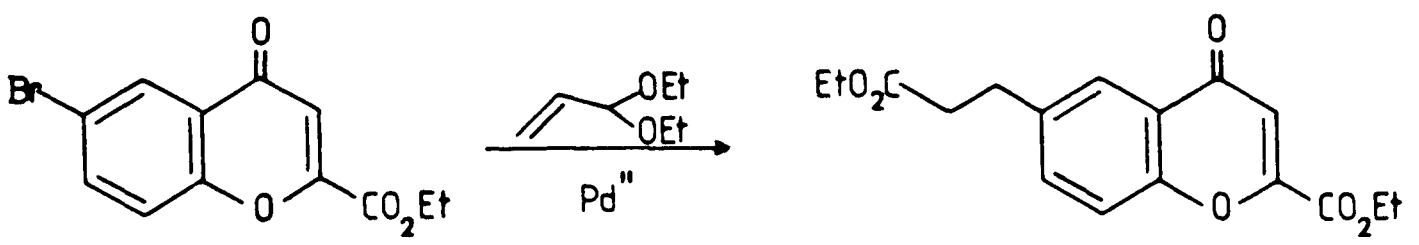
Analogous results were obtained with the 8-bromochromone 88. Thus a single product was isolated in 65% yield as pale yellow needles which was characterised as 8-(2-carboethoxychromone)-β-styrene 102, with 100% *E*-olefin stereochemistry.



88 102

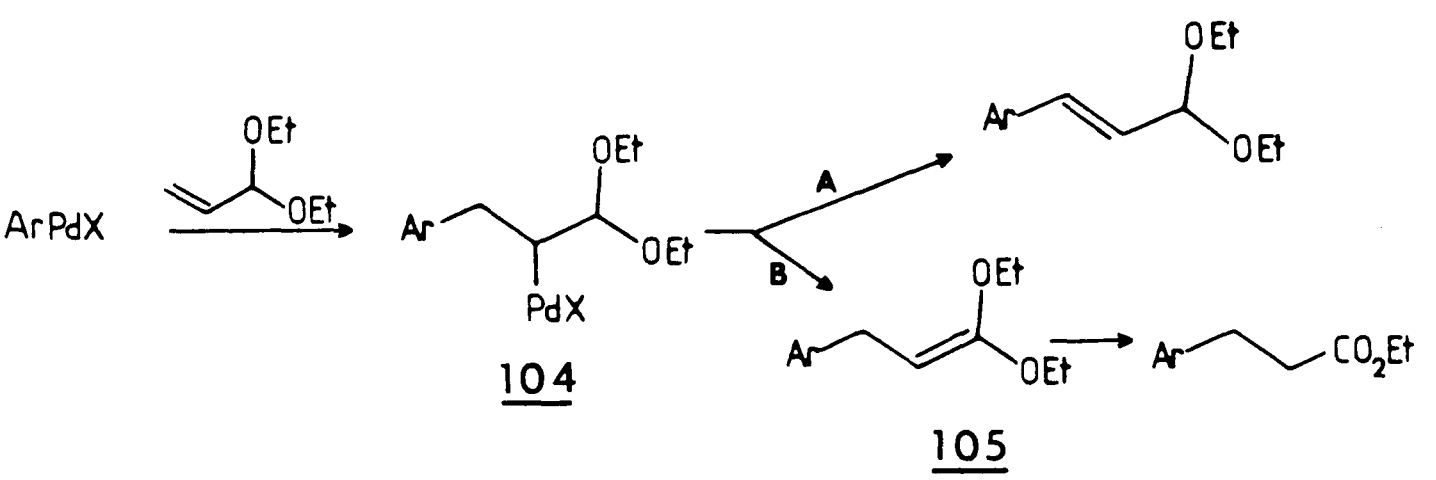
α,β-Unsaturated aldehydes undergo ready polymerisation upon heating and are therefore incompatible with the reaction conditions required for chromone vinylation. However, protection as their acetals renders them sufficiently stable to be used as substrates in the reaction.

Heating acrolein diethylacetal with the 6-bromochromone 87 under the standard conditions, after work-up, gave one major product and a mixture of several minor impurities. Chromatography followed by crystallisation gave the major product as white fluffy needles. This product exhibited a number of initially surprising spectroscopic features. The infrared spectrum contained an additional saturated ester absorption at 1725 cm^{-1} rather than the expected lower frequency α,β-unsaturated absorption and the ^{1}H n.m.r. spectrum contained no vinylic protons. Instead there were two two proton triplets (δ2.69 and 3.08) and an additional ethyl ester resonance. The two triplets could result from a two carbon methylene chain and the product was provisionally assigned as ethyl 3-[6-(2-carboethoxychromone)]propionate 103. This was confirmed by elemental analysis and a molecular ion m/z = 318 in the mass spectrum.



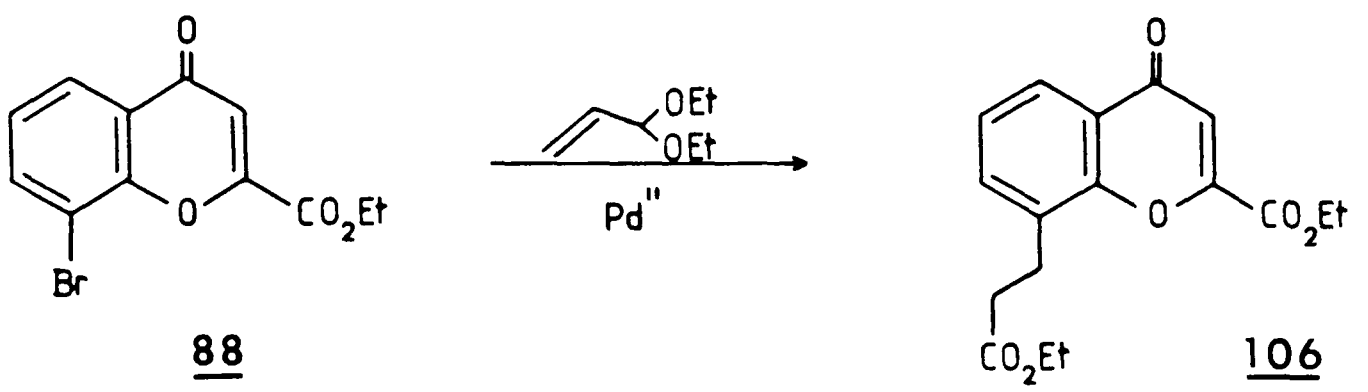
87 103

The formation of this saturated product rather than the expected vinylated product has previously been observed[60] and can be rationalised by considering the elimination of the palladium hydride species from the intermediate 104 after the addition of the aryl palladium species to the acrolein.



The intermediate 104 contains two hydrogens β to the palladium and therefore two possible modes of palladium hydride species elimination exist. From the observed product 103 path B must predominate, leading to the ketene acetal 105 which was hydrolysed to the saturated ester during the work-up.

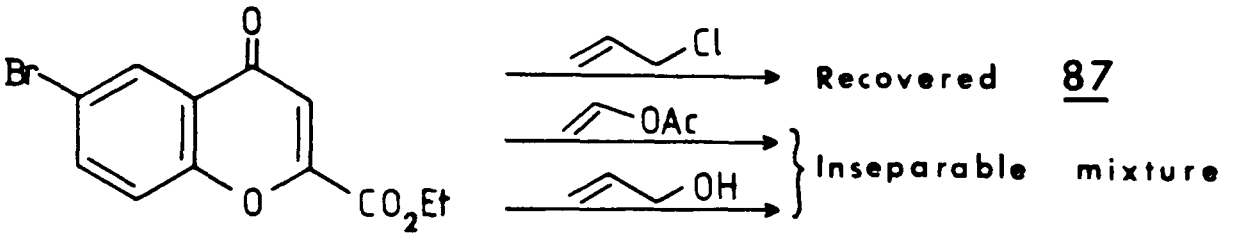
An analogous reaction was found for the 8-bromochromone 88. Thus heating with acrolein diethylacetal under identical conditions gave, after work-up, a saturated ester as the major product which was confirmed as ethyl 3-[8-(2-carbo-ethoxychromone)]propionate 106.



Attempts to couple the 6-bromochromone 87 with three other monosubstituted olefins were unsuccessful. Heating allyl chloride with the 6-bromochromone 87 led, after work-up, only to recovery of the chromone with no evidence for any coupled product. The failure of this reaction may have been due to the

preferential formation of a η^3-allyl palladium species rather than the palladium undergoing insertion into the C-X bond of the aryl bromide. Such a species would be unreactive towards aryl vinylation.

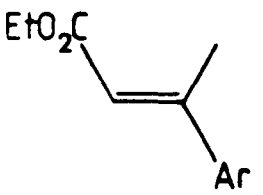
Heating the 6-bromochromone 87 with either vinyl acetate or allyl alcohol caused the opposite problem in that after work-up t.l.c. indicated the formation of several products. Unfortunately, no chromatographic separation of these could be achieved in either case. Allyl alcohol is known to undergo the vinylation reaction with simple halides to give both the expected vinylated product and the saturated aldehyde - arising from olefin isomerisation.[60] Vinyl acetate is similarly known to produce a mixture of products, largely through loss of the acetate group from an intermediate and further reaction.[61]



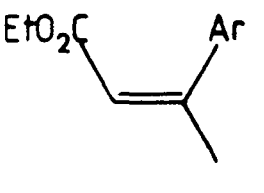
87

Having established the feasibility of the chromone vinylation reaction with monosubstituted olefins, a number of disubstituted vinyl esters were studied. Heating the 6-bromochromone 87 with ethyl crotonate under the standard conditions gave a single product as white needles after work-up. The infrared spectrum contained an additional ester absorption at 1725 cm^{-1} indicating the coupled product and this was confirmed by a molecular ion m/z = 320 in the mass spectrum. The ^1H n.m.r. spectrum contained a three proton singlet (δ1.60) from the methyl group, a one proton singlet (δ6.20) from the vinyl proton and the ethyl ester absorptions in addition to the expected chromone signals. Elemental analysis confirmed the product to be ethyl 3-[6-(2-carboethoxychromone)]-2-butenoate 107.

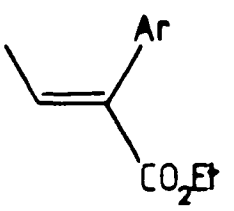
All four possible product stereochemistries 107A to D (arising from aryl addition to either end of the olefin) are consistent with this ^{1}H n.m.r. data.



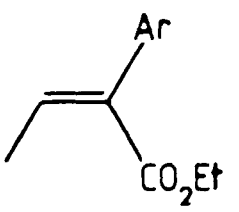
107A



107B

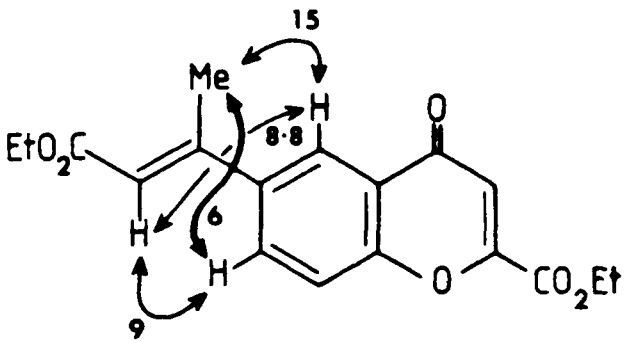


107C



107D

Two n.O.e. experiments were undertaken to solve this structural problem. Irradiation of the olefinic methyl group (δ1.60) gave a 6% intensity enhancement of the C7 chromone proton and a 15% enhancement of the C5 chromone proton. This result was consistent with either configuration 107A or B in which the methyl group is adjacent to the chromone ring, but not with either 107C or D in which an enhancement of the vinylic proton would be expected. To distinguish between these two possibilities the olefinic proton (δ6.20) was similarly irradiated. An 8.8% intensity enhancement was observed for the C5 chromone proton and a 9% enhancement for the C7 chromone proton - no change was observed in the methyl resonance. These results indicated the olefinic proton was also adjacent to the chromone ring and confirmed the product to have configuration 107A.

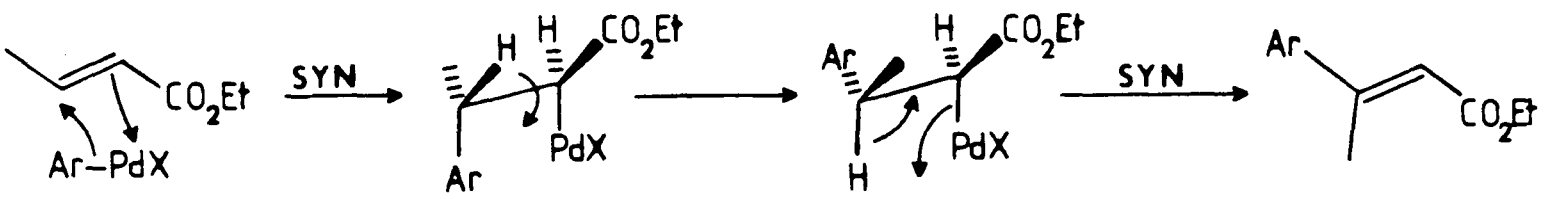


107A

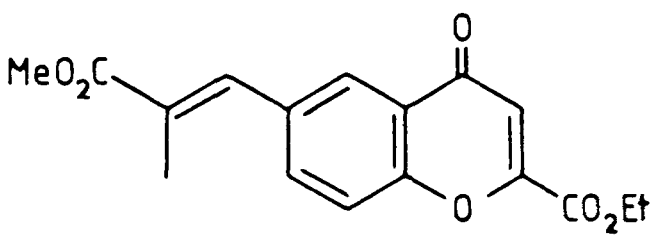
n.O.e enhancements (%) on irradiation

This result supports the generally accepted mechanism for the reaction as involving a *syn* addition and a *syn* elimination. Following the initial *syn* addition of the aryl-palladium species to the olefin, a *syn* elimination of a

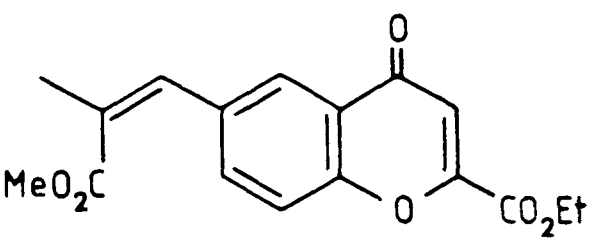
palladium hydride species (which requires a rotation to occur in the intermediate) results in the relationship between the two olefin substituents being reversed. Groups that were originally *anti* to each other, in the product have a *syn* relationship.



Heating the 6-bromochromone 87 with methyl methacrylate under the usual conditions gave, after work-up, a single product as a white crystalline solid. The infrared spectrum with an additional absorption of 1710 cm^{-1} indicated the desired coupled product as did the mass spectrum which contained a molecular ion at m/z = 316. The assignment of the product as methyl 3-[6-(2-carboethoxy)chromone]-2-methylpropenoate 108 was confirmed by elemental analysis. The ^1H n.m.r. spectrum although containing the expected methyl singlet (δ2.18), methoxy singlet (δ3.85) and vinyl proton singlet (δ7.73) did not allow an assignment of the stereochemistry as the chromone ring could be either *anti*, 108, or *syn*, 109, to the methyl ester substituent.



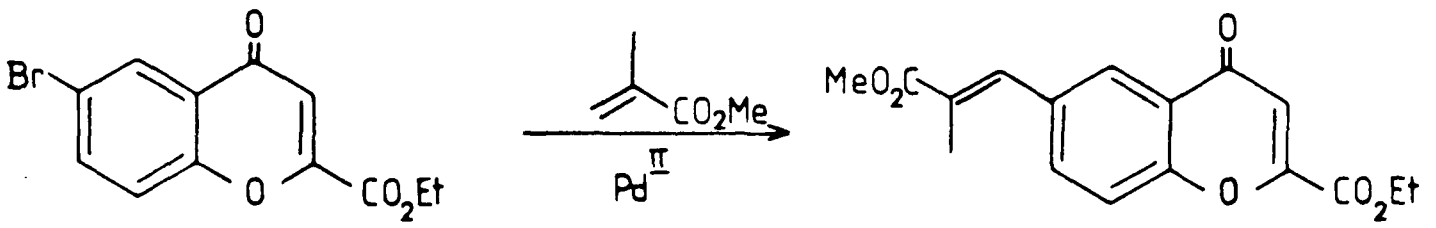
108



109

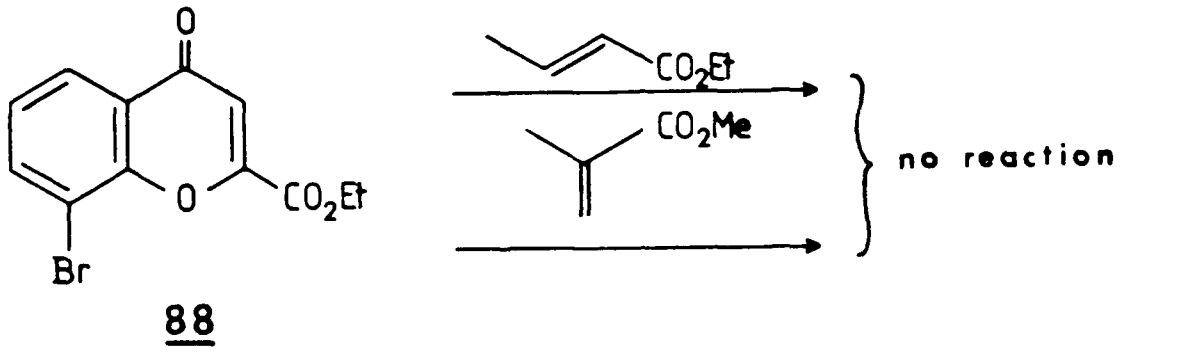
The structure of the product was again determined by two n.O.e. experiments. Irradiation of the methyl group (δ2.18) resulted in intensity enhancements of the C5 and C7 chromone protons (7 and 3% respectively). Irradiation of the vinyl proton (δ7.73) gave a moderate enhancement of the C5 proton (5%) and very small enhancements (<1%) of both the methoxy and

methyl protons. The presence of a strong enhancement between the methyl group and the chromone ring protons suggests a *syn* relationship. With the absence of any strong enhancement between the methyl and vinyl protons, the most consistent product geometry is 108.



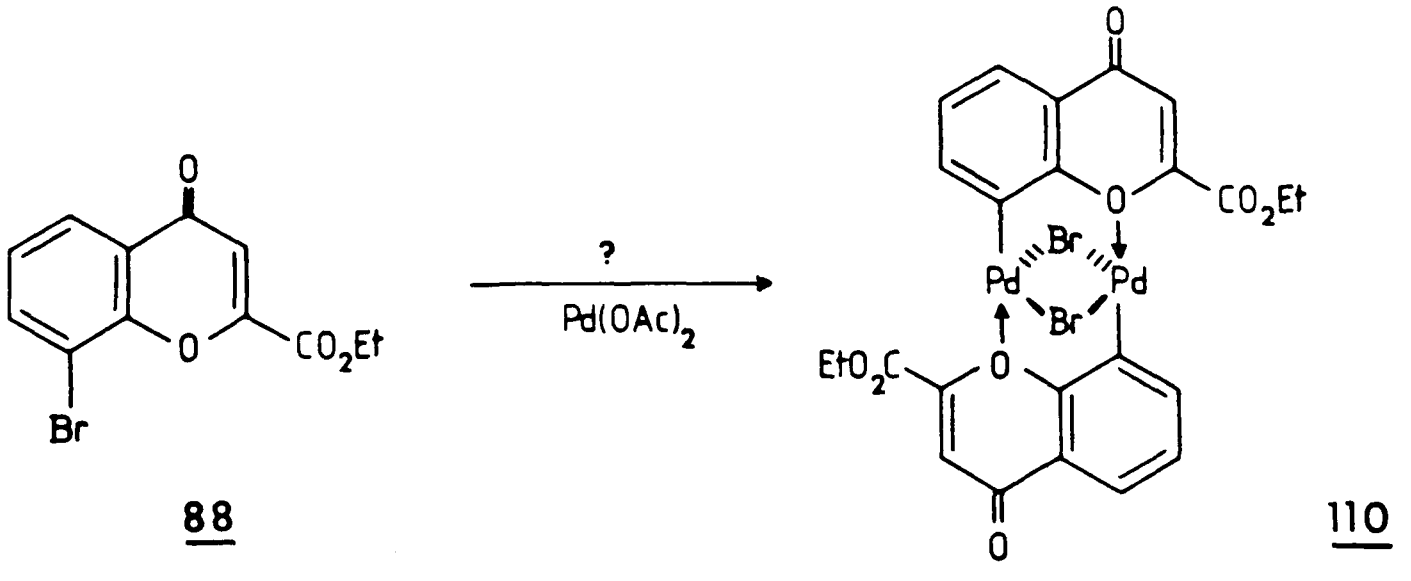
87 108

Attempts to perform the analogous coupling reactions of either ethyl crotonate or methyl methacrylate with the 8-bromochromone 88 under the standard conditions were unsuccessful. No vinylated chromone was isolated, starting material being recovered.



88

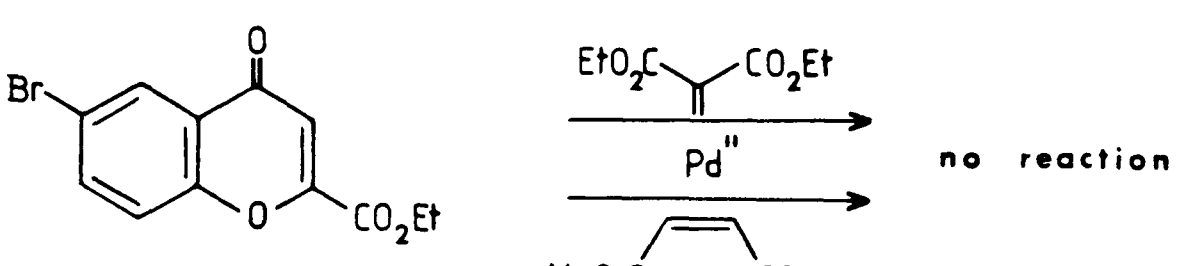
The failure of these two disubstituted olefins to undergo coupling with the 8-bromochromone 88 may be due to the formation of a stable palladium dimer species (such as complex 110) after it has undergone insertion into the carbon-bromine bond.



88 110

Disubstituted olefins are generally less reactive under the usual conditions for this coupling reaction than the corresponding mono-substituted compounds due to steric inhibition.[36] Should the chromone form the stable intermediate 110 the reduction in olefin reactivity on moving from mono- to disubstituted olefins could be sufficient to suppress the coupling reaction. The same problem is not found with the 6-bromo-chromone 87 since there is no adjacent chelating group.

Methylene diethyl malonate, prepared from formaldehyde and diethyl-malonate and dimethyl maleate both failed to react with the 6-bromochromone 87 under the standard vinylation conditions.



87

With the failure of both these olefins to couple with the more reactive 6-bromochromone 87, no attempts were made to vinylate the 8-bromo isomer 88.

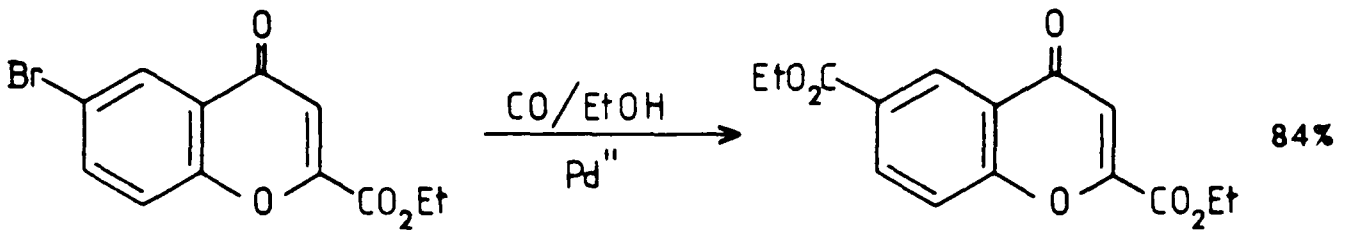
2(iii) Miscellaneous reactions

In addition to vinylation with olefins, there are a number of other reactions that an aryl halide can undergo following insertion of palladium (0) into the carbon-halogen bond (*cf.* introduction). A few such reactions were attempted with the 6-bromochromone 87.

Running the palladium catalysed reactions under a carbon monoxide atmosphere is known to result in CO insertion into the aryl-palladium bond. The resulting metal acyl may then be cleaved by donor solvents leading to overall carbonylation of the aryl halide.

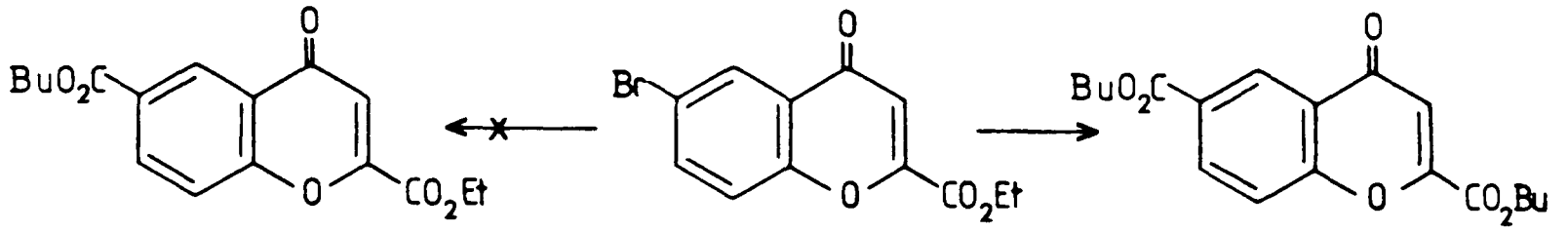
Heating the 6-bromochromone 87 under three atmospheres of carbon

monoxide in ethanol at 105°C with a tertiary amine base after work-up, gave a single product. The additional ethyl ester absorptions in the ^{1}H n.m.r. spectrum and a molecular ion m/z = 290 in the mass spectrum allowed this product to be identified as the known[62] diethyl 2,6-chromone dicarboxylate 111.



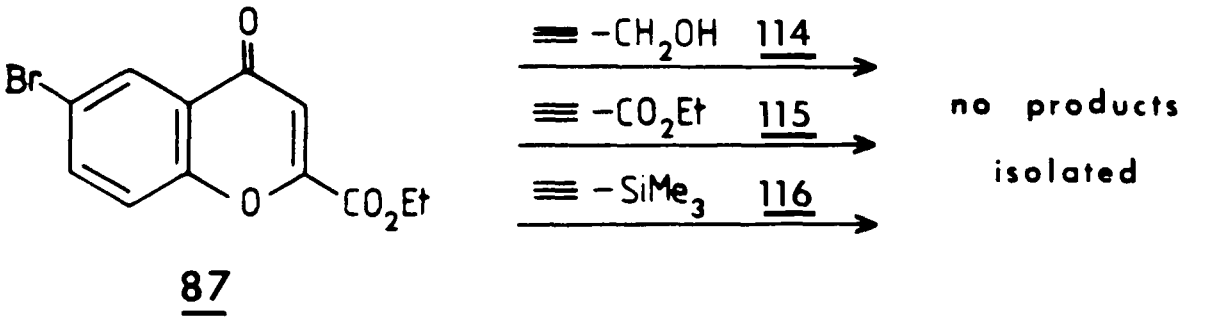
87 111

Repeating the reaction in n-butanol as a solvent led only to the dibutyl ester 112, identified by a molecular ion m/z = 346 in the mass spectrum. The non-isolation of the mixed ethyl-butyl ester 113 must be due to ester exchange.



113 87 112

Palladium is also known to catalyse the coupling of terminal acetylenes to aryl halides. Attempts to couple the 6-bromochromone 87 with propargyl alcohol 114,[63] ethyl propiolate 115 or trimethylsilylacetylene 116[54] under a variety of conditions failed to give any of the desired products. The isolated material in each case consisted of a mixture of several compounds which were inseparable.

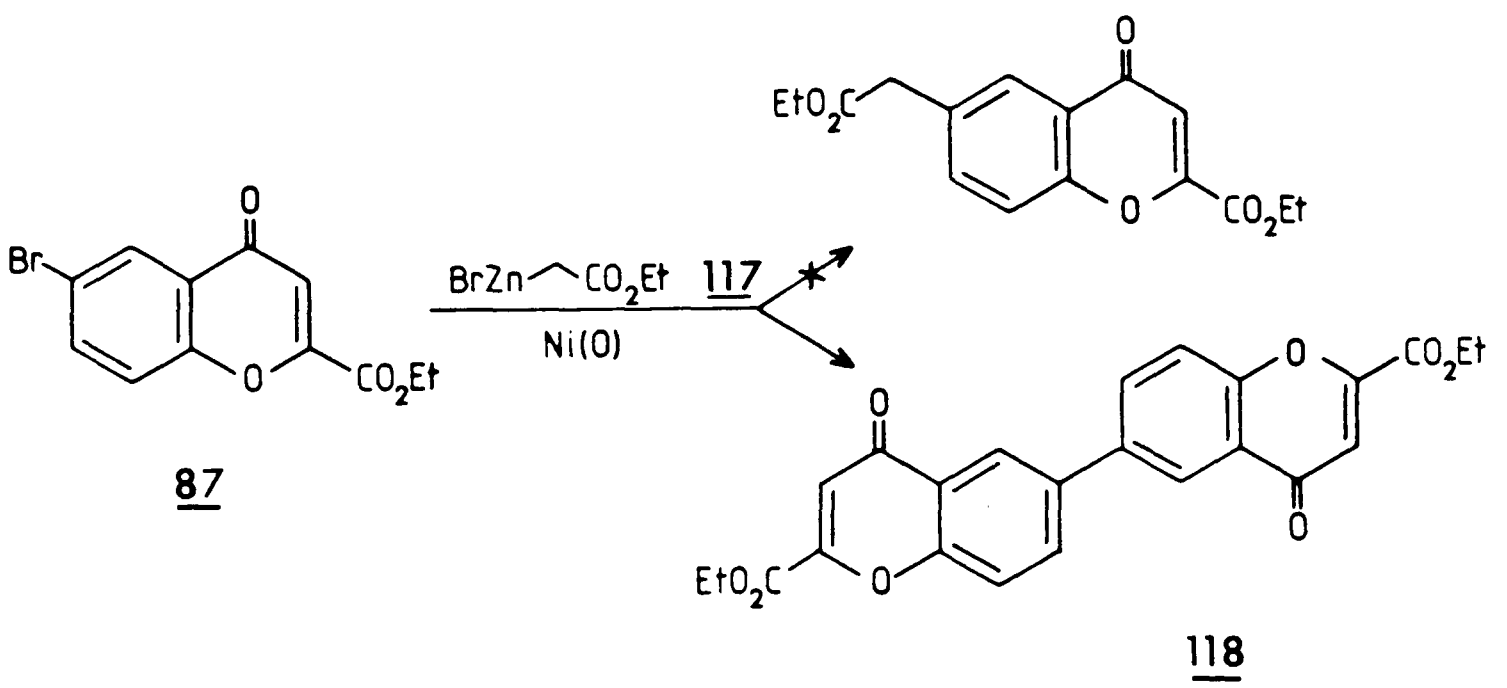


87

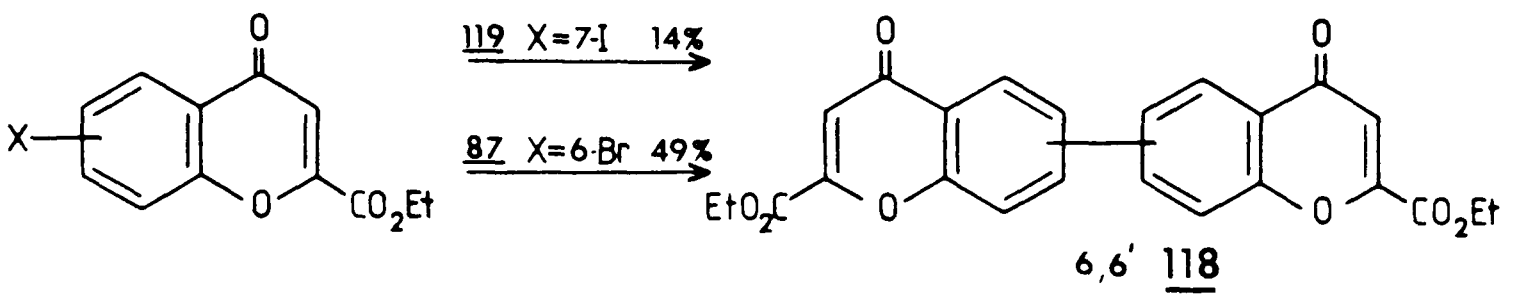
Palladium is not the only transition metal known to catalyse the cross-coupling of two organic molecules. Nickel species can often be used as an alternative to palladium catalysts with very similar results; they are particularly used for the coupling of Grignard reagents with alkyl halides.[64]

An attempt was made to couple the 6-bromochromone 87 with Reformatsky's reagent 117 using both palladium acetate tri-*o*-tolylphosphine and *tetrakis*(triphenylphosphine)palladium [52] as catalysts. In each case only starting material was recovered. The reaction was then repeated with a zero-valent nickel reagent, *tetrakis*(triphenylphosphine)nickel. This reagent, which has been used for the homocoupling of aryl halides to biaryls, is very air-sensitive and would require considerable care for its preparation. It was therefore generated *in situ* from nickel II chloride, triphenylphosphine and zinc.[65]

The reaction of a stoicheiometric amount of this reagent with the 6-bromochromone 87 and the Reformatsky reagent 117 led to a single product, highly fluorescent by t.l.c., and considerable quantities of triphenylphosphine being isolated after work-up. The ^{1}H n.m.r. spectrum of the product contained no additional resonances from the starting material. The aromatic protons, however, although exhibiting the same couplings had slight chemical shift differences when compared to the 6-bromochromone 87. This product was provisionally assigned as the novel 6,6'-*bis*-2-carboethoxychromone 118. This was confirmed by a molecular ion m/z = 434 in the mass spectrum and by elemental analysis. Preferential formation of the *bis*chromone had therefore occurred rather than cross-coupling with the Reformatsky reagent 117.



The dimer 118 was isolated in low yield (14%) from this reaction and it was therefore repeated without the superfluous Reformatsky reagent. Under identical conditions after work-up, the dimer 118 was isolated in 49% yield. This compared very favourably with the synthesis of the analogous 7,7' dimer in 14% yield which involves the Ullmann coupling of the iodide 119.[66]



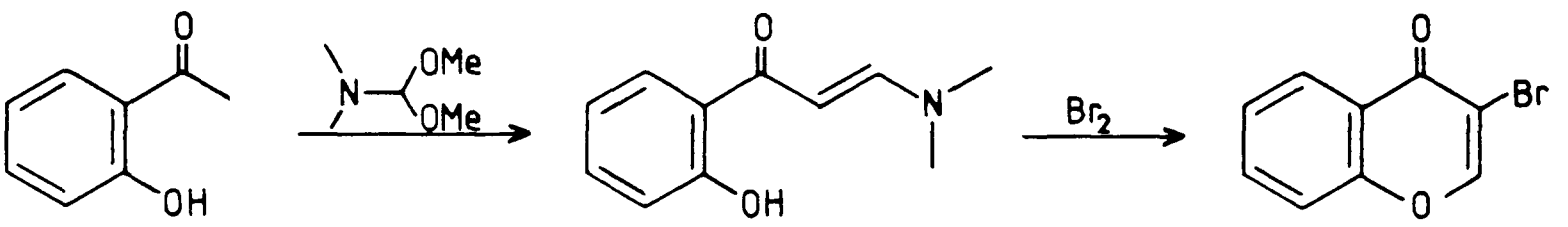
The stoicheiometric use of *tetrakis*(triphenylphosphine)nickel is inconvenient since the work-up generates four equivalents of triphenylphosphine which hinders the product isolation and purification. A method which uses a catalytic quantity of the nickel complex has been developed, regeneration of Ni(0) from Ni(II) being effected by zinc dust.[67] Repeating the coupling reaction of the 6-bromochromone 87 under these conditions gave poor results. The dimer 118 was still produced but it was contaminated by a number of impurities, from which it could not be separated.

3. Elaboration of 3-bromochromone

With the success of the vinylation reaction of the 6- and 8-bromochromones 87 and 88, it was decided to extend the studies to include 3-bromochromone 120 as a method of regiospecifically introducing substituents into a largely unfunctionalised system.

3(i) Synthesis

The desired compound 120 was synthesised according to a literature procedure.[68] Thus heating *o*-hydroxyacetophenone with dimethylformamide dimethyl acetal gave after chromatography, the bright yellow vinylogous amide 121. Treatment of a chloroform solution of this intermediate with bromine resulted in a cyclisation to give 3-bromochromone 120 in 59% overall yield.



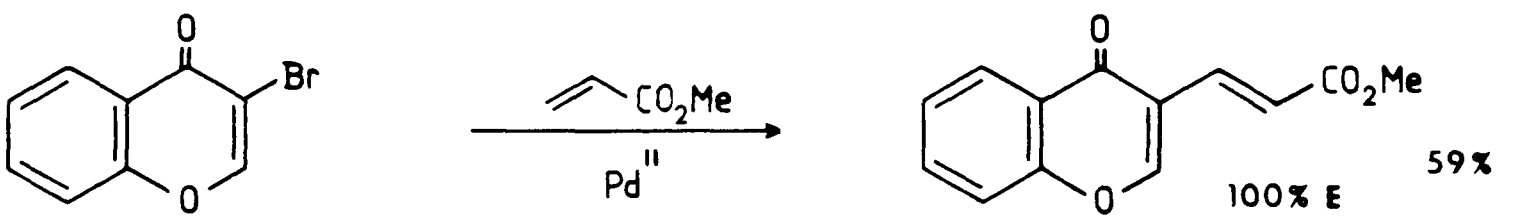
121 120

In contrast to the 6- and 8-bromochromones 87 and 88, not all the aromatic protons are clearly resolved in the ^{1}H n.m.r. spectrum of the 3-bromochromone 120. A singlet (δ8.24) can be assigned to the C2 proton and the doublet of doublets at δ8.26 due to one proton must arise from either the C5 or C8 proton; the splitting being due to a large *ortho* and a smaller *meta* aryl ring coupling. By analogy with the 6- and 8-bromo isomers this was assigned as the C5 proton. The remaining three protons C6, C7 and C8 were found as a one and a two proton multiplet (δ7.72 and 7.47) and could not be specifically assigned.

The infrared spectrum contained a pyrone carbonyl absorption at 1650 cm^{-1} and the mass spectrum two molecular ion peaks of equal intensity; m/z = 224 (^{79}Br) and 226 (^{81}Br).

3(ii) Vinylation

Heating a DMF solution of the 3-bromochromone 120 with methyl acrylate, triethylamine, a catalytic quantity of palladium acetate and triphenylphosphine under the standard conditions gave a single product by t.l.c. This was isolated after purification by chromatography on silica gel. The ^1H n.m.r. spectrum of the product contained the expected chromone aromatic resonances with the singlet for the C2 proton at δ8.16, indicating an unchanged substitution pattern. The new features in the spectrum were a two proton AB system (δ7.40, 7.26 J = 16 Hz) and a three proton singlet (δ3.78). These latter features are consistent with a methyl propenoate substituent and the product was assigned as *E*-methyl 3-(3-chromone)propenoate 122. Further confirmation was provided by the expected molecular ion m/z = 230 in the mass spectrum and by elemental analysis.

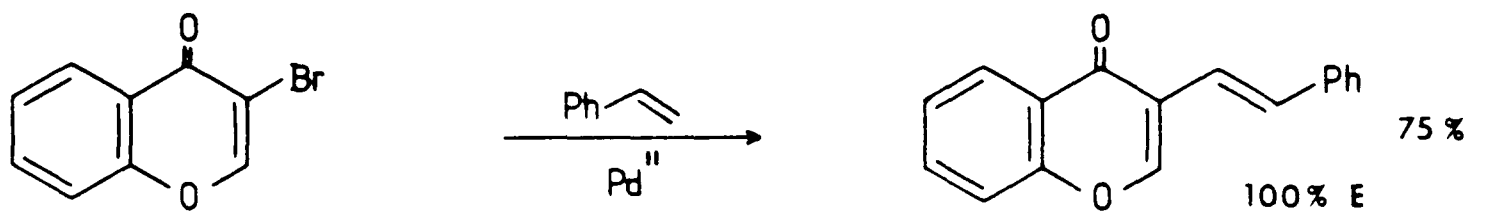


120 122

Once again the coupling constant between the two olefinic protons (16 Hz) confirms the double bond geometry as being *E*.

The parent acrylic acid is a known compound, one of a series of 3-chromone acrylic acids that have been tested for antiallergic activity.[69] Comparison with disodium cromoglycate (R Intal), the most widely prescribed compound, showed derivatives with alkyl and dimethylamine substituents to be at least as active as Intal. Significantly they were also found to be orally active, unlike Intal which is only active by inhallation.

The use of styrene as a substrate with the 3-bromochromone 120 under the standard vinylation conditions, after work-up, led to the formation of one product (75%) with 10% recovery of starting material. The aromatic region of the ^{1}H n.m.r. spectrum of this product consisted of a series of overlapping multiplets (δ7.67 - 7.18) with only the C2 and C5 protons resolved at the low field end and a new doublet (δ6.94) on the high field side. This new doublet (J = 16 Hz) was assumed to be one of the two olefinic protons from the expected vinylated product which was assigned as *E*-3-chromone-β-styrene 123. This was confirmed by a molecular ion *m/z* = 248 in the mass spectrum and by elemental analysis. Expansion of the aromatic region of the ^{1}H n.m.r. spectrum allowed the identification of the other olefinic proton doublet.



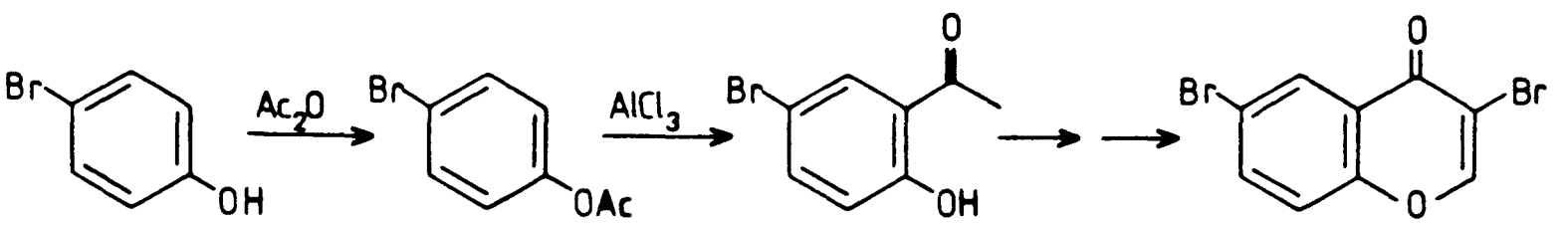
120 123

3(iii) 3,6-Dibromochromone

The ease with which the 3-bromochromone 120 underwent vinylation with methyl acrylate and styrene suggested the possibility of combining this with the similar reactivity of the 6-bromochromone 87. Vinylation of a dibromochromone should result in the simultaneous coupling of an olefin to the chromone system at two different sites.

The desired 3,6-dibromochromone 124 was synthesised *via* 5-bromo-2-hydroxyacetophenone 124A in an analogous manner to the preparation of 3-bromochromone 120 from *o*-hydroxyacetophenone. Compound 124A was prepared by *O*-acetylation of *p*-bromophenol 89 with acetic anhydride in pyridine, followed

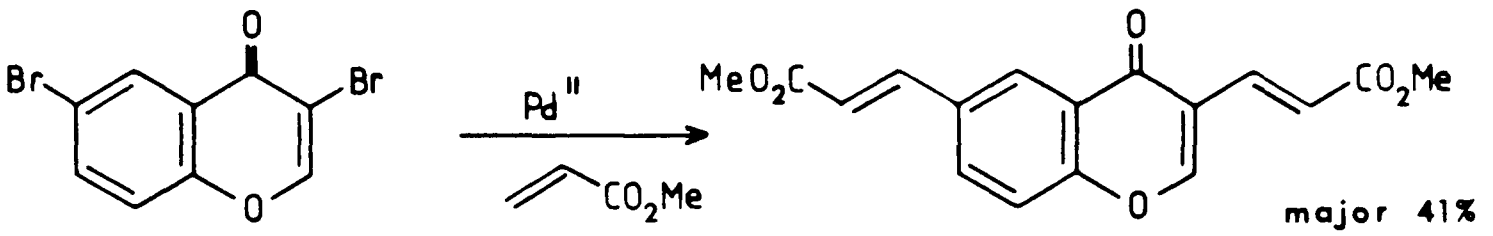
by heating with aluminium trichloride to give a Fries rearrangement. Subsequent conversion to 3,6-dibromochromone 124 was achieved in 37% overall yield from *p*-bromophenol 89.



89 124A 124

The ^{1}H n.m.r. spectrum of the dibromochromone 124 contained the familiar pattern of well resolved aromatic protons, the C2 proton occurring as a singlet (δ8.25) and the C5 proton as a doublet (δ8.35, J = 2 Hz) with a small *meta* coupling to the AB system of the C7 and C8 protons. The mass spectrum contained three molecular ions m/z = 302, 304 and 306 of intensity 1:2:1, characteristic of a dibromocompound.

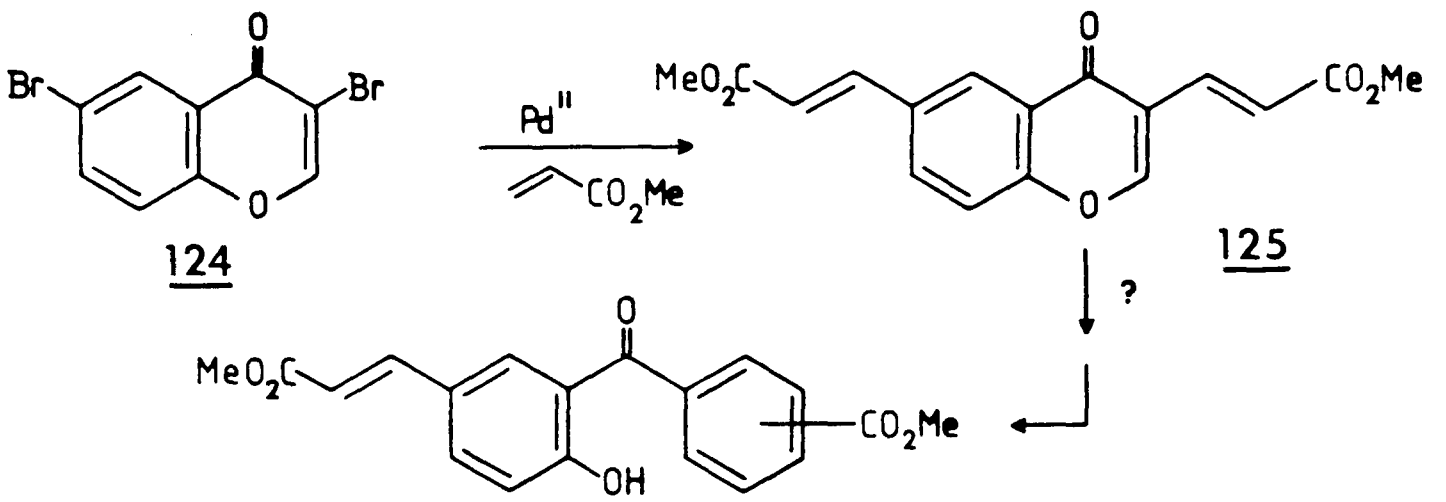
Heating the 3,6-dibromochromone 124 under the standard conditions required for vinylation with methyl acrylate gave after work-up, two products subsequently identified as compounds 125 (41%) and 126 (8%) together with a number of inseparable impurities. The ^{1}H n.m.r. spectrum of the major product 125 in addition to the expected chromone signals contained two, three proton singlets and four olefinic proton resonances as two doublets and an AB system. These features suggested product 125 to be the diacrylated chromone. This was confirmed by a molecular ion m/z = 314 in the mass spectrum, the novel compound being further characterised by elemental analysis. In common with the other vinylations identical coupling constants of 16 Hz within each pair of olefin resonances showed each double bond to have *E*-stereochemistry.



124 125

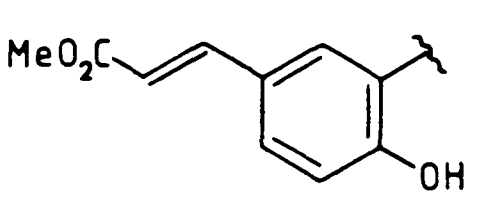
The identification of the minor product 126 proved to be more intriguing. The ^{1}H n.m.r. spectrum contained signals for sixteen protons (two more than the diacrylated product 125) and the mass spectrum a molecular ion at *m/z* = 340 (twenty-six mass units higher than compound 125), with the lack of an isotope pattern showing the compound contained no bromine. The ^{13}C n.m.r. spectrum contained signals for nineteen carbons (two more than compound 125) which combined with the other evidence indicated the overall addition of a C_2H_2 unit to the major product 125. An ester carbonyl absorption (1735 cm^{-1}) was present in the infrared spectrum which with two, three proton singlets in the ^{1}H n.m.r. spectrum suggested compound 126 contained two carbomethoxy groups. The other distinctive features in the ^{1}H n.m.r. spectrum were a singlet (δ12.16) which underwent exchange with D_2O and a doublet (δ6.25, J = 16 Hz) due to one proton. These suggested the presence of a phenol and an *E*-olefin respectively.

The most likely source of a C_2H_2 unit in the reaction mixture would be by an addition of excess methyl acrylate, followed by loss of the methyl ester. The phenol would probably have arisen by a cleavage of the pyrone ring. With eight aromatic protons, the spectral data therefore suggested 126 to be a benzophenone derivative, formed from the major product 125.

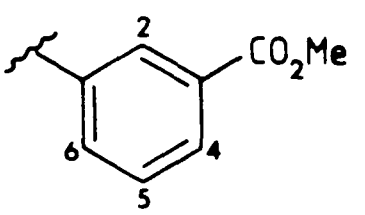


126

A change of solvent and an expansion of the aromatic region of the ^{1}H n.m.r. spectrum allowed the eight remaining protons to be resolved. A doublet (J = 16 Hz) was easily assigned as the other olefinic proton. A two proton AB system (J = 8 Hz) of which one pair of signals were further split into doublets, and a doublet with this corresponding small splitting (J = 2 Hz) were very similar to the resonances found in the chromone systems. They were therefore assigned to a 1,2,5 trisubstituted aromatic ring 127. The remaining protons were two triplets (J = 8 Hz and 1.5 Hz) and two doublets of triplets (J_d = 8 Hz, J_t = 1.5 Hz). These are consistent with a 1,3-disubstituted aromatic system 128. The triplet with the small coupling constant being H-2, with a *meta* coupling to H-4 and H-6 - while the other triplet is H-5 with a large *ortho* coupling to H-4 and H-6. The two doublets of triplets are therefore H-4 and H-6, which each have a large coupling to C5 and an identical coupling to the two protons *meta* to themselves.



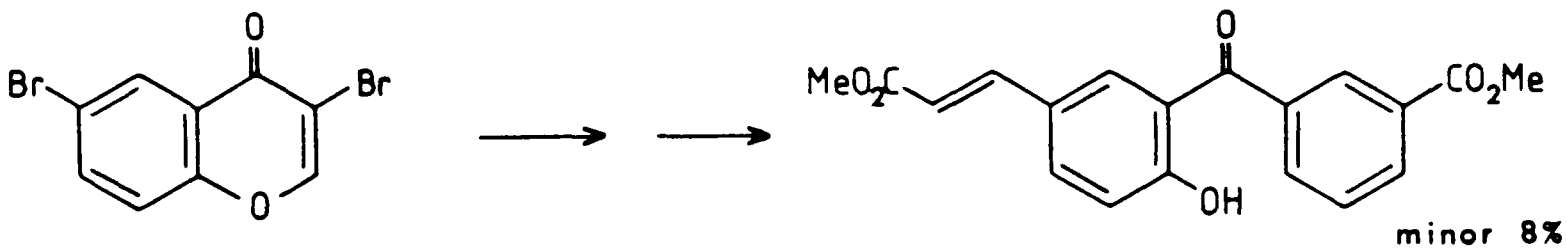
127



128

The aromatic fragments of 126

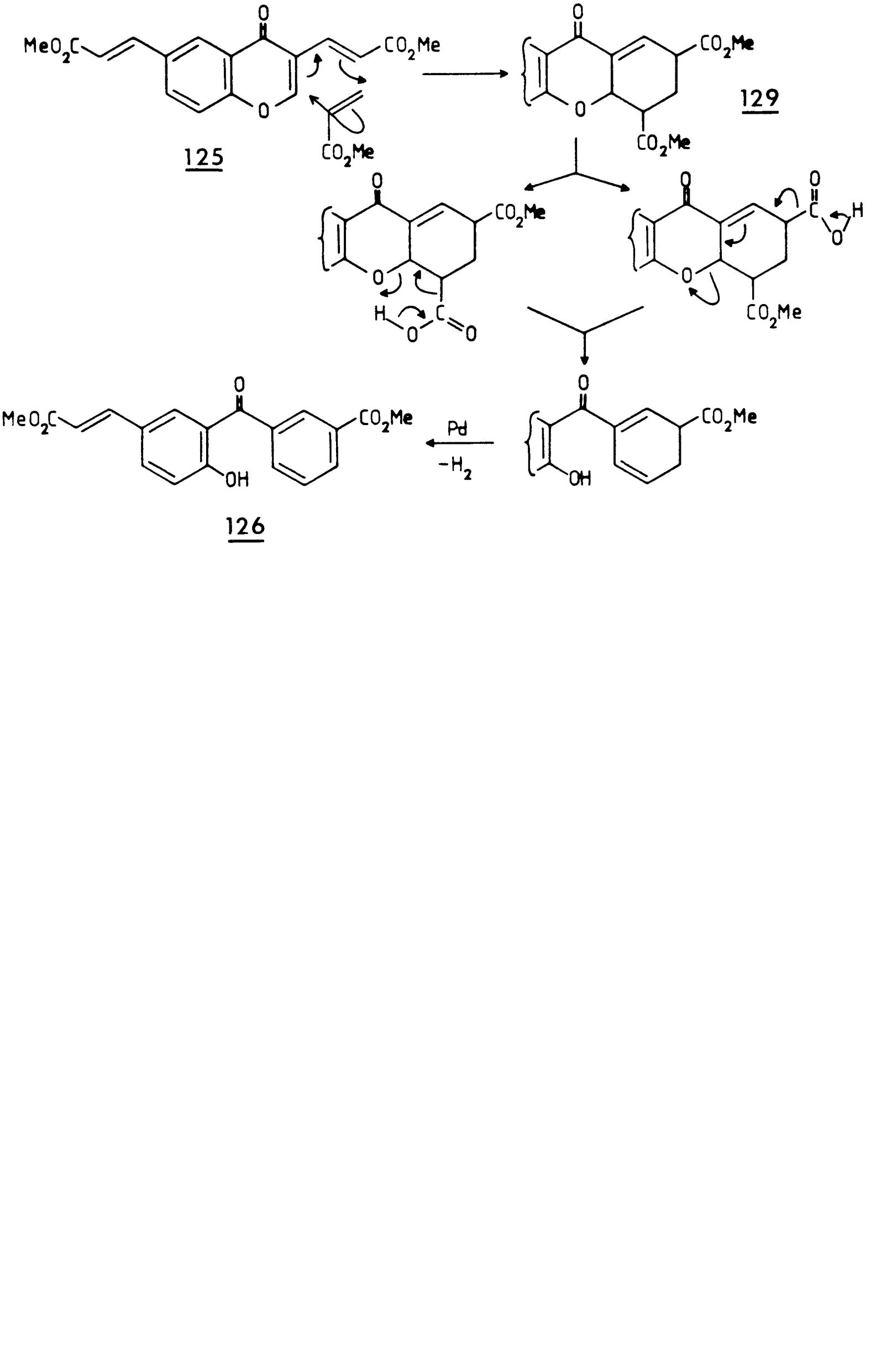
The minor product was therefore assigned as methyl 3-(3-carbomethoxybenzoyl)-4-hydroxycinnamate 126. This structure was supported by the ^{13}C n.m.r. spectrum which contained eight quaternary, nine tertiary and two primary carbons. The presence of nineteen distinct carbon resonances supports the location of the carbomethoxy group at C3 of the second aromatic fragment. If it was *para* to the carbonyl bridge then only seventeen signals would have been observed with the *ortho* and *meta* carbons being identical [*cf.* 6-(2-carboethoxychromone)-β-styrene 101]. Analysis of the mass spectrum, which contained the required molecular ion m/z = 340, gave further support to this structure with a fragment m/z = 205 formed by cleavage adjacent to the carbonyl group and loss of $C_6H_4CO_2Me$.



minor 8%

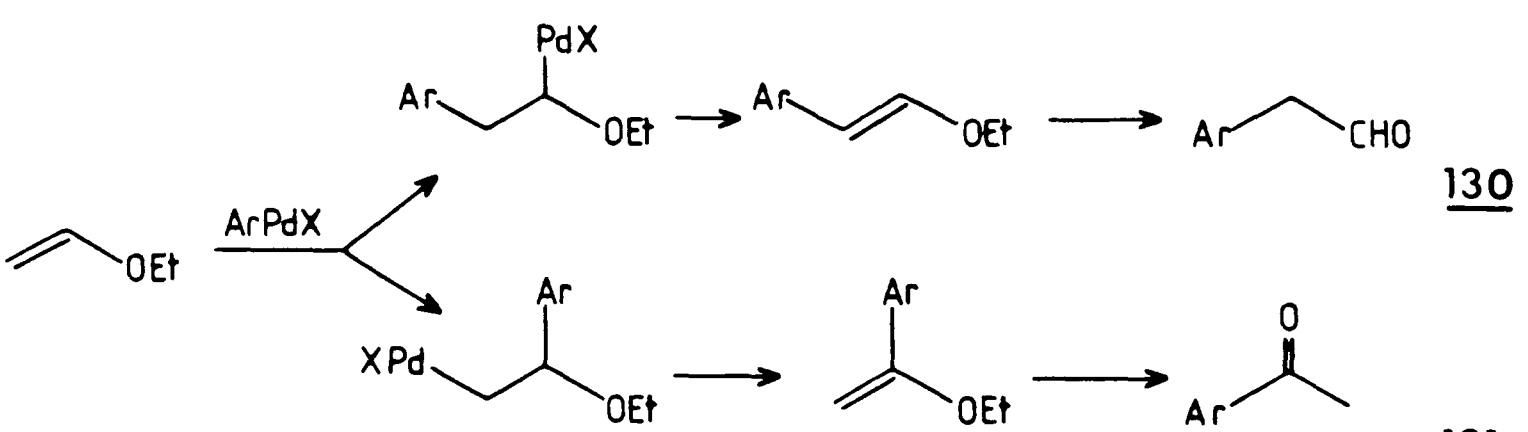
124 **126**

The probable mechanism for the formation of this minor product 126 involves an initial Diels-Alder addition of excess methyl acrylate to the diacrylated product 125, to produce a cyclohexene system 129. There are two possible orientations for this cycloaddition, either with the carbomethoxy group of methylacrylate *syn* or *anti* to the oxygen of the pyrone ring. The indicated *syn* orientation, to give 129, is the more likely both from the polarisation of the diene and the dieneophile and because subsequent loss of either ester group leads to the same product. The reverse orientation might be expected to lead to a mixture of two isomeric products. Following the Diels-Alder reaction mono-ester hydrolysis (of either ester) is followed by decarboxylation with concomitant ring opening. Dehydrogenation, presumably effected by metallic palladium in the reaction mixture, then gives the observed product 126.

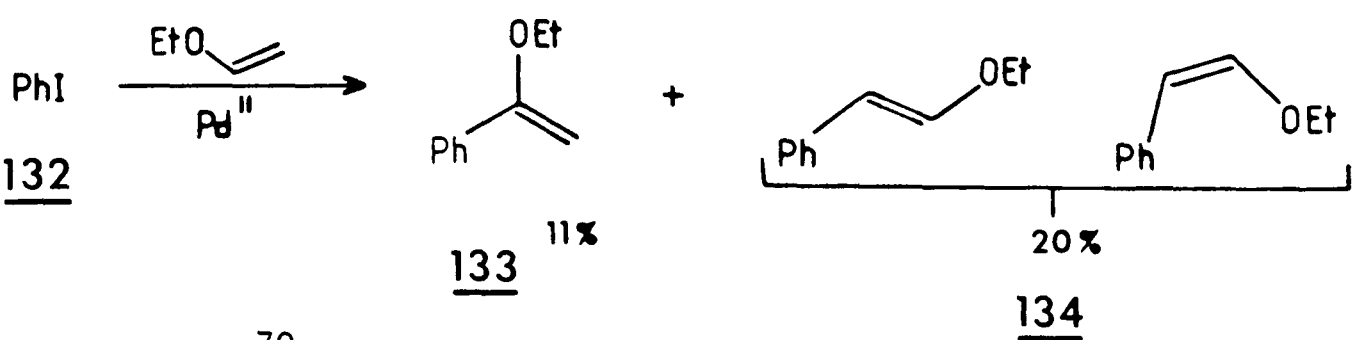

MeO2C
CO2Me
O
CO2Me
125
129
CO2Me
CO2Me
H
O
C
O
CO2Me
O
C
H
O
CO2Me
MeO2C
CO2Me
OH
Pd
-H2
OH
CO2Me
126

4. Acetylation of aryl halides

During the course of the bromochromone vinylations (I.2) we became interested in using ethyl vinyl ether as a substrate. There are two possible products from the reaction depending upon the orientation of addition of the arylpalladium species to the olefin. Addition to the terminal olefin carbon, followed by hydrolysis either subsequently or *in situ* would produce the saturated aldehyde 130. Conversely addition to C1 of the olefin after hydrolysis would give a methyl ketone 131.

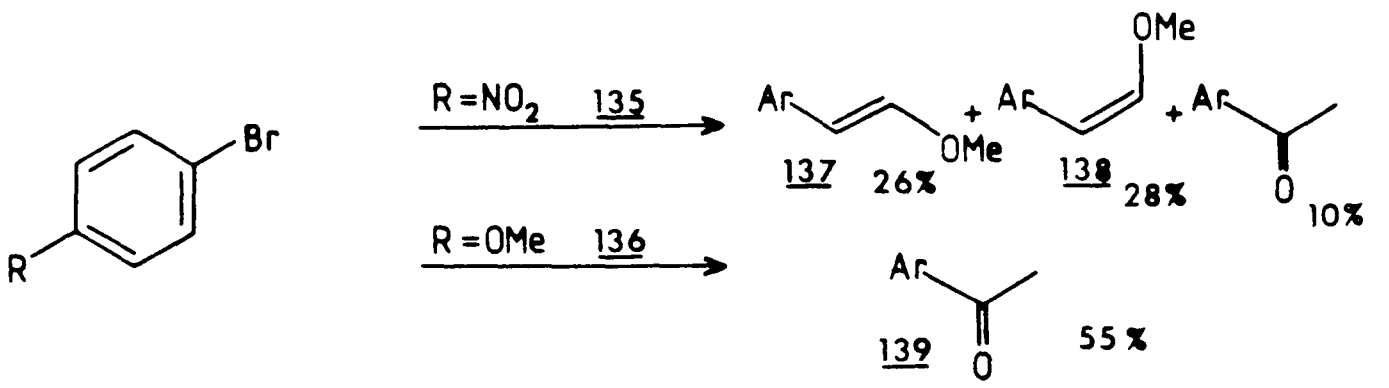


Either of these transformations, since they produce products not always readily accessible by other routes, would be desirable. A search of the literature revealed only two reports[61,70] on the use of alkyl vinyl ethers as substrates with aryl halides under the vinylation conditions and both contained some unusual results. The first paper[61] described the reaction between iodobenzene 132 and ethyl vinyl ether. The reported products were in low yield, a mixture of both the 1- and 2-arylated adducts 133 and 134 respectively, the latter being a mixture of *E*- and *Z*-isomers.



The second paper[70] contrasted the reaction of *p*-nitro 135 with that of *p*-methoxy bromobenzene 136 using methyl vinyl ether. Whilst the former

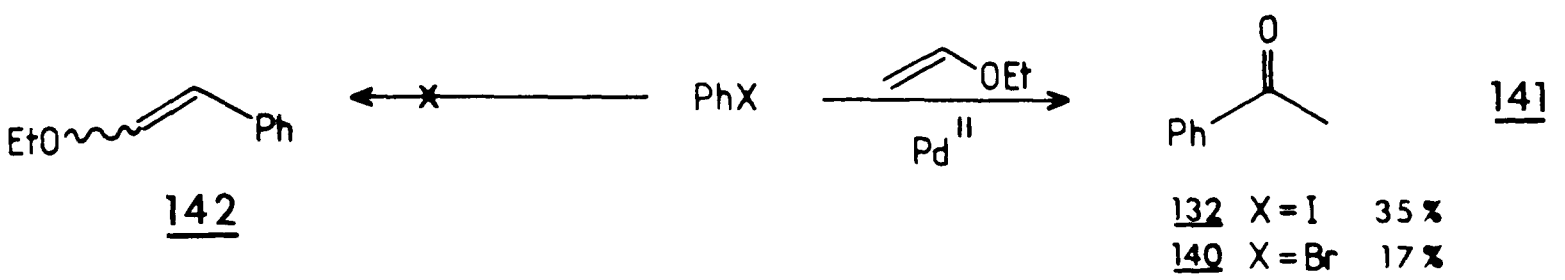
gave predominantly the 1-arylated adducts 137, and 138 in reasonable yield, the latter gave exclusively the substituted acetophenone 139. No trace of the other isomers were found.



With the limited number of examples in the literature of this reaction it was decided to examine its scope with some simple aryl halides, before proceeding to consider the bromochromone 87.

Utilising bromobenzene 140 under the standard vinylation reaction conditions with ethyl vinyl ether gave a single product. The ^{1}H n.m.r. spectrum contained a three proton singlet (δ2.55) and by comparison with an authentic sample this product was readily identified as acetophenone 141. The yield, however, was very low (17%).

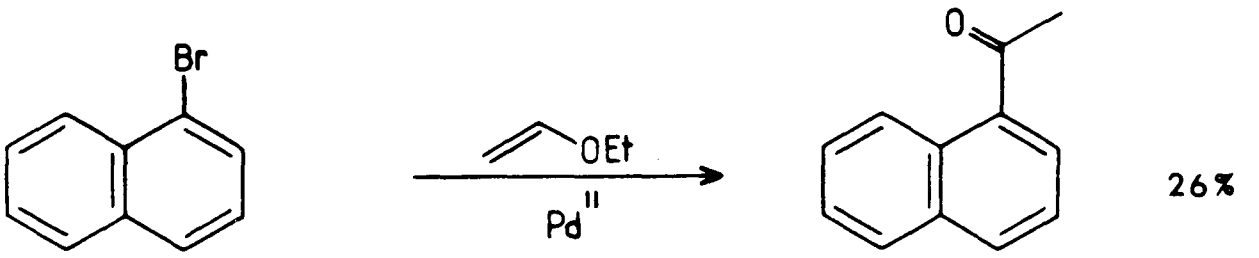
Aryl iodides generally react faster and give higher yields of products than the corresponding bromides for the vinylation reaction,[36] therefore an attempt was made to use iodobenzene 132 as a substrate. Acetophenone 141 was again isolated as the sole product from the reaction, with an improved, although still poor, yield of 35%.



In neither reaction was any 2-ethoxystyrene 142 (or its hydrolysis product) observed, which would result from addition to the less highly substituted end of the olefin. This is at variance with the result reported

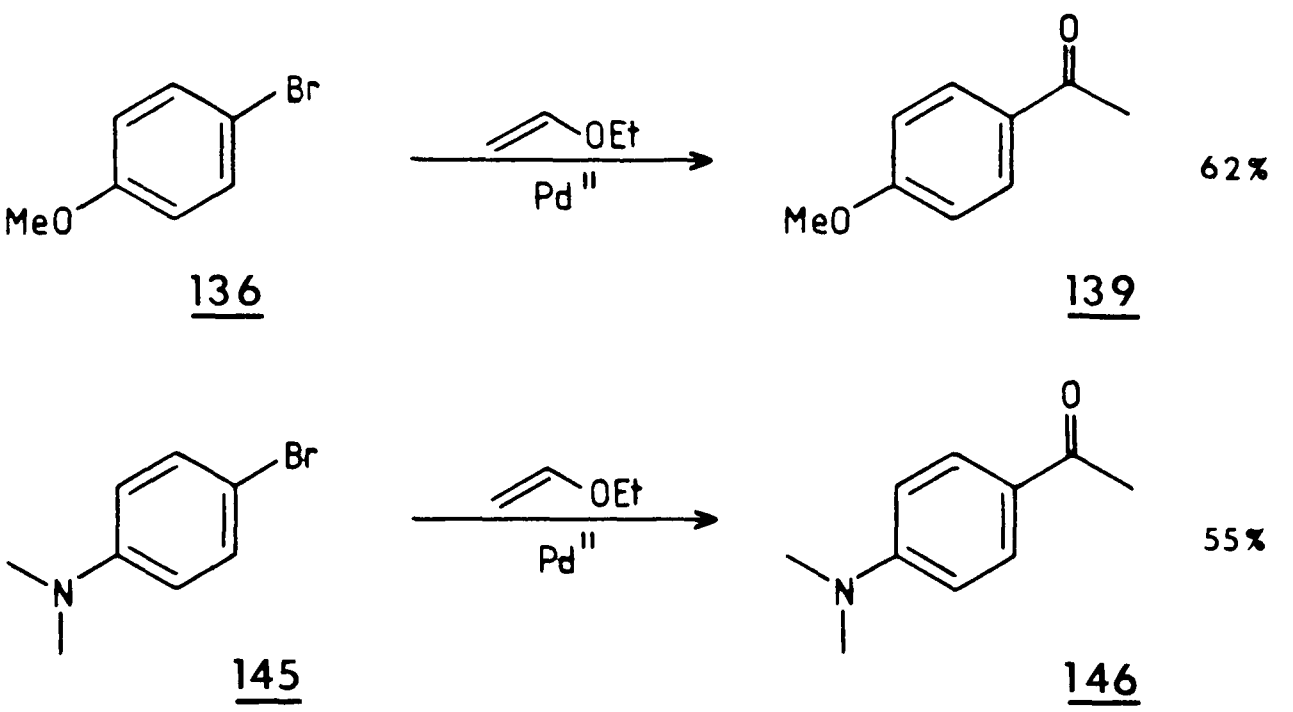
in the literature.[61] Changing the catalyst mixture from the usual palladium acetate, tri-*o*-tolylphosphine, to the preformed *bis*(triphenylphosphine)-palladium chloride did not improve the yield of acetophenone 141.

In a similar fashion to bromo- and iodobenzene, 1-bromonapthalene 143 gave a poor yield (26%) of 1-acetylnapthalene 144.



143 144

The change to aryl halides with electron donating groups brought an immediate improvement in the isolated yields of the substituted acetophenones. Heating *p*-bromoanisole 136 under the standard vinylation conditions gave, as reported,[70] *p*-methoxyacetophenone 139 in a slightly improved yield of 62%. *p*-Bromo-*N*,*N*-dimethylaniline 145 gave a similarly good yield (55%) of the *para*-substituted acetophenone 146.

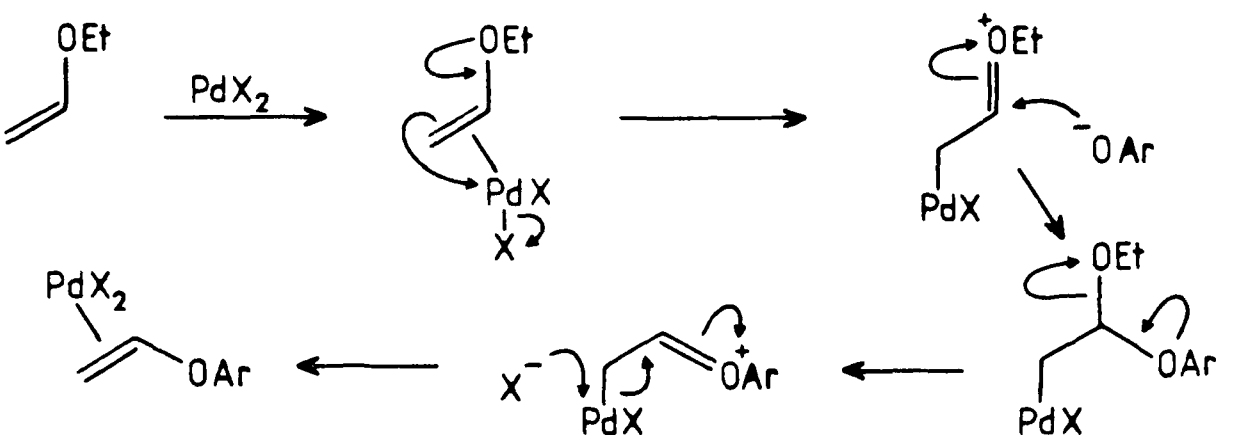


136 139

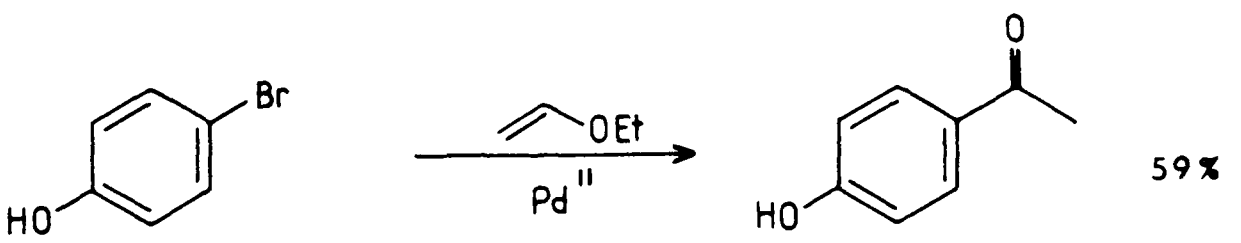
145 146

There have only been limited examples of the use of an aromatic halide containing a phenolic hydroxyl group as a substrate in the vinylation reaction.[36] Under the acetylation conditions it was anticipated that either

of two potential side reactions might predominate. The palladium could catalyse an ether exchange reaction between the ethyl vinyl ether and the phenoxide anion.

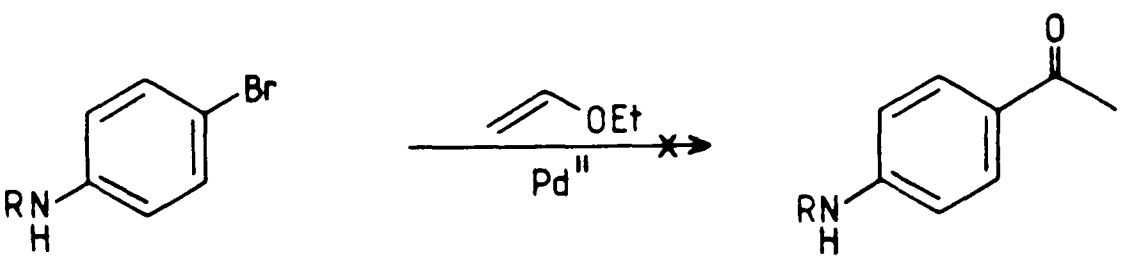


Alternatively the activated phenoxide anion could undergo phosphonium ion formation with the triarylphosphine required to stabilise the catalyst (p-bromophenol is about fifty times more reactive than bromobenzene).[60] It was found that the phenolic hydroxyl group was compatible with the reaction conditions and that protection (*e.g.* as its methyl ether) was not required. Thus p-bromophenol 89 and ethyl vinyl ether under the standard reaction conditions gave a 59% yield of p-hydroxyacetophenone 147.



89 **147**

The corresponding reaction of o-bromophenol 92 was poor. Only about 10% of the expected o-hydroxyacetophenone 148 was isolated along with 65% recovery of the starting material. With the successful acetylation of p-bromophenol 89 it was decided to use p-bromoaniline 149 as a substrate to see whether a free amino group was similarly compatible with the reaction conditions. None of the desired acetophenone was isolated either using p-bromoaniline 149, or when the amino group was protected as the N-acetyl derivative in p-bromoacetanilide 150.

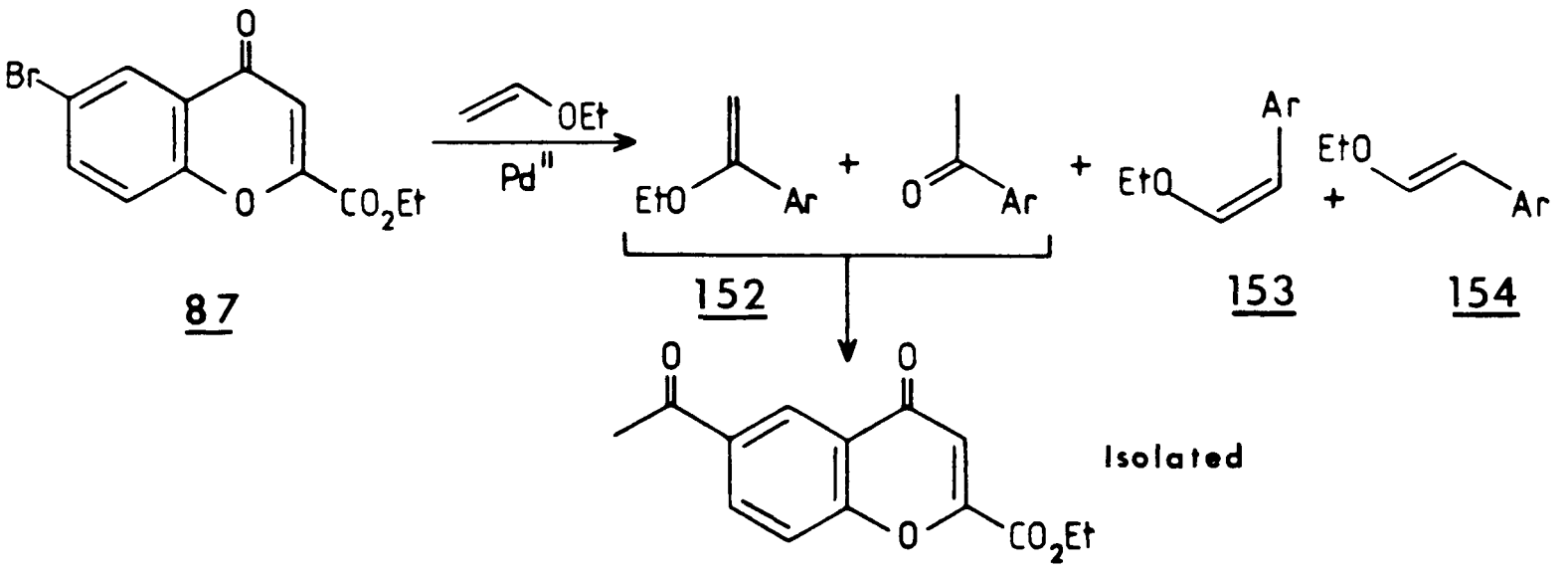


149 R = H
150 R = Ac

Having looked at the reactions of some simple aryl halides with ethyl vinyl ether and determined the sole products to be the substituted acetophenones, the 6-bromochromone 87 was used as a substrate. The crude product, obtained by precipitation of the reaction mixture by cold water, was shown by t.l.c. to be a mixture of several compounds. Attempts at chromatographic separation of these compounds on silica were, however, unsuccessful. This mixture was therefore subjected to hydrolysis, by stirring with trimethylsilyl iodide, since 2-ethoxystyrene derivatives are particularly resistant to acid hydrolysis. Chromatography on silica then allowed the isolation of one of the original products. Apart from the normal chromone resonances the only additional feature in the ^{1}H n.m.r. spectrum was a prominent three proton singlet (δ2.72) which suggested the product to be the known[71] 6-acetyl-2-carboethoxychromone 151. This was confirmed by a molecular ion m/z = 260 in the mass spectrum.

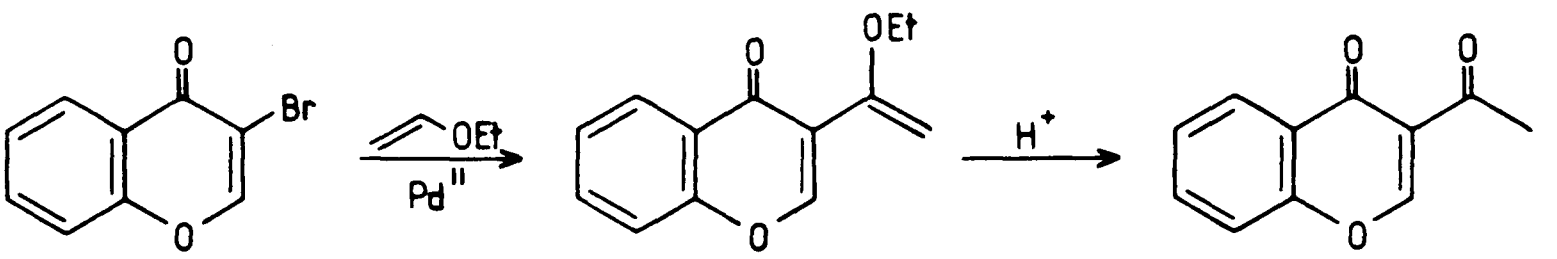
The isolation of this product indicated that addition of the chromone to the vinyl ether had occurred and assisted with the analysis of the original product mixture from the reaction. The ^{1}H n.m.r. spectrum of the less polar column fractions contained two ethyl ester quartets (δ4.45, 3.95) and two vinylic protons (J = 3 Hz). This small coupling is characteristic of geminal vinylic protons ($C=CH_2$) and with no other new resonances the product can be assigned as the unhydrolysed 1-arylated adduct 152.

The ^{1}H n.m.r. spectrum of the more polar column fractions in addition to the signals for the 6-acetylchromone 151 showed two sets of vinylic protons with coupling constants of 7 and 13 Hz as well as several ethyl ester quartets. The vinylic protons are characteristic of *Z*- and *E*-substituted olefins respectively and indicate this fraction to contain the 1-arylated adduct as a mixture of the two isomers 153 and 154. The 6-bromochromone 87 therefore gave a mixture of all four possible products upon reaction with ethyl vinyl ether.



151

The analogous reaction with the 3-bromochromone 120 under identical conditions, was worked-up by precipitation of the product from water, and filtering a dichloromethane solution of this product through a short plug of silica. T.l.c showed a single product and from the ^{1}H n.m.r. spectrum which contained two vinylic protons (δ5.70, 4.50, J = 3 Hz), characteristic of geminal protons, and resonances for an ethyl group, this product was assigned as 3-(1-ethoxyvinyl)chromone 155. Further purification by chromatography on silica resulted in the formation of two products, (by t.l.c.) suggesting that partial hydrolysis of the vinyl ether had occurred. Complete hydrolysis was achieved by brief treatment with acidic ethanol to give the known[72] 3-acetylchromone 156, readily identified by the three proton singlet (δ2.70) in the ^{1}H n.m.r. spectrum and other spectroscopic features.



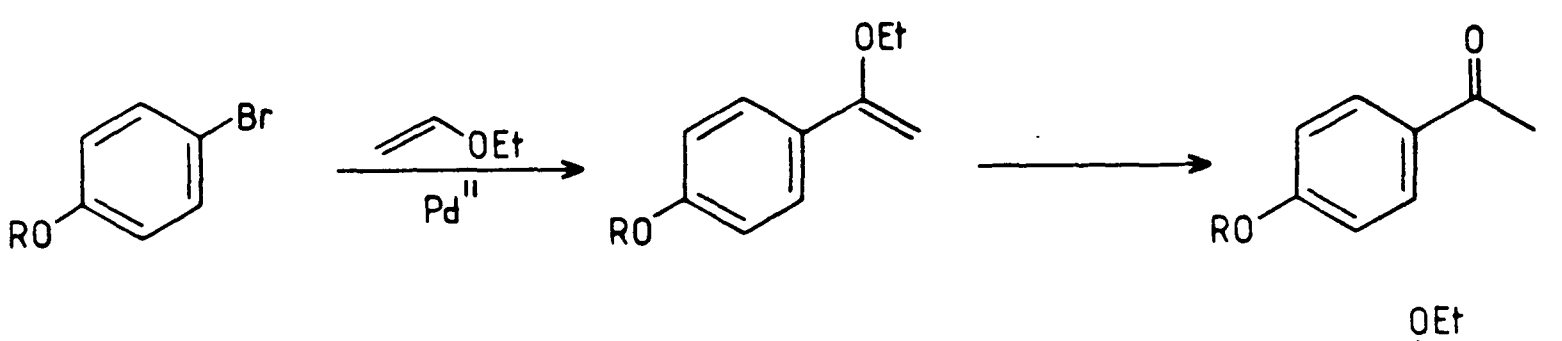
120 155 156

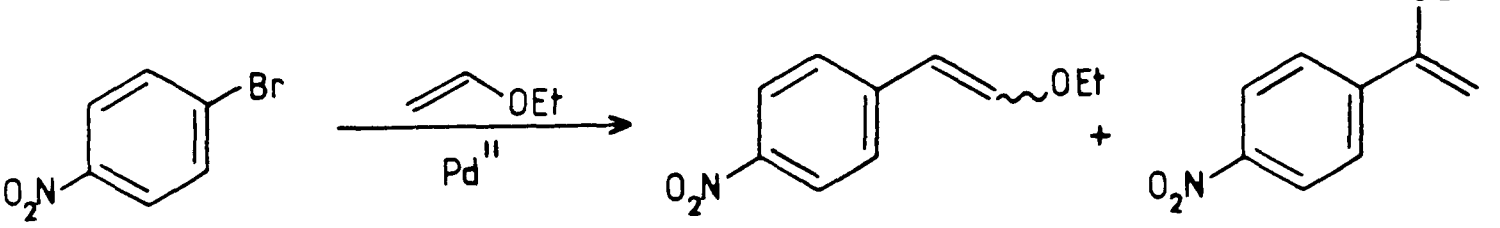
The palladium catalysed vinylation of aryl bromides with electron donating groups using ethyl vinyl ether thus leads to overall acetylation of the aryl halide. This reaction appears to be general and is therefore a viable route to regiospecifically acetylating an aromatic system. Standard Friedel-Crafts acetylations frequently require forcing conditions and can result in a mixture of isomeric products in addition to the problems of over-reaction. This method allows clean, regiospecific acetylation of any aromatic position and is currently under evaluation by Fisons Pharmaceuticals for the synthesis of intermediates required in the preparation of pharmacologically active compounds.

The orientation of addition of the aryl-palladium species to the olefin has been considered to be largely sterically controlled,although there is an electronic effect superimposed upon this which alters the regiochemistry of addition when the olefin contains electron donating substituents (*cf.* introduction).

For arenes containing electron donating substituents the results obtained suggest that their addition to ethyl vinyl ether is largely electronically controlled. Exclusive addition to C1, the more highly substituted end of the olefin, is observed. The electronic control arises from the polarisation of the arylpalladium bond, due to the electropositive metal. The addition to the olefin, although a concerted process, can formally be considered to involve an aryl anion and a palladium cation.

Electron donating groups on the arene will increase this polarisation by increasing the ring electron density. The polarisation of ethyl vinyl ether by mesomeric electron donation from the ethoxy group has the effect of increasing electron density at C2 of the olefin. This would account for the exclusive addition of the aryl group to the least electron rich olefin carbon (C1). With arenes containing electron withdrawing groups, the reduced polarisation of the arylpalladium bond reduces the effect of the electronic control and a mixture of C1 and C2 olefin addition is observed[70] due to the competing electronic and steric effects.





5. Experimental

All palladium (II) catalysed reactions were carried out in a glass Fischer-Porter pressure bottle (a small scale glass pressure apparatus) under a nitrogen atmosphere. Reactions involving the preparation or utilisation of palladium (0) or nickel (0) complexes were performed under an atmosphere of nitrogen using standard vacuum line and Schlenk tube techniques.[73]

Solvents

THF was distilled from sodium benzophenone ketyl under nitrogen. Dichloromethane was distilled from calcium hydride under nitrogen. DMF was heated (100°C) over calcium sulphate for 4 h and then distilled under reduced pressure (41°C, 0.1 mmHg) from a small quantity of fresh calcium sulphate. DMSO was heated (100°C) over calcium hydride for 6 h, then distilled under reduced pressure (80°C, 15 mmHg) from a fresh sample of calcium hydride.

Hexane refers to that fraction of light petroleum ether boiling between 67°C and 70°C. Other solvents were used as supplied.

All solvents were dried over $MgSO_4$ after extraction from aqueous solution and solvent removal or evaporation was carried out under reduced pressure.

Reagents

Zinc dust was activated by washing successively with portions of dilute aqueous hydrochloric acid, water, acetone and drying. *Tetrakis*(triphenylphosphine)palladium was prepared according to the

method of Coulson.[74] *Bis*(triphenylphosphine)palladium chloride was prepared by adding triphenylphosphine (2.4 equivalents) to a solution of palladium chloride in DMF at 140°C, cooling and collecting the resultant yellow precipitate.

Chromatography

T.l.c. was performed on aluminium sheets pre-coated with silica gel (Merck kieselgel 60 F_{254}). Column chromatography was performed on silica gel (Merck kieselgel 60 H).

Infrared spectra were recorded (as nujol mulls unless otherwise stated) on a Perkin-Elmer 297 instrument and were calibrated against polystyrene, 1601 cm^{-1}.

^{1}H N.m.r. spectra were obtained, in deuterochloroform unless otherwise stated, on a Brüker WH 300 (300 MHz) instrument. Those spectra at 60 MHz were obtained on a Hitachi-Perkin-Elmer R24B instrument and were referenced to internal tetramethylsilane. All chemical shifts are quoted as δ values.

^{13}C N.m.r. spectra were recorded on a Brüker AM 250 (62.89 MHz) instrument, in deuterochloroform. Quoted chemical shifts are from the broad-band decoupled spectrum, assignments are from the off-resonance spectrum.

Mass spectra were obtained by Dr. R.T. Aplin on V.G. Micromass VG ZAB IF instrument using electron impact techniques unless otherwise stated.

Melting points were recorded on a Kofler block and are uncorrected.

Elemental microanalyses were carried out by Dr. F.B. Strauss, the University of Manchester Microanalysis Service and by Fisons Pharmaceuticals plc.

6-Bromo-4-carboethoxycoumarin (91):
attempted preparation of 6-bromo-2-carboethoxychromone (87)[55]

A solution of *p*-bromophenol (89)(43.25 g, 0.25 mol), dimethylacetylene dicarboxylate (36 g, 0.25 mol) and benzyltrimethylammonium hydroxide (1 ml of a 40% solution in methanol) in ethanol (100 ml) was heated under reflux (15 min). Cooling failed to produce the expected precipitate,[55] so heating was continued (45 min). Subsequent cooling followed by solvent evaporation gave a viscous purple oil. This oil was dissolved in 50% aqueous ethanol (100 ml), sodium hydroxide (9 g, 0.23 mol) was added and the mixture heated under reflux (1 h). Solvent evaporation gave a viscous yellow oil which was dissolved in ethanol (270 ml), c.H_2SO_4 (45 ml) was added and the mixture heated under reflux (1 h). On cooling cream needles crystallised from the mixture, these were collected and dried to give 6-bromo-4-carboethoxycoumarin (91) (15.25 g, 21%). M.p. 122-5°C (Found: C, 48.8; H, 2.9. $C_{12}H_9BrO_4$ requires C, 48.5; H, 3.05%); $\nu_{max.}$ 3100 w (aryl-H), 1740 s (ester), 1720 s (lactone), and 1595 w cm^{-1} (olefin); ^1H n.m.r. δ8.49 (1H,d,J 2 Hz,H-5), 7.65, 7.24 (2H,ABX system, J_{AB} 8 Hz,J_{AX} 2 Hz,J_{BX} 0 Hz,H-7 and H-8), 7.00 (1H,s,H-3), 4.47 (2H,q, J 7 Hz,$C\underline{H}_2CH_3$), 1.45 (3H,t,J 7 Hz,$CH_2C\underline{H}_3$); irradiation of the Me δ_H 1.45 gave n.O.e's of 3.3% (CH_2), 0.8% (H-3), and 0.6% (H-5); *m/z* 296 (M^+,^{79}Br) and 298 (M^+,^{81}Br).

6-Bromo-2-carboethoxychromone (87)

p-Bromophenol (89) (8.65 g, 50 mmol) was added to a solution of dimethylacetylene dicarboxylate (7.2 g, 50 mmol) and tetra-*n*-butylammonium fluoride (1 crystal) in isopropanol (20 ml) and the mixture stirred (20°C, 19 h). Further dimethylacetylene dicarboxylate (0.72 g, 5 mmol)

was added when t.l.c. indicated incomplete reaction and the reaction mixture heated under reflux (100°C, 15 min). On cooling the 3-aryloxypropenoic ester (90) crystallised from the reaction mixture. This was collected and dried *in vacuo* (50°C, 15 mmHg) to give a mixture of dimethyl 4-bromophenoxy-maleate and fumarate (90) (11.06 g, 70%). ^{1}H n.m.r. (90 MHz) δ7.50 - 7.30 (2H,m,aryl-H), 6.95 - 6.70 (2H,m,aryl-H), 6.60 (1H,s,fumaric olefinic), 5.20 (1H,s,maleic olefinic), 3.70 (3H,s,OMe), 3.65 (3H,s,OMe).

The dimethyl esters (90) (10.88 g, 34 mmol) were dissolved in 50% aqueous ethanol (40 ml), sodium hydroxide (2.68 g, 67 mmol) was added and the reaction mixture heated under reflux (1 h). Acidification with c.HCl followed by solvent evaporation gave a yellow solid which was recrystallised from aqueous ethanol to give the diacid as a yellow powder (7.41 g, 75%). This was dissolved, with warming, in c.H_2SO_4 (15 ml) and the solution added dropwise to refluxing ethanol (100 ml). The resulting clear orange solution was then heated under reflux (for a further 30 min) during which crystallisation began. The reaction mixture was allowed to cool until crystallisation was complete. Collection of this product followed by recrystallisation from aqueous ethanol gave 6-bromo-2-carboethoxychromone (87) as fine white needles (6.20 g, 43% overall). M.p. 142-4°C (lit.,[56] 144-5°C); $\nu_{max.}$ 3060 w (aryl-H), 1735 s (ester), 1650 s (pyrone carbonyl), and 1610 m, 1600 m cm^{-1} (olefin); ^{1}H n.m.r. δ8.33 (1H,d,J 2 Hz,H-5), 7.83, 7.53 (2H,ABX system,J_{AB} 8 Hz,J_{AX} 2 Hz, J_{BX} 0 Hz,H-7 and H-8), 7.13 (1H,s,H-3), 4.48 (2H,q,J 7 Hz,$\underline{CH_2}CH_3$), 1.44 (3H,t,J 7 Hz,$CH_2\underline{CH_3}$) [lit.,[56] δ8.28 (1H,d,J 2.5 Hz,H-5), 7.85 (1H,dd, J 9 2.5 Hz,H-7), 7.52 (1H,d,J 9 Hz,H-8), 7.11 (1H,s,H-3)]; irradiation of the methyl δ_H 1.44 gave n.O.e's of 3.6% (CH_2) and 1.6% (H-3); *m/z* 296 (M^+,^{79}Br) and 298 (M^+,^{81}Br).

8-Bromo-2-carboethoxychromone (88)

o-Bromophenol (92) (15 g, 87 mmol) was reacted under analogous conditions to the synthesis of 6-bromo-2-carboethoxychromone (87) from *p*-bromophenol (89), to give the title compound (88) as fine white needles (14.4 g, 56% overall). M.p. 125-6°C (Found: C, 48.4; H, 3.1. $C_{12}H_9BrO_4$ requires C, 48.5; H, 3.05%); $\nu_{max.}$ 3090 w (aryl-H), 1735 s (ester), 1658 s (pyrone carbonyl), and 1620 m 1595 m cm^{-1} (olefin); ^1H n.m.r. δ8.12 (1H,dd,J 2,8 Hz,aryl-H), 7.95 (1H,dd,J 2,8 Hz,aryl-H), 7.32 (1H,t,J 8 Hz,H-6), 7.13 (1H,s,H-3), 4.47 (2H,q,J 7 Hz,$C\underline{H}_2CH_3$), 1.44 (3H,t,J 7 Hz,$CH_2C\underline{H}_3$); *m/z* 296 (M^+,^{79}Br) and 298 (M^+,^{81}Br).

General chromone vinylation procedure

The bromochromone (1.0 g, 3.4 mmol), triethylamine (0.53 ml, 3.8 mmol), the olefin and the catalyst were added to DMF (4 ml) in a Fischer-Porter bottle. The vessel was degassed by repeatedly pressurising and venting the apparatus. Finally, the vessel was placed under nitrogen pressure (3 atm) and the reaction mixture heated (120°C, 5 h). The warm reaction mixture was poured into aqueous sodium bicarbonate solution (35 ml) and the resulting precipitate collected and dried. Column chromatography (2% methanol - 98% dichloromethane) gave triarylphosphine followed by the vinylated chromone. Recrystallisation from dichloromethane-hexane, including treatment with decolourising charcoal, gave in each case analytically pure material.

E-Methyl 3-[6-(2-carboethoxychromone)]propenoate (93)

6-Bromo-2-carboethoxychromone (87) was heated with methyl acrylate

(0.35 ml, 3.9 mmol) and *bis*(triphenylphosphine)palladium chloride (47 mg; 2 mol %) to give the title compound (93) as a white crystalline powder (62 mg, 61%). M.p. 205-6°C (Found: C, 63.8; H, 4.7. $C_{16}H_{14}O_6$ requires C, 63.6; H, 4.7%); $\nu_{max.}$ 3060 w (aryl-H), 1735 s (ester), 1700 s (α,β-unsaturated ester), and 1660 br cm^{-1} (pyrone carbonyl); ^1H n.m.r. δ8.31 (1H,d,J 2 Hz,H-5), 7.88, 7.64 (2H,ABX system, J_{AB} 8 Hz, J_{AX} 2 Hz, J_{BX} 0 Hz,H-7 and H-8), 7.74 (1H,d,J 16 Hz, olefinic), 7.13 (1H,s,H-3), 6.53 (1H,d,J 16 Hz, olefinic), 4.48 (2H,q,J 7 Hz, $C\underline{H}_2CH_3$), 3.83 (3H,s,OMe), 1.45 (3H,t,J 7 Hz,$CH_2C\underline{H}_3$); *m/z* 302 (M^+).

3-[6-(2-Carboethoxychromone)]propenenitrile (94)

6-Bromo-2-carboethoxychromone (87) was heated with acrylonitrile (0.25 ml, 3.8 mmol) and *bis*(triphenylphosphine)palladium chloride (47 mg; 2 mol%) to give the title compound (94), an off-white powder, as a 3:1 mixture of *E*:*Z* isomers (505 mg, 55%). M.p. 190-200°C (Found: C, 67.0; H, 4.1; N, 5.1. $C_{15}H_{11}NO_4$ requires C, 67.0; H, 4.1; N, 5.2%); $\nu_{max.}$ 2215 w (nitrile), 1745 s (ester), and 1660 s cm^{-1} (pyrone carbonyl); ^1H n.m.r. (major *E*-isomer) δ8.27 (1H,d,J 2 Hz,H-5), 7.83, 7.69 (2H,ABX system, J_{AB} 8 Hz,J_{AX} 2 Hz,J_{BX} 0 Hz, H-7 and H-8), 7.48 (1H,d,J 16 Hz, olefinic), 7.15 (1H,s,H-3), 6.02 (1H,d,J 16 Hz, olefinic), 4.49 (2H,q,J 7 Hz,$C\underline{H}_2CH_3$), 1.46 (3H,t,J 7 Hz,$CH_2C\underline{H}_3$); (minor *Z*-isomer) δ8.51 (1H,dd,J 2 Hz, 8 Hz,H-7), 8.31 (1H,d,J 2 Hz,H-5), 7.72 (1H,d,J 11 Hz, olefinic), 7.23 (1H,s,H-3), 5.63 (1H,d,J 11 Hz, olefinic), ethyl ester and H-8 resonances identical to *E*-isomer; G.C. *m/z*: 12% 269 (M^+, *Z* isomer), and 88% 269 (M^+, *E* isomer).

E-Methyl 3-[8-(2-carboethoxychromone)]propenoate (99)

8-Bromo-2-carboethoxychromone (88) was heated with methyl acrylate

(0.35 ml, 3.9 mmol) and *bis*(triphenylphosphine)palladium chloride (47 mg; 2 mol%) to give a mixture of methyl 3-[8-(2-carboethoxy)chromone]propenoate (99) and unreacted 8-bromo-2-carboethoxychromone (88) by t.l.c. The use of palladium acetate (15 mg; 2 mol%) and tri-*o*-tolylphosphine (123 mg; 12 mol %) as the catalyst mixture gave 99 as white fluffy needles (770 mg, 76%). M.p. 157-8°C (Found: C, 63.8; H, 4.7. $C_{16}H_{14}O_6$ requires C, 63.6; H, 4.7%); $\nu_{max.}$ 3080 w (aryl-H), 1735 s (ester), 1720 s (α,β-unsaturated ester), and 1670 s cm^{-1} (pyrone carbonyl); ^1H n.m.r. δ8.22 (1H,dd,J 2 Hz, 8 Hz, aryl-H), 7.98 (1H,d,J 16 Hz, olefinic), 7.88 (1H,dd,J 2 Hz,8 Hz, aryl-H), 7.47 (1H,t,J 8 Hz,H-6), 7.16 (1H,s,H-3), 7.08 (1H,d,J 16 Hz, olefinic), 4.51 (2H,q,J 7 Hz,$C\underline{H}_2CH_3$), 3.86 (3H,s,OMe), 1.49 (3H,t,J 7 Hz,$CH_2C\underline{H}_3$); *m/z* 302 (M^+).

3-[8-(2-carboethoxychromone)]propenenitrile (100)

8-Bromo-2-carboethoxychromone (88) was heated with acrylonitrile (0.25 ml, 3.8 mmol), palladium acetate (15 mg; 2 mol %) and tri-*o*-tolylphosphine (123 mg; 12 mol %) to give the title compound (100), a white powder, as an 8:1 mixture of *E*:*Z* isomers (545 mg, 60%). M.p. 123-6°C (Found: C, 66.85; H, 4.4; N, 5.20. $C_{15}H_{11}NO_4$ requires C, 66.9; H, 4.1; N, 5.2 %); $\nu_{max.}$ 2215 w (nitrile), 1745 s (ester), and 1660 br cm^{-1} (pyrone carbonyl); ^1H n.m.r. (major *E*-isomer) δ8.24 (1H,dd,J 2 Hz,8 Hz, aryl-H), 7.81 (1H,dd,J 2 Hz,8 Hz, aryl-H), 7.64 (1H,d, J 16 Hz, olefinic), 7.50 (1H,t,J 8 Hz, H-6), 7.15 (1H,s,H-3), 6.66 (1H,d,J 16 Hz, olefinic), 4.51 (2H,q,J 7 Hz,$C\underline{H}_2CH_3$), 1.47 (3H,t,J 7 Hz,$CH_2C\underline{H}_3$); (minor *Z*-isomer) δ8.57 - 8.52 (1H,m,aryl-H), 8.29 - 8.21 (1H,m,aryl-H), 7.85 - 7.78 (1H,m), 7.58 - 7.50 (1H,m), 7.13 (1H,d,H-3), 5.76 (1H,d,J 11 Hz, olefinic), ester resonances identical; G.C. *m/z*: 11% 269 (M^+, *Z*-isomer) and 87% 269 (M^+, *E*-isomer).

E-6-(2-Carboethoxychromone)-β-styrene (101)

6-Bromo-2-carboethoxychromone (87) was heated with styrene (0.45 ml, 3.9 mmol), palladium acetate (15 mg; 2 mol %) and tri-*o*-tolylphosphine (82 mg; 8 mol %) to give the title compound (101) as fine pale yellow needles (720 mg, 67%). M.p. 194-5°C (Found: C, 75.1; H, 5.2. $C_{20}H_{16}O_4$ requires C, 75.0; H, 5.0%); $\nu_{max.}$ 1745 s (ester), 1650 s (pyrone carbonyl), and 1610 m cm^{-1} (conjugated olefin); ^1H n.m.r.δ8.24 (1H,d,J 2 Hz,H-5), 7.89, 7.62 (2H,ABX system,J_{AB} 8 Hz,J_{AX} 2 Hz,J_{BX} 0 Hz,H-7 and H-8), 7.51 (2H,d,J 7 Hz, aryl protons), 7.40 - 7.28 (3H,m, phenyl protons), 7.19, 7.13 (2H,AB system, J_{AB} 16 Hz, olefinic), 7.11 (1H,s,H-3), 4.45 (2H,q, J 7 Hz,$C\underline{H}_2CH_3$), 1.43 (3H,t,J 7 Hz,$CH_2C\underline{H}_3$); ^{13}C-{^1H} n.m.r. δ178.2 (C), 160.4 (C), 155.2 (C), 152.0 (C), 136.5 (C), 135.4 (C), 132.5 (CH), 130.8 (CH), 128.7 (CH), 128.1 (CH), 126.6 (CH), 126.3 (CH), 124.5 (C), 122.8 (CH), 119.1 (CH), 114.6 (CH), 62.9 (CH_2), 14.1 (CH_3); *m/z* 320 (M^+).

E-8-(2-carboethoxychromone)-β-styrene (102)

8-Bromo-2-carboethoxychromone (88) was heated with styrene (0.5 ml, 4.4 mmol), palladium acetate (15 mg; 2 mol %) and tri-*o*-tolylphosphine (123 mg; 12 mol %) to give the title compound (102) as pale yellow needles (705 mg, 65%). m.p. 141-2°C (Found: C, 75.2; H, 5.1. $C_{20}H_{16}O_4$ requires C, 75.0; H, 5.0%); $\nu_{max.}$ 3080 w (aryl-H), 1730 s (ester), 1660 s (pyrone carbonyl), and 1590 m 1580 m cm^{-1} (conjugated olefin); ^1H n.m.r. δ8.07 (1H,d,J 2 Hz, aryl-H), 7.94 (1H,dd,J 8 Hz,2 Hz, aryl-H), 7.57, 7.47 (2H,AB system, J_{AB} 16 Hz, olefinic), 7.60 - 7.55 (2H,m, phenyl protons), 7.45 - 7.29 (4H,m, phenyl protons & H-6), 7.13 (1H,s, H-3), 4.48 (2H,q,J 7 Hz, $C\underline{H}_2CH_3$), 1.47 (3H,t,J 7 Hz,$CH_2C\underline{H}_3$); ^{13}C-{^1H} n.m.r. δ178.2 (C), 160.3 (C), 152.9 (C), 151.8 (C), 136.9 (C), 132.8 (CH), 131.5 (CH), 128.7 (CH), 128.2 (CH),

127.9 (C), 126.7 (CH), 125.5 (CH), 124.7 (C), 124.3 (CH), 120.6 (CH), 114.3 (CH), 62.8 (CH_2), 14.0 (CH_3); *m/z* 320 (M^+).

Ethyl 3-[6-(2-carboethoxychromone)]propionate (103)

6-Bromo-2-carboethoxychromone (87) was heated with acrolein diethyl acetal (0.58 ml, 3.8 mmol), palladium acetate (15 mg; 2 mol %) and tri-*o*-tolylphosphine (123 mg; 12 mol %) to give initially a dark red oil. Extraction with dichloromethane (3x30 ml) followed by solvent evaporation gave a dark residue. This was purified according to the general procedure to give the title compound (103) as white fluffy needles (500 mg, 47%). M.p. 81-2°C (Found: C, 64.4; H, 5.7. $C_{17}H_{18}O_6$ requires C, 64.1; H, 5.7%); $\nu_{max.}$ 3060 w (aryl-H), 1725 s (ester), 1665 s (pyrone carbonyl), and 1625 m 1613m cm^{-1} (olefin); ^1H n.m.r. δ8.02 (1H,d,J 2 Hz, H-5), 7.61, 7.55 (2H,ABX system, J_{AB} 8 Hz,J_{AX} 2 Hz, J_{BX} 0 Hz, H-7 and H-8), 7.10 (1H,s, H-3), 4.47 (2H,q,J 7 Hz,$C\underline{H}_2CH_3$), 4.13 (2H,q,J 7 Hz,$C\underline{H}_2CH_3$), 3.07 (2H,t,J 6 Hz,CH_2), 2.69 (2H,t,J 6 Hz,CH_2), 1.44 (3H,t,J 7 Hz,$CH_2C\underline{H}_3$), 1.24 (3H,t,J 7 Hz,$CH_2C\underline{H}_3$); *m/z* 318 (M^+).

Ethyl 3-[8-(2-carboethoxychromone)]propionate (106)

8-Bromo-2-carboethoxychromone (88) was heated with acrolein diethyl acetal (0.60 ml, 3.9 mmol), palladium acetate (15 mg; 2 mol %) and tri-*o*-tolylphosphine (123 mg; 12 mol %) to give, after an analogous work-up to (103), the title compound (106) as cream rods (420 mg, 39%). M.p. 67-8°C (Found: C, 64.0; H, 5.45. $C_{17}H_{18}O_6$ requires C, 64.1; H, 5.7%); $\nu_{max.}$ 3060 w (aryl-H), 1743 s, 1725 s (ester), 1650 (pyrone carbonyl), and 1610 m 1600 m 1585 m cm^{-1} (olefin); ^1H n.m.r. δ8.05 (1H,dd,J 2 Hz,8 Hz,aryl-H),

7.62 (1H,dd,J 8 Hz,2 Hz,aryl-H), 7.36 (1H,t,J 8 Hz,H-6), 7.10 (1H,s,H-3), 4.46 (2H,q,J 7 Hz,CH_2CH_3), 4.11 (2H,q,J 7 Hz,CH_2CH_3), 3.26 (2H,t,J 6 Hz,CH_2), 2.81 (2H,t,J 6 Hz,CH_2), 1.44 (3H,t,J 7 Hz,CH_2CH_3), 1.21 (3H,t,J 7 Hz,CH_2CH_3); *m/z* 318 (M^+).

Attempted vinylation of 6-bromo-2-carboethoxychromone (87) with allyl chloride

Heating 6-bromo-2-carboethoxychromone (87) with allyl chloride (0.32 ml, 3.9 mmol), palladium acetate (15 mg; 2 mol %) and tri-*o*-tolylphosphine (123 mg; 12 mol %) led only to the recovery of the chromone (87) identified by comparison with an authentic sample.

Attempted vinylation of 6-bromo-2-carboethoxychromone (87) with vinyl acetate or allyl alcohol

Heating 6-bromo-2-carboethoxychromone (87) with palladium acetate (15 mg; 2 mol %), tri-*o*-tolylphosphine (123 mg; 12 mol %) and either vinyl acetate (0.35 ml, 3.8 mmol) or allyl alcohol (0.28 ml, 4.1 mmol) led in each case to complex product mixtures whose components could not be separated by column chromatography.

E-Ethyl 3-[6-(2-carboethoxychromone)]-2-butenoate (107A)

6-Bromo-2-carboethoxychromone (87) was heated with ethyl crotonate (0.50 ml, 4.0 mmol), palladium acetate (15 mg; 2 mol %) and tri-*o*-tolylphosphine (123 mg; 12 mol %) to give the title compound (107A) as white needles (340 mg, 31%). M.p. 124-5°C (Found: C, 65.6; H, 5.6. $C_{18}H_{18}O_6$ requires C, 65.45; H, 5.5%); $\nu_{max.}$ 3055 m (aryl-H), 1738 s 1720 s (ester), 1665 s (pyrone carbonyl), and 1630 m 1610 m cm^{-1} (olefin); ^1H n.m.r. δ

8.27 (1H,d,J 2 Hz,H-5), 7.84, 7.60 (2H,ABX system,J_{AB} 8 Hz,J_{AX} 2 Hz,J_{BX} 0 Hz, H-7 and H-8), 7.11 (1H,s,H-3), 6.20 (1H,d,J 1.5 Hz,vinyl), 4.45 (2H,q,J 7 Hz, $C\underline{H}_2CH_3$), 4.21 (2H,q,J 7 Hz,$C\underline{H}_2CH_3$), 2.60 (3H,d,J 1.5 Hz,Me), 1.42 (3H,t,J 7 Hz,$CH_2C\underline{H}_3$), 1.30 (3H,t,J 7 Hz,$CH_2C\underline{H}_3$); irradiation of the vinyl proton δ_H 6.20 gave n.O.e's of 9% (H-7), and 8.8% (H-5); irradiation of the methyl doublet δ_H 2.60 gave n.O.e's of 6% (H-7), and 15% (H-5); *m/z* 330 (M^+).

E-Methyl 3-[6-(2-carboethoxychromone)]-2-methylpropenoate (108)

6-Bromo-2-carboethoxychromone (87) was heated with methyl methacrylate (0.41 ml, 3.8 mmol), palladium acetate (15 mg; 2 mol %) and tri-*o*-tolylphosphine (123 mg; 12 mol %) to give the title compound (108) as white needles (305 mg, 29%). M.p. 139-40°C (Found: C, 64.3; H, 5.1. $C_{17}H_{16}O_6$ requires C, 64.55; H, 5.1%); $\nu_{max.}$ 3060 m (aryl-H), 1740 s (ester), 1710 s (α,β-unsaturated ester), 1665 s (pyrone carbonyl), and 1610 m cm^{-1} (olefin); ^1H n.m.r. δ8.22 (1H,d,J 2 Hz,H-5), 7.73 (1H,s,olefinic), 7.75, 7.65 (2H,ABX system,J_{AB} 8 Hz,J_{AX} 2 Hz,J_{BX} 0 Hz, H-7 and H-8), 7.15 (1H,s,H-3), 4.48 (2H,q,J 7 Hz,$C\underline{H}_2CH_3$), 3.85 (3H,s,OMe), 2.18 (3H,s,Me), 1.46 (3H,t,J 7 Hz, $CH_2C\underline{H}_3$); irradiation of the methyl δ_H 2.18 gave n.O.e's of 3.4% (H-7), and 7.1% (H-5); irradiation of vinyl proton δ_H 7.73 gave n.O.e's of 5.4% (H-5) 0.3% (OMe), and 0.9% (Me); *m/z* 316 (M^+).

Attempted vinylation of 8-bromo-2-carboethoxychromone (88) with ethyl crotonate and methyl methacrylate

Heating 8-bromo-2-carboethoxychromone (88) with palladium acetate (15 mg; 2 mol %), tri-*o*-tolylphosphine (123 mg; 12 mol %) and either ethyl crotonate (0.50 ml, 4 mmol) or methyl methacrylate (0.41 ml, 3.8 mmol)

led in each case only to the recovery of the bromochromone (88) identified by comparison with an authentic sample.

Attempted vinylation of 6-bromo-2-carboethoxychromone (87) with methylene diethyl malonate and dimethyl maleate

6-Bromo-2-carboethoxychromone (87) was heated with palladium acetate (15 mg; 2 mol %), tri-*o*-tolylphosphine (123 mg; 12 mol %) and either dimethyl maleate (0.48 ml, 3.8 mmol) or methylene diethyl malonate (0.65 g, 3.8 mmol) - prepared from diethyl malonate and paraformaldehyde.[75] In each case only unreacted starting material was recovered.

Diethyl-2,6-chromone dicarboxylate (111)

6-Bromo-2-carboethoxychromone (87) (0.5 g, 1.7 mmol) was added to a solution of palladium acetate (8 mg; 2 mol %), triphenylphosphine (18 mg; 4 mol %) and diisopropylethylamine (0.35 ml, 2 mmol) in ethanol (10 ml) in a small scale glass pressure apparatus. The vessel was degassed with carbon monoxide, by alternately pressurising and venting, placed under carbon monoxide pressure (3 atm.) and the reaction mixture heated with stirring (105°C, 24 h). The cool reaction mixture was poured into diethyl ether (200 ml) and filtered to remove the precipitated amine salt. Evaporation of the solvent gave a white powder which was recrystallised from ethyl acetate-hexane to give diethyl 2,6-chromone dicarboxylate (111) as white needles (410 mg, 84 %). M.p. 134-5°C (lit.,[62] 126-7°C); $\nu_{max.}$ 3060 m (aryl-H), 1740 s 1720 s (ester), 1655 s (pyrone carbonyl), and 1610 s cm^{-1} (olefin); ^1H n.m.r. δ8.86 (1H,d,J 2 Hz,H-5), 8.39 (1H,dd,J 2,8 Hz,H-7), 7.67 (1H,d,J 8 Hz,H-8), 7.14 (1H,s,H-3), 4.48 (2H,d,J 7 Hz,CH_2CH_3), 4.42 (2H,q, J 7 Hz,CH_2CH_3), 1.47 (3H,t,J 7 Hz,CH_2CH_3), 1.43 (3H,t,J 7 Hz,CH_2CH_3); *m/z* (IBEI) 290 (M^+).

Dibutyl-2,6-chromone dicarboxylate (112)

6-Bromo-2-carboethoxychromone (87) (0.5 g, 1.7 mmol) was heated under carbon monoxide pressure in *n*-butanol (10 ml) under identical conditions to the synthesis of the diethyl ester (111). An analogous work-up gave the title compound (112) as white needles (365 mg, 63 %). M.p. 99-100°C; ν_{max} 3060 w (aryl-H), 1740 s (ester), 1720 s (ester), 1650 s (pyrone carbonyl), 1615 m cm^{-1} (olefin); ^1H n.m.r. δ8.86 (1H,d,J 2Hz,H-5), 8.39 (1H,dd,J 2,8 Hz, H-7), 7.66 (1H,d,J 8 Hz,H-8), 7.14 (1H,s,H-3), 4.42 (2H,q,J 7 Hz,$OC\underline{H}_2$), 4.38 (2H,q,J 7 Hz,$OC\underline{H}_2$), 1.79 (4H,qu,J 7 Hz,$2xCH_2C\underline{H}_2CH_2CH_3$), 1.49 (4H,sx,J 7 Hz, $2xCH_2CH_2C\underline{H}_2CH_3$), 1.00 (6H,t,J 7 Hz,$2xCH_3$); *m/z* 346 ($M^+$).

Attempted coupling of 6-bromo-2-carboethoxychromone (87) with acetylenes.[54,63]

6-Bromo-2-carboethoxychromone (87) (1.0 g, 3.4 mmol) was added to a mixture of the acetylene, the catalyst, and triethylamine (0.60 ml, 4.3 mmol) in DMF (4 ml) in a Fischer-Porter bottle. The vessel was degassed by repeatedly pressurising and venting the apparatus, placed under nitrogen pressure and the mixture heated under a variety of conditions (see Table 1). The warm reaction mixture was poured into water (40 ml) to give a dark oil which was extracted with dichloromethane (3 x 30 ml). The organic fractions were combined, dried and the solvent evaporated. T.l.c. showed the presence of starting material (87) together with a number of products which were inseparable by column chromatography.

Table 1: acetylene coupling conditions

acetylene (mmol)	catalyst (mol %)	conditions °C	h	atm
$HC{\equiv}CCH_2OH$ (4.3) 114	$Pd(PPh_3)_2Cl_2$/CuI (2) (1)	50	28	1
		90	4	1
		125	3	5
	$Pd(OAc)_2$/P(*o*-tolyl)$_3$ (2) (12)	100	3	5
$HC{\equiv}CCO_2Et$ (4.0) 115	$Pd(OAc)_2$/P(*o*-tolyl)$_3$ (2) (12)	120	3½	5
$HC{\equiv}CSiMe_3$ (3.8) 116	$Pd(OAc)_2$/P(*o*-tolyl)$_3$ (2) (12)	90	3	5

Attempted coupling of the Reformatsky reagent (117) with 6-bromo-2-carboethoxychromone (87) using palladium acetate

Ethyl bromoacetate (0.45 ml, 4 mmol) was added to a suspension of activated zinc dust (250 mg, 3.8 mmol) in THF (10 ml) and the mixture heated (60°C, 30 min) until the metal dissolved to give a solution of the Reformatsky reagent (117). This solution was added to a mixture of palladium acetate (15 mg; 2 mol %), tri-*o*-tolylphosphine (123 mg; 12 mol %) and 6-bromo-2-carboethoxychromone (87) (1.0 g, 3.4 mmol) in a Fischer-Porter bottle. The vessel was degassed by repeatedly pressurising and venting the apparatus, placed under nitrogen pressure (5 atm) and the reaction mixture heated (120°C, 18 h). The warm reaction mixture was poured into water (40 ml)

and extracted with dichloromethane (3 x 30 ml). The combined organic fractions were dried and the solvent evaporated to give a mixture of tri-*o*-tolylphosphine and the starting material (87) identified by comparison with authentic samples.

Attempted coupling of the Reformatsky reagent (117) with 6-bromo-2-carboethoxychromone (87) using $Pd(PPh_3)_4$.[52]

Ethyl bromoacetate (0.45 ml, 4 mmol) was added to a suspension of activated zinc dust (240 mg, 3.7 mmol) in THF (10 ml) and the mixture heated (60°C, 30 min) until the metal dissolved to give a solution of the Reformatsky reagent (117). This solution was added to a mixture of *tetrakis*(triphenylphosphine)palladium (80 mg; 2 mol %), triethylamine (0.60 ml, 4.3 mmol) and 6-bromo-2-carboethoxychromone (87) (1.0 g, 3.4 mmol) under a nitrogen atmosphere and the reaction mixture heated (80°C, 43 h). T.l.c. showed the reaction mixture to contain only starting material (87) and no coupled product.

Attempted Ni(0) coupling of the Reformatsky reagent (117) with 6-bromo-2-carboethoxychromone (87)

Activated zinc dust (240 mg, 3.7 mmol) was added to a solution of ethyl bromoacetate (0.39 ml, 3.5 mmol) in DMF (8 ml) and the mixture heated, with stirring (60°C, 30 min) to give a solution of the Reformatsky reagent (117). Nickel (II) chloride (0.83 g, 3.5 mmol), and triphenylphosphine (3.67 g, 14 mmol) were added to a suspension of activated zinc dust (110 mg, 1.7 mmol) in DMF (18 ml), the mixture degassed with nitrogen and stirred with heating (50°C; 1 h) to give a red-brown slurry. 6-Bromo-2-carboethoxychromone (87) (1.0 g, 3.4 mmol) and the solution of the Reformatsky

reagent (117) were added to this slurry and heating continued (50°C; 2 h). The green reaction mixture was poured into aqueous ammonia solution (150 ml), extracted with dichloromethane (3 x 100 ml) and the combined organic fractions dried. Solvent evaporation gave a residue which was chromatographed (2% methanol in dichloromethane) to give triphenylphosphine and *bis*-6,6'-(2-carboethoxychromone) (118) as a white powder (100 mg, 14 %). M.p. 279-80°C (Found: C, 66.1; H, 4.2. $C_{24}H_{18}O_8$ requires C, 66.4; H, 4.2 %); $\nu_{max.}$ 3060 m (aryl-H), 1740 s (ester), 1660 s (pyrone carbonyl), and 1615 m cm^{-1} (olefin); ^1H n.m.r. δ8.46 (2H,d,J 2 Hz,H-5,5'), 8.07, 7.74 (4H,ABX system, J_{AB} 8 Hz,J_{AX} 2 Hz,J_{BX} 0 Hz,H-7,7' and H-8,8'), 7.16 (2H,s,H-3,3'), 4.48 4H,q,J 7 Hz,CH_2,CH_2'), 1.45 (6H,t,J 7 Hz,CH_3,CH_3'); *m/z* (I.B.E.I.) 434 (M^+).

Bis-6,6'-(2-carboethoxychromone) (118), using stoicheiometric Ni(0)[65]

To a suspension of activated zinc dust (110 mg, 1.7 mmol) in DMF (20 ml) were added nickel (II) chloride (0.83 g, 3.5 mmol) and triphenylphosphine (3.67 g, 14 mmol). The reaction mixture was degassed and heated with stirring under a nitrogen atmosphere (50°C; 1 h), to give a red-brown slurry. 6-Bromo-2-carboethoxychromone (87) (1.0 g, 1.7 mmol) was added and heating continued (3 h). The green reaction mixture was poured into aqueous ammonia solution (150 ml), extracted with dichloromethane and the combined organic extracts dried. Evaporation of the solvent followed by column chromatography (2% methanol - 98% dichloromethane) gave triphenylphosphine, followed by *bis*-6,6'-(2-carboethoxychromone) (118) (360 mg, 49%), identified by comparison with an authentic sample.

Bis -6,6'-(2-carboethoxychromone) (118); using Ni(0) catalytically[67]

To a suspension of activated zinc dust (120 mg, 1.8 mmol) in DMF (15 ml) were added nickel (II) chloride (42 mg; 5 mol %) and triphenylphosphine (365 mg; 40 mol %). The reaction mixture was degassed and heated under nitrogen (50°C; 10 min). 6-Bromo-2-carboethoxychromone (87) (1.0 g, 3.4 mmol) was added to this blood red solution and heating continued (50°C; 20 h). The mixture was poured into water (100 ml), extracted with dichloromethane (3 x 60 ml) and the combined organic fractions dried. Solvent evaporation gave a residue which was shown by t.l.c. to contain triphenylphosphine, unreacted starting material (87), the dimer (118) and a number of impurities. Column chromatography (2% methanol - 98% dichloromethane) gave an impure mixture of the dimer 118 (340 mg). Attempts at further purification were unsuccessful.

3-Bromochromone[68] (120)

o-Hydroxyacetophenone (4.0 g, 29 mmol) was added to DMF-dimethylacetal (5.25 g, 44 mmol) and the mixture heated (90°C; 2 h). Cooling followed by evaporation gave a light brown residue which was chromatographed (ethyl acetate) to give the vinylogous amide 121 as a bright yellow solid (4.38 g, 78%).

To an ice cold solution of 121 (2.3 g, 12 mmol) in chloroform (20 ml) was added dropwise a solution of bromine (1.92 g, 12 mmol) in chloroform (10 ml), and the mixture stirred (5 min). The reaction mixture was warmed, the solvent evaporated and the residue chromatographed (5% ethyl acetate in chloroform) to give a cream solid. This was recrystallised from dichloromethane-hexane to give 3-bromochromone 120 as cream needles (2.04 g, 59% overall; lit.,[68] 78%). M.p. 95 - 9°C (lit.,[68] 93-4°C); $\nu_{max.}$ 3060 m (aryl-H), 1648 s

(pyrone carbonyl), 1610 s, 1600 s,1560 m cm^{-1} (olefin) [lit.,[68] 3060 (C-H), 1665 (C=O), 1615 1600 1560 (C=C), 1370 and 1075 cm^{-1} (C-O)]; ^{1}H n.m.r. δ8.26 (1H,dd,J 2,8 Hz,H-5), 8.24 (1H,s,H-2), 7.74 - 7.69 (1H,m,aryl-H), 7.50 - 7.43 (2H,m,aryl-H) [lit.,[68] δ8.25 (1H,s,H-2), 8.30 - 8.10 (1H,m), 7.90 - 7.25 (3H,m)]; *m/z* 224 (M^{+}, ^{79}Br) and 226 (M^{+}, ^{81}Br).

E-Methyl 3-(3-chromone)propenoate (122)

3-Bromochromone (120) (500 mg, 2.2 mmol) was added to a mixture of methyl acrylate (0.30 ml, 3.3 mmol), triethylamine (0.45 ml, 3.2 mmol), palladium acetate (10 mg; 2 mol %) and triphenylphosphine (23 mg; 4 mol %) in DMF (2 ml) in a small scale glass pressure apparatus. The reaction mixture was degassed as with the general chromone vinylations and heated (120°C; 6 h). An analogous work-up gave *E*-methyl 3-(3-chromone)propenoate (122) as white needles (300 mg, 59%). M.p. 139-40°C (Found: C, 67.6; H, 4.3. $C_{13}H_{10}O_4$ requires C, 67.8; H, 4.4%); $\nu_{max.}$ 3060 w (aryl-H), 1725 s (α,β-unsaturated ester), 1660 s (pyrone carbonyl), and 1612 s 1560 m cm^{-1} (olefin); ^{1}H n.m.r. δ8.24 (1H,dd,J 2,8 Hz,H-5), 8.16 (1H,s,H-2), 7.74 - 7.61 (1H,m,aryl-H), 7.52 - 7.43 (2H,m,aryl-H), 7.40, 7.26 (2H,AB system,J_{AB} 16 Hz, olefinic), 3.78 (3H,s,OMe); $^{13}C\{^{1}H\}$ δ175.6 (C), 167.6 (C), 157.3 (CH), 155.3 (C), 135.5 (CH), 133.9 (CH), 126.1 (CH), 125.7 (CH), 124.0 (C), 121.6 (CH), 119.1 (CH), 118.0 (CH), 51.5 (CH_3); *m/z* 230 (M^{+}).

E-3-Chromone-β-styrene (123)

3-Bromochromone (120) (500 mg, 2.2 mmol) was added to a mixture of styrene (0.30 ml, 2.6 mmol), palladium acetate (10 mg; 2 mol %),

tri-*o*-tolylphosphine (81 mg; 12 mol %) and triethylamine (0.40 ml, 2.9 mmol) in DMF (3 ml) in a Fischer-Porter bottle. The mixture was degassed as for the general chromone vinylation procedure and heated (100°C; 5½ h). An analogous work-up gave recovered starting material (120) (50 mg, 10 %) followed by *E*-3-chromone-β-styrene (123) as white needles (370 mg, 75 % based on recovered starting material). M.p. 170-1°C (Found: C, 82.3; H, 4.8. $C_{17}H_{12}O_2$ requires C, 82.2; H, 4.9%); $\nu_{max.}$ 1640 s (pyrone carbonyl), and 1620 s 1610 s cm^{-1} (olefin); ^1H n.m.r. δ8.27 (1H,dd,J 2,8 Hz,H-5), 8.07 (1H,s,H-2), 7.67 - 7.60 (1H,m), 7.58 (1H,d,J 16 Hz,olefinic), 7.49 - 7.18 (7H,m), 6.94 (1H,d,J 16 Hz,olefinic); *m/z* 248 (M^+).

3,6-Dibromochromone (124)

p-Bromophenol (89) (10.0 g, 58 mmol) was added to a mixture of acetic anhydride (25 ml, 265 mmol) and pyridine (22 ml, 272 mmol) and the mixture heated (100°C; 2 h). The cool reaction mixture was poured into water (150 ml), acidified with dilute aqueous acid and extracted with diethyl ether (3 x 100 ml). The combined organic fractions were washed with saturated aqueous sodium bicarbonate solution (3 x 50 ml), dried and the solvent evaporated to give *o*-acetyl-*p*-bromophenol as a colourless oil (12.07 g, 97%). $\nu_{max.}$ 1770 s (ester) and 1590 w cm^{-1} (olefin); ^1H n.m.r. (60 MHz) δ7.65 - 7.40 (2H,m,aryl-H), 7.15 - 6.90 (2H,m,aryl-H), 2.25 (3H,s,$COCH_3$).

o-Acetyl-*p*-bromophenol (12.07 g, 56 mmol) was added to aluminium trichloride (11.25 g, 84 mmol) and the mixture heated (150°C; 3 h). Water (150 ml) was added slowly to the cool reaction mixture and the resulting solution extracted with diethyl ether (3 x 100 ml). The combined organic fractions were dried and the solvent evaporated to give an orange oil.

Distillation under reduced pressure gave a pale yellow solid which was recrystallised from aqueous ethanol to give 5-bromo-2-hydroxyacetophenone (124A) (7.50 g, 62%). $\nu_{max.}$ 1645 s cm^{-1} (carbonyl); ^1H n.m.r. (60 MHz) 7.80 (1H,d,J 2 Hz,H-6), 7.70 - 7.35 (1H,m,aryl-H), 6.95 - 6.75 (1H,m,aryl-H), 2.55 (3H,s,COMe).

5-Bromo-2-hydroxyacetophenone (124A)(1.0 g, 4.7 mmol) was added to DMF-dimethyl acetal (0.83 g, 7.0 mmol) and the mixture heated (100°C; 2 h). Cooling followed by evaporation gave a red-orange solid which was chromatographed (10% hexane in ethyl acetate) to give a yellow solid (1.0 g). This solid was dissolved in chloroform (10 ml), cooled (0°C) and a solution of bromine (0.60 g, 3.8 mmol) in chloroform (10 ml) added dropwise. The mixture was stirred (5 min), warmed to room temperature and the solvent evaporated. Chromatography (5% ethyl acetate in chloroform) gave 3,6-dibromochromone (124) as a pale yellow powder (860 mg, 36% overall). M.p. 137-8°C; $\nu_{max.}$ 1655 s (pyrone carbonyl) and 1600 m 1550 m cm^{-1} (olefin); ^1H n.m.r. (60 MHz) δ8.35 (1H,d,J 2 Hz,H-5), 8.20 (1H,s,H-2), 7.80, 7.35 (2H,ABX system, J_{AB} 9 Hz,J_{AX} 2 Hz,J_{BX} 0 Hz,H-7 and H-8); *m/z* (I.B.E.I.) 302 (M^+, $^{79}Br^{79}Br$ 50%), 304 (M^+, $^{79}Br^{81}Br$,100%) and 306 (M^+, $^{81}Br^{81}Br$ 50%).

Coupling of 3,6-dibromochromone (124) with methyl acrylate

3,6-Dibromochromone (124) (1.0 g, 3.3 mmol) was added to a mixture of methyl acrylate (0.68 ml, 7.5 mmol), triethylamine (1.06 ml, 7.6 mmol), palladium acetate (30 mg; 4 mol %) and tri-*o*-tolylphosphine (248 mg; 24 mol %) in DMF (4 ml) in a Fischer-Porter bottle. The vessel was degassed as with the general chromone vinylations and heated (120°C; 2½ h). After an analogous work-up two products were isolated; *E*,*E*-dimethyl 3,6-chromone dipropenoate (125) as a white powder (420 mg, 41%) and methyl 3-(3-carbomethoxybenzoyl)-4-hydroxycinnamate (126) as a pale yellow powder (85 mg, 8%).

(125): m.p. 210-15°C (Found: C, 64.65; H, 4.4. $C_{17}H_{14}O_6$ requires C, 65.0; H, 4.5 %); $\nu_{max.}$ 1725 s (α,β-unsaturated ester), 1655 s (pyrone carbonyl), and 1610 m 1560 w cm^{-1} (olefin); ^1H n.m.r. δ8.41 (1H,d,J 2 Hz,H-5), 8.13 (1H,s,H-2), 7.85, 7.51 (2H,ABX system,J_{AB} 8 Hz,J_{AX} 2 Hz,J_{BX} 0 Hz, H-7 and H-8), 7.77 (1H,d,J 16 Hz,olefinic), 7.41, 7.31 (2H,AB system,J_{AB} 16 Hz, olefinic), 6.55 (1H,d,J 16 Hz,olefinic), 3.85 (3H,s,OMe), 3.82 (3H,s,OMe); *m/z* 314 (M^+).

(126): m.p. 125-6°C; $\nu_{max.}$ 1735 s (ester), 1625 s (diaryl ketone), and 1580 w cm^{-1} (olefin); ^1H n.m.r. δ12.16 (1H,s,OH), 8.38 - 8.31 (2H,m) 7.93 - 7.87 (1H,m), 7.82 - 7.79 (1H,m), 7.71 - 7.65 (2H,m), 7.58 (1H,d,J 16 Hz, olefinic), 7.15 (1H,d,J 8 Hz), 6.26 (1H,d,J 16 Hz,olefinic), 4.00 (3H,s,OMe), 3.81 (3H,s,OMe); d^6-acetone (aromatic region) δ8.37 (1H,t,J 1.5 Hz,H-2'), 8.30 (1H,dt,J_d 8 Hz,J_t 1.5 Hz,H-6' or 4') 8.06 (1H,dt,J_d 8 Hz,J_t 1.5 Hz,H-4' or 6'), 8.01 (1H,dd,J 2,8 Hz,H-6), 7.91 (1H,d,J 2 Hz,H-2), 7.76 (1H,t,J 8 Hz, H-5'), 7.62 (1H,d,J 16 Hz,olefinic), 7.15 (1H,d,J 8 Hz,H-5); $^{13}C\{^1H\}$ n.m.r. δ200.2 (C), 167.2 (C), 165.9 (C), 164.9 (C), 143.2 (CH), 137.6 (C), 134.9 (CH), 133.8 (CH), 133.1 (CH), 133.0 (CH), 130.9 (C), 130.0 (CH), 128.8 (CH), 125.6 (C), 119.5 (CH), 118.8 (C), 116.6 (CH), 52.5 (CH_3), 51.7 (CH_3); *m/z* 340 (M^+) and 205 (M^+-$C_6H_4CO_2Me$), high resolution *m/z* **340·0946** $C_{19}H_{16}O_6$ requires **340·0947**.

General procedure for the acetylation of aryl halides with ethyl vinyl ether

To a mixture of palladium acetate (2 mol %), tri-*o*-tolylphosphine (8 mol %), triethylamine (1 ml, 7 mmol) and the aryl halide (1.0 g, ~5 mmol) in DMF (1 ml/mmol aryl halide) in a Fischer-Porter bottle was added ethyl vinyl ether (2 ml, 21 mmol). The reaction mixture was frozen, the vessel evacuated,filled with nitrogen and allowed to warm to room temperature.

Excess pressure was vented and the cycle was repeated twice, following which the mixture was heated (90°C; 3 h). The warm reaction mixture was poured onto water (45 ml) and extracted with diethyl ether (3 x 30 ml). The combined ether layers were washed with saturated brine solution (2 x 20 ml), dried and the solvent evaporated to give a dark residue. Column chromatography (diethyl ether-hexane) gave tri-*o*-tolylphosphine followed by the substituted acetophenone (table 2), identified by spectroscopic comparison with an authentic sample or by comparison of its ^{1}H n.m.r. spectrum with literature data.[76]

Table 2: Aryl halide acylations

Aryl halide, RX		Yield of substituted acetophenone
R	X	
Ph	Br (140)	17 (141)
	I (132)	35[a] (141)
1-napthyl	Br (143)	26 (144)
p-$Me_2NC_6H_4$	Br (145)	55[c] (146)
p-$MeOC_6H_4$	Br (136)	62 (139)
p-HOC_6H_4	Br (89)	59[b] (147)
o-HOC_6H_4	Br (92)	mixture of (92) +10% product
p-$H_2NC_6H_4$	Br (149)	no product isolated
p-$AcNHC_6H_4$	Br (150)	no reaction

a) Use of $Pd(PPh_3)_2Cl_2$ (2 mol %) as a catalyst led to no improvement in the yield.

b) Triethylamine (2 ml) was used and the reaction mixture acidified before diethyl ether extraction.

c) M.p. 103-4°C (lit.,[77] 104-5°C); $\nu_{max.}$ 1655 s cm^{-1}(carbonyl); ^{1}H n.m.r. (60 MHz) δ7.85-7.70 (2H,m,aryl-H), 6.65-6.50 (2H,m,aryl-H), 3.00 (6H,s, NMe_2), 2.45 (3H,s,COMe).

Reaction of 6-bromo-2-carboethoxychromone (87) with ethyl vinyl ether

6-Bromo-2-carboethoxychromone (87) (1.0 g, 3.4 mmol) was added to a mixture of palladium acetate (15 mg; 2 mol %), tri-*o*-tolylphosphine (123 mg; 12 mol %), triethylamine (0.65 ml, 4.7 mmol) and ethyl vinyl ether (2 ml, 21 mmol) in DMF (5 ml) in a Fischer-Porter bottle. The mixture was degassed by the freeze-pump method and the vessel heated (100°C; 3 h). The warm reaction mixture was poured into water (40 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic fractions were dried and the solvent evaporated. Column chromatography (2% methanol in dichloromethane) gave a mixture of products which were provisionally assigned from prominent features in their ^{1}H n.m.r. spectra: less polar fraction 2-carboethoxy-6-(1-ethoxyvinyl)chromone (152) δ4.75 (1H,d,J 3 Hz, vinylic), 4.45 (2H,q,J 7 Hz,$C\underline{H}_2CH_3$), 4.30 (1H,d,J 3 Hz,vinylic), 3.95 (2H,q,J 7 Hz,$C\underline{H}_2CH_3$), 1.45 (6H,t,J 7 Hz, 2 x $CH_2C\underline{H}_3$); middle fractions *Z*- and *E*- 2-carboethoxy-6-(2-ethoxyvinyl)chromone (153) and (154) respectively δ6.30 (1H,d,J 7 Hz,*Z*-olefin), 5.80 (1H,d,J 13 Hz,*E*-olefin) 5.25 (1H,d, J 7 Hz,*Z*-olefin); tail fractions (153), (154) and 6-acetyl-2-carboethoxychromone (151) δ2.70 (s,COMe). The three fractions were combined and dissolved in acetonitrile (10 ml). Trimethylsilylchloride (0.6 ml, 4.8 mmol) and sodium iodide (700 mg, 4.7 mmol) were added and the mixture stirred (20°C; 18 h) Water (40 ml) was added, the mixture extracted with dichloromethane and the combined organic fractions dried. Solvent evaporation and column chromatography (2% methanol in dichloromethane) gave 6-acetyl-2-carboethoxychromone (151) as an off-white powder (200 mg, 23%). M.p. 145-6°C (lit.,[71] 143-4°C); $\nu_{max.}$ 3070 w (aryl-H), 1730 s (ester), 1685 s (carbonyl), 1660 s (pyrone carbonyl) and 1605 s cm^{-1} (olefin); ^{1}H n.m.r. δ8.74 (1H,d,J 2 Hz,H-5), 8.38 (1H,dd,J 2,8 Hz,H-7), 7.70 (1H,d,J 8 Hz,H-8), 7.17 (1H,s,H-3), 4.50 (2H,q,J 7 Hz,$C\underline{H}_2CH_3$), 2.72 (3H,s,$COC\underline{H}_3$), 1.47 (3H,t,J 7 Hz,$CH_2C\underline{H}_3$); *m/z* (I.B.E.I.) 260 (M^+).

3-Acetylchromone (156)

3-Bromochromone (120) (0.5 g, 2.2 mmol) was added to a mixture of palladium acetate (10 mg; 2 mol %), tri-*o*-tolylphosphine (81 mg; 12 mol %), triethylamine (0.4 ml, 2.9 mmol) and ethyl vinyl ether (2 ml, 21 mmol) in DMF (3 ml) in a Fischer-Porter bottle. The mixture was degassed by the freeze-pump method and the vessel heated (100°C; 3 h). The warm reaction mixture was poured into water (30 ml) and extracted with dichloromethane (3 x 25 ml). The combined organic fractions were dried, filtered through silica and the solvent evaporated to give a mixture of tri-*o*-tolylphosphine and 3-(1-ethoxyvinyl)chromone (155). ^{1}H n.m.r. (60 MHz) δ8.50(1H,s,H-2), 7.75 - 7.10 (4H,m,H-5,H-8), 5.70 (1H,d,J 3 Hz,vinylic), 4.50 (1H,d,J 3 Hz, vinylic), 3.85 (2H,q,J 7 Hz,CH_2CH_3), 1.35 (3H,t,J 7 Hz,CH_2CH_3).

Column chromatography (dichloromethane) after elution of the tri-*o*-tolylphosphine gave a mixture of two products by t.l.c. This mixture was dissolved in ethanol (20 ml), 10% aqueous hydrochloric acid (1 ml) added and the solution shaken (5 min). Extraction with dichloromethane (3 x 30 ml), drying the combined organic fractions and evaporation gave a cream powder. This was crystallised from dichloromethane-hexane to give 3-acetylchromone (156) as off-white needles (290 mg, 69%). M.p. 126-7°C (lit.,[72] 129°C); $\nu_{max.}$ 3060 m (aryl-H), 1685 s (carbonyl), 1645 s (pyrone carbonyl), and 1610 s cm^{-1} (olefin); ^{1}H n.m.r. (60 MHz) δ8.55 (1H,s,H-2), 8.35 - 8.10 (1H,m), 7.80 - 7.25 (3H,m), 2.70 (3H,s,Me) [lit.,[72] δ8.55 (1H,s,H-2), 8.26 (1H,q,J 2.5,8 Hz,H-5), 7.56 - 7.17 (3H,m,H-6,7 and 8), 2.78 (3H,s,Me)]; *m/z* 188 (M^+).

Section II

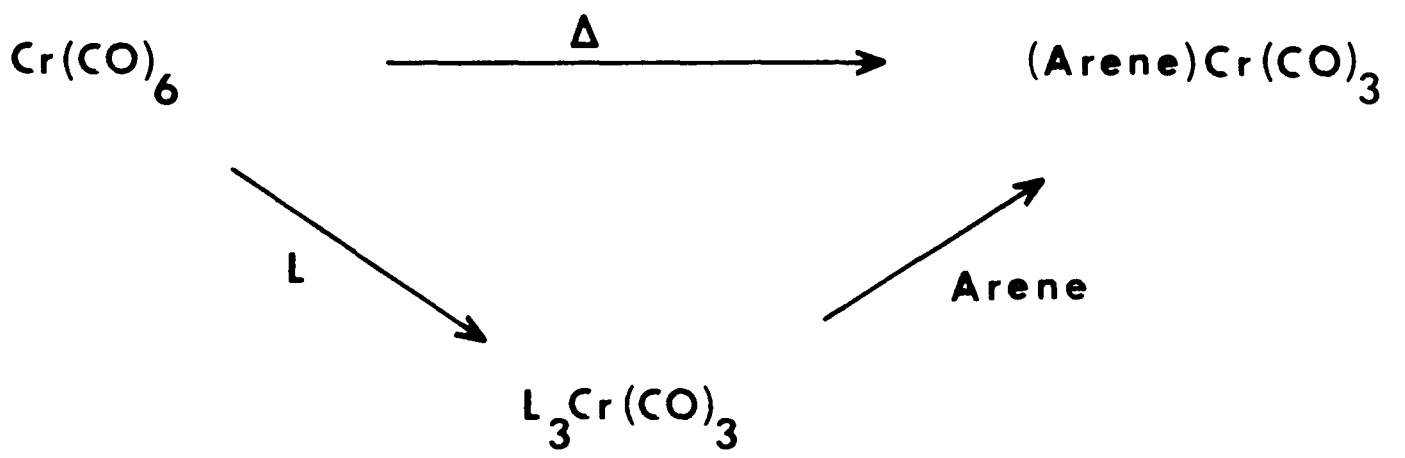
(η^6-BENZOPYRAN)$Cr(CO)_3$ COMPLEXES

1. Introduction to (η^6-arene)$Cr(CO)_3$ complexes

Whilst many transition metals form stable complexes with arenes, it is the neutral chromium tricarbonyl species that have attracted the most attention in the field of organic synthesis. This is predominantly due to the significant modifications in arene reactivity obtained by coordination to the metal unit, but it is also due to the ease with which the arene may be complexed and decomplexed. Both these latter features are important requirements for the use of any organometallic species in synthesis.

1(i) Synthesis

The two general methods for (η^6-arene)$Cr(CO)_3$* complex formation are either : direct thermolysis of the metal carbonyl in the presence of an arene,[78] or prior formation of an intermediate $L_3Cr(CO)_3$ (*e.g.* L=CH_3CN or pyridine) species which can then undergo L_3/arene exchange.[79]

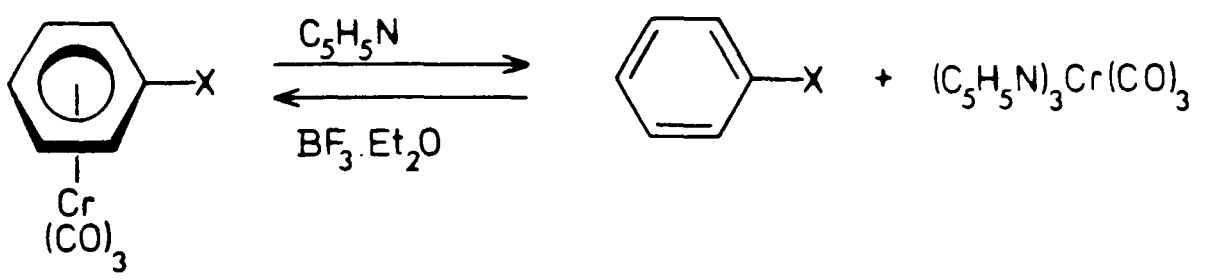


The former is the more common, with complexation usually being performed in an inert solvent at reflux under nitrogen; the loss of

* η^N: N is the number of carbon atoms of the hydrocarbon bonded to the metal. All $Cr(CO)_3$ complexes described in this thesis are η^6 complexes and henceforth this prefix will be omitted.

carbon monoxide helping to drive the reaction to completion. Donor solvents are commonly added to increase the rate of reaction; the most suitable solvent medium appears to be a 10:1 mixture of di-*n*-butyl ether and THF.[80] The mechanism of complexation has not been fully established but, by analogy with the reaction of molybdenum hexacarbonyl with arenes,[81] it is believed to proceed *via* an initial dissociation to form a $M(CO)_5$ species. Formation of an (η^2-arene)$M(CO)_5$ complex is probably followed by two stepwise displacements of further carbon monoxide ligands to yield the (η^6-arene)$M(CO)_3$ complex.

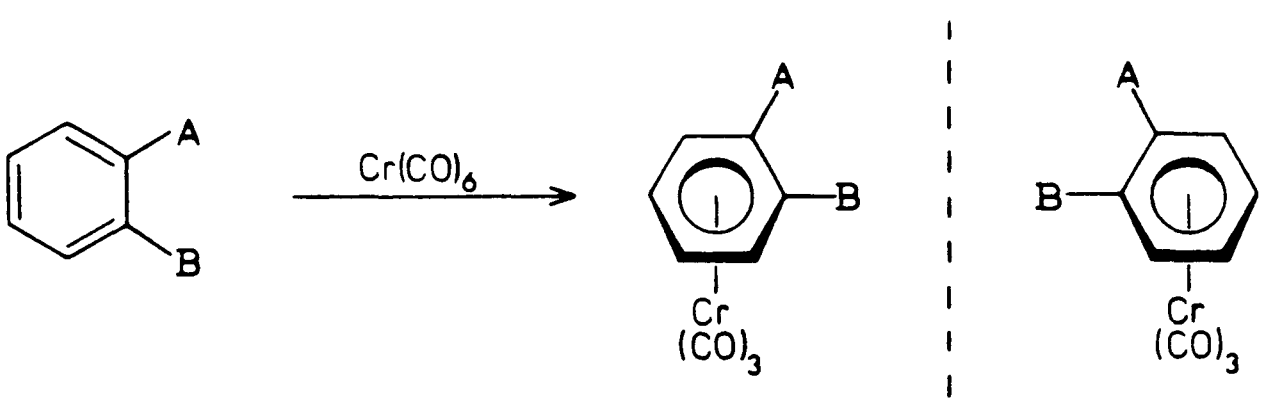
While direct coordination is compatible with many functional groups, some arenes are unstable to the required long reaction times (∿24 h) at high temperature (∿140°C). In particular, nitro groups are reduced to diazo species with concomitant oxidation of the metal. A different problem occurs with arenes, containing carboxylic acid substituents, which are generally insufficiently soluble in the reaction mixture for efficient complexation. The forcing thermal conditions can be avoided by the alternative method of complexation involving the prior formation of an intermediate $L_3Cr(CO)_3$ species; ligand-arene exchange then occurs under milder conditions.[79] The reaction is reversible and has been used for the decomplexation of arenes, thus allowing the metal unit to be recycled.[82]



Arene $Cr(CO)_3$ complexes are generally yellow to red diamagnetic solids, relatively stable to air. Solutions, however, undergo slow decomposition

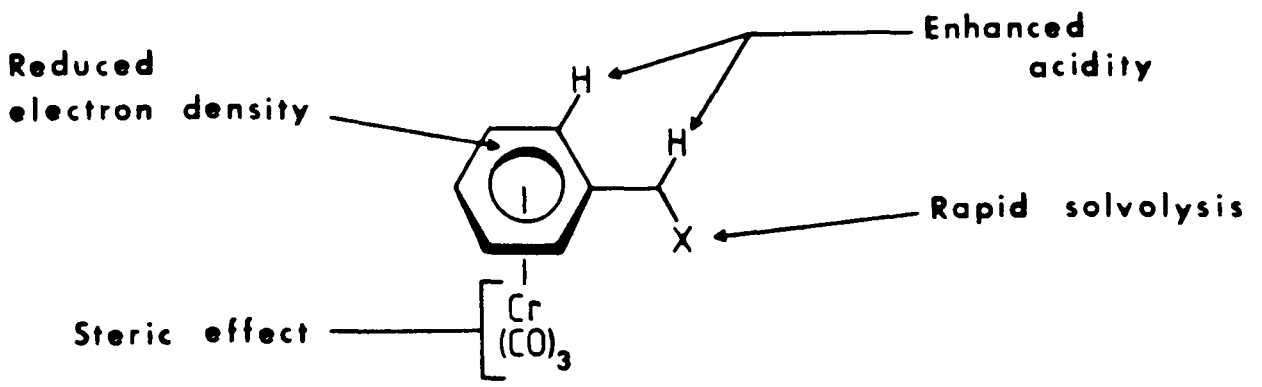
in air and all reactions are therefore performed under a nitrogen atmosphere.

All unsymmetrical *ortho* and *meta* disubstituted arenes are prochiral. Coordination of these arenes to the $Cr(CO)_3$ unit therefore generates complexes as pairs of enantiomers. Resolution of such complexes may be achieved by standard organic methods, if the arene possesses an appropriate functional group.[83]



1(ii) Modifications to arene reactivity

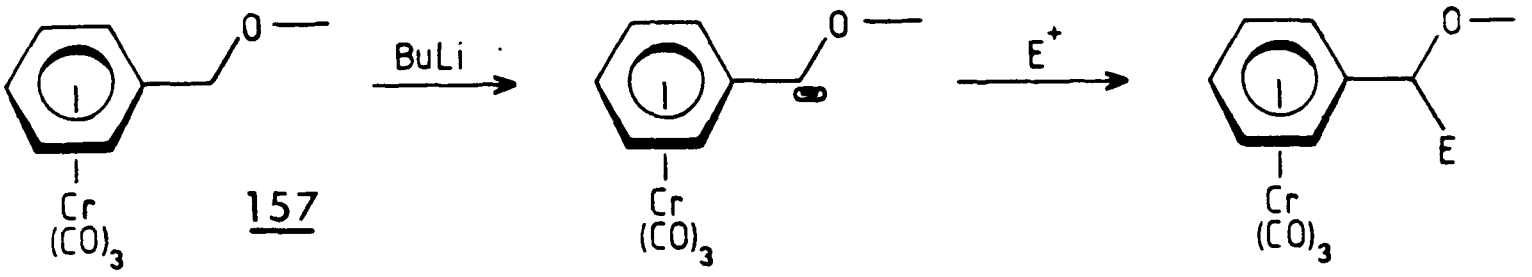
The figure below summarises the general changes in arene reactivity observed on coordination to the metal unit.



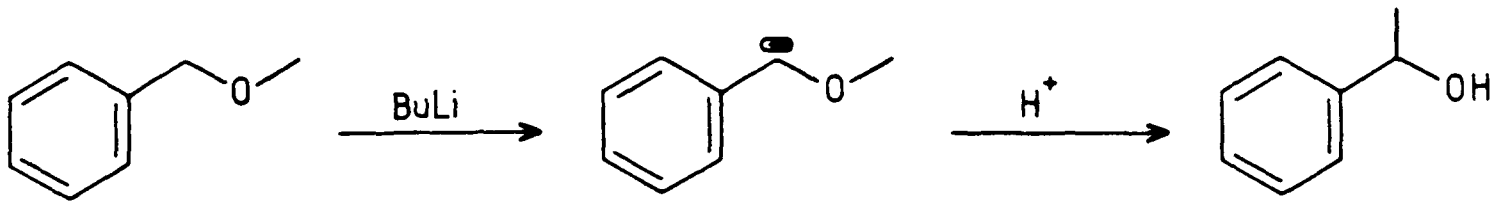
The electron withdrawing $Cr(CO)_3$ unit increases the acidity of both benzylic and ring protons. The former are more acidic due to resonance

stabilisation of the resultant anion by the metal unit, whereas the latter are more acidic due to inductive stabilisation. In each case this stabilisation is a result of electron donation from the arene to vacant metal orbitals, thus reducing the net negative charge on the arene. The magnitude of this effect can be seen by the increase in acidity of both benzoic acid[78] and phenol[84] upon complexation to the metal unit (pk_as from 5.7 and 11.0 to 4.8 and 7.1 respectively). The reduction in arene electron density by the metal unit is comparable to the introduction of a nitro group into the free arene.

Although both benzylic and ring protons are more acidic, by the suitable choice of conditions regioselective deprotonation can be effected.[85] We have used the ease of benzylic deprotonation and the stability of the resultant anion to functionalise (benzyl alkyl ether)$Cr(CO)_3$ complexes (*e.g.* 157),[86] The uncomplexed arene 158, undergoes the Wittig rearrangement when treated with strong base.

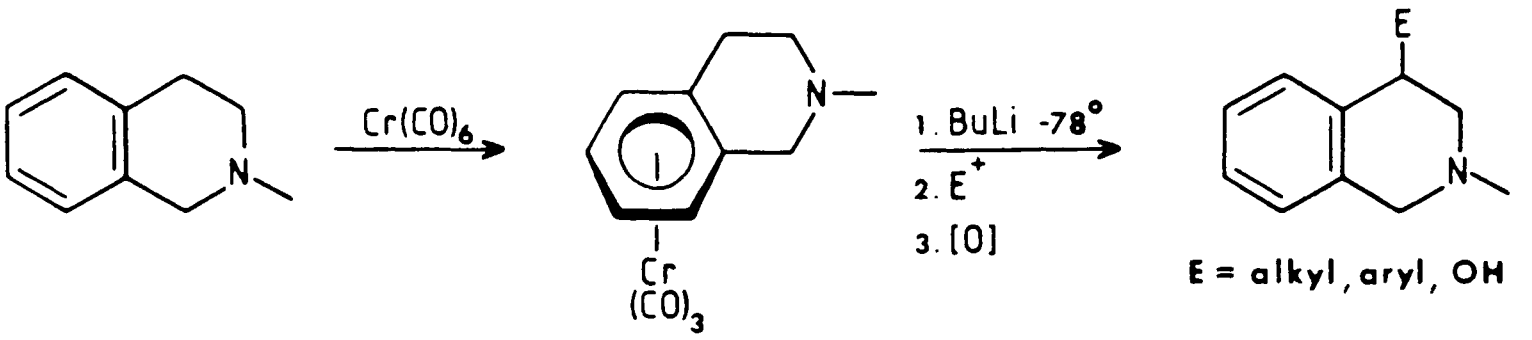


157



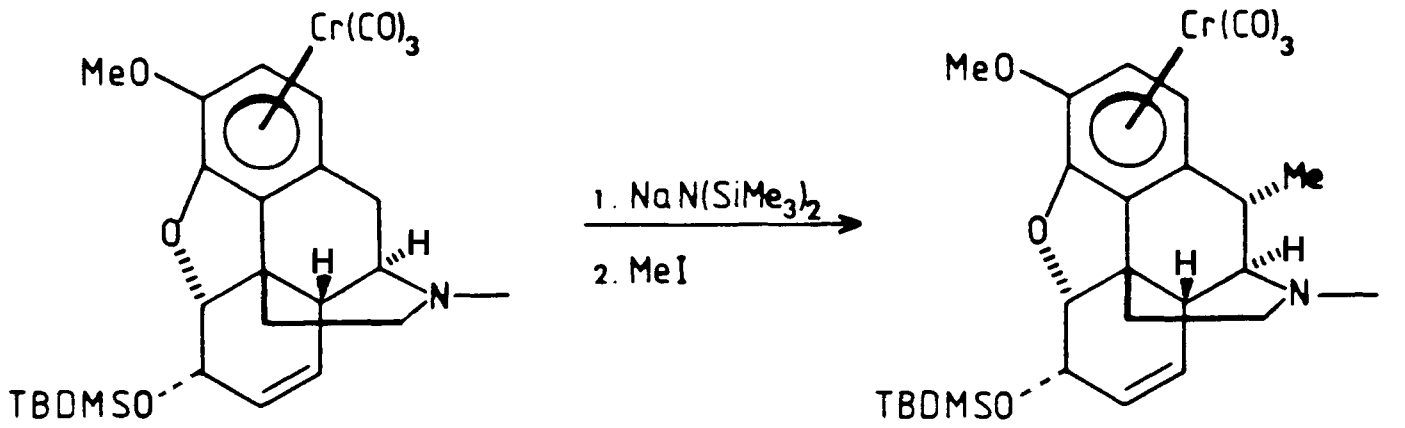
158

A variety of 4-substituted 1,2,3,4-tetrahydroisoquinolines 159 have been synthesised, from the parent compound 160 *via* their corresponding $Cr(CO)_3$ derivatives.[87]



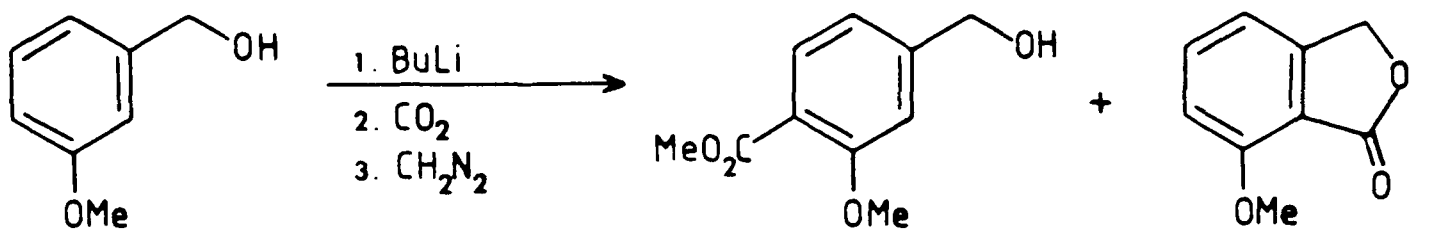
160 159

The steric bulk of the $Cr(CO)_3$ moiety results in reactants approaching the complex from the *exo* face, *i.e.* away from the metal. This is seen in the stereoselective trapping of the benzylic anion generated from the protected codeine derivative 161, with methyl iodide.[88]



161

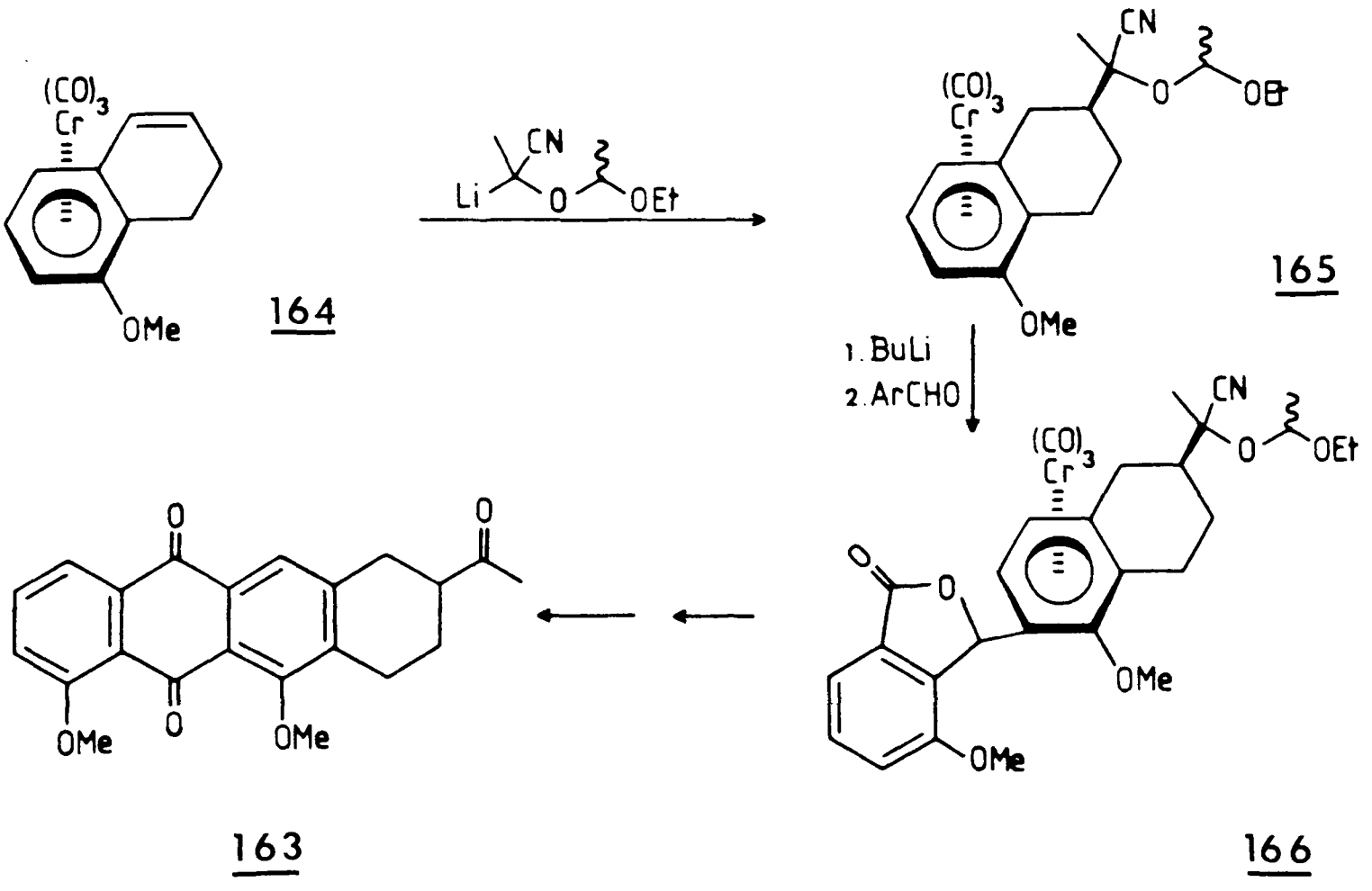
Ring deprotonation is usually highly regioselective, particularly if the complexed arene contains suitable *ortho* chelating groups. The regioselectivity observed is often different to that of the uncomplexed arene. *m*-Methoxybenzyl alcohol 162 is normally deprotonated at C2; coordination to the $Cr(CO)_3$ unit allows predominant C4 deprotonation.[89]



162

10 : 90
Complexed 77 : 23

An example utilising the stability of both benzylic and ring anions is found in the synthesis of the tetracycle 163 an intermediate for 11-deoxydaunomycinone.[90] The addition of a stabilised carbanion to the (dihydronapthalene)$Cr(CO)_3$ complex 164 gave complex 165 after subsequent quenching of the resultant benzylic anion. Regioselective ring deprotonation *ortho* to the methoxy group then allowed carbon-carbon bond formation to give the intermediate 166 with the required *ortho* substituent for subsequent ring fusion.



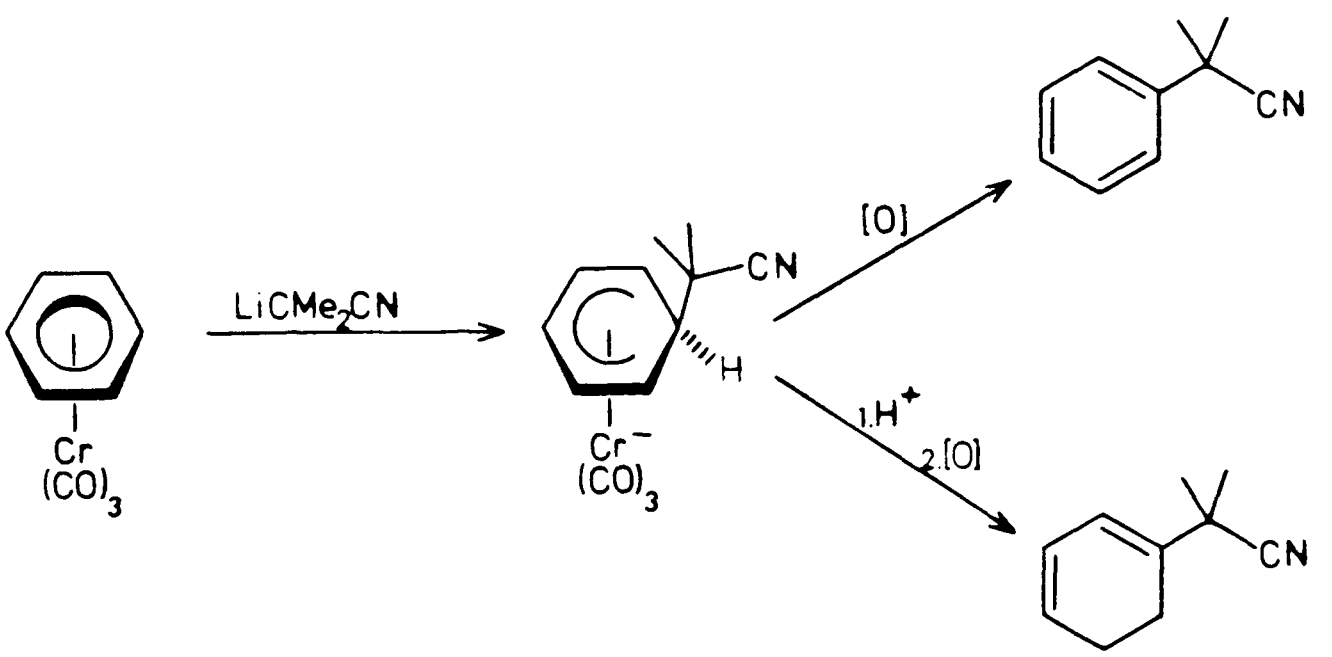
164

165

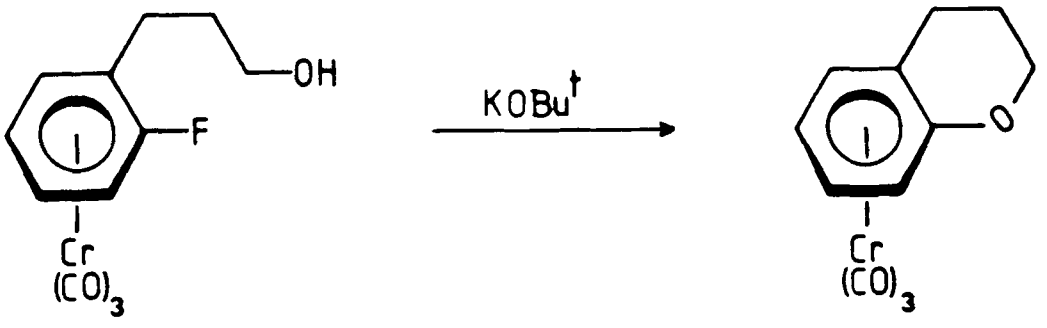
163

166

The reduction in ring electron density by the $Cr(CO)_3$ unit also activates the coordinated arene towards nucleophilic attack and is therefore an example of *umpolung*. A wide range of reactive carbon nucleophiles will add to the ring. Depending upon the conditions employed for the work-up, either substituted arenes or cyclohexadienes may be synthesised.[91]



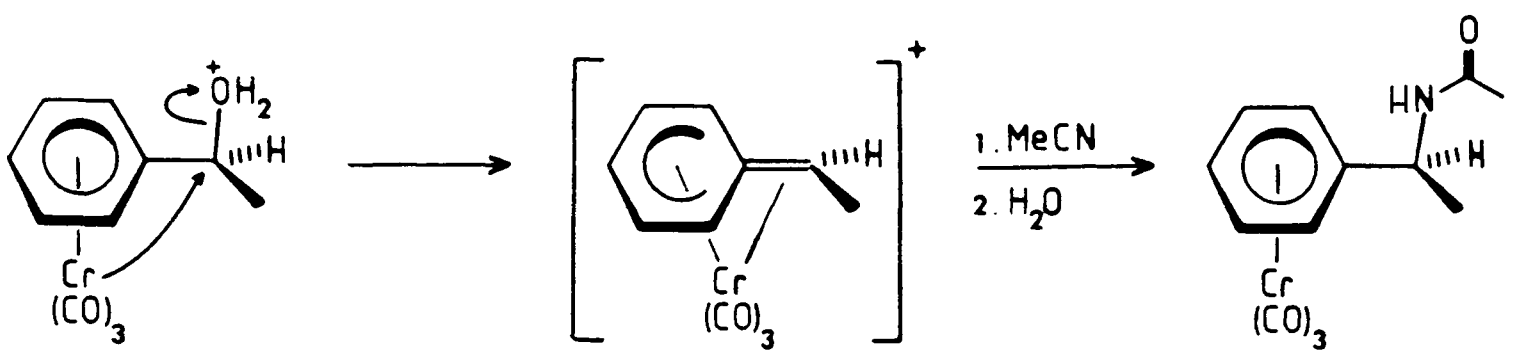
If the arene possesses a leaving group, ring attack by nucleophiles leads to overall nucleophilic substitution. (Haloarene)$Cr(CO)_3$ complexes are prone to these nucleophilic displacements; (chroman)$Cr(CO)_3$ 167 was first synthesised by an intramolecular displacement of fluoride.[92]



167

The metal unit can also act as a strong electron donor (by back donation from filled metal orbitals), resulting in the stabilisation of benzylic carbonium ions. Evidence for this is found in the rapid S_N1 solvolysis of

benzyl chlorides coordinated to the metal unit.[93] The stabilisation of benzylic carbonium ions proceeds with neighbouring group participation of the metal. Since the approach of a nucleophile is limited to the *exo*-face of the complex, due to the steric bulk of the metal, this enables the Ritter reaction on optically pure benzyl alcohols 168 to be achieved with complete retention of configuration.[94]



168

1(iii) Decomplexation

The two general methods for arene decomplexation from the metal unit, are either oxidation or displacement with other ligands (*vide supra*); the former is the more common. Whilst oxidising agents (such as I_2 or Ce^{IV})[95] can be employed, quantitative arene regeneration occurs on exposure of diethyl ether solutions of the complexes to air and sunlight.[96] The metal unit is oxidised from Cr(0) to Cr(III) which precipitates from solution. A filtration therefore gives a solution of the arene without the necessity for any further purification.

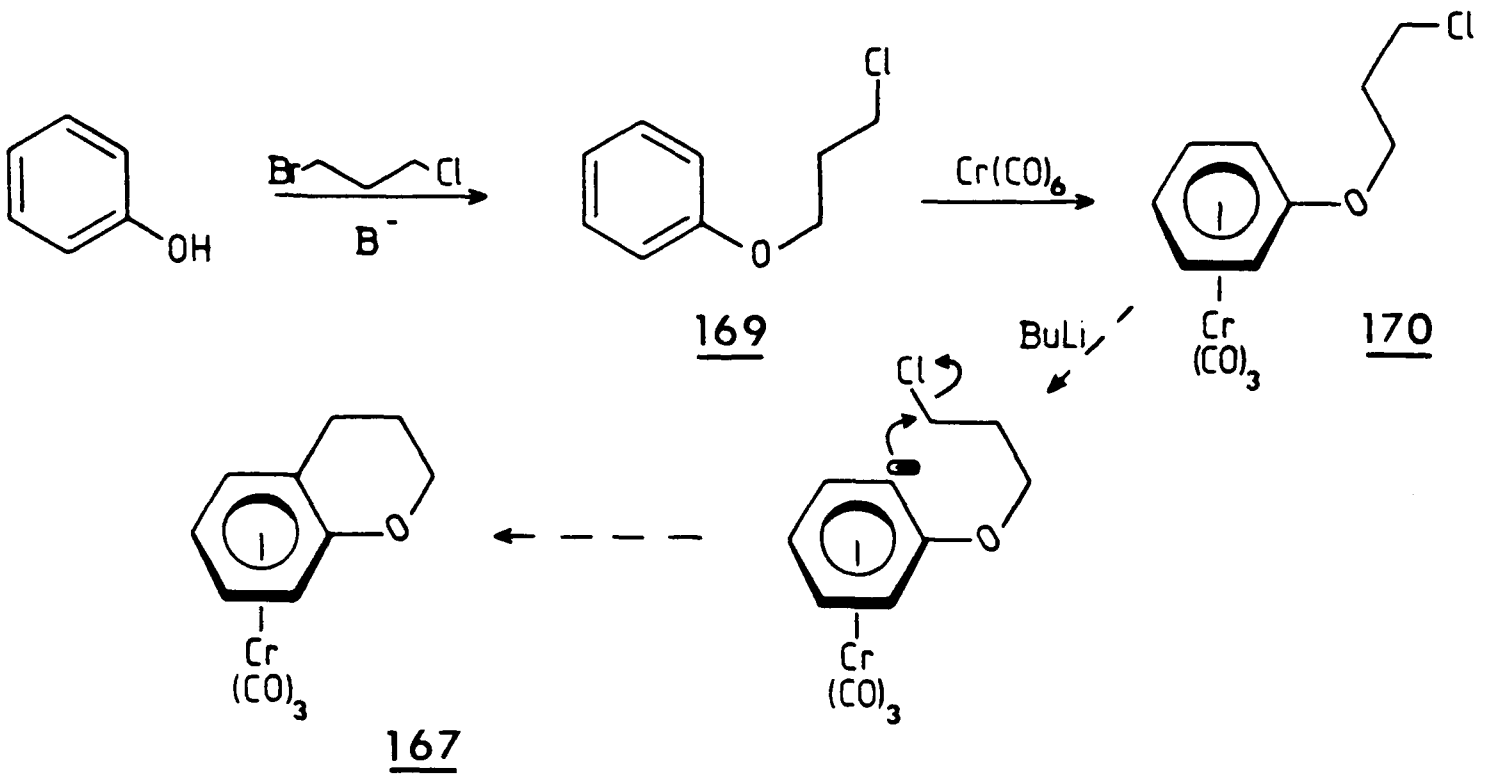
The $Cr(CO)_3$ moiety therefore provides a useful auxiliary for an arene and we decided to investigate whether the change in arene reactivity on coordination to the metal unit could be used to functionalise the chroman system. The increase in acidity of both the ring and benzylic protons should allow clean substituent introduction into either site - providing regiospecific deprotonation can be achieved.

2. Chroman functionalisation

2(i) (Chroman)$Cr(CO)_3$ synthesis

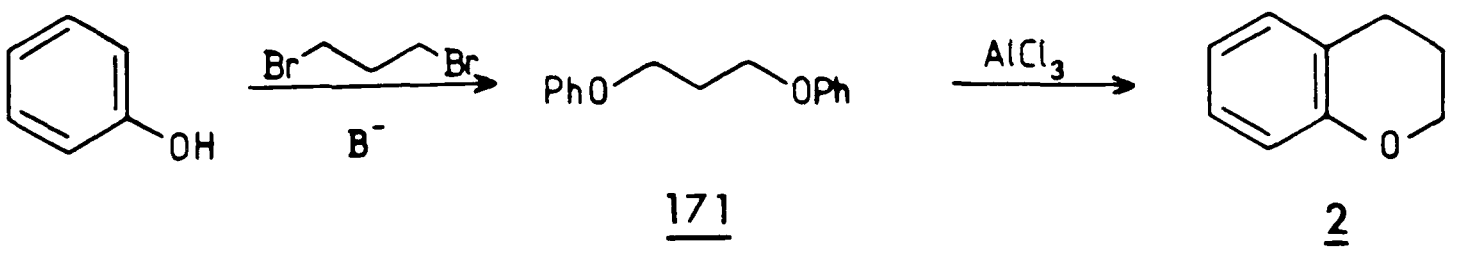
(Chroman)$Cr(CO)_3$ 167 is a known compound previously synthesised by an intramolecular aromatic nucleophilic displacement of fluoride by an alkoxide anion (see introduction).[92] The required fluoro-alcohol is not readily available commercially so the following route was devised. 1-Chloro-3-phenoxypropane 169 was synthesised by treatment of the phenoxide anion with 1-bromo-3-chloropropane. Heating this arene under reflux with excess chromium hexacarbonyl in a 10:1 mixture of di-*n*-butyl ether/THF gave a deep yellow solution characteristic of most (arene)$Cr(CO)_3$ complexes. After work-up a single yellow crystalline compound was isolated. This was readily identified as (1-chloro-3-phenoxypropane)$Cr(CO)_3$ 170 from the strong infrared absorptions in the region 1900 - 2000 cm^{-1} (characteristic of metal carbonyls) and the upfield shift of the aromatic protons (by about 2 ppm) in the ^1H n.m.r. spectrum. This large upfield shift from the free to the complexed arenes is another characteristic feature of (arene)$Cr(CO)_3$ complexes, and is thought to be due to the reduction in ring electron density caused by coordination to the metal unit. This therefore reduces the ring current, which results in a reduction in the deshielding magnetic field experienced by the aromatic protons. This novel compound was fully characterised and gave a satisfactory elemental analysis.

It was anticipated that (chroman)$Cr(CO)_3$ 167 could be synthesised from complex 170 by ring deprotonation with *n*-BuLi in THF at -78°C followed by intramolecular displacement of chloride. Deprotonation *ortho* to the oxygen substituent was expected to occur, by analogy with the deprotonation of (anisole)$Cr(CO)_3$ which proceeds regiospecifically *ortho* to the methoxy group.[97]

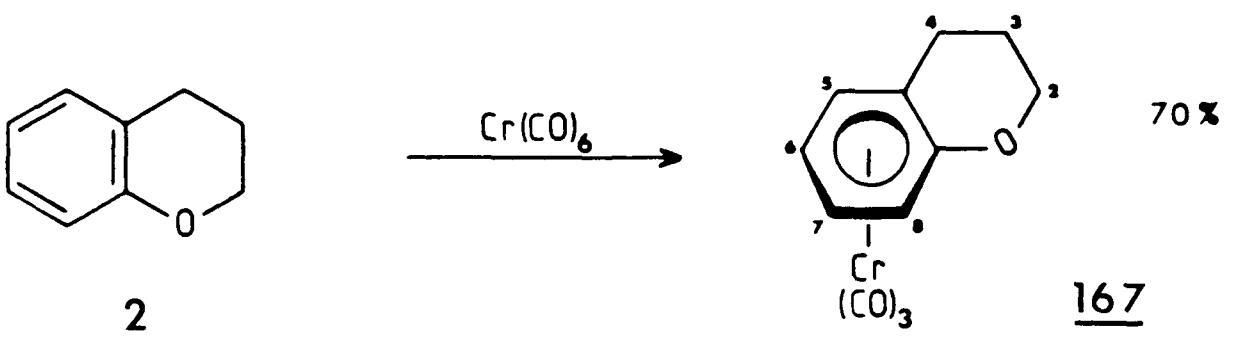


Unfortunately, attempts to effect this cyclisation were unsuccessful. Treatment of the complex 170 with *n*-BuLi at -78°C led, after work-up only to the recovery of the starting material. Repeating the reaction but allowing the mixture to warm to room temperature resulted in the decomposition of the complex with no product being isolated.

With the failure of this approach, direct complexation of the heterocycle with chromium hexacarbonyl was attempted. A sample of chroman 2 was prepared according to the method of Deady.[98] Heating a solution of sodium phenoxide with 1,3-dibromopropane gave 1,3-diphenoxypropane 171. Subsequent treatment with aluminium trichloride under Friedel-Crafts conditions resulted in a cyclisation to the desired heterocycle 2.



Heating chroman 2 under reflux with excess chromium hexacarbonyl in a 10:1 mixture of di-*n*-butyl ether/THF produced a yellow solution characteristic of (arene)$Cr(CO)_3$ complexes. After work-up, yellow crystals of the desired (chroman)$Cr(CO)_3$ 167, identified by comparison of its ^1H n.m.r. spectrum with the literature data,[92] were isolated in good yield (70%).



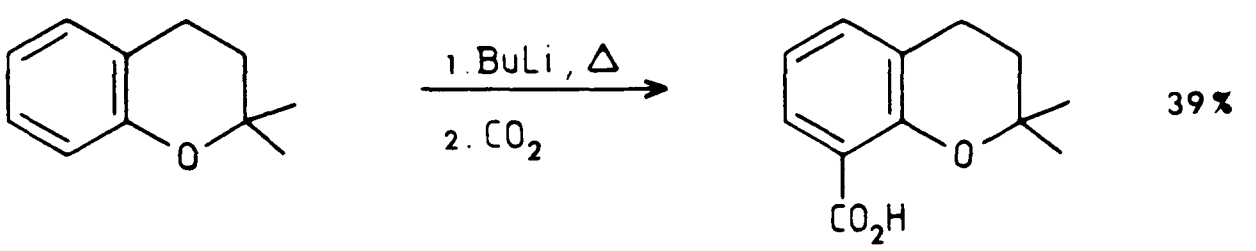
2 167

In the ^1H n.m.r. spectrum of (chroman)$Cr(CO)_3$ 167, all four of the aromatic protons, appear as discrete signals between δ4.5 and 5.5. They consist of two doublets (H-5 and H-8) and two triplets (H-6 and H-7), all with identical coupling constants of 6 Hz. The three sets of heterocyclic protons are also well resolved, with the C4 protons exhibiting a small and the C2 protons a larger low field shift from the C3 protons at δ2.0. The C3 protons are easily assigned as the high field set of resonances from the extensive coupling observed. The two protons are diastereotopic and couple to each other as well as the four adjacent protons, to give a highly complex pattern. Although they are also diastereotopic, less coupling is exhibited by the C2 and C4 protons since they only have two adjacent protons. The large chemical shift differences between the various sets of protons was found to be a general feature for these (benzopyran)$Cr(CO)_3$ complexes and frequently aided product identification.

With the synthesis of the required (chroman)$Cr(CO)_3$ 167 attempts were made to selectively functionalise the ring and benzylic positions.

2(ii) Ring functionalisation

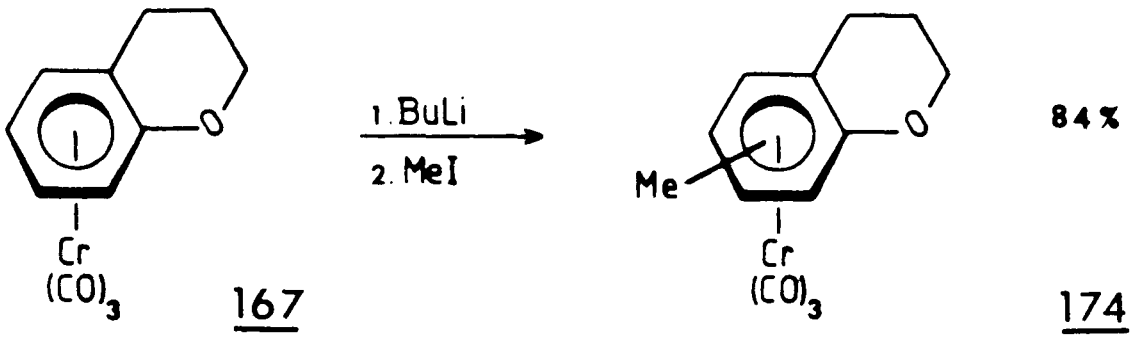
One example of ring metallation of a chroman derivative by a strong base has been reported.[99] Thus treatment of 2,2-dimethylchroman 172 with *n*-BuLi in ether under reflux followed by addition of carbon dioxide gave the 8-carboxylic acid 173, albeit in low yield (39%).



172 173

Presumably regiospecific deprotonation is observed due to chelation between the base and the *ortho* oxygen substituent before proton abstraction [*cf.* deprotonation of (anisole)$Cr(CO)_3$]. With an increase in ring proton acidity normally observed on arene coordination to the $Cr(CO)_3$ unit, coordination of chroman 2 was expected to facilitate this deprotonation. It was not clear however whether the regiochemistry of the reaction would be affected.

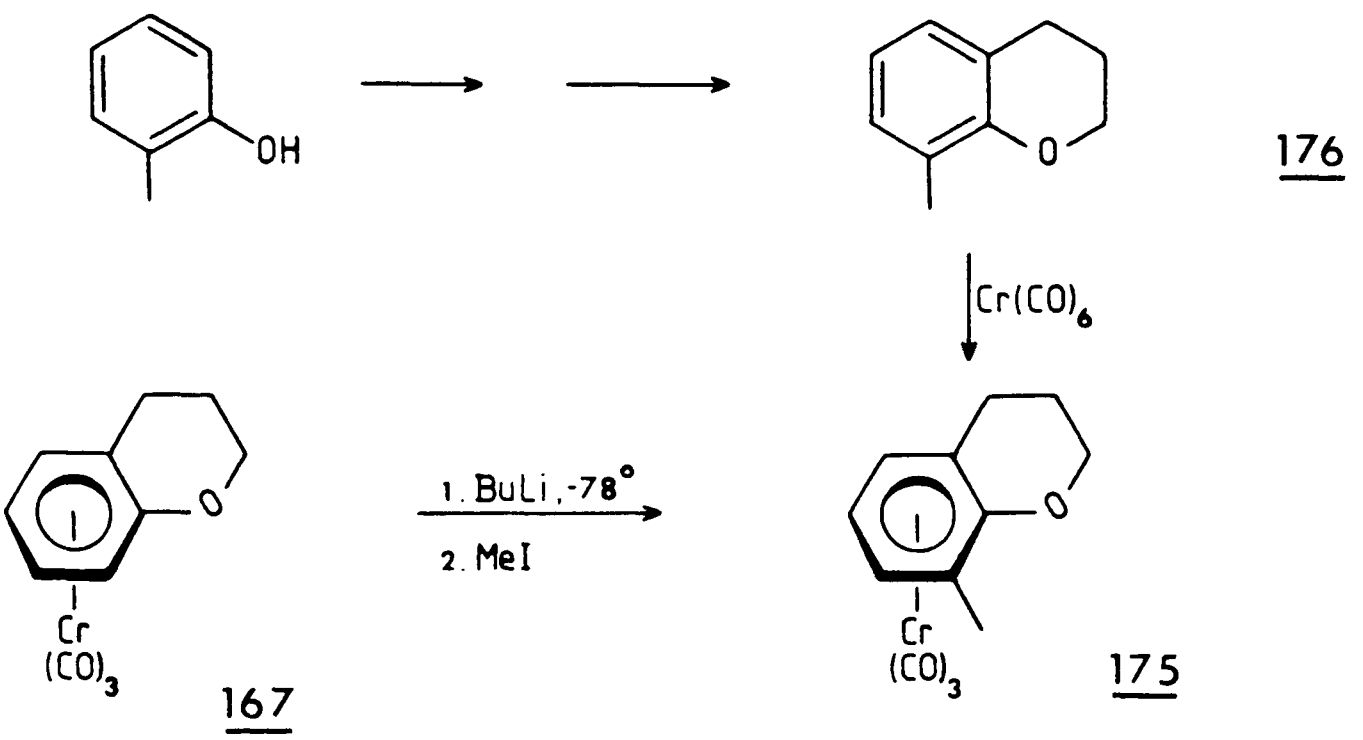
Treatment of a solution of (chroman)$Cr(CO)_3$ 167 in THF at -78°C with *n*-BuLi gave a yellow-orange colour characteristic of a ring anion. Methyl iodide was added and the reaction mixture subsequently quenched with methanol. After work-up, yellow crystals of a single product 174 were isolated in high yield. From a prominent three proton singlet (δ2.15) and a molecular ion *m/z* = 284 in the mass spectrum the product 174 contained a ring methyl group. The absence of a methyl doublet in the ^1H n.m.r. spectrum indicated that regioselective ring rather than benzylic substitution has occurred.



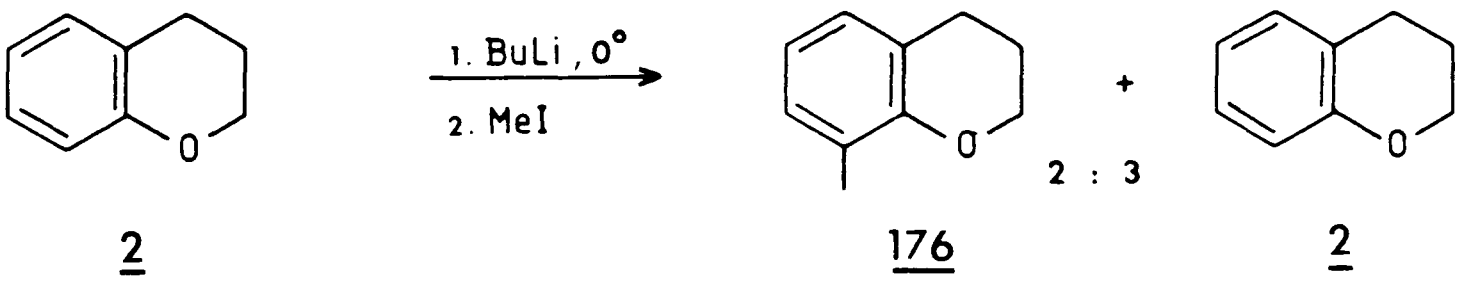
167 174

The three aromatic proton resonances in the ^{1}H n.m.r. spectrum consisted of two doublets and a triplet, each with identical coupling constants of 6 Hz. The observed couplings are characteristic of *ortho* aromatic proton couplings and indicate product 174 to contain three contiguous aromatic protons. This is only consistent with deprotonation and subsequent methylation having occurred at either C5 or C8. The alternative methylation sites (C6 or C7) would produce an aromatic proton resonance pattern similar to that found for the 6-bromochromone 87, consisting of a doublet with a small (J 2 Hz) *meta* coupling and an AB system with a large (J 6 Hz) *ortho* coupling one half of which was further split by the *meta* coupling. Although either C5 or C8 methylation had occurred, by analogy with the uncomplexed derivative 172 C8 deprotonation might be expected.

To assign unambiguously the structure of product 174 an authentic sample of (8-methylchroman)$Cr(CO)_3$ 175 was prepared by an alternative route. The free arene 176 was prepared from *o*-cresol in an analogous manner to the preparation of chroman 2 from phenol.[98] Direct complexation to the metal unit, by heating with chromium hexacarbonyl under the standard reaction conditions gave after work-up, (8-methylchroman)$Cr(CO)_3$ 175 in 60% yield. This novel product was fully characterised including by elemental analysis. Comparison of product 174 with this sample showed them to be identical in all respects. Deprotonation of (chroman)$Cr(CO)_3$ 167 had therefore occurred regiospecifically at C8.



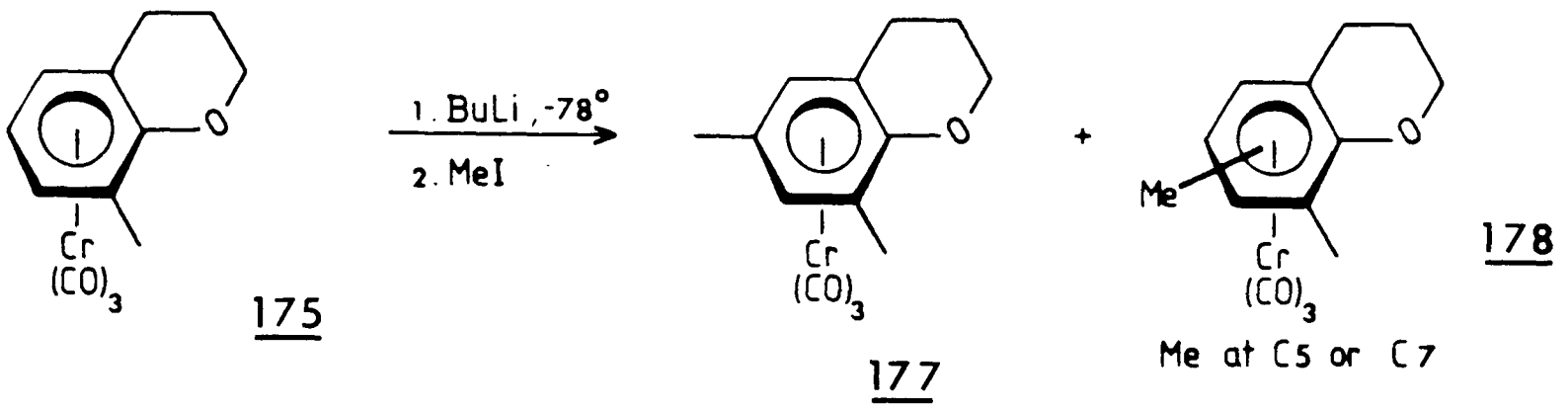
To compare this with the reactivity of the uncomplexed arene, a sample of chroman 2 was treated with *n*-BuLi followed by methyl iodide under identical conditions. At -78°C the arene was totally unreactive and only the starting material 2 was isolated. Repeating the reaction at 0°C resulted in partial methylation, to give a 3:2 mixture of the starting material 2 and 8-methylchroman 176. No clean substitution of the free arene could be achieved.



2 176 2

Treatment of (8-methylchroman)$Cr(CO)_3$ 175 with another equivalent of *n*-BuLi followed by methyl iodide resulted in further ring methylation. With no chelating group present in the ring to control the regiochemistry of deprotonation, a mixture of two isomers 177 and 178 was obtained. One isomer 177 could be identified from the ^1H n.m.r. spectrum as (6,8-dimethylchroman)$Cr(CO)_3$ 177 from the two remaining aromatic protons which exhibited

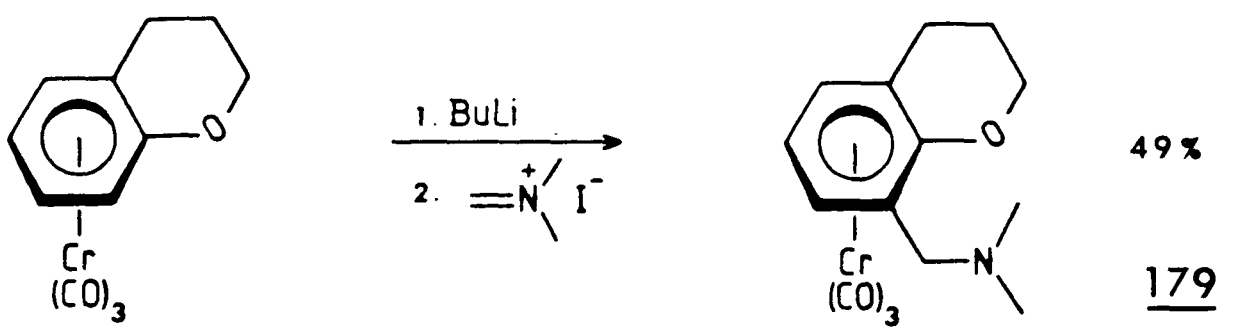
a small *meta* coupling. The two aromatic protons of the other isomer 178 exhibited a larger *ortho* coupling indicative of two adjacent protons, and would therefore correspond to either (5,8- or 7,8-dimethylchroman)$Cr(CO)_3$ 178. It was not possible, however, to distinguish between these two isomers.



175 177 178

Me at C5 or C7

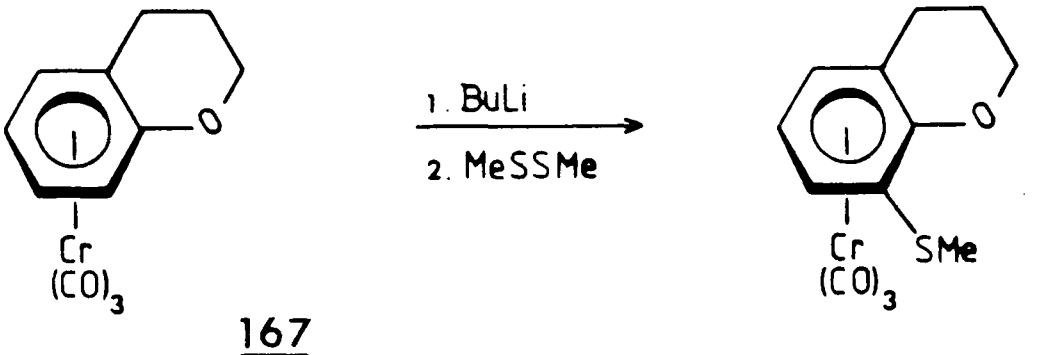
Addition of *n*-BuLi to (chroman)$Cr(CO)_3$ 167 followed by Eschenmoser's salt ($H_2C{=}N^+Me_2\ I^-$) produced a single product. The ^1H n.m.r. spectrum clearly showed that this electrophile had added to the ring anion from the six proton singlet at δ2.33 characteristic of the *N*,*N*-dimethylaminomethylene substituent. The three aromatic protons exhibited a similar pattern of resonances and couplings to that observed for (8-methylchroman)$Cr(CO)_3$ 175 and by analogy this novel compound was assigned as [8-(*N*,*N*-dimethylaminomethylene) chroman]$Cr(CO)_3$ 179. Further confirmation was provided by elemental analysis.



167 179

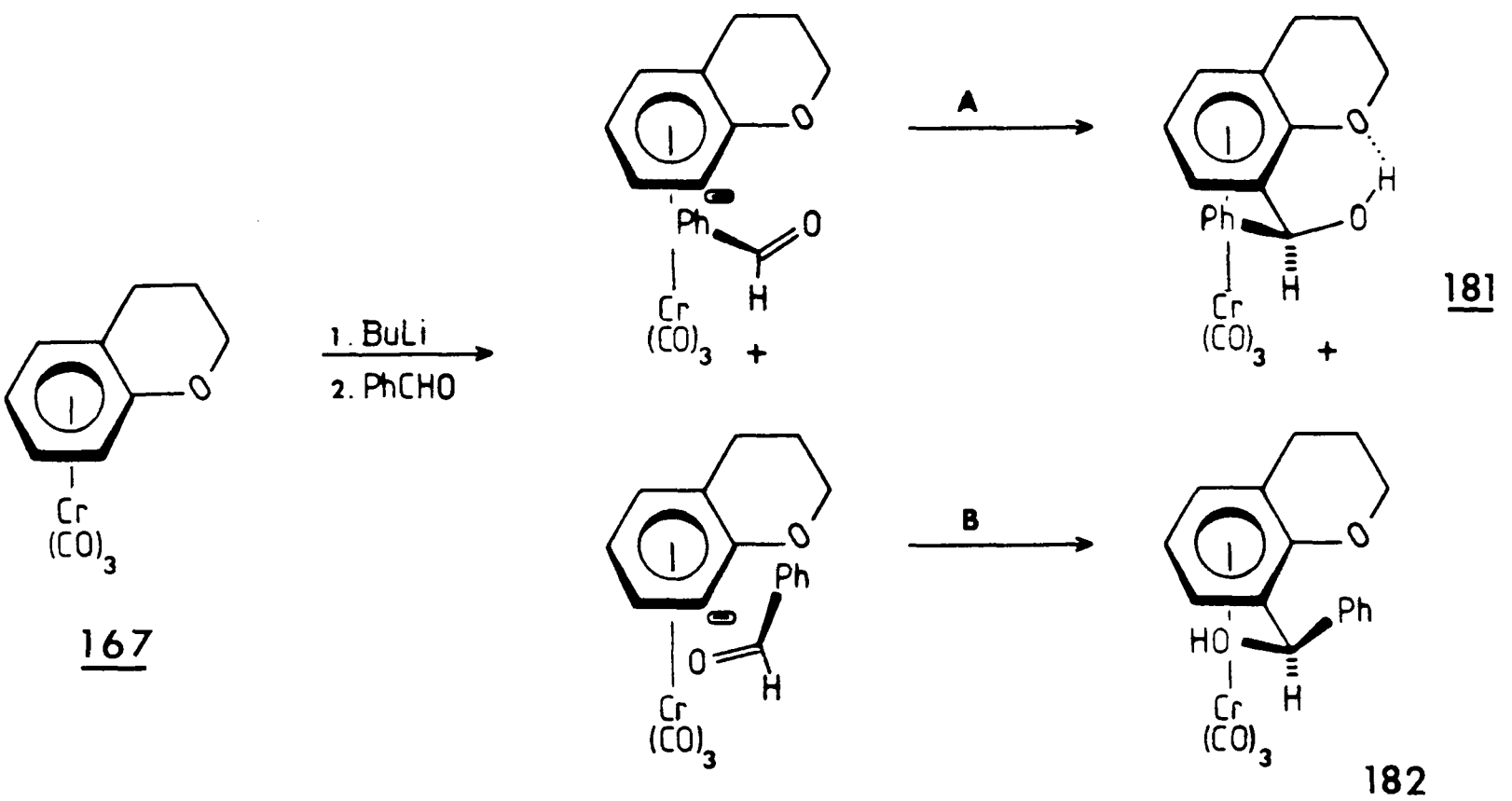
Methyl disulphide provides a source of electrophilic sulphur and its addition to a carbanion results in an overall oxidation of the C-H bond. Quenching the ring anion from (chroman)$Cr(CO)_3$ 167 with this reagent resulted in a ring thiomethylated product 180, readily identified from the molecular

ion m/z = 316 in the mass spectrum and a three proton singlet in the ^{1}H n.m.r. spectrum at δ2.43. By analogy with the formation of (8-methylchroman)$Cr(CO)_3$ 175, deprotonation *ortho* to the oxygen substituent was again presumed to have occurred and this novel product was assigned as (8-thiomethylchroman)$Cr(CO)_3$ 180, further confirmation being provided by elemental analysis.



167 180

Quenching the ring anion from (chroman)$Cr(CO)_3$ 167 with benzaldehyde led to the addition product, identified as the novel [8-(hydroxybenzyl)-chroman]$Cr(CO)_3$ by a molecular ion m/z = 376 in the mass spectrum. The ^{1}H n.m.r. spectrum however, contained two distinct sets of aromatic protons with identical couplings. The reaction generates a new chiral centre in the product and the two observed sets of resonances are consistent with the formation of the product as a mixture of two diastereoisomers 181 and 182. The approach of benzaldehyde to the ring anion is likely to occur with the smallest group (H) *syn* to the bulky $Cr(CO)_3$ moiety. With the phenyl group therefore *anti* to the metal unit, there are two possible conformations for the transition state. The addition can either occur with the carbonyl and the heterocyclic oxygen in a *syn* orientation (path A), or with the two groups in an *anti* orientation (path B).



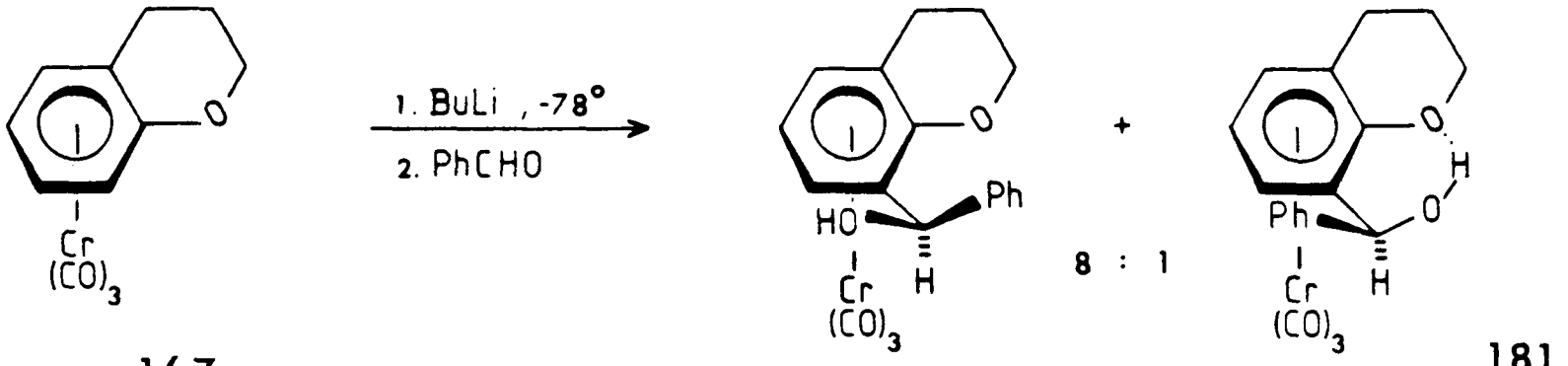
167

181

182

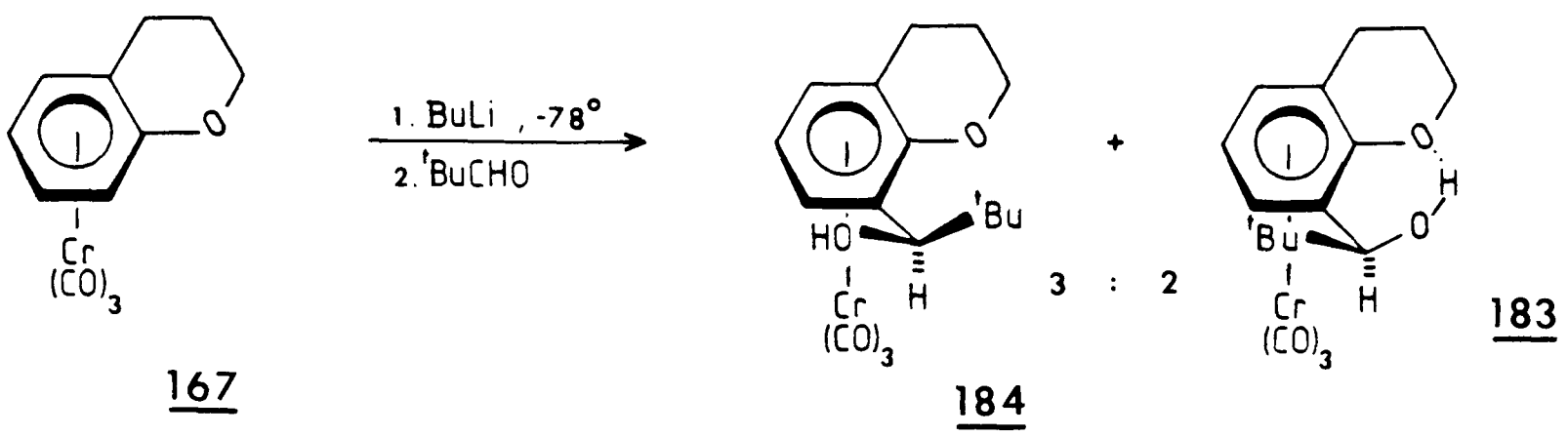
The formation of both diastereoisomers of the product (in a 8:1 ratio by integration of the two sets of aromatic protons) suggested that addition was occurring by both of these pathways. Pathway A, leading to diastereoisomer 181 occurs *via* chelation of the two oxygen atoms in the transition state and leads to a product diastereoisomer with an intramolecularly bonded hydroxyl group. An intramolecular hydrogen bond is not present in the other product diastereoisomer 182, derived from the transition state in which the two oxygens have an *anti* relationship, due to restricted rotation about the new C-C bond from steric interactions between the phenyl group and the metal unit. The two diastereoisomers 181 and 182 should therefore have very different polarities, since only one, 182, contains a free hydroxyl group. It was found that the two diastereoisomers 181 and 182 could easily be separated by column chromatography; the major, more polar diastereoisomer being isolated as a crystalline solid and fully characterised including by elemental analysis.

The solution infrared spectrum of this major diastereoisomer contained a sharp and a broad hydroxyl band, corresponding to the free and the hydrogen bonded OH absorptions. Increasing the dilution of the sample, resulted in a decrease in the relative intensity of the lower frequency hydrogen bonded OH band. This decrease is characteristic of an intermolecularly bonded group, since increasing the dilution with a non-polar solvent reduces the degree of intermolecular hydrogen bonding, and therefore the intensity of the absorption. Dilution should have no effect on an intramolecular hydrogen bond absorption. This implies that diastereoisomer 182 which possesses a free hydroxyl group is the major product from the reaction. This major product was the more polar diastereoisomer and its assignment as containing a free hydroxyl group is also consistent with the expected relative polarities of the two possible diastereoisomers.



167 182 181

The use of pivalaldehyde as the electrophile similarly produced the addition product, identified as the novel [8-(2,2-dimethyl-1-hydroxypropyl)-chroman]$Cr(CO)_3$ 183/184 together with some unreacted starting material 167. The failure of the anion to undergo complete addition was probably due to the sterically hindered nature of the aldehyde.



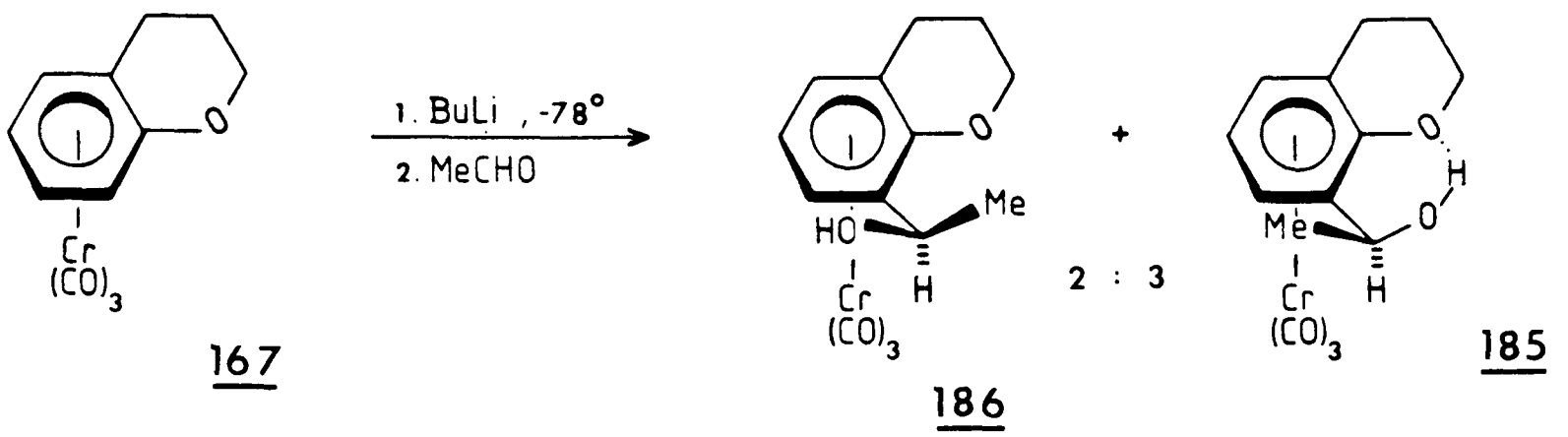
167 184 183

Two diastereoisomers 183 and 184 of the product were again observed in the reaction mixture, although with a greatly reduced selectivity of 3:2. The major, more polar diastereoisomer 184 (which by analogy with the hydroxybenzyl product 181/182 was assumed to have the free hydroxyl group) was similarly separated from the reaction mixture and fully characterised.

Attempts to use enolisable aldehydes as electrophiles with the anions derived from (arene)$Cr(CO)_3$ complexes have frequently been unsuccessful, with deprotonation of the electrophile occurring in preference to nucleophilic addition.[100] This problem has been overcome by dropwise addition of a dilute solution of the aldehyde to the anion and the method has been found to be applicable to (arene)$Cr(CO)_3$ anions.[101] Using this procedure acetaldehyde underwent smooth addition to the ring anion derived from (chroman)$Cr(CO)_3$ 167 to give the novel product [8-(1-hydroxyethyl)chroman]$Cr(CO)_3$ 185/186. No starting material was recovered, which would be the result of aldehyde enolisation.

The ratio of the two product diastereoisomers was 3:2 with the less polar diastereoisomer predominating, and the major diastereoisomer was easily separated by column chromatography and fully characterised including a satisfactory elemental analysis. The solution infrared spectrum of this

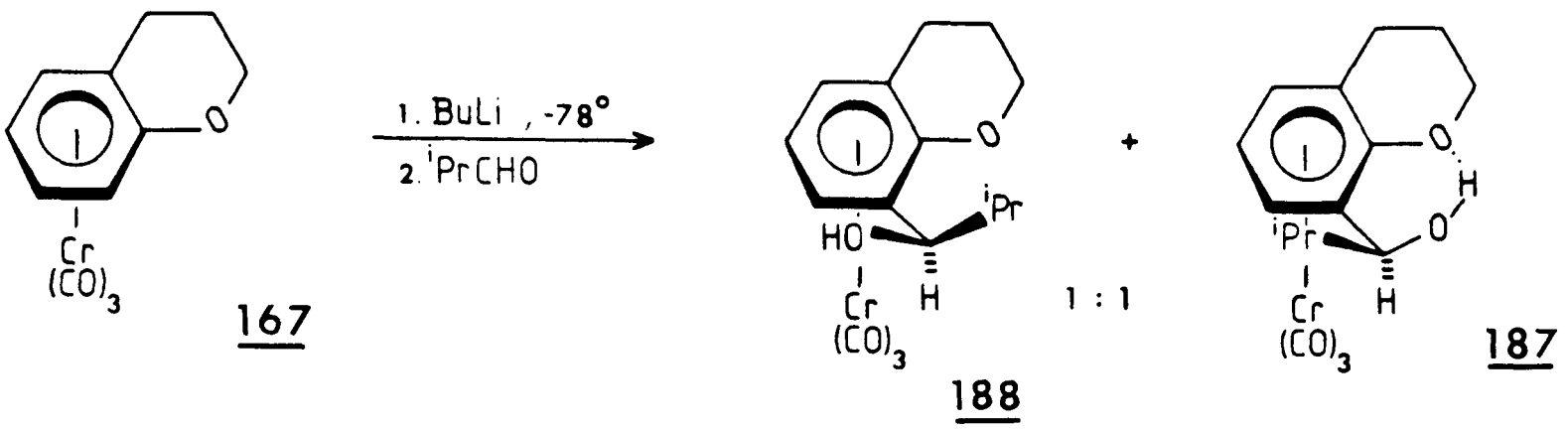
less polar diastereoisomer contained the expected two hydroxyl bands corresponding to the free and hydrogen bonded absorptions. Increasing the sample dilution produced no change in the relative intensities of the two bands, a result which is characteristic of an intramolecularly bonded hydroxyl group. This implies that diastereoisomer 185 which possesses the intramolecularly bonded hydroxyl group is the major product from the reaction.



167 186 185

This assignment of the less polar diastereoisomer as being complex 185, containing an intramolecularly hydrogen bonded OH group, is consistent with the previous assignment that the more polar diastereoisomer 182, from the addition of benzaldehyde, contained a free OH group.

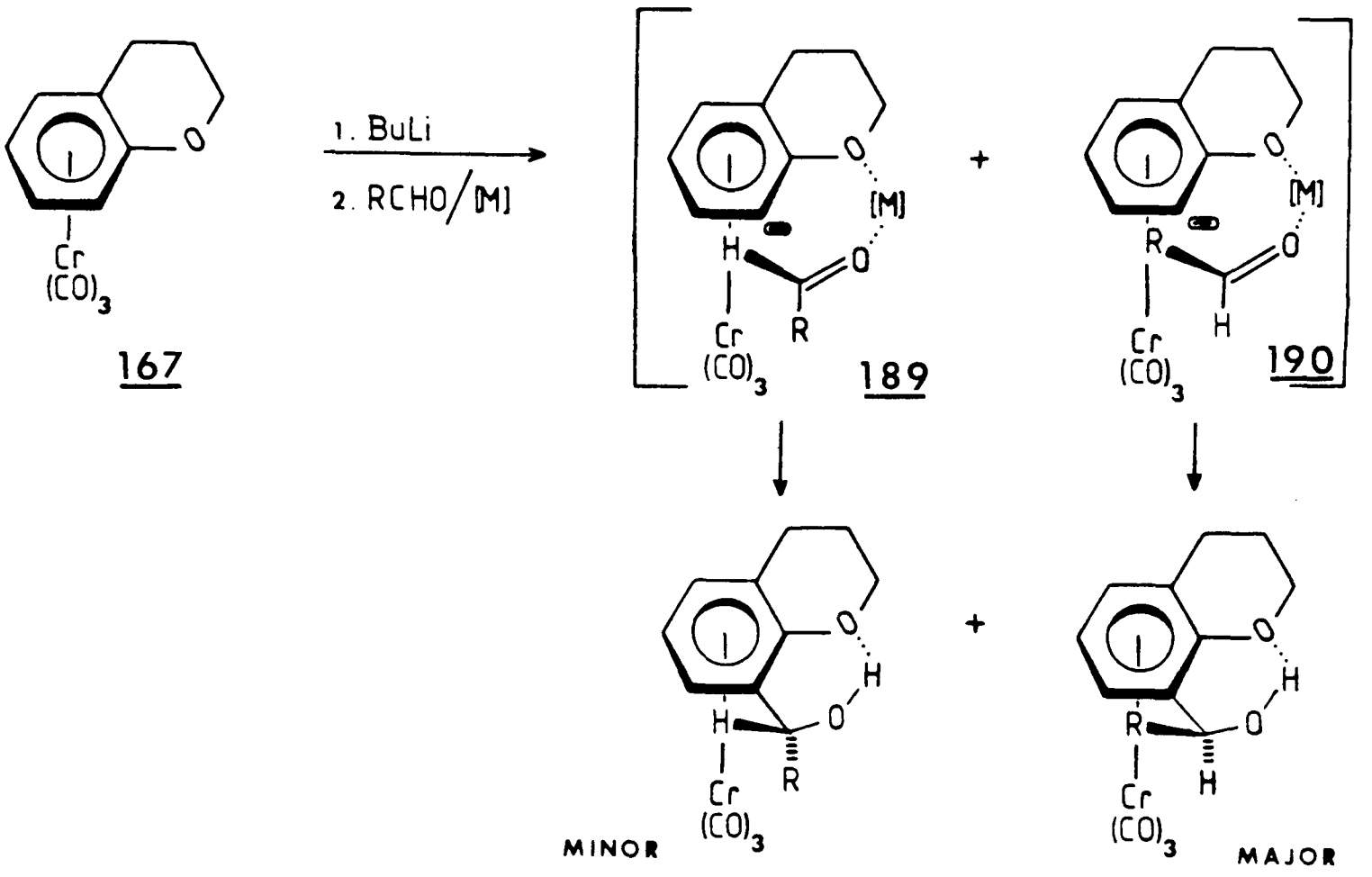
The addition of *iso*butyraldehyde to the ring anion derived from (chroman)$Cr(CO)_3$ 167 also proceeded smoothly to give [8-(1-hydroxy-2-methyl-propyl)chroman]$Cr(CO)_3$ 187/188 again without the recovery of any starting material 167. No selectivity, however, was observed and an equimolar ratio of the two diastereoisomers 187 and 188 was produced. The less polar diastereoisomer (identified as 187 by analogy with the previous additions) was again easily separated by column chromatography and characterised.



167 188 187

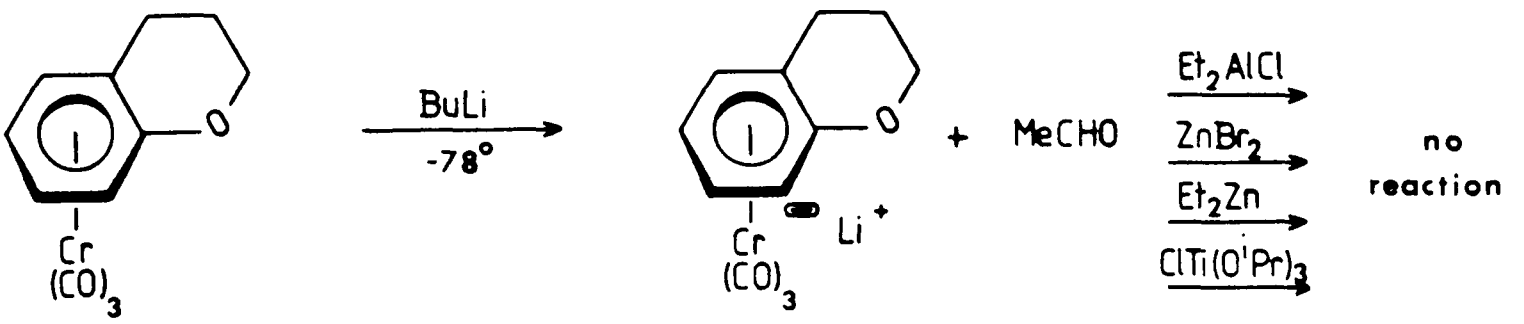
Of the four aldehydes used as substrates in the addition reaction, only benzaldehyde was found to give a modest degree of diastereoselectivity. Although the two product diastereoisomers could be separated in each case, the interest in asymmetric reactions in organic synthesis prompted us to investigate whether the predominant formation of one diastereoisomer could be achieved. It was anticipated that increased chelation between the oxygen of the heterocyclic ring and the aldehyde carbonyl oxygen could be achieved by the use of a better chelating metal counter-ion than lithium. There are then two possible orientations for the aldehyde substituent either *syn* 189 or *anti* 190 to the metal unit. On steric grounds the *anti* conformation 190 should predominate thus leading to the preferential formation of a single diastereoisomer.

A variety of reagents have been used in chelation controlled reactions, either to act as Lewis acids or to provide a different counter-ion *via* transmetallation of the initial lithium anion.[102]



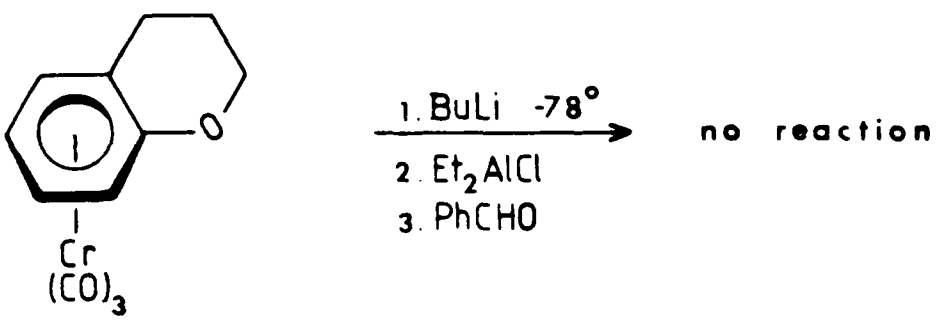
167

Both approaches, with the ring anion derived from (chroman)$Cr(CO)_3$ 167 using titanium, aluminium or zinc species were found to be unsuccessful. In each case the (arene)$Cr(CO)_3$ species was found to be totally unreactive and no addition to acetaldehyde was observed, starting material being recovered in each case.



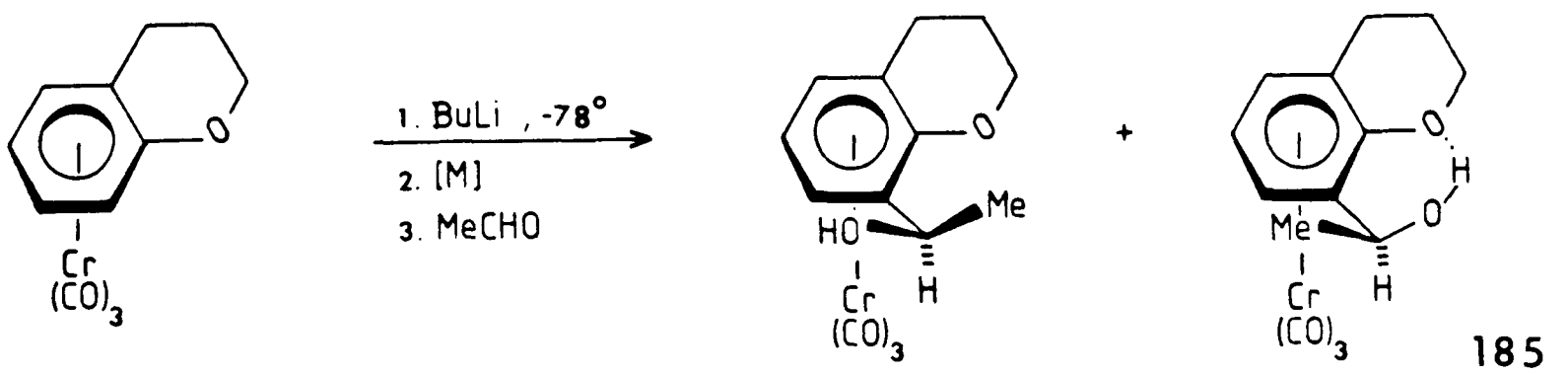
167

To check whether the recovery of starting material was due to enolisation of the aldehyde, benzaldehyde was added to a solution of the lithium ring anion that had been transmetallated with diethylaluminium chloride. Once again the starting material 167, was recovered, after quenching the reaction mixture with methanol, indicating that the transmetallated species was inert under the reaction conditions.



167

Organocerium reagents have been reported to react cleanly with enolisable aldehydes to give the addition products in high yield.[103] Transmetallation of the lithium ring anion from (chroman)$Cr(CO)_3$ 167 with cerium trichloride followed by addition of acetaldehyde gave, after work-up, the addition product 185/186 together with 30% recovery of the starting material 167. The diastereoisomer ratio was 1.3:1 with the more polar diastereoisomer 186 now predominating - a reversal of the selectivity observed for the addition of the lithium anion.



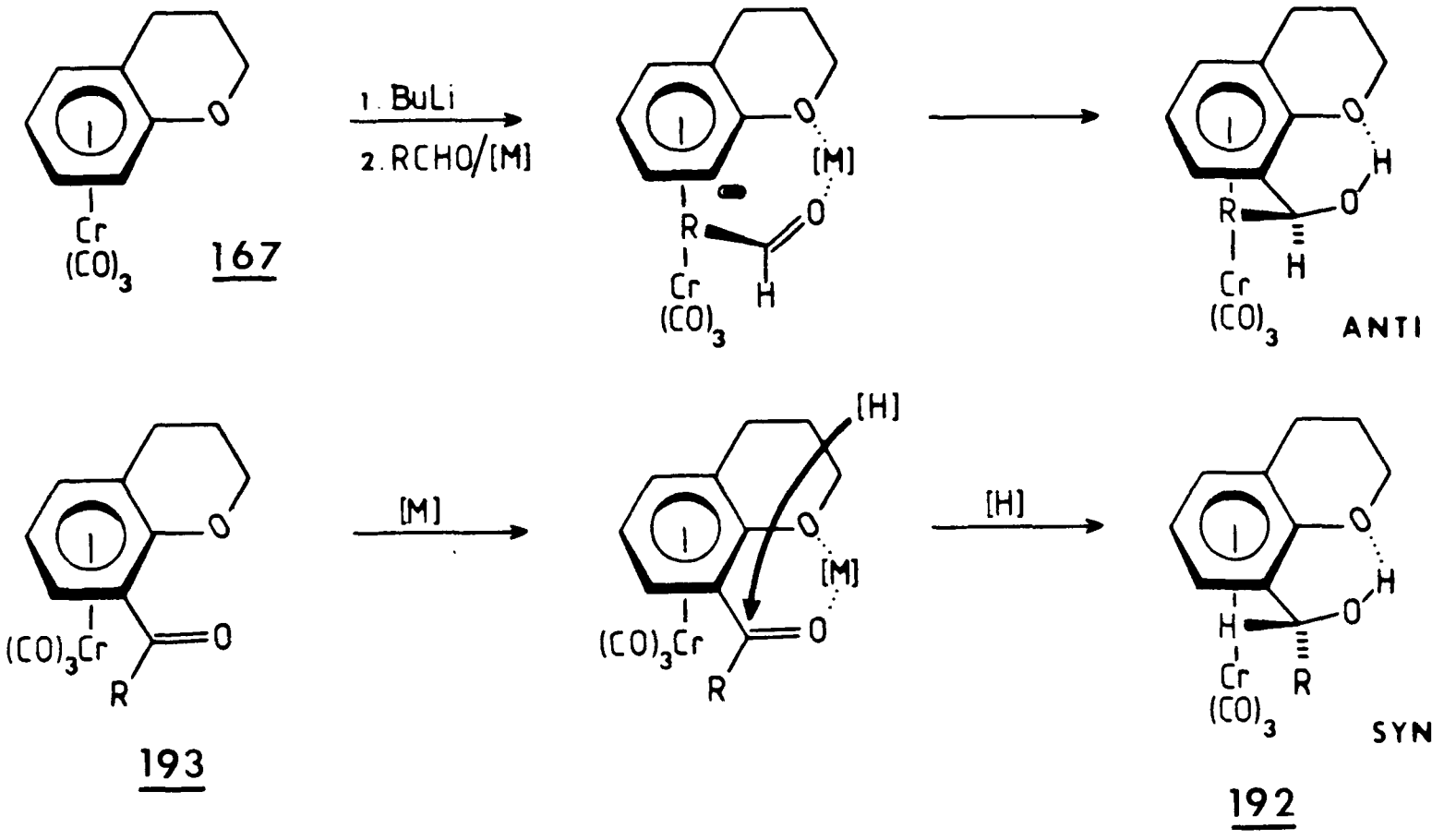
167

186

185

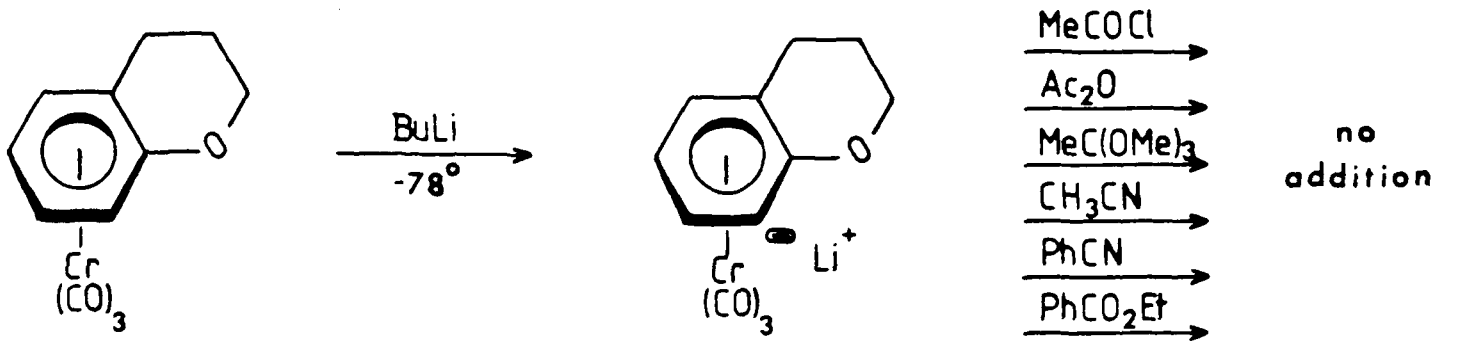
M = Li, 2 : 3
M = Ce, 1·3 : 1

It was originally anticipated that metal chelation in the addition of aldehydes to the ring anion would lead predominantly to one diastereoisomer of the addition product 191 with the aldehyde substituent *anti* to the metal unit. With the lack of success with these reactions, we decided to investigate the possibility of producing predominantly the other diastereoisomer 192 by reduction of the corresponding ketones 193. Chelation between the heterocyclic oxygen and the carbonyl group should lock the complex in the indicated conformation. The reducing agent would then approach the complex from the *exo* face, *i.e.* away from the bulky metal moiety, leading to predominantly the *syn* diastereoisomer 192.



167 191 193 192

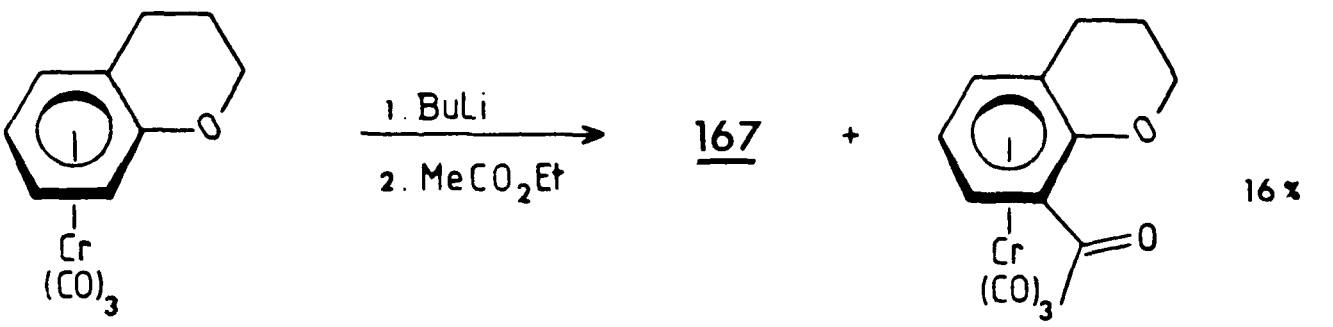
Attempts to synthesise the required ketones were made by the addition of a variety of carbonyl species or 'carbonyl equivalents' to the ring anion derived from (chroman)$Cr(CO)_3$ 167. With one exception these were all unsuccessful, only large amounts of the starting material 167 being recovered from each reaction.



167

The usual problems with these reactions are the addition of unreacted anion to the product, or enolisation of the carbonyl component.

The one successful reaction was from the addition of ethyl acetate to the ring anion. Whilst a substantial amount of starting material 167 was recovered from the reaction mixture, the novel (8-acetylchroman)$Cr(CO)_3$ 194 was also isolated as red needles, in low yield (16%).



167 194

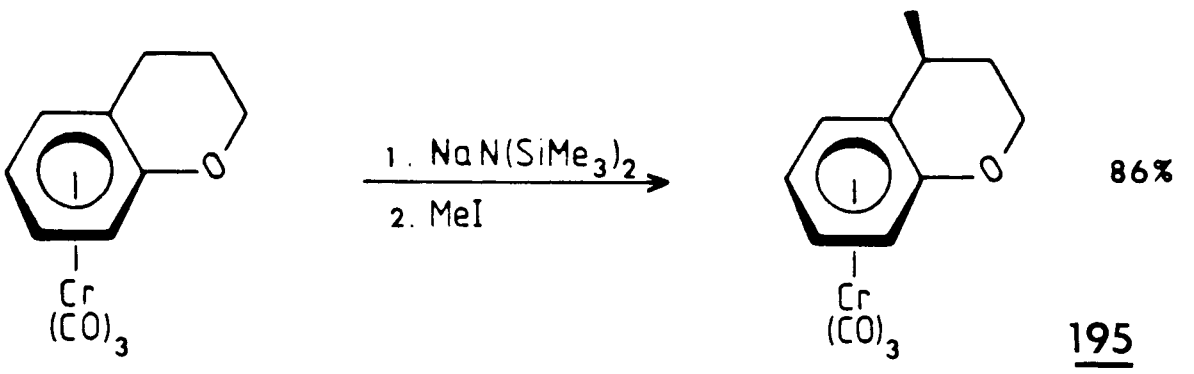
With the synthesis of only one ketone in such poor yield, no attempts were made to look at chelation control of the reduction to the alcohol and no further work was undertaken to control the diastereoselectivity of additions to the C8 ring anion.

2.3 Benzylic functionalisation

Having exploited the regiospecific ring deprotonation of

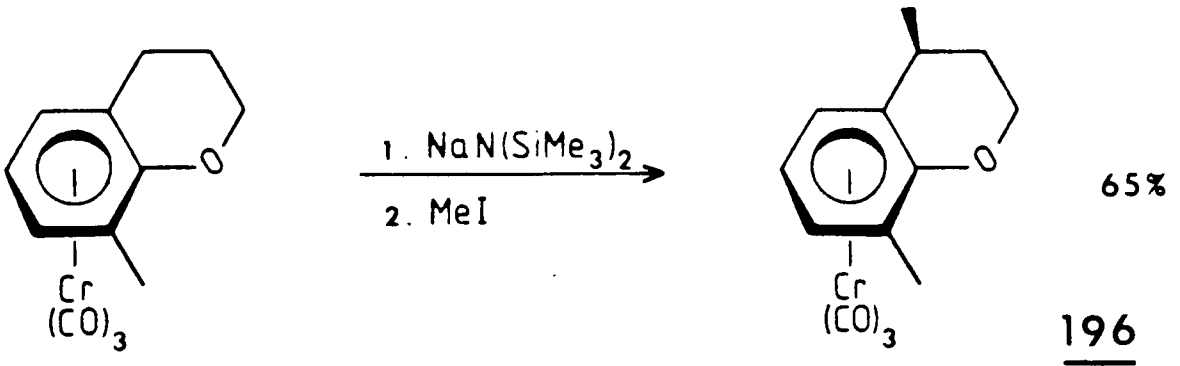
(chroman)$Cr(CO)_3$ 167 at C8, with the introduction of a range of substituents in high yield, attention was focussed on benzylic functionalisation. Coordination of the arene to the metal moiety increases the acidity of the benzylic, as well as the ring protons and benzylic deprotonation can normally be effected under thermodynamic conditions. This is a reaction that has no precedent on the uncomplexed arene.

Treatment of a solution of (chroman)$Cr(CO)_3$ 167 in DMF with sodium hexamethyldisilazide resulted in a rapid colour change of the reaction mixture from yellow to orange, suggesting that anion formation had occurred. Addition of methyl iodide to this solution resulted in an immediate colour change back to yellow and after work-up, a single product was isolated as yellow needles. The ^1H n.m.r. spectrum of this product contained four aromatic protons together with a three proton doublet characteristic of a secondary methyl group. Both the lower field (C2) and higher field (C3) two proton resonances were present in the spectrum, however there was only one C4 proton resonance. With a molecular ion m/z = 284 in the mass spectrum, this novel product was therefore identified as (4-methylchroman)$Cr(CO)_3$ 195 and subsequently characterised by elemental analysis. There was no sign of any ring methylated product and therefore regiospecific deprotonation and subsequent methylation had occurred at C4, the benzylic site. Two possible diastereoisomers of complex 195 exist, depending upon whether the methyl group is *syn* or *anti* to the metal unit. Only one methyl doublet was observed in the ^1H n.m.r. spectrum, consistent with complex 195 being a single diastereoisomer. By analogy with all other reactions of (arene)$Cr(CO)_3$ complexes the electrophile is assumed to have approached the anion from the *exo* face, leading exclusively to the *exo* methylated product.



167 195

(8-Methylchroman)$Cr(CO)_3$ 175 contains two sets of benzylic protons and deprotonation under thermodynamic conditions could occur at either site. Treatment of this complex 175 with sodium hexamethyldisilazide in DMF at room temperature followed by addition of methyl iodide gave, after work-up, a single product. The ^1H n.m.r. spectrum contained a three proton doublet at δ1.45 and a three proton singlet at δ2.17, rather than the resonances expected for an ethyl group which would have resulted from reaction at the C8 methyl group. This novel product was fully characterised as (4,8-dimethyl-chroman)$Cr(CO)_3$ 196, including by elemental analysis.

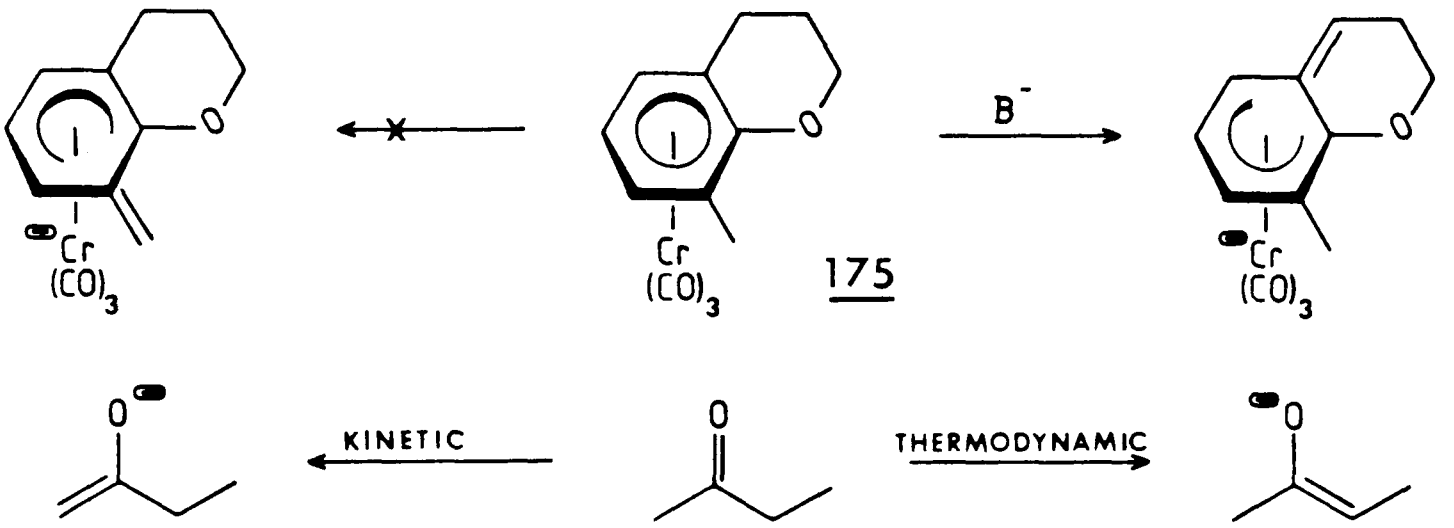


175 196

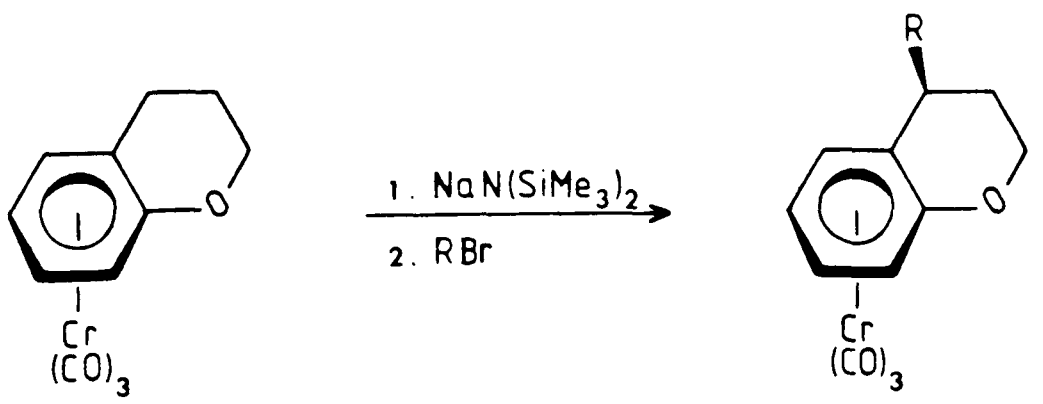
This result is in direct contrast to the deprotonation of complex 175 with *n*-BuLi which leads to ring methylated products.

Deprotonation at the secondary rather than the primary benzylic site can be rationalised by considering the stability of the resultant anions. The $Cr(CO)_3$ moiety stabilises benzylic anions *via* mesomeric donation of the electron density onto the metal unit to form an olefin type species.

Thermodynamic deprotonation, under equilibrium conditions, therefore occurs at the more highly substituted site due to the greater thermodynamic stability of a more highly substituted olefin. This is analogous to the deprotonation of 2-butanone to form its enolate. Kinetic deprotonation occurs at C1 whilst the most thermodynamically stable enolate is formed from deprotonation at C3.[104]

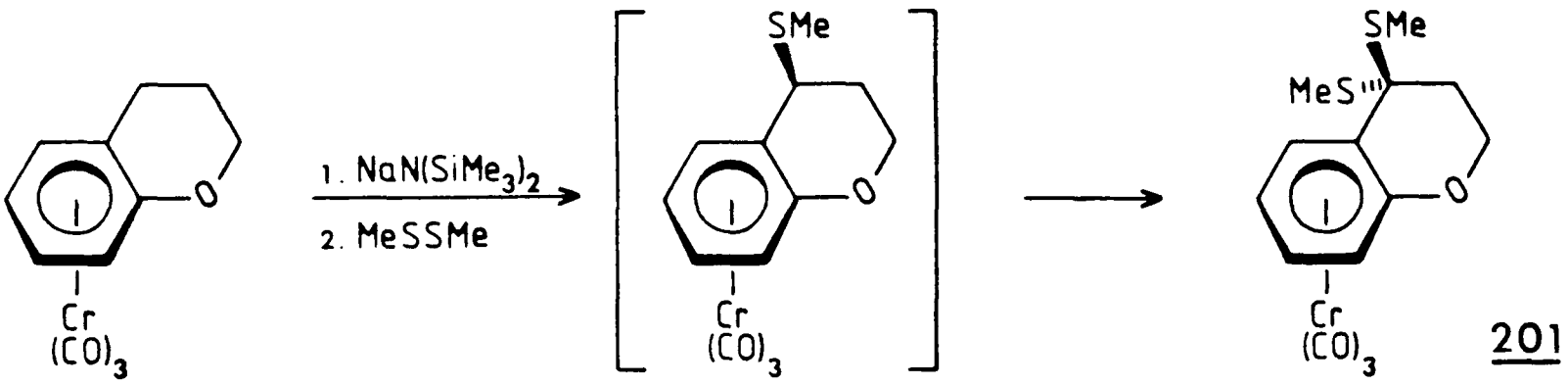


Treatment of the benzylic anion generated from (chroman)$Cr(CO)_3$ 167 with a number of carbon electrophiles led to the formation of the corresponding 4-substituted chroman complexes in good yield. Thus ethyl, allyl and benzyl bromide all underwent rapid addition to produce stereospecifically the novel *exo* substituted complexes 197 to 199 which were each characterised by elemental analysis. *Iso*propyl bromide failed to give the expected addition product. This is presumably due to deprotonation of the electrophile occurring in preference to nucleophilic addition.



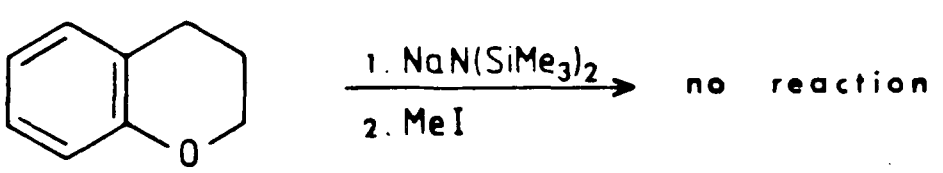
167

The use of methyl disulphide as an electrophile was by analogy with the reaction of the C8 ring anion, expected to produce (4-thiomethylchroman)-$Cr(CO)_3$ 200. The single product isolated from the reaction mixture, however, contained two, three proton singlets and no resonance for the remaining *endo* C4 proton. This suggested that disubstitution had occurred. A molecular ion *m/z*= 362 in the mass spectrum and elemental analysis confirmed this novel product to be (4,4-dithiomethylchroman)$Cr(CO)_3$ 201. In the mono-substituted complex 200 the remaining C4 proton would be very acidic and presumably the disubstituted product 201 arises *via* the formation of a second benzylic anion and subsequent quenching with excess electrophile.



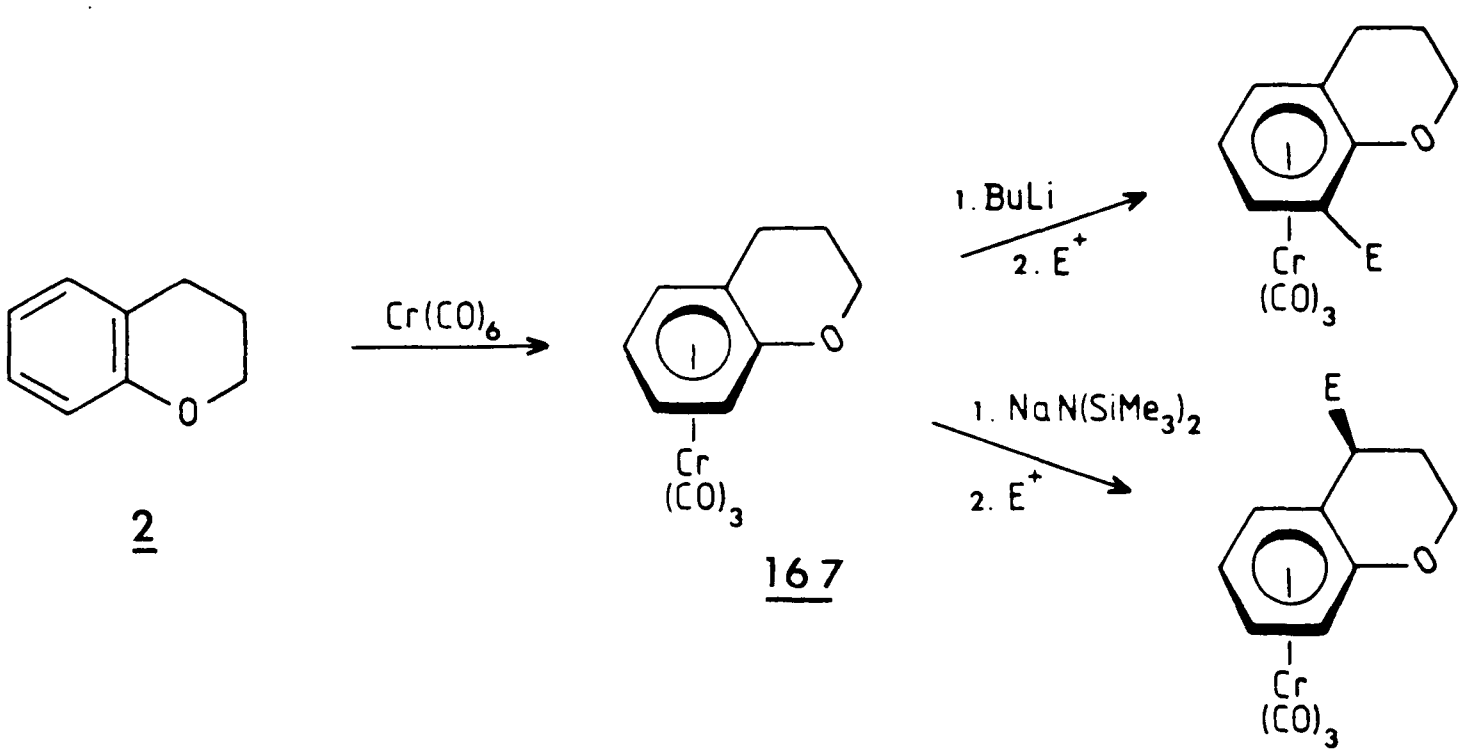
167 200 201

A number of electrophiles have been shown to add to the benzylic anion derived from (chroman)$Cr(CO)_3$ 167. To compare the reaction of the uncomplexed arene, a sample of chroman 2 was treated under identical conditions with sodium hexamethyldisilazide and methyl iodide. After work-up, only the starting material was recovered with no evidence for any ring or benzylic methylation.



2

Coordination of chroman 2 to the $Cr(CO)_3$ moiety therefore allows selective, regiospecific functionalisation of either the C8 ring or C4 benzylic sites with a variety of electrophiles. Under analogous conditions the free arene was found to be either totally inert or failed to give a clean reaction.

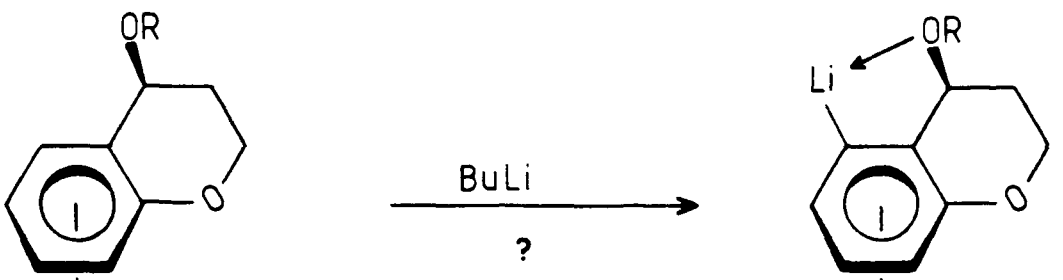


2

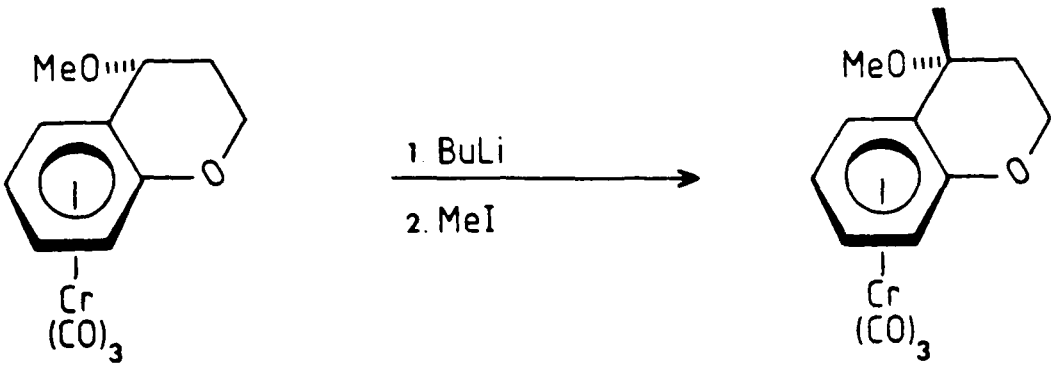
167

3. 4-Chromanol functionalisation

The work on (chroman)$Cr(CO)_3$ 167 has shown that selective functionalisation of the heterocycle can be achieved either at C4 (*via* a benzylic anion) or at C8 (*via* a ring anion). During the course of this work we were interested in the effect that other chelating groups in the complex might have on the site of ring deprotonation, particularly whether oxa substituents at C4 would alter the observed regiochemistry. With (chroman)$Cr(CO)_3$ 167 deprotonation at C8 presumably occurs by chelation of the base to the heterocyclic oxygen. With a C4 oxa substituent, chelation could occur either site and C5 deprotonation might be observed.

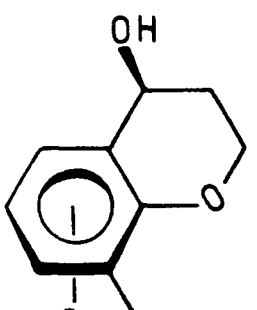


The only requirement for these complexes is that the oxa substituent be on the *exo* face of the complex, since the corresponding *endo* substituted complexes have been shown to undergo benzylic deprotonation with strong base.[105]

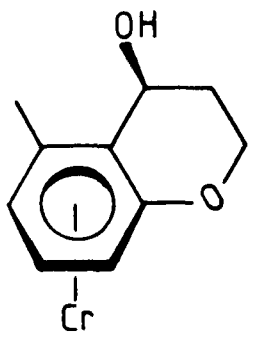


The corresponding deprotonation is not observed with the *exo* complexes because the removal of the *endo* proton requires the approach of the base from the face of the complex containing the metal unit. This is almost totally precluded, on steric grounds, and therefore ring deprotonation is observed. The only known case for *endo* deprotonation is with a thiomethyl substituent, under thermodynamic conditions [see section 2(ii)], due to the sulphur rendering the remaining pseudo-equatorial proton very acidic.

With potential deprotonation at either C5 or C8 the unambiguous synthesis of authentic samples of *exo*-(8-methyl-4-chromanol)$Cr(CO)_3$ 202 and *exo*-(5-methyl-4-chromanol)$Cr(CO)_3$ 203 was undertaken to allow positive product identification.



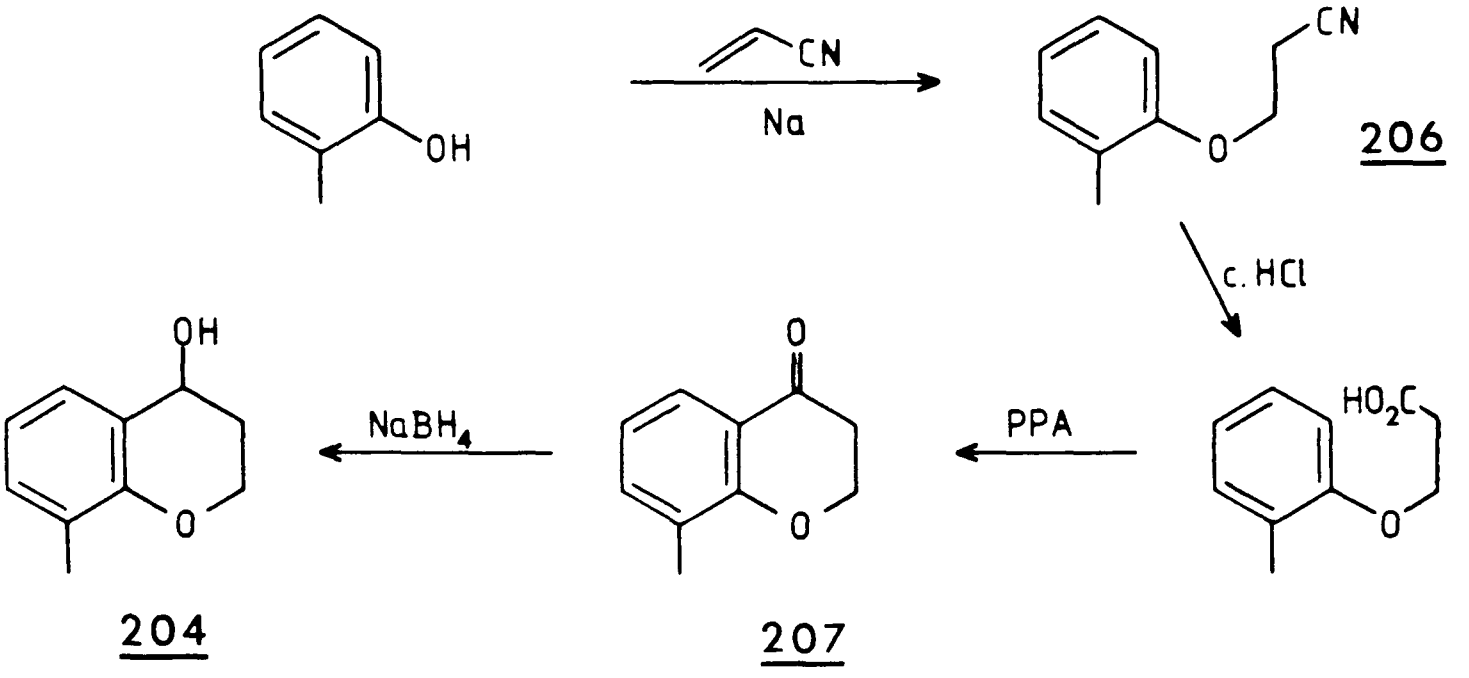
202



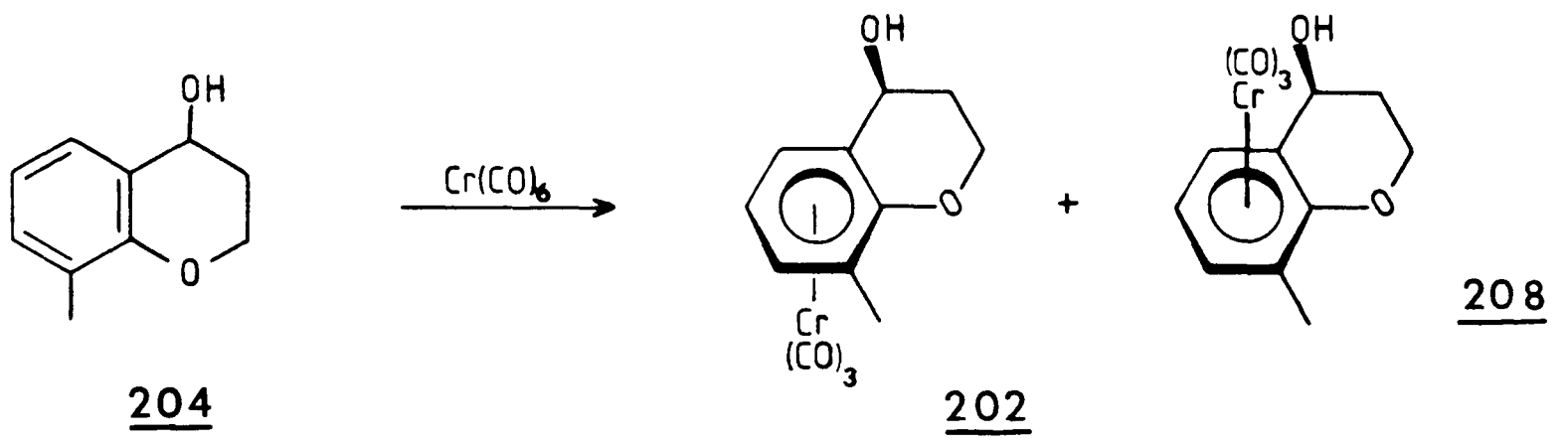
203

The free alcohols 204 and 205 were prepared from *o*- and *m*-cresol respectively. Treatment of the phenoxide anion from *o*-cresol with acrylonitrile produced *via* a Michael addition the 3-aryloxypropionitrile 206. Hydrolysis of this nitrile was effected by refluxing in concentrated hydrochloric acid and the resultant carboxylic acid cyclised to 8-methylchromanone 207 with polyphosphoric acid. Reduction of the ketone with sodium borohydride proceeded smoothly to give 8-methyl-4-chromanol 204.

Heating this arene 204 with chromium hexacarbonyl in a mixture of di-*n*-butyl ether/THF produced the deep yellow colour characteristic of most (arene)$Cr(CO)_3$ complexes and after work-up a single product was isolated as yellow needles. Two distinct sets of resonances could be

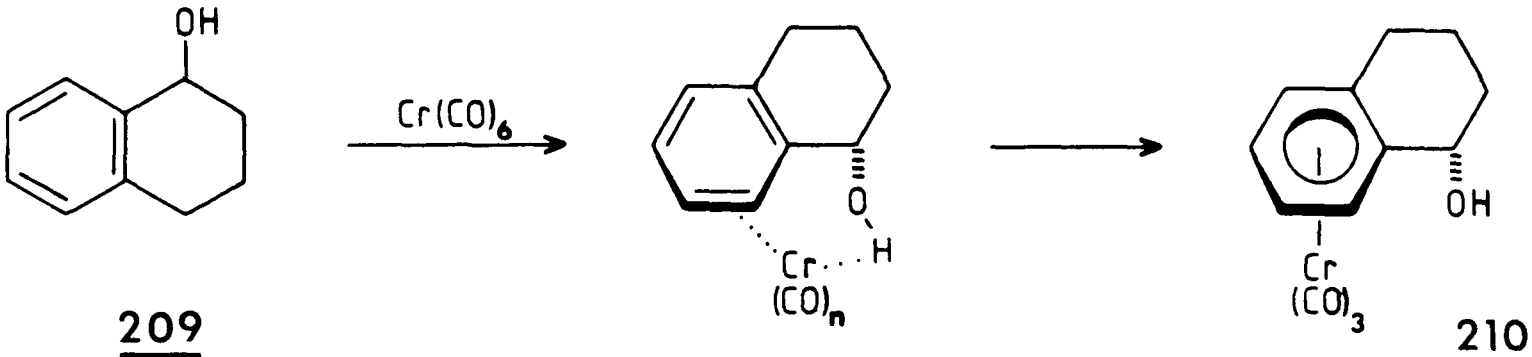


assigned to each aromatic proton in the ^1H n.m.r. spectrum. This is consistent with the formation of the product (8-methyl-4-chromanol)$Cr(CO)_3$ as a mixture of the two possible diastereoisomers 202 and 208 (ratio *ca.* 1:1), with the metal unit coordinated to either diastereotopic face of the arene.



204 202 208

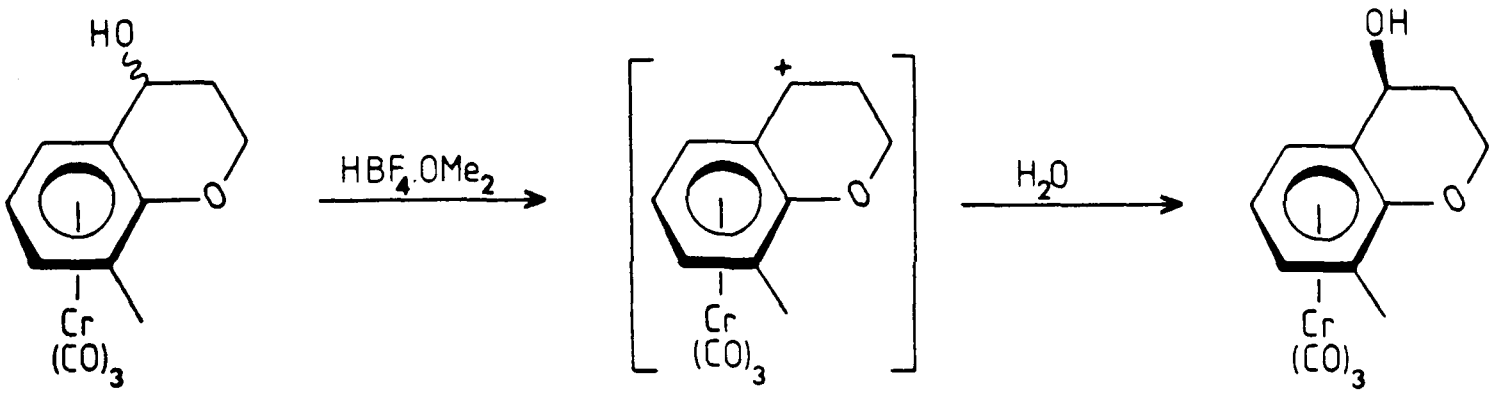
(1-Tetralol)$Cr(CO)_3$ 209 has been shown to undergo direct complexation to the $Cr(CO)_3$ moiety to produce exclusively the *endo* diastereoisomer 210.[101] This was rationalised by assuming intramolecular delivery of the metal unit to one face of the arene by hydrogen bonding with the hydroxyl group.



209 210

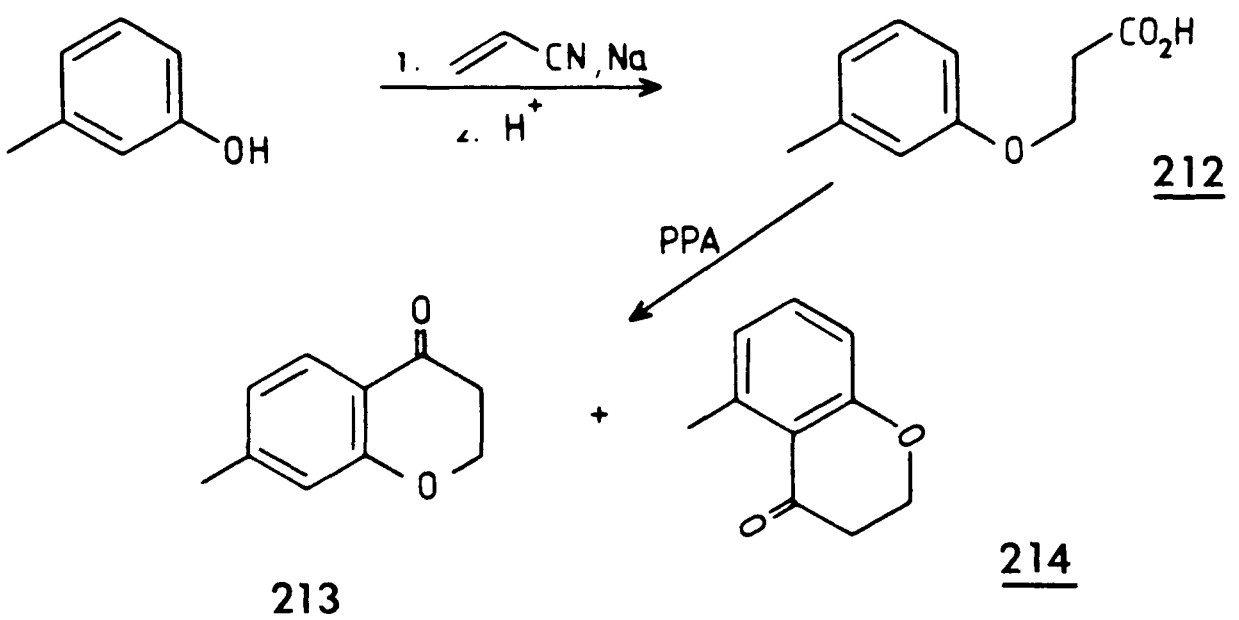
The absence of an analogous reaction with the 4-chromanol derivative 204 is presumably due to preferential chelation of the metal unit to the heterocyclic oxygen. There would then be little steric difference between the two faces of the arene.

The mixture of 4-chromanol diastereoisomers 202 and 208 was converted to exclusively the *exo* diastereoisomer 202 by treating a dichloromethane solution of this mixture with the dimethyl ether complex of tetrafluoroboric acid, followed by water.[106] The reaction proceeds *via* a benzylic carbonium ion 211, which is stabilised by the metal unit. Quenching this carbonium ion 211 with water results in the exclusive formation of the *exo* diastereoisomer 202 since the metal moiety completely shields the *endo* face of the complex 211 and the water can only add from the *exo* face.



202/208 211 202

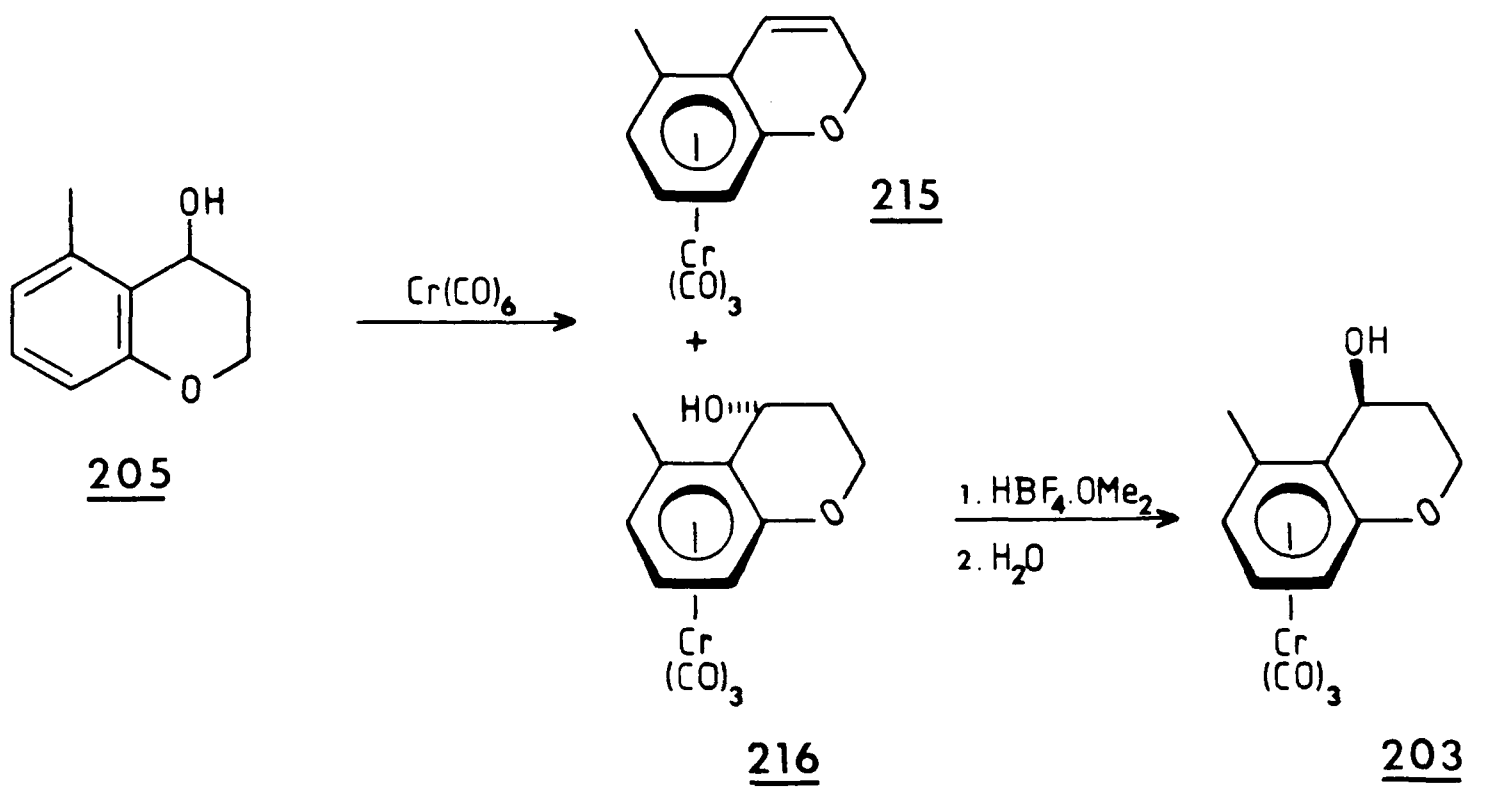
exo-(5-Methyl-4-chromanol)$Cr(CO)_3$ 203 was prepared in a similar fashion from *m*-cresol. The cyclisation of the 3-aryloxypropionic acid 212 however, gave rise to a 3:2 mixture of two isomeric chromanones 213 and 214, due to cyclisation both *ortho* and *para* to the ring methyl substituent.



These two isomers were separated by column chromatography and were identified from the aromatic proton resonances in their ^1H n.m.r. spectra. The spectrum of the major isomer contained a similar pattern to that observed for the 6-bromochromone 87, indicating the major isomer to be 7-methyl-chromanone 213. The spectrum of the minor isomer contained the two doublets and a triplet with equal coupling constants, characteristic of three contiguous protons and was therefore consistent with the minor product 214 being the desired 5-methylchromanone.

Reduction of this minor isomer 214 to the 4-chromanol 205 again proceeded smoothly with sodium borohydride. Direct complexation to the metal unit was attempted with chromium hexacarbonyl under the usual conditions. Unexpectedly, two products were isolated from this reaction in a ratio of 5:2. The ^1H n.m.r. spectrum of the major product contained only the C2

protons from the heterocyclic ring, with two additional vinyl protons. With a molecular ion *m/z* = 282 in the mass spectrum, this product was assigned as the dehydrated (5-methyl-3-chromene)$Cr(CO)_3$ 215. The minor product was found to be one diastereoisomer of the expected (5-methyl-4-chromanol)$Cr(CO)_3$ which was identified as the *endo* diastereoisomer 216 by complete epimerisation to the required *exo* diastereoisomer 203 with acid and water.

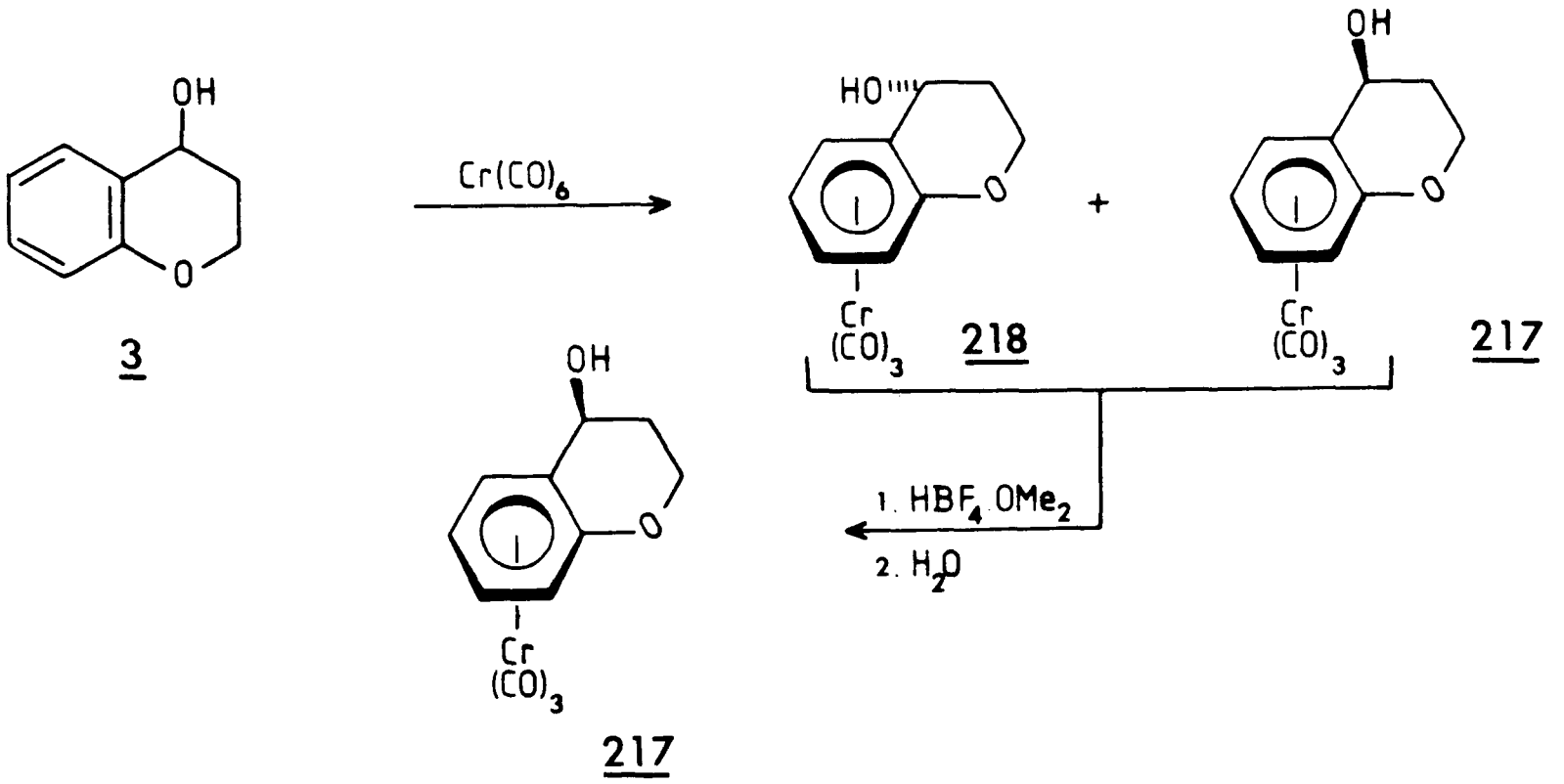


The dehydrated product may have arisen from an acid catalysed loss of hydroxide, and elimination from the resultant benzylic carbonium ion. Hydroxide loss from the *exo* alcohol would proceed at a much faster rate than from the corresponding *endo* alcohol due to anchimeric assistance from the metal unit. This would therefore be consistent with the exclusive formation of the *endo* alcohol diastereoisomer 216 in the product mixture.

The two authentic methylated alcohols 202 and 203 were found to have clearly different ^1H n.m.r. spectra, thus allowing positive identification of either C5 or C8 methylated products.

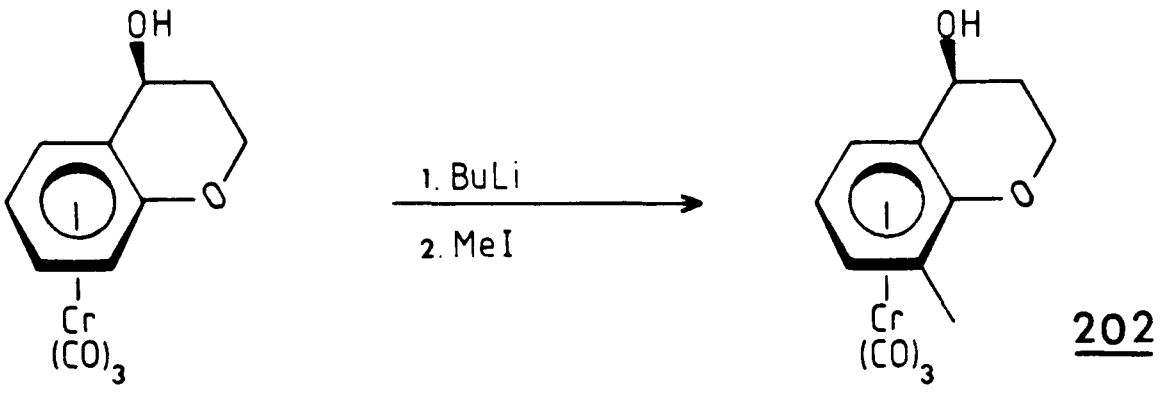
3(i) *via* the alcohol

(4-Chromanol)$Cr(CO)_3$ was prepared as an equimolar mixture of the two possible diastereoisomers 217 and 218 by direct complexation of the free arene 3 with chromium hexacarbonyl.[107] This mixture of diastereoisomers 217/218 was then converted into exclusively the *exo* diastereoisomer 217 by treatment with acid and water.



Treatment of *exo*-(4-chromanol)$Cr(CO)_3$ 217 with two equivalents of *n*-BuLi at -78°C, followed by methyl iodide gave, after work-up, a single product in good yield. The ^1H n.m.r. spectrum showed the product to be a ring methylated alcohol and it was found, by comparison to be identical with the ^1H n.m.r. spectrum of the authentic 8-methylated complex 202. Deprotonation and subsequent methylation had therefore occurred at C8.

The first equivalent of base deprotonates the alcohol to generate the alkoxide ion. Presumably a second deprotonation (at C5) would then be disfavoured due to the resultant coulombic repulsion between the two



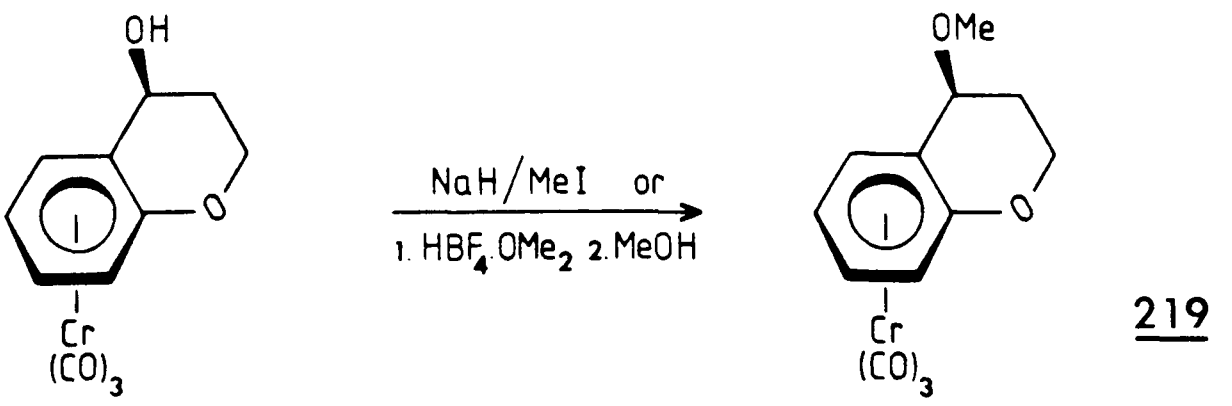
217 202

adjacent anions. Deprotonation at the alternative site (C8) gives rise to the observed product 202. The isolation of the alcohol 202 rather than the corresponding methyl ether is presumably due to the poor nucleophilicity of the alkoxide anion at low temperatures.

3(ii) *via* the methyl ether

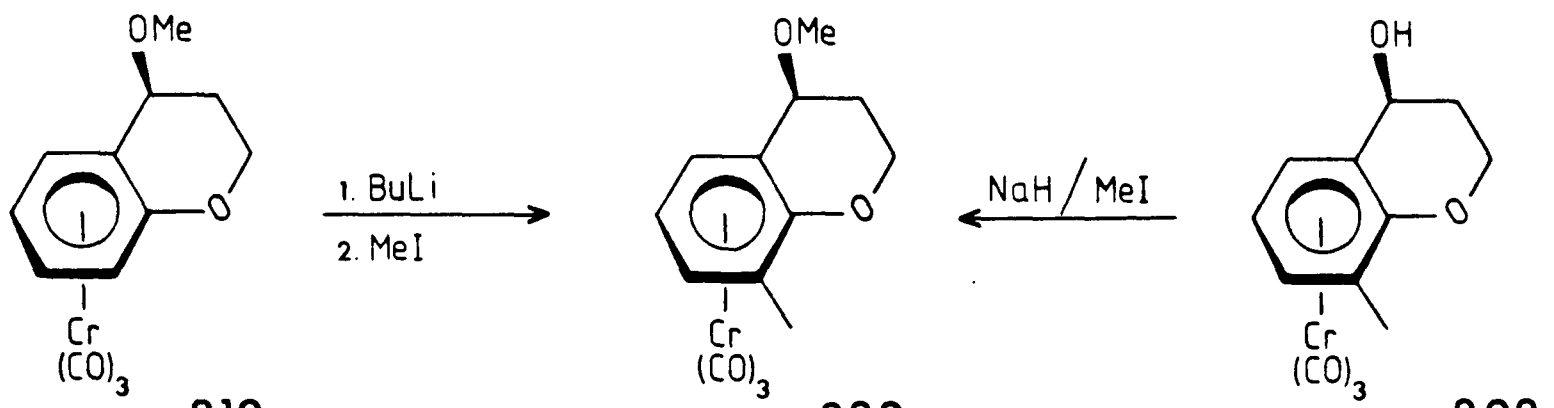
There has been only one previous study on the reaction of a 4-oxa substituted (chroman)$Cr(CO)_3$ derivative. It was reported[105] that treatment of *exo*-(4-chromanol methyl ether)$Cr(CO)_3$ 219 sequentially with *n*-BuLi and methyl iodide gave a ring methylated product. However, no positive product structure identification was made.

exo-(4-Chromanol methyl ether)$Cr(CO)_3$ 219 can be prepared either by methylation of the alcohol 217 with sodium hydride and methyl iodide or by quenching the benzylic carbonium ion derived from (4-chromanol)$Cr(CO)_3$ 217/218 with methanol.



217 219

Treatment of this complex 219 with *n*-BuLi at -78°C followed by methyl iodide, gave after work-up a ring methylated product readily identified from a three proton singlet at δ2.15 in the ^{1}H n.m.r. spectrum and a molecular ion *m/z* = 314 in the mass spectrum. A sample of authentic *exo*-(8-methyl-4-chromanol methyl ether)$Cr(CO)_3$ 220 was prepared by treatment of the authentic C8 methylated *exo*-alcohol 202 with sodium hydride and methyl iodide. A comparison of their ^{1}H n.m.r. spectra showed that the product derived from direct ring methylation and the authentic sample were identical.



219 220 202

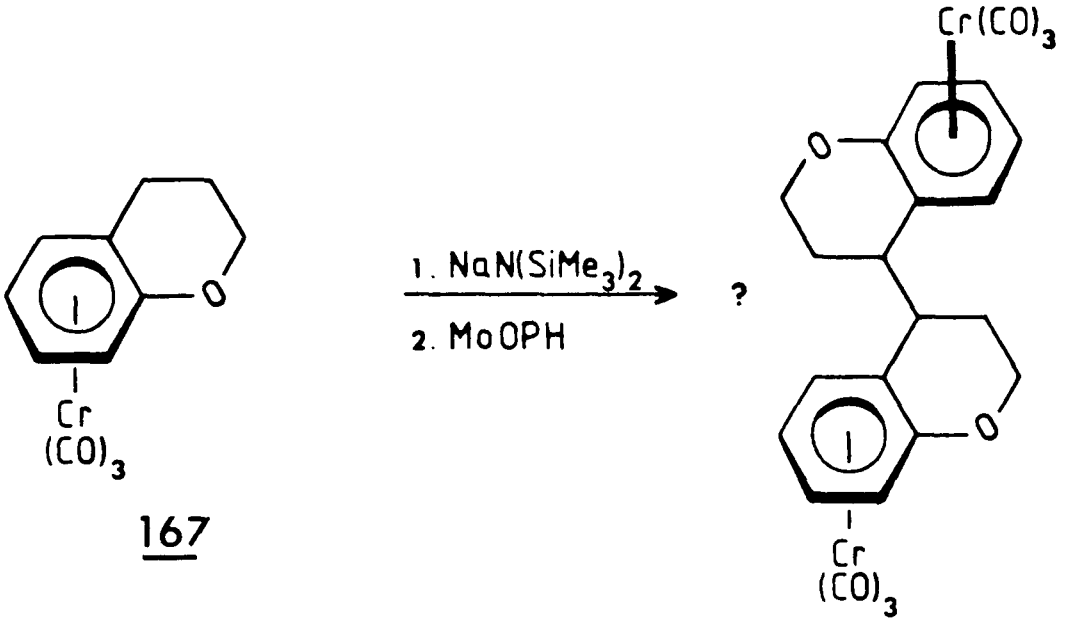
The C4 methoxy group therefore appears to have no effect upon the site of ring deprotonation.

3(iii) *via* silyl ethers

While investigating the functionalisation of (4-chromanol)$Cr(CO)_3$ considerable quantities of the pure *exo* diastereoisomer 217 were required. Although the required diastereoisomer was prepared by direct complexation of the alcohol 3, followed by conversion of the mixture of diastereoisomers 217 and 218 to the desired *exo* alcohol 217, the overall yield for this process was not high (40%) and two alternative approaches were considered.

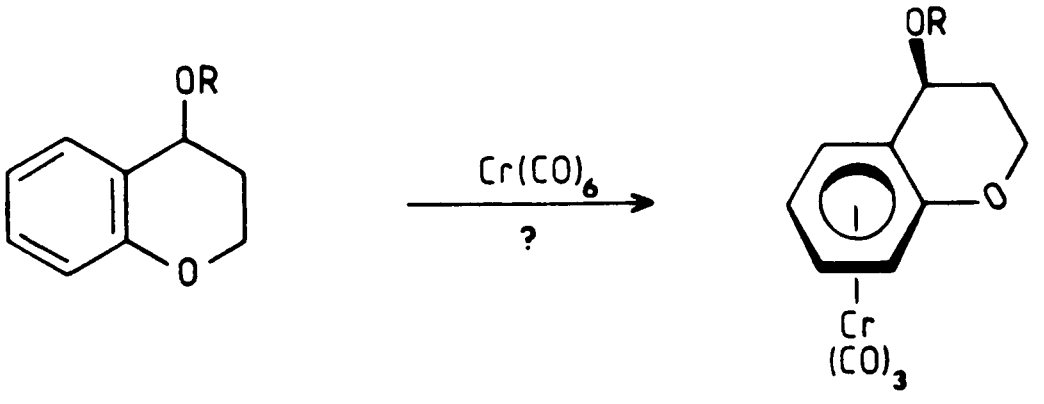
Benzylic functionalisation of (chroman)$Cr(CO)_3$ 167 *via* the C4 anion leads exclusive to the corresponding *exo* substituted complexes. The use of a source of electrophilic oxygen as a substrate under these conditions

might therefore produce the required *exo* alcohol 217. Oxodiperoxymolybdenum-(pyridine)hexaphosphoramide (MoOPH) is one such reagent which has been used for the oxidation of enolate anions to α-hydroxyketones[108] and for the oxidation of the benzylic position of (*N*-methyl-1,2,3,4-tetrahydroisoquinoline)-$Cr(CO)_3$.[87] Formation of the C4 anion from (chroman)$Cr(CO)_3$ 167 with sodium hexamethyldisilazide, followed by cooling to -40°C and treatment with MoOPH gave, after work-up a single product 221 and some recovered starting material 167. The ^1H n.m.r. spectrum of this product was uninterpretable, but from a molecular ion *m/z* = 538 in the mass spectrum the product 221 was tentatively assigned as the dimer formed by radical coupling of two (chroman)$Cr(CO)_3$ species. With no evidence for the formation of any alcohol, this approach was not pursued.



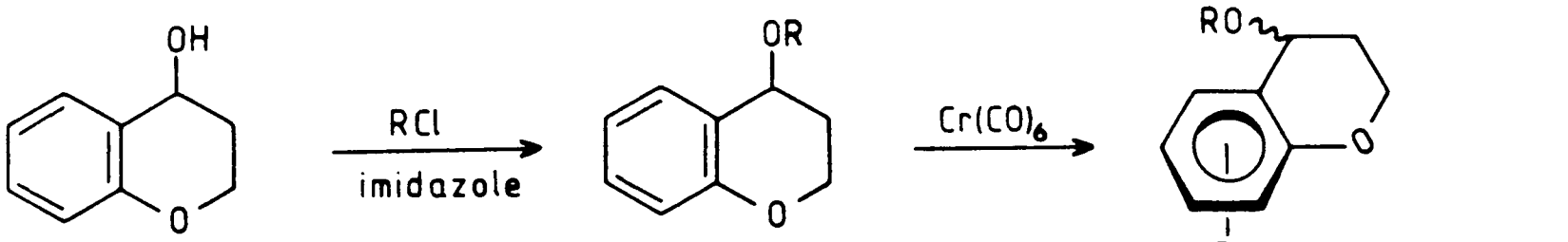
167 221

Coordination of the metal unit to the arene is affected by the steric environment and preferential coordination to one face has been observed.[88] As an alternative approach, it was thought that a bulky alcohol protecting group might inhibit the approach of the metal unit from one face of the arene, thus leading to predominantly one diastereoisomer of the product.



The two protecting groups chosen were *t*-butyldimethylsilyl (TBDMS) and tri-*i*-propylsilyl (TIPS), since they are reasonably stable to a wide range of conditions and yet can easily be removed under mild conditions to regenerate the parent alcohol.

Treatment of a solution of 4-chromanol 3 in DMF with either TBDMS-chloride or TIPS-chloride in the presence of imidazole[109] cleanly gave the silyl ethers 222 and 223. Heating these ethers with chromium hexacarbonyl, under the usual conditions for arene coordination to the metal unit, gave the desired $Cr(CO)_3$ complexes 224/225 and 226/227 as yellow crystals, which were fully characterised including by elemental analysis.

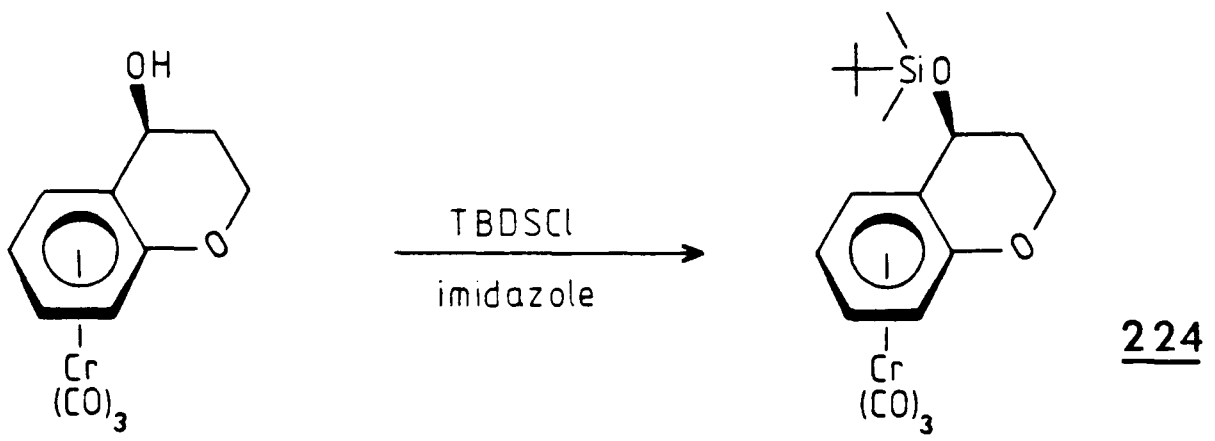


3 222/223 224/225 226/227

222 224 225 R = TBDMS 223 226 227 R = TIPS

The ^1H n.m.r. spectra of each of the product mixtures 224/225 and 226/227 contained two sets of signals for each aromatic proton. This is consistent with each product mixture containing both the *exo* and *endo* diastereoisomers. In each case the ratio, by integration, of these two

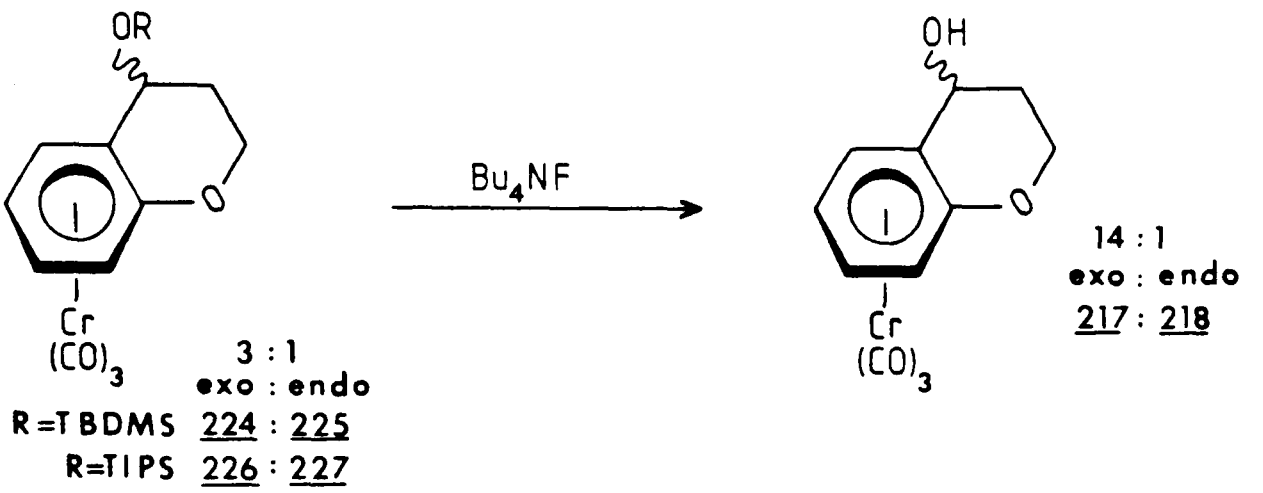
diastereoisomers was 3:1. An authentic sample of *exo*-(4-chromanol TBDMS ether)$Cr(CO)_3$ 224 was prepared from *exo*-(4-chromanol)$Cr(CO)_3$ 217 by treatment with TBDMS-chloride and imidazole.



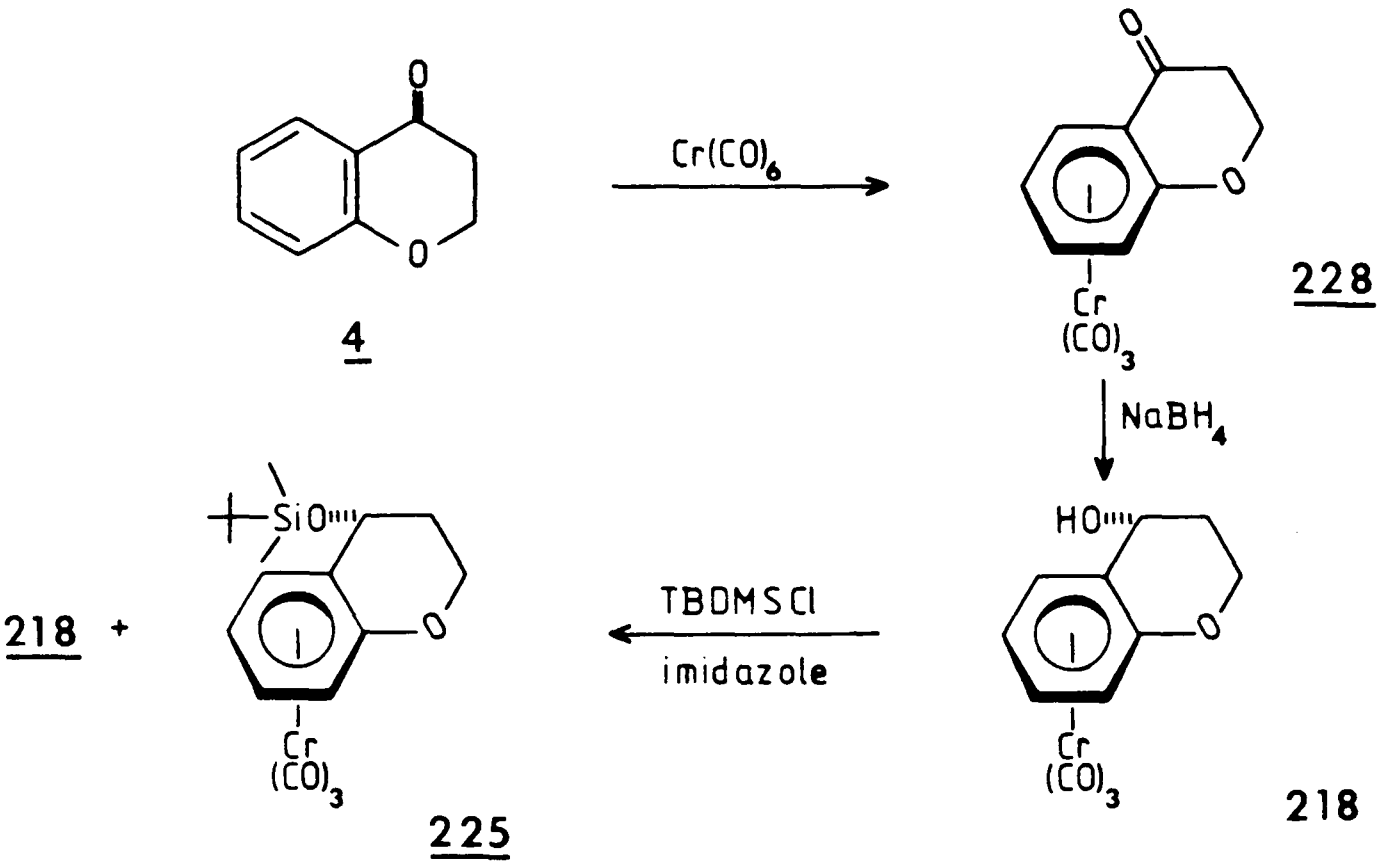
217 224

Comparison of the ^1H n.m.r. spectrum of this sample with that of the mixture of TBDMS ethers 224/225 formed by direct complexation, allowed the *exo* diastereoisomer to be identified as the major product. By analogy, the *exo* diastereoisomer was also presumed to be the major product in the direct complexation of the TIPS ethers. The use of bulky silyl protecting groups therefore increased the facial selectivity of coordination by the metal unit (from *ca.* 1:1 to 3:1), but failed to produce one diastereoisomer exclusively.

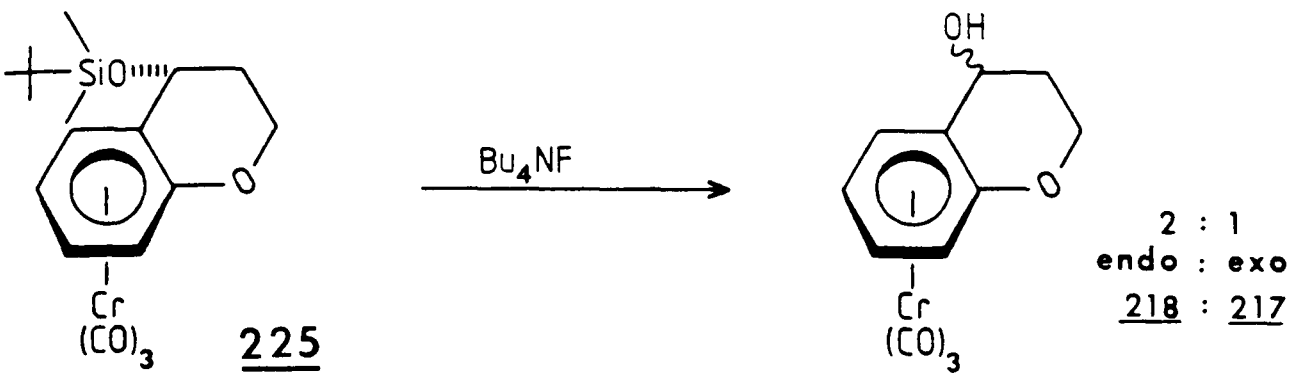
Treatment of a mixture of the two silyl ether complexes 224/225/226/227 with tetrabutylammonium fluoride in THF at room temperature resulted in the expected cleavage of the silyl ethers[109] to give (4-chromanol)$Cr(CO)_3$ 217/218. Deprotection of silyl ethers normally proceeds with cleavage of the Si-O bond and should therefore proceed with retention of stereochemistry from the silyl ether to the alcohol. Unexpectedly, the 3:1 mixture of *exo* : *endo* silyl ethers 224/226 : 225/227 gave a 14:1 mixture of *exo* : *endo* (4-chromanol)$Cr(CO)_3$ 217 : 218 in 71% yield.



An attempt to fractionally crystallise the major *exo* diastereoisomer 217 from this 14:1 mixture was unsuccessful, an isomer ratio of 12:1 being obtained in the isolated product. The mechanism for this loss of stereochemistry on silyl ether deprotection is uncertain, but may proceed *via* a chromium stabilised benzylic carbonium ion. To investigate this the pure *endo* silyl ether 225 was deprotected under identical conditions. The required diastereoisomer 225 was synthesised from a sample of *endo*-(4-chromanol)$Cr(CO)_3$ 218. Direct complexation of 4-chromanone 4 with chromium hexacarbonyl under the standard conditions gave, after work-up (4-chromanone)-$Cr(CO)_3$ 228 as red needles.[107] Reduction with sodium borohydride then led to a single diastereoisomer of the alcohol, by comparison with the mixture produced by direct complexation. This was different from the *exo* diastereoisomer 217 and was therefore identified as *endo*-(4-chromanol)$Cr(CO)_3$ 218. The stereospecific reduction to give the *endo* isomer 218 occurs as a result of the metal moiety completely shielding the lower face of the complex 228 thus limiting the approach of the reducing agent to the *exo* face. Treatment of this alcohol 218 with TBDMS-chloride and imidazole in DMF gave the required *endo*-(4-chromanol TBDMS ether)$Cr(CO)_3$ 225 together with some recovered starting material 218.

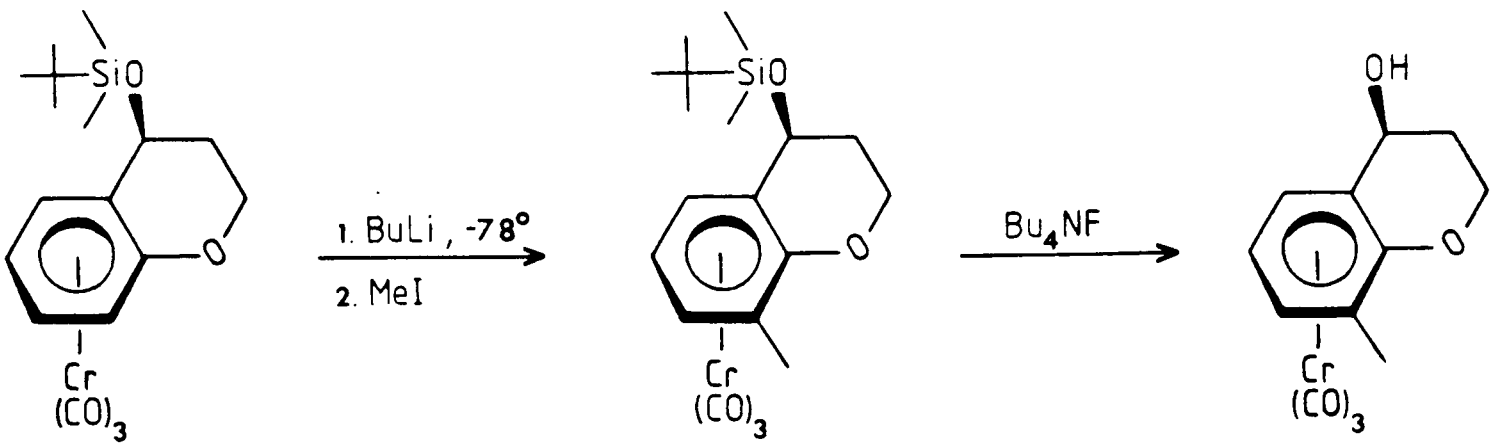


Deprotection of the *endo* silyl ether 225 under identical conditions to those used previously, generated a 2:1 mixture of the *endo* : *exo* alcohol 218 : 217 together with some decomplexed material. The formation of both alcohol diastereoisomers is consistent with the involvement of a benzylic carbonium ion, as a competing pathway to normal deprotection.



A sample of *exo*-(4-chromanol TBDMS ether)$Cr(CO)_3$ 224 was treated with *n*-BuLi at -78°C followed by methyl iodide. After work-up, a single product 229 was isolated together with some recovered starting material 224.

^{1}H n.m.r. spectroscopy clearly showed this product 229 to contain a ring methyl substituent from the three proton singlet at δ2.16. Cleavage of the silyl ether under the usual conditions allowed the resultant alcohol to be compared with the two authentic samples of the C8 and C5 methylated alcohols 202 and 203 previously prepared. The product was identical to complex 202 indicating that C8 deprotonation and subsequent methylation had occurred.



224 229 202

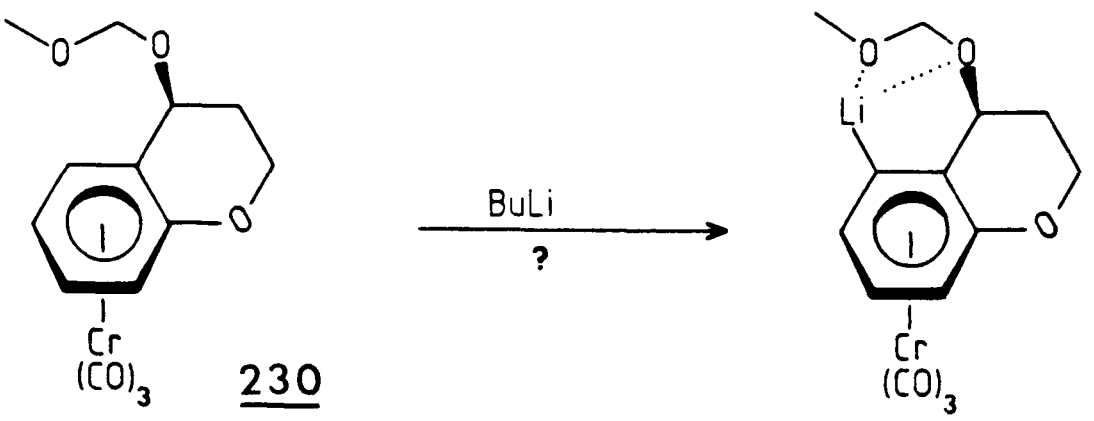
The deprotection of the *exo* silyl ether 229 gave exclusively the alcohol 202 with none of the epimeric *endo* diastereoisomer 208 being isolated. This is consistent with either the normal mechanism of deprotection *via* Si-O bond cleavage or a mechanism which involves the formation of a metal stabilised benzylic carbonium ion.

With the *exo* methyl ether 219 undergoing C8 deprotonation under identical conditions, it would have been surprising if any chelation had been observed to the bulky silyl ether.

3(iv) *via* the MOM ether

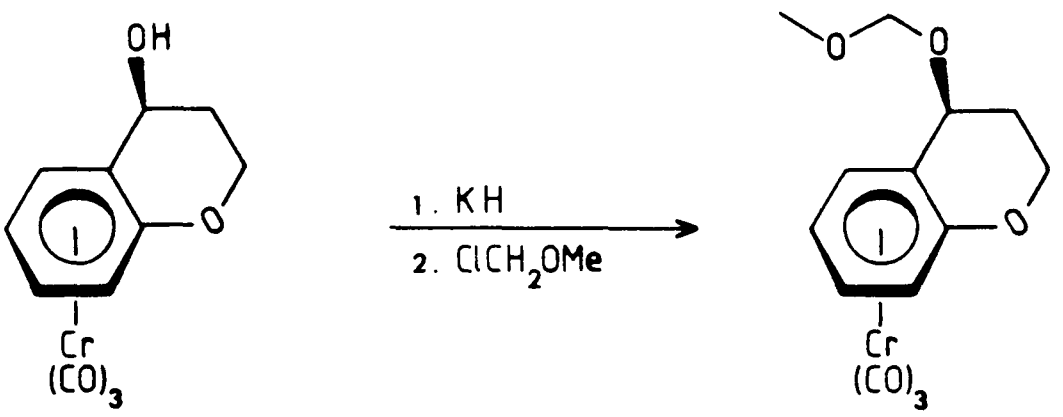
It was considered that protection of *exo*-(4-chromanol)$Cr(CO)_3$ 217 as its methoxymethyl (MOM) ether 230 might give a complex with a C4 substituent

capable of competing with the dominant chelating effect exerted by the heterocyclic oxygen in the previous complexes.



230

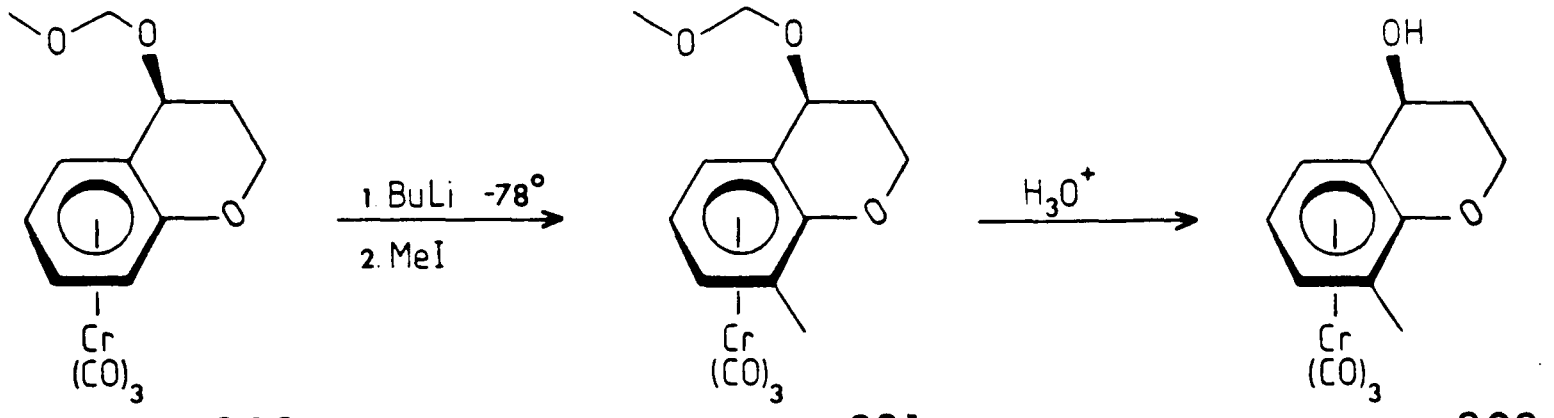
Treatment of *exo*-(4-chromanol)$Cr(CO)_3$ 217 with potassium hydride in THF generated the alkoxide anion. This was alkylated with chloromethyl methyl ether to give the MOM protected alcohol 230, readily identified from the methoxy (δ3.43) and methylene singlets (δ4.79) in the ^1H n.m.r. spectrum and a molecular ion m/z = 330 in the mass spectrum. A small amount of the starting material 217 was also recovered. Only one diastereoisomer of the product 230 was observed in the ^1H n.m.r. spectrum and since the reaction does not involve cleavage of the C-O alcohol bond, this structure was assigned as the *exo* isomer.



217 230

Treatment of this MOM ether 230 with *n*-BuLi in THF at -78°C followed by methyl iodide gave, after work-up, a single product 231. The ^1H n.m.r.

spectrum of this product clearly showed that ring methylation had occurred and that the product contained three contiguous aromatic protons. A molecular ion m/z = 344 in the mass spectrum provided further confirmation for ring methylation and this novel product was fully characterised including by elemental analysis. To distinguish between the two possibilities of C5 and C8 methylation, the MOM group was removed by acidic hydrolysis to generate the parent alcohol. This could proceed either by the normal mode of acetal hydrolysis or *via* formation of the corresponding metal stabilised benzylic carbonium ion. Comparison of the ^{1}H n.m.r. spectrum of this alcohol with those of the two authentic samples 202 and 203, clearly showed it to be identical to the 8-methylated alcohol 202. Deprotonation of the MOM ether 230 and subsequent methylation had therefore occurred at C8.



230 **231** **202**

The regiochemistry of the deprotonation of (chroman)$Cr(CO)_3$ 167 is therefore dominated by the chelating effect of the heterocyclic oxygen. Exclusive *ortho* deprotonation at C8 is observed and this is not affected by the presence of other oxa chelating groups at C4.

4. Experimental

For general experimental conditions see page 67.

All reactions involving the preparation or utilisation of (arene)$Cr(CO)_3$ complexes were performed under an atmosphere of nitrogen using standard vacuum line and Schlenk tube techniques.[73]

Solvents

Petrol refers to that fraction of petroleum ether boiling between 40° and 60°C. Di-*n*-butyl ether was dried over sodium and distilled before use.

Reagents

Sodium and potassium hydride were used as dispersions in oil (50% and 35% respectively). All aldehydes were dried over anhydrous calcium chloride before use. Acetyl chloride was dried by refluxing over P_2O_5 (3/4 h). Acetonitrile was dried over activated 4Å molecular sieves. *n*-BuLi was used as a 1.6 M solution in hexane. Chromium hexacarbonyl was steam distilled before use. Dilute aqueous acid refers to 10% aqueous hydrochloric acid. Sodium hexamethyldisilazide was prepared according to the method of Wannagat.[110]

Chromatography

All column chromatography and filtrations were performed on alumina (grade V) unless otherwise stated.

1-Chloro-3-phenoxypropane (169)

1-Bromo-3-chloropropane (18.5 g, 117 mmol) was added to a solution of potassium carbonate (14.7 g, 106 mmol) in acetone (100 ml) containing phenol (10 g, 106 mmol) and the mixture heated under reflux (36 h). The acetone was removed by distillation, water (100 ml) added and the mixture extracted with diethyl ether (3 x 60 ml). The combined organic fractions were washed with 5% aqueous sodium hydroxide solution (2 x 30 ml) and dried. Solvent evaporation gave a pale yellow oil which was distilled under reduced pressure to give the title compound (169) (11.19 g, 62%). B.p. 116-118°C, 15 mmHg; $\nu_{max.}$ (thin film) 3035 w (aryl-H), 1600 s 1585 s (phenyl), 1245 s and 1040 s cm^{-1} (Ph-O-C); ^1H n.m.r. (60 MHz) δ7.40 - 6.65 (5H,m,Ph), 4.00 (2H,t,J 6Hz,$OC\underline{H}_2$), 3.65 (2H,t,J 6Hz,$C\underline{H}_2Cl$), 2.15 (2H,qu,J 6Hz,$OCH_2C\underline{H}_2CH_2Cl$).

(1-Chloro-3-phenoxypropane)$Cr(CO)_3$ (170)

1-Chloro-3-phenoxypropane (169) (1.0 g, 5.9 mmol) and chromium hexacarbonyl (1.40 g, 6.4 mmol) were added to di-*n*-butyl ether (40 ml) containing THF (4 ml) and heated under reflux (24 h). The cooled solution was filtered and the solvent evaporated. Column chromatography (diethyl ether) followed by recrystallisation of the product from diethyl ether - hexane gave the title compound (170) as yellow plates (730 mg, 41%). M.p. 98-9°C (Found: C, 47.1; H, 3.5. $C_{12}H_{11}ClCrO_4$ requires C, 47.0; H, 3.6%); $\nu_{max.}$ 1955 s and 1860 s cm^{-1} (metal carbonyl); ^1H n.m.r. δ5.56 (2H,t,J 6Hz,*meta* aryl-H), 5.12 (2H,d,J 6Hz,*ortho* aryl-H), 4.88 (1H,t,J 6Hz,*para* aryl-H), 4.01 (2H,t,J 6Hz,$OC\underline{H}_2$), 3.70 (2H,t,J 6Hz,$C\underline{H}_2Cl$), 2.22 (2H,qu,J 6Hz,$OCH_2C\underline{H}_2CH_2Cl$); *m/z* (IBEI) 306 ($M^+$, ^{35}Cl), 308 (M^+,^{37}Cl).

Attempted cyclisation of (1-chloro-3-phenoxypropane)$Cr(CO)_3$ (170) to (chroman)$Cr(CO)_3$ (167)

n-BuLi (0.6 ml, 1 mmol) was added to a solution of (1-chloro-3-phenoxypropane)$Cr(CO)_3$ (170) (250 mg, 0.8 mmol) in THF (20 ml) at -78°C. After stirring (3 h), methanol (2 ml) was added and the reaction mixture warmed to room temperature. Solvent evaporation followed by column chromatography (diethyl ether) gave a single product identified as recovered starting material.

Repeating the reaction with identical quantities of reagents, but allowing the reaction mixture to warm to room temperature after stirring (2 h; -78°C), resulted only in decomposition. No complexed products were isolated.

Chroman (2) [98]

1,3-Dibromopropane (70 g, 0.35 mol) was added dropwise to an aqueous solution (100 ml) of phenol (150 g, 1.6 mmol) and sodium hydroxide (47 g, 1.2 mol). The mixture was heated under reflux (3 h) and then allowed to cool with stirring to give a cream precipitate of the 1,3 diphenoxypropane (171). This precipitate was collected, washed with 3% aqueous sodium hydroxide solution (2 x 100 ml), water (2 x 100 ml) and dried under reduced pressure (0.1 mmHg, 50°C) to give a cream solid (97 g).

Anhydrous aluminium trichloride (26.5 g, 0.2 mol) was added to a slurry of 1,3-diphenoxypropane (171) (35 g) in anhydrous benzene (300 ml) with stirring. The reaction mixture was heated under reflux (4 h) and poured onto ice-water (250 g). The organic layer was separated and the aqueous layer extracted with diethyl ether (3 x 100 ml). The combined

organic fractions were washed with 3% aqueous sodium hydroxide solution (3 x 150 ml), water (2 x 100 ml) and dried. Solvent evaporation gave a dark oil which was distilled under reduced pressure to give chroman (2) as a colourless oil (7.22 g, 43% overall; lit.,[98] 55%). B.p. 92-94°C, 15 mmHg (lit.,[98] b.p. 102-4°C, 20 mmHg); $\nu_{max.}$ (thin film) 3040 w, 3020 w (aryl-H), 1605 s 1595 s 1580 s (phenyl), and 1060 s cm^{-1} (C-O); ^{1}H n.m.r. (60 MHz) δ7.20 - 6.55 (4H,m,aryl-H), 4.10 (2H,t,J 5Hz,H-2), 2.70 (2H,t,J 6Hz,H-4), 2.20 - 1.60 (2H,m,H-3); *m/z* 134(M^+).

(Chroman)$Cr(CO)_3$ (167)

Chroman (2) (1.50 g, 11 mmol) was added to chromium hexacarbonyl (3.0 g, 13.6 mmol) in di-*n*-butyl ether (40 ml) containing THF (4 ml) and the mixture heated under reflux (26 h) in the absence of light. The cooled solution was filtered and the solvents evaporated. Column chromatography (diethyl ether-petrol) followed by recrystallisation of the product from diethyl ether-hexane gave the title compound (167) as yellow cubes (2.13 g, 70%; lit.,[92] 49%). M.p. 82-4°C (lit.,[92] 82-4°C); $\nu_{max.}$ 1950 s and 1850 br cm^{-1} (metal carbonyl); ^{1}H n.m.r. δ5.45 (1H,d,J 6Hz,aryl-H), 5.41 (1H,t,J 6Hz,aryl-H), 5.18 (1H,d,J 6Hz,aryl-H), 4.91 (1H,t,J 6Hz,aryl-H), 4.26 - 4.18 (1H,m,H-2), 4.11 - 4.04 (1H,m,H-2), 2.76 - 2.58 (2H,m,H-4), 2.19 - 2.06 (1H,m,H-3), 2.06 - 1.92 (1H,m,H-3) [lit.,[92](90 MHz) δ5.73 (1H,d), 5.64 (1H,t), 5.30 (1H,d), 5.11 (1H,t), 4.17 (2H,t,OCH_2), 2.69 (2H,m,H-4), 2.14 (2H,m,H-3)]; *m/z* (IBEI) 270 (M^+).

General procedure for ring functionalisation of (chroman)$Cr(CO)_3$ (167)

n-BuLi (0.6 ml, 1 mmol) was added to a solution of (chroman)$Cr(CO)_3$ (167) (200 mg, 0.75 mmol) in THF (20 ml) at -78°C to give a yellow-orange

solution of (8-lithiochroman)$Cr(CO)_3$. After stirring (2 h; -78°C), the electrophile was added and stirring continued (2 h; -78°C). Methanol (2 ml) was added, the reaction mixture warmed to 20°C, and the solvent evaporated. Column chromatography (diethyl ether-petrol, 1:1) followed by recrystallisation of the product (diethyl ether-hexane) gave in each case analytically pure C8 functionalised (chroman)$Cr(CO)_3$.

With aldehydes as the electrophiles, after THF evaporation the residue was dissolved in dichloromethane, filtered through a short plug of alumina and evaporated. The diastereoisomeric ratio was then determined from a ^1H n.m.r. spectrum of this material, by comparison of the integral values of the two sets of aromatic protons. Subsequent column chromatography allowed the separation of one diastereoisomer which in each case was fully characterised.

Methylation of (chroman)$Cr(CO)_3$ (167)

Methyl iodide (0.2 ml, 3.2 mmol) was added to a solution of (8-lithiochroman)$Cr(CO)_3$ prepared, according to the general procedure, from (chroman)-$Cr(CO)_3$ (167) (250 mg, 0.9 mmol) and *n*-BuLi (0.7 ml, 1.1 mmol). After work-up, (8-methylchroman)$Cr(CO)_3$ (175), identified by comparison of its spectroscopic data with those due to an authentic sample, was isolated as yellow crystals (220 mg, 84%).

8-Methylchroman (176)[98]

1,3-Dibromopropane (15 g, 74 mmol) was added dropwise to an aqueous solution (45 ml) of *o*-cresol (36 g, 330 mmol) and sodium hydroxide (10 g, 250 mmol), and the mixture heated under reflux (4 h). Water (50 ml) was added upon cooling and the reaction mixture extracted with diethyl ether (3 x 60 ml). The combined organic layers were washed with 5% aqueous sodium

hydroxide solution (3 x 30 ml), water (2 x 30 ml) and dried. Evaporation gave a yellow oil which was distilled under reduced pressure to give the diaryloxypropane as a pale yellow oil (13.23 g, 70 %). B.p. 180-90°C, 5 mmHg; ^{1}H n.m.r. (60 MHz) δ7.25 - 6.60 (8H,m,aryl-H), 4.15 (4H,t,J 6Hz,OCH_2), 2.50 - 2.10 (2H,m,$OCH_2CH_2CH_2O$), 2.20 (6H,s,ArMe).

This diaryloxypropane was converted to 8-methylchroman (176) by a similar procedure to that used for the preparation of chroman 2 (3.90 g, 35% overall; lit.,[98] 47%). B.p. 96-8°C, 15 mmHg (lit.,[98] b.p. 64-7°C, 2 mmHg); $\nu_{max.}$ (thin film) 3020 w (aryl-H), and 1595 m cm^{-1} (phenyl); ^{1}H n.m.r. (60 MHz) δ7.20 - 6.55 (3H,m,aryl-H), 4.20 (2H,t,J 5Hz,H-2), 2.80 (2H,t, J 6Hz,H-4), 2.20 (3H,s,ArMe), 2.30 -1.80 (2H,m,H-3); *m/z* 148 (M^+).

(8-Methylchroman)$Cr(CO)_3$ (175) by direct complexation

8-Methylchroman (176) (1.0 g, 6.8 mmol) and chromium hexacarbonyl (1.75 g, 8 mmol) were added to di-*n*-butyl ether (40 ml) containing THF (4 ml) and heated under reflux (24 h). The cooled solution was filtered and the solvents removed. Column chromatography (diethyl ether) gave the title compound (175) as yellow blocks (1.15 g, 60%). M.p. 69-70°C (Found: C, 55.0; H, 4.25. $C_{13}H_{12}CrO_4$ requires C, 54.9; H, 4.3%); $\nu_{max.}$ 1940 s and 1850 s cm^{-1} (metal carbonyl); ^{1}H n.m.r. δ5.32 (1H,d,J 6Hz,aryl-H), 5.25 (1H,d,J 6Hz,aryl-H), 4.97 (1H,t,J 6Hz,H-6), 4.27 - 4.07 (2H,m,H-4), 2.72 - 2.68 (2H,m,H-4), 2.15 (3H,s,ArMe), 2.22 - 1.92 (2H,m,H-3); *m/z* (IBEI) 284 (M^+).

Attempted methylation of chroman (2)

n-BuLi (2.5 ml, 4 mmol) was added to a solution of chroman (2) (500 mg, 3.7 mmol) in THF (15 ml) at -78°C. After stirring (2 h)

methyl iodide (0.4 ml, 6.4 mmol) was added and stirring continued (2 h). Methanol (2 ml) was added, the reaction mixture warmed to room temperature and evaporated. Water (20 ml) was added and the mixture extracted with diethyl ether (3 x 15 ml). The combined organic layers were dried and the solvent removed to give a pale yellow oil identified as the starting material (2).

The reaction was repeated, with the addition of *n*-BuLi (5 ml, 8 mmol) to an identical solution of chroman (2) in THF at 0°C. The reaction mixture was stirred (30 min), cooled to -78°C and methyl iodide (1 ml, 16 mmol) added. The reaction mixture was allowed to warm to room temperature and quenched with methanol (2 ml). An identical work-up gave a 3:2 mixture of chroman (2) and 8-methylchroman (176) identified by comparison of the ^{1}H n.m.r. spectrum of this mixture with those due to authentic samples.

Ring methylation of (8-methylchroman)$Cr(CO)_3$ (175)

n-BuLi (0.55 ml, 0.9 mmol) was added to a solution of (8-methylchroman)-$Cr(CO)_3$ (175) (200 mg, 0.7 mmol) in THF (20 ml) at -78°C. After stirring, (2 h), methyl iodide (0.4 ml, 6.4 mmol) was added and stirring continued (2 h). The reaction was worked-up according to the general procedure for ring functionalisation to give a 1:1 mixture of (6,8-dimethylchroman)$Cr(CO)_3$ (177) and (5,8- or 7,8-dimethylchroman)$Cr(CO)_3$ (178) as a yellow powder (110 mg, 52%). $\nu_{max.}$ 1960 s and 1890 s br cm^{-1} (metal carbonyl); ^{1}H n.m.r. δ5.36 [1H,d,J 6Hz,aryl-H (178)], 5.15 [1H,d,J 2Hz,aryl-H (177)], 5.07 [1H,d,J 2Hz,aryl-H (177)], 4.87 [1H,d,J 6Hz,aryl-H (178)], 4.23 - 4.08 (4H,m, H-2), 2.78 - 2.60 (4H,m,H-4), 2.17 (3H,s,ArMe), 2.14 (3H,s,ArMe), 2.11 (3H,s,ArMe), 2.08 (3H,s,ArMe), 2.07 - 1.92 (4H,m,H-3); *m/z* (IBEI) 298 (M^+).

[8-(*N*,*N*-dimethylaminomethylene)chroman]$Cr(CO)_3$ (179)

Eschenmoser's salt ($H_2C{=}\overset{+}{N}Me_2I^-$) (400 mg, 2.2 mmol) was dried by heating (80°C) under reduced pressure (0.1 mmHg). To this salt, cooled to -78°C, was added a solution of (8-lithiochroman)$Cr(CO)_3$ prepared according to the general procedure. After work-up, the title compound (179) was isolated as yellow crystals (120 mg, 49%). M.p. 71-2°C (Found: C, 55.05; H, 5.2; N, 4.0. $C_{15}H_{17}CrNO_4$ requires C, 55.05; H, 5.2; N, 4.3%); $\nu_{max.}$ 2780 w (NMe), 1950 s and 1850 br cm^{-1} (metal carbonyl); ^1H n.m.r. δ5.48 (1H,d,J 6Hz,aryl-H), 5.36 (1H,d,J 6Hz,aryl-H), 4.98 (1H,t,J 6Hz,H-6), 4.20 (2H,t,J 7Hz,H-2), 3.72 (1H,d,J 12.5Hz,C<u>H</u>NMe_2), 2.83 (1H,d,J 12.5Hz,C<u>H</u>NMe_2), 2.69 (2H,t,J 7Hz,H-4), 2.33 (6H,s,NMe_2), 2.17 - 1.96 (2H,m,H-3); *m/z* (NH_3 CI) 328 (M^++1).

(8-Thiomethylchroman)$Cr(CO)_3$ (180)

Methyl disulphide (0.2 ml, 2.2 mmol) was added to a solution of (8-lithiochroman)$Cr(CO)_3$ prepared according to the general procedure, to give the title compound (180) as orange needles (140 mg, 60%). M.p. 91-2°C (Found: C, 49.1; H, 3.5. $C_{13}H_{12}CrO_4S$ requires C, 49.4; H,3.8%); $\nu_{max.}$ 1950 s 1860 s and 1835 s cm^{-1} (metal carbonyl); ^1H n.m.r. δ5.50 (1H,d,J 6Hz,aryl-H), 5.32 (1H,d,J 6Hz,aryl-H), 4.94 (1H,t,J 6Hz,H-6), 4.40 - 4.30 (1H,m,H-2), 4.25 - 4.16 (1H,m,H-2), 2.83 - 2.63 (2H,m,H-4), 2.43 (3H,s,SMe), 2.25 - 2.10 (1H,m,H-3), 2.10 - 1.97 (1H,m,H-3); *m/z* (IBEI) 316 (M^+).

[8-(Hydroxybenzyl)chroman]$Cr(CO)_3$ (181)/(182)

Benzaldehyde (0.15 ml, 1.5 mmol) was added to a solution of

(8-lithiochroman)$Cr(CO)_3$ prepared according to the general procedure, to give the title compound as an 1:8 mixture of the two possible diastereoisomers (181) and (182) (270 mg, 96%). Column chromatography (dichloromethane) followed by recrystallisation from diethyl ether-hexane gave the major, more polar diastereoisomer (182) as yellow needles (210 mg, 60%). M.p. 157-8°C (Found: C, 60.4; H, 4.1. $C_{19}H_{16}CrO_5$ requires C, 60.7; H, 4.3%); $\nu_{max.}$ (CH_2Cl_2 solution) 0.76 M: 3580 m (free OH), 3430 w br (H-bonded OH), 0.37 M: 3580 m, 3430 vw br, 0.15 M: 3580 w, 1970 s and 1875 s cm^{-1} (metal carbonyl); ^1H n.m.r. δ7.64 - 7.33 (5H,m,Ph), 6.00 (1H,d,J 2Hz,CHOH), 5.43 (1H,d,J 6Hz, aryl-H), 4.82 (1H,d,J 6Hz,aryl-H), 4.75 (1H,t,J 6Hz,H-6), 4.42 - 4.23 (2H,m,OCH_2),3.09 (1H,d,J 2Hz,CHOH), 2.82 - 2.62 (2H,m,H-4), 2.25 - 2.00 (2H,m,H-3); *m/z* (IBEI) 376 (M^+). Minor diastereoisomer (181) ^1H n.m.r. δ5.96 (1H,d,J 2Hz,CHOH, 5.83 (1H,d,J 6Hz,aryl-H), 4.97 (1H,t,J 6Hz,H-6), 4.16 - 4.06 (2H,m,OCH_2), 2.20 (1H,d,J 2Hz,CHOH).

[8-(2,2-Dimethyl-1-hydroxypropyl)chroman]$Cr(CO)_3$ (183)/(184)

Pivalaldehyde (0.2 ml, 1.8 mmol) was added to a solution of (8-lithiochroman)$Cr(CO)_3$ prepared according to the general procedure, to give a 2:3 mixture of the two possible diastereoisomers (183) and (184), together with a 30% recovery of the starting material (167). Column chromatography (Al_2O_3 Grade I, dichloromethane-ethyl acetate, 1:1) followed by recrystallisation from diethyl ether-hexane gave the major, more polar diastereoisomer (184) as yellow needles. M.p. 154-5°C; $\nu_{max.}$ 3570 m (OH), 1950 s, 1875 s and 1855s cm^{-1} (metal carbonyl); ^1H n.m.r. δ5.40 (1H,d,J 6Hz,aryl-H), 5.33 (1H,d,J 6Hz,aryl-H), 4.83 (1H,t,J 6Hz,H-6), 4.35 - 4.28 (1H,m,H-2), 4.12 - 4.03 (1H,m,H-2), 3.81, 3.64 (2H,AB system, J_{AB} 10Hz,CHOH), 2.85 - 2.65 (2H,m,H-4), 2.26 - 2.10 (1H,m,H-3), 2.06 - 1.94 (1H,m,H-3), 0.98 (9H,s,^tBu);

m/z 356 (M^+), high resolution *m/z* **356·0767** $C_{17}H_{20}{}^{52}CrO_5$ requires **356·0766.** Less polar, minor diastereoisomer (183) ^1H n.m.r. δ5.70 (1H,d,J 6Hz,aryl-H), 5.48 - 5.41 (1H,m,aryl-H), 4.97 (1H,t,J 6Hz,H-6), 4.65 (1H,d,J 2Hz,CHOH), 1.52 (1H,d,J 2Hz,CHOH), 0.98 (9H,s,^{t}Bu).

[8-(1-Hydroxyethyl)chroman]$Cr(CO)_3$ (185)/(186)

A solution of acetaldehyde (0.3 ml, 5.4 mmol) in THF (10 ml) cooled to -78°C was added dropwise to a solution of (8-lithiochroman)$Cr(CO)_3$ prepared according to the general procedure. The title compound was isolated as a 3:2 mixture of the two possible diastereoisomers (185) and (186) (181 mg, 77%). Column chromatography (diethyl ether-petrol, 1:1) followed by recrystallisation from diethyl ether-hexane gave the major less polar diastereoisomer (185) as yellow needles. M.p. 76-7°C (Found: C, 53.5; H, 4.6. $C_{14}H_{14}CrO_5$ requires C, 53.5; H, 4.5%); $\nu_{max.}$ ($CHCl_3$ solution) 0.9 M: 3590 m (free OH), 3430 m br (H-bonded OH), 0.45 M: 3590 m, 3430 m br, 0.18 M: 3590 m, 3430 m br the relative intensities of the two bands were unchanged at the three concentrations, 1960 s and 1870 s cm^{-1} (metal carbonyl); ^1H n.m.r. δ5.73 (1H,d,J 6Hz,aryl-H), 5.42 (1H,d,J 6Hz, aryl-H), 5.05 - 4.97 (1H,m,CHOH), 5.00 (1H,t,J 6Hz,H-6), 4.27 - 4.08. (2H,m,OCH_2), 2.80 - 2.59 (2H,m,H-4), 2.18 - 1.93 (2H,m,H-3), 1.90 (1H,d,J 2Hz,CHOH), 1.45 (3H,d,J 7Hz,$CHCH_3$); *m/z* (IBEI) 314 (M^+). Minor diastereoisomer (186) ^1H n.m.r. δ5.61 (1H,d,J 6Hz,aryl-H); 5.46 (1H,d,J 6Hz,aryl-H), 5.04 - 4.96 (1H,m,CHOH), 4.91 (1H,t,J 6Hz,H-6), 4.33 - 4.13 (2H,m,OCH_2), 2.78 - 2.59 (2H,m,H-4), 2.18 - 1.98 (2H,m,H-3), 2.02 (1H,d,J 2Hz,CHOH), 1.52 (3H,d,J 7Hz,$CHCH_3$); *m/z* 314 (M^+).

[8-(1-Hydroxy-2-methylpropyl)chroman]$Cr(CO)_3$ (187)/(188)

A solution of *i*-butyraldehyde (0.3 ml, 3.3 mmol) in THF (10 ml), cooled to -78°C was added dropwise to a solution of (8-lithiochroman)$Cr(CO)_3$ prepared according to the general procedure. The title compound was isolated as a 1:1 mixture of the two possible diastereoisomers (187) and (188) (232 mg, 92%). Column chromatography (diethyl ether-petrol, 1:1) followed by recrystallisation from diethyl ether-hexane gave the less polar diastereoisomer (187) as yellow needles. M.p. 68-9°C; $\nu_{max.}$ 3440 br (OH), 1960 s and 1860 s cm^{-1} (metal carbonyl); ^1H n.m.r. δ5.68 (1H,d,J 6Hz,aryl-H), 5.42 (1H,d,J 6Hz,aryl-H), 4.99 (1H,t,J 6Hz,H-6), 4.75 - 4.71 (1H,m,CHOH), 4.27 - 4.07 (2H,m,OCH_2), 2.81 - 2.60 (2H,m,H-4), 2.19 - 1.84 (3H,m,$CHMe_2$ and H-3), 1.56 (1H,d,J 2Hz,CHOH), 1.00 (3H,d,J 7Hz,$CHCH_3$), 0.96 (3H,d,J 7Hz, $CHCH_3$); *m/z* 342 (M^+), high resolution *m/z* **342·0559** $C_{16}H_{18}{}^{52}CrO_5$ requires **342·0559**. More polar diastereoisomer (186) ^1H n.m.r. δ5.45 - 5.38 (2H,m,H-7 and H-5), 4.85 (1H,t,J 6Hz,H-6), 1.02 - 0.90 (6H,m,$CHMe_2$).

Addition of acetaldehyde to (8-lithiochroman)$Cr(CO)_3$; attempted chelation control with diethylaluminium chloride

a) *via* transmetallation

To a solution of (8-lithiochroman)$Cr(CO)_3$ at -78°C, prepared according to the general procedure, was added diethylaluminium chloride (0.8 ml of a 1.8 M solution in toluene, 1.44 mmol). The reaction mixture was warmed to -40°C and stirred (1 h) to effect transmetallation. The bright yellow solution was recooled to -78°C and a precooled solution of acetaldehyde (0.3 ml in 10 ml THF, 5.4 mmol) added dropwise. After stirring (2 h; -78°C) methanol (2 ml) was added, the mixture warmed to room temperature

and evaporated. A solution of saturated aqueous sodium bicarbonate (40 ml) was added and the mixture extracted with dichloromethane (3 x 30 ml). The combined organic fractions were filtered through a short plug of alumina and the solvent evaporated to give a yellow powder (170 mg, 85%) identified as recovered starting material (167).

b) as a Lewis acid

The reaction was repeated with the immediate addition of the acetaldehyde solution (at -78°C) following the addition of diethylaluminium chloride to the lithium anion. The reaction mixture was stirred (2 h; -78°C) and quenched with methanol (2 ml). An identical work-up gave only recovered starting material (167) as a yellow powder (165 mg, 83%).

Addition of acetaldehyde to (8-lithiochroman)$Cr(CO)_3$; attempted chelation control with zinc species

a) *via* transmetallation

To zinc bromide (250 mg, 1.1 mmol), dried by adding toluene (5 ml) and evaporating the resultant suspension, at -78°C was added a solution of (8-lithiochroman)$Cr(CO)_3$, prepared according to the general procedure. The reaction mixture was warmed to -40°C and stirred (1 h) to effect transmetallation. The solution was recooled to -78°C, a precooled solution of acetaldehyde (0.3 ml in 10 ml THF, 5.4 mmol) added dropwise and the mixture stirred (2 h; -78°C). Methanol (2 ml) was added, the reaction mixture warmed to room temperature and evaporated. The residue was extracted with dichloromethane (30 ml), filtered through a short plug of alumina and evaporated to give a yellow powder identified as recovered starting material (167) (181 mg, 90%).

b) as a Lewis acid

The reaction was repeated with the immediate addition of the acetaldehyde solution (at -78°C) following the addition of diethylzinc (0.45 ml of a 2.5 M solution in toluene, 1.1 mmol) to the lithium anion at -78°C. The reaction mixture was stirred (2 h; -78°C) and quenched with methanol (2 ml). An identical work-up gave only recovered starting material (167) as a yellow powder (158 mg 79%).

Addition of acetaldehyde to (8-lithiochroman)$Cr(CO)_3$; attempted chelation control with chlorotitanium tri*iso*propoxide

To a solution of (8-lithiochroman)$Cr(CO)_3$ at -78°C, prepared according to the general procedure, was added chlorotitanium tri*iso*propoxide (1.0 ml of a M solution, 1 mmol) to give a colour change from yellow-orange to red-black. After stirring (2 h; -78°C) a precooled solution of acetaldehyde (0.3 ml in 10 ml THF, 5.4 mmol) was added dropwise, during which the colour faded to a paler red, and stirring continued (2 h at -78°C). Methanol (2 ml) was added, the reaction mixture warmed to room temperature and concentrated (to 15 ml). Dilute aqueous acid (50 ml) was added, the mixture extracted with diethyl ether (3 x 30 ml) and the combined organic fractions evaporated. This residue was dissolved in dichloromethane (20 ml) and filtered through a short plug of alumina. Evaporation gave a yellow-orange oil (130 mg, 65%) identified as recovered starting material (167).

The reaction was repeated under similar conditions except that following the addition of acetaldehyde, the mixture was stirred at -40°C (3/4 h). With no colour change observed, the mixture was initially warmed to -10°C, then allowed to warm to 0°C (over 1 h). An identical work-up gave only recovered starting material (167) as a yellow powder (140 mg, 70%).

Addition of benzaldehyde to (8-lithiochroman)$Cr(CO_3$; attempted chelation control with diethylaluminium chloride

The reaction was carried out under identical conditions (a) to those employed for the addition of acetaldehyde to the transmetallated (8-lithiochroman)$Cr(CO)_3$ except that benzaldehyde (0.15 ml, 1.5 mmol) was used as the electrophile. An identical work-up gave a yellow oil, identified as a mixture of recovered starting material (167) and benzaldehyde.

Addition of acetaldehyde to (8-lithiochroman)$Cr(CO)_3$; attempted chelation control with cerium trichloride

The method employed was adapted from that reported by Imamoto.[103] $CeCl_3.7H_2O$ (330 mg, 0.9 mmol) was dried by heating under reduced pressure (140°C; 0.1 mmHg; 2 h). THF (10 ml) was added to the cooled powder, the resultant suspension stirred (1 h), then cooled to -78°C. To this suspension was added a solution of (8-lithiochroman)$Cr(CO)_3$, prepared according to the general procedure, and the mixture stirred (1½ h; -78°C). A precooled solution of acetaldehyde (0.3 ml in 10 ml THF, 5.4 mmol) was added dropwise and stirring continued (2 h at -78°C). The mixture was quenched with aqueous ammonium chloride solution (30 ml) and warmed to room temperature. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 20 ml). The combined organic fractions were evaporated and the residue chromatographed on alumina (diethyl ether-petrol, 1:1). Recovered starting material (167) was isolated as a yellow powder (50 mg, 25%), and [8-(1-hydroxyethyl)chroman]$Cr(CO)_3$ as a yellow oil (140 mg, 60%). This was identified and shown to be a 1:1.3 mixture of the two possible diastereoisomers (185) and (186) by comparison of its ^1H n.m.r. spectrum with that due to an authentic sample.

Attempted ring acylation of (chroman)$Cr(CO)_3$ (167)

A variety of electrophiles were added to solutions of (8-lithiochroman)-$Cr(CO)_3$, prepared according to the general procedure, to give in each case a colour change to red-orange. The reaction mixtures were stirred (2 h; -78°C), quenched with methanol (2 ml) and worked-up according to the general procedure, resulting in each case only in the isolation of the starting material (167).

The electrophiles used as substrates were acetyl chloride (0.2 ml, 2.8 mmol), acetic anhydride (0.25 ml, 2.6 mmol), ethyl benzoate (0.2 ml, 1.4 mmol), acetonitrile (1 ml, 19 mmol in 5 ml THF), benzonitrile (0.15 ml, 1.5 mmol) and trimethyl *ortho*acetate (0.3 ml, 2.4 mmol). The dilute acetonitrile solution was precooled (to -78°C) and added dropwise. For the latter three electrophiles after stirring (2 h; -78°C), the reaction mixture was quenched with dilute aqueous acid (5 ml), warmed to room temperature and stirred (1 h). Evaporation followed by a work-up according to the general procedure, led only to the isolation of recovered starting material (167).

(8-Acetylchroman)$Cr(CO)_3$ (194)

Ethyl acetate (0.15 ml, 1.5 mmol) was added to a solution of (8-lithiochroman)$Cr(CO)_3$ prepared according to the general procedure, to give the title compound (194) as red needles (38 mg, 16%). M.p. 89-90°C (Found: C,53.8; H, 3.9. $C_{14}H_{12}CrO_5$ requires C, 53.85; H, 3.9%); $\nu_{max.}$ 1960 s and 1880 s (metal carbonyl), 1660 s cm^{-1} (acetyl); ^1H n.m.r. 6.14 (1H,d,J 6Hz,aryl-H), 5.73 (1H,d,J 6Hz,aryl-H), 4.92 (1H,t,J 6Hz,H-6), 4.48 - 4.40 (1H,m,H-2), 4.23 - 4.13 (1H,m,H-2), 2.88 - 2.78 (1H,m,H-4), 2.67 - 2.57 (1H,m,H-4), 2.59 (3H,s,COMe), 2.26 - 1.98 (2H,m,H-3); *m/z* (IBEI) 312 (M^+).

General procedure for benzylic functionalisation of (chroman)$Cr(CO)_3$ (167)

Sodium hexamethyldisilazide (270 mg, 1.5 mmol) was added to a solution of (chroman)$Cr(CO)_3$ (167) (200 mg, 0.75 mmol) in DMF (15 ml) at room temperature, to give a solution of (4-sodiochroman)$Cr(CO)_3$. The resultant orange solution was stirred (10 min), the electrophile added (upon which an immediate colour change to yellow was observed) and stirring continued (10 min). The reaction mixture was quenched with methanol (2 ml), water (50 ml) was added and the mixture extracted with diethyl ether (3 x 30 ml). The combined organic fractions were evaporated and the residue chromatographed (diethyl ether-petrol, 1:1) to give the C4 substituted (chroman)$Cr(CO)_3$. Recrystallisation from diethyl ether-hexane gave analytically pure material in each case.

(4-Methylchroman)$Cr(CO)_3$ (195)

Methyl iodide (0.2 ml, 3.2 mmol) was added to a solution of (4-sodiochroman)$Cr(CO)_3$ according to the general procedure to give the title compound (195) as yellow crystals (180 mg, 86%). M.p. 79-80°C (Found: C, 54.7; H, 4.0. $C_{13}H_{12}CrO_4$ requires C, 54.9; H, 4.3%); $\nu_{max.}$ 1950 s, 1875 s and 1850 s cm^{-1} (metal carbonyl); ^1H n.m.r. δ5.55 (1H,d,J 6Hz,aryl-H), 5.42 (1H,t,J 6Hz,aryl-H), 5.18 (1H,d,J 6Hz,aryl-H), 4.92 (1H,t,J 6Hz,aryl-H), 4.23 - 4.07 (2H,m,OCH_2), 2.87 - 2.78 (1H,m,H-4), 2.29 - 2.17 (1H,m,H-3), 1.74 - 1.63 (1H,m,H-3), 1.33 (3H,d,J 7Hz,$CHCH_3$); *m/z* (IBEI) 284 (M^+).

(4,8-Dimethylchroman)$Cr(CO)_3$ (196)

Methyl iodide (0.4 ml, 6.4 mmol) was added to a mixture of (8-methylchroman)$Cr(CO)_3$ (175) (200 mg, 0.7 mmol) and sodium hexamethyldisilazide

(285 mg, 1.6 mmol) in DMF (15 ml) according to the conditions used for the general benzylic functionalisation procedure, to give the title compound (196) as yellow crystals (137 mg, 65%). M.p. 93-4°C (Found: C, 56.5; H, 4.8. $C_{14}H_{14}CrO_4$ requires C, 56.4; H, 4.7%); $\nu_{max.}$ 1955 s and 1850 br cm^{-1} (metal carbonyl); ^1H n.m.r. δ5.38-5.32 (2H,m,H-5 and H-7), 4.98 (1H,t,J 6Hz,H-6), 4.22 - 4.15 (2H,m,OCH_2), 2.96 - 2.83 (1H,m,H-4), 2.31 - 2.13 (1H,m,H-3), 2.17 (3H,s,$ArCH_3$), 1.76 - 1.64 (1H,m,H-3), 1.34 (3H,d,J 7Hz,$CHCH_3$); *m/z* (IBEI) 298 (M^+).

(4-Ethylchroman)$Cr(CO)_3$ (197)

Ethyl iodide (0.15 ml, 1.9 mmol) was added to a solution of (4-sodiochroman)$Cr(CO)_3$ prepared according to the general procedure to give the title compound (197) as yellow crystals (150 mg, 68%). M.p. 53-4°C (Found: C, 56.0; H, 4.7. $C_{14}H_{14}CrO_4$ requires C, 56.4; H, 4.7%); $\nu_{max.}$ 1955 s and 1870 br cm^{-1} (metal carbonyl); ^1H n.m.r. δ5.53 (1H,d,J 6Hz, aryl-H), 5.43 (1H,t,J 6Hz,aryl-H), 5.19 (1H,d,J 6Hz,aryl-H), 4.92 (1H,t,J 6Hz,aryl-H), 4.25 - 4.08 (2H,m,OCH_2) 2.63 - 2.53 (1H,m,H-4), 2.27 - 2.14 (1H,m,H-3), 1.88 - 1.72 (2H,m,CH_2CH_3), 1.67 - 1.50 (1H,m,H-3), 1.03 (3H,t,J 7Hz,CH_2CH_3); *m/z* (IBEI) 298 (M^+).

(4-Allylchroman)$Cr(CO)_3$ (198)

Allyl bromide (0.2 ml, 2.3 mmol) was added to a solution of (4-sodiochroman)-$Cr(CO)_3$ prepared according to the general procedure, to give the title compound (198) as a pale yellow powder (156 mg, 68%). M.p. 53-4°C (Found: C, 58.0; H, 4.6. $C_{15}H_{14}CrO_4$ requires C, 58.1; H, 4.55%); $\nu_{max.}$ 1945 s 1900 s and 1845 br cm^{-1} (metal carbonyl); ^1H n.m.r. δ5.88-5.73 (1H,m,olefinic), 5.55 (1H,d,J 6Hz,aryl-H), 5.44 (1H,t,J 6Hz,aryl-H), 5.21 - 5.07 (3H,m,aryl-H and 2 olefinic), 4.91 (1H,t,J 6Hz,aryl-H), 4.25 - 4.07 (2H,m,OCH_2), 2.78 - 2.70

(1H,m), 2.57 - 2.48 (1H,m), 2.38 - 2.30 (1H,m), 2.25 - 2.13 (1H,m), 1.88 - 1.78 (1H,m); *m/z* (IBEI) 310 (M^+).

(4-Benzylchroman)$Cr(CO)_3$ (199)

Benzyl bromide (0.2 ml, 1.7 mmol) was added to a solution of (4-sodiochroman)$Cr(CO)_3$ according to the general procedure, to give the title compound (199) as yellow blocks (160 mg, 60%). M.p. 97-8°C (Found: C, 63.4; H, 4.6. $C_{19}H_{16}CrO_4$ requires C, 63.3; H, 4.5%); $\nu_{max.}$ 1955 s and 1855 s cm^{-1} (metal carbonyl); ^1H n.m.r. δ7.49 - 7.23 (5H,m,phenyl), 5.53 (1H,t,J 6Hz,aryl-H), 5.24 (1H,d,J 6Hz,aryl-H), 5.19 (1H,d,J 6Hz,aryl-H), 4.92 (1H,t,J 6Hz,aryl-H), 4.38 - 4.21 (2H,m,OCH_2), 3.22 - 3.12 (1H,m,H-4), 3.07 - 2.87 (2H,m,CH_2Ph), 2.31 - 2.18 (1H,m,H-3), 1.92 - 1.80 (1H,m,H-3); *m/z* (NH_3DCI) 361 (M^++1).

(4,4-Dithiomethylchroman)$CrCO)_3$ (201)

Methyl disulphide (0.2 ml, 2.2 mmol) was added to a solution of (4-sodiochroman)$Cr(CO)_3$ prepared according to the general procedure, to give the title compound (201) as orange needles (110 mg, 41%). M.p. 96-7°C (Found: C, 46.7; H, 3.7. $C_{14}H_{14}CrO_4S_2$ requires C, 46.4; H, 3.9%); $\nu_{max.}$ 1975 s and 1890 br cm^{-1} (metal carbonyl); ^1H n.m.r. δ6.08 (1H,d, J 6Hz,aryl-H), 5.60 (1H,t,J 6Hz,aryl-H), 4.98 (1H,d,J 6Hz,aryl-H), 4.76 (1H,t,J 6Hz,aryl-H), 4.47 - 4.34 (2H,m,OCH_2), 2.63 - 2.53 (1H,m,H-3), 2.35 - 2.26 (1H,m,H-3), 2.25 (3H,s,SMe), 2.10 (3H,s,SMe); *m/z* 362 (M^+).

Attempted benzylic methylation of chroman (2)

Sodium hexamethyldisilazide (1.50 g, 8.2 mmol) was added to a solution of chroman (2) (500 mg, 3.7 mmol) in DMF (20 ml) at room temperature and

the mixture stirred (10 min). Methyl iodide (0.6 ml, 9.6 mmol) was added and stirring continued. Water (40 ml) was added, the mixture extracted with diethyl ether (3 x 30 ml), the combined organic fractions washed with dilute aqueous acid (20 ml), saturated brine solution (3 x 20 ml) and dried. Solvent evaporation gave a pale yellow oil (490 mg, 95%) identified as starting material (2).

3-(2-Methylphenoxy)propionitrile (206)

Acrylonitrile (45 ml, 0.68 mol) was added slowly to *o*-cresol (23 g, 0.21 mol) containing sodium metal (0.23 g, 0.01 mol) at 130°C and the mixture heated under reflux (15 h). Water (150 ml) was added to the cool solution and the mixture extracted with diethyl ether (3 x 150 ml). The combined organic layers were washed with 2 M aqueous sodium carbonate solution (3 x 80 ml),dried and evaporated. The resultant oil was distilled under reduced pressure to give the title compound (206) as a colourless oil (22.10 g, 64%). B.p. 98-100°C, 1 mmHg (lit.,[111] b.p. 165-6°C, 20 mmHg); $\nu_{max.}$ (liquid film) 2250 m cm^{-1} (nitrile); ^{1}H n.m.r. (60 MHz) δ7.25 - 6.60 (4H,m,aryl-H), 4.15 (2H,t,J 6Hz,OCH_2), 2.80 (2H,t,J 6Hz,CH_2CN), 2.35 (3H,s,ArMe).

8-Methyl-4-chromanone (207)

The procedure used was based on the method of Loudon.[112] A mixture of 3-(2-methylphenoxy)propionitrile (206) (2.60 g, 16 mmol) in 8 M hydrochloric acid (90 ml) was heated under reflux (2 h). On cooling a pale pink solid crystallised from the reaction mixture. The solid was collected, dissolved in aqueous sodium carbonate solution and this solution washed with diethyl ether (50 ml). Acidification with aqueous acid

gave a precipitate which was collected and dried to give 3-(2-methyl-phenoxy)propionic acid (1.53 g). The diethyl ether fraction was evaporated to give a pale oil. This oil was heated under reflux with 8 M hydrochloric acid (20 ml) and worked-up as above to give a further sample of the acid (300 mg, total yield 64%). $\nu_{max.}$ 2760 - 2500 w (carboxylic acid OH), 1690 s (carbonyl), 1600 m and 1590 m cm^{-1} (phenyl).

3-(2-Methylphenoxy)propionic acid (1.50 g, 8.3 mmol) was added in portions to polyphosphoric acid at 100°C and the mixture heated with stirring (2 h). The hot reaction mixture was poured onto ice-water (200 ml) and the mixture stirred until the gum dissolved. The resultant solution was extracted with diethyl ether (3 x 50 ml), the combined organic fractions washed with aqueous sodium bicarbonate solution (2 x 50 ml), water (50 ml) and dried. Solvent evaporation gave a yellow oil which was chromatographed on silica (hexane-diethyl ether) to give 8-methyl-4-chromanone (207) as a yellow oil (1.18 g, 87%). $\nu_{max.}$ 1690 s (carbonyl), and 1600 s cm^{-1} (phenyl); ^1H n.m.r. (60 MHz) δ7.85 - 7.60 (1H,m,aryl-H), 7.45 - 7.20 (1H,m,aryl-H), 6.85 (1H,t,J 6Hz,H-6), 4.50 (2H,t,J 6Hz,H-4), 2.75 (2H,t,J 6Hz,H-3) 2.20 (3H,s,ArMe); *m/z* 162 (M^+).

8-Methyl-4-chromanol (204)

Sodium borohydride (390 mg, 10.3 mmol) was added in portions to a solution of 8-methyl-4-chromanone (207) (1.10 g, 6.8 mmol) in a mixture of methanol-water (30 ml, 5:1). The mixture was stirred (20 min) and carefully quenched with dilute aqueous acid. Water (50 ml) was added, the mixture extracted with diethyl ether (3 x 50 ml) and the combined organic fractions dried. Solvent evaporation gave the title compound (204) as a pale yellow oil (1.06 g, 95%). $\nu_{max.}$ (liquid film) 3350 m br (OH), and 1595 m cm^{-1} (phenyl);

^{1}H n.m.r. (60 MHz) δ7.15 - 6.55 (3H,m,aryl-H), 4.55 (1H,t,J 4Hz,H-4), 4.15 (2H,t,J 6Hz,H-2), 3.15 (1H,s,OH), 2.15 (3H,s,ArMe), 2.05 - 1.70 (2H,m,H-3).

(8-Methyl-4-chromanol)$Cr(CO)_3$ (202)/(208)

8-Methyl-4-chromanol (204) (0.90 g, 5.5 mmol) and chromium hexacarbonyl (1.50 g, 6.8 mmol) were added to a mixture of di-*n*-butyl ether (40 ml) containing THF (4 ml) and the mixture heated under reflux (20 h) in the absence of light. The cooled solution was filtered and the solvents evaporated. Column chromatography (dichloromethane) followed by precipitation of the product from hexane gave the title compound as a mixture of the two diastereoisomers (202) and (208) (ratio *ca.* 1:1) (1.15 g, 70%). The *exo* diastereoisomer (202) was identified by comparison of the ^{1}H n.m.r. spectrum of this mixture with that of an authentic sample. $\nu_{max.}$ 3300 br (OH), 1945 s and 1855 s cm^{-1} (metal carbonyl); ^{1}H n.m.r. (C_6D_6) *exo* diastereoisomer (202) δ4.84 (1H,d,J 6Hz,aryl-H), 4.63 (1H,d,J 6Hz,aryl-H), 4.10 (1H,t,J 6Hz, H-6), 4.02 (1H,q,J 4Hz,H-4), 3.70 - 3.53 (2H,m,H-2), 1.80 (3H,s,ArMe), 1.78 - 1.67 (1H,m,H-3), 1.16 - 1.07 (1H,m,H-3), 1.00 (1H,d,J 4Hz,OH); *endo* diastereoisomer (208) δ5.08 (1H,d,J 6Hz,aryl-H), 4.74 (1H,d,J 6Hz,aryl-H), 3.97 (1H,t,J 6Hz,H-6), 3.85 - 3.78 (1H,m,H-4), 3.70 - 3.53 (1H,m,H-2), 3.28-3.19 (1H,m,H-2), 1.74 (3H,s,ArMe), 1.56 - 1.44 (1H,m,H-3), 1.40 (1H,d,J 8Hz,OH), 1.28 - 1.17 (1H,m,H-3); *m/z* (IBEI) 300 (M^+).

exo-(8-Methyl-4-chromanol)$Cr(CO)_3$ (202)

The method employed was adapted from that reported by Jaouen.[106] Tetrafluoroboric acid-dimethyl ether complex (0.3 ml, 3 mmol) was added to a solution of (8-methyl-4-chromanol)$Cr(CO)_3$ (202)/(208) (400 mg, 1.3 mmol)

in dichloromethane (30 ml) at -30°C. The resultant black solution was stirred (5 min; -30°C) and added dropwise with stirring to ice-water (80 ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 x 30 ml). The combined organic fractions were filtered through a short plug of alumina and evaporated. Column chromatography (dichloromethane) gave a minor fraction which was discarded and a major, more polar fraction. This second fraction was precipitated from hexane to give the product as yellow needles (227 mg, 57%). ^{1}H n.m.r. spectroscopy showed this product to be identical with one of the two diastereoisomers produced by direct complexation of the alcohol (204) and it was identified as the *exo* diastereoisomer (202). M.p. 118-9°C; $\nu_{max.}$ 3250 m br (OH), 1955 s and 1865 s cm^{-1} (metal carbonyl); *m/z* 300 (M^{+}), high resolution *m/z* **300·0091** $C_{13}H_{12}{}^{52}CrO_5$ requires **300·0090**.

7-Methyl- and 5-methylchromanone (213) and (214)

Acrylonitrile (45 ml, 0.68 mol) was added to *m*-cresol (25.0 g, 0.23 mol) containing sodium metal (0.25 g, 11 mmol) according to the procedure used for the preparation of 3-(2-methylphenoxy)propionitrile (206), to give after an analogous work-up 3-(3-methylphenoxy)propionitrile as a colourless oil (27.0 g, 72%). B.p. 118-20°C, 1 mmHg (lit.,[111] b.p. 161°C, 18 mmHg); $\nu_{max.}$ (liquid film) 2250 w cm^{-1} (nitrile); ^{1}H n.m.r. (60 MHz) 7.30 - 6.50 (4H,m,aryl-H), 4.05 (2H,t,J 6Hz,$OC\underline{H}_2$), 2.70 (2H,t,J 6Hz,$C\underline{H}_2CN$), 2.25 (3H,s,ArMe).

This nitrile (20 g, 12.4 mmol) was heated under reflux (2 h) with 8 M hydrochloric acid (60 ml). Cooling the mixture gave white crystals of the corresponding acid (212) which were collected and dried. (1.62 g, 73%). $\nu_{max.}$ 2800-2500 w (carboxylic OH), and 1690 s cm^{-1} (carbonyl).

The acid (212) (1.60 g, 8.8 mmol) was cyclised with polyphosphoric acid (50 g), according to the method used to prepare 8-methyl-4-chromanone (207), to give a 3:2 mixture of the two possible isomers (1.13 g, 78%). Column chromatography (silica; 20% diethyl ether in hexane) gave 5-methyl-4-chromanone (214) followed by 7-methyl-4-chromanone (213) both as off-white oils. Compound (214): $\nu_{max.}$ (liquid film) 1680 s (carbonyl), 1600 s and 1575 m cm^{-1} (aryl); ^1H n.m.r. δ7.30 (1H,t,J 8Hz,H-6), 6.83 (1H,d,J 8Hz, aryl-H), 6.80 (1H,d,J 8Hz,aryl-H), 4.48 (2H,t,J 6Hz,H-2), 2.80 (2H,t,J 6Hz,H-3), 2.64 (3H,s,ArMe); *m/z* 162 (M^+). Compound (213): $\nu_{max.}$ (liquid film) 1685 s (carbonyl), 1615 s, and 1565 m cm^{-1} (aryl); ^1H n.m.r. 7.78 (1H,d,J 8Hz,aryl-H), 6.83 (1H,d,J 8Hz,aryl-H), 6.77 (1H,s,H-8), 4.51 (2H,t,J 6Hz,H-2), 2.78 (2H,t,J 6Hz,H-3), 2.35 (3H,s,ArMe).

5-Methyl-4-chromanol (205)

Sodium borohydride (115 mg, 3 mmol) was added to 5-methyl-4-chromanone (214) (325 mg, 2 mmol), according to the procedure used for the reduction of 8-methyl-4-chromanone (207), to give after work-up, the title compound (205) as a white powder (320 mg, 97%). $\nu_{max.}$ 3370 m br (OH), 1600 w and 1585 w cm^{-1} (aryl); ^1H n.m.r. (60 MHz) δ7.20 - 6.55 (3H,m,aryl-H), 4.85 - 4.65 (1H,m,H-4), 4.30 - 4.00 (2H,m,H-2), 2.35 (3H,s,ArMe), 2.30 - 1.80 (2H,m,H-3); *m/z* 164 (M^+).

Complexation of 5-methyl-4-chromanol (205)

5-Methyl-4-chromanol (205) (320 mg, 2.0 mmol) and chromium hexacarbonyl (0.5 g, 2.3 mmol) were added to di-*n*-butyl ether (20 ml) containing THF (2 ml) and the mixture heated under reflux (15 h) in the absence of light. The cooled solution was filtered and the solvents removed.

Column chromatography (diethyl ether-dichloromethane) gave two fractions which were each precipitated from hexane to give (5-methyl-3-chromene)$Cr(CO)_3$ (215) as an orange powder 180 mg, 33%) and one diastereoisomer of (5-methyl-4-chromanol)$Cr(CO)_3$ as a yellow powder (75 mg, 13%). This latter compound was shown to be the *endo* diastereoisomer (216) by subsequent epimerisation to the *exo* diastereoisomer (203). Compound (215): M.p. 107-8°C; $\nu_{max.}$ 1950 s and 1850 s br cm^{-1} (metal carbonyl); ^1H n.m.r. (C_6D_6) δ5.67 (1H,m,vinyl), 5.07 - 5.00 (1H,m,vinyl), 4.56 (1H,m,aryl-H), 4.47 (1H,m,aryl-H), 4.41 (1H,m,aryl-H), 4.00 - 3.92 (2H,m,H-2), 1.61 (3H,s,ArMe); *m/z* 282 (M^+), high resolution *m/z* **281·9987** $C_{13}H_{10}{}^{52}CrO_4$ requires **281·9984**. Compound (216): $\nu_{max.}$ 1940 s 1900 s and 1845 s cm^{-1} (metal carbonyl); ^1H n.m.r. (C_6D_6) δ4.68 (1H,t,J 6Hz,H-6), 4.41 (1H,d,J 6Hz,aryl-H), 3.94 - 3.85 (1H,m,H-2), 3.80 (1H,d,J 6Hz,aryl-H), 3.73 - 3.68 (1H,m,H-4), 3.54 - 3.47 (1H,m,H-2), 1.83 (3H,s,ArMe), 1.29 (1H,d,J 7.5Hz,OH), 1.34 - 1.23 (1H,m,H-3), 1.14 - 1.07 (1H,m,H-3); *m/z* 300 (M^+).

exo-(5-Methyl-4-chromanol)$Cr(CO)_3$ (203)

endo-(5-Methyl-4-chromanol)$Cr(CO)_3$ (216) (75 mg, 0.25 mmol) was treated with tetrafluoroboric acid - dimethyl ether complex (0.1 ml, 1 mmol), according to the procedure used to prepare *exo*-(8-methyl-4-chromanol)$Cr(CO)_3$ (202), to give after work-up the title compound (203), as a yellow oil (56 mg, 75%). $\nu_{max.}$ (CH_2Cl_2 solution) 3590 w (OH), 1960 s and 1875 s cm^{-1} (metal carbonyl); ^1H n.m.r. (C_6D_6) δ4.71 (1H,t,J 6Hz,H-6), 4.53 (1H,d,J 6Hz, aryl-H), 4.10 - 4.03 (1H,m,H-4), 3.90 (1H,d,J 6Hz,aryl-H), 3.69 - 3.55 (2H,m,H-2), 1.92 (3H,s,ArMe), 1.98 - 1.85 (1H,m,H-3), 1.07 - 0.98 (1H,m,H-3), 0.82 (1H,d,J 4Hz,OH); *m/z* 300 (M^+).

(4-Chromanol)$Cr(CO)_3$ (217)/(218)[107]

4-Chromanol (3) (1.0 g, 6.6 mmol) was added to chromium hexacarbonyl (1.70 g, 7.7 mmol) in di-*n*-butyl ether (40 ml) containing THF (4 ml) and the mixture heated under reflux (22 h) in the absence of light. The cooled solution was filtered and the solvents evaporated. Column chromatography (diethyl ether-dichloromethane,1:2) followed by precipitation from hexane gave the title compound, a yellow powder, as an equimolar mixture of the two diastereoisomers (217) and (218) (1.20 g, 63%; lit.,[107] 73%); $\nu_{max.}$ 3480 br (OH), 1955 s and 1855 s cm^{-1} (metal carbonyl); *exo* diastereoisomer (217) ^1H n.m.r. (C_6D_6) δ4.95 (1H,d,J 6Hz,aryl-H), 4.68 - 4.49 (2H,m,aryl-H), 3.98 - 3.87 (2H,m), 3.67 - 3.48 (2H,m), 1.77 - 1.64 (1H,m,H-3), 1.13 - 1.03 (1H,m,H-3), 0.94 (1H,d,J 4Hz,OH) [lit.,[107] δ4.95 (1H,d), 4.68 - 4.49 (2H,m), 3.98 - 3.83 (2H,m), 3.77 - 3.50 (2H,m), 1.78 - 1.65 (1H,m), 1.25 - 1.05 (1H,m), 1.08 (1H,d)]; *endo* diastereoisomer (218) ^1H n.m.r. (C_6D_6) δ5.13 (1H,d,J 6Hz,aryl-H), 4.66 (1H,t,J 6Hz,aryl-H), 4.38 (1H,d,J 6Hz,aryl-H), 3.85 (1H,t,J 6Hz,aryl-H), 3.77 - 3.50 (2H,m), 3.24 - 3.15 (1H,m), 1.53 - 1.42 (1H,m,H-3), 1.33 (1H,d,J 7.5Hz,OH), 1.22 - 1.05 (1H,m) [lit.,[107] δ5.13 (1H,d), 4.68 - 4.49 (1H,m), 4.38 (1H,d), 3.98 - 3.83 (1H,m), 3.77 - 3.50 (2H,m), 3.24 - 3.15 (1H,m),1.53 - 1.42 (1H,m), 1.33 (1H,d), 1.22 - 1.05 (1H,m)]; *m/z* 286 (M^+).

exo-(4-Chromanol)$Cr(CO)_3$ (217)

A mixture of *exo*- and *endo*-(4-chromanol)$Cr(CO)_3$ (217)/(218) (440 mg, 1.5 mmol) was treated with tetrafluoroboric acid-dimethyl ether complex (0.35 ml, 3 mmol), according to the procedure used to prepare *exo*-(8-methyl-4-chromanol)$Cr(CO)_3$ (202), to give after work-up the title

compound (217) as yellow needles (235 mg, 60%). ^{1}H n.m.r. spectroscopy showed this product, by comparison to be identical to one of the two diastereoisomers (217) and (218) produced by direct complexation of the alcohol (3) and by analogy with similar work[106] it was assigned as the *exo* diastereoisomer (217). *m/z* 286 (M^+).

Ring methylation of *exo*-(4-chromanol)$Cr(CO)_3$ (217)

n-BuLi (1.2 ml, 1.9 mmol) was added to a solution of *exo*-(4-chromanol)-$Cr(CO)_3$ (217) (225 mg, 0.8 mmol) in THF (20 ml) at -78°C. After stirring (2 h; -78°C), methyl iodide (0.2 ml, 3.2 mmol) was added and stirring continued (2 h). Methanol (2 ml) was added, the reaction mixture warmed to room temperature and the solvents evaporated. Column chromatography (dichloromethane) followed by precipitation of the product from hexane gave *exo*-(8-methyl-4-chromanol)$Cr(CO)_3$ (202) (170 mg, 72%) identified by comparison of its ^{1}H n.m.r. spectrum with that of an authentic sample.

Methylation of *exo*-(4-chromanol methyl ether)$Cr(CO)_3$ (219)

n-BuLi (0.5 ml, 0.8 mmol) was added to a solution of *exo*-(4-chromanol methyl ether)$Cr(CO)_3$ (219)[113] (200 mg, 0.7 mmol) in THF (20 ml) at -78°C. After stirring (2 h; -78°C), methyl iodide (0.25 ml, 4 mmol) was added and stirring continued. Methanol (2 ml) was added, the reaction mixture warmed to 20°C and the solvents evaporated. Column chromatography (diethyl ether-petrol, 1:1) followed by crystallisation from diethyl ether-hexane gave *exo*-(methyl 8-methyl-4-chromanol ether)$Cr(CO)_3$ (220) as yellow needles (125 mg, 60%). This was identified by comparison of its ^{1}H n.m.r. spectrum with that of an authentic sample.

exo-(Methyl 8-methyl-4-chromanol ether)$Cr(CO)_3$ (220)

To sodium hydride (40 mg, 1.7 mmol) previously washed with petrol, was added THF (15 ml) and a catalytic quantity of 18-crown-6. A solution of *exo*-(8-methyl-4-chromanol)$Cr(CO)_3$ (202) (150 mg, 0.5 mmol) in THF (10 ml) containing methyl iodide (0.2 ml, 3.2 mmol) was added dropwise to this suspension and the mixture stirred (15 h). Methanol (2 ml) was added and the solvents evaporated. Column chromatography (diethyl ether-petrol, 1:1) followed by recrystallisation from diethyl ether-hexane gave the title compound (220) as a yellow powder (121 mg, 77%). M.p. 73-4°C; $\nu_{max.}$ 1960 s 1895 s and 1850 s cm^{-1} (metal carbonyl); ^1H n.m.r. δ5.54 (1H,d,J 6Hz,aryl-H), 5.47 (1H,d,J 6Hz,aryl-H), 4.90 (1H,t,J 6Hz,H-6), 4.28 - 4.23 (2H,m,H-2), 4.14 (1H,t,J 4Hz,H-4), 3.49 (3H,s,OMe), 2.40 - 2.24 (1H,m,H-3), 2.15 (3H,s,ArMe), 2.15 - 2.06 (1H,m,H-3); *m/z* 314 (M^+), high resolution *m/z* **314·0245** $C_{14}H_{14}{}^{52}CrO_5$ requires *m/z* **314·0246**.

Attempted hydroxylation of (chroman)$Cr(CO)_3$ (167)

The method employed was adapted from that reported by Vedejs.[108]

A solution of (4-sodiochroman)$Cr(CO)_3$ was prepared according to the general procedure for benzylic functionalisation and cooled to -40°C. MoOPH[114] (750 mg, 1.7 mmol) was added and the resultant red solution stirred (20 min; -40°C). A saturated solution of sodium sulphite (10 ml) was added and the reaction mixture warmed to room temperature. Addition of water (50 ml) was followed by extraction of the mixture with diethyl ether (3 x 30 ml). The combined organic layers were evaporated and the residue chromatographed (diethyl ether) to give recovered starting material (167) (75 mg, 38%) and a product tentatively identified as *bis*-4,4'-(chroman)$Cr(CO)_3$ (221) (55 mg, 28%). *m/z* 538 (M^+).

4-Chromanol TBDMS ether (222)

The method employed was adapted from that reported by Corey.[109]

TBDMS-chloride (600 mg, 4 mmol) was added to a solution of 4-chromanol (3) (500 mg, 3.3 mmol) and imidazole (545 mg, 8 mmol) in DMF (3 ml) and the mixture stirred (20 h; 20°C). The reaction mixture was partitioned between water-hexane (1:1, 50 ml) and the organic layer separated. Drying, followed by solvent evaporation gave the title compound (222) as a colourless oil (720 mg, 82%). ^{1}H n.m.r. (60 MHz) δ7.25-6.55 (4H,m,aryl-H), 4.70 (1H,t,J 5Hz,H-4), 4.35 - 4.00 (2H,m,H-2), 2.10 - 1.75 (2H,m,H-3), 0.85 (9H,s,^{t}Bu), 0.10 (6H,s,SiMe$_2$); *m/z* (NH_3 CI) 207 (M^+ - ^{t}Bu), 133 (M^+ - OTBDMS).

(4-Chromanol TBDMS ether)Cr(CO)$_3$ (224)/(225)

4-Chromanol TBDMS ether (222) (720 mg, 2.7 mmol) was added to chromium hexacarbonyl (720 mg, 3.3 mmol) in di-*n*-butyl ether (30 ml) containing THF (3 ml) and the mixture heated under reflux (25 h) in the absence of light. The cooled solution was filtered and the solvents evaporated. Column chromatography (diethyl ether-petrol, 1:3) followed by precipitation of the product from hexane gave the title compound as yellow blocks (870 mg, 80%). The ratio of the *exo* (224) : *endo* (225) diastereoisomers was 3:1 by comparison of the ^{1}H n.m.r. spectrum of this sample with those spectra of the authentic separate diastereoisomers. M.p. 82-3°C (Found: C, 54.4; H, 6.1. $C_{18}H_{24}CrO_5Si$ requires C, 54.0; H, 6.0%); $\nu_{max.}$ 1955 s and 1880 br cm^{-1} (metal carbonyl); *m/z* 400 (M^+).

(4-Chromanol TIPS ether)Cr(CO)$_3$ (226)/(227)

4-Chromanol (3) (500 mg, 3.3 mmol) was treated with TIPS-chloride

(770 mg, 4 mmol) and imidazole (545 mg, 8 mmol), according to the procedure used to prepared the corresponding TBDMS ether (222), to give after work-up 4-chromanol TIPS ether (223) as a colourless oil.

This oil was added to chromium hexacarbonyl (870 mg, 4 mmol) in di-*n*-butyl ether (40 ml) containing THF (4 ml) and the mixture heated under reflux (26 h) in the absence of light. The cooled solution was filtered and the solvents evaporated. Column chromatography (diethyl ether-petrol, 1:3) followed by precipitation of the product from hexane gave the title compound as yellow blocks (1.14 g, 77% overall). The ratio of the *exo* (226) : *endo* (227) diastereoisomers was 3:1; the major diastereoisomer being assigned as *exo* by analogy with (4-chromanol TBDMS ether)$Cr(CO)_3$ (224)/(225). M.p. 89-91°C (Found: C, 56.95; H, 6.8. $C_{21}H_{30}CrO_5Si$ requires C, 57.0; H, 6.8%); $\nu_{max.}$ 1970 s and 1900 s cm^{-1} (metal carbonyl); ^1H n.m.r. *exo* diastereoisomer (226) δ5.69 (1H,d,J 6Hz,aryl-H), 5.53 (1H,t,J 6Hz,aryl-H), 5.14 (1H,d,J 6Hz,aryl-H), 4.86 (1H,t,J 6Hz,aryl-H), 4.74 (1H,t,J 4Hz,H-4), 4.40 - 4.18 (2H,m,H-2), 2.39 - 2.25 (1H,m,H-3), 2.00 - 1.90 (1H,m,H-3), 1.33 - 1.08 (21H,m,Si^iPr_3); *endo* diastereoisomer (227) δ5.87 (1H,d,J 6Hz,aryl-H), 5.50 (1H,t,J 6Hz,aryl-H), 4.99 (1H,d,J 6Hz,aryl-H), 4.88 (1H,m), 4.81 (1H,m) other signals indistinguishable from those of the *exo* isomer; *m/z* (NH_3 CI) 443 (M^++1).

exo-(4-Chromanol TBDMS ether)$Cr(CO)_3$ (224)

The method employed was adapted from that reported by Corey.[109]

TBDMS-chloride (125 mg, 0.8 mmol) was added to a solution of *exo*-(4-chromanol)$Cr(CO)_3$ (217) (200 mg, 0.7 mmol) and imidazole (110 mg, 1.6 mmol) in DMF (3 ml) and the mixture stirred (18 h; 20°C). The reaction mixture was partitioned between water-hexane (1:1, 70 ml) and the organic

layer separated. Filtration of this organic layer through a short plug of alumina followed by solvent evaporation gave the title compound (224) as a yellow oil (240 mg, 86%). ^{1}H n.m.r. δ5.61 (1H,d,J 6Hz,aryl-H), 5.52 (1H,t,J 6Hz,aryl-H), 5.14 (1H,d,J 6Hz,aryl-H), 4.88 (1H,t,J 6Hz,aryl-H), 4.60 (1H,t,J 4Hz,H-4), 4.33 - 4.18 (2H,m,H-2), 2.33 - 2.22 (1H,m,H-3), 1.93 - 1.83 (1H,m,H-3), 0.92 (9H,s,^{t}Bu), 0.22 (3H,s,Me), 0.17 (3H,s,Me).

Deprotection of the mixture of silyl ethers(224)(225)(226)(227)

The method employed was adapted from that reported by Corey.[109] Tetra-*n*-butylammonium fluoride trihydrate (2.35 g, 7.5 mmol) was added to a mixture of (4-chromanol TBDMS ether)$Cr(CO)_3$ (224)/(225) (665 mg, 1.7 mmol) and (4-chromanol TIPS ether)$Cr(CO)_3$ (226)/(227) (915 mg, 2.1 mmol) in THF (50 ml) at room temperature. After stirring (15 h; 20°C), water (50 ml) was added, the reaction mixture concentrated (to 50 ml) and extracted with diethyl ether (3 x 30 ml). The combined organic layers were evaporated and filtered through a short plug of alumina. Precipitation from hexane gave a 14:1 mixture of *exo* (217) : *endo* (218) (4-chromanol)$Cr(CO)_3$ (753 mg, 71%), identified by comparison of its ^{1}H n.m.r. spectrum with those of the separate diastereoisomers.

(4-Chromanone)$Cr(CO)_3$[107] (228)

4-Chromanone (4) (1.0 g, 6.8 mmol) was added to chromium hexacarbonyl (1.65 g, 7.5 mmol) in di-*n*-butyl ether (40 ml) containing THF (4 ml) and the mixture heated under reflux (20 h) in the absence of light. The cooled solution was filtered and the solvents evaporated. Column chromatography (diethyl ether) followed by recrystallisation from diethyl ether-hexane

gave the title compound (228) as red needles (0.96 g, 50%; lit.,[107] 52%). $\nu_{max.}$ 1990 s 1960 s and 1875 br (metal carbonyl), and 1680 s cm^{-1} (carbonyl); ^1H n.m.r. δ6.18 (1H,d,J 6Hz,aryl-H), 5.76 (1H,t,J 6Hz,aryl-H), 5.22 (1H,d, J 6Hz,aryl-H), 5.03 (1H,t,J 6Hz,aryl-H), 4.59 - 4.40 (2H,m,H-2), 2.90 - 2.65 (2H,m,H-3) [lit.,[107](90 MHz) δ6.20 - 6.13 (1H,m), 5.80 - 5.65 (1H,m), 5.30 - 4.90 (2H,m), 4.60 - 4.35 (2H,m), 2.90 - 2.65 (2H,m)]; *m/z* 284 (M^+).

endo-(4-Chromanol)$Cr(CO)_3$ (218)[107]

Sodium borohydride (200 mg, 5.3 mmol) was added to a solution of (4-chromanone)$Cr(CO)_3$ (228) (400 mg, 1.4 mmol) in 15% aqueous THF (25 ml). An immediate colour change from red to yellow was observed. After stirring (10 min) the mixture was concentrated (to 10 ml) and carefully quenched with dilute aqueous acid (30 ml). The mixture was extracted with dichloromethane (3 x 15 ml) and the combined organic layers filtered through a short plug of alumina. Solvent evaporation gave the title compound as a yellow powder (210 mg, 53%). ^1H n.m.r. spectroscopy showed this product, by comparison to be identical to one of the two diastereoisomers (217) and (218) produced by direct complexation of the alcohol (3) and to be different from the *exo* isomer (217). It was therefore identified as *endo*-(4-chromanol)$Cr(CO)_3$ (218). *m/z* 286 (M^+).

endo-(4-Chromanol TBDMS ether)$Cr(CO)_3$ (225)

TBDMS-chloride (12.5 mg, 0.8 mmol) was added to a solution of *endo*-(4-chromanol)$Cr(CO)_3$ (218) (200 mg, 0.7 mmol) and imidazole (110 mg, 1.6 mmol) in DMF (3 ml) and the mixture stirred (21 h at 20°C). The reaction mixture was partitioned between water-hexane (1:1, 70 ml) and the organic layer separated and evaporated. Column chromatography (diethyl ether) gave the title compound (225) as a yellow powder (92 mg, 31%)

followed by unreacted starting material (218) (73 mg, 37%). Product (225): ^{1}H n.m.r. δ5.67 (1H,d,J 6Hz,aryl-H), 5.50 (1H,t,J 6Hz,aryl-H), 4.98 (1H,d,J 6Hz,aryl-H), 4.85 (1H,t,J 6Hz,aryl-H), 4.78 (1H,dd,J 5,8Hz,H-4), 4.39 - 4.31 (1H,m,H-2), 4.14 - 4.05 (1H,m,H-2), 2.23 - 2.03 (2H,m,H-3), 1.00 (9H,s,^{t}Bu), 0.23 (3H,s,Me), 0.18 (3H,s,Me); *m/z* 400 (M^+).

Deprotection of *endo*-(4-chromanol TBDMS ether)$Cr(CO)_3$ (225)

Tetra-*n*-butylammonium fluoride trihydrate (150 mg, 0.48 mmol) was added to a solution of *endo*-(4-chromanol TBDMS ether)$Cr(CO)_3$ (225) (70 mg, 0.18 mmol) in THF (15 ml) under identical conditions to those used for the deprotection of the mixture of silyl ethers (224) (225) (226) and (227). After work-up a 2:1 mixture of *endo* (218) : *exo* (217) (4-chromanol)$Cr(CO)_3$ (30 mg, 60%) was isolated as a yellow oil. This mixture was identified by comparison of its ^{1}H n.m.r. spectrum with those due to the separate diastereoisomers.

Methylation of *exo*-(4-chromanol TBDMS ether)$Cr(CO)_3$ (224)

n-BuLi (0.45 ml, 0.7 mmol) was added to a solution of *exo*-(4-chromanol TBDMS ether)$Cr(CO)_3$ (224) (240 mg, 0.6 mmol) in THF (20 ml) at -78°C. After stirring (2 h; -78°C), methyl iodide (0.1 ml, 1.6 mmol) was added and stirring continued (2 h). Methanol (2 ml) was added, the reaction mixture warmed to 20°C and the solvents evaporated. Column chromatography (diethyl ether-petrol, 1:3) gave a single fraction which could not be crystallised. Evaporation gave a 3:1 mixture of *exo*-(8-methyl-4-chromanol TBDMS ether)$Cr(CO)_3$ (229) and unreacted starting material (224) (total 180 mg). (229) ^{1}H n.m.r. δ5.45 (2H,d,J 6Hz,H-5 & 7), 4.93 (1H,t,J 6Hz,H-6), 4.66 (1H,t,J 4Hz,H-4), 4.37 - 4.18 (2H,m,H-2), 2.36 - 2.22 (1H,m,H-3), 2.16 (3H,s,ArMe), 1.95 - 1.83

(1H,m,H-3), 0.91 (9H,s,^{t}Bu), 0.21 (3H,s,SiMe), 0.18 (3H,s,SiMe); *m/z* 414 (M^+), 400 (M^+, starting material).

Deprotection of the ring methylated *exo*-(4-chromanol TBDMS ether)$Cr(CO)_3$ (229)

Tetra-*n*-butylammonium fluoride (250 mg, 0.8 mmol) was added to a solution of the product mixture (180 mg) obtained by methylation of *exo*-(4-chromanol TBDMS ether)$Cr(CO)_3$ (224) in THF (20 ml) and the mixture stirred (15 h; 20°C). The reaction mixture was concentrated (to 5 ml), water (30 ml) was added and the mixture extracted with diethyl ether (3 x 15 ml). The combined organic fractions were filtered through a short plug of alumina and the solvent evaporated to give a mixture of *exo*-(4-chromanol)$Cr(CO)_3$ (217) and *exo*-(8-methyl-4-chromanol)$Cr(CO)_3$ (202) (68 mg) identified by comparison of the ^{1}H n.m.r. spectrum with those of authentic samples.

exo-(4-Chromanol MOM ether)$Cr(CO)_3$ (230)

To potassium hydride (150 mg, 1.3 mmol) previously washed with petrol, was added THF (15 ml). A solution of *exo*-(4-chromanol)$Cr(CO)_3$ (217) (250 mg, 0.9 mmol) in THF (10 ml) was added dropwise to this suspension and the mixture stirred (1½ h; 20°C). A colour change from yellow to orange was observed while gas was evolved. Chloromethyl methyl ether (0.15 ml, 2 mmol) was added and stirring continued (15 h). The mixture was quenched with methanol (2 ml) and the solvent evaporated. Column chromatography (diethyl ether-petrol, 1:1) followed by crystallisation from diethyl ether-hexane gave the title compound (230) as yellow needles (150 mg, 52%) together with unreacted starting material (217) (40 mg, 20%). Product (230): ^{1}H n.m.r. δ5.73 (1H,d,J 6Hz,aryl-H), 5.55 (1H,t,J 6Hz,aryl-H),

5.13 (1H,d,J 6Hz,aryl-H), 4.85 (1H,t,J 6Hz,aryl-H), 4.79 (2H,s,OCH_2O), 4.47 (1H,t,J 4Hz,H-4), 4.30 - 4.18 (2H,m,H-2), 3.43 (3H,s,OMe), 2.41 - 2.28 (1H,m,H-3), 2.12 - 2.00 (1H,m,H-3); *m/z* 330 (M^+).

exo-(MOM 8-methyl-4-chromanol ether)$Cr(CO)_3$ (231)

n-BuLi (0.35 ml, 0.56 mmol) was added to a solution of *exo*-(4-chromanol MOM ether)$Cr(CO)_3$ (230) (150 mg, 0.45 mmol) in THF (20 ml) at -78°C. After stirring (2 h at -78°C), methyl iodide (0.2 ml, 3.2 mmol) was added and stirring continued. Methanol (2 ml) was added, the reaction mixture warmed to 20°C and the solvents evaporated. Column chromatography (diethyl ether) followed by crystallisation from diethyl ether-hexane gave the title compound (231) as yellow crystals (120 mg, 77%). M.p. 68-70°C (Found: C, 52.2; H, 4.55. $C_{15}H_{16}CrO_6$ requires C, 52.3; H, 4.7%); $\nu_{max.}$ 1955 s and 1860 s cm^{-1} (metal carbonyl); ^1H n.m.r. δ5.56 (1H,d,J 6Hz,aryl-H), 5.48 (1H,d,J 6Hz,aryl-H), 4.90 (1H,t,J 6Hz,H-6), 4.79 (2H,s,OCH_2O), 4.51 (1H,m,H-4), 4.33 - 4.23 (2H,m,H-2), 3.43 (3H,s,OMe), 2.42 - 2.26 (1H,m,H-3), 2.15 (3H,s,ArMe), 2.13 - 2.00 (1H,m,H-3); *m/z* 344 (M^+).

Deprotection of *exo*-(MOM 8-methyl-4-chromanol ether)$Cr(CO)_3$ (231)

Hydrochloric acid (6 M, 1 ml) was added to a solution of *exo*-(MOM 8-methyl-4-chromanol ether)$Cr(CO)_3$ (231) (40 mg, 0.1 mmol) in 25% aqueous THF (5 ml) and the mixture heated (6 h at 50°C). The mixture was concentrated (to 2 ml), water (5 ml)was added and the solution extracted with dichloromethane (3 x 10 ml). The organic fractions were filtered through a short plug of alumina and evaporated to give *exo*-(8-methyl-4-chromanol)$Cr(CO)_3$ (202) (20 mg, 59%) identified by comparison of its ^1H n.m.r. spectrum with that of an authentic sample.

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