Novel Methods for the Synthesis of Small Ring Systems

David Stephen Pugh

Thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

University of York

Department of Chemistry

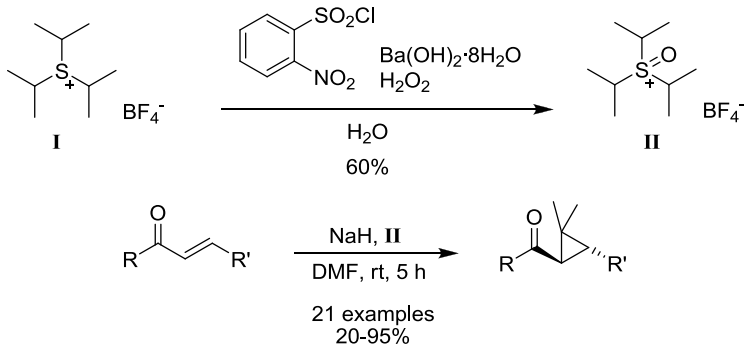
September 2011

Abstract

Chapter 1 briefly reviews telescoped reactions, in particular tandem oxidation processes, detailing the background to the development of the methodology presented here, and sets out the aims for the Thesis.

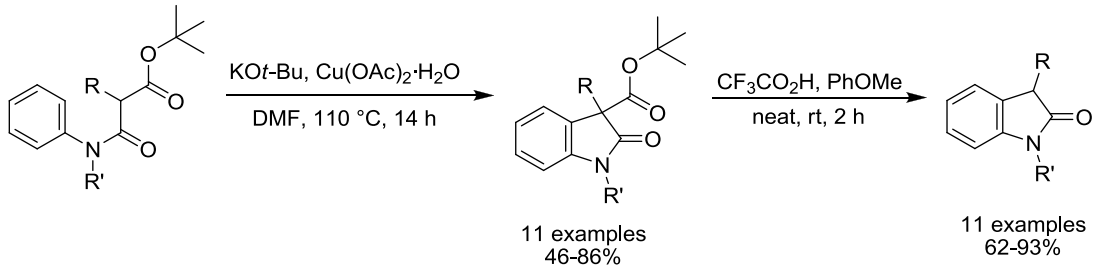
Chapter 2 reviews cyclopropanation methods and examines the preparation and use of tri*iso*propylsulfoxonium tetrafluoroborate **II** for the preparation of *gem*-dimethylcyclopropanes for a range of α,β-unsaturated compounds including ketones, esters, amides, nitriles and nitro-compounds (Scheme I). Chapter 2 also examines potential applications for the methodology, outlining a route towards the synthesis of chrysanthemic acid as well as attempts towards rearrangement methodology.

Scheme I:



Chapter 3 demonstrates the preparation of 3-substituted oxindoles from substituted anilides in a copper-mediated cyclisation-decarboxylation sequence (Scheme II).

Scheme II:



This sequence is demonstrated for a range of alkyl, aryl and heteroaryl substituents in the 3-position, with methyl, benzyl and PMB protection on the nitrogen atom. Further development of the copper-cyclisation methodology leading to a catalytic system is presented, along with initial work towards a decarboxylative allylation of oxindoles.

Contents

List of tables and figures

Acknowledgements

This thesis would not have been possible without the support of a great number of people. Firstly, to Professor Richard Taylor who gave me the opportunity to undertake a Ph.D, and provided much support and guidance through his supervision. To the many members of the Taylor group: Alan B, Alessia M, Alex C, Alexis P, Cat M, Dan H, Dave B, Graeme M, James C, James D, James R, Jan S, Jana L, Johannes K, Jon O, Katie G, Mark P, Melanie L, Mickael J, Mike E, Nicola C, Phil C, Pierre W, Reyhan B, Richard D, Richard P, Russ K, Sandra R, Stuart J, Subhrangsu R, Vilius F, Will B and Will U, who have all made working in the group an pleasure. In particular, I wish to thank Dr Mike Edwards for all his guidance, advice and proof reading the many drafts of this thesis, and to Graeme who looks after us all, maintaining every aspect of the labs.

Thanks to all those contributing to technical services in the department: Steve, Mike, Derek and Val in stores; Trevor, Ben and Karl for mass spec; Adrian and Rob and the national crystallography service for X-ray; Phil and Graeme for microanalysis; and especially Heather and Amanda for the NMR service. Also thanks to the workshops (glass, electrical and mechanical) who put everything back together each time we break things and to the EPSRC and the University of York for funding.

Thanks to all those who have contributed to providing distractions away from the lab, and particularly thanks to my family for their constant support and encouragement in everything I do.

Declaration

The research presented in this thesis was carried out at the University of York between October 2007 and September 2010. This work is, to the best of my knowledge, original, except where due reference has been made to other workers.

David Stephen Pugh

September 2011

Chapter 1: Telescoped reactions

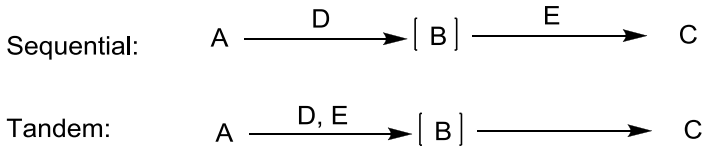
1.1 Telescoped processes

A telescoped reaction involves multiple reaction steps occurring in one reaction vessel, with no intermediate work-up or purification, offering environmental advantages through reduced solvent usage and elimination of a workup/purification procedure. Other advantages may also be obtained, such as access to unstable, volatile or highly toxic intermediates, which are formed and immediately used in the reaction.[1-4]

1.1.1 Sequential and tandem reactions

Telescoped (one-pot) reactions can be further broken down into sub-classes, sequential and tandem reactions. A sequential, one-pot reaction is one in which the reagents for the first step are added to the reaction vessel, and then the reaction monitored until reaching completion, before reagents for the subsequent step are added. Tandem reactions differ, in that all the reagents are present from the start and as the desired intermediate is formed, it is utilised immediately in the second step (Scheme 1).

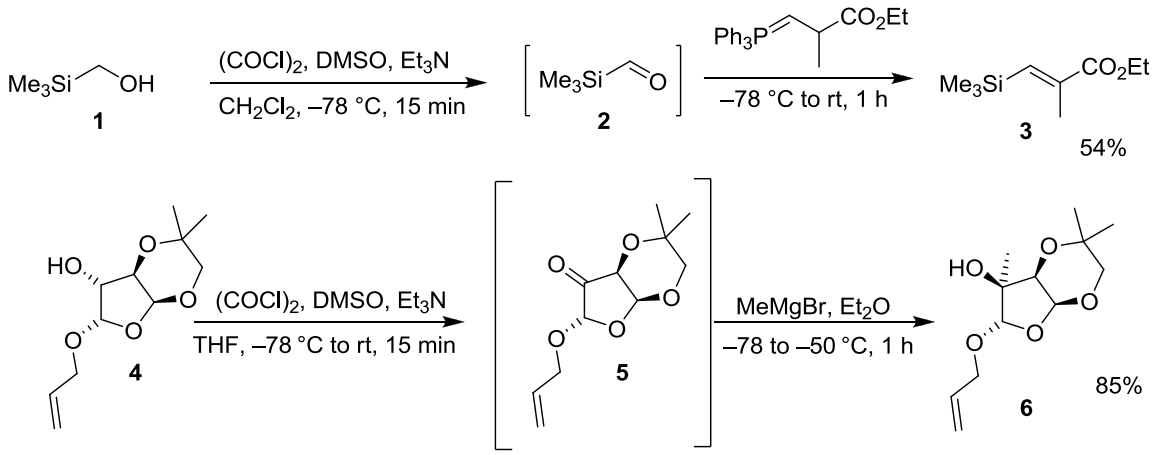
Scheme 1:



1.2 Development of tandem oxidation processes

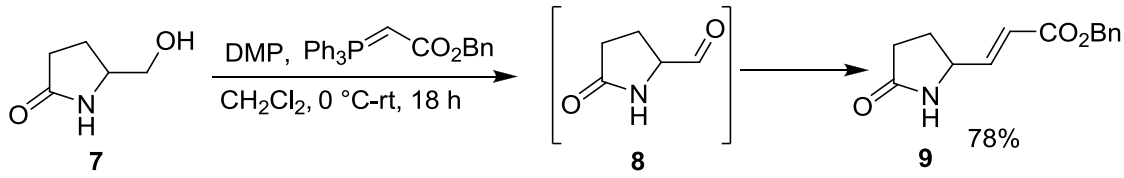
Tandem-oxidation processes (TOP) are a valuable telescoped reaction class, and are of major interest to the York group.[4] The first telescoped oxidation reaction sequences were reported by Norbeck and Ireland, who utilised a sequential Swern oxidation followed by Wittig or Grignard reactions (Scheme 2).[5]

Scheme 2:



The first tandem oxidation-Wittig process was reported two years later by Huang, using Dess-Martin periodinane as the oxidant (Scheme 3).[6]

Scheme 3:

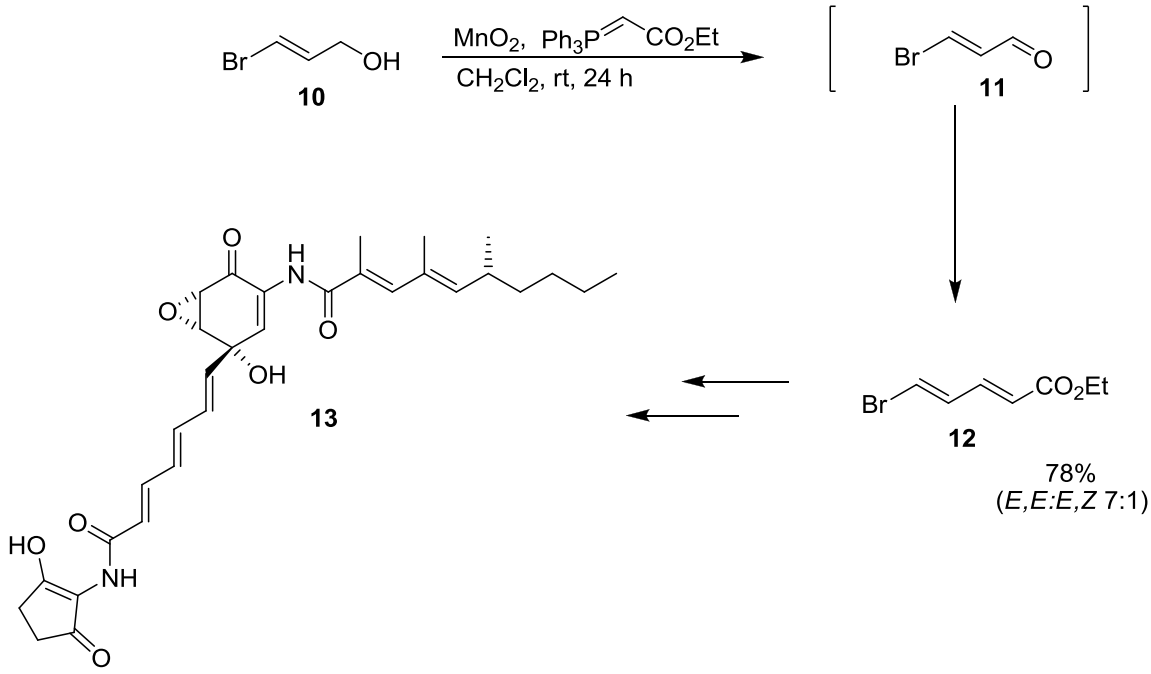


The York group made a number of contributions in this TOP area (Section 1.2.1), and subsequently several other tandem oxidation-Wittig reactions have been reported with oxidants including: IBX,[7] barium manganate,[8] TPAP-NMO,[9] PCC,[10] Parekh-Doering[11] and DMP.[12]

1.2.1 Tandem oxidation-Wittig processes

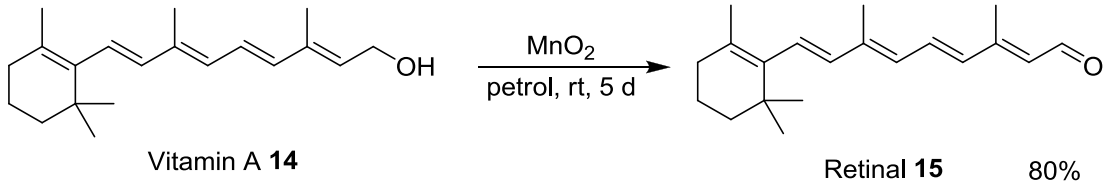
The Taylor group's first tandem oxidation reactions were used in the preparation of manumycin antibiotics (for example, **13**). Part of the synthesis required the use of (*E*)-3-bromopropenal **11**, a mutagenic, low-boiling aldehyde that was difficult to handle, and so instead alcohol **10** was utilised in a tandem oxidation-Wittig sequence (Scheme 4).[13]

Scheme 4:



Use of manganese dioxide as an organic oxidant dates from 1948, when it was used to prepare retinal **15** from vitamin A **14** (Scheme 5).[14]

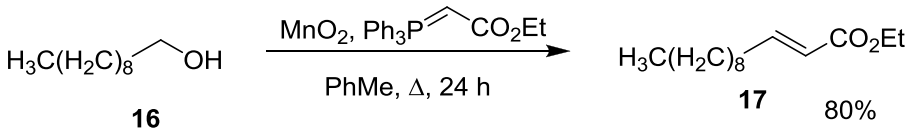
Scheme 5:



Activated manganese dioxide readily oxidises activated primary and secondary alcohols, and particularly α,β-unsaturated alcohols (with preservation of geometry),[15, 16] as well as oxidation of amines and aromatisation.[17] Oxidations are reported in a wide range of organic solvents (with the exceptions of alcohols and water), and frequently used solvents include: petroleum ethers, toluene, dichloromethane, chloroform, ether, THF and acetonitrile. A number of reviews have been published, including those from Evans,[18] Korshunov,[19] Fatiadi,[20, 21] and Soldatova.[22]

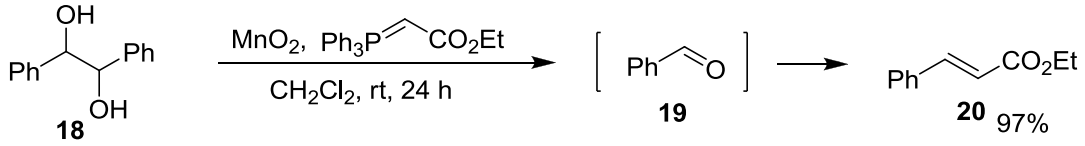
From the Taylor group's initial use, they went on to examine the scope and limitations with manganese dioxide tandem oxidation-Wittig reactions. This chemistry was particularly successful with activated alcohols,[23-32] although success was also found when using unactivated alcohols, for example, the use of decanol **16** (Scheme 6), although here higher temperatures and extended reaction times are required.[33]

Scheme 6:



Tandem oxidation-Wittig trapping has also been demonstrated using 1,2-diols, with oxidative cleavage followed by *in situ* aldehyde trapping with a Wittig ylide (Scheme 7).[34]

Scheme 7:

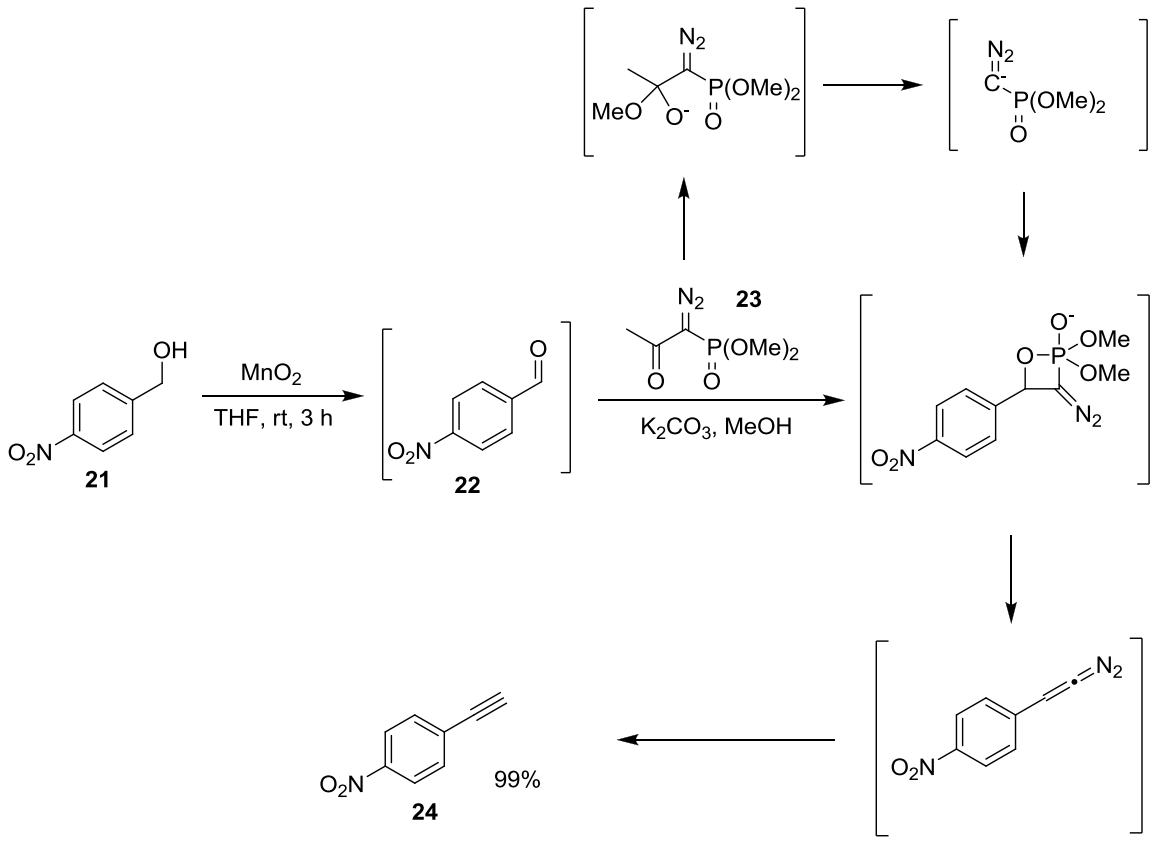


Following the success of tandem oxidation-Wittig reactions, other tandem oxidation processes utilising manganese dioxide were explored, giving facile, one-pot transformations from primary alcohols into alkynes,[35] allylic ketones,[36] esters,[37, 38] amides,[37, 38] imines,[39] amines,[39, 40] nitriles,[41] oximes,[42] heterocyclic compounds[32, 43-45] and cyclopropanes.[46] Selected examples are given in the following sections.

1.2.2 Tandem oxidation-alkyne formation

Sequential oxidation processes were developed for the conversion of alcohols into terminal alkynes, for example using the Bestmann-Ohira reagent **23** (Scheme 8).[35] The intermediate aldehyde undergoes a Seyferth-Gilbert homologation after loss of methyl acetate from the Bestmann-Ohira reagent.

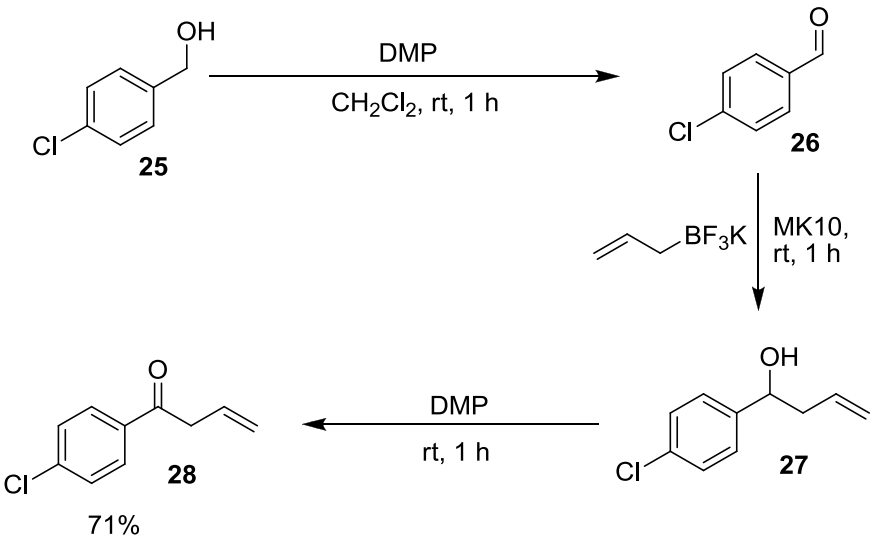
Scheme 8:



1.2.3 Telescoped oxidation-allylation processes

Another related tandem-oxidation process developed within the York group was for a tandem oxidation-allylation-oxidation process. It had been hoped to use manganese dioxide for this sequence, however it was quickly found that manganese dioxide was unable to oxidise the secondary alcohol formed, but the Dess-Martin periodinane proved capable, and this was utilised in the sequence (Scheme 9).[36]

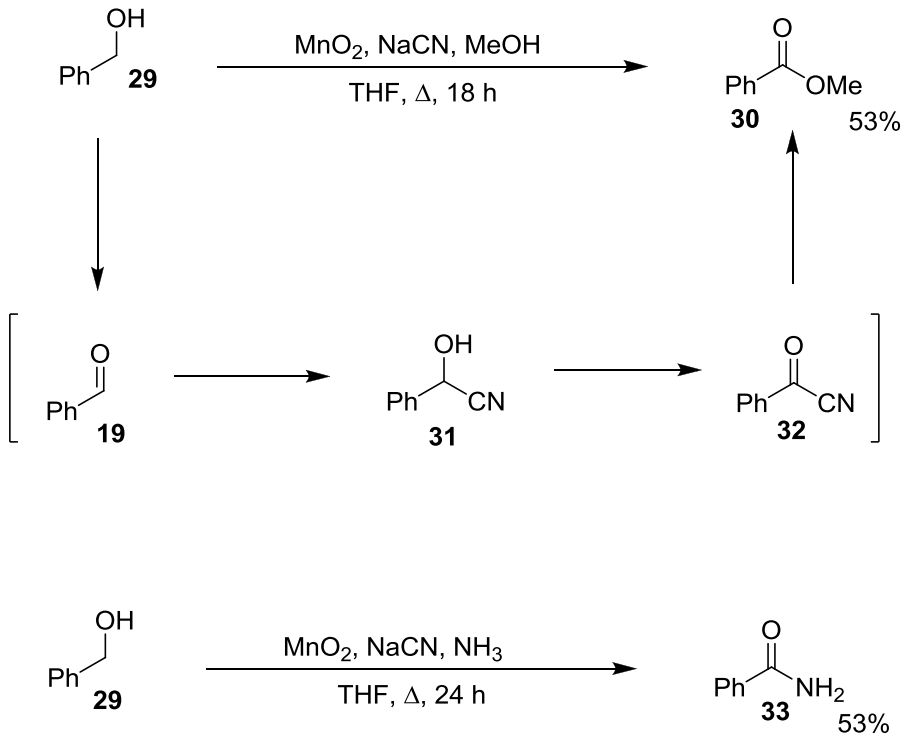
Scheme 9:



1.2.4 Tandem oxidation giving esters and amides

Direct conversion of alcohols into esters and amides has also been explored. Oxidation with manganese dioxide is followed by addition of cyanide to the intermediate aldehyde, to give a cyanohydrin, which is oxidised to the acyl cyanide and then substituted with an alcohol to give an ester, or an amine to give an amide (Scheme 10).[37, 38] This expands on the work of Corey and Gilman who developed these transformations from aldehydes.[47]

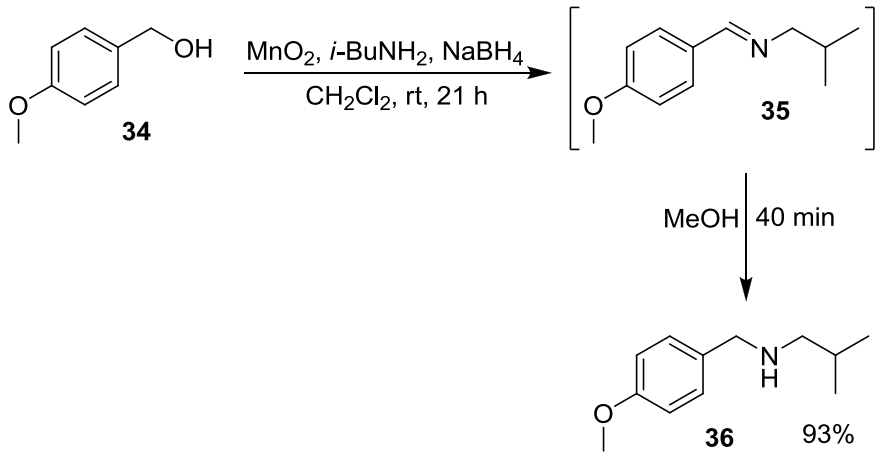
Scheme 10:



1.2.5 Tandem oxidation-imine formation

Trapping the aldehyde with primary amines gave access to imines,[39] which could then be reduced in the same pot to give secondary amines (Scheme 11).[39, 40]

Scheme 11:



Combining an oxidation and reduction step in a single pot is possible here due to the insolubility of the sodium borohydride in dichloromethane, and it only enters

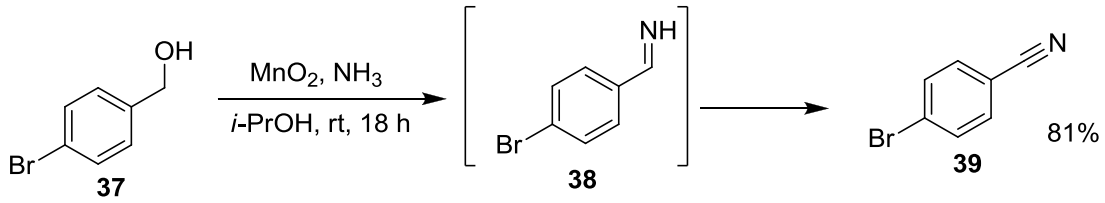
solution after addition of the methanol, facilitating the reductive amination step. If methanol is present from the start, no reaction is observed.[40]

Examples of tandem oxidation-imine formation with trapping by hydroxylamine in order to give oximes has also been demonstrated.[42]

1.2.6 Tandem oxidation-nitrile formation

One-pot conversion to nitriles has also been achieved, proceeding with imine formation and then *in situ* oxidation to the nitrile (Scheme 12).[41]

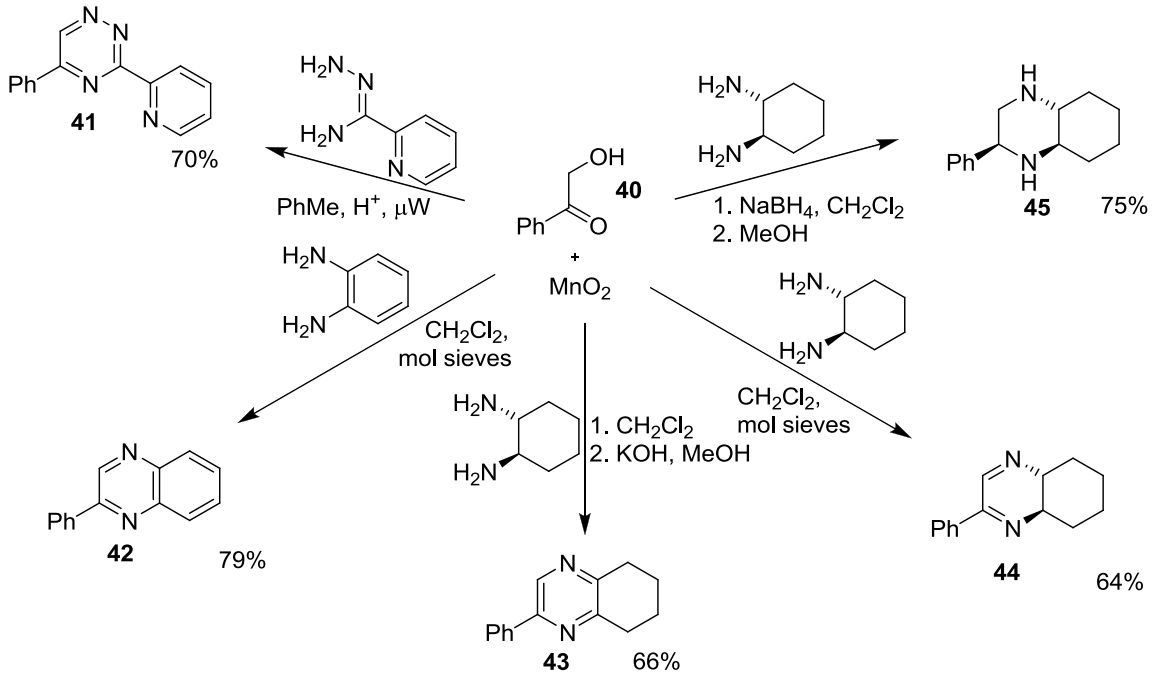
Scheme 12:



1.2.7 Formation of heterocycles

Perhaps the most useful application of TOP chemistry has been towards the synthesis of a range of heterocyclic scaffolds, using α-hydroxyketones and trapping with 1,2-diamines to give quinoxalines and related compounds (Scheme 13).[43-45]

Scheme 13:

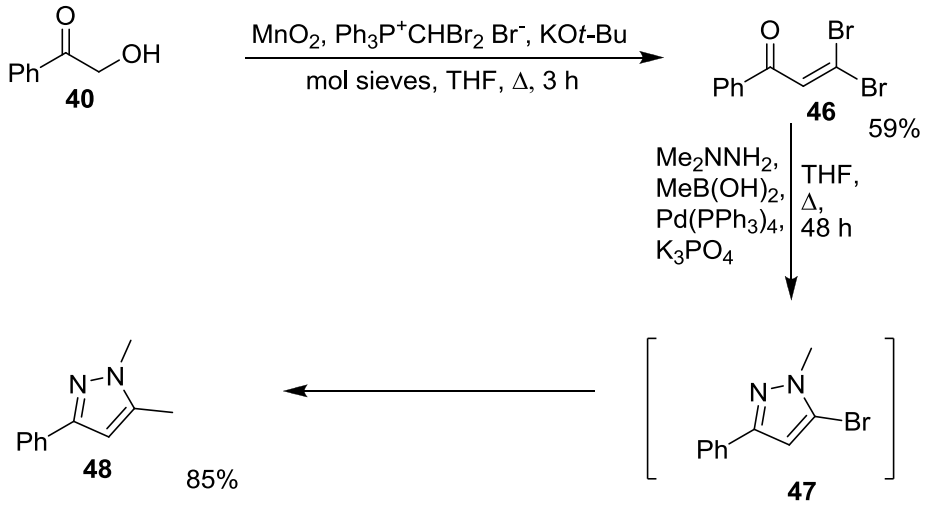


Here, pyrazines, quinoxalines, dihydropyrazines, piperazines and triazines are easily constructed from the oxidation of α-hydroxyketones which undergo double imine formation with diamines (and in the preparation of piperazines, subsequent reduction).

1.2.8 Tandem pyrazole formation-Suzuki coupling reactions

Beltran-Rodil developed a tandem pyrazole formation-Suzuki coupling reaction, which utilised some TOP-Wittig methodology.[32] Dibromoalkenes had previously been prepared from alcohols using TOP chemistry,[48] and this chemistry was applied to α-hydroxyketones to give β,β-dibromoenones. These compounds were then able to react with hydrazines to give bromopyrazoles, which underwent Suzuki coupling in one pot, giving a controlled, regioselective, pyrazole synthesis (Scheme 14).[32]

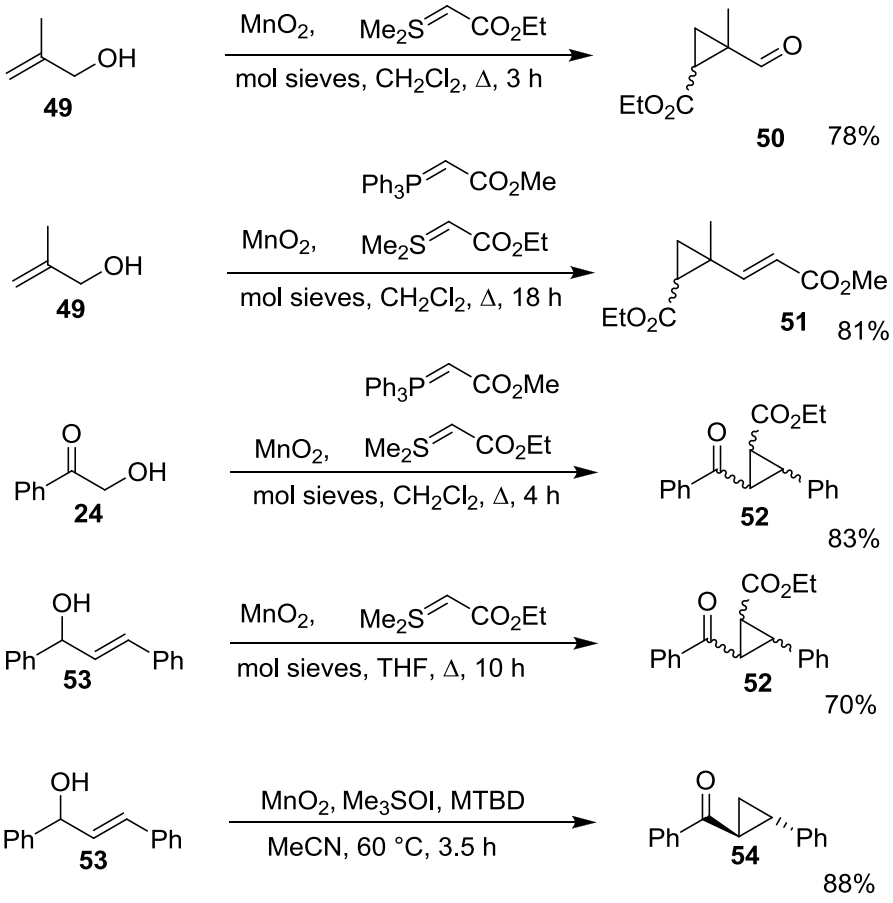
Scheme 14:



1.2.9 Tandem oxidation-cyclopropanation

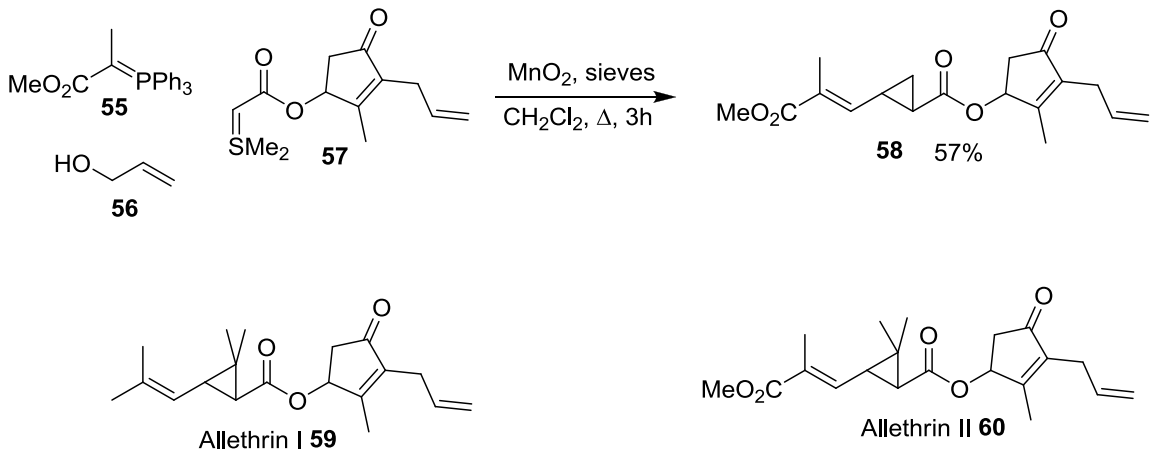
Of major relevance to this thesis, are tandem oxidation-cyclopropanation sequences. Here several complementary procedures have been developed (Scheme 15).[46] The first utilises Payne's cyclopropanation procedure[49] and oxidation of allylic alcohols to give cyclopropyl aldehydes, the second incorporates an *in situ* Wittig reaction on the aldehyde. The third reverses the order, constructing an alkene which then undergoes cyclopropanation. The final two examples feature oxidation of secondary alcohols with cyclopropanation, one using Payne's procedure[49] and the second utilising the Corey-Chaykovsky cyclopropanation.[50]

Scheme 15:



This methodology was utilised by the Taylor group in the synthesis of allethrin analogue **58** (Scheme 16).[46]

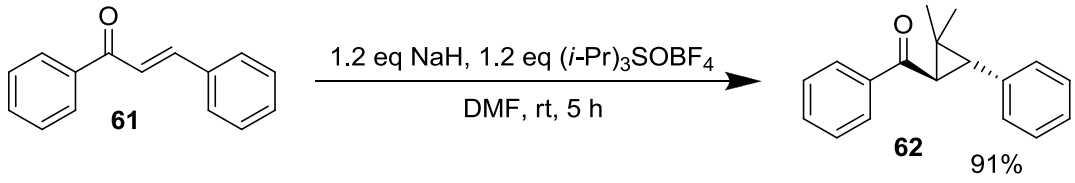
Scheme 16:



Here, allethrin analogue **58** is rapidly constructed in a tandem oxidation-cyclopropanation-Wittig reaction. This analogue differs from allethrin II **60** in the cyclopropane ring, where the ring would normally consist of a *gem*-dimethylcyclopropane.

This desire to develop a reagent capable of installing a *gem*-dimethylcyclopropane was explored in the York group by Paxton and Edwards. This led to the development of tri*iso*propylsulfoxonium tetrafluoroborate, which was shown to be capable of cyclopropanating electron-deficient alkenes (Scheme 17).

Scheme 17:



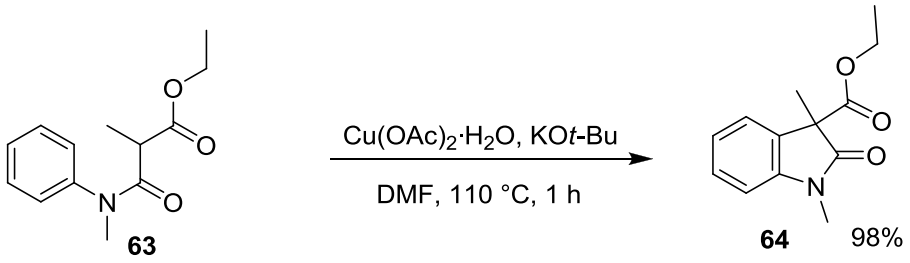
Chapter 2 discusses the developments in this methodology, from initial synthesis of the salt and demonstration of the scope for cyclopropanation and later developments of an improved salt synthesis.

1.3 Other tandem processes

1.3.1 Telescoped approaches to oxindoles

The preparation of oxindoles is another area of interest to the York group, with some tandem approaches having been developed. Perry examined the possibilities of a CH activation approach towards 3-substituted oxindoles, and ultimately obtained a copper-mediated process utilising a tandem alkylation-cyclisation route to oxindoles (Figure 1).[51]

Figure 1:



The continuation of this work, developing a cyclisation and decarboxylation route to 3-substituted oxindoles is discussed in Chapter 3.

1.4 Aims & objectives

The following aims and objectives are considered in the work contained in this thesis:

- To scale up the synthesis of tri*iso*propylsulfoxonium tetrafluoroborate. (Chapter 2)
- To demonstrate the scope of the reagent in the preparation of *gem*-dimethylcyclopropanes. (Chapter 2)
- To explore other synthetic applications of *gem*-dimethylcyclopropanes. (Chapter 2)
- To develop an anilide cyclisation and decarboxylation strategy for the synthesis of 3-substituted oxindoles. (Chapter 3)
- To consider approaches to prepare oxindoles with an unprotected nitrogen in the oxindole ring. (Chapter 3)
- To examine the large scale synthesis potential for oxindole preparation. (Chapter 3)

Chapter 2 – Preparation of *gem*-dimethylcyclopropanes

2.1 Cyclopropane functionality

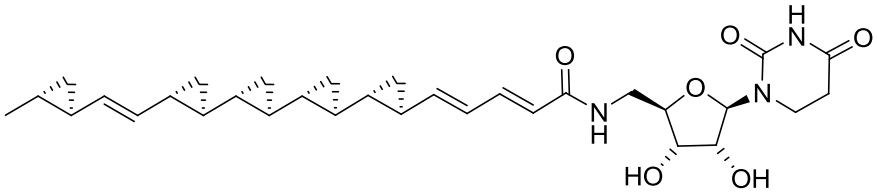
The cyclopropane functional group has been of great interest to synthetic chemists since the discovery of cyclopropane was published by Freund in 1882.[52, 53]

Cyclopropanes are the smallest ring system that can be formed, and offer unique characteristics due to the strained nature of the ring. The ring and torsional strain result in the cyclopropane bonds being considerably weaker than carbon-carbon bonds in other alkanes, including larger cycloalkanes, and results in the bonds sharing much in character with alkenes. A number of models have been reported in order to explain the bonding characteristics of cyclopropanes, including molecular orbital descriptions,[54] valence bond theories[55] and bent bond models.[56] A number of reviews have been published, examining the bond nature, and the methods used to describe the bonding in cyclopropanes, including those from Meijere,[57] Wiberg[58] and Palke.[59] The reactivity of cyclopropanes is unique as a result of the strained bonds, and undergo reactions that would otherwise not be expected from alkanes.[60, 61]

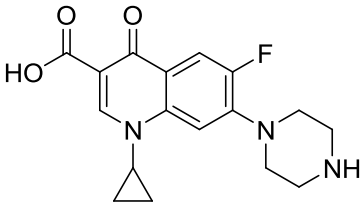
2.1.1 Prevalence in nature

The cyclopropyl structure is a common moiety found in nature, with methylene cyclopropanes being found in a wide variety of natural products,[62] however the *gem*-dimethylcyclopropane moiety is even more widespread.[63] Scheme 18 illustrates several cyclopropane and *gem*-dimethylcyclopropane containing natural products and pharmaceutical compounds.

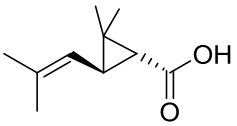
Scheme 18:



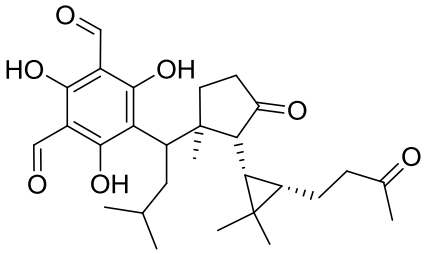
FR-900848 **65**



ciprofloxacin **66**



chrysanthemic acid **67**

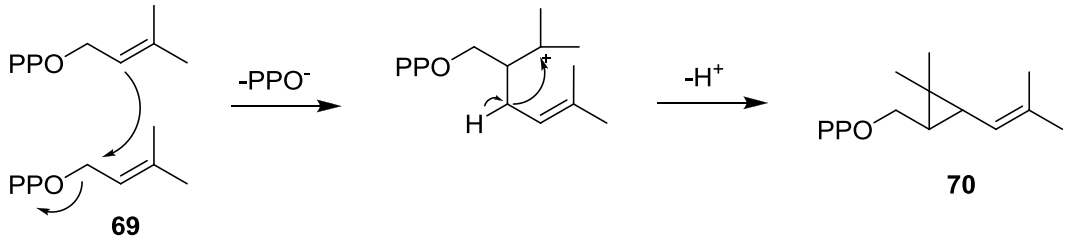


eucalyptone **68**

FR-900848 **65** is a compound extracted from *Streptoverticillium fervens* displaying a highly specific antibiotic activity against filamentous fungi, and contains five methylene cyclopropane rings.[12, 64] Ciprofloxacin **66** is a methylene cyclopropane containing antibiotic used in the treatment of food poisoning (for example, *Salmonella),* respiratory and urinary tract infections,[65] generating $194,300,000 in revenue, putting it in the top 200 drugs by retail sales in 2008.[66] Chrysanthemic acid **67** contains a *gem*-dimethylcyclopropane and is found in a number of plants, including pyrethrums and chrysanthemum.[67, 68] Derivatives of chrysanthemic acid are especially important to the pesticide industry, with these compounds generating billions of dollars in revenue.[69] Eucalyptone **68** is found in *Eucalyptus globulus* and demonstrates antibacterial activity.[70]

In nature, *gem*-dimethylcyclopropanes are likely to be constructed from terpenoid building blocks, for example from dimethylallyl pyrophosphate **69**, as suggested by Epstein and Poulter[71] (Scheme 19).

Scheme 19:

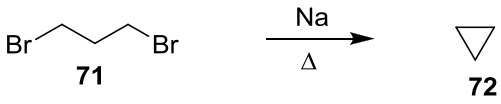


2.2 Synthesis of cyclopropanes

2.2.1 Wurtz type

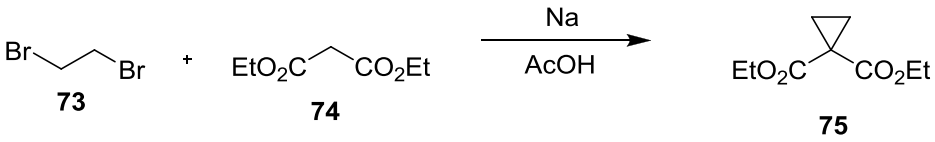
Methods for the synthesis of cyclopropanes are as old as our knowledge of their structure, and the first synthesis was from Freund. His synthesis of cyclopropanes was from 1,3-dibromopropane **71** and sodium, in an intramolecular Wurtz reaction (Scheme 20).[53]

Scheme 20:



Within a few years substituted cyclopropanes had been made by Perkin, using a related intermolecular reaction (Scheme 21).[72, 73]

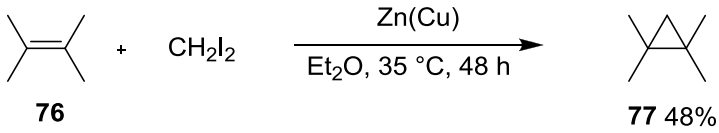
Scheme 21:



2.2.2 Simmons-Smith type

More recent routes to cyclopropanes often make use of carbene/metal carbenoid addition to alkenes, the first reported reaction still in widespread use is the Simmons-Smith cyclopropanation (Scheme 22).[74-76]

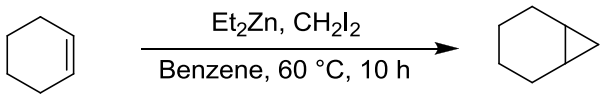
Scheme 22:



76 **77** 48%

Following their initial disclosure, many improvements to the reaction have been reported, from improved methods to prepare the zinc couple,[77, 78] preparations for active cyclopropanation species[79-82] and asymmetric variants.[83-85] In particular the developments of Furukawa, using diethylzinc are notable (Scheme 23).[86]

Scheme 23:

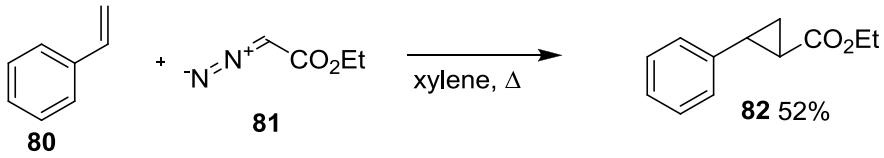


78 **79** 79%

2.2.3 From diazo compounds

Cyclopropanes are also commonly constructed through ring contraction, such as those formed from diazo compounds which can add across an alkene or alkyne to give a pyrazoline which subsequently loses nitrogen resulting in the formation of a cyclopropane. These can occur in one step, either directly[87, 88] (Scheme 24), or when catalysed by a metal such as rhodium,[89] copper[90] or ruthenium.[91]

Scheme 24:



80 **81** **82** 52%

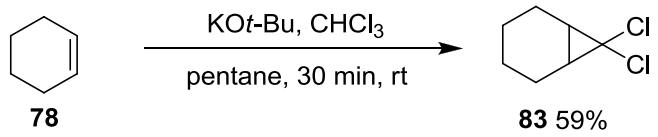
A detailed review covering diastereo and enantio-selective cyclopropanations, particularly using halomethylmetal and diazoalkane decompositions was published by the group of Charette in 2003.[92]

2.2.4 From dichlorocarbenes

Another important route to cyclopropanes is through the use of dichlorocarbenes derived from the action of a base with chloroform. The reaction was first

reported in 1954 by Doering and Hoffmann, who prepared cyclohexene-derived cyclopropanes (Scheme 25).[93]

Scheme 25:

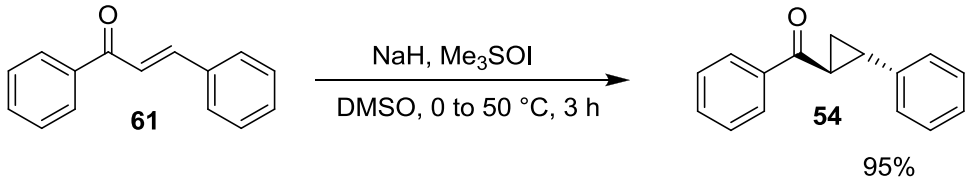


Doering and Hoffmann also reported the synthesis of *gem*-dibromocyclopropanes from bromoform in the same paper.[93] These *gem*-dihalocyclopropanes can then be converted into other functionalities (for example to cyclopropenes through elimination) or reduced to give methylene cyclopropanes.[94] A review on methods to prepare and the synthetic utility of *gem*-dihalocyclopropanes was published by Fedorynski in 2003.[95]

2.2.5 Using ylides

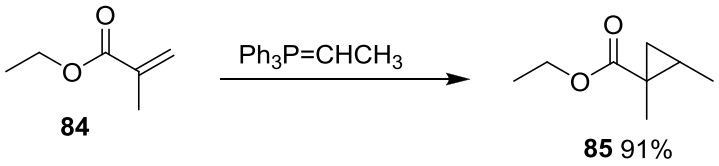
Another common approach to cyclopropanes is through the use of ylides. The first reports date from 1950,[96] but it was the work of Corey and Chaykovsky, reporting the use of dimethylsulfoxonium methylide in 1962 that started interest in this approach (Scheme 26).[50, 97]

Scheme 26:



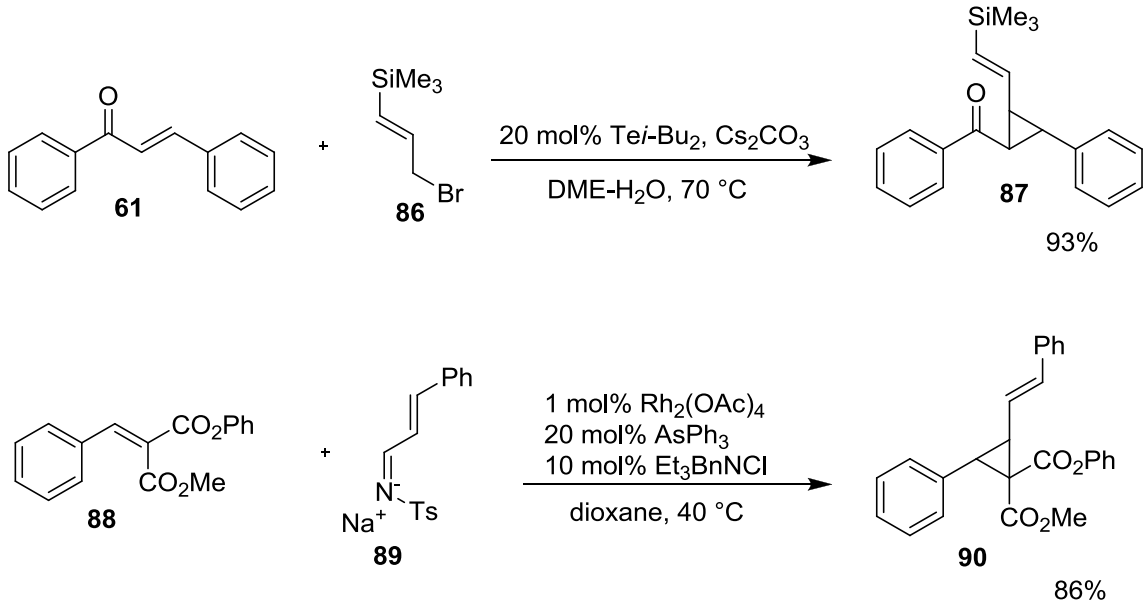
In the same year, Bestmann published an approach in which a nucleophilic phosphorus ylide undergoes conjugate addition with ethyl 2-methylacrylate **84** (Scheme 27).[98]

Scheme 27:



Subsequently, various other heteroatom ylides have been shown to cyclopropanate, including those based on arsenic[99] and tellurium.[100] Scheme 28 shows catalytic approaches with tellurium from Huang[101, 102] and arsenic from Tang.[103, 104]

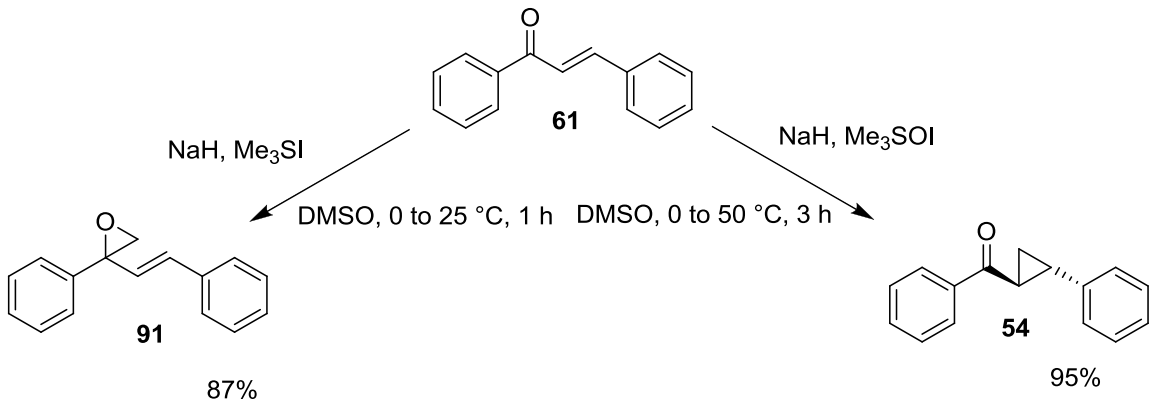
Scheme 28:



2.2.6 Sulfur ylides

Despite advances with other ylides, it is sulfur ylides that continue to generate the most interest. With Corey and Chaykovsky's development of trimethylsulfoxonium salts and their exploration into these and related compounds, conditions were developed for efficient cyclopropanation of olefins and epoxidation of carbonyls respectively. Corey showed that use of stabilised sulfur ylides (including sulfoxonium salts) favoured conjugate addition, and hence formation of cyclopropanes, whereas unstabilised ylides tend to lead to the formation of epoxides (Scheme 29).[97, 105]

Scheme 29:

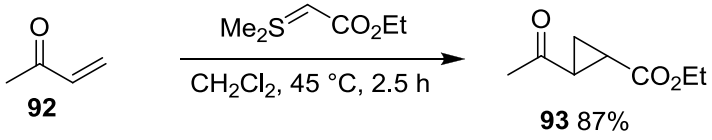


This change in addition regioselectivity comes from the type of nucleophile produced. Dimethylsulfonium methylide is an unstabilised anion, which results in irreversible 1,2-addition; whereas dimethylsulfoxonium methylide is a semi-stabilised ylide, making the initial 1,2-addition step reversible allowing 1,4-addition to proceed.

Although a variety of sulfonium salts were quickly developed,[106] offering different functionalities to be transferred to give substituted epoxides (including by Corey),[107] it is noteworthy that there are very limited corresponding reports for the development of alternative sulfoxonium salts. A number of reasons are likely for this: alkylation is reported to only be possible for sulfoxides in the case of methylation;[108] *O*-alkylation could compete with *S*-alkylation;[109] and there are limited reports for the oxidation of sulfonium salts (discussed later).

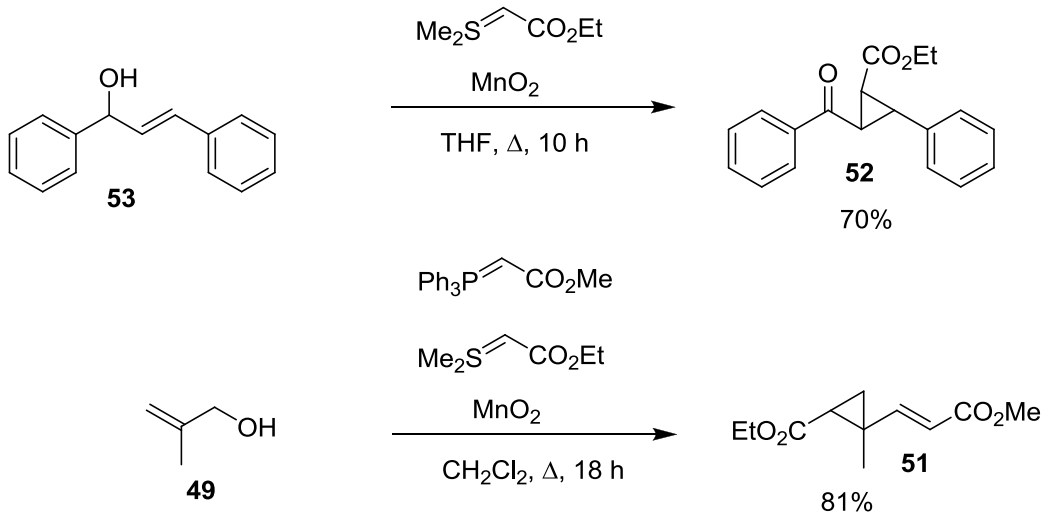
However, alternative stabilised ylides were quickly developed, offering the transfer of other functionalities than methylene. Of particular note were the developments of Payne, who developed ethyl (dimethylsulfuranylidene)acetate and demonstrated successful cyclopropanation (Scheme 30).[49]

Scheme 30:



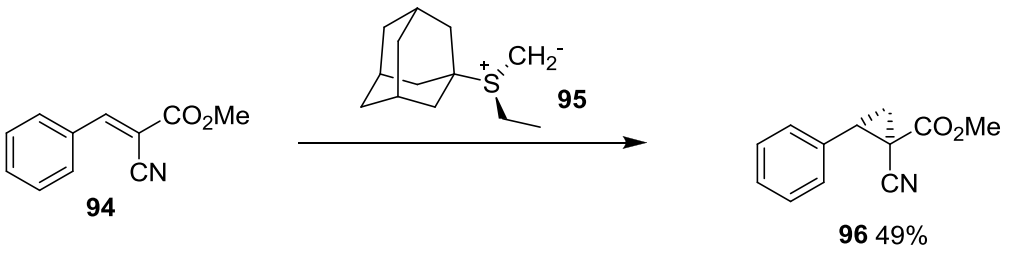
This approach has been of significant interest to our group previously, with the development of our Tandem Oxidation Processes chemistry (Scheme 31).[4, 46, 110] In the first scheme, an oxidation step of a secondary alcohol is telescoped with the cyclopropanation method of Payne, giving tri-substituted cyclopropanes. In the second scheme, a cyclopropanation and oxidation-Wittig reaction occur in a single pot process.

Scheme 31:



Novel sulfonium salts have continued to be developed, including the development of chiral salts giving optically active cyclopropanes, for example in the work of Trost (Scheme 32).[111]

Scheme 32:



Here, Trost prepared optically pure adamantylmethylethylsulfonium tetrafluoroborate by resolving as the L-malate salt and anion exchange. This sulfur chirality was then shown to be transferred to the carbon.

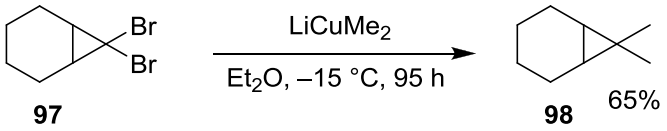
A detailed review of the use of ylides for cyclopropanation and epoxidation (in particular asymmetric reactions) has been published by Aggarwal.[112]

2.3 Synthesis of *gem*-dimethylcyclopropanes

2.3.1 Functional group conversion

The preparation of *gem*-dimethylcyclopropanes, can be achieved from either construction of the cyclopropane ring, or through suitable functional group interconversion. However, FGI approaches are limited because of the difficulties in introducing two methyl groups, although a limited number of examples do exist, such as the work of Corey in which *gem*-dibromocyclopropane **97** is converted (Scheme 33).[113]

Scheme 33:

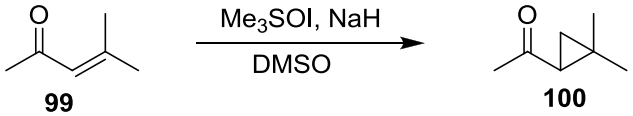


97 **98**

2.3.2 Substrate approaches

With the difficulties using FGI approaches, it is easier to construct the cyclopropane ring directly. For the preparation of *gem*-dimethylcyclopropanes, this can be achieved through choice of substrate, for example the approach of Marsh and coworkers using trimethylsulfoxonium iodide (Scheme 34),[114] but the methods to insert the *gem*-dimethyl groups in cyclopropanation are rather limited.

Scheme 34:

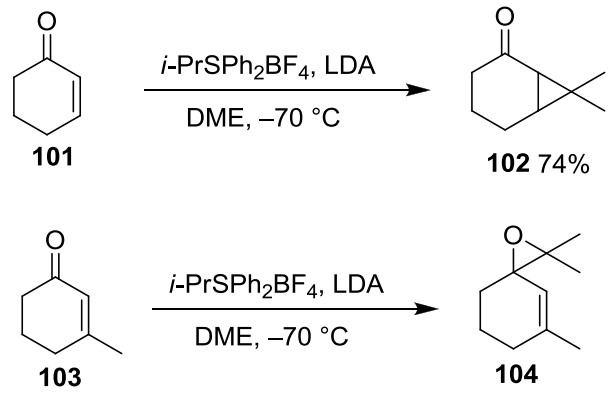


99 **100**

2.3.3 Ylide approaches

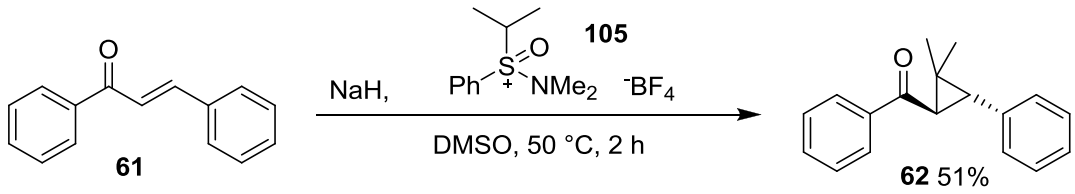
The majority of the reported routes to directly form *gem*-dimethylcyclopropanes involve the use of ylides, and several such ylides have been reported. The first such report came from Corey, in which an *iso*propyldiphenylsulfonium salt was prepared and used in the preparation of cyclopropanes. Whilst this approach is successful for many substrates (for example, cyclohexenone; Scheme 35), competitive epoxide formation limits its versatility, such as the reaction with 3-methyl-2-cyclohexenone **103** which gives mainly epoxide product **104** (Scheme 35).[115]

Scheme 35:



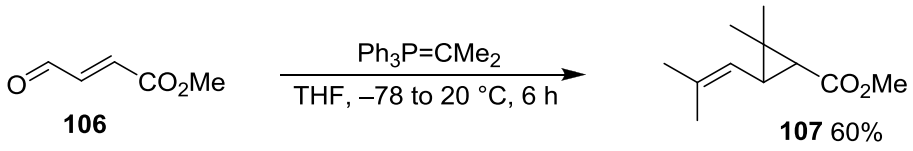
A few years later, Johnson[116] reported use of (dimethylamino)*iso*-propyl-*p*-tolylsulfoxonium tetrafluoroborate **105** (Scheme 36), but this method suffers from a difficult and very low yielding synthesis to obtain the required salt **105**, and few examples of cyclopropanation are reported .

Scheme 36:



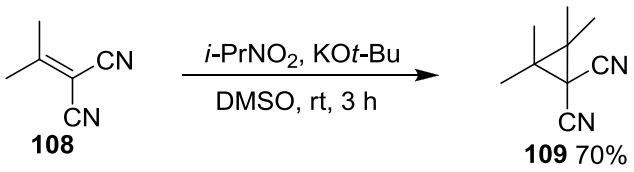
In 1976, Krief reported the use of the *iso*propylidene ylide for Corey-Chaykovsky type cyclopropanation of esters,[117, 118] but when aldehydes are present, a Wittig reaction occurs first (Scheme 37).

Scheme 37:



Ono and coworkers reported their use of 2-nitropropane (Scheme 38).[119] Whilst this approach is successful for some substrates, results are more disappointing for other compound classes, for example α,β-unsaturated ketones (chalcone **61** gives a 5% yield).

Scheme 38:

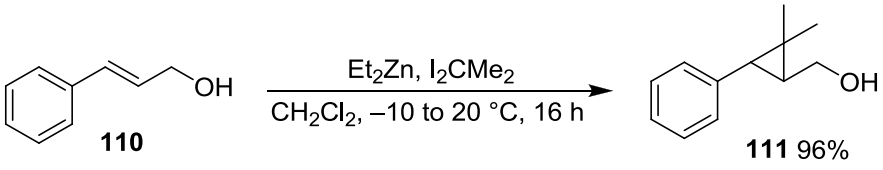


A related method, involving the metallation of 2-nitropropane was also reported by Krief in the same year,[120] along with a further system using lithium phenylsulfonyl-*iso*-propylide.[121]

2.3.4 Simmons-Smith approaches

Approaches that do not involve conjugate addition have also been reported. Charette reported a Simmons-Smith cyclopropanation using 2,2-diiodopropane for a range of allylic alcohols and ethers (Scheme 39).[122] Unfortunately, a significant drop in yield is observed when a phenyl substituent is not present.

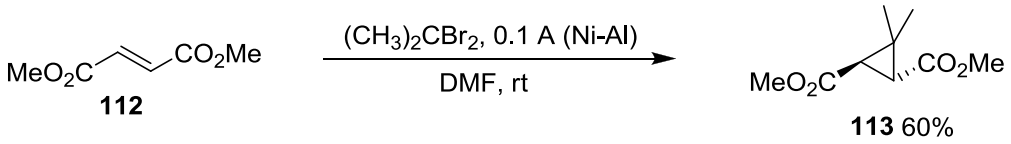
Scheme 39:



2.3.5 Electrochemical approaches

Leonel reported the use of dihalo compounds and electrochemistry to give cyclopropanes with fumarates and maleates (Scheme 40).[123]

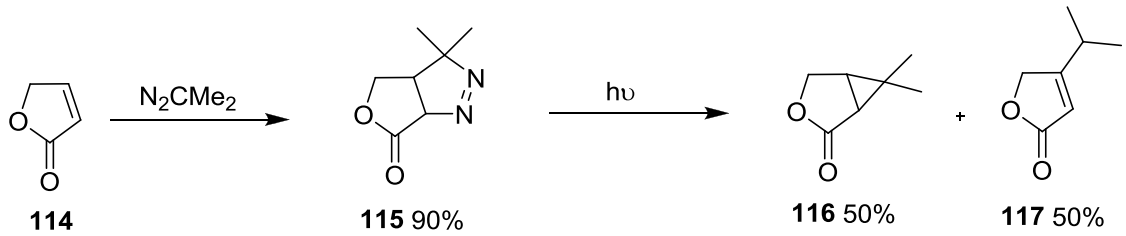
Scheme 40:



2.3.6 Ring-contraction approaches

Franck-Neumann reported use of 2-diazopropane to cyclopropanate fumarates *via* pyrazolines, with subsequent loss of nitrogen. The initial approach used thermal decomposition, but this gave exclusively *iso*-propylbutenolide **117**, whereas photolysis gave better results (Scheme 41).[124]

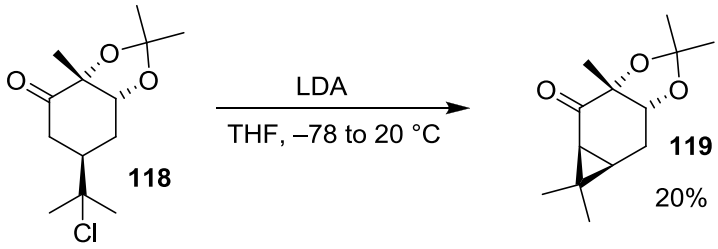
Scheme 41:



2.3.7 Intramolecular reactions

As an alternative to reagent based approaches, there are a number of intramolecular substitution reactions reported, such as the carvone-derived cyclopropane **119** reported by Selezneva and coworkers (Scheme 42).

Scheme 42:



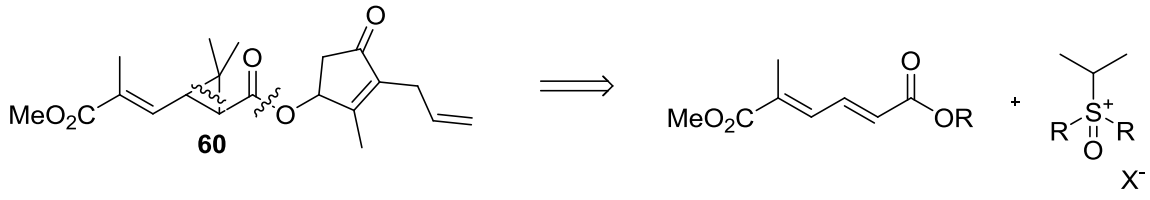
2.4 Ideas for a new reagent

Our search for a new *gem*-dimethyl cyclopropanation reagent was necessitated from our approaches towards a synthesis of allethrin II **60**, a potent synthetic insecticide. Our initial approach had produced the methylene cyclopropane analogue, making use of Tandem oxidation process / cyclopropanation (TOP-cyclopropanation) methodology (Scheme 43).[46]

Scheme 43:

However, in order to extend the synthesis to give allethrin II **60**, we required a compatible *gem*-dimethylcyclopropanation method. The proposed method was to prepare an *iso*propylidene transfer sulfoxonium salt such that alkenes could be converted into *gem*-dimethyl cyclopropanes (Scheme 44).

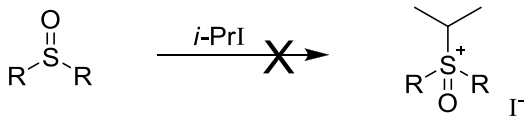
Scheme 44:



*Allethrin II **60**, and proposed disconnection.*

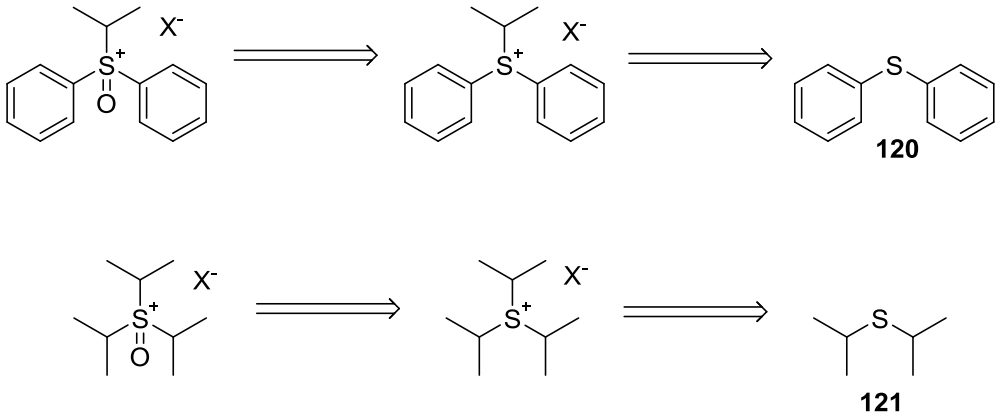
It is reported that alkylation of sulfoxides is only possible in the case of methylation,[108] which rules out preparation from diphenylsulfoxide or di-*iso*-propylsulfoxide (Scheme 45).

Scheme 45:



We envisaged a route involving the oxidation of a sulfonium salt. Two possible options were considered, diphenyl*iso*propylsulfoxonium salts or tri*iso*propylsulfoxonium salts (Scheme 46).

Scheme 46:



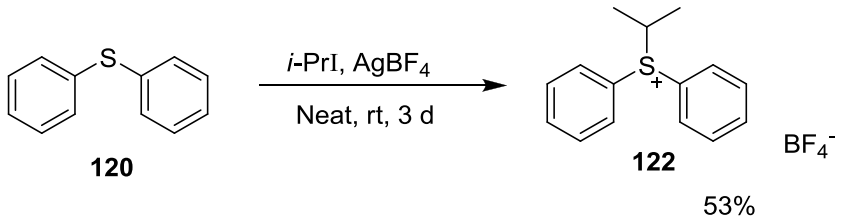
The diphenyl salts, despite having a much lower atom efficiency, offered the advantage that they would be formed from the readily available and cheap diphenyl sulfide (compared to di*iso*propyl sulfide). In addition, if a general synthesis could be found, then other sulfoxonium salts would be more easily accessible since only a small number of dialkyl sulfides are commercially available.

2.4.1 Preparation of *iso*propyl sulfonium salts

There are many methods reported in the literature for the synthesis of sulfonium salts, and indeed both of the desired sulfonium salts had been reported previously. Diphenyl*iso*propylsulfonium tetrafluoroborate had been prepared

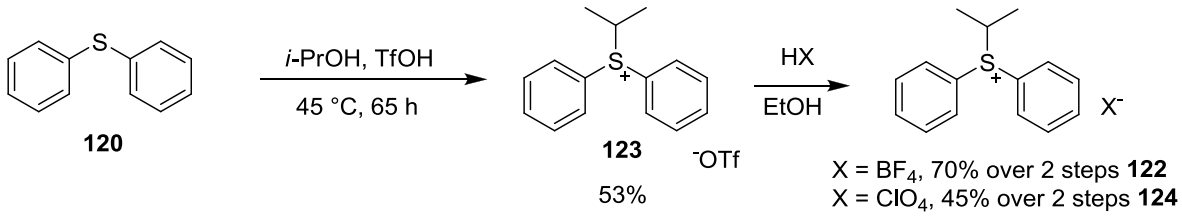
from diphenylsulfide **120** with *iso*propyl iodide and silver tetrafluoroborate (Scheme 47).[125]

Scheme 47:



Badet and Julia report a procedure using *iso*propanol and trifluoromethanesulfonic acid as a source of the *iso*propyl cation to alkylate diphenyl sulfide **120** to give the triflate salt **123** which can undergo anion exchange to give the tetrafluoroborate **122** or perchlorate **124** salts (desirable, as these are non-nucleophilic anions) (Scheme 48).[126]

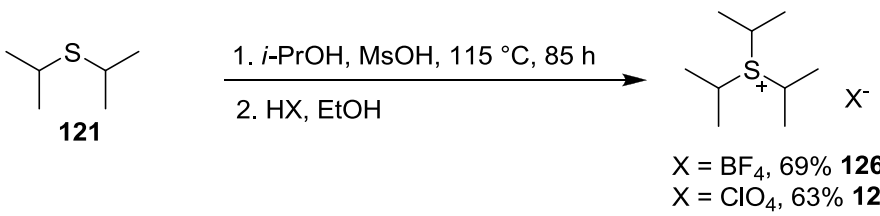
Scheme 48:



The repetition of the synthesis of sulfonium salt **122** (*via* Scheme 48) was noted to be difficult to reproduce, with only a 13% yield reported by Sen *et al*, possibly due to the lack of an experimental procedure from Badet and Julia.[127]

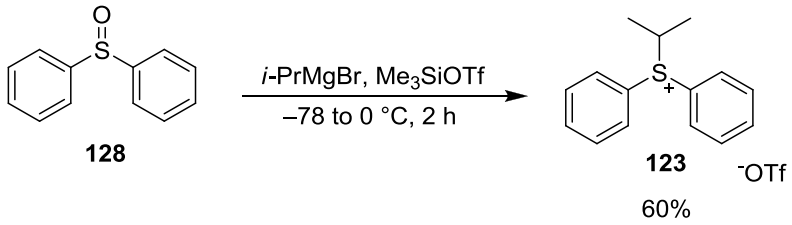
The synthesis of tri*iso*propylsulfonium salts from di*iso*propyl sulfide **121** was also disclosed in the same paper by Badet and Julia, utilising methanesulfonic acid with subsequent anion exchange (Scheme 49).

Scheme 49:



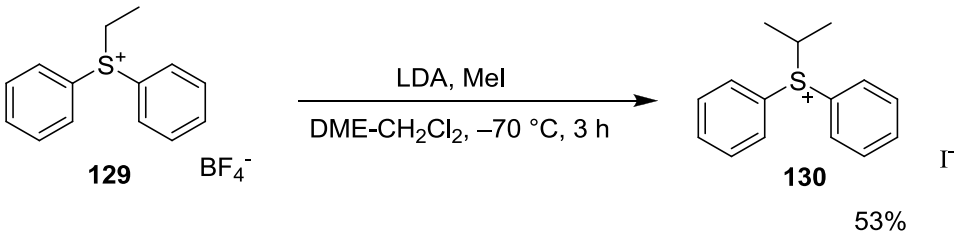
One other direct method for the synthesis of di*iso*propylsulfonium salts was reported by Miller *et al.*[128] In their synthesis, Grignard reagents were added to sulfoxides **128** using silicon reagents to give the desired triflate salt **123** in 60% yield (Scheme 50).

Scheme 50:



An indirect method for the synthesis of an *iso*propyl-containing sulfonium salt was reported by Corey and coworkers.[107] In their synthesis, ethyldiphenylsulfonium tetrafluoroborate **129** was alkylated with methyl iodide in the presence of base to give diphenyl*iso*propylsulfonium tetrafluoroborate **130** (Scheme 51).

Scheme 51:



Within the Taylor group, Paxton had successfully repeated methods for the synthesis of both the diphenyl*iso*propylsulfonium tetrafluoroborate **124** and tri*iso*propylsulfonium tetrafluoroborate **126** salts using silver tetrafluoroborate.[129]

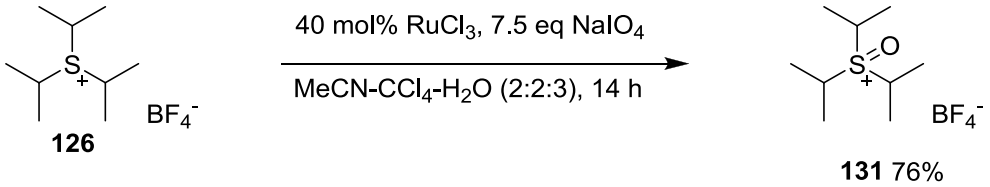
2.4.2 Oxidation of sulfonium salts.

The literature contains limited reports for the oxidation of sulfonium salts to sulfoxonium salts. The most prevalent method is through the use of aryl peracid salts, especially sodium perbenzoate and sodium *m*-chloroperbenzoate.[130-132] When these conditions were utilised by Paxton on both the diphenyl*iso*propyl

and tri*iso*propyl sulfonium salts, the results were disappointing. The use of diphenyl*iso*propylsulfonium tetrafluoroborate **124** gave no product, and the use of tri*iso*propylsulfonium tetrafluoroborate **126** gave only partial conversion.[129] After 5 iterations of exposing sulfonium salt **126** to *m*-CPBA/Na_2CO_3 around 80% conversion could be achieved, though with no means to separate the unreacted starting material.

Catalytic ruthenium dioxide with either bleach or sodium periodate has also been utilised in sulfonium salt oxidation, for the preparation of trimethylsulfoxonium salts.[133, 134] When Paxton applied this to diphenyl*iso*propyl sulfonium tetrafluoroborate **124**,[129] only decomposition was observed due to competing oxidation of the phenyl rings.[135, 136] More success was had when this was applied to the tri*iso*propyl salt **126**. Paxton managed to achieve complete oxidation using ruthenium dioxide in a process where the salt was exposed three times to the oxidation conditions.[129] Edwards later optimised the process, switching to the more readily soluble ruthenium trichloride and identifying the loadings required for full conversion (Scheme 52).[137]

Scheme 52:

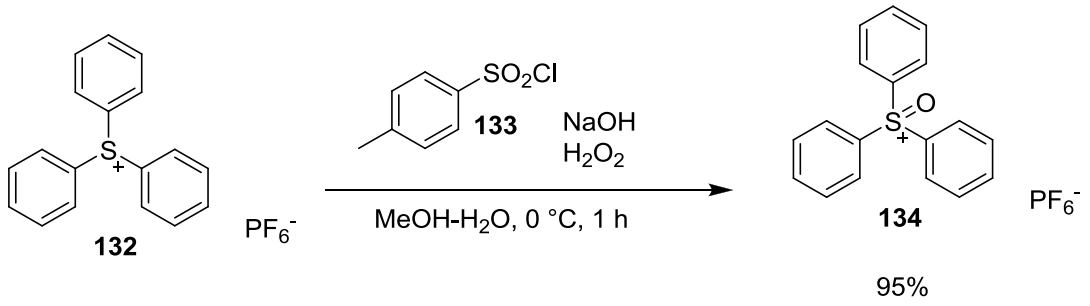


Whilst this is now a reliable route to tri*iso*propylsulfoxonium tetrafluoroborate **131**, the route is not ideal, using high loadings of ruthenium in order to push the oxidation to completion, resulting in a very high cost for the synthesis. At this point the priority was to examine the synthetic scope of the reagent, and further possible methods for oxidation were not explored.

Other methods for the oxidation of sulfonium salts reported in the literature include a patent from Ciba-Geigy which revealed several methods for the oxidation of triaryl sulfonium salts using peracids, and through the use of sulfonoperoxoic acids formed *in situ*.[138] Methods for the formation of sulfonoperoxoic acids involve the use of either *p*-toluenesulfonyl chloride **133**,

benzenesulfonyl chloride or *o*-nitrobenzenesulfonyl chloride with potassium superoxide or hydrogen peroxide in the presence of a base (Scheme 53).

Scheme 53:

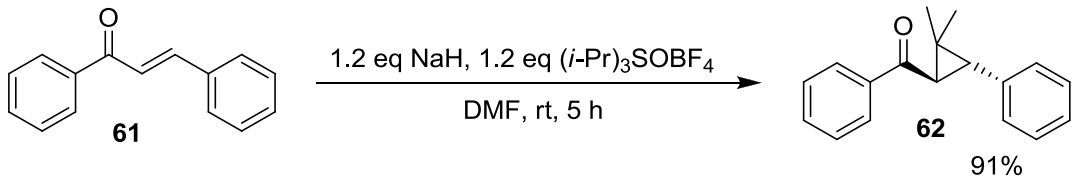


The numerous methods within this patent left scope for finding an alternative route for the synthesis of our desired sulfoxonium salt **126**.

2.4.3 Cyclopropanation of chalcone 61

The test substrate for cyclopropanation used by Paxton and Edwards was (*E*)-chalcone **61**, and optimisation of base and solvent by Edwards identified sodium hydride and DMF to be the favoured conditions, giving cyclopropane **62** in 91% yield (Scheme 54).[137]

Scheme 54:



A small range of other substrates had also been successfully cyclopropanated by Paxton prior to the optimisation of the cyclopropanation conditions.

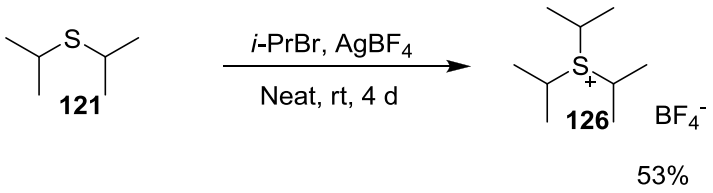
2.5 Cyclopropanation with tri*iso*propylsulfoxonium tetrafluoroborate 131

2.5.1 Initial synthesis of tri*iso*propylsulfoxonium tetrafluoroborate 131

On joining the project, the initial priorities were to repeat the synthesis of the sulfoxonium salt **126** and utilise the salt to demonstrate cyclopropanation with a range of substrates. Synthesis of tri*iso*propylsulfonium tetrafluoroborate **126**

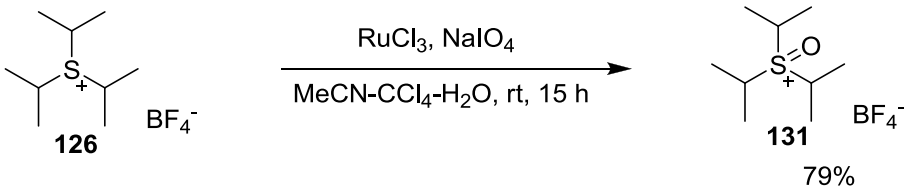
from di*iso*propyl sulfide **121** and 2-bromopropane (Scheme 55) was successful, giving sulfonium salt **126** in 53% yield.

Scheme 55:



Repeating, and scaling up Edwards' oxidation procedure gave access to the desired sulfoxonium salt **131** in 79% yield on a 25 mmol scale (Scheme 56).

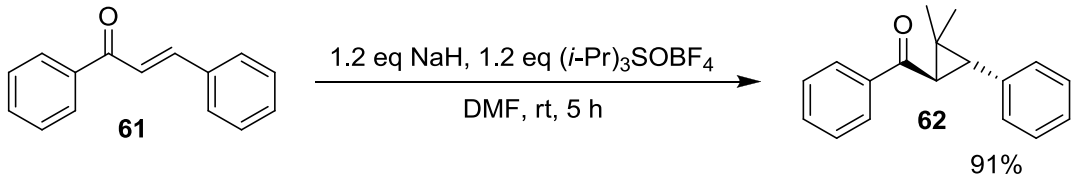
Scheme 56:



2.5.2 Reaction with chalcone

With multi-gram quantities of sulfoxonium salt **131** in hand, the cyclopropanation of chalcone **61** was repeated. Taking sodium hydride in DMF, followed by addition of (*E*)-chalcone **61** gave cyclopropane **62** in 91% after 2 hours (Scheme 57).

Scheme 57:

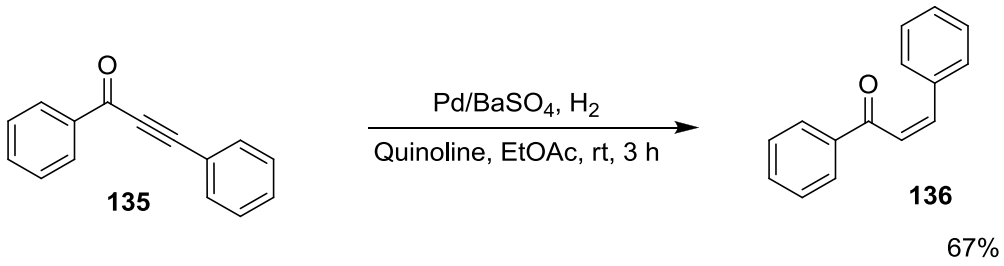


The cyclopropanation of (*E*)-chalcone **61** leads exclusively to the racemic *trans*-cyclopropane **62**. This is determined from proton NMR spectroscopy, with the cyclopropyl protons having a coupling constant of 6 Hz, which is consistent for a

trans-cyclopropane (the corresponding *cis*-cyclopropane would be expected to have a coupling constant in the range 7-13 Hz).[139]

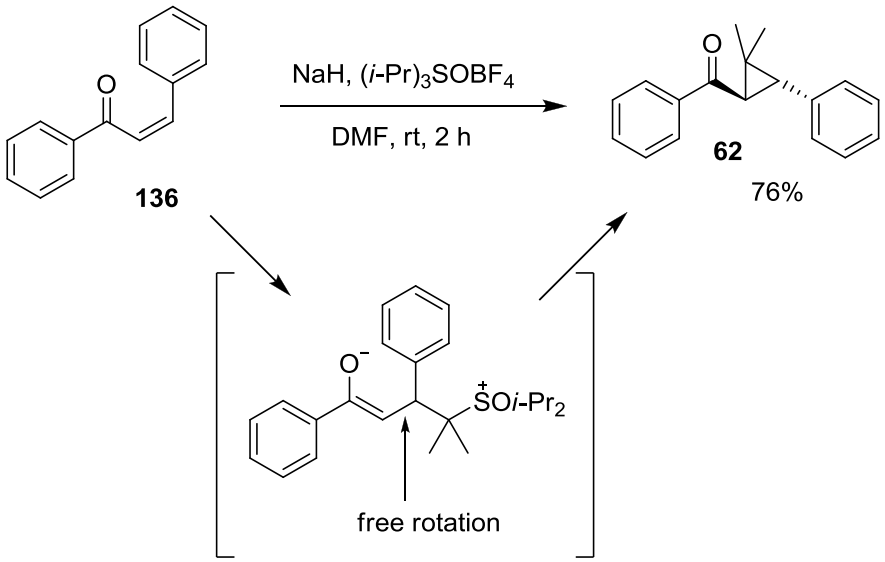
The outcome of this reaction using a (*Z*)-alkene was considered. (*Z*)-Chalcone **136** was eventually prepared from partial hydrogenation of diphenylpropynone **135**, using palladium on barium sulfate (Scheme 58; note, the use of Lindlar's catalyst led exclusively to the corresponding alkane). The structure was confirmed from a coupling constant indicative of a *cis*-alkene geometry (J = 13 Hz).

Scheme 58:



When (*Z*)-chalcone **136** was exposed to the cyclopropanation conditions, the same, exclusively *trans*-cyclopropane **62** was formed (indicated from a 6 Hz coupling constant) (Scheme 59). This implies that there is sufficient time for free rotation about the C-C single bond formed, before elimination of *iso*-propylsulfoxide, which results in the formation of the thermodynamically favoured *trans*-cyclopropane **62**.

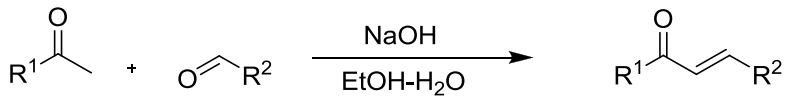
Scheme 59:

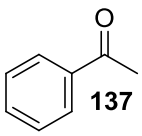
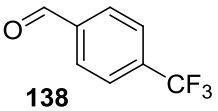
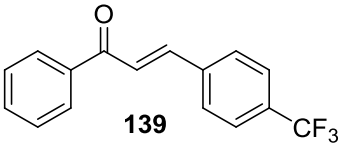
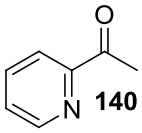
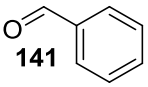
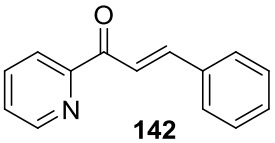
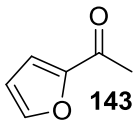
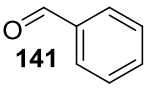
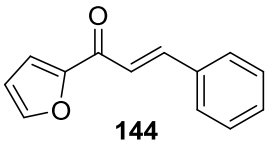


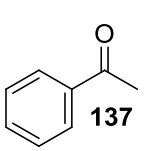
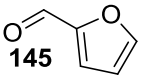
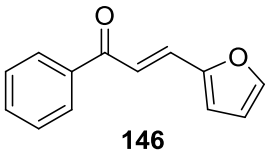
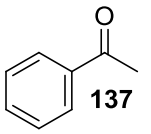
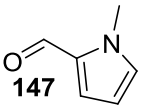
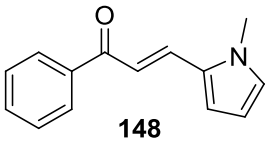
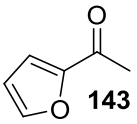
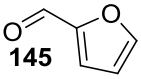
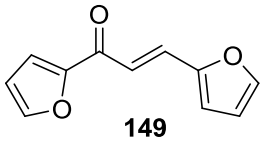
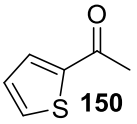
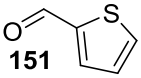
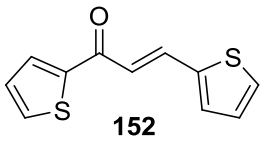
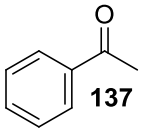
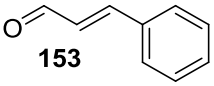
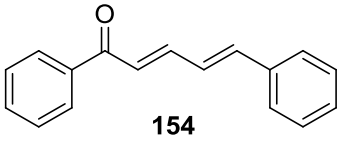
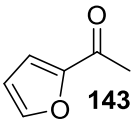
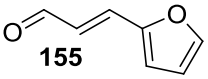
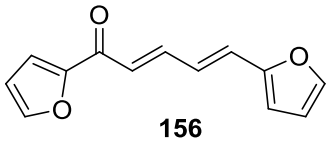
2.5.3 Preparation of chalcone analogues

A range of chalcone analogues were next prepared from aryl methyl ketones and aryl aldehydes *via* an aldol condensation, based on a procedure reported by Silva and co-workers[140] (Table 1).

Table 1: Preparation of chalcones

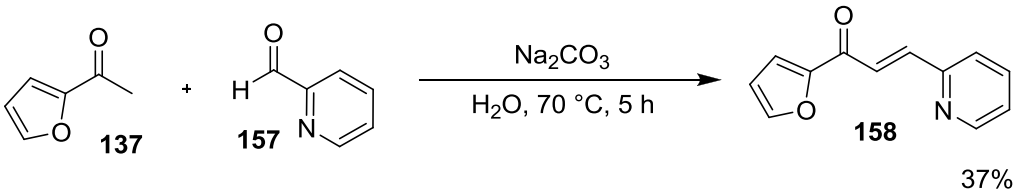


Entry	Ketone	Aldehyde	Product	Yield (%)
i				69
ii				20
iii				38

iv				99
v				64
vi				81
vii				83
viii				66
ix				79

A further chalcone, 1,4-diphenylbut-2-ene-1,4-dione **158**, was also prepared using conditions reported by Paxton[129] (Scheme 60).

Scheme 60:

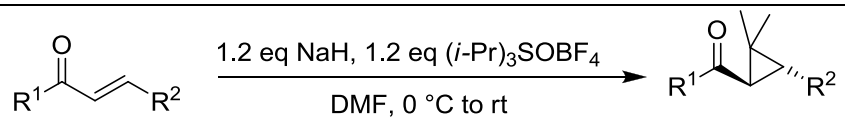


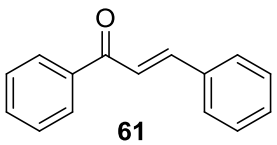
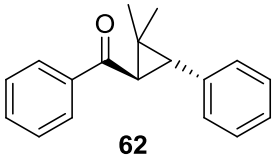
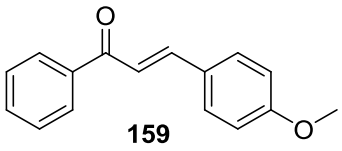
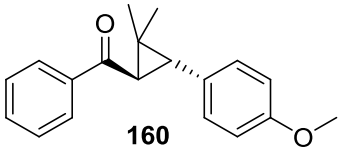
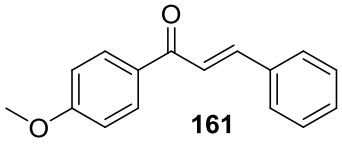
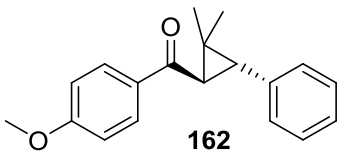
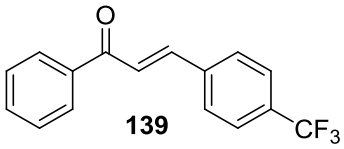
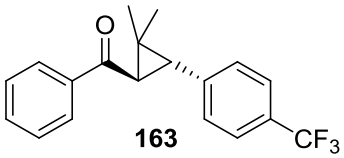
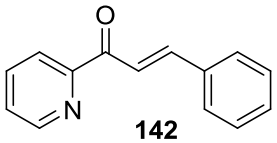
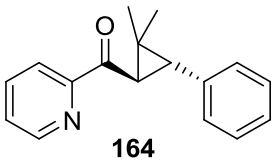
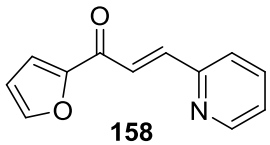
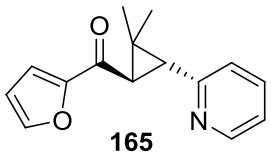
2.5.4 Cyclopropanation of chalcone analogues

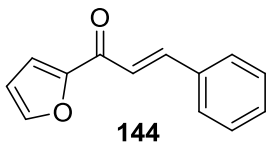
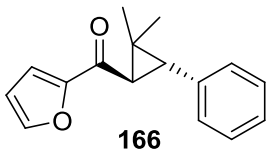
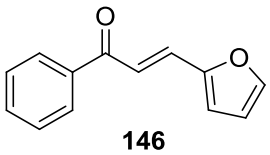
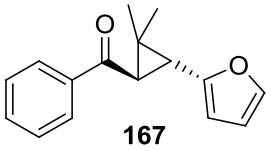
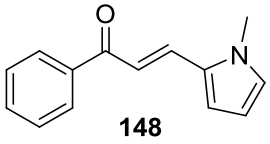
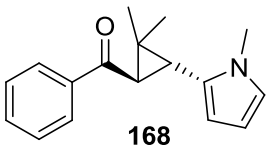
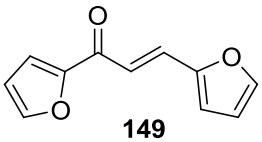
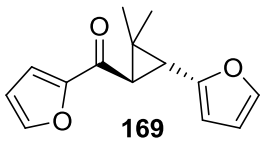
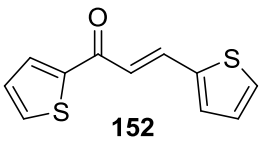
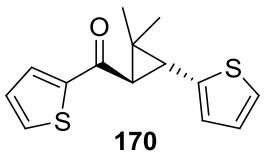
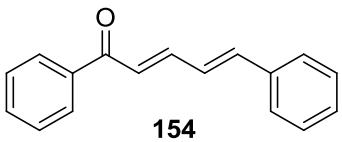
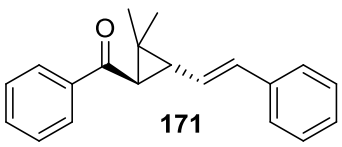
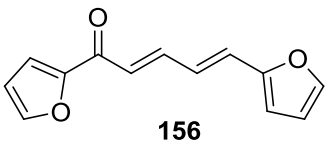
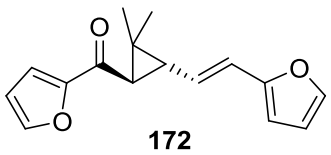
With the substrates prepared in Table 2, along with several commercially available chalcones, a selection of electron-rich, electron-deficient and various

heteroaromatic chalcones were selected in order to examine the scope of cyclopropanation of chalcones. Two dieneone examples were also utilised in order to examine the regioselectivity of the cyclopropanation. Under the original conditions, cyclopropanation was successful in all cases, generally in good yield.

Table 2: Cyclopropanation of chalcones



Entry	Chalcone	Product	Time (h)	Yield (%)
i	 **61**	 **62**	2	91
ii	 **159**	 **160**	3	94
iii	 **161**	 **162**	3	95
iv	 **139**	 **163**	0.5	93
v	 **142**	 **164**	1	89
vi	 **158**	 **165**	1	71

vii	 **144**	 **166**	1	67
viii	 **146**	 **167**	1	91
ix	 **148**	 **168**	1	85
x	 **149**	 **169**	1	82
xi	 **152**	 **170**	1	95
xii	 **154**	 **171**	1	88
xiii	 **156**	 **172**	1	60

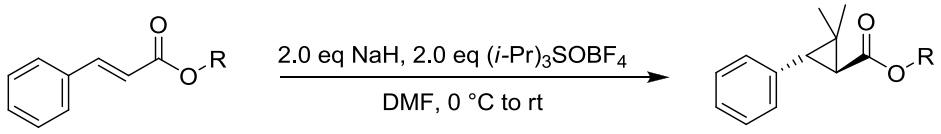
In all cases, as with chalcone itself, only *trans*-cyclopropanes were observed. The electronics of the alkene affect the time of the reactions. Where electron-donating groups were present on the aromatic rings (*p*-methoxy, Entries ii and iii), the reaction took longer to reach completion. Where an electron-withdrawing group was present (*p*-trifluoromethyl, Entry iv), the reaction proceeded much quicker. The reaction tolerated a range of heteroaromatic functionalities, including furans (Entries vi, vii, viii and x), pyridines (Entries v and vi) and thiophenes (Entry xi), all progressing to completion within an hour. Two dieneones (Entries xii and xiii) were examined, in order to explore the regiochemistry of the reaction, and in

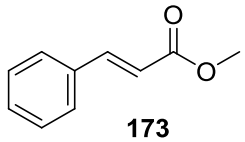
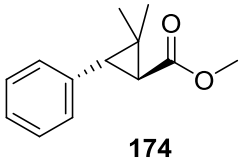
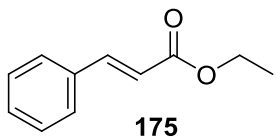
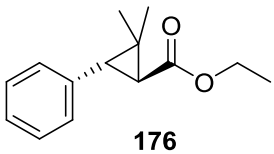
both cases only 1,4- rather than 1,6-addition was observed (with no trace of 1,6-addition found). This differs to the use of dimethylsulfonium methylide in which 1,6-addition is favoured.[141, 142]

2.5.5 Cyclopropanation of esters and amides

With the success of chalcones, we moved on to ester substrates, aware that these were likely to be more challenging, due to the more electron-rich nature of the alkene. The initial substrate selected was (*E*)-methyl cinnamate **173**, which offered disappointingly low yields, despite allowing long reaction times. Increasing the reaction temperature offered little improvement, but a marginal yield increase could be achieved through increasing the equivalents of sulfoxonium salt **131** and sodium hydride. The use of (*E*)-ethyl cinnamate **175** gave similar results (Table 3).

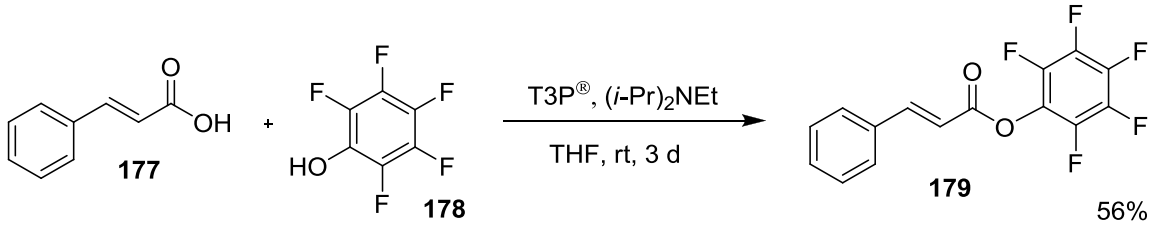
Table 3: Cyclopropanation of esters



Entry	Ester	Product	Time (h)	Yield (%)
i	 **173**	 **174**	40	25
ii	 **175**	 **176**	72	27

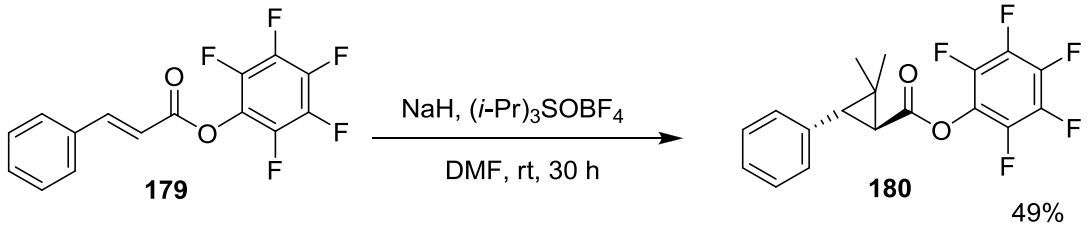
In order to enhance the electrophilicity of the double bond, the use of a more electron-poor ester was considered. A perfluorophenyl cinnamate ester **179** was formed from a T3P® coupling of cinnamic acid **177** and perfluorophenol **178** (Scheme 61).

Scheme 61:



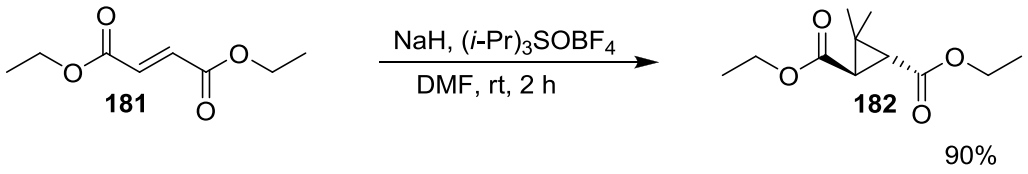
Use of this ester **179**, under the same conditions as for methyl cinnamate **173**, resulted in only a modest yield (potentially due to hydrolysis of the ester during work-up), but a significant improvement over the other esters (Scheme 62).

Scheme 62:



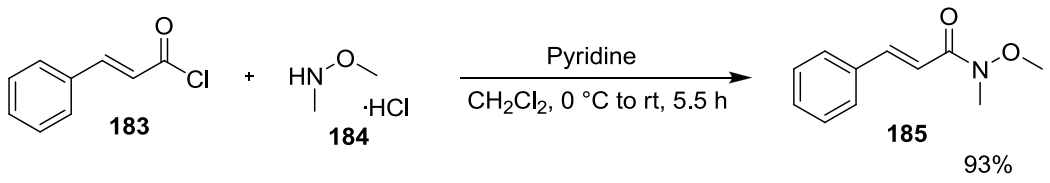
Use of a diester was also explored. Diethyl fumarate **181** was efficiently cyclopropanated under the ester conditions. With the ease of reaction with this substrate, the equivalents of reagents were lowered to those used for the chalcones, and cyclopropanation was equally successful (Scheme 63).

Scheme 63:



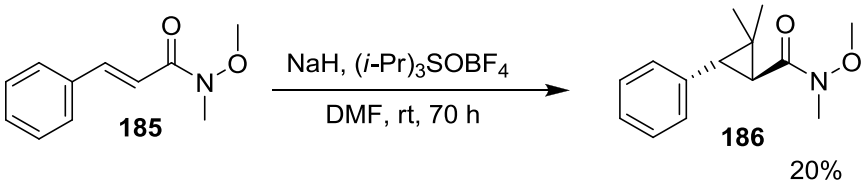
Despite the disappointing yields obtained for the esters, we were interested in the possibility of cyclopropanating a Weinreb amide, given the synthetic versatility of this functional group.[143] A suitable substrate **185** was prepared, based on the method reported by Nahm and Weinreb (Scheme 64).[143]

Scheme 64:



When this substrate was cyclopropanated using 2.0 equivalents of base and salt, the desired product **186** was obtained, albeit in low yield (Scheme 65).

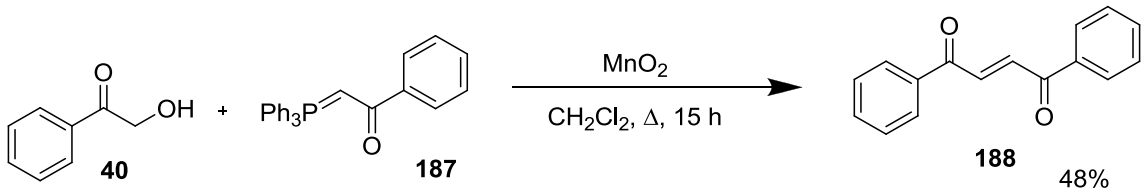
Scheme 65:



2.5.6 Cyclopropanation of other substrates

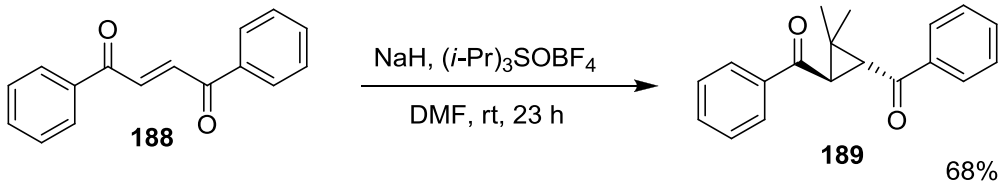
A range of other substrates were examined to further investigate the reaction scope. Predominantly, these are substrates Paxton had previously prepared and tested prior to isolation of pure sulfoxonium salt **131**. An enedione **188** was prepared using a tandem oxidation-Wittig reaction, following a procedure from Paxton (Scheme 66).[129]

Scheme 66:



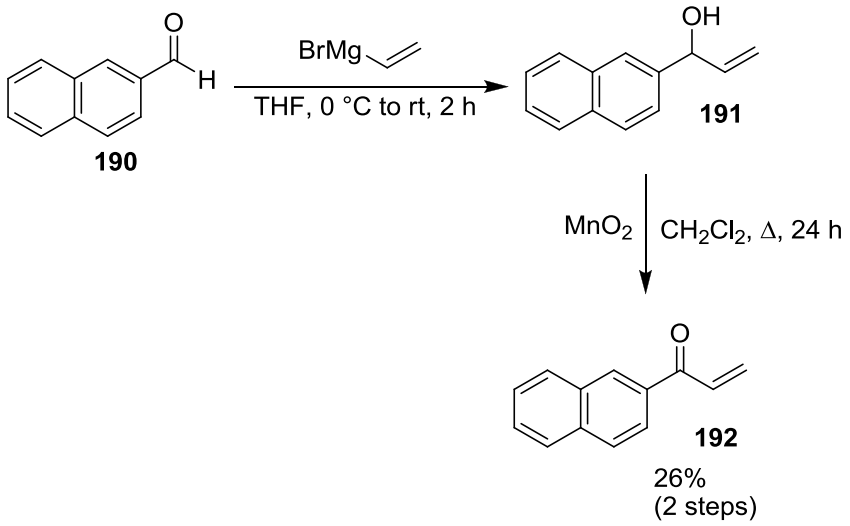
Enedione **188** was cyclopropanated in a modest 68% yield (Scheme 67), a similar finding to Paxton's reported 56% yield,[129] and a similar reduction in yield (compared to chalcone **61**) was observed by Johnson when preparing the analogous methylene cyclopropane.[144]

Scheme 67:



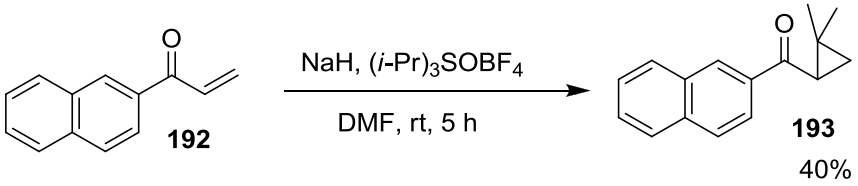
Again repeating a substrate from Paxton,[129] a terminal alkene was prepared by the addition of vinylmagnesium bromide to 2-naphthaldehyde **190** and subsequent oxidation (Scheme 68).

Scheme 68:



Subsequent cyclopropanation yielded the desired product **193** successfully, if in modest yield (Scheme 69), although Paxton reported a higher yield when the reaction was left for longer periods.[129]

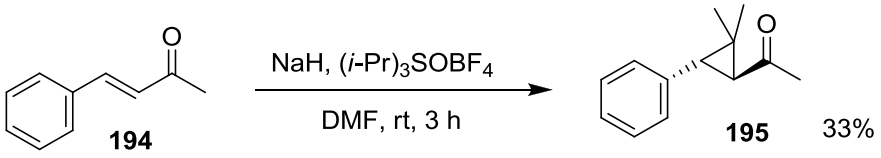
Scheme 69:



Paxton and Edwards had attempted to cyclopropanate several enolisable substrates with limited success. For example, Edwards obtained only 4% of the cyclopropane adduct of cyclohexenone, along with polymeric material, and Paxton had obtained 29% from the cyclopropanation of (*E*)-4-phenylbut-3-en-2-

one **194**. Repeating this cyclopropanation a similarly low yield of the desired cyclopropane **195** was obtained (Scheme 70).

Scheme 70:

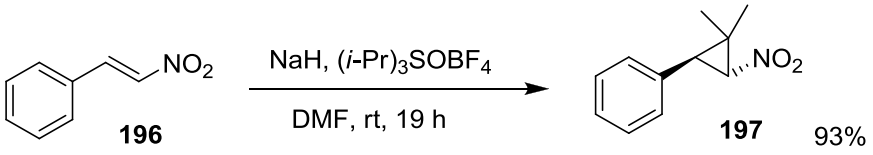


The enolisable nature of these substrates and the reaction conditions using sodium hydride as base are a possible cause for the disappointing yields. This differs somewhat to the Corey-Chaykovsky reaction, where for example, the cyclopropanation of cyclohexenone gives an 80% yield,[145] or (*E*)-4-phenylbut-3-en-2-one **194** gives a 61% yield.[146]

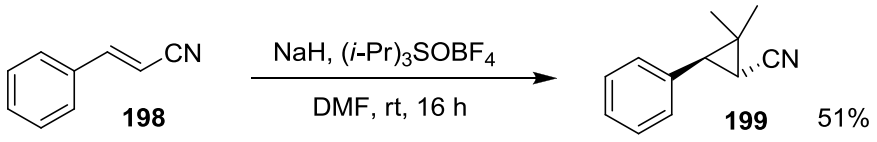
2.5.7 Cyclopropanation of non-carbonyl Michael acceptors

So far, all of the substrates examined had utilised a carbonyl group as the Michael acceptor, and so other electronically-activating groups were explored. (*E*)-Nitrostyrene **196** was cyclopropanated in good yield (Scheme 71) and this compares favourably to the Corey-Chaykovsky reaction of the methylene analogue where only a 57% yield is reported.[146] (*E*)-Cinnamonitrile **198** was also successful, if in more modest yield (Scheme 72), and interestingly here only the *trans*-cyclopropane **199** was observed, contrasting with the Corey-Chaykovsky cyclopropanation in which a 78:22 *cis:trans* ratio of the corresponding methylene compound was observed.[147, 148]

Scheme 71:



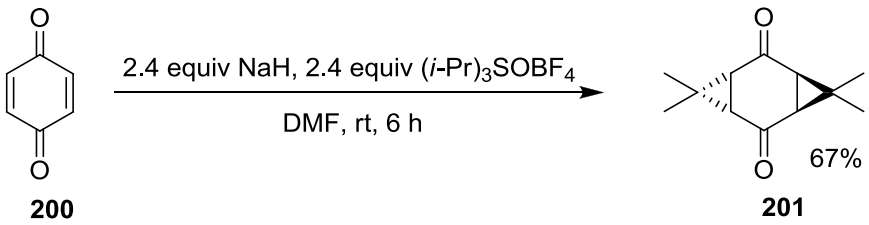
Scheme 72:



2.5.8 Double cyclopropanation

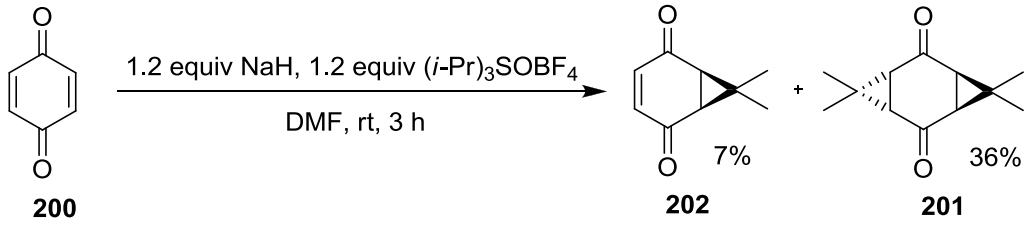
Edwards demonstrated a double cyclopropanation reaction on benzoquinone **200** using 2.4 equivalents of sulfoxonium salt **131** to give exclusively *bis*-cyclopropane **201** in good yield (Scheme 73; the stereochemistry was identified through X-ray crystal analysis).[137]

Scheme 73:



Repeating this cyclopropanation, but utilising only 1.2 equivalents of salt **131** (Scheme 74), still predominantly gave *bis*-cyclopropane **201**, with only a small quantity of the *mono*-cyclopropane **202**, along with unreacted starting material. This shows, as would be predicted, that the second cyclopropanation is more favourable than the initial cyclopropanation.

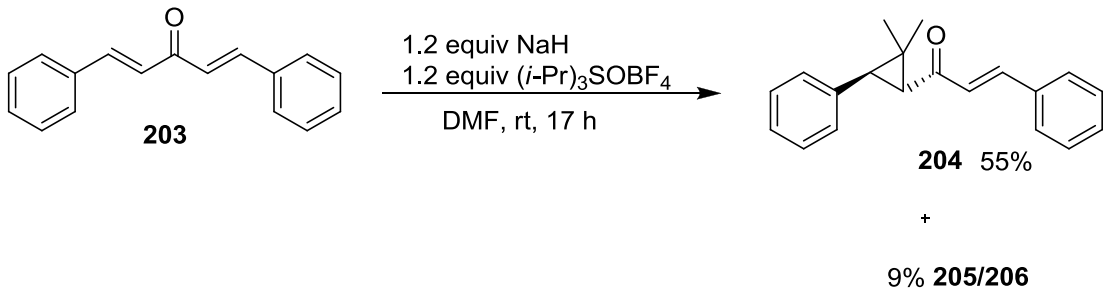
Scheme 74:



Taking a further substrate capable of undergoing double cyclopropanation, dibenzylidene acetone and exposing to a stoichiometric quantity of reagents (1.2

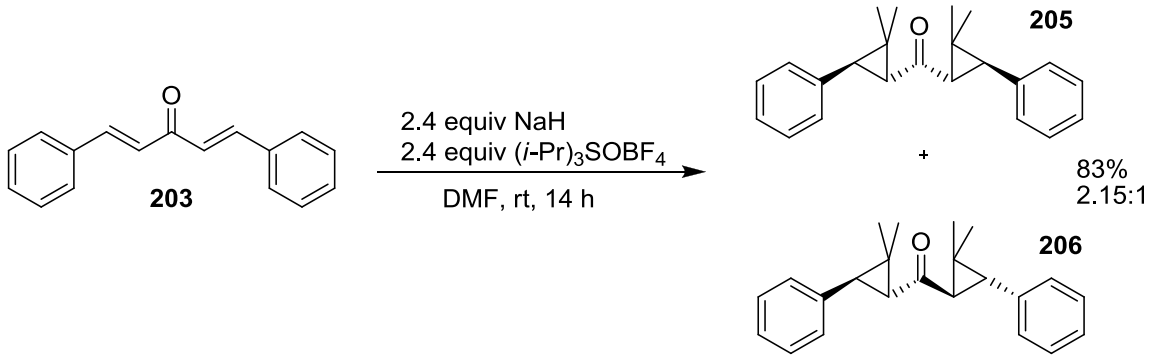
equivalents), gave predominantly the *mono*-cyclopropane **204** in 55% yield, along with 9% of the *bis*-cyclopropanes **205** and **206** as a mixture of diastereoisomers (2.15:1) (Scheme 75).

Scheme 75:



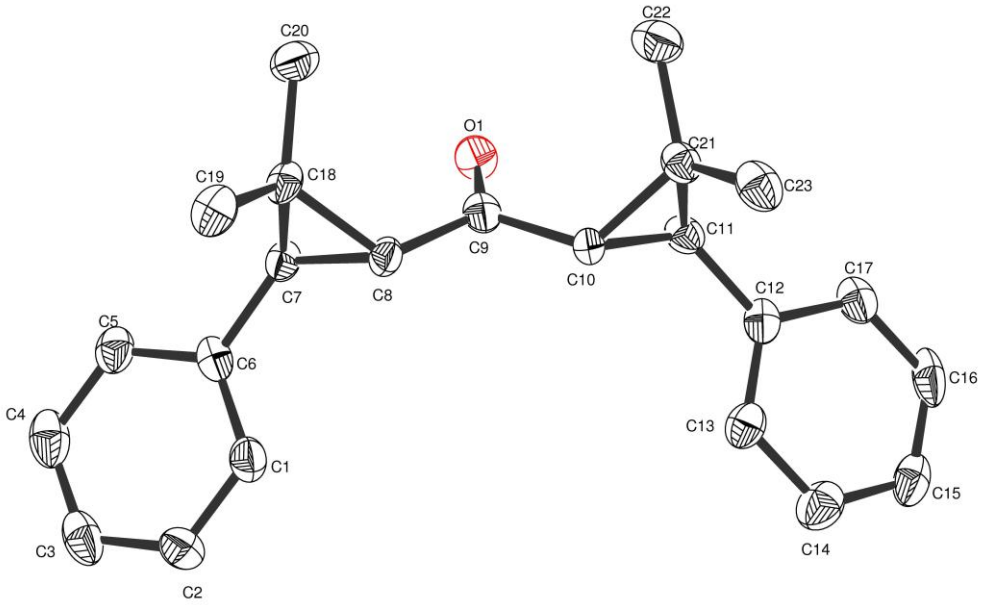
Increasing the reagent loadings to 2.4 equivalents resulted in exclusively the *bis*-cyclopropanes **205** and **206** as an inseparable 2.15:1 mixture of diastereoisomers (Scheme 76).

Scheme 76:



In order to determine the stereochemistry of the major isomer, the mixture of diastereoisomers was repeatedly recrystallised from EtOH-H_2O (× 10), until only the major isomer remained. A crystal suitable for X-ray diffraction was then grown by slow evaporation from methanol, and X-ray analysis showed the major isomer has *meso* structure **205** (Figure 2).

Figure 2:



*X-ray structure of **205** depicted in ORTEP-3 for windows. Displacement ellipsoids are shown at 50% probability. Hydrogen atoms omitted for clarity. CCDC number 698581.*

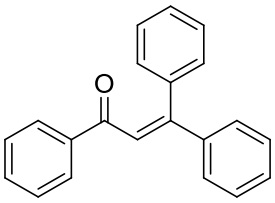
Further discussion on the crystallography for this structure can be found in Acta Crystallographica C.[149]

2.5.9 Unsuccessful substrates

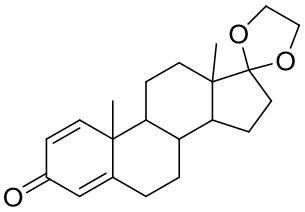
A small number of substrates failed to cyclopropanate to any extent, even under more forcing conditions (prolonged time, increased temperature). 1,3,3-Triphenylprop-2-en-1-one **207** (Figure 3) was prepared using a procedure from Dudley and co-workers,[150] and attempts to cyclopropanate gave no trace of product, with only starting material being recovered. Here, the conjugation between the aromatic rings, and the steric bulk around the alkene could be the cause of the unreactive nature.

Attempts to cyclopropanate a steroid substrate were similarly unsuccessful. 1,4-Androstadiene-3,17-dione **394** (see page 148) was taken and the cyclopentanone ketone protected as an acetyl using a procedure reported by Gentles and coworkers (Figure 3).[151] Even with prolonged heating no trace of cyclopropane could be found, and only slow decomposition was observed, possibly through similar polymerisation as had been seen with cyclohexenone.

Figure 3:



207



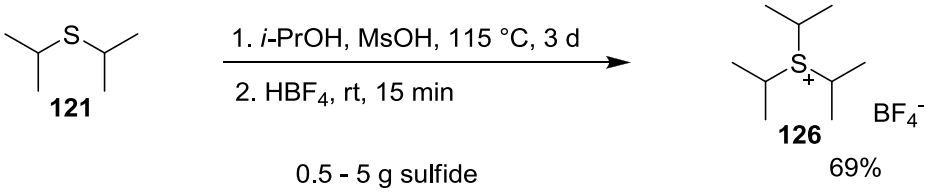
208

Unsuccessful cyclopropanation substrates.

2.5.10 Development of the sulfoxonium salt synthesis

Development of an improved synthesis for the sulfonium and sulfoxonium salts was desirable, particularly due to the high cost involved in the synthesis, and the large metal-waste stream. The sulfonium salt synthesis utilises stoichiometric silver tetrafluoroborate, with the silver serving to remove the bromide in the reaction, precipitating an equivalent of silver bromide waste for each equivalent of sulfonium salt. Badet and Julia[126] reported their acid-catalysed preparation of sulfonium salts (Scheme 50), but in our group isolation had proved problematic.[152] The problems stemmed from the isolation of the mesylate salt from the residual methanesulfonic acid in the reaction, with attempts having been made to distill off mesic acid (resulting in decomposition of the desired salt) and to extract the salt into dichloromethane from a diluted aqueous phase using batchwise and continuous extraction (yielding only trace amounts of sulfonium salt). Revisiting the synthesis, it was quickly identified that counter-ion exchange (with fluoroboric acid), prior to work-up, resulted in an organic-soluble salt **126** which was easily extracted into dichloromethane. This synthesis has now been shown to work reliably on a 5-50 mmol scale (Scheme 77).

Scheme 77:



With an improved and reliable sulfonium salt synthesis in hand, the oxidation step was revisited. The initial synthesis, using ruthenium trichloride as the oxidant, was shown to require 40 mol% ruthenium in order to push the reaction to completion.[137] At lower catalyst loadings, incomplete conversion occurred, resulting in a mixture of salts which were difficult to isolate.

Returning to the literature, alternative methods for the oxidation of sulfonium salts were sought, and several of these methods were screened on tri*iso*propylsulfonium tetrafluoroborate **126** (Table 4).

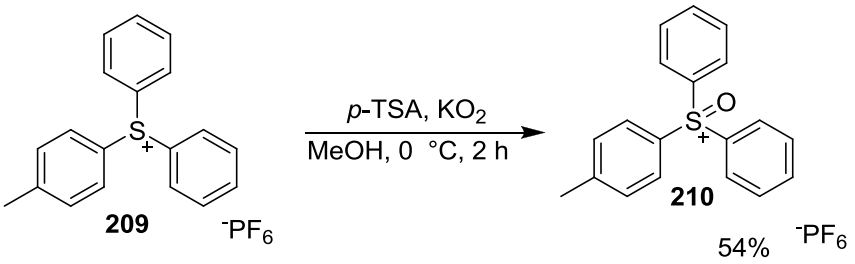
Table 4: Screening of oxidation conditions to give sulfoxonium salt **131**

Entry	Conditions	Solvent	Time	Conversion[a]
1	*m*-CPBA, Na_2CO_3	H_2O	64 h	21%
2	Trifluoroperacetic acid (TFPAA)	CH_2Cl_2	16 h	0%
3	H_2O_2	H_2O	16 h	0%
4	Oxone	H_2O	16 h	0%
5	Oxone	Acetone	16 h	0%
6	$WO_3 \cdot H_2O$, H_2O_2	H_2O	16 h	0%
7	$KMnO_4$	H_2O	15 h	0%
8	$KMnO_4$	Acetone	15 h	0%
9	KO_2	MeOH	16 h	0%
10	KO_2, 2-nitrobenzenesulfonyl chloride	MeOH	1 h	100%
11	Oxone, 2-nitrobenzenesulfonyl chloride	MeOH	1 h	0%
12	KO_2, *p*-TSA	MeOH	2 h	0%
13	H_2O_2, 2-nitrobenzenesulfonyl chloride	MeOH-H_2O	16 h	100%

[a] Determined using ^{1}H NMR spectroscopy.

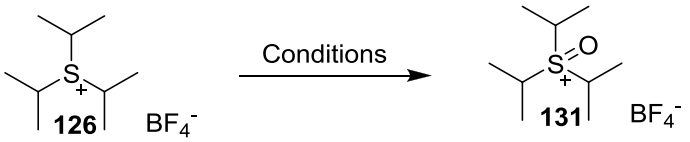
Sodium perbenzoate and *m*-CPBA/Na_2CO_3 have been shown[130] to oxidise a range of sulfonium salts, and this was the initial approach used by Paxton for the oxidation of tri*iso*propylsulfonium tetrafluoroborate **126**.[129] Paxton showed around 80% conversion could be achieved using 5-6 iterations of the reaction conditions, although with no means of cleanly isolating the desired product from the starting sulfonium salt **126**. Screening a range of oxidants known to oxidise sulfur compounds, no success was found (Table 4, Entries 1-9), until repeating methods patented by Ciba-Geigy.[138] This patent details the preparation of a variety of triarylsulfoxonium salts, primarily for use as photoinitiators, using peracids formed *in situ* (Scheme 78).

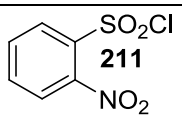
Scheme 78:



Utilising 2-nitrobenzenesulfonyl chloride **211**, and potassium superoxide or hydrogen peroxide with sodium hydroxide, complete conversion to the desired sulfoxonium salt **131** could be achieved (Table 5). However, isolation proved more problematic.

Table 5: Initial oxidation conditions



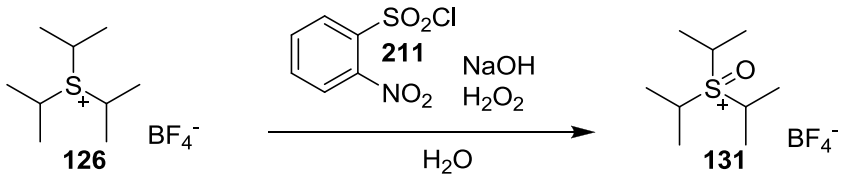
Entry	 211	Oxidant	Base	Solvent	Conversion[a]
i	5 equiv	12 equiv KO_2	-	MeOH	100%
ii	5 equiv	12 equiv H_2O_2	12 equiv NaOH	MeOH-H_2O	100%

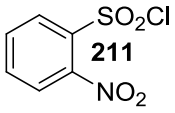
[a] Determined using ^{1}H NMR spectroscopy.

Whereas the triaryl salts had been isolated *via* filtration and washing with water, the aqueous solubility of the tri*iso*propyl salt **131** precluded this as an option. The isolation problem stems from the need to separate the product from the sulfonic acid, both compounds having similar solubilities in a range of solvents, and the large excesses of sulfonyl chloride **211** used prevented clean crystallisation of the desired product.

Consideration was given to the loadings, hoping that through reducing the loadings of the sulfonyl chloride **211**, isolation would be helped (Table 6).

Table 6: Attempts to reduce sulfonyl chloride **211** loadings



Entry		H_2O_2	NaOH	Solvent	Conversion[a]
i	5 equiv	12 equiv	12 equiv	MeOH-H_2O	100%
ii	0.5 equiv	12 equiv	12 equiv	MeOH-H_2O	67%
iii	2 equiv	12 equiv	12 equiv	MeOH-H_2O	80%

[a] Determined using ^{1}H NMR spectroscopy.

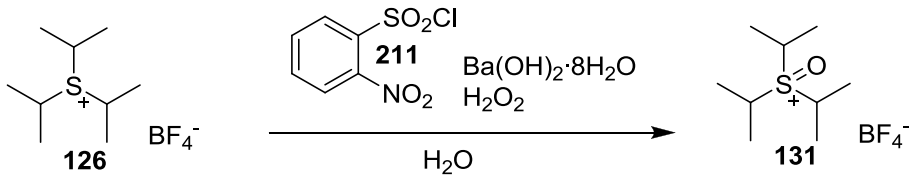
Unfortunately, it soon became apparent that high loadings of the sulfonyl chloride were necessary for the oxidation to proceed to full conversion.

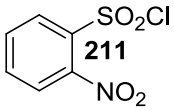
With the problems being due to the similar solubilities of the product and side-products, options were considered for reducing the solubility of the side-products. Use of barium salts was attempted to try to form an insoluble precipitate which could be removed *via* filtration. After carrying out the oxidation (as Table 6, Entry i), barium chloride was added (5 equiv), and the suspension formed was filtered, hoping to remove the side-product. This only gave partial success; the side-product was reduced, but not removed, and

recrystallisation remained unsuccessful. Repeating the process with the addition of further portions of barium chloride offered little improvement.

The next attempt was to replace the sodium hydroxide in the reaction with barium hydroxide, which enabled the separation of the desired salt from the sulfonic acid. Unfortunately, this change in base resulted in a significant drop in the conversion to a disappointing 56%. However, a breakthrough came from removing the methanol in the reaction and attempting the oxidation using only water as the solvent, possibly due to more barium hydroxide now being in solution. On a 1 mmol scale, after 1 hour, we were delighted to observe full conversion and an 83% isolated yield of **131** (Table 7, Entry i).

Table 7: Optimisation of the oxidation with barium hydroxide



Entry		H_2O_2	$Ba(OH)_2 \cdot 8H_2O$	Conversion[a]
i	5 equiv	12 equiv	12 equiv	100%
ii	2.5 equiv	6 equiv	6 equiv	100%
iii	1.5 equiv	3 equiv	5 equiv	98%
iv	2 equiv	3 equiv	6 equiv	100%

[a] Determined using ^{1}H NMR spectroscopy.

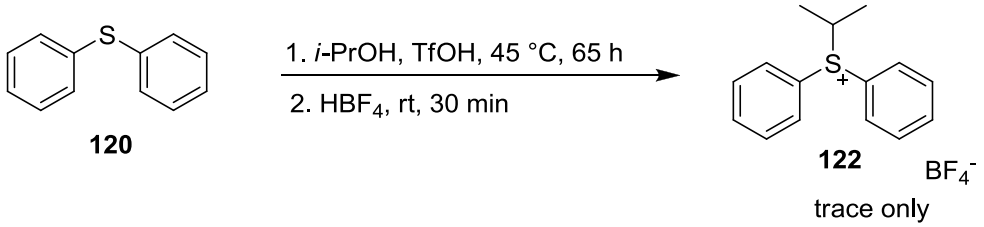
Optimisation of the loadings enabled a reduction in equivalents of reagents, and the procedure was successfully scaled up to 20 mmol, giving a 60% recrystallised yield. This offers improvement over the initial method, particularly in cost, through the elimination of high loadings of ruthenium.

2.5.11 Attempts towards *iso*propyldiphenylsulfoxonium salts

With a milder oxidation procedure now available, our initial target salt, *iso*propyldiphenyl sulfoxonium tetrafluoroborate **212** might now be feasible.

Attempting to repeat Badet and Julia's synthesis[126] (Scheme 79) of the sulfonium salt **122** proved problematic (despite applying what we had learnt from tri*iso*propyl sulfonium tetrafluoroborate **126**). Only trace amounts of the desired salt **122** could be isolated (as Sen had discovered trying to repeat the same synthesis[127]), along with significant quantities of unreacted diphenyl sulfide **120**.

Scheme 79:

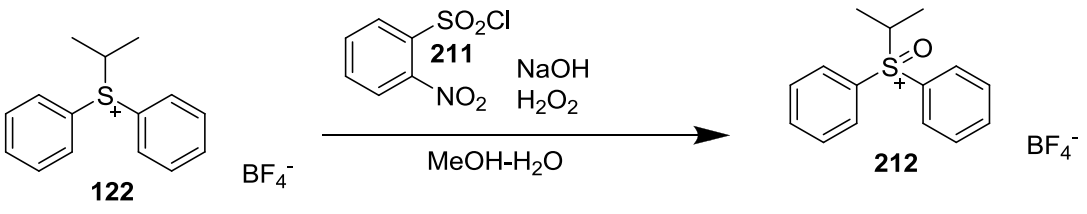


With the priority being to test the oxidation, we returned to Paxton's synthesis[129] and obtained the desired salt **122** in acceptable yield (Scheme 80).

Scheme 80:

Exposing sulfonium salt **122** to the initial oxidation conditions (sodium hydroxide rather than barium hydroxide), resulted in complete conversion into the desired sulfonium salt **212** (Scheme 81).

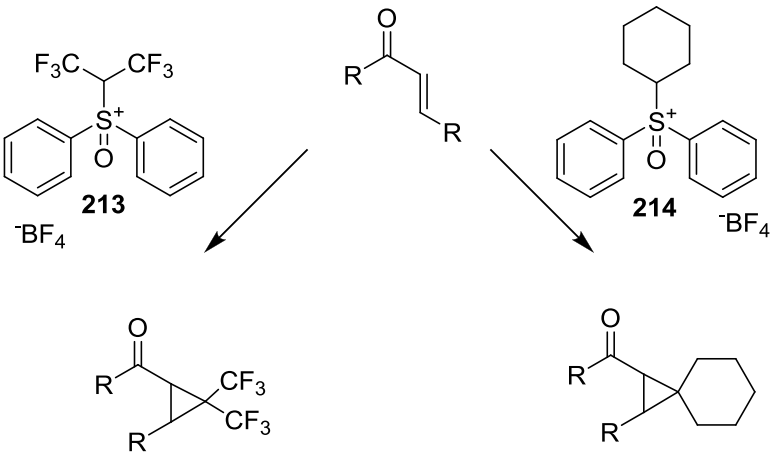
Scheme 81:



The compound could clearly be identified by proton NMR spectroscopy, but unfortunately, isolation again proved to be problematic, and to date this has not been overcome. As the sulfonium salt **212** is insoluble in water, the optimised conditions used for the tri*iso*propyl salt **131** are not able to be utilised.

If these isolation problems could be overcome, in principle a wide range of sulfoxonium salts could be developed to give a selection of cyclopropane substitutions, particularly if a general synthesis for alkyldiphenylsulfonium salts from diphenyl sulfide **120** and secondary alcohols could be found. Particular alcohols of interest could include the use of hexafluoro*iso*propanol to give *gem*-di(trifluoromethane) cyclopropanes or cyclohexanol to give spirocyclic cyclopropanes (Scheme 82).

Scheme 82:



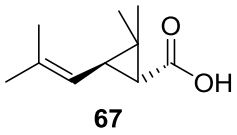
2.5.12 Studies towards chrysanthemic acid 67

With an efficient method for the preparation of *gem*-dimethylcyclopropanes, we went on to demonstrate the use of tri*iso*propylsulfoxonium tetrafluoroborate **131** as a synthetically useful reagent in target synthesis.

2.5.12.1 Chrysanthemic acid 67

Chrysanthemic acid **67** (Figure 4) is a naturally occurring terpene found in a variety of plants, and also as a substructure in a number of related natural products. Initially (+)-*trans*-chrysanthemic acid **37** was isolated from pyrethrum petals by Staudinger,[67] although subsequently all four possible stereoisomers of the cyclopropane **67** have all been isolated as natural products.[68]

Figure 4:

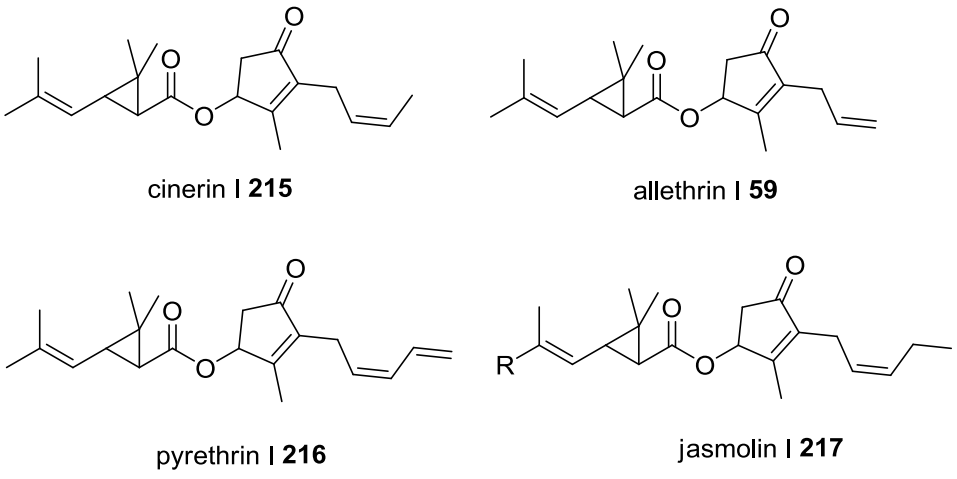


67

*Chrysanthemic acid **67** shown in the (+)-trans form.*

Chrysanthemic acid **67** is produced industrially as an intermediate in the synthesis of synthetic pyrethroids, particularly in the synthesis of allethrin I **59**. Allethrin I **59** is a synthetic analogue of cinerin I **215**, one of the active components in pyrethrum; a natural insecticide obtained from the dried flowers of pyrethrum, a member of the chrysanthemum family (Figure 5).[153]

Figure 5:



*Cinerin I **215**, allethrin I **59**, pyrethrin I **216** and jasmolin I **217**, members of the pyrethroid family.*

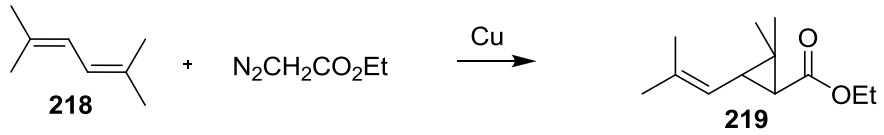
Allethrin I **59** was the first synthetic pyrethroid to be developed, cinerin I **215**, pyrethrin I **216** and jasmolin I **217** are all naturally occurring. Allethrin I **59** is

hugely successful, being much less prone to breakdown (due to their photolabile nature[154]) and being much more available than the limited supply of natural pyrethrins[153] Sales of allethrin I **59** and other synthetic pyrethrins[155] make these compounds a multi-billion dollar business.[69]

2.5.12.2 Previous syntheses of chysanthemic acid 67

There are numerous reported syntheses of chrysanthemic acid **67**, with the first being reported by Campbell and Harper in 1945 (Scheme 83) to give a mixture of all the possible isomers.[156]

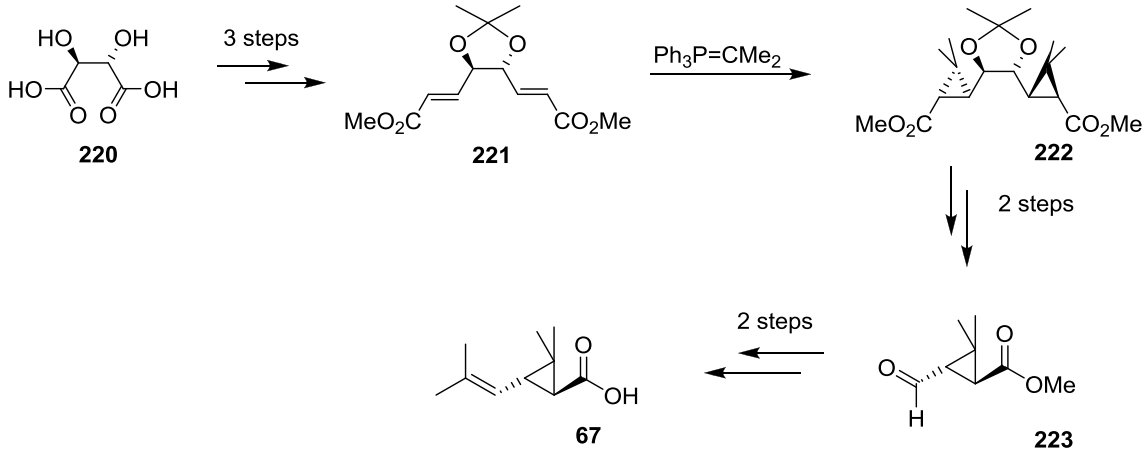
Scheme 83:



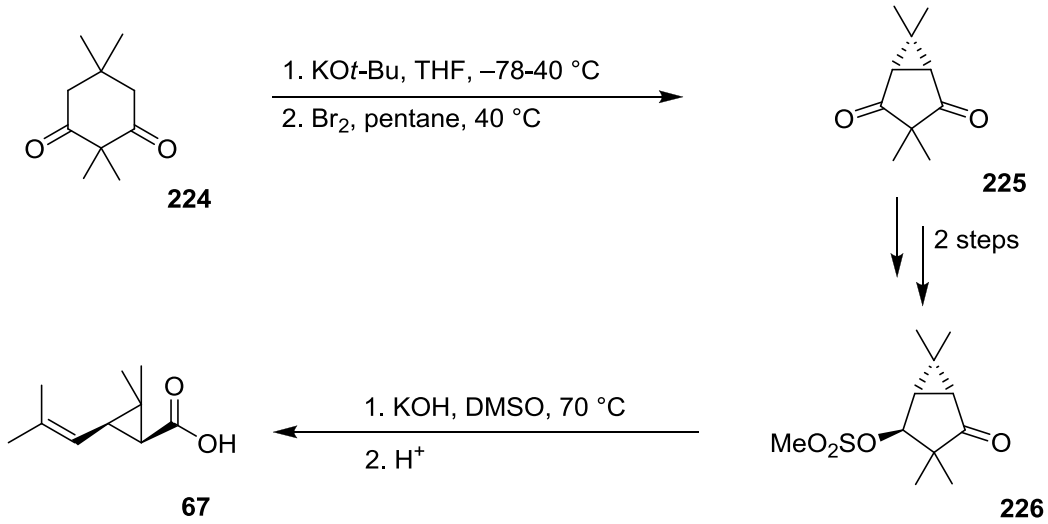
The first industrial scale syntheses made use of this same route, with the chrysanthemic acid **67** being taken forward to yield allethrin I **59**. By 1954, less than 10 years after the initial publication of the first route to chrysanthemic acid, around 1,000,000 kg of allethrin I **59** were being produced annually.[153] More recently the development of chiral ligands for the copper catalysis has led to enantiomerically pure syntheses of chrysanthemic acid, for example the use of chiral Schiff bases by Aratani.[157]

A number of syntheses have been reported making use of readily available enantiomerically pure compounds, such as Krief's approaches from tartaric acid **220** (Scheme 84)[158] or dimethyldimedone **224** (Scheme 85).[159]

Scheme 84:

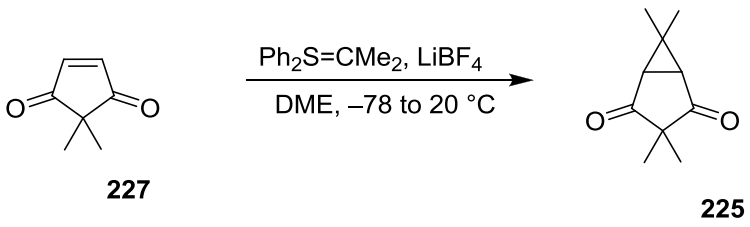


Scheme 85:



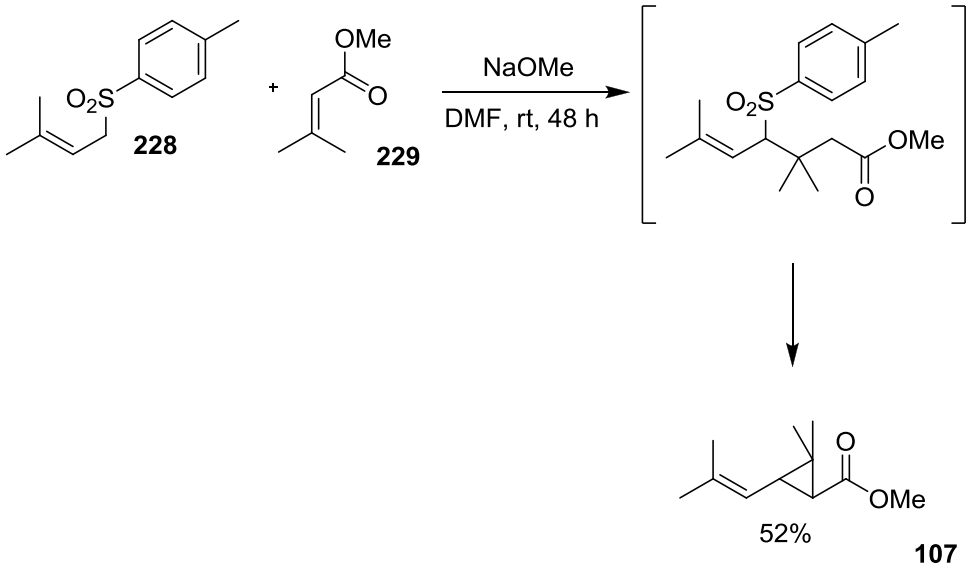
Krief published several improvements to his original synthesis,[160, 161] although one is particularly notable in which the cyclopropane ring is formed using a sulfurane acting on a cyclopentadienone ring (Scheme 86).

Scheme 86:



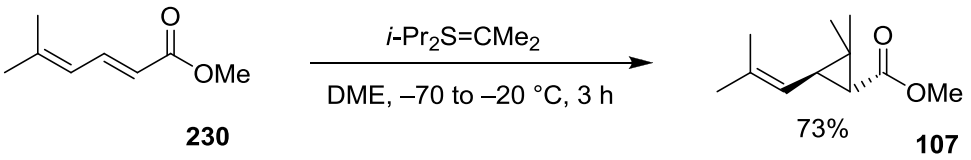
Several other sulfur chemistry approaches have also been reported, such as the synthesis reported by Martel and Huynh (Scheme 87).[162, 163]

Scheme 87:



In a closely related method to what we were hoping to achieve, Corey disclosed the use of sulfonium ylide cyclopropanation (Scheme 88).[115]

Scheme 88:



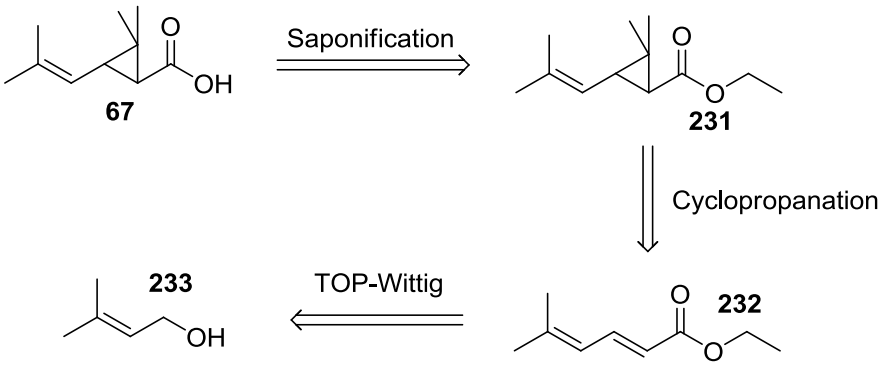
A number of chrysanthemic acid analogues have also been made, and these are well reviewed in the literature.[164]

2.5.12.3 Towards a new synthesis of chrysanthemic acid 67

For our approach towards **67**, we considered two possible disconnections to utilise our dimethyl cyclopropanation chemistry. The first involved cyclopropanation of the corresponding ethyl ester, to that of Corey's approach, in which ester **232** would hopefully be readily available from alcohol **233** using our

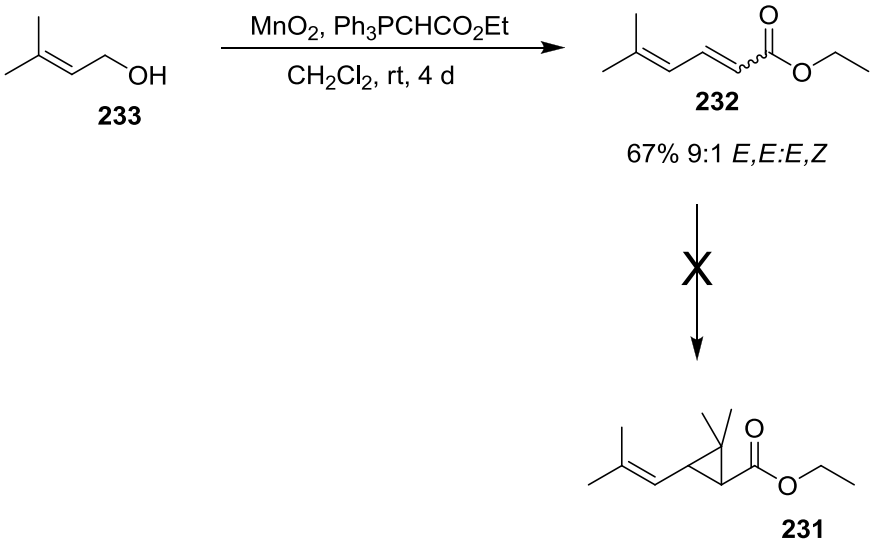
groups' Tandem Oxidation Procedure Wittig chemistry[4] (TOP-Wittig) (Scheme 89).

Scheme 89:



The one-pot oxidation olefination of dimethylallyl alcohol **233** worked successfully (Scheme 90), if slowly, though this is likely to be able to be optimised (for example, previous work has shown that molecular sieves are efficient at improving the rate of reaction).[4] The product **232** was obtained as a separable 9:1 ratio of *E*:*Z*-isomers, and although earlier results showed that both isomers should yield the same product, we opted to take only the *E*-isomer forward.

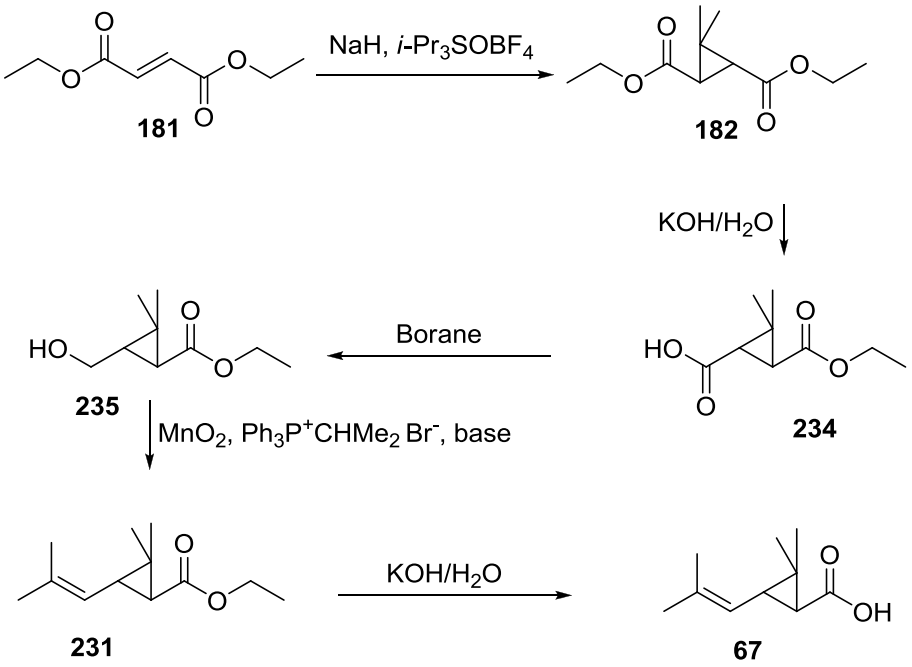
Scheme 90:



Unfortunately, when it came to the cyclopropanation of **232**, no traces of the product **231** could be found, despite numerous attempts. The work carried out with esters had led us to expect a low yield, due to the electron-rich nature of the alkene, but to have no discernible yield was disappointing.

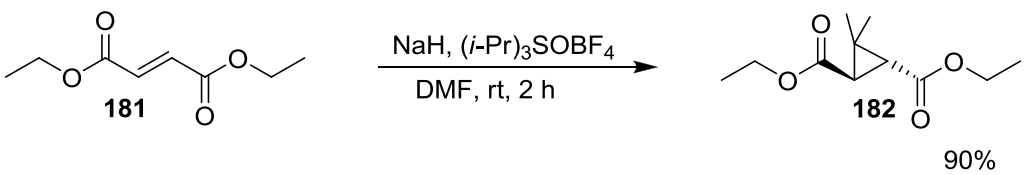
Our second approach is outlined in Scheme 91.

Scheme 91:



This approach makes use of the cyclopropanation product **182** of diethyl fumarate **181**, which we had been able to access with our methodology in near quantitative yield (Scheme 92).

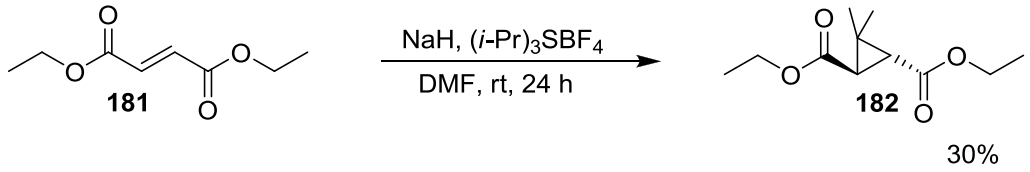
Scheme 92:



Whilst this compound **182** has been previously reported several times, the routes to synthesise it are either multi-step, or involve costly reagents/starting materials.[165, 166]

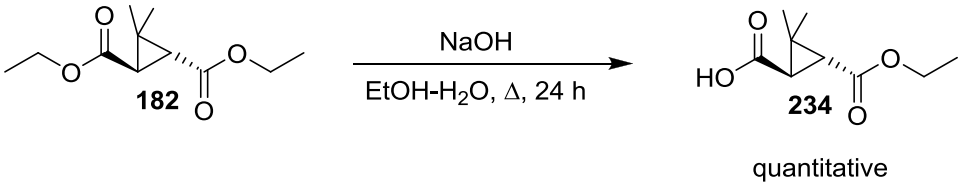
It is worth noting here, that on examining the use of the corresponding sulfonium salt **126**, the desired cyclopropane **182** can be obtained, albeit with low conversion (Scheme 93).

Scheme 93:



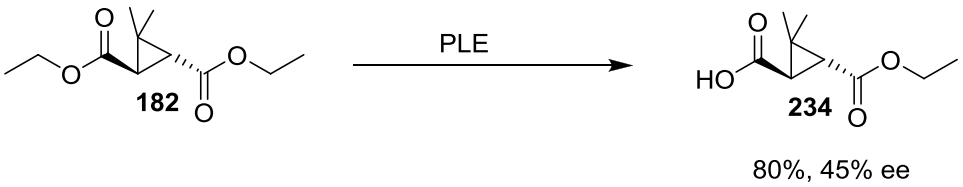
Mono-saponification of diester **182** was achieved in quantitative yield using alcoholic aqueous sodium hydroxide (Scheme 94).

Scheme 94:



It was envisaged that it would be possible to make the route enantioselective by carrying out an enzymatic cleavage of one of the ethyl esters, and indeed the literature contains a single report for the selective cleavage of **182** using pig-liver esterase (PLE), albeit in low enantiomeric excess (Scheme 95).[166]

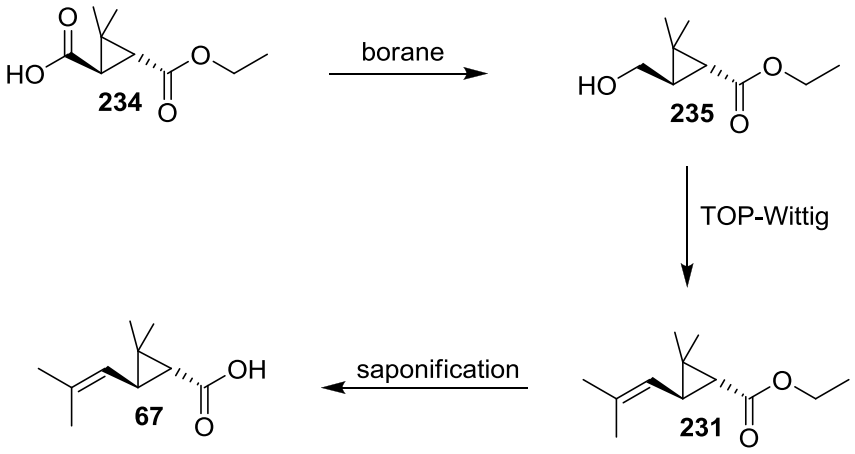
Scheme 95:



The same paper, however, reports much greater selectivity with the use of the corresponding dimethyl ester.

At this stage the project was handed over to Dr. Graeme McAllister, leaving a borane reduction, oxidation-Wittig and saponification in order to complete a synthesis of chrysanthemic acid (Scheme 96). This research is ongoing in our group.

Scheme 96:

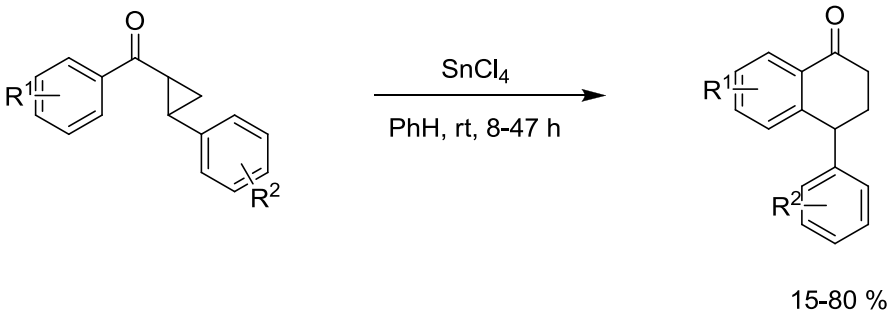


2.6 Cyclopropane rearrangement

2.6.1 Previous approaches

The rearrangement of cyclopropanes into alternative functionalities is well precedented, particularly ring expansion reactions.[61, 167] For example, Murphy and Wattanasin reported the conversion of cyclopropanes into tetralones (Scheme 97).[168]

Scheme 97:



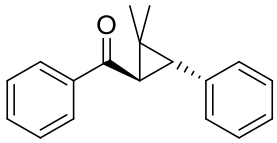
Having developed a route to *gem*-dimethylcyclopropanes, we were interested to investigate their potential in similar rearrangement processes, particularly as we

envisaged such processes would be further favoured by the Thorpe-Ingold effect.[169]

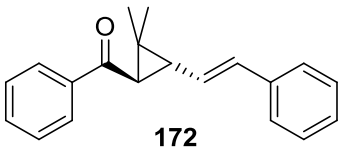
2.6.2 Initial catalyst screening

In order to examine potential rearrangements, we decided to screen a small number of cyclopropanes against a range of Lewis acids, and observe the reactions for the formation of any products. Cyclopropanes **62** and **172** from the two compound classes which had proved most facile to prepare were selected for the screening (Figure 6).

Figure 6:



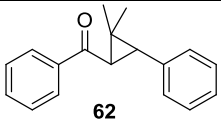
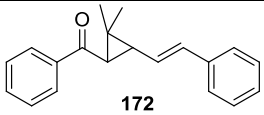
62



172

The method for screening was to stir a sample of the cyclopropane in 1,2-dichloroethane (DCE) at room temperature, monitoring the reactions with thin layer chromatography for any consumption of starting material, and potential formation of products. If after 24 h, no reaction had occurred, the sample was then heated to reflux and monitored for up to a further 24 h. The results from TLC and proton NMR spectroscopy then indicated any reactions worthwhile to scale up, in order to identify products. The results of the screening reactions are shown in Table 8.

Table 8: Catalyst screening for cyclopropane rearrangements

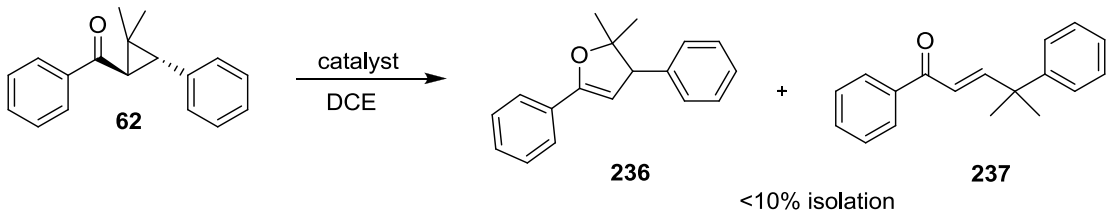
Entry	Lewis Acid	 62	 172
1[a]	$Au(PPh_3)Cl$	No reaction[c]	No reaction[c]
2[a]	$AuCl_3$	No reaction[c]	Consumption of SM
3[b]	$Ti(O\textit{i}\text{-}Pr)_4$	No reaction[c]	-
4[b]	$TiCl_4$	SM Consumed; product indicated	-
5[b]	$SnCl_4$	SM Consumed; product indicated	Consumption of SM
6[b]	$SnCl_2.2H_2O$	SM Consumed; product indicated[c]	Consumption of SM
7[b]	Me_2AlCl	No reaction[c]	Consumption of SM
8[a]	$InCl_3$	SM Consumed; product indicated [c]	-
9[a]	$HgCl_2$	No reaction[c]	-
10[b]	$ZnCl_2$	No reaction[c]	Consumption of SM
11[a]	$CeCl_3$	No reaction[c]	No reaction[c]
12[a]	$PdCl_2$	No reaction[c]	No reaction[c]
13[a]	AgOTf	Product spot indicated[c]	-
14[a]	$Cu(OTf)_2$	No reaction[c]	No reaction[c]
15[b]	TMSOTf	SM Consumed; product indicated	Consumption of SM

a) 0.10 mmol substrate in DCE (1 mL) in a sealed microwave tube. 20 mol% catalyst added.
b) 0.10 mmol substrate in DCE (1 mL) in a sealed microwave tube. 1 eq catalyst added.
c) After 24 h heated to reflux.

Chalcone-derived cyclopropane **62** gave rise to some promising reaction mixtures when analysed by TLC and proton NMR spectroscopy for several of the Lewis acids under investigation. Tin(IV) and titanium(IV) chlorides (Entries 4 and 5) and TMS triflate (Entry 15) were the most promising, with starting material being consumed rapidly to produce two distinct spots by TLC. Tin(II) and indium(III) chlorides (Entries 6 and 8) and silver(I) triflate (Entry 13) gave similar results after heating, although with silver(I) triflate the reaction did not go to completion. Dienone derived cyclopropane **172** was less promising, and where starting material was consumed, only baseline material was formed which showed no promise on proton NMR analysis.

On scaling up the reactions showing potential (Entries 4-6, 8 & 15), the same two products **236** and **237** were isolated in very low yields (Scheme 98).

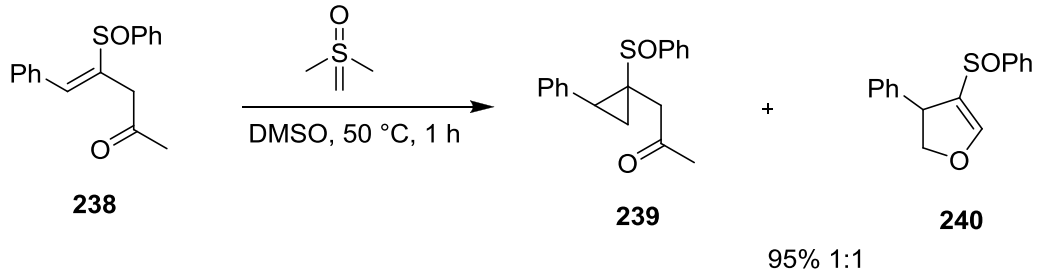
Scheme 98:



The first product **236** was a dihydrofuran, which rapidly decomposed on standing. The structure was easily assigned from the loss of the carbonyl stretch at 1660 cm^{-1} and the two dihydrofuran proton signals in the NMR spectra at δ 3.98 and 5.41 with a 3 Hz coupling.

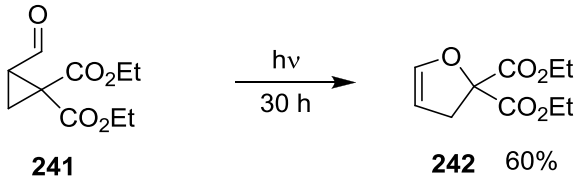
Dihydrofurans are found in a number of natural products[170] and there is precedent for their preparation from cyclopropanes.[171, 172] Piras *et al.*, whilst attempting to cyclopropanate sulfur-substituted enones, also observed the formation of dihydrofurans (Scheme 99).[171]

Scheme 99:



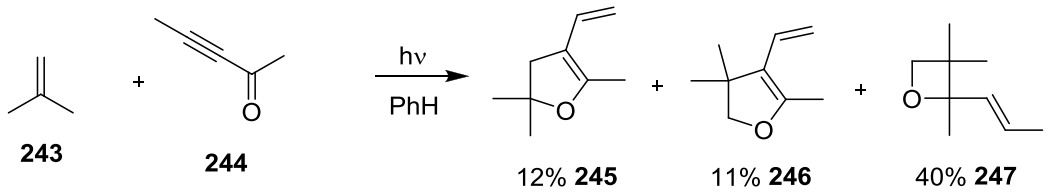
Engel also observed the formation of dihydrofurans from cyclopropanations when trying to form olefins *via* irradiation of cyclopropanes (Scheme 100).[172]

Scheme 100:



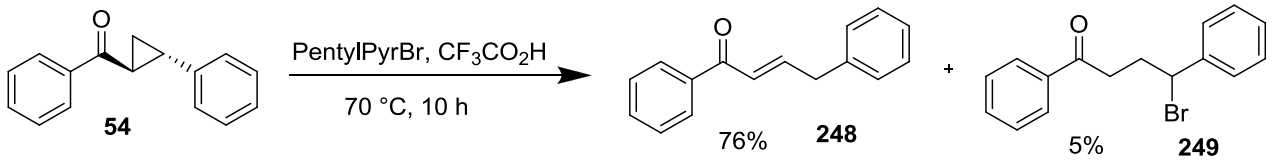
There are only a few reported examples of 2,3-dihydrofurans containing *gem*-dimethyl groups at the 2-position, such as the photochemically-formed examples reported by Agosta (Scheme 101).

Scheme 101:



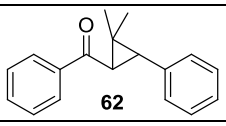
The enone system **237** is a much more widespread motif, and whilst this one is previously unknown,[173] it could presumably be accessed through aldol chemistry. Formation of this type of enone system from acid-catalysed cyclopropane rearrangement has been reported before by Dolbier Jr and coworkers.[174] They report the rearrangement of the methylene cyclopropane of chalcone **54** with TFA (Scheme 102).

Scheme 102:



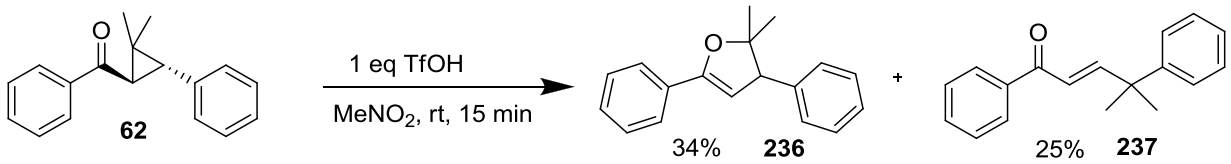
The successful Lewis acids have a significant factor in common; in the absence of rigorously anhydrous conditions they can hydrolyse to afford either hydrochloric or trifluoromethanesulfonic acid. Since this might be the "true" catalyst, the screening of these, and other, acids was attempted (Table 9).

Table 9: Acid screening for rearrangement of cyclopropane **62**

Entry	Acid	 **62**
1	CF_3SO_3H	~2:1:1 **62**:**236**:**237**
2	HCl	No reaction
3	CF_3CO_2H	No reaction
4	H_3PO_4	No reaction
5	*p*-TSA	No reaction

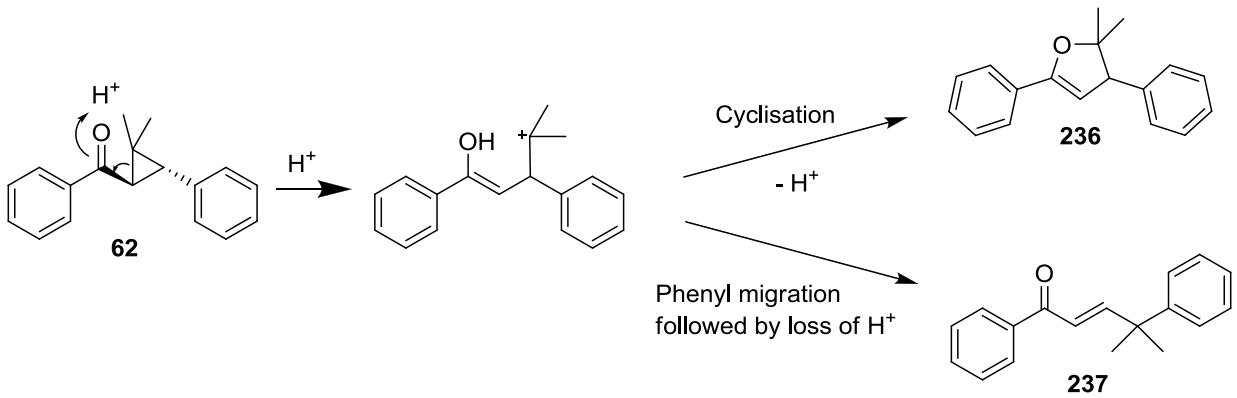
Use of trifluoromethanesulfonic acid (Table 9, Entry 1) gave formation of the same two products **236** and **237**, as had been observed from the reactions with Lewis acids. Combining this acid with use of a polar solvent (nitromethane), enabled higher isolated yields (Scheme 103), although dihydrofuran **236** still decomposed rapidly to baseline material.

Scheme 103:



A plausible mechanism for the formation of the two products **236** and **237** involves a common tertiary carbocation intermediate. From this intermediate either cyclisation can occur to give dihydrofuran **236** or phenyl migration occurs to give enone **237** (Scheme 104).

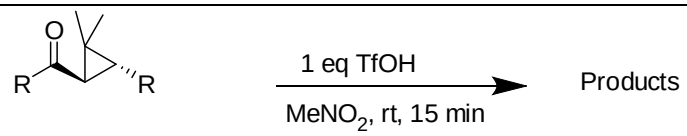
Scheme 104:

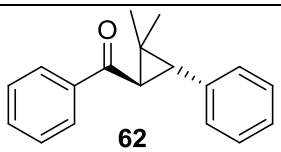
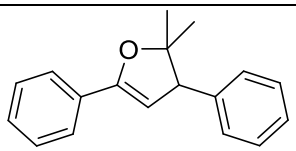
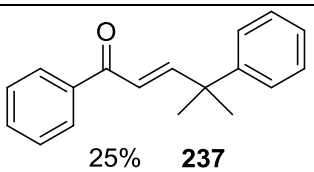
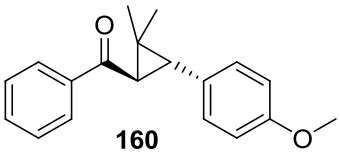
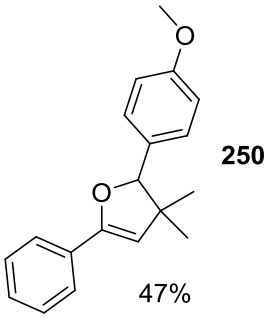
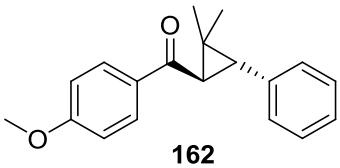
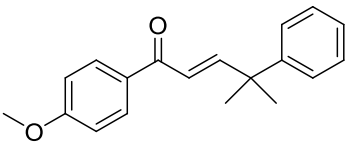
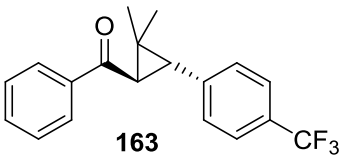
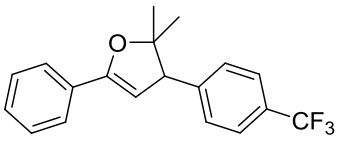
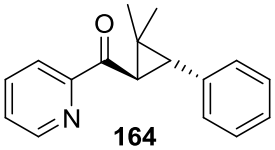
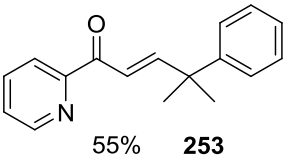


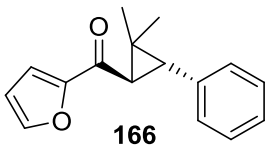
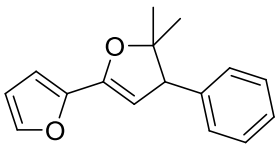
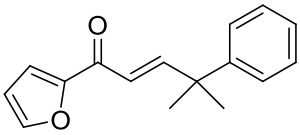
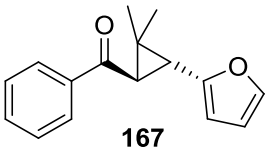
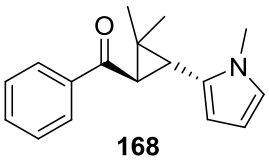
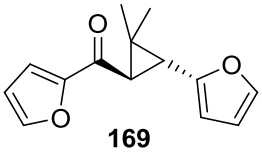
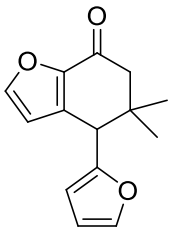
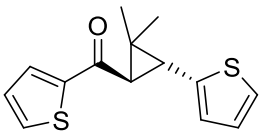
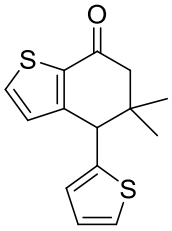
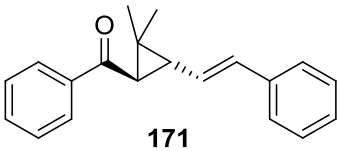
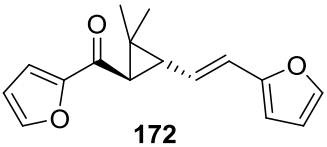
2.6.3 Scope of rearrangements

Prior to attempting any further optimisation of conditions, we decided to investigate if this conversion was a general process. Taking previously prepared cyclopropanes, and exposing these substrates to our reaction conditions gave the results summarised in Table 10.

Table 10: Rearrangement of chalcone-derived cyclopropanes

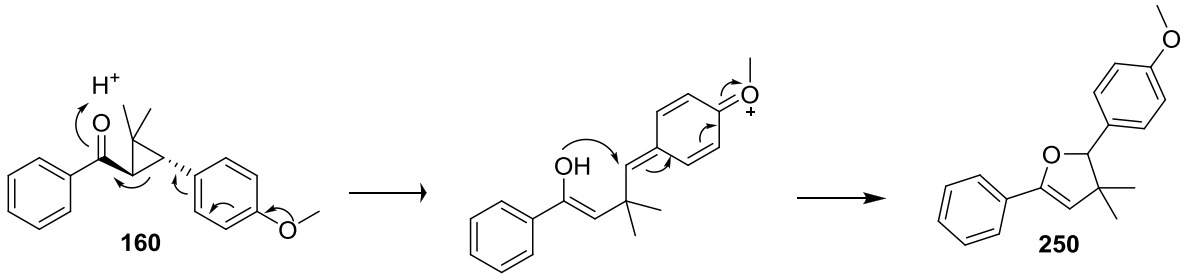


Entry	Substrate	Products	
1	 **62**	 34% **236**	 25% **237**
2	 **160**	 **250** 47%	
3	 **162**		 28% **251**
4	 **163**	 38% **252**	
5	 **164**		 55% **253**

6	 **166**	 9% **254**	 28% **255**
7	 **167**	SM consumed	
8	 **168**	SM consumed	
9	 **169**	 68% **256**	
10	 **170**	 55% **257**	
11	 **171**	SM consumed	
12	 **172**	SM consumed	

In contrast to the cyclopropane of chalcone (Entry 1), the use of the electron-donating analogue **110** (Entry 2) gave rise to a regioisomer of the dihydrofuran. Presumably this comes about through the mesomeric stabilisation offered from the *para*-methoxyphenyl ring being greater than that of the two methyl groups (Scheme 105), favouring this ring-opening selectivity.

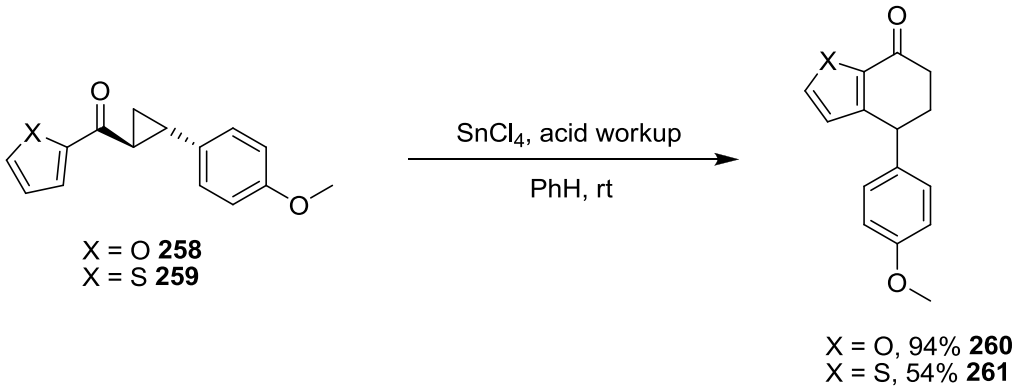
Scheme 105:



Changing to an electron-withdrawing ring substituent **163** (CF_3, Entry 4), returned the analogous dihydrofuran **252** to the diphenyl example (Entry 1), as would be predicted. For the examples listed where there is a phenyl substituent on the cyclopropane ring (Entries 1, 3, 5 & 6) the phenyl migration product was seen, giving rise to an enone system. Phenyl migration is possible due to the ring stabilising the positive charge. The substituted rings should also be able to undergo this migration, however, the *p*-CF_3 substituted ring **252** (Entry 4) would offer limited stabilisation and this pathway is probably disfavoured. For the *p*-OMe substituted cyclopropane **160** (Entry 2), this stabilisation should be increased, but it could be postulated that the pathway to form dihydrofuran **250** in this case occurs much more rapidly than the pathway required to form the corresponding enone.

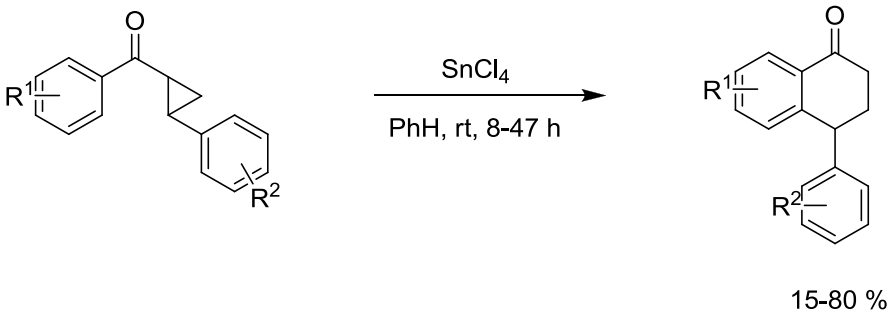
Another type of rearrangement was seen from the difuryl and dithiophenyl chalcone cyclopropanes **169** and **170** (Entries 9 & 10). This process is also known for the methylene cyclopropanes; Otto and coworkers[175] reported two tin(IV)-catalysed examples (Scheme 106).

Scheme 106:



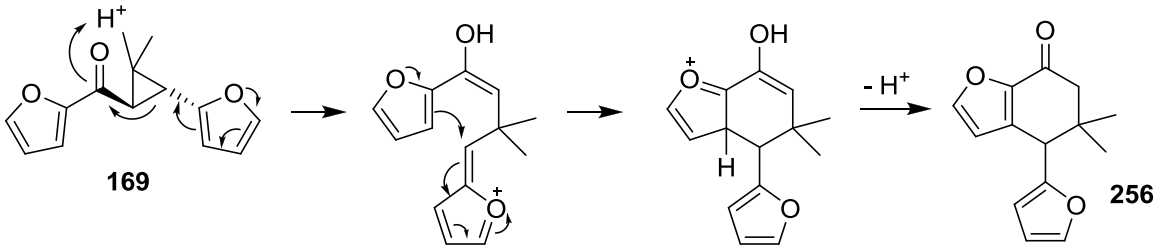
The same rearrangement process has also been reported by Murphy and coworkers for the synthesis of aryl-tetralones.[168, 176, 177] Their report highlights the need for both rings to have electron-donating substituents in order to assist the cyclopropane opening, and the intramolecular Friedel-Crafts reaction (Scheme 107).

Scheme 107:



A postulated mechanism for our transformation is outlined in Scheme 108.

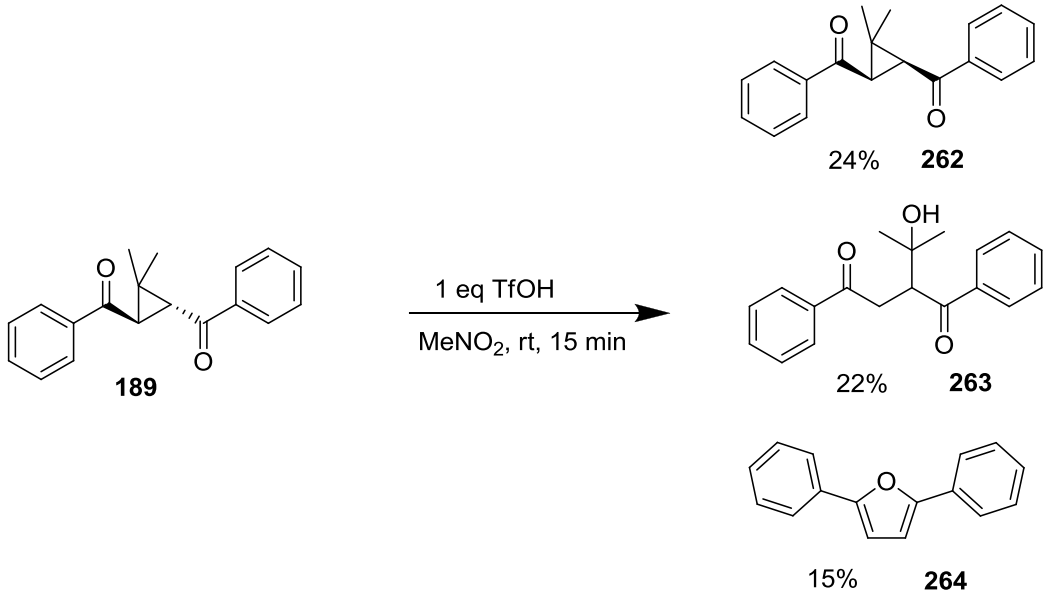
Scheme 108:



The remaining entries (Table 10, Entries 7,8,11 & 12) gave no identifiable products, or recovered starting material, with only baseline material being isolated. It should be noted that even in the successful examples, purification and stability of the products was problematic; the dihydrofurans in particular, decomposed rapidly on standing, as did several of the other products; probably contributing to the lower than ideal mass recoveries, and hampering attempts to fully characterise the products.

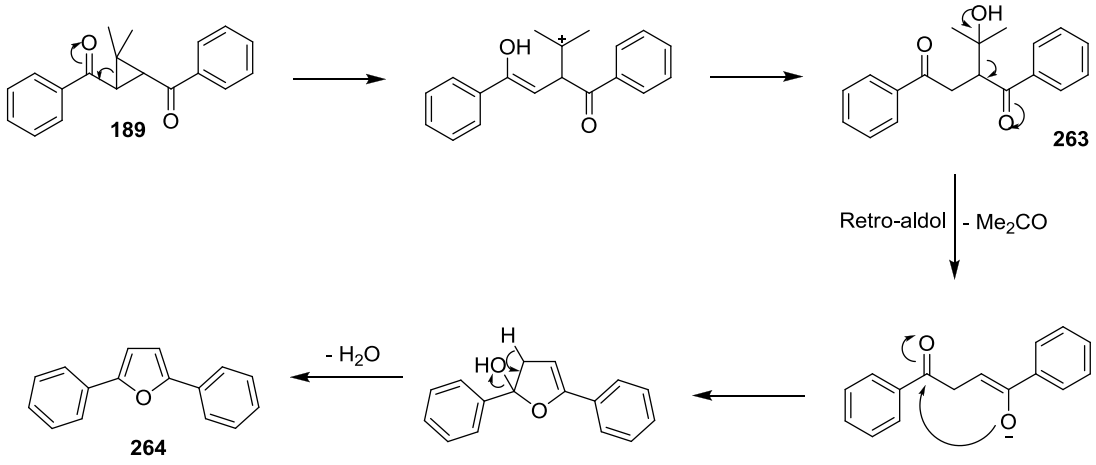
A further *gem*-dimethyl cyclopropane was also subjected to the trifluoromethanesulfonic acid rearrangement, diketone **189**. This gave rise to three products; a stereochemical inversion to the *cis*-cyclopropane **257**, as shown by the loss of the proton coupling for the cyclopropane protons as they are now equivalent (this structure has been reported by Zimmerman and Eberbach previously[178]) along with alcohol **263** and diphenylfuran **264** (Scheme 109).

Scheme 109:



A plausible mechanism for the formation of the diphenyl furan **264** going *via* alcohol **263** in a retro-aldol type process is shown in Scheme 110.

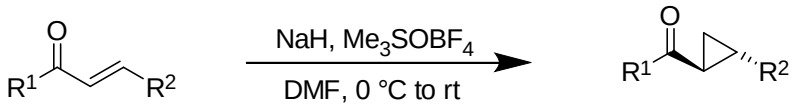
Scheme 110:

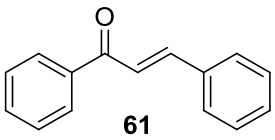
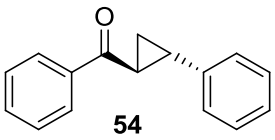
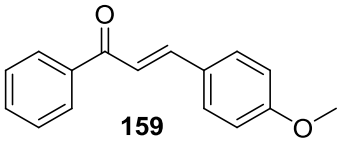
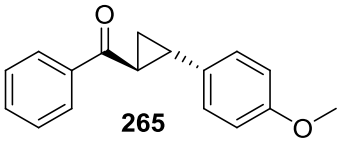
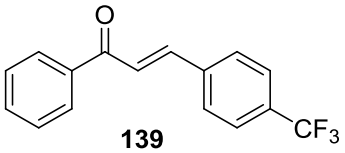
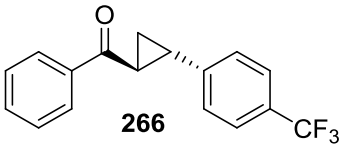
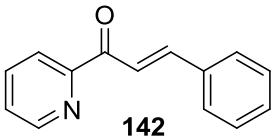
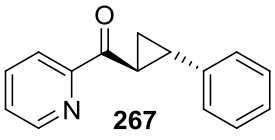
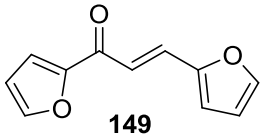
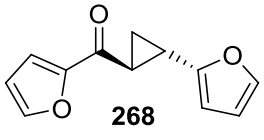


2.6.4 Rearragement of methylene cyclopropanes

Consideration was given next to reaction possibilities with cyclopropanes without the *gem*-dimethyl groups, with the expectation that cyclisation would not occur so readily. Preparation of several of these cyclopropanes was carried out using the Corey-Chaykovsky reagent under the same conditions as for the *gem*-dimethyl cyclopropanation (Table 11).

Table 11: Preparation of methylene cyclopropanes

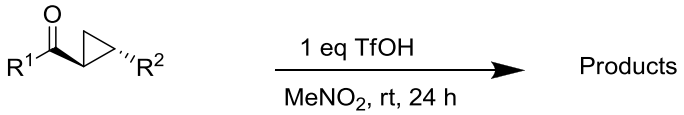


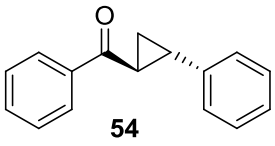
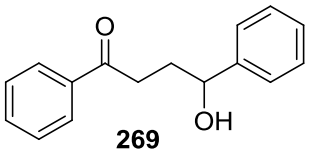
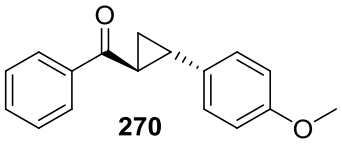
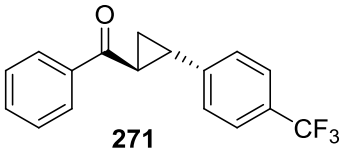
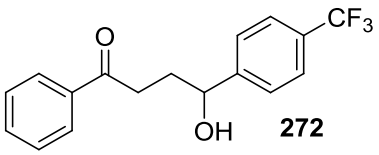
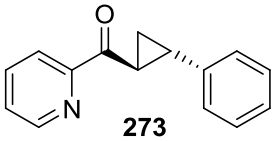
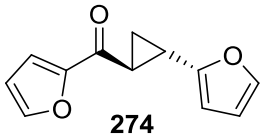
Entry	Chalcone	Product	Yield
1	 **61**	 **54**	86
2	 **159**	 **265**	94
3	 **139**	 **266**	90
4	 **142**	 **267**	76
5	 **149**	 **268**	93

When the *gem*-dimethyl cyclopropanes were exposed to the normal rearrangement conditions, the starting material had been entirely consumed

within 15 minutes. The methylene cyclopropanes displayed a reaction rate that was much slower that the *gem*-dimethylcyclopropanes, and even after 24 hours starting material was recovered (Table 12 Entries 1 and 3).

Table 12: Rearrangement of methylene cyclopropanes



Entry	Substrate	Products
1	 **54**	 **269** 48% + 25% RSM
2	 **270**	Nothing isolated
3	 **271**	 **272** 12% + 74% RSM
4	 **273**	Nothing isolated
5	 **274**	Nothing isolated

Murphy and coworkers have previously reported formation of alcohol **269** from chalcone-derived cyclopropane **54** with tin(IV) chloride in 90% yield. Presumably the cation formed from the cyclopropane opening is quenched on work-up to yield the alcohol. No formation of tetralones was observed in the above examples; the requirements for this to happen would be electron-donating substituents in both rings (consistent with the finding of Murphy and Otto).[168, 175] Only the difuryl example **274** fulfils this requirement, but here, opening of the

furyl rings, resulting in decomposition, appears to be faster than the intramolecular Friedel-Crafts process.

Whilst a range of interesting products were formed through these acid-catalysed rearrangements, the lack of selectivity along with purification and stability problems with the products hinders any synthetic use with this methodology.

2.7 Future work

If such a cyclopropanation approach to chrysanthemic acid **67** is successful, then particularly if combined with any future success with the development of diphenylalkyl sulfoxonium salts, it may become possible to easily synthesise analogues of chrysanthemic acid **67** for use in the synthesis of pyrethrins and related compounds.

Future work includes:

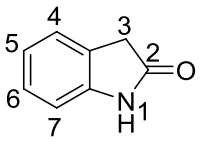
- Development of *iso*-propyldiphenylsulfoxonium tetrafluoroborate **212** and demonstrate its use in synthesis.
- Develop other sulfoxonium salts capable of transferring functionality in cyclopropanation.
- Complete synthesis of chrysanthemic acid **67**.
- Utilise alternative sulfoxonium salts in the synthesis to prepare analogues of chrysanthemic acid **67**.

Chapter 3: Preparation of 3-alkyloxindoles

3.1 Oxindoles

Oxindoles are a common structural motif in a wide variety of alkaloid natural products,[179] and are particularly prominent in the 3-alkenyl substituted form[180] or with a spirocycle on the 3-position.[181, 182]

Figure 7:

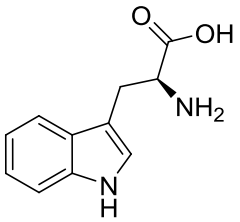


275

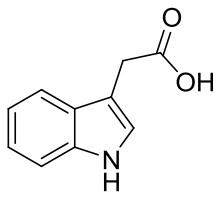
Structure of an oxindole with conventional numbering.[183]

Oxindoles are primarily constructed in nature from the oxidation of indoles.[184] Indoles are essential in nature, including the amino acid tryptophan **276**, and several important auxins (compounds coordinating plant growth) contain a core indole functionality (Figure 8).[185]

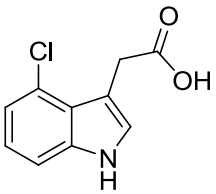
Figure 8:



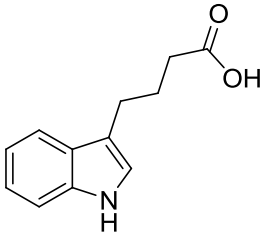
Tryptophan **276**



Indole-3-acetic acid **277**



4-Chloroindole-3-acetic acid **278**



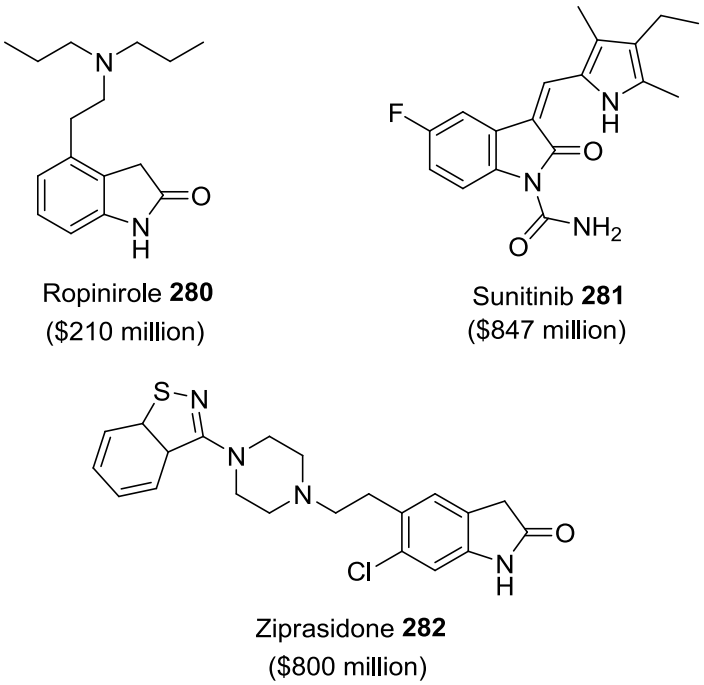
Indole-3-butyric acid **279**

The amino acid tryptophan and three auxins, all containing an indole functionality.

3.1.1 Use as pharmaceuticals

The bioactivity of oxindoles has led to much interest in these molecules as drug candidates, including as anti-cancer, anti-HIV, anti-inflammatory and protein-kinase inhibitor drugs.[186] Several of the best-selling drugs (as of 2008)[66] contain the oxindole structure (Figure 9).

Figure 9:



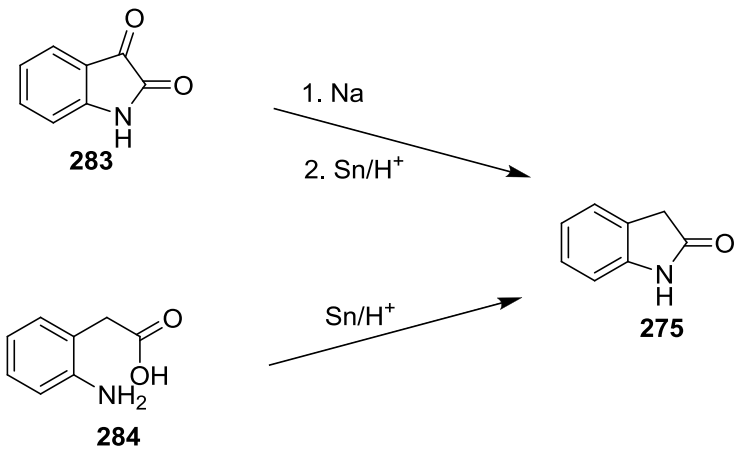
Top-selling pharmaceuticals containing the oxindole moiety, with revenue generated in 2008.[66]

Ropinirole **280**[187] (given orally as the hydrochloride salt) is a dopamine agonist developed by GlaxoSmithKline used primarily in the treatment of Parkinson's disease. Sunitinib **281**[188] is a tyrosine kinase inhibitor developed by Pfizer used in the treatment of renal and gastrointestinal tumours. Ziprasidone **282**[189] is marketed as Geodon® by Pfizer and given as either the hydrochloride (oral) or mesylate (intramuscular) salt in the treatment of bipolar disorder. In 2008 these three drugs generated nearly 2 billion dollars in retail sales.[66]

3.2 Synthetic approaches

The oxindole moiety **275** was first prepared by Baeyer through reduction of Isatin **283**, and its structure was confirmed *via* lactam formation with 2-aminophenylacetic acid **284** (Scheme 111).[190]

Scheme 111:

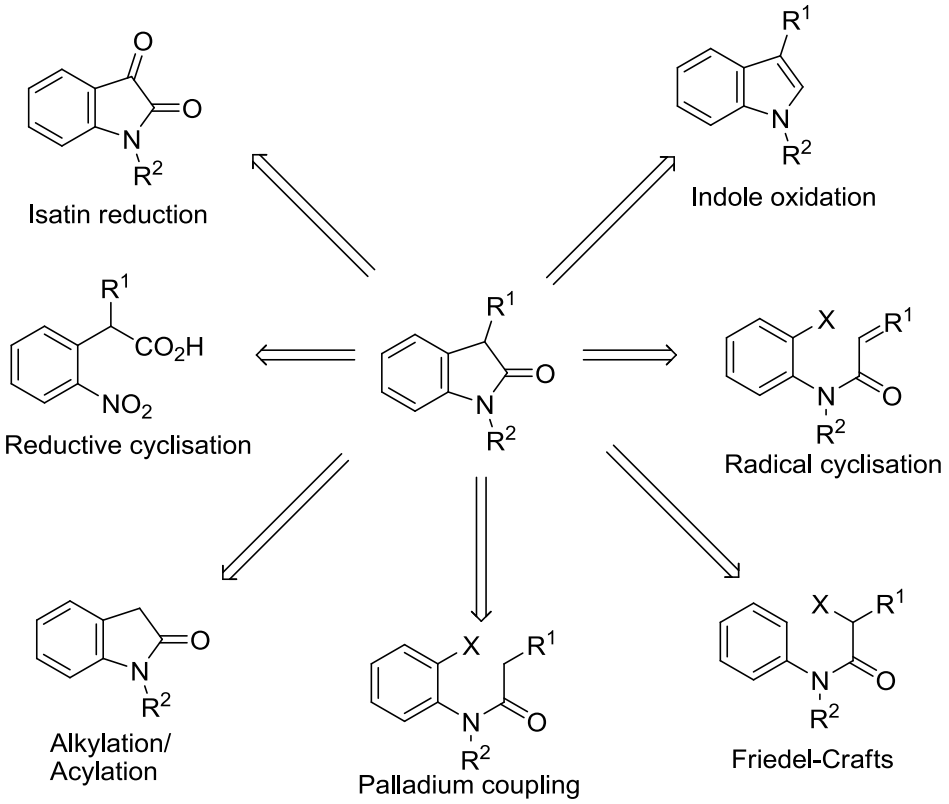


3.2.1 3-Substituted oxindoles

Following Baeyer's reports, many routes to substituted oxindoles were developed (a comprehensive review from 1945 covers the early approaches).[183] In more recent times, oxindoles have witnessed a resurgence in interest, with many reviews being published, such as those from Carreira, focusing on approaches to spirocyclic oxindoles,[184] Russel on the C-3 functionalisation of oxindoles,[191] and Zhou on asymmetric quaternary C-3 oxindoles.[192]

The main synthetic methods used to prepare 3-substituted oxindoles are outlined in Scheme 112.

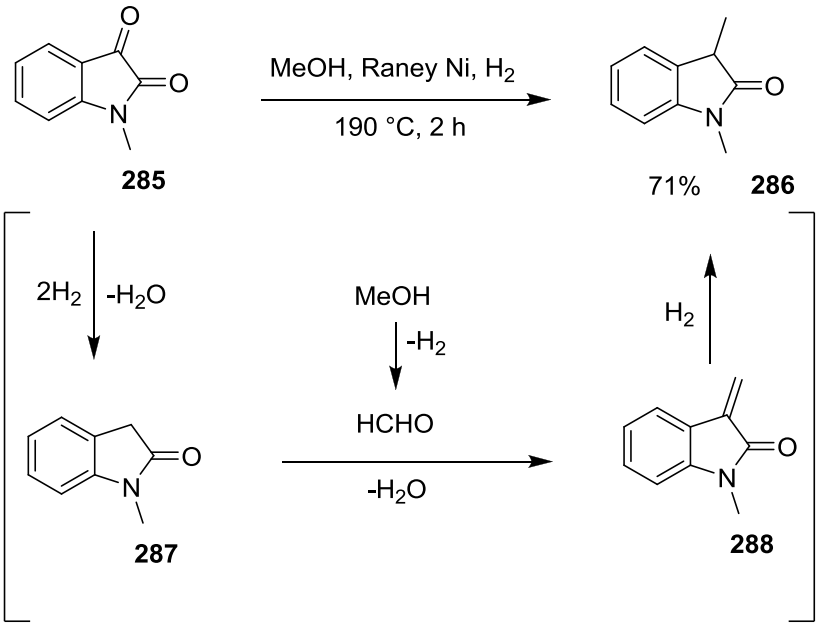
Scheme 112:



3.2.2 Isatin derived oxindoles

Reductive alkylation of isatin **283** to give 3-alkyloxindoles most commonly uses Raney nickel/hydrogen with alcohols as the alkylating agent, such as the method reported by Simig (Scheme 113).[193]

Scheme 113:

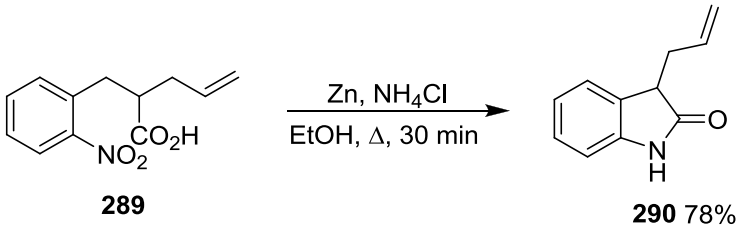


This approach is limited to the introduction of side-chains not liable to hydrogenation, reducing the scope of the method.

3.2.3 Reductive cyclisation

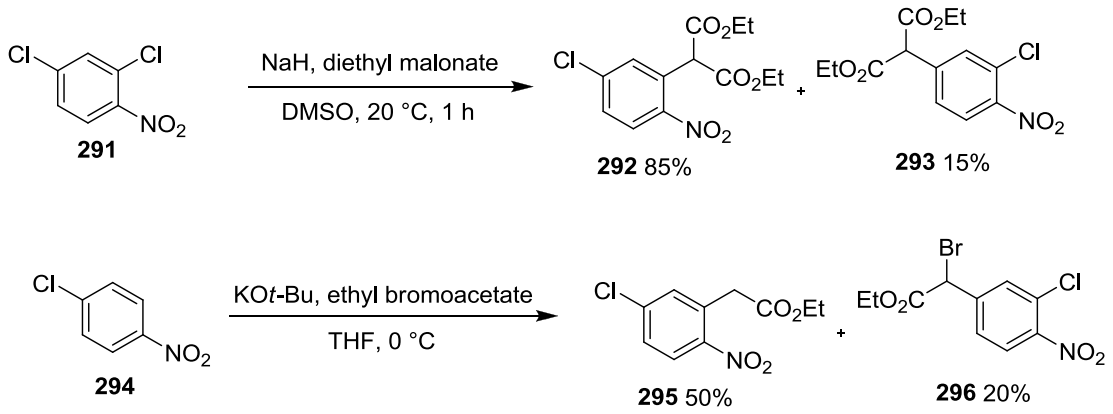
From the initial approaches of Baeyer, using a two-step reductive amination (reduction of the nitro group, followed by lactam formation), one pot reductive cyclisations have been developed. The approach of Kulkarni *et al.* in their syntheses of horsfiline and coerulescine includes the preparation of 3-allyloxindole **290** through reductive cyclisation (Scheme 114).[194]

Scheme 114:



Defrere had intended to use reductive amination in their process scale syntheses of oxindole derivatives, but abandoned this route following regioselectivity issues in the preparation of their substrates, despite trying several different routes, two of which are outlined here (Scheme 115).[195]

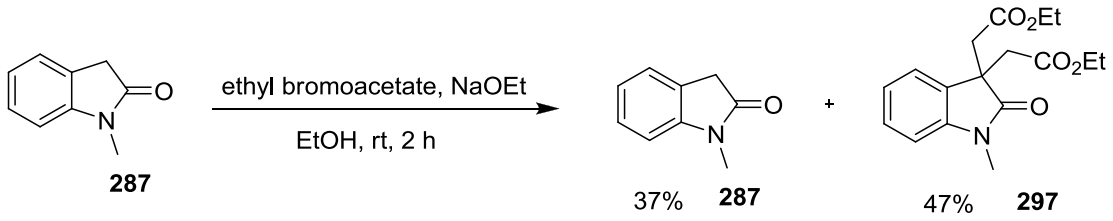
Scheme 115:



3.2.4 Alkylation of oxindoles

Alkylation (or acylation) of N-protected oxindoles would seem to offer a facile route to 3-substituted oxindoles, however this method commonly results in the formation of side products from double alkylation[196] (for example Scheme 116, where none of the mono-alkylation product was observed)[197] or *O*-alkylation,[198] and can lead to tedious separation of the products.

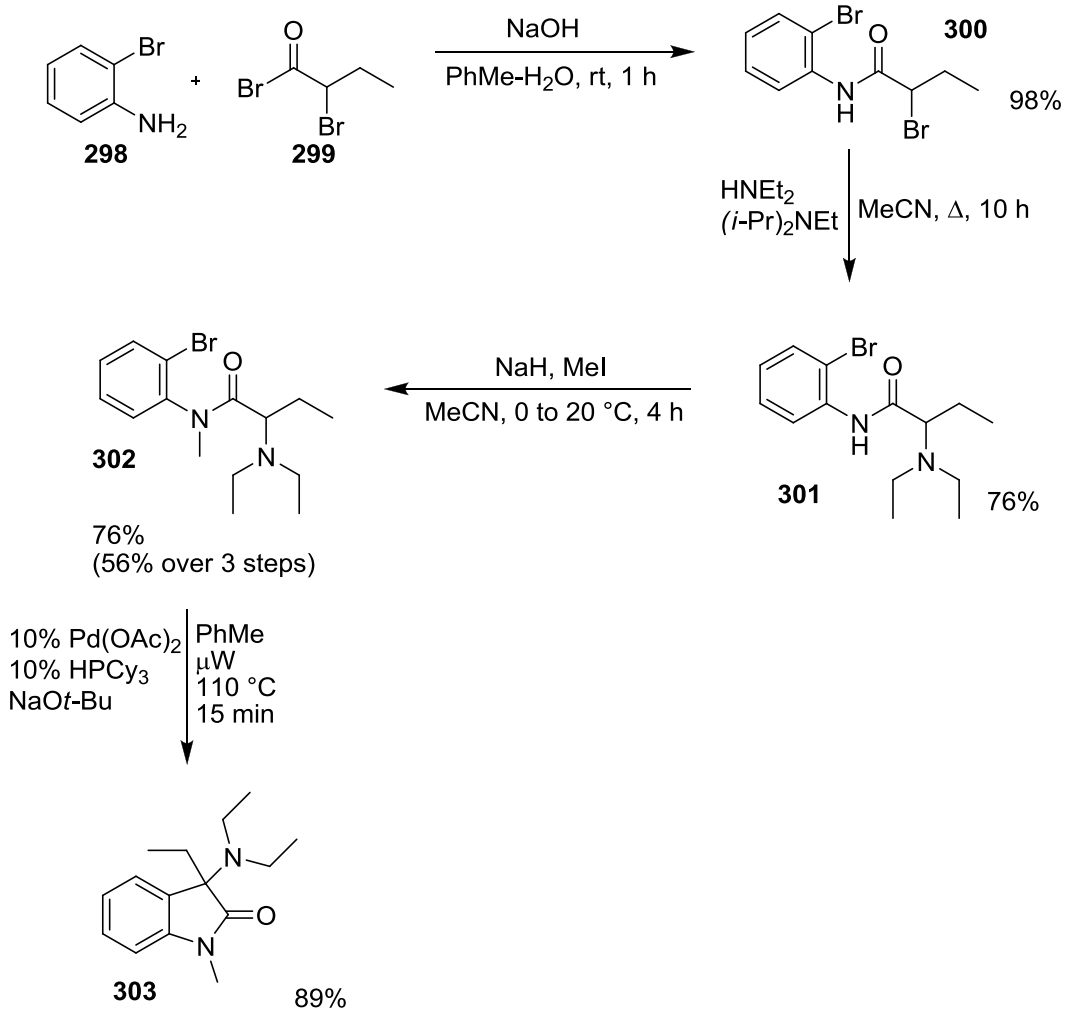
Scheme 116:



3.2.5 Palladium coupling approaches

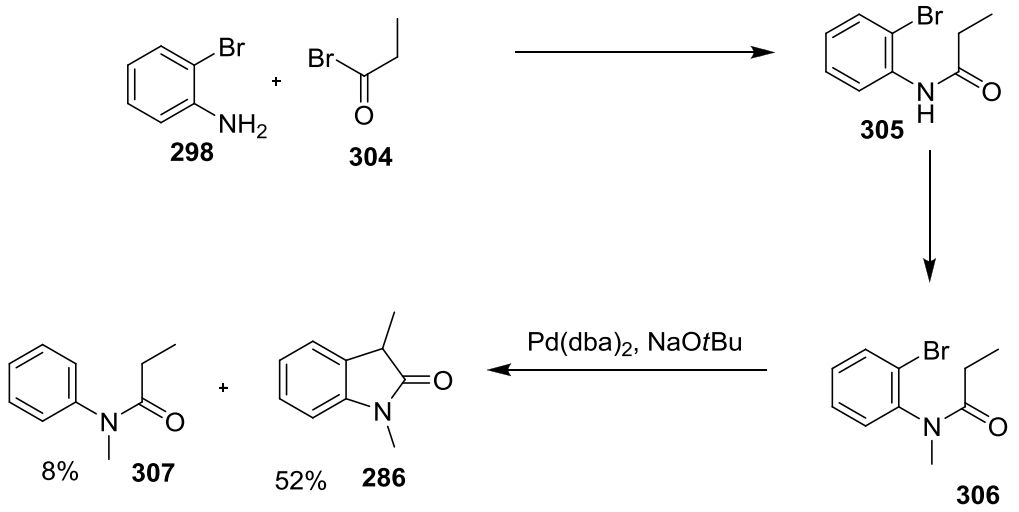
Enolate arylation approaches using palladium catalysts are an area of intensive research, with many groups publishing their routes to oxindoles. *Ortho*-halogenated anilides are common precursors for oxindole synthesis, although their preparation can involve multi-step syntheses. For example, Marsden's approach to oxindoles requires a 3 step preparation from bromobutyryl bromide **299** (Scheme 117).[199]

Scheme 117:



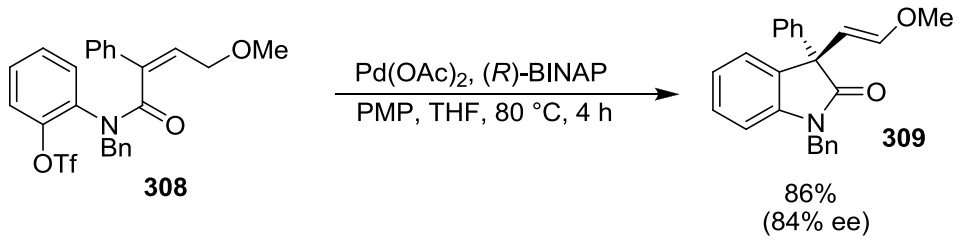
Hartwig uses a similar approach in which the oxindole precursors are assembled from *o*-bromoaniline **298** and acid halides (Scheme 118).[200]

Scheme 118:



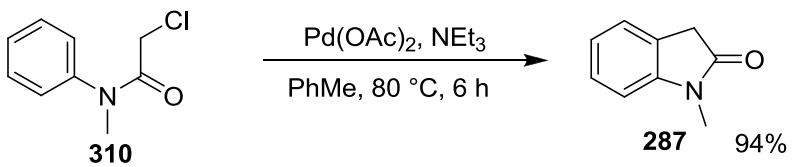
Intramolecular Heck reactions are also utilised in a similar fashion, with a many utilising chiral ligands offering asymmetric routes to oxindoles. Examples include the work of the Overman group (Scheme 119).[201] These asymmetric Heck routes were reviewed by Trost in 2009.[179]

Scheme 119:



Buchwald uses an approach in which the halogen is α to the oxygen in the amide, rather than on the aryl ring, to form oxindoles. However, here, no examples of 3-substituted oxindoles are demonstrated (Scheme 120).[202]

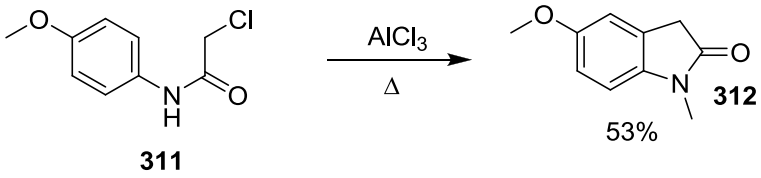
Scheme 120:



3.2.6 Friedel-Crafts approaches

Friedel-Crafts routes rely on similar substrates to those of Buchwald. Daisley reports the preparation of oxindoles through a Friedel-Crafts alkylation using aluminium trichloride (Scheme 121), although no 3-substituted examples are included.[203]

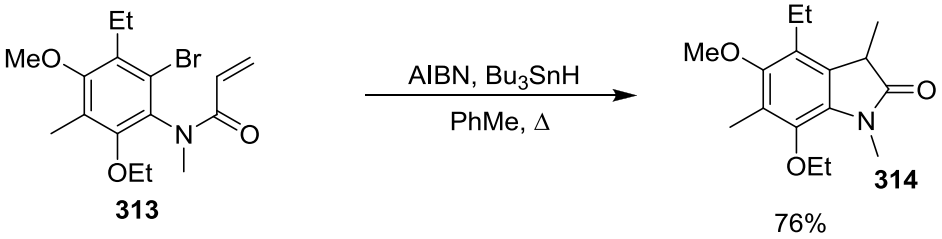
Scheme 121:



3.2.7 Radical cyclisation

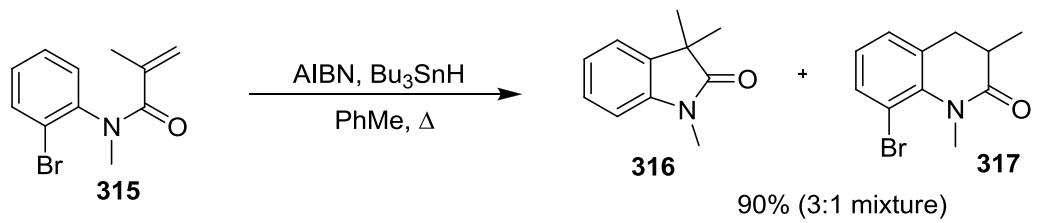
Jones and Storey used radical cyclisation in their approaches towards the synthesis of mytomycins.[204] Here the highly substituted anilide **313** undergoes 5-exo-trig cyclisation using tributyltin hydride as the hydrogen source (Scheme 122).[205]

Scheme 122:



More recently, Jones has reported examples in which oxindoles are formed in a 5-exo-trig reaction and dihydroquinolones are formed in a 6-endo-trig fashion (Scheme 123).[206, 207] Under Baldwin's rules both of these cyclisations are favoured.

Scheme 123:



3.2.8 Oxidation of indoles

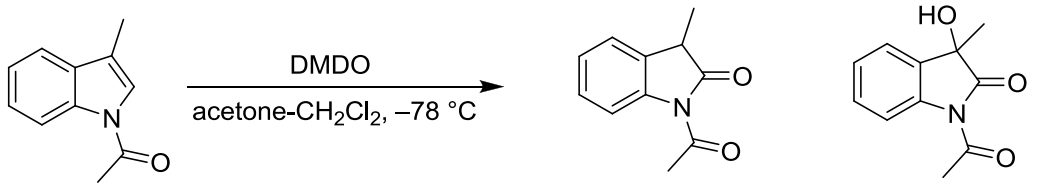
There are a number of routes reported for the oxidation of indoles to oxindoles, such as use of hydroxy radicals,[208] ammonium persulfate,[209] or enzymatic methods.[210, 211] For the oxidation of 3-substituted indoles, the prevailing method is the use of DMSO and HCl (for example, Scheme 124).[212, 213]

Scheme 124:

318 **286** 66%

Some oxidants used result in over-oxidation, such as the use of dimethyldioxirane, although in many cases separation is facile and yields are still good (Scheme 125).[214]

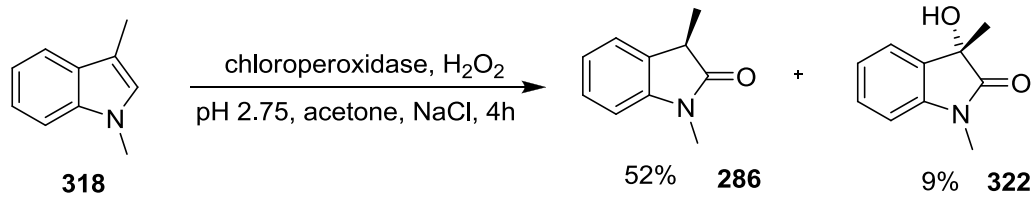
Scheme 125:



319 **320** 90% **321** 8%

The use of enzymatic oxidation is described in a number of reports,[210, 211, 215] giving access to enantiomerically pure material (although usually restricted to a single isomer), such as the use of chloroperoxidases obtained from *Caldariomyces fumago* (Scheme 126).[215]

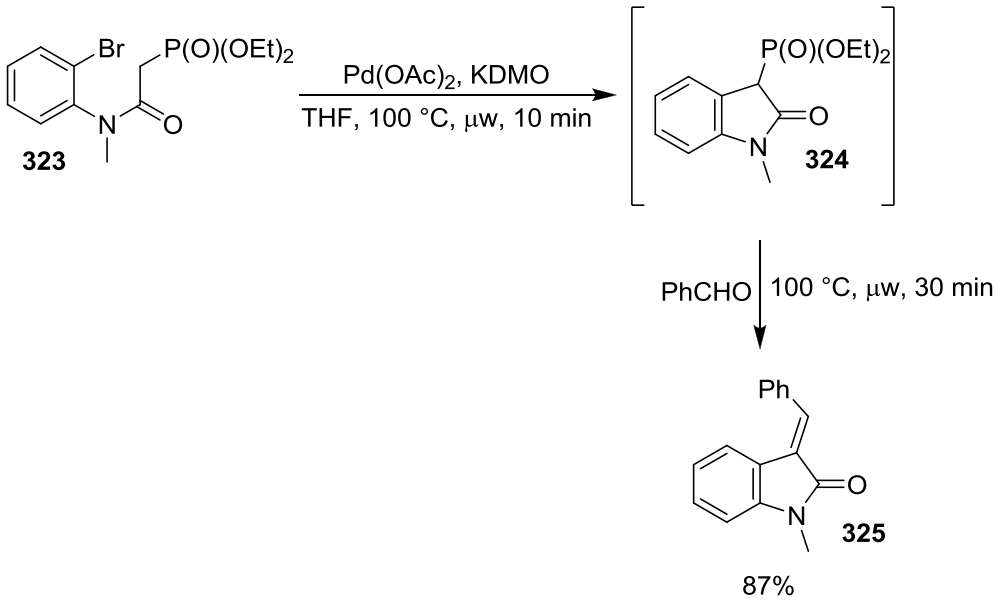
Scheme 126:



3.2.9 CH Activation

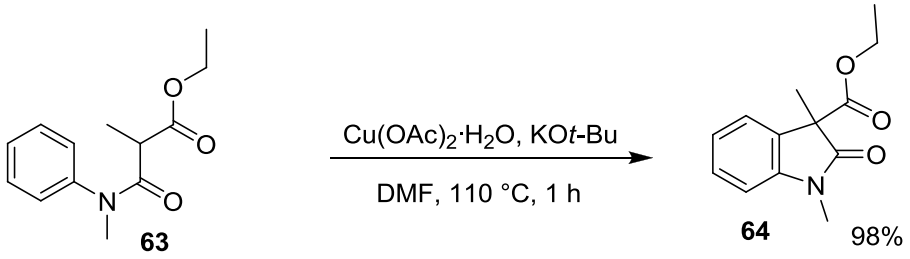
Within the Taylor group, Perry developed a telescoped enolate arylation / Horner-Wadsworth-Emmons coupling for the preparation of 3-alkenyl oxindoles (Scheme 127).[216, 217]

Scheme 127:



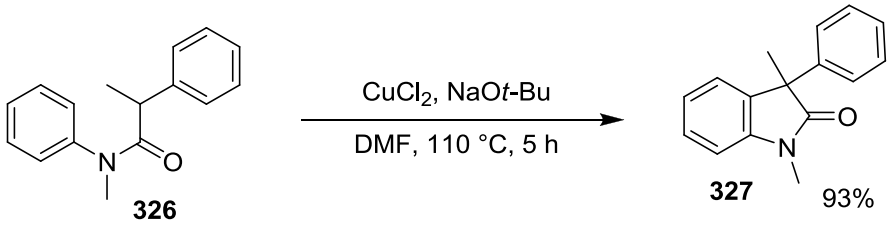
During this work, Perry looked at developing a CH activation route, removing the need for the aromatic halide. The initial approach was with a palladium(II)-catalysed intramolecular arylation of anilides (easily formed from anilines and malonates), in the presence of base, using a co-oxidant to turn over the palladium. Perry quickly found that the reaction was successful if copper(II) acetate was used, but only low yields were obtained using silver acetate as the co-oxidant. On running a control, removing the palladium, Perry discovered that the copper acetate was the actual catalyst. After optimisation this gave an efficient method for the preparation of 3-substituted oxindoles (Scheme 128).[51]

Scheme 128:



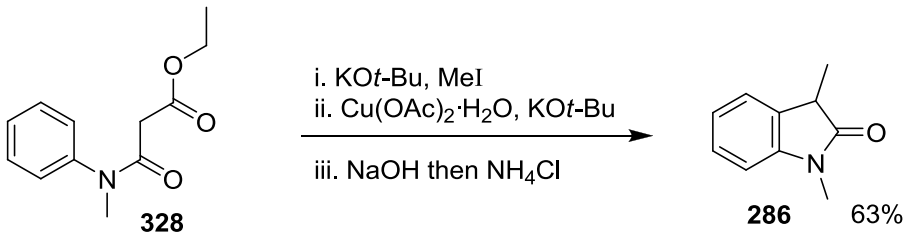
At the same time this work was being completed, Kündig disclosed his analogous results.[218] In their methodology anhydrous copper(II) chloride is utilised to prepare 3-aryl-3-alkyl oxindoles, although this method requires rigorously dry conditions (Scheme 129), contrasting with Perry's conditions which works even using laboratory reagent grade DMF.[51]

Scheme 129:



Perry also demonstrated a telescoped base-catalysed saponification/decarboxylation process in order to give access to mono-substituted oxindoles at the 3-position, but unfortunately, this proved not to be a general reaction (Scheme 130).[51]

Scheme 130:



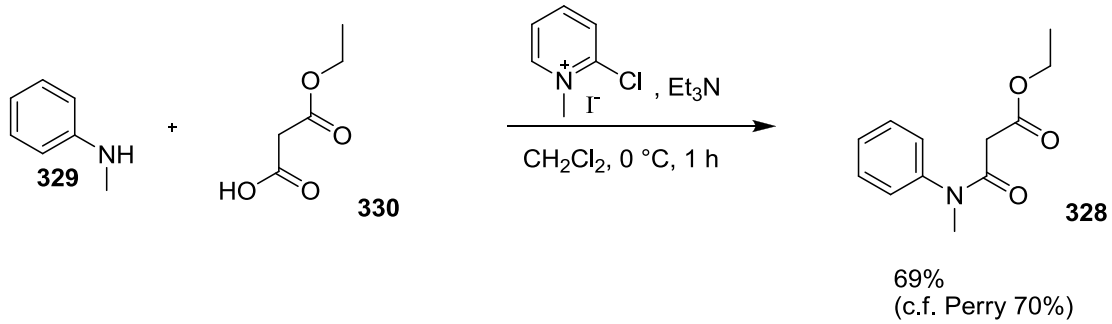
3.3 Proposed methodology

The aim of this project was to design a more general route to 3-alkyl oxindoles, by creating an analogous system in which we envisaged the formation of *tert*-butyl ester which could undergo acid-catalysed decarboxylation.

3.3.1 Ethyl ester oxindoles

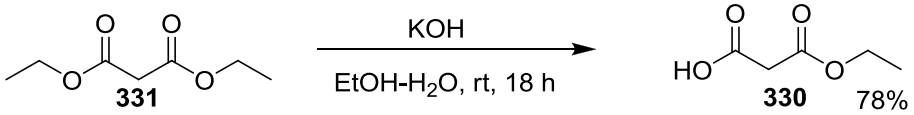
The starting point for this project was to repeat Perry's work (Scheme 128). The ethyl ester anilides are readily formed through the Mukaiyama amide coupling of *N*-methyl anilide **329** and ethyl malonate **330** in the same moderate yield as Perry had found (Scheme 131).

Scheme 131:



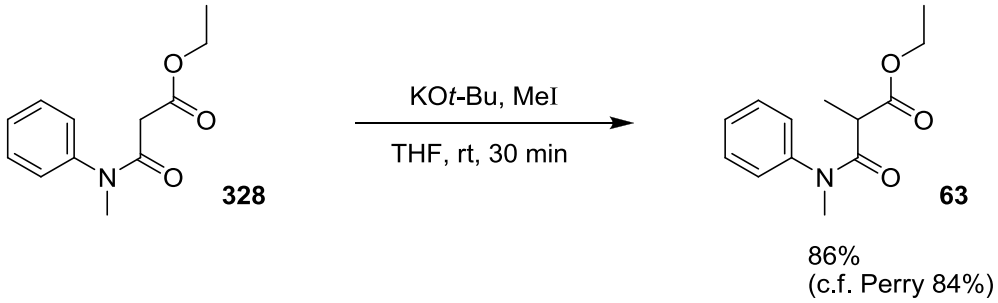
The ethyl malonate **330** was prepared from the facile mono-saponification of diethyl malonate **331** based on the procedure reported by Meijer (Scheme 132).[219]

Scheme 132:



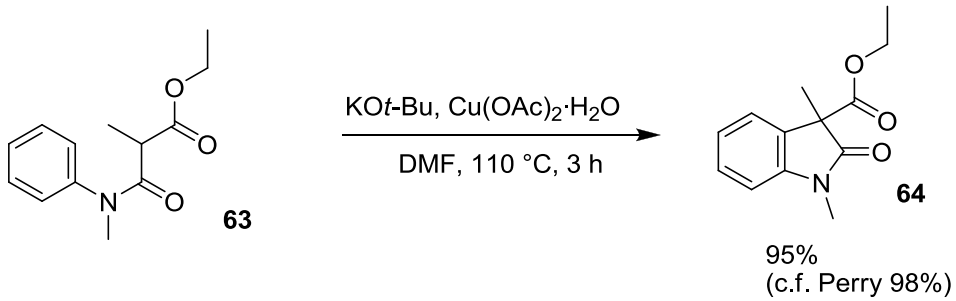
Alkylation with potassium *tert*-butoxide and methyl iodide then gave access to the required substrate **63** for cyclisation (Scheme 133).

Scheme 133:



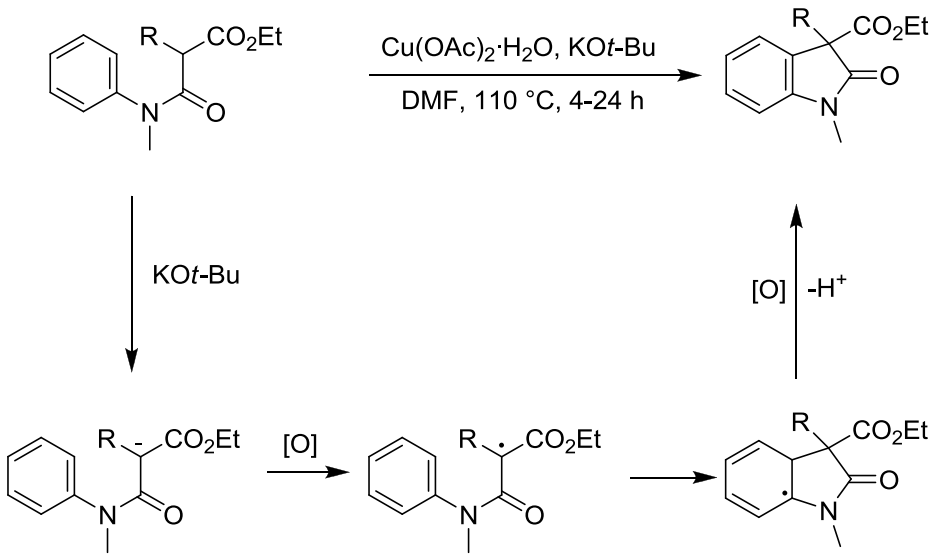
Repeating the cyclisation gave access to the desired oxindole **64** in similar yield to Perry (Scheme 134).

Scheme 134:



Our presumed mechanism for this reaction is outlined in Scheme 135. The first step is formal deprotonation of the anilide, followed by oxidation by the copper to give a radical, which can then undergo cyclisation onto the aryl ring, followed by a second oxidation and loss of a proton.

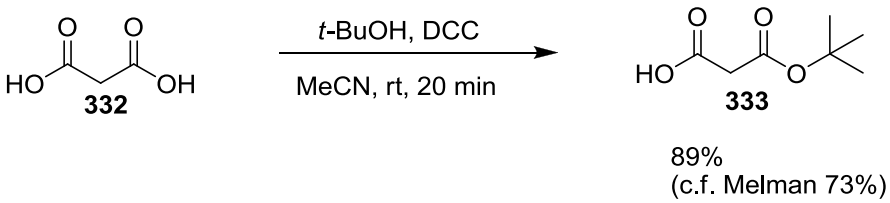
Scheme 135:



3.3.2 *tert*-Butyl ester oxindoles

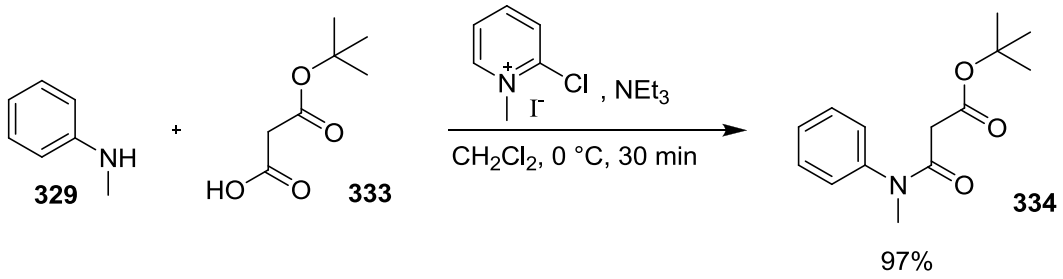
With these results, we then moved on to the analogous route for the preparation of 3-alkyl-3-*tert*-butyl oxindoles. A number of routes to *tert*-butyl malonate **333** are published,[220-222] and repeating the procedure of Melman[223] gave the desired malonate **333** in good yield (Scheme 136).

Scheme 136:



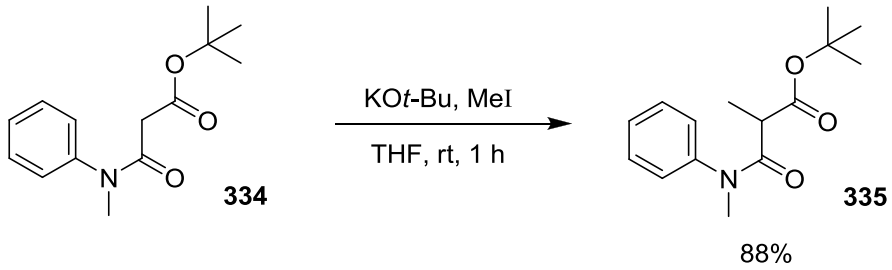
Forming the anilide from *N*-methyl aniline **329** and *tert*-butyl malonate **333** with Mukaiyama's reagent (as for the ethyl anilide preparation), gave the desired anilide **334** in essentially quantitative yield (Scheme 137; a significant increase over the ethyl anilide **328**).

Scheme 137:



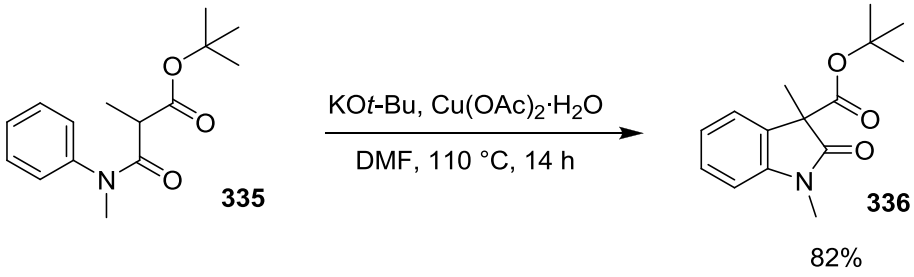
Alkylation with methyl iodide was straightforward, again occurring to give **335** in good yield (Scheme 138).

Scheme 138:



Taking this substrate **335** and exposing it to the original cyclisation conditions, we were delighted to observe the formation of the desired oxindole **336** in 82% yield, albeit with extended reaction times, presumably due to steric effects (Scheme 139).

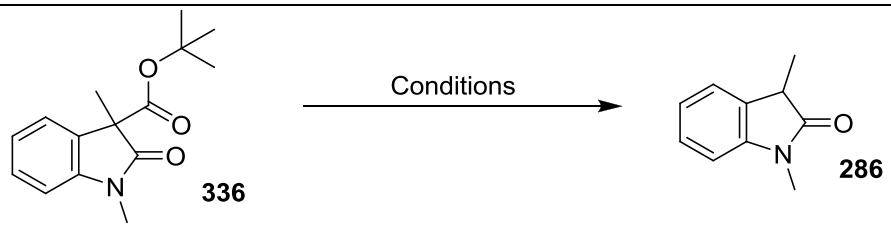
Scheme 139:



3.3.3 Decarboxylation studies

With our test oxindole substrate **336** now in hand, we were able to screen conditions for the dealkylation/decarboxylation:

Table 13: Screening of dealkylation/decarboxylation conditions of **336**.

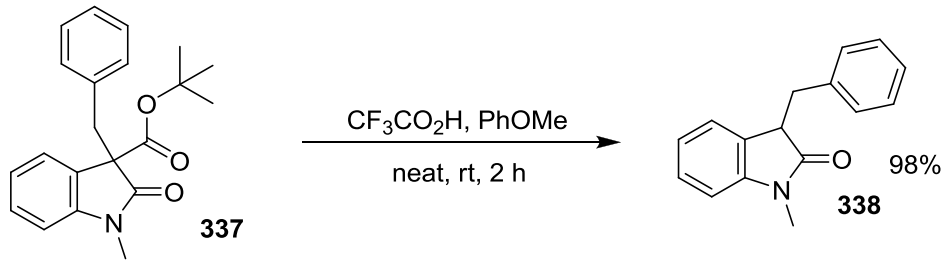


Entry	Conditions		Yield **286**
1	CF_3CO_2H/PhOMe	CH_2Cl_2, rt, 3 days	42%
2	CF_3CO_2H/PhOMe	CH_2Cl_2, reflux, 2 h	68%
3	CF_3CO_2H/PhOMe	CH_2Cl_2, reflux, 20 h	66%
4	**CF_3CO_2H/PhOMe**	**neat, rt, 2 h**	**78%**
5	*p*-TsOH	PhMe, 80 °C, 3 h	59%
6	*p*-TsOH	PhMe, 100 °C, 3 h	56%
7	HCl	EtOAc, rt, 14 h	Acid + **286**

Starting with a 9:1 mixture of CH_2Cl_2 : TFA (in the presence of anisole as a cation trap) (Entry 1) we slowly obtained the desired parent dimethyloxindole **286**, in a low yield (along with degradation products). Increasing the temperature (Entries 2 and 3) offered a modest yield increase and shortened reaction times, but the breakthrough came with the use of neat TFA (Entry 4), which gave the decarboxylated oxindole **286** in 78% after 2 h at rt. The use of *p*-toluenesulfonic acid (Entries 5 and 6) gave only moderate yields and use of HCl in EtOAc (Entry 7), gave only partial conversion to the acid, and did not promote the decarboxylation.

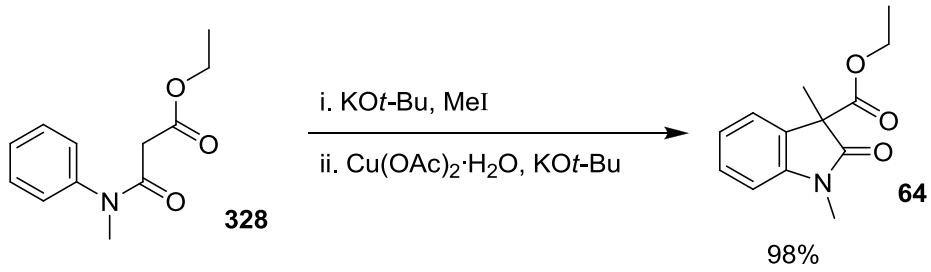
Preparing another substrate **337** to check the decarboxylation conditions, we were able to obtain a near-quantitative yield for the reaction of **338** (Scheme 140), as indicated by the loss of the ester stretch in the infrared spectra; carbonyl loss in the ^{13}C NMR spectra and loss of the 12 H singlet in the proton NMR spectra.

Scheme 140:



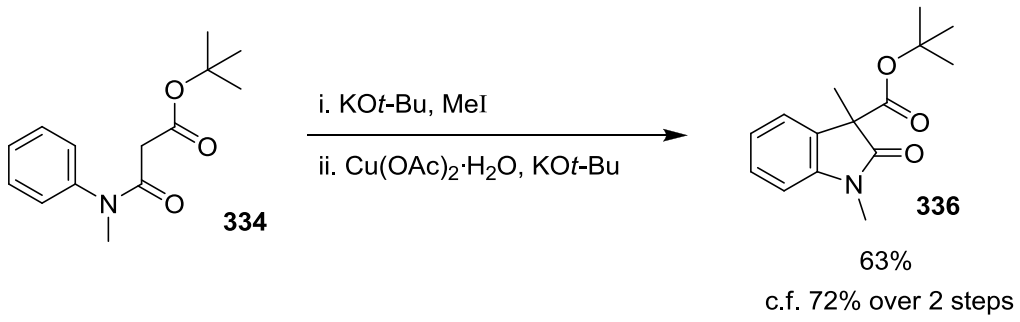
Returning to the cyclisation procedure, Perry had success with a tandem alkylation-cyclisation process, in which the alkylation was carried out in DMF with the copper(II) acetate present, and the reaction heated to 110 °C (Scheme 141).

Scheme 141:



With this in mind, we attempted a similar approach for the preparation of the *tert*-butyl oxindoles, but unfortunately obtained reduced yields (Scheme 142), and so we returned to separate steps.

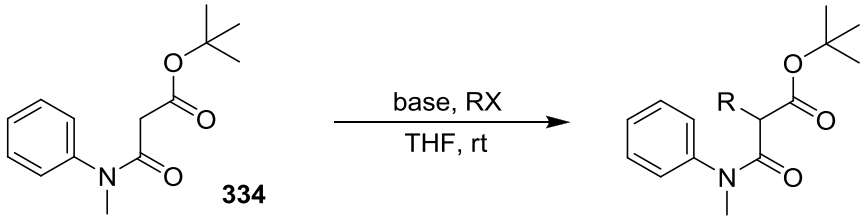
Scheme 142:

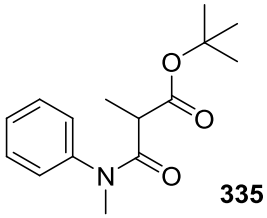
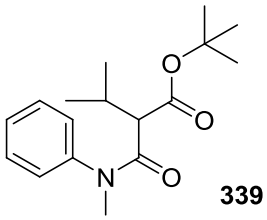
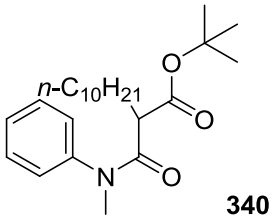
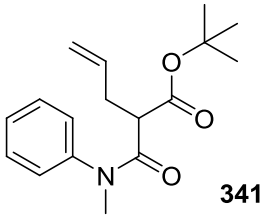
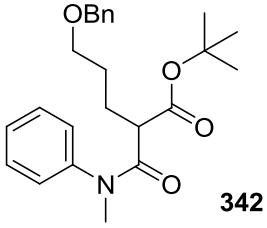


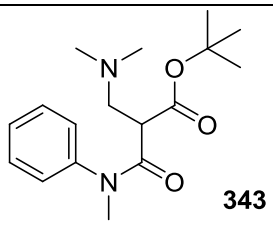
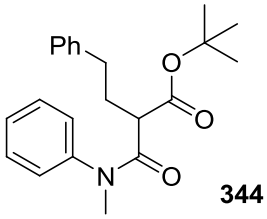
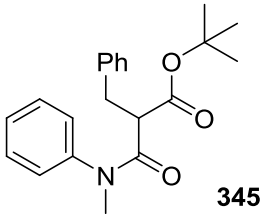
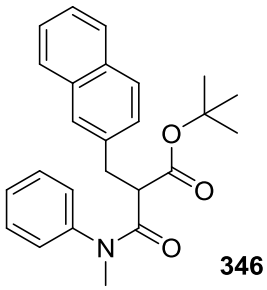
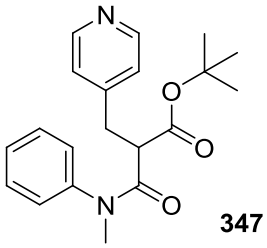
3.3.4 Scope of methodology

At this point we proceeded to examine the scope of the cyclisation-decarboxylation. First a selection of anilides were prepared through alkylation of the parent anilide **334** (Table 14).

Table 14: Alkylation of anilide **334**



Entry	Electrophile	Base	Product	Time (h)	Yield (%)
1	Methyl iodide	KO*t*-Bu	 **335**	1	88
2	2-Bromopropane	NaH	 **339**	72	55[a,b]
3	1-Decyl iodide	KO*t*-Bu	 **340**	24	88
4	Allyl bromide	KO*t*-Bu	 **341**	0.5	89
5	3-Bromopropyl benzyl ether	NaH	 **342**	18	26[a]

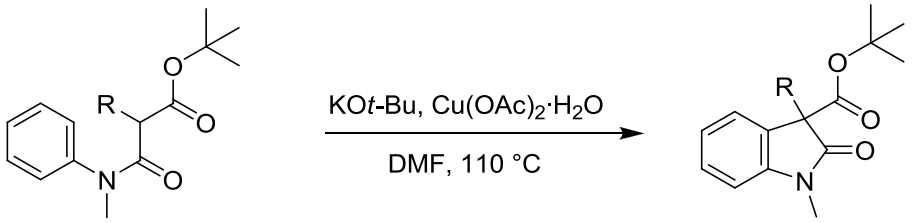
6	Eschenmoser's salt (=$N^+Me_2\ I^-$)	KO*t*-Bu	 **343**	14	40
7	Phenylethyl bromide	NaH	 **344**	14	63
8	Benzyl bromide	KO*t*-Bu	 **345**	0.5	93
9	2-Naphthyl bromide	KO*t*-Bu	 **346**	1	93
10	4-Pyridyl bromide hydrobromide	KO*t*-Bu	 **347**	48	46[c]

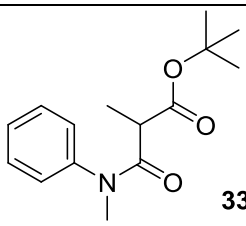
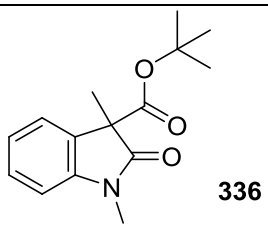
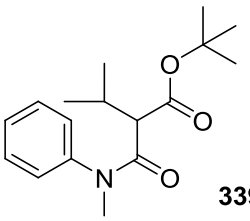
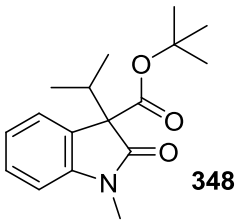
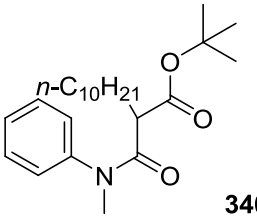
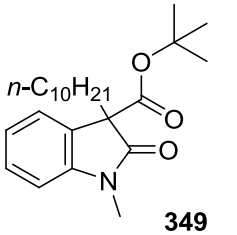
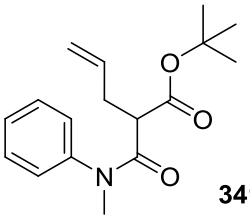
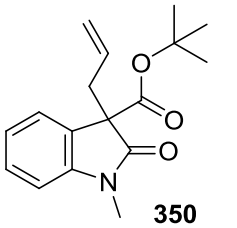
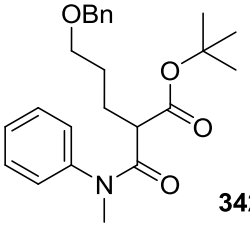
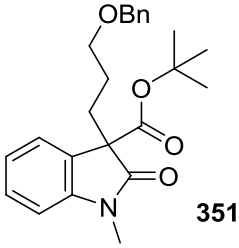
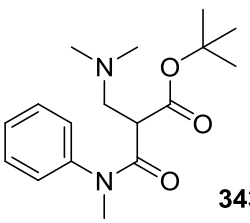
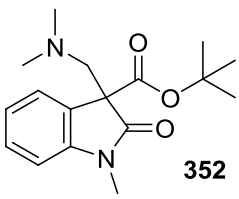
a) TBAI added
b) Reaction heated to reflux.
c) 2.2 eq base used.

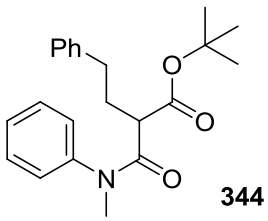
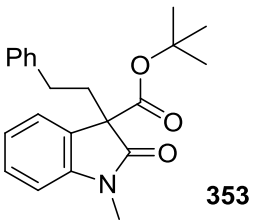
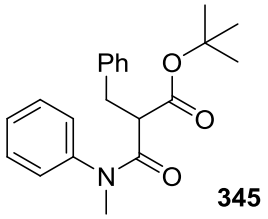
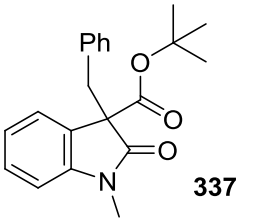
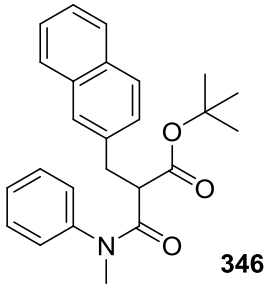
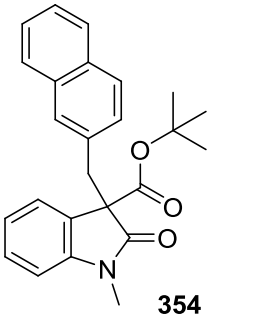
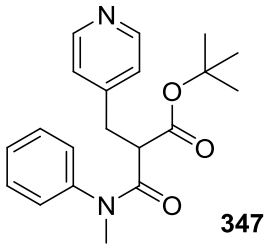
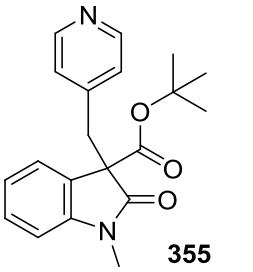
The desired substrates were prepared as shown in Table 14, and these preparations were not optimised, providing enough product could be obtained. Some of the preparations necessitated the use of a stronger base (NaH), TBAI as a catalyst, or heat to push the reactions to completion.

Exposing each substrate **335, 339-347** to the cyclisation conditions gave the results summarised in Table 15.

Table 15: Formation of *tert*-butyl oxindoles

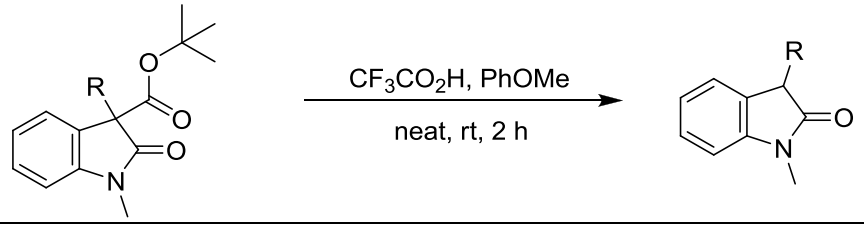


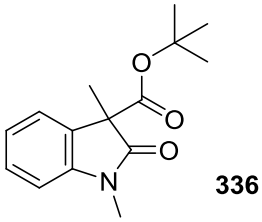
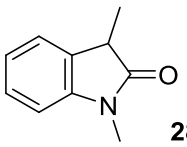
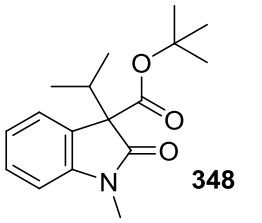
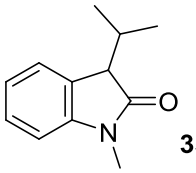
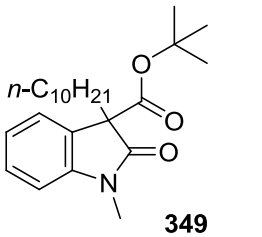
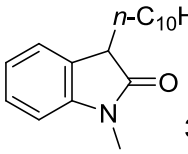
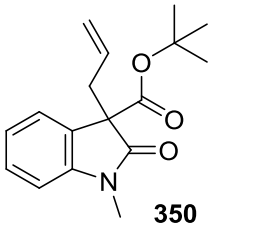
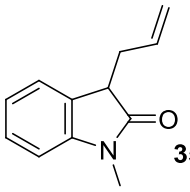
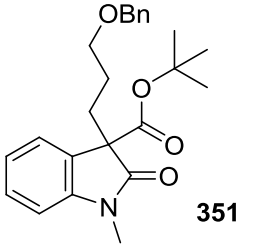
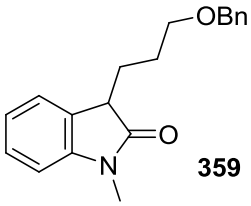
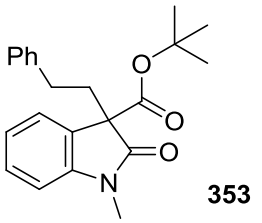
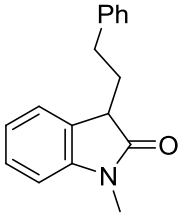
Entry	Starting material	Product	Time (h)	Yield (%)
1	 **335**	 **336**	14	82
2	 **339**	 **348**	72	46
3	 **340**	 **349**	15	76
4	 **341**	 **350**	14	59
5	 **342**	 **351**	18	65
6	 **343**	 **352**	3	0

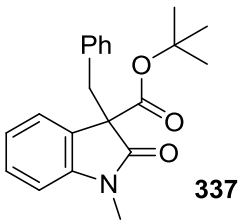
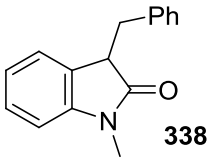
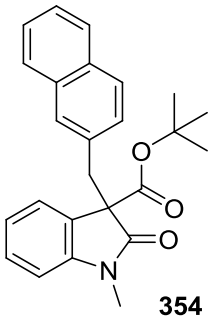
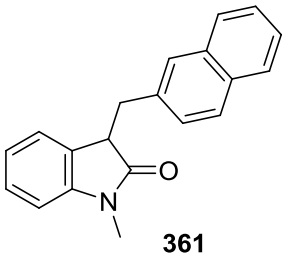
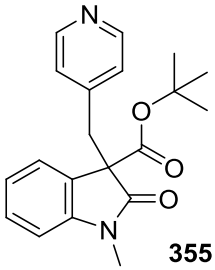
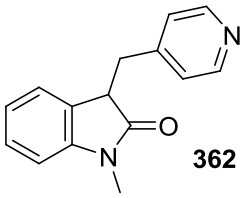
7	 **344**	 **353**	20	71
8	 **345**	 **337**	20	86
9	 **346**	 **354**	18	73
10	 **347**	 **355**	24	68

Use of *iso*-propyl anilide **339** (Entry 2) resulted in a much slower cyclisation in poor yield, presumably due to the steric effect with a secondary group. A long alkyl chain (Entry 3) was successful, as were use of an allyl group (Entry 4) and a benzyl protected alcohol (Entry 5). A tertiary amine substituent however failed to cyclise completely and only resulted in rapid degradation of the starting material (Entry 6). Use of aryl substituents (Entries 8 and 9) worked fine, as did a heterocyclic example (Entry 10). These oxindoles were then subjected to TFA to facilitate dealkylation/decarboxylation (Table 16).

Table 16: Dealkylation/decarboxylation of *tert*-butyloxindoles



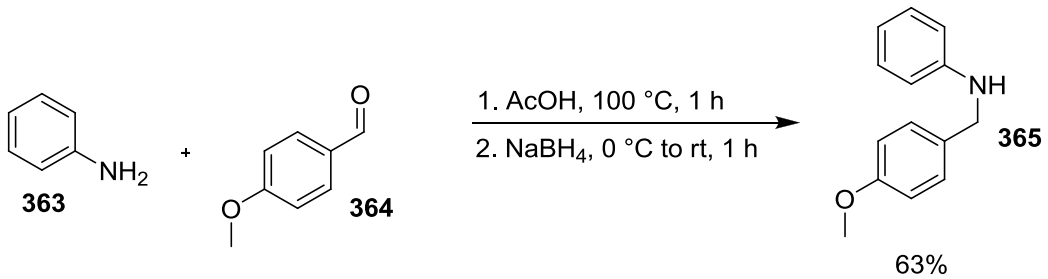
Entry	Product	Yield (%)
1	 **336**  **286**	78
2	 **348**  **356**	68
3	 **349**  **357**	90
4	 **350**  **358**	92
5	 **351**  **359**	86
6	 **353**  **360**	62

7	 **337**	 **338**	98
8	 **354**	 **361**	93
9	 **355**	 **362**	92

3.3.5 Cleavable N protecting groups

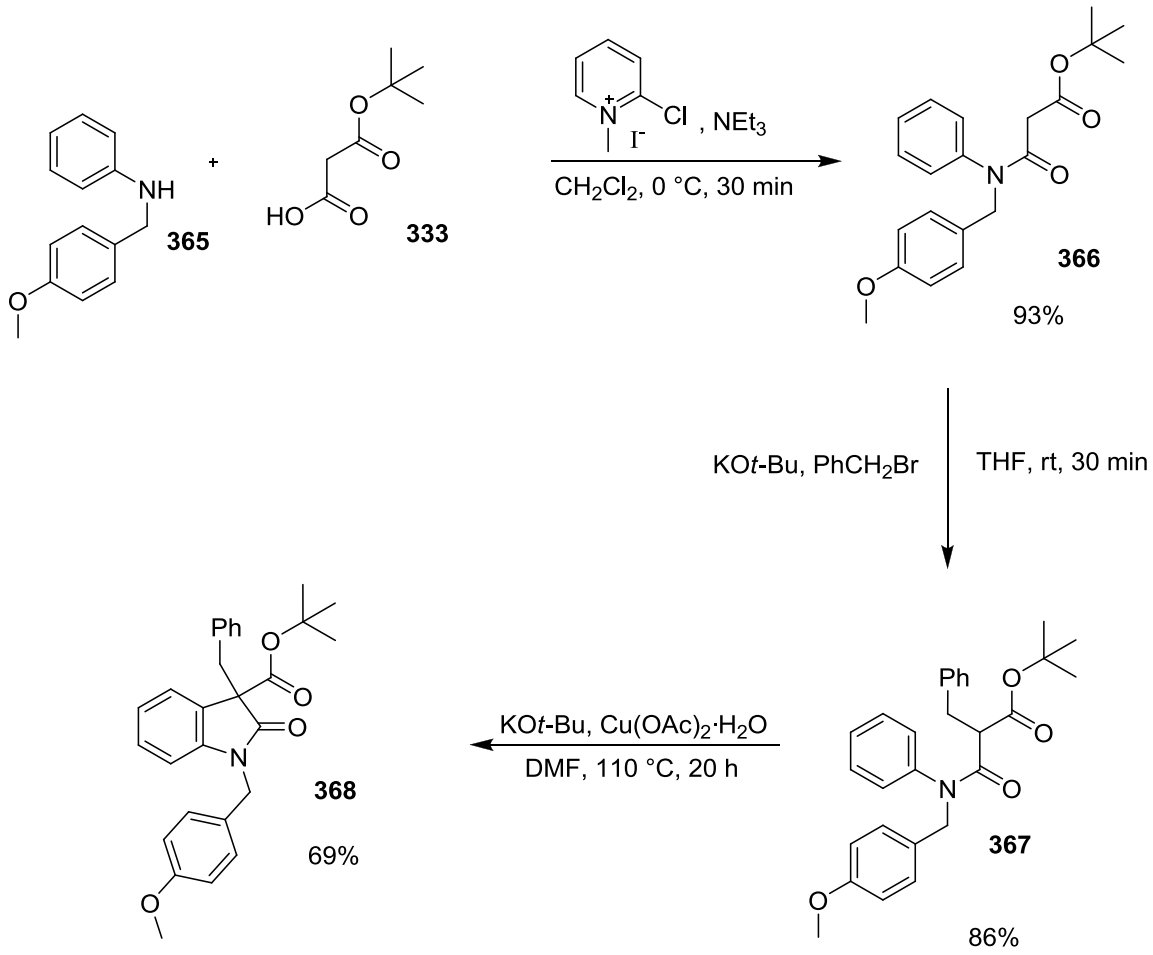
Following this success, we wanted to develop the methodology to prepare substrates with a removable nitrogen protecting group on the oxindole ring. A *para*-methoxybenzyl group was selected due to its acid-labile nature,[224] in order that decarboxylation and deprotection of the nitrogen could be performed in a single step. Aniline **365** was prepared through reductive amination, using the procedure of Abraham[225] (Scheme 143).

Scheme 143:



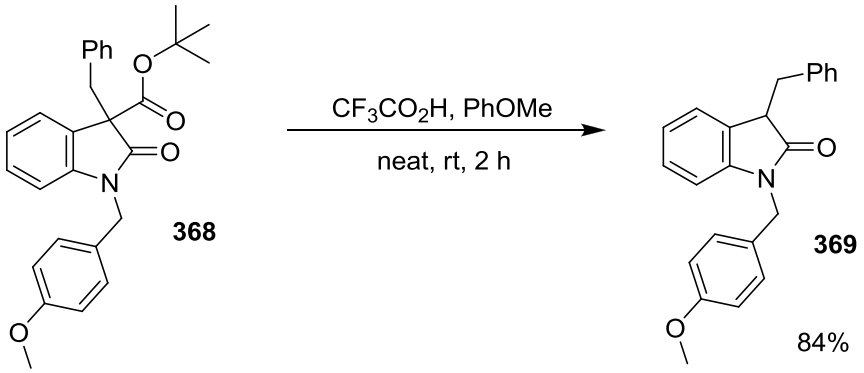
Coupling with *tert*-butyl malonate **333**, and alkylation with benzyl bromide was facile, and cyclisation proceeded in a 69% yield (Scheme 144).

Scheme 144:



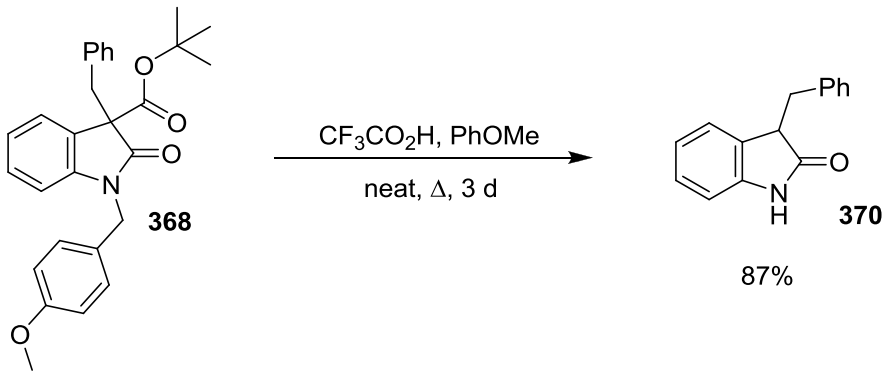
With the protected oxindole **368** in hand, we first attempted dealkylation/decarboxylation, using the conditions previously used and obtained solely the decarboxylated oxindole **369**, with no trace of the *N*-deprotected oxindole **370** (Scheme 145).

Scheme 145:



Repeating the reaction at elevated temperature, leaving the reaction longer to go to completion, resulted in the decarboxylation and deprotection of oxindole **368** (Scheme 146).

Scheme 146:



Attempts to remove the PMB protecting group, leaving the ester intact proved unsuccessful. Despite a number of attempts to oxidatively cleave the PMB group (with CAN or DDQ), only the rapid consumption of starting material was observered and no discernible products were obtained.

3.3.6 Methodology scale-up

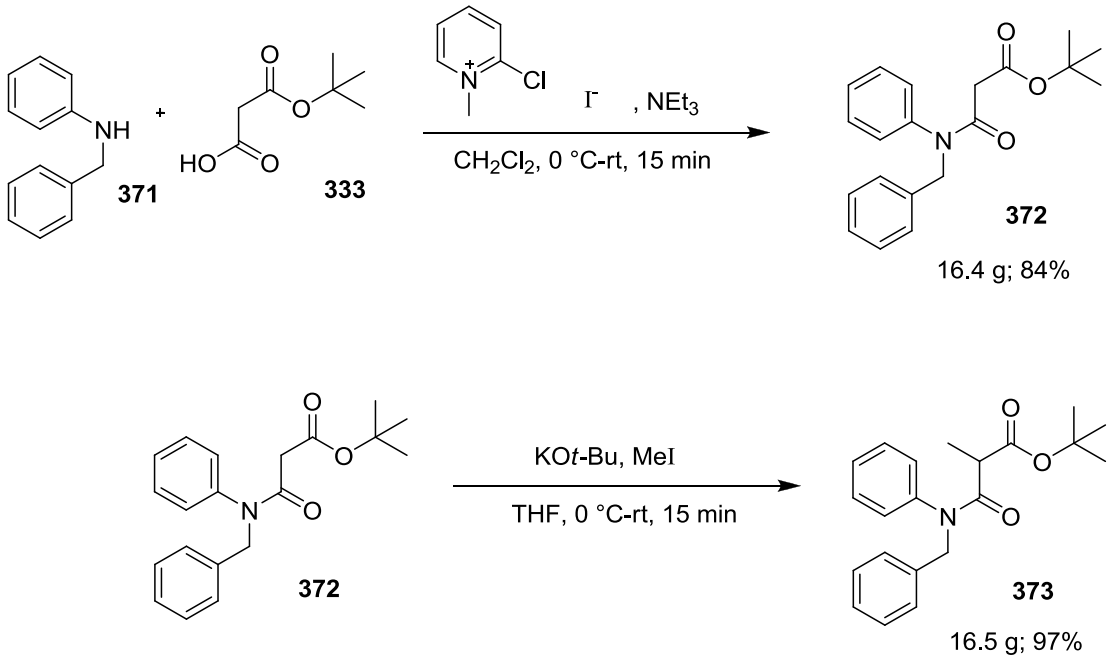
Following the publication of the oxindole formation/decarboxylation chemistry,[226] we considered whether this chemistry might be amenable to multi-gram synthesis.

The initial choice of target for this purpose was the PMB protected oxindole **368**, however it quickly became apparent that the cyclisation failed on a scale above ~5 mmol (earlier work had been on a 1 mmol scale), resulting in a large yield drop, despite consumption of starting material. Other products isolated appeared to indicate reactions occurring with the DMF following cleavage of the amide bond, and bond cleavage around the malonate.

Switching to *N*-methyl oxindole **337** the scale up was repeated. The anilide formation from the Mukaiyama coupling was able to be optimised for a 60 mmol scale (~15 g), although problems were initially encountered in the purification stage. It had been hoped to purify the anilide by distillation, which had been successful on a small scale, however upon increasing the volume to be distilled, decomposition of the product occurred in several of the attempts. Instead chromatography was optimised to use minimal silica and solvent. Benzylation to give **345** could be scaled up without problems (although distillation was also avoided), and the cyclisation step was attempted. This again resulted in problems; scale up was successful in good yield until around the 20 mmol mark, when again decomposition became a significant problem. However, work being carried out on a catalytic cyclisation process by Klein at the same time,[227] indicated that the benzyl substituted substrates were generally problematic. Klein found they were not representative, in that this substrate would not cyclise when most other substrates worked fine (further discussion on the catalytic process can be found later). In light of this, our approach focussed instead on methyl substituted anilide, though with an *N*-benzyl group.

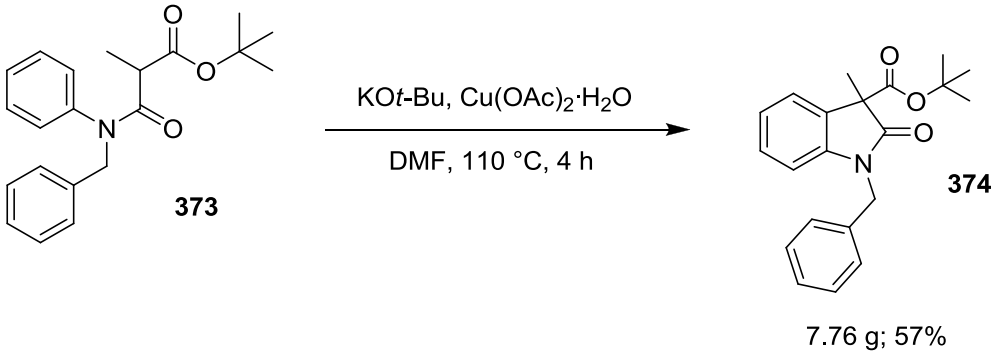
Preparation of the anilide **372** and subsequent alkylation with methyl iodide were straightforward, with the anilide being prepared on a 60 mmol scale and the alkylation on a 50 mmol scale (Scheme 147), utilising the knowledge gained from the previous scale-up procedures to simplify the workup/purification.

Scheme 147:



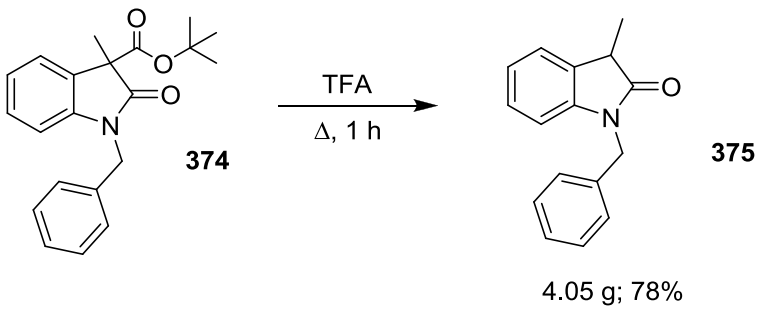
Cyclisation proceeded in moderate yield on a 40 mmol scale, if slightly reduced from those obtained on smaller scale (Scheme 148). On a large scale, removal of DMF becomes a greater challenge (and may contribute to the reduced yield); the work up necessitated the concentration of the DMF initially, rather than just dilution with water. The higher volumes also reduce the amount of air able to get into solution (due to a decrease in the surface area/volume ratio), which had been found to be important (*vide infra*).

Scheme 148:



tert-Butoxydecarboxylation was straightforward, giving the product **375** in a 78% recrystallised yield on a 22 mmol scale (Scheme 149).

Scheme 149:

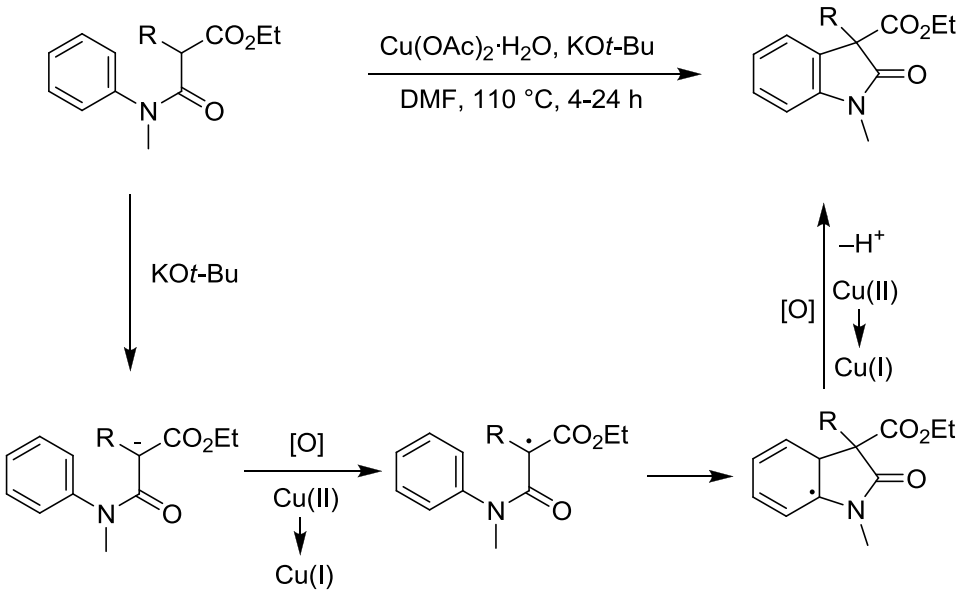


3.3.7 Developments in the cyclisation

This section of work was carried out jointly with Johannes Klein.[227]

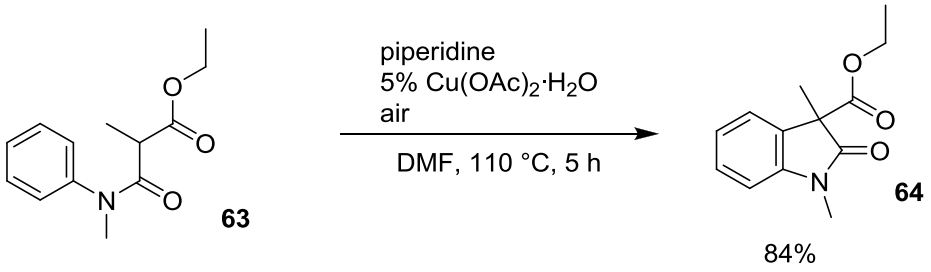
As the scale up work was proceeding, Klein was working on further exploring the copper-mediated cyclisation, producing a catalytic version. We had been aware, that if our mechanism (Scheme 150) was correct, then 2 equivalents of copper would be required. Contrast this with Kündig's work,[218] in which 2.2 equivalents of copper(II) chloride are used under rigorously inert conditions, whereas ours occurs with 1 equivalent under an atmosphere of air, it would seem likely that aerial re-oxidation of the copper(I) is occurring.

Scheme 150:



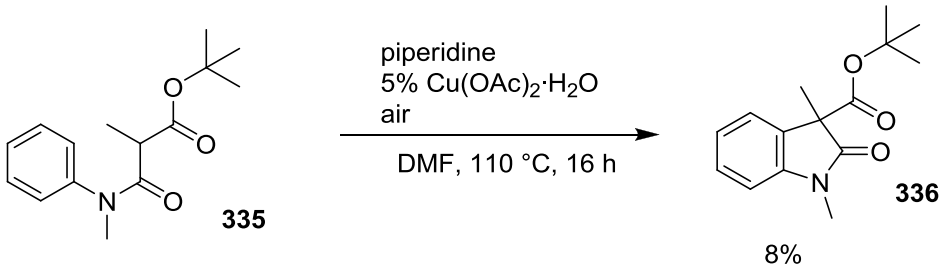
Klein found that copper loading could be reduced to 5% and KO*t*-Bu replaced by a large excess of piperidine (10 equivalents), to give an 84% yield (Scheme 151).

Scheme 151:



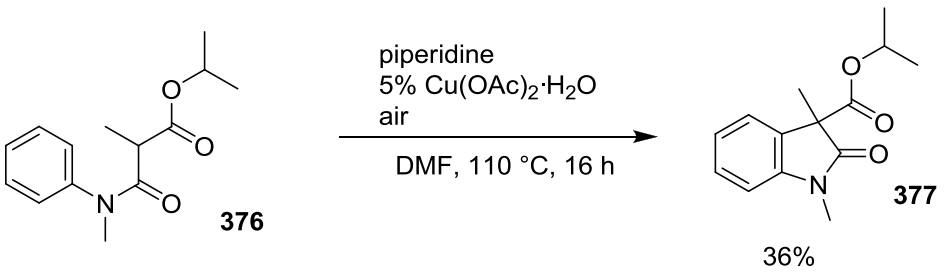
However, when testing Klein's conditions on the *tert*-butyl system only very low yields were obtained. For example, only 8% of oxindole **336** was obtained along with 48% starting material (Scheme 152). The same was also true when using benzyl substituents on the ethyl system.

Scheme 152:



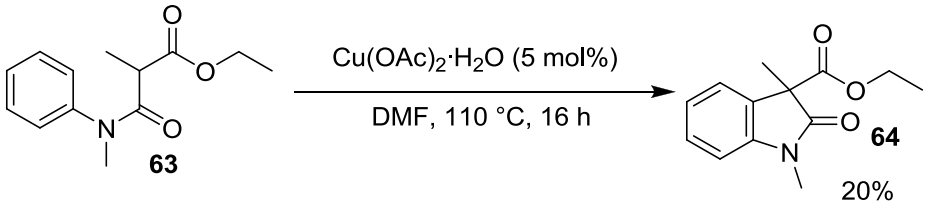
Preparing *iso*-propyl ester substrate **376**, and exposing to the reaction conditions gave a similar yield reduction of oxindole **377**, confirming that steric hindrance was a likely cause for the reduced yields (Scheme 153).

Scheme 153:



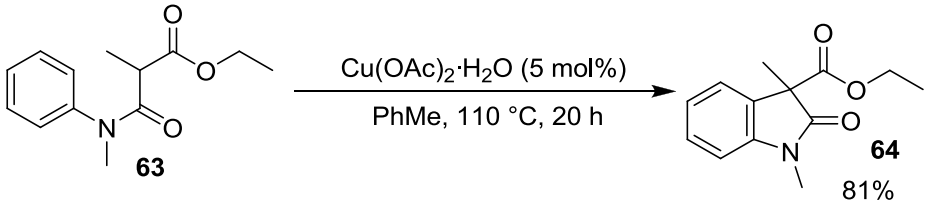
The major breakthrough came when carrying out a control reaction in the absence of base, after 16 h a 20% yield of **64** was obtained (Scheme 154).

Scheme 154:



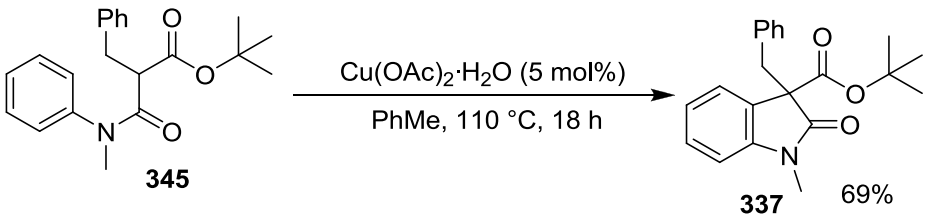
With DMF as the solvent at high temperatures, we were concerned that there may still be base present in the form of dimethylamine from the decomposition of DMF,[228] and so a second control reaction was carried out using toluene as the solvent (Scheme 155). With this unexpected result, Klein screened a variety of copper salts, but none were superior to copper(II) acetate.

Scheme 155:



Testing this system on the *tert*-butyl anilides, and selecting a benzyl substituent (anilide **345**), we were delighted to observe a 69% yield of **337** after 18 h (Scheme 156).

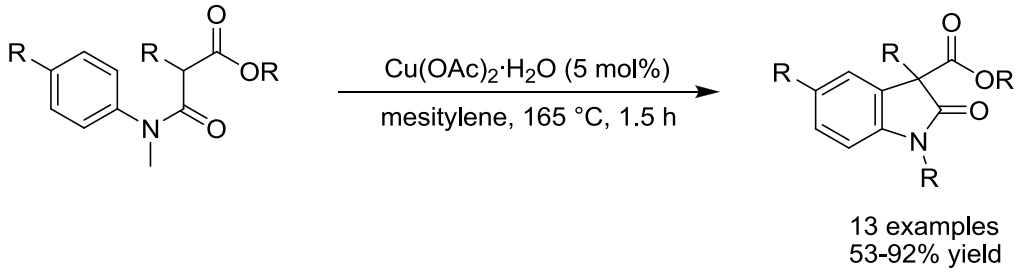
Scheme 156:



Klein continued to further optimise the conditions through the use of mesitylene as the reaction solvent, enabling higher reaction temperatures and shorter

reaction times. Using these conditions a range of substrates were examined, and the full results are published in Organic Letters (Scheme 157).[227]

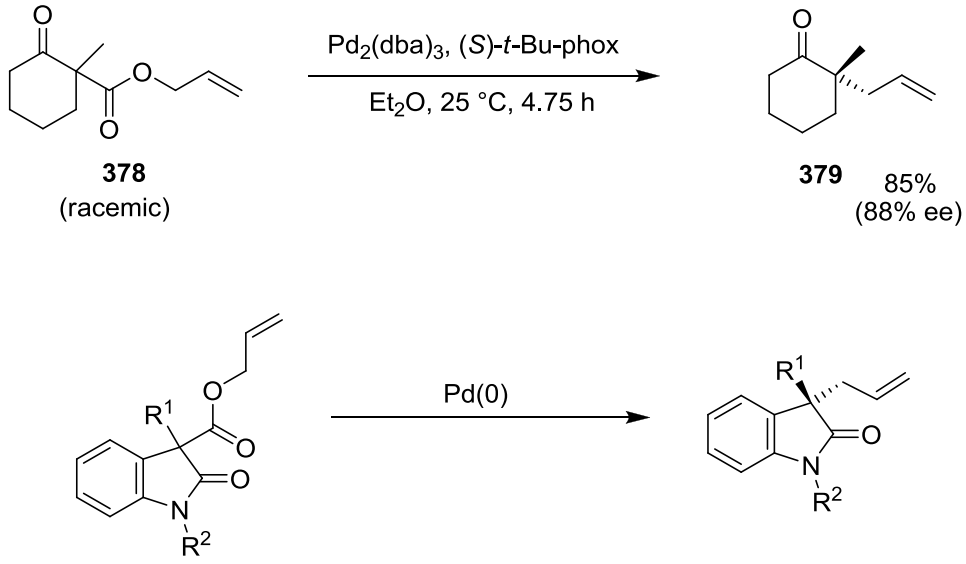
Scheme 157:



3.3.8 Preparation of 3-allyl-3-alkyl oxindoles

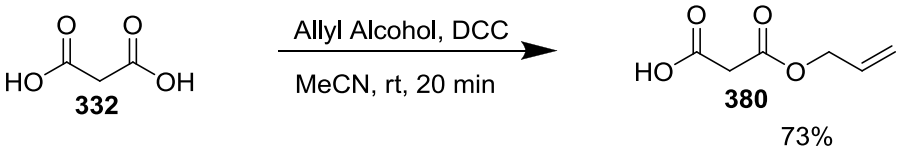
During the work on the *tert*-butyl ester oxindoles, an idea was conceived to examine the potential cyclisation of allyl esters with a view towards applying decarboxylative allylation[229] and the construction of a doubly substituted quaternary centre, in a similar method to that of Stoltz (Scheme 158).[230]

Scheme 158:



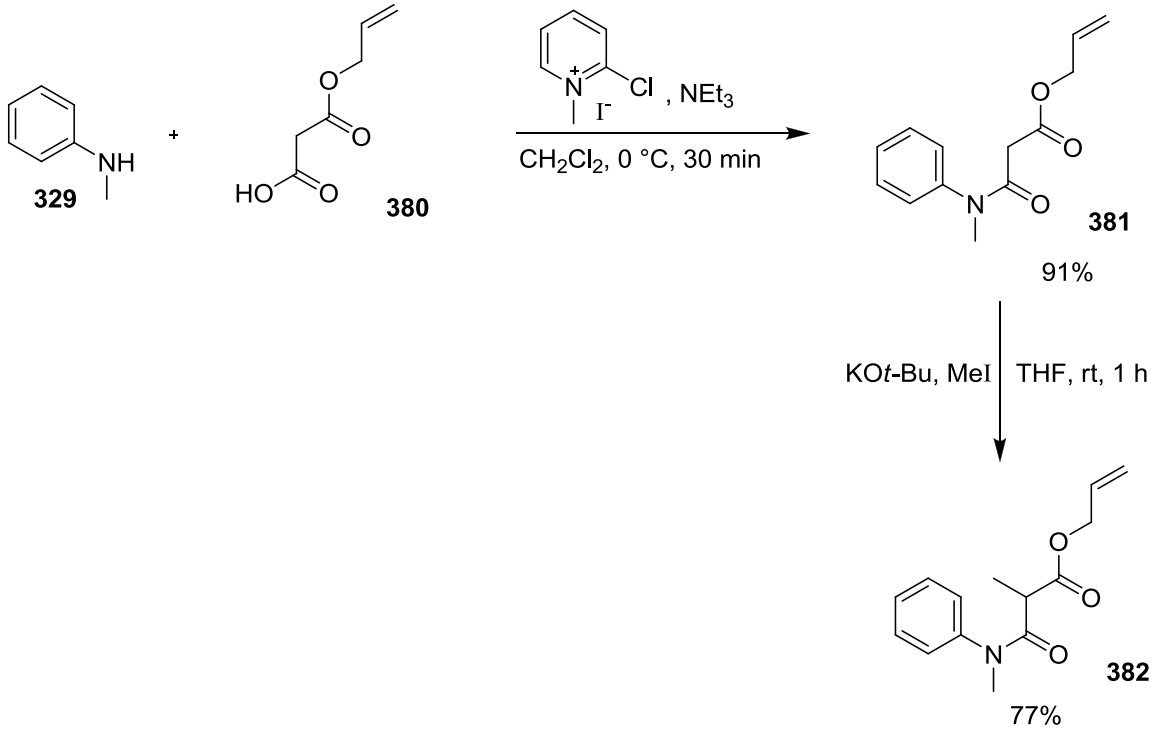
There are a few methods reported for the preparation of allyl malonate,[231] but we opted to adapt the method of Melman[223] which gave us access to allyl malonate **380** in 73% yield (Scheme 159).

Scheme 159:



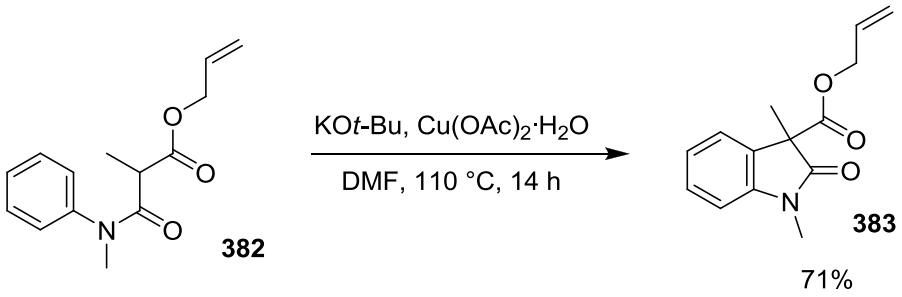
Preparation of the anilide and alkylation were trouble-free, giving a 91% yield of **381** from the Mukaiyama coupling and a 77% yield of **382** for methylation (Scheme 160).

Scheme 160:



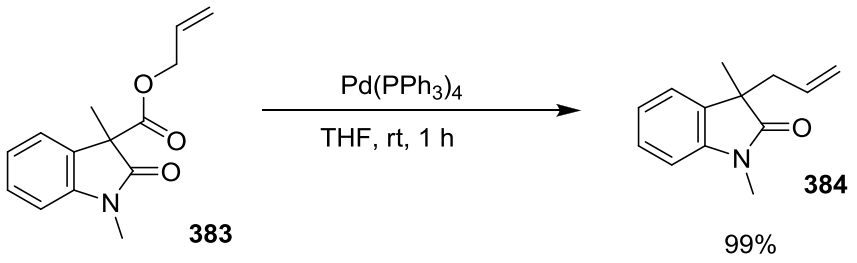
The key cyclisation occurred in 14 h under the original conditions to give a respectable 71% yield of oxindole **383**, a yield in line with those observed for the *tert*-butyl ester oxindoles (Scheme 161).

Scheme 161:



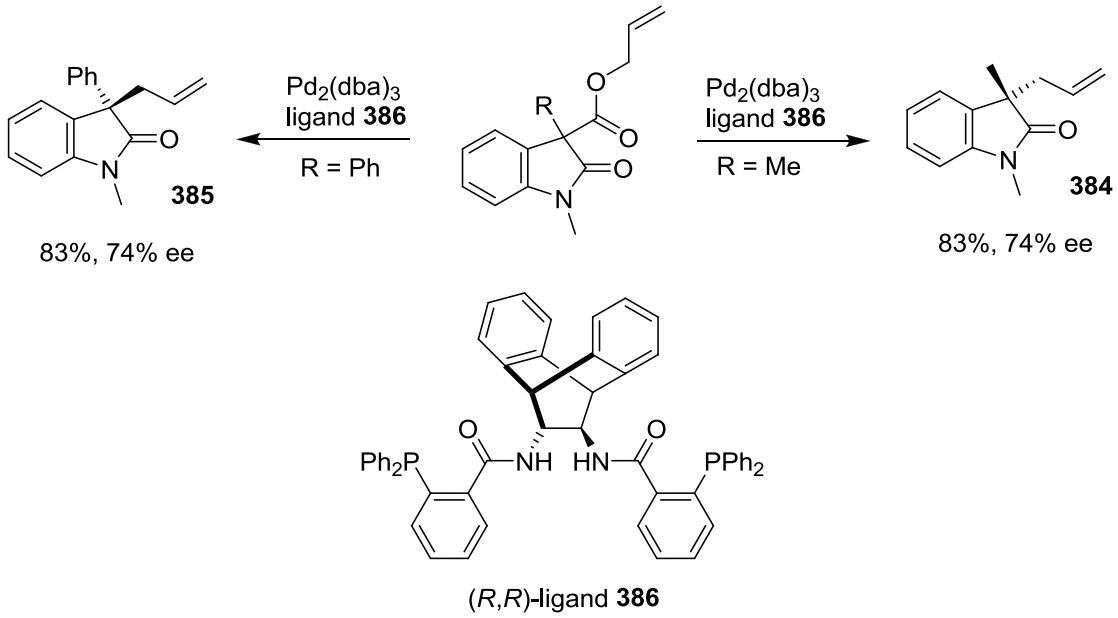
The first decarboxyallylation conditions we attempted (2% palladium tetrakistriphenylphosphine in THF), gave almost immediate conversion, and after workup we were delighted to obtain a quantitative yield of the desired all-carbon quaternary oxindole **384** (Scheme 162), clearly identifiable from the loss of the ester stretch at 1743 cm^{-1} in the IR spectrum.

Scheme 162:



This project was continued by Franckevicius, who went on to develop an asymmetric variant. Using the Trost ligand **386**, Franckevicius found that the selectivity depends on the size of the 3-substituent (Scheme 163).

Scheme 163:



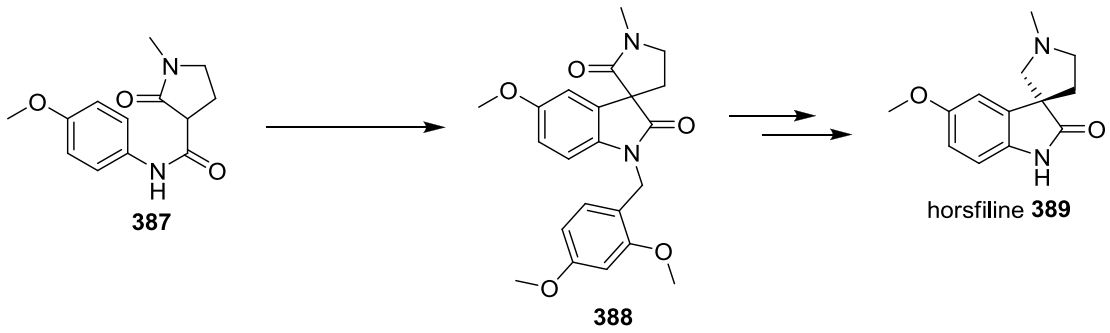
This work has now been published in Organic Letters.[232]

3.4 Summary and future work

A facile route to 3-substituted oxindoles using a copper-mediated anilide cyclisation and acid-catalysed dealkylation/decarboxylation scheme has been demonstrated. A catalytic variant has been developed jointly with Klein, and initial work towards a decarboxylative-allylation procedure are reported.

Having devised the basic methodology, future work in this area could involve the total synthesis of natural product targets. Particular targets of interest could be those containing a spirocyclic oxindole motif, which could be envisaged from an anilide incorporating a cyclic electron-withdrawing group, for example preparing the amide intermediate **388** used in Trost's synthesis of horsfiline **389** (Scheme 164).[233]

Scheme 164:



Chapter 4: Experimental

4.1 General experiments

All reagents were purchased from commercial sources and were used as supplied or prepared by methods detailed in the experimental. Petrol refers to light petroleum; bp 40-60 ^{o}C. Flash column chromatography was performed using Fluka silica gel 60 at a low positive pressure. Analytical thin layer chromatography was performed on aluminium sheets pre-coated with Merck silica gel 60 F_{254}, and visualised with ultraviolet light (254 nm), alcoholic *p*-anisaldehyde, aqueous potassium permanganate, aqueous phosphomolybdic acid or alcoholic vanillin solutions, as appropriate. Where necessary, diethyl ether, THF, CH_2Cl_2, DMF, MeCN and toluene were dried on an Innovative Technology Inc. PureSolv® Purification System. All melting points were taken on a Gallenkamp melting point apparatus. Proton magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz on a JEOL ECX400 or ECS400 spectrometer and are reported as follows: chemical shift δ (ppm) (number of protons, multiplicity, coupling constant J (Hz), assignment). The coupling constants are quoted to the nearest 0.5 Hz (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad) and are reported as measured splittings on each individual resonance. The residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) or acetone (δ_H = 2.05 ppm) was used as an internal reference. ^{13}C spectra were recorded at 100 MHz on a JEOL ECX400 spectrometer or at 125 MHz on a Bruker AV500 spectrometer. The central reference of $CDCl_3$ (δ_C = 77.0 ppm) or acetone (δ_C = 29.8 ppm) was used as an internal reference. ^{19}F spectra were recorded at 376 MHz on a JEOL ECX400 spectrometer or at 254 MHz on a JEOL EX270 spectrometer. ^{11}B spectra were recorded at 87 MHz on a JEOL EX270 spectrometer. Chemical shifts are reported in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H, or to 0.1 ppm for ^{13}C, ^{19}F and ^{11}B. ^{13}C spectra were verified using DEPT and where necessary HSQC experiments. ^{1}H spectra were verified where necessary using COSY experiments. Infrared spectra were recorded on a ThermoNicolet IR100 spectrometer as neat oils between NaCl disks. Absorption maxima are reported in wavenumbers (cm^{-1}) and only selected absorbencies are reported. Electrospray ionisation (ESI) mass spectra were recorded on a Bruker MicrOTOF spectrometer. Chemical Ionisation (CI) and

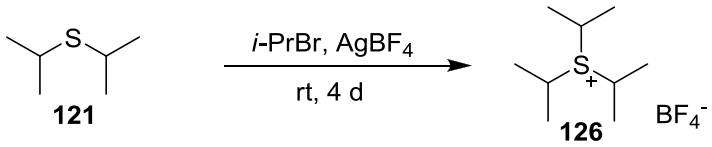
Electron Ionisation (EI) mass spectra were recorded on a Waters GCT Premier MS. Elemental analysis was conducted at the University of York on an Exeter Analytical CE-440 Elemental Analyser with samples weighed using a Sartorius SE2 analytical balance. All known products were characterised by NMR spectroscopy and comparison of key data with those published; novel products were fully characterised unless sufficient material was not available and/or decomposition had occurred. Where numbering is used to assign data to structures this is to aid assignment and it does not follow IUPAC numbering conventions.

4.2 Preparation of *gem*-dimethylcyclopropanes

4.2.1 Preparation of sulfoxonium salts

Tri*iso*propylsulfonium tetrafluoroborate 126

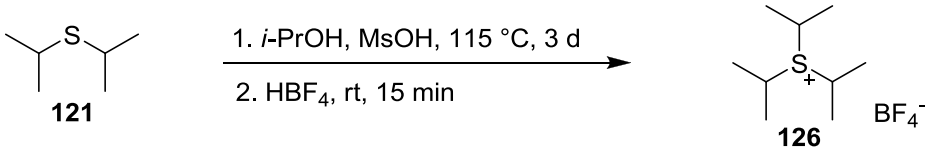
Initial approach:



A 250 mL pear-shaped flask with a stir bar, was charged with di*iso*propyl sulfide **121** (12.7 g, 107 mmol, 2.0 equiv), 2-bromopropane (26.3 g, 214 mmol, 4.0 equiv) and cooled to 0 °C (ice-bath). The mixture was stirred vigorously and silver tetrafluoroborate (10.4 g, 53.5 mmol, 1.0 equiv) added in small portions. On complete addition the flask was fitted with a rubber septum and balloon of argon, the ice-bath removed, and the reaction allowed to warm to room temperature with continuous stirring. After 4 days the mixture was passed through a celite topped column (SiO_2, 60 g, 50 mm Ø) and eluted with acetone (1 L) to give a cloudy white filtrate which was concentrated *in vacuo*, washed with diethyl ether (50 mL) and re-concentrated *in vacuo*. This green/brown tacky solid was suspended in diethyl ether (100 mL) and filtered, collecting and rewashing the solid with portions of diethyl ether (3 × 50 mL) to give a silver coloured precipitate. The residue was left to stand overnight in the light, before being suspended in hot methanol (100 mL), filtered through a pad of celite to remove residual silver and washed with further portions of methanol (150 mL).

Concentration *in vacuo* afforded a crude yellow/brown solid which was recrystallised from methanol/diethyl ether. The crude solid was dissolved in hot methanol (*ca.* 10 mL) and diethyl ether added dropwise with swirling until the mixture remained turbid. The mixture heated to redissolve the solid and then slowly cooled to 0 °C. The solid was collected *via* filtration, washed with diethyl ether (50 mL) and dried *in vacuo* to give 7.08 g (28.6 mmol, 53%) of **126** as cream coloured plates.

Improved procedure:



A 250 mL round-bottomed flask with a stir bar, was charged with di*iso*propyl sulfide **121** (7.3 mL, 5.91 g, 50.0 mmol, 1.0 equiv), *iso*-propanol (15 mL, 12.0 g, 200 mmol, 4.0 equiv) and methanesulfonic acid (32 mL, 48.1 g, 500 mmol, 10.0 equiv). A condenser was fitted and the mixture heated to 115 °C (oil-bath temperature) for 3 days (solution goes brown over 1 h, and effervesces). After this time the brown solution was cooled to room temperature, and 48% tetrafluoroboric acid in water (31 mL, 43.9 g, 500 mmol, 10.0 equiv) was added and the mixture stirred at room temperature for 15 min, then the mixture was transferred to a separating funnel with water (150 mL) and dichloromethane (150 mL). The layers were separated and the aqueous extracted with further portions of dichloromethane (2 × 150 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange solid. The crude compound was suspended in diethyl ether (100 mL) and filtered, collecting and washing the solid with portions of diethyl ether (2 × 50 mL) to give a colourless precipitate, which was recrystallised from methanol/diethyl ether.

The crude solid was dissolved in hot methanol (*ca.* 10 mL) and diethyl ether added dropwise with swirling until the mixture remained turbid (ca 15 mL). The mixture was heated to redissolve the solid and then slowly cooled to 0 °C The solid was collected *via* filtration, washed with diethyl ether (50 mL) and dried *in vacuo* to give 8.51 g (34.3 mmol, 69 %) of **126** as colourless plates.

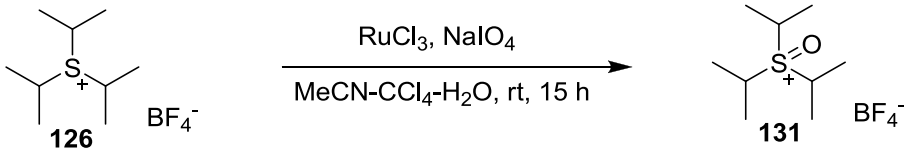
mp 167-170 °C (lit.[126] 194-195 °C); ν_{max}(film)/cm^{-1} 2972, 1464, 1338, 1259, 1163, 1046; δ_H(400 MHz; acetone-*d*$_6$) 1.66 (18 H, d, *J* 7.0 Hz, C*H*$_3$), 4.14, (3 H, septet, *J* 7.0 Hz, C*H*); δ_H(400 MHz; water-*d*$_2$) 1.55 (18 H, d, *J* 7.0 Hz, C*H*$_3$), 3.89, (3 H, septet, *J* 7.0 Hz, C*H*); δ_C(100 MHz; acetone-*d*$_6$) 20.8 (*C*H$_3$), 44.4 (*C*H); δ_B(87 MHz; acetone-*d*$_6$) -1.8; δ_F(376 MHz; acetone-*d*$_6$) -151.8; *m/z* (ESI) 161 ([$C_9H_{21}S$]$^+$), [HRMS (ESI): calcd. for $C_9H_{21}S$, 161.1358. Found: [$C_9H_{21}S$]$^+$, 161.1362 (2.1 ppm error)] [Found C, 43.27; H, 8.39. $C_9H_{21}BF_4S$ requires C, 43.56; H, 8.53%].

Obtained data in accordance with previously reported data.[129]

(DSP-II-11) (DSP-VII-23)

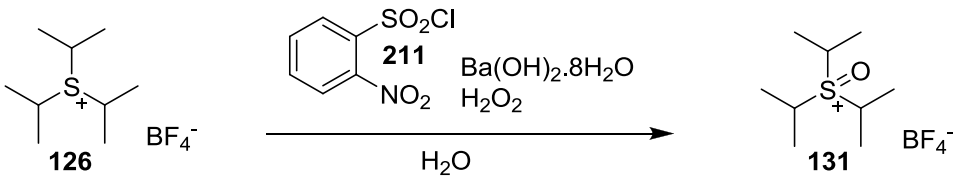
Tri*iso*propylsulfoxonium tetrafluoroborate 131

Initial approach:



A 250 mL pear-shaped flask with a stir bar, was charged with tri*iso*propyl sulfonium tetrafluoroborate **126** (6.20 g, 25.0 mmol, 1.0 equiv), acetonitrile (36 mL), carbon tetrachloride (36 mL) and water (54 mL). Ruthenium trichloride (2.07 g, 10.0 mmol, 0.4 equiv) was added and the mixture stirred for 10 min before the cautious addition of sodium periodate (40.1 g, 188 mmol, 7.5 equiv). The flask was loosely stoppered with a cork and stirred overnight (14 h). The grey/brown heterogeneous suspension was filtered through a celite pad, washed with water (400 mL) to give an orange filtrate. Methanol (50 mL) was added carefully to quench the residual RuO_4 and the mixture stirred for 5 min. The green suspension was concentrated *in vacuo* before being re-dissolved in acetone (400 mL) and stirred for 10 min. The suspension was filtered to remove inorganic solids and concentrated *in vacuo* to afford an orange powder which was recrystallised from methanol/diethyl ether. The crude solid was dissolved in hot methanol (*ca.* 10 mL) and diethyl ether added dropwise with swirling until the mixture remained turbid. The mixture was heated to redissolve the solid and then slowly cooled to 0 °C. The solid was collected *via* filtration, washed with diethyl ether (50 mL) and dried *in vacuo* to give 5.23 g (19.8 mmol, 79%) of **131** as colourless plates.

Improved procedure:

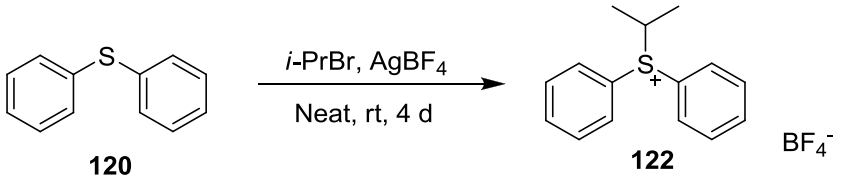


A 1 L two neck flask with a stir bar and thermometer, was charged with tri*iso*propyl sulfonium tetrafluoroborate **126** (4.96 g, 20.0 mmol, 1.0 equiv) and water (400 mL). The solution was placed in an ice-water bath and cooled to 0 °C. 2-Nitrobenzenesulfonyl chloride **211** (8.86 g, 40.00 mmol, 2.0 equiv) was added

followed by barium hydroxide octahydrate (18.9 g, 60.0 mmol, 3.0 equiv) to give a cream suspension. Hydrogen peroxide (30% *w/w*, 12.3 mL, 13.6 g, 120 mmol, 6.0 equiv) was then added dropwise over 1 h. On complete addition the suspension was stirred for a further h at 0 °C, then the ice bath removed and the reaction stirred overnight. After 18 h the cream suspension was filtered though a Celite pad (90 × 25 mm) washing with water (200 mL). The yellow aqueous solution was concentrated *in vacuo* to afford a yellow powder which was suspended in dichloromethane (100 mL), dried ($MgSO_4$), and filtered through a Celite pad (90 × 25 mm) washing with further portions of dichloromethane (3 × 50 mL). The colourless filtrate was concentrated *in vacuo* to give a colourless precipitate. This precipitate was dissolved in acetone (100 mL) and poured onto a silica column (50 g, 40 mm Ø) and eluted into a round-bottomed flask with acetone (500 mL). This filtrate was concentrated *in vacuo* to give a colourless solid which was recrystallised from methanol/diethyl ether. The crude solid was dissolved in the minimum amount of hot methanol (*ca.* 5 mL) and diethyl ether (*ca.* 5 mL) added dropwise with swirling until the mixture remained turbid. The suspension was heated to redissolve the solid and then slowly cooled to room temperature. The crystals were collected *via* filtration, washed with diethyl ether (50 mL) and dried *in vacuo* to give 3.12 g (11.8 mmol, 59 %) of **131** as colourless plates.

mp 114-116 °C; ν_{max}(film)/cm^{-1} 2977, 2924, 1462, 1198, 1166, 1047; δ_H(400 MHz; acetone-d_6) 1.71 (18 H, d, *J* 7.0 Hz, CH_3), 4.65 (3 H, septet, *J* 7.0 Hz, C*H*); δ_H(400 MHz; water-d_2) 1.62 (18 H, d, *J* 7.0 Hz, CH_3), 4.44 (3 H, septet, *J* 7.0 Hz, C*H*); δ_C(100 MHz; acetone-d_6) 15.7 (*C*H_3), 53.0 (*C*H); δ_B(87 MHz; acetone-d_6) -1.8; δ_F(376 MHz; acetone-d_6) -151.6; *m/z* (ESI) 177 ($[C_9H_{21}OS]^+$), [HRMS (ESI): calculated for $C_9H_{21}OS$, 177.1308; found $[C_9H_{21}OS]^+$, 177.1306 (0.6 ppm error)] [Found C, 40.93; H, 8.01. $C_9H_{21}BF_4OS$ requires C, 40.93; H, 8.01%].
Obtained data in accordance with previously reported data.[129]
(DSP-II-14) (DSP-VIII-7)

Diphenyl*iso*propylsulfonium tetrafluoroborate 122



120 **122**

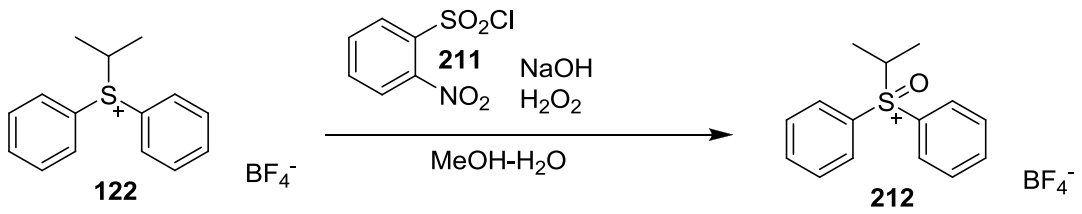
A 50 mL round-bottomed flask with a stir bar, was charged with diphenyl sulfide **120** (14.0 g, 75.0 mmol, 5.0 equiv), 2-bromopropane (2.95 g, 24.0 mmol, 1.6 equiv) and cooled to 0 °C (ice-bath). The mixture was stirred vigorously and silver tetrafluoroborate (2.92 g, 15.0 mmol, 1.0 equiv) added in small portions. On complete addition the flask was fitted with a rubber septum and balloon of argon, the ice-bath removed, and the reaction allowed to warm to room temperature with continuous stirring. After 3 days the mixture was poured onto a silica column (20 g, 20 mm Ø) topped with celite and washed with diethyl ether (100 mL) which was discarded. The salt was eluted with acetone (250 mL) to give a cloudy filtrate which was concentrated *in vacuo* to give a colourless oil. Diethyl ether (20 mL) was added to give a colourless suspension which was filtered, washing with further portions of diethyl ether (3 × 20 mL). The residue was suspended in hot methanol (20 mL) and filtered through a pad of celite to remove residual silver, washing with further portions of methanol (2 × 10 mL) and concentrated *in vacuo* to give a colourless solid which was recrystallised from methanol/diethyl ether. The crude solid was dissolved in the minimum amount of hot methanol (*ca.* 2 mL) and diethyl ether added dropwise with swirling until the mixture remained turbid. The mixture heated to redissolve the solid and then slowly cooled to 0 °C. The product was collected *via* filtration, washed with diethyl ether (20 mL) and dried *in vacuo* to give 2.11 g (6.67 mmol, 45%) of **122** as cream coloured plates.

mp 114-116 °C (lit.[127] 116-118 °C) ; δ_H(400 MHz; water-d_2) 1.44 (6 H, d, *J* 6.5 Hz, CH_3), 4.71, (1 H, septet, *J* 6.5 Hz, C*H*), 7.65-7.71 (4 H, m, Ar*H*) , 7.75-7.80 (2 H, m, Ar*H*), 7.91-7.95 (4 H, m, Ar*H*); δ_H(400 MHz; chloroform-*d*) 1.49 (6 H, d, *J* 6.5 Hz, CH_3), 5.02, (1 H, septet, *J* 6.5 Hz, C*H*), 7.64-7.73 (6 H, m, Ar*H*) , 8.07-8.12 (4 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[129]

(DSP-VII-10)

Diphenyl*iso*propylsulfoxonium tetrafluoroborate 212



A 50 round bottomed flask with a stir bar was charged with diphenyl*iso*propyl sulfonium tetrafluoroborate **122** (316 mg, 1.00 mmol, 1.0 equiv) and methanol (15 mL). The solution was placed in an ice-water bath to cool to 0 °C. 2-Nitrobenzenesulfonyl chloride (1.11 g, 5.00 mmol, 5.0 equiv) was added followed by a solution of sodium hydroxide (480 mg, 12.0 mmol, 12.0 equiv) and hydrogen peroxide (30% *w/w*, 1.35 mL, 12.0 mmol, 12.0 equiv) in water (10 mL), dropwise over 15 min to give a cream suspension. On complete addition the suspension was stirred for a further 15 min at 0 °C, then the ice bath removed and the reaction stirring continued. After 1 h the reaction was diluted with water (30 mL) and extracted with dichloromethane (3 × 20 mL) and dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a colourless solid. Attempts to isolate the product **212** have, to date, been unsuccessful. The proton NMR spectrum shows full conversion, but removal of the sulfonic acid by-products has proved difficult.

δ_H(400 MHz; chloroform-*d*) 1.56 (6 H, d, *J* 6.5 Hz, C*H*$_3$), 5.98, (1 H, septet, *J* 6.5 Hz, C*H*), 7.81-7.86 (6 H, m, Ar*H*) , 8.43-8.46 (4 H, m, Ar*H*).

(DSP-VII-80)

4.2.2 Preparation of chalcones

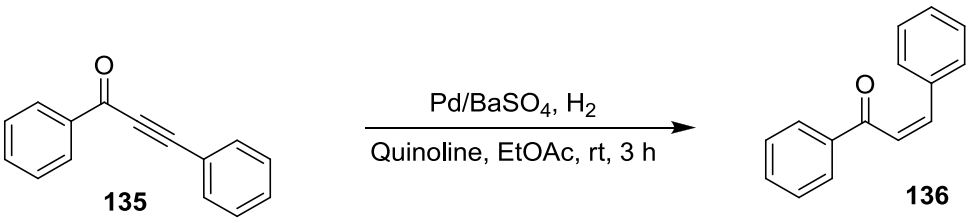
Method A: General procedure for the synthesis of chalcones

Based on a procedure from Silva and coworkers.[140]

A 250 mL round-bottomed flask with stirrer-bar was charged with ketone (20.0 mmol, 1.00 equiv), ethanol (40 mL) and aldehyde (22.0 mmol, 1.10 equiv). A solution of NaOH in water (10%, 40 mL) was added in a single portion. The resulting mixture was stirred at room temperature for the specified time. After this time, water (200 mL) and ice (200 g) was added. Where a solid precipitated, this was collected *via* filtration and recrystallised. Where a solid did not precipitate the solution was extracted with dichlloloromethane (3 × 200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product.

Solid products were recrystallised from the minimum amount of hot ethanol, allowed to cool slowly to room temperature then 0 °C. Crystals were collected via filtration, washed with pentane and dried *in vacuo*.

(*Z*)-Chalcone 136



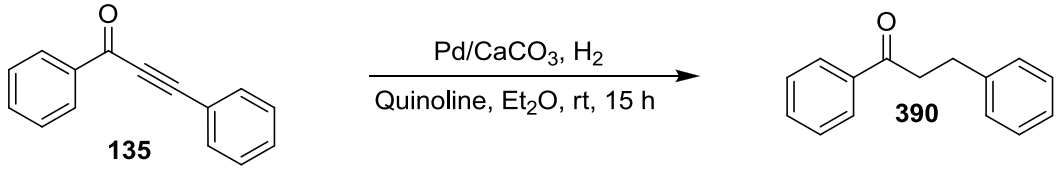
A 25 mL 3-neck round bottomed flask with stirrer-bar was charged with diphenylpropynone **135** (300 mg, 1.46 mmol, 1.0 equiv), 5% palladium on barium sulfate (155 mg, 0.073 mmol, 0.05 equiv) and quinoline (56 mg, 0.43 mmol, 0.30 equiv). A 3 way tap was fitted (one to vacuum, one to hydrogen) to the middle neck and septums to the other necks and the flask purged with hydrogen (5 x vacuum/hydrogen cycles). Ethyl acetate (10 mL) was added and the reaction stirred for 3 h before filtering through a sinter, washing with further portions of ethyl acetate (3 x 15 mL). The combined filtrates were concentrated *in vacuo* and purification by flash column chromatography (SiO_2, 15 g, 19:1 petrol/ethyl acetate, 20 mm Ø), gave 203 mg (0.97 mmol, 67%) of **136** as a yellow solid.

R_f 0.32 (9:1 petrol/ethyl acetate); mp 43-45 °C (lit.[234] 45-46 °C); δ_H(400 MHz; chloroform-*d*) 6.62 (1 H, d, *J* 13.0 Hz, C*H*), 7.01 (1 H, d, *J* 13.0 Hz, C*H*) 7.20-7.26 (3 H, m, Ar*H*), 7.35-7.42 (4 H, m, Ar*H*), 7.48-7.54 (2 H, m, Ar*H*), 7.94-7.99 (2 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[235]

(DSP-II-56)

1,3-Diphenylpropan-1-one 390



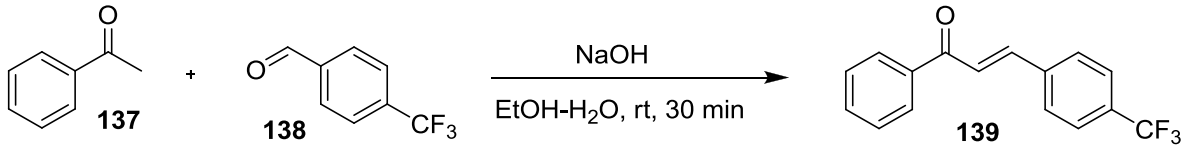
A 25 mL round bottomed flask with stir-bar was charged with diphenylpropynone **135** (300 mg, 1.46 mmol, 1.0 equiv), 5% palladium on calcium carbonate (155 mg, 1.46 mmol, 1.0 equiv, 5 mol% in Pd) and quinoline (56 mg, 0.43 mmol, 0.30 equiv). A 3 way tap was fitted (one to vacuum, one to hydrogen) and the flask purged with hydrogen (3 x vacuum/hydrogen cycles). Diethyl ether (10 mL) was added and the reaction stirred overnight. After 15 h the suspension was filtered through a sinter washing with further portions of diethyl ether (3 x 15 mL) and the combined filtrates concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 40 g, 9:1 petrol/ethyl acetate, 35 mm Ø), gave 230 mg (1.10 mmol, 74%) of **390** as colourless plates.

R_f 0.63 (3:1 petrol/ethyl acetate); mp 67-69°C (lit.[236] 72-73°C); δ_H(400 MHz; chloroform-*d*) 3.07 (2 H, t, *J* 8.0 Hz, CH_2), 3.31 (2 H, t, *J* 8.0 Hz, CH_2), 7.19-7.34 (5 H, m, Ar*H*), 7.43-7.48 (2 H, m, Ar*H*), 7.53-7.59 (1 H, m, Ar*H*), 7.94-7.98 (2 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[237]

(DSP-II-41)

(*E*)-1-Phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one 139



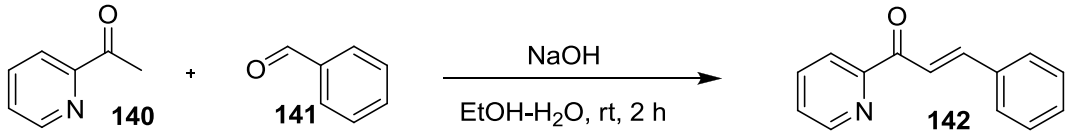
Reaction performed using method A using acetophenone **137** (2.40 g, 20.0 mmol, 1.0 equiv) and *p*-trifluoromethylbenzaldehyde **138** (3.83 g, 22.0 mmol, 1.1 equiv). The mixture was stirred at room temperature for 30 min. Recrystallisation following filtration gave 3.82 g (13.8 mmol, 69%) of **139** as pale yellow needles.

R_f 0.31 (9:1 petrol/ethyl acetate); mp 128-130 °C (lit[238] 128-129 °C); δ_H(400 MHz; chloroform-*d*) 7.50-7.56 (2 H, m, Ar*H*), 7.60 (1 H, d, *J* 16.0 Hz, C*H*), 7.59-7.65 (1 H, m, Ar*H*), 7.68 (2 H, d, *J* 8.0 Hz, Ar*H*), 7.75 (2 H, d, *J* 8.0 Hz, Ar*H*), 7.82 (1 H, d, *J* 16.0 Hz, C*H*), 8.01-8.06 (2 H, m, Ar*H*); δ_F(376 MHz; chloroform-*d*) -62.7.

Obtained data in accordance with previously reported data.[238]

(DSP-IV-96)

(*E*)-3-Phenyl-1-(pyridin-2-yl)prop-2-en-1-one 142



Reaction performed using method A using 2-acetylpyridine **140** (2.42 g, 20.0 mmol, 1.0 equiv) and benzaldehyde **141** (2.33 g, 22.0 mmol, 1.1 equiv). The mixture was stirred at room temperature for 2 h. Recrystallisation following filtration gave 840 mg (4.01 mmol, 20%) of **142** as pale green microcrystals.

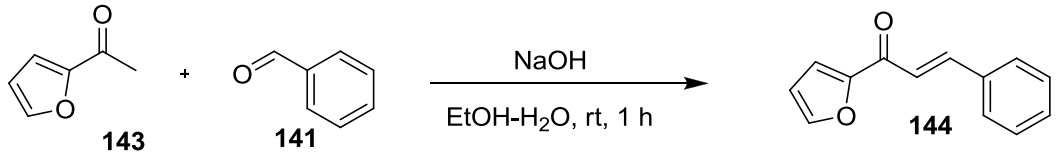
R_f 0.29 (3:1 petrol/ethyl acetate); mp 71-72 °C (lit.[239] 71-72 °C); ν_{max}(film)/cm^{-1} 3056, 1671, 1607, 1578, 1494, 1449, 1335, 1289, 1217, 1090, 1028, 994, 800, 753, 692, 672; δ_H(400 MHz; chloroform-*d*) 7.39-7.45 (3 H, m, Ph*H*), 7.49 (1 H, dd, *J* 7.5, 4.5 Hz, Pyr*H*), 7.71-7.76 (2 H, m, Ph*H*), 7.88 (1 H, ddd, *J* 8.0, 7.5, 1.5 Hz, Pyr*H*), 7.95 (1 H, d, *J* 16.0 Hz, C*H*), 8.20 (1 H, d, *J* 8.0 Hz, Pyr*H*), 8.31 (1 H,

d, *J* 16.0 Hz, C*H*), 8.75 (1 H, dd, *J* 4.5, 1.5 Hz, Pyr*H*); δ_C(100 MHz; chloroform-*d*) 120.8 (*C*H), 122.9 (PyrH), 126.9 (PyrH), 128.8 (PhH), 128.8 (PhH), 130.5 (PhH), 135.1 (Ph), 137.0 (PyrH), 144.8 (*C*H), 148.8 (PyrH), 154.2 (Pyr), 189.5 (*C*=O); *m/z* (ESI) 210 ($[MH]^+$) [HRMS (ESI): calculated for $C_{14}H_{12}NO$, 210.0913 Found: $[MH]^+$, 210.0917 (1.8 ppm error)].

Melting point in accordance with previously reported data.[239]

(DSP-IV-71)

(*E*)-1-(Furan-2-yl)-3-phenylprop-2-en-1-one 144



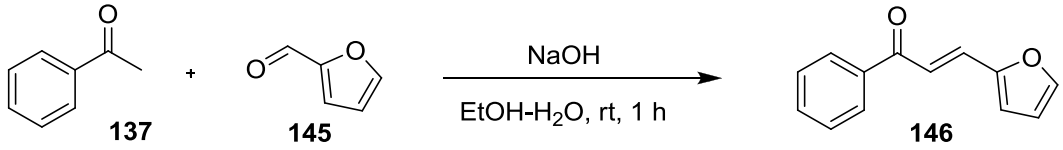
Reaction performed using method A using 2-acetylfuran **143** (2.20 g, 20.0 mmol, 1.0 equiv) and benzaldehyde **141** (2.33 g, 22.0 mmol, 1.1 equiv). The mixture was stirred at room temperature for 1 h. Recrystallisation following extraction gave 1.50 g (7.57 mmol, 38%) of **144** as colourless microcrystals.

R_f 0.38 (3:1 petrol/ethyl acetate); mp 83-85 °C (lit.[240] 94-95 °C); δ_H(400 MHz; chloroform-*d*) 6.60 (1 H, dd, *J* 3.5, 1.5 Hz, Fur*H*), 7.34 (1 H, dd, *J* 3.5, 1.0 Hz, Fur*H*), 7.41-7.44 (3 H, m, Ar*H*, Fur*H*), 7.46 (1 H, d, *J* 16.0 Hz, C*H*), 7.63-7.68 (3 H, m, Ar*H*), 7.89 (1 H, d, *J* 16.0 Hz, C*H*).

Obtained data in accordance with previously reported data.[240]

(DSP-IV-69)

(*E*)-3-(Furan-2-yl)-1-phenylprop-2-en-1-one 146

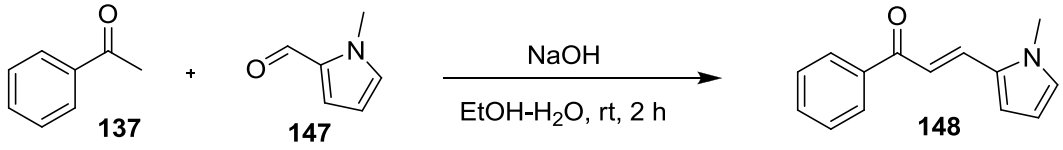


Reaction performed using method A using acetophenone **137** (2.40 g, 20.0 mmol, 1.0 equiv) and furfural **145** (2.33 g, 22.0 mmol, 1.1 equiv). Stirred The mixture was stirred at room temperature for 1 h. Extraction gave 3.92 g (19.8 mmol, 99%) of **146** as an orange oil which was used without further purification.

R_f 0.29 (9:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3125, 3062, 1663, 1603, 1551, 1476, 1448, 1389, 1330, 1284, 1263, 1224, 1180, 1155, 1079, 1014, 972, 928, 883, 777, 750, 701, 639; δ_H(400 MHz; chloroform-*d*) 6.51 (1 H, dd, *J* 3.5, 2.0 Hz, Fur*H*), 6.72 (1 H, d, *J* 3.5 Hz, Fur*H*), 7.46 (1 H, d, *J* 15.5 Hz, C*H*), 7.47-7.60 (4 H, m, Ph*H*, Fur*H*), 7.60 (1 H, d, *J* 15.5 Hz, C*H*), 8.01-8.05 (2 H, m, Ph*H*); δ_C(100 MHz; chloroform-*d*) 112.6 (FurH), 116.2 (FurH), 119.2 (*C*H), 128.4 (PhH), 128.6 (PhH), 130.6 (PhH), 132.7 (*C*H), 138.1 (Ph), 144.9 (FurH), 151.6 (Fur), 189.8 (*C*=O);*m/z* (ESI) 199 ([MH]$^+$) [HRMS (ESI): calculated for $C_{13}H_{11}O_2$, 199.0754 Found: [MH]$^+$, 199.0756 (1.4 ppm error)].

(DSP-IV-60)

(*E*)-3-(1-Methyl-*1H*-pyrrol-2-yl)-1-phenylprop-2-en-1-one 148



Reaction performed using method A using acetophenone **137** (2.40 g, 20.0 mmol, 1.0 equiv) and 1-methylpyrrole-2-carboxaldehyde **147** (2.40 g, 22.0 mmol, 1.1 equiv). The mixture was stirred at room temperature for 2 h. Recrystallisation following filtration gave 2.67 g (12.6 mmol, 63%) of **148** as yellow needles.

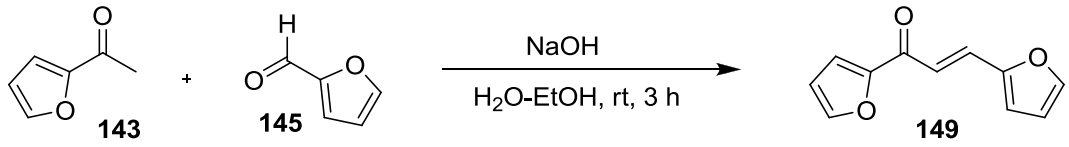
R_f 0.33 (3:1 petrol/ethyl acetate); mp 81-82 °C (lit.[241] 85 °C); ν_{max}(film)/cm^{-1} 3122, 3059, 2919, 1645, 1585, 1569, 1482, 1414, 1382, 1335, 1275, 1214, 1177,

1060, 1035, 1018, 966, 841, 774, 736, 699; δ_H(400 MHz; chloroform-*d*) 3.77 (3 H, s, C*H*$_3$), 6.22-6.24 (1 H, m, Pyr*H*), 6.81-6.83 (1 H, m, Pyr*H*), 6.84-6.87 (1 H, m, Pyr*H*), 7.31 (1 H, d, *J* 15.0 Hz, C*H*), 7.46-7.52 (2 H, m, Ar*H*), 7.54-7.59 (1 H, m, Ar*H*), 7.82 (1 H, d, *J* 15.0 Hz, C*H*), 7.99-8.03 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 34.4 (*C*H$_3$), 109.7 (PyrH), 112.4 (PyrH), 116.5 (*C*H), 127.8 (PyrH), 128.2 (PhH), 128.5 (PhH), 130.2 (Pyr), 132.2 (*C*H), 132.3 (PhH), 138.7 (Ph), 189.8 (*C*=O); *m/z* (ESI) 212 ([MH]$^+$) [HRMS (ESI): calculated for $C_{14}H_{14}NO$, 212.1070 Found: [MH]$^+$, 212.1075 (2.2 ppm error)].

Melting point in accordance with previously reported data.[241]

(DSP-IV-73)

(*E*)-1,3-Di(furan-2-yl)prop-2-en-1-one 149



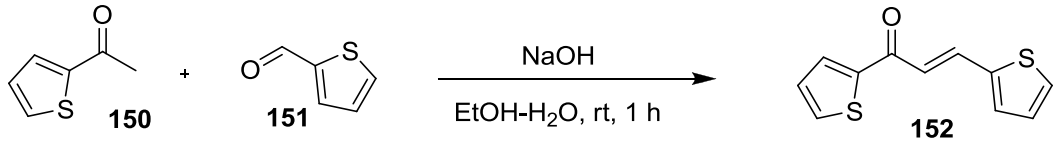
Reaction performed using method A using 2-acetylfuran **143** (2.20 g, 20.0 mmol, 1.0 equiv) and furfural **145** (2.11 g, 22.0 mmol, 1.1 equiv). The mixture was stirred at room temperature for 3 h. Recrystallisation following filtration gave 2.06 g (10.95 mmol, 55%) of **149** as pale brown microcrystals.

R_f 0.39 (1:1 petrol/ethyl acetate); mp 86-88 °C (lit.[242] 89-90 °C); ν_{max}(film)/cm^{-1} 1657, 1599, 1561, 1462, 1392, 1316, 1286, 1264, 1158, 1086, 1045, 1013, 972, 923, 882, 818, 755, 690; δ_H(400 MHz; chloroform-*d*) 6.51 (1 H, dd, *J* 3.5, 2.0 Hz, Fur*H*), 6.58 (1 H, dd, *J* 3.5, 2.0 Hz, Fur*H*), 6.72 (1 H, d, *J* 3.5 Hz, Fur*H*), 7.30 (1 H, d, *J* 15.5 Hz, C*H*), 7.31 (1 H, dd, *J* 3.5, 0.5 Hz, Fur*H*), 7.52 (1 H, d, *J* 2.0 Hz, Fur*H*), 7.62 (1 H, d, *J* 15.5 Hz, C*H*), 7.63 (1 H, dd, *J* 2.0, 0.5 Hz, Fur*H*); δ_C(100 MHz; chloroform-*d*) 112.5 (FurH), 112.7 (FurH), 116.4 (FurH), 117.4 (FurH), 118.8 (*C*H), 129.9 (*C*H), 145.0 (FurH), 146.5 (FurH), 151.5 (Fur), 153.7 (Fur), 177.7 (*C*=O); *m/z* (ESI) 211 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{11}H_8NaO_3$, 211.0366 Found: [MNa]$^+$, 211.0364 (0.5 ppm error)].

Obtained data in accordance with previously reported data.[243]

(DSP-II-74)

(*E*)-1,3-Di(thiophen-2-yl)prop-2-en-1-one 152



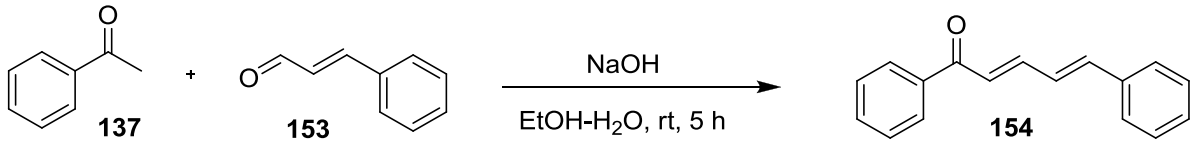
Reaction performed using method A using 2-acetylthiophene **150** (2.52 g, 20.0 mmol, 1.0 equiv) and 2-thiophenealdehyde **151** (2.47 g, 22.0 mmol, 1.1 equiv). The mixture was stirred at room temperature for 1 h. Recrystallisation following filtration gave 3.68 g (16.7 mmol, 84%) of **152** as yellow microcrystals.

R_f 0.41 (3:1 petrol/ethyl acetate); mp 95-97 °C (lit.[244] 95-97 °C); δ_H(400 MHz; chloroform-*d*) 7.09 (1 H, dd, *J* 5.0, 3.5 Hz, Thi*H*), 7.18 (1 H, dd, *J* 5.0, 4.0 Hz, Thi*H*), 7.21 (1 H, d, *J* 15.0 Hz, C*H*), 7.37 (1 H, d, *J* 3.5 Hz, Thi*H*), 7.43 (1 H, d, *J* 5.0 Hz, Thi*H*), 7.68 (1 H, dd, *J* 5.0, 1.0 Hz, Thi*H*), 7.85 (1 H, dd, *J* 4.0, 1.0 Hz, Thi*H*), 7.97 (1 H, d, *J* 15.0 Hz, C*H*).

Obtained data in accordance with previously reported data.[244]

(DSP-IV-70)

(2*E*,4*E*)-1,5-Diphenylpenta-2,4-dien-1-one 154



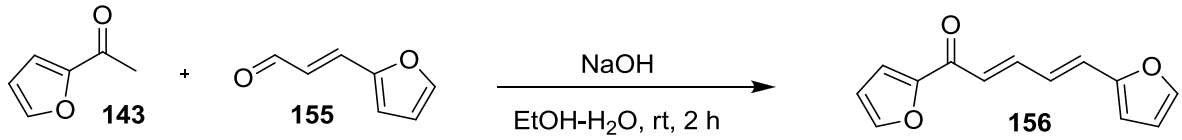
Reaction performed using method A using acetophenone **137** (1.20 g, 10.0 mmol, 1.0 equiv) and cinnamaldehyde **153** (1.59 g, 12.0 mmol, 1.2 equiv). The mixture was stirred at room temperature for 5 h. Recrystallisation following filtration gave 1.55 g (6.61 mmol, 66%) of **154** as orange-yellow plates.

R_f 0.33 (9:1 petrol/ethyl acetate); mp 95-97 °C (lit.[140] 102-103 °C); δ_H(400 MHz; chloroform-*d*) 7.02-7.05 (2 H, m, Ar*H*), 7.10 (1 H, d, *J* 15.0 Hz, C*H*), 7.30-7.41 (3 H, m, Ar*H*), 7.47-7.53 (4 H, m, Ar*H*), 7.55-7.65 (2 H, m, Ar*H*), 7.96-8.00 (2 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[140]

(DSP-IV-2)

(2*E*,4*E*)-1,5-Di(furan-2-yl)penta-2,4-dien-1-one 156



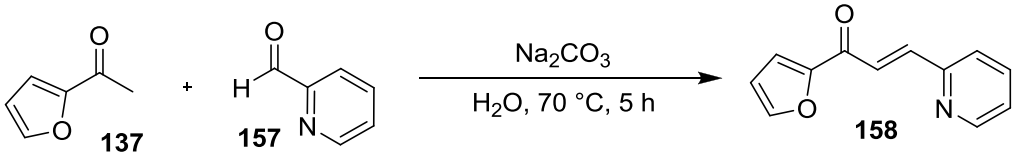
Reaction performed using method A using 2-acetylfuran **143** (2.20 g, 20.0 mmol, 1.0 equiv) and *E*-3-(2-Furyl)acrolein **155** (2.69 g, 22.0 mmol, 1.1 equiv). The mixture was stirred at room temperature for 2 h. Recrystallisation following filtration gave 3.36 g (15.7 mmol, 78%) of **156** as orange microcrystals.

R_f 0.08 (9:1 petrol/ethyl acetate); mp 75-77 °C (lit.[245] 80-81 °C); ν_{max}(film)/cm^{-1} 3214, 2920, 1647, 1584, 1467, 1393, 1335, 1271, 1152, 1086, 1044, 1012, 922, 882, 804, 758; δ_H(400 MHz; chloroform-*d*) 6.45 (1 H, dd, *J* 3.5, 2.0 Hz, Fur*H*), 6.49 (1 H, d, *J* 3.5 Hz, Fur*H*), 6.56 (1 H, dd, *J* 3.5, 2.0 Hz, Fur*H*), 6.77 (1 H, d, *J* 15.5 Hz, C*H*), 6.89 (1 H, dd, *J* 15.5, 11.5 Hz, C*H*), 6.97 (1 H, d, *J* 15.0 Hz, C*H*), 7.24 (1 H, d, *J* 3.5 Hz, Fur*H*), 7.45 (1 H, d, *J* 2.0 Hz, Fur*H*), 7.58 (1 H, dd, *J* 15.0, 11.5 Hz, C*H*), 7.61-7.62 (1 H, m, Fur*H*); δ_C(100 MHz; chloroform-*d*) 112.3 (FurH), 112.4 (FurH), 112.4 (FurH), 117.2 (FurH), 124.5 (*C*H), 125.1 (*C*H), 128.4 (*C*H), 143.5 (*C*H), 143.9 (FurH), 146.4 (FurH), 152.3 (Fur), 153.7 (Fur), 178.0 (*C*=O); *m/z* (ESI) 237 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{13}H_{10}NaO_3$, 237.0522 Found: [MNa]$^+$, 237.0530 (3.4 ppm error)].

Melting point in accordance with previously reported data.[245]

(DSP-IV-63)

(*E*)-1,4-Diphenylbut-2-ene-1,4-dione 158



Based on a procedure by Paxton.[129]

A 50 mL round-bottomed flask with stirrer-bar was charged with 2-acetylfuran **137** (583 mg, 5.30 mmol, 1.06 equiv), 2-pyridinecarboxaldehyde **157** (536 mg, 5.00 mmol, 1.0 equiv) and water (30 mL), a condenser fitted and the reaction heated to 70 °C. A solution of sodium carbonate (0.13 g, 1.3 mmol) in water (10 mL) was added and the stirring and heating continued. After 5 h the suspension was cooled to room temperature and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50 g, 2:1 petrol/ethyl acetate, 40 mm Ø) followed by recrystallisation from ethyl acetate/petrol gave 385 mg (2.11 mmol, 37%) of **158** as yellow plates.

R_f 0.44 (ethyl acetate); mp 69-70 °C (lit.[129] 68-69 °C); ν_{max}(film)/cm^{-1} 3126, 1660, 1611, 1566, 1464, 1432, 1394, 1328, 1259, 1158, 1087, 1045, 1012, 988, 884, 777; δ_H(400 MHz; chloroform-*d*) 6.60 (1 H, dd, *J* 3.5, 1.5 Hz, Fur*H*), 7.30 (1 H, ddd, *J* 7.5, 4.5, 1.5 Hz, Py*H*), 7.41 (1 H, d, *J* 3.5 Hz, Fur*H*), 7.48 (1 H, d, *J* 7.5 Hz, Py*H*), 7.67 (1 H, d, *J* 1.5 Hz, Fur*H*), 7.74 (1 H, td, *J* 7.5, 1.5 Hz, Py*H*), 7.83 (1 H, d, *J* 15.5 Hz, C*H*), 7.96 (1 H, d, *J* 15.5 Hz, C*H*), 8.68 (1 H, d, *J* 4.5 Hz, Py*H*); δ_C(100 MHz; chloroform-*d*) 112.7 (FurH), 118.6 (FurH), 124.6 (CH), 125.1 (PyH), 125.7 (PyH), 137.1 (PyH), 142.0 (CH), 147.2 (FurH), 150.2 (PyH), 153.0 (Fur), 153.6 (Py), 178.0 (*C*=O); *m/z* (ESI) 222 ($[MNa]^+$) [HRMS (ESI): calculated for $C_{12}H_9NNaO_2$, 222.0525 Found: $[MNa]^+$, 222.0521 (2.0 ppm error)].

Obtained data in accordance with previously reported data.[246]

(DSP-II-22)

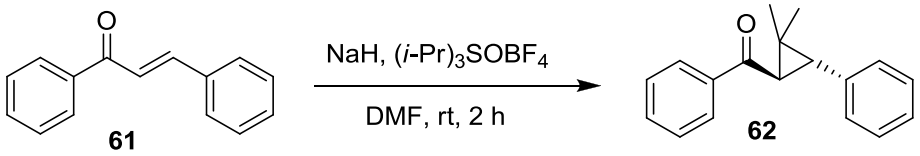
4.2.3 Cyclopropanation of chalcones

Method B: General procedure for the cyclopropanation of α,β-unsaturated carbonyl and related compounds

Based on a procedure by Paxton and Edwards.[152]

A 50 mL round bottomed flask with a stirrer-bar was charged with sodium hydride (60% *w/w* in mineral oil, 48 mg, 1.20 mmol, 1.2 equiv), a septum fitted and the flask purged with argon (balloon). Maintained under argon, as DMF (8 mL) added *via* syringe and the grey suspension cooled to 0 °C (ice-bath). The septum was briefly removed to add tri*iso*propylsulfoxonium tetrafluoroborate **131** (317 mg, 1.20 mmol, 1.2 equiv) and the suspension stirred for 5 min before the addition of a solution of the substrate (1.00 mmol, 1.0 equiv) in DMF (2 mL) *via* cannula. The mixture was stirred at 0 °C for 5 min before being warmed to room temperature and stirred continuously until the reaction was complete by TLC. On completion the solution was quenched with a saturated solution of ammonium chloride (10 mL), diluted with water (50 mL) and extracted with diethyl ether (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography yielded the desired compound.

(1*RS*, 3*RS*)-2,2-dimethyl-3-phenylcyclopropyl)(phenyl)methanone 62



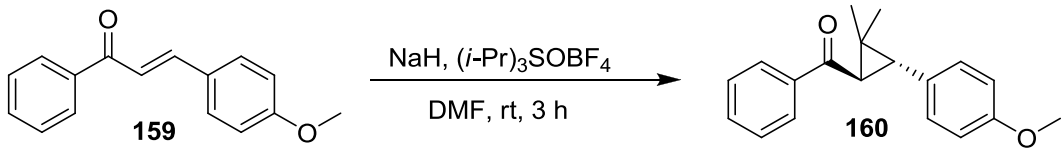
Reaction performed following method B using (*E*)-chalcone **61** (100 mg, 0.48 mmol, 1.0 equiv). The mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (SiO_2, 15 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 109 mg (0.44 mmol, 91%) of **62** as a cream coloured solid.

R_f 0.40 (9:1 petrol/ethyl acetate); mp 63-64 °C (lit.[137] 65-66 °C); δ_H(400 MHz; chloroform-*d*) 1.14 (3 H, s, CH_3), 1.28 (3 H, s, CH_3), 2.92 (1 H, d, *J* 6.0 Hz, C*H*), 3.13 (1 H, d, *J* 6.0 Hz, C*H*), 7.20-7.25 (3 H, m, Ar*H*), 7.27-7.33 (2 H, m, Ar*H*), 7.48-7.54 (2 H, m, Ar*H*), 7.56-7.62 (1 H, m, Ar*H*), 7.99-8.03 (2 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[137]

(DSP-II-17)

((1*RS*, 3*RS*)-3-(4-Methoxyphenyl)-2,2-dimethylcyclopropyl)(phenyl)methanone 160

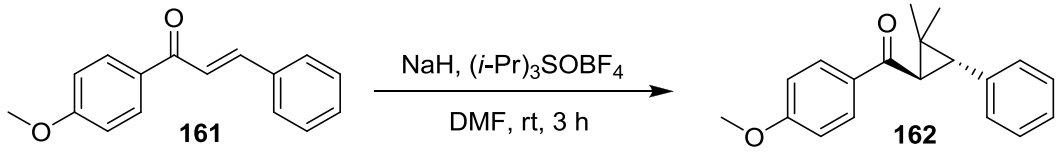


Reaction performed following method B using (*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one **159** (238 mg, 1.00 mmol, 1.0 equiv). The mixture was stirred at room temperature for 3 h. Purification by flash column chromatography (SiO_2, 15 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 265 mg, (0.94 mmol, 94%) of **160** as a colourless oil.

R_f 0.29 (9:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2944, 1668, 1612, 1580, 1514, 1449, 1420, 1377, 1338, 1286, 1246, 1203, 1177, 1111, 1035, 998, 830, 751, 728; δ_H(400 MHz; chloroform-*d*) 1.13 (3 H, s, CH_3), 1.26 (3 H, s, CH_3), 2.84 (1 H, d, *J* 6.0 Hz, C*H*), 3.06 (1 H, d, *J* 6.0 Hz, C*H*), 3.80 (3 H, s, OCH_3), 6.83 (2 H, d, *J* 8.5 Hz, ArH), 7.12 (2 H, d, *J* 8.5 Hz, ArH), 7.47-7.53 (2 H, m, Ar*H*), 7.55-

7.61 (1 H, m, Ar*H*), 7.98-8.02 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 20.2 (*C*H_3), 22.2 (*C*H_3), 33.0 *C*(CH_3)$_2$, 36.5 (*C*H), 37.8 (*C*H), 55.2 (O*C*H_3), 113.5 (ArH), 128.0 (ArH), 128.5 (ArH), 129.9 (Ar), 129.9 (ArH), 132.6 (ArH), 139.0 (Ar), 158.1 (ArOMe), 198.1 (*C*=O); *m/z* (ESI) 281 ([MH]$^+$) [HRMS (ESI): calculated for $C_{19}H_{21}O_2$, 281.1536 Found: [MH]$^+$, 281.1525 (4.0 ppm error)].
Obtained data in accordance with previously reported data.[247]
(DSP-IV-61)

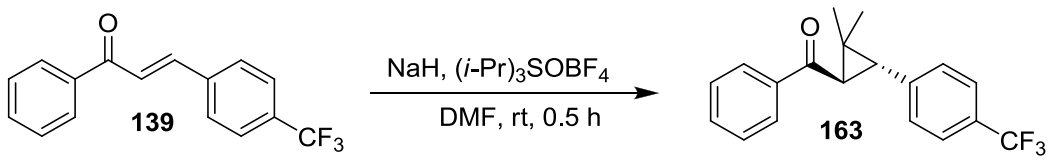
((1*RS*, 3*RS*)-2,2-Dimethyl-3-phenylcyclopropyl)(4-methoxyphenyl)methanone 162



Reaction performed following method B using (*E*)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one **161** (238 mg, 1.00 mmol, 1.0 equiv). The mixture was stirred at room temperature for 3 h. Purification by flash column chromatography (SiO_2, 15 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 265 mg, (0.95 mmol, 95%) of **162** as a colourless oil.

R_f 0.29 (9:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3027, 2943, 2870, 2840, 1660, 1601, 1576, 1509, 1456, 1424, 1377, 1340, 1310, 1244, 1213, 1170, 1111, 1061, 1029, 995, 974, 847, 806, 767, 726, 701; δ_H(400 MHz; chloroform-*d*) 1.08 (3 H, s, C*H*$_3$), 1.22 (3 H, s, C*H*$_3$), 2.83 (1 H, d, *J* 6.0 Hz, C*H*), 3.05 (1 H, d, *J* 6.0 Hz, C*H*), 3.86 (3 H, s, OC*H*$_3$), 6.94 (2 H, d, *J* 8.5 Hz, ArH), 7.15-7.28 (5 H, m, Ar*H*),7.96 (2 H, d, *J* 8.5 Hz, ArH); δ_C(100 MHz; chloroform-*d*) 20.3 (*C*H_3), 22.0 (*C*H_3), 32.2 (*C*(CH_3)$_2$), 36.6 (*C*H), 37.0 (*C*H), 55.4 (O*C*H_3), 113.6 (ArH), 126.2 (ArH), 128.0 (ArH), 128.9 (ArH), 130.2 (ArH), 131.9 (Ar), 137.9 (Ar), 163.1 (ArOMe), 196.2 (*C*=O); *m/z* (ESI) 281 ([MH]$^+$) [HRMS (ESI): calculated for $C_{19}H_{21}O_2$, 281.1536 Found: [MH]$^+$, 281.1539 (1.0 ppm error)].
(DSP-IV-84)

((1*RS*, 3*RS*)-2,2-Dimethyl-3-(4-(trifluoromethyl)phenyl)cyclopropyl)(phenyl)methanone 163

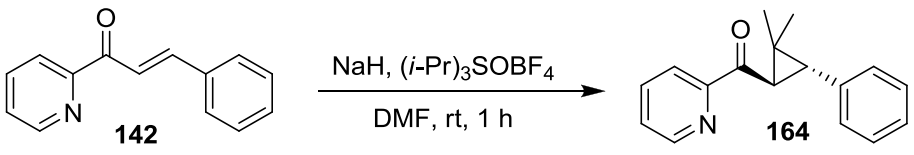


Reaction performed following method B using (*E*)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one **139** (276 mg, 1.00 mmol, 1.0 equiv). The mixture was stirred at room temperature for 30 min. Purification by flash column chromatography (SiO_2, 15 g, 19:1 petrol/ethyl acetate, 20 mm Ø), gave 297 mg, (0.93 mmol, 93%) of **163** as a colourless solid.

R_f 0.55 (9:1 petrol/ethyl acetate); mp 74-76 °C; ν_{max}(film)/cm^{-1} 2920, 1671, 1619, 1450, 1326, 1243, 1164, 1120, 1068, 1019, 689; δ_H(400 MHz; chloroform-*d*) 1.13 (3 H, s, C*H*$_3$), 1.28 (3 H, s, C*H*$_3$), 2.95 (1 H, d, *J* 6.0 Hz, C*H*), 3.15 (1 H, d, *J* 6.0 Hz, C*H*), 7.32 (2 H, d, *J* 8.5 Hz, ArH), 7.49-7.63 (5 H, m, Ph*H*), 8.00 (2 H, d, *J* 8.5 Hz, ArH); δ_C(100 MHz; chloroform-*d*) 20.2 (*C*H$_3$), 21.9 (*C*H$_3$), 32.8 (*C*(CH$_3$)$_2$), 36.4 (*C*H), 37.5 (*C*H), 124.2 (q, *J* 272 Hz, *C*F$_3$), 125.0 (q, *J* 4 Hz, ArH), 128.0 (ArH), 128.6 (q, *J* 32 Hz, Ar), 128.6 (ArH), 129.2 (ArH), 132.8 (ArH), 138.6 (Ar), 142.0 (Ar), 197.3 (*C*=O); δ_F(376 MHz; chloroform-*d*) -62.2; *m/z* (ESI) 319 ([MH]$^+$) [HRMS (ESI): calculated for $C_{19}H_{18}F_3O$, 319.1304 Found: [MH]$^+$, 319.1298 (1.9 ppm error)].

(DSP-IV-97)

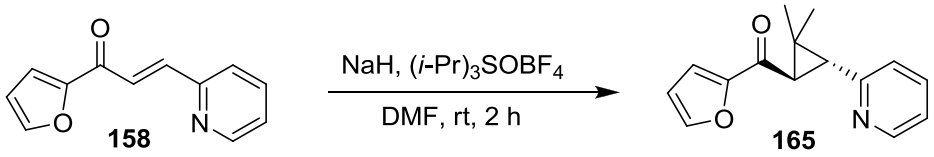
((1*RS*, 3*RS*)-2,2-Dimethyl-3-phenylcyclopropyl)(pyridin-2-yl)methanone 164



Reaction performed following method B using (*E*)-3-phenyl-1-(pyridin-2-yl)prop-2-en-1-one **142** (209 mg, 1.00 mmol, 1.0 equiv). The mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (SiO_2, 20 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 224 mg, (0.89 mmol, 89%) of **164** as a colourless oil.

R_f 0.30 (9:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3057, 2948, 2871, 1677, 1582, 1440, 1414, 1376, 1343, 1238, 1110, 1071, 1031, 997, 750, 733, 696; δ_H(400 MHz; chloroform-*d*) 1.11 (3 H, s, CH_3), 1.36 (3 H, s, CH_3), 3.10 (1 H, d, *J* 6.0 Hz, C*H*), 3.93 (1 H, d, *J* 6.0 Hz, C*H*), 7.19-7.33 (5 H, m, Ph*H*), 7.25 (1 H, dd, *J* 7.5, 5.0 Hz, Py*H*), 7.49 (1 H, ddd, *J* 8.0, 7.5, 2.0 Hz, Py*H*), 7.86 (1 H, d, *J* 8.0 Hz, Py*H*), 8.10 (1 H, dd, *J* 5.0, 2.0 Hz, Py*H*); δ_C(100 MHz; chloroform-*d*) 20.0 (*C*H_3), 22.2 (*C*H_3), 30.2 (*C*$(CH_3)_2$), 34.9 (*C*H), 40.0 (*C*H), 121.5 (PyH), 126.2 (PhH), 126.6 (PyH), 128.0 (PhH), 128.9 (PhH), 136.7 (PyH), 138.0 (Ph), 148.9 (PyH), 154.4 (Py), 198.7 (*C*=O); *m/z* (ESI) 252 ([MH]$^+$) [HRMS (ESI): calculated for $C_{17}H_{18}NO$, 252.1383 Found: [MH]$^+$, 252.1384 (0.3 ppm error)]. (DSP-IV-85)

(1*RS*, 3*RS*)-(Furan-2-yl)(-2,2-dimethyl-3-(pyridin-2-yl)cyclopropyl)methanone 165



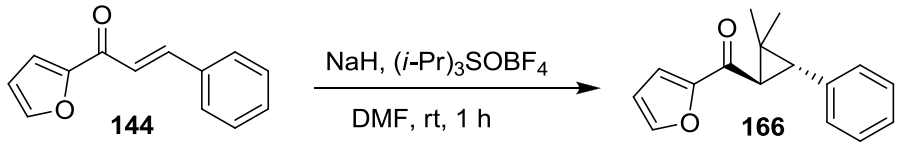
Reaction performed following method B using (*E*)-1-furan-2-yl-3-pyridin-2-ylpropenone **158** (100 mg, 0.48 mmol, 1.0 equiv). The mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (SiO_2, 15 g, 3:1 petrol/ethyl acetate, 25 mm Ø), gave 85 mg (0.35 mmol, 71%) of **165** as a brown solid.

R_f 0.34 (3:1 petrol/ethyl acetate); mp 64-65 °C; ν_{max}(film)/cm^{-1} 2921, 1659 (C=O), 1590, 1567, 1469, 1414, 1261, 1094, 1035, 752; δ_H(400 MHz; chloroform-*d*) 1.17 (3 H, s, CH_3), 1.31 (3 H, s, CH_3), 3.07 (1 H, d, *J* 6.0 Hz, C*H*), 3.44 (1 H, d, *J* 6.0 Hz, C*H*), 6.51-6.54 (1 H, m, Fur*H*), 7.08 (1 H, ddd, *J* 7.5, 5.0, 1.0 Hz, Pyr*H*), 7.25 (1 H, dd, *J* 2.0, 1.0 Hz, Py*H*), 7.27 (1 H, m, Fur*H*) 7.55 (1 H, dd, *J* 7.5, 2.0 Hz, Pyr*H*), 7.57-7.60 (1 H, m, Fur*H*), 8.49 (1 H, d, *J* 5.0 Hz, Pyr*H*). δ_C(100 MHz; chloroform-*d*) 20.3 (*C*H_3), 20.5 (*C*H_3), 34.7 (*C*H), 36.5 (*C*H), 38.4 (*C*$(CH_3)_2$), 112.1 (ArH), 116.7 (ArH), 121.1 (ArH), 124.4 (ArH), 135.8 (ArH), 146.1 (ArH), 148.7 (ArH), 154.0 (Ar), 157.4 (Ar), 186.3 (*C*=O); *m/z* (ESI) 264

([MNa]$^+$) [HRMS (ESI): calculated for $C_{15}H_{15}NNaO_2$, 264.0995 Found: [MNa]$^+$, 264.0997 (0.4 ppm error)].

(DSP-II-25)

((1*RS*, 3*RS*)-2,2-Dimethyl-3-phenylcyclopropyl)(furan-2-yl)methanone 166

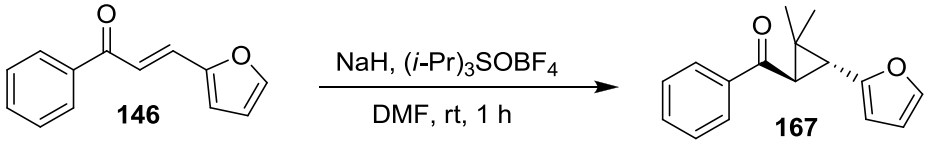


Reaction performed following method B using (*E*)-1-(furan-2-yl)-3-phenylprop-2-en-1-one **144** (198 mg, 1.00 mmol, 1.0 equiv). The mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (SiO_2, 15 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 161 mg, (0.67 mmol, 67%) of **166** as a colourless solid.

R_f 0.34 (9:1 petrol/ethyl acetate); mp 89-90 °C ν_{max}(film)/cm^{-1} 2985, 2951, 2919, 1656, 1568, 1466, 1419, 1389, 1343, 1258, 1162, 1097, 1039, 765, 718; δ_H(400 MHz; chloroform-*d*) 1.06 (3 H, s, C*H*$_3$), 1.34 (3 H, s, C*H*$_3$), 2.89 (1 H, d, *J* 6.0 Hz, C*H*), 3.07 (1 H, d, *J* 6.0 Hz, C*H*), 6.56-6.58 (1 H, m, FurH), 7.19-7.25 (4 H, m, Ar*H*, Fur*H*), 7.27-7.32 (2 H, m, Ar*H*), 7.61-7.63 (1 H, m, Fur*H*); δ_C(100 MHz; chloroform-*d*) 20.1 (*C*H$_3$), 22.3 (*C*H$_3$), 33.6 (*C*(CH$_3$)$_2$), 36.5 (*C*H), 38.1 (*C*H), 112.2 (FurH), 116.1 (FurH), 126.4 (PhH), 128.1 (PhH), 128.9 (PhH), 137.7 (Ph), 146.0 (FurH), 154.2 (Fur), 186.6 (*C*=O); *m/z* (ESI) 241 ([MH]$^+$) [HRMS (ESI): calculated for $C_{16}H_{17}O_2$, 241.1223 Found: [MH]$^+$, 241.1221 (0.8 ppm error)].

(DSP-IV-74)

(1*RS*, 3*RS*)-(3-(Furan-2-yl)-2,2-dimethylcyclopropyl)(phenyl)methanone 167



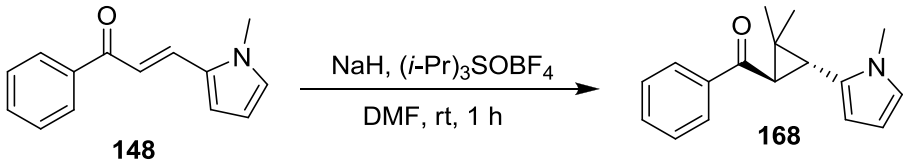
Reaction performed following method B using (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one **146** (198 mg, 1.00 mmol, 1.0 equiv). The mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (SiO_2, 15 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 217 mg, (0.91 mmol, 91%) of **167** as a colourless oil.

R_f 0.44 (9:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 1.21 (3 H, s, C*H*$_3$), 1.28 (3 H, s, C*H*$_3$), 2.91-2.97 (2 H, m, C*H*, C*H*), 6.09 (1 H, dd, *J* 3.0, 1.0 Hz, Fur*H*), 6.31 (1 H, dd, *J* 3.0, 2.0 Hz, Fur*H*), 7.31 (1 H, dd, *J* 2.0, 1.0 Hz, Fur*H*), 7.47-7.53 (2 H, m, Ph*H*), 7.56-7.61 (1 H, m, Ph*H*), 7.96-8.01 (2 H, m, Ph*H*); *m/z* (ESI) 241 ($[MH]^+$), 263 ($[MNa]^+$) [HRMS (ESI): calculated for $C_{16}H_{16}NaO_2$, 263.1043 Found: $[MNa]^+$, 263.1036 (2.3 ppm error)].

Obtained data in accordance with previously reported data.[129]

(DSP-IV-62)

((1*RS*, 3*RS*)-2,2-Dimethyl-3-(1-methyl-*1H*-pyrrol-2-yl)cyclopropyl)(phenyl)methanone 168



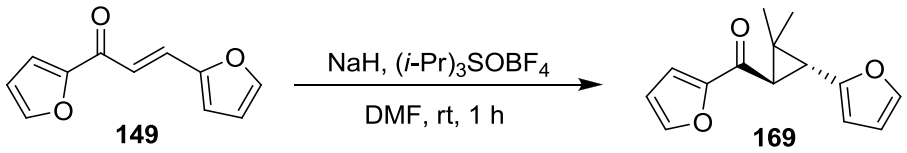
Reaction performed following method B using (*E*)-3-(1-methyl-1H-pyrrol-2-yl)-1-phenylprop-2-en-1-one **148** (211 mg, 1.00 mmol, 1.0 equiv). The mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (SiO_2, 20 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 217 mg, (0.85 mmol, 85%) of **168** as a yellow oil.

R_f 0.55 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3062, 2945, 2873, 1669, 1598, 1580, 1491, 1450, 1399, 1335, 1300, 1238, 1204, 1111, 1089, 1021, 982, 746, 691; δ_H(400 MHz; chloroform-*d*) 1.21 (3 H, s, C*H*$_3$), 1.26 (3 H, s, C*H*$_3$), 2.79 (1

H, d, *J* 6.0 Hz, C*H*), 2.82 (1 H, d, *J* 6.0 Hz, C*H*), 3.59 (3 H, s, NCH_3), 5.84-5.86 (1 H, m, PyrH), 6.01-6.04 (1 H, m, PyrH), 6.58-6.60 (1 H, m, PyrH), 7.47-7.53 (2 H, m, Ar*H*), 7.56-7.61 (1 H, m, Ar*H*), 7.97-8.00 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 19.6 (*C*H_3), 21.8 (*C*H_3), 29.0 (N*C*H_3), 32.6 (*C*$(CH_3)_2$), 33.8 (*C*H), 37.9 (*C*H), 106.4 (PyrH), 107.0 (PyrH), 121.7 (PyrH), 128.0 (PhH), 128.6 (PhH), 130.4 (Pyr), 132.7 (ArH), 138.7 (Ph), 197.5 (*C*=O); *m/z* (ESI) 254 ($[MH]^+$) [HRMS (ESI): calculated for $C_{17}H_{20}NO$, 254.1539 Found: $[MH]^+$, 254.1542 (1.1 ppm error)].

(DSP-IV-76)

Furan-2-yl((1*RS*, 3*RS*)-3-(furan-2-yl)-2,2-dimethylcyclopropyl)methanone 169



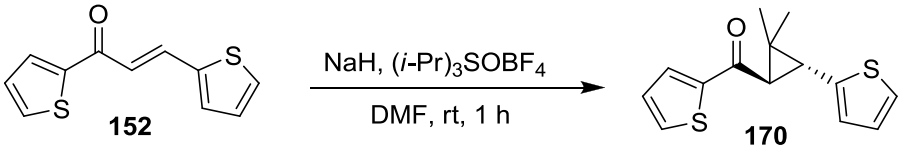
Reaction performed following method B using (*E*)-1,3-difuran-2-ylpropenone **149** (100 mg, 0.53 mmol, 1.0 equiv). The mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (SiO_2, 10 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 188 mg, (0.82 mmol, 82%) of **169** as a yellow oil.

R_f 0.23 (9:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 1.21 (3 H, s, CH_3), 1.26 (3 H, s, CH_3), 2.88 (1 H, d, *J* 6.0 Hz, C*H*), 2.91 (1 H, d, *J* 6.0 Hz, C*H*), 6.10 (1 H, dt, *J* 3.5, 1.0 Hz, Fur*H*), 6.30 (1 H, dd, *J* 3.5, 1.0 Hz, Fur*H*), 6.56 (1 H, dd, *J* 3.5, 1.0 Hz, Fur*H*), 7.22 (1 H, dd, *J* 3.5, 1.0 Hz, Fur*H*), 7.31 (1 H, dd, *J* 2.0, 1.0 Hz, Fur*H*), 7.61 (1 H, dd, *J* 2.0, 1.0 Hz, Fur*H*); δ_C(100 MHz; chloroform-*d*) 19.4 (*C*H_3), 22.0 (*C*H_3), 30.3 (*C*H), 33.2 (*C*$(CH_3)_2$), 36.9 (*C*H), 106.9 (FurH), 110.2 (FurH), 112.2 (FurH), 116.4 (FurH), 141.2 (FurH), 146.2 (FurH), 152.6 (Fur), 154.0 (Fur), 185.6 (*C*=O).

Obtained data in accordance with previously reported data.[137]

(DSP-II-78)

((1*RS*, 3*RS*)-2,2-Dimethyl-3-(thiophen-2-yl)cyclopropyl)(thiophen-2-yl)methanone 170

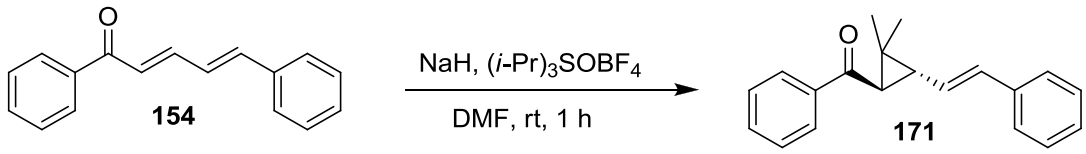


Reaction performed following method B using (*E*)-1,3-di(thiophen-2-yl)prop-2-en-1-one **152** (220 mg, 1.00 mmol, 1.0 equiv). The mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (SiO_2, 15 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 250 mg, (0.95 mmol, 95%) of **170** as a pale yellow oil.

R_f 0.60 (9:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3102, 2950, 2922, 2872, 1647, 1516, 1448, 1418, 1379, 1356, 1283, 1243, 1202, 1112, 1089, 1057, 968, 857, 818, 720, 698; δ_H(400 MHz; chloroform-*d*) 1.20 (3 H, s, C*H*$_3$), 1.28 (3 H, s, C*H*$_3$), 2.80 (1 H, d, *J* 5.5 Hz, C*H*), 3.07 (1 H, d, *J* 5.5 Hz, C*H*), 6.82 (1 H, dd, *J* 3.5, 1.0 Hz, Thi*H*), 6.84 (1 H, dd, *J* 5.0, 3.5 Hz, Thi*H*), 7.15 (1 H, dd, *J* 5.0, 1.0 Hz, Thi*H*), 7.17 (1 H, dd, *J* 5.0, 4.0 Hz, Thi*H*), 7.65 (1 H, dd, *J* 5.0, 1.0 Hz, Thi*H*), 7.79 (1 H, dd, *J* 4.0, 1.0 Hz, Thi*H*); δ_C(100 MHz; chloroform-*d*) 19.7 (*C*H$_3$), 22.1 (*C*H$_3$), 32.1 (*C*H), 33.5 (*C*(CH$_3$)$_2$), 40.1 (*C*H), 123.9 (ThiH), 125.6 (ThiH), 126.7 (ThiH), 128.1 (ThiH), 131.5 (ThiH), 133.2 (ThiH), 141.5 (Thi), 145.8 (Thi), 189.3 (*C*=O); *m/z* (ESI) 263 ([MH]$^+$) [HRMS (ESI): calculated for $C_{14}H_{15}OS_2$, 263.0559 Found: [MH]$^+$, 263.0562 (1.1 ppm error)].

(DSP-IV-75)

((1*RS*, 3*RS*)-2,2-Dimethyl-3-styrylcyclopropyl)(phenyl)methanone 171



Reaction performed following method B using (2*E*,4*E*)-1,5-diphenylpenta-2,4-dien-1-one **154** (351 mg, 1.50 mmol, 1.0 equiv). The mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (SiO_2, 30 g,

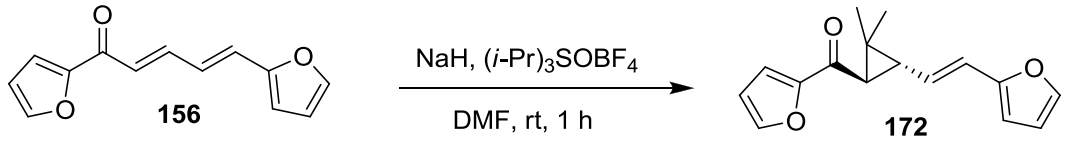
19:1 petrol/ethyl acetate, 30 mm Ø), gave 367 mg, (1.33 mmol, 88%) of **171** as a colourless solid.

R_f 0.42 (9:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 1.22 (3 H, s, CH_3), 1.43 (3 H, s, CH_3), 2.62-2.66 (2 H, m, CH, CH), 6.08 (1 H, dd, *J* 16.0, 8.0 Hz, CH), 6.61 (1 H, d, *J* 16.0 Hz, CH), 7.21 (1 H, tt, *J* 7.0, 1.5 Hz, ArH), 7.27-7.36 (4 H, m, ArH), 7.48 (2 H, t, *J* 7.5 Hz, ArH), 7.57 (1 H, tt, *J* 7.5, 1.5 Hz, ArH), 7.95 (2 H, dd, *J* 7.0, 1.5 Hz, ArH).

Obtained data in accordance with previously reported data.[137]

(DSP-IV-14)

Furan-2-yl((1*RS*, 3*RS*)-3-((E)-2-(furan-2-yl)vinyl)-2,2-dimethylcyclopropyl)methanone 172



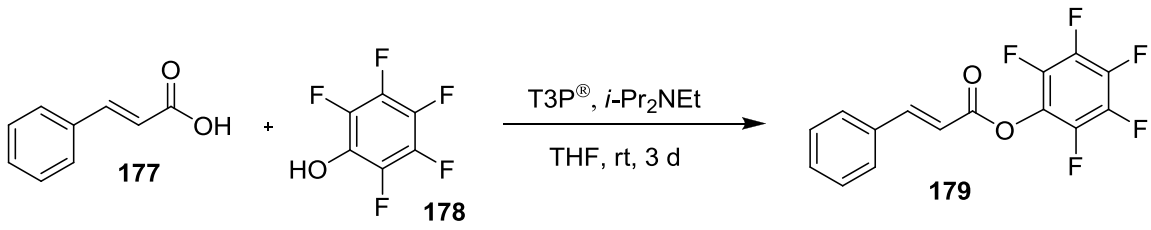
Reaction performed following method B using (2*E*,4*E*)-1,5-di(furan-2-yl)penta-2,4-dien-1-one **156** (214 mg, 1.00 mmol, 1.0 equiv). The mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (SiO_2, 15 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 155 mg, (0.60 mmol, 60%) of **172** as a colourless oil.

R_f 0.23 (9:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 1.26 (3 H, s, C*H*$_3$), 1.35 (3 H, s, C*H*$_3$), 2.52 (1 H, dd, *J* 9.0, 5.5 Hz, C*H*), 2.59 (1 H, d, *J* 5.5 Hz, C*H*), 6.00 (1 H, dd, *J* 15.5, 9.0 Hz, C*H*), 6.14 (1 H, d, *J* 3.5 Hz, Fur*H*), 6.34 (1 H, ddd, *J* 3.5, 2.0, 0.5 Hz, Fur*H*), 6.37 (1 H, d, *J* 15.5 Hz, C*H*) 6.53 (1 H, ddd, *J* 3.5, 1.5, 0.5 Hz, Fur*H*), 7.16 (1 H, ddd, *J* 3.5, 0.5, 0.5 Hz, Fur*H*), 7.30 (1 H, d, *J* 2.0 Hz, Fur*H*), 7.58 (1 H, dd, *J* 1.5, 0.5 Hz, Fur*H*); δ_C(100 MHz; chloroform-*d*) 19.7 (*C*H_3), 22.4 (*C*H_3), 33.7 (*C*$(CH_3)_2$), 37.8 (*C*H), 39.6 (*C*H), 106.7 (FurH), 111.2 (FurH), 112.2 (FurH), 116.1 (FurH), 120.2 (CH), 126.3 (CH), 141.4 (FurH), 146.0 (FurH), 152.8 (Fur), 154.0 (Fur), 186.1 (*C*=O); *m/z* (ESI) 279 ($[MNa]^+$) [HRMS (ESI): calculated for $C_{16}H_{16}NaO_3$, 279.0992 Found: $[MNa]^+$, 279.0991 (0.3 ppm error)].

(DSP-IV-64)

4.2.4 Preparation of ester and amide substrates

(*E*)-Perfluorophenyl cinnamate 179



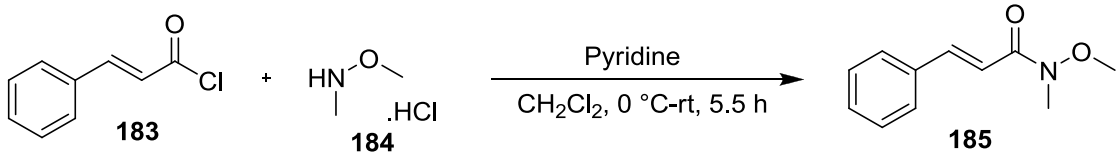
A 50 mL round-bottomed flask with stirrer-bar was charged with (*E*)-cinnamic acid **177** (644 mg, 4.35 mmol, 2.0 equiv), pentafluorophenol **178** (400 mg, 2.17 mmol, 1.0 equiv), a septum fitted and the flask purged with argon (balloon). The mixture was maintained under argon as THF (20 mL) added followed by di*iso*propylethylamine (1.40 g, 10.85 mmol, 5.0 equiv) and T3P® (50% w/w in toluene, 3.46 g, 5.43 mmol, 2.5 equiv) to give a colourless solution. After 3 days the reaction was diluted with ethyl acetate (100 mL) and washed with water (100 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 15 g, 19:1 petrol/ethyl acetate, 20 mm Ø), gave 384 mg (1.22 mmol, 56%) of **179** as a colourless solid.

R_f 0.62 (4:1 petrol/ethyl acetate); mp 84-85 °C, (lit.[248] 87-88 °C); ν_{max}(film)/cm^{-1} 1748, 1630, 1518, 1449, 1191, 1110, 997, 764; δ_H(400 MHz; chloroform-*d*) 6.65 (1 H, d, *J* 16.0 Hz, C*H*), 7.42-7.50 (3 H, m, Ar*H*), 7.59-7.64 (2 H, m, Ar*H*), 7.95 (1 H, d, *J* 16.0 Hz, C*H*); δ_C(100 MHz; chloroform-*d*) 114.3 (ArH), 125.3 (m, Ar), 128.7 (CH), 129.2 (CH), 131.6 (ArH), 133.6 (Ar), 138.0 (dm, *J* 241 Hz, ArF), 139.5 (dm, *J* 252 Hz, ArF), 141.4 (dm, *J* 255 Hz, ArF), 149.6 (ArH), 162.7 (*C*=O); δ_F(376 MHz; chloroform-*d*) -162.3, -158.1, -152.4; *m/z* (ESI) 337 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{15}H_7F_5O_2Na$, 337.0258 Found: [MNa]$^+$, 337.0272 (4.0 ppm error)].

Obtained data in accordance with previously reported data.[248]

(DSP-II-47)

_N_-Methoxy-_N_-methylcinnamoylamide 185



A 25 mL round-bottomed flask with stirrer-bar was charged with *N*,*O*-dimethylhydroxylamine hydrochloride **184** (281 mg, 2.88 mmol, 1.1 equiv), a septum fitted and the flask purged with argon (balloon). Maintained under argon as dichloromethane (10 mL) added and the suspension cooled to 0 °C (ice-bath). Pyridine (388 μL, 380 mg, 4.80 mmol, 2.0 equiv) was added and the suspension stirred for 20 min before addition of a solution of (*E*)-cinnamoyl chloride **183** (400 mg, 2.40 mmol, 1.0 equiv) in dichloromethane (5 mL) *via* syringe pump over 1.5 h. On complete addition the colourless solution was stirred for a further h at 0 °C before warming to room temperature and stirring for a further 3 h. The reaction was quenched by being poured into a saturated solution of sodium bicarbonate (30 mL) and stirred for 30 min before extracting with dichloromethane (3 x 20 mL). The combined organic extracts were washed with 10% aqueous hydrochloric acid (100 mL) and brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 434 mg (2.27 mmol, 93%) of **185** as a colourless solid.

R_f 0.42 (diethyl ether); mp 38-40 °C (lit.[249] 37-38 °C); δ_H(400 MHz; chloroform-*d*) 3.31 (3 H, s, NCH_3), 3.77 (3 H, s, OCH_3), 7.04 (1 H, d, *J* 16.0 Hz, C*H*), 7.35-7.42 (3 H, m, Ar*H*), 7.55-7.59 (2 H, m, Ar*H*) 7.73 (1 H, d, *J* 16.0 Hz, C*H*); δ_C(100 MHz; chloroform-*d*) 32.6 (N*C*H_3), 61.9 (O*C*H_3), 115.7 (CH), 128.0 (ArH), 128.8 (ArH), 129.8 (ArH), 135.1 (Ar), 143.4 (CH), 172.3 (C=O); *m/z* (ESI) 214 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{11}H_{13}NNaO_2$, 214.0838 Found: [MNa]$^+$, 214.0847 (3.8 ppm error)].

Obtained data in accordance with previously reported data.[250]

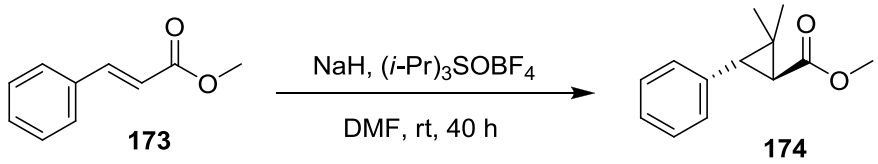
(DSP-II-85)

4.2.5 Cyclopropanation of esters and amides

Method C: General procedure for the cyclopropanation of α,β-unsaturated esters and amides.

A 25 mL round bottomed flask with a stirrer-bar was charged with sodium hydride (60% *w/w* in mineral oil, 49 mg, 1.23 mmol, 2.0 equiv), a septum fitted and the flask purged with argon (balloon). Maintained under argon, as DMF (4 mL) added *via* syringe and the grey suspension cooled to 0 °C (ice-bath). The septum was briefly removed to add tri*iso*propylsulfoxonium tetrafluoroborate **131** (326 mg, 1.23 mmol, 2.0 equiv) and the suspension stirred for 5 min before the addition of a solution of the substrate (0.62 mmol, 1.0 equiv) in DMF (1 mL) *via* cannula. The mixture was stirred at 0 °C for 5 min before being warmed to room temperature and stirred continuously until the reaction was complete by TLC. On completion the solution was quenched with a saturated solution of ammonium chloride (5 mL), diluted with water (25 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography yielded the desired compound.

Methyl (1*RS*, 3*RS*)-2,2-dimethyl-3-phenylcyclopropanecarboxylate 174



173 **174**

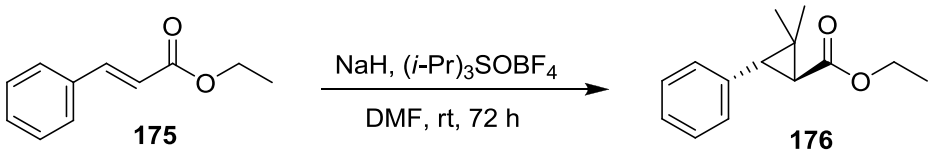
Reaction performed following method C using (*E*)-methyl cinnamate **173** (100 mg, 0.62 mmol, 1.0 equiv). The mixture was stirred at room temperature for 40 h. Purification by flash column chromatography (SiO_2, 15 g, 19:1 petrol/ethyl acetate, 20 mm Ø), gave 32 mg, (0.16 mmol, 25%) of **174** as a colourless oil.

R_f 0.41 (9:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 0.93 (3 H, s, CH_3), 1.39 (3 H, s, CH_3), 1.96 (1 H, d, *J* 6.0 Hz, C*H*), 2.70 (1 H, d, *J* 6.0 Hz, C*H*), 3.73 (3 H, s, OCH_3), 7.12-7.24 (3 H, m, Ar*H*), 7.27-7.32 (2 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[251]

(DSP-II-76)

Ethyl (1*RS*, 3*RS*)-2,2-dimethyl-3-phenylcyclopropanecarboxylate 176



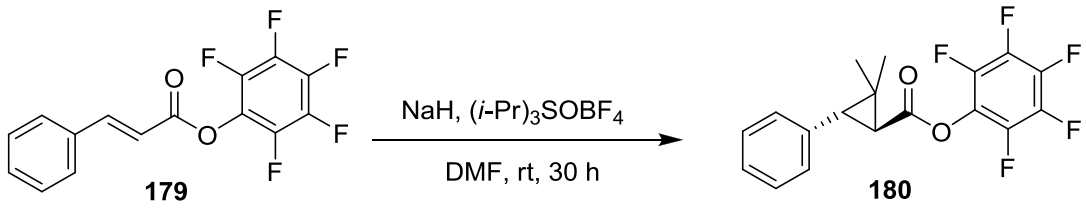
Reaction performed following method C using (*E*)-ethyl cinnamate **175** (100 mg, 0.57 mmol, 1.0 equiv). The mixture was stirred at room temperature for 72 h. Purification by flash column chromatography (SiO_2, 15 g, 19:1 petrol/ethyl acetate, 25 mm Ø), gave 34 mg (0.16 mmol, 27%) of **176** as a colourless oil.

R_f 0.64 (3:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 0.92 (3 H, s, C*H*$_3$), 1.30 (3 H, t, *J* 7.0 Hz, OCH$_2$C*H*$_3$) 1.38 (3 H, s, C*H*$_3$), 1.95 (1 H, d, *J* 6.0 Hz, C*H*), 2.69 (1 H, d, *J* 6.0 Hz, C*H*), 4.18 (2 H, m, OC*H*$_2$ CH$_3$), 7.14-7.22 (3 H, m, Ar*H*), 7.24-7.30 (2 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[252]

(DSP-II-35)

Perfluorophenyl (1*RS*, 3*RS*)-2,2-dimethyl-3-phenylcyclopropanecarboxylate 180

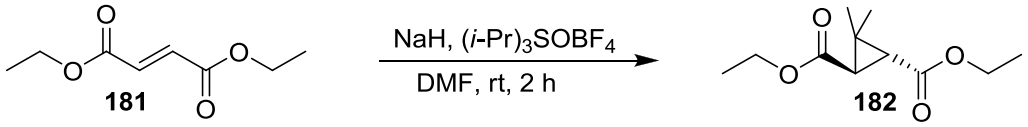


Reaction performed following method C using (*E*)-perfluorophenyl cinnamate **179** (100 mg, 0.32 mmol, 1.0 equiv). The mixture was stirred at room temperature for 30 h. Purification by flash column chromatography (SiO_2, 10 g, 40:1 petrol/diethyl ether, 25 mm Ø), gave 55 mg, (0.16 mmol, 49%) of **180** as a colourless oil.

R_f 0.43 (9:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3062, 3031, 2956, 2925, 2876, 1773, 1521, 1452, 1421, 1381, 1340, 1311, 1281, 1233, 1192, 1106, 1057, 1021, 999, 906, 862, 821, 765; δ_H(400 MHz; chloroform-*d*) 1.05 (3 H, s, C*H*$_3$), 1.45 (3

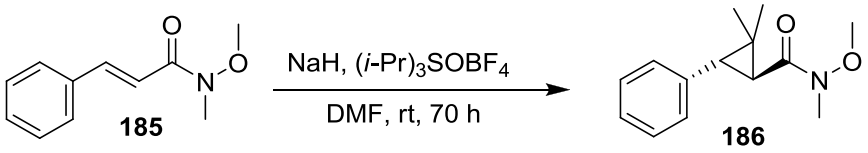
H, s, C*H*$_3$), 2.28 (1 H, d, *J* 6.0 Hz, C*H*), 2.87 (1 H, d, *J* 6.0 Hz, C*H*), 7.20-7.23 (2 H, m, Ar*H*), 7.25-7.28 (1 H, m, Ar*H*), 7.30-7.35 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 20.6 (*C*H$_3$), 21.8 (*C*H$_3$), 30.5 (*C*H), 31.8 (*C*(CH$_3$)$_2$), 39.2 (*C*H), 125.3 (m, Ar), 126.8 (ArH), 128.4 (ArH), 128.7 (ArH), 136.2 (Ar), 137.8 (dm, *J* 249 Hz, ArF), 139.3 (dm, *J* 253 Hz, ArF), 141.2 (dm, *J* 267 Hz, ArF), 168.3 (*C*=O); δ_F(254 MHz; chloroform-*d*) -162.4 (m), -158.3 (m), -152.4 (m); *m/z* (EI) 356 (M^+, 30%), 173 (100%), 158 (35%), 145 (80%), 91 (50%) [HRMS (EI): calculated for $C_{18}H_{13}F_5O_2$, 356.0836 Found: M^+, 356.0824 (3.4 ppm error)].
(DSP-II-53)

(1*RS*, 2*RS*)-Diethyl 3,3-dimethylcyclopropane-1,2-dicarboxylate 182



Reaction performed following method B using diethyl fumarate **181** (172 mg, 1.00 mmol, 1.0 equiv). The mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (SiO_2, 20 g, 4:1 petrol/diethyl ether, 20 mm Ø), gave 193 mg, (0.90 mmol, 90%) of **182** as a colourless oil.
R_f 0.54 (3:1 petrol/diethyl ether); ν_{max}(film)/cm^{-1} 2983, 2957, 1723, 1443, 1371, 1337, 1243, 1161, 1113, 1039; δ_H(400 MHz; chloroform-*d*) 1.27 (3 H, t, *J* 7.0 Hz, CH$_2$C*H*$_3$), 1.29 (3 H, s, C*H*$_3$), 2.21 (2 H, s, C*H*), 4.08-4.21 (4 H, m, C*H*$_2$); δ_C(100 MHz; chloroform-*d*) 14.2 (*C*H$_3$), 20.3 (*C*H$_3$), 30.2 (C), 33.5 (*C*H), 60.7 (*C*H$_2$), 170.4 (*C*=O); *m/z* (ESI) 237 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{11}H_{18}NaO_4$, 237.1097 Found: [MNa]$^+$, 237.1095 (0.8 ppm error)].
(DSP-VI-56)

(1*RS*, 3*RS*)-*N*-methoxy-*N*,2,2-trimethyl-3-phenylcyclopropanecarboxamide 186



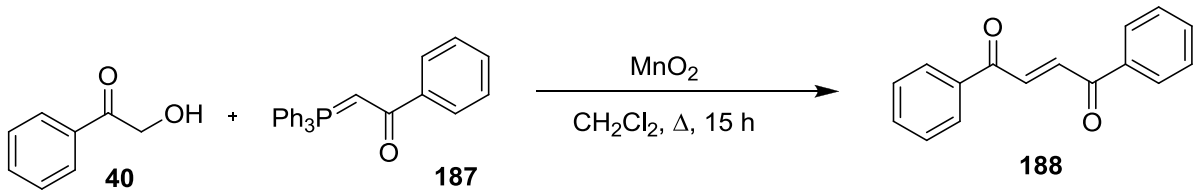
Reaction performed following method C using (*E*)-*N*-methoxy-*N*-methylcinnamamide **185** (100 mg, 0.48 mmol, 1.0 equiv). The mixture was stirred at room temperature for 70 h. Purification by flash column chromatography (SiO_2, 10 g, 2:1 petrol/ diethyl ether, 20 mm Ø), gave 25 mg, (0.11 mmol, 20%) of **186** as a colourless oil.

R_f 0.48 (diethyl ether); ν_{max}(film)/cm^{-1} 2939, 1656, 1442, 1369, 1177, 1113, 1000, 804, 765, 718; δ_H(400 MHz; chloroform-*d*) 0.96 (3 H, s, C*H*$_3$), 1.31 (3 H, s, C*H*$_3$), 2.43 (1 H, br s, C*H*), 2.78 (1 H, d, *J* 6.0 Hz, C*H*), 3.26 (3 H, s, NC*H*$_3$), 3.74 (3 H, s, OC*H*$_3$), 7.16-7.21 (3 H, m, Ar*H*), 7.25-7.29 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 20.6 (*C*H$_3$), 22.1 (*C*H$_3$), 28.6 (*C*(CH$_3$)$_2$), 29.6 (*C*H), 32.8 (NCH$_3$), 35.3 (*C*H), 61.6 (OCH$_3$), 126.1 (ArH), 128.0 (ArH), 128.9 (ArH), 138.0 (Ar), 172.3 (C=O); *m/z* (ESI) 256 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{14}H_{19}NNaO$, 256.1308 Found: [MNa]$^+$, 256.1312 (1.1 ppm error)].

(DSP-II-87)

4.2.6 Preparation of other substrates

(*E*)-1,4-Diphenylbut-2-ene-1,4-dione 188



Based on a procedure from Paxton.[129]

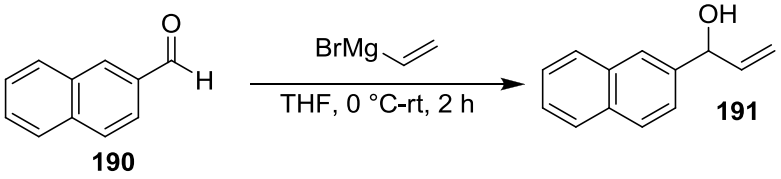
A 50 mL round-bottomed flask with stirrer-bar was charged with 2-hydroxyacetophenone **40** (442 mg, 3.25 mmol, 1.0 equiv), 1-phenyl-2-(triphenyl-λ^5-phosphanylidene)ethanone **187** (1.50 g, 3.90 mmol, 1.2 equiv) and dichloromethane (30 mL), a condenser fitted and the flask purged with argon (balloon). Manganese(IV) oxide (2.80 g, 32.5 mmol, 10 equiv) was added in a single portion and the reaction heated to reflux. After 15 h the black suspension was cooled and filtered through a celite pad washing with dichloromethane (30 mL) followed by ethyl acetate (30 mL) and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50 g, 9:1 petrol/ethyl acetate, 35 mm Ø) followed by recrystallisation from ethyl acetate/petrol gave 369 mg (1.56 mmol, 48%) of **188** as yellow needles.

R_f 0.42 (3:1 petrol/ethyl acetate); mp 109-110 °C (lit.[253] 110-111 °C); δ_H(400 MHz; chloroform-*d*) 7.51-7.56 (4 H, m, Ar*H*), 7.62-7.67 (2 H, m, Ar*H*), 8.02 (2 H, s, C*H*), 8.04-8.10 (4 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 129.0 (*C*H), 134.0 (ArH), 135.2 (ArH), 137.0 (Ar), 189.9 (*C*=O).

Obtained data in accordance with previously reported data.[254]

(DSP-II-21)

1-(Naphthalen-2-yl)prop-2-en-1-ol 191



190 **191**

Based on a procedure from Paxton.[129]

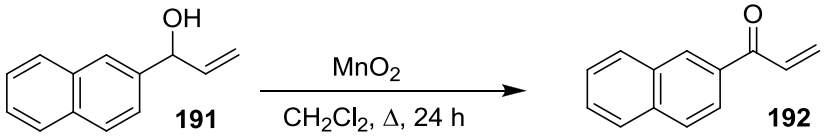
A 25 mL round-bottomed flask with stirrer-bar was charged with 2-naphthaldehyde **190** (781 mg, 5.00 mmol, 1.0 equiv) and THF (10 mL), the flask purged with argon (balloon) and cooled to 0°C (ice-bath) with stirring. To this a 1.0 M solution of vinyl magnesium bromide (7.5 mL, 5.50 mmol, 1.5 equiv) in THF was added dropwise over 10 min, the reaction allowed to warm to room temperature and stirred continuously. After 2 h the brown solution was quenched with a saturated solution of ammonium chloride (5 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a quantitative crude yield of **191** as a yellow oil which was taken through without purification to the next step.

R_f 0.37 (petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 2.13 (1 H, br s, O*H*), 5.24 (1 H, dt, *J* 10.5, 1.5 Hz, HC=CH_2), 5.37(1 H, d, *J* 6.0 Hz, C*H*(OH)), 5.40 (1 H, dt, J 17.0, 1.5 Hz, HC=CH_2), 6.12 (1 H, ddd, *J* 17.0, 10.5, 6.0 Hz, *H*C=CH_2), 7.48 (3 H, m, ArH), 7.83 (4 H, m, ArH).

Obtained data in accordance with previously reported data.[255]

(DSP-II-29)

1-(Naphthalen-2-yl)prop-2-en-1-one 192



Based on a procedure from Paxton.[129]

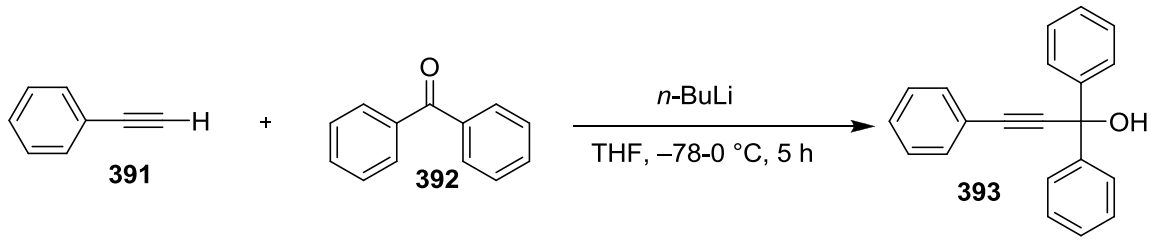
A 100 mL round-bottomed flask with stirrer-bar was charged with the obtained crude of 1-(naphthalen-2-yl)prop-2-en-1-ol **191** and manganese(IV) oxide (5.00 mmol, 4.34 g, 10 equiv), 4Å molecular sieves (5 g) and dichloromethane (30 mL). A condenser topped with an argon balloon was fitted and the reaction heated to reflux. After 24 h the black suspension was filtered through a celite pad, washing with dichloromethane (100 mL) and ethyl acetate (100 mL) and the combined organic extracts concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 50 g, 9:1 petrol/ethyl acetate, 40 mm Ø) gave 256 mg (1.40 mmol, 26% over 2 steps) of **192** as a bright yellow oil.

R_f 0.46 (3:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 5.98 (1 H, dd, *J* 10.5, 1.5 Hz, HC=C*H*$_2$), 6.50 (1 H, dd, *J* 17.0, 1.5 Hz, HC=C*H*$_2$), 7.32 (1 H, dd, *J* 17.0, 10.5 Hz, *H*C=CH$_2$), 7.53-7.67 (2 H, m, ArH), 7.85-8.06 (4 H, m, ArH), 8.46 (1 H, s, ArH).

Obtained data in accordance with previously reported data.[256]

(DSP-II-31)

1,1,3-Triphenylprop-2-yn-1-ol 393



Prepared using a procedure reported by Dudley and coworkers.[150]

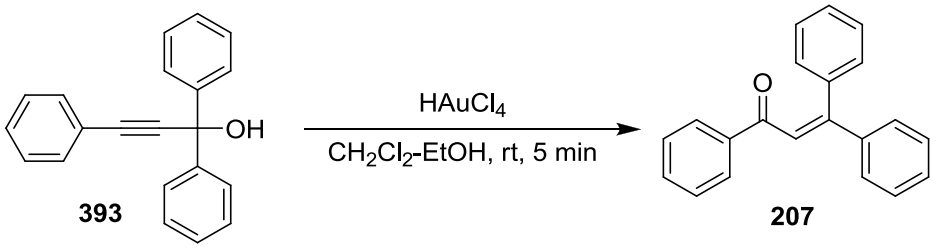
A 25 mL round-bottomed flask with a stir bar, was charged with phenyl acetylene **391** (1.53 g, 15.0 mmol, 2.0 equiv), a septum fitted, the flask purged with argon and cooled to –78 °C (CO_2/acetone). Maintained under argon as a 1.3 M solution of *n*-butyllithium in hexanes (9.2 mL, 12.0 mmol, 1.6 equiv) was added dropwise over a period of 10 min. The green solution was warmed to 0 °C (ice-bath) and stirred for 1 h before being recooled to –78 °C. To this benzophenone **392** (1.36 g, 7.5 mmol, 1.0 equiv) was added as a solution in THF (1 mL) by cannula and the mixture warmed to room temperature over 1 h. The yellow suspension was stirred for 4 h until the reaction was complete by TLC. The reaction was quenched with saturated ammonium chloride solution (25 mL) and extracted with ethyl acetate (2 x 20 mL). The organic layer was washed with water (30 mL), saturated aqueous sodium bicarbonate (30 mL), brine (30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 100 g, 19:1 petrol/ethyl acetate, 50 mm Ø), followed by recrystallisation from diethyl ether-petrol gave 977 mg (3.44 mmol, 46%) of **393** as colourless plates.

R_f 0.18 (9:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 2.95 (1 H, s, OH), 7.26-7.39 (9 H, m, Ar*H*), 7.50-7.55 (2 H, m, Ar*H*), 7.65-7.70 (4 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 74.8 (*C*Ph_2OH), 87.3 (*C*≡CPh), 91.7 (C≡*C*Ph), 122.6 (Ar), 126.3 (ArH), 128.0 (ArH), 128.6 (ArH), 128.6 (ArH), 128.9 (ArH), 132.0 (ArH), 145.3 (Ar).

Obtained data in accordance with previously reported data.[257]

(DSP-II-38)

1,3,3-Triphenylprop-2-en-1-one 207



Prepared using a procedure reported by Dudley and coworkers.[150]

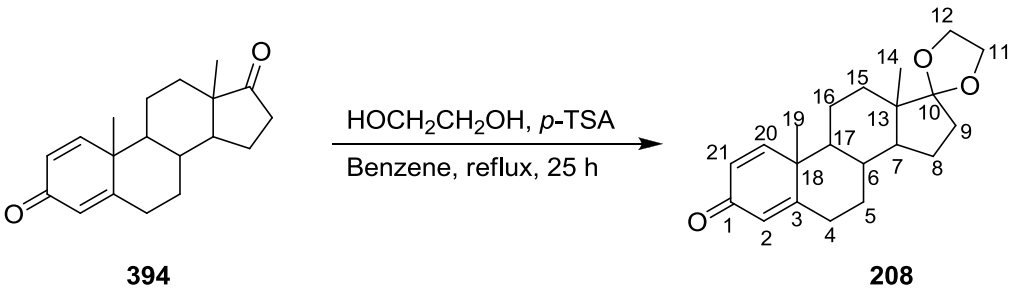
A 25 mL round-bottomed flask with stirrer-bar was charged with 1,1,3-triphenylprop-2-yn-1-ol **393** (200 mg, 0.70 mmol, 1.0 equiv) and dichloromethane (10 mL). To this colourless solution was added ethanol (0.20 mL, 3.50 mmol, 5.0 equiv) followed by hydrogen tetrachloroaurate(III) hydrate (55 mg, 0.14 mmol, 0.2 equiv) in a single portion to give an immediate yellow-orange solution. After 5 min the now yellow-green solution was filtered through a silica gel pad (10 g), eluting with petrol/ethyl acetate (4:1, 125 mL) and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 15 g, 30:1 petrol/ethyl acetate, 25 mm Ø), gave 145 mg (0.51 mmol, 71%) of **207** as a bright yellow oil.

R_f 0.22 (9:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 7.12 (1 H, s, C*H*), 7.16-7.20 (2 H, m, Ar*H*), 7.23-7.30 (3 H, m, Ar*H*), 7.35-7.41 (7 H, m, Ar*H*), 7.46-7.51 (1 H, m, Ar*H*), 7.89-7.93 (2 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[150]

(DSP-II-39)

1,4-Androstadiene-3,17-dione-17-ethylene-ketal 208



Prepared using the procedure reported by Gentles and coworkers.[151]

A 25 mL round-bottomed flask with stirrer-bar was charged with 1,4-androstadiene-3,17-dione **394** (350 mg, 1.23 mmol, 1.0 equiv), ethylene glycol

(83 μL, 1.47 mmol, 1.2 equiv), *p*-toluenesulfonic acid (3.5 mg, 0.018 mmol, 1.5 mol%) and benzene (18 mL), a Dean-Stark trap fitted and the reaction heated to reflux. After 18 h the reaction had not reached completion by TLC and a further portion of ethylene glycol (83 μL, 1.47 mmol, 1.2 equiv) and *p*-toluenesulfonic acid (3.5 mg, 0.018 mmol, 1.5 mol%) were added and the reaction heated for a further 7 h. The reaction was cooled to room temperature, 5 drops of 10% aqueous potassium hydroxide were added, and the organic layer washed with water (4 x 20 mL portions) until the aqueous washings were neutral by universal indicator paper. The organic layer was then dried (Na_2SO_4), filtered and a drop of pyridine added before concentrating *in vacuo* and azeotroping the solvent with portions of petrol (3 x 10 mL) to give 341 mg (0.97 mmol, 79%) of **208** as colourless prisms.

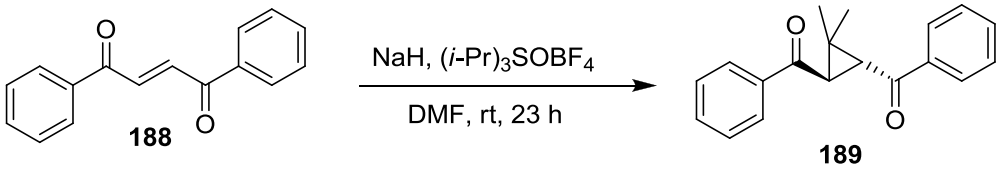
R_f 0.50 (ethyl acetate); mp 159-161 °C (lit.[151] 168-170 °C); ν_{max}(film)/cm^{-1} 2941, 1662, 1623, 1455, 1379, 1307, 1241, 1169, 1107, 1039, 937, 888, 814; δ_H(400 MHz; chloroform-*d*) 0.91 (3 H, s, *H-14*), 0.98-1.11 (2 H, m) 1.23 (3 H, s, *H-19*), 1.24-1.46 (3 H, m), 1.52-1.84 (6 H, m), 1.92-2.03 (2 H, m), 2.31-2.51 (2 H, m), 3.79-3.84 (4 H, m, *H-11*, *H-12*), 6.06 (1 H, s, *H-2*), 6.21 (1 H, d, *H-21*), 7.05 (1 H, d, *H-20*); δ_C(100 MHz; chloroform-*d*) 14.3 (*C-14*), 18.7 (*C-19*), 22.3 (*C-8*), 22.8 (*C-16*), 30.2 (*C-15*), 32.8 (*C-5*), 32.9 (*C-4*), 34.0 (*C-9*), 35.8 (*C-6*), 43.5 (*C-18*), 45.9 (*C-13*), 49.3 (*C-7*), 52.1 (*C-17*), 64.5 (*C-12*), 65.2 (*C-11*), 118.9 (*C-10*), 123.9 (*C-2*), 127.5 (*C-21*), 155.8 (*C-20*), 169.1 (*C-3*), 186.4 (*C-1*); *m/z* (ESI) 351 ($[MNa]^+$) [HRMS (ESI): calculated for $C_{21}H_{28}NaO_3$, 351.1931 Found: $[MNa]^+$, 351.1921 (1.9 ppm error)].

Obtained data in accordance with previously reported data.[151]

(DSP-II-24)

4.2.7 Cyclopropanation of other substrates

((1*RS*, 2*RS*)-3,3-Dimethylcyclopropane-1,2-diyl)bis(phenylmethanone) 189



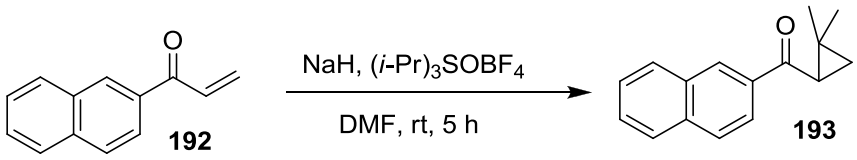
Reaction performed following method B using (*E*)-1,4-diphenylbut-2-ene-1,4-dione **188** (100 mg, 0.42 mmol, 1.0 equiv). The mixture was stirred at room temperature for 23 h. Purification by flash column chromatography (SiO_2, 15 g, 9:1 petrol/ethyl acetate, 25 mm Ø), gave 78 mg (0.28 mmol, 68%) of **189** as a colourless solid.

R_f 0.52 (3:1 petrol/ethyl acetate); mp 70-71 °C (lit.[116] 70-71 °C) δ_H(400 MHz; chloroform-*d*) 1.35 (6 H, s, C*H*$_3$), 3.54 (2 H, s, C*H*), 7.49-7.53 (4 H, m, Ar*H*), 7.58-7.62 (2 H, m, Ar*H*), 8.01-8.03 (4 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[116]

(DSP-II-23)

(±)-1,1a-Dihydro-1,1-dimethyl-7a*H*-cyclopropa[*b*]naphthalene-2,7-dione 193



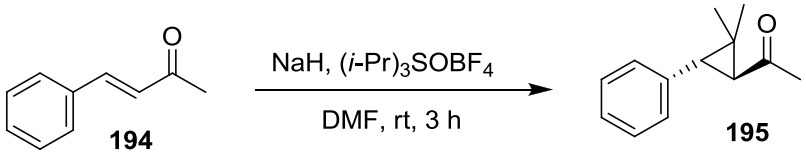
Reaction performed following method B using 1-(naphthalen-6-yl)prop-2-en-1-one **192** (100 mg, 0.55 mmol, 1.0 equiv). The mixture was stirred at room temperature for 5 h. Purification by flash column chromatography (SiO_2, 15 g, 9:1 petrol/ethyl acetate, 35 mm Ø), gave 53 mg, (0.23 mmol, 40%)) of **193** as a yellow oil.

R_f 0.58 (3:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 1.01 (1 H, dd, *J* 7.5, 4.0 Hz, C*H*), 1.12 (3 H, s, C*H*$_3$), 1.42 (3 H, s, C*H*$_3$), 1.58 (1 H, dd, *J* 5.5, 4.0 Hz, C*H*), 2.63 (1 H, dd, *J* 7.5, 5.5 Hz, C*H*), 7.52-7.62 (2 H, m, Ar*H*), 7.89 (2 H, t, *J* 8.0 Hz, Ar*H*), 7.98 (1 H, d, *J* 8.0 Hz, Ar*H*), 8.03 (1 H, dd, *J* 8.5, 1.5 Hz, Ar*H*), 8.46 (1 H, s, Ar*H*).

Obtained data in accordance with previously reported data.[137]

(DSP-II-33)

1-((1*RS*, 3*RS*)-2,2-Dimethyl-3-phenylcyclopropyl)ethanone 195



Reaction performed following method B using (*E*)-4-phenylbut-3-en-2-one **194** (100 mg, 0.68 mmol, 1.0 equiv). The mixture was stirred at room temperature for 3 h. Purification by flash column chromatography (SiO_2, 30 g, 9:1 petrol/ethyl acetate, 25 mm Ø), gave 44 mg, (0.23 mmol, 33%) of **195** as a colourless oil.

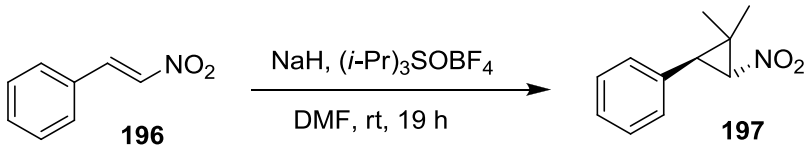
R_f 0.59 (3:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 0.97 (3 H, s, CH_3), 1.27 (3 H, s, CH_3), 2.30 (1 H, d, *J* 6.0 Hz, C*H*), 2.33 (3 H, s, CH_3), 2.84 (1 H, d, *J* 6.0 Hz, C*H*), 7.12-7.15 (2 H, m, Ar*H*), 7.17-7.22 (1 H, m, Ar*H*), 7.25-7.30 (2 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[258]

(DSP-II-18)

4.2.8 Cyclopropanation of non-carbonyl Michael acceptors

((1*SR*, 3*RS*)-2,2-Dimethyl-3-nitrocyclopropyl)benzene 197

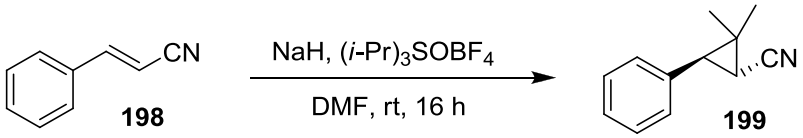


Reaction performed following method B using (*E*)-nitrostyrene **196** (mg, 0.67 mmol, 1.0 equiv). The mixture was stirred at room temperature for 19 h. Purification by flash column chromatography (SiO_2, 15 g, 9:1 petrol/ethyl acetate, 35 mm Ø), gave 123 mg, (0.64 mmol, 93%) of **197** as a colourless oil.

R_f 0.60 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3064, 3031, 2960, 2927, 2879, 2359, 1603, 1536, 1500, 1451, 1361, 1268, 1113, 1055, 1029, 952, 930, 862, 828, 770, 716, 700; δ_H(400 MHz; chloroform-*d*) 1.00 (3 H, s, CH_3), 1.48 (3 H, s, CH_3), 3.36 (1 H, d, *J* 4.5 Hz, C*H*), 4.47 (1 H, d, *J* 4.5 Hz, C*H*), 7.14-7.19 (2 H, m, Ar*H*), 7.25-7.35 (3 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 19.6 (*C*H_3), 20.7

(CH_3), 33.0 ($C(CH_3)_2$), 38.9 (*C*H), 70.3 (*C*H), 127.3 (Ar), 128.4 (Ar), 128.6 (Ar), 134.1 (Ar); *m/z* (CI) 209 ($[MNH_4]^+$, 78%), 145 (100%) [HRMS (CI): calculated for $C_{11}H_{17}N_2O_2$, 209.1290 Found: $[MNH_4]^+$, 209.1288 (1.1 ppm error)].
(DSP-II-30)

(1*RS*, 3*RS*)-2,2-Dimethyl-3-phenylcyclopropanecarbonitrile 199

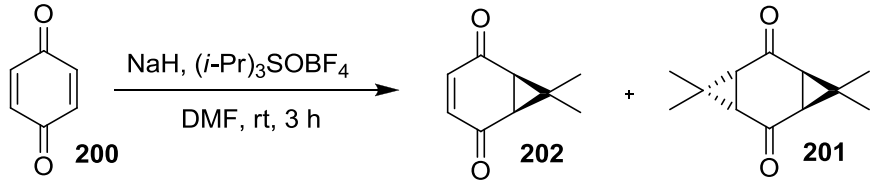


Reaction performed following method B using (*E*)-cinnamonitrile **198** (100 mg, 0.77 mmol, 1.0 equiv). The mixture was stirred at room temperature for 16 h. Purification by flash column chromatography (SiO_2, 15 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 71 mg, (0.42 mmol, 51%) of **199** as a yellow oil.
R_f 0.61 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3032, 2961, 2926, 2234 (C≡N), 1603, 1497, 1451, 1382, 1270; δ_H(400 MHz; chloroform-*d*) 0.91 (3 H, s, CH_3), 1.49 (3 H, s, CH_3), 1.63 (1 H, d, *J* 5.5 Hz, C*H*), 2.52 (1 H, d, *J* 5.5 Hz, C*H*), 7.12-7.16 (2 H, m, Ar*H*), 7.22-7.34 (3 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 15.1 (*C*H_3), 20.2 (*C*H_3), 23.8 ($C(CH_3)_2$), 26.5 (*C*H), 37.7 (*C*H), 120.5 (C≡N), 127.1 (Ar*H*), 128.4 (Ar*H*), 128.5 (Ar*H*), 135.2 (Ar); *m/z* (CI) 189 ($[MNH_4]^+$, 100%), [HRMS (CI): calculated for $C_{12}H_{17}N_2O_2$, 189.1392; found $[MNH_4]^+$, 189.1387 (2.6 ppm error)].
(DSP-II-36)

4.2.9 *Bis*-Cyclopropanation

7,7-dimethylbicyclo[4.1.0]hept-3-ene-2,5-dione 202

(2*RS*, 4*SR*, 6*SR*, 8*RS*)-4,4,8,8-Tetramethyltricyclo[5.1.0.$0^{0,0}$]octane-2,6-dione 201



A 50 mL round bottomed flask with a stirrer-bar was charged with sodium hydride (60% *w/w* in mineral oil, 44 mg, 1.11 mmol, 1.2 equiv), a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon, as DMF (8 mL) added *via* syringe and the grey suspension cooled to 0 °C (ice-bath). The septum was briefly removed to add tri*iso*propylsulfoxonium tetrafluoroborate **131** (293 mg, 1.11 mmol, 1.2 equiv) and the suspension stirred for 5 min before the addition of a solution of the benzoquinone **200** (100 mg, 0.93 mmol, 1.0 equiv) in DMF (2 mL) *via* cannula. The mixture was stirred at 0 °C for 5 min before being warmed to room temperature and stirred continuously until the reaction was complete by TLC. After 3 h stirring the solution was quenched with a saturated solution of ammonium chloride (10 mL), diluted with water (50 mL) and extracted with diethyl ether (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 15 g, 3:1 petrol/ethyl acetate, 20 mm Ø), 9 mg (0.06 mmol, 7%) of *mono*-adduct **202** was obtained as a cream solid and 64 mg (0.33 mmol, 36%) of *bis*-adduct **201** was obtained as brown needles.

Mono-adduct - 7,7-dimethylbicyclo[4.1.0]hept-3-ene-2,5-dione **202**

R_f 0.29 (3:1 petrol/ethyl acetate); mp 60-62 °C; ν_{max}(film)/cm^{-1} 1673, 1653, 1458, 1380, 1304, 1117, 1050; δ_H(400 MHz; chloroform-*d*) 1.34 (3 H, s, CH_3), 1.38 (3 H, s, CH_3), 2.33 (2 H, s, C*H*) 6.61 (2 H, s, C*H*); δ_C(100 MHz; chloroform-*d*) 15.6 (*C*H_3), 29.2 (*C*H_3), 39.4 (*C*(CH_3)$_2$), 140.7 (*C*H), 194.7 (*C*=O); *m/z* (EI) 150 (M^+,

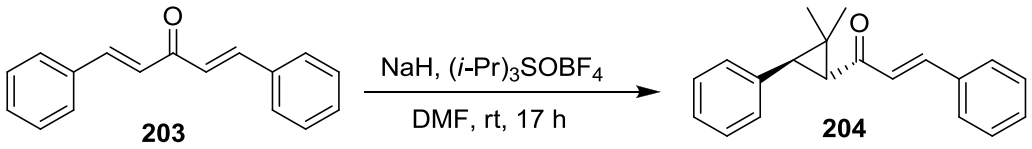
35%), 135 (100%), 107 (35%), 79 (60%), 77 (35%) [HRMS (EI): calculated for $C_9H_{10}O_2$, 150.0681 Found: M^+, 150.0675 (4.0 ppm error)].

Bis-adduct - (2RS, 4SR, 6SR, 8RS)-4,4,8,8-Tetramethyltricyclo[5.1.0.0^{0,0}]octane-2,6-dione **201**

R_f 0.23 (3:1 petrol/ethyl acetate); mp 162-164 °C (lit.[137] 155-158 °C); δ_H(400 MHz; chloroform-*d*) 1.26 (6 H, s, C*H*$_3$), 1.37 (6 H, s, C*H*$_3$), 1.97 (4 H, s, C*H*). Obtained data in accordance with previously reported data.[137]

(DSP-II-93)

(*E*)-1-((1*RS*,3*RS*)-2,2-Dimethyl-3-phenylcyclopropyl)-3-phenylprop-2-en-1-one 204



203 **204**

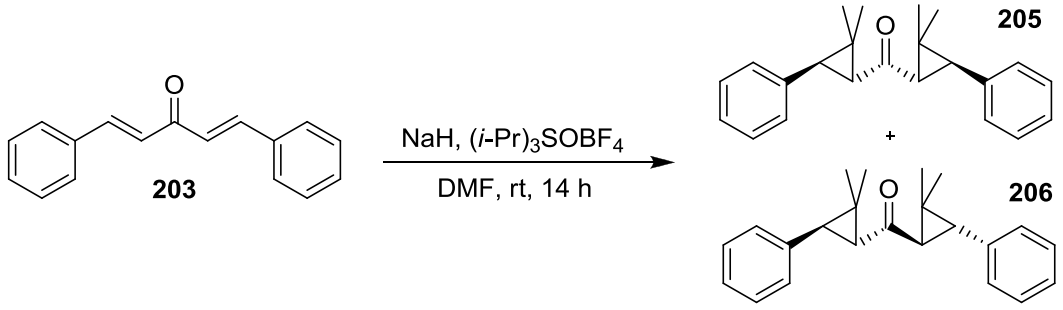
A 25 mL round bottomed flask with a stirrer-bar was charged with sodium hydride (60% *w/w* in mineral oil, 21 mg, 0.52 mmol, 1.2 equiv), a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon, as DMF (4 mL) added *via* syringe and the grey suspension cooled to 0 °C (ice-bath). The septum was briefly removed to add tri*iso*propylsulfoxonium tetrafluoroborate **131** (136 mg, 0.52 mmol, 1.2 equiv) and the suspension stirred for 5 min before the addition of a solution of dibenzylidene acetone **203** (100 mg, 0.43 mmol, 1.0 equiv) in DMF (1 mL) *via* cannula. The mixture was stirred at 0 °C for 5 min before being warmed to room temperature and stirred continuously until the reaction was complete by TLC. After 17 h the solution was quenched with a saturated solution of ammonium chloride (5 mL), diluted with water (25 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 15 g, 19:1 petrol/ethyl acetate, 25 mm Ø), 65 mg (0.24 mmol, 55%) of **204** was obtained as a colourless solid along with 13 mg (0.04 mmol, 9%) of the *bis*-addition products **205** and **206**.

R_f 0.52 (3:1 petrol/ethyl acetate); mp 75-76 °C; ν_{max}(film)/cm^{-1} 3082, 3058, 3027, 2975, 2945, 2921, 2869, 1672, 1647, 1606, 1576, 1495, 1448, 1418, 1377, 1342, 1304, 1282, 1234, 1202, 1179, 1107, 1055, 1029, 976, 913, 860, 801, 767; δ_H(400 MHz; chloroform-*d*) 1.06 (3 H, s, C*H*$_3$), 1.30 (3 H, s, C*H*$_3$), 2.56 (1 H, d, *J* 6.0 Hz, C*H*), 3.02 (1 H, d, *J* 6.0 Hz, C*H*), 6.96 (1 H, d, *J* 16.0 Hz, C*H*) 7.18-7.24 (3 H, m, Ar*H*), 7.26-7.32 (2 H, m, Ar*H*), 7.38-7.45 (3 H, m, Ar*H*), 7.57-7.62 (2 H, m, Ar*H*), 7.59 (1 H, d, *J* 16.0 Hz, C*H*); δ_C(100 MHz; chloroform-*d*) 20.2 (*C*H$_3$), 22.4 (*C*H$_3$), 33.3 (*C*(CH$_3$)$_2$), 38.1 (*C*H), 39.3 (*C*H), 126.4 (ArH), 128.1 (ArH), 128.2 (ArH), 128.4 (ArH), 129.0 (ArH), 129.0 (ArH), 130.4 (ArH), 134.7 (Ar), 137.9 (Ar) 141.9 (ArH), 197.3 (*C*=O); *m/z* (ESI) 299 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{20}H_{20}NaO$, 299.1406 Found: [MNa]$^+$, 299.1411 (1.7 ppm error)].

(DSP-II-45)

Bis((1*RS*, 3*RS*)-2,2-dimethyl-3-phenylcyclopropyl)methanone 205

((1*RS*, 3*RS*)-2,2-dimethyl-3-phenylcyclopropyl)((1*SR*, 3*SR*)-2,2-dimethyl-3-phenylcyclopropyl)methanone 206



A 25 mL round bottomed flask with a stirrer-bar was charged with sodium hydride (60% *w/w* in mineral oil, 128 mg, 3.22 mmol, 2.4 equiv), a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon, as DMF (10 mL) added *via* syringe and the grey suspension cooled to 0 °C (ice-bath). The septum was briefly removed to add tri*iso*propylsulfoxonium tetrafluoroborate **131** (850 mg, 3.22 mmol, 2.4 equiv) and the suspension stirred for 5 min before the addition of a solution of dibenzylidene acetone **203** (314 mg, 1.34 mmol, 1.0 equiv) in DMF (2 mL) *via* cannula. The mixture was stirred at 0 °C for 5 min before being warmed to room temperature and stirred continuously

until the reaction was complete by TLC. After 14 h the solution was quenched with a saturated solution of ammonium chloride (10 mL), diluted with water (50 mL) and extracted with diethyl ether (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 20 g, 19:1 petrol/ethyl acetate, 20 mm Ø), 350 mg (1.11 mmol, 83%) of **205** and **206** was obtained as a colourless solid, a mixture of 2 inseparable diastereoisomers (2.15:1). Repeated recrystallisation from EtOH-H_2O (× 10) gave only the major diastereomer and a crystal suitable for X-ray diffraction was obtained by slow evaporation from methanol.

R_f 0.30 (9:1 petrol/ethyl acetate; no separation); mp 55-57 °C. ν_{max}(film)/cm^{-1} 3027, 2972, 2950, 2919, 2871, 2361, 2338, 1666, 1602, 1579, 1497, 1443, 1422, 1375, 1278, 1103, 1070, 770; *m/z* (ESI) 341 ($[MNa]^+$) [HRMS (ESI): calculated for $C_{23}H_{26}NaO$, 341.1876 Found: $[MNa]^+$, 341.1882 (1.8 ppm error)].

*Major diastereoisomer – bis((1RS, 3RS)-2,2-dimethyl-3-phenylcyclopropyl)methanone **205***

δ_H(400 MHz; chloroform-*d*) 1.03 (6 H, s, C*H*$_3$), 1.29 (6 H, s, C*H*$_3$), 2.54 (2 H, d, *J* 6.0 Hz, C*H*), 2.93 (2 H, d, *J* 6.0 Hz, C*H*), 7.17-7.32 (10 H, m, Ar*H*); δ_C(125 MHz; chloroform-*d*) 20.6 (*C*H$_3$), 22.6 (*C*H$_3$), 33.7 (*C*(CH$_3$)$_2$), 38.6 (*C*H), 42.0 (*C*H), 126.3 (ArH), 128.1 (ArH), 128.9 (ArH), 138.0 (Ar), 205.2 (*C*=O); Structure configuration determined by single crystal X-ray crystallography - CCDC deposition number 698581.

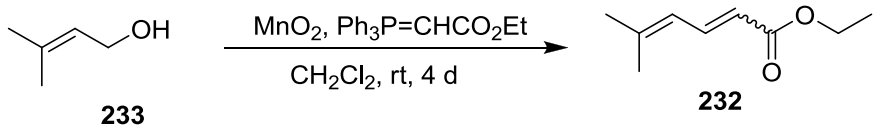
*Minor diastereoisomer – ((1RS, 3RS)-2,2-dimethyl-3-phenylcyclopropyl)((1SR, 3SR)-2,2-dimethyl-3-phenylcyclopropyl)methanone **206***

δ_H(400 MHz; chloroform-*d*) 1.05 (6 H, s, C*H*$_3$), 1.32 (6 H, s, C*H*$_3$), 2.50 (2 H, d, *J* 6.0 Hz, C*H*), 2.92 (2 H, d, *J* 6.0 Hz, C*H*), 7.17-7.32 (10 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 20.3 (*C*H$_3$), 22.4 (*C*H$_3$), 32.6 (*C*(CH$_3$)$_2$), 38.2 (*C*H), 41.9 (*C*H), 126.3 (ArH), 128.1 (ArH), 128.8 (ArH), 137.9 (Ar), 205.0 (*C*=O).

(DSP-II-67)

4.2.10 Approaches towards chrysanthemic acid

Ethyl 5-methylhexa-2,4-dienoate 232



233 **232**

A 250 mL round-bottomed flask with stirrer-bar was charged with 3-methylbut-2-en-1-ol **233** (861 mg, 10.0 mmol, 1.0 equiv), (carbethoxymethylene)triphenylphosphorane (4.18 g, 12.0 mmol, 1.2 equiv) and dichloromethane (100 mL). Manganese(IV) oxide (8.69 g, 100 mmol, 10.0 equiv) was added in a single portion and the flask stoppered and the black suspension was stirred at room temperature. After 4 days the mixture was filtered through a Celite pad, washing with ethyl acetate (100 mL) and concentrated *in vacuo* to give an orange oil. Purification by flash column chromatography (SiO_2, 50 g, 19:1 petrol/diethyl ether, 40 mm Ø), gave 950 mg (6.16 mmol, 62%) of *E*-**232** as a colourless oil along with 80 mg (0.52 mmol, 5.2%) of *Z*-**232** as a colourless oil.

E isomer

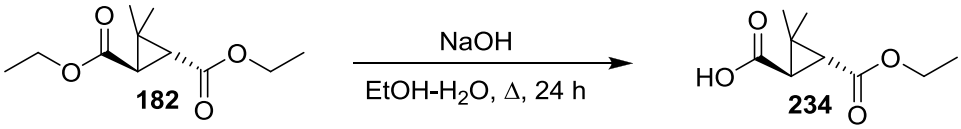
R_f 0.37 (19:1 petrol/diethyl ether); δ_H(400 MHz; chloroform-*d*) 1.29 (3 H, t, *J* 7.0 Hz, CH_2CH_3), 1.87 (3 H, s, CH_3), 1.89 (3 H, s, CH_3) 4.19 (2 H, q, *J* 7.0 Hz, CH_2), 5.75 (1 H, d, *J* 15.0 Hz, C*H*), 5.98 (1 H, dd, *J* 12.0 Hz, C*H*), 7.55 (1 H, dd, *J* 15.0, 12.0 Hz, C*H*); δ_C(100 MHz; chloroform-*d*) 14.3 (CH_3), 18.9 (CH_3), 26.5 (CH_3), 60.1 (CH_2), 118.5 (*C*H), 123.7 (*C*H), 141.0 (*C*H), 146.2 (*C*), 167.7 (*C*=O).

Z isomer

R_f 0.24 (19:1 petrol/diethyl ether); ν_{max}(film)/cm^{-1} 2921, 2852, 1729, 1600, 1461, 1378, 1268, 1120, 1074; δ_H(400 MHz; chloroform-*d*) 1.29 (3 H, t, *J* 7.0 Hz, CH_2CH_3), 1.85 (3 H, s, CH_3), 1.91 (3 H, s, CH_3) 4.17 (2 H, q, *J* 7.0 Hz, CH_2), 5.55 (1 H, d, *J* 12.0 Hz, C*H*), 6.85 (1 H, dd, *J* 12.0, 12.0 Hz, C*H*), 7.19 (1 H, d, *J* 12.0 Hz, C*H*); δ_C(100 MHz; chloroform-*d*) 14.3 (CH_3), 18.2 (CH_3), 26.9 (CH_3), 59.7 (CH_2), 114.7 (*C*H), 121.9 (*C*H), 140.5 (*C*H), 146.6 (*C*), 166.9 (*C*=O).

Obtained data in accordance with previously reported data.[259, 260]
(DSP-VII-31)

(1*RS*,3*RS*)-3-(Ethoxycarbonyl)-2,2-dimethylcyclopropanecarboxylic acid 234



A 25 mL round-bottomed flask with stirrer-bar was charged with (1*RS*, 2*RS*)-diethyl 3,3-dimethylcyclopropane-1,2-dicarboxylate **182** (536 mg, 2.50 mmol, 1.0 equiv) and ethanol (5 mL). A condenser was fitted and the solution heated to reflux. A solution of sodium hydroxide (100 mg, 2.50 mmol, 1.0 equiv) in water (1 mL) was added dropwise over 30 min. On complete addition the colourless solution was stirred at reflux overnight. After 24 h, the reaction was diluted with water (20 mL), quenched with a saturated solution of sodium bicarbonate (10 mL) and extracted with diethyl ether (2 × 20 mL). The aqueous layer was acidified to pH 1 with 10% hydrochloric acid (*ca* 5 mL) and extracted with ethyl acetate (2 × 20 mL). The ethyl acetate layers were combined and dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 465 mg (2.50 mmol, 100%) of **234** as a colourless solid.

R_f 0.41 (3:2 petrol/ethyl acetate); ν_{max}(film)/cm^{-1}2959, 1727, 1698, 1449, 1405, 1333, 1254, 1172, 1111, 845; δ_H(400 MHz; chloroform-*d*) 1.27 (3 H, t, *J* 7.0 Hz, CH_2CH_3), 1.31 (3 H, s, CH_3), 1.33 (3 H, s, CH_3), 2.23 (2 H, d, *J* 5.5 Hz, C*H*), 2.25 (2 H, d, *J* 5.5 Hz, C*H*), 4.08-4.22 (2 H, m, CH_2); δ_C(100 MHz; chloroform-*d*) 14.2 (CH_3), 20.4 (CH_3), 20.4 (CH_3), 31.2 (C), 33.2 (*C*H), 34.3 (*C*H), 60.9 (CH_2), 170.1 (*C*=O), 176.9 (*C*=O); *m/z* (ESI) 209 ([MNa]$^+$) [HRMS (ESI): calculated for $C_9H_{14}NaO_4$, 209.0784 Found: [MNa]$^+$, 209.0788 (1.6 ppm error)].
(DSP-VIII-10)

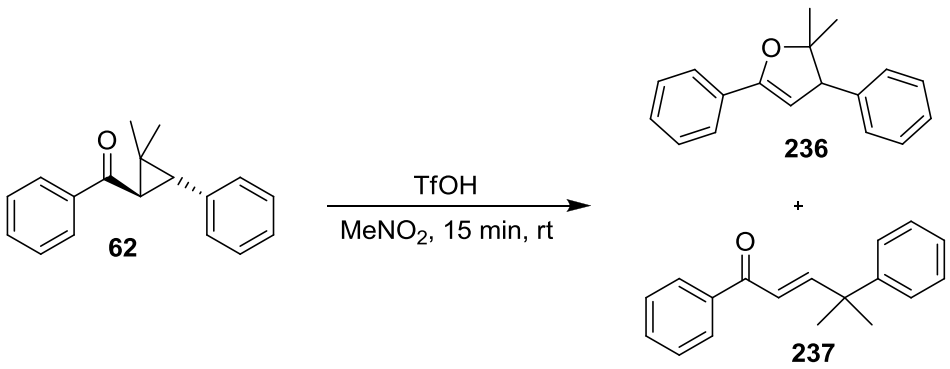
4.3 Cyclopropane rearrangement

4.3.1 Rearrangement of *gem*-dimethylcyclopropanes

Method D: General procedure for the rearrangement of *gem*-dimethyl cyclopropanes

A 25 mL round-bottomed flask with a stirrer-bar was charged with substrate (0.50 mmol, 1.0 equiv), a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon, as nitromethane (5 mL) added *via* syringe followed by a 10% *v/v* solution of trifluoromethanesulfonic acid (75 mg, 0.50 mmol, 1.0 equiv) in nitromethane. The mixture was stirred at room temperature for 15 min. The solution was quenched with a saturated solution of aqueous sodium bicarbonate (20 mL) and extracted with dichloromethane (10 mL). The organic layer was washed with 10% hydrochloric acid (10 mL) and brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Separation by flash column chromatography yielded the described compounds.

2,2-Dimethyl-3,5-diphenyl-2,3-dihydrofuran 236
(*E*)-4-Methyl-1,4-diphenylpent-2-en-1-one 237



Reaction performed following method D using (1*RS*, 3*RS*)-2,2-dimethyl-3-phenylcyclopropyl)(phenyl)methanone **62** (125 mg, 0.50 mmol, 1.0 equiv). Separation by flash column chromatography (SiO_2, 25 g, 19:1 petrol/diethyl ether, 20 mm Ø), gave 43 mg (0.17 mmol, 34%) of **236** as a colourless solid and 31 mg (0.12 mmol, 25%) of **237** as a colourless oil.

2,2-Dimethyl-3,5-diphenyl-2,3-dihydrofuran ***236***

R_f 0.48 (9:1 petrol/ethyl acetate); mp 92-95 °C; ν_{max}(film)/cm^{-1} 2973, 2928, 1493, 1450, 1367, 1278, 1246, 1129, 1055, 1026, 752, 699; δ_H(400 MHz; chloroform-*d*) 0.96 (3 H, s, CH_3), 1.59 (3 H, s, CH_3), 3.98 (1 H, d, *J* 3.0 Hz, C*H*), 5.41 (1 H, d, *J* 3.0 Hz, C*H*), 7.19-7.41 (8 H, m, Ar*H*), 7.62-7.70 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 24.5 (*C*H_3), 29.6 (*C*H_3), 59.0 (Ph*C*H), 87.6 (*C*(CH_3)$_2$), 98.8 (C=*C*H), 125.3 (ArH), 126.9 (ArH), 128.1 (ArH), 128.2 (ArH), 128.4 (ArH), 128.6 (ArH), 131.4 (Ar), 140.0 (Ar), 155.2 (Ph*C*O); *m/z* (ESI) 273 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{18}H_{18}NaO$, 273.1250 Found: [MNa]$^+$, 273.1258 (3.0 ppm error)].

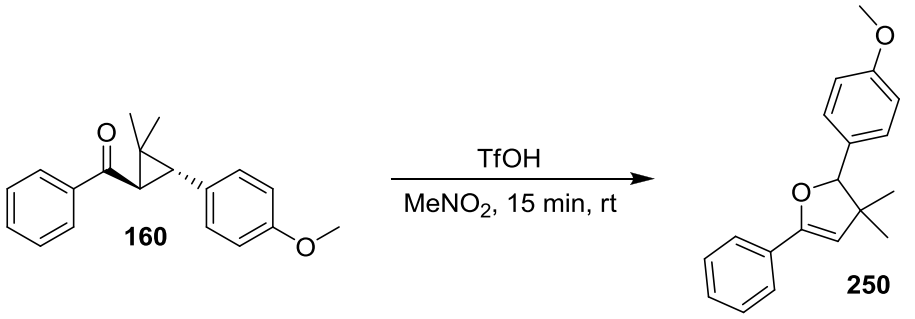
(DSP-II-83)

(E)-4-Methyl-1,4-diphenylpent-2-en-1-one ***237***

R_f 0.38 (9:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3059, 3030, 2968, 2928, 2872, 1721, 1669, 1616, 1579, 1494, 1447, 1384, 1365, 1330, 1298, 1233, 1212, 1179, 1102, 1074, 1019, 991, 764, 698; δ_H(400 MHz; chloroform-*d*) 1.55 (6 H, s, C(CH_3)$_2$), 6.83 (1 H, d, *J* 15.5 Hz, C*H*), 7.23 (1 H, d, *J* 15.5 Hz, C*H*), 7.20-7.27 (1 H, m, Ar*H*), 7.32-7.36 (4 H, m, Ar*H*), 7.44-7.50 (2 H, m, Ar*H*), 7.53-7.58 (1 H, m, Ar*H*), 7.88-7.93 (2 H, m, Ar*H*; δ_C(100 MHz; chloroform-*d*) 28.0 (C(*C*H_3)$_2$), 41.4 (*C*(CH_3)$_2$), 122.3 (*C*H), 126.2 (PhH), 126.4 (PhH), 128.4 (PhH), 128.5 (PhH), 128.5 (PhH), 132.6 (PhH), 138.0 (Ph), 146.4 (Ph), 157.8 (*C*H), 191.4 (*C*=O); *m/z* (ESI) 251 ([MH]$^+$) [HRMS (ESI): calculated for $C_{18}H_{19}O$, 251.1430 Found: [MH]$^+$, 251.1430 (0.2 ppm error)].

(DSP-IV-41)

2-(4-Methoxyphenyl)-3,3-dimethyl-5-phenyl-2,3-dihydrofuran 250

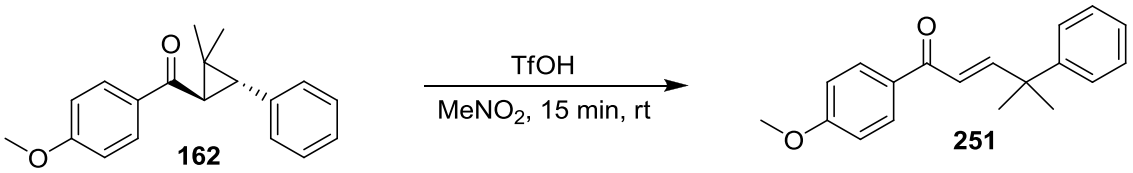


Reaction performed following method D using ((1*RS*, 3*RS*)-3-(4-methoxyphenyl)-2,2-dimethylcyclopropyl)(phenyl)methanone **160** (140 mg, 0.50 mmol, 1.0 equiv). Separation by flash column chromatography (SiO_2, 40 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 67 mg (0.24 mmol, 48%) of **250** as a colourless oil.

R_f 0.45 (9:1 petrol/ethyl acetate); δ_H(270 MHz; chloroform-*d*) 0.68 (3 H, s, CH_3), 1.33 (3 H, s, CH_3), 3.82 (3 H, s, OCH_3), 5.22 (1 H, s, C*H*), 5.36 (1 H, s, C*H*), 6.90 (2 H, d, *J* 8.5 Hz, ArH), 7.28-7.37 (5 H, m, Ar*H*), 7.63 (2 H, d, *J* 8.5 Hz, ArH); *m/z* (ESI) 281 ($[MH]^+$) [HRMS (ESI): calculated for $C_{19}H_{21}O_2$, 281.1536 Found: $[MH]^+$, 281.1529 (2.5 ppm error)].

(DSP-IV-67)

(*E*)-1-(4-Methoxyphenyl)-4-methyl-4-phenylpent-2-en-1-one 251

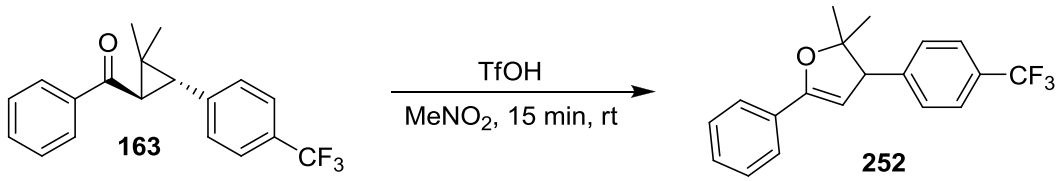


Reaction performed following method D using ((1*RS*, 3*RS*)-2,2-dimethyl-3-phenylcyclopropyl)(4-methoxyphenyl)methanone **162** (140 mg, 0.50 mmol, 1.0 equiv). Separation by flash column chromatography (alumina, 20 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 41 mg (0.15 mmol, 29%) of **251** as a colourless oil.

R_f 0.42 (9:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 1.55 (6 H, s, CH_3), 3.86 (3 H, s, OCH_3), 6.85 (1 H, d, *J* 15.5 Hz, C*H*), 6.95 (2 H, d, *J* 9.0 Hz, Ar*H*), 7.19-7.26 (1 H, m, PhH), 7.22 (1 H, d, *J* 15.5 Hz, C*H*), 7.31-7.38 (4 H, m, PhH)

7.94 (2 H, d, *J* 9.0 Hz, Ar*H*); δ_C(100 MHz; chloroform-*d*) 28.0 (*C*H_3), 41.3 (*C*$(CH_3)_2$), 55.4 (O*C*H_3), 113.7 (ArH), 121.9, 126.1 (ArH), 126.3, 128.3 (ArH), 130.8 (ArH), 130.9 (Ar), 146.6 (Ar), 156.7, 163.2 (Ar), 189.5 (*C*=O).
(DSP-IV-88)

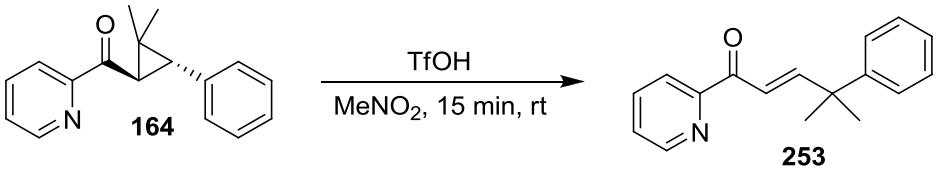
2,2-Dimethyl-5-phenyl-3-(4-(trifluoromethyl)phenyl)-2,3-dihydrofuran 252



Reaction performed following method D using ((1*RS*, 3*RS*)-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)cyclopropyl)(phenyl)methanone **163** (159 mg, 0.50 mmol, 1.0 equiv). Separation by flash column chromatography (SiO_2, 15 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 60 mg (0.19 mmol, 38%) of **252** as a colourless oil.

R_f 0.60 (9:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2921, 1419, 1326, 1165, 1125, 1068, 1021, 842; δ_H(400 MHz; chloroform-*d*) 0.96 (3 H, s, C*H*$_3$), 1.60 (3 H, s, C*H*$_3$), 4.02 (1 H, d, *J* 2.5 Hz, C*H*), 5.39 (1 H, d, *J* 2.5 Hz, C*H*), 7.31-7.41 (5 H, m, Ar*H*), 7.54-7.58 (2 H, m, Ar*H*), 7.64-7.68 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 24.5 (*C*H_3), 29.6 (*C*H_3), 58.7 (Ar*C*H), 87.4 (*C*$(CH_3)_2$), 98.0 (C=*C*H), 124.2 (q, *J* 272 Hz, *C*F_3), 125.1 (q, *J* 3.8 Hz, ArH) 125.3 (ArH), 128.3 (ArH), 128.7 (ArH), 128.9 (ArH), 129.2 (q, *J* 32.3 Hz, *C*CF_3), 131.5 (Ar), 145.3 (Ar), 155.9 (Ph*C*O); δ_F(376 MHz; chloroform-*d*) -62.2; *m/z* (ESI) 319 ($[MH]^+$) [HRMS (ESI): calculated for $C_{19}H_{18}F_3O$, 319.1304 Found: $[MH]^+$, 319.1298 (1.9 ppm error)].
(DSP-IV-98)

(*E*)-4-Methyl-4-phenyl-1-(pyridin-2-yl)pent-2-en-1-one 253



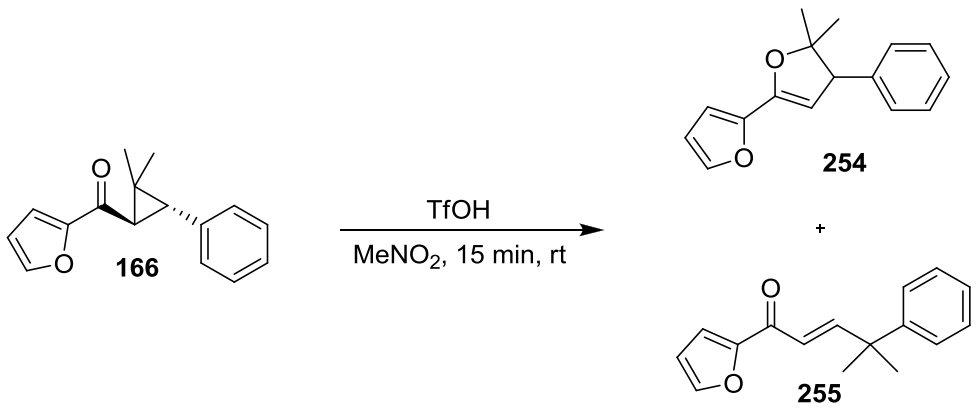
Reaction performed following method D using ((1*RS*, 3*RS*)-2,2-dimethyl-3-phenylcyclopropyl)(pyridin-2-yl)methanone **164** (126 mg, 0.50 mmol, 1.0 equiv). Separation by flash column chromatography (SiO_2, 15 g, 3:1 petrol/ethyl acetate, 20 mm Ø), gave 68 mg (0.27 mmol, 54%) of **253** as a colourless oil.

R_f 0.40 (9:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 0.58 (6 H, s, CH_3), 7.19-7.24 (1 H, m, Ph*H*), 7.29-7.38 (4 H, m, Ph*H*), 7.40 (1 H, d, *J* 16.0 Hz, C*H*), 7.47 (1 H, ddd, *J* 7.5, 5.0, 1.0 Hz, Py*H*), 7.68 (1 H, d, *J* 16.0 Hz, C*H*), 7.85 (1 H, ddd, *J* 8.0, 7.5, 1.5 Hz, Py*H*), 8.13 (1 H, ddd, *J* 8.0, 1.0, 1.0 Hz, Py*H*), 8.72 (1 H, ddd, *J* 5.0, 1.5, 1.0 Hz, Py*H*).

(DSP-IV-95)

2-(5,5-Dimethyl-4-phenyl-4,5-dihydrofuran-2-yl)furan 254

(*E*)-1-(Furan-2-yl)-4-methyl-4-phenylpent-2-en-1-one 255



Reaction performed following method D using ((1*RS*, 3*RS*)-2,2-dimethyl-3-phenylcyclopropyl)(furan-2-yl)methanone **166** (120 mg, 0.50 mmol, 1.0 equiv). Separation by flash column chromatography (alumina, 20 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 22 mg (0.09 mmol, 18%) of **254** as a yellow oil and 33 mg (0.14 mmol, 27%) of **255** as an orange oil.

2-(5,5-Dimethyl-4-phenyl-4,5-dihydrofuran-2-yl)furan ***254***

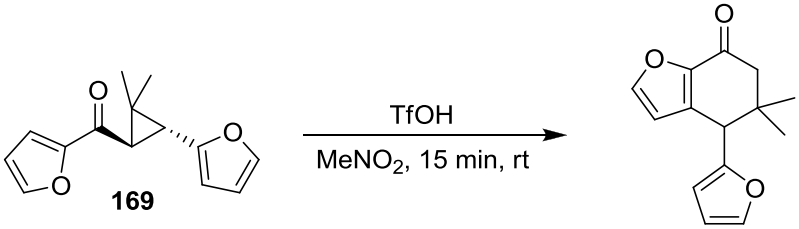
R_f 0.67 (9:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 0.94 (3 H, s, C*H*$_3$), 1.57 (3 H, s, C*H*$_3$), 3.97 (1 H, d, *J* 3.0 Hz, C*H*), 5.32 (1 H, d, *J* 3.0 Hz, C*H*), 6.44 (1 H, dd, *J* 3.5, 2.0 Hz, Fur*H*), 6.48-6.53 (2 H, m, Fur*H*), 7.20-7.32 (5 H, m, Ar*H*).

(E)-1-(Furan-2-yl)-4-methyl-4-phenylpent-2-en-1-one ***255***

R_f 0.41 (9:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3129, 2968, 1665, 1618, 1567, 1494, 1466, 1392, 1306, 1159, 1087, 1047, 1012, 799, 763, 701; δ_H(400 MHz; chloroform-*d*) 1.54 (6 H, s, C*H*$_3$), 6.55 (1 H, dd, *J* 3.5, 1.5 Hz, Fur*H*), 6.78 (1 H, d, *J* 15.5 Hz, C*H*), 7.21-7.25 (2 H, m, Ar*H*, Fur*H*), 7.32 (1 H, d, *J* 15.5 Hz, C*H*), 7.32-7.34 (4 H, m, Ar*H*), 7.61 (1 H, dd, *J* 1.5, 1.0 Hz, Fur*H*); δ_C(100 MHz; chloroform-*d*) 27.9 (*C*H$_3$), 41.2 (*C*(CH$_3$)$_2$), 112.3 (FurH), 117.6 (FurH), 121.2 (*C*H), 126.1 (ArH), 126.4 (ArH), 127.4, 128.4 (ArH), 146.4 (FurH), 153.4, 156.9 (*C*H), 178.5 (*C*=O).

(DSP-IV-87)

4-(Furan-2-yl)-5,5-dimethyl-5,6-dihydrobenzofuran-7(*4H*)-one 256



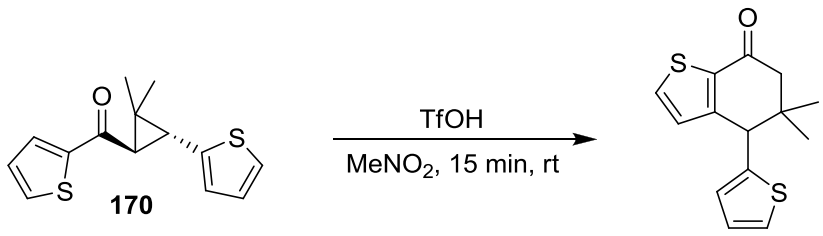
Reaction performed following method D using furan-2-yl((1*RS*, 3*RS*)-3-(furan-2-yl)-2,2-dimethylcyclopropyl)methanone **169** (115 mg, 0.50 mmol, 1.0 equiv). Separation by flash column chromatography (SiO_2, 15 g, 9:1 petrol/ethyl acetate, 20 mm Ø), gave 77 mg (0.33 mmol, 67%) of **256** as a pale yellow oil.

R_f 0.17 (9:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3123, 2963, 2929, 1683, 1598, 1508, 1467, 1443, 1414, 1389, 1372, 1307, 1278, 1252, 1172, 1121, 1072, 1046, 1012, 942, 889, 809, 780, 738, 700; δ_H(400 MHz; chloroform-*d*) 0.92 (3 H, s, C*H*$_3$), 1.18 (3 H, s, C*H*$_3$), 2.31 (1 H, d, *J* 16.5 Hz, C*H*$_2$), 2.70 (1 H, d, *J* 16.5 Hz,

C*H*$_2$), 4.08 (1 H, s, C*H*Fur), 6.08 (1 H, dd, *J* 3.0, 0.5 Hz, Fur*H*), 6.34 (1 H, dd, *J* 3.0, 2.0 Hz, Fur*H*), 6.70 (1 H, d, *J* 2.0 Hz, Fur*H*), 7.34 (1 H, d, *J* 2.0 Hz, Fur*H*) 7.36 (1 H, dd, *J* 2.0, 0.5 Hz, Fur*H*); δ_C(100 MHz; chloroform-*d*) 25.9 (*C*H$_3$), 28.4 (*C*H$_3$), 39.3 (*C*(CH$_3$)$_2$), 45.7 (*C*HFur), 50.3 (*C*H$_2$), 106.3 (FurH), 108.5 (FurH), 110.3 (FurH), 120.7 (Fur), 142.2 (FurH), 143.5 (FurH), 150.8 (Fur), 164.5 (Fur), 193.7 (*C*=O); *m/z* (ESI) 231 ([MH]$^+$) [HRMS (ESI): calculated for $C_{14}H_{15}O_3$, 231.1016 Found: [MH]$^+$, 231.1012 (1.7 ppm error)].

(DSP-IV-59)

5,5-Dimethyl-4-(thiophen-2-yl)-5,6-dihydrobenzo[b]thiophen-7(4H)-one 257

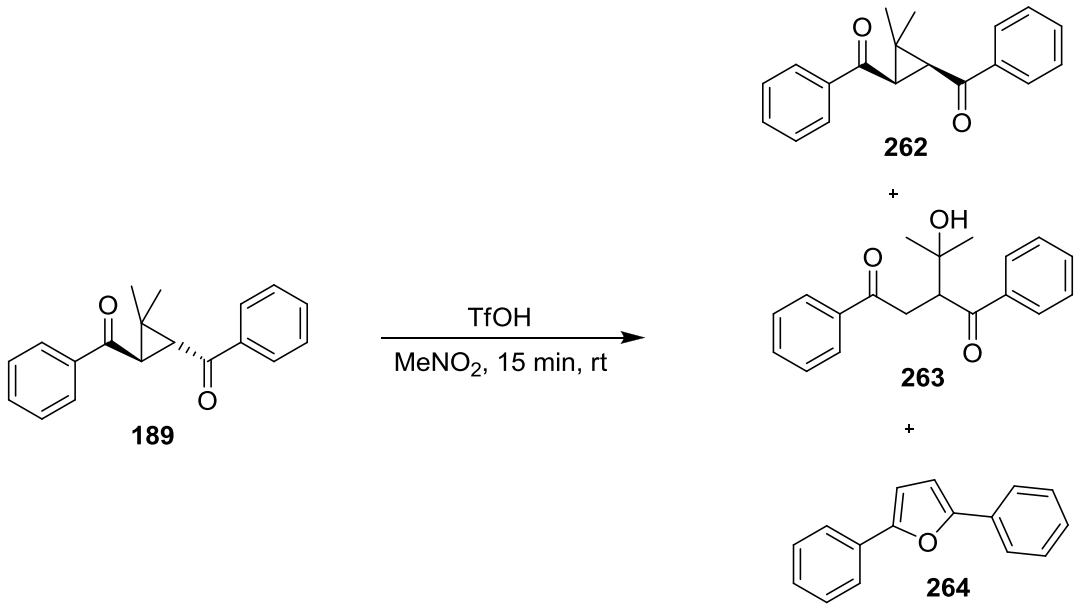


Reaction performed following method D using ((1*RS*, 3*RS*)-2,2-dimethyl-3-(thiophen-2-yl)cyclopropyl)(thiophen-2-yl)methanone **170** (131 mg, 0.50 mmol, 1.0 equiv). Separation by flash column chromatography (SiO_2, 20 g, 4:1 petrol/ethyl acetate, 20 mm Ø), gave 73 mg (0.28 mmol, 56%) of **257** as a yellow oil.

R_f 0.19 (9:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 1.11 (3 H, s, C*H*$_3$), 1.13 (3 H, s, C*H*$_3$), 2.94 (1 H, d, *J* 15.5 Hz, C*H*$_2$), 3.08 (1 H, d, *J* 15.5 Hz, C*H*$_2$), 4.95 (1 H, s, C*H*Thio), 6.97 (1 H, d, *J* 5.0 Hz, Thio*H*), 7.13 (1 H, dd, *J* 5.0, 4.0 Hz, Thio*H*), 7.23 (1 H, d, *J* 5.0 Hz, Thio*H*), 7.67 (1 H, d, *J* 5.0 Hz, Thio*H*) 7.22 (1 H, d, *J* 4.0 Hz, Thio*H*).

(DSP-IV-82)

((1*R*,2*S*)-3,3-Dimethylcyclopropane-1,2-diyl)bis(phenylmethanone) 262
2-(2-Hydroxypropan-2-yl)-1,4-diphenylbutane-1,4-dione 263
2,5-Diphenylfuran 264



Reaction performed following method D using ((1*RS*, 2*RS*)-3,3-dimethylcyclopropane-1,2-diyl)bis(phenylmethanone) **189** (69 mg, 0.25 mmol, 1.0 equiv). Separation by flash column chromatography (SiO_2, 20 g, 9:1 to 3:1 petrol/ethyl acetate, 20 mm Ø), gave 16 mg (0.06 mmol, 23%) of **262** as cream plates, 16 mg (0.05 mmol, 22%) of **263** as a colourless oil and 8 mg (0.04 mmol, 15%) of **264** as a colourless solid.

((1R,2S)-3,3-Dimethylcyclopropane-1,2-diyl)bis(phenylmethanone) ***262***

R_f 0.24 (3:1 petrol/ethyl acetate); mp 129-131 °C (lit.[261] 136-137 °C); ν_{max}(film)/cm^{-1} 3061, 2957, 1680, 1597, 1580, 1448, 1408, 1367, 1246, 1214, 1177, 1116, 1040, 1001, 761, 708, 690; δ_H(400 MHz; chloroform-*d*) 1.39 (3 H, s, C*H*$_3$), 1.52 (3 H, s, C*H*$_3$), 2.81 (2 H, s, C*H*), 7.40-7.46 (4 H, m, Ar*H*), 7.50-7.55 (2 H, m, Ar*H*), 7.93-7.96 (4 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 15.9 (*C*H$_3$), 28.4 (*C*H$_3$), 29.5 (*C*(CH$_3$)$_2$), 38.3 (*C*H), 127.9 (ArH), 128.5 (ArH), 132.7 (ArH), 138.2 (Ar), 195.7 (*C*=O); *m/z* (ESI) 279 ([MH]$^+$) [HRMS (ESI): calculated for $C_{19}H_{19}O_2$, 279.1380 Found: [MH]$^+$, 279.1383 (1.2 ppm error)].
Obtained data in accordance with previously reported data.[261]

2-(2-Hydroxypropan-2-yl)-1,4-diphenylbutane-1,4-dione ***263***

R_f 0.09 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3468 (br), 3061, 2975, 2931, 1677, 1597, 1580, 1448, 1370, 1218, 1181, 1000, 949, 907, 790, 745, 692; δ_H(400 MHz; chloroform-*d*) 1.24 (6 H, s, CH_3), 3.60 (1 H, d, *J* 18.5, 7.5 Hz, CH_2), 3.67 (1 H, dd, *J* 18.5, 4.5 Hz, CH_2), 4.32 (1 H, dd, *J* 7.5, 4.5 Hz, C*H*), 7.40-7.62 (6 H, m, Ar*H*), 7.95-7.99 (2 H, m, Ar*H*), 8.11-8.15 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 28.1 (*C*H_3), 29.3 (*C*H_3), 38.5 (*C*H_2), 48.6 (CH), 71.7 (*C*$(CH_3)_2$OH), 128.2 (ArH), 128.6 (ArH), 128.7 (ArH), 128.8 (ArH), 133.4 (ArH), 133.4 (ArH), 136.2 (Ar), 137.7 (Ar), 198.4 (*C*=O), 205.7 (*C*=O); *m/z* (ESI) 319 ($[MNa]^+$) [HRMS (ESI): calculated for $C_{19}H_{20}NaO_3$, 319.1305 Found: $[MNa]^+$, 319.1305 (0.0 ppm error)].

2,5-Diphenylfuran ***264***

R_f 0.72 (3:1 petrol/ethyl acetate); mp 81-84 °C (lit.[262] 83-85 °C); δ_H(400 MHz; chloroform-*d*) 6.75 (2 H, s, Fur*H*), 7.28 (2 H, tt, *J* 7.5, 1.5 Hz, Ph*H*), 7.42 (4 H, dd, *J* 8.0, 7.5 Hz, Ph*H*), 7.76 (4 H, dd, *J* 8.0, 1.5 Hz, Ph*H*); δ_C(100 MHz; chloroform-*d*) 107.2 (FurH), 123.7 (PhH), 127.3 (PhH), 128.7 (PhH), 130.7 (Ph), 153.3 (Fur); *m/z* (EI) 220 (M^+, 100%), 191 (5%), 115 (10%), 105 (5%), 77 (8%) [HRMS (EI): calculated for $C_{16}H_{12}O$, 220.0888 Found: $[M]^+$, 220.0884 (1.8 ppm error)].

Obtained data in accordance with previously reported data.[263].

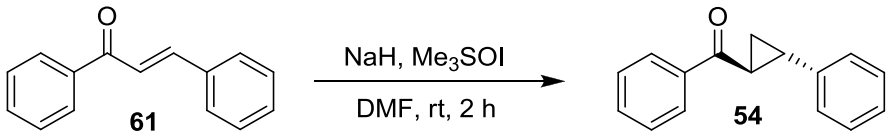
(DSP-IV-99)

4.3.2 Preparation of methylene cyclopropanes

Method E: General procedure for the methylene cyclopropanation of chalcones

A 50 mL round-bottomed flask with a stirrer-bar was charged with sodium hydride (60% *w/w* in mineral oil, 120 mg, 3.00 mmol, 1.2 equiv), a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon, as DMF (20 mL) added *via* syringe and the grey suspension cooled to 0 °C (ice-bath). The septum was briefly removed to add trimethylsulfoxonium iodide (660 mg, 3.00 mmol, 1.2 equiv) and the suspension stirred for 5 min before the addition of a solution of the substrate (2.50 mmol, 1.0 equiv) in DMF (5 mL) *via* cannula. The mixture was stirred at 0 °C for 5 min before being warmed to room temperature and stirred continuously until the reaction was complete by TLC. On completion the solution was quenched with a saturated solution of ammonium chloride (25 mL), diluted with water (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography yielded the desired compound.

Phenyl((1*SR*,2*SR*)-2-phenylcyclopropyl)methanone 54



Reaction performed following method E using (*E*)-chalcone **61** (1.00 g, 4.80 mmol, 1.0 equiv). The mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (SiO_2, 25 g, 19:1 petrol/ethyl acetate, 30 mm Ø), gave 920 mg (4.14 mmol, 86%) of **54** as a colourless solid.

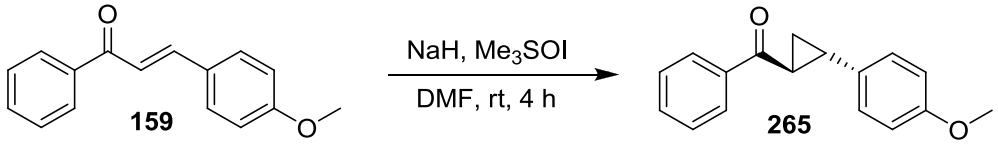
R_f 0.43 (9:1 petrol/ethyl acetate); mp 43-45 °C (lit.[264] 45-47 °C); δ_H(400 MHz; chloroform-*d*) 1.57 (1 H, ddd, *J* 8.0, 6.5, 4.0 Hz, CH_2), 1.93 (1 H, ddd, *J* 9.0, 5.5, 4.0 Hz, CH_2), 2.71 (1 H, ddd, *J* 9.0, 6.5, 4.0 Hz, C*H*), 2.91 (1 H, ddd, *J* 8.0, 5.5, 4.0 Hz, C*H*), 7.17-7.20 (2 H, m, Ar*H*), 7.23 (1 H, tt, *J* 7.5, 2.0 Hz, Ar*H*), 7.29-

7.35 (2 H, m, Ar*H*), 7.44-7.49 (2 H, m, Ar*H*), 7.57 (1 H, tt, *J* 7.5, 2.0 Hz, Ar*H*), 7.98-8.02 (2 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[129, 265]

(DSP-II-73)

((1*SR*,2*SR*)-2-(4-Methoxyphenyl)cyclopropyl)(phenyl)methanone 265



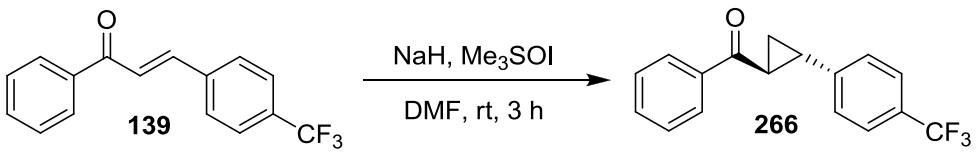
Reaction performed following method E using (*E*)-4-methoxychalcone **159** (701 mg, 2.50 mmol, 1.0 equiv). The mixture was stirred at room temperature for 4 h. Purification by flash column chromatography (SiO_2, 50 g, 9:1 petrol/ethyl acetate, 40 mm Ø), gave 590 mg (2.34 mmol, 94%) of **265** as a colourless solid.

R_f 0.28 (9:1 petrol/ethyl acetate); mp 38-40 °C (lit.[266] 37-38 °C); δ_H(400 MHz; chloroform-*d*) 1.52 (1 H, ddd, *J* 8.0, 6.5, 4.0 Hz, CH_2), 1.90 (1 H, ddd, *J* 9.0, 5.0, 4.0 Hz, CH_2), 2.67 (1 H, ddd, *J* 9.0, 6.5, 4.0 Hz, C*H*), 2.84 (1 H, ddd, *J* 8.0, 5.0, 4.0 Hz, C*H*), 3.80 (3 H, s, OCH_3), 6.86 (2 H, d, *J* 8.5 Hz, Ar*H*), 7.12 (2 H, d, *J* 8.5 Hz, Ar*H*), 7.46 (2 H, dd, *J* 8.0, 7.5 Hz, Ph*H*), 7.56 (1 H, t, *J* 7.5 Hz, Ph*H*), 7.99 (2 H, d, *J* 8.0 Hz, Ph*H*).

Obtained data in accordance with previously reported data.[267]

(DSP-V-7)

Phenyl((1*SR*,2*SR*)-2-(4-(trifluoromethyl)phenyl)cyclopropyl)methanone 266



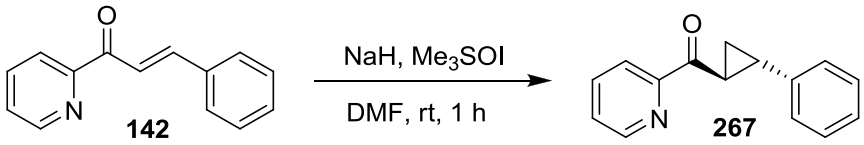
Reaction performed following method E using (*E*)-4-trifluoromethylmethoxychalcone **139** (691 mg, 2.50 mmol, 1.0 equiv). The mixture was stirred at room temperature for 3 h. Purification by flash column chromatography (SiO_2, 50 g, 9:1 petrol/ethyl acetate, 45 mm Ø), gave 658 mg (2.27 mmol, 91%) of **266** as a colourless solid.

R_f 0.67 (3:1 petrol/ethyl acetate); mp 57-60 °C; δ_H(400 MHz; chloroform-*d*) 1.59 (1 H, ddd, *J* 8.0, 6.5, 4.0 Hz, CH_2), 1.97 (1 H, ddd, *J* 9.0, 5.5, 4.0 Hz, CH_2), 2.75 (1 H, ddd, *J* 9.0, 6.5, 4.0 Hz, C*H*), 2.94 (1 H, ddd, *J* 8.0, 5.5, 4.0 Hz, C*H*), 7.47 (2 H, d, *J* 8.5 Hz, Ar*H*), 7.47 (2 H, t, *J* 7.5 Hz, Ph*H*), 7.57 (2 H, d, *J* 8.5 Hz, Ar*H*), 7.58 (1 H, dd, *J* 8.0, 7.5 Hz, Ph*H*), 7.99 (2 H, d, *J* 8.0 Hz, Ph*H*); δ_F(376 MHz; chloroform-*d*) -62.2.

Obtained data in accordance with previously reported data.[268]

(DSP-V-8)

((1*SR*,2*SR*)-2-Phenylcyclopropyl)(pyridin-2-yl)methanone 267



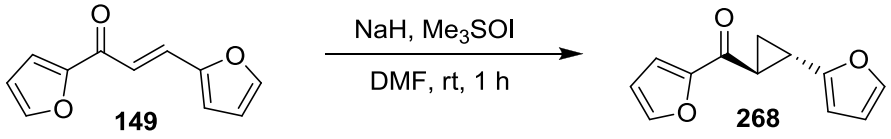
Reaction performed following method E using (*E*)-3-phenyl-1-(pyridin-2-yl)prop-2-en-1-one **142** (523 mg, 2.50 mmol, 1.0 equiv). The mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (SiO_2, 30 g, 9:1 petrol/ethyl acetate, 30 mm Ø), gave 423 mg (1.89 mmol, 76%) of **267** as colourless microcrystals.

R_f 0.48 (3:1 petrol/ethyl acetate); mp 78-80 °C (lit.[269] 80 °C); δ_H(400 MHz; chloroform-*d*) 1.61 (1 H, ddd, *J* 8.5, 6.5, 4.0 Hz, CH_2), 1.88 (1 H, ddd, *J* 9.0, 5.5, 4.0 Hz, CH_2), 2.75 (1 H, ddd, *J* 9.0, 6.5, 4.0 Hz, C*H*), 3.85 (1 H, ddd, *J* 8.5, 5.5, 4.0 Hz, C*H*), 7.18-7.23 (3 H, m, Ph*H*), 7.27-7.32 (2 H, m, Ph*H*), 7.47 (1 H, ddd, *J* 7.5, 5.0, 1.0 Hz, Py*H*), 7.84 (1 H, ddd, *J* 8.0, 7.5, 1.5 Hz, Py*H*), 8.07 (1 H, ddd, *J* 8.0, 1.0, 1.0 Hz, Py*H*), 8.70 (1 H, ddd, *J* 5.0, 1.5, 1.0 Hz, Py*H*); δ_C(100 MHz; chloroform-*d*) 21.0 (*C*H_2), 27.5 (*C*H), 30.7 (*C*H), 121.8 (PyH), 126.2 (PhH), 126.4 (PhH), 127.0 (PyH), 128.4 (PhH), 136.8 (PyH), 140.6 (Ph), 149.0 (PyH), 153.4 (Py), 199.5 (*C*=O); *m/z* (ESI) 224 ($[MH]^+$) [HRMS (ESI): calculated for $C_{15}H_{14}NO$, 224.1070 Found: $[MH]^+$, 224.1069 (0.6 ppm error)].

Melting point in accordance with previously reported data.[269]

(DSP-V-10)

Furan-2-yl((1*SR*,2*SR*)-2-(furan-2-yl)cyclopropyl)methanone 268



Reaction performed following method E using (*E*)-1,3-di(furan-2-yl)prop-2-en-1-one **149** (470 mg, 2.50 mmol, 1.0 equiv). The mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (SiO_2, 50 g, 9:1 petrol/ethyl acetate, 45 mm Ø), gave 474 mg (2.34 mmol, 94%) of **268** as a colourless oil.

R_f 0.23 (9:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 1.58 (1 H, ddd, *J* 8.5, 6.0, 3.5 Hz, C*H*$_2$), 1.78 (1 H, ddd, *J* 9.0, 5.5, 3.5 Hz, C*H*$_2$), 2.70 (1 H, ddd, *J* 9.0, 6.0, 4.0 Hz, C*H*), 2.93 (1 H, ddd, *J* 8.5, 5.5, 4.0 Hz, C*H*), 6.11 (1 H, d, *J* 3.0 Hz, Fur*H*), 6.30 (1 H, dd, *J* 3.0, 2.0 Hz, Fur*H*), 6.55 (1 H, dd, *J* 3.5, 1.5 Hz, Fur*H*), 7.25 (1 H, dd, *J* 3.5, 1.0 Hz, Fur*H*), 7.28 (1 H, d, *J* 2.0 Hz, Fur*H*), 7.61 (1 H, dd, *J* 1.5 Hz, Fur*H*).

Obtained data in accordance with previously reported data.[129]

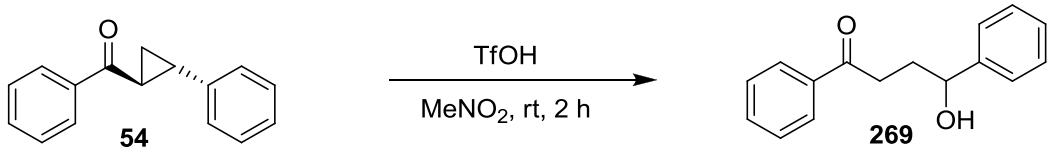
(DSP-V-9)

4.3.3 Rearrangement of methylene cyclopropanes

Method F: General procedure for the rearrangement of methylene cyclopropanes

A 25 mL round-bottomed flask with a stirrer-bar was charged with substrate (0.50 mmol, 1.0 equiv), a septum fitted and the flask purged with argon (balloon). Maintained under argon, as nitromethane (5 mL) added *via* syringe followed by a 10% solution of trifluoromethanesulfonic acid (75 mg, 0.50 mmol, 1.0 equiv) in nitromethane. The mixture was stirred at room temperature for 2 h. The solution was quenched with a saturated solution of sodium bicarbonate (20 mL) and extracted with dichloromethane (10 mL). The organic layer was washed with 10% hydrochloric acid (10 mL) and brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography yielded the desired compound and unreacted starting material.

4-Hydroxy-1,4-diphenylbutan-1-one 269



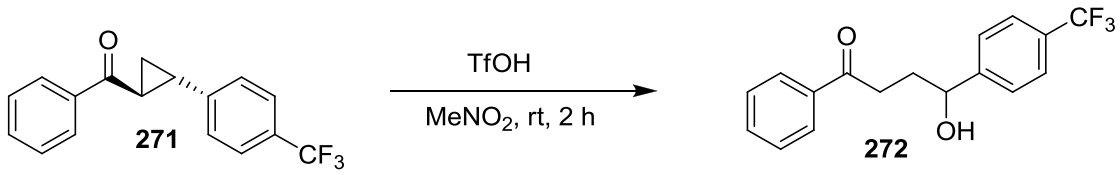
Reaction performed following method F using phenyl((1*SR*,2*SR*)-2-phenylcyclopropyl)methanone **54** (111 mg, 0.50 mmol, 1.0 equiv). Purification by flash column chromatography (SiO_2, 15 g, 3:1 petrol/ethyl acetate, 30 mm Ø), gave 58 mg (0.26 mmol, 48%) of **269** as a colourless solid along with 28 mg (0.13 mmol, 25%) of unreacted starting material **54**.

R_f 0.31 (3:1 petrol/ethyl acetate); mp 93-95 °C (lit.[270] 92-93 °C); δ_H(400 MHz; chloroform-*d*) 2.15-2.27 (2 H, m, C*H*$_2$), 3.13 (2 H, t, *J* 7.0 Hz, C*H*$_2$), 4.85 (1 H, dd, *J* 6.0, 6.0 Hz, C*H*(OH)), 7.26-7.31 (1 H, m, Ph*H*), 7.33-7.41 (4 H, m, Ph*H*), 7.43-7.48 (2 H, m, Ph*H*), 7.54-7.59 (1 H, m, Ph*H*), 7.94-7.97 (2 H, m, Ph*H*).

Obtained data in accordance with previously reported data.[271]

(DSP-V-36)

4-Hydroxy-1-phenyl-4-(4-(trifluoromethyl)phenyl)butan-1-one 272



Reaction performed following method F using phenyl((1*SR*,2*SR*)-2-(4-(trifluoromethyl)phenyl)cyclopropyl)methanone **271** (145 mg, 0.50 mmol, 1.0 equiv). Purification by flash column chromatography (SiO_2, 15 g, 3:1 petrol/ethyl acetate, 30 mm Ø), gave 18 mg (0.06 mmol, 12%) of **272** as a colourless solid along with 108 mg (0.37 mmol, 74%) of unreacted starting material **271**.

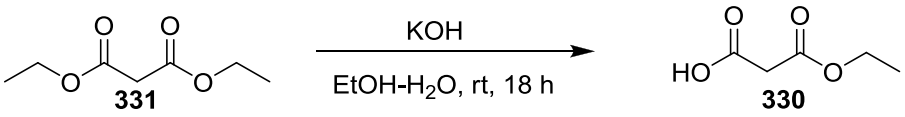
R_f 0.57 (3:1 petrol/ethyl acetate); mp 97-99 °C; δ_H(400 MHz; chloroform-*d*) 2.11-2.30 (2 H, m, C*H*$_2$), 2.82 (1 H, br s, O*H*), 3.07-3.22 (2 H, m, C*H*$_2$), 4.93 (1 H, dd, *J* 8.0, 4.5 Hz, C*H*(OH)), 7.44-7.53 (4 H, m, Ar*H*), 7.55-7.63 (3 H, m, Ar*H*), 7.93-7.97 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 33.0 (*C*H$_2$), 34.5 (*C*H$_2$), 72.9 (*C*H), 124.0 (q, *J* 238 Hz, *C*F$_3$), 125.4 (q, *J* 8 Hz, ArH), 126.0 (ArH), 128.1 (ArH), 128.6 (ArH), 129.7 (q, *J* 32 Hz, CCF$_3$), 133.4 (ArH), 136.6 (Ar), 148.4 (Ar), 200.6 (*C*=O).

(DSP-V-38)

4.4 Preparation of oxindoles

4.4.1 Preparation of ethyl ester oxindoles

***mono*-Ethyl malonate 330**



Based on the procedure of Meijer.[219]

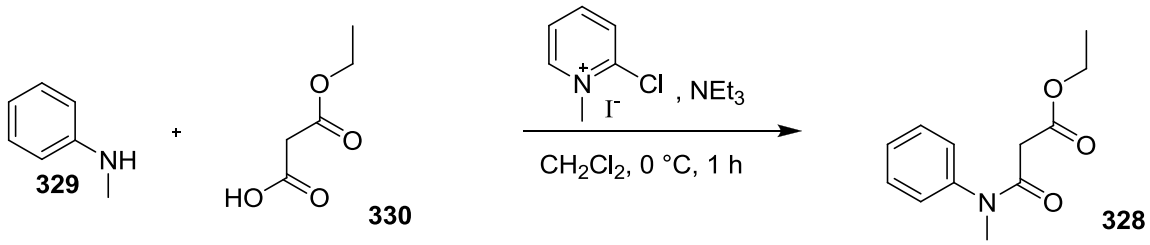
A 1 L pear-shaped flask with stirrer-bar was charged with diethyl malonate **331** (80.1 g, 500 mmol. 1.0 equiv) and ethanol (250 mL) and cooled to 0 °C (ice-bath). A solution of potassium hydroxide (28.1 g, 500 mmol, 1.0 equiv) in ethanol (350 mL) was added to give a viscous colourless suspension. Stirred at 0 °C for 1 h, then the ice-bath was removed and the suspension stirred overnight. After 18 h, diluted with water (300 mL) and concentrated to remove most of the ethanol. The aqueous layer was extracted with diethyl ether (2 × 250 mL) and the organic discarded. The aqueous was acidified to pH 1 with 37% hydrochloric acid (exotherm) and extracted with ethyl acetate (2 × 250 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to give **330** as colourless oil (51.8 g, 392 mmol, 78%).

δ_H(400 MHz; chloroform-*d*) 1.29 (3 H, t, *J* 7.0 Hz, C*H*$_3$), 3.43 (2 H, s, C*H*$_2$), 4.23 (2 H, q, *J* 7.0 Hz, C*H*$_3$), 10.64 (1 H, s, CO$_2$*H*).

Obtained data in accordance with previously reported data.[272]

(DSP-VII-7)

Ethyl 3-(methyl(phenyl)amino)-3-oxopropanoate 328



Based on the procedure of Perry.[51]

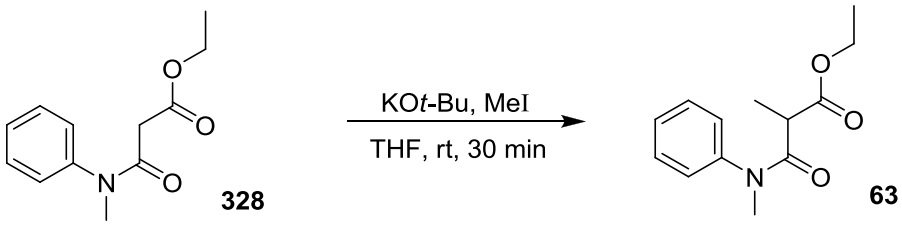
A 100 mL round-bottomed flask with stirrer-bar was charged with *N*-methylaniline **329** (1.00 g, 9.33 mmol, 1.0 equiv), a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as dichloromethane (40 mL) was added and the solution cooled to 0 °C (ice-bath). To this solution, ethyl malonate **330** (1.65 mL, 14.0 mmol, 1.5 equiv), 2-chloro-1-methylpyridinium iodide (7.15 g, 28.0 mmol, 3.0 equiv) and triethylamine (6.50 mL, 46.7 mmol, 5.0 equiv) were added to give a bright yellow suspension. The mixture was stirred at 0 °C for 1 h, before the reaction was quenched with 10% hydrochloric acid (20 mL). The resulting organic layer was washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (SiO_2, 90 g, 1:1 petrol/ethyl acetate, 65 mm Ø), gave 1.40 g (6.33 mmol, 69%) of **328** as a colourless oil.

R_f 0.39 (1:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 1.23 (3 H, t, *J* 7.0 Hz, CH_2CH_3), 3.20 (2 H, s, CH_2), 3.31 (3 H, s, NCH_3), 4.12 (2 H, q, *J* 7.0 Hz, CH_2CH_3) 7.22-7.25 (2 H, m, Ar*H*), 7.33-7.38 (1 H, m, Ar*H*), 7.40-7.45 (2 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[51]

(DSP-V-1)

Ethyl 2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoate 63



Based on the procedure of Perry.[51]

A 250 mL round-bottomed flask with stirrer-bar was charged with ethyl 3-(methyl(phenyl)amino)-3-oxopropanoate **328** (1.11 g, 5.00 mmol, 1.0 equiv), a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as THF (60 mL) was added. Septum briefly removed to add potassium *tert*-butoxide (617 mg, 5.50 mmol, 1.1 equiv) to give a yellow solution which was stirred for 5 min before the dropwise addition of methyl iodide (0.33 mL, 5.25 mmol, 1.05 equiv) over 1 min to give a colourless suspension which was stirred at room temperature. After 30 min the reaction was quenched by the addition of a saturated solution of ammonium chloride (30 mL) and extracted with ethyl acetate (30 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (SiO_2, 50 g, 7:3 petrol/ethyl acetate, 40 mm Ø), gave 1.03 g (4.38 mmol, 86%) of **63** as a colourless oil.

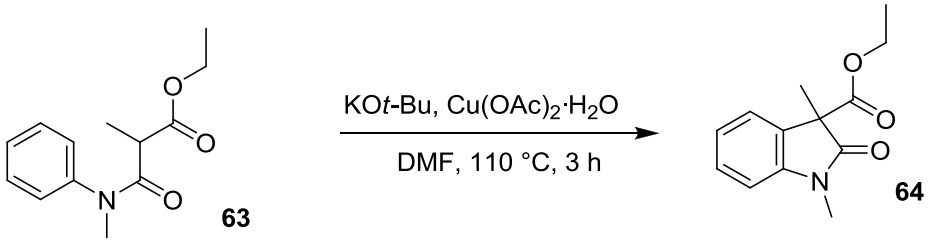
R_f 0.47 (1:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 1.23 (3 H, t, *J* 7.0 Hz, OCH_2CH_3), 1.30 (3 H, d, *J* 7.0 Hz, CH_3), 3.30 (3 H, s, NCH_3), 3.40 (1 H, q, *J* 7.0 Hz, C*H*), 4.03-4.17 (2 H, m, CH_2CH_3), 7.23-7.27 (2 H, m, Ar*H*), 7.34-7.46 (3 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[51]

(DSP-V-2)

Ethyl 1,3-dimethyl-2-oxoindoline-3-carboxylate 64

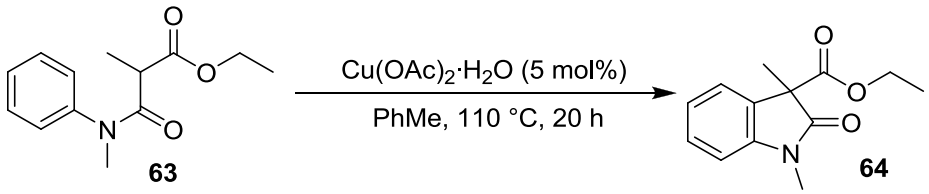
Initial approach:



Based on the procedure of Perry.[51]

A 25 mL round-bottomed flask with stirrer-bar was charged with ethyl 2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoate **63** (118 mg, 0.50 mmol, 1.0 equiv), DMF (10 mL), potassium *tert*-butoxide (62 mg, 0.55 mmol, 1.1 equiv) and copper(II) acetate monohydrate (100 mg, 0.50 mmol, 1.0 equiv). A condenser topped with an argon balloon was fitted and the green suspension heated to 110 °C. The mixture was stirred at this temperature for 3 h before cooling to room temperature and quenching the reaction with a saturated solution of ammonium chloride (10 mL). The solution was diluted with water (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with brine (2 × 30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (SiO_2, 20 g, 3:1 petrol/ethyl acetate, 20 mm Ø), gave 112 mg (0.48 mmol, 95%) of **64** as a colourless oil.

Catalytic procedure:



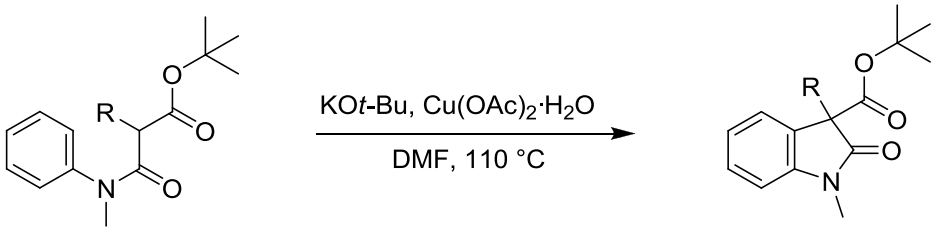
A 25 mL round-bottomed flask with stirrer-bar was charged with ethyl 2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoate **63** (118 mg, 0.50 mmol, 1.0 equiv), copper(II) acetate monohydrate (5 mg, 0.025 mmol, 0.05 equiv) and toluene (10 mL). A condenser was fitted and the blue-green suspension heated to 110 °C. The mixture was stirred at this temperature for 20 h before cooling to room temperature and quenching the reaction with with water (20 mL). The organic layer was washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography

(SiO_2, 20 g, 3:1 petrol/ethyl acetate, 20 mm Ø), gave 94 mg (0.40 mmol, 81%) of **64** as a colourless oil.

R_f 0.31 (3:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 1.34 (3 H, t, CH_2CH_3), 1.66 (3 H, s, CH_3), 3.26 (3 H, s, NCH_3), 4.05-4.20 (2 H, m, CH_2CH_3) 6.87 (1 H, dd, *J* 7.5, 1.0 Hz, Ar*H*), 7.07 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.26 (1 H, dd, *J* 7.5, 1.0 Hz, Ar*H*), 7.32 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*).
Obtained data in accordance with previously reported data.[51]
(DSP-V-4)(DSP-VII-12)

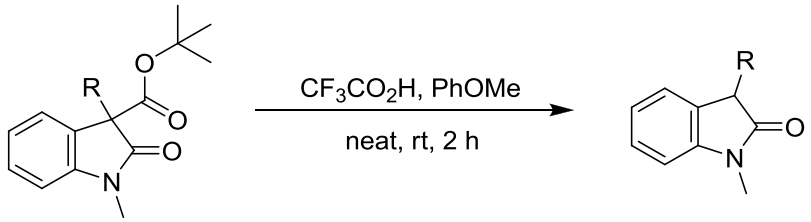
4.4.2 Preparation of *tert*-butyl ester oxindoles

Method G: General procedure for the copper(II) mediated cyclisation of anilides to give oxindoles



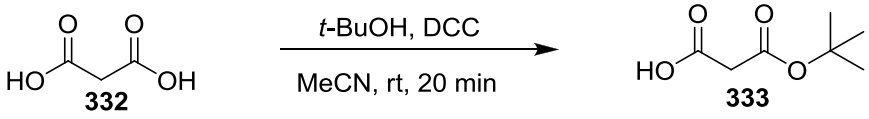
A 25 mL round-bottomed flask with stirrer-bar was charged with substrate (0.50 mmol, 1.00 equiv), DMF (10 mL), potassium *tert*-butoxide (62 mg, 0.55 mmol, 1.1 equiv) and copper(II) acetate monohydrate (100 mg, 0.50 mmol, 1.0 equiv). A condenser topped with a drying tube ($CaCl_2$) was fitted and the reaction heated to 110 °C until the reaction was complete by TLC. On completion the green-brown suspension was cooled to room temperature and the quenched by addition of a saturated solution of ammonium chloride (10 mL). The mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with brine (2 × 30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography yielded the desired compound.

Method H: General procedure for decarboxylative preparation of oxindoles



A 25 mL round-bottomed flask with stirrer-bar was charged with substrate (0.25 mmol, 1.0 equiv), anisole (82 μL, 0.75 mmol, 3.0 equiv), and a septum with argon balloon fitted. TFA (1 mL) was added and the brown solution stirred at room temperature. After 2 h the stirrer-bar was removed and the mixture concentrated *in vacuo*. Purification by flash column chromatography yielded the desired compound.

***tert*-Butyl malonate 333**



Based on a procedure by Melman.[223]

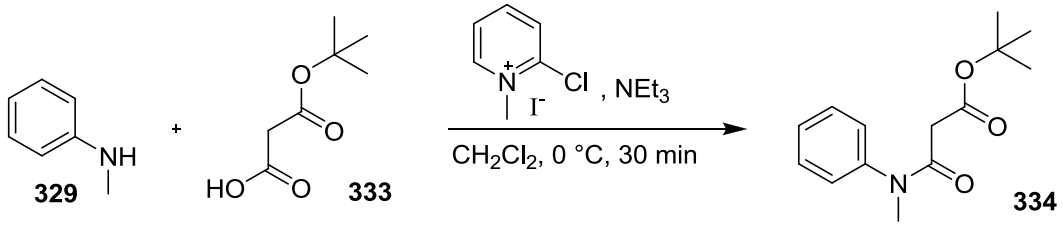
A 250 mL round-bottomed flask with stirrer-bar was charged with malonic acid **332** (5.20 g, 50.0 mmol. 1.0 equiv), acetonitrile (150 mL) and *tert*-butanol (9.60 mL, 100 mmol, 2.0 equiv), a septum fitted and the flask purged with argon (balloon). A solution of dicyclohexylcarbodiimide (11.4 g, 55.0 mmol, 1.1 equiv) in acetonitrile (55 mL) was added *via* cannula to give a white suspension. Stirred at room temperature for 30 min before filtering to give a colourless solution which was concentrated *in vacuo* to give a colourless oil. The oil was taken into solution with diethyl ether (250 mL) and extracted with saturated aqueous sodium bicarbonate (2 × 100 mL). The aqueous layer was acidified to pH 1 by addition of a 10% solution of hydrochloric acid (70 mL) and extracted with ethyl acetate (2 × 175 mL). The combined ethyl acetate layers were dried (Na_2SO_4), filtered and concentrated to give **333** as a colourless oil (7.11 g, 44.4 mmol, 89%).

δ_H(400 MHz; chloroform-*d*) 1.49 (9 H, s, C(C*H*$_3$)$_3$), 3.35 (2 H, s, C*H*$_2$).

Obtained data in accordance with previously reported data.[223]

(DSP-V-19)

***tert*-Butyl 3-(methyl(phenyl)amino)-3-oxopropanoate 334**

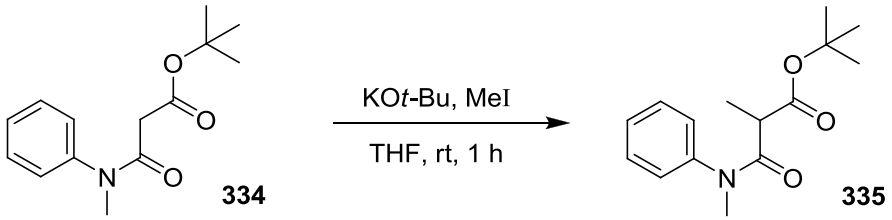


A 100 mL round-bottomed flask with stirrer-bar was charged with *N*-methylaniline **329** (1.61 g, 15.0 mmol, 1.0 equiv), a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as dichloromethane (60 mL) was added and the solution cooled to 0 °C (ice-bath).

To this solution, *tert*-butylmalonate **333** (2.31 mL, 16.5 mmol, 1.1 equiv), 2-chloro-1-methylpyridinium iodide (4.22 g, 16.5 mmol, 1.1 equiv) and triethylamine (10.5 mL, 75.0 mmol, 5.0 equiv) were added to give a bright yellow suspension. The mixture was stirred at 0 °C for 30 min before the reaction was quenched with 10% hydrochloric acid (50 mL). The resulting organic layer was washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an orange oil. Purification by flash column chromatography (SiO_2, 50 g, 3:1 petrol/ethyl acetate, 40 mm Ø), gave 3.63 g (14.6 mmol, 97%) of **334** as a colourless oil.

R_f 0.29 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2978, 2934, 1735, 1665, 1595, 1496, 1455, 1423, 1383, 1326, 1253, 1217, 1152, 1121, 959, 852, 774, 703; δ_H(400 MHz; chloroform-*d*) 1.41 (9 H, s, C(C*H*$_3$)$_3$), 3.13 (2 H, s, C*H*$_2$), 3.30 (3 H, s, NC*H*$_3$), 7.21-7.25 (2 H, m, Ar*H*), 7.32-7.38 (1 H, m, Ar*H*), 7.39-7.44 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 27.9 (C(*C*H$_3$)$_3$), 37.4 (N*C*H$_3$), 42.7 (*C*H$_2$), 81.5 (O*C*(CH$_3$)$_3$), 127.3 (ArH), 128.1 (ArH), 129.8 (ArH), 143.7 (Ar), 166.4 (*C*=O), 167.0 (*C*=O); *m/z* (ESI) 250 ([MH]$^+$) [HRMS (ESI): calculated for $C_{14}H_{20}NO_3$, 250.1438 Found: [MH]$^+$, 250.1436 (0.7 ppm error)] [Found C, 67.21; H, 7.67; N, 5.81%. $C_{14}H_{19}NO_3$ requires C, 67.45; H, 7.68; N, 5.62%].
(DSP-V-89)

***tert*-Butyl 2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoate 335**



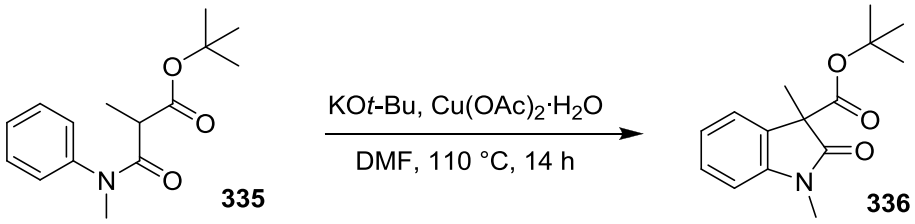
A 50 mL round-bottomed flask with stirrer-bar was charged with *tert*-butyl 3-(methyl(phenyl)amino)-3-oxopropanoate **334** (499 mg, 2.00 mmol, 1.0 equiv) a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as THF (20 mL) was added. The septum was briefly removed to add potassium *tert*-butoxide (247 mg, 2.20 mmol, 1.1 equiv) to give a yellow solution which was stirred for 5 min before dropwise addition of methyl iodide (130 μL, 2.10 mmol, 1.05 equiv) over 1 min to give a colourless

suspension which was stirred at room temperature. After 1 h the reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (SiO_2, 50 g, 3:1 petrol/ethyl acetate, 45 mm Ø), gave 470 mg (1.78 mmol, 88%) of **335** as a colourless oil.

R_f 0.62 (1:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2979, 2937, 1738, 1662, 1595, 1496, 1456, 1419, 1385, 1370, 1321, 1253, 1221, 1156, 1122, 1031, 919, 884, 849, 775, 738, 701, 673; δ_H(400 MHz; chloroform-*d*) 1.25 (3 H, d, *J* 7.0 Hz, C*H*$_3$), 1.42 (9 H, s, C(C*H*$_3$)$_3$), 3.29 (3 H, s, NC*H*$_3$), 3.31 (1 H, q, *J* 7.0 Hz, C*H*), 7.22-7.26 (2 H, m, Ar*H*), 7.33-7.38 (1 H, m, Ar*H*), 7.39-7.46 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 14.1 (*C*H$_3$), 27.9 (C(*C*H$_3$)$_3$), 37.6 (N*C*H$_3$), 44.3 (*C*H), 81.1 (O*C*(CH$_3$)$_3$), 127.5 (ArH), 128.0 (ArH), 129.8 (ArH), 143.8 (Ar), 169.9 (*C*=O), 170.5 (*C*=O); *m/z* (ESI) 264 ([MH]$^+$) [HRMS (ESI): calculated for $C_{15}H_{22}NO_3$, 264.1594 Found: [MH]$^+$, 264.1599 (2.0 ppm error)].

(DSP-V-14)

tert-Butyl 1,3-dimethyl-2-oxoindoline-3-carboxylate 336



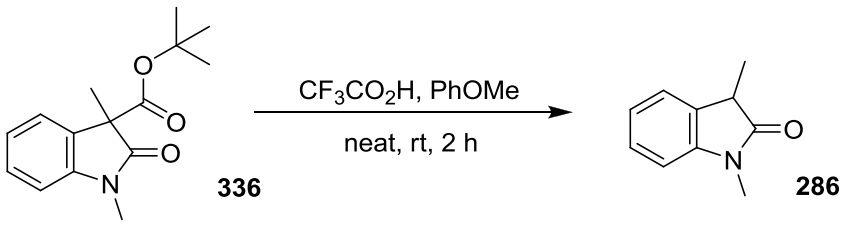
A 100 mL round-bottomed flask with stirrer-bar was charged with *tert*-Butyl 2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoate **335** (526 mg, 2.00 mmol, 1.0 equiv), DMF (40 mL), potassium *tert*-butoxide (247 mg, 2.20 mmol, 1.1 equiv) and copper(II) acetate monohydrate (399 mg, 2.00 mmol, 1.0 equiv). A condenser topped with an argon balloon was fitted and the reaction heated to 110 °C. After 14 h the reaction was cooled to room temperature and the reaction by addition of a saturated solution of ammonium chloride (40 mL). The mixture was diluted with water (80 mL) and extracted with ethyl acetate (120 mL). The organic layer was washed with brine (2 × 120 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a pale yellow oil. Purification by flash column

chromatography (SiO_2, 50 g, 3:1 petrol/ethyl acetate, 30 mm Ø), gave 428 mg (1.64 mmol, 82%) of **336** as a colourless oil.

R_f 0.39 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2979, 2933, 1737, 1663, 1611, 1494, 1471, 1371, 1347, 1304, 1254, 1161, 1119, 1064, 1029, 931, 842, 751; δ_H(400 MHz; chloroform-*d*) 1.34 (9 H, s, C(C*H*$_3$)$_3$), 1.61 (3 H, s, C*H*$_3$), 3.24 (3 H, s, NC*H*$_3$), 6.85 (1 H, dd, *J* 7.5, 1.0 Hz, Ar*H*), 7.06 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.24 (1 H, dd, *J* 7.5, 1.0 Hz, Ar*H*), 7.31 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*); δ_C(100 MHz; chloroform-*d*) 19.7 (*C*H$_3$), 26.4 (NCH$_3$), 27.7 (C(*C*H$_3$)$_3$), 56.0 (*C*(CH$_3$)), 82.2 (O*C*(CH$_3$)$_3$), 108.2 (ArH), 122.7 (ArH), 122.7 (ArH), 128.7 (ArH), 130.6 (Ar), 143.7 (Ar), 168.6 (*C*=O), 175.5 (*C*=O); *m/z* (ESI) 262 ([MH]$^+$) [HRMS (ESI): calculated for $C_{15}H_{20}NO_3$, 262.1438 Found: [MH]$^+$, 262.1440 (0.9 ppm error)].

(DSP-V-15)

1,3-Dimethylindolin-2-one 286



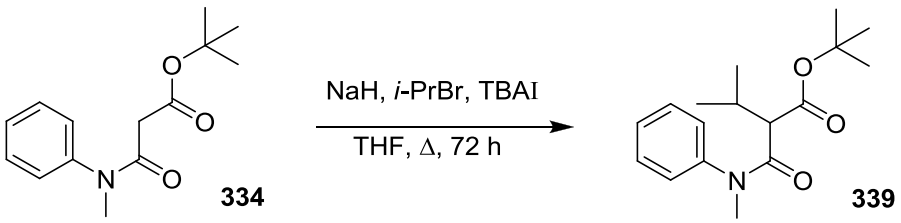
Reaction performed following method H using *tert*-butyl 1,3-dimethyl-2-oxoindoline-3-carboxylate **336** (65 mg, 0.25 mmol, 1.0 equiv). The mixture was stirred at rt for 2 h. Purification by flash column chromatography (SiO_2, 15 g, 1:1 petrol/ethyl acetate, 30 mm Ø), gave 32 mg (0.20 mmol, 79%) of **286** as colourless needles.

R_f 0.27 (3:1 petrol/ethyl acetate); mp 115-117 °C (lit.[273] 122-123 °C) δ_H(400 MHz; chloroform-*d*) 1.47 (3 H, d, *J* 7.5 Hz, C*H*$_3$), 3.21 (3 H, s, NC*H*$_3$), 3.43 (1 H, q, *J* 7.5 Hz, C*H*), 6.83 (1 H, dd, *J* 7.5, 1.0 Hz, Ar*H*), 7.06 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.24 (1 H, dd, *J* 7.5, 1.0 Hz, Ar*H*), 7.28 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*).

Obtained data in accordance with previously reported data.[274]

(DSP-V-16)

***tert*-Butyl 3-methyl-2-(methyl(phenyl)carbamoyl)butanoate 339**

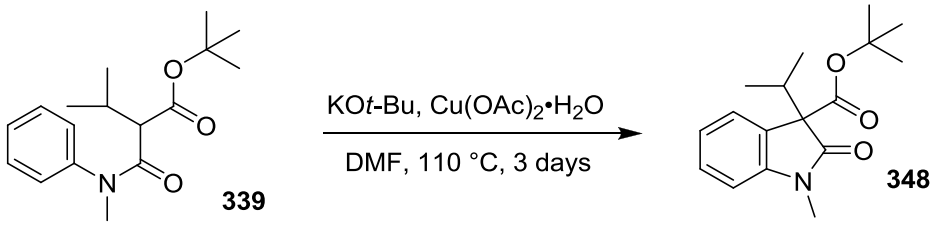


A 50 mL round-bottomed flask with stirrer-bar was charged with sodium hydride (132 mg, 3.30 mmol, 1.1 equiv), a septum fitted and the flask purged with argon (balloon). Maintained under argon as THF (20 mL) was added and the suspension cooled to 0 °C (ice-bath). A solution of *tert*-butyl 3-(methyl(phenyl)amino)-3-oxopropanoate **334** (748 mg, 3.00 mmol, 1.0 equiv) in THF (10 mL) was added dropwise *via cannula* to give a pale yellow solution which was stirred for 5 min before addition of 2-bromopropane (295 μL, 3.15 mmol, 1.05 equiv) and tetrabutylammonium iodide (222 mg, 0.60 mmol, 0.20 equiv). The resulting suspension was stirred at 0 °C for 15 min before a condenser, topped with an argon balloon, was fitted and the reaction heated to reflux. After 72 h the reaction was cooled to room temperature and quenched by the addition of a saturated solution of ammonium chloride (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with a saturated solution of brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (SiO_2, 50 g, 4:1 petrol/ethyl acetate, 40 mm Ø), gave 478 mg (1.64 mmol, 55%) of **339** as a colourless oil.

R_f 0.42 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2968, 2934, 2874, 1740, 1660, 1595, 1496, 1471, 1419, 1370, 1299, 1251, 1155, 1118, 1040, 997, 917, 866, 836, 775, 738, 701; δ_H(400 MHz; chloroform-*d*) 1.14 (3 H, d, *J* 6.5 Hz, C*H*$_3$), 1.19 (3 H, d, *J* 6.5 Hz, C*H*$_3$), 1.73 (9 H, s, C(C*H*$_3$)$_3$), 2.67-2.77 (1 H, m, C*H*(CH$_3$)$_2$), 3.25 (1 H, d, *J* 9.5 Hz, C*H*), 3.59 (3 H, s, NC*H*$_3$), 7.49-7.53 (2 H, m, Ar*H*), 7.63-7.75 (3 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 20.2 (*C*H$_3$), 20.3 (*C*H$_3$), 27.7 (C(*C*H$_3$)$_3$), 29.4 ((CH$_3$)$_2$C*H*), 37.5 (N*C*H$_3$), 57.1 (*C*H), 81.2 (O*C*(CH$_3$)$_3$), 128.1 (ArH), 128.2 (ArH), 129.9 (ArH), 144.1 (Ar), 169.0 (*C*=O), 169.1 (*C*=O); *m/z* (ESI) 314 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{17}H_{25}NNaO_3$, 314.1727 Found: [MNa]$^+$, 314.1720 (2.0 ppm error)].

(DSP-V-67)

***tert*-Butyl 3-*iso*propyl-1-methyl-2-oxoindoline-3-carboxylate 348**

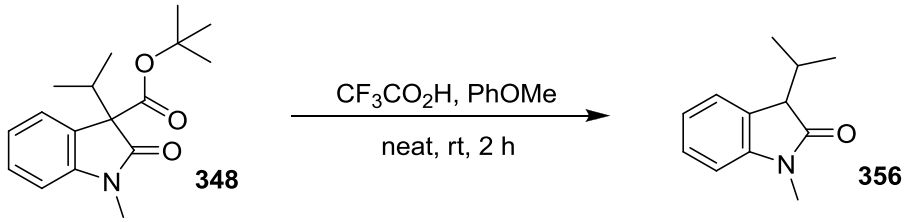


Reaction performed following method G using *tert*-butyl 3-methyl-2-(methyl(phenyl)carbamoyl)butanoate **339** (146 mg, 0.50 mmol, 1.0 equiv). Stirred at 110 °C for 72 h. Purification by flash column chromatography (SiO_2, 20 g, 7:2:1 petrol/dichloromethane/ethyl acetate, 30 mm Ø), gave 66 mg (0.23 mmol, 46%) of **348** as a yellow oil.

R_f 0.41 (4:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3056, 2971, 2936, 2879, 1719, 1610, 1492, 1470, 1370, 1349, 1253, 1156, 1122, 1085, 1025, 974, 858, 836, 809, 750; δ_H(400 MHz; chloroform-*d*) 0.75 (3 H, d, *J* 7.0 Hz, C*H*$_3$), 1.09 (3 H, d, *J* 7.0 Hz, C*H*$_3$), 1.41 (9 H, s, C(C*H*$_3$)$_3$), 2.69 (1 H, qq, *J* 7.0, 7.0 Hz, C*H*(CH$_3$)$_2$), 3.19 (3 H, s, NC*H*$_3$), 6.80 (1 H, d, *J* 7.5 Hz, ArH), 7.05 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.25-7.33 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 17.0 (*C*H$_3$), 17.1 (*C*H$_3$), 26.0 (N*C*H$_3$), 27.8 (C(*C*H$_3$)$_3$), 34.8 ((CH$_3$)$_2$*C*H), 64.1 (*C*), 82.2 (O*C*(CH$_3$)$_3$), 107.7 (ArH), 122.3 (ArH), 123.9 (ArH), 128.0 (Ar), 128.5 (ArH), 144.1 (Ar), 168.0 (*C*=O), 173.2 (*C*=O); *m/z* (ESI) 312 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{17}H_{23}NNaO_3$, 312.1570 Found: [MNa]$^+$, 312.1565 (1.6 ppm error)].

(DSP-V-74)

3-*Iso*propyl-1-methylindolin-2-one 356

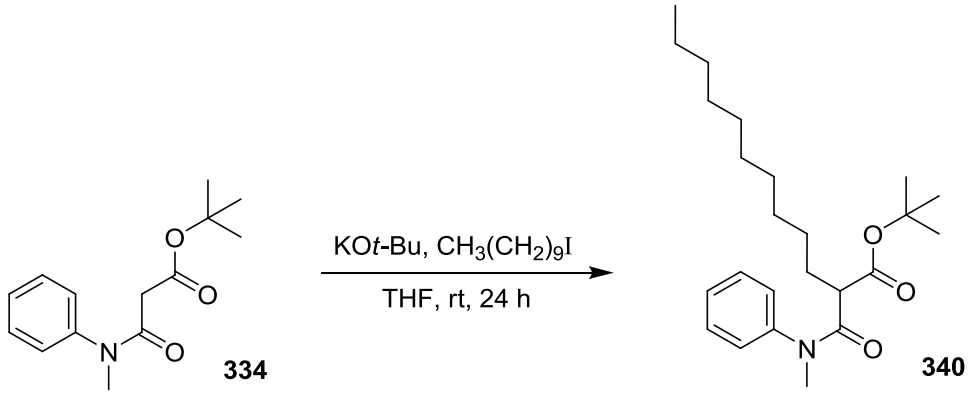


Reaction performed following method H using *tert*-butyl 3-*iso*propyl-1-methyl-2-oxoindoline-3-carboxylate **348** (58 mg, 0.20 mmol, 1.0 equiv). Purification by flash column chromatography (SiO_2, 20 g, 3:1 petrol/ethyl acetate, 25 mm Ø), gave 26 mg (0.14 mmol, 68%) of **356** as a yellow oil.

R_f 0.53 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3055, 2961, 2933, 2876, 1711, 1612, 1439, 1468, 1421, 1374, 1349, 1302, 1261, 1203, 1127, 1086, 1021, 969, 929, 865, 752, 731; δ_H(400 MHz; chloroform-*d*) 0.85 (3 H, d, *J* 7.0 Hz, C*H*$_3$), 1.10 (3 H, d, *J* 7.0 Hz, C*H*$_3$), 2.51 (1 H, qqd, *J* 7.0, 7.0, 3.5 Hz, C*H*$(CH_3)_2$), 3.20 (3 H, s, NC*H*$_3$), 3.37 (1 H, d, *J* 3.5 Hz, C*H*), 6.82 (1 H, dd, *J* 7.5, 1.5 Hz, ArH), 7.04 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.26-7.31 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 17.9 (*C*H$_3$), 19.8 (*C*H$_3$), 25.9 (N*C*H$_3$), 30.7 ($(CH_3)_2$*C*H), 51.6 (*C*H), 107.7 (ArH), 122.0 (ArH), 124.3 (ArH), 127.7 (Ar), 127.7 (ArH), 144.7 (Ar), 177.3 (*C*=O); *m/z* (ESI) 212 ($[MNa]^+$) [HRMS (ESI): calculated for $C_{12}H_{15}NNaO$, 212.1046 Found: $[MNa]^+$, 212.1041 (2.2 ppm error)].

(DSP-V-84)

***tert*-Butyl 2-(methyl(phenyl)carbamoyl)dodecanoate 340**

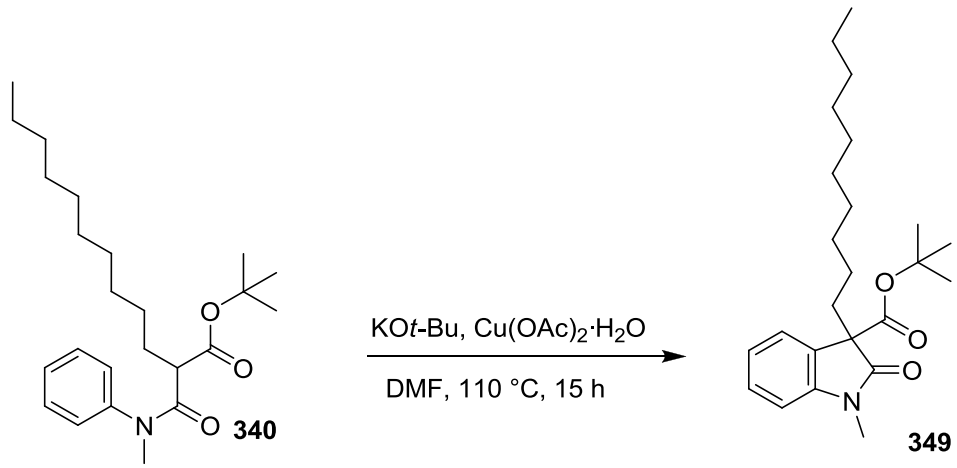


A 50 mL round-bottomed flask with stirrer-bar was charged with *tert*-butyl 3-(methyl(phenyl)amino)-3-oxopropanoate **334** (499 mg, 2.00 mmol, 1.0 equiv) a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as THF (20 mL) was added. Septum briefly removed to add potassium *tert*-butoxide (247 mg, 2.20 mmol, 1.1 equiv) to give a yellow solution which was stirred for 5 min before dropwise addition of 1-iododecane (0.45 mL, 2.10 mmol, 1.05 equiv) over 1 min to give a colourless suspension which was stirred at room temperature. After 24 h the reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a colourless oil. Purification by flash column chromatography (SiO_2, 50 g, 9:1 petrol/ethyl acetate, 40 mm Ø), gave 683 mg (1.75 mmol, 88%) of **340** as a colourless oil.

R_f 0.54 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2925, 2855, 1741, 1663, 1596, 1496, 1457, 1370, 1256, 1152, 1121, 848, 774, 701; δ_H(400 MHz; chloroform-*d*) 1.05-1.33 (19 H, m, C*H*$_2$), 1.42 (9 H, s, C(C*H*$_3$)$_3$), 1.70-1.88 (2 H, m, C*H*$_2$), 3.21 (1 H, dd, *J* 8.5, 6.0 Hz, C*H*), 3.30 (3 H, s, NC*H*$_3$), 7.21-7.25 (2 H, m, Ar*H*), 7.32-7.38 (1 H, m, Ar*H*), 7.39-7.45 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 14.0 (*C*H$_3$), 22.6 (*C*H$_2$), 27.3 (*C*H$_2$), 27.9 (C(*C*H$_3$)$_3$), 29.2 (*C*H$_2$), 29.3 (*C*H$_2$), 29.3 (*C*H$_2$), 29.4 (*C*H$_2$), 29.5 (*C*H$_2$), 29.5 (*C*H$_2$), 31.8 (*C*H$_2$), 37.5 (N*C*H$_3$), 49.8 (*C*H), 81.1 (O*C*(CH$_3$)$_3$), 127.6 (ArH), 127.9 (ArH), 129.6 (ArH), 143.7 (Ar), 169.3 (*C*=O), 169.5 (*C*=O); *m/z* (ESI) 390 ([MH]$^+$) [HRMS (ESI): calculated for $C_{24}H_{40}NO_3$, 390.3003 Found: [MH]$^+$, 390.3008 (0.8 ppm error)].

(DSP-V-87)

tert-Butyl 3-decyl-1-methyl-2-oxoindoline-3-carboxylate 349

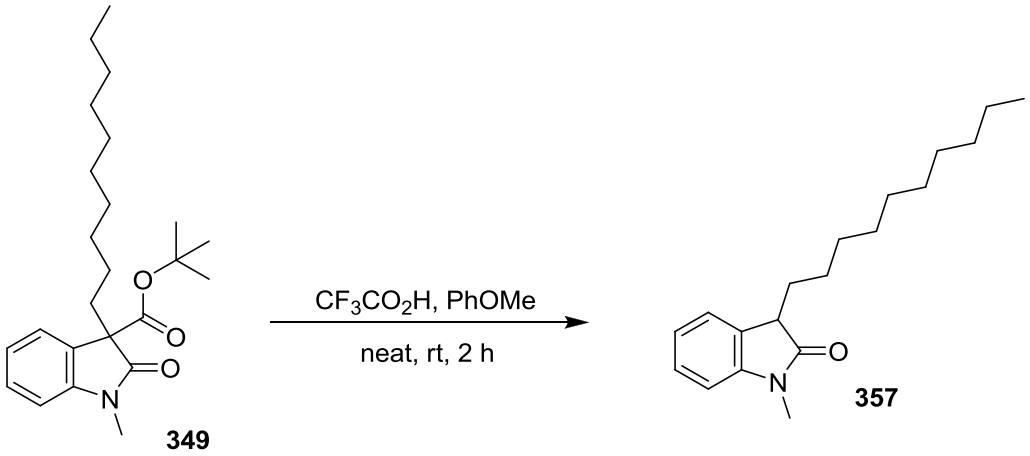


Reaction performed following method G using *tert*-butyl 2-(methyl(phenyl)carbamoyl)dodecanoate **340** (195 mg, 0.50 mmol, 1.0 equiv). The mixture was stirred at 110 °C for 15 h. Purification by flash column chromatography (SiO_2, 20 g, 4:1 petrol/ethyl acetate, 20 mm Ø), gave 147 mg (0.38 mmol, 76%) of **349** as a yellow oil.

R_f 0.48 (4:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2926, 2855, 1723, 1611, 1492, 1469, 1371, 1347, 1251, 1158, 1124, 1084, 750; δ_H(400 MHz; chloroform-*d*) 0.83-1.30 (19 H, m, C*H*$_2$, C*H*$_3$), 1.35 (9 H, s, C(C*H*$_3$)$_3$), 2.05-2.25 (2 H, m, C*H*$_2$), 3.23 (3 H, s, NC*H*$_3$), 6.83 (1 H, dd, *J* 7.5, 1.0 Hz, Ar*H*), 7.06 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.24 (1 H, dd, *J* 7.5, 1.0 Hz, Ar*H*), 7.30 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*); δ_C(100 MHz; chloroform-*d*) 13.9 (*C*H$_3$), 22.4 (*C*H$_2$), 23.4 (*C*H$_2$), 26.0 (N*C*H$_3$), 27.5 (C(*C*H$_3$)$_3$), 29.0 (*C*H$_2$), 29.0 (*C*H$_2$), 29.3 (*C*H$_2$), 29.3 (*C*H$_2$), 29.4 (*C*H$_2$), 31.6 (*C*H$_2$), 33.7 (*C*H$_2$), 60.3 (*C*), 81.8 (O*C*(CH$_3$)$_3$), 107.9 (ArH), 122.4 (ArH), 122.8 (ArH), 128.4 (ArH), 128.5 (Ar), 144.0 (Ar), 168.2 (*C*=O), 174.3 (*C*=O); *m/z* (ESI) 410 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{24}H_{37}NNaO_3$, 410.2666 Found: [MNa]$^+$, 410.2666 (1.1 ppm error)].

(DSP-V-94)

3-Decyl-1-methylindolin-2-one 357

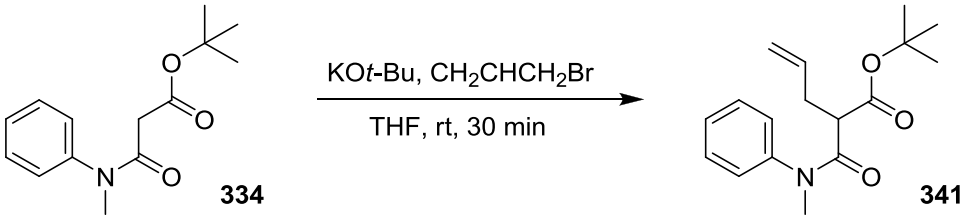


Reaction performed following method H using *tert*-butyl 3-decyl-1-methyl-2-oxoindoline-3-carboxylate **349** (97 mg, 0.25 mmol, 1.0 equiv). Purification by flash column chromatography (SiO_2, 10 g, 4:1 petrol/ethyl acetate, 20 mm Ø), gave 65 mg (0.23 mmol, 90%) of **357** as a yellow oil.

R_f 0.32 (4:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3055, 2924, 2854, 1715, 1613, 1493, 1468, 1375, 1345, 1258, 1127, 1087, 1020, 750; δ_H(400 MHz; chloroform-*d*) 0.87 (3 H, t, *J* 7.0 Hz, C*H*$_3$), 1.20-1.35 (16 H, m, C*H*$_2$), 1.81-2.01 (2 H, m, C*H*$_2$), 3.20 (3 H, s, NC*H*$_3$), 3.42 (1 H, t, *J* 6.0 Hz, C*H*), 6.82 (1 H, d, *J* 7.5 Hz, Ar*H*), 7.05 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.23-7.30 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 14.0 (*C*H$_3$), 22.6 (*C*H$_2$), 25.8 (*C*H$_2$), 26.0 (N*C*H$_3$), 29.2 (*C*H$_2$), 29.3 (*C*H$_2$), 29.5 (*C*H$_2$), 29.5 (*C*H$_2$), 29.5 (*C*H$_2$), 30.6 (*C*H$_2$), 31.8 (*C*H$_2$), 45.5 (*C*H), 107.8 (ArH), 122.1 (ArH), 123.7 (ArH), 127.6 (ArH), 129.3 (Ar), 144.3 (Ar), 177.9 (*C*=O); *m/z* (ESI) 288 ([MH]$^+$) [HRMS (ESI): calculated for $C_{19}H_{30}NO$, 288.2322 Found: [MH]$^+$, 288.2321 (0.6 ppm error)].

(DSP-V-97)

tert-Butyl 2-(methyl(phenyl)carbamoyl)pent-4-enoate 341

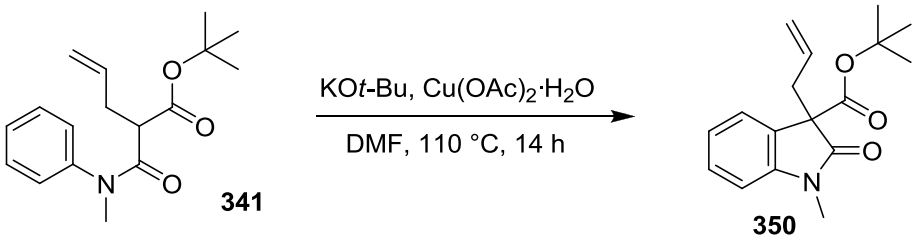


A 50 mL round-bottomed flask with stirrer-bar was charged with *tert*-butyl 3-(methyl(phenyl)amino)-3-oxopropanoate **334** (499 mg, 2.00 mmol, 1.0 equiv) a septum fitted and the flask purged with argon (balloon). Maintained under argon as THF (20 mL) was added. The septum was briefly removed to add potassium *tert*-butoxide (247 mg, 2.20 mmol, 1.1 equiv) to give a yellow solution which was stirred for 5 min before dropwise addition of allyl bromide (185 μL, 2.10 mmol, 1.05 equiv) over 1 min to give a colourless suspension which was stirred at room temperature. After 30 min the reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a colourless oil. Purification by flash column chromatography (SiO_2, 30 g, 4:1 petrol/ethyl acetate, 35 mm Ø), gave 518 mg (1.79 mmol, 89%) of **341** as a colourless oil.

R_f 0.41 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3073, 2978, 2931, 1737, 1661, 1595, 1496, 1420, 1371, 1333, 1260, 1154, 1120, 1037, 999, 918, 847, 774, 701; δ_H(400 MHz; chloroform-*d*) 1.41 (9 H, s, C(C*H*$_3$)$_3$), 2.44-2.63 (2 H, m, C*H*$_2$), 3.28 (3 H, s, NC*H*$_3$), 3.30 (1 H, dd, *J* 9.0, 6.0 Hz, C*H*), 4.97 (1 H, dd, *J* 17.0, 1.0 Hz, =C*H*$_2$), 5.01 (1 H, dd, *J* 10.5, 1.0 Hz, =C*H*$_2$), 5.64 (1 H, dddd, *J* 17.0, 10.5, 7.0, 7.0 Hz, =C*H*), 7.19-7.24 (2 H, m, Ar*H*), 7.32-7.38 (1 H, m, Ar*H*), 7.38-7.44 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 27.9 (C(*C*H$_3$)$_3$), 33.6 (CH*C*HCH), 37.6 (N*C*H$_3$), 49.6 (CO*C*HCO), 81.5 (O*C*(CH$_3$)$_3$), 117.0 (=*C*H$_2$) 127.8 (PhH), 128.0 (PhH), 128.7 (PhH), 135.0 (=*C*H), 143.6 (PhH), 168.7 (*C*=O), 168.8 (*C*=O); *m/z* (ESI) 312 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{17}H_{23}NNaO_3$, 312.1570 Found: [MNa]$^+$, 312.1568 (0.7 ppm error)].

(DSP-V-50)

tert-Butyl 3-allyl-1-methyl-2-oxoindoline-3-carboxylate 350

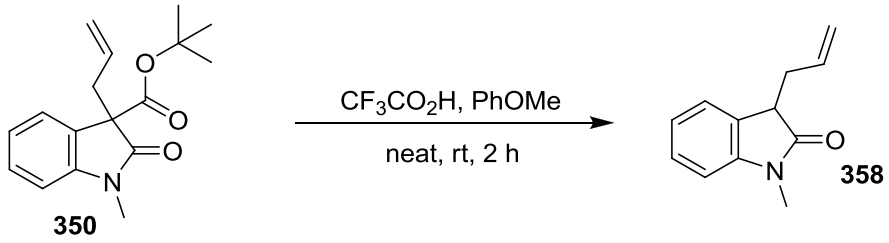


Reaction performed following method G using *tert*-butyl 2-(methyl(phenyl)carbamoyl)pent-4-enoate **341** (145 mg, 0.50 mmol, 1.0 equiv). Stirred at 110 °C for 14 h. Purification by flash column chromatography (SiO_2, 18 g, 7:2:1 petrol/dichloromethane/ethyl acetate, 20 mm Ø), gave 85 mg (0.30 mmol, 59%) of **350** as a colourless oil.

R_f 0.41 (7:2:1 petrol/dichloromethane/ethyl acetate); ν_{max}(film)/cm^{-1} 2977, 2919, 2851, 1735, 1656, 1611, 1493, 1470, 1370, 1349, 1251, 1155, 1106, 750; δ_H(400 MHz; chloroform-*d*) 1.36 (9 H, s, C(C*H*$_3$)$_3$), 2.92 (1 H, ddd, *J* 7.0, 2.0, 1.0 Hz, C*H*$_2$), 2.92 (1 H, ddd, *J* 7.0, 2.0, 1.0 Hz, C*H*$_2$), 3.21 (3 H, s, NC*H*$_3$), 4.91 (1 H, dddd, *J* 10.0, 2.0, 1.0, 1.0 Hz, =C*H*$_2$), 5.02 (1 H, dd, *J* 17.0, 2.0 Hz, =C*H*$_2$), 6.39 (1 H, dddd, *J* 17.0, 10.0, 7.0, 7.0 Hz, =C*H*), 6.82 (1 H, dd, *J* 7.5, 0.5 Hz, Ar*H*), 7.06 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.26 (1 H, ddd, *J* 7.5, 1.0, 0.5 Hz, Ar*H*), 7.30 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*); δ_C(100 MHz; chloroform-*d*) 26.3 (NCH$_3$), 27.7 (C(*C*H$_3$)$_3$), 38.1 (*C*H$_2$), 60.1 (*C*), 82.4 (O*C*(CH$_3$)$_3$), 108.1 (ArH), 119.4 (=*C*H$_2$), 122.5 (ArH), 123.3 (ArH), 128.1 (ArH), 128.8 (ArH), 131.4 (=*C*H), 144.2 (Ar), 167.8 (*C*=O), 173.9 (*C*=O); *m/z* (ESI) 310 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{17}H_{21}NNaO_3$, 310.1414 Found: [MNa]$^+$, 310.1400 (4.4 ppm error)].

(DSP-V-51)

3-Allyl-1-methylindolin-2-one 358

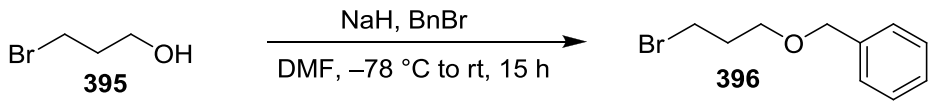


Reaction performed following method H using *tert*-butyl 3-allyl-1-methyl-2-oxoindoline-3-carboxylate **350** (72 mg, 0.25 mmol, 1.0 equiv). Purification by flash column chromatography (SiO_2, 20 g, 3:1 petrol/ethyl acetate, 30 mm Ø), gave 43 mg (0.23 mmol, 92%) of **358** as a colourless oil.

R_f 0.36 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3056, 2934, 1713, 1641, 1613, 1494, 1470, 1438, 1420, 1376, 1349, 1251, 1127, 1087, 1020, 996, 918, 751; δ_H(400 MHz; chloroform-*d*) 2.54 (1 H, ddd, *J* 14.0, 7.5, 7.5 Hz, C*H*$_2$), 2.83 (1 H, ddd, *J* 14.0, 6.0, 5.0 Hz, C*H*$_2$), 3.11 (3 H, s, NC*H*$_3$), 3.48 (1 H, dd, *J* 7.5, 5.0 Hz, C*H*), 5.04 (1 H, dd, *J* 10.0, 2.0 Hz, =C*H*$_2$), 5.10 (1 H, dd, *J* 17.0, 2.0 Hz, =C*H*$_2$), 5.69-5.81 (1 H, m, =C*H*), 6.82 (1 H, d, *J* 8.5 Hz, Ar*H*), 7.04 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.25-7.31 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 26.1 (NC*H*$_3$), 34.9 (*C*H$_2$), 45.2 (*C*H), 107.9 (ArH), 117.9 (=*C*H$_2$), 122.2 (ArH), 124.2 (ArH), 127.9 (ArH), 128.6 (Ar), 134.1 (=*C*H), 144.3 (Ar), 177.2 (*C*=O); *m/z* (ESI) 188 ([MH]$^+$) [HRMS (ESI): calculated for $C_{12}H_{14}NO$, 188.1070 Found: [MH]$^+$, 188.1068 (0.8 ppm error)].

(DSP-V-70)

((3-Bromopropoxy)methyl)benzene 396



Based on a procedure by Janda.[275]

A 100 mL round-bottomed flask with stirrer-bar was charged with sodium hydride (288 mg, 12.0 mmol. 1.2 equiv), a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as DMF (30 mL) was added, followed by benzyl bromide (1.25 mL, 10.5 mmol, 1.05 equiv). The solution was cooled to –78 °C (CO_2/acetone) and 3-bromopropan-1-ol **395** (0.90

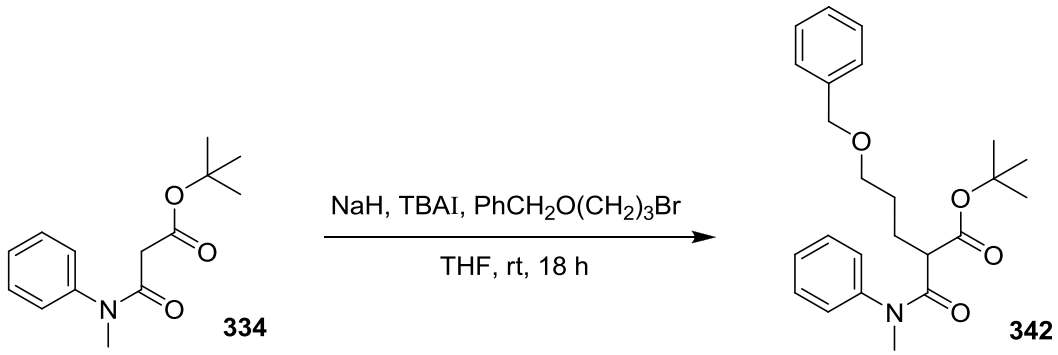
mL, 10.0 mmol, 1.0 equiv) added dropwise over 30 min. The mixture was stirred at –78 °C for 1 h, then allowed to warm to room temperature overnight (14 h). The reaction was quenched with water (30 mL) and extracted with hexane (3 × 30 mL). The combined organic layers were washed with brine (2 × 20 mL) and dried ($MgSO_4$), filtered and concentrated to give **396** as a colourless liquid (1.91 g, 8.33 mmol, 83%). The crude material was used without purification.

δ_H(400 MHz; chloroform-*d*) 2.14 (2 H, tt, *J* 6.5, 6.0 Hz, CH_2), 3.54 (2 H, t, *J* 6.5 Hz, CH_2), 3.61 (2 H, t, *J* 6.0 Hz, CH_2), 4.52 (2 H, s, CH_2), 7.27-7.42 (5 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[275]

(DSP-V-91)

***tert*-Butyl 5-(benzyloxy)-2-(methyl(phenyl)carbamoyl)pentanoate 342**



334 **342**

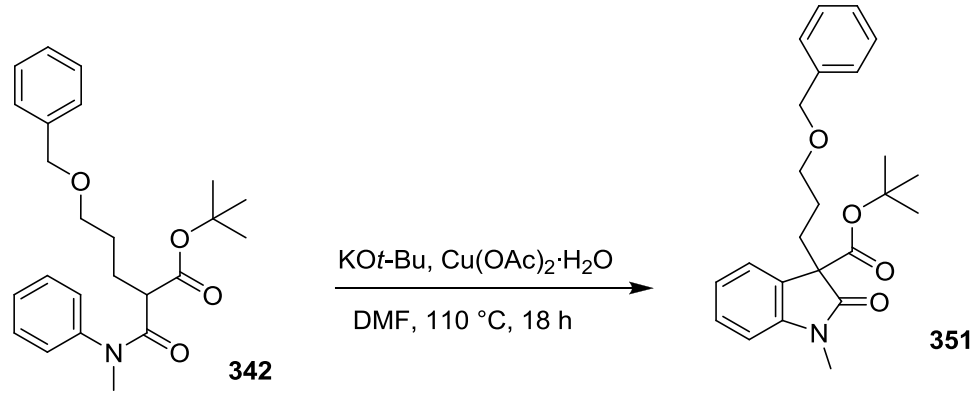
A 50 mL round-bottomed flask with stirrer-bar was charged with sodium hydride (132 mg, 3.30 mmol, 1.10 equiv), a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as THF (20 mL) was added and the suspension cooled to 0 °C (ice-bath). A solution of *tert*-butyl 3-(methyl(phenyl)amino)-3-oxopropanoate **334** (748 mg, 3.00 mmol, 1.0 equiv) in THF (10 mL) was added dropwise *via cannula* to give a pale yellow solution which was stirred for 5 min before addition of ((3-Bromopropoxy)methyl)benzene **396** (722 mg, 3.15 mmol, 1.05 equiv) and tetrabutylammonium iodide (222 mg, 0.60 mmol, 0.20 equiv). The resulting suspension was stirred at 0 °C for 15 min before warming to room temperature and the stirring continued. After 18 h the reaction was quenched by the addition of a saturated solution of ammonium chloride (20 mL) and extracted with ethyl

acetate (30 mL). The organic layer was washed with a saturated solution of brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (SiO_2, 50 g, 3:1 petrol/ethyl acetate, 40 mm Ø), gave 313 mg (0.79 mmol, 26%) of **342** as a colourless oil.

R_f 0.27 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2976, 2934, 2863, 1736, 1661, 1595, 1496, 1453, 1370, 1253, 1153, 1118, 848, 775, 740, 701; δ_H(400 MHz; chloroform-*d*) 1.42 (9 H, s, C(C*H*$_3$)$_3$), 1.44-1.60 (2 H, m, C*H*$_2$), 1.80-1.98 (2 H, m, C*H*$_2$), 3.26 (1 H, dd, *J* 8.5, 6.0 Hz, C*H*), 3.29 (3 H, s, NC*H*$_3$), 3.32-3.39 (2 H, m, OC*H*$_2$), 4.24 (2 H, s, OC*H*$_2$), 7.20-7.44 (10 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 26.1 (*C*H$_2$), 27.5 (*C*H$_2$), 27.9 (C(*C*H$_3$)$_3$), 37.6 (N*C*H$_3$), 49.6 (*C*H), 70.0 (O*C*H$_2$), 72.9 (O*C*H$_2$), 81.3 (O*C*(CH$_3$)$_3$), 127.5 (ArH), 127.6 (ArH), 127.7 (ArH), 128.0 (ArH), 128.3 (ArH), 129.7 (ArH), 138.4 (Ar), 143.6 (Ar), 169.1 (*C*=O), 169.3 (*C*=O); *m/z* (ESI) 398 ([MH]$^+$) [HRMS (ESI): calculated for $C_{24}H_{32}NO_4$, 398.2326 Found: [MH]$^+$, 398.2324 (1.1 ppm error)].

(DSP-V-92)

tert-Butyl 3-(3-(benzyloxy)propyl)-1-methyl-2-oxoindoline-3-carboxylate 351



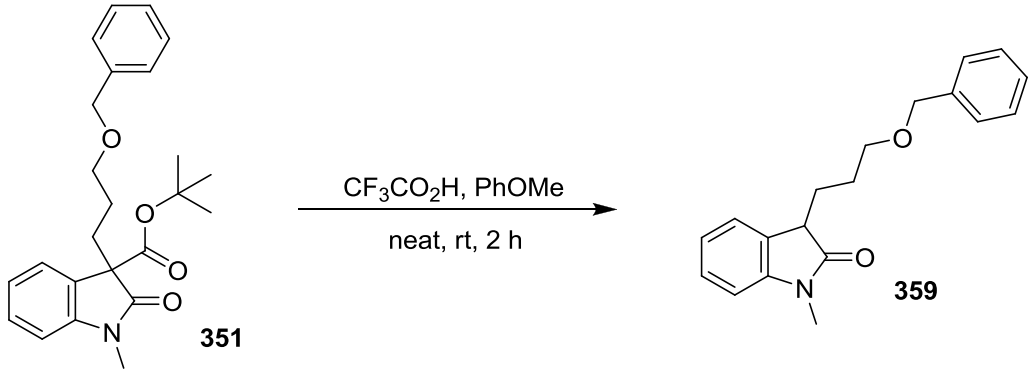
Reaction performed following method G using *tert*-butyl 5-(benzyloxy)-2-(methyl(phenyl)carbamoyl)pentanoate **342** (199 mg, 0.50 mmol, 1.0 equiv). The mixture was stirred at 110 °C for 18 h. Purification by flash column chromatography (SiO_2, 20 g, 3:1 petrol/ethyl acetate, 20 mm Ø), gave 128 mg (0.32 mmol, 65%) of **351** as a yellow oil.

R_f 0.53 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2977, 2934, 2860, 1717, 1610, 1493, 1471, 1370, 1349, 1250, 1158, 1116, 914, 735, 699; δ_H(400 MHz;

chloroform-*d*) 1.20-1.40 (2 H, m, CH_2), 1.35 (9 H, s, C(CH_3)$_3$), 2.17-2.32 (2 H, m, CH_2), 3.21 (3 H, s, NCH_3), 3.34-3.39 (2 H, m, OCH_2), 4.40 (2 H, s, OCH_2) 6.82 (1 H, dd, *J* 7.5, 1.0 Hz, Ar*H*), 7.05 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.22-7.34 (7 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 24.0 (*C*H$_2$), 26.1 (N*C*H$_3$), 27.5 (C(*C*H$_3$)$_3$), 30.3 (*C*H$_2$), 59.9 (*C*), 69.7 (O*C*H$_2$), 72.6 (O*C*H$_2$), 82.0 (O*C*(CH$_3$)$_3$), 108.0 (ArH), 122.5 (ArH), 122.9 (ArH), 127.3 (ArH), 127.4 (ArH), 128.1 (ArH), 128.2 (Ar), 128.6 (ArH), 138.2 (Ar), 144.0 (Ar), 168.1 (*C*=O), 174.2 (*C*=O); *m/z* (ESI) 418 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{24}H_{29}NNaO_4$, 418.1989 Found: [MNa]$^+$, 418.1986 (0.6 ppm error)].

(DSP-V-95)

3-(3-(Benzyloxy)propyl)-1-methylindolin-2-one 359

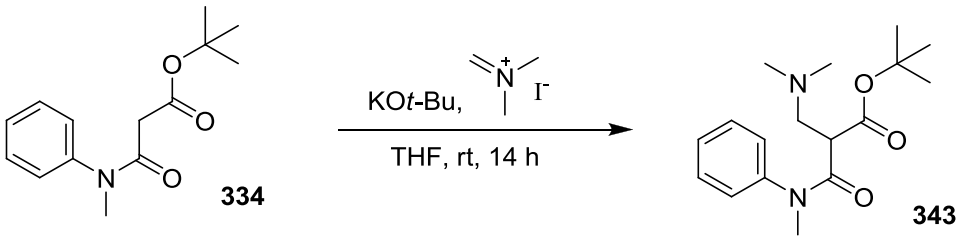


Reaction performed following method H using *tert*-butyl 3-(3-(benzyloxy)propyl)-1-methyl-2-oxoindoline-3-carboxylate **351** (99 mg, 0.25 mmol, 1.0 equiv). Purification by flash column chromatography (SiO_2, 13 g, 3:1 petrol/ethyl acetate, 20 mm Ø), gave 64 mg (0.22 mmol, 86%) of **359** as a yellow solid.

R_f 0.20 (4:1 petrol/ethyl acetate); mp 90-92 °C; ν_{max}(film)/cm^{-1} 3057, 2928, 2857, 1710, 1612, 1493, 1469, 1374, 1347, 1260, 1094, 1023, 750, 699; δ_H(400 MHz; chloroform-*d*) 1.60-1.76 (2 H, m, CH_2), 1.96-2.10 (2 H, m, CH_2), 3.19 (3 H, s, NCH_3), 3.43-3.52 (3 H, m, C*H*, OCH_2), 4.60 (2 H s, OCH_2), 6.81 (1 H, d, *J* 7.5 Hz, Ar*H*), 7.04 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.23-7.36 (7 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 25.9 (*C*H$_2$), 26.0 (N*C*H$_3$), 27.2 (*C*H$_2$), 45.1 (*C*H), 69.9 (O*C*H$_2$), 72.8 (O*C*H$_2$), 107.8 (ArH), 122.2 (ArH), 123.8 (ArH), 127.4 (ArH), 127.5 (ArH), 127.8 (ArH), 128.2 (ArH), 128.9 (Ar), 138.3 (Ar), 144.2

(Ar), 177.7 (*C*=O); *m/z* (ESI) 296 ($[MH]^+$) [HRMS (ESI): calculated for $C_{19}H_{22}NO_2$, 296.1645 Found: $[MH]^+$, 296.1650 (1.1 ppm error)].
(DSP-V-98)

tert-Butyl 2-((dimethylamino)methyl)-3-(methyl(phenyl)amino)-3-oxopropanoate 343



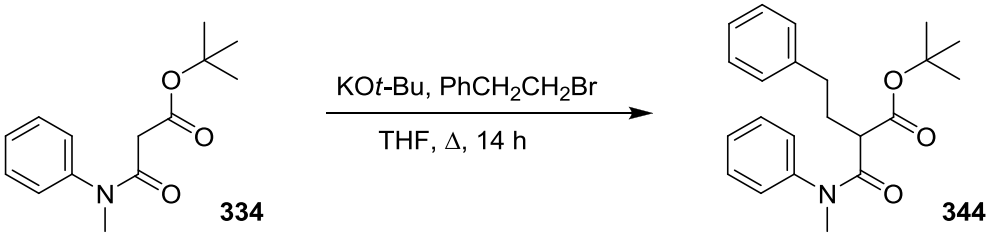
A 50 mL round-bottomed flask with stirrer-bar was charged with *tert*-butyl 3-(methyl(phenyl)amino)-3-oxopropanoate **334** (499 mg, 2.00 mmol, 1.0 equiv) a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as THF (20 mL) was added. Septum briefly removed to add potassium *tert*-butoxide (247 mg, 2.20 mmol, 1.1 equiv) to give a yellow solution which was stirred for 5 min before addition of Eschenmoser's salt (389 mg, 2.10 mmol, 1.05 equiv) in a single portion to give a yellow suspension which was stirred at room temperature. After 14 h the reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (SiO_2, 50 g, 1:1 petrol/ethyl acetate to 9:1 ethyl acetate/methanol, 35 mm Ø), gave 246 mg (0.80 mmol, 40%) of **343** as a yellow oil.

R_f 0.47 (9:1 ethyl acetate/methanol); ν_{max}(film)/cm^{-1} 2976, 2940, 2823, 2771, 1734, 1660, 1595, 1496, 1458, 1369, 1253, 1152, 1117, 1044, 846, 775, 701; δ_H(400 MHz; chloroform-*d*) 1.42 (9 H, s, C(CH_3)$_3$), 2.05 (6 H, s, N(CH_3)$_2$), 2.58 (1 H, dd, *J* 12.5, 5.5 Hz, CH_2), 2.93 (1 H, dd, *J* 12.5, 9.0 Hz, CH_2), 3.30 (3 H, s, NCH_3), 3.43 (1 H, dd, *J* 9.0, 5.5 Hz, C*H*), 7.27-7.31 (2 H, m, Ar*H*), 7.32-7.37 (1 H, m, Ar*H*), 7.39-7.45 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 27.9 (C(CH_3)$_3$), 37.7 (NCH_3), 45.7 (N(CH_3)$_2$), 48.6 (*C*H), 58.8 (CH_2), 81.5 (O*C*(CH_3)$_3$), 127.9 (ArH), 128.0 (ArH), 129.6 (ArH), 143.7 (Ar), 168.3 (*C*=O),

168.6 (*C*=O); *m/z* (ESI) 307 ($[MH]^+$) [HRMS (ESI): calculated for $C_{17}H_{27}N_2O_3$, 307.2016 Found: $[MH]^+$, 307.2007 (3.0 ppm error)].

(DSP-V-55)

tert-Butyl 2-(methyl(phenyl)carbamoyl)-4-phenylbutanoate 344



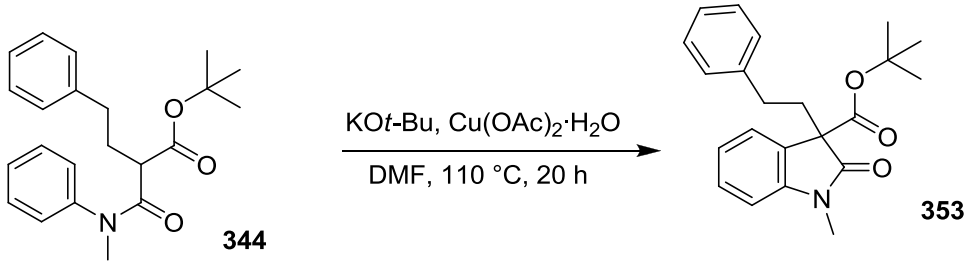
A 50 mL round-bottomed flask with stirrer-bar was charged with sodium hydride (88 mg, 2.20 mmol, 1.1 equiv), a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as THF (15 mL) was added and the suspension cooled to 0 °C (ice-bath). A solution of *tert*-butyl 3-(methyl(phenyl)amino)-3-oxopropanoate **334** (499 mg, 2.00 mmol, 1.0 equiv) in THF (5 mL) was added dropwise *via cannula* to give a pale yellow solution which was stirred for 5 min before dropwise addition of (2-bromoethyl)benzene (287 μL, 2.10 mmol, 1.05 equiv) over 5 min. The resulting suspension was stirred at 0 °C for 15 min before a condenser, topped with an argon balloon, was fitted and the reaction heated to reflux. After 14 h the reaction was cooled to room temperature and quenched by the addition of a saturated solution of ammonium chloride (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (SiO_2, 35 g, 3:1 petrol/ethyl acetate, 30 mm Ø), gave 442 mg (1.25 mmol, 63%) of **344** as a colourless oil.

R_f 0.39 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3062, 3027, 2976, 2932, 1735, 1662, 1596, 1496, 1454, 1420, 1385, 1254, 1148, 1119, 1031, 965, 847, 774, 736; δ_H(400 MHz; chloroform-*d*) 1.43 (9 H, s, C(CH_3)$_3$), 2.13 (2 H, m, CH_2), 2.46-2.61 (2 H, m, CH_2), 3.26 (1 H, dd, *J* 7.0, 7.0 Hz, C*H*), 3.30 (3 H, s, NCH_3), 7.05-7.10 (2 H, m, Ar*H*), 7.11-7.18 (3 H, m, Ar*H*), 7.19-7.25 (2 H, m, Ar*H*), 7.30-7.38 (3 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 27.9 (C(CH_3)$_3$), 30.9 (CH_2), 33.4 (CH_2), 37.6 (NCH_3), 49.4 (*C*H), 81.4 (O*C*(CH_3)$_3$), 125.9 (ArH),

127.6 (ArH), 127.9 (ArH), 128.3 (ArH), 128.3 (ArH), 129.7 (ArH), 141.2 (Ar), 143.5 (Ar), 169.1 (*C*=O), 169.2 (*C*=O); *m/z* (ESI) 376 ($[MNa]^+$), 354 ($[MH]^+$) [HRMS (ESI): calculated for $C_{22}H_{28}NO_3$, 354.2064 Found: $[MH]^+$, 354.2063 (0.1 ppm error)].

(DSP-V-54)

***tert*-Butyl 1-methyl-2-oxo-3-phenethylindoline-3-carboxylate 353**

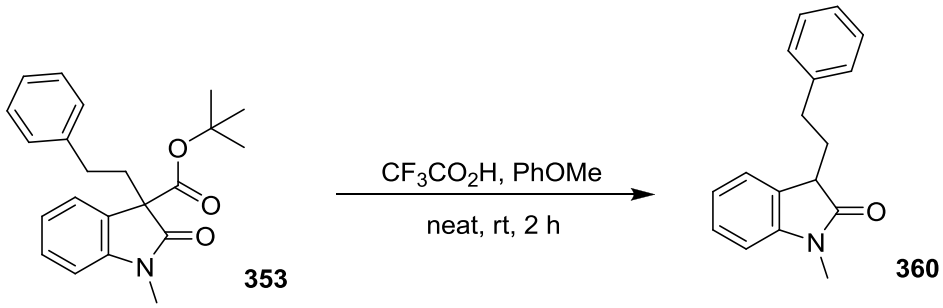


Reaction performed following method G using *tert*-butyl 2-(methyl(phenyl)carbamoyl)-4-phenylbutanoate **344** (177 mg, 0.50 mmol, 1.0 equiv). The mixture was stirred at 110 °C for 20 h. Purification by flash column chromatography (SiO_2, 20 g, 3:1 petrol/ethyl acetate, 20 mm Ø), gave 125 mg (0.36 mmol, 71%) of **353** as a colourless oil.

R_f 0.44 (3:1 petrol /ethyl acetate); ν_{max}(film)/cm^{-1} 2976, 2931, 1736, 1717, 1610, 1493, 1471, 1370, 1346, 1248, 1155, 1090, 1022, 985, 844, 751, 700; δ_H(400 MHz; chloroform-*d*) 1.37 (9 H, s, C(CH_3)$_3$), 2.22-2.62 (4 H, m, CH_2, CH_2), 3.23 (3 H, s, NCH_3), 6.56 (1 H, d, *J* 7.5 Hz, Ar*H*), 7.05-7.16 (4 H, m, Ar*H*), 7.19-7.25 (2 H, m, Ar*H*), 7.28-7.36 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 26.3 (N*C*H$_3$), 27.7 (C(*C*H$_3$)$_3$), 30.1 (*C*H$_2$), 35.6 (*C*H$_2$), 60.3 (*C*), 82.4 (O*C*(CH$_3$)$_3$), 108.2 (ArH), 122.7 (ArH), 123.1 (ArH), 125.9 (ArH), 128.3 (ArH), 128.3 (Ar), 128.4 (ArH), 128.9 (ArH), 141.0 (Ar), 144.3 (Ar), 168.1 (*C*=O), 174.2 (*C*=O); *m/z* (ESI) 374 ($[MNa]^+$) [HRMS (ESI): calculated for $C_{22}H_{25}NNaO_3$, 374.1727 Found: $[MNa]^+$, 374.1716 (2.7 ppm error)].

(DSP-V-66)

1-Methyl-3-(phenethyl)indolin-2-one 360

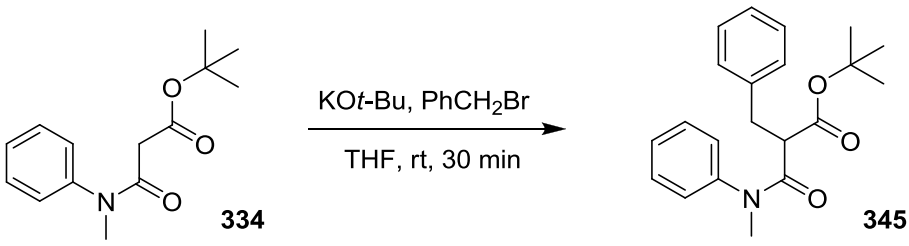


Reaction performed following method H using *tert*-butyl 1-methyl-2-oxo-3-phenethylindoline-3-carboxylate **353** (88 mg, 0.25 mmol, 1.0 equiv). Purification by flash column chromatography (SiO_2, 20 g, 3:1 petrol/ethyl acetate, 20 mm Ø), gave 39 mg (0.16 mmol, 62%) of **360** as a colourless oil.

R_f 0.36 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3057, 3027, 2925, 2859, 1710, 1612, 1493, 1469, 1421, 1376, 1346, 1261, 1126, 1089, 1023, 925, 750, 700; δ_H(400 MHz; chloroform-*d*) 2.26 (2 H, m, CH_2), 2.61-2.79 (2 H, m, CH_2), 3.19 (3 H, s, NCH_3), 3.48 (1 H, dd, *J* 6.0, 6.0 Hz, C*H*), 6.50 (1 H, d, *J* 7.5 Hz, Ar*H*), 7.07 (1 H, dd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.15-7.20 (3 H, m, Ar*H*), 7.23-7.32 (4 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 26.1 (N*C*H_3), 31.9 (*C*H_2), 32.3 (CH_2), 44.9 (*C*H), 108.0 (ArH), 122.3 (ArH), 123.8 (ArH), 126.0 (ArH), 127.9 (ArH), 128.3 (ArH), 128.5 (ArH), 128.9 (Ar), 141.2 (Ar), 144.4 (Ar), 177.6 (*C*=O); *m/z* (ESI) 274 ($[MNa]^+$) [HRMS (ESI): calculated for $C_{17}H_{17}NNaO$, 274.1202 Found: $[MNa]^+$, 274.1202 (2.9 ppm error)].

(DSP-V-71)

***tert*-Butyl 2-benzyl-3-(methyl(phenyl)amino)-3-oxopropanoate 345**



A 50 mL round-bottomed flask with stirrer-bar was charged with *tert*-butyl 3-(methyl(phenyl)amino)-3-oxopropanoate **334** (499 mg, 2.00 mmol, 1.0 equiv) a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as THF (20 mL) was added. The septum was briefly

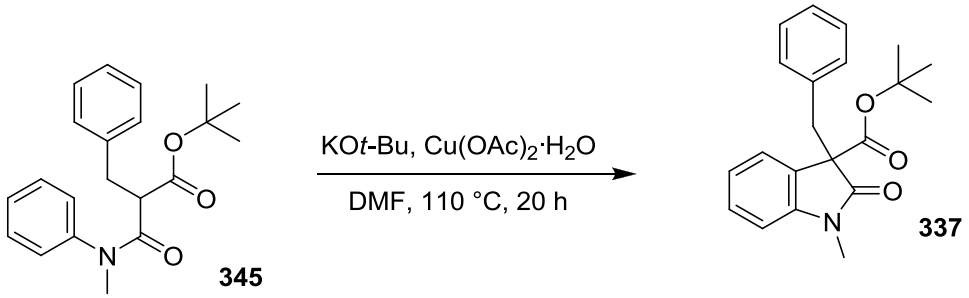
removed to add potassium *tert*-butoxide (247 mg, 2.20 mmol, 1.1 equiv) to give a yellow solution which was stirred for 5 min before dropwise addition of benzyl bromide (251 μL, 2.10 mmol, 1.05 equiv) over 1 min to give a colourless suspension which was stirred at room temperature. After 30 min the reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (SiO_2, 50 g, 3:1 petrol/ethyl acetate, 45 mm Ø), gave 634 mg (1.87 mmol, 93%) of **345** as a colourless oil.

R_f 0.67 (1:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3062, 3029, 2976, 2933, 1738, 1659, 1596, 1452, 1420, 1385, 1370, 1258, 1148, 1118, 1032, 846, 772, 750, 700; δ_H(400 MHz; chloroform-*d*) 1.45 (9 H, s, C(C*H*$_3$)$_3$), 3.01 (1 H, dd, *J* 13.5, 5.0 Hz, C*H*$_2$), 3.18 (3 H, s, NC*H*$_3$), 3.18 (1 H, dd, *J* 13.5, 10.5 Hz, C*H*$_2$), 3.45 (1 H, dd, *J* 10.5, 5.0 Hz, C*H*), 6.60 (2 H, br s, Ar*H*), 7.01-7.06 (2 H, m, Ar*H*), 7.21-7.27 (6 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 27.9 (C(*C*H$_3$)$_3$), 35.2 (*C*H$_2$), 37.3 (N*C*H$_3$), 51.7 (*C*H), 81.5 (O*C*(CH$_3$)$_3$), 126.4 (ArH), 127.6 (ArH), 127.8 (ArH), 128.3 (ArH), 129.2 (ArH), 124.4 (ArH), 138.7 (Ar), 143.3 (Ar), 168.5 (*C*=O), 168.8 (*C*=O); *m/z* (ESI) 362 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{21}H_{25}NNaO_3$, 362.1727 Found: [MNa]$^+$, 362.1728 (0.4 ppm error)] [Found C, 74.06; H, 7.35; N, 3.95%. $C_{21}H_{25}NO_3$ requires C, 74.31; H, 7.42; N, 4.13%].

(DSP-V-21)

tert-Butyl 3-benzyl-1-methyl-2-oxoindoline-3-carboxylate 337

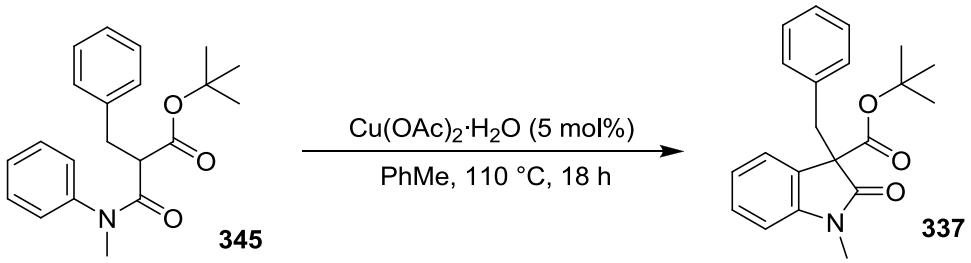
Initial approach:



Reaction performed following method G using *tert*-Butyl 2-benzyl-3-(methyl(phenyl)amino)-3-oxopropanoate **345** (170 mg, 0.50 mmol, 1.0 equiv). Stirred at 110 °C for 20 h. Purification by flash column chromatography (SiO_2,

50 g, 7:2:1 petrol/dichloromethane/ethyl acetate, 45 mm Ø), gave 146 mg (0.43 mmol, 86%) of **337** as a yellow solid.

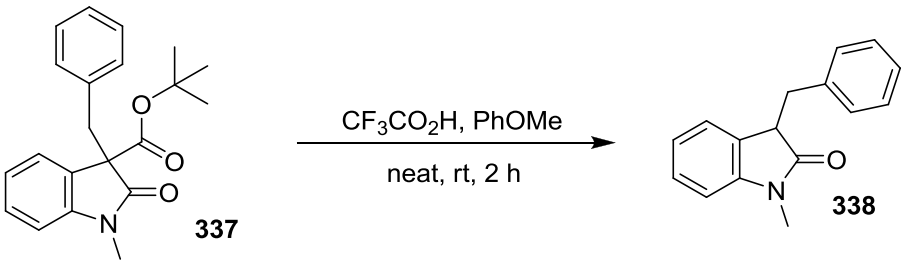
Catalytic procedure:



A 25 mL round-bottomed flask with stirrer-bar was charged with *tert*-butyl 2-benzyl-3-(methyl(phenyl)amino)-3-oxopropanoate **345** (170 mg, 0.50 mmol, 1.0 equiv), copper(II) acetate monohydrate (5 mg, 0.025 mmol, 0.05 equiv) and toluene (10 mL). A condenser topped was fitted and the blue-green suspension heated to 110 °C. The mixture was stirred at this temperature for 18 h before cooling to room temperature and quenching the reaction with with water (20 mL). The organic layer was washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (SiO_2, 50 g, 7:2:1 petrol/dichloromethane/ethyl acetate, 45 mm Ø), gave 116 mg (0.34 mmol, 69%) of **337** as a colourless oil.

R_f 0.50 (7:2:1 petrol/dichloromethane/ethyl acetate); mp 77-79 °C; ν_{max}(film)/cm^{-1} 2975, 2921, 1717, 1610, 1493, 1470, 1370, 1351, 1251, 1155, 1127, 1089, 997, 847, 748, 699; δ_H(400 MHz; chloroform-*d*) 1.39 (9 H, s, C(C*H*$_3$)$_3$), 2.94 (3 H, s, NC*H*$_3$), 3.47 (1 H, d, *J* 13.5 Hz, C*H*$_2$), 3.51 (1 H, d, *J* 13.5 Hz, C*H*$_2$), 6.56 (1 H, dd, *J* 7.5, 1.0 Hz, Ar*H*), 6.83-6.87 (2 H, m, Ar*H*), 6.97-7.07 (4 H, m, Ar*H*), 7.20 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.31 (1 H, dd, *J* 7.5, 1.0 Hz, Ar*H*); δ_C(100 MHz; chloroform-*d*) 26.0 (NCH$_3$), 27.8 (C(*C*H$_3$)$_3$), 39.7 (*C*H$_2$), 61.8 (*C*), 82.5 (O*C*(CH$_3$)$_3$), 108.0 (ArH), 122.3 (ArH), 123.6 (ArH), 126.6 (ArH), 127.5 (ArH), 127.9 (Ar), 128.7 (ArH), 129.9 (ArH), 134.8 (Ar), 144.1 (Ar), 168.1 (*C*=O), 173.7 (*C*=O); *m/z* (ESI) 360 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{21}H_{23}NNaO_3$, 360.1570 Found: [MNa]$^+$, 360.1565 (1.3 ppm error)] [Found C, 74.82; H, 6.93; N, 4.15%. $C_{21}H_{23}NO_3$ requires C, 74.75; H, 6.87; N, 4.15%].
(DSP-V-23)

3-Benzyl-1-methylindolin-2-one 338



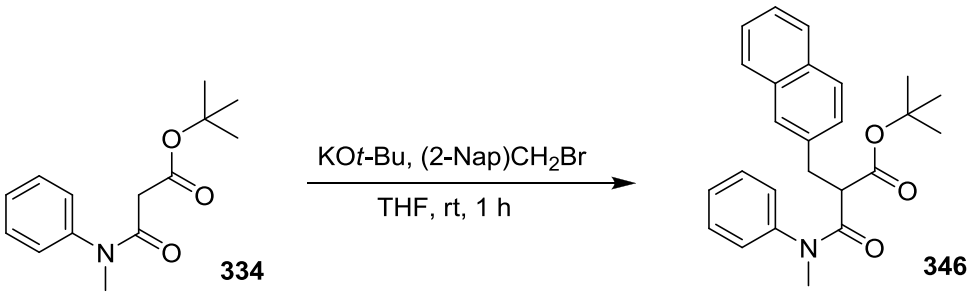
Reaction performed following method H using *tert*-butyl 3-benzyl-1-methyl-2-oxoindoline-3-carboxylate **337** (84 mg, 0.25 mmol, 1.0 equiv). Purification by flash column chromatography (SiO_2, 20 g, 3:1 petrol/ethyl acetate, 20 mm Ø), gave 85 mg (0.24 mmol, 98%) of **338** as a yellow solid.

R_f 0.33 (3:1 petrol/ ethyl acetate); mp 61-63 °C (lit. 69-70 °C); δ_H(400 MHz; chloroform-*d*) 2.87 (1 H, dd, *J* 13.5, 9.5 Hz, C*H*$_2$), 3.16 (3 H, s, NC*H*$_3$), 3.50 (1 H, dd, *J* 13.5, 4.5 Hz, C*H*$_2$), 3.72 (1 H, dd, *J* 9.5, 4.5 Hz, C*H*), 6.71-6.77 (2 H, m, Ar*H*), 6.91 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.15-7.18 (2 H, m, Ar*H*), 7.19-7.28 (4 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[276]

(DSP-V-69)

***tert*-Butyl 3-(methyl(phenyl)amino)-2-(naphthalen-2-ylmethyl)-3-oxopropanoate 346**



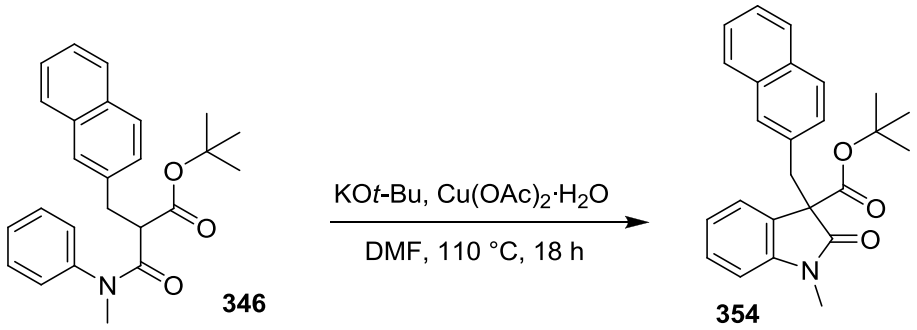
A 50 mL round-bottomed flask with stirrer-bar was charged with *tert*-butyl 3-(methyl(phenyl)amino)-3-oxopropanoate **334** (499 mg, 2.00 mmol, 1.0 equiv) a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as THF (20 mL) was added. Septum briefly removed to add potassium *tert*-butoxide (247 mg, 2.20 mmol, 1.1 equiv) to give a yellow

solution which was stirred for 5 min before addition of 2-(bromomethyl)naphthalene (464 mg, 2.10 mmol, 1.05 equiv) in a single portion to give a yellow suspension which was stirred at room temperature. After 1 h the reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a pale yellow oil. Purification by flash column chromatography (SiO_2, 50 g, 3:1 petrol/ethyl acetate, 35 mm Ø), gave 725 mg (1.86 mmol, 93%) of **346** as a colourless oil.

R_f 0.42 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3057, 2976, 2933, 1737, 1657, 1596, 1496, 1449, 1422, 1386, 1369, 1333, 1265, 1148, 1119, 909, 846, 817, 773, 732, 700; δ_H(400 MHz; chloroform-*d*) 1.46 (9 H, s, C(C*H*$_3$)$_3$), 3.12 (3 H, s, NC*H*$_3$), 3.19 (1 H, dd, *J* 13.5, 5.0 Hz, C*H*$_2$), 3.34 (1 H, dd, *J* 13.5, 10.5 Hz, C*H*$_2$), 3.59 (1 H, dd, *J* 10.5, 5.0 Hz, C*H*), 6.51 (2 H, br s, Ar*H*), 7.09-7.17 (3 H, m, Ar*H*), 7.20-7.25 (1 H, m, Ar*H*), 7.42-7.50 (3 H, m, Ar*H*), 7.71-7.75 (2 H, m, Ar*H*), 7.80-7.84 (1 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 28.0 (C(*C*H$_3$)$_3$), 35.4 (*C*H$_2$), 37.3 (N*C*H$_3$), 51.7 (*C*H), 81.6 (O*C*(CH$_3$)$_3$), 125.4 (ArH), 125.9 (ArH), 127.5 (ArH), 127.6 (ArH), 127.6 (ArH), 127.6 (ArH), 127.7 (ArH), 127.8 (ArH), 127.8 (ArH), 130.0 (ArH), 132.2 (Ar), 133.5 (Ar), 136.2 (Ar), 143.3 (Ar), 168.5 (*C*=O), 168.8 (*C*=O); *m/z* (ESI) 412 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{25}H_{27}NNaO_3$, 412.1883 Found: [MNa]$^+$, 412.1890 (1.7 ppm error)].

(DSP-V-57)

***tert*-Butyl 1-methyl-3-(naphthalen-2-ylmethyl)-2-oxoindoline-3-carboxylate 354**

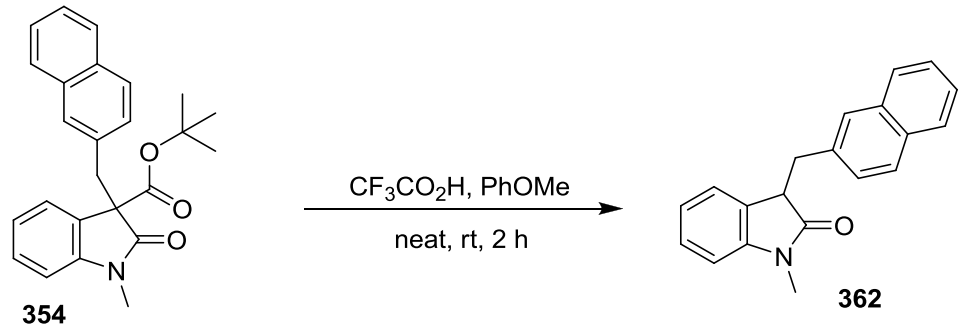


Reaction performed following method G using *tert*-butyl 3-(methyl(phenyl)amino)-2-(naphthalen-2-ylmethyl)-3-oxopropanoate **346** (195 mg, 0.50 mmol, 1.0 equiv). The mixture was stirred at 110 °C for 18 h. Purification by flash column chromatography (SiO_2, 15 g, 7:2:1 petrol/dichloromethane/ethyl acetate, 20 mm Ø), gave 141 mg (0.36 mmol, 73%) of **354** as a colourless gum.

R_f 0.44 (3:1 petrol /ethyl acetate); ν_{max}(film)/cm^{-1} 3056, 2978, 2932, 1734, 1715, 1610, 1493, 1471, 1370, 1351, 1306, 1251, 1155, 1086, 997, 909, 750; δ_H(400 MHz; chloroform-*d*) 1.41 (9 H, s, C(C*H*$_3$)$_3$), 2.89 (3 H, s, NC*H*$_3$), 3.64 (1 H, d, *J* 13.5 Hz, C*H*$_2$), 3.69 (1 H, d, *J* 13.5 Hz, C*H*$_2$), 6.50 (1 H, d, *J* 7.5 Hz, Ar*H*), 6.98 (1 H, dd, *J* 8.5, 2.0 Hz, Ar*H*), 7.06 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.17 (1 H, ddd, *J* 7.5, 7.5, 1.5 Hz, Ar*H*), 7.33-7.37 (3 H, m, Ar*H*), 7.38 (1 H, ddd, *J* 7.5, 1.5, 0.5 Hz, Ar*H*), 7.48 (1 H, d, *J* 8.5 Hz, Ar*H*), 7.60 (1 H, dd, *J* 6.0, 3.5 Hz, Ar*H*), 7.67 (1 H, dd, *J* 6.0, 3.5 Hz, Ar*H*); δ_C(100 MHz; chloroform-*d*) 26.1 (NC*H*$_3$), 27.8 (C(*C*H$_3$)$_3$), 39.7 (*C*H$_2$), 61.8 (*C*), 82.6 (O*C*(CH$_3$)$_3$), 108.1 (ArH), 122.3 (ArH), 123.6 (ArH), 125.4 (ArH), 125.5 (ArH), 126.9 (ArH), 127.3 (ArH), 127.7 (ArH), 127.8 (Ar), 128.3 (ArH), 128.8 (ArH), 128.8 (ArH), 132.1 (Ar), 132.5 (Ar), 132.9 (Ar), 144.1 (Ar), 168.1 (*C*=O), 173.8 (*C*=O); *m/z* (ESI) 410 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{25}H_{25}NNaO_3$, 410.1727 Found: [MNa]$^+$, 410.1731 (0.6 ppm error)].

(DSP-V-61)

1-Methyl-3-(naphthalen-2-ylmethyl)indolin-2-one 362

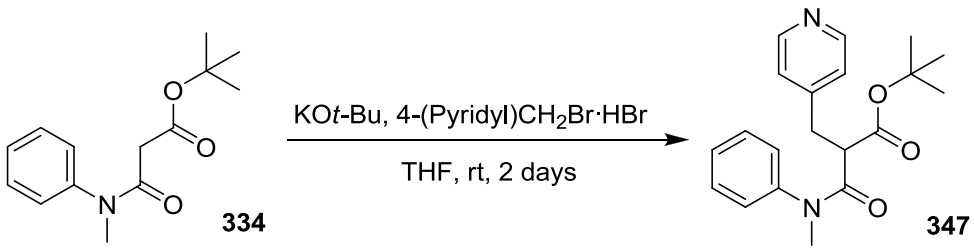


Reaction performed following method H using *tert*-butyl 1-methyl-3-(naphthalen-2-ylmethyl)-2-oxoindoline-3-carboxylate **354** (97 mg, 0.25 mmol, 1.0 equiv). Purification by flash column chromatography (SiO_2, 20 g, 4:1 petrol/ethyl acetate, 25 mm Ø), gave 67 mg (0.23 mmol, 93%) of **362** as a yellow solid.

R_f 0.39 (3:1 petrol/ethyl acetate); mp 91-93 °C; ν_{max}(film)/cm^{-1} 3053, 2920, 2853, 1709, 1612, 1493, 1469, 1422, 1375, 1350, 1256, 1127, 1089, 750, 732; δ_H(400 MHz; chloroform-*d*) 3.04 (1 H, dd, *J* 13.5, 9.5 Hz, C*H*$_2$), 3.17 (3 H, s, NC*H*$_3$), 3.67 (1 H, dd, *J* 13.5, 4.5 Hz, C*H*$_2$), 3.84 (1 H, dd, *J* 9.5, 4.5 Hz, C*H*), 6.71-6.77 (2 H, m, *J* 7.5 Hz, Ar*H*), 6.88 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.21 (1 H, dd, *J* 8.0, 8.0 Hz, Ar*H*), 7.34 (1 H, dd, *J* 8.5, 1.5 Hz, Ar*H*), 7.43-7.47 (2 H, m, Ar*H*), 7.60 (1 H, br s, Ar*H*), 7.73-7.82 (3 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 26.2 (N*C*H$_3$), 37.0 (*C*H$_2$), 46.9 (*C*H), 107.9 (ArH), 122.1 (ArH), 124.5 (ArH), 125.5 (ArH), 126.0 (ArH), 127.6 (ArH), 127.6 (ArH), 127.6 (ArH), 127.9 (Ar), 127.9 (ArH), 128.0 (ArH), 128.3 (Ar), 132.3 (Ar), 133.3 (Ar), 135.5 (Ar), 144.1 (Ar), 177.0 (*C*=O); *m/z* (ESI) 310 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{20}H_{17}NNaO$, 310.1202 Found: [MNa]$^+$, 310.1196 (1.6 ppm error)].

(DSP-V-68)

***tert*-Butyl 3-(methyl(phenyl)amino)-3-oxo-2-(pyridin-4-ylmethyl)propanoate 347**

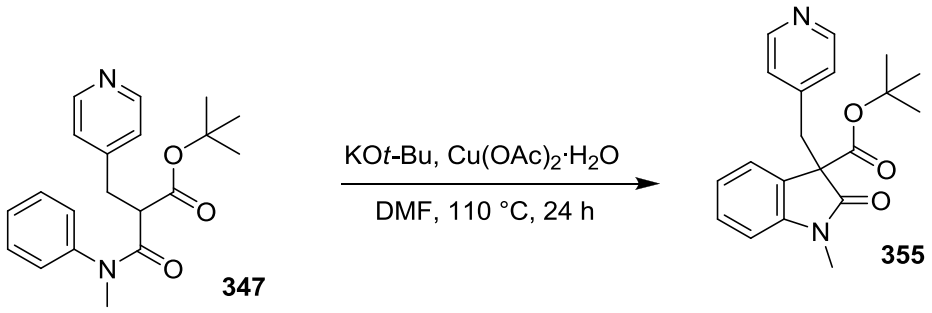


A 50 mL round-bottomed flask with stirrer-bar was charged with *tert*-butyl 3-(methyl(phenyl)amino)-3-oxopropanoate **334** (499 mg, 2.00 mmol, 1.0 equiv) a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as THF (20 mL) was added. The septum was briefly removed to add potassium *tert*-butoxide (538 mg, 4.40 mmol, 2.2 equiv) to give a yellow solution which was stirred for 5 min before addition of 2-(bromomethyl)pyridine hydrobromide (531 mg, 2.10 mmol, 1.05 equiv) in a single portion to give a yellow suspension which was stirred at room temperature. After 2 days the reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a pale yellow oil. Purification by flash column chromatography (SiO_2, 50 g, 1:3 petrol/ethyl acetate, 35 mm Ø), gave 313 mg (0.92 mmol, 46%) of **347** as a colourless oil, along with 76 mg (0.30 mmol, 15%) recovered starting material.

R_f 0.21 (1:3 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2977, 2934, 1737, 1658, 1599, 1560, 1496, 1449, 1417, 1387, 1371, 1332, 1281, 1220, 1150, 1120, 1072, 995, 845, 810, 775, 733, 702; δ_H(400 MHz; chloroform-*d*) 1.42 (9 H, s, C(C*H*$_3$)$_3$), 2.98 (1 H, dd, *J* 13.5, 5.0 Hz, C*H*$_2$), 3.13 (1 H, dd, *J* 13.5, 10.0 Hz, C*H*$_2$), 3.15 (3 H, s, NC*H*$_3$), 3.46 (1 H, dd, *J* 10.0, 5.0 Hz, C*H*), 6.71 (2 H, br s, Py*H*), 6.96 (2 H, br s, Ph*H*), 7.25-7.30 (3 H, m, Ph*H*), 8.48 (2 H, d, *J* 6.0 Hz, Py*H*); δ_C(100 MHz; chloroform-*d*) 27.9 (C(*C*H$_3$)$_3$), 34.5 (*C*H$_2$), 37.4 (N*C*H$_3$), 50.7 (*C*H), 82.0 (O*C*(CH$_3$)$_3$), 124.6 (PyH), 127.3 (PhH), 128.1 (ArH), 129.6 (PhH), 143.0 (Ph), 147.8 (Py), 149.6 (PyH), 167.9 (*C*=O), 168.1 (*C*=O); *m/z* (ESI) 341 ([MH]$^+$) [HRMS (ESI): calculated for $C_{20}H_{25}N_2O_3$, 341.1860 Found: [MH]$^+$, 341.1868 (2.4 ppm error)].

(DSP-V-80)

***tert*-Butyl 1-methyl-2-oxo-3-(pyridin-4-ylmethyl)indoline-3-carboxylate 355**

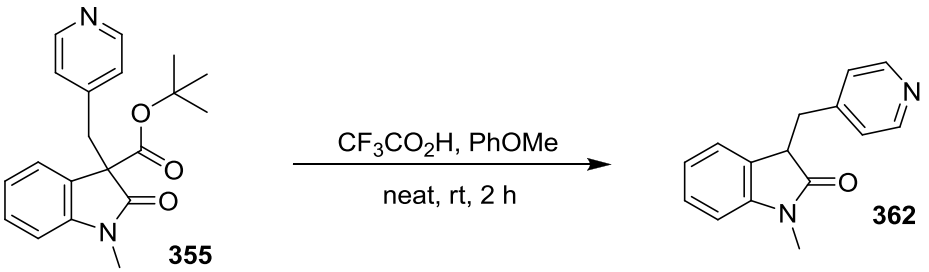


Reaction performed following method G using *tert*-butyl 3-(methyl(phenyl)amino)-3-oxo-2-(pyridin-4-ylmethyl)propanoate **347** (170 mg, 0.50 mmol, 1.0 equiv). The mixture was stirred at 110 °C for 24 h. Purification by flash column chromatography (SiO_2, 20 g, 1:3 petrol/ethyl acetate, 25 mm Ø), gave 115 mg (0.34 mmol, 68%) of **355** as a yellow solid.

R_f 0.41 (1:3 petrol/ethyl acetate); mp 159-161 °C; ν_{max}(film)/cm^{-1} 2977, 2934, 1720, 1608, 1491, 1461, 1415, 1370, 1350, 1256, 1155, 1124, 1082, 1056, 995, 841, 808, 764, 685; δ_H(400 MHz; chloroform-*d*) 1.38 (9 H, s, C(C*H*$_3$)$_3$), 2.98 (3 H, s, NC*H*$_3$), 3.45 (1 H, d, *J* 13.0 Hz, C*H*$_2$), 3.53 (1 H, d, *J* 13.0 Hz, C*H*$_2$), 6.61 (1 H, d, *J* 7.5 Hz, Ar*H*), 6.82 (2 H, br s, Py*H*), 7.08 (1 H, d, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.24 (1 H, d, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.32 (1 H, d, *J* 7.5, 1.0 Hz, Ar*H*), 8.27 (2 H, br s, Py*H*); δ_C(100 MHz; chloroform-*d*) 25.9 (N*C*H$_3$), 27.5 (C(*C*H$_3$)$_3$), 38.5 (*C*H$_2$), 60.9 (*C*), 82.7 (O*C*(CH$_3$)$_3$), 108.2 (ArH), 122.5 (ArH), 123.1 (ArH), 125.1 (br, PyH), 126.9 (Ar), 129.1 (ArH), 143.8 (Ar), 143.9 (Py), 148.8 (PyH), 167.4 (*C*=O), 173.1 (*C*=O); *m/z* (ESI) 339 ([MH]$^+$) [HRMS (ESI): calculated for $C_{20}H_{23}N_2O_3$, 339.1703 Found: [MH]$^+$, 339.1692 (3.3 ppm error)].

(DSP-V-85)

1-Methyl-3-(pyridin-4-ylmethyl)indolin-2-one 362



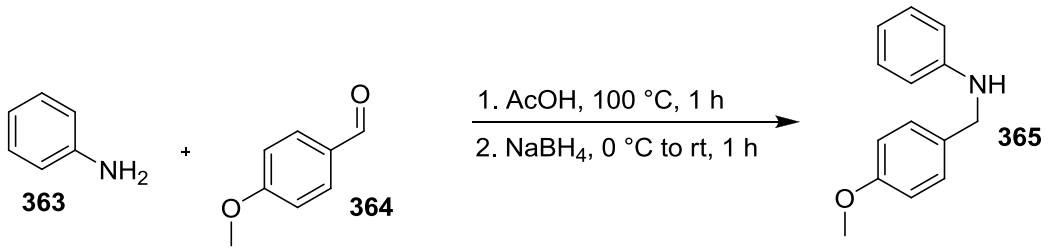
Reaction performed following method H using *tert*-butyl 1-methyl-2-oxo-3-(pyridin-4-ylmethyl)indoline-3-carboxylate **355** (85 mg, 0.25 mmol, 1.0 equiv). Purification by flash column chromatography (SiO_2, 20 g, 1:3 petrol/ethyl acetate → 9:1 ethyl acetate/methanol, 20 mm Ø), gave 55 mg (0.23 mmol, 92%) of **362** as an orange gum.

R_f 0.41 (1:3 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2919, 1694, 1612, 1470, 1378, 1197, 1129, 756, 719; δ_H(400 MHz; chloroform-*d*) 3.12 (3 H, s, NC*H*$_3$), 3.39 (1 H, dd, *J* 13.5, 6.5 Hz, C*H*$_2$), 3.47 (1 H, dd, *J* 13.5, 5.5 Hz, C*H*$_2$), 3.87 (1 H, dd, *J* 6.5, 5.5 Hz, C*H*), 6.77 (1 H, d, *J* 8.0 Hz, Ar*H*), 7.02-7.11 (2 H, m, Ar*H*), 7.29 (1 H, ddd, *J* 8.5, 8.0, 1.0 Hz, Ar*H*), 7.40 (2 H, d, *J* 5.5 Hz, Py*H*), 8.57 (2 H, d, *J* 5.5 Hz, Py*H*); δ_C(100 MHz; methanol-*d*$_4$) 26.5 (N*C*H$_3$), 36.9 (*C*H$_2$), 46.8 (*C*H), 109.9 (ArH), 124.0 (ArH), 125.3 (ArH), 128.1 (Ar), 128.9 (PyH), 129.9 (ArH), 143.2 (PyH), 145.3 (Ar), 159.5 (Py), 178.0 (*C*=O); *m/z* (ESI) 239 ($[MH]^+$) [HRMS (ESI): calculated for $C_{15}H_{15}N_2O$, 239.1179 Found: $[MH]^+$, 239.1185 (2.4 ppm error)].

(DSP-V-96)

4.4.3 Preparation of *N*-*para*-methoxybenzyl oxindoles

_N_-(4-Methoxybenzyl)aniline 363

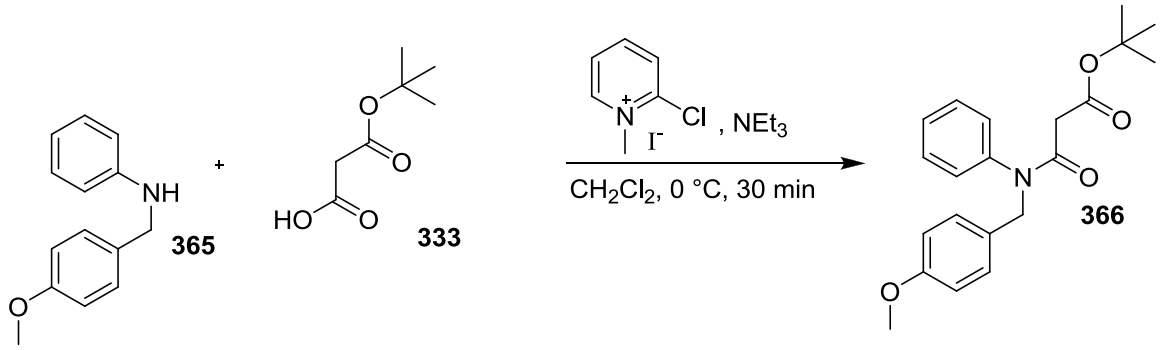


A 100 mL round-bottomed flask with stir-bar was charged with aniline **363** (4.66 g, 50.00 mmol, 1.0 equiv), *p*-anisaldehyde aniline **364** (6.81 g, 50.0 mmol, 1.0 equiv) and acetic acid (25 mL) was added. A condenser was fitted and the solution heated to 100 °C for 1 h. After this time the solution was cooled to room temperature and concentrated to remove most of the acetic acid. Ethanol (50 mL) was added and the solution cooled to 0 °C (ice-bath), before addition of sodium borohydride (2.27 g, 60.0 mmol, 1.2 equiv) in small portions over 10 min. On complete addition the ice bath was removed and the suspension stirred at room temperature for 1 h. The crude material was loaded directly onto a silica column (50 g, 40 mm Ø) and eluted with 9:1 petrol/ethyl acetate, to give a brown solid. The crude solid was recrystallised from MeOH and the crystals were collected *via* filtration, washing with portions of pentane to give 6.72 g (31.5 mmol, 63%) of **365** as colourless needles.

R_f 0.30 (9:1 petrol/ethyl acetate); mp 65-66 °(lit.[277] 63.5-64 °C); δ_H(400 MHz; chloroform-*d*) 3.81 (3 H, s, OC*H*$_3$), 4.07 (1 H, br s, N*H*), 4.26 (2 H, s, C*H*$_2$), 6.65 (2 H, dd, *J* 8.5, 1.0 Hz, Ph*H*), 6.73 (1 H, tt, *J* 7.5, 1.0 Hz, Ph*H*), 6.89 (2 H, d, *J* 8.5 Hz, Ar*H*), 7.19 (2 H, dd, *J* 8.5, 7.5 Hz, Ph*H*), 7.30 (2 H, d, *J* 8.5 Hz, Ar*H*); δ_C(100 MHz; chloroform-*d*) 47.8 (*C*H$_2$), 55.3 (*C*H$_3$), 112.9 (ArH), 114.0 (ArH), 117.6 (ArH), 128.8 (ArH), 129.2 (ArH), 131.3 (Ar), 148.1 (Ar), 158.8 (*C*OCH$_3$). Obtained data in accordance with previously reported data.[278]

(DSP-VI-6)

tert-Butyl 3-((4-methoxybenzyl)(phenyl)amino)-3-oxopropanoate 366

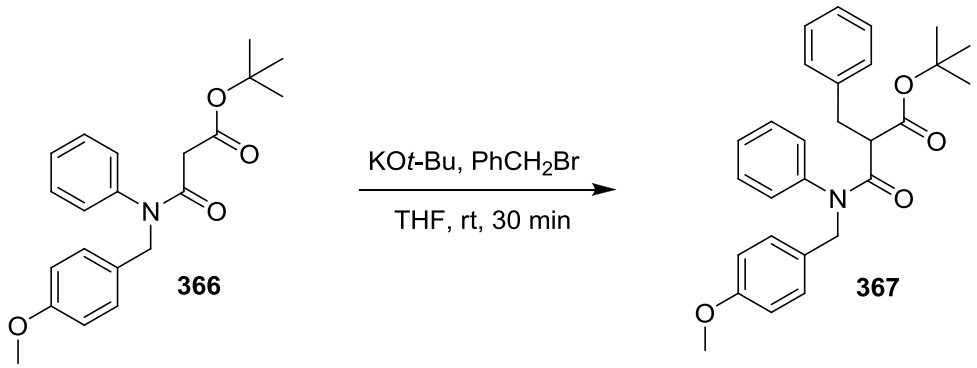


A 250 mL round-bottomed flask with stirrer-bar was charged with *N*-(4-methoxybenzyl)aniline **365** (6.40 g, 30.0 mmol, 1.0 equiv), a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as dichloromethane (120 mL) was added and the solution cooled to 0 °C (ice-bath). To this solution, *tert*-butylmalonate **333** (5.1 mL, 33.0 mmol, 1.1 equiv), 2-chloro-1-methylpyridinium iodide (8.43 g, 33.0 mmol, 1.1 equiv) and triethylamine (21 mL, 15.2 g, 150 mmol, 5.0 equiv) were added to give a bright yellow suspension. The mixture was stirred at 0 °C for 90 min before the reaction was quenched with 10% hydrochloric acid (60 mL). The resulting organic layer was washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a brown oil. Purification by flash column chromatography (SiO_2, 100 g, 3:1 petrol/ethyl acetate, 40 mm Ø), gave 9.87 g (27.8 mmol, 93%) of **366** as a colourless oil.

R_f 0.25 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2979, 2935, 2837, 1734, 1662, 1614, 1594, 1513, 1495, 1397, 1369, 1247, 1176, 1147, 1037, 957, 845, 779, 757, 702; δ_H(400 MHz; chloroform-*d*) 1.41 (9 H, s, C(C*H*$_3$)$_3$), 3.11 (2 H, s, C*H*$_2$), 3.77 (3 H, s, OC*H*$_3$), 4.84 (2 H, s, NC*H*$_2$), 6.78 (2 H, d, *J* 8.5 Hz, Ar*H*), 6.99 (2 H, dd, *J* 6.5, 3.0 Hz, Ph*H*), 7.13 (2 H, d, *J* 8.5 Hz, Ar*H*), 7.28-7.32 (3 H, m, Ph*H*); δ_C(100 MHz; chloroform-*d*) 27.8 (C(*C*H$_3$)$_3$), 42.9 (*C*H$_2$), 55.2 (N*C*H$_2$), 55.0 (O*C*H$_3$), 81.4 (O*C*(CH$_3$)$_3$), 113.6 (ArH), 128.1 (PhH), 128.4 (PhH), 129.1 (Ar), 129.5. (PhH), 130.1 (ArH), 141.7 (Ph), 158.8 (*C*OCH$_3$), 166.1 (*C*=O), 166.8 (*C*=O); *m/z* (ESI) 356 ([MH]$^+$) [HRMS (ESI): calculated for $C_{21}H_{26}NO_4$, 356.1856 Found: [MH]$^+$, 356.1852 (1.1 ppm error)].

(DSP-VI-7)

***tert*-Butyl 2-benzyl-3-((4-methoxybenzyl)(phenyl)amino)-3-oxopropanoate 367**

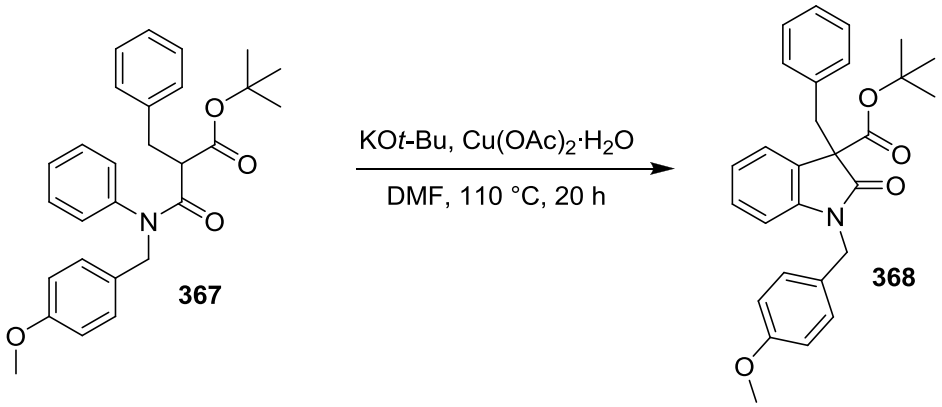


A 100 mL round-bottomed flask with stirrer-bar was charged with *tert*-Butyl 3-((4-methoxybenzyl)(phenyl)amino)-3-oxopropanoate **366** (1.78 g, 5.00 mmol, 1.0 equiv) a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as THF (50 mL) was added. The septum was briefly removed to add potassium *tert*-butoxide (672 mg, 5.50 mmol, 1.1 equiv) to give a yellow solution which was stirred for 5 min before dropwise addition of benzyl bromide (0.63 mL, 5.25 mmol, 1.05 equiv) over 15 min to give a colourless suspension which was stirred at room temperature. After 30 min the reaction was quenched by the addition of a saturated solution of ammonium chloride (25 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (SiO_2, 50 g, 3:1 petrol/ethyl acetate, 30 mm Ø), gave 1.92 g (4.31 mmol, 86%) of **367** as a colourless gum.

R_f 0.38 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2976, 2934, 1737, 1655, 1612, 1594, 1512, 1494, 1452, 1400, 1368, 1328, 1278, 1247, 1176, 1147, 1034, 845, 753, 733, 700; δ_H(400 MHz; chloroform-*d*) 1.43 (9 H, s, C(C*H*$_3$)$_3$), 3.02 (1 H, dd, *J* 13.0, 4.5 Hz, C*H*$_2$), 3.23 (1 H, dd, *J* 13.0, 11.0 Hz, C*H*$_2$), 3.38 (1 H, dd, *J* 11.0, 4.5 Hz, C*H*), 3.77 (3 H, s, OC*H*$_3$), 4.54 (1 H, d, *J* 14.0 Hz, NC*H*$_2$), 4.86 (1 H, d, *J* 14.0 Hz, NC*H*$_2$), 6.74 (2 H, d, *J* 8.5 Hz, Ar*H*), 7.00 (2 H, d, *J* 8.5 Hz, Ar*H*), 7.03-7.24 (10 H, m, Ph*H*); δ_C(100 MHz; chloroform-*d*) 27.9 (C(*C*H$_3$)$_3$), 35.0 (*C*H$_2$), 51.7 (*C*H), 52.2 (NCH$_2$), 55.1 (OCH$_3$) 81.5 (O*C*(CH$_3$)$_3$), 113.4 (ArH), 126.3 (ArH), 127.9 (ArH), 128.2 (ArH), 128.8 (ArH), 129.0 (ArH), 129.2

(Ar), 129.3 (ArH), 130.1 (ArH), 138.5 (Ar), 141.4 (Ar), 158.7 (*C*OCH$_3$), 168.4 (*C*=O), 168.4 (*C*=O); *m/z* (ESI) 468 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{28}H_{31}NNaO_4$, 468.2145 Found: [MNa]$^+$, 468.2155 (2.0 ppm error)].
(DSP-VI-8)

***tert*-Butyl 3-benzyl-1-(4-methoxybenzyl)-2-oxoindoline-3-carboxylate 368**



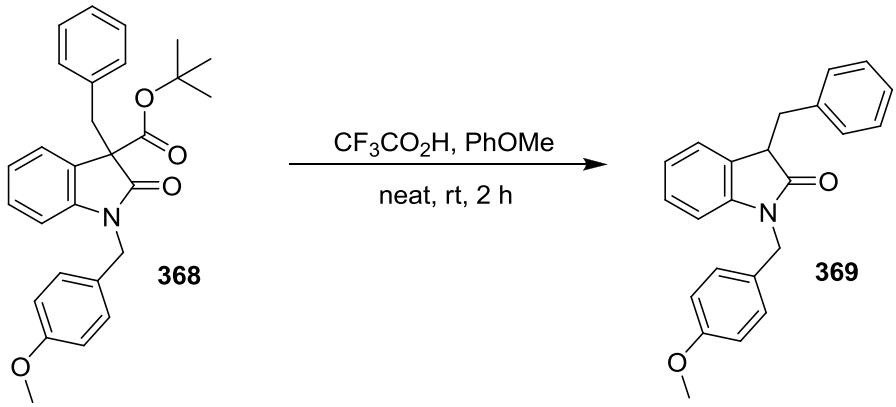
A 50 mL round-bottomed flask with stirrer-bar was charged with *tert*-butyl 2-benzyl-3-((4-methoxybenzyl)(phenyl)amino)-3-oxopropanoate **367** (446 mg, 1.00 mmol, 1.0 equiv), DMF (20 mL), potassium *tert*-butoxide (123 mg, 1.10 mmol, 1.1 equiv) and copper(II) acetate monohydrate (200 mg, 1.00 mmol, 1.0 equiv). A condenser topped with an argon balloon was fitted and the reaction heated to 110 °C. After 14 h the reaction was cooled to room temperature and the quenched by addition of a saturated solution of ammonium chloride (20 mL). The mixture was diluted with water (40 mL) and extracted with ethyl acetate (60 mL). The organic layer was washed with brine (2 × 60 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a brown oil. Purification by flash column chromatography (SiO_2, 50 g, 4: petrol/ethyl acetate, 40 mm Ø), gave 304 mg (0.69 mmol, 69%) of **368** as a yellow solid.

R_f 0.46 (3:1 petrol/ethyl acetate); mp 99-101 °C; ν_{max}(film)/cm^{-1} 3032, 2978, 2932, 1735, 1610, 1513, 1490, 1466, 1366, 1250, 1155, 1035, 912, 846, 733, 700; δ_H(400 MHz; chloroform-*d*) 1.40 (9 H, s, C(C*H*$_3$)$_3$), 3.54 (1 H, d, *J* 13.5 Hz, C*H*$_2$), 3.60 (1 H, d, *J* 13.5 Hz, C*H*$_2$), 3.74 (3 H, s, OC*H*$_3$), 4.59 (1 H, d, *J* 16.0 Hz, NC*H*$_2$), 4.68 (1 H, d, *J* 16.0 Hz, NC*H*$_2$), 6.38 (1 H, d, *J* 7.0 Hz, Ar*H*), 6.66-6.68 (3 H, m, Ar*H*), 6.89 (2 H, d, *J* 7.0 Hz, Ar*H*), 7.00-7.12 (6 H, m, Ar*H*), 7.38 (1 H, d, *J* 7.0 Hz, Ar*H*); δ_C(100 MHz; chloroform-*d*) 27.7 (C(*C*H$_3$)$_3$), 39.1 (*C*H$_2$), 42.8

(N*C*H$_3$), 55.2 (O*C*H$_3$), 61.8 (*C*), 82.6 (O*C*(CH$_3$)$_3$), 109.3 (ArH), 113.9 (ArH), 122.3 (ArH), 123.3 (ArH), 126.6 (ArH), 127.2 (Ar), 127.8 (ArH), 127.9 (Ar), 127.9 (ArH), 128.7 (ArH), 130.2 (ArH), 134.9 (Ar), 143.3 (Ar), 158.7 (Ar), 168.3 (*C*=O), 173.6 (*C*=O); *m/z* (ESI) 466 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{28}H_{29}NNaO_4$, 466.1989 Found: [MNa]$^+$, 466.1995 (1.4 ppm error)].

(DSP-VI-11)

3-Benzyl-1-(4-methoxybenzyl)indolin-2-one 369



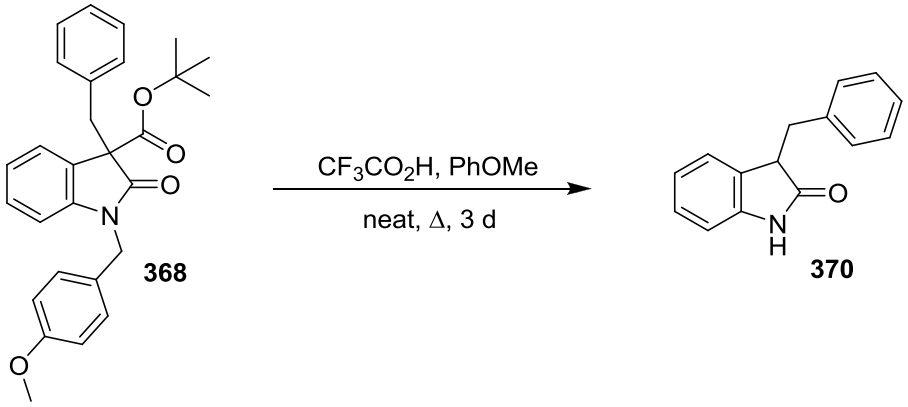
A 25 mL round-bottomed flask with stirrer-bar was charged with *tert*-butyl 3-benzyl-1-(4-methoxybenzyl)-2-oxoindoline-3-carboxylate **368** (110 mg, 0.25 mmol, 1.0 equiv), anisole (82 μL, 0.75 mmol, 3.0 equiv), and a septum with argon balloon fitted. TFA (1 mL) was added and the brown solution stirred at room temperature. After 2 h the stirrer-bar was removed and the mixture concentrated to give a yellow oil. Purification by flash column chromatography (SiO_2, 15 g, 3:1 petrol/ethyl acetate, 20 mm Ø), gave 72 mg (0.21 mmol, 84%) of **369** as a yellow oil.

R_f 0.50 (1:1 petrol/ ethyl acetate); δ_H(400 MHz; chloroform-*d*) 3.11 (1 H, dd, *J* 13.5, 8.0 Hz, C*H*$_2$), 3.50 (1 H, dd, *J* 13.5, 4.5 Hz, C*H*$_2$), 3.76 (3 H, s, C*H*$_3$), 3.83 (1 H, dd, *J* 8.0, 4.5 Hz, C*H*), 4.58 (1 H, d, *J* 15.5 Hz, C*H*$_2$), 4.96 (1 H, d, *J* 15.5 Hz, C*H*$_2$), 6.58 (1 H, d, *J* 8.0 Hz, Ar*H*), 6.74 (1 H, d, *J* 9.0 Hz, Ar*H*), 6.89 (1 H, d, *J* 9.0 Hz, Ar*H*), 6.91-6.93 (2 H, m, Ar*H*), 7.08-7.14 (3 H, m, Ar*H*), 7.20-7.22 (3 H, m, Ar*H*); *m/z* (ESI) 366 ([MNa]$^+$) [HRMS (ESI): calculated for $C_{23}H_{21}NNaO_2$, 366.1465 Found: [MNa]$^+$, 366.1459 (1.4 ppm error)].

Obtained data in accordance with previously reported data.[279]

(DSP-VI-13)

3-Benzyloxindole 370



A 25 mL round-bottomed flask with stirrer-bar was charged with *tert*-butyl 3-benzyl-1-(4-methoxybenzyl)-2-oxoindoline-3-carboxylate **368** (110 mg, 0.25 mmol, 1.0 equiv), anisole (82 μL, 0.75 mmol, 3.0 equiv), and a condenser fitted. TFA (1 mL) was added and the brown solution was heated to reflux. After 3 days the stirrer-bar was removed and the mixture concentrated to give an orange gum. Purification by flash column chromatography (SiO_2, 15 g, 3:1 petrol/ethyl acetate, 20 mm Ø), gave 49 mg (0.22 mmol, 87%) of **370** as a pale yellow solid.

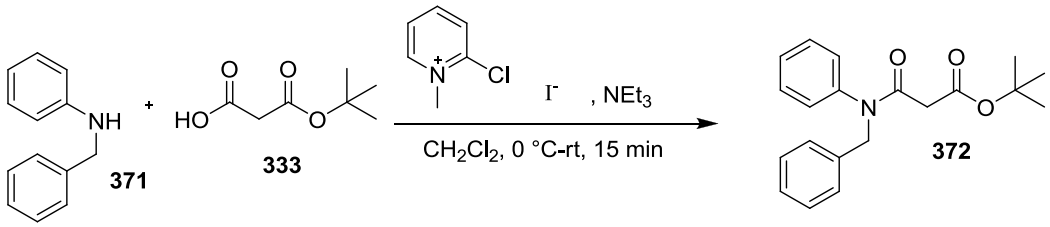
R_f 0.24 (2:1 petrol/ ethyl acetate); mp 123-125 °C (lit.[280] 129-130 °C); δ_H(400 MHz; chloroform-*d*) 2.95 (1 H, dd, *J* 13.5, 9.0 Hz, CH_2), 3.49 (1 H, dd, *J* 13.5, 4.5 Hz, CH_2), 3.75 (1 H, dd, *J* 9.0, 4.5 Hz, C*H*), 6.75 (1 H, d, *J* 7.5 Hz, CH_2), 6.79 (1 H, d, *J* 7.5 Hz, CH_2), 6.90 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.13-7.19 (3 H, m, Ar*H*), 7.21-7.28 (3 H, m, Ar*H*).

Obtained data in accordance with previously reported data.[280]

(DSP-VI-23)

4.4.4 Preparation of *N*-benzyl oxindoles

tert-Butyl 3-(benzyl(phenyl)amino)-3-oxopropanoate 372

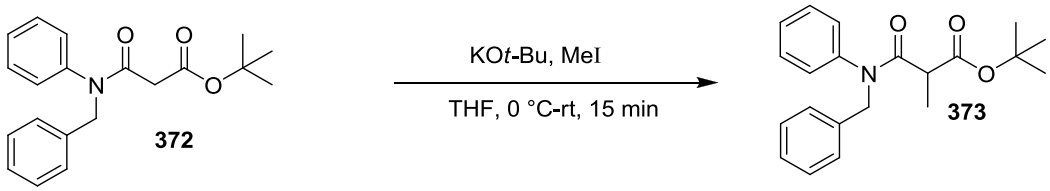


A 250 mL 2-neck round bottomed flask (B24 open neck; B14 with thermometer adaptor and −10 - 60 °C thermometer fitted) with a stirrer bar was charged with *N*-benzylaniline **371** (11.0 g, 60.0 mmol, 1.0 equiv), dichloromethane (120 mL) and *tert*-butyl malonate **333** (10.1 mL, 10.6 g, 66.0 mmol, 1.1 equiv) to give a pale yellow solution. The flask was placed in an ice-water bath to give an internal temperature of 3 °C. 2-Chloro-1-methylpyridinium iodide (16.9 g, 66.0 mmol, 1.1 equiv) was added in a single portion to give a yellow suspension and an exotherm to 10 °C. The mixture was stirred for 5 min until the temperature had returned to 3 °C, before addition of triethylamine (17.6 mL, 24.3 g, 240 mmol, 4.0 equiv) *via* syringe maintaining the temperature below 10 °C (*ca.* 10 min) to give a yellow solution. On complete addition the ice bath was removed and the reaction allowed to warm to room temperature. After 15 min the yellow solution was quenched by the addition of an aqueous 3 M HCl solution (60 mL) to give a biphasic solution which was stirred for 5 min before transferring to a 500 mL separating funnel, washing the flask with an additional portion of dichloromethane (50 mL). The combined organic layers were separated and washed with a saturated solution of sodium bicarbonate (60 mL) and brine (120 mL), dried (Na_2SO_4), filtered and concentrated to afford 16.89 g of a yellow oil. Purification by flash column chromatography (SiO_2, 180 g, 3:1 to 1:1 petrol/Et_2O, 60 mm Ø), gave 16.44 g (50.5 mmol, 84%) of **372** as a colourless oil.

R_f 0.39 (1:1 petrol/diethyl ether); ν_{max}(film)/cm^{-1} 2979, 2933, 1732, 1664, 1595, 1495, 1397, 1368, 1329, 1147, 701; δ_H(400 MHz; chloroform-*d*) 1.42 (9 H, s, (C*H*$_3$)$_3$), 3.14 (2 H, s, C*H*$_2$), 4.91 (2 H, s, C*H*$_2$), 7.00-7.04 (2 H, m, Ar*H*), 7.20-7.27 (5 H, m, Ar*H*), 7.29-7.34 (3 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 27.9

(($CH_3)_3$), 42.9 (CH_2), 52.9 (CH_2), 81.6 (*C*), 127.3 (ArH), 128.3 (ArH), 128.3 (ArH), 128.3 (ArH), 128.7 (ArH), 129.5 (ArH), 137.0 (Ar), 141.8 (Ar), 166.3 (*C*=O), 166.8 (*C*=O); *m/z* (ESI) 326 ($[MH]^+$) [HRMS (ESI): calculated for $C_{20}H_{24}NO_3$, 326.1751 Found: $[MH]^+$, 326.1759 (2.4 ppm error)] [Found C, 73.58; H, 7.16; N, 4.32%. $C_{20}H_{23}NO_3$ requires C, 73.82; H, 7.12; N, 4.30%]. (DSP-VII-42)

tert-Butyl 3-(benzyl(phenyl)amino)-2-methyl-3-oxopropanoate 373

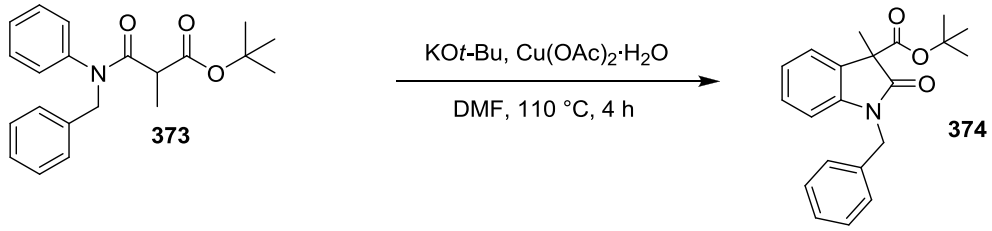


A 250 mL 2-neck round bottomed flask (B24 septum and argon balloon; B14 with thermometer adaptor and −10 - 60 °C thermometer fitted) with a stirrer bar was charged with *tert*-butyl 3-(benzyl(phenyl)amino)-3-oxopropanoate **372** (16.3 g, 50.0 mmol, 1.0 equiv) and tetrahydrofuran (100 mL) to give a pale yellow solution. The flask was placed in an ice-water bath to give an internal temperature of 3 °C. Potassium *tert*-butoxide (6.17 g, 55.0 mmol, 1.1 equiv) was added to give a colourless suspension and an exotherm to 10 °C. The reaction was stirred until the temperature had returned to 3 °C (*ca.* 5 min), before addition of methyl iodide (3.4 mL, 7.61 g, 52.5 mmol, 1.05 equiv) *via* syringe over 30 min, maintaining the temperature below 10 °C to give a colourless suspension. On complete addition, the ice bath was removed and the mixture stirred for 15 min. After this time the cream suspension was quenched with a saturated solution of ammonium chloride (50 mL) and transferred to a 250 mL separating funnel. The washings were transferred with water (20 mL) and diethyl ether (100 mL). The organic layer was separated and washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 18.0 g of an orange oil. Purification by flash column chromatography (SiO_2, 180 g, 7:3 petrol/diethyl ether, 60 mm Ø), gave 16.5 g (48.7 mmol, 97%) of **373** as a colourless sticky oil. R_f 0.58 (1:1 petrol/diethyl ether); ν_{max}(film)/cm^{-1} 2979, 2936, 1739, 1661, 1595, 1495, 1454, 1398, 1369, 1326, 1248, 1152, 848, 736, 701; δ_H(400 MHz;

chloroform-*d*) 1.28 (3 H, d, *J* 7.0 Hz, C*H*$_3$), 1.41 (9 H, s, (C*H*$_3$)$_3$), 3.27 (1 H, q, *J* 7.0 Hz, C*H*), 4.58 (1 H, d, *J* 14.5 Hz, C*H*$_2$), 5.22 (1 H, d, *J* 14.5 Hz, C*H*$_2$), 7.01-7.04 (2 H, m, Ar*H*), 7.21-7.26 (5 H, m, Ar*H*), 7.30-7.34 (3 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 13.9 (*C*H$_3$), 27.8 ((*C*H$_3$)$_3$), 44.3 (*C*H), 52.9 (*C*H$_2$), 81.1 (*C*), 127.6 (ArH), 128.2 (ArH), 128.2 (ArH), 128.4 (ArH), 128.7 (ArH), 129.5 (ArH), 137.3 (Ar), 141.9 (Ar), 169.7 (*C*=O), 170.3 (*C*=O); *m/z* (ESI) 340 ([MH]$^+$) [HRMS (ESI): calculated for $C_{21}H_{26}NO_3$, 340.1907 Found: [MH]$^+$, 340.1916 (2.5 ppm error)] [Found C, 74.19; H, 7.46; N, 4.12%. $C_{21}H_{25}NO_3$ requires C, 74.13; H, 7.42; N, 4.13%].

(DSP-VII-48)

***tert*-Butyl 1-benzyl-3-methyl-2-oxoindoline-3-carboxylate 374**



A 2 L 2-neck round bottomed flask (B24 septum and argon balloon; B19 with thermometer adaptor and 0 - 300 °C thermometer fitted) with a stirrer bar was charged with *tert*-butyl 3-(benzyl(phenyl)amino)-2-methyl-3-oxopropanoate **373** (13.58 g, 40.0 mmol, 1.0 equiv) and *N*,*N*-dimethylformamide (800 mL) to give a colourless solution. Potassium *tert*-butoxide (4.94 g, 44.0 mmol, 1.1 equiv) was added to give a yellow solution. The mixture was stirred for 5 min before addition of copper(II) acetate monohydrate (7.99 g, 40.0 mmol, 1.0 equiv) in a single portion to give a green-blue suspension, which was placed in a 110 °C oil-bath. After 4 h the green suspension was cooled to room temperature and concentrated *in vacuo* to approximately 1/10th volume. The brown suspension was poured into a 1 L separating funnel, washing in with water (300 mL), 3 M hydrochloric acid (100 mL) and diethyl ether (200 mL) to give a brown organic and green aqueous layers. The layers were separated and the aqueous layer extracted with further portions of diethyl ether (2 × 200 mL). The combined organic layers were washed with a saturated solution of sodium bicarbonate (200

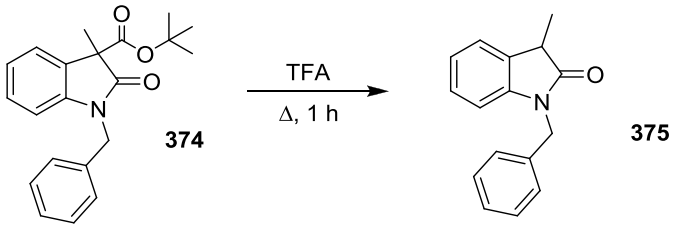
mL) and brine (2 × 200 mL). Dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 14.7 g of a brown oil.

Purification by flash column chromatography (SiO_2, 120 g, 4:1 petrol/diethyl ether, 60 mm Ø), followed by collection of the product on a sinter, using portions of hexane (3 × 50 mL) gave 7.76 g (23.0 mmol, 57%) of **374** as a colourless solid.

R_f 0.36 (2:1 petrol/diethyl ether); mp 106-107 °C; ν_{max}(film)/cm^{-1} 2980, 2932, 1735, 1609, 1490, 1466, 1368, 1254, 1157, 1115, 749, 697; δ_H(400 MHz; chloroform-*d*) 1.36 (9 H, s, (C*H*$_3$)$_3$), 1.67 (3 H, s, C*H*$_3$), 4.66 (1 H, d, *J* 16.0 Hz, C*H*$_2$), 5.22 (1 H, d, *J* 16.0 Hz, C*H*$_2$), 6.69 (1 H, d, *J* 7.5 Hz, Ar*H*), 7.02 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.17 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.22-7.34 (6 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 19.9 (*C*H$_3$), 27.7 ((*C*H$_3$)$_3$), 43.6 (*C*H$_2$), 55.9 (*C*), 82.4 (*C*), 109.3 (ArH), 122.6 (ArH), 122.7 (ArH), 127.1 (ArH), 127.5 (ArH), 128.6 (ArH), 128.6 (ArH), 130.7 (Ar), 135.6 (Ar), 142.7 (Ar), 168.7 (*C*=O), 175.6 (*C*=O); *m/z* (ESI) 338 ([MH]$^+$) [HRMS (ESI): calculated for $C_{21}H_{24}NO_3$, 338.1751 Found: [MH]$^+$, 338.1745 (1.7 ppm error)] [Found C, 74.67; H, 6.84; N, 4.11%. $C_{21}H_{23}NO_3$ requires C, 74.75; H, 6.87; N, 4.15%].

(DSP-VII-52)

1-Benzyl-3-methylindolin-2-one 375.



A 100 mL 1-neck round bottomed flask (B14 with condenser fitted) with a stirrer bar was charged with *tert*-butyl 1-benzyl-3-methyl-2-oxoindoline-3-carboxylate **374** (7.42 g, 22.0 mmol, 1.0 equiv) and trifluoroacetic acid (11 mL) to give a yellow solution which was placed in an oil-bath held at 75 °C. After 1 h the brown solution was cooled to room temperature, transferred to a 250 mL round bottomed flask using dichloromethane (3 × 20 mL) and concentrated *in vacuo* to yield a brown oil. Ethanol (50 mL) was added to dissolve the oil and then

concentrated *in vacuo* to give a colourless solid. Purification by recrystallization (ethanol) gave 4.05 g (17.1 mmol, 78%) of **375** as colourless prisms.

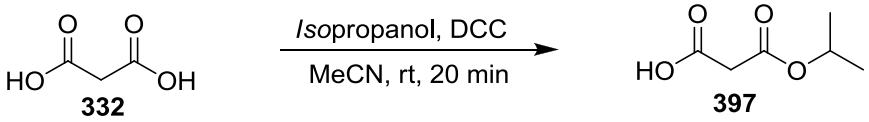
R_f 0.47 (1:1 petrol/diethyl ether); mp 120-121 °C (lit.[281] 112-114 °C); ν_{max}(film)/cm^{-1} 3053, 3031, 2922, 1714, 1611, 1488, 1466, 1452, 1358, 1211, 1172, 979, 747, 697; δ_H(400 MHz; chloroform-*d*) 1.55 (3 H, d, *J* 7.5 Hz, C*H*$_3$), 3.55 (1 H, q, *J* 7.5 Hz, C*H*), 4.88 (1 H, d, *J* 16.0 Hz, C*H*$_2$), 4.93 (1 H, d, *J* 16.0 Hz, C*H*$_2$), 6.73 (1 H, d, *J* 7.5 Hz, Ar*H*), 7.03 (1 H, dd, *J* 7.5, 7.5 Hz, Ar*H*), 7.16 (1 H, dd, *J* 7.5, 7.5 Hz, Ar*H*), 7.23-7.35 (6 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 15.5 (*C*H$_3$), 40.4 (*C*H), 43.5 (*C*H$_2$), 108.9 (ArH), 122.3 (ArH), 123.5 (ArH), 127.2 (ArH), 127.5 (ArH), 127.7 (ArH), 128.6 (ArH), 130.5 (Ar), 135.9 (Ar), 142.9 (Ar), 178.6 (*C*=O); *m/z* (ESI) 238 ([MH]$^+$) [HRMS (ESI): calculated for $C_{16}H_{16}NO$, 238.1226 Found: [MH]$^+$, 238.1230 (1.5 ppm error)] [Found C, 80.86; H, 6.41; N, 5.89%. $C_{16}H_{15}NO$ requires C, 80.98; H, 6.37; N, 5.90%].

Obtained data in accordance with previously reported data.[281]

(DSP-VII-70)

4.4.5 Preparation of *iso*-propyl ester oxindoles

iso-Propyl malonate 397



Based on a procedure by Melman.[223]

A 250 mL pear-shaped flask with stirrer-bar was charged with malonic acid **332** (5.20 g, 50.0 mmol. 1.0 equiv), acetonitrile (150 mL) and *iso*-propanol (7.70 mL, 100 mmol, 2.0 equiv), a septum fitted and the flask purged with argon (balloon). A solution of dicyclohexylcarbodiimide (11.4 g, 55.0 mmol, 1.1 equiv) in acetonitrile (55 mL) was added *via* cannula to give a white suspension. The mixture was stirred at room temperature for 30 min before filtering to give a colourless solution which was concentrated *in vacuo* to give a colourless oil. The oil was taken into solution with diethyl ether (250 mL) and extracted with

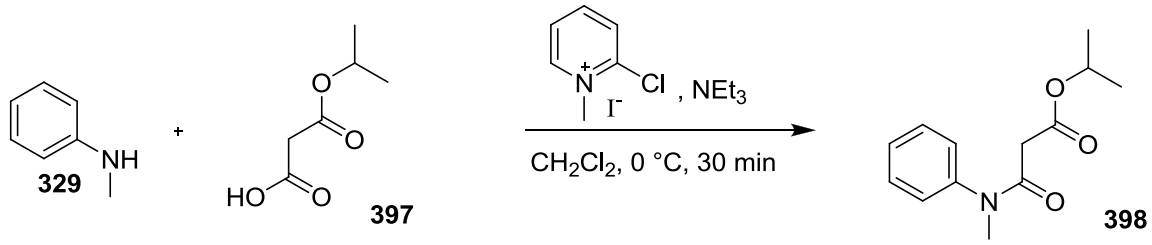
saturated aqueous sodium bicarbonate (2 × 100 mL). The aqueous layer was acidified to pH 1 by addition of a 10% solution of hydrochloric acid (70 mL) and extracted with ethyl acetate (2 × 175 mL). The combined ethyl acetate layers were dried (Na_2SO_4), filtered and concentrated to give **397** as a colourless oil (5.26 g, 36.0 mmol, 72%).

R_f 0.35 (1:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 1.28 (6 H, d, *J* 6.5 Hz, CH(C*H*$_3$)$_2$), 3.41 (2 H, s, C*H*$_2$), 5.11 (1 H, septet, *J* 6.5 Hz, C*H*(CH$_3$)$_2$); δ_C(100 MHz; chloroform-*d*) 21.5 (CH(*C*H$_3$)$_2$), 41.1 (CH$_2$), 69.8 (*C*H(CH$_3$)$_2$), 166.4 (*C*=O), 171.8 (*C*=O); *m/z* (ESI) 169 ([MNa]$^+$) [HRMS (ESI): calculated for $C_6H_{10}NaO_4$, 169.0471 Found: [MNa]$^+$, 169.0472 (0.1 ppm error)].

Obtained data in accordance with previously reported data.[272]

(DSP-VI-33)

***iso*-Propyl 3-(methyl(phenyl)amino)-3-oxopropanoate 398**

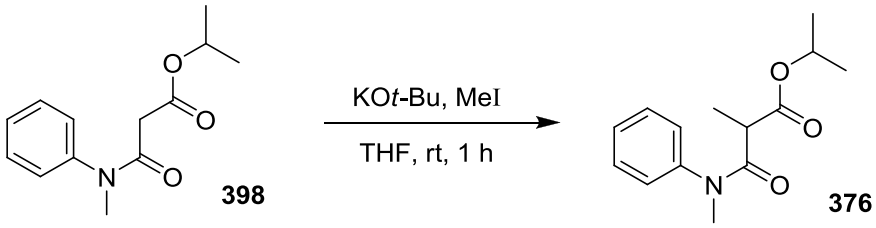


A 100 mL round-bottomed flask with stirrer-bar was charged with *N*-methylaniline **329** (1.07 g, 10.0 mmol, 1.0 equiv) and dichloromethane (20 mL) was added and the solution cooled to 0 °C (ice-bath). To this solution, *iso*-propylmalonate **397** (1.61 g, 11.0 mmol, 1.1 equiv), 2-chloro-1-methylpyridinium iodide (2.81 g, 11.0 mmol, 1.1 equiv) and triethylamine (5.60 mL, 40.0 mmol, 4.0 equiv) were added to give a bright yellow suspension. The mixture was stirred at 0 °C for 30 min before the reaction was quenched with 10% hydrochloric acid (10 mL). The resulting organic layer was washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an orange oil. Purification by flash column chromatography (SiO_2, 50 g, 1:1 petrol/ethyl acetate, 40 mm Ø), gave 2.16 g (9.19 mmol, 92%) of **398** as a colourless oil.

R_f 0.38 (1:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3062, 2982, 2938, 1733, 1664, 1595, 1496, 1453, 1420, 1382, 1314, 1250, 1206, 1174, 1106, 971, 775, 756, 703, 663; δ_H(400 MHz; chloroform-*d*) 1.18 (6 H, d, *J* 6.5 Hz, C*H*(CH_3)$_2$), 3.15 (2 H, s, C*H*$_2$), 3.28 (3 H, s, NC*H*$_3$), 4.96 (1 H, septet, *J* 6.5 Hz, C*H*(CH_3)$_2$), 7.20-7.24 (2 H, m, Ar*H*), 7.31-7.43 (3 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 21.6 (CH(*C*H$_3$)$_2$), 37.4 (N*C*H$_3$), 41.8 (*C*H$_2$), 68.7 (O*C*H(CH_3)$_2$), 127.2 (ArH), 128.2 (ArH), 129.8 (ArH), 143.4 (Ar), 166.1 (*C*=O), 167.2 (*C*=O); *m/z* (ESI) 236 ([MH]$^+$) [HRMS (ESI): calculated for $C_{13}H_{18}NO_3$, 236.1281 Found: [MH]$^+$, 236.1282 (0.2 ppm error)].

(DSP-VI-36)

iso-Propyl 2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoate 376



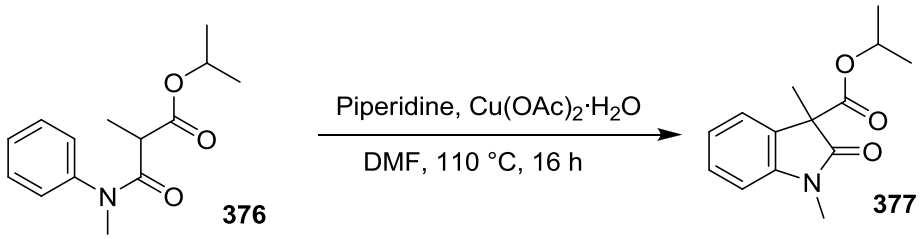
A 50 mL round-bottomed flask with stirrer-bar was charged with *iso*-propyl 3-(methyl(phenyl)amino)-3-oxopropanoate **398** (707 mg, 3.00 mmol, 1.0 equiv) a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as THF (10 mL) was added. The septum was briefly removed to add potassium *tert*-butoxide (370 mg, 3.30 mmol, 1.1 equiv) to give a yellow solution which was stirred for 5 min before the dropwise addition of methyl iodide (196 μL, 3.15 mmol, 1.05 equiv) over 1 min to give a colourless suspension which was stirred at room temperature. After 20 min the reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (SiO_2, 50 g, 3:2 petrol/ethyl acetate, 40 mm Ø), gave 684 mg (2.74 mmol, 91%) of **376** as a colourless oil.

R_f 0.50 (1:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2982, 2939, 1736, 1663, 1595, 1496, 1455, 1419, 1383, 1313, 1251, 1203, 1109, 1030, 777, 702; δ_H(400 MHz; chloroform-*d*) 1.18 (6 H, t, *J* 6.5 Hz, CH(C*H*$_3$)$_2$), 1.28 (3 H, d, *J* 7.0 Hz, C*H*$_3$),

3.28 (3 H, s, NC*H*$_3$), 3.36 (1 H, q, *J* 7.0 Hz, C*H*), 4.93 (1 H, septet, *J* 6.5 Hz, C*H*(CH$_3$)$_2$), 7.22-7.25 (2 H, m, Ar*H*), 7.33-7.38 (1 H, m, Ar*H*), 7.39-7.44 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 14.0 (*C*H$_3$), 21.5 (CH(*C*H$_3$)$_2$), 21.6 (CH(*C*H$_3$)$_2$), 37.6 (N*C*H$_3$), 43.6 (*C*H), 68.5 (O*C*H(CH$_3$)$_2$), 127.5 (ArH), 128.1 (ArH), 129.8 (ArH), 143.6 (Ar), 170.1 (*C*=O), 170.3 (*C*=O); *m/z* (ESI) 250 ([MH]$^+$) [HRMS (ESI): calculated for $C_{14}H_{20}NO_3$, 250.1438 Found: [MH]$^+$, 250.1444 (2.6 ppm error)].

(DSP-VI-44)

iso-Propyl 1,3-dimethyl-2-oxoindoline-3-carboxylate 377



A 50 mL round-bottomed flask with stirrer-bar was charged with *iso*-propyl 2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoate **376** (100 mg, 0.40 mmol, 1.0 equiv), copper(II) acetate monohydrate (4 mg, 0.02 mmol, 0.05 equiv) and DMF (8 mL) to give a blue solution. Once all the copper was dissolved, piperidine (395 μL, 4.00 mmol, 10.0 equiv) was added. A condenser topped with a drying tube was fitted and the reaction heated to 110 °C. After 16 h the reaction was cooled to room temperature and the quenched by addition of a saturated solution of ammonium chloride (20 mL). The mixture was diluted with water (40 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a brown oil. Purification by flash column chromatography (SiO_2, 20 g, 7:2:1 petrol/dichloromethane/ethyl acetate, 30 mm Ø), gave 36 mg (0.15 mmol, 36%) of **377** as a colourless oil.

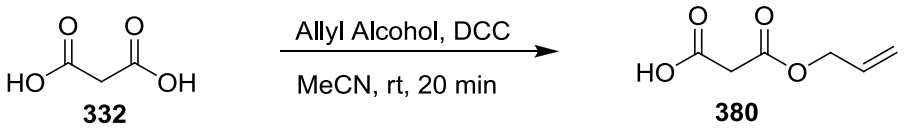
R_f 0.37 (3:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2983, 2936, 1737, 1610, 1494, 1471, 1375, 1347, 1252, 1101, 1029, 937, 907, 824; δ_H(400 MHz; chloroform-*d*) 1.07 (3 H, d, *J* 6.5 Hz, CH(C*H*$_3$)$_2$), 1.17 (3 H, d, *J* 6.5 Hz, CH(C*H*$_3$)$_2$), 1.63 (3 H, s, C*H*$_3$), 3.23 (3 H, s, NC*H*$_3$), 4.96 (1 H, qq, *J* 6.5, 6.5 Hz, C*H*(CH$_3$)$_2$), 6.85 (1 H, dd, *J* 7.5, 1.0 Hz, Ar*H*), 7.04 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.23 (1 H, dd, *J* 7.5, 1.0 Hz, Ar*H*), 7.30 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*); δ_C(100 MHz;

chloroform-*d*) 19.9 (*C*H_3) , 21.2 (CH(*C*H_3)$_2$), 21.4 (CH(*C*H_3)$_2$), 26.4 (N*C*H_3), 55.2 (*C*(CH$_3$)), 69.4 (O*C*H(CH$_3$)$_2$), 108.3 (ArH), 122.7 (ArH), 122.8 (ArH), 128.8 (ArH), 130.2 (Ar), 143.5 (Ar), 169.1 (*C*=O), 175.2 (*C*=O); *m/z* (ESI) 248 ([MH]$^+$) [HRMS (ESI): calculated for $C_{14}H_{18}NO_3$, 248.1281 Found: [MH]$^+$, 248.1287 (2.3 ppm error)].

(DSP-VI-52)

4.4.6 Preparation of allyl ester oxindoles

Allyl malonate 380



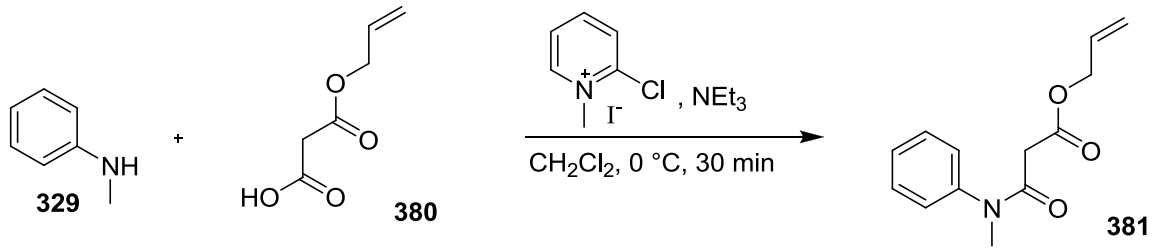
332 **380**

A 500 mL round-bottomed flask with stirrer-bar was charged with malonic acid **332** (5.20 g, 50.0 mmol. 1.0 equiv), acetonitrile (150 mL) and allyl alcohol (6.8 mL, 100 mmol, 2.0 equiv). A solution of dicyclohexylcarbodiimide (11.4 g, 55.0 mmol, 1.1 equiv) in acetonitrile (55 mL) was added *via* cannula to give a white suspension. Stirred at room temperature for 30 min before filtering to give a colourless solution which was concentrated *in vacuo* to give a colourless oil. The oil was taken into solution with diethyl ether (250 mL) and extracted with saturated aqueous sodium bicarbonate (2 × 100 mL). The aqueous layer was acidified to pH 1 by addition of a 10% solution of hydrochloric acid (70 mL) and extracted with ethyl acetate (2 × 175 mL). The combined ethyl acetate layers were dried (Na_2SO_4), filtered and concentrated to give **380** as a colourless oil (5.23 g, 36.3 mmol, 73%).

R_f 0.31 (1:1 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3491, 3089, 2951, 2666, 1741, 1414, 1372, 1323, 1277, 1158, 993, 936; δ_H(400 MHz; chloroform-*d*) 3.47 (2 H, s, C*H*$_2$), 4.66 (2 H, ddd, *J* 6.0, 1.5, 1.5 Hz, C*H*$_2$), 5.27 (1 H, dddd, *J* 10.5, 1.5, 1.5, 1.5 Hz, =C*H*$_2$), 5.34 (1 H, dddd, *J* 16.5, 1.5, 1.5, 1.5 Hz, =C*H*$_2$), 5.91 (1 H, dddd, *J* 16.5, 10.5, 6.0, 6.0 Hz, C*H*); δ_C(100 MHz; chloroform-*d*) 40.9 (*C*H$_2$), 66.4 (*C*H$_2$), 119.1 (=*C*H$_2$), 131.1 (*C*H), 166.2 (*C*=O), 171.9 (*C*=O); *m/z* (ESI) 167 ([MNa]$^+$) [HRMS (ESI): calculated for $C_6H_8NaO_4$, 167.0315 Found: [MNa]$^+$, 167.0315 (0.1 ppm error)].

(DSP-VI-37)

Allyl 3-(methyl(phenyl)amino)-3-oxopropanoate 381

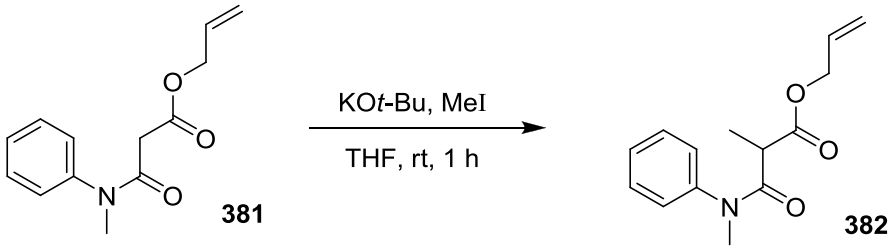


A 50 mL round-bottomed flask with stirrer-bar was charged with *N*-methylaniline **329** (1.07 g, 10.0 mmol, 1.0 equiv), dichloromethane (20 mL) and the solution cooled to 0 °C (ice-bath). To this solution, allylmalonate **380** (2.82 mL, 11.0 mmol, 1.1 equiv) and 2-chloro-1-methylpyridinium iodide (2.81 g, 11.0 mmol, 1.1 equiv) were added to give a bright yellow suspension, followed by triethylamine (10.5 mL, 75.0 mmol, 5.0 equiv) dropwise over 10 min. Stirred at 0 °C for 5 min before warming to room temperature and stirring for 30 min. The reaction was quenched with 10% hydrochloric acid (10 mL). The resulting organic layer was washed with saturated sodium bicarbonate solution (10 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an orange oil. Purification by flash column chromatography (SiO_2, 50 g, 3:2 petrol/ethyl acetate, 40 mm Ø), gave 2.12 g (9.09 mmol, 91%) of **381** as a colourless oil.

R_f 0.39 (3:2 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 3063, 2943, 1742, 1664, 1595, 1496, 1422, 1384, 1310, 1241, 1157, 1121, 992, 930, 776, 702; δ_H(400 MHz; chloroform-*d*) 3.24 (2 H, s, CH_2), 3.31 (3 H, s, NCH_3), 4.57 (2 H, ddd, *J* 6.0, 1.5, 1.5 Hz, OCH_2), 5.23 (1 H, ddd, *J* 10.5, 1.5, 1.5 Hz, =CH_2), 5.30 (1 H, dddd, *J* 17.0, 1.5, 1.5, 1.5 Hz, =CH_2), 5.87 (1 H, dddd, *J* 17.0, 10.5, 1.5, 1.5 Hz, =C*H*), 7.21-7.25 (2 H, m, Ar*H*), 7.33-7.45 (3 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 37.4 (NCH_3), 41.4 (CH_2), 65.8 (OCH_2), 118.6 (=CH_2), 127.2 (ArH), 128.3 (ArH), 129.9 (ArH), 131.6 (=CH), 143.4 (Ar), 165.8 (*C*=O), 167.3 (*C*=O); *m/z* (ESI) 234 ($[MH]^+$) [HRMS (ESI): calculated for $C_{13}H_{16}NO_3$, 234.1125 Found: $[MH]^+$, 234.1132 (2.5 ppm error)].

(DSP-VI-40)

Allyl 2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoate 382

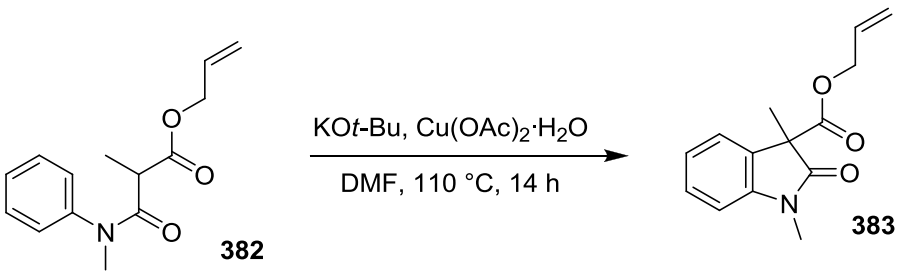


A 50 mL round-bottomed flask with stirrer-bar was charged with allyl 3-(methyl(phenyl)amino)-3-oxopropanoate **381** (1.17 g, 5.00 mmol, 1.0 equiv), a septum fitted and the flask purged with argon (balloon). The flask was maintained under argon as THF (10 mL) was added. The septum was briefly removed to add potassium *tert*-butoxide (0.62 g, 5.50 mmol, 1.1 equiv) to give a yellow solution which was stirred for 5 min before dropwise addition of methyl iodide (0.33 mL, 5.25 mmol, 1.05 equiv) over 1 min to give a colourless suspension which was stirred at room temperature. After 1 h the reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL) and extracted with ethyl acetate (10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (SiO_2, 50 g, 3:2 petrol/ethyl acetate, 40 mm Ø), gave 953 mg (3.85 mmol, 77%) of **382** as a colourless oil.

R_f 0.46 (3:2 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2987, 2941, 1744, 1661, 1595, 1496, 1456, 1420, 1385, 1313, 1250, 1189, 1122, 1092, 1029, 998, 972, 931, 776, 702; δ_H(400 MHz; chloroform-*d*) 1.32 (3 H, d, *J* 7.0 Hz, C*H*$_3$), 3.30 (3 H, s, NC*H*$_3$), 3.44 (1 H, q, *J* 7.0 Hz, C*H*), 4.49-4.60 (2 H, m, OC*H*$_2$), 5.22 (1 H, dddd, *J* 10.5, 1.5, 1.5, 1.5 Hz, =C*H*$_2$), 5.29 (1 H, dddd, *J* 17.0, 1.5, 1.5, 1.5 Hz, =C*H*$_2$), 5.87 (1 H, dddd, *J* 17.0, 10.5, 1.5, 1.5 Hz, =C*H*), 7.22-7.26 (2 H, m, Ar*H*), 7.34-7.39 (1 H, m, Ar*H*), 7.40-7.45 (2 H, m, Ar*H*); δ_C(100 MHz; chloroform-*d*) 13.9 (*C*H$_3$), 37.4 (NCH$_3$), 43.2 (*C*H), 65.4 (OCH$_2$), 117.9 (=*C*H$_2$), 127.2 (ArH), 128.0 (ArH), 129.7 (ArH), 131.6 (=*C*H), 143.3 (Ar), 169.7 (*C*=O), 170.1 (*C*=O); *m/z* (ESI) 248 ([MH]$^+$) [HRMS (ESI): calculated for $C_{14}H_{18}NO_3$, 248.1281 Found: [MH]$^+$, 248.1281 (4.7 ppm error)].

(DSP-VI-41)

Allyl 1,3-dimethyl-2-oxoindoline-3-carboxylate 383

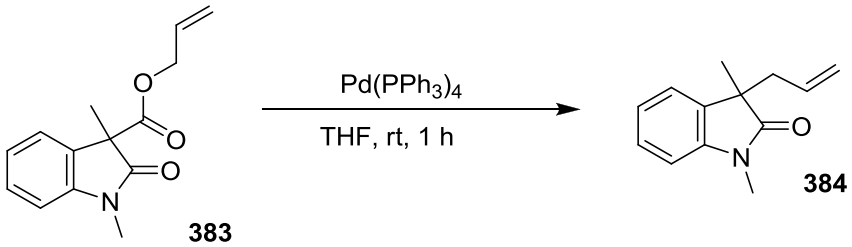


A 100 mL round-bottomed flask with stirrer-bar was charged with allyl 2-methyl-3-(methyl(phenyl)amino)-3-oxopropanoate **382** (495 mg, 2.00 mmol, 1.00 equiv), DMF (40 mL), potassium *tert*-butoxide (247 mg, 2.20 mmol, 1.1 equiv) and copper(II) acetate monohydrate (399 mg, 2.00 mmol, 1.0 equiv). A condenser with a drying tube (drierite®) was fitted and the reaction heated to 110 °C. After 17 h the reaction was cooled to room temperature and the reaction quenched by addition of a saturated solution of ammonium chloride (20 mL). The mixture was diluted with water (80 mL) and extracted with ethyl acetate (80 mL). The organic layer was washed with brine (2 × 80 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a pale yellow oil. Purification by flash column chromatography (SiO_2, 50 g, 3:1 petrol/ethyl acetate, 30 mm Ø), gave 347 mg (1.41 mmol, 71%) of **383** as a colourless oil.

R_f 0.57 (3:2 petrol/ethyl acetate); ν_{max}(film)/cm^{-1} 2984, 2936, 1743, 1718, 1610, 1493, 1471, 1451, 1374, 1348, 1223, 1106, 1029, 971, 930, 753; δ_H(400 MHz; chloroform-*d*) 1.68 (3 H, s, C*H*$_3$), 3.26 (3 H, s, NC*H*$_3$), 4.54-4.57 (2 H, m, OC*H*$_2$), 5.09-5.16 (2 H, m, =C*H*$_2$), 5.76 (1 H, dddd, *J* 17.0, 10.5, 5.5, 5.5 Hz, =C*H*), 6.87 (1 H, br d, *J* 7.5 Hz, Ar*H*), 7.07 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.26 (1 H, dd, *J* 7.5, 1.0 Hz, Ar*H*), 7.33 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*); δ_C(100 MHz; chloroform-*d*) 19.8 (*C*H$_3$), 26.3 (N*C*H$_3$), 54.8 (*C*), 65.7 (O*C*H$_2$), 108.3 (ArH), 117.6 (=*C*H$_2$), 122.6 (ArH), 122.7 (ArH), 128.8 (ArH), 129.7 (Ar), 131.1 (=*C*H) 143.4 (Ar), 169.1 (*C*=O), 174.8 (*C*=O); *m/z* (ESI) 246 ([MH]$^+$) [HRMS (ESI): calculated for $C_{14}H_{16}NO_3$, 246.1125 Found: [MH]$^+$, 246.1125 (1.2 ppm error)].

(DSP-VI-43)

3-Allyl-1,3-dimethylindolin-2-one 384



A 10 mL round-bottomed flask with stirrer-bar was charged with tetrakistriphenylphospine palladium (12 mg, 0.01 mmol, 0.02 equiv), a septum with argon balloon fitted and degassed THF (0.75 mL) added. A solution of allyl 1,3-dimethyl-2-oxoindoline-3-carboxylate **383** (123 mg, 0.50 mmol, 1.0 equiv), in THF (0.25 mL) was added dropwise via cannula and the resulting solution stirred at room temperature. After 1 h the stirrer-bar was removed and the mixture concentrated to give a brown oil which was immediately purified by flash column chromatography (SiO_2, 10 g, 3:1 petrol/ethyl acetate, 20 mm Ø), to give 100 mg (0.49 mmol, 99%) of **384** as a colourless oil.

R_f 0.27 (3:1 petrol/ethyl acetate); δ_H(400 MHz; chloroform-*d*) 1.37 (3 H, s, CH_3), 2.50-2.54 (2 H, m, OCH_2), 3.20 (3 H, s, NCH_3), 4.90-5.02 (1 H, m, =CH_2), 5.44 (1 H, dddd, *J* 17.0, 10.0, 7.0, 7.0 Hz, =C*H*), 6.83 (1 H, br d, *J* 7.5 Hz, Ar*H*), 7.06 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*), 7.20 (1 H, dd, *J* 7.5, 1.0 Hz, Ar*H*), 7.27 (1 H, ddd, *J* 7.5, 7.5, 1.0 Hz, Ar*H*).

Obtained data in accordance with previously reported data.[282]

(DSP-VI-45)

Chapter 5: Publications

5.1 Chronological list of authored publications

An Improved gem-Dimethylcyclopropanation Procedure Using Triisopropylsulfoxonium Tetrafluoroborate.
Michael G. Edwards, Richard J. Paxton, David S. Pugh, and Richard J. K. Taylor, Synlett, 2008, 521-524.

Gem-Dimethylcyclopropanation using Triisopropylsulfoxonium Tetrafluoroborate: Scope and Limitations.
Michael G. Edwards, Richard J. Paxton, David S. Pugh, Adrian C. Whitwood, and Richard J. K. Taylor, Synthesis, 2008, 3279-3288.

Gem-Dimethylcyclopropanation of Dibenzylideneacetone Using Triisopropyl Sulfoxonium Tetrafluoroborate.
Michael G. Edwards, David S. Pugh, Adrian C. Whitwood, and Richard J. K. Taylor, Acta Crystallographica Section C, 2009, **65**, o39-o41.

The Preparation of Substituted Pyrazoles from β,β-Dibromo-enones by a Tandem Condensation/Suzuki-Miyaura Cross-Coupling Process.
Sandra Beltrán-Rodil, Michael G. Edwards, David S. Pugh, Mark Reid and Richard J. K. Taylor, Synlett, 2010, 602-606.

Preparation of 3-Alkyl-Oxindoles by Copper(II)-Mediated C-H, Ar-H Coupling Followed by Decarboxyalkylation.
David S. Pugh, Johannes E. M. N. Klein, Alexis Perry and Richard J. K. Taylor, Synlett, 2010, 934-938.

First C−H Activation Route to Oxindoles using Copper Catalysis.
Johannes E. M. N. Klein, Alexis Perry, David S. Pugh and Richard J. K. Taylor, Org. Lett., 2010, 12, 3446.

A one pot oxidation / allylation / oxidation sequence for the preparation of β,γ-unsaturated ketones directly from primary alcohols.
Catherine L. Moody, David S. Pugh and Richard J. K. Taylor, Tetrahedron Lett., 2011, 52, 2511.

Asymmetric Decarboxylative Allylation of Oxindoles.
Villius Franckevicius, James D. Cuthbertson, Mark Pickworth, David S. Pugh and Richard J. K. Taylor, Org. Lett., 2011, 13, 4264.

An Improved *gem*-Dimethylcyclopropanation Procedure Using Triisopropylsulfoxonium Tetrafluoroborate

Michael G. Edwards, Richard J. Paxton, David S. Pugh, Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York, YO10 5DD, UK
Fax +44(1904)434523; E-mail: rjkt1@york.ac.uk

Received 1 December 2007

Abstract: A new procedure for the cyclopropanation of α,β-unsaturated carbonyl compounds and related systems is described which employs triisopropylsulfoxonium tetrafluoroborate and sodium hydride in dimethylformamide. Using this reagent, a range of α,β-unsaturated ketones (and an ester and a vinyl nitro example) has been converted into the corresponding *gem*-dimethylcyclopropyl carbonyl compounds; in addition, a preliminary result is described in which an activated alcohol is converted directly into a *gem*-dimethylcyclopropyl ketone by a one-pot tandem oxidation–cyclopropanation sequence, albeit in low yield.

Key words: cyclopropanes, cyclopropanation, tandem oxidation procedures, sulfoxonium salts, ruthenium tetroxide

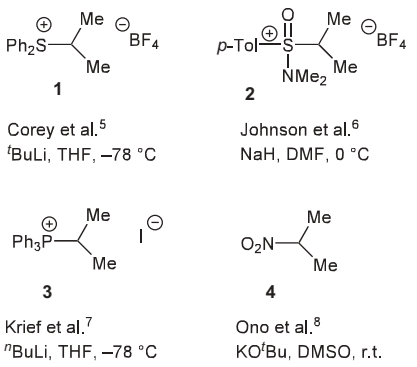


Figure 1

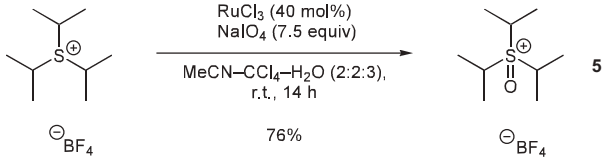
In recent years there has been a revival of interest in cyclopropanation chemistry with the development of efficient carbenoid sources and the application of organocatalysis to provide several elegant enantioselective syntheses.[1,2] This is a testament to both the prevalence of the cyclopropane unit in nature[1] and the utility of functionalised cyclopropanes as synthetic building blocks.[2] Although the parent methylene cyclopropane is present in numerous natural products, the *gem*-dimethylcyclopropane group is a more common structural motif.[3] There are numerous procedures available to prepare *gem*-dimethylcyclopropanes,[4] but it is noteworthy that only a limited number involve isopropyl transfer to electron-deficient alkenes (Figure 1).[5–8] The first such procedure was reported by Corey and Jautelat and utilised diphenylsulfonium isopropylide (**1**).[5] This reagent efficiently produces *gem*-dimethylcyclopropanes from unsaturated esters and amides but with α,β-unsaturated ketones, epoxide formation can compete (for example, 3-methyl-2-cyclohexenone gives mainly the unsaturated epoxide[5a]). In addition, the use of a strong base and low temperatures is required. In 1973, Johnson's group disclosed the use of (dimethylamino)isopropyl-*p*-tolyloxosulfonium tetrafluoroborate (**2**) for the *gem*-dimethylcyclopropanation of *trans*-1,2-dibenzoylethene and *trans*-chalcone.[6] However the synthesis of salt **2** was difficult and low-yielding and the scope of the procedure has not been demonstrated. More recently, it has been shown that the cyclopropanation of unsaturated esters can be achieved using the isopropyl phosphorane **3**[7] and the nitro compound **4**,[8] but again the scope of these reagents has not been determined (e.g. there are no examples of the use with α,β-unsaturated ketones).

As part of our continuing programme in telescoped processes and tandem oxidation processes (TOP),[9] we have recently become interested in developing improved routes to functionalised cyclopropanes.[10,11] First, a tandem procedure was designed for the one-pot oxidation–cyclopropanation of allylic alcohols using MnO_2 in conjunction with stabilised sulfuranes such as (carbethoxymethylene)dimethylsulfurane.[10] We went on to develop an improved procedure for the dimethylsulfoxonium methylide cyclopropanation of α,β-unsaturated ketones using trimethylsulfoxonium iodide and 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine (MTBD).[11]

As an extension for our natural product programme, we also required a method for the nucleophilic *gem*-dimethylcyclopropanation of α,β-unsaturated ketones that would eliminate competitive epoxide formation (via reaction of the ketone), proceed under mild reaction conditions, and be applicable to a range of Michael acceptors. It is well established that the ylide derived from treatment of a sulfoxium salt with base can undergo nucleophilic cyclopropanation of α,β-unsaturated alkenes (the Corey–Chaykovsky reaction) via alkylidene transfer.[12] We therefore explored the preparation and reactions of a triisopropylsulfoxonium salt. As the S-alkylation of sulfoxides is successful only in the case of methylation,[13] it was necessary to synthesise such a salt by oxidation of the triisopropylsulfonium salt[14] (itself derived from diisopropyl sulfide). Unfortunately, the literature contains few reports on the oxidation of sulfonium salts to sulfoxonium salts. The best method, aqueous sodium *m*-chloroperbenzoate,[15]

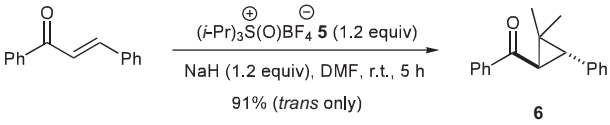
SYNLETT 2008, No. 4, pp 0521–0524
Advanced online publication: 12.02.2008
DOI: 10.1055/s-2008-1042761; Art ID: D39107ST

was not useful for this substrate because the oxidation could not be driven to completion. We reasoned that the use of a more powerful oxidant could overcome the slow oxidation of the sterically encumbered sulfonium salt. Ruthenium tetroxide[16] has been applied to the oxidation of many organic functionalities and, after optimisation of the classical Sharpless conditions ($RuCl_3$, MeCN–CCl_4–H_2O),[17] we found that with 40 mol% of $RuCl_3$ and 7.5 equivalents of $NaIO_4$, triisopropylsulfoxonium could be prepared, after recrystallisation from MeOH–Et_2O, in 76% yield[18] (Scheme 1).



Scheme 1

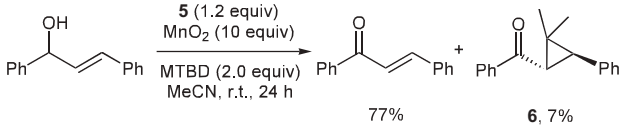
With the sulfoxonium salt in hand, the cyclopropanation of α,β-unsaturated ketones was explored; the initial experiments were conducted under literature conditions for dimethylsulfoxonium methylide cyclopropanation (NaH in DMF).[12d] We were delighted to observe that, after five hours at room temperature, the *gem*-dimethylcyclopropane adduct of chalcone[6] was obtained in 91% yield (Scheme 2). Most notably, only a single diastereomer, the *trans*-product, was obtained. Following this success, a range of α,β-unsaturated ketones was examined as cyclopropanation substrates (Table 1).



Scheme 2

The results illustrated in Table 1 indicate that cyclopropanation of a wide range of α,β-unsaturated ketones proceeds readily in 33–93% yield.[19,20] The results demonstrate a tolerance for both cyclic and acyclic substrates; high yields being obtained in both series. Even in the cases where moderate yields were obtained, there was no evidence for any of the epoxide (1,2-addition products). Moreover, in all examples studied, only a single diastereomer of product, the *trans*-cyclopropane, was obtained. Most notably, (2*E*,4*E*)-1,5-diphenylpenta-2,4-dien-1-one (entry 3) afforded only the 1,4-mono-addition product **8** in 85% yield. Electron-poor and electron-rich α,β-unsaturated ketones both seem to participate reasonably well as evidenced by the successful use of both (*E*)-1,4-diphenylbut-2-ene-1,4-dione (entry 7) and chromone (entry 9). Even a terminal vinyl group could be successfully cyclopropanated (entry 4). The reaction appears to tolerate heterocyclic functionality (entry 2) and the use of (*E*)-2-nitrostyrene illustrates the use of electron-withdrawing groups other than carbonyls. In contrast to the use of dimethylsulfoxonium methylide,[12] enolisable substrates can be problematic leading to alternative condensation byproducts and a lower yield (entries 5 and 6). Furthermore, the use of cyclohexenone led to only 4% of the desired product. Presumably, the slower rate of cyclopropanation, due to the steric encumberance of an ylide bearing three isopropyl groups, renders deprotonation a competitive alternative for the basic ylide.

After developing a successful method for cyclopropanation via isopropyl transfer we briefly investigated a one-pot MnO_2 oxidation–cyclopropanation reaction[11] (Scheme 3). This procedure produced chalcone in 77% yield along with a 7% yield of the oxidized/cyclopropanated adduct **6**. We are currently optimising these conditions.



Scheme 3

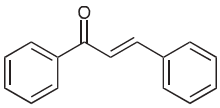
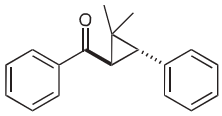
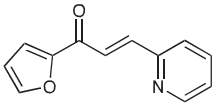
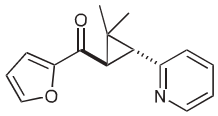
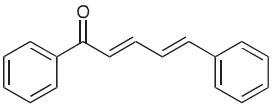
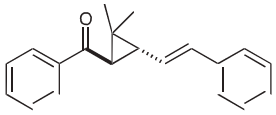
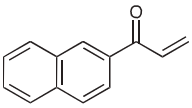
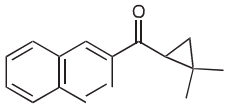
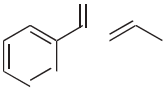
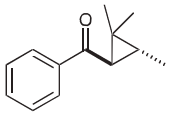
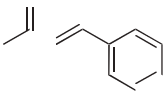
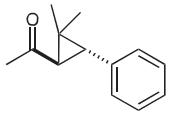
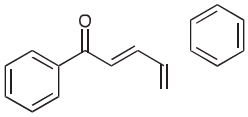
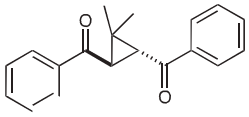
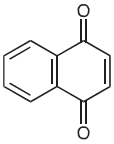
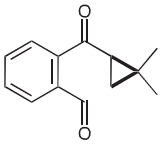
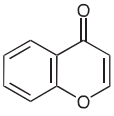
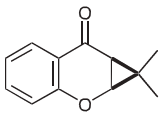
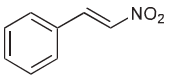
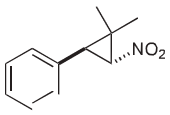
Acknowledgment

We are grateful to the EPSRC for studentship support (R. J. P. and D. S. P.) and Elsevier Science for postdoctoral support (M. G. E.).

References and Notes

(1) See, for example: (a) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589. (b) Pietruszka, J. *Chem. Rev.* **2003**, *103*, 1051.
(2) See, for example: (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (b) Fedorynski, M. *Chem. Rev.* **2003**, *103*, 1099. (c) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133. (d) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151.
(3) For a recently reported example of a *gem*-dimethylcyclopropane natural product, see: Gao, S.; Liu, H.-Y.; Wang, Y.-H.; He, H.-P.; Wang, J.-S.; Di Y, T.; Li, C.-S.; Fang, X.; Hao, X.-J. *Org. Lett.* **2007**, *9*, 3453.
(4) For alternative routes to *gem*-dimethylcyclopropanes, see: (a) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 3911. (b) Franck-Neumann, M. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 65. (c) Sengmany, S.; Léonel, E.; Paugam, J. P.; Nédélec, J.-Y. *Tetrahedron* **2002**, *58*, 271. (d) Charette, A. B.; Wilb, N. *Synlett* **2002**, 176; and references cited therein.
(5) (a) Corey, E. J.; Jautelat, M. *J. Am. Chem. Soc.* **1967**, *89*, 3913. (b) Corey, E. J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.* **1967**, *8*, 2325. (c) Tang, C. S. F.; Rapoport, H. *J. Org. Chem.* **1973**, *38*, 2806. (d) For a recent asymmetric variant, see: Mamai, A.; Madalengoitia, J. S. *Tetrahedron Lett.* **2000**, *41*, 9009.
(6) Johnson, C. R.; Janiga, E. R. *J. Am. Chem. Soc.* **1973**, *95*, 7692.
(7) (a) Devos, M. J.; Krief, A. *Tetrahedron Lett.* **1979**, *20*, 1515. (b) Krief, A.; Dubois, P. *Tetrahedron Lett.* **1993**, *34*, 2691.
(8) Ono, N.; Yanai, T.; Hamamoto, I.; Kamimura, A.; Kaji, A. *J. Org. Chem.* **1985**, *50*, 2806.

Table 1 Cyclopropanation Using Triisopropylsulfoxonium Tetrafluoroborate **5** and NaH in DMF[a]

Entry	Substrate	Product	Time (h)	Yield (%)[b]
1		 **6**	5	91
2		 **7**	2	71
3		 **8**	4	85
4		 **9**	24	53
5		 **10**	1.5	53
6		 **11**	2	33
7		 **12**	23	68
8		 **13**	3	92
9		 **14**	3	95
10		 **15**	17	93

[a] Using 1.2 equiv *i*-$Pr_3S(O)BF_4$ in DMF at r.t.
[b] Isolated yield of chromatographically homogeneous material; >95% *trans*-isomers by ^1H NMR spectroscopy.

(9) Taylor, R. J. K.; Reid, M.; Foot, J. S.; Raw, S. A. *Acc. Chem. Res.* **2005**, *38*, 851.
(10) (a) Oswald, M. F.; Raw, S. A.; Taylor, R. J. K. *Org. Lett.* **2004**, *6*, 3997. (b) Oswald, M. F.; Raw, S. A.; Taylor, R. J. K. *Chem. Commun.* **2005**, 2253. (c) McAllister, G. D.; Oswald, M. F.; Paxton, R. J.; Raw, S. A.; Taylor, R. J. K. *Tetrahedron* **2006**, *62*, 6681.
(11) Paxton, R. J.; Taylor, R. J. K. *Synlett* **2007**, 633.
(12) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867. (b) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782. (c) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. (d) Yanovskaya, L. A.; Dombrovsky, V. A.; Chizhov, O. S.; Zolotarev, B. M.; Subbotin, O. A.; Kucherov, V. F. *Tetrahedron* **1972**, *28*, 1565.
(13) See, for example: (a) Major, R. T.; Hess, H.-J. *J. Org. Chem.* **1958**, *23*, 1563. (b) Kobayashi, M.; Kamiyama, K.; Minato, H.; Oishi, Y.; Takada, Y.; Hattori, Y. *Bull Chem. Soc. Jpn.* **1972**, *45*, 3703.
(14) Badet, B.; Julia, M. *Tetrahedron Lett.* **1979**, *20*, 1101.
(15) (a) Mori, M.; Takeuchi, H.; Minato, H.; Kobayashi, M.; Yoshida, M.; Matsuyama, H.; Kamigata, N. *Phosphorus, Sulfur Silicon Relat. Elem.* **1990**, *47*, 157. (b) There is also a more recent report on the use of RuO_2/$NaIO_4$ for the oxidation of trimethylsulfonium salts: Forrester, J.; Jones, R. V. H.; Preston, P. N.; Simpson, E. S. C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2289.
(16) Martín, V. S.; Palazón, J. M.; Rodríguez, C. M.; Nevill, C. R. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; John Wiley: New York, **2004**.
(17) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(18) **Preparation of Triisopropylsulfoxonium Tetrafluoroborate**
A 250 mL round-bottomed flask with stirrer bar was charged with triisopropylsulfonium tetrafluoroborate[14] (6.20 g, 25.0 mmol, 1.0 equiv), and then MeCN (36 mL), CCl_4 (36 mL), and H_2O (54 mL) were added via syringe. The resulting biphasic solution was stirred vigorously and ruthenium(III) chloride (2.07 g, 10.0 mmol, 0.40 equiv) added in a single portion. The mixture was stirred for 10 min and then $NaIO_4$ (40.10 g, 187.5 mmol, 7.5 equiv) was added in 5 portions over ca. 5 min to the brown-coloured solution. The flask was loosely stoppered with a cork and the mixture vigorously stirred overnight at r.t. (14 h). The resulting grey-brown heterogeneous suspension was filtered through a Celite® pad (3 cm × 70 mm Ø) and washed with H_2O (400 mL). The yellow filtrate was stirred vigorously and MeOH (50 mL) added to quench the residual RuO_4. The green suspension was concentrated under reduced pressure to remove the water present (60 °C) and the grey solid residue suspended in acetone (400 mL). The reaction mixture was stirred for a further 10 min and filtered to remove the residual inorganic solids. Concentration of the filtrate under reduced pressure afforded a yellow-orange powder that was recrystallised from MeOH–Et_2O. The crude solid was dissolved in 10 mL of boiling MeOH and Et_2O added until the solution remained turbid. The mixture was then re-heated until homogeneous and allowed to cool, to afford the title compound as colourless plates (5.06 g, 76%); mp 108–109 °C. IR (acetone): ν_{max} = 3427, 1699, 1642, 1462, 1369, 1235, 1198, 1049 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ = 1.79 (d, J = 7.0 Hz, 18 H, CH_3), 4.73 (sept, J = 7.0 Hz, 3 H, CH). ^{13}C NMR (100 MHz, acetone-d_6): δ = 15.7 (CH_3), 53.0 (CH). ^{19}F NMR (254 MHz, acetone-d_6): δ = –151.6. ^{11}B NMR (87 MHz, acetone-d_6): δ = –1.9. ESI-MS: *m/z* (%) = 177 (100) [M^+]. HRMS–FAB: *m/z* calcd for $C_9H_{21}OS$: 177.1308 (0.4 ppm error); found: 177.1308 [M^+]. Anal. Calcd for $C_9H_{21}BF_4OS$: C, 40.93; H, 8.01. Found: C, 40.76; H, 7.85.
(19) All known products were characterised by NMR spectroscopy and comparison of key data with those published; novel products were fully characterised.
(20) **Representative Procedure for Cyclopropanation of α,β-Unsaturated Carbonyl Compounds (Table 1, Entry 1)**
A 25 mL round-bottomed flask with stirrer bar was charged with NaH (60% dispersion in mineral oil, 23 mg, 0.57 mmol, 1.2 equiv), sealed with a rubber septum and purged with argon. The flask was maintained under argon and anhyd DMF (4 mL) was added. The vigorously stirred suspension was cooled to 0 °C, the septum briefly removed and triisopropylsulfoxonium tetrafluoroborate (152 mg, 0.57 mmol, 1.2 equiv) added in a single portion. The mixture was stirred for 5 min before the addition of a solution of (*E*)-chalcone (100 mg, 0.48 mmol) in DMF (1 mL) dropwise by cannula. The cooling bath was removed and the brown-coloured solution allowed to stir at r.t. until the reaction was deemed to be complete by TLC (5 h). The reaction was quenched by the addition of sat. aq NH_4Cl (5 mL), diluted with H_2O (20 mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed in vacuo. The residue was purified by column chromatography (PE–Et_2O, 19:1) to afford *trans*-(2,2-dimethyl-3-phenylcyclopropyl)-phenylmethanone (**6**) as a cream-coloured solid (109 mg, 91%); mp 63–64 °C. R_f = 0.29 (PE–Et_2O, 19:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 2.91 (d, J = 6.0 Hz, 1 H, CH), 3.12 (d, J = 6.0 Hz, 1 H, CH), 7.20–7.24 (m, 3 H, ArH), 7.28–7.32 (m, 2 H, ArH), 7.49–7.53 (m, 2 H, ArH), 7.57–7.61 (m, 1 H, ArH),7.99–8.02 (m, 2 H, ArH). Data consistent with those reported in the literature.[6]

PAPER 3279

gem-Dimethylcyclopropanation Using Triisopropylsulfoxonium Tetrafluoroborate: Scope and Limitations

Michael G. Edwards, Richard J. Paxton, David S. Pugh, Adrian C. Whitwood, Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York, YO10 5DD, UK
Fax +44(1904)434523; E-mail: rjkt1@york.ac.uk

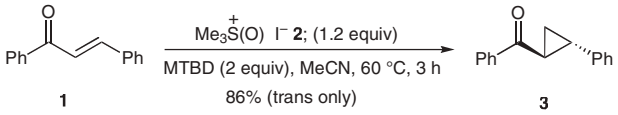
Received 13 June 2008

Abstract: A new nucleophilic isopropyl transfer reagent, triisopropylsulfoxonium tetrafluoroborate, has been prepared and evaluated. Thus, using this reagent and NaH in DMF, a range of electron deficient alkenes, including several chalcone analogues, α,β-unsaturated ketones, dienones and quinones, plus α,β-unsaturated esters, nitrile, sulfone and nitro examples, have been converted into the corresponding *gem*-dimethylcyclopropane compounds.

Key words: cyclopropanes, cyclopropanation, sulfoxonium salts, ruthenium tetraoxide

Classical procedures for the preparation of cyclopropanes from alkenes include Simmons–Smith methodology[1] and the addition of dihalocarbenes (generated from haloforms).[2] For the cyclopropanation of electron-deficient alkenes, Corey and Chaykovsky developed a methylene transfer process using sulfoxonium ylides.[3] This latter transformation has been widely used in organic synthesis,[4] and is the basis of a number of modern asymmetric cyclopropanation procedures.[4,5]

Our interest in new synthetic approaches to cyclopropanes[6,7] led to the recent development of an improved procedure for the cyclopropanation of α,β-unsaturated ketones (e.g., the conversion of chalcone **1** into cyclopropane **3**, Scheme 1) using trimethylsulfoxonium iodide (**2**) and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD).[7]



Scheme 1

Although methylenecyclopropanes are present in many natural products, the *gem*-dimethylcyclopropane motif is even more prevalent. Figure 1 shows representative natural products possessing a *gem*-dimethylcyclopropane group: allethrin II (**4**) is a typical pyrethroid insecticide,[8] (–)-taylorione (**5**) was extracted from the liverwort *Mylia Taylorii* found in the Austrian alps,[9] and the novel cyclohexanone diterpenoid (+)-lathyranone A (**6**) was recently isolated from the seeds of *E. lathyris*.[10]

There are a number of procedures available for the preparation of *gem*-dimethylcyclopropanes from electron-rich alkenes,[11] but for a natural product target we required a nucleophilic isopropylidene transfer approach. The first such procedure was reported by Corey and Jautelat and utilised diphenylsulfonium isopropylide derived from salt **7**[12] (Figure 2). This reagent efficiently produces *gem*-dimethylcyclopropanes from unsaturated esters and amides, but with α,β-unsaturated ketones, epoxide formation can compete (e.g., 3-methylcyclohex-2-enone gives mainly the unsaturated epoxide[12a]). In addition, the use of a strong base and low temperature is required. In 1973, Johnson's group disclosed the use of (dimethylamino)isopropyl-*p*-tolyloxosulfonium tetrafluoroborate (**8**) for the *gem*-dimethylcyclopropanation of (*E*)-1,2-dibenzoylethene and (*E*)-chalcone.[13] However, the synthesis of salt **8** was difficult and low yielding, and the scope of the procedure has not been demonstrated. More recently, it has been shown that the cyclopropanation of unsaturated esters can be achieved using the isopropyl phosphorane **9**[14] and the nitro compound **10**,[15] but again the scope of these reagents has not been determined (e.g., there are no examples of their use with α,β-unsaturated ketones).

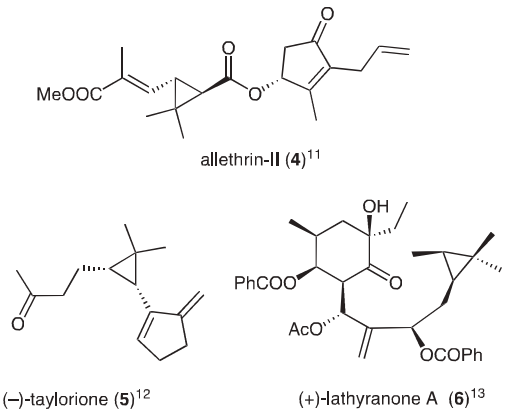


Figure 1 Some natural products containing *gem*-dimethylcyclopropyl group

We therefore decided to develop a new procedure for the nucleophilic *gem*-dimethylcyclopropanation of electron-deficient alkenes. Ideally, we required an isopropylidene transfer reagent that was readily available, would react under mild conditions, be applicable to a range of Michael acceptors, and would avoid competitive epoxide formation with α,β-unsaturated ketones.

SYNTHESIS 2008, No. 20, pp 3279–3288
Advanced online publication: 25.09.2008
DOI: 10.1055/s-0028-1083165; Art ID: P06408SS

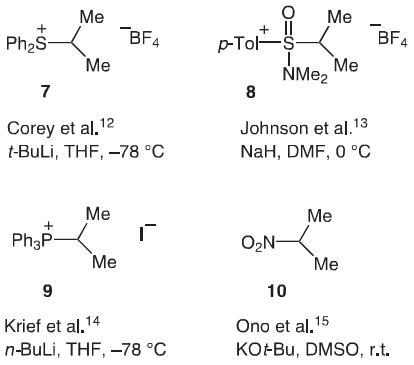
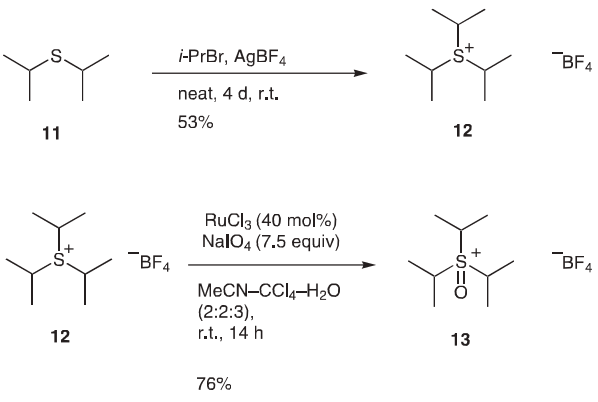


Figure 2 Reagents reported for *gem*-dimethylcyclopropanation

Sulfoxonium ylides favour 1,4-additon over 1,2-addition,[3,4,7] and we therefore decided to investigate the preparation and reactions of isopropylsulfoxonium salts. Given the availability of diphenylisopropylsulfonium tetrafluoroborate (**7**),[12] initial efforts involved the attempted oxidation of the corresponding sulfonium salt. This approach had the additional advantage that the phenyl substituents would be nontransferable groups derived from the inexpensive diphenyl sulfide. Unfortunately, all attempts to oxidise salt **7**, using either *m*-CPBA/Na_2CO_3[16] or RuO_2/$NaIO_4$,[17] gave none of the corresponding sulfoxonium salt and resulted only in degradation due to competing oxidation of the aryl rings.[18]

We therefore turned our attention to the preparation of the corresponding triisopropylsulfoxonium salt **13**.[19] As the S-alkylation of sulfoxides is successful only in the case of methylation,[20] it was necessary to carry out the oxidation of a triisopropylsulfonium salt. Badet and Julia[21] reported the preparation of triisopropylsulfonium tetrafluoroborate (**12**) from diisopropyl sulfide and isopropanol in the presence of methanesulfonic acid with subsequent anion exchange, but this procedure proved problematic in our hands. Instead, an alternative method using diisopropyl sulfide, 2-bromopropane, and silver tetrafluoroborate was developed to afford the desired salt **12** directly (Scheme 2).



Scheme 2

Oxidation of triisopropylsulfonium tetrafluoroborate (**12**) to give the triisopropylsulfoxonium salt **13** was the next issue to be addressed. The literature contains few reports on the oxidation of sulfonium salts to sulfoxonium salts, but the method reported by Kamigata and co-workers, using aqueous sodium *m*-chloroperbenzoate[16] seemed most appropriate. Unfortunately, when this procedure was applied to sulfonium salt **12** the reaction could not be driven to completion; at room temperature, only 36% conversion could be obtained and attempts to heat the reaction in the presence of a radical scavenger[22] proved futile. We reasoned that the use of a more powerful oxidant could overcome the slow oxidation of the sterically encumbered sulfonium salt **12**. RuO_4[17] has been applied to the oxidation of many organic functionalities, and optimisation studies were carried out to find the best conditions to oxidise the sulfonium salt **12** (Table 1).

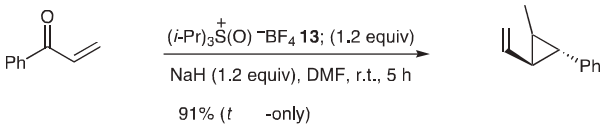
Table 1 Oxidation of Triisopropylsulfonium Tetrafluoroborate (**12**)[a]

Entry	Catalyst (mol%)	Oxidant (equiv)	Time (h)	Conversion to **13** (%)[b]
1	RuO_2 (20)	$NaIO_4$ (5)	16	63
2	RuO_2 (20)	$NaBrO_3$ (5)	16	59
3	RuO_2 (20)	NaOCl (5)	16	25
4	RuO_2 (20)	Oxone (5)	16	0
5	$RuCl_3$ (20)	$NaIO_4$ (5)	16	80
6	$RuCl_3$ (30)	$NaIO_4$ (7.5)	20	93
7	$RuCl_3$ (40)	$NaIO_4$ (5)	20	96

[a] Using triisopropylsulfonium tetrafluoroborate **12** (0.1 mmol) at 0.2 M concentration in MeCN–CCl_4–H_2O (2:2:3) with stirring at r.t.
[b] As determined by ^{1}H NMR spectroscopy.

As can be seen from the results presented in Table 1, the use of RuO_2 with a range of oxidants gave only moderate yields of sulfoxonium salt **13** at best (entries 1–4). However, use of the classic Sharpless conditions ($RuCl_3$/$NaIO_4$ in MeCN–CCl_4–H_2O)[23] gave much improved yields (entries 5–7), and with $RuCl_3$ (40 mol%) and $NaIO_4$ (5 equiv) the conversion was essentially quantitative (entry 7). Based on these results, triisopropylsulfonium tetrafluoroborate (**12**) was oxidised to the triisopropylsulfoxonium salt **13** on a 6 g scale in a 76%, recrystallised, yield (Scheme 2).

With the sulfoxonium salt **13** in hand, we explored its use as an isopropylidene transfer reagent with chalcone **1**. Several solvent/base combinations were investigated, but the use of NaH in DMF proved to be the best by far. Thus, after 5 hours at room temperature, the *gem*-dimethylcyclopropane adduct of chalcone **14** was obtained in 91% yield with no sign of any epoxide by-product (Scheme 3). Notably, only the *trans*-isomer was obtained, as shown by an H,H coupling constant of 6.0 Hz (which is consistent with the published value[24]).



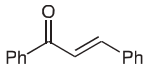
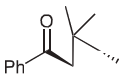
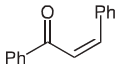
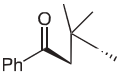
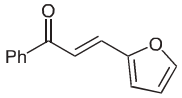
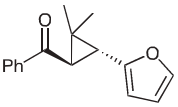
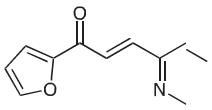
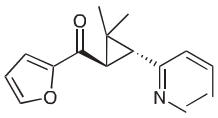
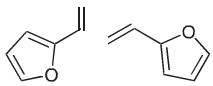
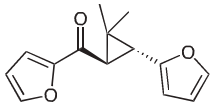
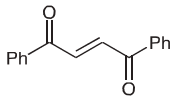
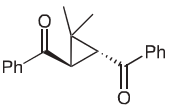
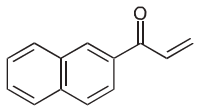
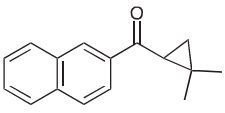
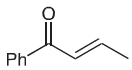
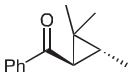
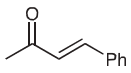
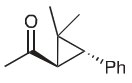
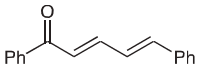
Scheme 3

Given the success of the chalcone reaction we moved on to examine a range of acyclic α,β-unsaturated ketones in the above dimethylcyclopropanation procedure (Table 2). With (*E*)-chalcone **1** giving only *trans*-cyclopropane **14** (entry 1), we first investigated the dimethylcyclopropanation of (*Z*)-chalcone **15**:[25] in this case (entry 2) the same *trans*-cyclopropane **14** was formed, as expected, indicating the potential for free rotation in the intermediate adduct.

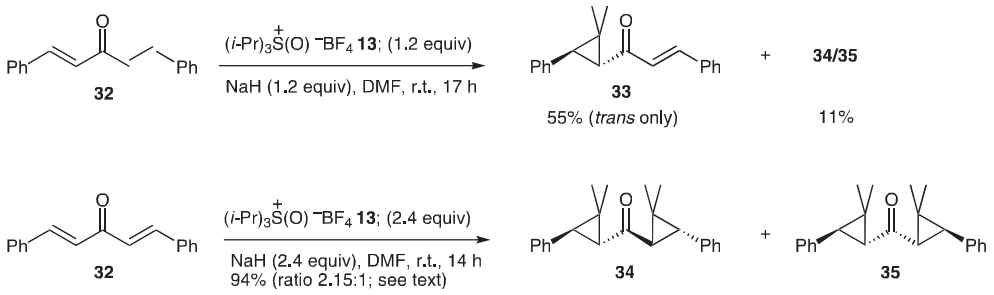
Heterocyclic chalcone analogues **16**, **18**, and **20**, and an enedione analogue **22** were studied next and in all cases fair to good yields of the corresponding dimethylcyclopropanes were obtained (entries 3–6). The simple acyclic enones **24**, **26**, and **28** were studied next (entries 7–9). Notably, the monosubstituted enone **24** underwent cyclopropanation giving adduct **25** in 53% yield, although the reaction was slow. The yields of the cyclopropanated products **27** and **29** were also modest (although in these cases the low yields could be attributed to the enolisable nature of the substrates **26** and **28**).

Finally in this group, dienones **30** and **32** were studied. With dienone **30**, only the alkene adjacent to the carbonyl group underwent dimethylcyclopropanation affording *trans*-cyclopropane **31** in excellent yield (entry 10). In contrast, under the standard conditions, dibenzylideneacetone (**32**) gave a mixture of the expected dimethylcyclopropane **33** together with two inseparable diastereomers of the bis-cyclopropyl adducts **34** and **35** (Scheme 4). With excess sulfoxonium salt, the bis-ad-

Table 2 Cyclopropanation of Acyclic Enones Using Triisopropylsulfoxonium Tetrafluoroborate (**13**) and NaH in DMF[a]

Entry	Substrate		Product		Time (h)	Yield (%)[b]
1	**1**		**14**		5	91
2	**15**		**14**		2	76
3	**16**		**17**		2	52
4	**18**		**19**		2	71
5	**20**		**21**		1	71
6	**22**		**23**		23	68
7	**24**		**25**		24	53
8	**26**		**27**		1.5	53
9	**28**		**29**		2	33
10	**30**		**31**		4	85

[a] Using *i*-$Pr_3S(O)BF_4$ (1.2 equiv) in DMF at r.t.
[b] Isolated yield of chromatographically homogeneous material; >95% *trans*-isomers by ^1H NMR spectroscopy.



Scheme 4

ducts **34** and **35** were formed in 94% yield as an inseparable mixture of diastereomers (2.15:1; we were unable to assign the structure of the major diastereomer).

The dimethylcyclopropanatations of cyclic enones were studied next (Table 3). Indenone polymerised under the reaction conditions and cyclohexenone (**36**) produced the known[3a] adduct **37** in extremely low yield (entry 1). However, naphthoquinone (**38**) and chromone (**40**) produced the expected adducts, **39** and **41**, in excellent yields (entries 2 and 3).

Interestingly, with benzoquinone, only a low yield of the monocyclopropane **43** was observed and double addition was preferred even using sulfoxonium salt **13** in approximately stoichiometric quantities (1.2 equiv, entry 4). With excess sulfoxonium salt, the biscyclopropane was observed as the only product and as a single diasteromer; X-ray crystallography confirmed this product to be the *trans*-diastereomer **44** (Figure 3).

Non-ketone Michael acceptors were also examined (Table 4). Under the standard conditions, methyl cin-

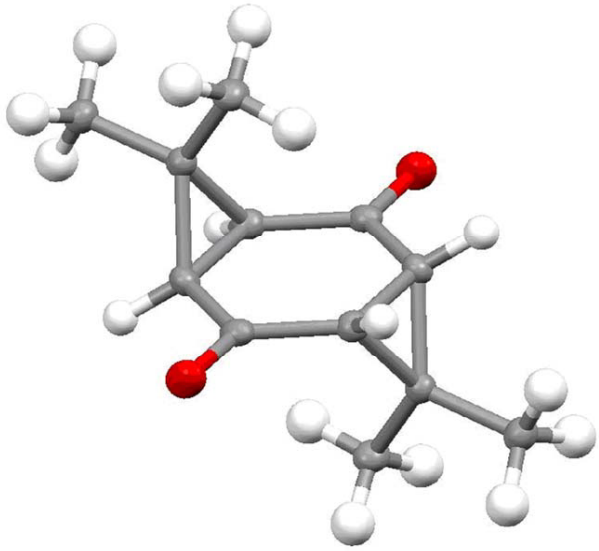
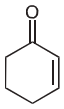
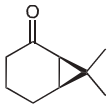
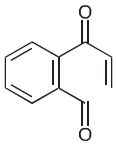
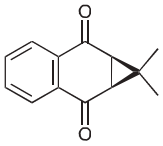
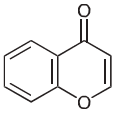
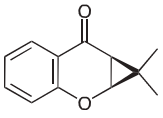
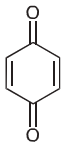
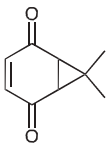
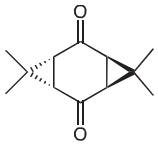


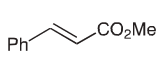
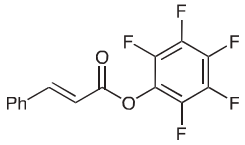
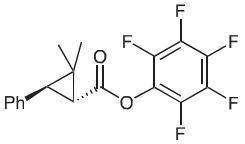
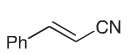
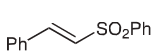
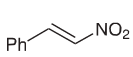
Figure 3 X-ray crystal structure of bis-cyclopropane **44** (depicted in Mercury 1.4.2)

Table 3 Cyclopropanation of Cyclic Enones Using Triisopropylsulfoxonium Tetrafluoroborate (**13**) and NaH in DMF[a]

Entry	Substrate	Product	Time (h)	Yield (%)[b]
1	**36** 	**37** 	4	4
2	**38** 	**39** 	3	92
3	**40** 	**41** 	3	95
4[c]	**42** 	**43**  **44** 	3	**43**: 7 **44**: 36

[a] Using *i*-$Pr_3S(O)BF_4$ (1.2 equiv) in DMF at r.t.
[b] Isolated yield of chromatographically homogeneous material; >95% *trans*-isomers by ^1H NMR spectroscopy.
[c] Use of *i*-$Pr_3S(O)BF_4$ (2.4 equiv) in DMF at r.t. for 6 h gave only **44** (67%).

Table 4 Cyclopropanation of Non-ketone Acceptors Using Triisopropylsulfoxonium Tetrafluoroborate (**13**) and NaH in DMF[a]

Entry	Substrate		Product		Time (h)	Yield (%)[b]
1	**45**		**46**		40	52[c]
2	**47**		**48**		30	49[c]
3	**49**		**50**		16	51
4	**51**		**52**		24	45
5	**53**		**54**		17	93

[a] Using *i*-$Pr_3S(O)BF_4$ (1.2 equiv) in DMF at r.t.
[b] Isolated yield of chromatographically homogeneous material; >95% *trans*-isomers by ^1H NMR spectroscopy.
[c] Using *i*-$Pr_3S(O)BF_4$ (2.0 equiv).

namate (**45**) and pentafluorophenyl cinnamate (**47**) produced adducts **46** and **48** in around 50% yield (entries 1 and 2). Similar yields were obtained using cinnamonitrile (**49**) and 2-phenylsulfonylstyrene (**51**) producing dimethylcyclopropanes **50** and **52**, respectively, whereas nitrostyrene (**53**) underwent an extremely successful transformation giving adduct **54** in 93% yield (entries 3–5).

In summary, we have described the preparation of triisopropylsulfoxonium tetrafluoroborate (**13**) and its use as an isopropylidene transfer reagent for the *gem*-dimethylcyclopropanation of electron-deficient alkenes. Good to excellent yields were obtained with a range of cyclic and acyclic α,β-unsaturated ketones, quinones, a dienone, chromone, and with nitrostyrene. In addition, modest yields were obtained from unsaturated esters, nitriles, and sulfones; it should be noted that all of these processes have been carried out using the standard conditions (NaH, DMF) derived for chalcone and so higher yields may be possible with further optimisation. In the ketone examples, epoxide formation was never observed as a side reaction. However, enolisable substrates do present a problem with reagent **13**; this contrasts to the use of dimethylsulfoxonium methylide[3a,c] and diphenylsulfonium isopropylide[12a] [e.g., the latter reagent effects the conversion of cyclohexenone (**36**) into adduct **37** in 74% yield].[12a] These facts suggest that with reagent **13**, steric effects may slow down the initial addition process, or may favour reversible addition, resulting in side reactions with enolisable substrates. We are currently examining the use of triisopropylsulfoxonium tetrafluoroborate (**13**) in natural product synthesis.

PE refers to light petroleum ether; bp 40–60 °C. All reagents were used as supplied by the manufacturers, or prepared by literature methods. Flash column chromatography was performed using Fluka silica gel 60 at a low positive pressure. Analytical TLC was performed on aluminum sheets pre-coated with Merck silica gel 60 F_{254}, and visualised with ultraviolet light (254 nm), alcoholic *p*-anisaldehyde, aq $KMnO_4$, or alcoholic vanillin solutions, as appropriate. All melting points were taken on a Gallenkamp apparatus. ^1H NMR spectra were recorded at 400 MHz on a Jeol ECX400 spectrometer and are reported as follows: chemical shift δ (ppm) [multiplicity, coupling constant *J* (Hz), number of protons, assignment]. The coupling constants are quoted to the nearest 0.1 Hz and are reported as measured splittings on each individual resonance. The residual protic solvent $CHCl_3$ ($\delta_H = 7.26$) or acetone ($\delta_H = 2.05$) was used as an internal reference. ^{13}C NMR spectra were recorded at 100 MHz on a Jeol ECX400 spectrometer or at 125 MHz on a Bruker AV500 spectrometer. The central reference of $CDCl_3$ ($\delta_C = 77.0$) or acetone ($\delta_C = 29.8$) was used as an internal reference. ^{19}F spectra were recorded at 376 MHz on a Jeol ECX400 spectrometer or at 254 MHz on a Jeol EX270 spectrometer. ^{11}B spectra were recorded at 87 MHz on a Jeol EX270 spectrometer. Chemical shifts are reported in parts per million (ppm) to the nearest 0.01 ppm for ^1H, or to 0.1 ppm for ^{13}C, ^{19}F, and ^{11}B. IR spectra were recorded on a ThermoNicolet IR100 spectrometer between NaCl disks. Absorption maxima are reported in wavenumbers (cm^{-1}) and only selected absorbencies are reported. Mass spectra and accurate mass measurements were recorded on a Micromass Autospec spectrometer. All known products were characterised by NMR spectroscopy and comparison of key data with those published; new products were fully characterised.

Triisopropylsulfonium Tetrafluoroborate (12)

A 250 mL pear-shaped flask with a stirrer bar, was charged with diisopropyl sulfide (12.65 g, 107 mmol, 2.0 equiv) and 2-bromopropane (26.32 g, 214 mmol, 4 equiv) and cooled to 0 °C (ice-bath). The mixture was stirred vigorously and $AgBF_4$ (10.41 g, 53.5 mmol, 1 equiv) added in small portions. On complete addition the flask was fitted with a rubber septum and balloon of argon, the ice-bath was removed and the reaction allowed to warm to r.t. with continuous stirring. After 4 d, the mixture was passed through a pre-

packed silica column (60 g, 50 mm diam.) topped with Celite and eluted with acetone (1 L) to give a cloudy white filtrate, which was concentrated in vacuo. The residue was suspended in Et_2O (100 mL), filtered, washed with Et_2O (3 × 25 mL) to give a silver-coloured precipitate. The solid was left to stand overnight in the light, before being suspended in hot MeOH (100 mL) and filtered through a pad of Celite to remove residual silver, washed with further MeOH (150 mL) and concentrated in vacuo to give a yellow/brown solid that was recrystallised from MeOH–Et_2O. The product was collected by filtration, washed with Et_2O (50 mL), and dried in vacuo to give the title compound **12**; yield: 7.1 g (53%); mp 167–170 °C; cream-coloured plates.

IR (NaCl): 2972, 1464, 1388, 1259, 1163, 1046 cm^{-1}.

^1H NMR (400 MHz, acetone- d_6): δ = 1.66 (d, J = 7.0 Hz, 18 H, CH_3), 4.14 (sept, J = 7.0 Hz, 3 H, CH).

^{13}C NMR (100 MHz, acetone-d_6): δ = 20.8 (CH_3), 44.4 (CH).

^{19}F NMR (254 MHz, acetone-d_6): δ = –151.8.

^{11}B NMR (87 MHz, acetone-d_6): δ = –1.8.

MS (FAB): m/z = 161 [$(i\text{-Pr})_3S^+$].

HRMS-FAB: m/z calcd for $C_9H_{21}S$: 161.1364; found: 161.1360 (2.5 ppm error).

Anal. Calcd for $C_9H_{21}BF_4S$: C, 43.56; H, 8.53. Found: C, 43.85; H, 8.06.

Triisopropylsulfoxonium Tetrafluoroborate (13)

A 250 mL round-bottomed flask with stirrer bar was charged with triisopropylsulfonium tetrafluoroborate (**12**; 6.20 g, 25.0 mmol, 1.0 equiv) and then MeCN (36 mL), CCl_4 (36 mL), and H_2O (54 mL) were added via a syringe. The resulting biphasic solution was stirred vigorously and $RuCl_3$ (2.07 g, 10.0 mmol, 0.40 equiv) was added in a single portion. The mixture was stirred for 10 min and then $NaIO_4$ (40.10 g, 187.5 mmol, 7.5 equiv) was added in 5 portions over ~5 min to the brown-coloured solution. The flask was loosely stoppered with a cork and the mixture stirred vigorously overnight at r.t. (14 h). The resulting grey-brown heterogeneous suspension was filtered through a Celite pad (3 cm × 70 mm diam.) and washed with H_2O (400 mL). The yellow filtrate was stirred vigorously and MeOH (50 mL) was added to quench the residual RuO_4. The green suspension was concentrated under reduced pressure to remove the H_2O present (60 °C) and the grey solid residue suspended in acetone (400 mL). The mixture was stirred for a further 10 min and filtered to remove the residual inorganic solids. Concentration of the filtrate under reduced pressure afforded a yellow-orange powder that was recrystallised from MeOH–Et_2O giving the title compound **13**; yield: 5.6 g (76%); mp 108–109 °C; colourless plates.

IR (NaCl): 3427, 1699, 1642, 1462, 1369, 1235, 1198, 1049 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 1.79 (d, J = 7.0 Hz, 18 H, CH_3), 4.73 (sept, J = 7.0 Hz, 3 H, CH).

^{13}C NMR (100 MHz, acetone-d_6): δ = 15.7 (CH_3), 53.0 (CH).

^{19}F NMR (254 MHz, acetone-d_6): δ = –151.6.

^{11}B NMR (87 MHz, acetone-d_6): δ = –1.9.

MS (ESI): m/z = 177 [$(i\text{-Pr})_3SO^+$].

HRMS-FAB: m/z calcd for $C_9H_{21}OS$: 177.1308; found: 177.1308 (0.4 ppm error).

Anal. Calcd for $C_9H_{21}BF_4OS$: C, 40.93; H, 8.01. Found: C, 40.76; H, 7.85.

Cyclopropanation of α,β-Unsaturated Carbonyl Compounds; [(1*RS*,3*RS*)-2,2-Dimethyl-3-phenylcyclopropyl](phenyl)methanone (14); Typical Procedure (Table 2, Entry 1)

A 25 mL round-bottomed flask with stirrer bar was charged with NaH (60% dispersion in mineral oil, 23 mg, 0.57 mmol, 1.2 equiv), sealed with a rubber septum, and purged with argon. The flask was maintained under argon and anhyd DMF (4 mL) was added. The stirred suspension was cooled to 0 °C, the septum briefly removed and triisopropylsulfoxonium tetrafluoroborate (**13**; 152 mg, 0.57 mmol, 1.2 equiv) was added in a single portion. The mixture was stirred for 5 min before the addition of a solution of (*E*)-chalcone (**1**; 100 mg, 0.48 mmol) in DMF (1 mL) dropwise by a cannula. The cooling bath was removed and the brown-coloured solution allowed to stir at r.t. until the reaction was deemed to be complete by TLC (5 h). The reaction was quenched by the addition of sat. aq NH_4Cl (5 mL), diluted with H_2O (20 mL), and extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed in vacuo. The residue was purified by column chromatography (PE–Et_2O, 19:1) to afford **14** as a cream-coloured solid; yield: 109 mg (91%); mp 63–64 °C (Lit.[13] mp 65–66 °C); R_f = 0.39 (PE–EtOAc, 3:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 2.91 (d, J = 6.0 Hz, 1 H, CH), 3.12 (d, J = 6.0 Hz, 1 H, CH), 7.20–7.24 (m, 3 H, ArH), 7.28–7.32 (m, 2 H, ArH), 7.49–7.53 (m, 2 H, ArH), 7.57–7.61 (m, 1 H, ArH), 7.99–8.02 (m, 2 H, ArH).

Data in accord with reported values.[24]

A similar procedure was followed for all other examples (which were carried out on a scale of 0.24–1.34 mmol).

[(1*RS*,3*RS*)-2,2-Dimethyl-3-(furan-2-yl)cyclopropyl](phenyl)methanone (17)

Yield: 15 mg (52%); colourless oil; R_f = 0.51 (PE–EtOAc, 3:1).

IR (film): 2925, 1670, 1449, 1241, 909, 733, 689 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 2.91–2.95 (m, 2 H, CH), 6.08 (d, J = 3.0 Hz, 1 H, ArH), 6.30 (dd, J = 3.0, 2.0 Hz, 1 H, ArH), 7.30 (dd, J = 0.5, 2.0 Hz, 1 H, ArH), 7.47–7.51 (m, 2 H, ArH), 7.55–7.60 (m, 1 H, ArH), 7.97–7.99 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3 (CH_3), 21.5 (CH_3), 29.4 (CH), 32.4 (C), 37.7 (CH), 107.0 (ArCH), 110.4 (ArCH), 128.3 (ArCH), 128.8 (ArCH), 133.1 (ArCH), 138.9 (ArC), 141.5 (ArCH), 153.2 (ArC), 197.7 (C=O).

MS (ESI): m/z = 263 $[M + Na]^+$, 241 $[M + H]^+$.

HRMS-ESI: m/z calcd for $C_{16}H_{17}O_2$ $[M + H]^+$: 241.1229; found: 241.1223 (3.2 ppm error).

[(1*RS*,3*RS*)-2,2-Dimethyl-3-(pyridin-2-yl)cyclopropyl](furan-2-yl)methanone (19)

Yield: 41 mg (71%); yellow solid; mp 64–65 °C; R_f = 0.19 (PE–EtOAc, 3:1).

IR (NaCl): 2924, 1657, 1591, 1568, 1468, 1415, 1261, 909, 733 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 3.10 (d, J = 6.0 Hz, 1 H, CH), 3.46 (d, J = 6.0 Hz, 1 H, CH), 6.57 (dd, J = 3.5, 1.5 Hz, 1 H, ArH), 7.12 (ddd, J = 7.5, 5.0, 1.0 Hz, 1 H, ArH), 7.27 (dd, J = 3.5, 1.0 Hz, 1 H, ArH), 7.28 (dt, J = 8.0, 1.0 Hz, 1 H, ArH), 7.57 (dd, J = 7.5, 2.0 Hz, 1 H, ArH), 7.60 (dd, J = 1.5, 1.0 Hz, 1 H, ArH), 8.53 (ddd, J = 5.0, 1.5, 1.0 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1 (CH_3), 20.2 (CH_3), 34.6 (CH), 36.4 (CH), 38.3 (C), 112.3 (ArCH), 116.9 (ArCH), 121.3 (ArCH), 124.7 (ArCH), 136.2 (ArCH), 146.5 (ArCH), 149.1 (ArCH), 154.5 (ArC), 157.9 (ArC), 187.0 (C=O).

MS (ESI): m/z = 242 $[M + H]^+$.

HRMS-ESI: m/z calcd for $C_{15}H_{16}NO_2$ $[M + H]^+$: 242.1103; found: 242.1176 (1.8 ppm error).

[(1*RS*,3*RS*)-2,2-Dimethyl-3-(furan-2-yl)cyclopropyl](furan-2-yl)methanone (21)
Yield: 89 mg (71%); colourless oil; R_f = 0.44 (PE–EtOAc, 3:1).

IR (film): 3134, 2954, 2874, 1661, 1569, 1469, 1415, 1378, 1257, 1098, 1035, 1015, 761 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 2.86–2.91 (m, 2 H, CH), 6.09 (d, J = 3.0 Hz, 1 H, ArH), 6.27 (dd, J = 3.0, 2.0 Hz, 1 H, ArH), 6.55 (dd, J = 3.5, 1.5 Hz, 1 H, ArH), 7.21 (dd, J = 3.5, 0.5 Hz, 1 H, ArH), 7.30 (dd, J = 2.0, 1.0 Hz, 1 H, ArH), 7.60 (dd, J = 1.5, 0.5 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0 (CH_3), 21.7 (CH_3), 29.9 (CH), 32.9 (C), 36.7 (CH), 107.0 (ArCH), 110.4 (ArCH), 112.4 (ArCH), 116.7 (ArCH), 141.5 (ArCH), 146.5 (ArCH), 153.0 (ArC), 154.3 (ArC), 186.2 (C=O).

MS (CI): m/z = 284 $[M + NH_4]^+$, 231 $[M + H]^+$, 135.

HRMS-CI: m/z calcd for $C_{14}H_{15}O_3$ $[M + H]^+$: 231.1021; found: 231.1014 (2.9 ppm error).

[(1*RS*,2*RS*)-3,3-Dimethylcyclopropane-1,2-diyl]bis(phenylmethanone) (23)
Yield: 78 mg (68%); colourless solid; mp 70–71 °C; R_f = 0.45 (PE–EtOAc, 3:1).

IR (NaCl): 2887, 2254, 1662, 1449, 1346, 1254, 909, 731, 650 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 6 H, CH_3), 3.54 (s, 2 H, CH), 7.49–7.53 (m, 4 H, ArH), 7.58–7.62 (m, 2 H, ArH), 8.01–8.03 (m, 4 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8 (CH_3), 35.6 (C), 38.3 (CH), 128.5 (ArCH), 128.9 (ArCH), 133.4 (ArCH), 138.5 (ArC), 197.0 (C=O).

MS (ESI): m/z = 301 $[M + Na]^+$.

HRMS-ESI: m/z calcd for $C_{19}H_{18}O_2$ + Na $[M + Na]^+$: 301.1205; found: 301.1199 (3.15 ppm error).

(2,2-Dimethylcyclopropyl)(naphthalen-2-yl)methanone (25)
Yield: 38 mg (53%); colourless oil; R_f = 0.53 (PE–EtOAc, 3:1).

IR (film): 3059, 2924, 2870, 1666, 1627, 1465, 1394, 1376, 1275, 1180, 1117, 1000, 808 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (dd, J = 7.5, 4.0 Hz, 1 H, CH), 1.14 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.59 (dd, J = 5.5, 4.0 Hz, 1 H, CH), 2.65 (dd, J = 7.5, 5.5 Hz, 1 H, CH), 7.55–7.63 (m, 2 H, ArH), 7.92 (t, J = 8.0 Hz, 2 H, ArH), 8.01 (d, J = 7.5 Hz, 1 H, ArH), 8.05 (dd, J = 8.5, 1.5 Hz, 1 H, ArH), 8.48 (s, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2 (CH_3), 21.8 (CH_2), 28.7 (C), 28.8 (CH_3), 32.7 (CH), 124.3 (ArCH), 126.9 (ArCH), 128.0 (ArCH), 128.4 (ArCH), 128.5 (ArCH), 129.6 (ArCH), 129.8 (ArCH), 132.8 (ArC), 135.6 (ArC), 136.7 (ArC), 199.0 (C=O).

MS (ESI): m/z = 225 $[M + H]^+$.

HRMS-ESI: m/z calcd for $C_{16}H_{17}O$ $[M + H]^+$: 225.1279; found: 225.1274 (2.75 ppm error).

[(1*RS*,3*RS*)-2,2,3-Trimethylcyclopropyl)phenylmethanone (27)
Yield: 20 mg (53%); colourless oil; R_f = 0.52 (PE–EtOAc, 3:1).

IR (film): 2920, 1665, 1449, 1378, 1344, 1243, 1214, 1090, 1025, 910 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.10 (s, 3 H, CH_3), 1.16 (d, J = 6.5 Hz, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.81 (m, 1 H, CH), 2.11 (d, J = 5.5 Hz, 1 H, CH), 7.44–7.47 (m, 2 H, ArH), 7.52–7.56 (m, 1 H, ArH), 7.90–7.92 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7 (CH_3), 19.9 (CH_3), 20.8 (CH_3), 27.5 (CH), 31.9 (C), 40.2 (CH), 128.1 (ArCH), 128.7 (ArCH), 132.6 (ArCH), 139.6 (ArC), 199.7 (C=O).

MS (ESI): m/z = 189 $[M + H]^+$.

HRMS-ESI: m/z calcd for $C_{13}H_{17}O$ $[M + H]^+$: 189.1279; found: 189.1274 (2.6 ppm error).

1-[(1*RS*,3*RS*)-2,2-Dimethyl-3-phenylcyclopropyl]ethanone (29)
Yield: 44 mg (33%); colourless oil; R_f = 0.53 (PE–EtOAc, 3:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.97 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 2.29 (d, J = 6.0 Hz, 1 H, CH), 2.33 (s, 3 H, CH_3), 2.85 (d, J = 6.0 Hz, 1 H, CH), 7.13–7.16 (m, 2 H, ArH), 7.19–7.22 (m, 1 H, ArH), 7.26–7.30 (m, 2 H, ArH).

Data in accord with reported values.[26]

[(1*RS*,3*RS*)-2,2-Dimethyl-(3*E*)-styrylcyclopropyl](phenyl)methanone (31)
Yield: 117 mg (85%); colourless solid; mp 66–69 °C; R_f = 0.54 (PE–Et_2O, 9:1).

IR (NaCl): 3059, 3027, 2947, 2923, 2781, 1664, 1597, 1579, 1494, 1449, 1413, 1378, 1353, 1278, 1227, 1178, 1111, 1053, 1022, 961, 862, 822, 767, 716, 691 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 2.62–2.66 (m, 2 H, CH, CH), 6.08 (dd, J = 15.9, 4.0 Hz, 1 H, CH), 6.61 (d, J = 15.9 Hz, 1 H, CH), 7.21 (tt, J = 7.3, 1.5 Hz, 1 H, ArH), 7.28–7.36 (m, 4 H, ArH), 7.48 (t, J = 7.3 Hz, 2 H, ArH), 7.57 (tt, J = 7.3, 1.3 Hz, 1 H, ArH), 7.95 (dd, J = 7.3, 1.3 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0 (CH_3), 22.2 (CH_3), 33.1 (C), 36.7 (CH), 40.3 (CH), 125.8 (ArCH), 127.0 (ArCH), 127.5 (CH), 127.9 (ArCH), 128.5 (ArCH), 128.5 (ArCH), 131.7 (CH), 132.5 (ArCH), 137.3 (ArC), 138.8 (ArC), 197.5 (C=O).

MS (ESI): m/z = 299 $[M + Na]^+$, 277 $[M + H]^+$.

HRMS-ESI: m/z calcd for $C_{20}H_{21}O$ $[M + H]^+$: 277.1587; found: 277.1591 (1.5 ppm error).

(*E*)-1-[(1*RS*,3*RS*)-2,2-Dimethyl-3-phenylcyclopropyl]-3-phenylprop-2-en-1-one (33)
Yield: 65 mg (55%); colourless solid; 75–76 °C; R_f = 0.52 (PE–EtOAc, 3:1).

IR (NaCl): 3082, 3058, 3027, 2975, 2945, 2921, 2869, 1672, 1647, 1606, 1576, 1495, 1448, 1418, 1377,1342, 1304, 1282, 1234, 1202, 1179, 1107, 1055, 1029, 976, 913, 860, 801, 767 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.06 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 2.56 (d, J = 5.9 Hz, 1 H, CH), 3.02 (d, J = 5.9 Hz, 1 H, CH), 6.96 (d, J = 16.2 Hz, 1 H, CH) 7.18–7.24 (m, 3 H, ArH), 7.26–7.32 (m, 2 H, ArH), 7.38–7.45 (m, 3 H, ArH), 7.57–7.62 (m, 2 H, ArH), 7.59 (d, J = 16.2 Hz, 1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.2 (CH_3), 22.4 (CH_3), 33.3 (C), 38.1 (CH), 39.3 (CH), 126.4 (ArCH), 128.1 (ArCH), 128.2 (ArCH), 128.4 (ArCH), 129.0 (ArCH), 129.0 (ArCH), 130.4 (ArCH), 134.7 (ArC), 137.9 (ArC), 141.9 (ArCH), 197.3 (C=O).

MS (ESI): m/z = 299 $[M + Na]^+$.

HRMS-ESI: m/z calcd for $C_{20}H_{20}O$ + Na $[M + Na]^+$: 299.1406; found: 299.1411 (1.7 ppm error).

Bis[(1*RS*,3*RS*)-2,2-dimethyl-3-phenylcyclopropyl]methanone (34) and [(1*RS*,3*RS*)-2,2-dimethyl-3-phenylcyclopropyl][(1*S*,3*S*)-2,2-dimethyl-3-phenylcyclopropyl]methanone (35)
Yield: 350 mg (94%); colourless solid; inseparable mixture of diastereoisomers (2.15:1); mp 58–60 °C; R_f = 0.63 (PE–EtOAc, 3:1; no separation).

IR (NaCl): 3027, 2972, 2950, 2919, 2871, 2361, 2338, 1666, 1602, 1579, 1497, 1443, 1422, 1375, 1278, 1103, 1070, 770 cm^{-1}.

MS (ESI): *m*/*z* = 341 $[M + Na]^+$.

HRMS-ESI: *m*/*z* calcd for $C_{23}H_{26}O$ + Na $[M + Na]^+$: 341.1876; found: 341.1882 (1.82 ppm error).

Major Diastereoisomer
^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 6 H, CH_3), 1.29 (s, 6 H, CH_3), 2.54 (d, *J* = 6.1 Hz, 2 H, CH), 2.93 (d, *J* = 6.1 Hz, 2 H, CH), 7.17–7.32 (m, 10 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6 (CH_3), 22.6 (CH_3), 33.7 (C), 38.6 (CH), 42.0 (CH), 126.3 (ArCH), 128.1 (ArCH), 128.9 (ArCH), 138.0 (ArC), 205.2 (C=O).

Minor Diastereoisomer
^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (s, 6 H, CH_3), 1.32 (s, 6 H, CH_3), 2.50 (d, *J* = 6.1 Hz, 2 H, CH), 2.92 (d, *J* = 6.1 Hz, 2 H, CH), 7.17–7.32 (m, 10 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3 (CH_3), 22.4 (CH_3), 32.6 (C), 38.2 (CH), 41.9 (CH), 126.3 (ArCH), 128.1 (ArCH), 128.8 (ArCH), 137.9 (ArC), 205.0 (C=O).

(1*RS*,6*SR*)-7,7-Dimethylbicyclo[4.1.0]heptan-2-one (37)
Yield: 3 mg (4%); colourless oil; R_f = 0.68 (PE–EtOAc, 3:1)

^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.40–1.85 (m, 6 H), 1.95–2.00 (m, 1 H), 2.15–2.20 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.7 (CH_3), 18.8 (CH_2), 25.8 (CH_2), 27.6 (C), 29.3 (CH_3), 30.9 (CH), 34.6 (CH), 40.0 (CH_2), 210.0 (C=O).

Data in accord with reported values.[27]

1,1a-Dihydro-1,1-dimethyl-7a*H*-cyclopropa[*b*]naphthalene-2,7-dione (39)
Yield: 92 mg (92%); beige solid; mp 109–111 °C; R_f = 0.32 (PE–EtOAc, 9:1).

IR (NaCl): 3041, 2949, 2924, 1675, 1592, 1361, 1325, 1297 (s), 1189, 1117, 1039, 1019, 996, 912, 849, 813, 749 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 2.54 (s, 2 H, CH), 7.68–7.72 (m, 2 H, ArH), 8.02–8.05 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0 (CH_3), 29.4 (CH_3), 33.4 (CH), 40.3 (CH), 126.5 (ArCH), 134.1 (ArCH), 134.6 (ArC), 192.9 (C=O).

MS (ESI): *m*/*z* = 223 $[M + Na]^+$, 201 $[M + H]^+$.

HRMS-ESI: *m*/*z* calcd for $C_{13}H_{13}O_2$ $[M + H]^+$: 201.0910; found: 201.0908 (1.0 ppm error).

(1a*SR*,7a*SR*)-1,1-Dimethyl-1,1a-dihydrocyclopropa[*b*]chromen-7(7a*H*)-one (41)
Yield: 89 mg (95%); colourless solid; mp 96–98 °C; R_f = 0.26 (PE–Et_2O, 9:1).

IR (NaCl): 3036, 2996, 2959, 2927, 1658, 1606, 1578, 1462, 1337, 1231, 1126, 1055, 994, 887, 763 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.06 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.91 (d, *J* = 6.4 Hz, 1 H, CH), 4.19 (d, *J* = 6.4 Hz, 1 H, CH), 6.89 (d, *J* = 8.5 Hz, 1 H, ArH), 6.95 (ddd, *J* = 8.0, 7.5, 1.0 Hz, 1 H, ArH), 7.43 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1 H, ArH), 7.88 (dd, *J* = 8.0, 1.5 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3), 19.2 (C), 25.3 (CH_3), 33.8 (CH), 66.6 (CH), 116.8 (ArCH), 119.7 (ArC), 120.9 (ArCH), 126.2 (ArCH), 135.8 (ArCH), 159.9 (ArC), 188.4 (C=O).

MS (ESI): *m*/*z* = 211 $[M + Na]^+$, 189 $[M + H]^+$.

HRMS-ESI: *m*/*z* calcd for $C_{12}H_{13}O_2$ $[M + H]^+$: 189.0919; found: 189.0910 (4.6 ppm error).

7,7-Dimethylbicyclo[4.1.0]hept-3-ene-2,5-dione (43)
Yield: 9 mg (7%); brown-coloured needles; mp 60–62 °C; R_f = 0.39 (PE–EtOAc, 3:1).

IR (NaCl): 1673, 1653, 1458, 1380, 1304, 1117, 1050 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 2.33 (s, 2 H, CH) 6.61 (s, 2 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6 (CH_3), 29.2 (CH_3), 39.4 (C), 140.7 (CH), 194.7 (C=O).

MS (EI): *m*/*z* = 150 $[M]^+$.

HRMS-EI: *m*/*z* calcd for $C_9H_{10}O_2$ $[M]^+$: 150.0681; found: 150.0675 (4.0 ppm error).

(2*RS*,4*SR*,6*SR*,8*RS*)-4,4,8,8-Tetramethyltricyclo[5.1.0.$0^{0,0}$]octane-2,6-dione (44)
Yield: 64 mg (67%); cream-coloured solid; mp 155–158 °C; R_f = 0.22 (PE–EtOAc, 4:1).

IR (NaCl): 2990, 2959, 2931, 1672, 1453, 1366, 1344, 1303, 1276, 1123, 1044, 904, 885, 851, 731 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 6 H, CH_3), 1.32 (s, 6 H, CH_3), 1.91 (s, 4 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.7 (CH_3), 28.7 (CH_3), 31.6 (C), 39.7 (CH), 201.6 (C=O).

MS (ESI): *m*/*z* = 215 $[M + Na]^+$, 193 $[M + H]^+$.

HRMS-ESI: *m*/*z* calcd for $C_{12}H_{17}O_2$ $[M + H]^+$: 193.1223; found: 193.1226 (1.8 ppm error).

Crystals suitable for X-ray diffraction were obtained by dissolving **44** in a minimal volume of CH_2Cl_2 and layering with hexane.[28]

Methyl (1*RS*,3*RS*)-2,2-Dimethyl-3-phenylcyclopropanecarboxylate (46)
Yield: 70 mg (52%); colourless oil; R_f = 0.41 (PE–EtOAc, 9:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.93 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.96 (d, *J* = 6.0 Hz, 1 H, CH), 2.70 (d, *J* = 6.0 Hz, 1 H, CH), 3.73 (s, 3 H, OCH_3), 7.12–7.24 (m, 3 H, ArH), 7.27–7.32 (m, 2 H, ArH).

Data in accord with reported values.[29]

Pentafluorophenyl (1*RS*,3*RS*)-2,2-Dimethyl-3-phenylcyclopropanecarboxylate (48)
Yield: 55 mg (49%); colourless oil; R_f = 0.51 (PE–EtOAc, 3:1).

IR (film): 3062, 3031, 2956, 2925, 2876, 1773, 1521, 1452, 1421, 1381, 1340, 1311, 1281, 1233, 1192, 1106, 1057, 1021, 999, 906, 862, 821, 765 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 2.28 (d, *J* = 5.8 Hz, 1 H, CH), 2.87 (d, *J* = 5.8 Hz, 1 H, CH), 7.20–7.23 (m, 2 H, ArH), 7.25–7.28 (m, 1 H, ArH), 7.30–7.35 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6 (CH_3), 21.8 (CH_3), 30.5 (CH), 31.8 (C), 39.2 (CH), 125.3 (m, C), 126.8 (ArCH), 128.4 (ArCH), 128.7 (ArCH), 136.2 (ArC), 137.8 (dm, *J* = 249 Hz,

ArCF), 139.3 (dm, J = 253 Hz, ArCF), 141.2 (dm, J = 267 Hz, ArCF), 168.3 (C=O).

^{19}F NMR (254 MHz, acetone-d_6): δ = –162.4, –158.3, –152.4.

MS (EI): m/z = 356 $[M]^+$.

HRMS-EI: m/z calcd for $C_{18}H_{13}F_5O_2$ $[M]^+$: 356.0836; found: 356.0824 (3.4 ppm error).

(1*RS*,3*RS*)-2,2-Dimethyl-3-phenylcyclopropanecarbonitrile (50)
Yield: 71 mg (51%); pale yellow oil; R_f = 0.61 (PE–EtOAc, 3:1).

IR (film): 3032, 2961, 2926, 2234, 1603, 1497, 1451, 1382, 1270, 1195, 1117, 1061, 1029, 971, 850, 800, 742, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 1.63 (d, J = 5.6 Hz, 1 H, CH), 2.52 (d, J = 5.6 Hz, 1 H, CH), 7.12–7.16 (m, 2 H, ArH), 7.23–7.34 (m, 3 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 (CH_3), 20.2 (CH_3), 23.8 (C), 26.5 (CH), 37.7 (CH), 120.5 (CN), 127.1 (ArCH), 128.4 (ArCH), 128.5 (ArCH), 135.2 (ArC).

MS (CI): m/z = 189 $[M + NH_4]^+$.

HRMS-CI: m/z calcd for $C_{12}H_{17}N_2$ $[M + NH_4]^+$: 189.1392; found: 189.1387 (2.6 ppm error).

[(1*SR*,3*RS*)-2,2-Dimethyl-3-(phenylsulfonyl)cyclopropyl]benzene (52)
Yield: 63 mg (45%); colourless solid; mp 88–90 °C; R_f = 0.35 (PE–EtOAc, 3:1).

IR (NaCl): 3429, 3062, 3028, 2958, 2923, 1447, 1306, 1148, 1087, 702, 689, 608 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (s, 3 H, CH_3), 1.66 (s, 3 H, CH_3), 2.60 (d, J = 6.0 Hz, 1 H, CH), 3.09 (d, J = 6.0 Hz, 1 H, CH), 7.00–7.02 (m, 2 H, ArH), 7.22–7.26 (m, 3 H, ArH), 7.57–7.61 (m, 2 H, ArH), 7.65–7.69 (m, 1 H, ArH), 7.98–8.00 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 (CH_3), 21.9 (CH_3), 29.4 (C), 36.3 (CH), 49.7 (CH), 127.3 (ArCH), 127.5 (ArCH), 128.6 (ArCH), 128.7 (ArC), 128.8 (ArCH), 129.5 (ArCH), 133.6 (ArCH), 135.6 (ArC).

MS (ESI): m/z = 287 $[M + H]^+$.

HRMS-ESI: m/z calcd for $C_{17}H_{19}O_2S$ $[M + H]^+$: 287.1106; found: 287.1100 (1.2 ppm error).

[(1*SR*,3*RS*)-2,2-Dimethyl-3-nitrocyclopropyl]benzene (54)
Yield: 123 mg (93%); pale yellow oil; R_f = 0.60 (PE–EtOAc, 3:1).

IR (film): 3064, 3031, 2960, 2927, 2879, 2359, 1603, 1536, 1500, 1451, 1361, 1268, 1113, 1055, 1029, 952, 930, 862, 828, 770, 716, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 3.36 (d, J = 4.6 Hz, 1 H, CH), 4.47 (d, J = 4.6 Hz, 1 H, CH), 7.14–7.19 (m, 2 H, ArH), 7.25–7.35 (m, 3 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6 (CH_3), 20.7 (CH_3), 33.0 (C), 38.9 (CH), 70.3 (CH), 127.3 (ArCH), 128.4 (ArCH), 128.6 (ArCH), 134.1 (ArC).

MS (CI): m/z = 209 $[M + NH_4]^+$, 145.

HRMS-CI: m/z calcd for $C_{11}H_{17}N_2O_2$ $[M + NH_4]^+$: 209.1290; found: 209.1288 (1.1 ppm error).

Acknowledgment

We are grateful to the EPSRC for studentship support (R.J.P. and D.S.P.) and Elsevier Science for postdoctoral support (M.G.E.). We also acknowledge the EPSRC National Crystallography Service at the University of Southampton for data collection.

References

(1) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256.
(2) Kostikov, R. R.; Molchanov, A. P.; Khlebnikov, A. F. *Russ. Chem. Rev.* **1989**, *58*, 654.
(3) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867. (b) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782. (c) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. (d) Yanovskaya, L. A.; Dombrovsky, V. A.; Chizhov, O. S.; Zolotarev, B. M.; Subbotin, O. A.; Kucherov, V. F. *Tetrahedron* **1972**, *28*, 1565.
(4) For a review, see: Aggarwal, V. K.; Li, A.-H.; Dai, L.-X. *Chem. Rev.* **1997**, *97*, 2341.
(5) For recent asymmetric examples, see: (a) Papageorgiou, C. D.; Cubillo de Dios, M. A.; Ley, S. V.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 4641. (b) Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240.
(6) (a) Oswald, M. F.; Raw, S. A.; Taylor, R. J. K. *Org. Lett.* **2004**, *6*, 3997. (b) Oswald, M. F.; Raw, S. A.; Taylor, R. J. K. *Chem. Commun.* **2005**, 2253. (c) McAllister, G. D.; Oswald, M. F.; Paxton, R. J.; Raw, S. A.; Taylor, R. J. K. *Tetrahedron* **2006**, *62*, 6681.
(7) Paxton, R. J.; Taylor, R. J. K. *Synlett* **2007**, 633.
(8) Hossain, M. M.; Suzuki, T.; Sato, I.; Takewaki, T.; Suzuki, K.; Kobayashi, H. *Life Sci.* **2005**, *77*, 795; and references cited therein.
(9) von Reuss, S. H.; Wu, C.-L.; Muhle, H.; Konig, W. A. *Phytochemistry* **2004**, *65*, 2277; and references cited therein.
(10) Gao, S.; Liu, H.-Y.; Wang, Y.-H.; He, H.-P.; Wang, J.-S.; Di, Y.-T.; Li, C.-S.; Fang, X.; Hao, X.-J. *Org. Lett.* **2007**, *9*, 3453.
(11) (a) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 3911. (b) Franck-Neumann, M. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 65. (c) Sengmany, S.; Léonel, E.; Paugam, J. P.; Nédélec, J.-Y. *Tetrahedron* **2002**, *58*, 271. (d) Charette, A. B.; Wilb, N. *Synlett* **2002**, 176; and references cited therein.
(12) (a) Corey, E. J.; Jautelat, M. *J. Am. Chem. Soc.* **1967**, *89*, 3912. (b) Corey, E. J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.* **1967**, *8*, 2325. (c) Tang, C. S. F.; Rapoport, H. *J. Org. Chem.* **1973**, *38*, 2806. (d) For an asymmetric variant, see: Mamai, A.; Madalengoitia, J. S. *Tetrahedron Lett.* **2000**, *41*, 9009.
(13) Johnson, C. R.; Janiga, E. R. *J. Am. Chem. Soc.* **1973**, *95*, 7692.
(14) (a) Devos, M. J.; Krief, A. *Tetrahedron Lett.* **1979**, *20*, 1515. (b) Krief, A.; Dubois, P. *Tetrahedron Lett.* **1993**, *34*, 2691.
(15) Ono, N.; Yanai, T.; Hamamoto, I.; Kamimura, A.; Kaji, A. *J. Org. Chem.* **1985**, *50*, 2806.
(16) Mori, M.; Takeuchi, H.; Minato, H.; Kobayashi, M.; Yoshida, M.; Matsuyama, H.; Kamigata, N. *Phosphorus, Sulfur Silicon Relat. Elem.* **1990**, *47*, 157.
(17) (a) Martín, V. S.; Palazón, J. M.; Rodríguez, C. M.; Nevill, C. R. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, **2004**. (b) For its use in the preparation of a sulfoxonium salt, see: Forrester, J.; Jones, R. V. H.; Preston, P. N.; Simpson, E. S. C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2289.
(18) (a) Djerassi, C.; Engle, R. R. *J. Am. Chem. Soc.* **1953**, *75*, 3838. (b) Berkowitz, L. M.; Rylander, P. N. *J. Am. Chem. Soc.* **1958**, *80*, 6682.

(19) Preliminary communication: Edwards, M. G.; Paxton, R. J.; Pugh, D. S.; Taylor, R. J. K. *Synlett* **2008**, 521.
(20) See, for example: (a) Major, R. T.; Hess, H.-J. *J. Org. Chem.* **1958**, *23*, 1563. (b) Kobayashi, M.; Kamiyama, K.; Minato, H.; Oishi, Y.; Takada, Y.; Hattori, Y. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3703.
(21) Badet, B.; Julia, M. *Tetrahedron Lett.* **1979**, *20*, 1101.
(22) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T.; Inoue, S.; Sugiura, S.; Kakoi, H. *J. Chem. Soc., Chem Commun.* **1972**, 64.
(23) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(24) Lui, K.-H.; Sammes, M. P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 457.
(25) (a) Noyce, D. S.; Pryor, W. A.; King, P. A. *J. Am. Chem. Soc.* **1959**, *81*, 5423. (b) For the hydrogenation of the corresponding alkyne we employed 5% Pd on $BaSO_4$ and 30% quinoline in EtOAc (3 h).
(26) Armesto, D.; Ortiz, M. J.; Agarrabeitia, A. R.; Martín-Fontecha, M. *Org. Lett.* **2005**, *7*, 2687.
(27) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O. *Tetrahedron* **1992**, *44*, 9767.
(28) CCDC-687178 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; E-mail: admin@ccdc.cam.ac.uk].
(29) Kohmoto, S.; Kasimura, H.; Nishio, T.; Iida, I.; Kishikawa, K.; Yamamoto, M.; Yamada, K. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1565.

Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

gem-Dimethylcyclopropanation of dibenzylideneacetone using triisopropyl sulfoxonium tetrafluoroborate

Michael G. Edwards, David S. Pugh, Adrian C. Whitwood and Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York YO10 5DD, England
Correspondence e-mail: rjkt1@york.ac.uk

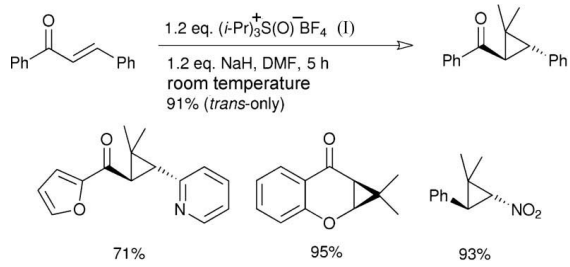
Received 21 October 2008
Accepted 12 December 2008
Online 10 January 2009

The reaction between dibenzylideneacetone (dba) and triisopropyl sulfoxonium tetrafluoroborate has been reinvestigated. The stereochemistry of the major diasteromeric bis(*gem*-dimethylcyclopropane) adduct has now been assigned as [(1*RS*,3*RS*)-2,2-dimethyl-3-phenylcyclopropyl][(1*SR*,3*SR*)-2,2-dimethyl-3-phenylcyclopropyl]methanone, $C_{23}H_{26}O$, by X-ray crystallographic studies on a twinned crystal. The asymmetric unit contains two molecules of the adduct, the conformations of which differ in the orientation of the phenyl ring relative to the adjacent cyclopropanated double bond. The carbonyl groups of each adduct are aligned approximately along the *a* axis and in opposite directions to each other. The molecules pack to give a sinusoidal pattern along the *b* axis. This is the first acyclic bis(dimethylcyclopropyl) ketone for which an X-ray crystal structure determination has been reported, and is also the first bis-cyclopropanated dba analogue. The knowledge that the major diastereomer has the *meso* structure (and therefore the confirmation that the minor isomer is the racemate) will prove invaluable in future studies to utilize bis(dimethylcyclopropyl) ketones as reagents, in rearrangement processes, and as potential ligands and ligand precursors in organometallic chemistry.

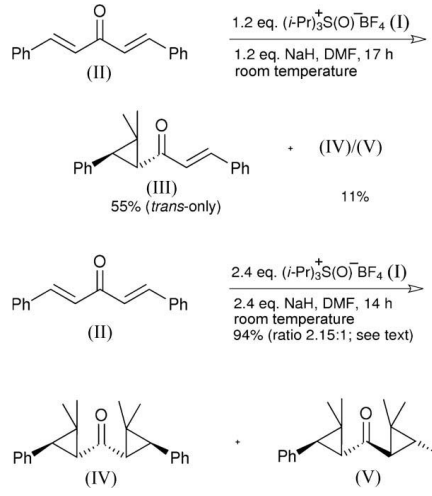
Comment

We recently reported the preparation of triisopropyl sulfoxonium tetrafluoroborate, (I), and its use as an isopropylidene transfer reagent for the *gem*-dimethylcyclopropanation of a range of electron-deficient alkenes (Edwards *et al.*, 2008). Good to excellent yields were obtained with a range of cyclic and acyclic α,β-unsaturated ketones and related systems (see first scheme).

The dimethylcyclopropanation of dienones was also studied. Interestingly, dibenzylideneacetone, (II), gave a mixture of the expected dimethylcyclopropane derivative, (III), together with two inseparable diastereomers of the bis-cyclopropyl adducts, (IV) and (V) (see top part of second scheme). With excess sulfoxonium salt, the bis-adducts (IV) and (V) were formed in 94% yield as an inseparable mixture of diastereomers (2.15:1), but we were unable to assign the structure of the major diastereoisomer.



We have now repeated the bis(dimethylcyclopropanation) of dibenzylideneacetone in order to clarify the stereochemical outcome of this reaction (see bottom part of second scheme). Repeated recrystallization (ten times) of the (IV)/(V) mixture from ethanol–water, and analysis by ^{1}H NMR spectroscopy, produced a pure sample of the major diastereomeric product. X-ray crystallographic analysis then confirmed that the major product was the title *meso* isomer, (IV) (Fig. 1).



The asymmetric unit contains two molecules of the adduct (IV) with differing conformations. The carbonyl groups of each adduct are aligned approximately along the *a* axis and in opposite directions to each other. The conformation of the individual molecules is such that there is almost a mirror plane of symmetry along the carbonyl axis, perpendicular to the C8/C9/C10/O1 plane (this is also true for the plane perpendicular to C31/C32/C33/O2, although the correspondence is less good).

The differences between the two conformations are significant, with the r.m.s. best fit for overlap of the heavy atoms being 0.252 Å. Closer inspection reveals that the major difference is in the orientation of the phenyl ring relative to the adjacent cyclopropanated double bond. For one adduct, both rings are twisted with approximately equivalent angles of −15.6 (10) and 16.5 (10)°. In the other, one phenyl ring and bond are almost coplanar, the angles being 2.8 (11) and

 doi:10.1107/S0108270108042431

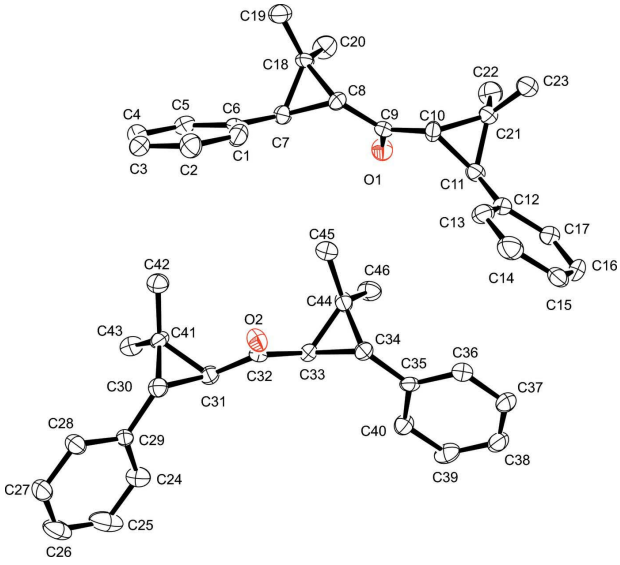


Figure 1
A view of the asymmetric unit of compound (IV), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

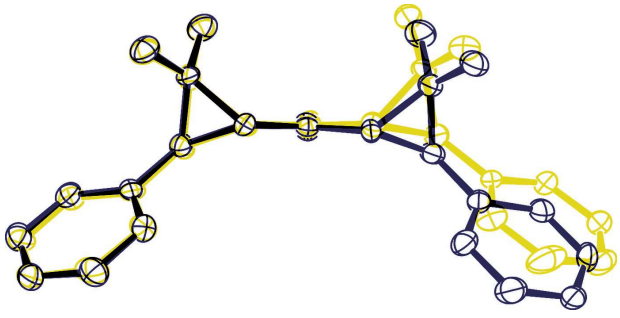


Figure 2
Overlaid crystal structures of the two independent molecules of (IV) (H atoms omitted), highlighting the significant conformational differences of one half of each molecule. [In the electronic version of the paper, molecule 1 (atoms C1–C23/O1) is coloured blue, dark here, and molecule 2 (atoms C24–C46/O2) is coloured yellow, light here.]

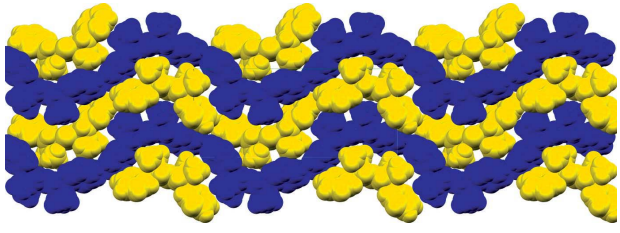


Figure 3
A packing diagram for (IV), viewed along the *a* axis. The different colours denote the two different molecular conformations (*cf.* Fig. 2).

−13.5 (10)°. This difference is also reflected in the angle between the planes for each pair of cyclopropane and phenyl groups; the angles are 58.8 (6) and 59.2 (6)° for the first adduct, and 61.5 (5) and 65.9 (6)° for the second. It is notable that for the second conformer, half of the molecule has an orientation closely similar to that of the first conformer, whilst the remainder is significantly different. This is clearly illustrated in Fig. 2.

The packing of the molecules within the crystal structure also shows some interesting behaviour. Each conformer is arranged to form a sinusoidal pattern orientated along the *b* axis (Fig. 3). Analysis of the packing shows that there are no intermolecular π–π interactions (neither face-to-face nor edge-to-face) as there are no pairs of atoms which are significantly closer (0.2 Å) than the sum of their van der Waals radii.

A search of the Cambridge Structural Database (Version 5.29, with August 2008 update; Allen, 2002) reveals that only 29 crystal structures have been reported previously which contain the cyclopropyl–carbonyl–cyclopropyl (CyP–CO–CyP) sequence. All but three of these have the (CyP–CO–CyP) moiety as part of a cyclic structure, with the majority being derived from 1,4-benzoquinone. Only two structures are reported which have two dimethylcyclopropyl groups, one being derived from benzoquinone (Edwards *et al.*, 2008) and the other based on tropone (Cetinkaya *et al.*, 1982). Thus, the crystal structure of (IV), with the dimethylcyclopropyl groups and carbonyl group in an acyclic arrangement, appears to be the first of its type to be reported.

Experimental

[(1*RS*,3*RS*)-2,2-Dimethyl-3-phenylcyclopropyl][(1*SR*,3*SR*)-2,2-dimethyl-3-phenylcyclopropyl]methanone, (IV), and [(1*RS*,3*RS*)-2,2-dimethyl-3-phenylcyclopropyl][(1*RS*,3*RS*)-2,2-dimethyl-3-phenylcyclopropyl]methanone, (V), were prepared as follows.

A 25 ml round-bottomed flask equipped with a stirrer bar was charged with sodium hydride (60% dispersion in mineral oil, 111 mg, 2.78 mmol, 2.4 equivalents), sealed with a rubber septum and purged with argon. The flask was maintained under argon and anhydrous *N*,*N*-dimethylformamide (10 ml) was added. The stirred suspension was cooled to 273 K (ice bath), the septum briefly removed and triisopropyl sulfoxonium tetrafluoroborate (735 mg, 2.78 mmol, 2.4 equivalents) added in a single portion. The mixture was stirred for 5 min before the addition of a solution of dibenzylideneacetone (272 mg, 1.16 mmol, 1.0 equivalents) in *N*,*N*-dimethylformamide (5 ml) dropwise by cannula. The cooling bath was removed and the yellow solution stirred at room temperature until the reaction was shown to be complete by thin-layer chromatographic analysis (14 h). The reaction was quenched by the addition of saturated aqueous NH_4Cl (15 ml), diluted with water (60 ml) and extracted with Et_2O (3 × 50 ml). The combined organic extracts were dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by column chromatography (petrol/Et_2O, 19:1 *v*/*v*) to afford 350 mg (94%) of a colourless solid, a chromatographically inseparable mixture of diastereoisomers (IV) and (V) (2.15:1) (m.p. 331–333 K). Analysis: R_F = 0.63 (petrol–EtOAc, 3:1 *v*/*v*; no separation); IR (NaCl, ν, cm^{-1}): 3027, 2972, 2950, 2919, 2871, 2361, 2338, 1666, 1602, 1579, 1497, 1443, 1422, 1375, 1278, 1103, 1070, 770; MS (ESI): *m*/*z* = 341 $[M + Na]^+$; HRMS–ESI: *m*/*z* $[M + Na]^+$ calculated for $C_{23}H_{26}NaO$: 341.1876; found: 341.1882 (1.82 p.p.m. error). Repeated recrystallization (ten times) from EtOH–H_2O (EtOH with *ca.* 5–10% H_2O added dropwise) gave a single diastereomer; X-ray analysis identified this as (IV)

(m.p. 336–338 K). Analysis: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (*s*, 6H, CH_3), 1.29 (*s*, 6H, CH_3), 2.54 (*d*, J = 6.1 Hz, 2H, CH), 2.93 (*d*, J = 6.1 Hz, 2H, CH), 7.17–7.32 (*m*, 10H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.6 (CH_3), 22.6 (CH_3), 33.7 (C), 38.6 (CH), 42.0 (CH), 126.3 (ArH), 128.1 (ArH), 128.9 (ArH), 138.0 (Ar), 205.2 (C=O).

Crystal data

$C_{23}H_{26}O$
M_r = 318.44
Monoclinic, $P2_1$
a = 5.7287 (7) Å
b = 27.517 (4) Å
c = 11.9206 (17) Å
β = 91.881 (8)°
V = 1878.1 (4) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.07 mm^{-1}
T = 120 (2) K
0.28 × 0.24 × 0.02 mm

Data collection

Bruker–Nonius APEXII CCD diffractometer on κ-goniostat
Absorption correction: multi-scan (*TWINABS*; Sheldrick, 2007)
T_{min} = 0.454, T_{max} = 0.999
6207 measured reflections
4341 independent reflections
3685 reflections with $I > 2\sigma(I)$
R_{int} = 0.072

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.087
$wR(F^2)$ = 0.186
S = 1.24
4341 reflections
442 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.38 e Å^{-3}
$\Delta\rho_{min}$ = −0.36 e Å^{-3}

The crystal was discovered to be nonmerohedrally twinned by a 180° rotation about the [$\bar{1}$00] direction. The orientation matrix for each twin component was determined using *DIRAX* (Duisenberg, 1992), allowing a HKLF 5 file (*SHELXL97*; Sheldrick, 2008) to be prepared. The twin fraction refined to 0.470 (3). H atoms were placed using a riding model, with C—H = 0.98 (CH_3), 0.95 (aromatic CH) or 1.00 Å (aliphatic CH). They were refined isotropically with U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(C_{methyl}).

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *DENZO* (Otwinowski & Minor, 1997) and *COLLECT*; data reduction: *DIRAX* (Duisenberg, 1992), *DENZO*, *COLLECT* and *EVALCCD* (Duisenberg *et al.*, 2003); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Version 2.02; Farrugia, 1997) and *Mercury* (Version 1.4.2; Macrae *et al.*, 2008); software used to prepare material for publication: *PLATON* (Spek, 2003).

The authors are grateful to the EPSRC for studentship support (DSP) and to Elsevier Science for postdoctoral support (MGE). We also acknowledge the EPSRC National Crystallography Service at the University of Southampton for data collection and processing.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM3069). Services for accessing these data are described at the back of the journal.

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Cetinkaya, B., Binger, P. & Krüger, C. (1982). *Chem. Ber.* **115**, 3414–3421.
Duisenberg, A. J. M. (1992). *J. Appl. Cryst.* **25**, 92–96.
Duisenberg, A. J. M., Kroon-Batenburg, L. M. J. & Schreurs, A. M. M. (2003). *J. Appl. Cryst.* **36**, 220–229.
Edwards, M. G., Paxton, R. J., Pugh, D. S., Whitwood, A. C. & Taylor, R. J. K. (2008). *Synthesis*, pp. 3279–3288.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Macrae, C. F., Bruno, I. J., Chisholm, J. A., Edgington, P. R., McCabe, P., Pidcock, E., Rodriguez-Monge, L., Taylor, R., van de Streek, J. & Wood, P. A. (2008). *J. Appl. Cryst.* **41**, 466–470.
Nonius (1998). *COLLECT*. Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Sheldrick, G. M. (2007). *TWINABS*. Version 2007/2. Bruker AXS Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.

Preparation of 3-Alkyl-Oxindoles by Copper(II)-Mediated C–H, Ar–H Coupling Followed by Decarboxyalkylation

David. S. Pugh, Johannes E. M. N. Klein, Alexis Perry, Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York YO10 5DD, UK
Fax +44(1904)434523; E-mail: rjkt1@york.ac.uk

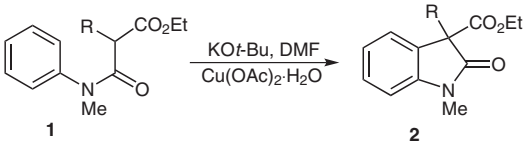
Received 14 December 2009

Dedicated to Professor Saverio Florio in celebration of his 70th birthday

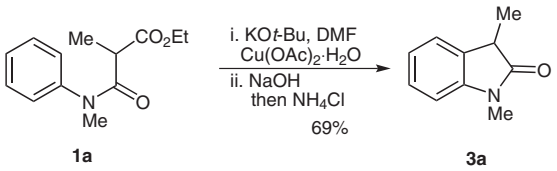
Abstract: A novel route for the conversion of anilides into 3-alkyl-oxindoles is described in which a copper(II)-mediated cyclization process is followed by an acid-mediated decarboxyalkylation. Scope and limitation studies are reported together with a telescoped variant which incorporates in situ *N*-deprotection.

Key words: oxindoles, 3-alkyl-oxindoles, anilides, cyclisation, copper(II) catalysis, C–H activation, decarboxyalkylation

We recently developed a novel copper(II)-mediated route for the conversion of anilides **1** into 3-alkyl-3-carboethoxy-oxindoles **2** by a formal C–H, Ar–H coupling process as shown in Scheme 1.[1,2] In the case of the 3-methylated example **1a** it proved possible to carry out a 'one-pot' cyclisation–decarboxyalkylation process to produce 3-methyl-oxindole (**3a**) in reasonable yield (Scheme 2).[1]



Scheme 1



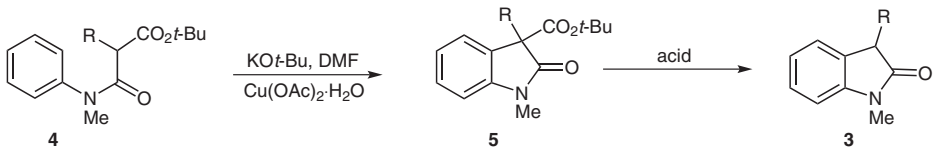
Scheme 2

In view of the utility of 3-alkylated oxindoles as synthetic building blocks[3] and as drug candidates,[4] and given the low yields often observed in the 3-alkylation of oxindoles,[3f] we attempted to generalize this procedure. Unfortunately, the base-mediated saponification–decarboxylation sequence proved to be unsuccessful with other 3-alkyl-3-carboethoxy-oxindoles **2** (e.g., 3-allyl and 3-benzyl analogues); such problems during basic procedures are precedented.[3g,h] As shown in Scheme 3, we therefore proposed the use of the corresponding *tert*-butyl esters **4** to evaluate their utility[5] in the copper(II)-mediated cyclization process with a view to exploring an acid-mediated route to 3-alkyl-oxindoles **3**.

To test this approach, anilide **4a** (R = Me) was prepared as shown in Scheme 4.[6] Thus, Mukaiyama coupling[7] of *N*-methylaniline (**6**) and *tert*-butyl malonate (**7**) gave amide **8** in essentially quantitative yield. Alkylation using methyl iodide also proceeded efficiently to give cyclization precursor **4a**. The key copper(II)-mediated cyclization was investigated next using the $Cu(OAc)_2 \cdot H_2O$–DMF procedure developed earlier.[1] We were delighted to observe the formation of oxindole **5a** in good yield using these conditions. The second crucial step in this sequence, the acid-mediated decarboxyalkylation to produce 3-methyl-oxindole (**3a**), proved to be relatively straightforward (Scheme 4). This transformation could be achieved using several acids but neat TFA (with anisole as a cation trap)[8] at room temperature proved to be the most effective.

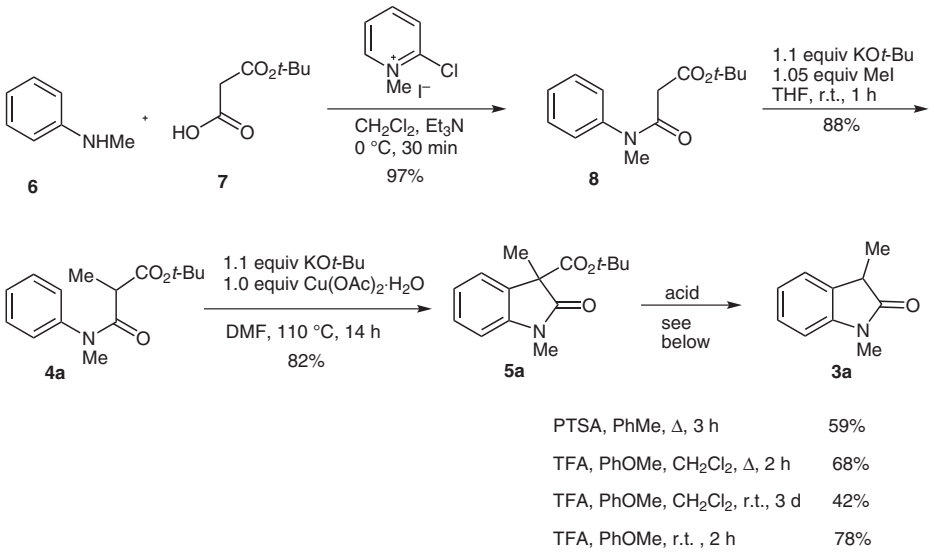
Having established the viability of the copper(II)-mediated cyclization route on *tert*-butyl ester **4a** and the decarboxyalkylation of *tert*-butyl ester **5a**, we went on to explore the scope of this cyclisation–decarboxyalkylation sequence with a range of anilides **4**[9] (Table 1).

As can be seen, this cyclisation–decarboxyalkylation sequence was used to prepare a range of 3-substituted oxindoles including those with saturated alkyl substituents (entries 1–3), allyl, benzyl, phenethyl, and naphthylmethyl substituents (entries 4–7), as well as the benzyloxypro-



Scheme 3

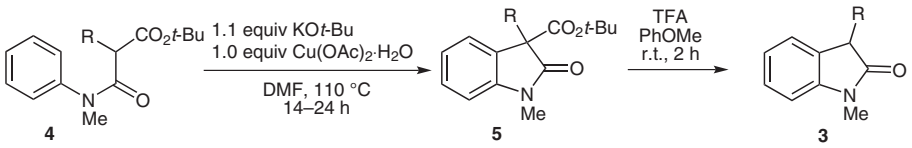
SYNLETT 2010, No. 6, pp 0934–0938
Advanced online publication: 18.02.2010
DOI: 10.1055/s-0029-1219392; Art ID: D36209ST



Scheme 4

pyl (entry 8) and 4-pyridylmethyl (entry 9) examples. All reactions proceeded in the expected manner in fair to excellent yield. The conditions devised for **4a** and **5a** (Scheme 4) were employed in all examples; it is likely that the lower yields could be improved with further optimization studies. One notable observation from this study is the profound steric effect observed for the cyclization of the isopropyl system with oxindole **5c** being obtained in only 42% yield after a reaction time of 72 hours.

Table 1 Scope of the Cyclisation–Decarboxyalkylation Sequence



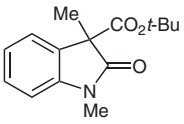
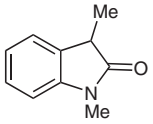
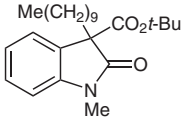
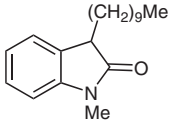
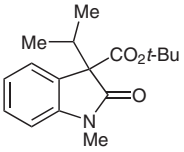
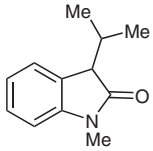
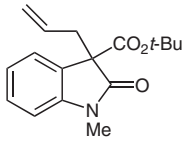
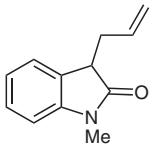
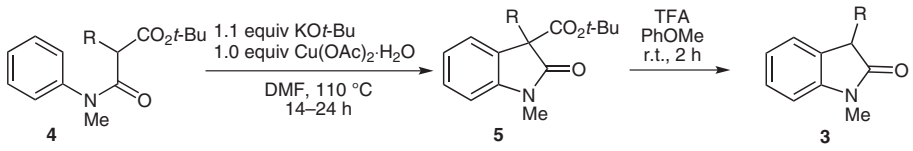
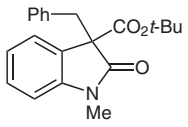
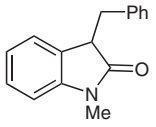
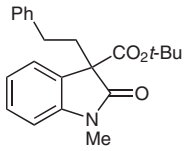
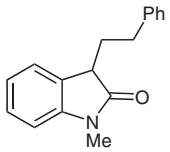
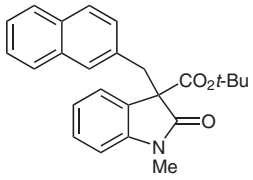
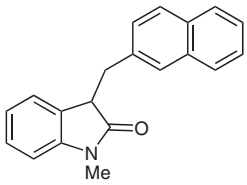
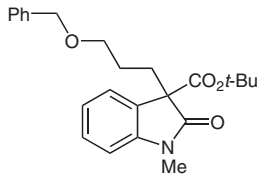
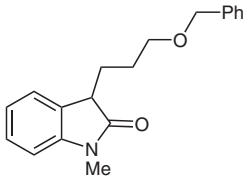
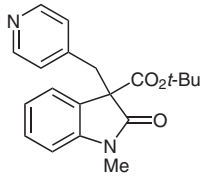
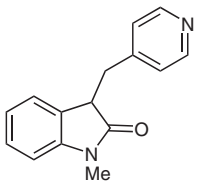
Entry	Cyclisation product **5**	Yield **5** (%)	3-Alkyl-oxindole **3**	Yield **3** (%)
1	 **5a**	82	 **3a**	78
2	 **5b**	76	 **3b**	90
3	 **5c**	46[a]	 **3c**	68
4	 **5d**	59	 **3d**	92

Table 1 Scope of the Cyclisation–Decarboxyalkylation Sequence (continued)



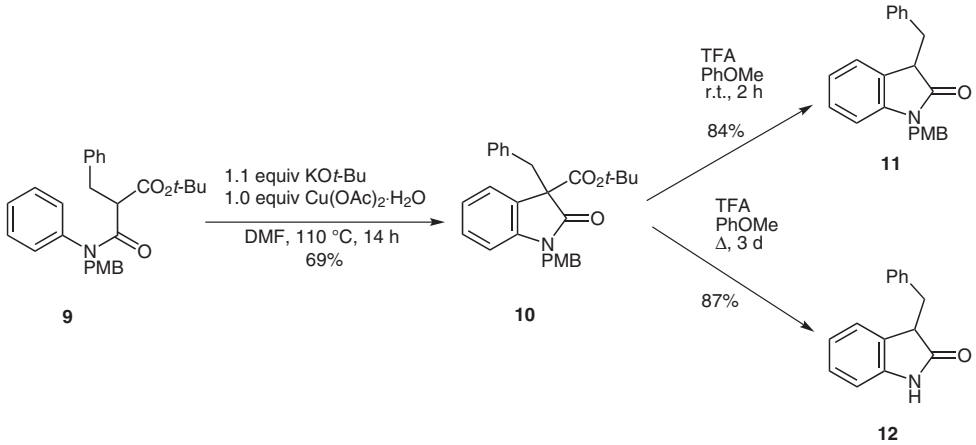
Entry	Cyclisation product **5**	Yield **5** (%)	3-Alkyl-oxindole **3**	Yield **3** (%)
5	 **5e**	93	 **3e**	98
6	 **5f**	71	 **3f**	62
7	 **5g**	73[10]	 **3g**	93[11]
8	 **5h**	65	 **3h**	86
9	 **5i**	68	 **3i**	92

[a]A reaction time of 72 h was required.

Finally, we briefly explored the utility of this methodology for the preparation of unprotected oxindoles (Scheme 5). Thus, we established that *p*-methoxybenzyl (PMB) protection is compatible with the copper(II)-mediated cyclization (**9** → **10**) and then investigated deprotection protocols.

Treatment of oxindole **10** using the TFA and room temperature conditions developed earlier, for 2 hours, gave efficient decarboxyalkylation producing the *N*-PMB-protected 3-benzyl-oxindole **11** in excellent yield. The use of a higher temperature and a longer reaction time gave both decarboxyalkylation and *N*-deprotection producing 3-benzyl-oxindole **12** in 87% yield. The complementarity of these deprotection procedures should be of value when the product oxindoles are required for further synthetic elaboration.

In summary, an inexpensive and operationally straightforward sequence for the conversion of readily available anilides **4** into 3-substituted-*N*-methyl-oxindoles **3** has been developed, based on a copper(II)-mediated C–H, Ar–H coupling process followed by decarboxyalkylation. This procedure is compatible with alkyl, arylalkyl, and functionalized substituents and can also be utilized to prepare 3-substituted oxindoles in the N–H form. We are currently applying this new methodology in natural product areas.



Scheme 5

Acknowledgment

We thank the ESPRC for postgraduate (D.S.P., EP/E041302/1) and postdoctoral (A.P., EP/029841/1) support. We are also grateful to the University of York Wild fund for additional postgraduate funding (J.E.M.N.K.).

References and Notes

(1) Perry, A.; Taylor, R. J. K. *Chem. Commun.* **2009**, 3249.

(2) For related processes, see: (a) Jia, Y.-X.; Kündig, E. P. *Angew. Chem. Int. Ed.* **2009**, *48*, 1636. (b) Miura, T.; Ito, Y.; Murakami, M. *Chem. Lett.* **2009**, *38*, 328. (c) Liang, J.; Chen, J.; Du, F.; Zeng, X.; Li, L.; Zhang, H. *Org. Lett.* **2009**, *11*, 2820. (d) Teichert, A.; Jantos, K.; Harms, K.; Studer, A. *Org. Lett.* **2004**, *6*, 3477.

(3) (a) Bui, T.; Borregan, M.; Barbas, C. F. III. *Org. Lett.* **2009**, *11*, 8935. (b) Qian, Z.-Q.; Zhou, F.; Du, T.-P.; Wang, B.-L.; Ding, M.; Zhao, X.-L.; Zhou, J. *Chem. Commun.* **2009**, 6753. (c) Jiang, K.; Peng, J.; Cui, H.-L.; Chen, Y.-C. *Chem. Commun.* **2009**, 3955. (d) Kato, Y.; Furutachi, M.; Chen, Z.; Mitsunuma, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9168. (e) Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593. (f) Nakazawa, N.; Tagami, K.; Iimori, H.; Sano, S.; Ishikawa, T.; Nagao, Y. *Heterocycles* **2001**, *55*, 2157. (g) Miah, S.; Moody, C. J.; Richards, I. C.; Slawin, A. M. Z. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2405. (h) Damavandy, J. A.; Jones, R. A. Y. *J. Chem. Soc., Perkin Trans. 1* **1981**, 712.

(4) (a) Shimazawa, R.; Kuriyama, M.; Shirai, R. *Bioorg. Med. Chem. Lett.* **2009**, *18*, 3350. (b) Rizzi, E.; Cassinelli, G.; Dallavalle, S.; Lanzi, C.; Cincinelli, R.; Nannei, R.; Cuccuru, G.; Zunino, F. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3962.

(5) (a) Henderson, D.; Richardson, K. A.; Taylor, R. J. K.; Saunders, J. *Synthesis* **1983**, 996; and references therein. (b) Successful decarboxyalkylation of related systems under acidic conditions is precedented: Tani, M.; Matsumoto, S.; Aida, Y.; Arikawa, S.; Nakane, A.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull.* **1994**, *42*, 443.

(6) All novel compounds were fully characterised..

(7) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, *4*, 1163.

(8) Millemaggi, A.; Perry, A.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2009**, 2947.

(9) Prepared by the alkylation of amide **8** using the route shown in Scheme 4; all yields were greater than 88% with the exceptions of *i*-Pr (**5c**, 55%), $PhCH_2CH_2$ (**5f**, 63%), $PhCH_2O(CH_2)_3$ (**5h**, 69%), and 4-$PyCH_2$ (**5i**, 46%).

(10) **Representative Procedure for the Copper-Mediated Cyclisation: *tert*-Butyl 1-Methyl-3-(naphthalen-2-yl-methyl)-2-oxoindoline-3-carboxylate (5g)**
A 100 mL round-bottomed flask fitted with a condenser and stirrer-bar was charged with *tert*-butyl ester **4g** (R = naphthalen-2-yl-methyl, 195 mg, 0.50 mmol) and DMF (10 mL). KO*t*-Bu (62 mg, 0.55 mmol) was added in a single portion, followed by copper(II) acetate monohydrate (100 mg, 0.50 mmol). The green-black suspension was heated to 110 °C (oil bath temperature) over 15 min. After stirring at 110 °C for 18 h, the reaction was cooled to r.t. and quenched with a sat. solution of NH_4Cl (10 mL), diluted with H_2O (20 mL), and extracted with EtOAc (20 mL). The organic layer was washed with a sat. brine solution (2 × 20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to give an orange oil. Purification by flash column chromatography (SiO_2, 7:2:1 PE–CH_2Cl_2–EtOAc) gave product **5g** (141 mg, 73%) as a colorless gum; R_f = 0.44 (3:1 PE–EtOAc). IR (film): ν_{max} = 3056, 2978, 2932, 1734, 1715, 1610, 1493, 1471, 1370, 1351, 1306, 1251, 1155, 1086, 997, 909, 750 cm^{-1}. ^1H NMR (400 MHz, $CHCl_3$-d_1): δ = 1.41 (9 H, s, CMe_3), 2.89 (3 H, s, NMe), 3.64 (1 H, d, *J* = 13.5 Hz, CH_2), 3.69 (1 H, d, *J* = 13.5 Hz, CH_2), 6.50 (1 H, d, *J* = 7.5 Hz, ArH), 6.98 (1 H, dd, *J* = 8.5, 2.0 Hz, ArH), 7.06 (1 H, ddd, *J* = 7.5, 7.5, 1.0 Hz, ArH), 7.17 (1 H, ddd, *J* = 7.5, 7.5, 1.5 Hz, ArH), 7.33–7.37 (3 H, m, ArH), 7.38 (1 H, ddd, *J* = 7.5, 1.5, 0.5 Hz, ArH), 7.48 (1 H, d, *J* = 8.5 Hz, ArH), 7.60 (1 H, dd, *J* = 6.0, 3.5 Hz, ArH), 7.67 (1 H, dd, *J* = 6.0, 3.5 Hz, ArH). ^{13}C NMR (100 MHz, $CHCl_3$-d_1): δ = 26.1 (NMe), 27.8 (CMe_3), 39.7 (CH_2), 61.8 (C), 82.6 [O*C*$(CH_3)_3$], 108.1 (ArH), 122.3 (ArH), 123.6 (ArH), 125.4 (ArH), 125.5 (ArH), 126.9 (ArH), 127.3 (ArH), 127.7 (ArH), 127.8 (Ar), 128.3 (ArH), 128.8 (2 × ArH), 132.1 (Ar), 132.5 (Ar), 132.9 (Ar), 144.1 (Ar), 168.1 (C=O), 173.8 (C=O). ESI-MS: *m/z* = 410 $[MNa]^+$. ESI-HRMS: *m/z* calcd for $C_{25}H_{25}NNaO_3$: 410.1727; found: 410.1731 $[MNa]^+$; 0.6 ppm error.

(11) **Representative Procedure for Decarboxyalkylation: 1-Methyl-3-(naphthalen-2-ylmethyl) indolin-2-one (3g)**
A 10 mL round-bottomed flask with stirrer bar was charged with *tert*-butyl ester **5g** (97 mg, 0.25 mmol) and anisole (82 μL, 0.75 mmol), a septum was fitted and the flask purged with argon(balloon). TFA (1 mL) was added, and the resulting brown solution was stirred for 2 h. The reaction mixture was concentrated in vacuo to give a yellow gum. Purification by flash column chromatography (SiO_2, 4:1 PE–EtOAc) gave oxindole **3g** (67 mg, 93%) as a yellow solid.

R_f = 0.39 (3:1 PE–EtOAc); mp 91–93 °C. IR (film): ν_{max} = 3053, 2920, 2853, 1709, 1612, 1493, 1469, 1422, 1375, 1350, 1256, 1127, 1089, 750, 732 cm^{-1}. ^1H NMR (400 MHz, $CHCl_3$-d_1): δ = 3.04 (1 H, dd, *J* = 13.5, 9.5 Hz, CH_2), 3.17 (3 H, s, NMe), 3.67 (1 H, dd, *J* = 13.5, 4.5 Hz, CH_2), 3.84 (1 H, dd, *J* = 9.5, 4.5 Hz, CH), 6.71–6.77 (2 H, m, *J* = 7.5 Hz, ArH), 6.88 (1 H, ddd, *J* = 7.5, 7.5, 1.0 Hz, ArH), 7.21 (1 H, dd, *J* = 8.0, 8.0 Hz, ArH), 7.34 (1 H, dd, *J* = 8.5, 1.5 Hz, ArH), 7.43–7.47 (2 H, m, ArH), 7.60 (1 H, br s, ArH), 7.73–7.82 (3 H, m, ArH). ^{13}C NMR (100 MHz, $CHCl_3$-d_1): δ = 26.2 (NMe), 37.0 (CH_2), 46.9 (CH), 107.9 (ArH), 122.1 (ArH), 124.5 (ArH), 125.5 (ArH), 126.0 (ArH), 127.6 (3 × ArH), 127.9 (2 × ArH), 128.0 (ArH), 128.3 (Ar), 132.3 (Ar), 133.3 (Ar), 135.5 (Ar), 144.1 (Ar), 177.0 (C=O). ESI-MS: *m/z* = 310 $[MNa]^+$. ESI-HRMS: *m/z* calcd for $C_{20}H_{17}NNaO$: 310.1202; found: 310.1196 $[MNa]^+$; 1.6 ppm error.

ORGANIC LETTERS

2010
Vol. 12, No. 15
3446−3449

First C−H Activation Route to Oxindoles using Copper Catalysis

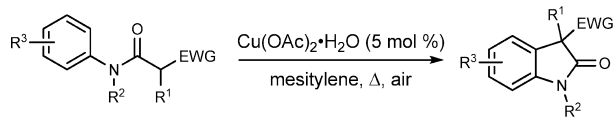
Johannes E. M. N. Klein, Alexis Perry, David S. Pugh, and Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York, YO10 5DD, United Kingdom

rjkt1@york.ac.uk

Received June 2, 2010

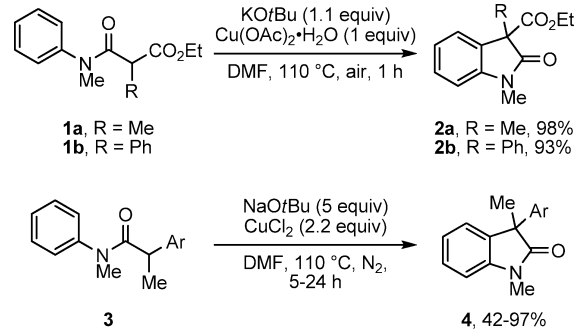
ABSTRACT



The preparation of 3,3-disubstituted oxindoles by a formal C−H, Ar−H coupling of anilides is described. Highly efficient conditions have been identified using catalytic (5 mol %) $Cu(OAc)_2 \cdot H_2O$ with atmospheric oxygen as the reoxidant; no additional base is required, and the reaction can be run in toluene or mesitylene. Optimization studies are reported together with a scope and limitation investigation based on variation of the anilide precursors. The application of this methodology to prepare a key intermediate for the total synthesis of the anticancer, analgesic oxindole alkaloid Horsfiline is also described.

Substituted oxindoles form the cornerstone of numerous natural products and bioactive lead compounds.[1,2] We recently reported an efficient new route to 3,3-disubstituted oxindoles from anilides using potassium *t*-butoxide as base and stoichiometric $Cu(OAc)_2 \cdot H_2O$ in DMF (e.g., **1** → **2**, Scheme 1).[3] This coupling process employs inexpensive reagents and does not require anhydrous conditions or the use of an inert atmosphere (other electron-withdrawing groups, such as nitrile and phosphonate, could also be employed in this sequence). This procedure is closely related to the one, also reported in 2009, by Kündig's group (e.g., **3** → **4**, Scheme 1) in which 3-aryl-3-alkyl-oxindoles **4** were prepared by a $CuCl_2$-mediated cyclization process (although in this aryl variant, Schlenk techniques, anhydrous conditions and an inert atmosphere are required).[4]

Scheme 1. Stoichiometric Approaches to Oxindoles[3,4]



The transformations shown in Scheme 1 are remarkable, and synthetically valuable, as they generate quaternary all-carbon centers via a formal double C−H activation process.[5]

(1) For reviews on the properties of oxindoles and synthetic routes, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Cerchiaro, G.; da Costa Ferreira, A. M. *J. Braz. Chem. Soc.* **2006**, *17*, 1473. (c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (d) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003.

(2) For recent approaches to oxindoles, see: (a) Luan, X.; Wu, L.; Drinkel, E.; Mariz, R.; Gatti, M.; Dorta, R. *Org. Lett.* **2010**, *12*, 1912. (b) Wei, Q.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 1008. (c) Reddy, V. J.; Douglas, C. J. *Org. Lett.* **2010**, *12*, 952. (d) Yasui, Y.; Kamisaki, H.; Ishida, T.; Takemoto, Y. *Tetrahedron* **2010**, *66*, 1980. (e) Liang, J.; Chen, J.; Du, F.; Zeng, X.; Li, L.; Zhang, H. *Org. Lett.* **2009**, *11*, 2820. (f) Peng, P.; Tang, B.-X.; Pi, S.-F.; Liang, Y.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 3569. (g) Song, R.-J.; Liu, Y.; Li, R.-J.; Li, J.-H. *Tetrahedron Lett.* **2009**, *50*, 3912.

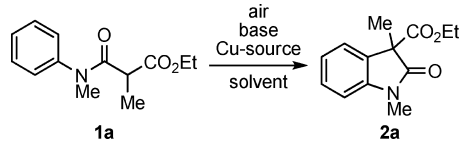
(3) (a) Perry, A.; Taylor, R. J. K. *Chem. Commun.* **2009**, 3249. See also: (b) Pugh, D. S.; Klein, J. E. M. N.; Perry, A.; Taylor, R. J. K. *Synlett* **2010**, 934.

(4) Jia, Y.-X.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1636.

(5) For a copper catalysed, double C-H coupling route to indoles, see: Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8078.

10.1021/ol1012668
Published on Web 07/14/2010

Table 1. Oxindole Preparation using Stoichiometric and Catalytic Cu(II)[a,b]



1a **2a**

entry	base	Cu-source	solvent (temp)	time	yield
i	KO*t*Bu (1.1 equiv)	$Cu(OAc)_2{\cdot}H_2O$ (1 equiv)	DMF (110 °C)	1 h	98%
ii	KO*t*Bu (1.1 equiv)	$Cu(OAc)_2{\cdot}H_2O$ (5 mol %)	DMF (110 °C)	16 h	(14%)
iii	Piperidine (10 equiv)[c]	$Cu(OAc)_2{\cdot}H_2O$ (5 mol %)	DMF (110 °C)	5 h	(87%)84%
iv	–	$Cu(OAc)_2{\cdot}H_2O$ (5 mol %)	DMF (110 °C)	16 h	(20%)
v	–	$Cu(OAc)_2{\cdot}H_2O$ (5 mol %)	PhMe (110 °C)	20 h	81%
vi	–	$Cu(OTf)_2$[d] (5 mol %)	PhMe (110 °C)	24 h	(75%)
vii	–	***$Cu(OAc)_2{\cdot}H_2O$*** (5 mol %)	***Mesitylene (165 °C)***[e]	***1.5 h***	***92%***
viii	–	$Cu(OAc)_2{\cdot}H_2O$ (5 mol %)	Mesitylene (165 °C)[f]	1.5 h	(<5%)

[a] Unless stated otherwise, the base (if used) was added to a mixture of the substrate and the copper salt in the solvent specified; then a reflux condenser fitted with a drying tube was inserted and the reaction heated for the time indicated. [b] Yields in parentheses determined using NMR spectroscopy against an internal standard (1,1,2,2-tetrachloroethane). [c] With piperidine (1 equiv), the reaction was still incomplete after 16 h giving **2** in 47% NMR yield. [d] The following copper salts (5 mol %) also effected the required transformation: $CuBF_4{\cdot}4H_2O$, 67%; $Cu(acac)_2$, 62%; $[Me(CH_2)_3CH(Et)CO_2]_2Cu$, 63%; $Cu(TC)_2{\cdot}$MeOH, 70%; CuOAc, 51%; CuTC, 53%). A UK 1p coin (1980) also gave oxindole **2** (57%, 5 h). Little or no cyclization was observed using $CuCl_2$, $CuBr_2$, $CuSO_4$, $CuCl_2$(phen), Cu_2O, CuO, and CuCl. [e] No product formation was observed in the absence of $Cu(OAc)_2{\cdot}H_2O$ (or when the $Cu(OAc)_2{\cdot}H_2O$ was replaced by KOAc). [f] Degassed and under an argon atmosphere.

Preliminary mechanistic studies[3,4] indicated that the cyclization proceeds via deprotonation, radical generation, and then homolytic aromatic substitution. Such a sequence involves two separate one-electron oxidation processes, which would require the use of 2 equiv of a Cu(II) source.

We were intrigued by the possibility that the above cyclization reactions could be carried out using catalytic quantities of Cu(II) salts by the use of a stoichiometric reoxidant, preferably atmospheric oxygen, to recycle the putative Cu(I) intermediate.[6] Such a catalytic approach, which would be of great value for larger scale processes, seemed plausible given that the original reaction shown in Scheme 1 used just 1 equiv of $Cu(OAc)_2{\cdot}H_2O$ and the reaction vessel was open to the air. The preliminary studies toward the development of a Cu(II)-catalyzed procedure for oxindole synthesis are shown in Table 1.

Repeating the original[3] stoichiometric $Cu(OAc)_2{\cdot}H_2O$/KO*t*Bu/DMF conditions gave a near quantitative yield for the conversion of anilide **1** into 3,3-disubstituted oxindole **2** after 1 h at 110 °C (entry i), whereas the use of 5 mol % $Cu(OAc)_2{\cdot}H_2O$ under the same conditions resulted in only 14% yield of oxindole **2** after 16 h (entry ii). However, this partial success (ca. 3 turnovers) in DMF was in contrast to the fact that little or no cyclization was observed when $Cu(OAc)_2{\cdot}H_2O$ was employed in other solvents such as THF or MeCN. Replacement of KO*t*Bu by organic bases was investigated next and a dramatic improvement was realized using $Cu(OAc)_2{\cdot}H_2O$/piperidine/DMF (entry iii); with an excess of piperidine (10 equiv) an 84% yield of oxindole **2** was isolated with a reaction time of only 5 hours.

We next carried out a control reaction in the absence of added base but were amazed to observe that oxindole **2** was still formed in approximately 20% yield (entry iv). Initially, we reasoned that the thermal decomposition of DMF at elevated temperature would release dimethylamine,[7] which could act as the base. However, changing the solvent to toluene (entry v), again using 5 mol % $Cu(OAc)_2{\cdot}H_2O$ with no added base, resulted in a much improved 81% isolated yield after 20 h at 110 °C.

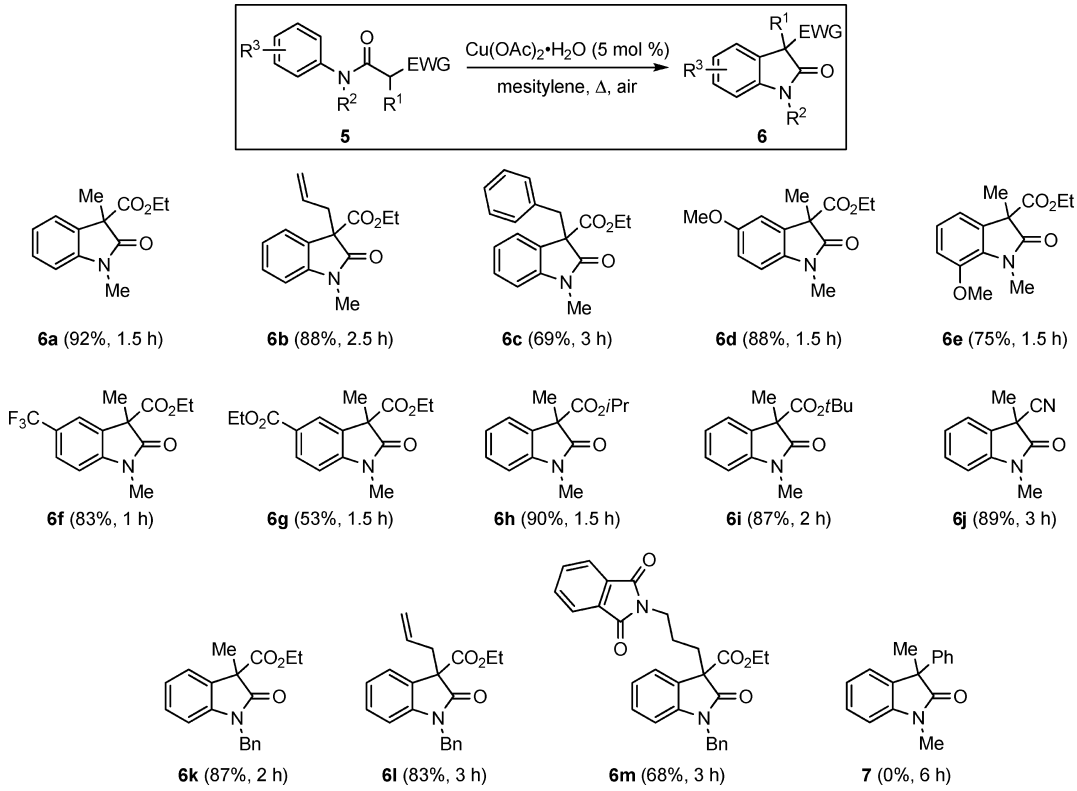
With this remarkable result in hand, we set out to further optimize this reaction by varying the copper source whilst keeping toluene as solvent. A range of copper salts were screened and several were successful with $Cu(OTf)_2$ giving the best result (entry vi) but none were superior to $Cu(OAc)_2{\cdot}H_2O$. It is also noteworthy, given its use by Kündig et al.,[4] that $CuCl_2$ was completely ineffective for this transformation. In addition, replacement of toluene as solvent by mesitylene at reflux gave a dramatic improvement in yield and a reduction of reaction time (92%, 1.5 h; entry vii). Finally in this preliminary study, the importance of aerial oxidation was confirmed (entry viii); when the reaction was carried out using the mesitylene conditions but with degassing under an argon atmosphere, less than 5% of oxindole **2** was formed.

Having devised an efficient cyclization procedure using catalytic $Cu(OAc)_2{\cdot}H_2O$ in mesitylene, we went on to test the substrate scope using differently substituted anilides **5** (Scheme 2). As can be seen, several α-carbonyl substituents were compatible with the cyclization conditions producing oxindoles **6a**−**6c** in good yields. In addition, substitution of the aryl ring with electron donating groups (4-OMe and 2-OMe) made little difference, with oxindoles **6d** and **6e** being isolated in 88 and 75% yield, respectively. Furthermore

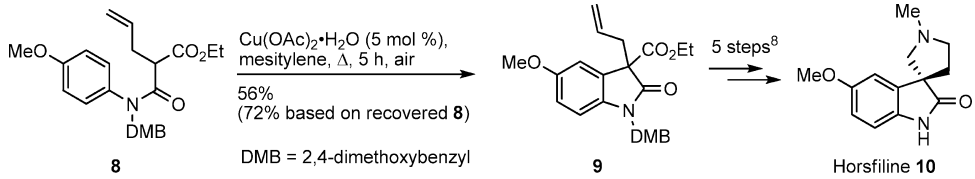
(6) For a review on aerobic copper catalysis, see: (a) Gamez, P.; Aubel, P. G.; Driessen, W. L.; Reedijk, J. *Chem. Soc. Rev.* **2001**, *30*, 376. For more recent references, see: (b) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (c) Villalobos, J. M.; Srogl, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 15734.

(7) Muzart, J. *Tetrahedron* **2009**, *65*, 8313.

Scheme 2. Scope and Limitations of the Catalytic $Cu(OAc)_2 \cdot H_2O$ Procedure



Scheme 3. Preparation of a Horsfiline Precursor **9**



electron withdrawing groups such as 4-CF_3 and 4-CO_2Et were also tolerated under the reaction conditions, giving oxindoles **6f** and **6g** in 83 and 53% yield, respectively. Changing the ester group from ethyl to *iso*-propyl or *tert*-butyl was also allowed with the expected oxindoles **6h** and **6i** being formed in excellent yield; the latter result emphasizes the compatibility of the $Cu(OAc)_2 \cdot H_2O$/mesitylene system with acid-labile groups. In addition, this catalytic procedure was shown to be compatible with other activating groups by the preparation of nitrile **6j** in excellent yield. All of the examples mentioned to date contained *N*-Me groups but formation of the *N*-benzyl systems **6k**−**6m** was equally straightforward. Finally, we explored the cyclization of the less activated *N*-methyl-*N*-2-diphenylpropanamide but no trace of oxindole **7** was observed even after a reaction time of 6 h (and so Kundig's stoichiometric $CuCl_2$/NaO*t*Bu conditions[4] are favored in such aryl-activated cases).

The above observations seem to be consistent with the original mechanistic proposal for the stoichiometric process, that is, enolization followed by radical generation and then homolytic aromatic substitution. In the catalytic process, oxygen in air is the terminal oxidant recycling Cu(I) to Cu(II) and the enolization (possibly assisted by copper(II) chelation) is presumably effected by the substrate. It should be noted that the reactions do not appear to increase in acidity as they progress and so the hydrogens are presumably lost as water.

Trost and Brennan recently published a new synthesis of the anticancer, analgesic oxindole alkaloid Horsfiline **10**, which proceeded by way of oxindole **9** (Scheme 3).[8] To showcase the utility of the Cu(II)-mediated Ar−H/C-H coupling sequence developed herein, we prepared intermediate **9** from readily available anilide **8** in 56% unoptimised yield (72% based on recovered **8**) using the $Cu(OAc)_2 \cdot H_2O$/mesitylene procedure. Once again, these conditions were compatible with a sensitive protecting

(8) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027.

group (DMB) which is easily cleaved under acidic or oxidative conditions.

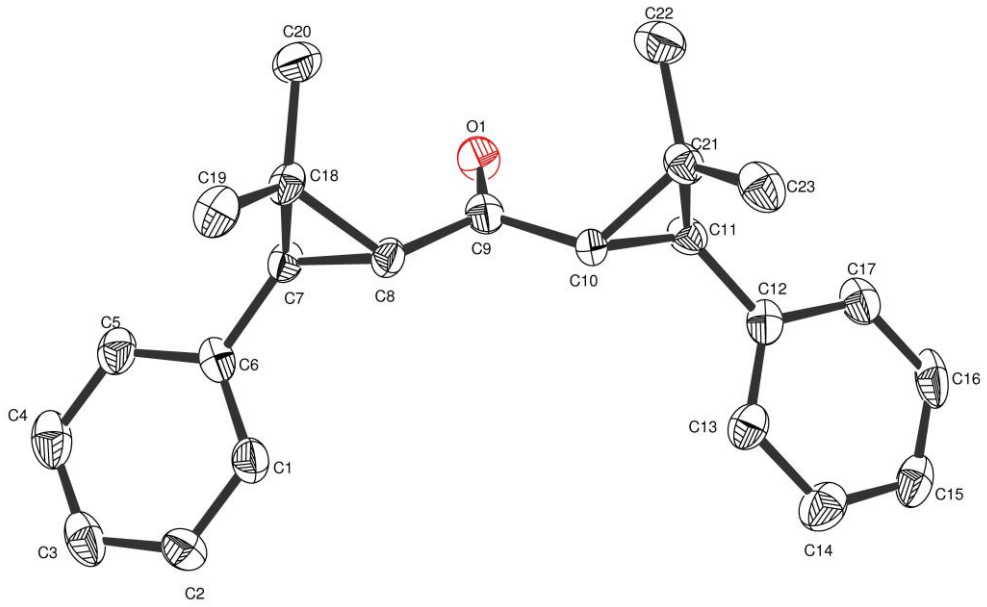
In summary, we have developed an operationally straightforward double C−H activation route to 3,3-disubstituted oxindoles that employs catalytic $Cu(OAc)_2 \cdot H_2O$ and atmospheric oxygen as the reoxidant; no additional base is required, and the reaction can be run in toluene or mesitylene. The mesitylene conditions have been utilized with a range of substrates, including several containing acid-labile groups, to establish the general utility of the process.

Acknowledgment. We thank the EPSRC for postgraduate (D.S.P., EP/E041302/1) and postdoctoral (A.P., EP/029841/1) support. We are also grateful to the University of York Wild fund for additional postgraduate support (J.E.M.N.K.).

Supporting Information Available: Experimental procedures and spectroscopic data for oxindoles **6a**−**6m** and **9** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1012668

Appendix 1: X-ray crystal data for *bis((1RS, 3RS)-2,2-dimethyl-3-phenylcyclopropyl)methanone 205*



CCDC deposition number 698581

Table 1. Crystal data and structure refinement for 2008src0750.

Identification code	2008src0750	
Empirical formula	C23 H26 O	
Formula weight	318.44	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 5.7287(7) Å	α= 90°.
	b = 27.517(4) Å	β= 91.881(8)°.
	c = 11.9206(17) Å	γ = 90°.
Volume	1878.1(4) $Å^3$	
Z	4	
Density (calculated)	1.126 Mg/m^3	

Absorption coefficient	0.067 mm^{-1}
F(000)	688
Crystal size	0.28 x 0.24 x 0.02 mm^3
Theta range for data collection	3.42 to 27.533°.
Index ranges	-7<=h<=7, 0<=k<=35, 0<=l<=15
Reflections collected	4341
Independent reflections	4341 [R(int) = 0.0000]
Completeness to theta = 27.73°	95.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.999 and 0.454
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4341 / 1 / 442
Goodness-of-fit on F^2	1.236
Final R indices [I>2sigma(I)]	R1 = 0.0865, wR2 = 0.1634
R indices (all data)	R1 = 0.1140, wR2 = 0.1856
Absolute structure parameter	3(5)
Largest diff. peak and hole	0.377 and -0.362 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 2008src0750. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	9241(13)	2555(3)	6841(6)	31(2)
C(2)	10482(13)	2186(3)	6358(6)	32(2)
C(3)	9779(15)	1710(3)	6449(6)	38(2)
C(4)	7830(15)	1604(3)	7051(7)	39(2)
C(5)	6542(14)	1975(3)	7534(6)	31(2)
C(6)	7264(12)	2458(2)	7438(5)	23(1)
C(7)	5830(12)	2845(2)	7963(5)	24(1)
C(8)	6792(12)	3358(2)	8125(5)	23(1)
C(9)	5224(12)	3767(2)	7808(5)	25(1)
C(10)	6435(12)	4233(2)	7563(5)	22(1)
C(11)	5097(12)	4620(2)	6905(5)	25(1)
C(12)	6203(13)	4881(2)	5979(6)	26(2)
C(13)	8184(12)	4727(3)	5465(6)	29(2)
C(14)	9188(15)	4979(3)	4594(6)	40(2)
C(15)	8106(15)	5393(3)	4180(6)	36(2)
C(16)	6079(17)	5556(3)	4656(7)	40(2)
C(17)	5146(14)	5308(2)	5541(6)	32(2)
C(18)	6286(12)	3023(2)	9137(5)	24(1)
C(19)	8379(12)	2821(3)	9771(6)	31(2)
C(20)	4285(13)	3153(3)	9868(6)	35(2)
C(21)	5715(12)	4718(2)	8104(6)	26(1)
C(22)	3819(13)	4717(3)	8966(7)	37(2)
C(23)	7676(14)	5067(3)	8386(6)	33(2)
O(1)	3116(8)	3729(2)	7726(4)	31(1)
C(24)	2532(13)	1695(3)	332(6)	33(2)
C(25)	1880(17)	1415(4)	-582(7)	49(2)
C(26)	3394(17)	1045(3)	-938(7)	45(2)
C(27)	5426(17)	966(3)	-334(6)	39(2)
C(28)	6064(14)	1249(2)	582(6)	32(2)
C(29)	4559(13)	1618(2)	932(5)	25(1)
C(30)	5358(11)	1906(2)	1929(5)	23(1)
C(31)	3921(12)	2309(2)	2417(6)	24(1)
C(32)	5165(12)	2769(2)	2732(5)	24(1)

C(33)	3582(12)	3180(2)	3029(5)	23(1)
C(34)	4585(11)	3695(2)	2971(5)	22(1)
C(35)	3206(12)	4103(2)	2472(5)	21(1)
C(36)	4072(13)	4575(3)	2663(6)	30(2)
C(37)	2826(16)	4967(3)	2203(6)	38(2)
C(38)	797(16)	4902(3)	1584(6)	37(2)
C(39)	-55(13)	4436(3)	1394(6)	33(2)
C(40)	1191(12)	4043(3)	1839(6)	27(2)
C(41)	4367(12)	1843(2)	3088(5)	24(1)
C(42)	6060(12)	1844(3)	4075(6)	29(2)
C(43)	2280(13)	1513(3)	3208(6)	32(2)
C(44)	4066(12)	3478(2)	4100(6)	24(1)
C(45)	6020(12)	3336(3)	4910(6)	29(2)
C(46)	1921(12)	3669(3)	4677(6)	31(2)
O(2)	7276(8)	2806(2)	2757(4)	28(1)

Table 3. Bond lengths [Å] and angles [°] for 2008src0750.

C(1)-C(2)	1.376(10)
C(1)-C(6)	1.383(10)
C(1)-H(1)	0.9500
C(2)-C(3)	1.377(11)
C(2)-H(2)	0.9500
C(3)-C(4)	1.378(12)
C(3)-H(3)	0.9500
C(4)-C(5)	1.395(11)
C(4)-H(4)	0.9500
C(5)-C(6)	1.395(10)
C(5)-H(5)	0.9500
C(6)-C(7)	1.496(9)
C(7)-C(18)	1.497(9)
C(7)-C(8)	1.525(9)
C(7)-H(7)	1.0000
C(8)-C(9)	1.481(9)
C(8)-C(18)	1.553(8)
C(8)-H(8)	1.0000
C(9)-O(1)	1.213(8)
C(9)-C(10)	1.491(9)
C(10)-C(11)	1.516(9)
C(10)-C(21)	1.543(9)
C(10)-H(10)	1.0000
C(11)-C(12)	1.477(10)
C(11)-C(21)	1.485(9)
C(11)-H(11)	1.0000
C(12)-C(13)	1.374(10)
C(12)-C(17)	1.413(9)
C(13)-C(14)	1.389(10)
C(13)-H(13)	0.9500
C(14)-C(15)	1.381(11)
C(14)-H(14)	0.9500
C(15)-C(16)	1.384(12)
C(15)-H(15)	0.9500
C(16)-C(17)	1.379(11)
C(16)-H(16)	0.9500

C(17)-H(17)	0.9500
C(18)-C(19)	1.503(10)
C(18)-C(20)	1.506(10)
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800
C(20)-H(20C)	0.9800
C(21)-C(23)	1.509(10)
C(21)-C(22)	1.520(10)
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-C(29)	1.361(10)
C(24)-C(25)	1.376(11)
C(24)-H(24)	0.9500
C(25)-C(26)	1.410(13)
C(25)-H(25)	0.9500
C(26)-C(27)	1.366(13)
C(26)-H(26)	0.9500
C(27)-C(28)	1.382(10)
C(27)-H(27)	0.9500
C(28)-C(29)	1.403(10)
C(28)-H(28)	0.9500
C(29)-C(30)	1.489(9)
C(30)-C(31)	1.509(9)
C(30)-C(41)	1.521(9)
C(30)-H(30)	1.0000
C(31)-C(32)	1.495(9)
C(31)-C(41)	1.527(9)
C(31)-H(31)	1.0000
C(32)-O(2)	1.213(8)
C(32)-C(33)	1.499(9)
C(33)-C(34)	1.531(9)

C(33)-C(44)	1.535(9)
C(33)-H(33)	1.0000
C(34)-C(35)	1.485(9)
C(34)-C(44)	1.511(9)
C(34)-H(34)	1.0000
C(35)-C(40)	1.368(10)
C(35)-C(36)	1.407(10)
C(36)-C(37)	1.395(10)
C(36)-H(36)	0.9500
C(37)-C(38)	1.367(12)
C(37)-H(37)	0.9500
C(38)-C(39)	1.387(11)
C(38)-H(38)	0.9500
C(39)-C(40)	1.391(9)
C(39)-H(39)	0.9500
C(40)-H(40)	0.9500
C(41)-C(42)	1.500(9)
C(41)-C(43)	1.512(10)
C(42)-H(42A)	0.9800
C(42)-H(42B)	0.9800
C(42)-H(42C)	0.9800
C(43)-H(43A)	0.9800
C(43)-H(43B)	0.9800
C(43)-H(43C)	0.9800
C(44)-C(45)	1.505(9)
C(44)-C(46)	1.522(9)
C(45)-H(45A)	0.9800
C(45)-H(45B)	0.9800
C(45)-H(45C)	0.9800
C(46)-H(46A)	0.9800
C(46)-H(46B)	0.9800
C(46)-H(46C)	0.9800

C(2)-C(1)-C(6)	121.0(7)
C(2)-C(1)-H(1)	119.5
C(6)-C(1)-H(1)	119.5
C(1)-C(2)-C(3)	120.8(7)
C(1)-C(2)-H(2)	119.6

C(3)-C(2)-H(2)	119.6
C(2)-C(3)-C(4)	119.1(7)
C(2)-C(3)-H(3)	120.5
C(4)-C(3)-H(3)	120.5
C(3)-C(4)-C(5)	120.6(7)
C(3)-C(4)-H(4)	119.7
C(5)-C(4)-H(4)	119.7
C(4)-C(5)-C(6)	120.0(7)
C(4)-C(5)-H(5)	120.0
C(6)-C(5)-H(5)	120.0
C(1)-C(6)-C(5)	118.4(7)
C(1)-C(6)-C(7)	123.2(6)
C(5)-C(6)-C(7)	118.4(6)
C(6)-C(7)-C(18)	122.9(6)
C(6)-C(7)-C(8)	120.8(6)
C(18)-C(7)-C(8)	61.8(4)
C(6)-C(7)-H(7)	113.9
C(18)-C(7)-H(7)	113.9
C(8)-C(7)-H(7)	113.9
C(9)-C(8)-C(7)	117.3(6)
C(9)-C(8)-C(18)	121.5(6)
C(7)-C(8)-C(18)	58.2(4)
C(9)-C(8)-H(8)	115.8
C(7)-C(8)-H(8)	115.8
C(18)-C(8)-H(8)	115.8
O(1)-C(9)-C(8)	123.2(7)
O(1)-C(9)-C(10)	121.9(6)
C(8)-C(9)-C(10)	114.9(6)
C(9)-C(10)-C(11)	118.4(6)
C(9)-C(10)-C(21)	121.9(6)
C(11)-C(10)-C(21)	58.1(4)
C(9)-C(10)-H(10)	115.4
C(11)-C(10)-H(10)	115.4
C(21)-C(10)-H(10)	115.4
C(12)-C(11)-C(21)	122.5(6)
C(12)-C(11)-C(10)	120.4(6)
C(21)-C(11)-C(10)	61.9(4)
C(12)-C(11)-H(11)	114.1

C(21)-C(11)-H(11)	114.1
C(10)-C(11)-H(11)	114.1
C(13)-C(12)-C(17)	116.2(7)
C(13)-C(12)-C(11)	124.3(6)
C(17)-C(12)-C(11)	119.4(7)
C(12)-C(13)-C(14)	123.2(7)
C(12)-C(13)-H(13)	118.4
C(14)-C(13)-H(13)	118.4
C(15)-C(14)-C(13)	119.2(8)
C(15)-C(14)-H(14)	120.4
C(13)-C(14)-H(14)	120.4
C(14)-C(15)-C(16)	119.6(7)
C(14)-C(15)-H(15)	120.2
C(16)-C(15)-H(15)	120.2
C(17)-C(16)-C(15)	120.3(7)
C(17)-C(16)-H(16)	119.8
C(15)-C(16)-H(16)	119.8
C(16)-C(17)-C(12)	121.5(7)
C(16)-C(17)-H(17)	119.3
C(12)-C(17)-H(17)	119.3
C(7)-C(18)-C(19)	117.5(6)
C(7)-C(18)-C(20)	120.4(6)
C(19)-C(18)-C(20)	114.0(6)
C(7)-C(18)-C(8)	60.0(4)
C(19)-C(18)-C(8)	116.4(6)
C(20)-C(18)-C(8)	118.3(6)
C(18)-C(19)-H(19A)	109.5
C(18)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(18)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(18)-C(20)-H(20A)	109.5
C(18)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
C(18)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5

C(11)-C(21)-C(23)	118.8(6)
C(11)-C(21)-C(22)	119.9(6)
C(23)-C(21)-C(22)	113.1(6)
C(11)-C(21)-C(10)	60.1(4)
C(23)-C(21)-C(10)	115.9(6)
C(22)-C(21)-C(10)	119.2(6)
C(21)-C(22)-H(22A)	109.5
C(21)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(21)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(21)-C(23)-H(23A)	109.5
C(21)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(21)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(29)-C(24)-C(25)	122.2(8)
C(29)-C(24)-H(24)	118.9
C(25)-C(24)-H(24)	118.9
C(24)-C(25)-C(26)	119.2(8)
C(24)-C(25)-H(25)	120.4
C(26)-C(25)-H(25)	120.4
C(27)-C(26)-C(25)	118.6(7)
C(27)-C(26)-H(26)	120.7
C(25)-C(26)-H(26)	120.7
C(26)-C(27)-C(28)	121.6(8)
C(26)-C(27)-H(27)	119.2
C(28)-C(27)-H(27)	119.2
C(27)-C(28)-C(29)	119.6(8)
C(27)-C(28)-H(28)	120.2
C(29)-C(28)-H(28)	120.2
C(24)-C(29)-C(28)	118.6(7)
C(24)-C(29)-C(30)	124.8(6)
C(28)-C(29)-C(30)	116.5(6)
C(29)-C(30)-C(31)	122.9(6)
C(29)-C(30)-C(41)	123.4(6)

C(31)-C(30)-C(41)	60.6(4)
C(29)-C(30)-H(30)	113.4
C(31)-C(30)-H(30)	113.4
C(41)-C(30)-H(30)	113.4
C(32)-C(31)-C(30)	117.2(6)
C(32)-C(31)-C(41)	120.6(6)
C(30)-C(31)-C(41)	60.1(4)
C(32)-C(31)-H(31)	115.8
C(30)-C(31)-H(31)	115.8
C(41)-C(31)-H(31)	115.8
O(2)-C(32)-C(31)	122.9(6)
O(2)-C(32)-C(33)	122.8(6)
C(31)-C(32)-C(33)	114.3(6)
C(32)-C(33)-C(34)	117.2(6)
C(32)-C(33)-C(44)	120.3(6)
C(34)-C(33)-C(44)	59.1(4)
C(32)-C(33)-H(33)	116.1
C(34)-C(33)-H(33)	116.1
C(44)-C(33)-H(33)	116.1
C(35)-C(34)-C(44)	122.5(6)
C(35)-C(34)-C(33)	121.4(6)
C(44)-C(34)-C(33)	60.6(4)
C(35)-C(34)-H(34)	114.0
C(44)-C(34)-H(34)	114.0
C(33)-C(34)-H(34)	114.0
C(40)-C(35)-C(36)	119.1(6)
C(40)-C(35)-C(34)	124.0(6)
C(36)-C(35)-C(34)	116.9(6)
C(37)-C(36)-C(35)	118.5(7)
C(37)-C(36)-H(36)	120.8
C(35)-C(36)-H(36)	120.8
C(38)-C(37)-C(36)	121.8(8)
C(38)-C(37)-H(37)	119.1
C(36)-C(37)-H(37)	119.1
C(37)-C(38)-C(39)	119.8(7)
C(37)-C(38)-H(38)	120.1
C(39)-C(38)-H(38)	120.1
C(38)-C(39)-C(40)	118.8(7)

C(38)-C(39)-H(39)	120.6
C(40)-C(39)-H(39)	120.6
C(35)-C(40)-C(39)	122.1(7)
C(35)-C(40)-H(40)	119.0
C(39)-C(40)-H(40)	119.0
C(42)-C(41)-C(43)	114.8(6)
C(42)-C(41)-C(30)	117.5(6)
C(43)-C(41)-C(30)	118.3(6)
C(42)-C(41)-C(31)	120.1(6)
C(43)-C(41)-C(31)	115.7(6)
C(30)-C(41)-C(31)	59.3(4)
C(41)-C(42)-H(42A)	109.5
C(41)-C(42)-H(42B)	109.5
H(42A)-C(42)-H(42B)	109.5
C(41)-C(42)-H(42C)	109.5
H(42A)-C(42)-H(42C)	109.5
H(42B)-C(42)-H(42C)	109.5
C(41)-C(43)-H(43A)	109.5
C(41)-C(43)-H(43B)	109.5
H(43A)-C(43)-H(43B)	109.5
C(41)-C(43)-H(43C)	109.5
H(43A)-C(43)-H(43C)	109.5
H(43B)-C(43)-H(43C)	109.5
C(45)-C(44)-C(34)	120.7(6)
C(45)-C(44)-C(46)	113.2(6)
C(34)-C(44)-C(46)	116.9(6)
C(45)-C(44)-C(33)	120.4(6)
C(34)-C(44)-C(33)	60.3(4)
C(46)-C(44)-C(33)	115.7(6)
C(44)-C(45)-H(45A)	109.5
C(44)-C(45)-H(45B)	109.5
H(45A)-C(45)-H(45B)	109.5
C(44)-C(45)-H(45C)	109.5
H(45A)-C(45)-H(45C)	109.5
H(45B)-C(45)-H(45C)	109.5
C(44)-C(46)-H(46A)	109.5
C(44)-C(46)-H(46B)	109.5
H(46A)-C(46)-H(46B)	109.5

C(44)-C(46)-H(46C)	109.5
H(46A)-C(46)-H(46C)	109.5
H(46B)-C(46)-H(46C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 3. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 2008src0750. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	37(4)	24(3)	30(4)	4(3)	1(3)	5(3)
C(2)	27(4)	32(4)	36(4)	-2(3)	2(3)	5(3)
C(3)	56(5)	29(4)	28(4)	-2(3)	-10(4)	14(4)
C(4)	59(5)	25(4)	32(4)	-2(3)	-12(4)	0(4)
C(5)	39(4)	29(4)	24(4)	5(3)	-4(3)	1(3)
C(6)	31(4)	21(3)	17(3)	-3(3)	-11(3)	3(3)
C(7)	28(3)	21(3)	23(3)	2(3)	0(3)	-4(3)
C(8)	29(3)	20(3)	20(3)	4(3)	1(3)	0(3)
C(9)	35(4)	23(3)	16(3)	-3(3)	-3(3)	1(3)
C(10)	28(3)	16(3)	24(3)	1(2)	5(3)	1(3)
C(11)	29(4)	25(3)	21(3)	-4(3)	-1(3)	3(3)
C(12)	35(4)	22(3)	21(3)	0(3)	-6(3)	-2(3)
C(13)	33(4)	30(3)	24(3)	5(3)	-3(3)	-3(3)
C(14)	50(5)	40(4)	28(4)	-1(3)	4(3)	-10(4)
C(15)	61(5)	26(3)	20(3)	-2(3)	-2(3)	-16(4)
C(16)	70(6)	18(3)	32(4)	5(3)	-10(4)	4(4)
C(17)	46(5)	26(4)	23(4)	-2(3)	-5(3)	5(3)
C(18)	36(4)	22(3)	14(3)	1(2)	-3(3)	-5(3)
C(19)	32(4)	34(4)	27(4)	4(3)	-6(3)	-5(3)
C(20)	33(4)	41(4)	32(4)	5(3)	9(3)	2(3)
C(21)	30(3)	24(3)	23(3)	-2(3)	-2(3)	3(3)
C(22)	35(4)	40(4)	36(4)	-3(3)	5(3)	8(4)
C(23)	41(4)	30(4)	28(4)	-5(3)	-6(3)	5(3)
O(1)	25(2)	30(3)	37(3)	-1(2)	-1(2)	-1(2)
C(24)	33(4)	39(4)	26(4)	-1(3)	-2(3)	0(3)
C(25)	53(5)	68(6)	26(4)	-3(4)	-5(4)	-25(5)
C(26)	73(6)	40(4)	22(4)	-4(3)	2(4)	-31(5)
C(27)	71(6)	25(4)	23(4)	-2(3)	8(4)	1(4)
C(28)	48(4)	25(3)	22(4)	-3(3)	1(3)	-4(3)
C(29)	42(4)	18(3)	14(3)	1(2)	4(3)	1(3)
C(30)	21(3)	25(3)	23(3)	0(3)	1(3)	3(3)
C(31)	22(3)	24(3)	26(4)	0(3)	-6(3)	4(3)
C(32)	37(4)	22(3)	13(3)	-2(2)	-4(3)	3(3)

C(33)	27(3)	19(3)	22(3)	2(2)	-3(3)	2(3)
C(34)	21(3)	22(3)	23(3)	1(3)	-2(3)	3(3)
C(35)	25(3)	26(3)	13(3)	1(2)	-1(2)	-1(3)
C(36)	39(4)	28(4)	22(3)	-1(3)	-3(3)	1(3)
C(37)	67(6)	26(4)	21(4)	5(3)	4(4)	3(4)
C(38)	62(5)	29(4)	22(4)	5(3)	6(4)	15(4)
C(39)	25(4)	44(4)	30(4)	7(3)	-2(3)	12(3)
C(40)	27(4)	25(3)	29(4)	3(3)	-1(3)	1(3)
C(41)	29(3)	24(3)	19(3)	4(3)	-2(3)	7(3)
C(42)	28(4)	30(4)	27(4)	0(3)	-4(3)	-1(3)
C(43)	35(4)	36(4)	26(4)	4(3)	-1(3)	1(3)
C(44)	22(3)	20(3)	29(4)	-4(3)	-3(3)	1(3)
C(45)	31(4)	31(4)	25(4)	-2(3)	-4(3)	-1(3)
C(46)	30(4)	39(4)	24(4)	-2(3)	3(3)	4(3)
O(2)	27(3)	26(2)	32(3)	-7(2)	1(2)	1(2)

Table 4. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 2008src0750.

	x	y	z	U(eq)
H(1)	9749	2882	6763	37
H(2)	11841	2261	5956	38
H(3)	10625	1457	6101	46
H(4)	7360	1276	7139	47
H(5)	5173	1900	7927	37
H(7)	4137	2835	7732	29
H(8)	8476	3403	7956	28
H(10)	8127	4204	7393	27
H(11)	3411	4541	6757	30
H(13)	8902	4434	5718	35
H(14)	10601	4868	4287	47
H(15)	8749	5565	3572	43
H(16)	5325	5840	4372	48
H(17)	3763	5426	5864	38
H(19A)	7932	2525	10167	47
H(19B)	8965	3063	10316	47
H(19C)	9604	2745	9245	47
H(20A)	2988	3282	9400	53
H(20B)	4796	3400	10415	53
H(20C)	3768	2862	10264	53
H(22A)	3063	5037	8976	55
H(22B)	4517	4647	9710	55
H(22C)	2656	4468	8769	55
H(23A)	7054	5399	8422	50
H(23B)	8846	5050	7806	50
H(23C)	8403	4980	9114	50
H(24)	1532	1951	552	39
H(25)	428	1469	-969	59
H(26)	3008	856	-1583	54
H(27)	6426	709	-549	47
H(28)	7514	1196	972	38
H(30)	7071	1976	1948	28

H(31)	2307	2348	2084	29
H(33)	1903	3143	2787	27
H(34)	6285	3706	2807	26
H(36)	5474	4626	3095	35
H(37)	3403	5287	2322	46
H(38)	-26	5175	1286	45
H(39)	-1464	4387	967	39
H(40)	624	3724	1699	33
H(42A)	6652	1514	4204	43
H(42B)	5268	1957	4743	43
H(42C)	7365	2062	3923	43
H(43A)	1268	1535	2531	48
H(43B)	1405	1613	3862	48
H(43C)	2813	1177	3309	48
H(45A)	6484	3618	5367	44
H(45B)	7358	3223	4492	44
H(45C)	5489	3075	5401	44
H(46A)	2336	3962	5105	46
H(46B)	1344	3420	5187	46
H(46C)	700	3747	4111	46

Table 5. Torsion angles [°] for 2008src0750.

C(6)-C(1)-C(2)-C(3)	0.5(11)
C(1)-C(2)-C(3)-C(4)	-1.2(11)
C(2)-C(3)-C(4)-C(5)	2.0(11)
C(3)-C(4)-C(5)-C(6)	-2.0(11)
C(2)-C(1)-C(6)-C(5)	-0.5(11)
C(2)-C(1)-C(6)-C(7)	-178.9(7)
C(4)-C(5)-C(6)-C(1)	1.2(10)
C(4)-C(5)-C(6)-C(7)	179.8(6)
C(1)-C(6)-C(7)-C(18)	-90.0(9)
C(5)-C(6)-C(7)-C(18)	91.5(8)
C(1)-C(6)-C(7)-C(8)	-15.6(10)
C(5)-C(6)-C(7)-C(8)	165.9(6)
C(6)-C(7)-C(8)-C(9)	134.8(6)
C(18)-C(7)-C(8)-C(9)	-111.8(7)
C(6)-C(7)-C(8)-C(18)	-113.4(7)
C(7)-C(8)-C(9)-O(1)	20.5(10)
C(18)-C(8)-C(9)-O(1)	-47.2(9)
C(7)-C(8)-C(9)-C(10)	-157.8(6)
C(18)-C(8)-C(9)-C(10)	134.5(6)
O(1)-C(9)-C(10)-C(11)	-16.6(10)
C(8)-C(9)-C(10)-C(11)	161.7(6)
O(1)-C(9)-C(10)-C(21)	51.6(10)
C(8)-C(9)-C(10)-C(21)	-130.1(7)
C(9)-C(10)-C(11)-C(12)	-135.1(6)
C(21)-C(10)-C(11)-C(12)	113.1(7)
C(9)-C(10)-C(11)-C(21)	111.8(7)
C(21)-C(11)-C(12)-C(13)	90.6(9)
C(10)-C(11)-C(12)-C(13)	16.5(10)
C(21)-C(11)-C(12)-C(17)	-92.1(8)
C(10)-C(11)-C(12)-C(17)	-166.2(6)
C(17)-C(12)-C(13)-C(14)	2.6(10)
C(11)-C(12)-C(13)-C(14)	179.9(7)
C(12)-C(13)-C(14)-C(15)	-3.1(12)
C(13)-C(14)-C(15)-C(16)	1.6(11)
C(14)-C(15)-C(16)-C(17)	0.2(11)
C(15)-C(16)-C(17)-C(12)	-0.7(12)

C(13)-C(12)-C(17)-C(16)	-0.7(10)
C(11)-C(12)-C(17)-C(16)	-178.2(7)
C(6)-C(7)-C(18)-C(19)	4.1(9)
C(8)-C(7)-C(18)-C(19)	-106.1(7)
C(6)-C(7)-C(18)-C(20)	-142.6(7)
C(8)-C(7)-C(18)-C(20)	107.2(7)
C(6)-C(7)-C(18)-C(8)	110.2(7)
C(9)-C(8)-C(18)-C(7)	104.6(7)
C(9)-C(8)-C(18)-C(19)	-147.4(7)
C(7)-C(8)-C(18)-C(19)	108.0(7)
C(9)-C(8)-C(18)-C(20)	-6.0(9)
C(7)-C(8)-C(18)-C(20)	-110.6(7)
C(12)-C(11)-C(21)-C(23)	-4.9(10)
C(10)-C(11)-C(21)-C(23)	105.0(7)
C(12)-C(11)-C(21)-C(22)	141.5(7)
C(10)-C(11)-C(21)-C(22)	-108.6(7)
C(12)-C(11)-C(21)-C(10)	-109.9(7)
C(9)-C(10)-C(21)-C(11)	-105.7(7)
C(9)-C(10)-C(21)-C(23)	144.4(7)
C(11)-C(10)-C(21)-C(23)	-109.8(7)
C(9)-C(10)-C(21)-C(22)	3.9(10)
C(11)-C(10)-C(21)-C(22)	109.6(7)
C(29)-C(24)-C(25)-C(26)	-2.2(12)
C(24)-C(25)-C(26)-C(27)	2.4(12)
C(25)-C(26)-C(27)-C(28)	-2.6(12)
C(26)-C(27)-C(28)-C(29)	2.4(11)
C(25)-C(24)-C(29)-C(28)	2.0(11)
C(25)-C(24)-C(29)-C(30)	-179.8(7)
C(27)-C(28)-C(29)-C(24)	-2.1(10)
C(27)-C(28)-C(29)-C(30)	179.6(6)
C(24)-C(29)-C(30)-C(31)	2.8(11)
C(28)-C(29)-C(30)-C(31)	-179.0(6)
C(24)-C(29)-C(30)-C(41)	76.8(9)
C(28)-C(29)-C(30)-C(41)	-105.0(7)
C(29)-C(30)-C(31)-C(32)	-135.8(6)
C(41)-C(30)-C(31)-C(32)	111.4(6)
C(29)-C(30)-C(31)-C(41)	112.8(7)
C(30)-C(31)-C(32)-O(2)	-10.4(10)

C(41)-C(31)-C(32)-O(2)	59.3(9)
C(30)-C(31)-C(32)-C(33)	170.3(6)
C(41)-C(31)-C(32)-C(33)	-120.0(7)
O(2)-C(32)-C(33)-C(34)	20.9(9)
C(31)-C(32)-C(33)-C(34)	-159.8(6)
O(2)-C(32)-C(33)-C(44)	-47.5(9)
C(31)-C(32)-C(33)-C(44)	131.9(6)
C(32)-C(33)-C(34)-C(35)	137.0(6)
C(44)-C(33)-C(34)-C(35)	-112.3(7)
C(32)-C(33)-C(34)-C(44)	-110.7(6)
C(44)-C(34)-C(35)-C(40)	-86.4(9)
C(33)-C(34)-C(35)-C(40)	-13.5(10)
C(44)-C(34)-C(35)-C(36)	94.3(8)
C(33)-C(34)-C(35)-C(36)	167.3(6)
C(40)-C(35)-C(36)-C(37)	0.4(10)
C(34)-C(35)-C(36)-C(37)	179.8(6)
C(35)-C(36)-C(37)-C(38)	0.4(11)
C(36)-C(37)-C(38)-C(39)	-0.6(12)
C(37)-C(38)-C(39)-C(40)	-0.1(11)
C(36)-C(35)-C(40)-C(39)	-1.2(11)
C(34)-C(35)-C(40)-C(39)	179.5(6)
C(38)-C(39)-C(40)-C(35)	1.0(11)
C(29)-C(30)-C(41)-C(42)	137.6(7)
C(31)-C(30)-C(41)-C(42)	-110.5(7)
C(29)-C(30)-C(41)-C(43)	-7.3(9)
C(31)-C(30)-C(41)-C(43)	104.7(7)
C(29)-C(30)-C(41)-C(31)	-112.0(7)
C(32)-C(31)-C(41)-C(42)	0.2(10)
C(30)-C(31)-C(41)-C(42)	106.0(7)
C(32)-C(31)-C(41)-C(43)	145.1(6)
C(30)-C(31)-C(41)-C(43)	-109.1(7)
C(32)-C(31)-C(41)-C(30)	-105.9(7)
C(35)-C(34)-C(44)-C(45)	-139.6(7)
C(33)-C(34)-C(44)-C(45)	109.8(7)
C(35)-C(34)-C(44)-C(46)	4.8(9)
C(33)-C(34)-C(44)-C(46)	-105.7(7)
C(35)-C(34)-C(44)-C(33)	110.5(7)
C(32)-C(33)-C(44)-C(45)	-4.8(10)

C(34)-C(33)-C(44)-C(45)	-110.3(7)
C(32)-C(33)-C(44)-C(34)	105.4(7)
C(32)-C(33)-C(44)-C(46)	-146.9(7)
C(34)-C(33)-C(44)-C(46)	107.6(7)

Abbreviations

A	Ampere
Ac	Acetyl
AIBN	2,2′-Azo*bis*(2-methylpropionitrile)
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
Bu	Butyl
ca	*Circa*
Calcd.	Calculated
CAN	Ceric ammonium nitrate
CI	Chemical ionisation
conc.	Concentrated
CPBA	Chloroperbenzoic acid
δ	Chemical shift
Δ	Heat/reflux
d	Doublet
DBA	Dibenzylideneacetone
DCC	*N,N*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DEPT	Distortionless enhancement by polarisation transfer
Ø	Diameter

DMAP	4-*N*,*N*-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
EI	Electron ionisation
ESI	Electrospray ionisation
Et	Ethyl
eq	Equivalent
Fur	Furyl
g	Gram(s)
h	Hour(s)
HRMS	High resolution mass spectrometry
hν	Light
Hz	Hertz
i	*Iso*
IBX	Iodoxybenzoic acid
IPA	*iso*-Propyl alcohol
IR	Infra-red
J	Coupling constant
KDMO	Potassium 3,7-dimethyl-3-octylate
L	Litre(s)
LDA	Lithium di*iso*propylamide
Lit.	Literature

m	Multiplet
m	*Meta*
M	Molar
M^+	Molecular ion
Me	Methyl
min	Minute(s)
MK10	Montmorillonite K10
mL	Millilitre(s)
mmol	Millimole
mol sieves	Molecular sieves
mp	Melting point
Ms	Methanesulfonic
MS	Mass spectrometry
MTBD	7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
μW	Microwave
m/z	Mass to charge ratio
n	Normal
Nap	Naphthyl
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic resonance
o	*Ortho*
p	*Para*
PCC	Pyridinium chlorochromate
Ph	Phenyl
PhMe	Toluene

PLE	Pig-liver esterase
PMB	*para*-Methoxybenzyl
ppm	Parts per million
PPO	Pyrophosphate
Pr	Propyl
Py	Pyridine
Pyr	Pyridyl
q	Quartet
R	Alkyl group (unspecified)
R_f	Retention factor
rt	Room temperature
RSM	Recovered starting material
s	Singlet
(*S*)-*t*-Bu-phox	(*S*)-4-*tert*-Butyl-2-[2-(diphenylphosphino)phenyl]-2-oxazoline
t	Triplet
t	*Tert*
T3P	Propylphosphonic anhydride
Tf	Trifluoromethanesulfonic
TFA	Trifluoroacetic acid
TFPAA	Trifluoroperacetic acid
THF	Tetrahydrofuran
Thi	Thiophenyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TOP	Tandem Oxidation Process

TPAP	Tetra-*n*-propylammonium perruthenate
TSA	Toluenesulfonic acid
v	Volume
w	Weight

References

1. L. F. Tietze, G. Brasche and K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, 2006.
2. P. J. Parsons, C. S. Penkett and A. J. Shell, *Chem. Rev.*, 1996, **96**, 195-206.
3. T.-L. Ho, *Tandem Organic Reactions*, Wiley-Interscience, 1992.
4. R. J. K. Taylor, M. Reid, J. Foot and S. A. Raw, *Acc. Chem. Res.*, 2005, **38**, 851-869.
5. R. E. Ireland and D. W. Norbeck, *J. Org. Chem.*, 1985, **50**, 2198-2200.
6. C. C. Huang, *J. Labelled Compd. Rad.*, 1987, **24**, 675-681.
7. D. Crich, D. Crich and X.-S. Mo, *Synlett*, 1999, 67-68.
8. S. Shuto, S. Niizuma and A. Matsuda, *J. Org. Chem.*, 1998, **63**, 4489-4493.
9. R. N. MacCoss, E. P. Balskus and S. V. Ley, *Tetrahedron Lett.*, 2003, **44**, 7779-7781.
10. A. R. Bressette and L. C. Glover Iv, *Synlett*, 2004, 738-740.
11. F. R. Pinacho Crisóstomo, R. Carrillo, T. s. Martín, F. García-Tellado and V. S. Martín, *J. Org. Chem.*, 2005, **70**, 10099-10101.
12. A. G. M. Barrett, D. Hamprecht and M. Ohkubo, *J. Org. Chem.*, 1997, **62**, 9376-9378.
13. L. Alcaraz, G. Macdonald, J. P. Ragot, N. Lewis and R. J. K. Taylor, *J. Org. Chem.*, 1998, **63**, 3526-3527.
14. S. Ball, T. W. Goodwin and R. A. Morton, *Biochem. J.*, 1948, **42**, 516-523.
15. R. J. Gritter and T. J. Wallace, *J. Org. Chem.*, 1959, **24**, 1051-1056.
16. E. P. Papadopoulos, A. Jarrar and C. H. Issidorides, *J. Org. Chem.*, 1966, **31**, 615-616.
17. H. J. Knölker, *J. Prakt. Chem.*, 1995, **337**, 75-77.
18. R. M. Evans, *Quart. Rev. Chem. Soc.*, 1959, **13**, 61-70.
19. S. P. Korshunov and L. I. Vereshchagin, *Russ. Chem. Rev.*, 1966, **35**, 942-957.
20. A. J. Fatiadi, *Synthesis*, 1976, 65-104.

21. A. J. Fatiadi, *Synthesis*, 1976, 133-167.
22. A. Soldatenkov, K. Polyanskii, N. Kolyadina and S. Soldatova, *Chem. Heterocycl. Compd.*, 2009, **45**, 633-657.
23. X. Wei and R. J. K. Taylor, *Tetrahedron Lett.*, 1998, **39**, 3815-3818.
24. X. Wei and R. J. K. Taylor, *J. Org. Chem.*, 1999, **65**, 616-620.
25. K. A. Runcie and R. J. K. Taylor, *Chem. Commun.*, 2002, 974-975.
26. L. Blackburn, C. Pei and R. J. K. Taylor, *Synlett*, 2002, 215-218.
27. L. Blackburn, H. Kanno and R. J. K. Taylor, *Tetrahedron Lett.*, 2003, **44**, 115-118.
28. M. Reid, D. J. Rowe and R. J. K. Taylor, *Chem. Commun.*, 2003, 2284-2285.
29. S. A. Raw, M. Reid, E. Roman and R. J. K. Taylor, *Synlett*, 2004, 819-822.
30. S. Lang and R. J. K. Taylor, *Tetrahedron Lett.*, 2006, **47**, 5489-5492.
31. R. J. K. Taylor, L. Campbell, G. D. McAllister, R. Webster and M. Lautens, *Org. Synth.*, 2008, **85**, 15-26.
32. S. Beltran-Rodil, M. G. Edwards, D. S. Pugh, M. Reid and R. J. K. Taylor, *Synlett*, 2010, 602-606.
33. L. Blackburn, X. Wei and R. J. K. Taylor, *Chem. Commun.*, 1999, 1337-1338.
34. H. S. Outram, S. A. Raw and R. J. K. Taylor, *Tetrahedron Lett.*, 2002, **43**, 6185-6187.
35. E. Quesada and R. J. K. Taylor, *Tetrahedron Lett.*, 2005, **46**, 6473-6476.
36. C. L. Moody, D. S. Pugh and R. J. K. Taylor, *Tetrahedron Lett.*, 2011, **52**, 2511-2514.
37. J. S. Foot, H. Kanno, G. M. P. Giblin and R. J. K. Taylor, *Synlett*, 2002, 1293-1295.
38. J. S. Foot, H. Kanno, G. M. P. Giblin and R. J. K. Taylor, *Synthesis*, 2003, 1055-1064.
39. L. Blackburn and R. J. K. Taylor, *Org. Lett.*, 2001, **3**, 1637-1639.
40. H. Kanno and R. J. K. Taylor, *Tetrahedron Lett.*, 2002, **43**, 7337-7340.
41. G. D. McAllister, C. D. Wilfred and R. J. K. Taylor, *Synlett*, 2002, 1291-1292.
42. H. Kanno and R. J. K. Taylor, *Synlett*, 2002, 1287-1290.

43. S. A. Raw, C. D. Wilfred and R. J. K. Taylor, *Chem. Commun.*, 2003, 2286-2287.
44. S. Laphookhieo, S. Jones, S. A. Raw, Y. F. Sainz and R. J. K. Taylor, *Tetrahedron Lett.*, 2006, **47**, 3865-3870.
45. C. D. Wilfred and R. J. K. Taylor, *Synlett*, 2004, 1628-1630.
46. G. D. McAllister, M. F. Oswald, R. J. Paxton, S. A. Raw and R. J. K. Taylor, *Tetrahedron*, 2006, **62**, 6681-6694.
47. E. J. Corey, N. W. Gilman and B. E. Ganem, *J. Am. Chem. Soc.*, 1968, **90**, 5616-5617.
48. E. Quesada, S. A. Raw, M. Reid, E. Roman and R. J. K. Taylor, *Tetrahedron*, 2006, **62**, 6673-6680.
49. G. B. Payne, *J. Org. Chem.*, 1967, **32**, 3351-3355.
50. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1962, **84**, 867-868.
51. A. Perry and R. J. K. Taylor, *Chem. Commun.*, 2009, 3249-3251.
52. A. Freund, *J. Prakt. Chem.*, 1882, **26**, 367-377.
53. A. Freund, *Monatsh. Chem.*, 1882, **3**, 625-635.
54. A. D. Walsh, *Trans. Faraday Soc.*, 1949, **45**, 179-190.
55. C. A. Coulson and W. E. Moffitt, *J. Chem. Phys.*, 1947, **15**, 151.
56. L. Pauling, *J. Am. Chem. Soc.*, 1931, **53**, 1367-1400.
57. A. de Meijere, *Angew. Chem. Int. Ed.*, 1979, **18**, 809-826.
58. K. B. Wiberg, *Acc. Chem. Res.*, 1996, **29**, 229-234.
59. J. G. Hamilton and W. E. Palke, *J. Am. Chem. Soc.*, 1993, **115**, 4159-4164.
60. M. Y. Lukina, *Russ. Chem. Rev.*, 1962, **31**, 419-439.
61. H. N. C. Wong, M. Y. Hon, C. W. Tse, Y. C. Yip, J. Tanko and T. Hudlicky, *Chem. Rev.*, 1989, **89**, 165-198.
62. L. A. Wessjohann, W. Brandt and T. Thiemann, *Chem. Rev.*, 2003, **103**, 1625-1648.
63. S. Gao, H.-Y. Liu, Y.-H. Wang, H.-P. He, J.-S. Wang, Y.-T. Di, C.-S. Li, X. Fang and X.-J. Hao, *Org. Lett.*, 2007, **9**, 3453-3455.
64. M. Yoshida, M. Ezaki, M. Hashimoto, M. Yamashita, N. Shigematsu and M. Okuhara, *J. Antibiot.*, 1990, **43**, 748-754.
65. *British National Formulary*, 2008, **56**, 321-322.

66. N. A. McGrath, M. Brichacek and J. T. Njardarson, *J. Chem. Ed.*, 2010, **87**, 1348-1349.
67. H. Staudinger and L. Ruzicka, *Helv. Chim. Acta*, 1924, **7**, 177-201.
68. I. G. M. Campbell and S. H. Harper, *J. Sci. Food. Agr.*, 1952, **3**, 189-192.
69. R. Faust, *Angew. Chem. Int. Ed.*, 2001, **40**, 2251-2253.
70. K. Osawa, H. Yasuda, H. Morita, K. Takeya and H. Itokawa, *Phytochemistry*, 1995, **40**, 183-184.
71. W. W. Epstein and C. D. Poulter, *Phytochemistry*, 1973, **12**, 737-747.
72. W. H. Perkin, *J. Chem. Soc., Trans.*, 1885, **47**, 801-855.
73. W. A. Bone and W. H. Perkin, *J. Chem. Soc., Trans.*, 1895, **67**, 108-119.
74. H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, 1958, **80**, 5323-5324.
75. H. E. Simmons, T. L. Cairns, S. A. Vladuchick and C. M. Hoiness, *Organic Reactions*, 1973, **20**, 1-131.
76. A. B. Charette and A. Beauchemin, *Simmons-Smith Cyclopropanation Reaction*, John Wiley & Sons, Inc., 2004.
77. R. Shank and H. Shechter, *J. Org. Chem.*, 1959, **24**, 1825-1826.
78. J. M. Denis, C. Girard and J. M. Conia, *Synthesis*, 1972, 549-551.
79. G. Wittig and K. Schwarzenbach, *Angew. Chem.*, 1959, **71**, 652-652.
80. J. Furukawa, N. Kawabata and J. Nishimura, *Tetrahedron Lett.*, 1966, **7**, 3353-3354.
81. S. E. Denmark and J. P. Edwards, *J. Org. Chem.*, 1991, **56**, 6974-6981.
82. A. Voituriez, L. E. Zimmer and A. B. Charette, *J. Org. Chem.*, 2010, **75**, 1244-1250.
83. H. Takahashi, M. Yoshioka, M. Ohno and S. Kobayashi, *Tetrahedron Lett.*, 1992, **33**, 2575-2578.
84. H. Shitama and T. Katsuki, *Angew. Chem. Int. Ed.*, 2008, **47**, 2450-2453.
85. H. Y. Kim, A. E. Lurain, P. Garcia-Garcia, P. J. Carroll and P. J. Walsh, *J. Am. Chem. Soc.*, 2005, **127**, 13138-13139.
86. J. Furukawa, N. Kawabata and J. Nishimura, *Tetrahedron*, 1968, **24**, 53-58.
87. H. M. Walborsky and L. Plonsker, *J. Am. Chem. Soc.*, 1961, **83**, 2138-2144.

88. C. Kaiser, J. Weinstock, M. P. Olmstead, W. E. Parham, W. E. Noland, P. Cahill and T. S. Straub, *Org. Synth.*, 1970, **50**, 94-96.
89. R. Paulissen, H. Reimlinger, E. Hayez, A. J. Hubert and P. Teyssié, *Tetrahedron Lett.*, 1973, **14**, 2233-2236.
90. R. G. Salomon, M. F. Salomon and T. R. Heyne, *J. Org. Chem.*, 1975, **40**, 756-760.
91. G. Maas, *Chem. Soc. Rev.*, 2004, **33**, 183-190.
92. H. l. n. Lebel, J.-F. o. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977-1050.
93. W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, 1954, **76**, 6162-6165.
94. M.-X. Wang, G.-Q. Feng and Q.-Y. Zheng, *Adv. Synth. Catal.*, 2003, **345**, 695-698.
95. M. Fedorynski, *Chem. Rev.*, 2003, **103**, 1099-1132.
96. F. Krollpfeiffer and H. Hartmann, *Chem. Ber.*, 1950, **83**, 90-98.
97. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353-1364.
98. H. J. Bestmann and F. Seng, *Angew. Chem. Int. Ed.*, 1962, **1**, 116-117.
99. H. Yaozeng, S. Yanchang, F. G. A. Stone and R. West, in *Advances in Organometallic Chemistry*, Academic Press, 1982, vol. 20, pp. 115-157.
100. Y.-Z. Huang, Y. Tang and Z.-L. Zhou, *Tetrahedron*, 1998, **54**, 1667-1690.
101. Y.-Z. Huang, Y. Tang, Z.-L. Zhou, W. Xia and L.-P. Shi, *J. Chem. Soc., Perkin Trans. 1*, 1994, 893-896.
102. Y. Tang, S. Ye, Z.-Z. Huang and Y.-Z. Huang, *Heteroatom Chem.*, 2002, **13**, 463-466.
103. H. Jiang, X.-L. Sun, C.-Y. Zhu, L.-X. Dai and Y. Tang, *Tetrahedron*, 2008, **64**, 5032-5035.
104. H. Jiang, X. Deng, X. Sun, Y. Tang and L.-X. Dai, *J. Org. Chem.*, 2005, **70**, 10202-10205.
105. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1962, **84**, 3782-3783.
106. K. W. Ratts and A. N. Yao, *J. Org. Chem.*, 1966, **31**, 1185-1188.
107. E. J. Corey, M. Jautelat and W. Oppolzer, *Tetrahedron Lett.*, 1967, **8**, 2325-2328.
108. R. Major and H.-J. Hess, *J. Org. Chem.*, 1958, **23**, 1563-1564.

109. N. J. Leonard and C. R. Johnson, *J. Am. Chem. Soc.*, 1962, **84**, 3701-3710.
110. M. F. Oswald, S. A. Raw and R. J. K. Taylor, *Chem. Commun.*, 2005, 2253-2255.
111. B. M. Trost and R. F. Hammen, *J. Am. Chem. Soc.*, 1973, **95**, 962-964.
112. A.-H. Li, L.-X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341-2372.
113. E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.*, 1967, **89**, 3911-3912.
114. J. N. Pitts, D. G. Marsh, K. Schaffner and A. Tuinman, *J. Am. Chem. Soc.*, 1971, **93**, 333-338.
115. E. J. Corey and M. Jautelat, *J. Am. Chem. Soc.*, 1967, **89**, 3912-3914.
116. C. R. Johnson and E. R. Janiga, *J. Am. Chem. Soc.*, 1973, **95**, 7692-7700.
117. M. J. Devos, L. Hevesi, P. Bayet and A. Krief, *Tetrahedron Lett.*, 1976, **17**, 3911-3914.
118. M. J. De Vos and A. Krief, *Tetrahedron Lett.*, 1983, **24**, 103-106.
119. N. Ono, T. Yanai, I. Hamamoto, A. Kamimura and A. Kaji, *J. Org. Chem.*, 1985, **50**, 2806-2807.
120. A. Krief, L. Hevesi, G. Chaboteaux, P. Mathy, M. Sevrin and M. J. De Vos, *J. Chem. Soc., Chem. Commun.*, 1985, 1693-1695.
121. A. Krief and M. J. De Vos, *Tetrahedron Lett.*, 1985, **26**, 6115-6116.
122. A. B. Charette and N. Wilb, *Synlett*, 2002, 176-178.
123. S. Sengmany, E. Léonel, J. P. Paugam and J.-Y. Nédélec, *Tetrahedron*, 2002, **58**, 271-277.
124. M. Franck-Neumann, *Angew. Chem. Int. Ed.*, 1968, **7**, 65-66.
125. H. Matsuyama, T. Nakamura and M. Iyoda, *J. Org. Chem.*, 2000, **65**, 4796-4803.
126. B. Badet and M. Julia, *Tetrahedron Lett.*, 1979, **20**, 1101-1104.
127. S. E. Sen, Y. z. Zhang and S. L. Roach, *J. Org. Chem.*, 1996, **61**, 9534-9537.
128. R. D. Miller, A. F. Renaldo and H. Ito, *J. Org. Chem.*, 1988, **53**, 5571-5573.
129. R. J. Paxton, *Development of novel tandem oxidation processes*, 2008, **Ph.D Thesis**, University of York.

130. M. Mori, H. Takeuchi, H. Minato, M. Kobayashi, M. Yoshida, H. Matsuyama and N. Kamigata, *Phosphorus Sulfur Silicon Relat. Elem.*, 1990, **47**, 157-164.
131. M. Kobayashi, K. Umemura, N. Watanabe and H. Matsuyama, *Chem. Lett.*, 1985, **14**, 1067-1070.
132. K. Okuma, H. Takeuchi, H. Ohta and H. Matsuyama, *Bull. Chem. Soc. Jap.*, 1991, **64**, 315-317.
133. *United States Pat.*, 4625065, 1986.
134. J. Forrester, R. V. H. Jones, P. N. Preston and E. S. C. Simpson, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2289-2291.
135. C. Djerassi and R. R. Engle, *J. Am. Chem. Soc.*, 1953, **75**, 3838-3840.
136. L. M. Berkowitz and P. N. Rylander, *J. Am. Chem. Soc.*, 1958, **80**, 6682-6684.
137. M. G. Edwards, R. J. Paxton, D. S. Pugh, A. C. Whitwood and R. J. K. Taylor, *Synthesis*, 2008, 3279-3288.
138. *United States Pat.*, 5576461, 1996.
139. W. Fresenius, J. F. K. Huber, E. Pungor, G. A. Rechnitz, W. Simon and T. S. West, *Spectral data for structure determination of organic compounds*, Springer-Verlag, 1989.
140. D. C. G. A. Pinto, A. M. S. Silva, A. Levai, J. A. S. Cavaleiro, T. Patonay and J. Elguero, *Eur. J. Org. Chem.*, 2000, 2593-2599.
141. Y. G. Gololobov, A. N. Nesmeyanov, V. P. lysenko and I. E. Boldeskul, *Tetrahedron*, 1987, **43**, 2609-2651.
142. E. Piers, J. Banville, C. K. Lau and I. Nagakura, *Can. J. Chem.*, 1982, **60**, 2965-2975.
143. S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815-3818.
144. C. R. Johnson, M. Haake and C. W. Schroeck, *J. Am. Chem. Soc.*, 1970, **92**, 6594-6598.
145. J. Cossy, N. Furet and S. BouzBouz, *Tetrahedron*, 1995, **51**, 11751-11764.
146. J. A. Ciaccio and C. E. Aman, *Synth. Commun.*, 2006, **36**, 1333-1341.
147. R. F. Borne, M. L. Forrester and I. W. Waters, *J. Med. Chem.*, 1977, **20**, 771-776.
148. M.-X. Wang and G.-Q. Feng, *New J. Chem.*, 2002, **26**, 1575-1583.

149. M. G. Edwards, D. S. Pugh, A. C. Whitwood and R. J. K. Taylor, *Acta Crystallogr. C*, 2009, **65**, o39-o41.
150. D. A. Engel and G. B. Dudley, *Org. Lett.*, 2006, **8**, 4027-4029.
151. M. J. Gentles, J. B. Moss, H. L. Herzog and E. B. Hershberg, *J. Am. Chem. Soc.*, 1958, **80**, 3702-3705.
152. M. G. Edwards, R. J. Paxton, D. S. Pugh and R. J. K. Taylor, *Synlett*, 2008, 521-524.
153. H. J. Sanders and A. W. Taff, *Ind. Eng. Chem.*, 1954, **46**, 414-426.
154. T. R. Roberts and D. H. Hutson, in *Metabolic Pathways of Agrochemicals: Part 2 Insecticides and Fungicides*, The Royal Society of Chemistry, 1999, pp. 579-726.
155. M. Elliott and N. F. Janes, *Chem. Soc. Rev.*, 1978, **7**, 473-505.
156. I. G. M. Campbell and S. H. Harper, *J. Chem. Soc.*, 1945, 283-286.
157. T. Aratani, *Pure Appl. Chem.*, 1985, **57**, 1839-1844.
158. A. Krief, W. Dumont and P. Pasau, *Tetrahedron Lett.*, 1988, **29**, 1079-1082.
159. A. Krief, D. Surleraux and H. Frauenrath, *Tetrahedron Lett.*, 1988, **29**, 6157-6160.
160. A. Krief, D. Surleraux and N. Ropson, *Tetrahedron: Asymmetry*, 1993, **4**, 289-292.
161. A. Krief, T. Ollevier and W. Dumont, *J. Org. Chem.*, 1997, **62**, 1886-1890.
162. J. Martel and C. Huynh, *Bull. Chim. Soc. Fr.*, 1967, 985-986.
163. P. F. Schatz, *J. Chem. Ed.*, 1978, **55**, 468-470.
164. D. Arlt, M. Jautelat and R. Lantzsch, *Angew. Chem. Int. Ed.*, 1981, **20**, 703-722.
165. I. J. Jakovac, H. B. Goodbrand, K. P. Lok and J. B. Jones, *J. Am. Chem. Soc.*, 1982, **104**, 4659-4665.
166. P. Walser, P. Renold, V. N'Goka, F. Hosseinzadeh and C. Tamm, *Helv. Chim. Acta*, 1991, **74**, 1941-1952.
167. C. A. Carson and M. A. Kerr, *Chem. Soc. Rev.*, 2009, **38**, 3051-3060.
168. W. S. Murphy and S. Wattanasin, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2920-2926.

169. R. M. Beesley, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc., Trans.*, 1915, **107**, 1080-1106.
170. A. T. Merritt and S. V. Ley, *Nat. Prod. Rev.*, 1992, **9**, 243-287.
171. A. M. Bernard, A. Frongia, P. P. Piras, F. Secci and M. Spiga, *Org. Lett.*, 2005, **7**, 4565-4568.
172. C. R. Engel, A. F. d. Krassny, A. Bélanger and G. Dionne, *Can. J. Chem.*, 1973, **51**, 3263-3271.
173. *Reaxys literature search, September 2011*.
174. W. Xu, W. R. Dolbier and J. Salazar, *J. Org. Chem.*, 2008, **73**, 3535-3538.
175. L. Greiner-Bechert, T. Sprang and H.-H. Otto, *Monatsh. Chem.*, 2005, **136**, 635-653.
176. W. S. Murphy and K. Hantawong, *J. Chem. Res. (S)*, 1988, 318-319.
177. W. S. Murphy and S. Wattanasin, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1029-1035.
178. H. E. Zimmerman and W. Eberbach, *J. Am. Chem. Soc.*, 1973, **95**, 3970-3976.
179. B. M. Trost and M. K. Brennan, *Synthesis*, 2009, 3003-3025.
180. A. Millemaggi and R. J. K. Taylor, *Eur. J. Org. Chem.*, 2010, 4527-4547.
181. C. V. Galliford and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2007, **46**, 8748-8758.
182. A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schurmann, H. Preut, S. Ziegler, D. Rauh and H. Waldmann, *Nat. Chem.*, 2010, **2**, 735-740.
183. W. C. Sumpter, *Chem. Rev.*, 1945, **37**, 443-479.
184. C. Marti and Erick M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209-2219.
185. T. Koshiba, Y. Kamiya and M. Iino, *Plant Cell Physiol.*, 1995, **36**, 1503-1510.
186. S. R. S. Rudrangi, V. K. Bontha, V. R. Manda and S. Bethi, *Asian J. Res. Chem.*, 2011, **4**, 335-338.
187. *British National Formulary*, 2008, **56**, 264.
188. *British National Formulary*, 2008, **56**, 476.
189. *Food and Drug Administration, U.S. Gov.*, NDA 21483.
190. A. Baeyer and C. A. Knop, *Liebigs Ann.*, 1866, **140**, 1-38.

191. J. S. Russel, *Top. Het. Chem.*, 2011, **26**, 397-431.

192. F. Zhou, Y.-L. Liu and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381-1407.

193. B. Volk and G. Simig, *Eur. J. Org. Chem.*, 2003, 3991-3996.

194. M. G. Kulkarni, A. P. Dhondge, S. W. Chavhan, A. S. Borhade, Y. B. Shaikh, D. R. Birhade, M. P. Desai and N. R. Dhatrak, *Beilstein J. Org. Chem.*, 2010, **6**, 876-879.

195. F. Broeders, L. Defreİ€re, M.-F. Deltent, F. Driessens, F. d. r. Gilson, L. Grooters, X. Ikonomakos, F. d. r. Limauge, E. Sergeef and N. Verstraeten, *Org. Process Res. Dev.*, 2009, **13**, 442-449.

196. A. S. Kende and J. C. Hodges, *Synth. Commun.*, 1982, **12**, 1-10.

197. E. Wenkert, N. K. Bhattacharyya, T. L. Reid and T. E. Stevens, *J. Am. Chem. Soc.*, 1956, **78**, 797-801.

198. E. Wenkert, A. K. Bose and T. L. Reid, *J. Am. Chem. Soc.*, 1953, **75**, 5514-5516.

199. S. P. Marsden, E. L. Watson and S. A. Raw, *Org. Lett.*, 2008, **10**, 2905-2908.

200. K. H. Shaughnessy, B. C. Hamann and J. F. Hartwig, *J. Org. Chem.*, 1998, **63**, 6546-6553.

201. A. B. Dounay, K. Hatanaka, J. J. Kodanko, M. Oestreich, L. E. Overman, L. A. Pfeifer and M. M. Weiss, *J. Am. Chem. Soc.*, 2003, **125**, 6261-6271.

202. E. J. Hennessy and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 12084-12085.

203. A. H. Beckett, R. W. Daisley and J. Walker, *Tetrahedron*, 1968, **24**, 6093-6109.

204. K. Jones and J. M. D. Storey, *Arkivoc*, 2000, **5**, 755-768.

205. K. Jones and J. M. D. Storey, *Tetrahedron Lett.*, 1993, **34**, 7797-7798.

206. K. Jones, M. Thompson and C. Wright, *J. Chem. Soc., Chem. Commun.*, 1986, 115-116.

207. K. Jones, S. A. Brunton and R. Gosain, *Tetrahedron Lett.*, 1999, **40**, 8935-8938.

208. T. Kaneko, M. Matsuo and Y. Iitaka, *Chem. Pharm. Bull.*, 1981, **29**, 3499-3506.

209. P. Manini, M. d'Ischia, M. Milosa and G. Prota, *J. Org. Chem.*, 1998, **63**, 7002-7008.

210. S. Hu, J. Huang, L. Mei, Q. Yu, S. Yao and Z. Jin, *J. Mol. Catal. B: Enzym.*, 2010, **67**, 29-35.

211. R. Lichtenecker and W. Schmid, *Monatsh. Chem.*, 2009, **140**, 509-512.

212. S. A. Shaw, P. Aleman, J. Christy, J. W. Kampf, P. Va and E. Vedejs, *J. Am. Chem. Soc.*, 2005, **128**, 925-934.

213. S. Takase, I. Uchida, H. Tanaka and H. Aoki, *Tetrahedron*, 1986, **42**, 5879-5886.

214. X. Zhang and C. S. Foote, *J. Am. Chem. Soc.*, 1993, **115**, 8867-8868.

215. R. G. Alvarez, I. S. Hunter, C. J. Suckling, M. Thomas and U. Vitinius, *Tetrahedron*, 2001, **57**, 8581-8587.

216. A. Millemaggi, A. Perry, A. C. Whitwood and R. J. K. Taylor, *Eur. J. Org. Chem.*, 2009, 2947-2952.

217. J. Lubkoll, A. Millemaggi, A. Perry and R. J. K. Taylor, *Tetrahedron*, 2010, **66**, 6606-6612.

218. Y.-X. Jia and E. P. Kündig, *Angew. Chem. Int. Ed.*, 2009, **48**, 1636-1639.

219. J. H. K. K. Hirschberg, R. A. Koevoets, R. P. Sijbesma and E. W. Meijer, *Chem. Eur. J.*, 2003, **9**, 4222-4231.

220. Y. Saito, T. Watanabe, H. Hashimoto and J. Yoshimura, *Carbohydr. Res.*, 1987, **169**, 171-188.

221. F. Gao, X. Yan, T. Shakya, O. M. Baettig, S. Ait-Mohand-Brunet, A. M. Berghuis, G. D. Wright and K. Auclair, *J. Med. Chem.*, 2006, **49**, 5273-5281.

222. V. I. Tararov, A. Korostylev, G. Konig and A. Borner, *Synth. Commun.*, 2006, **36**, 187-191.

223. R. Shelkov, M. Nahmany and A. Melman, *J. Org. Chem.*, 2002, **67**, 8975-8982.

224. P. J. Kocienski, *Protecting Groups*, 3rd edn., Thieme, 2005.

225. R. J. Abraham, G. R. Bedford and B. Wright, *Org. Mag. Res.*, 1982, **18**, 45-52.

226. D. S. Pugh, J. E. M. N. Klein, A. Perry and R. J. K. Taylor, *Synlett*, 2010, 934-938.

227. J. E. M. N. Klein, A. Perry, D. S. Pugh and R. J. K. Taylor, *Org. Lett.*, 2010, **12**, 3446-3449.
228. J. Muzart, *Tetrahedron*, 2009, **65**, 8313-8323.
229. J. Tsuji and I. Minami, *Acc. Chem. Res.*, 1987, **20**, 140-145.
230. J. T. Mohr, D. C. Behenna, A. M. Harned and B. M. Stoltz, *Angew. Chem. Int. Ed.*, 2005, **44**, 6924-6927.
231. C.-n. Xia, H.-b. Li, F. liu and W.-x. Hu, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 6553-6557.
232. V. Franckevicius, J. D. Cuthbertson, D. S. Pugh and R. J. K. Taylor, *Org. Lett.*, 2011, **13**, 4264-4267.
233. B. M. Trost and M. K. Brennan, *Org. Lett.*, 2006, **8**, 2027-2030.
234. R. E. Lutz and R. H. Jordan, *J. Am. Chem. Soc.*, 1950, **72**, 4090-4091.
235. H. E. Zimmerman and A. Pushechnikov, *Eur. J. Org. Chem.*, 2006, 3491-3497.
236. R. Adams, J. W. Kern and R. L. Shriner, *Org. Synth.*, Collective Volume 1, 101-102.
237. M. S. Kwon, N. Kim, S. H. Seo, I. S. Park, R. K. Cheedrala and J. Park, *Angew. Chem. Int. Ed.*, 2005, **44**, 6913-6915.
238. U. B. Roland, A. Markus and J. J. M. Thomas, *Chem. Eur. J.*, 2006, **12**, 9081-9094.
239. C. S. Marvel, L. E. Coleman and G. P. Scott, *J. Org. Chem.*, 1955, **20**, 1785-1792.
240. Y.-M. Lin, Y. Zhou, M. T. Flavin, L.-M. Zhou, W. Nie and F.-C. Chen, *Bioorg. Med. Chem.*, 2002, **10**, 2795-2802.
241. W. Herz and J. A. Y. Brasch, *J. Org. Chem.*, 1958, **23**, 1513-1516.
242. K. Alexander and G. H. Smith, *J. Am. Chem. Soc.*, 1949, **71**, 735-737.
243. A. S. Demir, C. Tanyeli, A. Cagir, M. N. Tahir and D. Ulku, *Tetrahedron: Asymmetry*, 1998, **9**, 1035-1042.
244. H.-H. Ko, L.-T. Tsao, K.-L. Yu, C.-T. Liu, J.-P. Wang and C.-N. Lin, *Bioorg. Med. Chem.*, 2003, **11**, 105-111.
245. K. Alexander, L. S. Hafner, G. H. Smith and L. E. Schniepp, *J. Am. Chem. Soc.*, 1950, **72**, 5506-5507.

246. Y. Jahng, L.-X. Zhao, Y.-S. Moon, A. Basnet, E.-k. Kim, H. W. Chang, H. K. Ju, T. C. Jeong and E.-S. Lee, *Bioorg. Med. Chem.*, 2004, **14**, 2559-2562.

247. J. Lachheb, M.-T. Martin and A.-K. Khemiss, *Tetrahedron Lett.*, 1999, **40**, 9029-9031.

248. L. A. Babadzhanova, N. V. Kirij, Y. L. Yagupolskii, W. Tyrra and D. Naumann, *Tetrahedron*, 2005, **61**, 1813-1819.

249. T. Hiyama, G. B. Reddy, T. Minami and T. Hanamoto, *Bull. Chem. Soc. Jap.*, 1995, **68**, 350-363.

250. L. De Luca, G. Giacomelli and M. Taddei, *J. Org. Chem.*, 2001, **66**, 2534-2537.

251. S. Kohmoto, H. Kasimura, T. Nishio, I. Iida, K. Kishikawa, M. Yamamoto and K. Yamada, *J. Chem. Soc., Perkin Trans. 2*, 1994, 1565-1568.

252. S. Ahmad, L. M. Doweyko, S. Dugar, N. Grazier, K. Ngu, S. C. Wu, K. J. Yost, B. C. Chen, J. Z. Gougoutas, J. D. DiMarco, S. J. Lan, B. J. Gavin, A. Y. Chen, C. R. Dorso, R. Serafino, M. Kirby and K. S. Atwal, *J. Med. Chem.*, 2001, **44**, 3302-3310.

253. M. J. Janssen, F. Wiegman and H. J. Kooreman, *Tetrahedron Lett.*, 1966, **7**, 6375-6381.

254. C.-S. Chien, T. Kawasaki, M. Sakamoto, Y. Tamura and Y. Kita, *Chem. Pharm. Bull.*, 1985, **33**, 2743-2749.

255. J. Barluenga, F. J. Fananas, R. Sanz, C. Marcos and M. Trabada, *Org. Lett.*, 2002, **4**, 1587-1590.

256. J.-i. Matsuo and Y. Aizawa, *Chem. Commun.*, 2005, 2399-2401.

257. R. Sanz, A. Martínez, J. M. Álvarez-Gutiérrez and F. Rodríguez, *Eur. J. Org. Chem.*, 2006, 1383-1386.

258. D. Armesto, M. J. Ortiz, A. R. Agarrabeitia and M. Martin-Fontecha, *Org. Lett.*, 2005, **7**, 2687-2690.

259. N. Balu, J. V. Thomas and S. V. Bhat, *J. Med. Chem.*, 1991, **34**, 2821-2823.

260. N. Shimojuh, Y. Imura, K. Moriyama and H. Togo, *Tetrahedron*, 2011, **67**, 951-957.

261. L. A. Paquette and L. M. Leichter, *J. Am. Chem. Soc.*, 1971, **93**, 5128-5136.
262. M. Egi, K. Azechi and S. Akai, *Org. Lett.*, 2009, **11**, 5002-5005.
263. K. C. Nicolaou, J. Hao, M. V. Reddy, P. B. Rao, G. Rassias, S. A. Snyder, X. Huang, D. Y. K. Chen, W. E. Brenzovich, N. Giuseppone, P. Giannakakou and A. O'Brate, *J. Am. Chem. Soc.*, 2004, **126**, 12897-12906.
264. W. Pablo and M. Olaf, *Helv. Chim. Acta*, 2003, **86**, 865-893.
265. E. J. Enholm and Z. J. Jia, *J. Org. Chem.*, 1997, **62**, 9159-9164.
266. L. A. Yanovskaya, V. A. Dombrovsky, O. S. Chizhov, B. M. Zolotarev, O. A. Subbotin and V. F. Kucherov, *Tetrahedron*, 1972, **28**, 1565-1573.
267. J. A. Ciaccio and C. E. Aman, *Synth. Commun.*, 2006, **36**, 1333-1341.
268. I. Nicolas, P. L. Maux and G. Simonneaux, *Tetrahedron Lett.*, 2008, **49**, 2111-2113.
269. M. Cussac, A. Boucherle and J. L. Pierre, *Bull. Chim. Soc. Fr.*, 1974, **7**, 1442-1445.
270. R. E. Lutz and J. S. Gillespie, *J. Am. Chem. Soc.*, 1950, **72**, 2002-2005.
271. J. Bach, R. Berenguer, J. Garcia, M. López, J. Manzanal and J. Vilarrasa, *Tetrahedron*, 1998, **54**, 14947-14962.
272. P. C. Bulman Page, J. P. G. Moore, I. Mansfield, M. J. McKenzie, W. B. Bowler and J. A. Gallagher, *Tetrahedron*, 2001, **57**, 1837-1847.
273. C. Ollivier, T. Bark and P. Renaud, *Synthesis*, 2000, 1598-1602.
274. C. I. Altinis Kiraz, T. J. Emge and L. S. Jimenez, *J. Org. Chem.*, 2004, **69**, 2200-2202.
275. J. Hasserodt, K. D. Janda and R. A. Lerner, *J. Am. Chem. Soc.*, 1997, **119**, 5993-5998.
276. B. M. Trost and Y. Zhang, *J. Am. Chem. Soc.*, 2006, **128**, 4590-4591.
277. J. H. Billman and J. W. McDowell, *J. Org. Chem.*, 1961, **26**, 1437-1440.
278. B. Sreedhar, P. S. Reddy and D. K. Devi, *J. Org. Chem.*, 2009, **74**, 8806-8809.
279. T. Jensen and R. Madsen, *J. Org. Chem.*, 2009, **74**, 3990-3992.
280. R. Grigg, S. Whitney, V. Sridharan, A. Keep and A. Derrick, *Tetrahedron*, 2009, **65**, 4375-4383.

281. J. E. Thomson, A. F. Kyle, K. A. Gallagher, P. Lenden, C. Concellon, L. C. Morrill, A. J. Miller, C. Joannesse, A. M. Z. Slawin and A. D. Smith, *Synthesis*, 2008, 2805-2818.

282. M. K. G. Mekhael and H. Heimgartner, *Helv. Chim. Acta*, 2003, **86**, 2805-2813.