Asymmetric reduction of substituted indanes as scaffolds for the

synthesis of potential drug candidates

A Dissertation Submitted for the Degree of Doctor of Philosophy

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University of Sheffield

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Dedication

This piece of work is dedicated to my husband Dasuki Imam Galadanci for 'always being there for me, my children who patiently persevered with lonely days and my loving mother Khadija Ibrahim Hassan for her unconditional love and prayers at all times.

Contents

Declaration

This dissertation records the work carried out in the Department of Chemistry, University of Sheffield, between January 2017 and November 2022 and is original except where acknowledged by reference. No part of this work is being, nor has been, submitted for a degree, diploma or any other qualification at any other university.

Acknowledgement

All praise and gratitude are due to Allah the Lord of the Universe, the sublime owner of absolute Knowledge who made it possible for this task to be accomplished. I wish to express my profound gratitude to Prof Simon Jones for giving me the opportunity to undertake a PhD in his research group. His invaluable support throughout this arduous journey is well appreciated.

I would also like to thank both past and present members of the Jones group for their help throughout my studies. I will always cherish the friendship we had with Najwa and Shuwen also not forgetting the untiring assistance I got from Haneesh and Ali who lightened our moods with doses of comic relief in the lab .

Abbreviations & commonly used terms

app	**Apparent**
br s	**Broad singlet**
Cy	**Cyclohexyl**
DCE	**1,2-dichloroethene**
DCM	**Dichloromethane**
DEAB	**N,N-diethylaniline borane**
DEMP	**Diethylmethyl phosphonate**
DIPEA	**N,N- diisopropylethyl amine**
DMF	**Dimethyl formamide**
DMMP	**Dimethylmethyl phosphonate**
DMP	**Dess-Martin periodinane**
DPEN	**1,2-Diphenylethane-1,2-diamine**
d	**Doublet**
dd	**Doublet of doublets**
ddd	**Doublet of doublet of doublets**
dddd	**Doublet of doublet of doublet of doublets**
dt	**Doublet of triplets**
DtBPF	**1,1'-bis(di-*tert*-butylphosphino)ferrocene**
E1cB	**Elimination, unimolecular conjugate base.**
er	**Enantiomeric ratio**
FA	**Formic acid**
FT-IR	**Fourier transform infrared spectroscopy**
h	**Hour**
HPLC	**High pressure liquid chromatography**

Hz	**Hertz**
IPA	***iso*-propyl alcohol (propan-2-ol)**
KHMDS	**Potassium bis (trimethylsilyl)amide**
LDA	**Lithium diisopropylamide**
LED	**Light emitting diode**
m	**Multiplet**
MHz	**Mega hertz**
Mpt	**Melting point**
m/z	**Mass to charge ratio**
NaOtBu	**Sodium *tert*-butoxide**
n-BuLi	**Normal butyllithium**
NMR	**Nuclear magnetic resonance**
NOE	**Nuclear Overhauser effect**
ONf	**Nitrosyl fluoride**
OTf	**Trifluoro methanesulfonate**
PCC	**Pyridinium Chlorochromate**
$Pd_2(dba)_3$	**Tris(dibenzylideneacetone)dipalladium**
$Pd(OAC)_2$	**Palladium(II)acetate**
q	**Quartet**
ROE	**Rotating-frame Overhauser Enhancement**
s	**Selectivity factor**
s	**Singlet**
TEA	**Triethylamine**
THF	**Tetrahydrofuran**
TLC	**Thin layer chromatography**

TFA	**Trifluoroacetic acid**
TMS	**Tetramethylsilane**
t_R	**Retention time**
Ts	***p*-toluene sulfonyl**
UV	**Ultra-violet**
X-Phos	**Dicyclohexyl[2',4',6'-tris(propan-2-yl)[1,1'-biphenyl]-2-yl]phosphane**

Abstract

The indanone core is ubiquitous to a host of isolated natural compounds that have shown significant biological activities against HIV, cancer, malaria, diabetes, respiratory disorders and many more.[1] Isopaucifloral F and its isomer Paucifloral F have the indanone cores embedded in their structures. The former is found in grapes, nuts and other plants with medicinal properties and is a potential candidate for osteoporosis.[2,3] It is reported to have interesting pharmacological and biological activities including antioxidant, anticancer, antifungal and antibacterial properties. The latter (Paucifloral F), is a promising anti-viral agent. Among the most privileged indanones, are the 3-substituted indanones which can be transformed into a variety of biologically active compounds.[4,5,6] A new method for the synthesis of 3-aryl-2-phosphoryl indanones was developed for the first time using modified Heck cyclisation conditions.
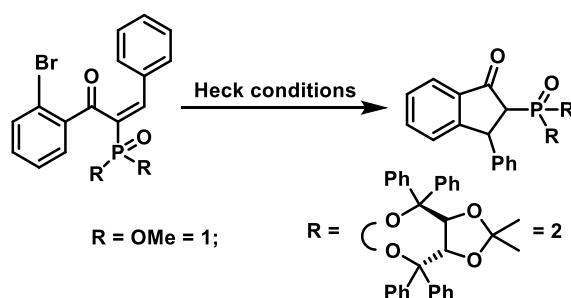
The strategy was adopted after many unsuccessful Nazarov cyclisation attempts of phosphorylated chalcones that were obtained from Knoevenagel condensation of β-ketophosphonates previously synthesised by the phosphono-Claisen condensation of aryl esters and alkyl phosphonates.
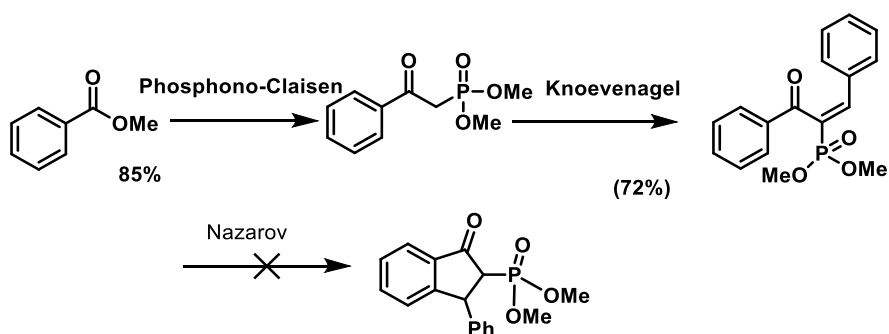
Different types of 3-aryl indanones were also synthesized *via* classical Heck reaction of 2-bromo chalcones and kinetic resolution (KR) *via* asymmetric reduction of the prepared 3-aryl indanone cores using amino indanol catalysts was investigated for the first time on these types of systems. 50% ee was achieved on the major *cis* indanol while the minor had better enantioselectivity of 88%.

54

Conditions
(up to 100% product conversion)

74

75

(1*S*, 3*S*) [α]$_D^{25}$ = +10.0
(c 1.0, CHCl$_3$); 50% ee

(1*R*, 3*S*) [α]$_D^{25}$ = +18.0
(c 1.0, CHCl$_3$); 88% ee
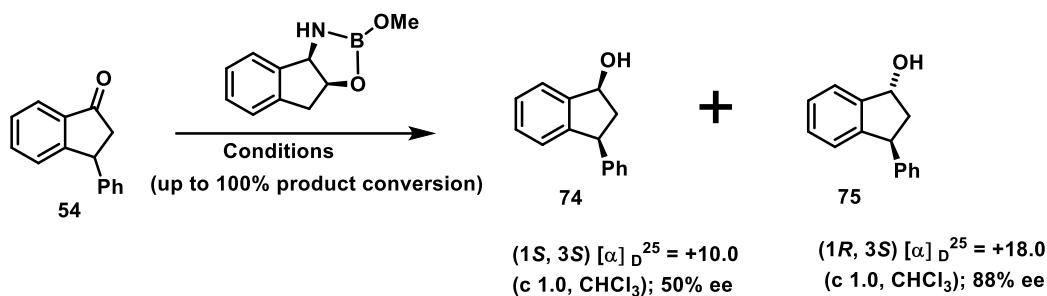
Reproducibility issues necessitated the use of an alternative reducing agent. Room temperature reaction of DPEN-based Ru(II) catalysts 10 mol% had a remarkable outcome at 50% conversion providing almost exclusively the *cis* isomer with dr > 95:5 (*cis/trans*), excellent ee of 94% and 82% ee on unreacted starting material on simple and substituted indanones.

54 Ph

Ru cat (*S,S*)
HCO$_2$H/Et$_3$N
30 °C/18 h

74 Ph
(1*S*, 3*S*), 98% ee

Recovered SM **77**
(*R*), 94% ee
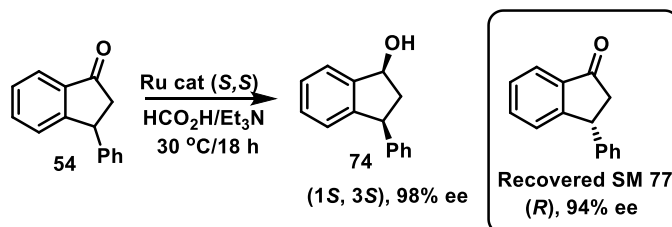
Chapter 1.0

1.1 Natural products as sources of drugs or potential drug candidates

Earth is endowed with vast vegetation having almost 500,000 species of plants. Of these, only a small fraction (10%) are used by both humans and animals as food.[7,8] The use of natural products from animals, plants, and microorganisms for the management of both humans and animal diseases is as old as humanity based on folklore evidence of ancient Egyptians, Greek, Babylonians [9] and a lot of non-documented claims which are known by oral tradition. Many natural products extracts are sources of important drugs[10] with examples of plant based compounds that have been used for ethnomedicinal purposes including Khellin which was isolated from *Ammi visnaga (L) Lamk*., which led to the development of a bronchodilator sodium chromoglycate; the isolation of quinine, a potent antimalarial drug from the bark of *Cinchona* species like *C. officinalis*), which was used by natives in the Amazon and brought to Europe in the early 1600s and paved the way to the syntheses of antimalarial drugs.[11,12]

Intermediates or end-products of biochemical processes in plants are termed as metabolites. They have been broadly categorised into primary and secondary metabolites based on their functions.[12] The primary plant metabolites are vital for growth of the host plant and its development[13] examples of which are carbohydrates, proteins, fats, and oils. Secondary metabolites on the other hand, are not required for use by the host plant but they are formed in response to some external stimuli, although recent genetic studies have established their multifunctionality in regulation of the biochemical processes of the plant as well as primary metabolites in the wider sense.[10]

Plants have a well-defined system of self-defence mitigating the effects from external elements like pests, disease causing fungi and bacteria by synthesising secondary metabolites known as phytoalexins.[14] These phytoalexins from both terrestrial and marine sources have been explored by various researchers and utilised in the management or healing of diseases.[15] Examples can be found

in the work of the German pharmacist Friedrich Serturner which dates back to almost two centuries ago when he isolated morphine from opium seed pods from the plant *Papaver somniferum* which was found to have pharmacological effect on the central nervous system (CNS) as a strong analgesic, but problems of overdependence which causes addiction, euphoria and respiratory depression necessitated search for relatively safer alternatives with similar beneficial features.[8]

Another example is Taxol which was isolated from the bark of yew tree and found to have cytotoxic effects against cancer cell lines L1210, P388, and P1534 in mouse models.[16]   This led to over cultivation of yew trees which was damaging to the ecosystem and at the same time not meeting the demand of the growing world population. It was demonstrated that 10, 000 kg of the tree bark was able to produce only 1 kg of Taxol.[16,17] This prompted the search for more efficient ways of synthesising it and other natural product-based compounds with proven biological importance.[16]

Another prominent phytoalexin found to have significant biological activities is resveratrol (Figure 1) that has been isolated from numerous plants since its first discovery in 1940 from the roots of white hellebore (*Veratrum grandiflorum O. Loes*).[17,18]
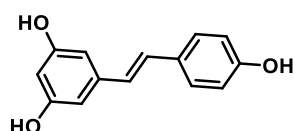
Figure 1. Resveratrol [19, 20,21, 22]

It is believed to be implicated in biochemical processes like anti-aging and anti-inflammatory mechanisms**,** heart disease, cancer and many more.[1] Studies backed by clinical trials reveal its presence in reducing the incidences of acute pancreatitis although its exact role cannot be ascertained due to its poor drug-like property [23, 24] and fast metabolic activity. A host of biologically important compounds which are believed to be biosynthetic products have demonstrated better potency than the parent compound. [22,25] This paved way to the synthesis of compounds having more advanced structures than resveratrol by various researchers while at the same time optimising the

parent structure.[1] It is interesting to note that a lot of these products have either the indane or indanone structures as part of their basic framework (Figure 2).

tefludazine
anti-psychotic

indatraline
Anti-depressant & cocaine addiction

(+)-Iranadalone
anti-hypertensive

pallidol (estrogen-like activity)

caraphenol C (asthenia syndrome & vascular hypertension)

parthenocissin A

Quadrangularin A (anti-cancer agent, anti-ulcer, anti-ostereoporotic)
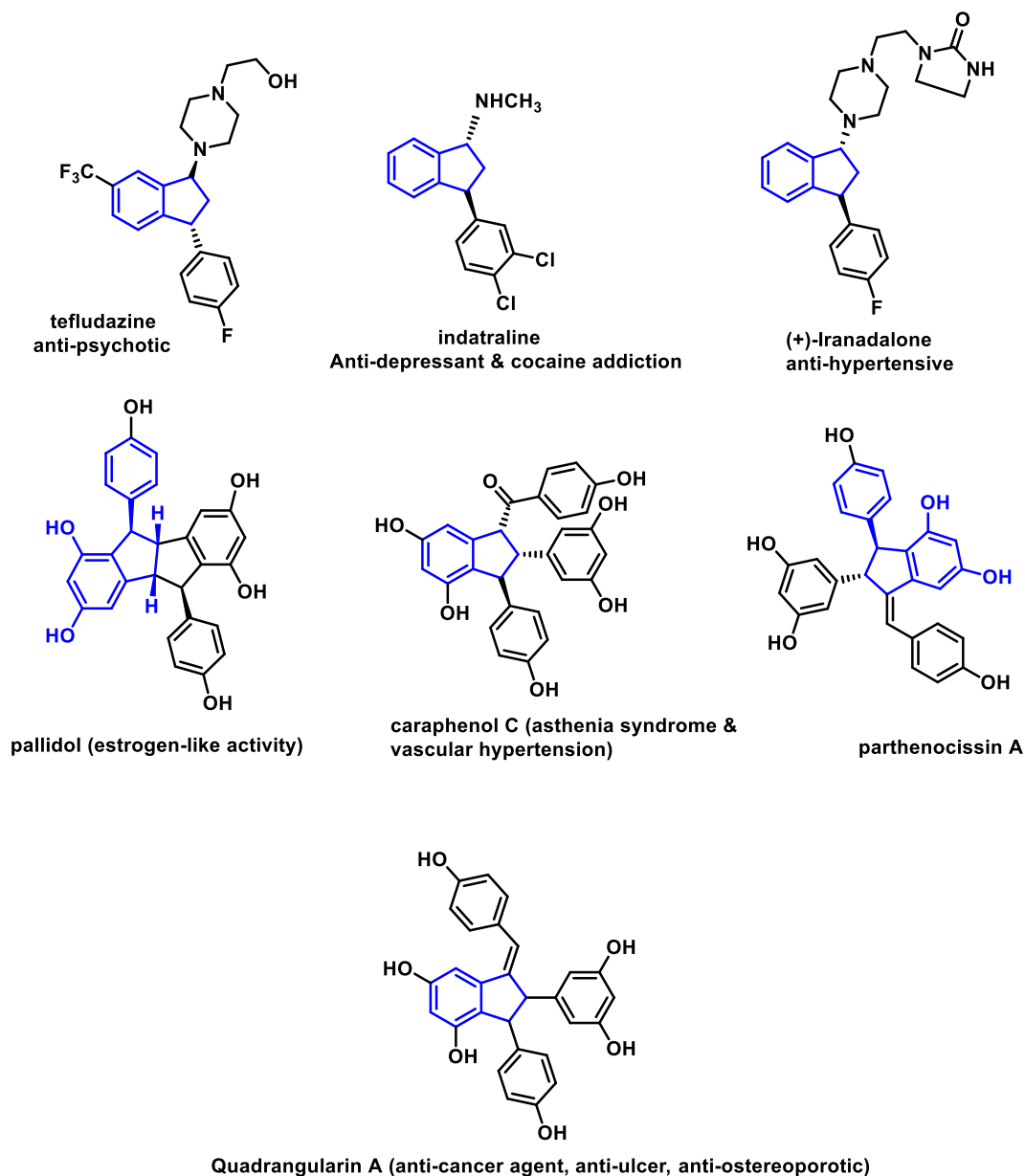
Figure 2. Aryl indane-derivatives used in drug therapy[26]

Realising the immense importance of the indanone structure found in a lot of pharmacologically active natural and synthesised compounds or intermediates in synthesis, studies pertaining to indanones has been undertaken with keen interest by many research groups.

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1.2 The indanone core

The indanone core is ubiquitous to a host of isolated natural compounds that have shown significant biological activities against HIV, cancer, malaria, diabetes, respiratory disorders and many more.[1] It comprises of a cyclopentanone ring that is fused to a benzene ring **1** (Figure 3). A closely related group of compounds are the indanes that are made up of a benzene ring fused with a cyclopentane ring **2** (Figure 3). Both group of compounds have been identified as important structural molecules that occur in a wide range of both natural and synthetic molecules[27] and as such, they have been adopted in the synthesis of many bioactive lead components that find use in medicine, and the pharmaceutical industry.[28]
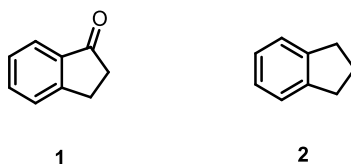

Figure 3. 1 = indanone; 2 = indane

A promising anti-viral agent Paucifloral F and its isomer isopaucifloral F which is a potential candidate for osteoporosis[2,3] have the indanone core embedded in their structure (Figure 5). Isopaucifloral F which is found in grapes, nuts and other plants with medicinal properties is reported to have interesting pharmacological and biological activities including antioxidant, anticancer, antifungal and antibacterial properties.[1] Another indanone-based natural product is afzeliindanone (Figure 4) which was isolated from the roots of the plant Scot Elliot (*Uvaria afzelii*) and is used by locals in West Africa as an antibacterial drug.[19]
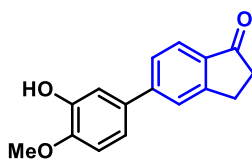
Figure 4. Afzeliindanone [19]

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Due to the prevalence of the indanone cores in a lot of biologically significant structures (Figure 5), many new synthetic routes to prepare the indanone core as an intermediate in the synthesis of drugs currently used in conventional medicine are available.[26]

Figure 5. Aryl indanone-derivatives used in drug therapy.[26]

The compounds have marked similarities and differ only in the patterns to which the various substituents are attached on the core. This provides motivation of having a general strategy to produce the indanone scaffold that allows for late-stage functionalisation, thereby generating an array of indanone-based synthetic molecules (Figure 5).

1.3 Indanone-based compounds used in conventional medicine

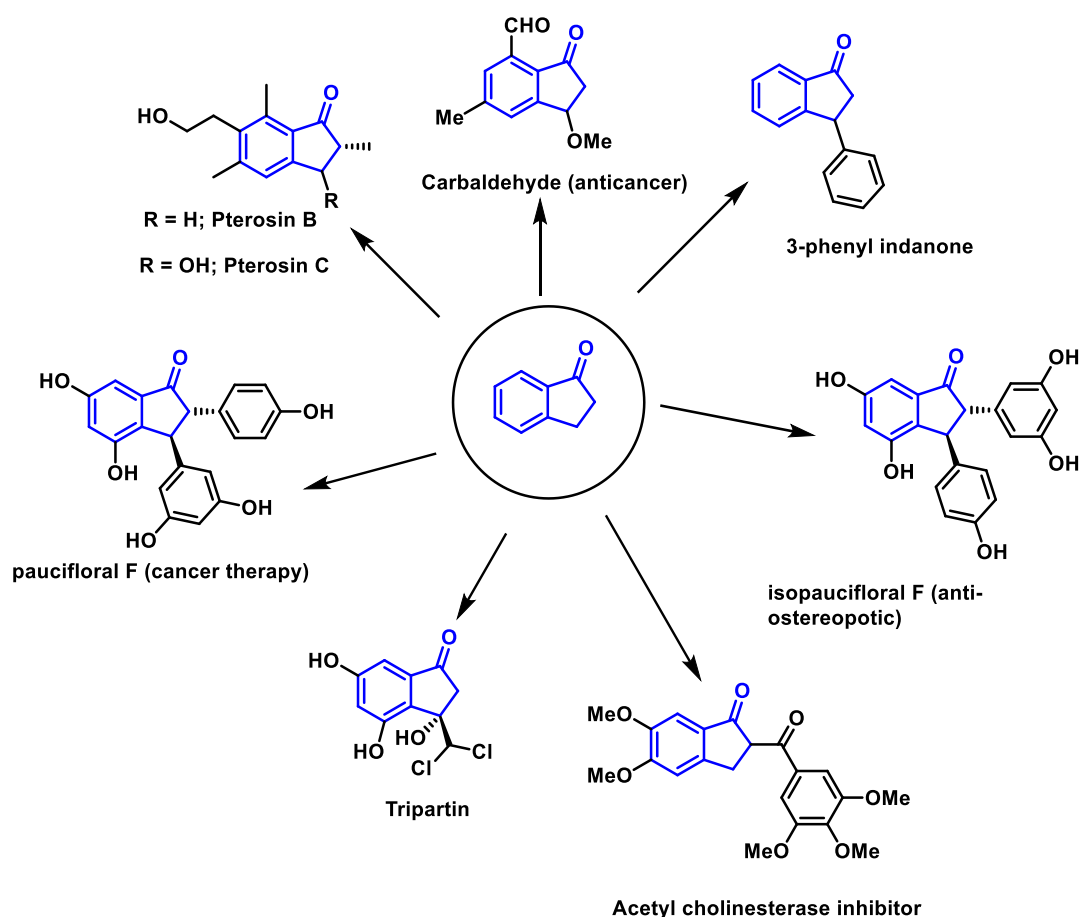Drug antimicrobial resistance is a cause for major concern globally. According to 2019 reports from the centres for disease control Atlanta USA, 35,900 deaths occur annually because of antibiotic resistance out of 2.8 million new infections per year. This is a serious challenge that demands addressing by finding new antimicrobial agents.[29] A series of indanone-derived analogues were synthesised and screened for preliminary *invitro* antimicrobial testing against a broad spectrum of Gram positive and negative bacteria, and some fungi. Interestingly, all the synthesised compounds had good to medium activities against Gram-positive bacteria *Staphylococcus aureus* and the two Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*.[26] Similarly, the Sosnik group derivatised thiosemicarbazones from 1-indanone (Figure 6) which were found to be effective against the hepatitis C virus, and also displayed anti-tumour activities in some malignant cancer cells.[30,31]

Figure 6. Benzylidene indanones as multitarget ligands for tumours [30 , 31]

Another indanone-derived analogue presently used in conventional medical practice is donepezil which is registered with the US food and drug administration as an acetylcholinesterase (AChE) inhibitor for the treatment of Alzheimer's disease [30 , 26 , 32]
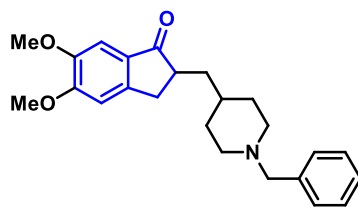
Figure 7. Donepezil for Alzheimer's treatment. [30 , 26 , 32]

Indanone-based compounds have been shown to have potency against many cancer lines. The vinyl indanone (Figure 8) is used as an anti-inflammatory drug that impairs the action of the enzyme lipoxygenase responsible for causing cell inflammation in humans by converting arachidonic acid into leukotrienes.[33 , 34 , 27]
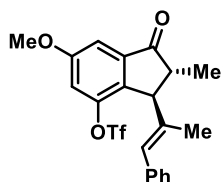
Figure 8. Human lipoxygenase (HLO) inhibitor [33]

Similarly, the Balczewski group synthesised indanone compounds (Figure 9) and some of them were found to have good cytotoxic effects against Hela and K562 cancer cell lines.[34 , 27]

Figure 9. Substituted Indanones against Hela and K562 [34 , 27]

A library of novel gallic acid derived indanones (Figure 10) were synthesised and screened *in vitro* and found to have toxicity against some human cancer lines. Among the compounds, the analogue with 4-NO$_2$ had the highest potency against MCF-7 cell lines within the range of 3-10 μM at IC$_{50}$. [35, 36]
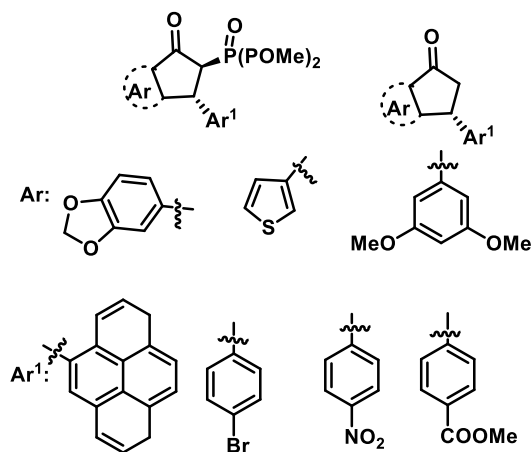

R = 4-NO$_2$ 4-COOCH$_3$

R = 4-N-(CH$_3$)$_2$ R = 4-CONH$_2$

R = 4-COOH
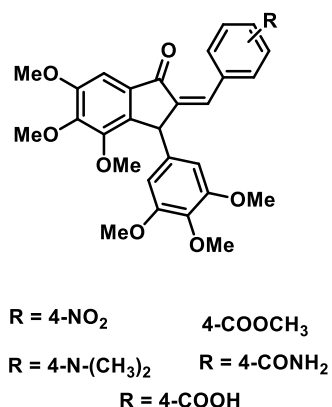
Figure 10. Gallic acid derived indanones as anticancer drugs.[34]

Previously synthesised compounds by the same group (Figure 11) exhibited comparable cytotoxicity to various human cancer cell lines at IC$_{50}$ = 0.01 μM-2.2 μM reducing tumour growth by about 45-50%.[37,38,39]

(a)   (b)
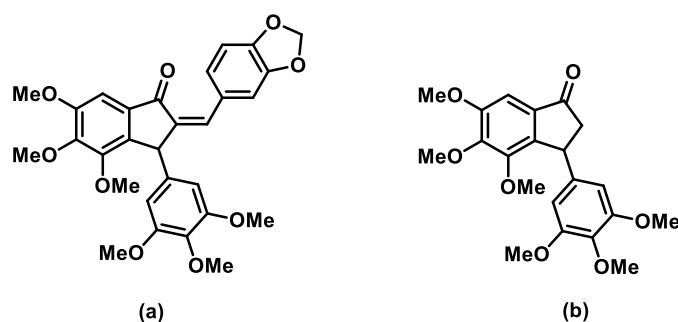
Figure 11. Gallic acid derived indanones as anticancer drugs [37,38, 39]

Bertrand and co-workers[26] synthesised indanone-derived analogues which were screened against malignant lung cell lines H661 of which some were found to have moderate activities. Antiproliferative activity was recorded for the synthesised compounds (Figure 12) after 48 h with IC$_{50}$ values between 20-25 μM.[26]
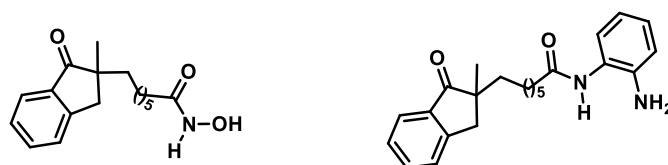
Figure 12. Indanone-derived active analogues against malignant cell lines H661[26]

1.4 Methods of synthesizing indanones

The first reported synthesis of 1-indanone in 1927 was *via* the Friedel-Crafts reaction of phenylpropanoic acid chloride with aluminum chloride in benzene (90% yield).[27] Subsequently Price and Lewis (1939) undertook the synthesis of 1-indanone from the carboxylic acid in which unsubstituted 1-indanone **1** was obtained in 27% yield by exposing phenylpropanoic acid to acidic conditions (20% sulfuric acid) at 140 °C (Scheme 1).[40]
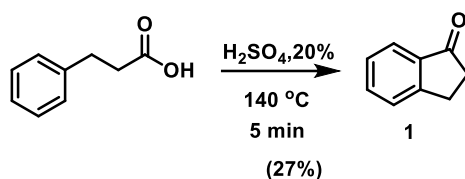

Scheme 1. Synthesis of 1-indanone via acid-based intra molecular cyclization.

An improvement in the product yield (76%) was achieved at a low temperature of −100 °C by using n-BuLi for cyclization of 3-(2-bromophenyl)propionic acid **15** (Scheme 2).[28]
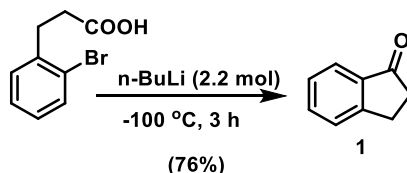
Scheme 2. Synthesis of 1-indanone *via* cyclization of 3-(2-bromophenyl)propionic acid. [28]

1-Indanones can also be obtained by photochemical reactions in very good yields within a short period of reaction time. The 1-indanone **4** was obtained in 94% yield by photolysis of the cyclopentenone **3** in 30 minutes. Interestingly, the cyclohexanone **5** took longer to cyclise (3.5 h) than the cyclopentenone counterpart (Scheme 3).[27]
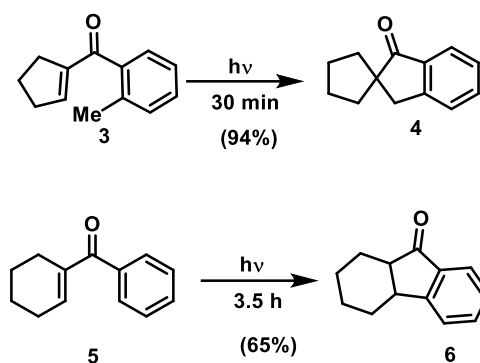
Scheme 3. Photocatalytic synthesis of 1-indanones. [27]

Similarly, the Larock group demonstrated the palladium catalysed synthesis of indanones in an atmosphere of carbon monoxide from unsaturated aryl halides which produced products with good to excellent yields (Scheme 4).[41]
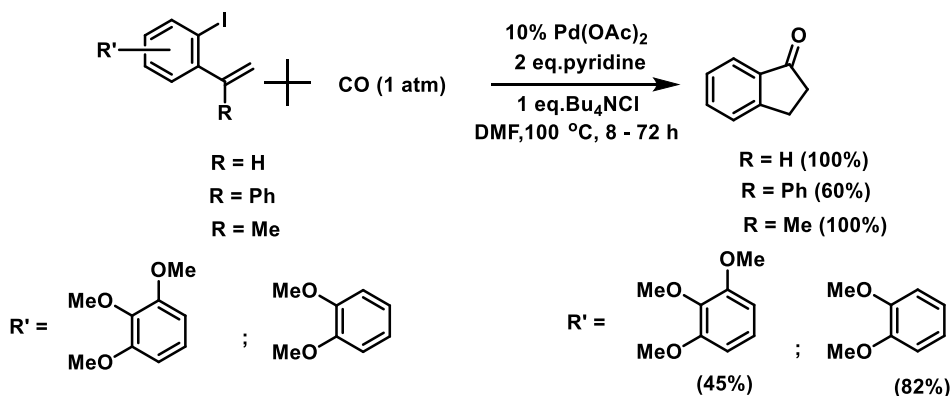
Scheme 4. Synthesis of indanones via carbonylative cyclisation of aryl iodides. [41]

Other protocols in the synthesis of indanones involve the use of *trans* substituted chalcone epoxides as demonstrated by Ahmed and co-workers *via* an intramolecular indium (III)-chloride mediated Friedel–Crafts alkylation to produce only *cis* configured 2-hydroxyindan-1-one derivatives in very good yields (up to 95%) (Scheme 5). [42]

R¹ = H, R² = H
R¹ =H, R² = 4-Cl
R¹ =H, R² = 3-NO₂
R¹ =H, R² = 4-Br

R¹ = H, R² = H (95%)
R¹ =H, R² = 4-Cl (95%)
R¹ =H, R² = 3-NO₂ (94%)
R¹ =H, R² = 4-Br (92%)
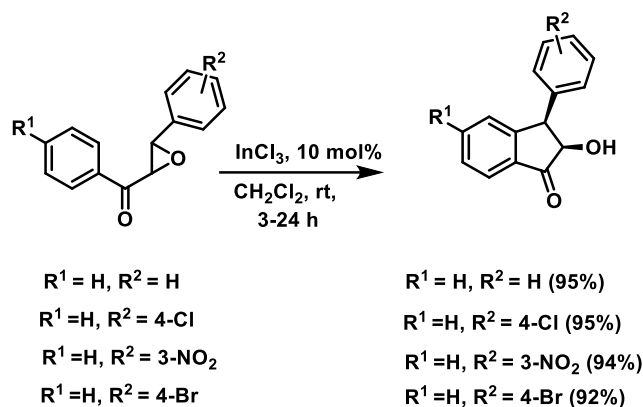
Scheme 5. Synthesis of 2-hydroxyindan-1-one derivatives from chalcone epoxides. [42]

Synthesis of 3-aryl-1-indanone derivatives **9** was accomplished from a one-pot stereoselective reaction of aldehydes **8** and alkyne derivatives **7**. The reaction was facilitated by antimony pentafluoride (SbF₅) and ethanol in DCE to produce high yields of *trans*-2,3-disubstituted indanones as the only isomers (Scheme 6). [44]

R¹ = Me, R² = Ph
R¹ = Me, R² = *t*-Bu
R¹ = Me, R² = Et
R¹ = *n*-Bu, R² = *t*-Bu
R¹ = *n*-Bu, R² = *i*-Pr

R¹ = Me, R² = Ph (78%)
R¹ = Me, R² = *t*-Bu (89%)
R¹ = Me, R² = Et (75%)
R¹ = *n*-Bu, R² = *t*-Bu (82%)
R¹ = *n*-Bu, R² = *i*-Pr (38%)
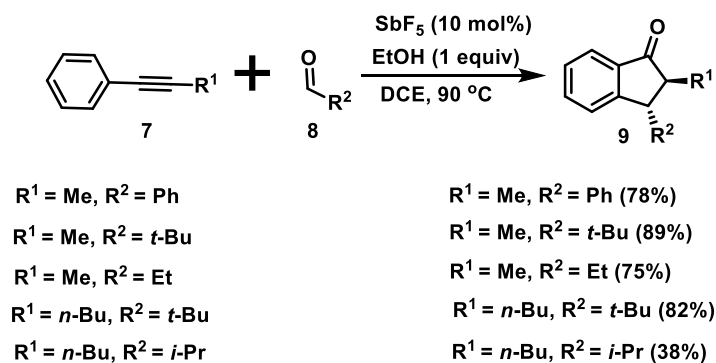
Scheme 6. Synthesis of 3-aryl indanones from aromatic aldehydes and alkyne derivatives.[44]

Zhu *et* al; [45] have reported a novel protocol of the synthesis of a broad range of indanones *via* photoredox reaction using an iridium complex as the catalyst and employing hydrogen-radical (HRS) decarboxylative strategy to effect the cyclisation (Scheme 7). They highlighted the importance of using water as an important additive which served a dual purpose of furnishing both hydrogen and

as a HRS source. The claim was supported by mechanistic experiments and density functional theory (DFT) calculations .
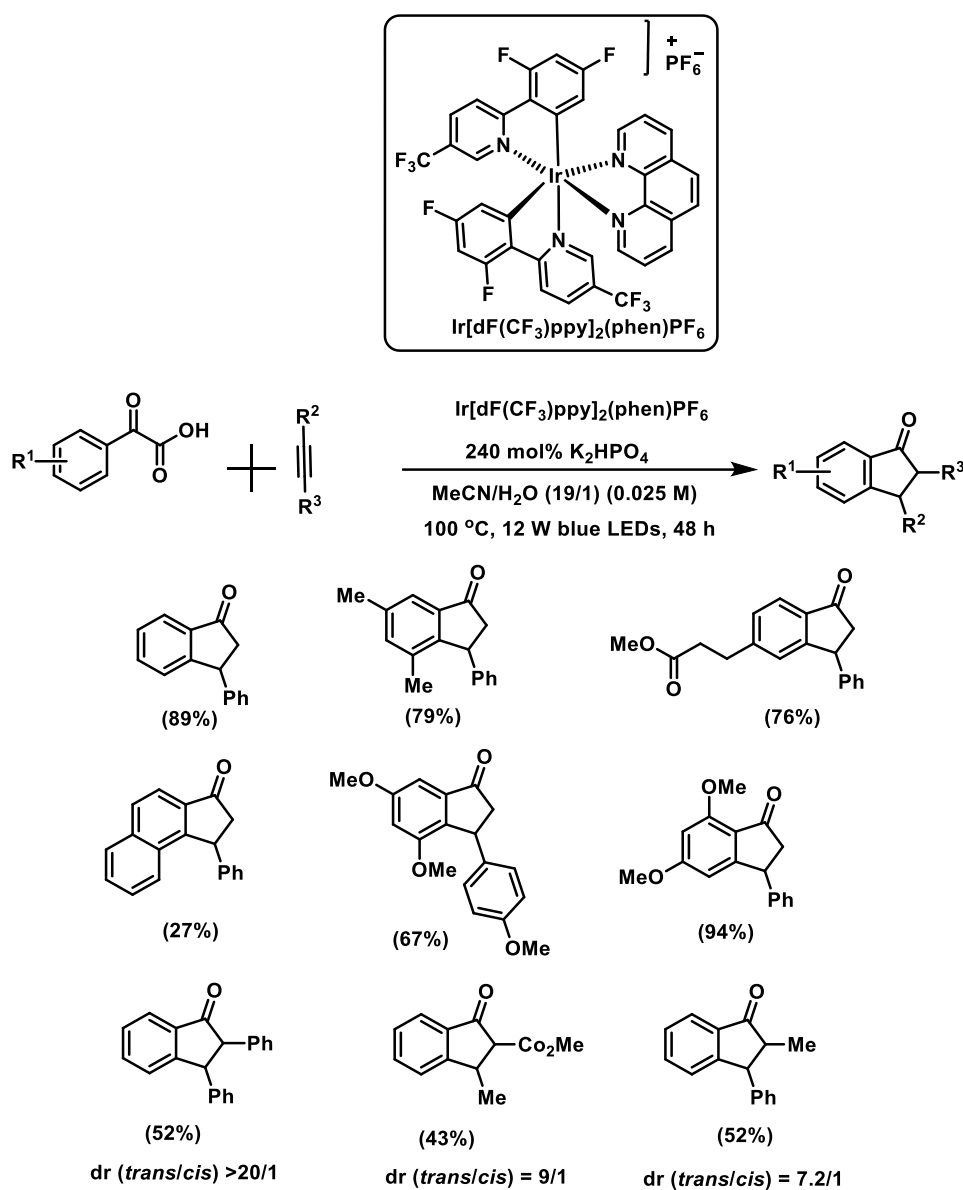
Scheme 7. Photoredox synthesis of indanones *via* hydrogen-radical shuttle. [45]

1.5 Nazarov cyclization

Nazarov cyclization is a powerful method for the synthesis of alicyclic compounds with 5 carbon atoms.[46,47] A high yield of indanones (52-90%) related to combretastin A-4 was reported by Lawrence and co-workers (Scheme 8).[48] Chalcones were dissolved in neat TFA and heated for 4 h

inside sealed tubes. They observed that when the chalcones were subjected to microwave heating, the indanones were formed within 20 minutes The indanones showed antiproliferative properties like that of combretastin A-4 when they were exposed to human leukaemia cell lines. [48]
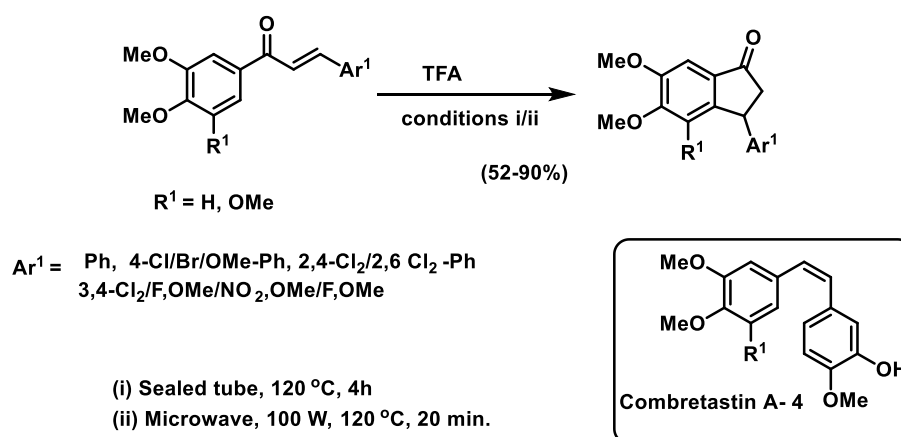
Scheme 8. TFA-mediated synthesis of indanones. [48]

Frontier and Eisenberg have described the highly reactive iridium-BINAP catalyst system with one equivalent of antimony hexafluoride (AgSbF$_6$) as an additive to facilitate the Nazarov cyclisation of vinyl phosphonates with product yield up to 97% (Scheme 9). Although chiral BINAP constituted a large part of the catalyst system, poor enantioselectivity of less than 15% was achieved. [49]
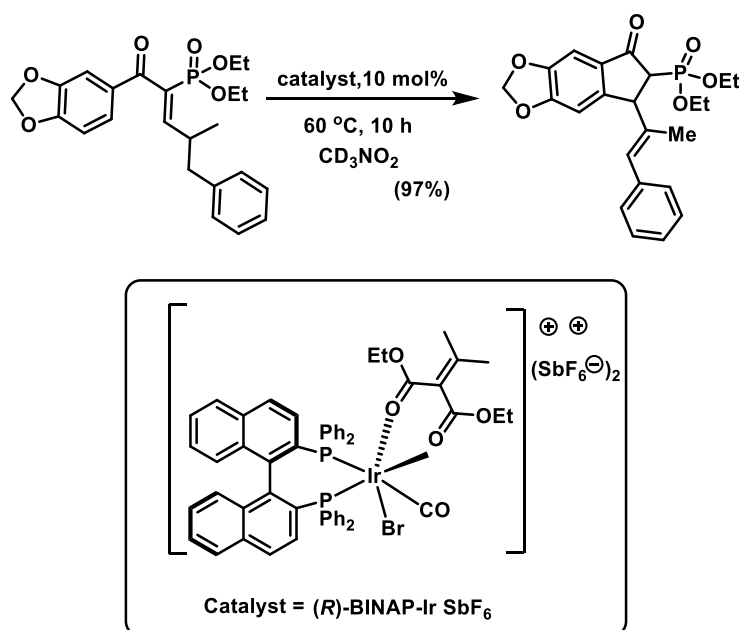
Scheme 9. Cyclisation of aryl vinyl phosphonate. [49]

In a related finding, Xu and Yu [50] reported the enantioselective synthesis of 3-aryl-1-indanones *via* the 1,4 cyclisation of pinacolborane chalcones catalysed by a rhodium/monophospho complex (Scheme 10). An array of pinacolborane chalcone derivatives that differ in both steric and electronic properties were examined, which provided the indanones in very good to excellent yields (82–95%) with high enantioselectivities (81–95% ee).
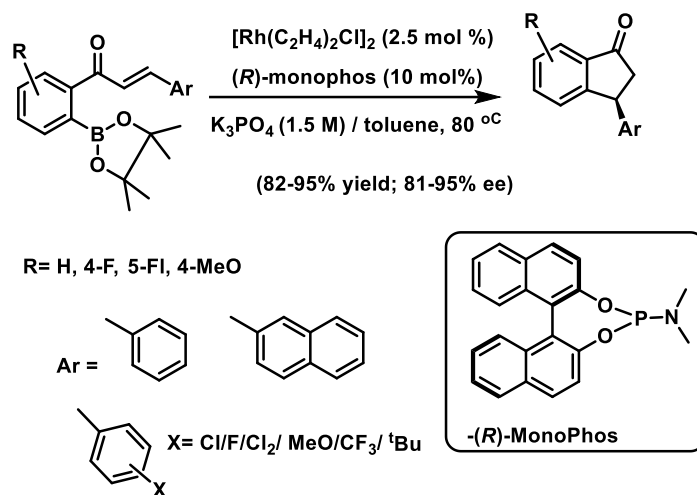
Scheme 10. Rhodium-catalysed synthesis of chiral 3-Aryl-1-indanones. [50]

Similarly, Tang *et al*;[51] reported the use of methyl *p*-tolyl sulfoxide in a controlled Nazarov cyclisation manner to achieve 3-arylindanones in high yields with excellent enantioselectivities. The starting material was prepared by a Claisen-like condensation of enantiomerically pure methyl *p*-tolyl sulfoxide **10** with methyl 3,5-dimethoxybenzoate to produce the β-ketosulfoxide **11** in excellent yield. Knoevenagel condensation proceeded smoothly with 3,5-dimethoxybenzaldehyde using a substoichiometric amount of piperidine and acetic acid to yield the desired enone **12** (Scheme 11).[51]
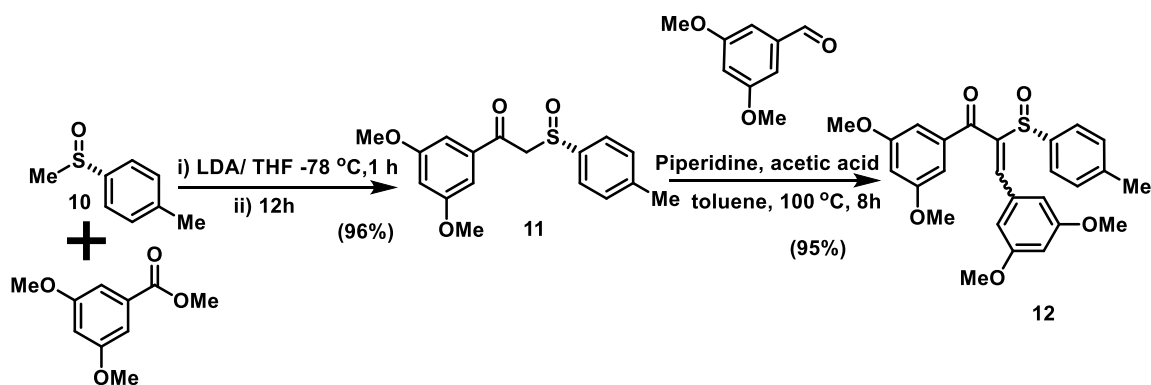
Scheme 11. Chalcone synthesis via Knoevenagel condensation of β-keto aryl sulfoxide. [51]

The sulfoxide chalcone **12** was subjected to optimal Nazarov conditions to yield the corresponding sulfinyl-substituted indanone **13** with high diastereoselectivity (99:1) which underwent reductive cleavage of the stereodirecting group to afford 95% yield of the desired highly enantioenriched indanone **14** (98% ee) (Scheme 12). [52]
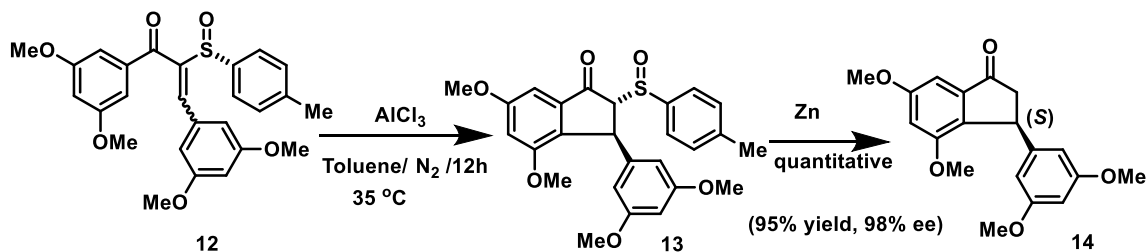
Scheme 12. Sulfoxide-based enantioselective synthesis of 3-aryl indanone [52]

Using the same protocol, they were able to test the scope of the reaction with a range of electron donating and withdrawing aryl groups which yielded the products in moderate to very good yield (68-93%) with high enantioselectivities of up to 99% ee (Scheme 13).[51]
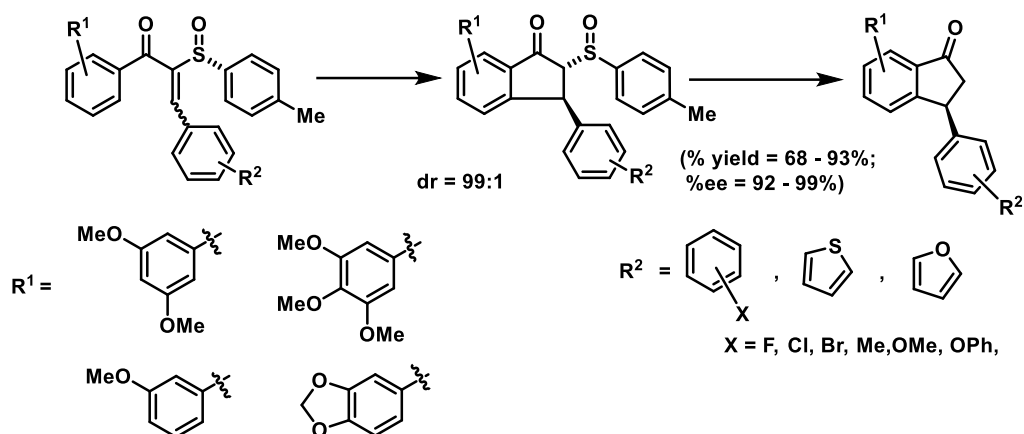
Scheme 13. Scope of the sulfoxide-based enantioselective synthesis of 3- aryl indanones [51]

1.5 Hypothesis and Aims:

Due to the desirable outcomes achieved by the Tang group, their procedure was adopted in this project but modified using phosphorus stereodirecting group instead of sulfur. The hypothesis was whether chiral phosphonates which could be easily made by the use of chiral alkoxy ester side chains on phosphorus atom (Figure 13a) would work as well or even better than the sulfoxides. Alternatively, stereodirecting groups bearing P-stereogenic centre such as (Figure 13b) may exert good stereocontrol.
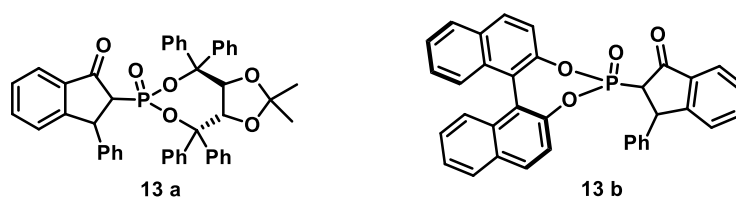
Figure 13. Chirality stereo directing on indanones *via* chiral phosphonates

To test the hypothesis, the protocol developed by Sczesna and co-workers of synthesising 3-aryl-1-indanones **18** and novel 3-aryl-2-phosphoryl-substituted **17** indanones was proposed to evaluate this in achiral systems before moving to chiral ones. The key step was the Nazarov cyclisation of phosphorylated **15** and non-phosphorylated **16** chalcones which were prepared *via* base-mediated Knoevenagel reaction (Scheme 14).[27] If the approach is successful, the indanone framework could be developed for further elaboration towards synthesis of the natural product isopaucifloral F.

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Thereafter, the use of different starting materials will be explored which will generate a library of potential novel biologically active indanones that could pave way for further elaboration.
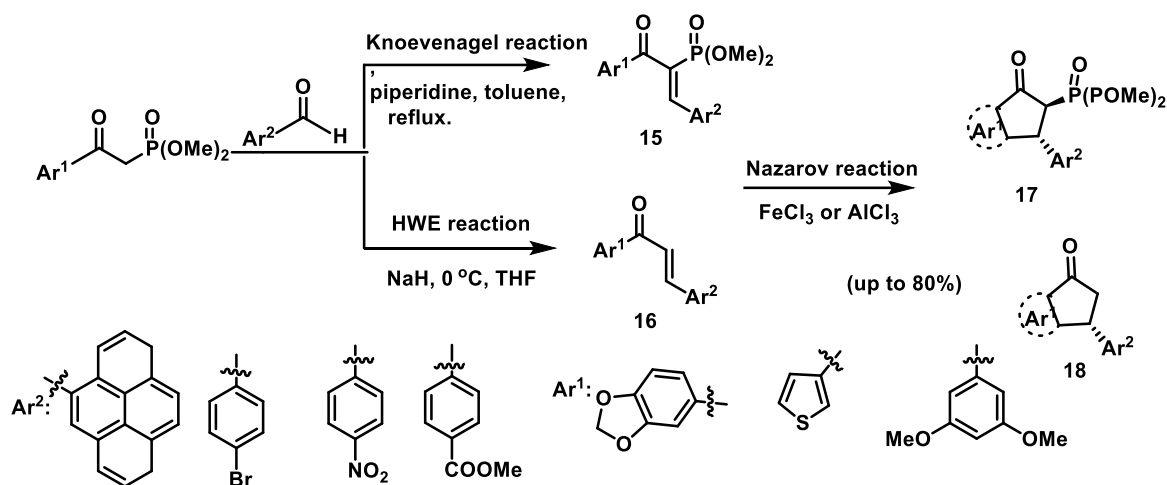
Scheme 14. Nazarov reaction of 3-aryl-2-phosphonate chalcones [51]

1.6 Retrosynthetic plan

The retrosynthetic disconnection of **19** started at **C-2** to arrive at a substituted indanone **20** which was envisioned to be assembled *via* Nazarov cyclisation of the chalcone **21** as the key stage in the synthetic plan.
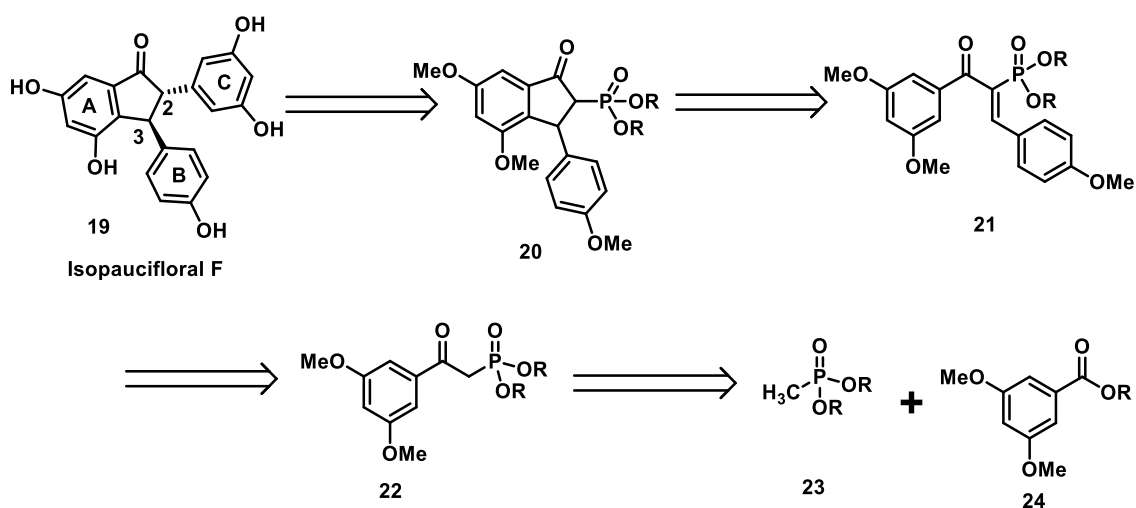
Scheme 15. Retrosynthetic approach to the synthesis of *i***-Paucifloral F with Nazarov cyclisation as key stage of forming indanone scaffolds**

Subsequent α-arylation of the indanone would produce the protected precursor molecule to arrive at isopaucifloral F **19** and its analogues after deprotection. The phosphorylated chalcone **21** could be assembled in a Knoevenagel fashion from *β*- ketophosphonate **22** and *p*-methoxy benzaldehyde. Further simplification of the *β*-ketophosphonate *via* a retro phosphono-Claisen was expected to give a methyl phosphonate ester **23** and an aryl ester **24** which are both commercially available cheap starting materials.

Chapter 2.0

2.1 Synthesis of substituted indanones

2.2 Introduction

The synthesis of C-P bonds has gained significant relevance in the field of organic chemistry due to the importance of organophosphorus compounds as building blocks in the synthesis of biologically active compounds.[54,55] An important class of the organophosphorus compounds are the *β-*ketophosphonates which have been reported to have varied biological properties, like thyroid receptor ligands, cholinesterase inhibitors used in the treatment of Alzheimers disease, glaucoma, parasitic infections, inhibition of cancer cell proliferation, in addition to their diverse synthetic applications. [56, 57]

2.3 General methodologies for synthesis of β -keto phosphonates

The traditional protocol for the synthesis of β-ketophosphonates is Arbuzov reaction of alkyl halides and trialkylphosphites (Scheme 16). [58, 59]
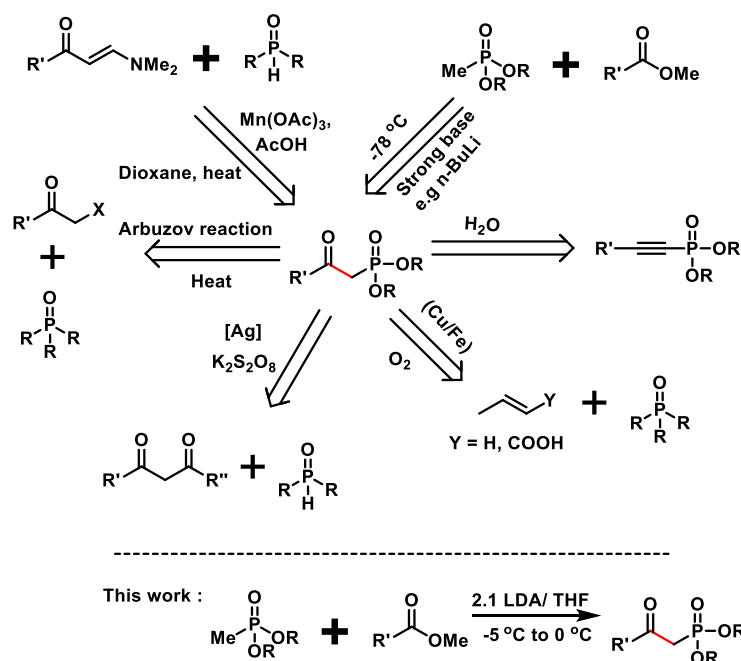
Scheme 16. Summary of synthetic routes to β -keto phosphonates. [58, 59]

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Other procedures have been reported by various research groups like the hydration of acetylenic phosphonates in the presence of transition metals, [60] [61] and Mn(OAc)$_3$-mediated reactions of enaminones and phosphonic acids [59] (Scheme 16). Others that rely on catalysts for activation are limited by catalyst reuse and recycling or losing a relatively large amount of catalysts during work-up and laborious procedures. [54] Although there are numerous procedures, a common one involves the Claisen condensation of dialkyl phosphonates with carboxylate esters at -78 °C. [62] However, it has drawbacks in having to deal with unwanted side reactions which affect the product yields (Scheme 17). [62]
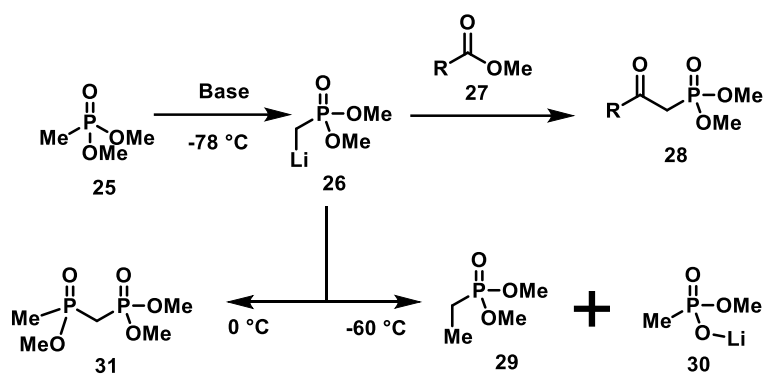
Scheme 17. Condensation of LiCH$_2$PO(OMe)$_2$ with Esters. [62]

The first step of the condensation reaction of synthesis of β-ketophosphonate involves deprotonating the phosphonate ester **25** at -78 °C which leads to formation of **26** after which the compound **28** is synthesised following the addition of ester **27**. In order to drive the reaction to completion, addition of a second equivalent of base or the anion **26** is required which will ensure deprotonation of the more acidic compound **28.** The formation of unwanted side reactions like dimerization of **26** to **31** or intermolecular alkyl transfer from **26** to **29** and **30** coupled with the operational temperature at -78 °C are a great concern for large-scale synthesis although it has previously been used in these regards.[62]

As a way of mitigating the loss in product yield, Maloney and Chung developed milder reaction conditions at a temperature range of -5 to 0 °C which they presumed would curtail formation of side

products [65] thereby enhancing product yields. It is on this premise, that the method in this work was adapted for the synthesis of *β*-ketophosphonates.

2.3.1 Synthesis of *β*-ketophosphonates
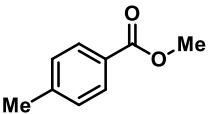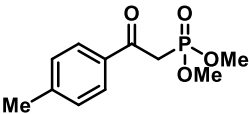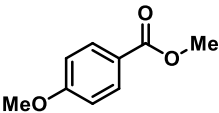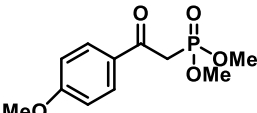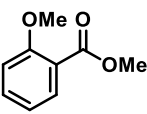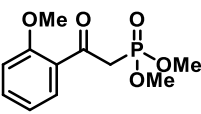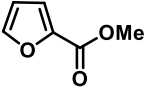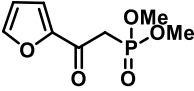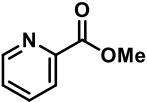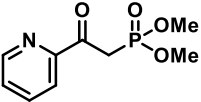
2.3.2 The model substrate
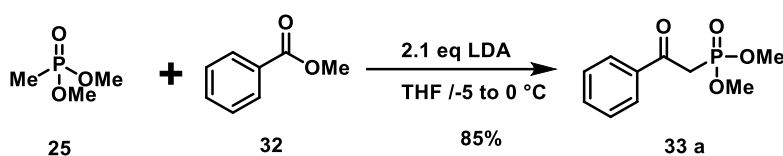
Scheme 18. Synthesis of β-ketophosphonates with the model substrate

The starting material required for the synthesis of substituted *β*-ketophosphonates which would subsequently be functionalised to isopaucifloral F and its analogues are not commercially available but can be prepared by a series of steps. As a proof-of-concept experiment, an LDA mediated phosphono-Claisen condensation of dimethyl methylphosphonate **25** was conducted at -5 $^{\circ}$C followed by addition of an aryl ester **32**. A second equivalent of LDA was required to deprotonate the acidic *β*-ketophosphonate product which is typical with Claisen condensation (Scheme 18). The product **33 a** was formed after an aqueous work up as confirmed by ^{1}H and ^{31}P NMR analysis revealing the presence of a methylene proton signal (CH_2) at δ_H 3.65 ppm which coupled with the phosphorus atom thereby splitting the signal into a doublet with a coupling constant of J_{PH} 22.9 Hz. Purification by flash column chromatography afforded 85% yield of pure material. To further explore the scope of the reaction, other aryl esters bearing electron donating groups (Table 1, entries 1-3), and heterocycles, (entries 4-5) were examined with the same protocol. They all proceeded well to give the desired compounds (**33 b - f**) in moderate to very good yields.

Table 1. Preparation of β-ketophosphonates 33 b - f

Entry	Substrate	Product	Yield (%)	33 b - f
1.			77	b
2.			94	c
3.			65	d
4.			55	e
5.			66	f

Conditions: In all reactions 1 eq of DMMP was added to 2.1 eq. of LDA in THF at -5 °C - 0 °C followed by dropwise addition of the corresponding aryl ester then left to stir until complete consumption of starting materials as determined by TLC analysis.

2.4 Knoevenagel condensation

Knoevenagel olefination was the next step pursued in this work, and was first attempted following a literature precedence (Scheme 19). [66]

2.4.1 Synthesis of the model chalcone
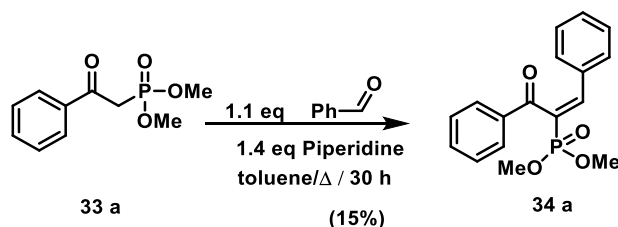
Scheme 19. Synthesis of chalcones. [66]
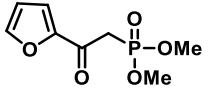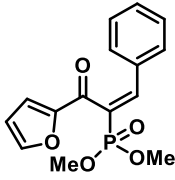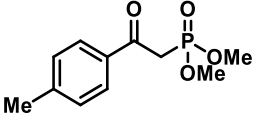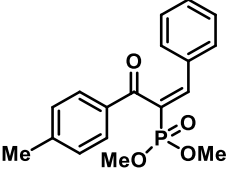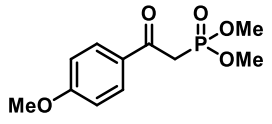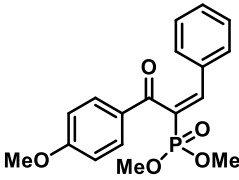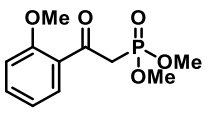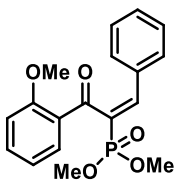
A mixture of *β*-ketophosphonate **33 a**, benzaldehyde and piperidine was examined under Dean-Stark conditions. The product **34 a** was obtained in 15% yield after flash column chromatography (Scheme 19). Subsequent efforts to optimise the reaction could not give a higher yield, even though literature reports have attested to the feasibility of the protocol with a range of β-ketophosphonates which generated a library of alkenes with excellent yields.[66] This was a cause for concern that necessitated review of the protocol after several failed attempts and non-reproducibility.

By changing various parameters in the reaction, starting first with the catalyst loading, it was discovered that by reducing the amount of catalyst from 1.4 equivalents to 0.2 equivalents, a drastic change in the reaction outcome was recorded where the product **34 a** was isolated in 72% yield (Scheme 20) which could not be improved or replicated in the previous set of experiments. The identity of the product was confirmed by the presence of a doublet at *δ* 7.86 with an integral of a single proton characteristic of proton β to phosphonate and $^3J_{HP} = 26.0$ Hz. The stereoselectivity of the resulting chalcone was assigned as *E* configuration based on ^{1}H NMR analysis and comparisons with literature values of similar compounds from the works of Zhang *et al*.[67] The newly established reaction conditions of using 0.2 equivalents of piperidine as a base catalyst, 1.1 equivalent of benzaldehyde, in toluene under Dean-stark conditions were deemed as optimal which were then applied to a range of β-keto phosphonates to test the efficacy and scope of the amended reaction procedure generating various phosphonate chalcones with reasonable yields (Table 2, entries 1-4).
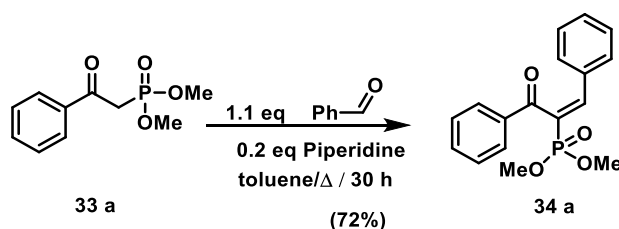
Scheme 20. Optimisation of the Knoevenagel synthesis of phosphonate chalcones

Table 2. Knoevenagel condensation of β-keto phosphonates 34 b - e

Entry	Substrate	Product	Yield (%)	34 b - e
1			55	b
2			89	c
3			81	d
4			51	e

Conditions: 1.1 eq of benzaldehyde, 0.2eq of piperidine was added to 1.0 eq of corresponding β-ketophosphonate in dry toluene under N_2 atmosphere and heated under Dean-Stark conditions for 30 h.

2.5 Attempted Nazarov cyclisation

A literature protocol for the synthesis of 3-aryl-2-phosphoryl-1-indanones *via* Nazarov cyclisations was adopted.[66] In order to test the applicability of the established protocol, the chalcone analogues (**34 b - e**) generated from previous experiments (Table 2, entries 1-4) were investigated under the reported optimal conditions of using $AlCl_3$ in toluene at room temperature for 24 hours. Surprisingly, there were no products formed in each instance, but starting materials were returned instead. Repeated attempts of synthesising the indanones proved unsuccessful with no products formed but starting materials were returned. Investigations into the reaction conditions were hence

necessitated which might give an insight into the failure of the reaction. The need to come up with a model substrate for use in the screening exercise was warranted. To this effect, *p*-tolyl chalcone phosphonate **34 c** was considered and selected as the model substrate due to its relative simplicity and at the same time it was relatively more electron rich on the A ring due to an inductive effect from the attached methyl substituent on the ring compared to chalcone **34 a**.
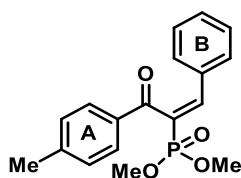
34 c

Figure 14. p-tolyl chalcone phosphonate as the new model substrate

The model substrate was screened under the adopted optimal conditions with 2 eq of FeCl$_3$ in DCM at reflux (Table 3, entry 1) and AlCl$_3$ in toluene at room temperature (Table 3, entry 2) in separate experiments.[66] Here also, it did not yield any product but starting materials were returned just like its counterparts from the previous experiments. This raises cause for concerns as the literature precedence reported obtaining up to 90% of product yield.[66] Other optimal reaction conditions that had good outcomes in the synthesis of indanones from other protocols [69,70] were explored for this model substrate (Table 3, entries 3-5).

Table 3. Screening of reaction conditions for the failed Nazarov cyclisation reaction on *p*-tolyl chalcone phosphonate

Entry	Lewis acid	Concentration (M)	Time (h)	Temp (°C)	Solvent	Conversion (%)[a]
1	FeCl$_3$	0.003	05	reflux	DCM	0
2	AlCl$_3$	0.004	24	20	Toluene	0
3	AlCl$_3$	0.5	24	80	DCE	0
4	ZnBr$_2$	0.5	24	80	DCE	0
5	Cu(OTf)$_2$	0.5	5	80	DCE	0

Conditions: 1.0 eq *p*-tolyl chalcone phosphonate dissolved in solvent, 2.0 eq of Lewis acid added, heated at the specified temperature and time; Key; [a] % conversion of starting material (Sm) to product as determined ^{1}H & ^{31}P NMR spectral assessments of crude reaction mixture.

These involved increasing the concentration, the temperature of the reaction and changing Lewis acids.[69] Cu(OTf)$_2$ was demonstrated to effect catalysis in Nazarov cyclizations of various aryl vinyl enones by Frontier and co-workers, although Cu(ClO$_4$)$_2$ was employed for some substrates bearing electron withdrawing groups.[70] Most of the substrates cyclized with just 2mol% of Cu(OTf)$_2$ at 45 °C, but the sulfonate and phosphonate substrates were sluggish and only started cyclizing when the temperature was raised to 80 °C.[70] Applying these conditions on the model substrate **34 c**, did not yield any product but starting material was returned and as such, an investigation into different reaction conditions was carried out with the hope of finding the right set of conditions that might form the product (Table 4).
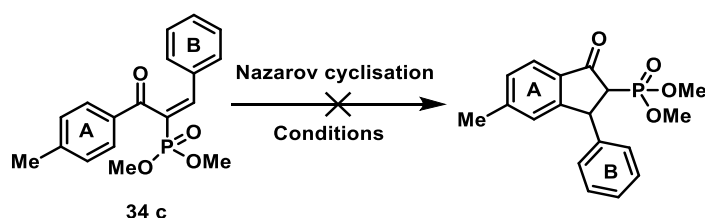
Table 4. Further screening of reaction conditions for the failed Nazarov cyclisation reaction on *p*-tolyl chalcone phosphonate

Entry	Lewis or Bronsted acid	Concentration (M)	Time (h)	Temp (°C)	Solvent	Conversion (%)[a]
1	$AlCl_3$	1.0	5	20	Toluene	0
2	$AlCl_3$	1.0	24	60	Toluene	0
3	$AlCl_3$	1.0	24	Reflux	Toluene	10
4	$FeCl_3$	1.0	24	Reflux	DCM	0
5	$FeBr_3$	1.0	24	40	DCM	0
6	$TiCl_4$	1.0	24	Reflux	Toluene	0[b]
7	TFA	0.80	24	120	Toluene	0
8	$In(OTf)_3$/DPP	0.004	0.3	RT	Toluene	0

Conditions: 1.0 eq *p*-tolyl chalcone phosphonate dissolved in solvent, 2.0 eq of Lewis acid added, heated at the specified temperature and time. Key; [a] % conversion of starting material (Sm) to product as determined ^{1}H & ^{31}P NMR spectral assessments of crude reaction mixture; [b] degradation of Sm.

A further increase in concentration to 1.0 M and temperature rise to 60 °C did not yield any product either (Table 4, entry 2). When the reaction was heated at reflux, a 10% conversion of the starting material to give product was noticed as evidenced by peak integral calculations of ^3J vicinal protons in the ^{1}H and ^{31}P NMR spectra of the crude reaction mixture (Table 4, entry 3). Further screening of different reaction parameters by following other literature precedents with respect to a change in Lewis acid or in combination with a Bronsted acid, solvent, concentration, temperature range including microwave conditions[48] and time were carried out for the ring closure (Table 4, entries 4-8). No products were formed in all instances, and degradation of starting material was evident in an instance although the identity of side-products was not verified (Table 4, entry 6).

Several hypotheses to investigate the failure to form the cyclised material were then examined. The first postulate suggests that an S_N2 -like reaction might be occurring at the phosphorus atom, where Cl⁻ originating from the Lewis acid may be attacking the methyl phosphonate ester *via* an S_N2 process

thereby generating a phosphonate anion that might be lost in the aqueous phase, although no literature precedent to support this proposal has been found (Scheme 21).
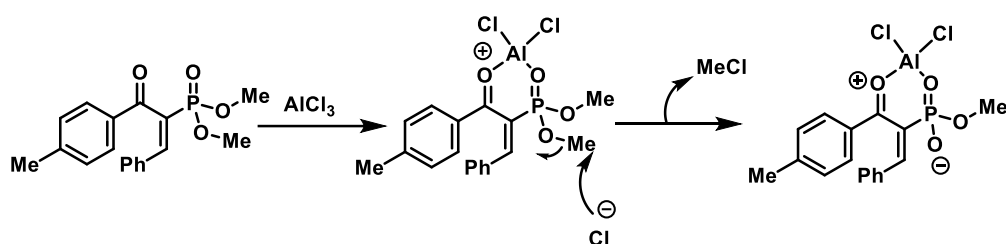
Scheme 21. Presumed generation of a phosphonate anion

To test this hypothesis, use of a non-nucleophilic counter ion was considered and as such, aluminium triflate Al(OTf)$_3$ was employed. No product was formed when the temperature was raised to 60 °C, but a slight conversion of starting material to product (Table 5, entries 1 & 2) was seen at reflux.

Table 5: Screening bulky LA counterion for attempted Nazarov cyclisation

Entry	Lewis Acid	Concentration (M)	Time (h)	Temp (°C)	Solvent	Conversion (%)[a]
1	Al(OTf)$_3$	1.0	24	60	Toluene	0
2	Al(OTf)$_3$	1.0	24	Reflux	Toluene	5

Conditions: 1.0 eq *p*-tolyl chalcone phosphonate dissolved in solvent, 2.0 eq of Al(OTf)$_3$, heated at the specified temperature and time, Key; [a] % conversion of starting material (Sm) to product as determined ^{1}H & ^{31}P NMR spectral assessments of crude reaction mixture

Although the use of Al(OTf)$_3$ showed an indication of product formation, it was only in a disappointing 5% conversion of starting material. Results from the table revealed that the reaction protocol did not produce any meaningful outcome greater than 5% conversion (Table 5, Entries 1-2) as depicted by integral calculations of the ^{1}H NMR spectrum of the crude reaction mixture. This suggests that the Cl$^-$ was unlikely the cause of the problem.

The second possibility was to assess the effect of steric bulk that could prevent the S$_N$2 -like reaction from happening. Accordingly, the need to synthesise bulkier groups was pursued where ethyl and

diisopropyl chalcones were considered for these investigations (Scheme 22). However, the prerequisite starting material, diisopropyl methylphosphonate (DIMP) **36** needed for the phosphono-Claisen condensation was not commercially available and was prepared by base catalysed esterification of dichloromethyl phosphonate **35** which was obtained from treatment of DMMP **25** with $SOCl_2$ in pyridine at reflux as a moderate 65% yield (Scheme 22).
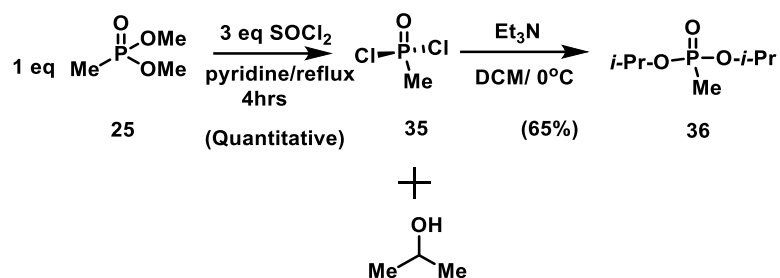
Scheme 22. Synthesis of Diisopropyl methylphosphonate

The chalcones *p*-tolyl ethyl β-ketophosphonate **40** and *p*-tolyl diisopropyl β-ketophosphonate **41** were then each prepared over two steps from condensation of methyl *p*-tolyl benzoate with DEMP **36** and DIMP **37** with good yields of 83% and 90%, respectively. The identity of the products as single *E* alkenes were each confirmed by the magnitude of the *J* values in the ^{1}H NMR spectrum assessment of the crude reaction mixtures and were found to be consistent with literature results.[67] Applying optimum conditions for the Nazarov cyclisation did not yield the cyclisation material in both cases as evidenced by ^{1}H and ^{31}P NMR results but starting material was returned (Scheme 23).
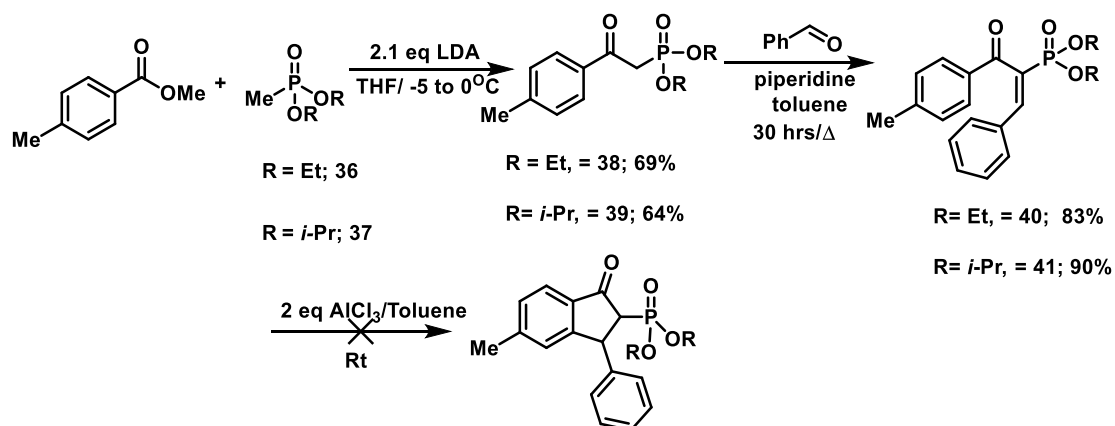
Scheme 23. Steric bulk assessment on phosphonate chalcones

It can be inferred from the outcome of these two results that steric hinderance was not a deterrent to the cyclisation of the chalcone and as such, a third hypothesis which investigated on the electronic nature of the **A** ring of the chalcone was put forward. It was proposed that the electron donating groups on the **A** ring will stabilise the developing positive charge on the intermediate **42** at the transition state thereby lowering the energy state which will facilitate the rate of the cyclisation (Scheme 24). Testing this necessitated making more electron rich substrates and as such *ortho* (*o*), *meta* (*m*), and *para* (*p*)- methoxy-substituted diethyls were considered for these investigations.

R' = Electron-donating groups

42
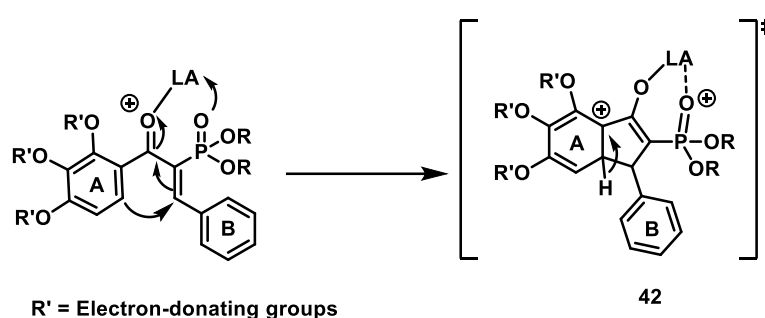
Scheme 24. Stabilisation of developing +ve charge by electron-donating substituents

In order to prepare these substrates, the prerequisite ester **43** methyl-*m*-methoxybenzoate was synthesised in a classical Fischer esterification reaction from *m*-methoxy methyl benzoic acid (Scheme 25). It was initially made by direct acid catalysis where molecular sieves were added to drive the thermodynamically controlled reaction to completion with an obtained yield of 80% (**method i**), while the second approach was carried out by dropwise addition of thionyl chloride which gave 95% product yield (**method ii**). Though both procedures gave excellent yields of esters with the first route being more atom efficient, the second method was more straight forward requiring no traditional work up and as such it was adopted.
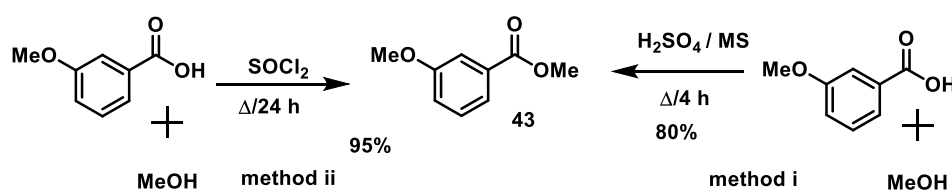
Scheme 25. Synthesis of Methyl-*m*-methoxyl benzoate

Next, the corresponding substrates **44 - 46** for each chalcone were separately synthesised by coupling diethyl methyl phosphonate (DEMP) **36** with their corresponding esters, which were then transformed into their respective *E* chalcones **47 - 49** *via* Knoevenagel olefination. Their configurations were confirmed by the magnitude of the *J* values in the ^{1}H NMR spectra of the crude reaction mixture and were found to be consistent with literature values. [48] They were then purified by column chromatography and optimal Nazarov conditions were applied to them, but the outcomes remained the same as in previous failed reactions (Scheme 26).
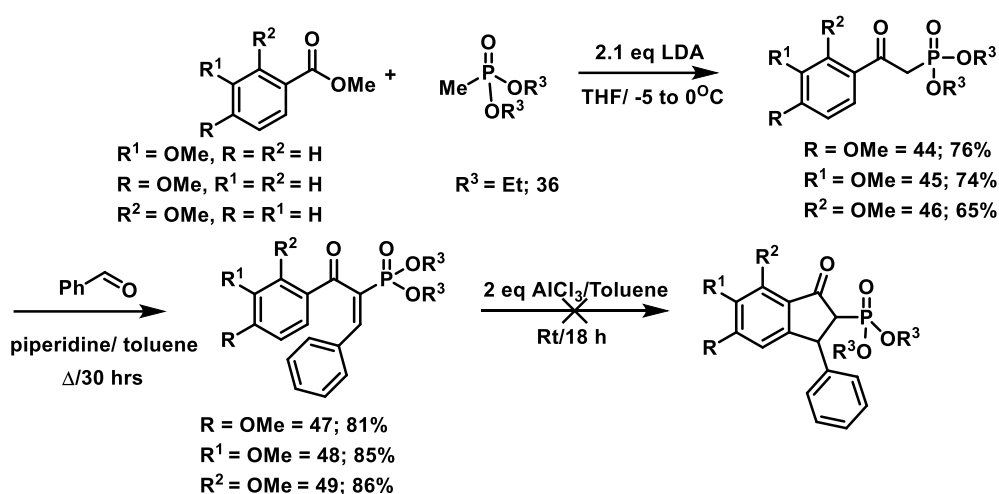
Scheme 26. Synthesis of different methoxy substituted phosphono-chalcones and their attempted Nazarov reactions

It is now clear evidence that getting Nazarov cyclisation to work as the key step of synthesizing indanones in this project has so far proved unsuccessful despite being published in literature. The reason is unclear, however a point to note is the substrates used in this work were different from the ones quoted in literature which might be partly responsible for the failure in replicating the procedure. Given the practicality and relative simplicity of the procedure, more studies are needed in the future to adequately understand the reason behind non-replication of the procedure. To circumvent this issue, a new strategy was adopted.

2.6 Hypothesis

Owing to the remarkable success of the Heck reaction in producing multicyclic compounds and quarternary stereocenters (Scheme 27),[71] the principle governing standard Heck conditions was adopted for the synthesis of 3-aryl-2-phosphoryl indanones in this project. If successful, this will be the first time it is reported in the synthesis of 2-phosphoryl-1-indanones.
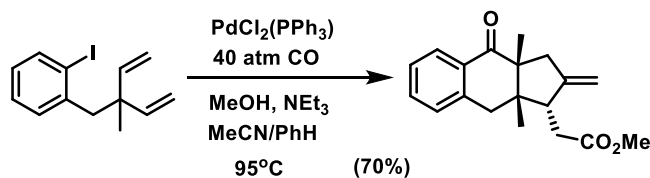
Scheme 27. Synthesis of multicyclic compounds with multiple stereocenters *via* Heck Cyclisation[71]

2.7 Model substrate:

The synthesis of a model achiral substrate to first evaluate Heck cyclisation reaction to form the desired 2-phosphoryl-3-aryl chalcone was attempted (Scheme 28).
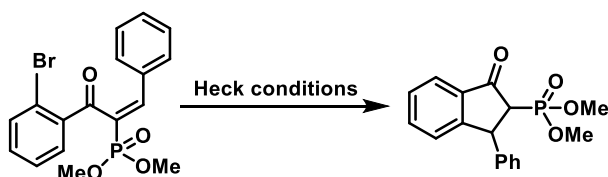
Scheme 28. Synthesis of 2-phosphoryl-3-aryl indanone *via* standard Heck reaction conditions

Preparation of the β-keto phosphonate **51** was prepared as in the previous chapter for the corresponding non-bromo β-keto phosphonate analogues (Chapter 2.3.1) but with a slight modification in the order of addition of the reactants as developed by Maloney and Chung as they have reported the instant formation of the products with excellent yields after complete addition of starting materials. A precooled solution of previously made LDA was added dropwise to a mixture of the phosphonate **25** and methyl-2-bromo benzoate **50** in THF at -5°C, and the reaction mixture was left to stir at 0 °C following its complete addition (Scheme 29).
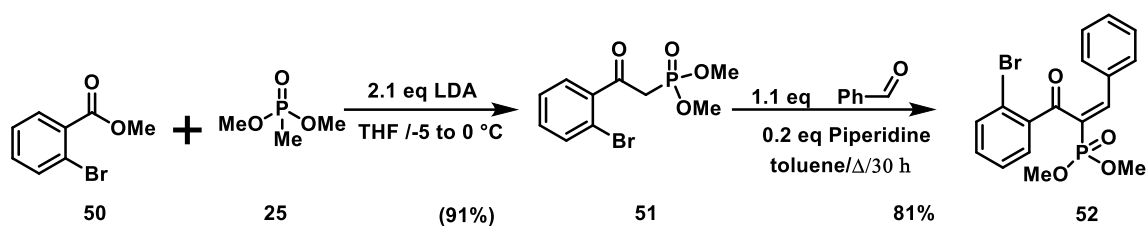
Scheme 29. Synthesis of 2'-bromo-2-phosphoryl-3-aryl chalcone

The reaction was complete within 15 minutes with an excellent yield (91%) of the β-keto phosphonate **51** which was confirmed from the ^{1}H and ^{31}P NMR spectra. These reaction conditions were hence deemed optimal given the excellent reaction outcome. The next step was the Knoevenagel condensation of β-keto phosphonate **51** with benzaldehyde under Dean-Stark conditions to produce chalcone **52** as the key intermediate. A very good yield (81%) of the bromo chalcone was obtained after purification and confirmed by the ^{1}H and ^{31}P NMR spectra. The stereoselectivity of the resulting chalcone was assigned as *E* configuration based on ^{1}H NMR analysis and compared with the literature data of similar compounds.[67] With the chalcone **52** in hand, the next compound to be made was the target molecule which was envisaged to be formed by exposing the chalcone to standard Heck conditions (Scheme 30).
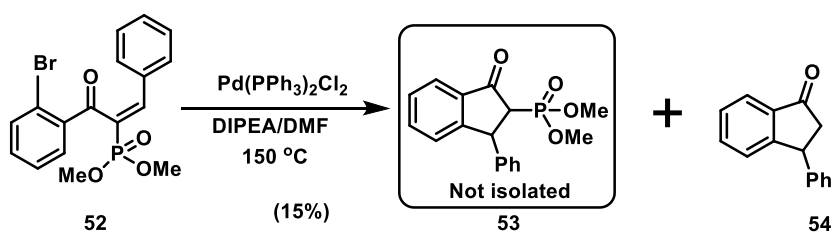
Scheme 30. Attempted synthesis of 2-phosphoryl-3-phenyl-1-indanone *via* Heck reaction

Surprisingly, there was no trace of the desired compound **53**, but the presence of a dephosphorylated 3-phenyl indanone **54** was evident with a modest yield of 15% (Table 6, entry 1) as evidenced by ^{1}H NMR spectroscopic data analysis which matches literature data.[50, 4,72,73,74] This was a rather unexpected outcome. Although the desired compound was not formed, the need to explore the reaction further was considered. Concentration of the reaction mixture was the first

parameter to be assessed. It was observed that at low concentrations between 0.03 M and 0.07 M, the dephosphorylated product **54** was exclusively formed (Table 6, entries 1-3). With a slight increase in the concentration, a trace of the phosphorylated compound **53** was observed as seen in the ^{1}H and ^{31}P NMR spectra in addition to indanone **54** in the subsequent reactions (Table 6, entries 4 & 5). These outcomes were indications suggesting that the more dilute conditions facilitated the dephosphorylation and as such a 10 fold concentration increase (0.3 M) compared to the first entry was considered. Interestingly, a mixture of both products **53** and **54** was realised although the yield was modest for both products (Table 6, entry 6). The reproducibility of the reaction at 0.3 M under the same conditions, was re-examined for the second time and the same outcome was obtained.

Table 6. Attempted synthesis of 2-phosphoryl-3-phenyl-1-indanone via Heck reaction

Entry	Concentration (M)	REACTION OUTCOME	
		Dephosphorylated	Phosphorylated (% yield [c])
1	0.03	15	0
2	0.05	26	0
3	0.07	29	0
4	0.08	30	05
5	0.10	40	05
6	0.30 [d]	15	18
7	0.30*[a.b]	0	0
8	0.30*[b]	0	0

Conditions: All reactions were done under standard Heck conditions for 48 hours;*reaction time is 24 hours,[a] 5mol% catalyst, [b] different bottle of DIPEA; [c] % yield of inseparable mixture of diastereomers from column chromatography and determined by ^{1}H and ^{31}P NMR analysis; [d] done in duplicate

A mixture of diastereomers in the ratio of (major/minor; 60:40) as seen from the ^{1}H NMR spectrum was formed, which could not be separated by flash column chromatography on silica gel. However, the dephosphorylated product **54** was obtained as a clean product each time the reaction was carried out. This was rather disappointing, but notwithstanding, a need for further optimisation was necessary to allow the reaction to reach its full potential. Maintaining the same concentration at 0.3 M but with a fivefold increase in catalyst loading (5 mol%), the desired product failed to form (Table 6, entry 7). In order to understand what might be responsible for this disappointing outcome, the same conditions that led to the formation of both compounds in entry 6 were revisited, but surprisingly the expected compound **53** still did not form (Table 6, entry 8). This was rather strange because the products were formed in the initial duplicate trials with even lower catalyst loading. The only difference was that in these instances (entries 7 & 8), the base used was from a different bottle, suggesting its quality may have deteriorated.

2.8 Synthesis of enantioenriched phosphoryl indanone 58

Although novel compound **53** could not be purified efficiently using silica gel flash column chromatography, the reaction worked, and an enantioenriched TADDOL derived methyl phosphonate **55** was employed for the next condensation reaction. It was hypothesised that this auxiliary could control the stereochemistry of the indanone during Heck reaction (Scheme 31).

The prerequisite keto phosphonate **56** was first made by phosphono-Claisen condensation of the bromo ester **50** with methyl phosphonate **55**, previously prepared and available in the group by Ali Hussein Raheemah**.** Surprisingly, the adopted optimum conditions used in the synthesis of the previous β-keto phosphonate **51** were not applicable in this instance, instead the starting material was returned (Table 7, entry 1).

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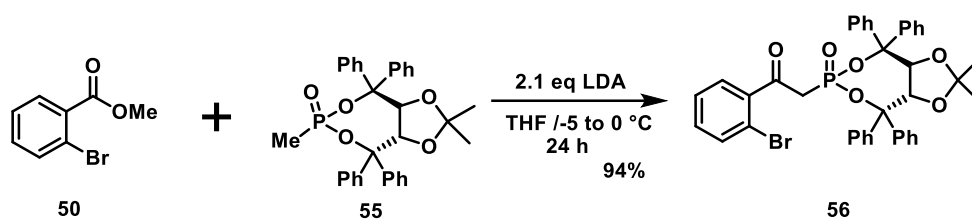
Scheme 31. Synthesis of TADDOL-derived β-keto phosphonate

Table 7. Probing the phosphono-Claisen reaction

Entry	[a] Reaction 1 (minutes)	[b] Reaction 2 (hours)	[c] Yield (%)
1	15	0.25	[d]SM
1	15	01	[d]SM
2	15	24	40
3	40	01	[d]SM
4	40	24	94

Reaction conditions: [a]LDA was made by adding DIPA (2.2 equiv) + *n*-BuLi (2.2 equiv) THF (10 mL) at -78 °C and left to stir for the times stated. [b] In a different reaction flask, Taddol-derived methyl phosphonate (1.1 equiv) + methyl-2-bromobenzoate (1.0 equiv) in 10 mL THF at -5 °C to 0 °C followed by dropwise addition of LDA. [c] Product yields after purification by column chromatography. [d] Returned starting material

It was anticipated that the product of interest might be formed if the reaction was given more time to run and as such it was extended for one hour. Here again, it failed to yield the product of interest unfortunately, but the starting material was returned for the second time (Table 7, entry 2). However, when the reaction time was extended for 24 hours, a modest yield of the desired product (40%) was formed although there was incomplete consumption of starting material (entry 3), suggestive that the reaction was time dependent. Additionally, it was speculated that the time taken for LDA formation (reaction 1) was not sufficient to bring about complete enolization of the phosphonate **55**, and which if fully formed, might push the reaction to completion otherwise not requiring an extended time for reaction 2. Here again, starting material was returned (Table 7, entry 3). Pleasingly, when both reactions 1 and 2 were extended, a yield of 94% was obtained which did

not require purification (Table 7, entry 4), and in turn was used in the synthesis of the key intermediate **57** *via* Knoevenagel condensation (Scheme 32).
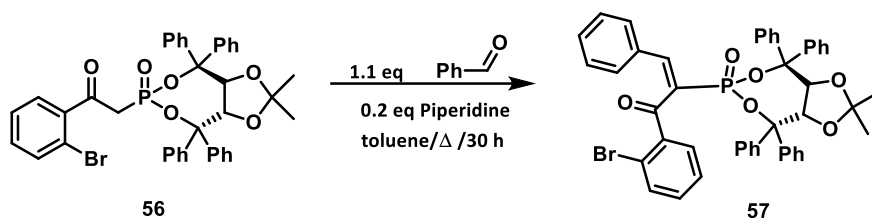
Scheme 32. Synthesis of TADDOL-derived bromo chalcone

The formed β-keto phosphonate **56** was put under Dean stark conditions with benzaldehyde for 30 hours. The yield obtained was relatively poor (12%) (Table 8, entry 1) compared to compound **52** which was obtained from the same reaction conditions. The generous amount of residual starting returned (65%) was suggestive of the reaction requiring more time and as such, 48 hours was decided for the next attempt. A disappointing 20% product yield was obtained after purification with 50% unreacted starting material (Table 8, entry 2). Although more starting material appears to be consumed in the second trial as compared to the first case, there was still an indication of more time requirement for a possible complete reaction. At the third attempt, there was complete consumption of starting material after 5 days, and an excellent yield of 95% of the *E* isomer was obtained following purification by column chromatography (Table 8, entry 3).

Table 8. Optimisation of Knoevenagel condensation reaction

Entry	Time (hrs)	% yield	SM (%)
1	30	12	65
2	48	20	50
3	120	95	-

Conditions: 1.1 eq of benzaldehyde, 0.2eq of piperidine was added to 1.0 eq of corresponding β-ketophosphonate in dry toluene under N$_2$ atmosphere and heated under Dean-Stark conditions for the stipulated time

After the successful formation of the prerequisite key intermediate **57,** it was then exposed to the optimum Heck conditions used for the synthesis of dimethyl phosphonate indanone **53**. It was interesting to note that the desired compound **58** was formed efficiently at different range of concentrations, between very dilute (0.02 M) to more concentrated (1.00 M) media over 24 hours which was not the case in the model substrate. Similarly, there was no evidence of any dephosphorylated product in this instance (Scheme 33).
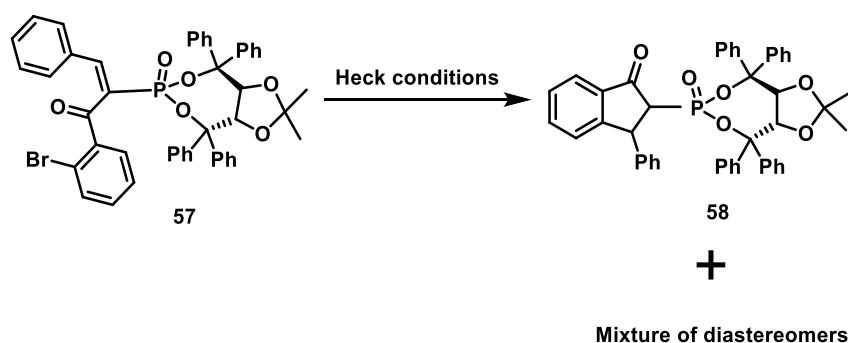
Scheme 33. Synthesis of TADDOL-derived 3-phenyl indanone

Although there was full conversion of starting material to product in all instances, separation of the different diastereomers by normal flash column chromatography however proved challenging except for a modest amount (18%) that was isolated but the rest of the mixture could not be purified. Several attempts were made to obtain crystals for X-ray analysis but amorphous solids were returned, even after purification using preparative HPLC. An alternative route to the synthesis of indanones was hence required.

2.9 Possible reaction mechanism

Suggested reaction pathways may be used to propose a mechanism that might be responsible for both the phosphorylated and dephosphorylated products in the modified Heck procedure (Scheme 34):
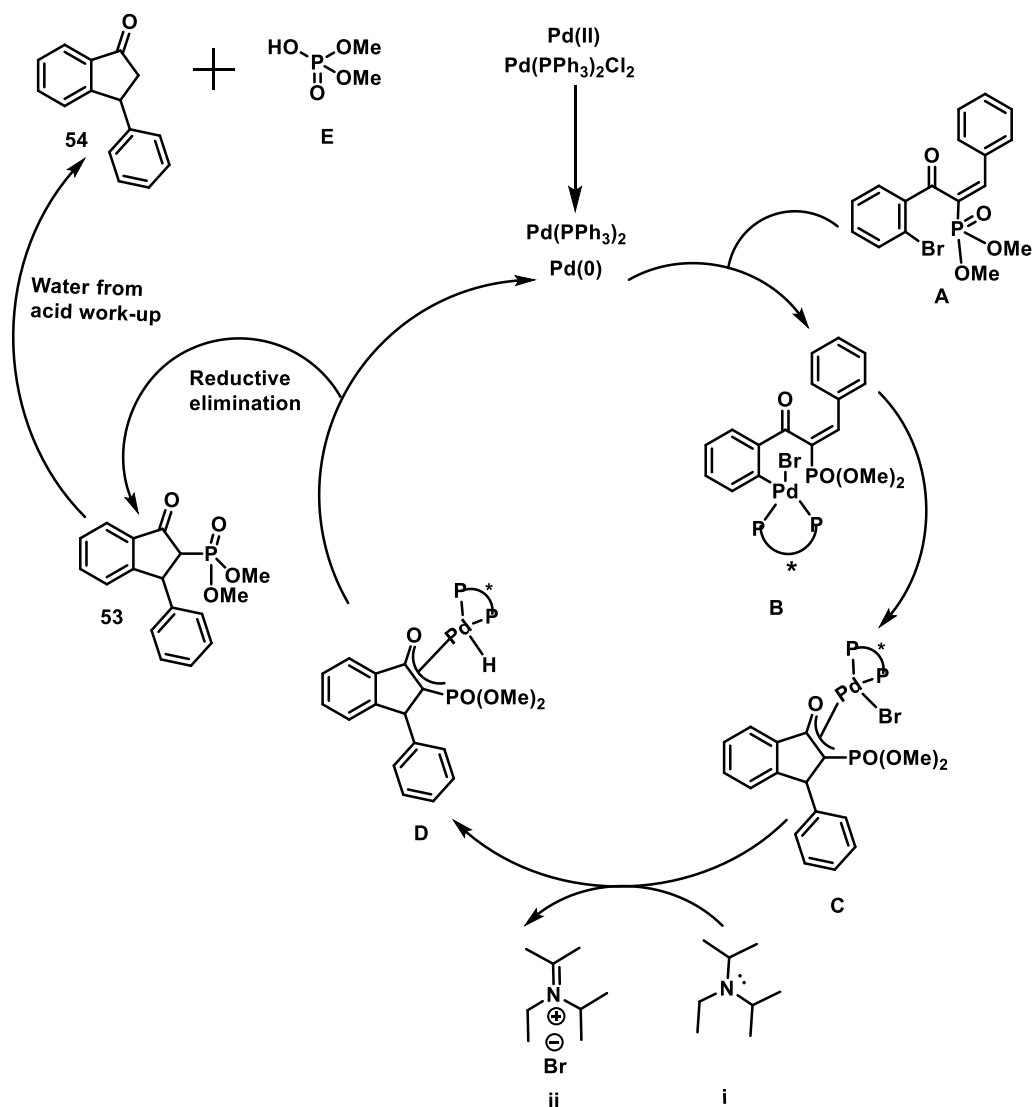
Scheme 34. Proposed catalytic palladium cycle in the synthesis of phosphorylated and dephosphorylated indanones

A possible reaction mechanism for the formation of the indanone molecules **53** and **54** may be proposed by analogy to the intermolecular reductive Heck reaction of aryl iodides with α,β-unsaturated ketones as explained by Cacchi et al. [75], [76], [77], [78] The initial oxidative addition of the aryl chalcone halide (**A**) to Pd (0) phosphine complex (**B**), coordination and insertion of the olefin part of the molecule on to the complex in a *syn* manner generates the π-oxa-allyl cyclic C- Pd-enolate cation (**C**). Due to the *cis* configuration of the cyclic intermediate **C** and absence of β-hydrogen *syn* to the palladium centre, β-hydride elimination is prevented as evidenced from the literature. [76], [79], [80], [81]

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It has been reported that having a substituent at β-position of the substrate compound or by addition of a hydrogen source to the reaction mixture [82] additionally hampers β-hydride elimination and as such, a proposal that explains hydride transfer from DIPEA (i) is made, thereby forming an iminium ion (ii) and the palladium (II) hydride complex (D). [76,83] This is further supported by mechanistic study on palladium catalysed reductive Heck reaction of aryl iodides to enones using DIPEA as a reductant which revealed the formation of palladium alkyl hydride complex. [84,85]

The phosphorylated indanone **53** is subsequently formed by collapse of the palladium II hydride complex (**D**) *via* reductive elimination and regeneration of Pd (0). The use of an organic amine base is reported to be responsible for directing the reaction towards conjugate addition rather than direct addition [78] and also as a reductant that maintains the catalytic cycle that reduces palladium (II) to palladium (0). [86,87] Likewise, water serves a dual purpose with a nucleophilic attack on the phosphorus atom in **53** which could lead to loss of the phosphate **E** and formation of the dephosphorylated indanone **54** and at the same time, as a hydride source as supported by deuterium-labelling experiments. [80,81,84]

2.10 Conclusions:

A new protocol for the synthesis of 2-phosphoryl-3-aryl indanones has been developed using modified Heck reaction conditions which was not reported in literature prior to this. Synthesis of two novel 2-phosphoryl-3-phenyl indanones was attempted and indication of product formation was seen from spectral assessments of the crude mixture which shows the feasibility of the reaction although isolating clean materials proved challenging. An unexpected but interesting side product was discovered where the dephosphorylated 3-phenyl indanone **F** was formed alongside the expected products. Further work is needed to fully understand the intrinsic nature of the reaction and explore the potential of the methodology.

Chapter 3.0

3.1 Heck cyclisation.

The Heck reaction has been identified as an effective tool for the synthesis of C-C bonds between alkyl or vinyl halides which are catalysed by palladium sources in the presence of a base.[77, 88] Since the independent breakthroughs by Heck and Mizoroki in the 1970s,[89] the exploration on its general mechanism, reaction conditions, applications in natural and drug-like synthesis has been an area pursued by many organic chemists.[81]

Since then, other variations of the conjugate additions using other organometallic catalysts ensued like the rhodium catalysed asymmetric synthesis of 3-aryl-1-indanones[50] by Morehead and the intramolecular hydroacylation of 2-vinyl benzaldehyde[73 ,90] and Hayashi.[77]

Subsequent studies by Zhou *et al*; revealed the palladium catalysed conjugate addition of enones and enals with aryl halides where β-hydride elimination can be suppressed with the right solvent choice, in which formates and alkyl amines acted as the proton sources.[91]

3.2 Synthesis of simple and substituted indanones.

Various research groups have employed the reductive Heck cyclisation for the synthesis of 3-aryl indanones generating both racemic and asymmetric products in moderate to good yields.[28] Buchwald *et al.* studied the asymmetric reductive Heck reactions of *o*-bromochalcone derivatives facilitated by the chiral ligand (*R*)-3,5-XylMeOBIPHEP and proton sponge as the base of choice and hydride source in which indanones were produced with good yields and good to excellent enantioselectivities (Scheme 35).[76]
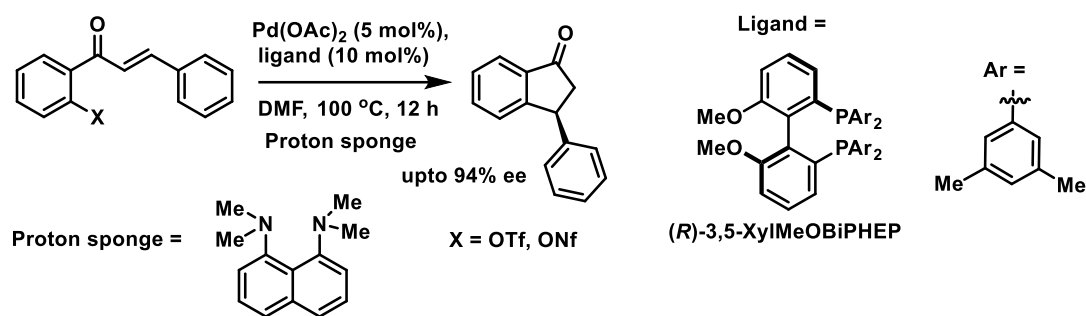
Scheme 35. Asymmetric reductive Heck cyclisation[76]

Using the same protocol, a wide range of indanones containing electron withdrawing or donating groups on either or both rings **A** and **B** were formed that had comparable product yield and enantioselectivity to the unsubstituted indanone (Figure 15).
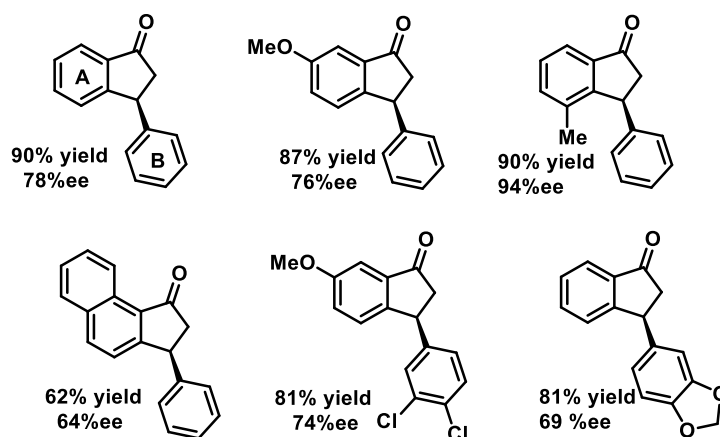
Figure 15. Scope of asymmetric reductive Heck cyclisation of some 3-aryl indanones[76]

Although the procedure delivered enantioenriched products for simple indanones, the methoxy substituted derivatives which are related to those required for the isopaucifloral F substrate, gave only moderate ee (76% and 74%) [76] and as such, a racemic version of this reaction was adopted and chosen as a strategy towards obtaining the indanone cores after which their asymmetric induction will be undertaken.

3-Phenyl indanone **54** was chosen as the model substrate that could be used to assess the efficiency of the reaction without any interference from attached substituents on both **A** and **B** phenyl rings which could be synthesised over two steps from 2-bromoacetophenone (Scheme 36).
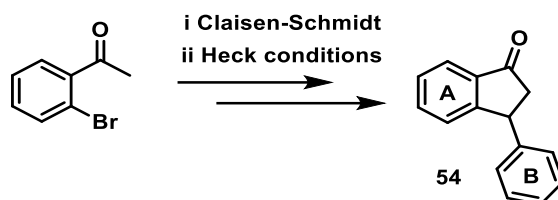
Scheme 36. Synthesis of 3-Aryl indanone as the model substrate *via* intramolecular Heck reaction

3.2.1 Claissen-Scmidt condensation

Chalcones have diverse methods of preparation but a commonly used method is *via* the Claisen–Schmidt reaction [93] due to good yields and simplicity compared to other methods. [94] It generally involves condensation of acetophenone and aldehyde derivatives which is facilitated by either acid or base catalysis.[94]

3.2.2 Synthesis of the model substrate

2'-Bromo chalcone **59** was synthesised *via* the Claissen-Scmidt condensation of 2-bromoacetophenone and benzaldehyde under basic conditions following a standard literature[67] protocol (Scheme 37). The identity of the product as a single *E* alkene was ascertained by the magnitude of the *J* values in the ¹H NMR spectrum assessment of the crude reaction mixture and was found to be consistent with literature results.[95] The pure material was isolated in an almost quantitative yield (97%) after flash column chromatography.
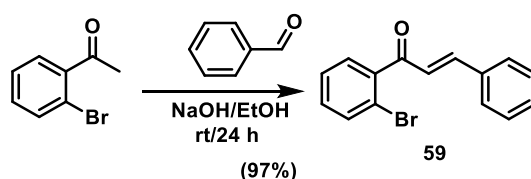
Scheme 37. Aldol condensation reaction

In order to assess the scope of the reaction, substituted 3-aryl indanones were also prepared. 2′-Bromo-3,5-dimethoxy-substituted chalcone **64** was required as an intermediate for isopaucifloral F indanone but due to high cost of purchasing the methoxy substituted ketone starting material, it was instead prepared over 4 steps starting from inexpensive commercially available starting material 3,5-dimethoxy benzaldehyde **60** (Scheme 38).
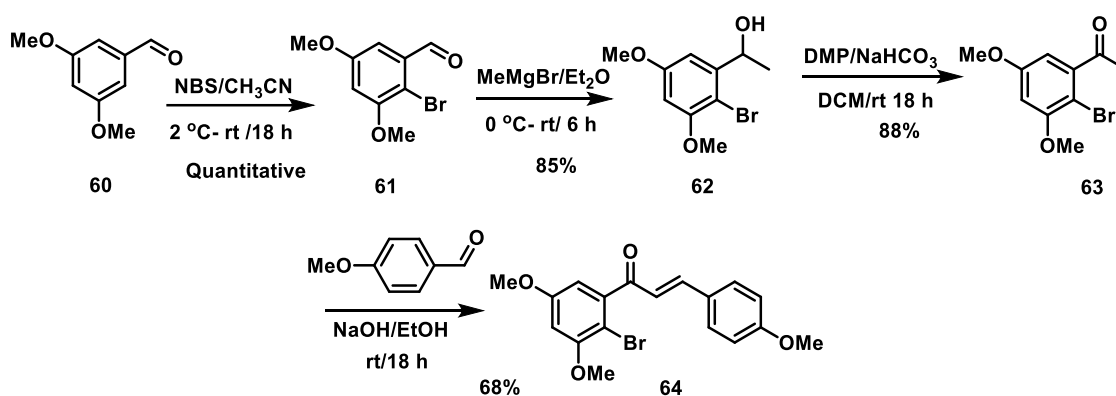
Scheme 38. Synthesis of substituted chalcone for *i*-paucifloral F

Direct bromination of **60** with NBS following a literature precedence[96] provided a quantitative yield of the desired mono brominated compound **61** as a single regioisomer that did not require further purification. The identity of the aldehyde was established by ^{1}H NMR analysis which matches literature data,[96,98] which is in-line with what would be expected on the grounds of steric and electronic factors. Grignard addition with methylmagnesium bromide afforded the corresponding alcohol **62** and was recrystallised from chloroform in 85% yield. Subsequent Dess-Martin oxidation furnished 88% yield of the ketone **63** which underwent Claisen-Schmidt condensation with *p*-anisaldehyde to furnish the 3,5-dimethoxy-substituted chalcone **64** as the only isomer, again confirmed as the *E*-isomer by the magnitude of the *J* values in the ^{1}H NMR spectrum.

The 4,6-dimethoxy-substituted chalcone **70** was also targeted which will subsequently serve as an intermediate for the isopaucifloral F indanone analogue. The starting material employed for this

purpose was 3,5-dimethoxybromobenzene **65**. A Friedel Crafts acylation was first attempted but the

desired product was formed in only 25% yield after extensive column chromatography with several

other side products evident (Scheme 39). Analysis of the ^{1}H NMR data of the product **66** and the

major side product which was later identified as 4-bromo-2,6-dimethoxy-phenylethanone **67** was

consistent with data from literature.[99]
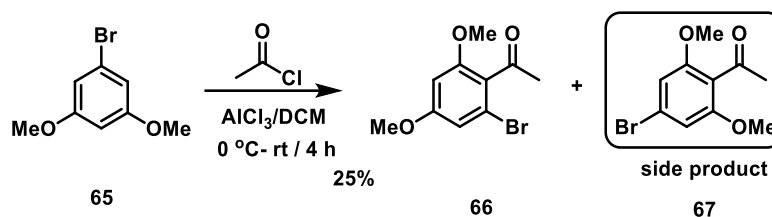
Scheme 39. Friedel-Craft acylation of 3,5-dimethoxybromobenzene

The outcome of a Friedel-Crafts reaction usually consists of a mixture of products because both the

bromine and methoxy substituents on the aromatic ring of the starting material are expected to

direct the incoming electrophile towards *ortho* and *para* positions. However, the low yield of the

preferred product was discouraging considering the number of steps required before the substituted

indanone is formed. This strategy was considered as unproductive and the earlier procedure

employed for the isopaucifloral F chalcone **64** was adopted as the preferred route even though it

had more reaction steps.
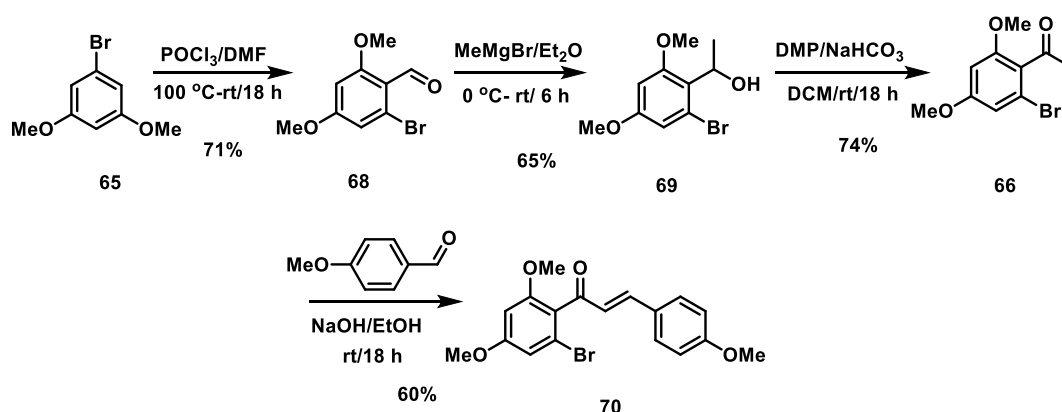
Scheme 40. Synthesis of substituted chalcone for *i*-paucifloral F analogue

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The synthesis commenced by Vilsmeier-Haack formylation of the starting material **65** following a reported protocol from the literature (Scheme 40). [99, 100] Gratifyingly, 71% yield of the corresponding aldehyde **68** was obtained as the only regioisomer after flash column chromatography as confirmed from interpretation of its ^{1}H NMR spectrum which matched literature data,[99, 100] although the formation of other side products cannot be ruled out due to directing group effects of the substituents on the benzene ring of the starting material **65**. It is also interesting to note that the obtained product yield (71%) has a substantial improvement on the reported yield in literature (33%) [99] for the same reaction and isomer. Subsequent Grignard addition on the aldehyde provided a modest yield of 65% adduct **69**. Dess-Martin oxidation on the alcohol provided 74% ketone **66** which was purified by recrystallisation. The substituted chalcone **70** was subsequently obtained by base catalysed Claisen-Schmidt reaction of ketone **66** with *p*-methoxy benzaldehyde to give a 60% yield of the desired enone (Scheme 40).

3.2.3 Synthesis of 3-aryl indanone.

With the chalcone **59** in hand, conditions for reductive Heck cyclisation were investigated (Scheme 41). The indanone model substrate **54** was synthesised using standard Heck reaction conditions as reported in the literature [76] and confirmed by the ^{1}H NMR spectrum of the crude reaction mixture where a modest yield of 35% was obtained after chromatography. Encouraged by the outcome, an optimisation study was conducted by changing the reaction parameters with the hope of obtaining better yields (Table 9).
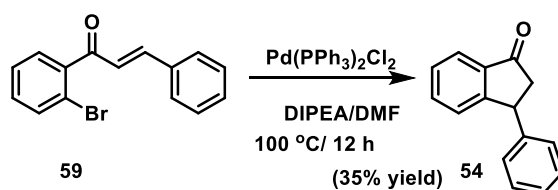
Scheme 41. Synthesis of 3-aryl indanone as the model substrate *via* intramolecular Heck reaction

Table 9. Optimisation of reaction conditions for the model Heck reaction

Entry #	Time (h)	Temperature (°C)	Catalyst Loading (equivalent)	Solvent	Concentration (M)	Yield (%)
1	12	100	0.05	DMF	0.25	35
2	18	100	0.05	DMF	0.25	50
3	18	100	0.05	DMF/PhCO$_2$H	0.25	40
4 [a]	18	100	0.05	DMF	0.10	50
5	02	100	0.05	DMF	0.10	0
6	02	150	0.01	DMF	0.10	54
7	18	65	0.01	THF	0.95	0
8	18	80	0.01	CH$_3$CN	0.95	0
9 [b]	18	150	0.01	DMF	0.95	0
10	18	150	0.01	DMF	0.10	50

Conditions: All reactions were done under an inert atmosphere of N$_2$ using 1.0 eq of model substrate dissolved in DMF, Pd(PPh$_3$)$_2$Cl$_2$ catalyst except specified, 2.0 eq of DIPEA except specified [a] Pd(OAc)$_2$/PPh$_3$; [b]

base used was proton sponge =

From the table, it was observed that an increase in time, gave an improved product yield (Table 9, entry 2). However, a decrease in product yield was recorded when an additive was added (Table 9, entry 3). It was interesting to note that an increase in temperature improved on the product yield even at a lower catalyst loading and shorter reaction time (Table 9, entry 6), but an increase in concentration or changing the base had a detrimental effect on the reaction outcome as compared to entry 2 (Table 9, entries 7- 9). Also, worthy to note was that a catalyst change did not yield higher product output as compared to the second entry (Table 9, entry 4). No product was formed when the solvent was changed from DMF to either THF or CH$_3$CN (Table 9, entries 7 and 8). Although some results comparable to the second entry were obtained in the table with varied conditions, the best

reaction conditions were the choice of DMF as a solvent at a concentration of 0.10 M, heating at reflux for 2 hours, and 1 mol% of the catalyst Pd (PPh$_3$) providing 54% yield of the product after flash column chromatography on silica gel (Table 9, entry 6) and as such, were adopted as optimal. The formation of the indanone molecule **54** can be explained with a plausible mechanism (Scheme 42) by analogy to the intermolecular reductive Heck reaction of aryl iodides with α, β-unsaturated ketones as explained by Cacchi et al.[75,76,77,78] which was earlier explained in Scheme **34** on page **40**.

Another possibility of forming the indanone molecule **54** could arise after a possible Cα-Pd heterolytic bond cleavage of the cyclic C- Pd-enolate cation (C), followed by rapid protonation[87] from acid work up or iminium ion (ii),[78] and subsequent conversion of Pd (II) to Pd (0) by the base (i). Although the reductive Heck product **54** is the major compound formed, formation of the classical Heck product as a side product may not be entirely ruled out, which might be the reason for the relative low yield as explained by Cacchi *et al*; that a trace amount of the Heck product is often noticed even in the presence of a strong hydride donor like DIPEA .[77,101]
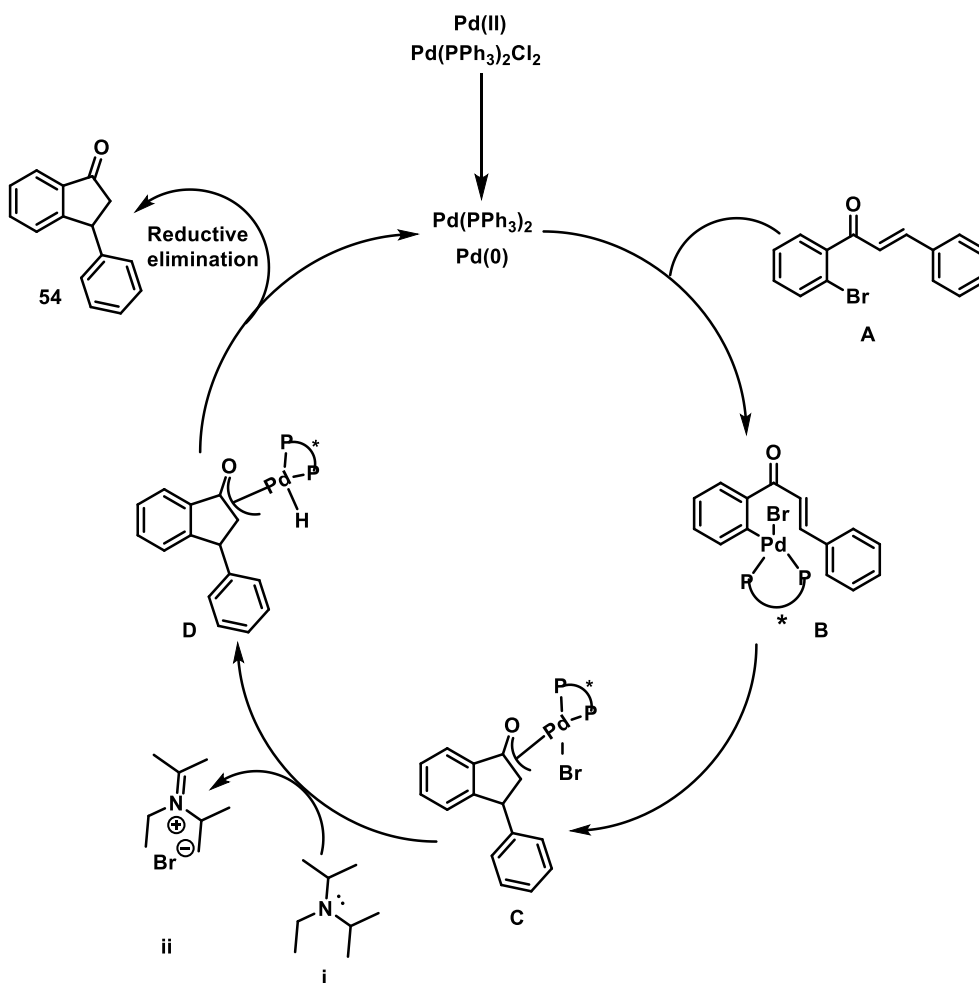
Scheme 42. Plausible scheme for reductive Heck cyclisation

3.2.4 Syntheses of substituted indanones as scaffolds for isopaucifloral F and its analogue

R^1 = OMe, R^2 = H; 64

R^1 = H, R^2 = OMe; 70

R^1 = OMe, R$_2$ = H, 71; 8%

R^2 = OMe, R$_2$ = H, 72; 13%
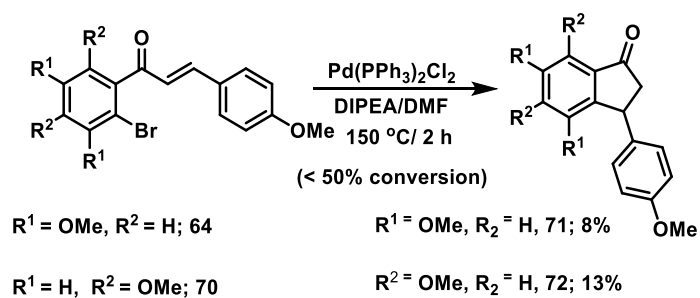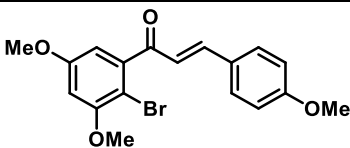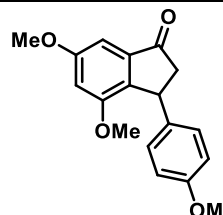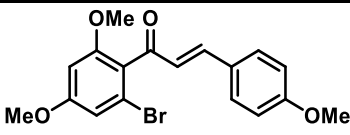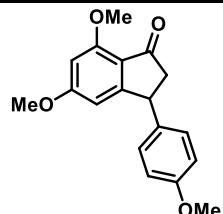
Scheme 43. Syntheses of substituted indanones as scaffolds for isopaucifloral F and its analogue

Although, the synthesis of target **71** has been reported from other protocols,[51,2] the reaction

conditions were not without some drawbacks like harsh acidic conditions or high temperatures, and

use of bulky ligands that are air or moisture sensitive. As such, it was synthesised using standard

Heck reaction conditions as reported in the literature.[76] Indanone **72** on the other hand is a novel compound with no literature precedent. Having established the optimum reaction conditions from the previous synthesis of the model indanone core in table **9** with some success, the same protocol was replicated on methoxy substituted chalcone intermediates to assess the scope of the reaction (Scheme 43). Using this procedure, < 20% of products was obtained as evidenced by ^{1}H NMR spectral assessment of the crude reaction mixtures and as such, an optimisation study was pursued to improve on the yields (Table 10).

Table 10. Optimisation of Heck reaction conditions for substituted indanones

| Entry	Substrate	Product	Time (h)	Cat.loading (Equiv)	Conc (M)	Yield (%)[a]
1			(i) 02	0.01	0.10	08
			(ii) 18	0.01	0.10	33
			(iii) 18	0.05	0.50	25
			(iv) 48	0.01	0.10	>95%[b]
2			(i) 2	0.01	0.10	13
			(ii) 18	0.01	0.10	50
			(iii) 18	0.05	0.50	10
			(iv) 48	0.01	0.10	>95%[b]

Conditions: All reactions were done under an inert atmosphere of N$_2$ using 1.0 eq of model substrate dissolved in DMF, 0.01 eq of Pd source, 2.0 eq of DIPEA were added and heating was done at reflux, [a] Column chromatography done, [b] clean material which did not require column chromatography

Due to the presence of unconsumed starting materials (Table 10, entries 1i, 2i), it was anticipated that either more reaction time should be given or an increase in catalyst loading might ensure their full consumption, and as such the reactions were left overnight. There were marked improvements

50

in the reaction outcomes of both substrates with about 50% and 60% conversion of the starting materials to products that afforded 33% and 50% yields of clean materials, respectively after purification (entries 2ii and 3ii). These results were encouraging and suggestive of the reaction being time-dependent and as such the effect of time was investigated together with additional catalyst loading and increased concentration. At first, the reactions were performed for 18 hours, 5 mol% catalyst, and reduced amounts of solvent. The reaction outcomes were deleterious in comparison to the previous outcome giving reduced yields of 22% and 13%, respectively (entries 1iii and 2iii). These results were perhaps lower because of reduced solubility of the substrates in the solvents due to higher concentrations. As such, the next set of experiments were performed as in the original conditions of 0.1 M but extending the reaction time to 48 hours which gave complete conversion of starting materials and provided the products in quantitative yields as evidenced from ^{1}H and ^{13}C NMR spectral analyses that did not require any further purification (entries 1iv and 2iv). These set of new conditions were taken as optimal for the substituted chalcones which provided the 4,6 and 5,7-dimethoxy substituted indanones **71, 72** for the isopaucifloral F and its analogue, respectively.

With the successful syntheses of indanones **54, 71, 72,** the next stage to be undertaken in this project work is their asymmetric induction to produce enantioenriched molecules with good selectivity by using some standard protocols. Some efforts have been directed along asymmetric reduction[102] and the kinetic resolution of indanones.[103]

Chapter 4.0

4.1 Asymmetric reduction

The asymmetric reduction of prochiral ketones is one of the most prominent reactions for synthesising enantioenriched chiral alcohols that could be used as end products of a reaction or as intermediates that can be further functionalised into other compounds of pharmaceutical importance. [104] The use of chiral catalysts is one of the ways to achieve this and is relatively cheap and practically easy compared to other protocols. [105] Usually, a small quantity of the catalyst is required for the transformation and a catalytic cycle becomes complete once the starting material is consumed and the catalyst dissociates from the compound.

4.2 Oxazaborolidine catalysts.

The search for a cost-effective catalyst with a high reactivity and enantioselectivity has been an area that attracted a lot of research and discussions in the field of organic chemistry. Previous efforts initiated by Itsuno [106] and Corey [40] on asymmetric borane reduction using chiral oxazaborolidine catalysts (CBS reduction) have been identified as viable solutions employed in the asymmetric reduction of prochiral ketones with reported high yields, predictable configurations and excellent enantioselectivities that can be predicted from the relative positioning of substituents on the prochiral ketone (Scheme 44).[107,108]
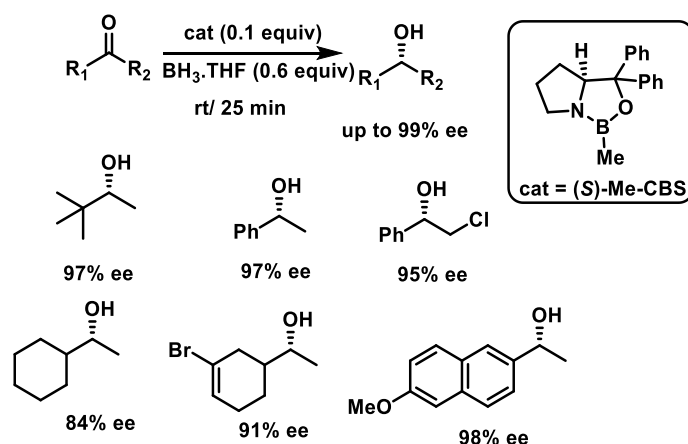
Scheme 44. CBS reduction of prochiral ketones[107,108]

There have been numerous reports of oxazaborolidine reductions, [109], [110], [111], [112] however of direct relevance to this project is the work of Wang and co-workers where they developed prolinol based chiral dendrimer catalysts and applied them in the asymmetric borane reduction of ketones. [109], [113] When tested on indanones, the reaction yielded products of almost (1:1) ratio between the *cis* and *trans* indanol isomers in which the *trans* isomers had an enantiomeric excess of between 91 - 96% and interpreted as products of matched reactions while the *cis* isomers had an ee of 78 - 82% from mismatched reactions (Scheme 45).[110]

R' = Ph, Me, Cy, *n*-butyl, *t*-butyl

1 = (structure)

R = Dendrimer chains

R' = Me; *cis* = 82% ee, *trans* = 95% ee

R' = Ph; *cis* = 78% ee, *trans* = 91% ee

R' = Cy; *cis* = 78% ee, *trans* = 93% ee

R' = *n*-butyl; *cis* = 80% ee, *trans* = 94% ee

R' = *t*-butyl; *cis* = 80% ee, *trans* = 96% ee
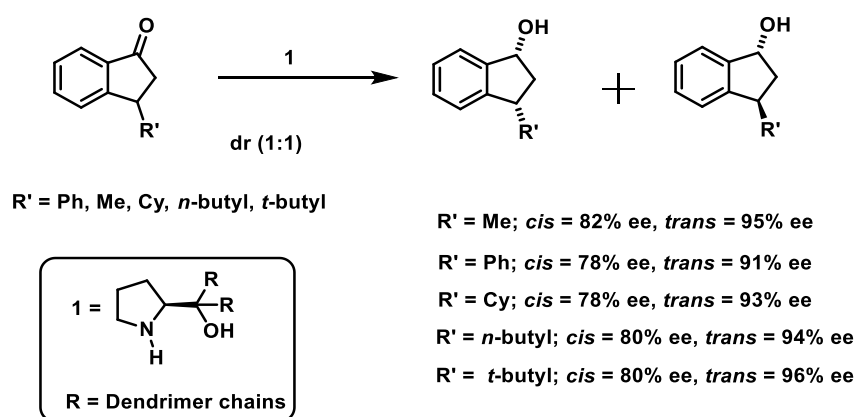
Scheme 45. Asymmetric reduction of indanones using prolinol-derived chiral dendrimers [110]

The relative configuration of the diastereoisomers was established by 2D ^{1}H-^{1}H NOESY experiments on the respective indanol diastereoisomers in which correlations were established between protons at C-1 and C-3 of the *cis* indanol suggesting same orientation while these were absent in the *trans* isomer (Figure 16).
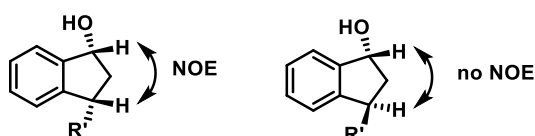
Figure 16. nOe experiments of *cis* and *trans* indanols [110]

The absolute configuration of the *trans* indanol at C-3 was confirmed by oxidation of the isolated *cis* isomer and comparison with the specific rotation of the derived ketone with known compounds in the literature (Scheme 46). [110]

cis isomer
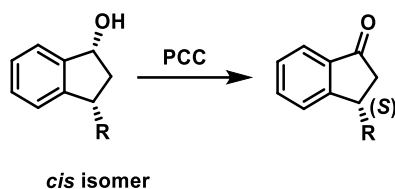
Scheme 46. Establishing absolute configuration of *cis* indanol[110]

Other research groups have used CBS catalysts and have applied them in the asymmetric synthesis of indanone based compounds of biological interest. For example, Clark *et al.* reported the CBS-derived asymmetric reduction of a substituted indenone using -(*R*)-MeCBS 5 mol%/ BH$_3$·THF (1.1 equivalent) to produce the corresponding (*S*)- indenol in 90% yield and 94% ee (Scheme 47)[107]
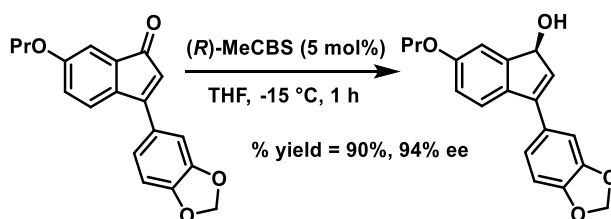
Scheme 47. CBS-derived asymmetric reduction of indanone[107]

In a closely related development, the enantioselective reduction of an indenone was achieved with (*S*)-Me-CBS catalyst (5 mol %)/BH$_3$·THF (1.05 equiv) to produce the corresponding (*R)*- indenol in high yield and enantioselectivity (95% yield, 97% ee) (Scheme 48). [89] The importance of fast quenching the reaction mixture as a measure of attaining high enantioselectivity was stressed by the authors due to susceptibility of the product to racemization with long reaction times.[89]
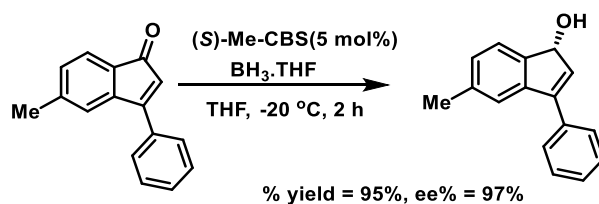
Scheme 48. Me-CBS reduction on 3-Phenyl-5-methyl-1-indenone[89]

Inspired by the work of Clark [107] & Hedberg [89] the Yao group reported the asymmetric conjugate reduction of 3-aryl indenones by first employing the use of CBS derived catalysts of different configurations (*R*)-MeCBS and (*S*)-Me-CBS to generate the stereospecific corresponding allylic indenols and their subsequent treatment with DABCO/Et$_3$N to form different enantiomers of the indanols in high yield and excellent enantioselectivity (89% yield, 99% ee) and (86% yield, 98% ee), respectively, after hydride rearrangements (Scheme 49). [114] Here also, fast quenching of the reaction was necessary to circumvent the issue of isomerisation and degradation of the highly unstable intermediate allylic indenols.
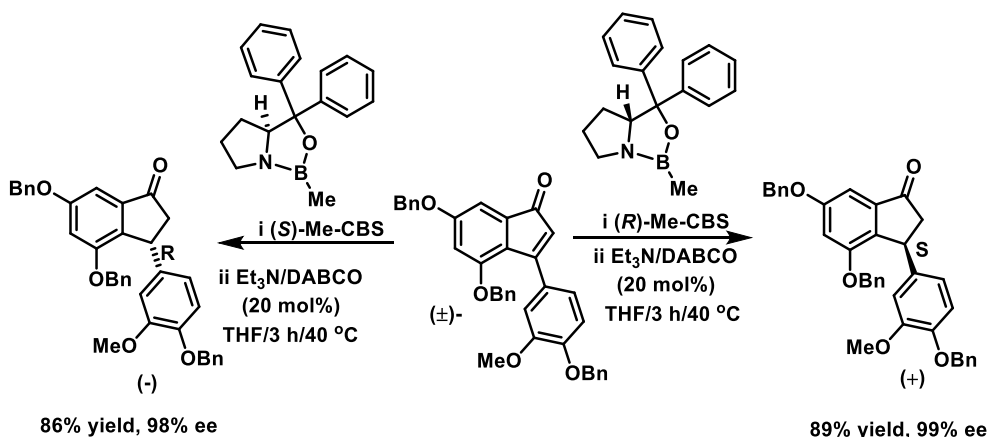
Scheme 49. Enantioselective reduction of substituted indenone with CBS catalyst[114]

A similar asymmetric reduction of 3-(3,4-dichlorophenyl)-2,3-dihydro-1H-inden-1-one by using 5 equivalent of (*S*)-Me-CBS and 2.0 equivalent DEAB which produced the corresponding (1*R*,3*S*)-*trans* indanol in 45% yield, >99% ee while the (1*R*,3*R*)-*cis* diastereomer had 46% yield, >91% ee was reported (Scheme 50).[115]
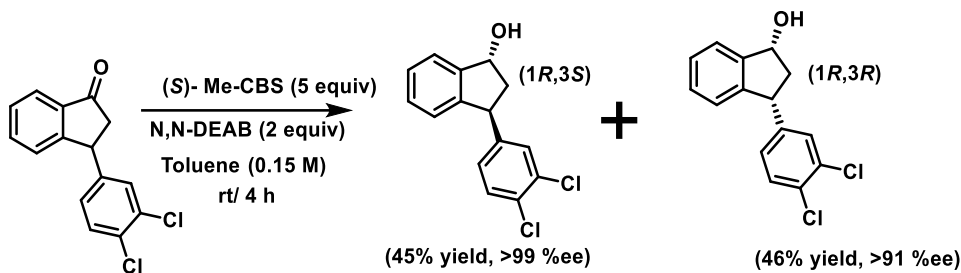
Scheme 50. Me-CBS asymmetric reduction of -3-(3,4-dichlorophenyl)-2,3-dihydro-1H-inden-1-one

Other CBS catalysts which have shown comparable outcomes with the Itsuno catalysts[109,110,111, 112] have continued to be used in various asymmetric synthetic applications. Of interest are those derived from optically pure (1R,2S) and (1S,2R) cis-1-amino-2-indanols. They have been used successfully in the Jones research group on different types of systems, but this is the first attempt they are used on 3-phenyl indanone systems. Hence it was proposed to try their application on these systems to see if similar or better results could be obtained compared to those noted earlier.

4.2.1 Asymmetric reduction of 3-aryl indanones.

With successful synthesis of the indanone core **54** as a model substrate for further functionalisation, it was first reduced with sodium borohydride where a racemic mixture of diastereoisomers was obtained in 75:25 ratio corresponding to (major/minor) isomers. Then another sample of compound **54** was subjected to a literature procedure[116] that employed the use of 0.5 mol% amino indanol-derived oxazaborolidine catalyst **55** loading in dry THF at 0 °C which was allowed to warm up to room temperature over 2.5 hours (Scheme 51, Table 11).
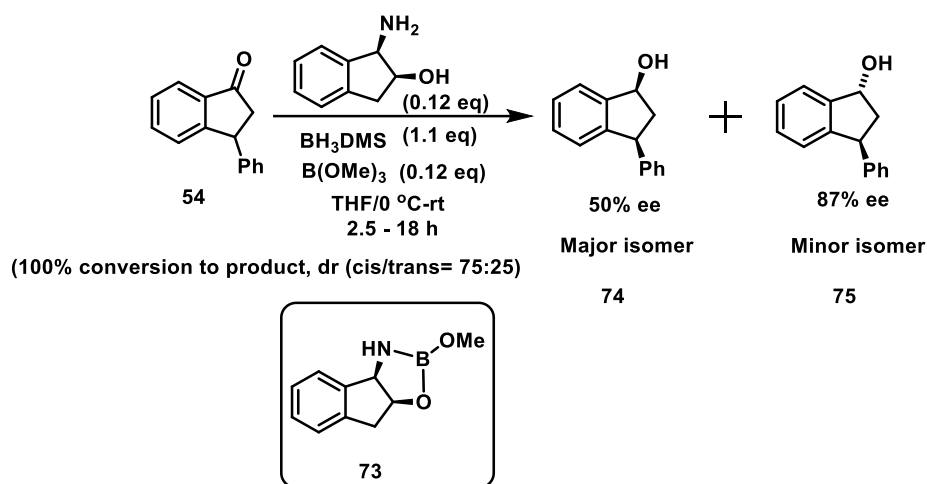
Scheme 51. Asymmetric reduction of 3-pheny indanone with CBS-derived amino indanol

The results reveal full conversion of the starting material **54** to yield the indanols **74 and 75** as determined by the ^{1}H NMR spectrum of the crude reaction mixture. The spectral interpretation also revealed that the product was a pair of major and minor diastereoisomers with a dr of (75:25). The enantiomeric excess (ee) of the crude mixture was determined by chiral HPLC analysis and was found to be only 50% for the major isomer while the minor isomer had an ee of 87%. In order to isolate the diastereoisomers, purification by flash column chromatography was attempted which proved unsuccessful after several attempts, but when preparative HPLC was employed, the individual isomers were efficiently separated and characterised as *cis* and *trans* diastereoisomers which matched with literature NMR data. [117, 89, 28, 77] An optimisation study aimed at improving the outcomes of the reaction was investigated (Table 11).

Table 11. Results of optimisation conditions of asymmetric induction of 3-aryl indanones

# no.	Time (h)	Concentration (M)	Temp (°C)	Conversion to product (%)	dr (cis:trans [c] Crude	ee (%) [d] (*cis*) Crude	ee(%)[f] (*trans*) Crude
1)	2.5	0.5	0	100	83:17	18	58
2)	2.5	0.5	0 [b]	100	83:17	01	3
3)	2.5	0.5	0 [a]	100	75:25	14	52
4)	2.5	0.5	0 *	100	83:17	08	15
5)	2.5	0.5	-78	19	>95:5	02	N/A
6)	2.5	0.05	0	100	83:17	07	52
7)	0.5	0.5	0	100	75:25	19	57
8)	1	0.5	0	100	82:18	06	29
9)	2.5	0.5	-40	69	89:11	04	20
10)	2.5	0.5	0**	100	83:17	02	44

All reactions were done in THF, catalyst used (1R, 2S)-*cis*-amino indanol, [a] =1:1 equimolar quantity of (1R, 2S) & (1S, 2R), * catalyst used (1S, 2R)-*cis*-amino indanol, [b]Reaction done in Et$_2$O, **Reaction done in dioxane; [c] determined by analysis of the crude(*cis*:*trans*) ^{1}H NMR spectrum; [d]ee% of the major (*cis*) isomer determined by HPLC analysis of the crude mixture on a Chiralcel OJ column; mobile phase: haxane/isopropanol(90:10); flow rate: 1.0 mL/min; detector: UV 254 nm

A second attempt under the same reaction conditions with the aim of obtaining a replicate of the representative reaction however, did not produce the same outcome. At full conversion of the starting material to product, the dr obtained was 83:17 for the major/minor isomers from NMR spectral interpretation of the crude reaction mixture and HPLC analysis revealed a disappointing 18% ee for the major isomer and 58% for the minor isomer (Table 11, entry 1). More optimisations were

carried out by changing the reaction conditions. Changing the solvent to Et_2O (Table 6, entry 2), or the use of dioxane (Table 11, entry 10) had a deleterious effect on the ee of the *cis* and *trans* isomers compared to the previous experiment in entry 1, although it kept the dr at 83:17.

When the opposite enantiomer of (1*S*, 2*R*)-*cis*-amino indanol was used however, a decrease in enantio-enrichment was observed in the product (Table 11, entry 4). This was rather surprising because technically as a pair of catalyst enantiomers, the same or similar outcome was expected which turned out not to be the case. This could be attributed to either an impure form of the catalyst was used, or a possible mislabelling of the catalyst container.

It was also interesting to note that when an equimolar quantity of both catalyst enantiomers was used, a comparable dr of 75:25 (major/minor) isomers was deduced from ^{1}H NMR spectral analysis as expected, with a comparable ee of 14% for the major isomer and 52% for the minor isomer (Table 11, entry 3). The catalyst mixture was envisaged to be racemic and as such no enantio-selection was expected. Here again, the reason could be because either or both catalysts used were in their impure forms which may have contributed to the enantio-differentiation in the products.

Considering the full conversion of starting material to product obtained in all the reactions so far, it was evident that the reaction was occurring at a fast rate which could be the reason why enantioselectivity was not high. A decrease in the reaction temperature was considered as a measure of slowing the reaction. As such, the reaction was performed at -40 ^{o}C which led to an incomplete conversion of starting material to product (69%), but the ee of the major/minor isomers dropped to 4% for the major and 20% for the minor isomer (Table 11, entry 9). A further reduction in the temperature to -78 ^{o}C led to 19% conversion of starting material providing almost exclusively the major diastereoisomer with a dr >95:5, but the ee of the major isomer dropped further to 2% (Table 11, entry 5). Although a decrease in temperature slowed the reaction the preferred isomer was produced as seen in entry 5, but at the same time it led to a decrease in the ee.

With the aim of boosting the ee of the product, a decrease in the reaction time was then considered as another measure of slowing the reaction but maintaining the initial reaction temperature of 0 °C. After 1 hour of reaction, complete conversion of the starting material to product was realised with no improvement in the ee (Table 11, entry 8). Also, it was noted that 30 minutes was enough time to bring about complete conversion of starting material as seen in entry 7, with a comparable value in the %ee of the major isomer (19%), minor(57%) as compared to entry 1 with 18% for the major and 58 % for the minor isomer. It is important to point out here, that recovered starting materials isolated in cases where incomplete conversion occurred, did not have any enantioselectivity imparted on them.

4.3 Determination of absolute and relative stereochemistry.
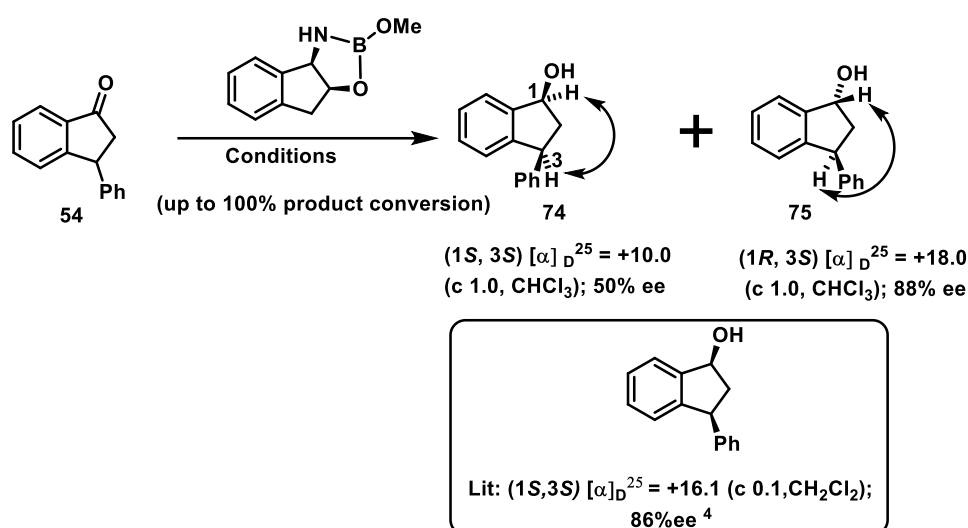
Scheme 52. Stereochemistry assignment of 3-phenyl indanols

The identity of the major isomer of alcohol **74** was proposed as the *cis* isomer and the absolute configuration as (1*S*, 3*S*) from analytical measurements $[\alpha]_D^{25}$ +10.0 (*c* 1.0 in CHCl$_3$) for a sample of 50% ee based on comparison with a reported value for a known compound in the literature [(1*S*, 3*S*) $[\alpha]_D^{23}$ +16.1 (*c* 0.1 in CH$_2$Cl$_2$)] for a sample of 86% ee (Scheme 52).[4]

The minor alcohol **75** with analytical measurements $[\alpha]_D^{25}$ +18.0 (*c* 1.0 in CHCl$_3$)] for a sample of 88% ee was proposed as the *trans* isomer based on comparison with ^{1}H NMR spectral interpretation of a

known racemic compound in the literature which was reported for the first time.[34] Although its optical rotation could not be found in the literature, its relative configuration was presumed as 1*R*, 3*S*, as would be expected from Corey's prediction of the proposed CBS mechanism.[118, 119, 120]

Additionally, the coupling constants between C-1 and C-3 protons of the major isomer in the 3-phenyl indanol (J = 8.4) suggests a H-C-C-H dihedral angle of around 0° which is typical for *cis* protons in a 5-membered ring system while that of the minor isomer of the same product has a coupling constant (J = 7.4) suggestive of a H-C-C-H dihedral angle close to 120° which is also characteristic of *trans* protons in a 5-membered ring system.

Considering the optimisation reactions carried out so far (Table 11), but with still more to be done for the reaction to reach its full capacity, coupled with very low enantioselectivity of the product, challenges in separating the mixtures and inefficient time utilisation, the reaction could not be optimised further with this catalyst system as such, an alternative reducing agent that could be employed for the effective resolution of the indanone substrates was sought.

4.4 Classical kinetic resolution.

Kinetic resolution (KR) continues to be used as one of the most amenable strategies for obtaining pure enantioenriched chiral compounds. Historically, it is considered as the earliest strategy for obtaining pure enantioenriched chiral compounds.[121] Its utility is based on the relative difference in reaction rates of the pair of enantiomers of a racemate substrate when they are exposed to a chiral environment.[122] In an efficient KR, the fast-reacting enantiomer gets transformed into its corresponding enantioenriched product leaving the slow reacting enantiomer behind unreacted which may be recovered as enantiomerically enriched[122] or gets transformed into product at a certain conversion level (Scheme 53).[123]

$$SM_R \xrightarrow{\ k_R\ } P_R \qquad SM_R, SM_S = \text{starting material enantiomers}$$

$$k_R \gg k_S$$

$$SM_S \xrightarrow{\ k_S\ } P_S \qquad P_R, P_S = \text{Product enantiomers}$$
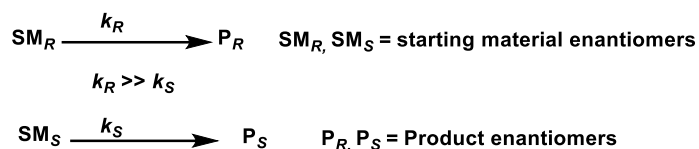
Scheme 53. Simple illustration of a classical kinetic resolution of a racemic substrate

Some of the advantages of this method lies in its simplicity, compatibility with many chiral substrates and enantioselective methodologies,[121] and can be done on a large scale.[124] It has an added advantage of producing two categories of enantioenriched materials (product and recovered starting material) from a cheaper racemic starting material compared to their commercial pure enantioenriched versions when the reaction is controlled to about 50% conversion (Scheme 53). Additionally, the enantioenrichment of the desired product may be raised to a higher value by increasing the % conversion of the racemic starting material during a chemical reaction when desired.[124,125]

4.5 Asymmetric transfer hydrogenation (ATH) - assisted KR

Reduction of prochiral ketones to optically active chiral alcohols *via* hydrogen transfer from organic reducing agents like 2-propanol or formic acid is known as asymmetric transfer hydrogenation (ATH).[127] The use of formic acid has been demonstrated to provide a higher product conversion and better enantioenriched products than 2.[127,128] The non-enzymatic KR of racemic compounds facilitated by chiral catalysts is an alternative method of producing enantioenriched products and starting materials in KR experiments as exemplified by the KR of racemic alcohols and amines [127,122] ATH assisted KR provides an alternative to asymmetric hydrogenation due to its relative simplicity and practicability compared to high pressure needed in providing molecular hydrogen. [4, 129,130] The use of ruthenium and rhodium catalysts in the ATH of enantioenriched 1-or 2-indanols where hydrogen was furnished from an azeotropic mixture of formic acid/triethyl amine have been reported[79] however, no report was found on KR of 3-aryl indanones at the time of writing this document which led to the basis of pursuing this strategy. The efficiency of the 1st generation ruthenium catalyst

(RuCl (Tsdpen) in the synthesis of optically active alcohols *via* asymmetric reduction has also been documented.[127,131,132,133] A characteristic of the RuCl(Tsdpen)-(η6-arene) catalyst is the stereocontrol achieved at the carbonyl group where any interaction between the catalyst metal centre with any substituents at the α or β positions of the carbonyl group is precluded due to the saturated 18-electron coordination of the chiral Ru II catalyst complex with the diamine ligands which leads to excellent enantioselectivity.[132]

4.6 ATH-assisted KR of indanones.

The Buchwald group reported the kinetic resolution of *N*-methyl imines derived substituted indanones by using hydrosilylation conditions catalysed by a chiral titanocene previously developed by the group (Scheme 54). Reactions were performed at varied temperatures (-30 $^{\circ}$C to 15 $^{\circ}$C) and highly enantioenriched indanones were recovered in up to 93% ee along with the reduced amines.[103]
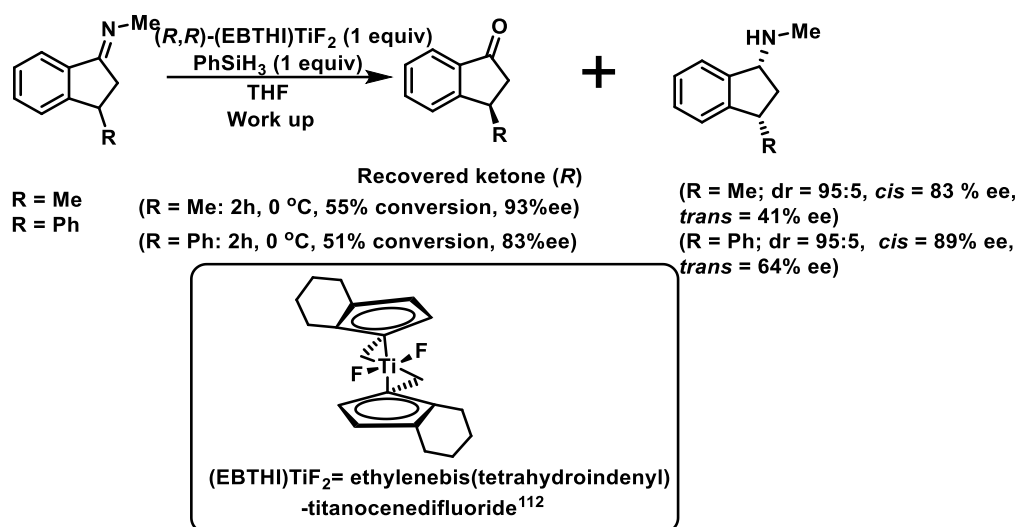
Scheme 54. Synthesis of 3-phenyl indanones via kinetic resolution of *N*-methyl imines[103]

The ruthenium-based Mohar's catalyst containing the benzosultam (*syn*-ULTAM) ligand effected a dynamic kinetic resolution (DKR) in the ATH reaction of 3-methoxycarbonyl-1-indanone with a substrate/catalyst factor of 200 (Scheme 55). The optimum reaction conditions of 40 $^{\circ}$C, 6 hours and an azeotropic mixture of HCO$_2$H/Et$_3$N (5:2) provided the product *cis*-(1*R*,3*S*)-3-methoxycarbonyl-1- with a very good level of diastereoselectivity (95:5) and excellent enantioselectivity (100%)[134,135]
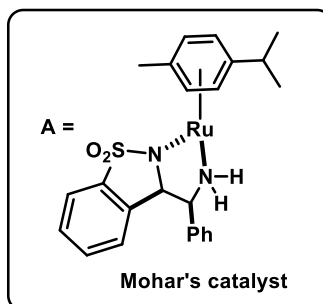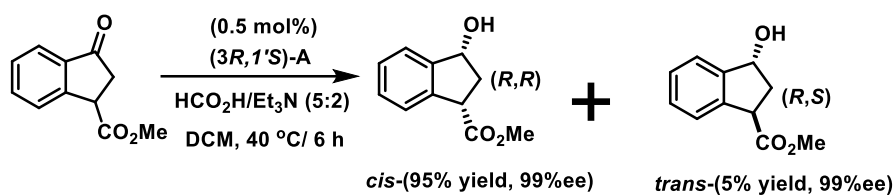
Scheme 55. ATH-DKR of *rac*-3-methoxycarbonyl-1-indanone[134]

Similarly, tethered Ru–TsDPEN complex was employed for the DKR-ATH of *cis*-β-heteroaryl amino indanones. The corresponding indanols were obtained using a substrate/catalyst ratio of 1000 which was carried out in DCM and using an azeotropic mixture of HCO_2H/Et_3N (5:2). A very good yield of the *cis* substituted-indanols (91%) was obtained with an excellent enantioselectivity of about 92% (Scheme 56).[136]
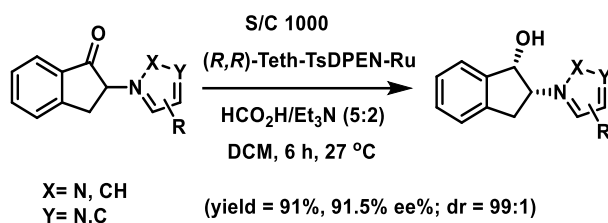
Scheme 56. DKR-ATH of α-heteroalkyl amino indanones.[136]

Similar efforts have revealed literature precedence of a DPEN-based Ru(II) catalysed reduction and has proven to be effective in the DKR–ATH on racemic 2 or 3-substituted indanone systems in an azeotropic mixture (3:2) of HCO_2H/Et_3N giving the *cis*-2 or 3-substituted-indanols with a dr = 44:50:6:0 and excellent ee's (>99.9% each) (Scheme 57). [135,137]
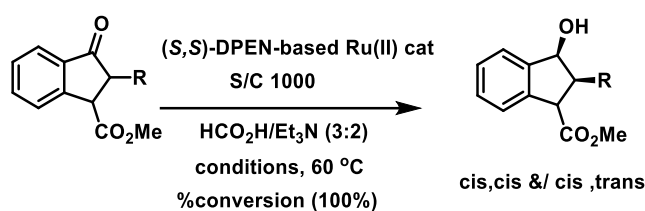
R = Me (dr = 85:15)

R = *i*Pr (dr > 99:1)

R = Cy (dr > 99:1)

R = Ph (dr = 97:3)

R = Me; 2h; dr = 44:50:6:0; ee% >99.5%

R = *i*Pr; 24 h; dr = 95:5:0:0; ee% >99.5%

R = Cy; 24 h; dr = 95:5:0:0; ee% >99.5%

R = Ph; 24 h; dr = 98:2:0:0; ee% >99.9%

Scheme 57. Ru(II)-Catalyzed DKR–ATH of racemic 2,3-disubstituted Indanones [135,137]

In a related finding, ATH assisted DKR/lactonization of carboxylic acid-derived 1-indanone derivatives using 0.2 mol % of oxo-tethered (*R*,*R*)-ruthenium Ts-DENEB catalyst in an azeotropic mixture of formic acid/ triethylamine (5:2) was reported (Scheme 58).[138] The *syn* lactone was exclusively obtained in 83% yield, with an excellent enantioselectivity > 99% ee. Other substituted analogues were exposed to similar reaction conditions and the corresponding lactones were obtained with high diastereoselectivities and enantioselectivities in the range of 94–96% ee.

R = H; yield =85%, ee = 99%, 60 °C, 9 h

yield =78%, ee = 94%, 60 °C, 7 h

yield =72%, ee = 96%, 60 °C, 7 h

yield =76%, ee = 96%, 40 °C, 12 h
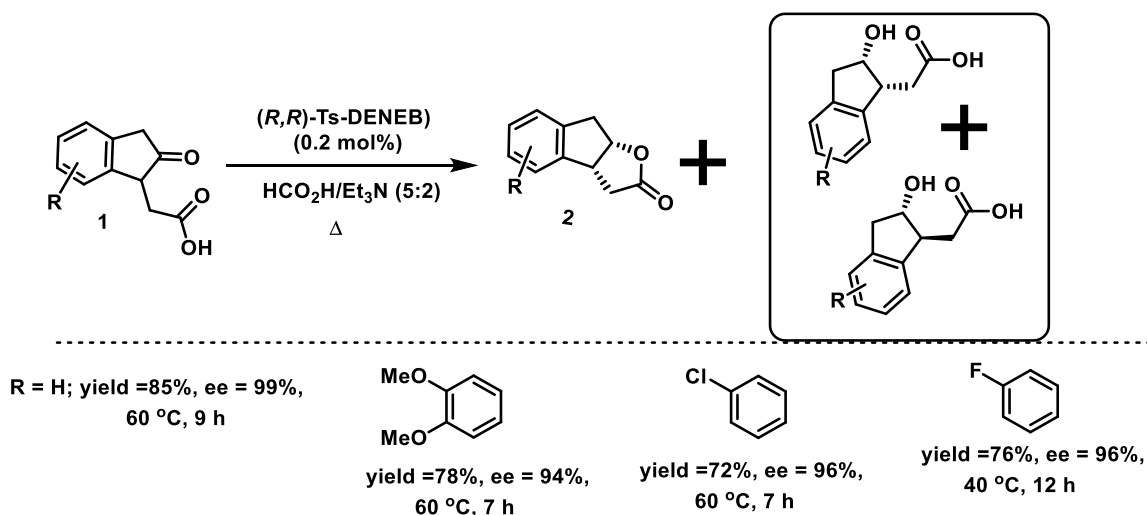
Scheme 58. ATH assisted DKR/lactonization of 1-indanone derivatives[138]

Despite the numerous reports on the use of chiral transition metal catalysts in the ATH of 1-indanones or 2-substituted-1- indanones were hydrogen was furnished from the azeotropic mixture of formic acid/triethyl amine, no literature precedence was found on ATH-assisted KR of 3-aryl-1-

indanones to produce the corresponding 3-aryl-1-indanols. The realisation motivated this research work in assessing the ATH-assisted KR of the 3-aryl-indanones by using one of the first generation Noyori catalysts RuCl [(R,R or S,S)Ts-dpen] p-cymene (Scheme 59).

However, whilst this work was in progress, Lee and co-workers reported the first ATH-KR on the 3-aryl indanone systems using the new generation oxo-tethered ruthenium based-Ts-DENEB catalyst. (Scheme 59). The use of both (R,R)-Ts DENEB and (S,S)-Ts DENEB catalysts in MeOH at room temperature, using a combination of a 1 : 5 mixture of HCO_2H and Et_3N as the hydrogen source was employed providing cis-3-arylindanols with high levels of diastereoselectivities and enantioselectivities (up to 99% ee) and enantioenriched recovered starting materials (up to 99% ee).[79]
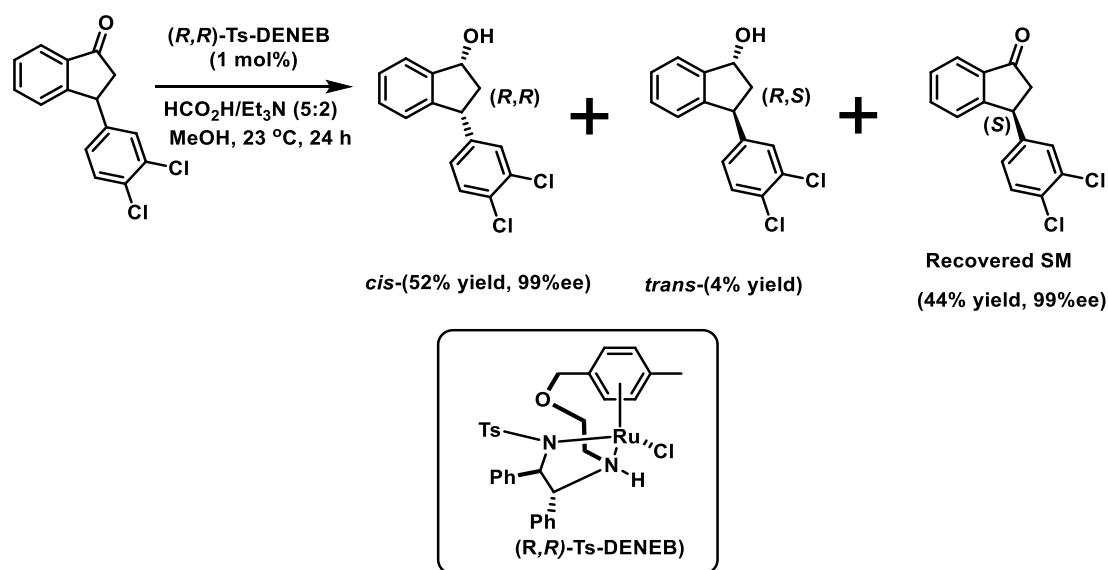
Scheme 59. ATH-KR of 3-aryl indanone[79]

At the initial stage of the asymmetric reduction of indanones, the model substrate of 1-indanone **1** was chosen based upon commercial availability which was exposed to literature conditions[132] using Ru(II) catalysts 1 or 2 with an S/C (substrate/catalyst = 900) in (HCO_2H/Et_3N; 3.1:2.6) at 30 °C in 24 hours for both unsubstituted and 3-phenyl indanones (Scheme 60).
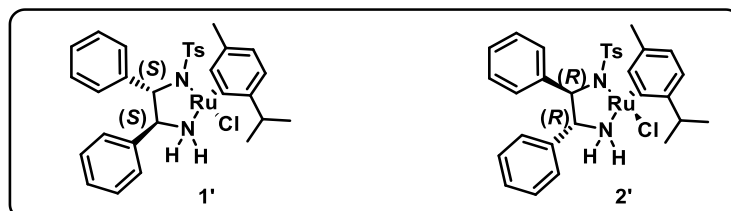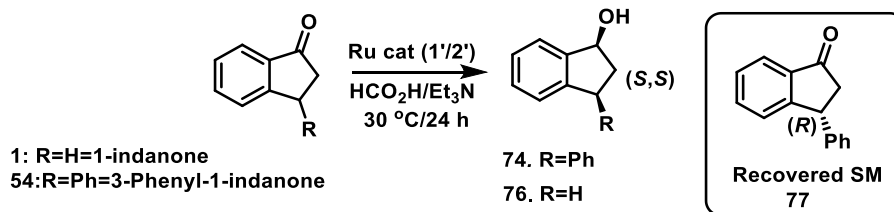
Scheme 60.Asymmetric reduction on indanone model substrates using ruthenium complexes

The reaction conditions gave only 20% conversion of the starting material to product as observed from the ^{1}H NMR spectrum of the unpurified mixture, with chiral HPLC analysis showing 40% ee of the desired product (Table 12, entry 1).

Table 12. Optimisation of ruthenium catalyst reduction on indanone model substrates

Ent	Subst	Cat	Cat loading (mol%)	FA: TEA	Conc (M)	Conv (%)[d]	Indanol (**56: 57**) (*cis*:*trans*)[e]	ee(%)[f] *cis* **74**	ee (%)[f] *trans* **75**	SM **77** ee (%)[g]	s[h]
1	1	1'	0.1	3.1:2.6	2.1	20	N/A	40	N/A	-	N/A
2[a]	1	1'	0.1	3.1:2.6	2.1	50	N/A	72	N/A	-	N/A
3	1	2'	0.1	3.1:2.6	9.5	32	N/A	92	N/A	-	N/A
4	1	1'	0.1	2:5	2.1	20	N/A	95	N/A	-	N/A
5	1	1'	1.0	3.1:2.6	2.1	94	N/A	100	N/A	-	N/A
6	54	1'	0.1	3.1:2.6	2.1	60	>95:5	98	N/A	71	5.7
7	54	2'	0.1	3.1:2.6	1.0	57	75:25	>99	50	92	17.6
8 **	54	2'	0.1	3.1:2.6	1.0	57	86:14	>91	54	98	29.6
9	54	2'	0.5	5:2	1.0	58	86:14	79	49	94	18.0
10[b]	54	1'	0.1	3.1 2.6	2.1	46	>95:5	93	N/A	74	31.5
11[c]	54	1'	0.1	3.1:2.6	2.1	71	80:20	98	32	90	6.0

Conditions: All reactions were done in 24 h except [a] = 72 h; [b] = 6 h; [c] = 48 h; reaction temperature was 30 ºC throughout except* = 35 ºC; ** = 40 ºC; DCM (0.5 mL) was added to aid in dissolving reaction mixture; (%)[d] Product conversions and (%)[e] diastereomeric ratios were calculated from ^{1}H NMR spectrum of crude reaction mixture; (%)[f] from chiral HPLC measurements; [g] = recovered starting material; selectivity factor (s[h]) was determined using Kagan's equation[139]; Ent = entry, Cat = catalyst, Subst = substrate.

An optimisation study was carried out to improve the reaction outcome. An increase in time from 24 hours to 72 hours increased the conversion to 50%, with an improvement in the ee of the product to 72% ee (entry 2). However, reducing the volume of the solvent increasing the concentration to 9.5

M from 2.1 M, led to a decrease in product formation (32% conversion of starting material) but with a significant improvement in the ee of the product to 92% (entry 3).

Altering composition of the hydrogen source was considered and as such, acidity was reduced by changing the FA/TEA mixture from (3.1:2.6) to (2.0:5.0) but it did not improve on the conversion (20%), although an excellent ee of 95% of the product was obtained (entry 4). A final parameter that was screened was an increase in catalyst loading to 1 mol% from the original 0.1 mol% that was used in all previous entries (entries 1-4). Pleasingly, there was a marked improvement in both conversion to product (94%) and enantioselectivity (100% ee) (entry 5). Since isopaucifloral F and its analogues are derived from 3-aryl indanones, it was deemed appropriate to have a second model substrate that bears some resemblance to them and as such, 3-phenyl indanone **54** was chosen which was prepared over two steps from 2-bromoacetophenone as mentioned in the previous section (Scheme 41).

Starting with a catalyst loading of 0.1 mol% led to 60% conversion of starting material producing almost exclusively one single isomer of the corresponding alcohol as seen in the ^{1}H NMR spectrum of the unpurified reaction mixture with an ee of 98% of the product, and 71% ee of the unreacted starting material from HPLC analyses and a selectivity factor (*s*) of 5.7 (entry 6). This is a clear manifestation of a classical kinetic resolution (KR) with enantioselectivity being imparted on both product and unreacted starting material.

Since a decrease in product conversion from starting material **1** was recorded when the reaction was conducted at higher concentration (entry 3), further optimisation was performed by diluting the reaction medium which led to a decrease in concentration to 1.0 M. A slight decrease in conversion of starting material from 60% to 57%, producing a mixture of diastereoisomers (*cis/trans*) in the ratio of 75:25 as seen from the ^{1}H NMR spectrum was recorded (entry 7). There was an increase in selectivity to 17.6 and a marked improvement in the ee of the unreacted starting material to 92% in

contrast to the first instance which gave 71% ee. However, the ee of the major isomer was about the same as in the previous experiment (>99%) (entry 7).

Increasing the reaction temperature to 40 $^{\circ}$C gave a better dr (86:14) at 57% conversion with an improved ee of >91% for the *cis* isomer and a higher ee of the minor isomer at 54%. Here again, the *s* factor increased to a higher value of 29.6 compared to the previous entry, with an improvement in the ee of the unreacted starting material to 98% ee (entry 8).

Other studies which included an increase in catalyst loading or a change in the ratio of formic acid to triethylamine were also investigated (entry 9). Here too, similar results to the previous entry were obtained with a 58% conversion of starting material to product, but a decrease in ee% of the *cis* diastereoisomer to 79%, and thus a selectivity factor of 18.0.

By monitoring the reaction with respect to time, it was observed that 6 hours was enough time to bring about 46% conversion of the starting material thereby providing the best selectivity so far up to 31.5, with excellent diastereoselectivity (>95:5) affording 93% ee of the *cis* isomer and 74% ee unreacted starting material (entry 10). However, when the reaction time was increased to 48 h, the diastereoselectivity dropped thereby providing a dr of 80:20 (*cis/trans* isomers) with a 71% conversion as seen from the ^{1}H NMR spectrum of the unpurified reaction mixture and the *s* factor also dropped to 6.0. HPLC analysis revealed 98% and 32% ee values for the (*cis/trans*) isomers, respectively, and the starting material had 90% ee (entry 11).

Selectivity factors (*s*) from 5.7 and 31.5 were obtained from the various optimisation experiments (entries 6-11) in the table. From all the results so far, the best *s* was achieved as 31.7 which was recorded at 46% product conversion (entry 7). It can thus be inferred that this conversion is the optimum for KR to be achieved with the 3-phenyl indanone system.

4.7 Determination of absolute and relative stereochemistry.

The identity of the indanol **76** as [R= H, $[\alpha]_D^{25}$ +31.3 (*c* 1.5 in CHCl$_3$)] for a sample of 100% ee was proposed as *S* by comparing its optical rotation with the reported value of a known compound in literature [R= H, $[\alpha]_D^{25}$ +21.4 (*c* 1.0 in CHCl$_3$)] for a sample of 88% ee,[140] as well as its opposite isomer $[\alpha]_D^{24}$ -30.4 (*c* 1.96 in CHCl$_3$) for a sample of 97% ee.[75] (Scheme 61)
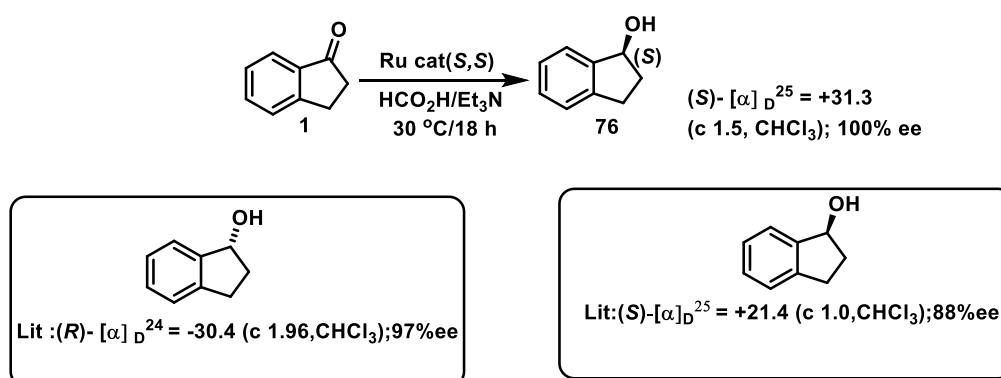
Scheme 61. Relative and absolute stereochemistry assignments of 1-indanol from asymmetric reduction on 1-indanone

Similarly, the identity of the major isomer of alcohol **74** was proposed as (1*S*, 3*S*) $[\alpha]_D^{25}$ = +9.0 (*c* 1.0 in CHCl$_3$) for a sample of 98% ee based on comparison with a reported value for a known compound in the literature [(1*S*, 3*S* $[\alpha]_D^{25}$ = +16.1 (*c 0.1* in CH$_2$Cl$_2$)] for a sample of 86% ee.[4]
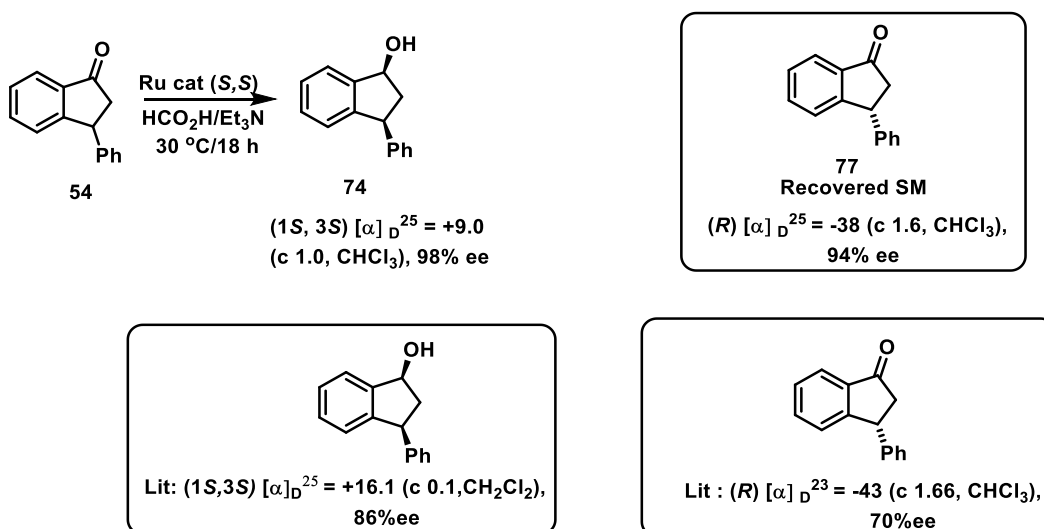
Scheme 62. Relative and absolute stereochemistry assignments of 3-phenyl-1-indanol from asymmetric reduction on 3-phenyl-1-indanone

Based on the interpretations and proposals above, the recovered starting material **42 a** $[\alpha]_D^{25} = -38$ (c 1.6 in $CHCl_3$) for a sample of 94% ee was assigned an R configuration with respect to optical rotation and ^{1}H NMR data of a related compound reported in the literature $[\alpha]_D^{25} = -43.0$ (c 1.66 in $CHCl_3$)] for a sample of 70% ee.[141]

The rationalisation of the stereochemical outcome of the ATH assisted kinetic resolution can be explained by analogy to the simple asymmetric reduction of acetophenone using the (*S,S*)-ruthenium catalyst complex which produced (*S*)- 1-phenylethanol in 96 - 98% ee.[142,143] The basis for the enantioselectivity is believed to be as a consequence of multiple CH-π interactions between the η^6 arene ligand of the catalyst and the phenyl part of the acetophenone molecule in the transition state (Scheme 63).

These electrostatic interactions stabilise the diastereomeric structures (in the transition state) where the electron-deficient $C(sp^2)H$ at the ortho or benzylic $C(sp^3)H$ at meta positions of the *p*-cymene ring interact with the benzene ring of the acetophenone molecule (Scheme 63).
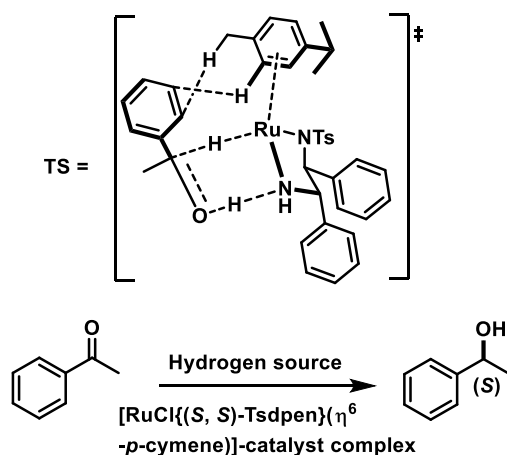
Scheme 63. Stereochemical model for the asymmetric reduction of acetophenone[142,143]

Thus, in the ATH reaction of the 3-phenyl indanone using ruthenium catalyst *p*-cymene, the major *cis* indanol **74** may be favoured in preference to the minor trans isomer due to these multiple interactions between the catalyst and the aromatic ring of the indanone while the 3-aryl substituent of the indanone **54** keeps away from the reaction site (Scheme 64).[138,136,134]
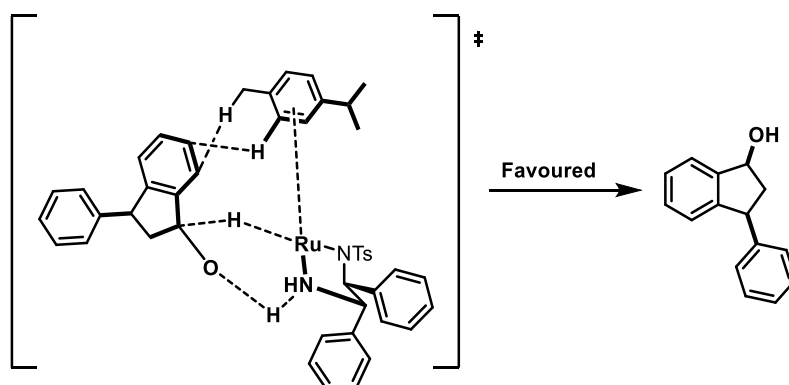
Scheme 64. Proposed asymmetric induction model in the ATH-KR of racemic indanone 54 with *S,S* ruthenium *p*-cymene

However, the transition state reason that leads to formation of the minor isomer is not favoured energetically due to steric hindrance between the phenyl groups of the catalyst and the substituent at C-3 of the indanone ring.[138,136,134]

4.8 Investigation of the scope of the asymmetric reduction on 3-substituted indanones

The scaffolds for isopaucifloral A and its analogues, which are the dimethoxy substituted indanones **71, 72** were subjected to the previous established optimal conditions from table 12 and it was surprising to find <10% conversion of starting material was achieved, even after extending it to 24 h (Scheme 65, entry 1).
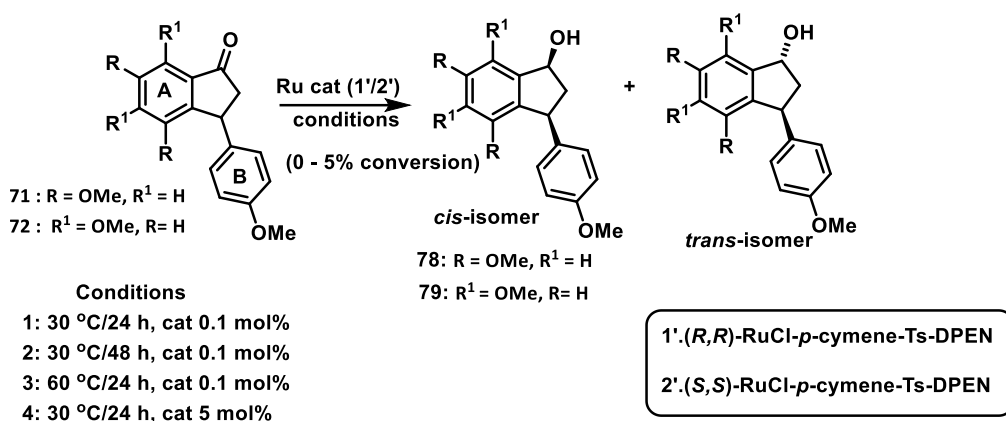
Scheme 65. Optimisation of ATH conditions on dimethoxy substituted indanones

An optimisation study with the intent of improving on the reaction outcome was initiated. An increase in reaction time to 48 h, temperature to 60 °C, or catalyst loading to 5 mol% did not improve the reaction outcomes (Scheme 64, entries 2-4). It was hypothesised that unfavourable steric interactions between the methoxy substituents and the catalyst or other substances in the reaction mixture might be operating which may impede the reaction from reaching its full potential and as such, substrate screening on both the **A** & **B** rings of the disubstituted indanone **71, 72** was initiated.

4.8.1 Synthesis of the indanone cores 71, 72

The synthesis of ring **A** with methoxy substituent at either position **5** or **6** of the indanone ring was proposed which will allow comparison based on subsequent asymmetric reductions with the isopaucifloral A indanones. The intermittent commercial supply and high cost of the ketone starting materials **80, 87** used in the syntheses of the requisite chalcones **83, 88** which would ultimately

74

undergo Heck cyclisation to form 4-methoxy indanone and 5-methoxy indanone necessitated their preparations.
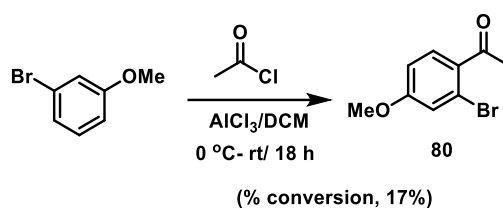
Scheme 66. Synthesis of o-bromo-*p*-methoxy acetophenone

The starting material 3-bromo-anisole was exposed to standard Friedel-Crafts acylation reaction conditions that provided the corresponding 2-bromo-4-methoxyacetophenone **80** as a yellow oil with a disappointing 17% yield obtained after several attempts (Scheme 66). Its identity was confirmed by comparing its ^{1}H NMR spectral analysis data with a known compound as reported in the literature.[62,144,145] Substituent effect on the benzene ring of the starting material could be responsible for the poor yield of the product of choice thereby yielding other side products. A previous strategy of ketone synthesis that had successful outcomes in the earlier part of this project (Scheme 38) was revisited and hence pursued though it had more reaction steps Thus, the requisite ketones 2-bromo-4-methoxy acetophenone **80** and 2-bromo-5-methoxy acetophenone **87**, were each synthesised from their corresponding commercially available aldehydes **81, 85** over two steps, respectively (Scheme 67).
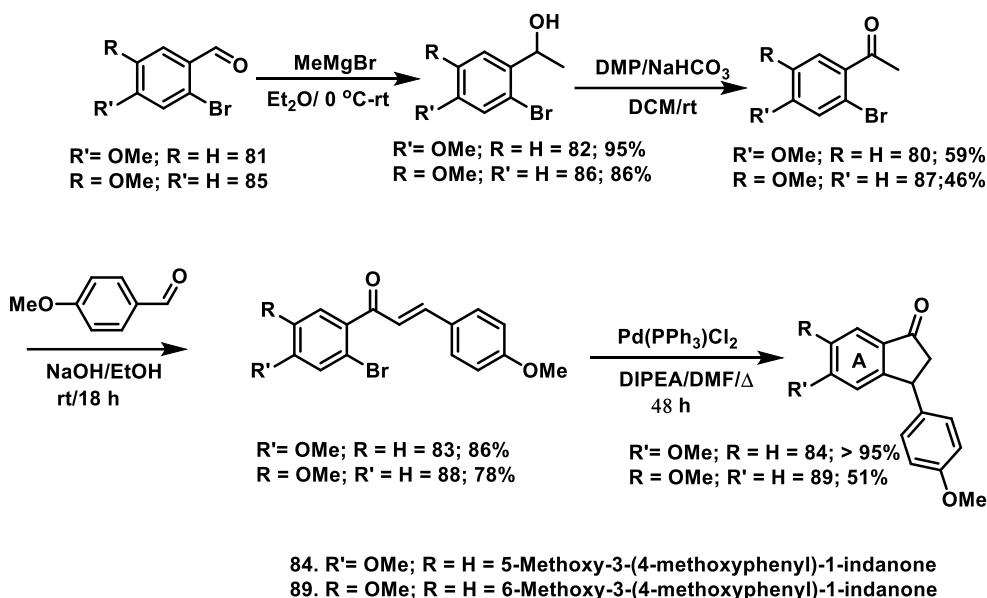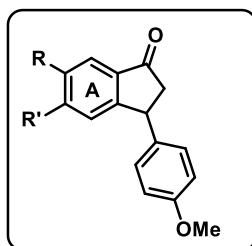
Scheme 67. Syntheses of methoxy substituted indanones

The indanone cores **84, 89** were accessed under standard Heck conditions of their respective chalcones **83, 88** which provided good to excellent yields. The chalcones were made by the Claisen-Schmidt condensation under basic conditions following a standard literature protocol as explained in the previous chapter, and their identities were ascertained as single *E* alkenes by the magnitude of the *J* values in the ^{1}H NMR spectrum assessment of the crude reaction mixture which were found to be consistent with literature results.[147,148]

4.8.2 Ring B synthesis.

The next indanone ring B **91** was accessed over two steps from commercially available starting materials. Claisen-Schmidt reaction between 2-bromoacetophenone and *p*-anisaldehyde produced 72% of the desired alkene **90** after column chromatography and confirmed as the *E*-isomer, again by

the magnitude of the *J* values in the ^{1}H NMR spectrum of the product which subsequently

underwent Heck cyclisation (Scheme 68).
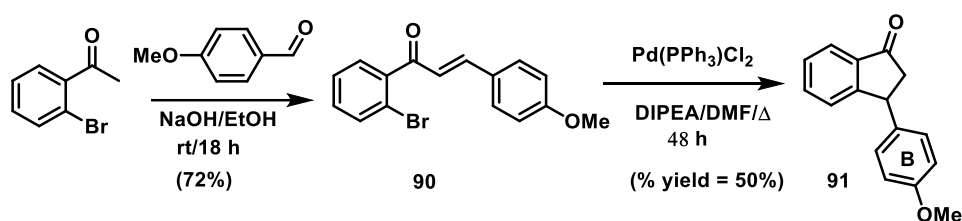
Scheme 68. Synthesis of indanone ring B

 Although the yield of the purified indanone material obtained after column chromatography was

just 50%, it was enough for the upcoming KR assessment and as such there was no need to carry out

further optimisation experiments.

4.8.3 Assessing substituted indanones for asymmetric reduction

The synthesised indanones were ready to be screened for asymmetric reduction following their

successful syntheses. The developed optimum conditions for the substituted indanone model

substrate were applied to indanone **91** with a view to screening ring **B** (Scheme 69).
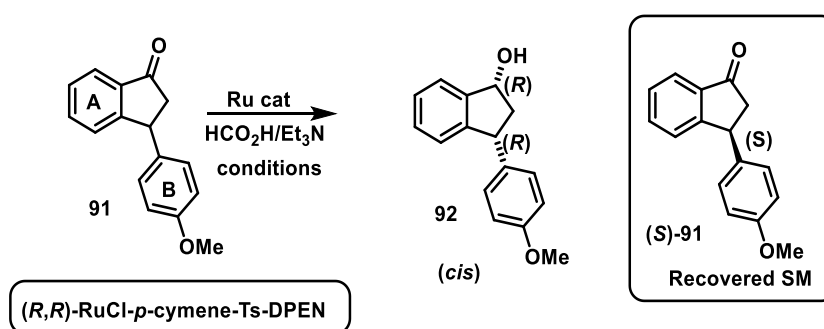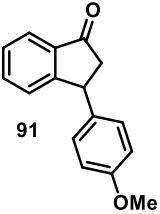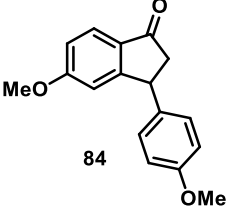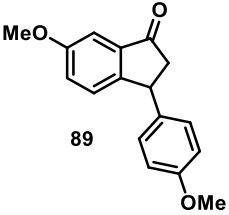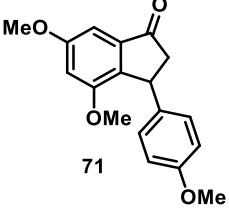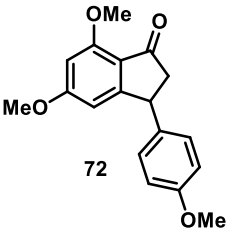
Scheme 69. Screening of different substituted indanones on ATH

There was a 50% conversion of the starting material with excellent diastereoselectivity >95:5

producing the *cis* isomer **92** as interpreted from ^{1}H spectroscopic analysis of the crude reaction

mixture which matched with results in the literature.[79] Also, excellent ee's of both the corresponding

indanol 92% and unreacted indanone 96% were obtained from chiral HPLC measurements

respectively (Table 13, entry 1). These results are suggestive of the fact that the **B** ring does not interfere with the asymmetric reduction of the indanones since good reaction outcomes were able to be achieved in contrast to prior outputs from the other di-substituted indanones. This is in line with recent finding by the Lee group where they reported that substituent differences in either position or electronics on the 3-phenyl ring do not have a noticeable effect on the reaction outcome.[79]

Table 13. Results of ATH screening on different substituted indanones.

Entry	Indanone	Conversion (%)[c]	Indanol (cis:trans)[d]	ee (%)[e] (cis)	Recovered SM ee (%)[f]	s[g]
1	**91**	50	>95:5	92	96	195.5
2	**84**	<5 (i)	Cis	NA	04	NA
		63[a]* (ii)	70:30	71[a]	93[a]	10.8
3	**89**	<5 (i)	Cis	04	NA	NA
		71[a]*(ii)	60:40	60[a]	49[a]	2.7
4	**71**	0-8 (i)	Cis	NA	NA	NA
		57[a]*(ii)	72:25[a]	80	88	13.9
		50[b]* (iii)	>95:5	94[b]	82[b]	26
5	**72**	0-5 (i)	Cis	NA	NA	NA
		50[a]*(ii)	>95:5 [a]	33	53	5.4
		50[b]*(iii)	>95:5 [b]	ND	ND	ND

Conditions: All reactions were done in 24 h; except [a] = 30 ºC/22 hrs; [b] = rt/22 hrs; reaction temperature was 30 ºC throughout; FA/TEA (3.1:2.6) was added to the substrate/catalyst mixture; DCM (0.5 mL) added throughout to enhance solubility of reaction mixture; * = 10 mol% of catalyst; (%)[c] Product conversions and (%)[d] diastereomeric ratios were calculated from ^{1}H NMR spectrum of crude reaction mixture; [e,f] = measured fom chiral HPLC measurements; (s) = selectivity factor was determined using Kagan's equation; [139] **NA = not applicable; ND = not determined (HPLC separation couldn't be achieved despite many attempts).**

The next set of indanones to be screened and tested based on the hypothesis with respect to ring **A** were **84, 89** which had a single methoxy substituent on their **A** rings in addition to an existing methoxy substituent on the **B** ring each. It was interesting to note that, under the same conditions previously employed for the indanone **91,** the indanone **84**, had less than 5% conversion of the starting material to product (Table 13, entry 2i). With an aim to optimise the reaction outcome and allow for reasonable reaction time, the catalyst loading was increased to 10 mol% and the reaction was not terminated until there was complete consumption of the starting material as evidenced by TLC analysis. Pleasingly, there was 63% conversion of the ketone with a dr of 70:30 *cis/trans* indanols and 71% ee on the major (*cis*) isomer **93** and an excellent ee on the unreacted ketone 93% **(S)-84** (entry 2ii). The next indanone to be assessed was **89**. Just like its counterpart indanone **84** here also, less than 5% conversion of the starting material was recorded (entry 3i). Similarly, with a catalyst loading adjustment to 10 mol%, there was 71% product conversion, dr 60:40 (cis/trans) indanols, ee of (60%) on the *cis* isomer **94** and the unreacted starting material **(S)-89** (49%) (entry 3ii), though the enantioselectivity were not as high as in the previous entry (entry 3ii). Results from ring **A** assessment suggest that the methoxy substituents on ring A could have some participatory role like coordinating to the catalyst thereby reducing the efficiency of the reaction.

With these positive outcomes, the need to push the isopaucifloral F indanone cores for the asymmetric ruthenium reduction once again was revisited by repeating the reaction performed earlier (Scheme 64, entry 1) which provided the same results as expected (entries 4i & 5i). The new set of conditions from table 13 of 10 mol% catalyst loading was then applied. It was pleasing to discover a 57% conversion of starting material with a dr of 75:25 (*cis/trans*) that had an ee of 80% on the *cis* isomer and 88% on the unreacted starting material (entry 4ii). The next substituted indanone **72** was exposed to the same reaction conditions and had a relatively similar % conversion (60%), but with a much higher dr >95:5 (*cis/trans*), and lower ee's of indanol and returned starting material (33% and 53%), respectively (entry 5ii). The need to optimise further on the reaction outcomes was carried out. Repeating the experiments on the same substrates at room temperature had

remarkable outcomes with a 50% conversion, dr >95:5 (*cis/trans*), excellent ee of 94% of the major product **78** and 82% ee on unreacted starting material **(S)-71** (entry 4iii). It was disappointing to observe that although the isopaucifloral F analogue indanone **72** had a similar outcome at 50% conversion of starting material to product, and producing almost exclusively the *cis* isomer with a dr >95:5 (*cis/trans*), the ee of the product **79** (33%) and recovered starting material **(S)-72** (53%) however were not good (entry 5iii) under the same reaction conditions that had good outcomes for its counterpart indanone **71** (entry 4iii). From results of the asymmetric inductions on different substituted indanones conducted, moderate selectivity levels of about 3–14 were recorded (entries 2-5) but the best *s* factor of about 196 was recorded in entry 1.

5.1 Total synthesis towards isopaucifloral F & analogues.

Since the isolation of isopaucifloral F from plants, it has been shown to have significant biological properties like antioxidant, anti-inflammatory, antimicrobial, and many more.[1] Due to its significance in the field of medicine and the pharmaceutical industries, different efforts for its synthesis and other analogues have been pursued by several research groups.

Motivated by the biosynthetic route, Synder *et al*. developed the total synthesis of racemic isopaucifloral F[149] along with other analogues. A previously synthesised intermediate alcohol was treated with TFA and subsequently quenching it with K_2CO_3 yielded the *trans*-2,3-diaryl indanol in 93% yield from which isopaucifloral F (72%) was synthesised in two steps (Scheme 70).
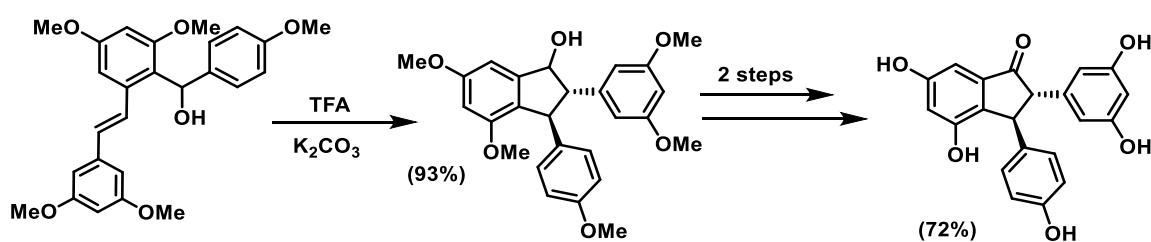
Scheme 70. Synthesis of (±)- isopaucifloral F[149]

Similarly, the Zhong group developed a concise synthesis of racemic isopaucifloral F by utilising commercially available 3,5-dimethoxybenzoic acid **95** as the starting material. Exposure to lithium-naphthalide, produced the dimer **96** which was obtained in 55% yield. Subsequent HWE reaction and cyclisation with BF_3 ensured, to provide the *trans* methylated isopaucifloral F precursor **97** in 85% yield, which was deprotected with BBr_3 to give the target molecule **19** in 54% yield (Scheme 71).[23]
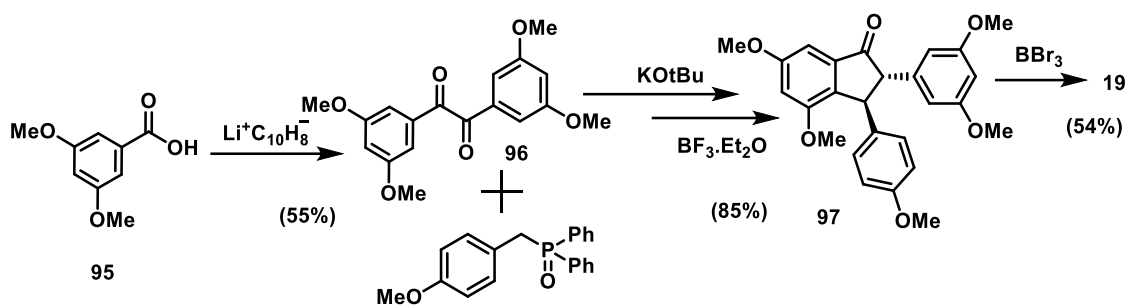
Scheme 71. Concise Synthesis of (±)- isopaucifloral F [23]

Another synthesis of the isopaucifloral F precursor was developed by the Du group through a novel ortho halogenation strategy of arylnitriles. The cyano group on the benzene ring being electron withdrawing and *meta* directing was manipulated *via* the use of a palladium source to regioselectively direct *ortho*-iodination of substituted benzonitriles. The starting material was treated with *N*-iodosuccinimide (NIS) to produce the corresponding 2-iodinated product **98** in 88% yield. The requisite biaryl alkyne **99** was obtained in 83% yield from Sonogashira coupling reaction of a substituted benzene and an acetylenic benzene. Subsequently, combination of the iodinated compound **98** and biaryl alkyne **99** under palladium reaction conditions, provided the precursor isopaucifloral F molecule in 43% yield together with its regioisomer paucifloral F (30%) (Scheme 72).[150]
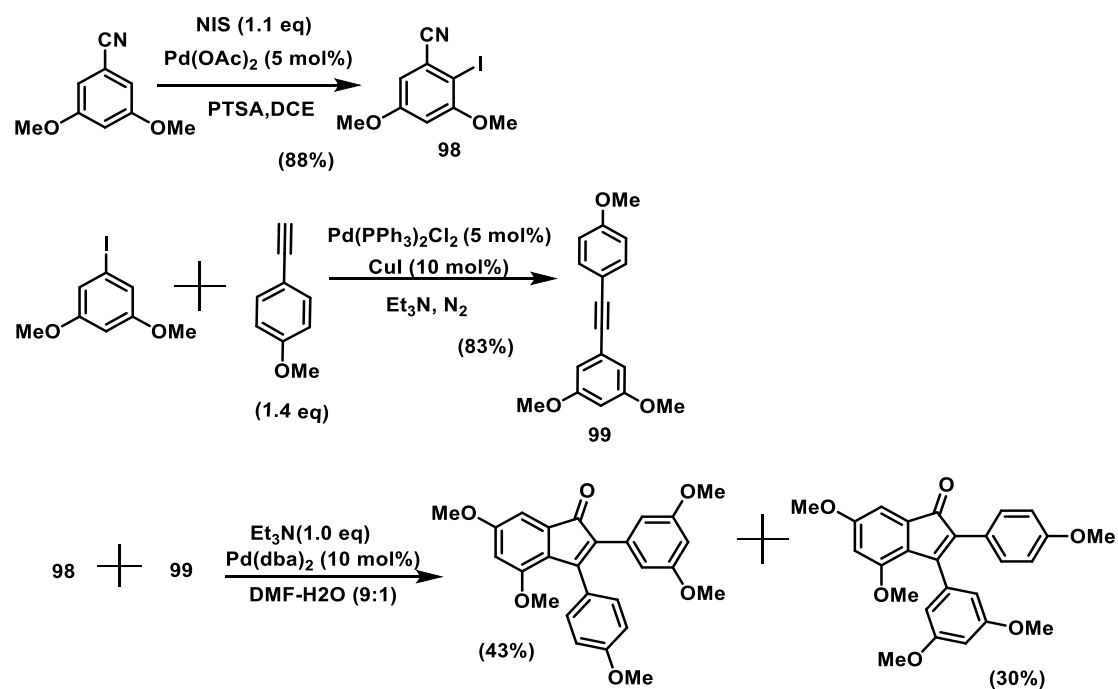
Scheme 72. Synthesis of precursors isopaucifloral F [150]

Similarly, the total synthesis of racemic isopaucifloral F was reported by Anand *et al*; by exploring intramolecular 1,6-hydroolefination strategy. The intermediate *p*-quinone methide **100** which was synthesised over two steps from commercially available materials was transformed into more complex structures. The reaction was carried out in toluene and facilitated by the catalyst Bi(OTf)$_3$ which provided 75% yield of 2,3-diaryl substituted indene **101**. Further functionalisation of the indene molecule produced almost exclusively a single isomer of the isopaucifloral F precursor **102** (dr = 96:4) in 96% yield over four steps. Thereafter, stepwise deprotection of methoxy groups and tert-butyl groups was done with excess of BBr$_3$ and AlCl$_3$ respectively to furnish (±)-isopaucifloral F in 65% yield over two steps, and 13% overall yield (Scheme 73).[151]
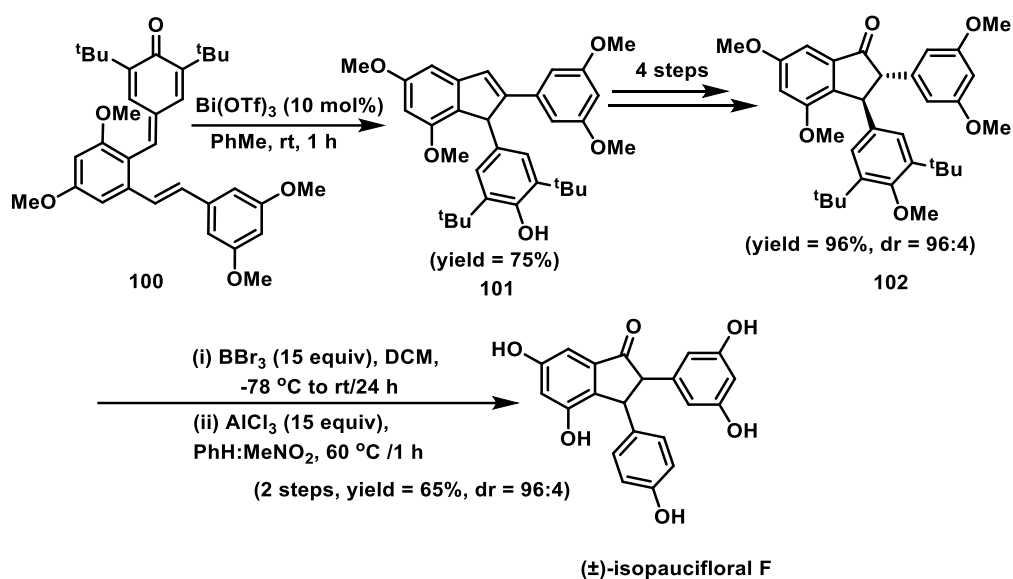
Scheme 73. Total synthesis of (±)-isopaucifloral F[151]

Recently, the formal synthesis of isopaucifloral F was reported *via* a hydrogen radical-shuttle (HRS) assisted decarboxylative cyclisation strategy.[45] The methodology was illustrated with photocatalysis of a mixture of carbonyl compounds and alkynes in water. Under an inert atmosphere of N_2, the reaction flask containing substituted benzoylformic acid **103** and phenylacetylene **104** was irradiated with blue LEDs at 100 °C, and catalysed by an iridium based catalyst in a mixture of acetonitrile and water (19:1) (Scheme 74). Indanone **71** was formed in 67% yield which was further functionalised by following existing protocol[2] where the *trans* arylated isopauciflorol F precursor **97** was synthesised in 87% yield.[45] The target compound **19** was proposed to be obtained by demethylation using standard protocol.[45]
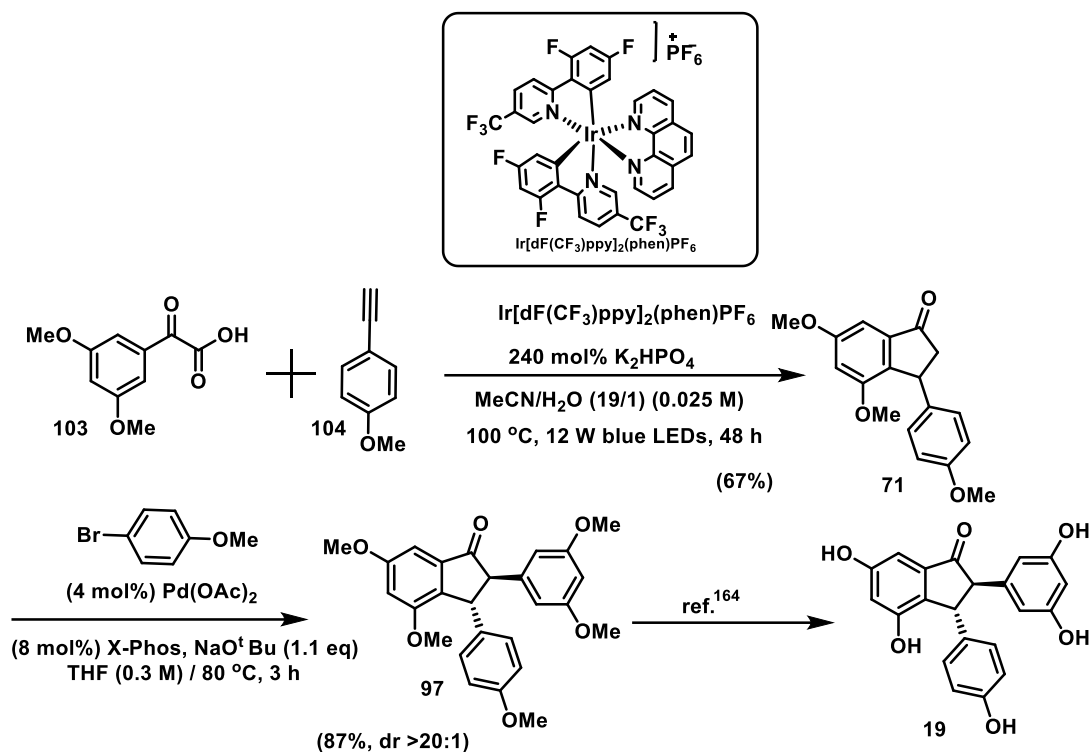
Scheme 74. Formal synthesis of isopaucifloral F[45]

The enantioselective sulfoxide-based total synthesis of (+)-isopaucifloral F was pursued by Tang *et al* in which highly enantioenriched substituted 3-aryl indanone **71** (99% ee) was synthesised in good yield (90%) by Knoevenagel condensation/Nazarov cyclisation (as previously described in section 1.4 of this work). Thereafter, it was derivatised to give 81% yield of the 2,3- diaryl *trans* indanone which was then deprotected with BBr$_3$ to give 54% yield of (+)-isopaucifloral F (Scheme 75).[51]
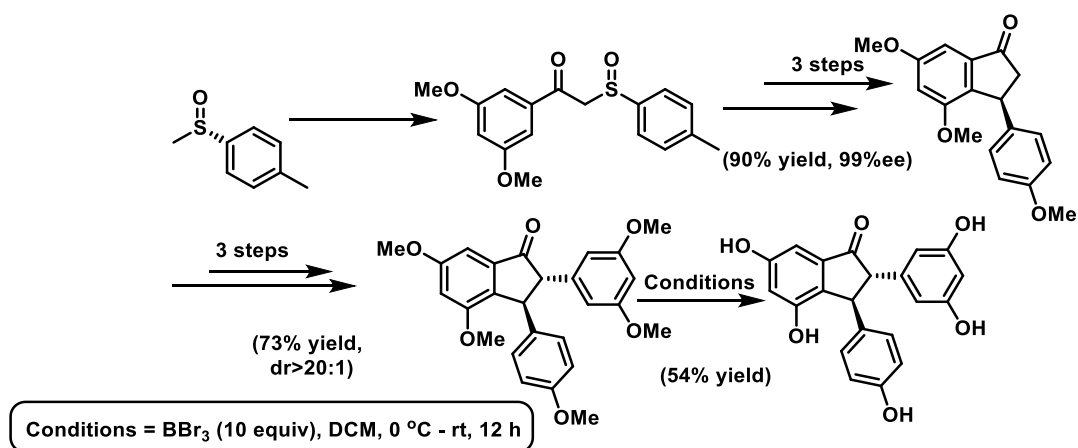
Scheme 75. Enantioselective synthesis of (+)-isopaucifloral F[51]

Despite the diverse approaches towards the synthesis of isopaucifloral F by many research groups, the synthesis of enantioenriched isopaucifloral F is still an area that needs attention. Since only one report was found in the literature, the asymmetric formal synthesis of isopaucifloral F was considered by derivatising previously synthesised indanones *via α*-arylation.

5.2 Making the C ring *via α*-arylation.

The use of transition metals in creating C-C bonds in compounds has continued to generate interest in the field of synthetic chemistry particularly in drug syntheses where molecules with different ring systems are made. The use of palladium catalysts has been employed as a powerful tool for C-H activation, especially for *α*-arylation reactions of carbonyl compounds. They provide versatile routes for installing a great variety of aryl and heteroaryl groups at the *α*-position in carbonyl compounds. [153, 154, 155]

Yang and co-workers developed a novel protocol of α-arylating indanone cores in the concise synthesis of racemic paucifloral F. They reported the use of $Pd_2(dba)_3$ catalyst with the ligand DtBPF as the best combination that produced up to 77% product yield of the α-arylated indanone **106** together with a dehydrogenated compound **107** as an unwanted side product having a selectivity ratio of 5:1 respectively (Scheme 76).[20]
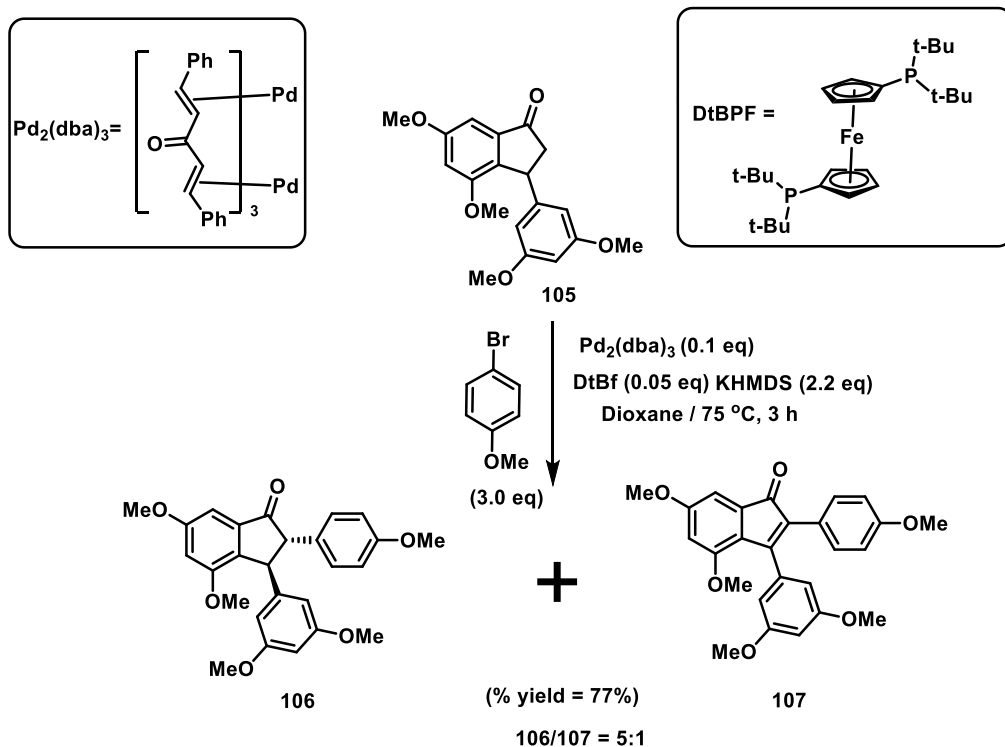
Scheme 76. Synthesis of α-arylated indanones.[20]

Interestingly, the *trans* isomer was the only product isolated from the reaction due to thermodynamic control and mode of quenching the reaction at high temperature. They postulated that steric bulk posed by the methoxy substituents on the phenyl group at the β-position of the indanone ring could also play some key role in dictating the direction to which the arylated product is attached.[20] The stereochemistry of the *trans* product **106** was ascertained *via* 2-D NMR experiments. In the first ROESY experiment, the correlation between ROE signals of protons at C-8 and C-26 was established. Similarly, another correlation of ROE signals between the protons at C-7 and C-17 were also observed in the second experiment (Figure 17).[20]
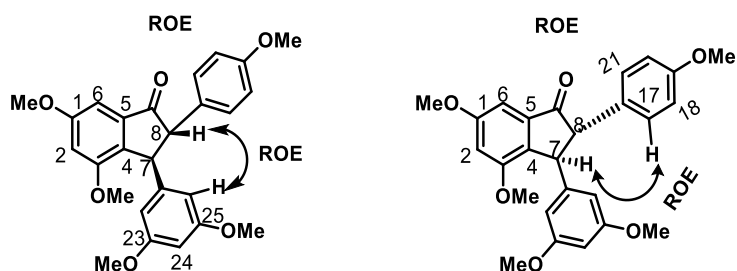
Figure 17. ROESY analysis of compound 106[20]

5.3 Palladium-catalyzed α-arylation

Inspired by the work of Yang and co-workers, the Lee group developed an alternative approach towards synthesis of the asymmetric version of (+)-paucifloral-F. They first attempted literature conditions developed by Buchwald by using (Pd(OAc)$_2$ (4 mol %), X-Phos (8 mol %), NaOtBu (1.5 equiv), 80 °C, 3 h) in the Pd-catalyzed α-arylation of carbonyl substrates.[2] They reported a mixture of four products that they were able to isolate on silica gel flash column chromatography. These included the *trans*-**106** and *cis*-**106** coupled products, which were present in about 3:1 ratio as determined by ^{1}H NMR spectroscopic analysis. Amongst the products formed, were the α-hydroxy compound **108** whose structure was previously elucidated by Sarpong[145] with traces of 1-indenone **107** (Scheme 77).[2]
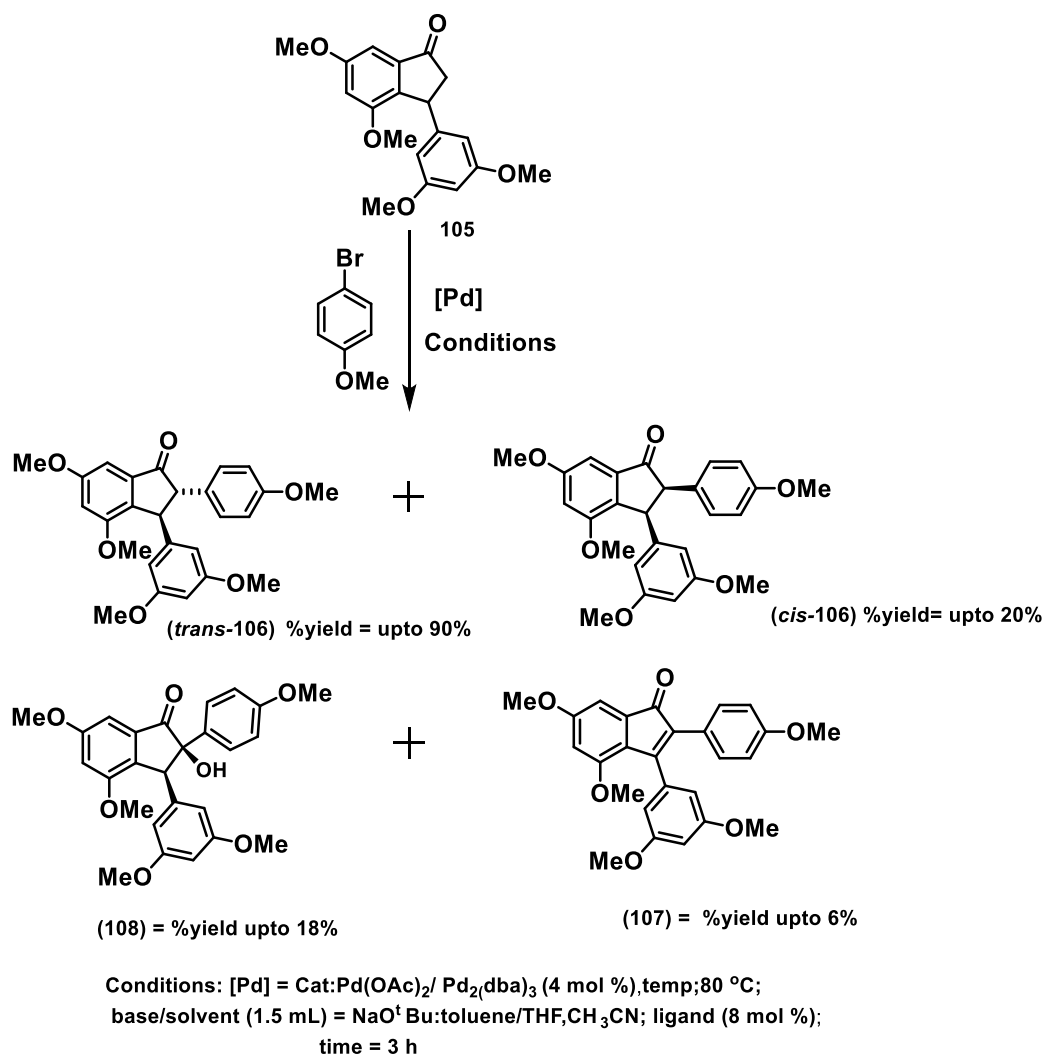
Scheme 77. Palladium-catalyzed α-arylation[2]

An investigative protocol which gave more insight to understanding formation of α-hydroxy **108** as one of the side products was carried out. It involved exposing the *trans* product **106** under basic conditions where 80% α-hydroxy product was formed (Scheme 78).[2] This supports the earlier claim they had of suspecting the use of excess base as being responsible for the unwanted side product in the reaction (Scheme 78).
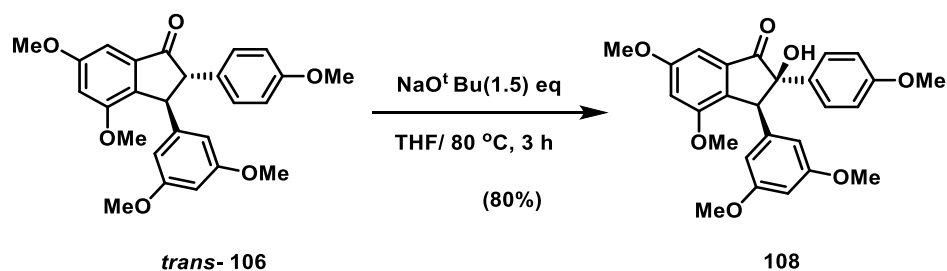
Scheme 78. Formation of α-hydoxy-1-indanones in excess base[2]

Another possibility of the production of the α-hydroxy side product could be the participation of molecular oxygen from air as one of the oxidants (Scheme 79)[2] because the reaction was not carried under inert conditions. Also, it has been established that enolates that result from perarylated indanones, undergo oxygenation very fast contrary to simple indanones that seldom do that.[145]
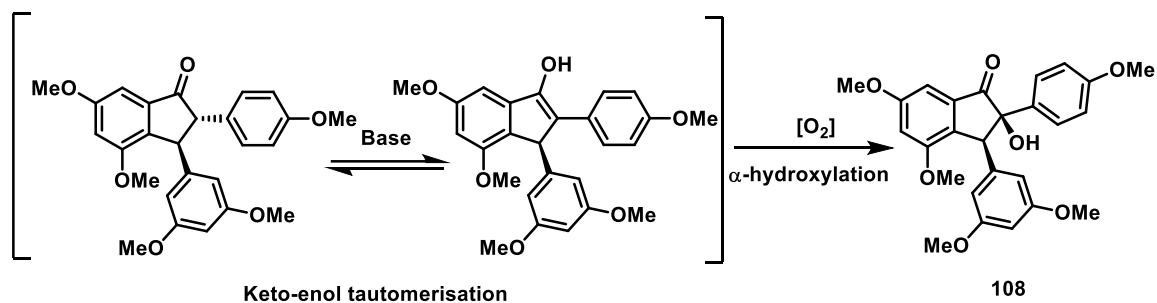
Scheme 79. Proposal for formation of α-hydoxy-1-indanone

In line with investigating the amount and type of base used, the Lee group observed that when the reaction was performed with KOtBu instead of NaOtBu and at the same time reducing the quantity added from the previous 1.5 eq to 1.1 eq, the desired α-arylated compound was not seen, instead the α-hydroxylated product **109** (63%) and its reduced form **110** (20%) were formed (Scheme 80).
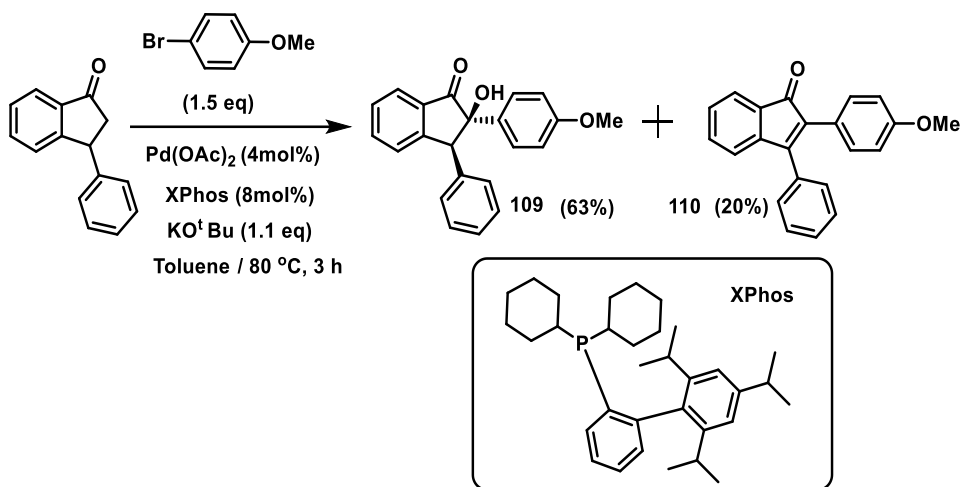
Scheme 80. Formation of α-hydoxy-1-indanones in toluene[2]

To this effect, they came up with optimum conditions by reducing the amount of base, temperature of the reaction, and solvent change from toluene to THF which ultimately produced only the compound of choice (α-arylated *trans* product), thereby curtailing formation of the side product to the barest minimum (Scheme 81).
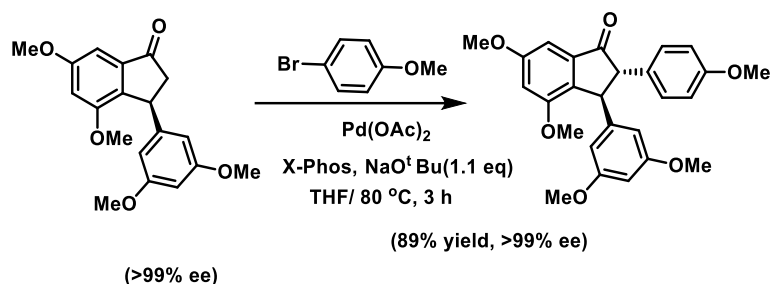
Scheme 81. Applying optimised conditions for the synthesis of trans- α-arylated substituted indanone[2]

5.4 Synthesis of *trans*-2-(3,5-dimethoxyphenyl)-3-phenyl-2,3-dihydroindan-1-one.

Following the successful syntheses of various types of both racemic and chiral 3-aryl indanone cores from previous reactions, there was a need to further functionalise them and incorporate the third ring which will subsequently form the target molecule isopaucifloral F and or its analogues. The

model indanone substrate **54** was subjected to the optimised reaction conditions developed by the Lee group of using Pd(OAc)$_2$/X-Phos, 1.1 eq of in THF at 80 ^{o}C for 3 h.[2] Surprisingly, there was no evidence of new material detected from TLC of the reaction mixture after 3 hours. However, a small indication of product formation was seen after 5 hours together with some unconsumed starting material. It was therefore left overnight for possible consumption of all starting material and pleasingly, the α-arylated compound **111** was isolated in modest yield of 61% from silica gel flash column chromatography (Scheme 82).

R = R'= R" H; 54
R = R" = OMe; R' = H; 71
R' = R" = OMe; R = H; 72

R = R'= R" = H; 111 = 61%
R = R" = OMe; R' = H; 97 = 62%
R' = R" OMe; R = H; 112 = 32%
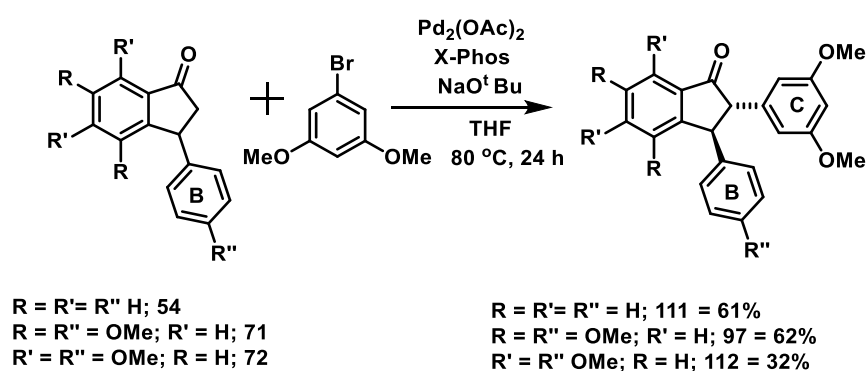
Scheme 82. α -arylation of methoxy-substituted indanones.

The identity was proposed to be the *trans* isomer as indicated by ^{1}H NMR spectra evidence with the coupling constant $^3J_{H2-H3}$ as 5 Hz and by analogy to a previously isolated lone α-arylated *trans* isomer by the Sun group as the more stable dynamic product ($^3J_{H2-H3}$ = 4.7 Hz)[156] as previously reported by Marco *et al*;[157] in the synthesis of 2,3-diaryl indanone. Given the experimental conditions of high temperature and a long reaction time as conditions for operating under dynamic control, formation of the *trans* isomer **111** as the major product was expected which will be more energetically favoured. However, identification of other products that were also isolated along with the major product was not pursued.

5.5 α-Arylation of dimethoxy substituted indanones

The substituted methoxy indanones **71, 72** were also exposed to the same protocol that produced the α-arylated model substrate **111** with formation of desired products **112** and **97** in modest yields of 32% and 62%, respectively (Scheme 82). An interesting observation here was the relative low value of the coupling constant $^3J_{H2\text{-}H3}$ = 2.5 Hz as compared to that observed from the unsubstituted model substrate ($^3J_{H2\text{-}H3}$ = 5.0 Hz) but nonetheless, it matches reported data of $^3J_{H2\text{-}H3}$ = 2.6 Hz for *trans*-dimethoxy indanone substrates in the literature.[22,157] A possible suggestion is the induced steric strain caused by interaction between the bulky methoxy substituents on the newly formed **C** ring with the existent ring **B** which could make the H-C-C-H dihedral angle smaller.

5.6 Conclusion.

Following the successful syntheses of various types of both racemic and enantioenriched chiral 3-aryl indanone cores from previous reactions, onward elaboration towards the formal asymmetric synthesis of the target molecule isopaucifloral F was pursued. By adapting existing literature protocol as developed by the Lee group[2] and subsequent modifications, this led to the synthesis of the simple *trans* isomer **111** in 61% yield from the model substrate **54** as the major energetically favoured isomer given the experimental conditions operating under dynamic control. Substituted dimethoxy analogues **97, 112** were also formed in modest yields of 62% and 32% respectively. Prior to this work, the compounds **111** and **112** were not found in the literature.

Chapter 6.0

6.1 Conclusion and Future work

Different protocols for the synthesis of 3-aryl-2-phosphoryl indanones and 3-aryl-indanones have been assessed in this project. The initial attempt was to employ Nazarov cyclisation of phosphorylated chalcones previously obtained from Knoevenagel condensation of β-ketophosphonates as the key step (Scheme 83).
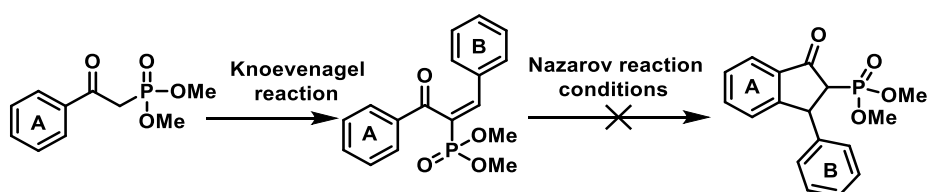
Scheme 83. Synthesis of 3-aryl-2-phosphoryl indanones *via* Nazarov cyclisation

However, after unsuccessful Nazarov cyclisation attempts, a new method for the synthesis of 3-aryl-2-phosphoryl indanones was developed using modified Heck cyclisation (Scheme 84).
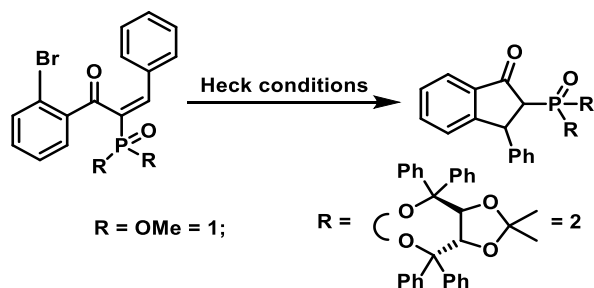
Scheme 84. Modified Heck reaction towards synthesis of 3-aryl-2-phosphoryl indanones

In the developed method, there was full conversion of starting material to product in all instances but separation of the different diastereoisomers by flash column chromatography proved challenging except for a modest amount (18%) of clean material (**2**) that was isolated. Also several preparative HPLC attempts to obtain crystals for X-ray analysis failed.

Another change in strategy was necessitated which led to the synthesis of different types of 3-aryl indanones *via* classical Heck reaction of 2-bromo chalcones. Subsequent kinetic resolution (KR) *via* asymmetric reduction of the prepared 3-aryl indanone cores using amino indanol catalysts was investigated for the first time on these types of systems although the use of other CBS-derived catalysts has been reported in the literature[127,158] (Scheme 51).
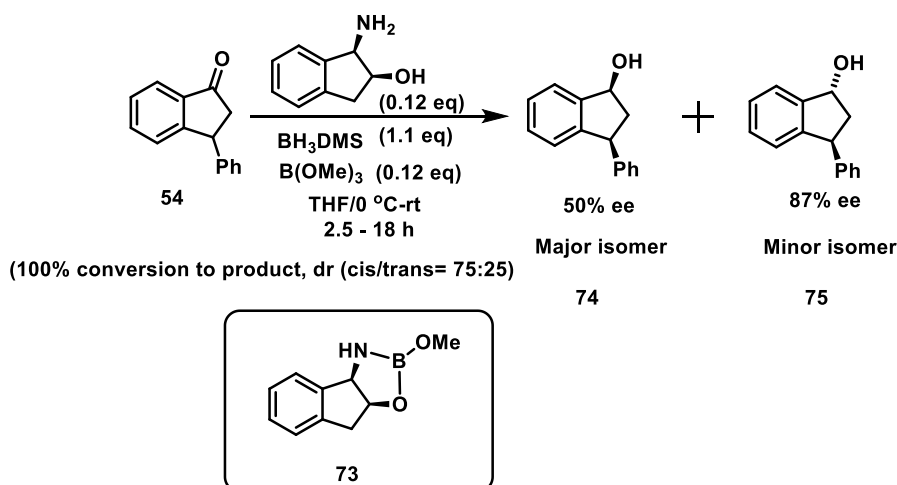
Scheme 51. Asymmetric reduction of 3-pheny indanone with CBS-derived amino indanol

Non-reproducibility of the reaction outcome even after several optimisation reactions and poor ee values from subsequent trials (Table 11) necessitated the use of an alternative reducing agent that could be employed for the effective resolution of the indanone substrates.

Pleasingly, modified literature conditions with DPEN-based Ru(II)[132] led to the development of an efficient ATH-KR on the 3-phenyl indanones with excellent outcomes. Prior to this time, the ATH-KR of 3-phenyl indanones using DPEN-based Ru(II) catalysts has not been reported (Scheme 85).
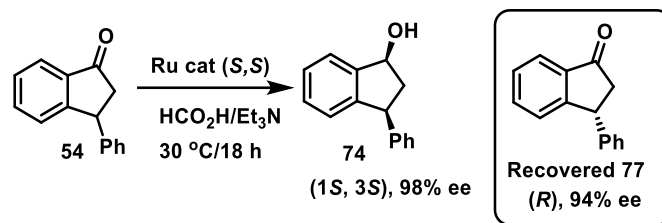
Scheme 85. ATH-KR of 3-phenyl indanone

A major advantage of this protocol is that enantioenriched *cis*-3-phenyl indanols and 3-arylindanones were formed in a single step. Interestingly, the dimethoxy substituted-3-aryl indanones were effectively resolved at room temperature with 10 mol% catalyst loading to give a 50% conversion, dr >95:5 (*cis/trans*), excellent ee of 94% and 82% ee on unreacted starting material. This strategy provides an option for synthesising substituted enantioenriched chiral indanones which could be used as intermediates for further elaborations into compounds of interest that may be used as drug leads in a single step.

The synthetic utility of the enantioenriched chiral 3-aryl indanone cores from previous reactions was demonstrated by carrying out some transformations which are not straightforward to make or would otherwise require multiple steps. NaBH$_4$ reduction on an enantioenriched 3-phenyl indanone produced the corresponding indanol with comparable enantioselectivity and DMP oxidation of a *cis* alcohol yielded the chiral indanone with about the same ee value (Scheme 86).
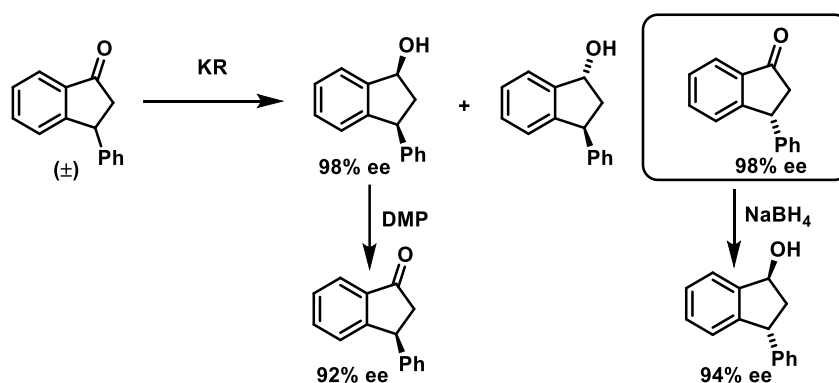
Scheme 86. Synthetic utility of KR indanone products

In the case of the enantioenriched substituted indanones, the synthetic utility was demonstrated by incorporating a third ring on the resolved dimethoxy substituted indanone *via* α-arylation to form the precursor isopaucifloral *F* molecule. Expectedly, there was no significant erosion on the ee of the product (Scheme 87). The formal synthesis of isopaucifloral F has been achieved and all that would be required is demethylation of the precursor **109**.
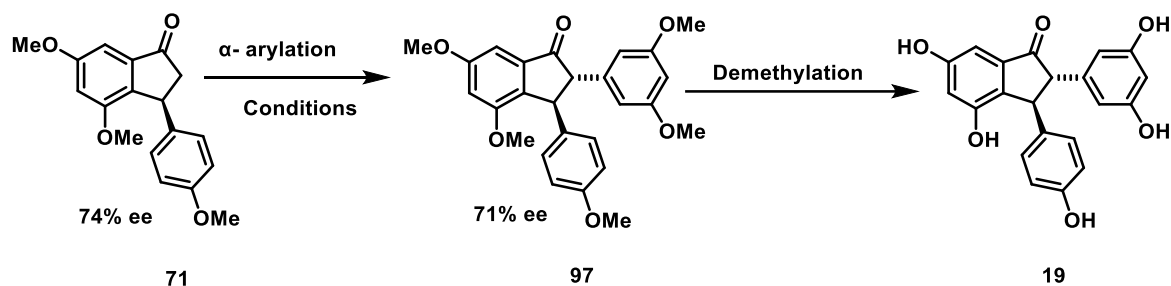
Scheme 87. Formal synthesis of isopaucifloral F

6.2 Future work

Since the ATH-KR has yielded highly enantioenriched indanols along with their corresponding indanones, it will be interesting to assess their biological activities and subsequently their higher functionalised products.

Additionally, the modified Heck cyclisation procedure developed for the synthesis of 3-aryl-2-phosphoryl indanones successfully revealed full conversion of starting materials to products but isolating the products remained a challenge. Investigation into the optimised conditions by expanding the substrate scope on both A and B rings of the indanone could provide better diastereoselectivity and perhaps may lead to an effective isolation of more materials thereby yielding crystals for X-ray analysis. To test the efficiency of the chirality control by the enantioenriched stereogenic phosphonate, reductive cleavage of the phosphoryl group could be attempted and the resulting 3-aryl indanone assessed with respect to its yield and enantioselectivity. Moreover, a library of analogues could be generated which may have some biological potency that could be utilised as drug candidates.

Chapter 7.0

Experimental

General

Unless otherwise stated, all reactions were performed under an inert atmosphere of nitrogen or argon in flame dried glassware with magnetic stirring. Dry solvents were obtained from the Grubbs dry solvent facility in the department. Commercially available starting materials were purchased from Alfa Aesar, Fluorochem or Sigma–Aldrich and used directly unless specified. TLC was carried out using Merck aluminium TLC sheets (silica gel 60 F254), visualisation of TLC plates was performed using a UV lamp or developed in $KMnO_4$ or PMA dips and heating. Flash column chromatography was performed using Fluorochem Limited Silica Gel 40-63μ 60Å as the stationary phase. Columns were typically packed as a slurry, and the eluent equilibrated with the appropriate solvent system prior to use.

The reactions done at sub-zero temperatures of -78 °C were cooled by means of an acetone/dry ice bath, -40 °C by CH_3CN/dry ice with occasional CH_3CN topping to maintain the temperature, -5 °C by an ice/salt bath, while those at 0 °C were carried out in an ice bath. n-BuLi was used as a solution in hexanes and was titrated weekly against 1,3-diphenyl-2-propanone tosyl hydrazine [159] ^1H, ^{13}C NMR and ^{31}P spectra were recorded in $CDCl_3$ or MeOD on Bruker 100 or 400 MHz spectrometers. Chemical shifts were recorded on the δ scale relative to the TMS (tetramethylsilane, δ = 0 ppm) reference point and coupling constant (J) values were reported in Hz. Infrared spectra were obtained using a PerkinElmer RX1 FT-IR spectrometer. Liquid chromatographic mass spectrometry (LCMS) was performed using electron ionisation (EI), electrospray ionisation (ES or ESI), affinity purification (AP) or direct infusion using either a Walter ITC Premier XE instrument or a Micromass LCT instrument. Specific rotations were performed on an Optical Activity Ltd. AA-10 automatic polarimeter at 589 nm (Na D-line) and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Melting points were measured on a Gallenkamp apparatus. Enantioenriched compounds were separated on a Gilson HPLC with an ABI

Analytical Spectroflow 783 UV detector and preparative HPLC was done with Waters XBridge C18 (250 × 4.6 mm column). The specifications of chiral columns used for different compounds and the setting of the wavelength detector is mentioned in the individual experimental details. The same solvent system of n-hexane and IPA was used as the mobile phase in all experiments but with variations in their proportionality as described in the different individual experiments. Absolute configuration of the products was determined by comparison with known compounds from literature.

Preparation of β-keto phosphonates.

General procedure A for representative compound 33 a-f

Dimethyl (2-oxo-2-phenylethyl) phosphonate 33 a [54, 62, 160, 161, 65, 162, 57]
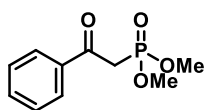
A solution of n-butyllithium (2.00 mL, 2.80 mmol, 1.40 M in hexanes) was added to a stirred solution of DIPA (0.40 mL, 0.30 g, 2.93 mmol) in THF (10 mL) at -78 °C under an atmosphere of argon. After 40 minutes, DMMP (0.20 mL, 1.47 mmol) was added to the reaction mixture at -5 °C, followed by portion wise addition of ethyl benzoate (0.20 g, 1.33 mmol). After complete addition of the ester, the reaction mixture was stirred between -5 to 0 °C until complete consumption as determined by TLC. The reaction mixture was then carefully quenched with 1M HCl to adjust the pH to ca. 4 and diluted with EtOAc (30 mL). The aqueous layer was separated and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (3 × 30 mL) and brine (30 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo* to yield the crude product that was purified by flash column chromatography on silica gel eluting with EtOAc (R$_f$ = 0.35) to give the title compound as a pale yellow oil (0.23 g, 77%); ^{1}H NMR (400 MHz; CDCl$_3$) δ$_H$ 3.56 (2H, d, J_{HP} 22.6, CH_2), 3.67 (6H, d J_{HP} 11.22 × OCH_3), 7.38 (2H, t, J 5.1, 2 × ArCH), 7.47-7.52 (1H, m, ArCH), 7.88-7.92 (2H, m, 2 × ArCH); ^{13}C

NMR (100 MHz; CDCl$_3$) δ_C 37.3 (d, J_{CP} 131.5, CH_2), 53.1 (2 × OCH_3, d, J_{CP} 6.5)128.6 (2 × ArCH), 128.9 (2

× ArCH), 133.7 (ArCH), 136.3 (d, J_{CP} 2.5 ArC), 191.8 (ArCO, d, J_{CP} 6.4); ^{31}P NMR (CDCl$_3$, 162 MHz);

δ22.86. All data were in accordance with literature. [54, 62, 160, 161, 65, 162, 57]

Dimethyl[2-(4-methylphenyl)-2-oxoethyl)] phosphonate 33 b [54, 161, 65]
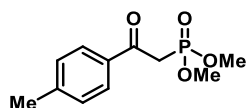
Prepared according to the general procedure **A** using a solution of n-BuLi (14.7 mL, 14.0 mmol, 0.95

M in hexanes), solution of DIPA (2.10 mL, 14.7 mmol) in THF (40 mL), DMMP (0.80 mL, 7.33 mmol),

methyl-*p*-tolyl benzoate (1.00 g, 6.66 mmol). The residue was purified by flash column

chromatography on silica gel eluting with EtOAc (R$_f$ = 0.21) to give the title compound as a pale

yellow oil (1.25 g, 77 %); ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 2.43 (3H, s, CH_3), 3.63 (2H, d, J_{HP} 22.6, CH_2),

3.79 (6H, d, J_{HP} 11.2, 2 × OCH_3), 7.29 (2H, d, J 8.1, 2 × ArCH), 7.91 (2H, d, J 8.1, 2 × ArCH); ^{13}C NMR

(100 MHz; CDCl$_3$) δ_C 21.7 (CH_3), 37.4 (CH_2, d, J_{CP} 131.2), 53.1 (d, J_{CP} 6.4, 2 × CH_3), 129.1 (2 × ArCH),

129.4 (2 × ArCH), 134.0 (ArC, d, J_{CP} 2.7), 144.8 (ArC), 191.4 (d, J_{CP} 6.7, ArCO); ^{31}P NMR (CDCl$_3$; 162

MHz): δ 23.06 (s). All data were in accordance with literature. [54, 161, 65]

Dimethyl[2-(4-methoxyphenyl)-2-oxoethyl]phosphonate 33 c [54, 161]
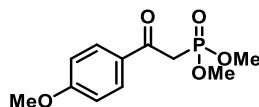
Prepared according to the general procedure **A** using a solution of n-butyl lithium (5.70 mL, 13.0

mmol, 2.28 M in hexanes), a solution of DIPA (1.90 mL, 13.6 mmol) in THF (30 mL), DMMP (0.70 mL,

6.78 mmol), ethyl *p*-anisate (1.00 g, 6.17 mmol). The residue was purified by flash column

chromatography on silica gel eluting with EtOAc (R$_f$ = 0.19) to give the title compound as a pale

yellow oil (1.52 g, 94%): ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 3.61 (2H, d, J_{HP} 22.6, CH_2), 3.80 (6H, d, J_{HP} 11.2,

2 × OCH_3), 3.90 (3H, s, OCH_3), 6.97 (2H, d, J 9.0, 2 × ArCH), 8.01 (2H, d, J 9.0, 2 × ArCH); ^{13}C NMR (100

MHz; CDCl$_3$) δ_C 37.3 (CH_2, d, J $_{CP}$ 131.0), 53.2 (d, J $_{CP}$ 6.5, 2 × OCH_3), 55.6 (OCH_3), 113.9 (2 × ArCH),

129.5 (ArC, d, J_{cp} 2.9), 131.5 (2 × ArCH), 164.1 (ArC), 190.1 (ArCO, d, J $_{CP}$ 7.1); ^{31}P NMR (CDCl$_3$, 162

MHz); δ 23.23. All data were in accordance with literature. [54,161]

Dimethyl[2-(2-methoxyphenyl)-2-oxoethyl] phosphonate 33 d [62]
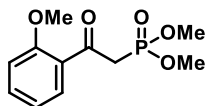
Prepared according to the general procedure **A** using a solution of n-butyl lithium (8.00 mL, 15.2

mmol, 1.90 M in hexanes), a solution of DIPA (2.20 mL, 15.9 mmol) in THF (20 mL), at -78 ^{o}C under an

atmosphere of argon. After 40 minutes, DMMP (0.90 mL, 7.94 mmol), methyl o-anisate (1.20 g, 7.22

mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R$_f$

= 0.17) to give the title compound as a pale yellow oil (1.21 g, 65%); ^{1}H NMR (400 MHz; CDCl$_3$) δ_H

3.76 (6H, d, J_{HP} 11.2, 2 × OCH_3), 3.84 (2H, d, J_{HP} 21.6, CH_2), 3.96 (3H, s, OCH_3), 6.98 - 7.06 (2H, m, ArH),

7.48-7.54 (1H, m, ArH), 7.76 (1H, dd J 7.7, 1.8, ArH); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 41.7 (CH_2, d, J $_{CP}$

132.2), 52.9 (d, J_{CP} 6.4, 2 × OCH_3), 55.70 (OCH_3), 111.6 (ArCH), 120.9 (ArCH), 130.0 (ArC), 131.0 (ArCH),

134.5 (ArCH), 158.8 (ArC), 193.0 (ArCO, d, J $_{CP}$ 7.2); ^{31}P NMR (CDCl$_3$; 162 MHz) δ 24.19. All data were

in accordance with the literature. [62]

Dimethyl[2-(2-furyl)-2-oxoethyl)]phosphonate 33 e [65]
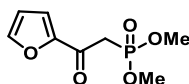
Prepared according to the general procedure **A** using a solution of n-BuLi (8.70 mL, 19.8 mmol, 2.28

M in hexanes), DIPA (2.90 mL, 20.8 mmol) in THF (30 mL), DMMP (1.10 mL, 10.4 mmol), methyl-2-

furoate (1.10 mL, 9.44 mmol). The residue was purified by flash column chromatography on silica

gel eluting with EtOAc (R$_f$ = 0.18) to give the title compound as a golden-brown oil (1.14 g, 55 %); ^{1}H

NMR (400 MHz; CDCl$_3$) δ_H 3.53 (2H, d, J_{HP} 22.6, CH_2), 3.81 (6H, d, J_{HP} 11.2, 2 × OCH_3), 6.60 (1H, dd, J 3.8, 1.7, ArCH), 7.33 (1H, dd, J 3.8 0.8, ArCH), 7.65 (1H, dd, J 1.7, 0.8 , ArCH); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 37.1 (CH_2, d, J_{CP} 131.2), 53.1 (d, J_{CP} 6.4, 2 × OCH_3), 112.9 (ArCH), 119.1 (ArCH), 147.4 (ArCH), 152.1 (d, J_{CP} 3.2, ArC), 179.7 (d, J_{CP} 6.8, ArCO); ^{31}P NMR (CDCl$_3$; 162 MHz): δ 22.33 (s). All data were in accordance with literature [8] except at: δ_H 7.33 (1H, d, J 3.6 ArH) and 7.65 (1H, d, J 0.9ArH).

Dimethyl (2-oxo-2-pyridin-3ylethyl) phosphonate 33 f [62]
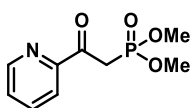
Prepared according to the general procedure A using a solution of n-BuLi (6.80 mL, 15.5 mmol, 2.28 M in hexanes) was added to a stirred solution of DIPA (2.30 mL, 16.3 mmol) in THF (30 mL), DMMP (0.90 mL, 8.10 mmol), ethyl-2-picolinate (1.00 mL, 7.40 mmol), The residue was purified by flash column chromatography on silica gel eluting with EtOAc (Rf =0.19), to give the title compound as a pale yellow oil (1.12 g, 66%); 1H NMR (400 MHz; CDCl3) δH 3.80 (6H, d, J PH 11.2, 2 × OCH3), 4.05 (2H, d, J PH 22.6, CH2), 7.50- 7.55 (1H, m, ArH), 7.88 (1H, td, J 7.8, 1.7, ArH), 8.10 (1H, br d, J 7.8, ArH), 8.71- 8.74 (1H, m, ArH); 13C NMR (100MHz; CDCl3) δC 37.3 (CH2, d, JCP 131.0), 53.1 (2 × OCH3, d, J CP 6.2), 122.4 (ArCH), 127.9 (ArCH), 137.1 (ArCH) , 149.0 (ArCH), 152.0 (d, JCP 2.7, ArC), 193.6 (ArCO, d, JCP 7.0); 31P NMR (CDCl3; 162MHz); δ 23.7. All data were in accordance with literature.[62]

Diethyl-[2-(4-methylphenyl)-2-oxoethyl)]phosphonate 38 [54, 65, 163, 59]
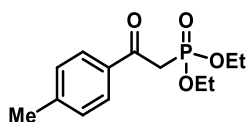
Prepared according to the general procedure **A** using a solution of n-BuLi (10.0 mL, 14.0 mmol, 1.46 M in hexanes), solution of DIPA (2.10 mL, 14.7 mmol) in THF (20 mL), DEMP (1.10 mL, 7.33 mmol), methyl-*p*-toluate (1.00 g, 6.66 mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R_f = 0.19) to give the title compound as a pale yellow oil (1.24 g, 69%); ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 1.28 (6H, t, *J* 7.1, 2 × OCH$_2$C*H*$_3$), 2.41 (3H, s, C*H*$_3$), 3.60 (2H, d, J_{HP} 22.7, C*H*$_2$), 4.08 - 4.18 (4H, m, 2 × C*H*$_2$O), 7.27 (2H, d, *J* 8.8, 2 × ArC*H*), 7.91 (2H, d, *J* 8.8, 2 × ArC*H*); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 16.3 (d*, J* $_{CP}$ 6.3, 2 × *C*H$_3$), 21.7 (*C*H$_3$), 38.4 (*C*H$_2$, d, *J* $_{CP}$ 129.9), 62.6 (*C*H$_2$, d, *J* $_{CP}$ 6.5), 129.2 (Ar*C*H), 129.3 (Ar*C*H), 134.1 (Ar*C,* d*, Jcp* 1.8), 144.6 (Ar*C*), 191.5 (d, *J* $_{CP}$ 6.6 Ar*C*O); ^{31}P NMR (162 MHz; CDCl$_3$) δ_P 20.18. All Data were in accordance with literature. [54, 65, 163, 59]

**Diisopropyl[2-(4-methylphenyl)-2-oxoethyl)] phosphonate 39** [163]
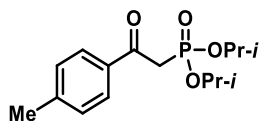
Prepared according to the general procedure **A** using a solution of n-BuLi (5.60 mL, 14.0 mmol, 2.50 M in hexanes), DIPA (2.10 mL, 14.7 mmol) in THF (20 mL), methyl-*p*-toluate (1.00 g, 6.66 mmol. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether/EtOAc (1:2) (R_f = 0.19), to give the title compound as a pale yellow oil (1.27 g, 64%): ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 1.29 (12H, dd, *J* 6.2, 3.8, 2 × 6*H*), 2.42 (3H, s, C*H*$_3$), 3.57 (2H, d, *J* 22.9, C*H*$_2$), 4.67-4.80 (2H, m, 2 × C*H*), 7.27 (2H, d, *J* 8.3, 2 × ArC*H*), 7.93 (2H, d, *J* 8.3, 2 × ArC*H*); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 21.7 (*C*H$_3$), 23.8 (2 × d, J_{CP} 5.2, 3.8, C*C*H$_3$), 39.6(d, J_{CP} 130.3, *C*H$_2$), 71.4 (d, J_{CP} 6.7, 2 × *C*H), 129.2 (2 × Ar*C*H), 129.3 (2 × Ar*C*H), 134.3 (Ar*C* d, *Jcp* 1.5)*,* 144.4 (Ar*C*), 191.7 (d, *J* $_{CP}$ 6.6, Ar*C*O); ^{31}P NMR (CDCl$_3$; 162 MHz); *δ* 18.01. All Data were in accordance with literature. [163]

Diethyl [2-(4-methoxyphenyl)-2-oxoethyl] phosphonate 44 [163, 54, 164]

Prepared according to the general procedure **A** using a solution of n-BuLi (4.90 mL, 11.7 mmol, 2.37 M in hexanes), solution of DIPA (1.70 mL, 12.2 mmol) in THF (20 mL), DEMP (0.90 mL, 6.10 mmol), methyl-*p*-toluate (1.00 g, 5.55 mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R_f = 0.2) to give the title compound as a pale yellow oil (1.2 g, 76%); ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 1.27 (6H, t, *J* 7.1, 2 × C*H$_3$*), 3.57 (2H, d, J_{HP} 22.7, C*H$_2$*), 3.86 (3H, s, OC*H$_3$*), 4.08 - 4.16 (4H, m, 2 × OC*H$_2$*), 6.93 (2H, d, *J* 8.6, 2 × ArC*H*), 7.98 (2H, d, *J* 8.6, 2 × ArC*H*); ^{13}C NMR (100MHz; CDCl$_3$) δ_C 16.3 (d, *J* $_{CP}$ 6.3, *C*H$_3$), 38.3 (d, *J* $_{CP}$ 129.7, *C*H$_2$), 55.5 (s, O*C*H$_3$), 62.6 (d, *J* cp 6.5, 2 × O*C*H$_2$), 113.7 (2 × Ar*C*H), 129.6 (Ar*C*, d, *Jcp* 1.7), 131.5 (2 × Ar*C*H), 164 (Ar*C*), 190.3 (d , J_{CP} 6.4, Ar*C*O); ^{31}P NMR (CDCl$_3$, 162 MHz): δ 20.39. All data were in accordance with literature. [163, 54, 164, 163]

**Diethyl [2-(3-methoxyphenyl)-2-oxoethyl] phosphonate 45** [162, 163]
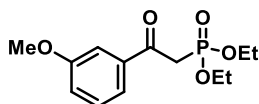
Prepared according to the general procedure **A** using a solution of n-BuLi (1.10 mL, 2.50 mmol, 2.37 M in hexanes), a solution of DIPA (0.40 mL, 2.60 mmol) in THF (10mL), DEMP (0.20 mL, 1.30 mmol), methyl-*m*-anisate (0.20 g, 1.20 mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R_f = 0.20) to give the product as a pale yellow oil (0.25 g, 74%); ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 1.29 (6H, t, *J* 7.1, 2 × OC*H$_3$*), 3.62 (2H, d, J_{HP} 22.7, C*H$_2$*), 3.85 (3H, br s, OC*H$_3$*), 4.09 - 4.19 (4H, m, 2 × OC*H$_2$*), 7.11- 7.15 (1H, m, ArC*H*), 7.38 (1H, t, *J* 7.9 Ar*H*), 7.53 (1H, d, *J* 1.6, ArC*H*), 7.57 – 7.61 (1H, m, ArC*H*); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 16.2 (d, J_{CP} 6.3, 2 × O*C*H$_3$), 38.6 (d, J_{CP} 130.2, *C*H$_2$CO), 55.4 (O*C*H$_3$), 62.6 (d, J_{CP} 6.5, 2 × *C*H$_2$), 112.8 (Ar*C*H), 120.4 (Ar*C*H), 121.9 (Ar*C*H), 129.6

(ArCH), 137.9 (d, J_{CP} 2.1, ArC), 159.8 (ArC), 191.8 (ArCO, d, J_{CP} 6.6); ^{31}P NMR (CDCl$_3$, 162 MHz); δ 19.92. All data were in accordance with literature. [162, 163]

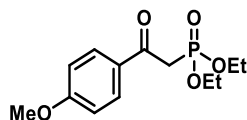## Diethyl [2-(2-methoxyphenyl)-2-oxoethyl] phosphonate 46 [57]
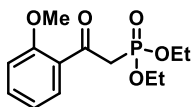
Prepared according to the general procedure **A** using a solution of n-BuLi (5.30 mL, 12.6 mmol, 2.37 M in hexanes), a solution of DIPA (1.90 mL, 13.2 mmol) in THF (20 mL), DEMP (1.00 g, 6.62 mmol), methyl-*o*-anisate (1.00 g, 6.02 mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R$_f$ = 0.19) to give the title compound as a pale yellow oil (1.12 g, 65%); ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 1.26 (6H, t, J 7.1, 2 × CH$_3$), 3.84 (2H, d, J_{HP} 21.9, CH$_2$), 3.94 (3H, s, OCH$_3$), 4.07 - 4.15 (4H, quint, J_{HP} 5.8, 2 × OCH$_2$), 6.96 – 7.04 (2H, m, ArH), 7.50 (1H, ddd, J 8.4, 7.5, 1.8 ArH), 7.73 (1H, dd, J 7.5 1.8, ArH); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 16.3 (d, J_{CP} 6.4, 2 × CH$_3$), 42.5 (d, J_{CP} 130.1, CH$_2$CO), 55.6 (OCH$_3$), 62.2 (d, J_{CP} 6.4, 2 × CH$_2$), 111.5 (ArCH), 120.8 (ArCH), 127.8 (ArC, d, J 2.3), 131.0 (ArCH), 134.2 (ArCH), 158.6 (ArC), 193.5 (ArCO, d, J_{CP} 7.2); ^{31}P NMR (CDCl$_3$, 162 MHz); δ 21.17. All data were in accordance with literature. [57]

Synthesis of Knoevenagel products 34 a-e

General procedure B for Representative compound

Phosphonic acid, *P*-[(*1E*)-1-benzoyl-2-phenylethyl] dimethyl ester 34 a [67]
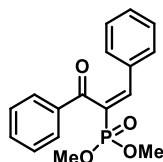
Benzaldehyde (0.20 mL, 2.40 mmol) was added to a stirred solution of β-ketophosphonate **33 a** (0.50 g, 2.19 mmol) in dry toluene (30 mL). Piperidine (~0.05mL, 0.44 mmol) was added, and the resulting solution was heated for 30 hours under Dean-Stark conditions. The reaction mixture was cooled and

concentrated to yield the crude product which was purified by flash column chromatography on silica gel eluting with petroleum-ether/EtOAc = 1:2 (R_f = 0.30) to afford the title compound as a yellow liquid (0.50 g, 72%); ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 3.81 (6H, d, J 11.2, 2 × OCH_3), 7.18-7.26 (3H, m, 3 × ArCH), 7.29 -7.34 (2H, m, ArCH), 7.36- 7.41 (2H, m, ArCH) 7.50 - 7.55 (1H, m, ArCH), 7.86 (1H, d, J_{PH} 26.0, PC=CH), 7.93-7.97 (2H, m, 2 × ArCH); ^{13}C NMR (100MHz; CDCl$_3$) δ_C 53.20 (2 × OCH$_3$, d J_{CP} 5.8), 128.7 (4 × ArCH), 129.6 (2 × ArCH), 129.9 (2 × ArCH), 130.3 (ArCH), 130.5 (ArC), 133.4 (d, J_{CP} 21.4, PC=CH), 134.0 (ArCH), 135.4 (d, J_{cp} 2.7, ArC), 147.2 (HC=CP, d, J_{cp} 5.9), 195.5 (ArC=O, d, J_{CP} 8.3); ^{31}P NMR (CDCl$_3$, 162 MHz); δ 17.06. All Data were in accordance with literature. [67]

P-[(*1E*)-1-Furanoyl-2-phenylethyl] phosphonic acid dimethyl ester 34 b
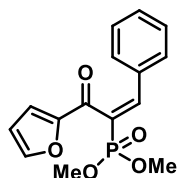
Prepared according to the general procedure **B** using benzaldehyde (0.30 mL, 2.52mmol), a solution of β-ketophosphonate **33 e** (0.50 g, 2.29 mmol) in dry toluene (20 mL) and piperidine (0.05 mL, 0.46 mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R_f = 0.32), to afford the title compound (0.42 g, 60%) as deep yellow crystals. Mpt 59 – 61 °C; ν_{max} (ATR / cm^{-1}); 3076, 3004, 1640, 1460, 1251; ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 3.84 (6H, d, J 11.3, 2 × OCH_3), 6.42 (1H, dd, J 3.6, 1.7, ArCH), 7.08 (1H, d, J 3.4 ArCH), 7.24 -7.38 (5H, m, 5 × ArCH), 7.56 (1H, d, J_{Hp} 1.6, ArCH), 7.85 (1H, d, J_{Hp}25.3, CH=CH); ^{13}C NMR (100MHz; CDCl$_3$) δ_C 53.2 (OCH$_3$, d J_{CP} 5.7), 112.6 (ArCH), 121.3 (ArCH), 127.9 (ArC), 128.8 (2 × ArCH), 129.7 (2 × ArCH), 130.4 (ArCH), 133.5 (d, J_{CP} 21.1, PC=CH , 148.0 (ArCH), 148.5 (PC=CH, d J_{cp} 6.3), 151.7 (ArC, d, J_{CP}4.1),182.0 (ArCO, d J_{CP} 9.5); ^{31}P NMR (CDCl$_3$, 162 MHz) δ_P 16.76; *m/z* (ESI$^+$) 307.0738 (100%, MH$^+$. C$_{15}$H$_{16}$O$_5$P requires 307.0730), 239 (10), 121 (5).

P - [*1E*)-1-*p*-tolyl-2-phenylethyl] phosphonic acid dimethyl ester 34 c
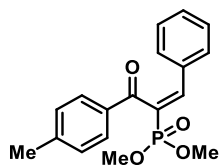
Prepared according to the general procedure **B** using benzaldehyde (0.10 mL, 0.91 mmol), a solution of β-ketophosphonate **33 b** (0.20 g, 0.83 mmol) in dry toluene (30 mL), and piperidine (~0.02 mL 0.17 mmol. The residue was purified by flash column chromatography on silica gel eluting petroleum ether/ EtOAc = 1:2 (R_f = 0.30) to afford the title compound (0.23 g, 84%) as yellow crystals; ν_{max} (ATR / cm^{-1}); 2928, 2859, 1661, 1259, 1029 ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 2.36 (3H, s, ArCH_3), 3.80 (6H, d, *J* 11.3, 2 × OCH_3), 7.15 -7.27 (5H, m, 5 × ArC*H*), 7.32 (2H, d, *J* 7.5, 2 × ArC*H*), 7.79 (1H, d, J_{HP} (19.6), C=C*H*), 7.85 (2H, d, *J* 7.5, 2 × ArC*H*); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 21.8 (*C*H$_3$, s), 53.2 (d, *J* $_{CP}$ 5.8, 2 × O*C*H$_3$), 128.7 (2 × Ar*C*H), 129.5 (2 × ArCH), 129.8 (2 × Ar*C*H), 129.9 (2 × ArCH), 130.2 (ArCH), 130.6 (Ar*C*), 133.0 (d, J_{CP} 2.6 Ar*C*), 133.5 (d, J_{CP} 21.8, P*C*=CH), 145.1 (Ar*C*), 146.8 (d, J_{CP} 5.8, PC=*C*H), 195.1 (d, J_{CP} 8.1, Ar*C*O); ^{31}P NMR (CDCl$_3$, 162 MHz); *δ* 17.23; *m/z* (ESI$^+$) 353, 331.1098 (100%, MH$^+$. C$_{18}$H$_{20}$O$_4$P requires 331.1094), 214 (8), 121 (10).

Phosphonic acid, *P*-[*(1E*)-1-*p*-anisyl-2-phenylethyl] dimethyl ester 34 d
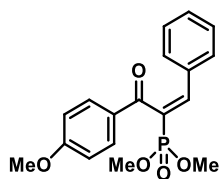
Prepared according to the general procedure **B** using benzaldehyde (0.20 mL, 1.70 mmol), a solution of β-ketophosphonate **33 c** (0.40 g, 1.55 mmol) in dry toluene (30 mL) and piperidine (~0.05 mL, 0.60 mmol). The residue was purified by flash column chromatography on silica gel eluting with petroleum ether/EtOAc = 1:4 (R_f = 0.24), to afford the title compound as yellow crystals (0.41g, 81% yield); Mpt. 105.3 -107 °C; ν_{max} (ATR / cm^{-1}); 2947, 1645, 1595, 1573, 1572; ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 3.81 (6H, d, J_{HP} 11.3, OCH_3), 3.84 (3H, s, OCH_3), 6.86 (2H, d, *J* 9.0, 2 x ArC*H*), 7.20-7.36 (5H, m, 5 x

ArC*H*), 7.81 (1H, d, J_{PH} 26.0, PC=C*H*), 7.94 (2H, d, *J* 9.0,   2 x ArC*H*]; ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 53.2

(OC*H*$_3$, d, J_{CP} 5.7), 55.5 (OC*H*$_3$), 114.0 (ArC*H*), 128.6 (d, Ar*C*, J_{CP} 2.4), 128.7 (ArC*H*), 128.9 (Ar*C*), 129.9

(2 x ArC*H*), 130.2 (2 x ArC*H*), 130.6 (Ar*C*), 132.1 (2 x ArC*H*), 133.5 (d, J_{CP} 21.9, P*C*=CH), 146.6 (ArC*H*, d,

J_{CP} 6.0, PC=*C*H), 164.3 (Ar*C*), 193.8 (Ar*C*O, d, J_{CP} 8.3); ^{31}P NMR (162 MHz; CDCl$_3$) δ_P 17.36; *m/z* (ESI$^+$)

347.1052 (100%, MH$^+$. C$_{18}$H$_{20}$O$_5$P requires 347.1043).

Phosphonic acid, *P*-[*(1E)*-1-O-anisyl-2-phenylethyl]dimethyl ester 34 e
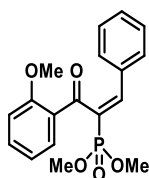
Prepared according to the general procedure **B** using benzaldehyde (0.40 mL, 3.41 mmol), a solution

of β-ketophosphonate **33 d** (0.80 g, 3.10 mmol) in dry toluene (60 mL) and piperidine (~0.10 mL, 0.62

mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R$_f$

= 0.33) to afford the title compound (0.52 g, 51 %) as a yellow semi-solid ν$_{max}$ (ATR /cm^{-1}) 3007, 1661,

1596,1243, 1027; ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 3.80 (6H, d, J_{HP} 11.3, 2 × OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$),

6.86 (1H, d, *J* 8.3, ArC*H*), 6.90-6.94 (1H, m, ArC*H*), 7.18-7.25 (3H, m, 3 × ArC*H*), 7.31 -7.35 (2H, m, 2 ×

ArC*H*), 7.40 - 7.45 (1H, m, ArC*H*), 7.72 (1H, d, J_{HP} 25.7, PC=C*H*), 7.78 (1H, dd, *J* 7.8, 1.8, ArC*H*). [13]C

NMR (100MHz; CDCl$_3$) δ_C 53.1 (2 × *C*H$_3$, d, J_{CP} 5.7), 55.7 (OC*H*$_3$), 111.8 (ArC*H*), 120.3 (ArC*H*), 126.5 (d,

J_{CP} 3.1, Ar*C*), 128.3 (2 × ArC*H*), 129.6 (2 × ArC*H*), 129.8(ArC*H*), 132.0 (ArC*H*), 132.0 (ArC*H*), 133.9

(HC=*C*P, d J_{cp} 21.8), 134.8 (ArC*H*), 146.1 (H*C*=CP, d J_{cp} 6.3), 159.6 (2 × Ar*C*), 191.3 (Ar*C*O, d, J_{cp} 8.3); [31]P

NMR (CDCl$_3$, 162 MHz); *δ* 17.45; *m/z* (ESI$^+$) 347.1043 (100%, M+H$^+$. C$_{18}$H$_{20}$O$_5$P requires 347.1045).

Dichloromethylphosphonate 35 [166, 167]
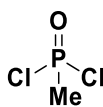
Thionylchloride (12.2 mL) was added dropwise to DMMP (6.70 mL) in a flask equipped with a short pathway condenser, calcium chloride guard and magnetic stirrer at 0 °C over a period of 30 minutes. Pyridine (0.50 mL) was then added, and the reaction mixture was heated at reflux for 4 hours. The mixture was left to cool, thereafter excess $SOCl_2$ was removed by vacuum distillation. The title compound was collected as a light-yellow liquid at 68 -78 °C and 275 Torr; b.pt lit. [167] 162 °C at 760 mm Hg) which turned into a semi-solid when refrigerated (6.00 g, 97%); ^{1}H NMR (400 MHz; $CDCl_3$) δ_H (2.53 (3H, d, J_{HP} 16.4, CH_3); ^{13}C NMR (100MHz; $CDCl_3$) δ_C 30.1 (d, J_{cp} 105.5, CH_3); ^{31}P NMR (162 MHz; $CDCl_3$) δ_P 43.4. All data were in accordance with literature [166]

Diisopropyl methyl phosphonate 36 [168]
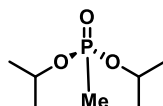
IPA (9.50 mL, 125 mmol) and triethylamine (21.6 mL, 156 mmol) in dry DCM (20 mL) were added first dropwise to a flask containing DCMP (5.70 mL, 62.5 mmol) *via* a pressure-equalising dropping funnel at 0 °C and then added normally after 10 minutes. The reaction mixture was kept stirring for 2 hours after which it was carefully quenched with water (30 mL). The aqueous layer was separated and extracted with DCM (3 × 30 mL). The combined organic layers were washed with water (3 × 20 mL) and brine (30 mL), then dried over $MgSO_4$, filtered, and concentrated to yield a brown oil which was identified as the title compound that was used for the next step without further purification (7.29 g, 65%) ; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.21-1.27(12H, m, 4 × CH_3), 1.31-1.44 (3H, m, CH_3), 4.60 - 4.69 (2H, m, 2 × C(CH)); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 12.6 (CH_3, d, J_{CP} 145.4), 23.9 (br s, CH_3), 70.0 (d, Jcp 6.1, CH); ^{31}P NMR ($CDCl_3$; 162 MHz) δ 28.41 with a side product at 30.18 ppm (major/minor =

19:1). All data were in accordance with literature [168] except δ_H at 1.29 and 1.42 were reported as doublets.

### Phosphonic acid, *P* - [*1E*)-1-*p*-tolyl-2-phenylethyl] diethyl ester 40 [67]
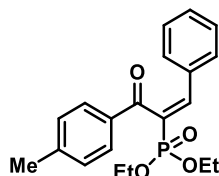
Prepared according to the general procedure **B** using benzaldehyde (0.20 mL, 2.04 mmol), a solution of β-ketophosphonate **38** (0.50 g, 1.85 mmol) in dry toluene (30 mL) and piperidine ~0.05 mL, 0.37 mmol). The residue was purified by flash column chromatography on silica gel eluting with petroleum-ether/ EtOAc = 1:2 (R$_f$ = 0.30), to afford the title compound (0.57 g, 83 %) as a yellow liquid. ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 1.28 (6H, t, *J* 7.0, 2 × OCH$_2$C*H$_3$*), 2.37 (3H, s, ArC*H$_3$*), 4.16 (4H, quint, *J$_{HP}$* 7.3, 2 × CH$_2$), 7.18 (2H, d, *J* 8.1, 2 × ArC*H*), 7.22 -7.26 (3H, m, 3 × ArC*H*) 7.30 -7.35 (2H, m, 2 × ArC*H*), 7.79 (1H, d, *J$_{HP}$* 26.0, ArC=C*H*), 7.86 (2H, d, *J* 8.1, 2 × ArC*H*); ^{13}C NMR (100MHz; CDCl$_3$) δ_C 16.1 (d, *J$_{CP}$* 6.7, 2 × *C*H$_3$), 21.8 (O*C*H$_3$), 62.8 (d, *J$_{CP}$* 5.7, 2 × O*C*H$_2$), 128.7 (2 × Ar*C*H), 129.0 (Ar*C*H), 129.2 (Ar*C*H), 129.3 (2 × Ar*C*H), 129.8 (d, *J* 4.8, 2 × Ar*C*H), 130.1 (Ar*C*H), 130.3 (Ar*C*), 133.2 (d, *J$_{CP}$* 2.3, H*C*=*C*P), 133.8 (Ar*C*), 144.9 (Ar*C*), 145.9 (d, *J$_{CP}$* 5.9, H*C*=CP), 195.3 (d, *J$_{CP}$* 8.1, Ar*C*O); ^{31}P NMR (CDCl$_3$, 162 MHz) δ 14.05. All data were in accordance with literature. [67]

Phosphonic acid, *P* - [*1E*)-1-*p*-tolyl-2-phenylethyl] diisopropyl ester 41
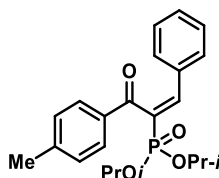
Prepared according to the general procedure **B** using benzaldehyde (0.10 mL, 1.11 mmol), a solution of β-ketophosphonate **39** (0.30 g, 1.01 mmol) in dry toluene (30 mL), and piperidine (~0.03 mL, 0.30 mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R$_f$

= 0.45) to afford the title compound (0.35 g, 90%) as a yellow liquid; ν_{max} (ATR/cm^{-1}) 2979, 1661, 1605, 1374, 1247; ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 1.27 (12H, dd, J_{PH} 6.0, 2.3, 2 × O(CH_3)$_2$, 2.34 (3H, s, CH_3), 4.67-4.79 (2H, m, 2 × CH), 7.14 (2H, d, J 8.1, 2 × ArCH), 7.16 - 7.22 (3H, m, 3 × ArCH), 7.28 - 7.33 (2H, m, 2 × ArCH), 7.75 (1H, d, J_{HP} 26.0, PC=CH), 7.85 (2H, d, J 8.1, 2 × ArCH); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 21.7 (CH_3, s), 23.8 (dd, J_{CP} 20.8, 4.6, CCH_3, 4 × CH_3), 71.7 (d, J_{CP} 6.1, 2 × OCH), 128.6 (2 × ArCH), 129.2 (4 × ArCH), 129.8 (3 × ArCH), 131.7 (ArC), 133.4 (d, J_{CP} 3.1 ArC), 133.8 (ArC), 144.6 (ArC), 145.0 (d, J_{CP} 6.1 HC=CP), 195.4 (d, J_{CP} 8.3, ArCO); ^{31}P NMR (162 MHz; CDCl$_3$) δ_P 11.5; m/z (ESI$^+$) 599.2 (35%), 303.1 (18%), 345.1 (15%), 387.172 (90, MH$^+$. C$_{22}$H$_{27}$O$_4$P requires 387.1732), 191.5 (5%).

Methyl- *o* –anisate 43 [169]
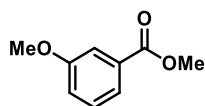
SOCl$_2$ (5.00 mL, 3.63 mmol) was added dropwise to a stirred solution of *m*-anisyl benzoic acid (0.50 g, 3.30 mmol) in methanol (3.30 mL, 0.15 mmol) at 0 ^{o}C, and left to warm up to room temperature. After complete addition of the chloride, the reaction mixture was heated at reflux for 18 h, cooled to room temperature then concentrated *in vacuo* to yield the crude product which did not require further purification (0.52 g, 95%) as a light pink oil; ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 3.86 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 7.11 (1H, dd, J 7.9, 2.4, ArCH), 7.35 (1H, t, J 7.9, ArCH), 7.56-7.59 (1H, m, ArCH), 7.65 (1H, d, J 7.9, ArH); ^{13}C NMR (100MHz; CDCl$_3$) δ_C 52.1 (s, OCH_3), 55.3 (s, OCH_3), 114.0 (ArCH), 119.3 (ArCH), 121.9 (ArCH), 129.4 (ArCH), 131.4 (ArC), 159.5 (ArC), 166.9 (ArCO). All data were in accordance with literature [169]

Phosphonic acid, *P*-[(1*E*)-1-*p*-anisyl-2-phenylethyl] diethyl ester 47 [67]
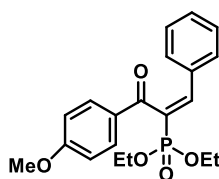
Prepared according to the general procedure **B** using benzaldehyde (0.20 mL 1.92 mmol), a solution of β-ketophosphonate **44** (0.50 g, 1.75 mmol) in dry toluene (30 mL) and piperidine (~0.03 mL, 0.35 mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R_f = 0.43) to afford the title compound as a yellow liquid (0.53 g, 81% yield); ^{1}H NMR (400 MHz; CDCl₃) δ_H 1.27 (6H, t, *J* 7.1, 2 x OCH₂C*H₃*), 3.82 (3H, s, OC*H₃*), 4.10 - 4.20 (4H, m, 2 x CH₂), 6.84 (2H, d, *J* 9.0, 2 x ArC*H*), 7.17 -7.26 (3H, m, 3 x ArC*H*), 7.30 – 7.35 (2H, m, 2 x ArC*H*), 7.76 (1H, d, J_{PH} 26.1, C=C*H*), 7.93 (2H, d, *J* 9.0, 2 x ArC*H*); ^{13}C NMR (100 MHz; CDCl₃) δ_C 16.2 (d, J_{CP} 6.7, 2 x OC*H₃*,), 55.5 (OC*H₃*), 62.8 (d, *J* 5.7, 2 x *C*H₂), 113.8 (Ar*C*H), 128.7 (2 x Ar*C*H), 128.8 (Ar*C*), 129.8 (Ar*C*H), 130.1 (Ar*C*H), 132.1 (2 x Ar*C*H), 130.6 (Ar*C*), 132.1 (2 x Ar*C*H), 133.7 (d, J_{CP} 22.0 C=*C*P), 133.6 (Ar*C*), 145.7 (C=*C*H, d, J_{CP} 5.9), 164.2 (Ar*C*O); ^{31}P NMR (162 MHz; CDCl₃) δ_P 14.17. All data were in accordance with literature. [67]

Phosphonic acid, *P*-[(1*E*)-1-*m*-anisyl-2-phenylethyl] diethyl ester 48
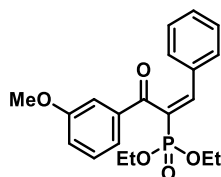
Prepared according to the general procedure **B** using benzaldehyde (0.20 mL, 1.92 mmol), a solution of β-ketophosphonate **45** (0.50 g, 1.75 mmol) in dry toluene (30 mL) and piperidine (~0.03 mL, 0.35 mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R_f = 0.45), to afford the title compound as a deep yellow viscous oil (0.55 g, 85% yield); ν max (ATR / cm⁻¹) 2982, 1699, 1664, 1582, 1257; ^{1}H NMR (400 MHz; CDCl₃) δ_H 1.25 - 1.31 (6H, m, 2 x C*H₃*), 3.82 (3H, s, OC*H₃*), 4.11 - 4.21 (4H, m, 2 x OCH₂), 7.07 (1H, ddd *J* 6.7, 2.5, 1.2, ArC*H*), 7.20 – 7.27 (4H, m, ArC*H*), 7.29 – 7.34 (2H, m, 2 x ArC*H*), 7.51 – 7.54 (2H, m, 2 x ArC*H*), 7.82 (1H, d, J_{PH} 25.9, C=C*H*); ^{13}C NMR (100 MHz; CDCl₃) δ_C 16.1 (d, J_{CP} 6.8, 2 x OC*H₃*,), 55.4 (OC*H₃*), 62.8 (d, *J* 5.7, 2 x *C*H₂), 112.9 (Ar*C*H), 120.9 (Ar*C*H), 122.8 (Ar*C*H), 128.7 (2 × Ar*C*H), 129.6 (Ar*C*H), 129.8 (2 × Ar*C*H), 130.2 (Ar*C*H), 131.8 (Ar*C*), 133.6 (d, J_{CP} 21.7, C=*C*P), 136.9 (d, Ar*C* , J_{CP} 2.5), 146.3 (d, J_{CP} 5.8, H*C*=CP), 159.8 (Ar*C*), 195.5 (d,

J_{CP} 8.8, ArCO); ^{31}P NMR (162 MHz; CDCl$_3$) δ_P 14.17;   m/z (ESI$^+$) 376 (8%), 375.1356 (95, M+H$^+$.

C$_{20}$H$_{23}$O$_5$P requires 375.1368).

**Phosphonic acid, P-[(1E)-1-o-anisyl-2-phenylethyl] diethyl ester 49**
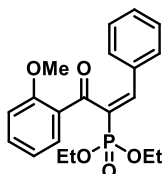
Prepared according to the general procedure **B** using benzaldehyde (0.20 mL, 1.92 mmol), a solution

of β-ketophosphonate **46** (0.50 g, 1.75 mmol) in dry toluene (30 mL) and piperidine (~0.03 mL, 0.35

mmol). The material obtained was purified by flash column chromatography on silica gel eluting with

EtOAc (R$_f$ = 0.41) to afford the title compound as a yellow liquid (0.56 g, 86% yield); v $_{max}$ (ATR / cm$^-$

^{1}) 3462, 2983, 1665, 1593, 1019; ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 1.26 (6H, t, J 7.1, 2 x CH_3), 3.80 (3H, s,

OCH_3), 4.10 - 4.19 (4H, m, 2 x OCH_2), 6.84 – 6.92 (2H, m, 2 x ArCH), 7.18 -7.23 (3H, m, 3 x ArCH), 7.32

– 7.34 (2H, m, 2 x ArCH), 7.39 - 7.43 (1H, m, ArCH), 7.67 (1H, d, J_{PH} 25.6, C=CH), 7.74 – 7.78 (1H, m,

ArCH); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 16.1 (d, J_{CP} 6.8, 2 x CH_3), 55.6 (OCH$_3$), 62.5 (d, J 5.6, 2 x OCH$_2$),

111.7 (ArCH), 120.2 (ArCH), 126.8 (d, J_{CP} 2.5, ArC), 128.3 (3 x ArCH), 129.7 (ArCH), 129.8 (ArCH), 132.0

(ArCH), 134.0 (d, J_{CP} 21.5, C=CP), 134.6 (ArCH), 134.7 (ArC), 145.5 (C=CH, d, J_{CP} 6.3), 159.5 (ArC), 194.4

(d, J 9.3, ArCO); ^{31}P NMR (162 MHz; CDCl$_3$) δ_P 14.40; m/z (ESI$^+$) 459 (5%),   397.1 (95, M - 2H$^+$),

375.1356 (50, M+H$^+$. C$_{20}$H$_{24}$O$_5$P requires 375. 1367), 227.6 (30).

Modified Heck procedure:

1. Synthesis of 2-bromo phosphonates

Dimethyl [2-(2-bromophenyl)-2-oxo-2-phenylethyl)] phosphonate 51
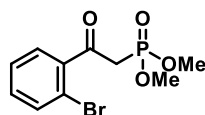
A solution of n-butyllithium (11.2 mL, 22.4 mmol, 2.0 M in hexanes) was added to a stirred solution of DIPA (3.30 mL, 23.5 mmol) in THF (30 mL) at -78 °C under an atmosphere of argon and allowed to stir for 40 minutes. In a separate flask, methyl-2-bromobenzoate (1.50 mL, 10.7 mmol) and DMMP (1.30 mL, 11.7 mmol) were stirred in THF (5.00 mL) at -5 °C followed by dropwise addition of the solution from the first flask. The reaction mixture was stirred between -5 to 0 °C until complete consumption of the starting material as determined by TLC. The reaction mixture was then carefully quenched with 1M HCl to adjust the pH to ca. 4 and diluted with EtOAc (50 mL). The aqueous layer was separated and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (3 × 50 mL) and brine (50 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo* to give the crude product which was purified by dry-flash column chromatography on silica gel eluting with EtOAc (R$_f$ = 0.25) to give the title compound as a yellow solid (3.0 g, 92%) Mpt 79.4-80.1 °C; v$_{max}$ (ATR, cm^{-1}) 2962, 2916, 1688, 1258, 1022; ^{1}H NMR (400 MHz; CDCl$_3$) δ$_H$ 3.72 (2H, d, J_{HP} 22.2, CH_2), 3.78 (6H, d J_{HP} 11.3 × OCH_3), 7.34 (1H, td J 7.7, 1.4, ArCH), 7.41 (1H, td J 7.7, 1.4, ArCH), 7.56 (1H, dd, J 7.8, 1.4, ArCH), 7.63 (1H, dd, J 7.8, 1.4, ArCH); ^{13}C NMR (100 MHz; CDCl$_3$) δ$_C$ 41.0 (d, J_{CP} 129.4, CH$_2$), 53.1 (2 × OCH$_3$, d, J_{CP} 6.4), 119.0 (ArC), 127.6 (ArCH), 129.7 (ArCH), 132.3 (ArCH), 133.8 (ArCH), 140.6 (ArC), d, J_{CP} 2.3), 194.9 (ArCO, d, J_{CP} 7.1); ^{31}P NMR (CDCl$_3$, 162 MHz); δ 21.74; *m/z* (ESI$^+$) 637 (95%), 328.9549 (80, M+ Na$^+$. C$_{10}$H$_{12}$^{81}BrNaO$_4$P requires 328.956), 309 (60, MH$^+$), 195.

2-((3a*R*,8a*R*)-2,2-Dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)-[1-(2-bromophenyl)] ethenone 56
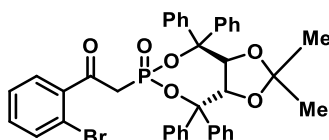
A solution of n-butyllithium (4.90 mL, 9.77 mmol, 2.0 M in hexanes) was added to a stirred solution of DIPA (1.40 mL, 10.2 mmol) in THF (20 mL) at -78 °C under an atmosphere of argon and allowed to stir for 40 minutes. In a separate flask methyl-2-bromobenzoate (0.65 mL, 4.65 mmol) and DMMP (2.30 mL, 5.12 mmol) were stirred in THF (10 mL) at -5 °C followed by dropwise addition of the contents of the first flask. The reaction mixture was stirred between -5 to 0 °C until complete consumption of the starting material as determined by TLC. The reaction mixture was then carefully quenched with 1M HCl to adjust the pH to ca. 4 and diluted with EtOAc (50 mL). The aqueous layer was separated and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (3 × 50 mL) and brine (50 mL), dried over MgSO₄, filtered, and concentrated *in vacuo* to yield the crude product that was purified by flash column chromatography on silica gel eluting with Hexane/EtOAc (2:1) (R_f = 0.31) to give the title compound as a yellow solid (3.10 g, 94% yield) mp 165.7 °C; $[\alpha]_D^{25}$ = -16 (*c* 1 in CHCl₃); ν_{max} (ATR)/cm^{-1}: 3060, 2990, 1695, 1448, 1429; ^{1}H NMR (400 MHz, CDCl₃) δ_H 0.56 (3H, s, CH₃), 0.80 (3H, s, C*H₃*), 3.73 (1H, dd, J_{HP} 22.9, J_{HH} 14.7, C*H*P), (1H, dd, J_{HP} 22.9, J_{HH} 14.7, C*H*P), 5.26 (1H, d, *J* 7.9, C*H*-O), 5.54 (1H, d, *J* 7.9, C*H*-O), 7.06 (1H, dd, *J* 7.6, 1.8, ArC*H*), 7.20 - 7.4 (16H, m, ArC*H*), 7.47 - 7.61 (7H, m, ArC*H*); ^{13}C NMR (100 MHz, CDCl₃) δ_C 26.5 (s, CH₃), 26.9 (s, C*H₃*), 43.4 (d, J_{C-P} 139.0, CH₂P), 79.0 (d, J_{C-P} 2.7, *C*H-O), 79.5 (d, J_{C-P} 2.7, *C*H-O), 87.7 (d, J_{C-P} 7.9, *C*-O-P), 90.9 (d, J_{C-P} 11.8, *C*-O-P), 114.1 [*C*(CH₃)], 126.8 (3 × Ar*C*H), 127.2 (d, *J* 5.9, 2 × Ar*C*H), 127.4 (2 × Ar*C*H), 127.6 (Ar*C*H), 127.7 (d, *J* 8.6, Ar*C*H), 128.2 (3 × Ar*C*H), 128.3 (4 × Ar*C*H), 128.7 (2 × Ar*C*H), 129.6 (3 × Ar*C*H), 130.3 (Ar*C*H), 132.3 (Ar*C*H), 133.7 (Ar*C*H), 139.4 (Ar*C*, *J* 1.9), 139.4 (Ar*C*), 139.5 (Ar*C*), 140.5 (d, *J* 2.1, Ar*C*), 143.5 (Ar*C*), 144.1 (d, *J* 6.2, Ar*C*), 193.9 (d, J_{C-P} 8.1, *C*=O); ^{31}P NMR (162 MHz, CDCl₃) δ 11.95; *m/z* (ESI$^+$) 1441 (20), 733.1184 (80%, M+Na$^+$.C₃₉H₃₄ ^{81}BrNa O₆P requires 733.1156), 431 (95) , 373 (55), 282(40).

2. Knoevenagel products:

## (*E*)-Dimethyl (3-(2-bromophenyl)-3-oxo-1-phenylprop-1-en-1-yl) phosphonate 52
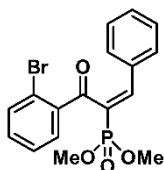
Prepared according to the general procedure **B** using benzaldehyde (0.70 mL, 6.40 mmol), a solution

of **51** (1.80 g, 5.80 mmol) in dry toluene (100 mL) and piperidine (0.11 mL, 1.20 mmol). The residue

was purified by flash column chromatography on silica gel eluting with EtOAc (R_f = 0.29) to afford the

title compound as a yellow liquid (0.86 g, 38 %); v_{max} (ATR /cm^{-1}) 2953, 2851, 1668, 1601, 1574; ^{1}H

NMR (400 MHz; CDCl$_3$) δ_H 3.86 (6H, d, J_{HP} 11.3, 2 × OCH_3), 7.18 -7.20 (2H, m, 2 × ArCH), 7.24 -7.26

(3H, m, 3 × ArCH), 7.32 -7.34 (2H, m, 2 × ArCH), 7.56 - 7.58 (1H, m, ArCH), 7.65 -7.67 (1H, m, ArCH),

7.97 (1H, d, J_{HP} 24.9, PC=CH). ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 53.4 (2 × CH$_3$, d, J_{CP} 5.9), 122.1 (ArCH),

127.0 (ArCH), 128.5 (2 × ArCH), 129.7 (2 × ArCH), 130.1 (ArCH), 130.5 (ArC), 131.3 (ArC), 132.0

(ArCH), 133.4 (HC=CP, d J_{cp} 21.0), 134.8 (ArCH), 136.8 (d, J_{CP} 3.1, ArC), 149.9 (HC=CP, d J_{cp} 6.5), 194.0

(ArCO, d, J_{cp} 8.7); ^{31}P NMR (CDCl$_3$, 162 MHz); δ 16.9; *m/z* (ESI$^+$) 813 (95%), 481 (2), 419 (75%),

397.0024 (80, M+H$^+$. C$_{17}$H$_{17}$^{81}BrO$_4$P requires 397.0032), 239 (30).

## (*E*)-2'-(3a*R*,8a*R*)-2,2-Dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)-[3-(2-bromophenyl)-3-oxo-1-phenylprop-1-ene-1-yl) phosphonate

45
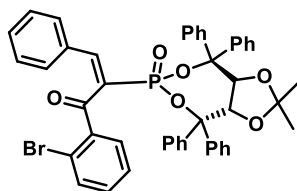
Prepared according to the general procedure **B** using benzaldehyde (0.20 mL, 2.32 mmol), a solution of β-ketophosphonate **56** (1.50 g, 2.11 mmol) in dry toluene (100 mL) and piperidine (~0.04 mL, 0.42 mmol). The residue was purified by flash column chromatography on silica gel first eluting with hexane/EtOAc (4:1), followed by EtOAc (100%) (R_f = 0.25) to give the title compound as a yellow solid (2.01 g, 95% yield) mp 165.7 °C - 167.5 °C; $[\alpha]_D$ [25] -16 (c 1 in CHCl$_3$); ν_{max} (ATR)/cm^{-1}: 3061, 2991, 1669, 1602, 1448; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 0.49 (3H, s, CH_3), 0.90 (3H, s, CH_3), 5.28 (1H, d, J 8.0, CH-O), 5.61 (1H, d, J 8.0, CH-O), 7.00 - 7.07 (1H, m, ArCH), 7.10 - 7.25 (9H, m, 9 × ArCH), 7.26- 7.40 (12H, m, 12 × ArCH), 7.44 - 7.51 (2H, m, 2 × ArCH), 7.31 - 7.35 (5H, m, 5 × ArCH), 8.00 (1H, d, J_{HP} 27.4, PC=CH); ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 26.2 (s, CH$_3$), 27.1 (s, CH$_3$), 79.2 (d, J_{CP} 2.7, CH-O), 79.5 (d, J_{CP} 2.7, CH-O), 90.6 (d, J_{CP} 5.4, C-O-P), 91.3 (d, J_{CP} 7.3, C-O-P), 113.6 [C(CH$_3$)$_2$], 126.5 (ArCH), 126.8 (d, J 3.6, 2 × ArCH), 127.2 (2 × ArCH), 127.3 (2 × ArCH), 127.4 (2 × ArCH), 127.5 (ArCH), 127.7 (4 × ArCH), 128.1 (d, J 8.7, ArCH), 128.4 (2 × ArCH), 128.8 (ArCH), 129.0 (2 × ArCH), 129.8 (3 × ArCH), 130.0 (2 × ArCH), 130.4 (ArCH), 132.5 (ArCH), 132.8 (ArCH), 133.5 (HC=CP, d, J_{cp} 21.8), 134.6 (ArCH), 137.0 (d, J_{CP} 4.1, ArC), 139.7 (ArC), 143.6 (d, J_{CP} 7.6, ArC), 150.0 (d, J_{cp} 7.9, (HC=CP), 143.7 (ArC), 144 (ArC), 149 (ArC), 150 (ArC), 193.1 (d, J_{CP} 8.4, C=O); ^{31}P NMR (162 MHz, CDCl$_3$) δ 8.00; *m/z* (TOF MS ES$^+$) 838 (5), 822 (7, [81]Br) 819.1467 (100%, M+Na$^+$. C$_{46}$H$_{38}$ O$_6$Na [79]BrP requires 819.1487), 802 (32), 789 (10).

3. **3-phenyl-1-indanones**

   a. **(1-Oxo-3-phenyl-indan-2-yl)-phosphonic acid dimethyl ester 53**
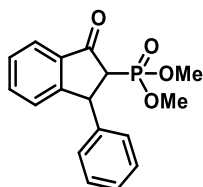
Chalcone **52** (0.13 g, 0.33 mmol) was dissolved in dry DMF (1.0 mL) in a flamed dried two-necked flask, to which Pd(Ph$_3$P)$_2$Cl$_2$ (~0.002 g, 0.003 mmol) was added under N$_2$. Diisopropylethylamine (0.10 mL, 0.66 mmol) was introduced and the stirred reaction mixture heated at reflux for 48 h. The reaction was cooled to room temperature and quenched by addition of 1 M HCl (10 mL). Brine (30

mL) and EtOAc (10 mL) were added. The organic layer was separated, washed with brine (3 × 20 mL), and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 1 M HCl (10 mL), brine (30 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo* to give a reddish-brown solid 0.08 g. There was full conversion of the starting material to product as determined by ^{1}H NMR spectrum. The residue was subjected to flash column chromatography on silica gel (n-Hexane/EtOAC 1:3 as eluent; (R$_f$ = 0.71) to afford the dephosphorylated indanone as a brown liquid which turned to solid on standing (0.02 g, 20%), phosphorylated indanone (R$_f$ = 0.26) as a mixture of diastereoisomers major/minor (60:40) to give the title compound as a beige solid (0.01 g, 10%) which could not be purified further on silica gel despite several attempts; Selected data; ^{1}H NMR (400 MHz;CDCl$_3$): δ$_H$ 3.29 (1H, dd, J_{HP} 26.5, J_{HH} 3.7, HCP), 3.67 (3H, d, J_{HP} 11.4, CH$_3$), 3.81 (3H, d, J_{HP} 11., CH$_3$), 4.98 (1H, dd, J_{HP} 16.3, J_{HH} 3.7, CH), 7.00 – 7.03 (2H, m, 2 × ArCH), 7.30 - 7.35 (5H, m, 5 × ArCH), 7.43-7.49 (4H, m, 4 × ArCH; ^{31}P NMR (162 MHz, CDCl$_3$) δ24.

b. 3-Phenyl-2,3-dihydro-1H-indan-1-one 54 [72, 73, 50, 74, 4]

Data as reported under standard Heck products [72, 73, 50, 74, 4]

2-(2,2-Dimethyl-6-oxo-4,4,8,8-tetraphenyl-tetrahydro-6λ^5-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)-3-phenyl-indan-1-one
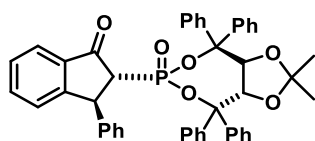
Chalcone **57** (0.06 g, 0.07 mmol) was dissolved in dry DMF (1.0 mL) in a flamed dried two-necked flask, to which Pd(Ph$_3$P)$_2$Cl$_2$ (0.0005 g, 0.0007 mmol) was added under N$_2$. Diisopropylethylamine (~ 0.02 mL, 0.14 mmol) was introduced the stirred reaction mixture heated at reflux for 48 h. The mixture was cooled to room temperature and quenched by addition of 1 M HCl (1.0 mL). Brine (5 mL) and EtOAc (5 mL) were added. The organic layer was separated, washed with brine (3 × 10 mL), and

the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M HCl (10 mL), brine (20 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The residue was subjected to flash column chromatography on silica gel (n-Hexane/EtOAC 2:1 as eluent; R$_f$ = 0.33) to give the title compound as a beige solid (0.09 g, 18%); [α]$_D$ ^{25} -250 (c 0.2 in CHCl$_3$); v$_{max}$ (ATR)/cm-^{1} : 2924, 1718, 1448, 1372, 1018; ^{1}H NMR (400 MHz;CDCl$_3$): δ$_H$ 0.55 (3H, s, C*H*$_3$), 0.78 (3H, s, C*H*$_3$), 3.38 (1H, dd, *J*$_{HP}$ 26.7, *J*$_{HH}$ 3.5, *H*CP),5.09 (1H, dd, *J*$_{HP}$ 17.7, *J*$_{HH}$ 3.5, C*H*), 5.27 (1H, d, *J* 7.9, C*H*-O), 5.54 (1H, d, *J* 7.8, C*H*-O), 7.00 – 7.03 (2H, m, 2 × ArC*H*), 7.09 - 7.15 (5H, m, 5 × ArC*H*), 7.22- 7.28 (6H, m, 6 × ArC*H*), 7.30 – 7.37 (9H, m, 9 × ArC*H*), 7.53 -7.58 (7H, m, 7 × ArC*H*); ^{13}C NMR (100 MHZ; CDCl$_3$) δ$_C$ 26.5 (*C*H$_3$), 27.1 (*C*H$_3$), 31.8 (*C*H), 56.9 (*J*$_{CP}$ 144.2, H*C*P), 78.9 (d, *J*$_{C-P}$ 2.8, *C*H-O), 79.0 (d, *J*$_{C-P}$ 2.8, *C*H-O), 98.6 (d, *J*$_{C-P}$ 8.6, *C*-O-P), 98.7 (d, *J*$_{C-P}$ 5.9, *C*-O-P), 113.9 [*C*(CH$_3$)], 124.2 (Ar*C*H), 126.9 (d, *J* 5.1, 2 × Ar*C*H), 127.1 (Ar*C*H), 127.2 (Ar*C*H), 127.3 (Ar*C*H), 127.6 (4 × Ar*C*H), 127.7 (Ar*C*H), 127.8 (2 × Ar*C*H), 128.0 (3 × Ar*C*H), 128.1 (Ar*C*H), 128.2 (3 × Ar*C*H), 128.9 (2 × Ar*C*H), 129.2 (2 × Ar*C*H), 129.9 (2 × Ar*C*H), 135.2 (Ar*C*H), 135.4 (2 × Ar*C*H), 136.2 (Ar*C*), 139.6 (Ar*C*), 140.1 (Ar*C*), 143.5 (Ar*C*), 144.3 (Ar*C*), 157.5 (Ar*C*), 158.0 (Ar*C*), 198.3 (d, *J*$_{C-P}$ 6.5, *C*=O); ^{31}P NMR (162 MHz, CDCl3) δ14.9; *m/z* (ESI+ MS) 1460 (100% 922 (22), 850 (45), 741.2381 (97, M+Na$^+$. C$_{46}$H$_{39}$NaO$_6$P requires 741.2376), 742 (46), 536 (25), 431 (44), 289 (44), 121 (17).

Standard Heck procedure:

General procedure C for the Synthesis of (*E*)-2'-Bromo chalcones

Representative compound 59

(*E*)-2'-Bromophenyl-3-phenyl-2-propen-1-one 59 [14 , 170 , 95]
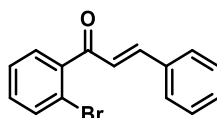
o-Bromoacetophenone (0.10 g, 0.5 mmol) was dissolved in EtOH (10 mL). Benzaldehyde (~0.05 mL, 0.50 mmol) and NaOH (2.50 M, 4.00 mL) were added to the solution at room temperature. The

mixture was stirred for 3 h, neutralised with dilute HCl to pH = 3 and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water (10 mL), brine (3 × 10 mL), dried with Na$_2$SO$_4$, filtered and the solvents evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether/ EtOAc = 9:1) to give the compound as a yellow oil R$_f$ = 0.38 (0.12 g, 97%); ^{1}H NMR (400MHz; CDCl$_3$) δ_H 7.13 (1H, d, *J* 16.1, C*H*=CH), 7.34-7.39 (1H, m, ArC*H*), 7.42-7.48 (6H, m, 6 × ArC*H*), 7.57 - 7.60 (2H, m, 2 × ArC*H*), 7.68 (1H, br d, *J* 7.6, CH=C*H*); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 119.5 (Ar*C*), 126.2 (Ar*C*H), 127.4 (Ar*C*H), 128.6 (2 × Ar*C*H), 129.0 (2 × Ar*C*H), 129.2 (Ar*C*H),130.9 (Ar*C*H), 131.4 (Ar*C*H), 133.5 (*C*H=*C*H), 134.4 (Ar*C*), 141.2 (Ar*C*), 146.7 (OC*C*H=CH), 194.8 (Ar*C*O). All data were in accordance with literature. [14][170][95]

(*E*)-2'-Bromophenyl-3-(4-methoxyphenyl)-2-propen-1-one 90 [89],[95]
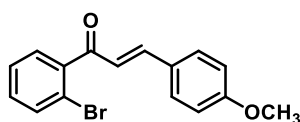
Prepared according to the general procedure **C** using *o*-Bromoacetophenone (0.10 g, 0.5 mmol) in EtOH (10 mL), *p*-anisaldehyde (0.05 mL, 0.50 mmol) and NaOH (2.50 M, 4.00 mL). The residue was purified by flash column chromatography on silica gel (Hexane / EtOAc = 9:1)) to give the title compound as a yellow flaky solid R$_f$ = 0.43 (0.12 g, 76 %); Mp 87 − 89 °C (lit [95] 88 - 90 °C); ^{1}H NMR (400MHz; CDCl$_3$) δ_H 3.87 (3H, s, OC*H$_3$*), 6.94 (2H, d, *J* 8.8, 2 × ArC*H*), 6.99 (1H, d, *J* 16.3, CH=C*H*), 7.31 - 7.37 (1H, m, ArC*H*), 7.38 - 7.44 (3H, m, 2 × ArC*H*, C*H*=CH), 7.53 (2H, d, *J* 8.8, 2 × ArC*H*), 7.66 (1H, d, *J* 7.9, ArC*H*); ^{13}C NMR (100 MHZ; CDCl$_3$) δ_C 55.5 (O*C*H$_3$), 114.5 (2 × Ar*C*H), 119.5 (Ar*C*), 124.0 (*C*=C), 127.1 (Ar*C*), 127.3 (Ar*C*H), 129.1 (Ar*C*H),130.5 (2 × Ar*C*H), 131.2 (Ar*C*H), 133.4 (Ar*C*H), 141.4 (Ar*C*), 146.7 0 (C=*C*), 162.0 (Ar*C*), 194.8 (Ar*C*O). All data were in accordance with literature. [89],[95]

(*E*)-2'-Bromo-4-methoxyphenyl 3'-(4'-methoxyphenyl)-2-propen-1-one 83 [147]
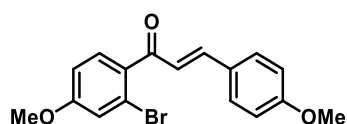
Prepared according to the general procedure **C** using 2'-Bromo-4'-methoxyacetophenone **80** (0.50 g, 2.01 mmol) in EtOH (40 mL), *p*-anisaldehyde (0.20 mL, 2.01 mmol) and NaOH (3.00 M, 20.0 mL). The solution was filtered *in vacuo*, residue was washed with water (3 x 20 mL) and dried to give the title compound as a yellow flaky solid that did not require further purification (0.50 g, 78%); Mpt = 87- 89 °C (Lit. *Arch. Pharm. (Weinheim)*, 1994, **327**, 547–561. 88-90 °C); ^{1}H NMR (400MHz; CDCl$_3$) δ_H 3.87 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.92 - 6.97 (3H, m, 2 × ArC*H*, C*H*=CH), 7.07 (1H, d, *J* 15.9, CH=C*H*CO), 7.20 (1H, d, *J* 2.4, ArC*H*), 7.46 (1H, d, *J* 8.2, ArC*H*), 7.49 (1H, d, *J* 8.2, ArC*H*), 7.55 (2H, d, *J* 8.7, 2 × ArC*H*); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 55.4 (OCH$_3$), 55.7 (OCH$_3$), 113.2 (*C*H=CHCO), 114.5(2 × Ar*C*H), 118.9 (Ar*C*H), 121.0(Ar*C*) 124.0 (Ar*C*H), 127.4(Ar*C*) , 130.3 (2 × Ar*C*H), 131.0 (Ar*C*H), 133.7 (Ar*C*), 145.4 (CH=*C*HCO), (161.4(Ar*C*), 161.8 (Ar*C*), 193.5(*C*=O). All data were in accordance with literature.[147]

(*E*)-2'-Bromo-5'-methoxyphenyl-3-(4-methoxyphenyl)-2-propen-1-one 88
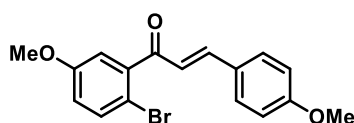
Prepared according to the general procedure **C** using 2'-Bromo-5'-methoxyacetophenone **87** (0.50 g, 2.14 mmol) in EtOH (40 mL), *p*-anisaldehyde (0.30 mL, 2.14 mmol) and NaOH (3.00 M, 20.0 mL)The solution was filtered *in vacuo*, residue was washed with water (3 x 20 mL) and dried to give the title compound as a white flaky solid that did not require further purification (R$_f$ = 0.38)(0.64 g, 86%); v_{max} (ATR, cm^{-1}) 2936, 1634, 1599, 1323, 1238; Mpt. 126.5 – 128 °C; ^{1}H NMR (400MHz; CDCl$_3$) δ_H 3.87 (3H, s, OC*H*$_3$), 3.88 (3H, s, OC*H*$_3$), 6.93 – 6.95 (3H, m, 3 × ArC*H*) 7.07 (1H, d, *J* 16.0, C*H*=CH) 7.20 (1H, d, *J* 2.4, ArC*H*), 7.42 (1H, d, *J* 16.0, CH=C*H*CO), 7.48 - 7.50 (1H, m, ArCH), 7.54-7.56 (2H, m, 2 × ArC*H*); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 55.4 (OCH$_3$), 55.7 (OCH$_3$), 113.2 (C=C), 114.5 (2 × ArC*H*), 118.9 (Ar*C*H), 121.0 (Ar*C*), 124.0 (Ar*C*H), 127.4 (Ar*C*), 130.3 (2 × ArC*H*), 130.5 (C=C), 133.7 (Ar*C*), 133.6 (Ar*C*), 145.4 (Ar*C*H) 161.4 (Ar*C*), 193.5 (Ar*C*O); *m/z* (ESI$^+$) 370 (5%), 369 (55), 367 (8), 348 (15), 347.0277 (95, MH$^+$. C$_{17}$H$_{15}$ ^{79}BrO$_3$ requires 347.0291).

(*E*)-2'-Bromo-3,5-dimethoxyphenyl-(4'-methoxyphenyl)-2-propen-1-one 64 [89]
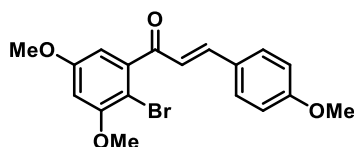
Prepared according to the general procedure **C** using 2'-Bromo-3,5-dimethoxyacetophenone **63** (4.00 g, 15.4mmol) in EtOH (310 mL), *p*-anisaldehyde (2.10 mL, 15.4 mmol) and NaOH (2.50 M, 125 mL).The solution was filtered *in vacuo*, the residue washed with water (3 x 20 mL), then dried to give the title compound as white crystalline powder that did not require further purification (3.52 g, 60%); Mpt. 139 – 141 °C; ^{1}H NMR (400MHz; CDCl$_3$): δ_H 3.85 (3H, s, OCH_3), 3.87 (s, 3H, s, OCH_3), 3.94 (3H, s, OCH_3), 6.53 (1H, d, *J* 2.7, ArCH), 6.59 (1H, d, *J* 2.7, ArCH), 6.90 - 6.96 (3H, m, 2 × ArCH, CH=CH), 7.38 (1H, d, *J* 16.1, OCCH=CH), 7.53 (2H, d, *J* 8.8, 2 × ArCH); ^{13}C NMR (100 MHz;CDCl$_3$): δ_C 55.5 (OCH_3), 55.8 (OCH_3), 56.5 (OCH_3), 100.9 (CH=CH), 104.4 (ArCH), 114.5 (2 × ArCH), 124.0, (ArCH), 127.1 (ArC), 130.5 (2 × ArCH), 143.4 (ArC), 147.0(OCCH=CH), 156.8 (ArC), 160.0 (2 × ArC), 162.0 (ArC), 195.2 (ArCO). All data were in accordance with literature.[89] except δ_H 6.56 which was reported as a multiplet and melting point was not reported.

(*E*)2'-Bromo-4,6-dimethoxyphenyl-(4'-methoxyphenyl)-2-propen-1-one 70
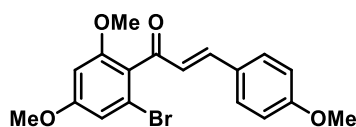
Prepared according to the general procedure **C** using 2'-Bromo-4,6-dimethoxyacetophenone **66** (0.10 g, 0.31 mmol) in EtOH (5.00 mL), *p*-anisaldehyde (0.05 mL, 0.31 mmol) and NaOH (2.50 M, 2.00 mL). The residue was purified by flash column chromatography on silica gel (Hexane/EtOAc 3:1 as eluent R$_f$ = 0.15) to give the title compound as a yellow flaky solid (0.07 g, 60%); Mpt 88-90 °C; ν$_{max}$ (ATR, cm^{-1}) 2938, 1645, 1597, 1252, 1173; ^{1}H NMR (400MHz; CDCl$_3$): δ_H 3.77 (s, 3H, s, OCH_3), 3.84 (3H,s, OCH_3), 3.85 (3H, s, OCH_3), 6.48 (1H, d, *J* 2.1, ArCH), 6.75 (1H, d, *J* 2.1, ArCH), 6.83 (1 H, d, *J* 16.1, CH=CHCO), 6.91 (2H, d, *J* 8.8, 2 × ArCH), 7.26 (1 H, d, *J* 16.1, CH=CHCO), 7.50 (2H, d, *J* 8.8, 2 ×

ArC*H*); ^{13}C NMR (100 MHz; CDCl$_3$): δ_C 55.3 (*C*H$_3$), 55.4 (*C*H$_3$), O*C*H$_3$ (56.0), 98.3 (*C*H=*C*H), 109.0 (Ar*C*H), 114.4 (2 × Ar*C*H), 120.4 (Ar*C*), 123.9 (Ar*C*), 125.6 (Ar*C*H), 130.1 (Ar*C*), 130.4 (2 × Ar*C*H), 146.2 (O*C*C*H*=CH), 158.5 (Ar*C*), 161.3 (Ar*C*), 161.8 (Ar*C*), 194.6 (Ar*C*O); *m/z* (M+2H)[+] 401 (5%), 379 (100, MH[+]. C$_{18}$H$_{17}$O$_4$[79]Br requires 379.0365).

Synthesis of 2'-Bromo benzaldehyde derivatives.

2-Bromo-4,6-dimethoxybenzaldehyde 68 [99, 100, 171,]
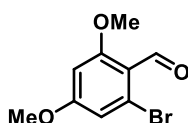
Phosphorylchloride (5.40 mL, 57.6 mmol) was added to dry DMF (12.0 mL) at room temperature. The mixture was heated to 100 °C for 1 h then cooled to room temperature. A solution of 1-bromo-3,5-dimethoxybenzene **65** (5.00 g, 23.0 mmol) in dry DMF (8.00 mL) was added dropwise. When the addition was complete, the reaction mixture was heated for 4 h at 100 °C. The mixture was cooled, poured on ice, stirred for 1 h and extracted with DCM (3 × 7 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. The residue was purified by dry flash column chromatography on silica gel (petroleum ether/EtOAc 3:1; R$_f$ = 0.21) as yellowish-white crystals (4.03 g, 71%); Mpt. 84.5 °C - 85.5 °C (Lit. *J. Korean Chem. Soc.*, 2015, **59**, 471– 474. 83 - 85 °C); ^{1}H NMR (400 MHz;CDCl$_3$): δ_H 3.89 (3H, s, OC*H$_3$*), 3.92 (3H, s, OC*H$_3$*), 6.46 (1H, d, *J* 2.3, ArC*H*), 6.81 (1H, d, *J* 2.3, ArC*H*), 10.34 (1H, s, C*H*O); ^{13}C NMR (100 MHz;CDCl$_3$): δ_C 55.9 (O*C*H$_3$), 56.1 (O*C*H$_3$), 98.2 (Ar*C*H), 111.5 (Ar*C*H), 127.5 (2 × Ar*C*), 163.6 (Ar*C*), 164.5 (Ar*C*), 189.2 (*C*HO). All data were in accordance with literature. [99, 100, 171]

1-(2-Bromo-3,5-dimethoxyphenyl) benzaldehyde 61 [96, 172, 98]
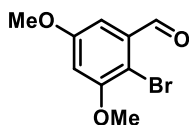
NBS (8.56 g, 48.1 mmol) was added in small portions to an ice-cold stirring solution of 3,5-dimethoxybenzaldehyde **60** (8.00 g, 48.14 mmol) in CH_3CN (100 mL) over 15 minutes. The reaction mixture was kept stirring at 2 $^{\circ}$C and left to warm up to room temperature for 18 hours. The solvent was evaporated *in vacuo*, and residue was dissolved in boiling water (100 mL) containing NaOH (2.20 g, 53.0 mmol). The solution was cooled to 10 $^{\circ}$C and acidified with excess 1 M HCl to pH to ca. 3. The precipitate that formed was filtered, washed with water (50 mL) and dried. The title compound was obtained as a white flaky solid which did not require further purification (11.30 g, 96%) Mpt 95 − 97 $^{\circ}$C Lit. [173] 94.8 - 95.7 $^{\circ}$C, Lit. [98] 114 - 115 $^{\circ}$C); ^{1}H NMR (400 MHz; $CDCl_3$) δ_H; 3.87 (3H, s, CH_3), 3.94 (3H, s, CH_3), 6.73 (1H, d, *J* 2.8), 7.06 (1H, d, *J* 2.8), 10.44 (1H, s, CHO); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 55.8 (OCH_3), 56.9 (OCH_3), 103.4 (ArCH), 105.9 (ArCH), 109.2 (ArC), 134.7 (ArC), 157.1 (ArC), 160.0 (ArC), 192.1 (ArCHO). All data were in accordance with literature. [96, 172, 98, 173]

Synthesis of 2'-Bromobenzyl ethanol derivatives.

1-(2'-Bromo-4,6-dimethoxyphenyl) ethanol 69 [99]
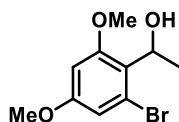
MeMgBr (2.70 mL, 8.20 mmol, 3M in Et_2O) was added to a solution of 2-Bromo-4,6-dimethoxybenzaldehyde **68** (1.00 g, 4.08 mmol) in Et_2O (30 mL) at 0 $^{\circ}$C and allowed to warm up to room temperature. The reaction mixture was left stirring at room temperature 6 h. It was quenched with saturated NH_4Cl at 0 $^{\circ}$C. The layers were separated, and the aqueous phase extracted with Et_2O

(3 × 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo to give the desired product as a light-yellow viscous oil which did not need further purification (1.05 g, 99%); ^{1}H NMR (400 MHz; CDCl$_3$): δ_H 1.53 (3H, d, J 6.7 CH_3), 3.67 - 3.76 (1H, br s, OH), 3.80 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 5.27-5.35 (1H, m, CH (OH)), 6.47 (1H, d, J 2.4, ArCH), 6.71 (1H, d, J 2.4, ArCH); ^{13}C NMR (100 MHz; CDCl$_3$): δ_C 23.0 (CH_3), 55.6 (OCH_3), 55.7 (OCH_3), 60.4 (ArC), 70.6 (CH), 99.3 (ArCH), 109.2 (ArCH), 123.0 (2 × ArC), 159.5 (ArC). All data were in accordance with literature. [99]

1-(2'-Bromo-3,5-dimethoxyphenyl) ethanol 62 [99]
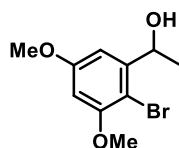
MeMgBr (2.70 mL, 8.20 mmol, 3 M in Et$_2$O) was added to a solution of 2-bromo-3,5-dimethoxybenzaldehyde **61** (1.00 g, 4.08 mmol) in Et$_2$O (30 mL) at 0 ^{o}C and allowed to warm up to room temperature. The reaction mixture was left stirring at room temperature 6 h. It was quenched with saturated NH$_4$Cl (5 mL) at 0 ^{o}C. The layers were separated, and the aqueous phase extracted with Et$_2$O (3 × 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated *in vacuo* to give the desired product as a beige solid which did not need further purification (0.91 g, 85%); Mpt 75 - 78 ^{o}C (Lit. [96]76 - 78 ^{o}C); ^{1}H NMR (400 MHz; CDCl$_3$): δ_H 1.49 (3H, d, J 6.4, CH_3), 1.98 (1H, d, J 3.3, OH), 3.85 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.27-5.35 (1H, m, CH(OH)), 6.44 (1H, d, J 2.8, ArCH), 6.83 (1H, d, J 2.8, ArCH); ^{13}C NMR (100 MHz; CDCl$_3$): δ_C 23.4 (CH_3), 55.6 (OCH_3), 56.4 (OCH_3), 69.4 CH(OH), 98.8 (2 × ArCH), 101.9 (ArC), 102.4 (2 × ArCH), 146.9 (ArC), 156.4 (ArC), 160.2 (ArC). All data were in accordance with literature. [99]

1-(2'-Bromo-4-methoxyphenyl) ethanol 82 [174, 175]
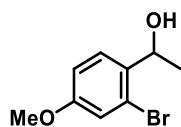
MeMgBr (6.80 mL, 20.5 mmol, 3 M in Et$_2$O) was added to a solution of 2-Bromo-4 methoxybenzaldehyde **81** (2.00 g, 9.30 mmol) in Et$_2$O (30 mL), at 0 °C. The reaction mixture was left stirring at room temperature for 5h, monitored with TLC and quenched with saturated NH$_4$Cl (5 mL) at 0 °C. The layers were separated, and the aqueous phase extracted with Et$_2$O (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo* to give the desired product as a pale yellow viscous oil which did not require further purification (1.85 g, 86%); ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 1.44 (3H, d, *J* 6.4, C*H$_3$*), 2.55 (1H, br s, O*H*), 3.80 (3H, s, OC*H$_3$*), 5.17 (1H, q, *J* 6.3, C*H* (OH)), 6.88 (1H, dd, *J* 8.7, 2.6, ArC*H*), 7.06 (1H, d, *J* 2.6, ArC*H*); 7.50 (1H, d, *J* 8.7, ArC*H*); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 23.7 (*C*H$_3$), 55.5 (O*C*H$_3$), 68.6 (*C*H(OH)), 113.9 (Ar*C*H), 117.7 (Ar*C*H), 122.0 (Ar*C*), 127.2 (Ar*C*H), 136.7 (Ar*C*), 159.1 (Ar*C*). All Data were in accordance with literature [174, 175]

1-(2'-Bromo-5-methoxyphenyl) ethanol 86 [53, 174]
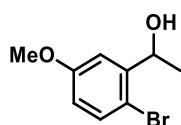
MeMgBr (6.80 mL, 20.5 mmol, 3M in Et$_2$O) was added to a solution of 2-Bromo-5-methoxybenzaldehyde **85** (2.00 g, 9.30 mmol) in Et$_2$O (30 mL) at 0 °C and allowed to warm up to room temperature. The reaction mixture was left stirring at room temperature 5 h. It was quenched with saturated NH$_4$Cl (5 mL) at 0 °C. The layers were separated, and the aqueous phase extracted with Et$_2$O (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO4, filtered, and concentrated *in vacuo* to give the desired product as a pale yellow solid which did not need further purification (2.08 g, 95%) Mpt (92 - 94 °C); ^{1}H NMR (400 MHz; CDCl$_3$): δ_H 1.46

(3H, d, J 6.3 CH_3), 2.24 (1H, br s, OH), 3.80 (3H, s, OCH_3), 5.15-5.25 (1H, m, CH(OH)), 6.90 (1H, dd, J 8.6, 2.5, ArCH), 7.07 (1H, d, J 2.5, ArCH), 7.48 (1H, d, J 8.6, ArCH); ^{13}C NMR (100 MHz; CDCl$_3$): δ$_C$ 23.6 (CH_3), 55.5 (OCH_3), 69.2 (CH(OH)), 111.8 (ArC), 112.0 (ArCH), 114.7 (ArCH), 133.2(ArCH), 145.8 (ArC), 159.4 (ArC). All Data were in accordance with literature, but mpt was not found reported. [53, 174]

Synthesis of 2'-Bromo acetophenone derivatives.

1-(2-Bromo-4,6-dimethoxyphenyl) ethenone 66 [99]
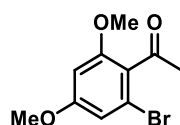
Acetyl chloride (0.20 mL, 2.5 mmol) was added dropwise to a cooled stirring suspension of AlCl$_3$ (0.40 g, 2.80 mmol) in dry DCM (6 mL) at 0 ^{o}C. The mixture was left stirring for 30 mins and the temperature maintained at 0 ^{o}C, followed by slow addition of 1-bromo-3,5-dimethoxy benzene **65** (0.50 g, 2.30 mmol) in DCM (4 mL). The reaction mixture was quenched by addition of saturated NH$_4$Cl solution (5 mL), diluted with water (10 mL) and saturated NaHCO$_3$ (5 mL), which was extracted with DCM (3 x 20 mL). The combined organic layers were washed with NaHCO$_3$ solution (20 mL), brine (20 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. The title compound was obtained as a yellow oil (0.60 g, 25%) after a flash column chromatography on silica gel using (petroleum ether / EtOAc 93:7) as eluent (R$_f$ = 0.50); ^{1}H NMR (400 MHz; CDCl$_3$) δ$_H$ 2.52 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.43 (1H, d, J 2.1), 6.70 (1H, d, J 2.1); ^{13}C (100 MHz; CDCl$_3$); CH_3 (31.8), 55.7 (OCH_3), 55.9 (OCH_3), ArCH (98.2), 109.0 (ArCH) , 118.7 (ArC), 157.0 (ArC), 161.3 (ArC), 202.0 (ArCO). All data were in accordance with literature.[99]

1- (2'-Bromo-3,5-dimethoxyphenyl) ethanone 63 [63.89]
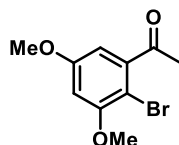
NaHCO$_3$ (5.63 g, 67.0 mmol) was added to a stirred solution of 1-(2-bromo-3,5-dimethoxyphenyl)ethanol **62** (5.00 g, 19.1 mmol) in DCM (0.1 M, 500 mL), followed by Dess-Martin periodinane (DMP, 12.2 g, 28.7 mmol) at room temperature. After 18 hours, the reaction mixture was quenched with saturated Na$_2$SO$_3$ (20 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 150 mL). The combined organic layers were washed with water (3 × 150 mL) and brine (100 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo* to yield the crude product that was recrystallised from EtOH to give the title compound (4.36 g, 88%) as a pale yellow liquid purified by flash column chromatography on silica gel using hexane /EtOAc 1:1) as eluent (R$_f$ = 0.07); ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 2.60 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.49 (1H, d, *J* 2.7, ArC*H*), 6.55 (1H, d, *J* 2.7, ArC*H*); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 30.7 (*C*H$_3$), 55.7 (O*C*H$_3$), 56.5 (O*C*H$_3$), 98.9 (Ar*C*), 101.2 (Ar*C*H), 103.8 (Ar*C*H), 144.3 (Ar*C*), 156.9 (Ar*C*), 160.1 (Ar*C*), 202.4 (Ar*C*O). All data were in accordance with literature. [63, 89]

2'-Bromo-5-methoxyphenyl ethanone 87 (a) [64, 68] in a 90:10 mixture with 1-(3-Methoxyphenyl ethanone 87 (b) [96]

a   (a:b = 90:10)   b
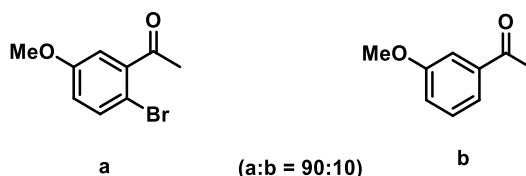
NaHCO$_3$ (1.10 g, 13.0 mmol) was added to a stirred solution of 2-(bromo-5-methoxyphenyl) ethanol **86** (1.00 g, 4.33 mmol) in DCM (0.1 M, 50 mL), followed by Dess-Martin periodinane (2.40 g, 5.63 mmol) at room temperature. After 18 hours, the reaction mixture was quenched with saturated Na$_2$SO$_3$ (10 mL). The organic layer was separated, washed with brine (3 × 10 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo* to give the residue which was purified by flash column chromatography on silica gel using hexane / EtOAc (4:1) as eluent (R$_f$ = 0.32) to give the title compound as a pale yellow oil as a 90:10 (^{1}H by NMR) mixture of compounds a, b (0.46 g, 46%); The peaks for the major compound were selected and characterized thus; ^{1}H NMR (400 MHz; CDCl$_3$) δ_H 2.60 (3H, s, CH_3), 3.79 (3H, s, OCH_3), 6.83 (1H, dd, *J* 8.8, 3.1, ArCH), 6.96 (1H, d, *J* 3.1, ArCH); 7.45 (1H, d, *J* 8.8, ArCH); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 30.3 (CH_3), 55.7 (OCH_3), 109.0 (ArC), 114.2 (ArCH), 117.8 (ArCH), 134.5 (ArCH), 131.6 (ArCH), 142.2 (ArC), 158.8 (ArC), 201.1 (ArCO). All data were in accordance with literature.[4, 64, 68]

1- (2'-Bromo-4-methoxyphenyl) ethanone 80[97]
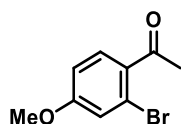
NaHCO$_3$ (5.63 g, 67.0 mmol) was added to a stirred solution of 1-(2-bromo-4-methoxyphenyl)ethanol **82** (1.00 g, 4.33 mmol) in DCM (0.1 M, 50 mL), followed by Dess-Martin periodinane (DMP) (2.40 g, 5.63 mmol) at room temperature. After 18 hours, the reaction mixture was quenched with saturated Na$_2$SO$_3$ (10 mL). The organic layer was separated, washed with brine (3 × 10 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (using hexane / EtOAc 4:1 as eluent R$_f$ =0.30) to give the title compound as a yellow oil (0.46 g, 46%); ^{1}H NMR (400 MHz; CDCl$_3$): δ_H 2.64 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 6.89 (1H, dd, *J* 8.7, 2.4, ArCH), 7.16 (1H, d, *J* 2.4, ArCH), 7.60 (1H, d, *J* 8.7, ArCH); ^{13}C NMR (100 MHz; CDCl$_3$): δ_C 29.9

(CH_3), 55.7 (OCH$_3$), 112.9 (ArCH), 119.6 (ArCH), 121.0 (ArC), 131.6 (ArCH), 132.4 (ArC), 161.8 (ArC), 156.9 (ArC), 160.1 (ArC), 198.7 (ArCO). All data were in accordance with literature. [97]

Synthesis of 3-aryl indanones.

3-Phenyl-2,3-dihydro-1H-indan-1-one 54 [72, 73, 50, 74,4]
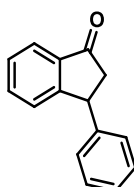
2-Bromophenyl-3'-phenyl-2-propen-1-one **59** (0.07 g, 0.25 mmol) was dissolved in dry DMF (2.0 mL, 0.12 M) in a flamed dried two-necked flask, to which Pd(Ph$_3$P)$_2$Cl$_2$ (0.01 g, 0.01 mmol) was added under N$_2$. Diisopropylethylamine (0.06 g,0.50 mmol) was introduced to the reaction mixture, stirred, and heated at reflux for 18 h. The mixture was cooled to room temperature and quenched by addition of 1 M HCl (5 mL). Brine (10 mL) and EtOAc (10 mL) were added. The organic layer was separated, washed with brine (3 × 20 mL), and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 1 M HCl (10 mL), brine (50 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The residue was subjected to flash column chromatography on silica gel (petroleum ether/EtOAC 10:1 as eluent; R$_f$= 0.23) to give the title compound as a beige solid (0.02 g, 50%); R$_f$ product=0.14 (petroleum ether/EtOAc, 10:1); ^{1}H NMR (400 MHz;CDCl$_3$): δ_H 2.72 (1H, dd, J 19.3, 3.9, CHH); 3.27 (1H, dd, J 19.3 8.1, CHH), 4.61 (1H, dd, J 8.1, 3.9, CH), 7.15 (2H, d, J 8.5, ArCH), 7.25-7.37(4H, m, 4 × ArCH), 7.45 (1H, t, J 7.4, ArCH), 7.58 (1H, td, J 7.6, 1.2. ArCH), 7.84 (1H, d, J 7.7, ArCH); ^{13}C NMR (100 MHZ; CDCl$_3$) δ_C 44.5 (CH), 46.9 (CH$_2$), 123.4 (ArCH), 126.9 (ArCH), 127 (ArCH), 127.7(2 × ArCH),127.9 (ArCH), 128.9 (2 × ArCH), 135.1 (ArCH), 136.8 (ArC), 143.7 (ArC), 158.0 (ArC), 206.1 (ArCO). All data were in accordance with literature. [72, 73, 50, 74, 4, 4 79]

3-(4-methoxy)-phenyl-2,3-dihydro-1*H*-indan-1-one 91 [77, 76, 74]
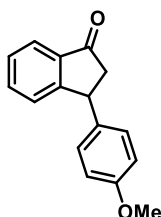
2-Bromophenyl-3'-(-4-methoxyphenyl)-2-propen-1-one **90** (0.13 g, 0.41 mmol) was dissolved in dry DMF (0.5 mL, 0.12 M) in a flamed dried two-necked flask, to which Pd(Ph$_3$P)$_2$Cl$_2$ (0.003 g, 0.004 mmol) was added under N$_2$. Diisopropylethylamine (0.11 g, 0.82 mmol) was introduced to the reaction mixture, stirred, and heated at reflux for 18 h. The mixture was cooled to room temperature and quenched by addition of 1 M HCl (7 mL), brine (10 mL) and EtOAc (10 mL). The organic layer was separated and washed with brine (3 × 20 mL), and the aqueous extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 1M HCl (5 mL), brine (50 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The residue was subjected to flash column chromatography on silica gel (Hex/EtOAc; 10:1) as eluent (R$_f$ = 0.23) to give the title compound as a yellow solid (0.03 g, 50%) Mpt 73 - 75 °C [lit.[126] 76 °C, 75 - 77 °C, [76] 71 - 73 °C [78], 72.7 - 73.1 °C; [79] ^{1}H NMR (400 MHz;CDCl$_3$): δ_H 2.68 (1H, dd, *J* 19.2, 3.9, CH*H*); 3.24 (1H, dd, *J* 19.2 8.0, C*H*H), 3.82 (3H, s, OC*H$_3$*), 4.56 (1H, dd, *J* 8.0, 3.9, C*H*Ar), 6.87(2H d, *J* 8.7, 2 × ArC*H*), 7.07 (2H d, *J* 8.7, 2 × ArC*H*), 7.30 (1H, br s, ArC*H*), 7.43 (1H, t, *J* 7.6 ArC*H*), 7.56 - 7.62 (1H, m, ArC*H*), 7.83 (1H, d, *J* 7.6); ^{13}C NMR (100 MHZ; CDCl$_3$) δ_C 43.7 (OCH$_3$), 47.0 (*C*H$_2$), 55.3(*C*H), 114.3 (2 × Ar*C*H), 123.4 (Ar*C*H), 126.8 (Ar*C*H), 127.0 (Ar*C*H), 128.6 (2 × Ar*C*H), 135.1 (Ar*C*H), 135.8 (Ar*C*), 136.7 (Ar*C*), 158.0 (Ar*C*), 206.1(Ar*C*O). All data were in accordance with literature. [77, 76, 74]

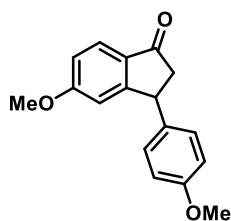## 2,3-Dihydro-5-methoxy-3-(4-methoxyphenyl)-1H-indan-1-one 84 [117]

2-Bromo-4-methoxyphenyl-3'-(4-methoxyphenyl)-2-propen-1-one **83** (0.50 g, 1.44 mmol) was dissolved in dry DMF (0.12 M) in a flamed dried two-necked flask, to which $Pd(Ph_3P)_2Cl_2$ (0.01 g, 0.01 mmol) was added under N_2. Diisopropylethylamine (0.50 g, 2.90 mmol) was introduced and the reaction mixture stirred whilst heating at reflux for 48 h. The mixture was cooled to room temperature and quenched by addition of 1 M HCl (10 mL), brine (20 mL) and EtOAc (20 mL). The organic layer was separated and washed with brine (3 × 20 mL), and the aqueous extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 1M HCl (10 mL), brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was subjected to flash column chromatography on silica gel (eluting with petrol/EtOAc 2:1; R_f = 0.10) to give the title compound as a beige solid (0.20 g, 51%); R_f product = 0.14; Mpt 92 - 94 °C (Lit. [79] 91 – 93 °C); v_{max} (ATR, cm^{-1}) ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 2.65 (1H, dd, *J* 19.0, 3.8, CH*H*), 3.27 (1H, dd, *J* 19.0 8.0, C*H*H), 3.82 (6H, d, *J* 1.6, 2 × OC*H*$_3$), 4.48 (1H, dd, *J* 8.0, 3.8, C*H*Ar), 6.67 (1H, br s, ArC*H*), 6.88 (2H, d, *J* 8.7, 2 × ArC*H*), 6.94 - 6.98 (1H, m, ArC*H*), 7.07 (2H, d, *J* 8.7, 2 × ArC*H*), 7.76 (1H, d, *J* 8.5); ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 43.7 (*C*H), 55.3 (OCH$_3$), 55.7 (OCH$_3$), 47.3 (*C*H$_2$), 109.7 (Ar*C*H), 114.3 (2 × Ar*C*H), 116.0 (Ar*C*H), 125.1 (Ar*C*H), 128.7 (2 × Ar*C*H), 130.2 (Ar*C*), 135.7 (Ar*C*), 158.5 (Ar*C*), 161.3 (Ar*C*), 165.6 (Ar*C*), 204.3 (Ar*C*O). (ESI+) 559 (50%), 307 (5), 291.0992 (55, M+Na$^+$), 269.1172 (95, M+H$^+$. C$_{17}$H$_{17}$O$_3$ requires 269.1172, 195 (25), 175 (8). All data were in accordance with literature. [117]

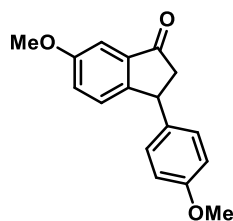## 2,3-Dihydro-6-methoxy-3-(4-methoxyphenyl)-1H-indan-1-one 89 [117, 148]

2-Bromo-5-methoxyphenyl-3'-(4-methoxyphenyl)-2-propen-1-one **88** (0.60 g, 1.73 mmol) was dissolved in dry DMF (0.12 M) in a flamed dried two-necked flask, to which Pd(Ph$_3$P)$_2$Cl$_2$ (0.01 g, 0.02 mmol) was added under N$_2$. Diisopropylethylamine (0.60 g, 3.50 mmol) was introduced to the reaction mixture, stirred, and heated at reflux for 48 h. The mixture was cooled to room temperature and quenched by addition of 1 M HCl (10 mL), brine (20 mL) and EtOAc (20 mL). The organic layer was separated and washed with brine (3 × 20 mL), and the aqueous extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 1M HCl (10 mL), brine (50 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The residue was subjected to flash column chromatography on silica gel (Hexane/EtOAC 2:1) as eluent (R$_f$ = 0.38) to give the title compound as a brown liquid (0.20 g, 51%); ν$_{max}$ (ATR, cm^{-1}) 2934, 1706, 1608, 1489, 1028; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 2.67 (1H, dd, *J* 19.2, 3.6, CH*H*); 3.26 (1H, dd, *J* 19.2 7.8, C*H*H), 3.81 (3H, s, OC*H*$_3$), 3.88 (3H, s, OC*H*$_3$), 4.50 (1H, dd, *J* 7.8, 3.6, C*H*Ar), 6.84 - 6.88 (2H, d, *J* 8.7, 2 × ArC*H*), 7.03 - 7.07 (2H, d, *J* 8.7, 2 × ArC*H*), 7.18 (1H, br s), 7.24 – 7.24 (1H, m, ArC*H*) 7.30 (1H, s, ArC*H*); ^{13}C NMR (100 MHZ, CDCl$_3$): δ_C 43.0 (*C*H), 47.8 (*C*HH), 55.3 (O*C*H$_3$), 55.5 (O*C*H$_3$), 104.3 (Ar*C*H), 114.5 (2 × Ar*C*H), 116.0 (Ar*C*H), 124.5 (Ar*C*H), 127.6 (Ar*C*H), 128.5 (Ar*C*H), 137.9 (Ar*C*), 140.0 (Ar*C*), 151.2 (Ar*C*),158.5 (Ar*C*), 159.7 (Ar*C*), 206.2 (Ar*C*O). All data were in accordance with literature. [117, 148]

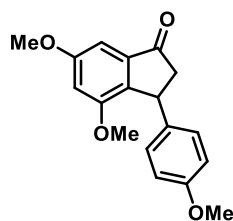**4,6-Dimethoxy-3-(4-methoxyphenyl)- 2,3-dihydro-1H-indan-1-one 71** [89]

2-Bromo-3,5-dimethoxyphenyl-3'-(4-methoxypheny)-2-propen-1-one **64** (1.00 g, 2.65 mmol) was dissolved in dry DMF (0.90 M, 3.00 mL) in a flamed dried two-necked flask, to which Pd(Ph$_3$P)$_2$Cl$_2$ (0.02 g, 0.03 mmol) was added under N$_2$. Diisopropylethylamine (0.69 g, 5.30 mmol) was added to the reaction mixture, stirred, and heated at reflux for 48 h. The mixture was cooled to room temperature, quenched with 1 M HCl (20 mL) and diluted with EtOAc (40 mL). The organic layer was separated, washed with brine (4 × 100 mL), and the aqueous layer further extracted with EtOAC (3 × 80 mL). The combined organic layers were washed sequentially with 1 M HCl (10 mL), brine (100 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using (petroleum ether/EtOAc as eluent 4:1; R$_f$ = 0.20) to give the title compound as a beige solid (0.80 g, quantitative >98%) Mpt. 119 - 121 $^{\circ}$C Lit. [51] (124-125 $^{\circ}$C); R$_f$ product = 0.19 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz;CDCl$_3$): δ_H 2.60 (1H, dd, *J* 19.2, 2.2, CH*H*), 3.21 (1H, dd, *J* 19.2, 7.9, C*H*H), 3.70 (3H, s, OC*H$_3$*), 3.8 (3H, s, OC*H$_3$*), 3.9 (3H, s, OC*H$_3$*), 4.55 (1H, dd *J* 7.9, 2.2, ArC*H*), 6.65 (1H, d, *J* 2.1, ArC*H*), 6.80 (2H, d, *J*, 8.8, 2 × ArC*H*); 6.87 (1H, d , *J* 2.1), ;6.99 (2H, d, *J* 8.8, 2 × ArC*H*); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 40.5 (*C*H), 47.8 (*C*H$_2$), 55.2 (O*C*H$_3$), 55.6 (O*C*H$_3$), 55.8 (O*C*H$_3$), 95.8 (Ar*C*H), 106.2 (Ar*C*H), 113.8 (2 × Ar*C*H), 128.0 (2 × Ar*C*H), 136.0 (Ar*C*), 139.0 (Ar*C*), 139.8 (Ar*C*), 157.9 (Ar*C*), 158 (Ar*C*), 161.6 (Ar*C*), 206.6 (Ar*C*O). All data were in accordance with literature. [89, 51]

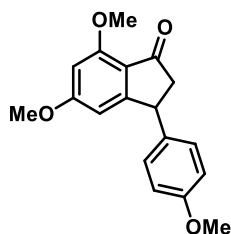**5,7-Dimethoxy-3-(4-methoxyphenyl)- 2,3-dihydro-1H-indn-1-one 72**

2-Bromo-4,6-dimethoxyphenyl-3'-(4-methoxypheny)-2-propen-1-one **70** (0.95 g, 2.52 mmol) was dissolved in dry DMF (0.11 M, 5.0 mL) in a flamed dried two-necked flask, to which Pd(Ph$_3$P)$_2$Cl$_2$ (0.02 g, 0.03 mmol) was added under N$_2$. Diisopropylethylamine (0.90 mL, 5.04 mmol) was added to the reaction mixture, stirred with heating at reflux for 48 h. The mixture was cooled to room temperature, quenched with 1 M HCl (10 mL) and dissolved with EtOAc (30 mL). The organic layer was washed with brine (4 × 20 mL), and the aqueous extracted with EtOAc (3 × 30 mL). The combined organic layers were washed sequentially with 1 M HCl (10 mL), brine (50 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using (petroleum ether/EtOAc as eluent 1:1; R$_f$ = 0.18) to give the title compound as a yellowish-brown solid (0.62 g, 82%), Mpt. 153.4 - 155.8 °C; ν$_{max}$ (ATR, cm^{-1}) 2937, 1694, 1600, 1510, 1470; ^{1}H NMR (400 MHz;CDCl$_3$): δ_H 2.63 (1H, dd, *J* 18.7, 3.9, CH*H*), 3.17 (1H, dd, *J* 18.7, 8.1, C*H*H), 3.79 (3H, s, OC*H$_3$*), 3.82 (3H, s, OC*H$_3$*), 3.97(3H, s, OC*H$_3$*), 4.39 (1H, dd, *J* 8.1 3.9, C*H*), 6.24 (1H d, *J* 1.3, ArC*H*), 6.35 (1H, d*,* *J* 1.3 ArC*H*), 6.87 (2H, d, *J* 8.7, 2 × ArC*H*), 7.07 (2H, d, *J* 8.7, 2 × ArC*H*); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 43.6 (*C*H), 47.7 (*C*H$_2$), 55.3 (O*C*H$_3$), 55.8(O*C*H$_3$), 55.9(O*C*H$_3$), 97.9 (Ar*C*H), 101.7 (Ar*C*H), 114.3 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 135.8 (2 × Ar*C*), 159.0 (Ar*C*), 163.5 (2 × Ar*C*), 167.2 (Ar*C*), 202.1 (Ar*C*O); *m/z* (ESI$^+$) 339 (12%), 321 (100), 299.1278 (91, M+H$^+$. C$_{18}$H$_{19}$O$_4$ requires 299.1278), 210 (28), 190 (16).

Synthesis of indanols

General representative procedure D for the synthesis of racemate indanols.

Solid NaBH$_4$ was added to a solution of the corresponding 1-indanone in MeOH at room temperature and was stirred for 4 h. The solvent was removed at the end of the reaction and the residue was treated with ice-cold water, acidified with conc. HCl to adjust the pH to ca. 2. The organic layer was removed while the aqueous layer was extracted with EtOAc (× 3). The combined organic layers were washed with brine,dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using (petroleum ether/ EtOAc 3:1) as eluent R$_f$ = 0.20) to give the title compound.

General procedure E for the asymmetric reduction of indanones using *cis* -amino indanol catalyst

A solution of *cis*-(1*R*, 2*S*)-1-amino indan-2-ol in dry THF was stirred under N$_2$, followed by addition of trimethylborate which was stirred at rt for 30 min. A solution of borane dimethyl sulfide complex in THF was added drop wise, cooled to 0 °C, and a solution of the corresponding 1-indanone in THF was added to the reaction mixture sequentially, stirred for 2.5 hrs while maintaining the temperature at 0 °C. The reaction was quenched with MeOH and allowed to warm up to RT for 10 min. The mixture was diluted by addition of water, the organic layer was removed while the aqueous layer was extracted with DCM. The combined organic layers were separated and washed with 1M HCl, dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using (Hexane / EtOAc) as eluent to give the compound as a solid.

General procedure F for the asymmetric transfer hydrogenation accompanying kinetic resolution.

A mixture of triethylamine and formic acid, was added to a mixture of the corresponding 1-indanone and RuCl [(*p*-cymene)-(S,S)-Ts-dpen], and the mixture was stirred at 30 °C for 24 h under N$_2$. The reaction mixture was left to warm up to RT and then quenched with NaHCO$_3$. It was then diluted with EtOAc, the organic layer was removed while the aqueous layer was extracted with EtOAc. The

combined organic layers were separated and washed with brine, dried over Na$_2$SO$_4$, passed through a silica gel pad, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using (n-Hexane / EtOAc 4:1) as eluent (R$_f$ = 0.18) to give the resulting indanol and unreacted remaining indanone.

(S)-2,3-dihydro-1H-inden-1-ol 76 [110, 127, 152]
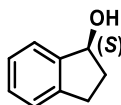
(i). Prepared according to the general procedure E using *cis* amino indanol:

Yellow oil (0.05 g, 89%); ^{1}H NMR (400MHz, CDCl$_3$): δ$_H$ 1.74 (1H, d, *J* 6.3, O*H*), 1.98 *H* (1H, dddd, *J* 13.4, 8.4, 6.5, 5.3, HC(OH)CH*H*), 2.52 [1H, dddd, *J* 13.4, 8.4, 6.5, 5.3, HC (OH) C*H*H) , 2.80 - 2.90 (1H, m, ArCH*H*), 3.09 (1H, ddd, *J* 15.9, 8.4, 5.3, ArC*H*H), 5.28 (1H, q, *J* 5.3, C*H*(OH), 7.24-7.28 (3H, m, 3 × ArC*H*), 7.45 (1H, d, *J* 5.4, ArC*H*); ^{13} C (100 MHz; CDCl$_3$) : δ$_c$ 29.8 (*C*H$_2$), 35.9 (Ar*C*H$_2$), 76.4 (H*C*OH), 124.3 (Ar*C*H), 124.9 (Ar*C*H), 126.7 (Ar*C*H), 128.3 (Ar*C*H) , 143.3 (Ar*C*), 145.1 (Ar*C*); [α]^{25}$_D$ = +26.0 (*c* 1.0, CHCl$_3$) **Chiral HPLC:** Cellulose 3 column; (hexane/*i*-PrOH 90:10); flow rate = 0.5 mL/min; detection at 254 nm; t$_R$ (major) = 9.75 min, t$_R$ (minor) = 6.24 min, for a sample of 65% ee. Lit. [127] [α]^{25}$_D$ = +15.7 (*c* 1.0, CHCl$_3$) for a sample of 88% ee.

(ii). Prepared according to general procedure F using ruthenium catalyst.

The residue was purified by flash column chromatography on silica gel using (n-hexane / EtOAc 4:1) as eluent (R$_f$ = 0.18) to give the title compound as a white solid; 0.29 g, 57%); [α]^{25}$_D$ = +31.3 (c 1.5, CHCl$_3$) for a sample of 100% ee, **Chiral HPLC:** Cellulose 3 column; (hexane/*i*-PrOH 90:10); flow rate = 0.5 mL/min; detection at 254 nm; t $_R$ (major)t= 9.5 min, t$_R$ (minor) = 6.0 min. Lit. [127] [α]^{23}$_D$ + 30.9 (c 1.99, CHCl$_3$) for a sample of 92% ee; Lit. [75] [α]^{23}$_D$ +28.7 (c 0.023, CHCl$_3$), 99% ee by HPLC (Chiralcel OB (hexane/*i*-PrOH 90:10); (0.5 mL/min), t$_R$ (major) = 18.6 min, t$_R$ (minor) =12.9 min.

(1*S*,3*S*)-3-phenyl-2,3-dihydro-1H-inden-1-ol 74 [4, 29, 77, 79,110]
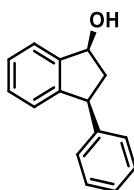
(i). Prepared according to general procedure F using ruthenium catalyst to give the title compound as a white solid (mixture of diastereomers (dr 83:17 major/minor). The isomers were separated *via* preparative HPLC using waters XBridge C18 (250 × 4.6 mm column) at a flow rate of 1mL/min over 20 min (CH$_3$CN: H$_2$O/ 45:55) as eluent to give the title compound as a white solid (40 mg, 40% yield, 98% ee); Mpt = 93 - 95 °C Lit. [147] = 94.5 - 95 °C; ^{1}H NMR (400 MHz; CDCl$_3$): δ$_H$ 1.92 (1H, d, *J* 7.6, O*H*), 1.98 (1H, ddd, *J* 12.9, 9.3, 7.8, CH*H*), 3.07 (1H, dt, *J* 12.9, 7.8 C*H*H), 4.22 (1H, t, *J* 7.8, *H*CAr), 5.33 (1H, dd, *J* 9.3, 7.8 C*H* (OH), 6.98 (1H, d, *J* 7.4, ArC*H*), 7.24 -7.28 (4H, m, 4 × ArC*H*), 7.30 - 7.38(3H, m, 3 × ArC*H*), 7.51 (1H, d, *J* 7.4, ArC*H*); ^{13}C (100 MHz; CDCl$_3$): δ$_c$ 47.3 (*C*HH), 48.3 (*C*HCH$_2$), 75.1 (*H*COH), 123.7 (Ar*C*H), 125.1 (Ar*C*H), 126.6 (Ar*C*H), 127.2 (Ar*C*H), 128.3 (Ar*C*H × 2), 128.4 (Ar*C*H), 128.6 (2 × Ar*C*H), 145.3 (Ar*C*); 145.6 (2 × Ar*C*); **Chiral HPLC**: Cellulose 2, (hexane/*i*-PrOH 90:10), flow rate = 0.5 mL/min, detection at 254nm, t$_R$ (major) = 5.7 min, t$_R$ (minor) = 9.6 min; [α]$_D$^{25} = + 9.0 (c 1.0, CHCl$_3$); 98% ee compared with Lit.[4] (1*S*,3*S*)-3-phenyl-2,3-dihydro-1H-indan-1-ol; [α]$_D$^{25} = +16.1 (c 0.1,CH$_2$Cl$_2$); 86% ee. All data were in accordance with literature. [110, 4, 29, 79 , 77]

(*R*)-3-Phenyl-2,3-dihydro-1H-inden-1-one 77
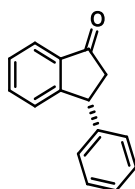
(*R*)- [α]$_D$^{25} = -38.0 (c 1.6, CHCl$_3$), 94% ee, chiral cellulose-2 column (*n*-hexane/*i*-propanol = 95:5, 1.00 mL/min, 254 nm), t$_R$ (major) = 11.8 min, t$_R$ (minor) = 13.0 min, R$_f$ product = 0.14 compared with Lit.

[α]$_D$ ^{23} = -25 (c = 0.4, CHCl$_3$), 97% ee; Lit.[141] [α]$_D$ ^{23} = - 43.0 (c 1.66, CHCl$_3$), 70% ee ; Lit. [89] [α]$_D$ ^{23} = - 49 (c 1.0, CHCl$_3$), 91% ee.

For the opposite enantiomer-(*S*)- Lit.[4] [α]$_D$ ^{25} = +64.9 (c = 0.4, CH$_2$Cl$_2$), 93% ee; Lit. [76] [α]$_D$ ^{25} = + 48 (c = 0.76, CHCl$_3$), 78% ee.

(1*R*,3*S*)-3-phenyl-2,3-dihydro-1H-inden-1-ol 75 [34]
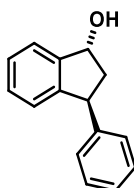
Prepared according to the general procedure B using a solution of *cis*-(1*R*, 2*S*)-1-amino indan-2-ol.

The residue was purified by flash column chromatography on silica gel using (petroleum ether/EtOAc 3:1) as eluent (R$_f$ = 0.20) to give the title compound as a white solid (mixture of diastereomers 83:17 major/minor). The isomers were separated *via* preparative HPLC using waters X Bridge C18 (250 × 4.6 mm column) at a flow rate of 1mL/min over 20 min (CH$_3$CN: H$_2$O/ 45:55) as eluent to give the title compound as a white solid; Mp = 83.5 – 85.0 °C; (20 mg, 11% yield, 87% ee); ^{1}H NMR (400MHz; CDCl$_3$): δ$_H$ 1.74 (1H, d, *J* 5.8, O*H*), 2.43 (1 H, dt, *J* 13.7, 7.3, (CH*H*), 2.58 (1 H, ddd, *J* 13.7, 7.3, 3.0, (C*H*H), 4.66 (1H, t, *J* 7.3, *H*C(Ar), 5.40 – 5.46 (1H, m, *H*C (OH), 7.04 - 7.08 (1H, m, ArC*H*) , 7.14 - 7.18 (2H, m, 2 × ArC*H*), 7.22-7.27 (1H , m, ArC*H*), 7.29 - 7.35 (4H, m, 4 × ArC*H*), 7.48 - 7.53 (1H, m, ArC*H*); ^{13}C NMR (100 MHz;CDCl$_3$): 46.4 (*C*H$_2$), 48.9 (*C*H(Ar)), 75.4 (*C*H(OH)), 124.4, (Ar*C*H), 125.5(Ar*C*H), 126.5(Ar*C*H), 127.4 (Ar*C*H) , 127.9 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 129.0 (Ar*C*H), 144.7 (Ar*C*), 144.9 (Ar*C*), 146.8 (Ar*C*); Chiral HPLC: Cellulose 2, (hexane/i-PrOH 90:10), flow rate = 0.5 mL/min; detection at 254 nm; t$_R$ (major) = 11.0 min, t$_R$ (minor) = 7.3 min; Optical rotation: [α]^{25} $_D$ = +18.0 (c 1.0, CHCl$_3$), for a sample of 87% ee. All data were in accordance with the literature [34] but optical rotation was not reported.

(1*R*,3*R*)-3-Phenyl-(4-methoxy-phenyl)-2,3-dihydro-1H-inden-1-ol 92 [147, 79]
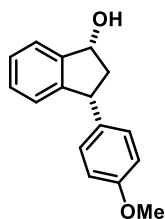
Beige solid (0.02 g, 40%); $[\alpha]_D^{25}$ = -12 (c 1.0, CHCl$_3$), 92% ee Lit. [79] $[\alpha]_D^{28}$ = -20.6 (c 2.5, CH$_2$Cl$_2$),99% ee;

mpt = 110.5 - 112 °C lit. [79] = 110.8 - 111.3 °C), (lit. [29] = 114 °C); v_{max} (ATR, cm^{-1}) 3335, 2930, 1611,

1512, 1247; ^{1}H NMR (400 MHz; CDCl$_3$): δ_H 1.89 - 1.98 (2H, m, CH*H*, O*H*), 3.03 (1H, dt, *J* 12.9, 8.0,

C*H*H), 3.83 (3H, s, OC*H*$_3$), 4.17 (1H, t, *J* 8.0, C*H*Ar), 5.26 – 5.34 (1H, m, C*H*(OH)), 6.89 (2H, d, *J* 8.6, 2 ×

ArC*H*), 6.97 (1H, d, *J* 7.5, ArC*H*), 7.15 - 7.20 (2H, d, *J* 8.6, 2 × ArC*H*), 7.24 - 7.35 (2H, m, 2 × ArC*H*), 7.50

(1H, d, *J* 7.5, ArC*H*); ^{13}C (100 MHz; CDCl$_3$): δ_c 47.4 (*C*HH), 47.5 (O*C*H$_3$), 55.3 (H*C*Ar), 75.1 (H*C*OH), 114.0

(2 × Ar*C*H), 123.6 (Ar*C*H), 125.0 (Ar*C*H), 127.1 (Ar*C*H), 128.3 (Ar*C*H), 129.2 (2 × Ar*C*H), 136.4 (Ar*C*),

145.2 (Ar*C*), 146.0 (Ar*C*), 158.3 (Ar*C̲*); m/z (ESI$^+$) 445 (2%), 325 (5), 279 (8), 263.1041 (50. M+Na$^+$.

C$_{16}$H$_{16}$NaO$_2$ requires 263.1043), 223 (95), 152 (15); **Chiral HPLC**: Cellulose 2, (hexane/i-PrOH 90:10),

flow rate = 0.5 mL/min; detection at 254 nm; t_R (major) = 8.1 min, t_R (minor) = 10.7 min.

3-(*S*)- (4-Methoxyphenyl)-2,3-dihydro-1H-inden-1-one (*S*)-91 [79, 4]
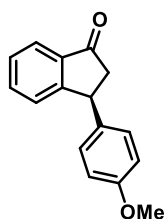
Yellow solid (0.10 g, 50%); $[\alpha]_D^{25}$ = +28.4, 53% ee); Lit.[79] $[\alpha]_D^{20}$ (c 2.1, CH$_2$Cl$_2$) = + 69.7, >99% ee; Lit [4].

$[\alpha]^{25}_D$ = +59.1 (c = 0.6, CH$_2$Cl$_2$), 84% ee; Lit [76]. $[\alpha]^{25}_D$ = +41.1 (c 0.6, CHCl$_3$), 70% ee; **Chiral HPLC**:

Cellulose 2, (hexane/i-PrOH 90:10), flow rate = 0.5 mL/min; detection at 254 nm; t_R (major) = 18.1

min, t_R (minor) = 16.2 min.

(1*R*,3*R*)-5-Methoxy-3-(4-methoxyphenyl)-2,3-dihydro-1H-inden-1-ol 93
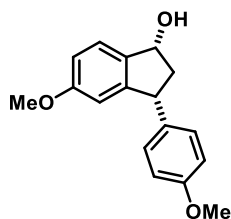
White solid (20 mg, 23%) Mpt = 94 - 98 °C; $[\alpha]^{25}_{D}$ = + 12.5 (c 1.0, CHCl$_3$), 71% ee; v_{max} (ATR, cm^{-1}) 3343, 2957, 1612, 1509, 1247; ^{1}H NMR (400MHz; CDCl$_3$): δ$_H$ 1.89 - 1.97 (2H, m, CH*H*, O*H*), 3.02 (1 H, dt, *J* 13.0, 7.5, C*H*H), 3.74 (3H, s, OCH$_3$), 3.83 (3H, s, OCH$_3$), 4.14 (1H, t, *J* 7.5, C*H*Ar) 5.25 (1H, t, *J* 7.5, C*H*(OH), 7.5 (1H, d, *J* 1.7, ArC*H*), 6.85 - 6.90 (3H, m, ArC*H*), 7.20 (2H, d, *J* 8.3, 2 × ArC*H*), 7.39 (1H, d, *J* 8.3, ArC*H*); ^{13} C (100 MHz; CDCl$_3$) : δ$_c$ 47.6 C*H*(OH), 47.7(*C*H$_2$), 55.3 (O*C*H$_3$), 55.4 (O*C*H$_3$),74.6 (H*C*Ar), 109.8, (Ar*C*H) 113.7 (Ar*C*H), 114.0 (2 × Ar*C*H), 124.6 (Ar*C*H), 129.2 (2 × Ar*C*H), 136.4 (Ar*C*), 137.6 (2 × Ar*C*), 158.3 (Ar*C*), 160.4 (Ar*C*); *m/z* (ESI$^+$) 293 (10%), 253 (90),   299.1148 (10, M-H$_2$O$^+$. C$_{17}$H$_{18}$O$_3$ requires 293.1141); **Chiral HPLC**: Cellulose 2, (hexane/i-PrOH 90:10), flow rate = 0.5 mL/min; detection at 254 nm; t$_R$ (major) = 12.1 min, t$_R$ (minor) = 16.2 min.

For the recovered starting material:

(*S*)- 5-Methoxy-3-(4-methoxyphenyl)-2,3-dihydro-1H-inden-1-one (*S*)-84
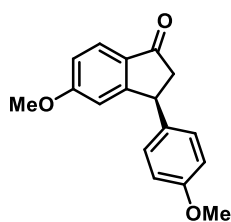
(mpt 96 - 98 °C, $[\alpha]_{D}^{25}$ = -10.4 (c 1.0, CHCl$_3$), 93% ee; **Chiral HPLC**: Cellulose-2 column (*n*-hexane/*i*-propanol = 90:10, flow rate = 1.00 mL/min, 254 nm, t$_R$ (major) = 34.6 min, t$_R$ (minor) = 40.0 min

(1*R*, 3*R*)-3-(4-methoxyphenyl)-6-methoxy-2,3-dihydro-1H-inden-1-ol 94
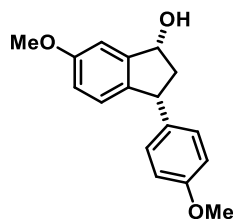
Brown solid (16 mg, 32%); 50% ee; v_{max} (ATR, cm^{-1}) 3386, 2926, 1609, 1511, 1246; ^{1}H NMR (400MHz; CDCl$_3$): δ_H 1.75 -1.92 (2H, m, CH*H*, O*H*), 3.03 (1 H, dt, *J* 13.0, 7.5, (C*H*H), 3.83 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 4.12 (1H, t, *J* 7.5, C*H*Ar) 5.25 (1H, q, *J* 7.5, C*H*(OH), 6.80 - 6.91 (4H, m, 4 × ArC*H*), 7.03 (1H, d, *J* 2.3, ArC*H*), 7.17 (2H, d, *J* 8.7, 2 × ArC*H*); ^{13}C (100 MHz; CDCl$_3$) : δ_c 46.8 (*C*H(OH), 47.9 (*C*H$_2$), 55.3 (O*C*H$_3$), 55.5 (O*C*H$_3$),75.1 (H*C*Ar), 108.0 (Ar*C*H), 114.0 (2 × Ar*C*H), 115.2 (Ar*C*H), 125.8 (Ar*C*H), 129.1 (2 × Ar*C*H), 136.7 (Ar*C*),137.9 (Ar*C*), 146.6 (Ar*C*), 158.3 (Ar*C*), 159.4 (2 × Ar*C*) ; *m/z* (ESI$^+$) 309 (5%), 293.1148 (20, MH$^+$. C$_{17}$H$_{19}$O$_3$ requires 293.1153), 253 (95), 167 (8); **Chiral HPLC:** Cellulose 2, (hexane/i-PrOH 90:10), flow rate = 0.5 mL/min; detection at 254 nm; t_R (major) = 11.3 min, t_R (minor) = 16.7 min.

For the recovered starting material:

(3*S*)- 3-(4-methoxyphenyl)-6-methoxy-2,3-dihydro-1H-inden-1-one (*S*)-89

Dark-brown liquid (0.22 g, 48%); 49% ee; **Chiral HPLC:** Cellulose-2 column (*n*-hexane/*i*-propanol = 90:10, flow rate = 0.50 mL/min, 254 nm, t_R (major) = 20.6 min, t_R (minor) = 18.9 min

(1*R*, 3*R*)- 4,6-Dimethoxy-(-3-(4-methoxyphenyl)-2,3-dihydro-1H-inden-1-ol 78
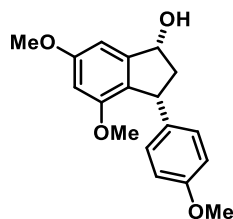
White solid (0.04 g, 41%), 98% ee; Mpt 109 - 111.5 °C; $[\alpha]_D^{25}$ = + 9.0 (c 1.0, CHCl$_3$); ^{1}H NMR (400MHz; CDCl$_3$): δ_H 1.77 (1H, d, *J* 7.3, O*H*), 1.96 (1 H, dt, *J* 12.9, 4.4, CH*H*), 2.96 (1H, dt, *J* 12.9, 7.3, C*H*H), 3.62 (3H, s, OC*H$_3$*), 3.80 (3H, s, OC*H$_3$*), 3.86 (3H, s, OC*H$_3$*), 4.29 (1H, dd, *J* 7.3, 4.4, C*H*Ar), 5.13 – 5.18 (1H, m, C*H* (OH), 6.41 (1H, d, *J* 2.0, ArC*H*), 6.66 (1H, d, *J* 2.0, ArC*H*), 6.82 (2H, d, *J* 8.7, 2 × ArC*H*), 7.10 (2H, d, *J* 8.7, 2 × ArC*H*); ^{13}C (100 MHz; CDCl$_3$) : δ_c 45.2 (*C*HOH), 46.4 (*C*HH), 55.2 (O*C*H$_3$), 55.6 (O*C*H$_3$), 55.8 (O*C*H$_3$), 76.1 (*C*HAr), 99.6 (2 × Ar*C*H), 113.6 (2 × Ar*C*H), 125.5 (Ar*C*), 128.3 (2 × Ar*C*H), 138.3 (Ar*C*), 147.5 (Ar*C*), 157.2 (Ar*C*), 157.7 (Ar*C*), 161.4 (Ar*C*); m/z (ESI$^+$) 324 (15%), 323.1254 (100, M+Na$^+$. C$_{18}$H$_{20}$O$_4$Na requires 323.1241), 320 (15); **Chiral HPLC**: Cellulose 2, (hexane/*i*-PrOH 95:5), flow rate = 1.0 mL/min, detection at 254nm, t$_R$ (major) = 51.9 min, t$_R$ (minor) = 54.8 min.
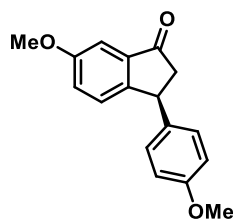
(3*S*)- 4,6-Dimethoxy-3-(4-methoxyphenyl)-2,3-dihydro-1H-inden-1-one (*S*)-71
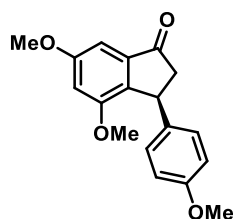
White solid (0.03 g, 37%), 121 -123 °C Lit.^{03} 124 -125 °C, Lit .^{2}125 -126 °C; $[\alpha]_D^{25}$ = - 30 (c 0.14, CHCl$_3$); 88% ee **Chiral HPLC**, Lux 3u Cellulose-2 column; hexane: i-PrOH/95:5; flow rate = 1.0 mL/min; detection at 254 nm; t$_R$ (major) = 31.3min, t$_R$ (minor) = 33.9 min, Lit.^{51} 3(*S*)-$[\alpha]^{20}_D$ = +36° (c 0.14, CHCl$_3$), 99% ee.

(1*R*, 3*R*)- 5,7-Dimethoxy-(-3-(4-methoxyphenyl)-2,3-dihydro-1H-inden-1-ol 79
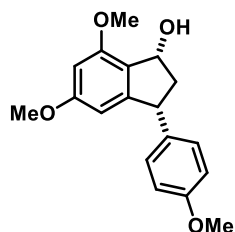
Brown solid (18 mg, 22%, 33% ee); v_{max} (ATR, cm^{-1}) 3454, 2934, 1600, 1511, 1141; ^{1}H NMR (400MHz; CDCl$_3$): δ_H 1.99 - 2.06 (1H, m, (CH*H*), 2.85 (1H, br s, O*H*), 2.94 – 3.01 (1H, m, C*H*H), 3.71 (3H, s, OC*H$_3$*), 3.82 (3H, s, OC*H$_3$*), 3.90 (3H, s, OC*H$_3$*), 4.13 (1H, t, *J* 7.3 C*H*Ar), 5.45 (1H, t, *J* 7.3 C*H* (OH), 6.09 (1H, d, *J* 1.5, ArC*H*), 6.36 (1H, d, *J* 1.5, ArC*H*), 6.88 (2H, d, *J* 8.7, 2 × ArC*H,* 7.18 - 7.20 (2H, d, *J* 8.7, 2 × ArC*H*); ^{13}C (100 MHz; CDCl$_3$) : δ_c 31.0(*C*H (OH), 44.9 (*C*HH), 48.7 (O*C*H$_3$), 55.3 (O*C*H$_3$), 55.6 (O*C*H$_3$), 73.2 (*C*HAr), 97.3 (Ar*C*H), 100.8 (Ar*C*H), 114.0 (2 × Ar*C*H), 125.1 (Ar*C*), 129.2 (2 × Ar*C*H), 136.8 (Ar*C*), 149.1 (Ar*C*), 156.9 (Ar*C*), 158.2 (Ar*C*), 162.0 (Ar*C*); *m/z* (ESI$^+$) 324 (10%), 323.1254 (100%. M+Na$^+$. C$_{18}$H$_{20}$O$_4$ Na requires 323.1241); **Chiral HPLC:** Cellulose 2, (hexane/i-PrOH 95:5), flow rate = 0.5 mL/min; detection at 254 nm; t_R (major) = 49.7 min, t_R (minor) = 62.3 min.

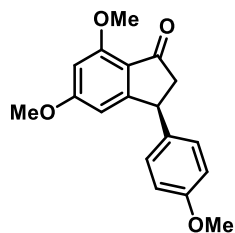## (3*S*)- 5,7-Dimethoxy-3-(4-methoxyphenyl)-2,3-dihydro-1H-inden-1-one (*S*)-72

Yellowish-brown solid; Mpt (109 - 110 ^{o}C); 53% ee; **Chiral HPLC:** Cellulose 2, (hexane/i-PrOH 95:5), flow rate = 0.5 mL/min; detection at 254 nm; t_R (major) = 26.8 min, t_R (minor) = 25.1 min.

α-arylation experiments

***trans*- 2-(3,5-Dimethoxyphenyl)-3-phenyl-2,3-dihydroinden-1-one 111**
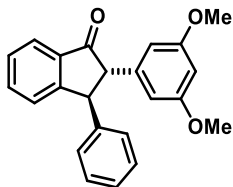
A mixture of 3-phenyl-2,3-dihydro-1H-inden-1-one (0.12 g, 0.60 mmol), 1-bromo-3,5-dimethoxy benzene **65** (0.20 g, 0.86 mmol), Pd(OAc)$_2$ (0.5 mol%, 0.02 mmol), X-Phos (0.02 g, 0.05 mmol), and NaO^{t}Bu (0.06 g, 0.64 mmol) were added sequentially to a 2-necked flame dried flask which was purged with N$_2$. THF (1.5 mL) was added then the reaction mixture was heated at 80 °C for 18 h under N$_2$. It was cooled to room temperature and filtered through a short pad of silica gel while rinsing with EtOAc (10 mL). The solution was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel using (petroleum ether / EtOAc 9:1) as eluent (R$_f$ = 0.07) to give the title compound as a light yellow oil (0.12 g, 61%); ν$_{max}$ (ATR, cm^{-1}) 2825, 1714, 1594; ^{1}H NMR (400 MHz; MeOD): δ$_H$ 3.72 (6H, s, 2 × OC*H*$_3$), 3.82 (1H, d, *J* 5.0, C*H*CO), 4.64 (1H, d, *J* 5.0, C*H*), 6.26 (2H, d, *J* 2.2, 2 × ArC*H*), 6.42 (1H, t, *J* 2.2, ArC*H*), 7.15 (2H, d, *J* 8.4, 2 × ArC*H*), 7.26 - 7.37 (4H, m, ArC*H*), 7.55 (1H, t, *J* 7.5, ArC*H*), 7.72 (1H, t, *J* 7.5, ArC*H*), 7.85 (1H, d, *J* 7.7, ArC*H*); ^{13}C NMR (100 MHz; MeOD) δ$_C$ 54.3(2 × OC*H*$_3$), 54.5 (H*C*Ar), 64.8 (*C*HCO), 98.7 (Ar*C*H), 106.2 (2 × Ar*C*H), 123.3 (Ar*C*H), 126.5 (Ar*C*H), 126.9 (Ar*C*H), 127.7 (Ar*C*H), 128.1 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 135.5 (Ar*C*H), 135.8 (Ar*C*), 140.4 (Ar*C*), 142.4 (Ar*C*), 156.7 (Ar*C*), 161.2 (2 × Ar*C*), 205.8 (Ar*C*O); *m/z* (ESI$^+$) 536 (10%), 383 (23), 367 (79), 345.1494 (100, MH$^+$. C$_{23}$H$_{21}$O$_3$ requires 345.1485), 233 (11), 213 (23).

***trans*-2-(3,5-Dimethoxyphenyl)-4,6-dimethoxy-3-(4- methoxyphenyl)-2,3-dihydroinden-1-one 97** [22,]

A mixture of 2,3-dihydro-4,6-dimethoxy-3-(4-methoxyphenyl)-1H-inden-1-one **71** (0.10 g, 0.34 mmol), 1-bromo-3,5-dimethoxy benzene (0.11 g, 0.50 mmol), $Pd(OAc)_2$ (0.5 mol%, 0.01 mmol), X-Phos (0.01 g, 0.03 mmol), and NaO^tBu (0.04 g, 0.37 mmol) were added sequentially to a 2-necked flame dried flask which was purged with N_2. THF (2.5 mL) was added then the reaction mixture was heated at 80 °C for 18 h under N_2. It was cooled to room temperature and filtered through a short pad of silica gel while rinsing with EtOAc (10 mL). The solution was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel using (petroleum ether / EtOAc, 2:1) as eluent (R_f = 0.26) to give the title compound as a beige solid (0.05 g, 32%); ^{1}H NMR (400 MHz; CDCl3): δ_H 3.63 (1H, d, *J* 2.7, C*H*CO), 3.68 (3H, s, OC*H*3), 3.76 (6H, s, 2 × OC*H*3), 3.80 (3H, s, OC*H*3), 3.90 (3H, s, OC*H*3), 4.53 (1H, d, *J* 2.7, C*H*Ar), 6.26 (2H, d, *J* 2.2, 2 × ArC*H*), 6.38 (1H, t, *J* 2.2, ArC*H*), 6.71 (1H, d, *J* 2.0, ArC*H*), 6.81 (2H, d, *J* 8.4, 2 × ArC*H*), 6.92 (1H, d, *J* 2.0, ArC*H*), 6.96 (2H, d, *J* 8.4, 2 × ArC*H*; ^{13}C NMR (100 MHz; CDCl3) δ_C 50.9 (CO*C*H), 55.2 (O*C*H3), 55.3 (2 × O*C*H3), 55.6 (O*C*H3), 55.8 (O*C*H3), 65.4 (H*C*Ar), 96.5 (Ar*C*H), 98.9 (Ar*C*H), 106.1 (2 × Ar*C*H), 106.7 (Ar*C*H), 113.8 (2 × Ar*C*H), 128.0 (2 × Ar*C*H), 135.5 (Ar*C*) 138.5 (Ar*C*), 138.6 (Ar*C*), 141.6 (Ar*C*), 157.8 (Ar*C*), 158.2 (Ar*C*) ,161.0 (2 × Ar*C*), 161.9 (Ar*C*), 205.5 (Ar*C*O). All data were in accordance with literature [2] except the aromatic region [22] where it was reported as one entity thus: δ_H 6.23-6.96 (9H, m).

Derivatisation: Typical procedure for α-arylation

Deep pink solid (0.12 g, 81%), $[\alpha]_D^{25}$ = +40 (c 0.14, CHCl3) Lit. [2] $[\alpha]_D^{20}$ = +137 (c 0.4, MeOH), 230 nm; 71% ee; **Chiral HPLC:** Cellulose 2, (hexane/i-PrOH 90:10), flow rate = 1.0 mL/min; detection at 254 nm; t_R (major) = 27.5min, t_R (minor) = 47.6 min
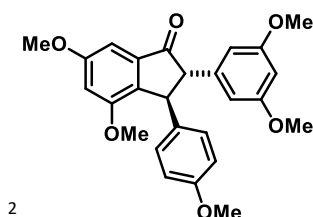
trans-2-(3,5-dimethoxyphenyl)-5,7-dimethoxy-3-(4- methoxyphenyl)-2,3-dihydroinden-1-one 112
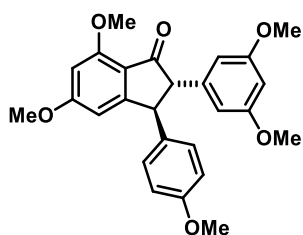

A mixture of 2,3-dihydro-5,7-dimethoxy-3-(4-methoxyphenyl)-1H-inden-1-one (0.20 g, 0.60 mmol), 1-bromo-3,5-dimethoxy benzene **72** (0.20 g, 0.90 mmol), Pd(OAc)$_2$ (0.5 mol%, 0.02 mmol), X-Phos (0.02 g, 0.05 mmol), and NaO^{t}Bu (0.06 g, 0.63 mmol), were added sequentially to a 2-necked flame dried flask which was purged with N$_2$. THF (2.5 mL) was added then the reaction mixture was heated at 80 ^{o}C for 18 h under N$_2$. It was cooled to room temperature and filtered through a short pad of silica gel while rinsing with EtOAc (10 mL). The solution was concentrated in *vacuo*, and the residue was purified by flash column chromatography on silica gel using (Petrol / EtOAc, 1:2) as eluent (R$_f$ = 0.23) to give the title compound as a yellow solid (0.15 g, 60%); ν$_{max}$ (ATR, cm^{-1}) 3014, 1662, 1599, 1241; ^{1}H NMR (400 MHz; CDCl$_3$): δ_H 3.56 (1H, d, *J* = 5.5, C*H*CO), 3.77 (3H, s, OC*H$_3$*), 3.82 (6H, s, 2 × OC*H$_3$*) 3.92 (6H, s, 2 × OC*H$_3$*), 4.73 (1H, d, *J* = 5.5, C*H*Ar),6.21 (1H, d, *J* 1.9, ArC*H*), 6.26 (1H, d, *J* 1.9, ArC*H*), 6.77 (2H, d, *J* 8.8, 2 × ArC*H*), 6.83 - 6.87 (3H, m, 3 × ArC*H*), 7.02 (2H, d, *J*, 8.8, 2 × ArC*H*); ^{13}C NMR (100 MHz; CDCl$_3$) δ_C 50.3 (CO*C*H), 55.3 (O*C*H$_3$), 55.7 (2 × O*C*H$_3$), 55.8 (2 × O*C*H$_3$), 58.5 (H*C*Ar), 96.9 (Ar*C*H), 97.9 (Ar*C*H), 103.9 (Ar*C*H), 113.9 (2 × Ar*C*H), 114.2 (2 × Ar*C*H), 129.6 (2 × Ar*C*H), 134.5 (Ar*C*), 158.3 (Ar*C*), 158.6 (Ar*C*), 158.9 (Ar*C*), 159.1 (Ar*C*) ,160.2 (Ar*C*), 161.7 (Ar*C*), 166.9 (2 × Ar*C*), 200.4 (Ar*C*O); *m/z* (ESI$^+$) 493 (20%), 473 (25), 457 (95), 435.1806 (100, M+H$^+$. C$_{26}$H$_{26}$O$_6$ requires 435.1802), 144 (15), 9213 (18).

References

1   S. Faiz, M. Yousaf, A. F. Zahoor, S. A. R. Naqvi, A. Irfan, G. Zaman, S. Ali, R. Naqvi, A. Irfan and G. Zaman, *Synth. Commun.*, 2017, **47**, 1121–1135.

2   B. H. Lee, Y. L. Choi, S. Shin and J.-N. Heo, *J. Org. Chem*, 2011, **76**, 6611–6618.

3   X.-D.Hao, J. Chang, B.-Y.Qin, C. Zhong, Z.-B.Chu, J. Huang, W.-J.Zhou and X. Sun, *Eur. J. Med. Chem.*, 2015, **102**, 26–38.

4   J. Yan, Y. Nie, F. Gao, Q. Yuan, F. Xie and W. Zhang, *Tetrahedron*, 2021, **84**, 1–8.

5   L. Yang and H. Huang, *Catal. Sci. Technol*, 2012, **2**, 1099–1112.

6   J. A. Lowe, D. L. Hageman, S. E. Drozda, S. Mclean, D. K. Bryce, R. T. Crawford, S. Zorn, J. Morrone and J. Bordner, *J. Med. Chem*, 1994, **37**, 3789–3811.

7   A. W. Al-Shahwany, *Biomed. Biotechnol.*, 2014, **2**, 20–28.

8   D. E. Moerman, *J. Ethnopharmacol.*, 1996, **52**, 1–22.

9   D. A. Dias, S. Urban and U. Roessner, *Metabolites*, 2012, **2**, 303–336.

10   M. Erb and D. J. Kliebenstein, *Plant Physiol.*, 2020, **184**, 39–52.

11   G. M. Cragg and D. J. Newman, *Biochimica et. Biophysica Acta*, 2013, **1830**, 3670–3695.

12   M. Zaynab, M. Fatima, Y. Sharif, M. H. Zafar, H. Ali and K. A. Khan, *Microb. Pathog.*, 2019, **137**, 103728.

13   F. R Bhuiyan, S. Howlader, T. Raihan and M.Hasan, Frontiers in Med., 2020, **7**, 1 - 26.

14   S. M. Colegate and R. J. Molyneux, *Bioactive Natural Products*: *Detection, Isolation, and Structural Determination*, CRC Press, Taylor and Francis Group, Fl, Boca Raton, 2008, 250.

15   B. B. Mishra and V. K. Tiwari, *Eur. J. Med. Chem.*, 2011, **46**, 4769–4807.

16   I. Ojima, A. Kamath and J. D. Seitz in *Natural Products in Medicinal Chemistry: Taxol, Taxoids, and Related Taxanes,* ed. S. Hanessian Wiley Blackwell, 2014, 127–180.

17   S. J. R. Croteau, *Appl Microbiol Biotechnol*, 2001, **57**, 13–19.

18   M. H. Keylor, B. S. Matsuura and C. R. J. Stephenson, *Chem. Rev*, 2015, **115**, 8976–9027.

19   N. Ahmed, in *Studies in Natural Products Chemistry: Synthetic Advances in the Indane Natural Product Scaffolds as Drug Candidates*, Elsevier, 2016, **51**, 383 - 434

20   Y. Yang, D. Philips and S. Pan, *J. Org. Chem.*, 2011, **76**, 1902–1905.

21   W. R. Sawadogo, M. Schumacher, M.-H. Teiten, M. Dicato and M. Diederich, *Biochem. Pharmacol.*, 2012, **84**, 1225–1240.

22   C. Zhong, X. H. Liu, X. D. Hao, J. Chang and X. Sun, *Eur. J. Med. Chem.*, 2013, **62**, 187–198.

23   C. Zhong, X. H. Liu, J. Chang, J. M. Yu and X. Sun, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 4413–4418.

24   J. B. Baell, *J. Nat. Prod.*, 2016, 79, 616–628.

25   S. H. Lee, N. H. Shin, S. H. Kang, J. S. Park, S. R. Chung, K. R. Min and Y. Kim, *Planta Med.*, 1998, **64**, 204–207.

26   S. A. Patil & R. Patil, *Eur. J. Med. Chem.*, 2017, **138**, 182–198.

27   M. Turek, D. Szczęsna, M. Koprowski and P. Bałczewski, *Beilstein J. Org. Chem*, 2017, **13**, 451–494.

28   L. Zhu, Z.-G. Xi, J. Lv and S. Luo, *Org. Lett.,* 2013, **15***,* 4496-4499.

29   J. A. Barltrop, R. M. Acheson, P. G. Philpott, K.E. MacPhee and and J. S. Hunt., *J.Chem.Soc*, 1956, 2928–2940.

30   R. J. Glisoni, D. A. Chiappetta, L. M. Finkielsztein, A. G. Moglioni, A. Sosnik, A. G. Moglioni Bc

and A. Sosnik, *New J. Chem.*, 2010, **34**, 2047–2058.

31   R. A. Finch, M.-C. Liu, S. P. Grill, W. C. Rose, R. Loomis, K. M. Vasquez, Y.-C. Cheng and A. C. Sartorelli, *Biochem. Pharmacol.*, 2000, **59**, 983–991.

32   H. Sugimoto, *Chem. Biol. Interact.*, 2008, **175**, 204–208.

33   P. N. Carlsen, C. Jiang, I. R. Herrick and A. J. Frontier, *Tetrahedron*, 2015, **71**, 5886–5896.

34   N. G. Leónard, W. N. Palmer, M. R. Friedfeld, M. Máté, M. Bezdek and P. J. Chirik, *ACS Catal.*, 2019, **9**, 9034–9044.

35   A.Singh, K. Fatima, A. Srivastava, S. Khwaja, D.Priya, Arjun Singh, G.Mahajan, S.Alam, A.K. Saxena, D. M. Mondhe, S. Luqman, D. Chanda, F. Khan and A.S. Negi, *Chem Biol Drug Des*, 2016, **88**, 625–634.

36   J. C. J. M. D. S. Menezes, *RSC Adv*, 2017, **7**, 9357 - 9372

37   A. Singh, K. Fatima, A. Singh, A. Behl, M. J. Mintoo, M. Hasanain, R. Ashraf, S. Luqman, K. Shanker, D. M. Mondhe, J. Sarkar, D. Chanda and A. S. Negi, *Eur. J. Pharm. Sci.*, 2015, **76**, 57–67.

38   D. Chanda, S. Bhushan, S. K. Guru, K. Shanker, Z. A. Wani, B. A. Rah, S. Luqman, D. M. Mondhe, A. Pal and A. S. Negi, *Eur. J. Pharm. Sci.*, 2012, **47**, 988–995.

39   H. O. Saxena, U. Faridi, S. Srivastava, J. K. Kumar, M. P. Darokar, S. Luqman, C. S.Chanotiya, V. Krishna, A. S. Negi and S.P. S. Khanuja, *Bioorg. Med. Chem. Lett*, 2008, **18**, 3914–3918.

40   J. Kaldun, A. Krimalowski and M. Breuning, *Tetrahedron Lett.*, 2016, **57**, 2492–2495.

41   S. V Gagnier and R. C. Larock, *J. Am. Chem. Soc*, 2003, **125**, 4804–4807.

42   N. Ahmed, *Synthesis (Stuttg).*, 2011, **15**, 2471–2477.

43   R. Sun, Y. Liu, Y. Zhang, L. Xiong and Q. Wang, *J. Agric. Food Chem*, 2011, **59**, 2471–2477.

44   A. Saito, M.Umakoshi, N.Yagyu, and Yuji Hanzawa, *Org. Lett.*, 2008, **10**, 1783–1785.

45   B. Yang, S.-J. Li, Y. Wang, Y. Lan and S. Zhu, *Nat. Commun.*, 2021, **12**, 5257.

46   W.T. Spencer, T. Vaidya and A. J. Frontier, *Eur. J. Org. Chem*, 2013, 3621–3633.

47   A. J. Frontier and C. Collison, *Tetrahedron*, 2005, **61,** 7577-7606.

48   N. J. Lawrence, E. S. M. Armitage, B. Greedy, D. Cook, S. Ducki and A. T. McGown, *Tetrahedron Lett.*, 2006, **47**, 1637–1640.

49   T. Vaidya, A. C. Atesin, I. R. Herrick, A. J. Frontier, R. Eisenberg, T. Vaidya, A. C. Atesin, I. R. Herrick, A. J. Frontier and R. Eisenberg, *Angew. Chem. Int. Ed*, 2010, **49**, 3363–3366.

50   Y.-N. Yu and M.-H. Xu, *J. Org. Chem*, 2013, **78**, 2736–2741.

51   M.-L. Tang, P. Peng, Z.-Y. Liu, J. Zhang, J.-M. Yu, X. Sun, *Chem. Eur. J*, 2016, **22**, 14535–14539.

52   S. Weckesser, K. Engel, B. S-Haarhaus, A. Wittmer, K. Pelz and C. M. Schempp, *Phytomed*, 2007, **14**, 508–516.

53   R. Réka, J. Faggyas, E. D. D. Calder, C. Wilson and A. Sutherland, *J.Org.Chem*, 2017, **82**, 11585–11593.

54   F. M. Moghaddam, M. Daneshfar, R. Azaryan and J. L. Pirat, *Catal. Commun.*, 2020, **141**, 106015.

55   C. Wang, K. Huang, J. Ye and W.-L. Duan, *J. Am. Chem. Soc*, 2021, **143**, 5690.

56   A. Dudzik, W. Snoch, P. Borowiecki, J. Opalinska-Piskorz, M. Witko, J. Heider and M. Szaleniec, *Appl. Microbiol. Biotechnol.*, 2015, **99**, 5055–5069.

57   V. Cavallaro, Y. F. Moglie, A. P. Murray and G. E. Radivoy, *Bioorg. Chem.*, 2018, **77**, 420–428.

58   A. K. Bhattacharya and G. Thyagarajan, *Chem. Rev*, 1981, **81**, 415–430.

59   P. Zhou, B. Hu, L. Li, K. Rao, J. Yang and F. Yu, *JOC*, 2017, **82**, 13268–13276.

60   D.Baran, X.Sun, Z. Sun, M.Han, J. Han, W.He, J. Chen, H.Deng, M. Shao, H.Zhang and W.Cao, *Chin.J.Org.Chem*, 2019, 192-199.

61   J. Xiang, N. Yi, R. Wang, L. Lu, H. Zou, Y. Pan and W. He, *Tetrahedron*, 2015, **71**, 694–699.

62   K. M. Maloney and J. Y. L. Chung, *J. Org. Chem.*, 2009, **74**, 7574–7576.

63   B. H. Lee, Y. L. Choi, S. Shin and J.-N. Heo, *J. Org. Chem*, 2011, **76**, 6611-6618.

64   M. Kreibich, M. Gemander, D. Peter, D. B. Yadav, C. B. De Koning, M. A. Fernandes, I. R. Green, W. A. L. Van Otterlo and R. Brückner, *Eur. J. Org. Chem*, 2020, 2929–2955

65   R. R. Milburn, K. McRae, J. Chan, J. Tedrow, R. Larsen and M. Faul, *Tetrahedron Lett.*, 2009, **50**, 870–872.

66   D.Szczęsnaa, M. Koprowski, E. R-Sokołowskab, B. Marciniakb and P.Bałczewski, *Synlett*, 2016, **28**, 113–116.

67   X.-Q. Pan, J.-P. Zou, G.-L. Zhang and W. Zhang, *Chem. Commun*, 2010, **46**, 1721–1723.

68   P. K. Pramanick, Z. L. Hou and B. Yao, *Tetrahedron*, 2017, **73**, 7105–7114.

69   W. He, X. Sun, A. J. Frontier, M. Bendikov, H. M. Duong, K. Starkey, K. N. Houk, E. A. Carter and F. Wudl, *J. Am. Chem. Soc*, 2003, **125**, 14278–14279.

70   A. J. Frontier and J. J. Hernandez, *Acc. Chem. Res*, 2020, **53**, 1822–1832.

71   R. Knowles, *The Intramolecular Heck Reaction*, MacMillan Group Meeting July 14th 2004.

72   T. Kumon, M. Shimada, J. Wu, S. Yamada and T. Konno, *Beilstein J. Org. Chem.*, 2020, **16**, 2193–2200.

73   G. Yue, K. Lei, H. Hirao and J. S. Zhou, *Angew. Chemie*, 2015, **54**, 6531–6535.

74   Y.Liu, L.Chen, Y.Liu, P.Liu and B.Dai, *J. Chem. Res.*, 2018, **42**, 40–43.

75   S. Hashiguchi, A. Fujii, K.-J. J. Haack, K. Matsumura, T. Ikariya and R. Noyori, *Angew. Chem. Int.*

Ed, 1997, **36**, 288–290.

76   A. Minatti, X. Zheng and S. L. Buchwald, *J.Org.Chem*, 2007, **72**, 9253–9258.

77   N. Parveen and G. Sekar, *Adv. Synth. Catal.*, 2019, **361**, 4581–4595.

78   A. Püschl, H. C. Rudbeck, A. Faldt, A. Confante and J. Kehler, *Synthesis (Stuttg).*, 2005, **2**, 291–295.

79   S. Park and H.-K. Lee, *RSC Adv.*, 2021, **11**, 23161–23183.

80   S. Mannathan, S. Raoufmoghaddam, J. N. H. Reek, J. G. De Vries, and A. J. Minnaard, *ChemCatChem*, 2015, **7**, 3923–3927.

81   A. N. Reznikov, M. A. Ashatkina and Y. N. Klimochkin, *Org. Biomol. Chem*, 2021, **19**, 5673–5701.

82   B.-C. Tang, W.-X. Lin, X.-L. Chen, C. He, J.-T. Ma, Y.-D. Wu, Y. Lan and A.-X. Wu, *Nat. Commun.*, 2020, **11**, 5662.

83   G. R. Konopelski, J.P., Kent S. Chu and Negrete, *J.O.C*, 1991, **56**, 1355–1357.

84   S. Mannathan, S. Raoufmoghaddam, J. N. H. Reek, J. G. de Vries and A. J. Minnaard, *ChemCatChem*, 2016, **8**, 2572.

85   S.Raoufmoghaddam, S.Mannathan, A. J. Minnaard, J. G. de Vries and J. N. H. Reek, *Chem. Eur. J*, 2015, **21**, 18811–18820.

86   H. Hagiwara, Y. Eda, K. Morohashi, T. Suzuki, M. Ando and N. Ito, *Tetrahedron Lett.*, 1998, **39**, 4055–4058.

87   A. Cacchi, S and Arcadi, *J. Org. Chem*, 1983, **48**, 4236–4240.

88   X.-F. Wu, P. Anbarasan, H. Neumann and M. Beller, *Nobel Prize Chem.*, 2010, **49**, 9047–9050.

89   X. Qin, M. Wen, Y. Lee and J. S. Zhou, *Org. Lett*, 2019, **21**, 5990–5994.

90   K. Kundu, J. V Mccullagh and A. T. Morehead, *J. Org. Chem*, 2004, **5**, 1075–1082.

91   G. Yue, K. Lei, H. Hirao and A. Jianrong Zhou, *Angew.Chem.*, 2015, **127**, 6631–6635.

92   B. Hu, S. Xing, J. Ren and Z. Wang, *Tetrahedron*, 2010, **66**, 5671–5674.

93   M. Ceylan and H. Gezegen , *Turkish J. Chem.*, 2008, **32**, 55–61.

94   A. Rammohan, J. S. Reddy, G. Sravya, C.N. Rao and G. V. Zyryanov, *Environ. Chem. Lett.*, 2020, **18**, 433–458.

95   X.-D. Fei, Z. Zhou, W. Li, Y.-M. Zhu and J.-K. Shen, *Eur. J. Org. Chem.*, 2012, 3001–3008.

96   L. Mahendar and G. Satyanarayana, *J.Org.Chem*, 2016, **81**, 7685–7691.

97   B. Hu, S. Xing, J. Ren and Z. Wang, *Tetrahedron*, 2010, **66**, 5671–5674.

98   B. Shen, D. Löffler, G. Reischl, H. J. Machulla and K. P. Zeller, *J. Fluor. Chem.*, 2009, **130**, 216–224.

99   M. Weber, K. Owens, A. Masarwa and R. Sarpong, *Org. Lett*, 2015, **17**, 5432–5435.

100   M. Won, S. Kwon and T.-H. H. Kim, *J. Korean Chem. Soc.*, 2015, **59**, 471–474.

101   A. Amorese, A. Arcadi, E. Bernocchi, S. Cacchi, S. Cerrini, W. Fedeli and G. Ortar, *Tetrahedron*, 1989, **45**, 813–828.

102   M. D. Barker, R. A. Dixon, S. and Jones and B. J. Marsh, *Chem. Commun.*, 2008, 2218–2220.

103   J. Yun and S. L. Buchwald, *J.Org.Chem*, 2000, **65**, 767–774.

104   F. Hollmann, D. J. Opperman and C. E. Paul, *Angew. Chem., Int. Ed*, 2021, **60**, 5644–5665.

105   K. Nakamura, R. Yamanaka, T. Matsuda and T. Harada, *Tetrahedron Asymmetry*, 2003, **14**, 2659–2681.

106   E. J. Corey, R.K. Bakshi, and S.Shibata, *J. Am. Chem. Soc*, 1987, **109**, 5551–5553.

107   E. J. Corey and C. J. Helal, *Angew. Chemie Int. Ed.*, 1998, **37**, 1986–2012.

108   E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen and V. K. Singh, *J. Am. Chem. Soc*, 1987, **109**, 7925–7926.

109   X. Y. Liu, X. Y. Wu, Z. Chai, Y. Y. Wu, G. Zhao and S.Z. Zhu, *J.Org.Chem*, 2005, **70**, 7432–7435.

110   G. Wang, C. Zheng and G. Zhao, *Tetrahedron: Asymmetry*, 2006, **17**, 2074–2081.

111   S. Lemouzy, L. Giordano, D. Hérault and G. Buono, *Eur. J. Org. Chem*, 2020, 3351–3366.

112   J.P. Konopelski, K.S. Chu, and G.R. Negrete, *J. Org. Chem,* 1991, **56**, 1357-1359.

113   C. Chen and R. A. Reamer, *Tetrahedron: Asymmetry*, 1990, **10**, 293–294.

114   C. Shang, Y. Kang, Q. Yang, Q. Zhu and C. Yao, *Adv. Synth. Catal.*, 2019, **361**, 3768–3776.

115   S. H. Lee, S. J. Park, I. S. Kim and Y. H. Jung, *Tetrahedron*, 2013, **69**, 1877–1880.

116   M. D. Barker, R. A. Dixon, S. Jones and B. J. Marsh, *Chem.Comm*, 2008, 2218-2220.

117   W. M. Clark, A. J. Kassick, M. A. Plotkin, A. M. Eldridge and I. Lantos, *Org. Lett.*, 1996, **69**, 1839–1842.

118   E. J. Corey and C. J. Helal, *Tetrahedron Lett.*, 1995, **36**, 9153–9156.

119   L. P. Linney, C. R. Self and I. H. Williams, *J. Chem. Soc., Chem. Commun.*, 1994, 1651–1652.

120   G. J. Quallich and T. M. Woodall, *Tetrahedron Lett.*, 1993, **34**, 4145–4148.

121   E. Vedejs and and M. Jure, *Angew. Chem. Int. Ed*, 2005, **44**, 3974–4001.

122   H. Pellissier, *Adv. Synth. Catal.*, 2011, **353**, 1613–1666.

123   J. R. Dehli and V. Gotor, *Chem. Soc. Rev*, 2002, **31**, 365–370.

124   G. Qabaja, A. R. Benavides, S. Liu and K. S. Petersen, *J.Org.Chem*, 2015, **80**, 133–140.

125   V. S. Martin, S.S.Woodard, T.Katsuki, Y.Yamada, M.Ikeda, and K. B.Sharpless, *J. Am. Chem. Soc.*

1981, **103** , 6237-6240

126   S. Yoshimatsu and K. Nakata, *Adv. Synth. Catal.*, 2019, **361**, 4679–4684

127   A.Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, and R.Noyori, *J. Am. Chem. Soc*, 1996, **118**,

2521–2522.

128   C. S. G. Seo and R. H. Morris, *Organometallics*, 2019, **38**, 2022.

129   D.-S. Wang, Q.-A. Chen, S.-M. Lu and Y.-G. Zhou, *Chem. Rev*, 2012, **112**, 2557–2590.

130   T. Touge,T. Hakamata, H. Nara, T. Kobayashi, N. Sayo, T. Saito, Y. Kayaki, and T. Ikariya, *J. Am.*

Chem. Soc, 2011, **133**, 14960–14963.

131   F. Chen, Z. Ding, Y. He, J. Qin, T. Wang and Q.-H. Fan, *Tetrahedron*, 2012, **68**, 5248–5257.

132   M. Watanabe, K. Murata and T. Ikariya, *J. Org. Chem*, 2002, **67**, 1712–1715.

133   Y. Zheng, J. A. Martinez-Acosta, M. Khimji, L. C. A. Barbosa, G. J. Clarkson and M. Wills,

ChemCatChem, 2021, **13**, 4384–4391.

134   S. Rast, B. Modec, M. Stephan and B. Mohar, *Org. Biomol. Chem*, 2016, **14**, 2112–2120.

135   A. E. Cotman, B. Modec and B. Mohar, *Org. Lett*, 2018, **20**, 2921–2924.

136   V. K. Vyas and B. M. Bhanage, *Org Lett*, 2016, **18**, 6436–6439.

137   A. E. Cotman, D. Cahard and B. Mohar, *Angew. Chemie Int. Ed.*, 2016, **55**, 5294–5298.

138   T. Touge, K. Sakaguchi, N. Tamaki, H. Nara, T. Yokozawa, K. Matsumura and Y. Kayaki, *J. Am.*

Chem. Soc, 2019, **141**, 16354–16361.

139   M. D. Greenhalgh, J. E. Taylor and A. D. Smith, *Tetrahedron*, 2018, **74**, 5554–5560.

140   J. S. Yadav, B. V. Subba Reddy, C. Sreelakshmi and A. B. Rao, *Synthesis (Stuttg).*, 2009, **11**,

1881–1885.

141 Y. Natori, M. Anada, S. Nakamura, H. Nambu and S. Hashimoto, *Heterocycles*, 2006, **70**, 635–646.

142 A. Matsuoka, C. A. Sandoval, M. Uchiyama, R. Noyori, H. Naka, *Chem. Asian J*, 2015, **10**, 112–115.

143 R. Noyori, M. Yamakawa and S. Hashiguchi, *J.O.C*, 2001, **66**, 7931–7944.

144 X.-H. Li, B.-H. Zheng, C.-H. Ding and X.-L. Hou, *Org. Lett*, 2013, **15**, 6086–6089.

145 J. L. Jeffrey and R. Sarpong, *Org. Lett*, 2009, **11**, 5450–5453.

146 T. Ito, F. Z. Marques, M. A. Markus, B. J. Morris, M. A. Khan, S. G. Nabi, S. Prakash and A. Zaman, *Org Lett*, 2013, **15**, 4118–4121.

147 T. Kammermeier and W. Wiegrebe, *Arch. Pharm. (Weinheim)*, 1994, **327**, 547–561.

148 C. M. Brennan, I. Hunt, T. C. Jarvis, C. D. Johnson and P. D. McDonnell, *Can. J. Chem.*, 1990, **68**, 1780–1785.

149 S. A. Snyder, A. L. Zografos and Y. Lin, *Angew. Chem. Int. Ed*, 2007, **46**, 8186–8191.

150 B. Du, X. Jiang and P. Sun, *J.Org.Chem*, 2013, **78**, 2786–2791.

151 A. S. Jadhav, Y. A. Pankhade, R. Hazra and R. V. Anand, *J.Org.Chem*, 2018, **83**, 10107–10119.

152 A. H. Abazid, N. Clamor and B. J. Nachtsheim, *ACS Catal.*, 2020, **10**, 8042–8048.

153 J. Krishna, A. Gopi, K. Reddy and G. Satyanarayana, *Synth. Commun.*, 2014, **44**, 2103–2111.

154 H.-J. Xu, Y.-Q. Zhao and X.-F. Zhou, *J.Org. Chem*, 2011, **76**, 8036–8041.

155 M. B. Díaz-Valenzuela, S. D. Phillips, M. B. France, M. E. Gunn and M. L. Clarke, *Chem.,Eur. J.*, 2009, **15**, 1227–1232.

156 J. Zhu, C. Zhong, H. F. Lu, G. Y. Li and X. Sun, *Synlett*, 2008, 458–462.

157   C. Zhong, J. Zhu, J. Chang and X. Sun, *Tetrahedron Lett.*, 2011, **52**, 2815–2817.

158   W. M. Clark, A. M. T-Eldridge, G. Kris Huang, L. N. Pridgen, M. A. Olsen, R. J. Mills, I. Lantos and N. H. Baine, *J. Am. Chem. Soc*, 1998, **120**, 4550–4551.

159   Z. Liu, R. J. Deeth, J. S. Butler, A. Habtemariam, M. E. Newton and P. J. Sadler, *Angew. Chemie - Int. Ed.*, 2013, **52**, 4194 –4197.

160   X. Liu, J. Wen, L. Yao, H. Nie, R. Jiang, W. Chen and X. Zhang, *Org. Lett*, 2020, **22**, 4812–4816.

161   G. Y. Zhang, C. K. Li, D. P. Li, R. S. Zeng, A. Shoberu and J. P. Zou, *Tetrahedron*, 2016, **72**, 2972–2978.

162   L.-J. Liu, W.-M. Wang, L. Yao, F.-J. Meng, Y.-M. Sun, H. Xu, Z.-Y. Xu, Q. Li, C.-Q. Zhao and L.-B. Han, *J. Org. Chem*, 2017, **82**, 11990–12002.

163   X. Chen, X. Li, X.-L. Chen, L.-B. Qu, J.-Y. Chen, K. Sun, Z.-D. Liu, W.-Z. Bi, Y.-Y. Xia, H.-T. Wu and Y.-F. Zhao, *Chem. Commun.*, 2015, **51**, 3846–3849.

164   X. Chen, X. Chen, X. Li, C. Qu, L. Qu, W. Bi, K. Sun and Y. Zhao, *Tetrahedron*, 2017, **73**, 2439–2446.

165   S. Yoshimatsu, A. Yamada and K. Nakata, *J.O.C*, 2018, **83**, 452–458.

166   H. Fakhraian, M. Zarinehzad and H. Ghadiri, *Org. Prep. Proced. Int.*, 2005, **37**, 377–385.

167   B. A. M Kinnea and E. A. Perren, *J. Chem. Soc.,* 1952, 3437–3445.

168   A. Jasiak, G. Y. Mielniczak, K. Owsianik, M. Koprowski, D. Krasowska and J. J. Drabowicz, *J.O.C*, 2019, **84**, 2619–2625.

169   C. Liu, J. Wang, L. Meng, Y. Deng, Y. Li and A. Lei, *Angew.Chem.*, 2011, **123**, 5250–5254.

170   L. Peng, M. Gao, X. Cai, R. Zhang, K. Li, G. Feng, A. Tong and B. Liu, *J. Mater. Chem. B*, 2015, **3**, 9168–9172.

171   W.-R. Yang, Y.-S. Choi and J.-H. Jeong, *Org. Biomol. Chem*, 2017, **15**, 3074.

172   A. Takada, Y. Hashimoto, H. Takikawa, K. Hikita and K. Suzuki, *Angew. Chem. Int. Ed*, 2011, **50**, 2297–2301.

173   X-J.Xu, T.Zeng, Z-X. Huang, X-F. Xu, J. Lin, and W-M. Chen, *J. Nat. Prod*, 2018, **81**, 2621 -2629.

174   X. Chang, P. Ma, H. Chen, C. Li and P. Wang, *Angew. Chemie Int. Ed.*, 2020, **59**, 8937–8940.

175   A. Casnati, M. Fontana, E. Motti and N. D. Ca', *Org. Biomol. Chem.*, 2019, **17**, 6165.