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The Selective Palladium-Catalysed Decarboxylative Coupling of Nucleophiles in the Presence of Propargylic Electrophiles

This thesis is submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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1. Abstract

The Selective Palladium-Catalysed Decarboxylative Coupling of Nucleophiles in the Presence of Propargylic Electrophiles

This thesis is submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in October 2017.

This thesis describes the development of a palladium-catalysed chemo- and regioselective decarboxylative coupling of 1,3-dicarbonyl compounds and nitrogen nucleophiles in the presence of propargylic electrophiles.

The first part of this thesis focuses on the palladium-catalysed cross-coupling reaction involving two 1,3-dicarbonyl compounds in a regio- and chemoselective manner *via* an allylic linker. The reaction is applied to a wide range of substrates and forms two C–C bonds and installs two all-carbon quaternary centres. Mechanistic studies to help deduce the mechanism of the reaction are described, which shows that by utilising a propargyl enol carbonate as one of the coupling partners, the regioselectivity of this process can be predictably controlled.

The second part of this thesis focuses on the palladium-catalysed cross-coupling reaction of 1,3-dicarbonyl compounds with indole, pyrrole, imidazole and pyrazole nucleophiles *via* an allylic linker. Despite the weakly acidic nature of *N*-heterocycles, the reaction proceeds with good efficiency, complete regio- and chemoselectivity and broad substrate scope. Mechanistic studies have also been carried out to help deduce the mechanism of the reaction.

The third part of this thesis centres around the development of the palladium-catalysed cross-coupling reaction of two 1,3-dicarbonyl compounds in an enantioselective manner. Focus is given to the enantioselective *alkenylation* and enantioselective *allylic alkylation* reactions. Optimisation of the reaction conditions as well as the expansion of the substrate scope is described.

Finally, a discussion of future work, comprehensive conclusions as well as experimental procedures for the preparation of new compounds, backed up by full analytical characterisation, are disclosed.

2. Table of Contents

3. Acknowledgements

I would like to thank Dr. Vilius Franckevičius for the fantastic opportunity to undergo my PhD at Lancaster University. I have to say even though it has been one of the hardest challenges I have ever had to face, it has also been one of the most enjoyable. With no two days the same, each day in the laboratory was always interesting. You always pushed me to do my best even when it didn't seem like anything would work out in the lab, and even though there were some extremely tough times, the feeling of satisfaction at the end cannot be matched by anything else. While things haven't always been easy I really to believe I am a better chemist as well as a better person because of all the experiences I have had, and I cannot thank you enough for the opportunity.

As well as my supervisor, who was always there throughout, everyone else in the chemistry department made me feel welcome throughout my time and were always helpful when I needed advice. This includes all the students and staff in the chemistry department at Lancaster University. I must give a special mention to David Rochester, who has run my mass spec samples, as well as helped me use the Chiral HPLC machine, as well as Geoff Akien for being the eyes and ears of the NMR machine, which I used all too frequently. I also thank Nathan Halcovitch for running the X-ray crystallography data for 2 of the 3 compounds, as well as Daniel Kitson who also contributed to a small part of the project.

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4. List of Abbreviations

ADMET	absorption, distrubtion, metabolism, excretion and toxicity
Å	angstrom
Ac	acetyl
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
^{o}C	degrees Celsius
c	concentration
Cbz	carboxybenzyl
COSY	^{1}H correlation spectroscopy (NMR)
Cy	cyclohexyl
[D]	deuterated compound
δ	chemical shift (NMR)
dba	dibenzylideneacetone
Dbcot	dibenzo[a,e]cyclooctatetraene
DEPT	distortionless enhancement by polarisation transfer (NMR)
DMA	dimethylacetamide
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DPEphos	bis[(2-diphenylphosphino)phenyl] ether
Dppb	2-bis(diphenylphosphino)butane
Dppe	1,2-bis(diphenylphosphino)ethane
Dppf	1,1-bis(diphenylphosphino)ferrocene
Dppp	1,3-bis(diphenylphosphino)propane

d.r	diastereomeric ratio
E	entegen (opposite, *trans*)
ee	enantiomeric excess
ESI	electrospray ionisation (HRMS)
EPSRC	Engineering and Physical Sciences Research Council
Et	ethyl
FTIR	fourier transform infrared spectroscopy (IR)
G	gram(s)
h	hours
HMBC	heteronuclear multiple bond correlation (NMR)
HMDS	bis(trimethylsilyl)amine
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrscopy
HSQC	heteronuclear single quantum coherence spectroscopy (NMR)
IUPAC	International Union of Pure and Applied Chemistry
^{i}Pr	*iso*-propyl
IPA	*iso*-propanol
IR	infrared
IT	ion trap
J	coupling constant (NMR)
L	litre(s)
LC	liquid chromatography
LCMS	liquid chromatography mass spectroscopy
M	metre(s)
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
Mol	mole(s)
m.p.	melting point
Ms	methylsulfonyl
MTBE	methyl *tert*-butyl ether
Mts	2,4,6-trimethylbenzenesulfonyl
MW	molecular weight

N	number
n.d.	not determined
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Ns	nitrobenzenesulfonyl
Nuc	undefined nucleophile
o-	*ortho* (isomer)
Log P	partition coefficient
p-	para (isomer)
Ph	phenyl
Ppm	parts per million
R	undefined substituent
R_F	retention factor
r.r.	regioisomeric ratio
rt	room temperature
S.M.	starting material
t (*tert*)	tertiary (isomer)
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
Tf	triflyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TOF	time of flight
t_R	retention time (HPLC)
Ts	*para*-toluenesulfonyl
Z	zusammen (together, *cis*)

5. Introduction

One of the most important accomplishments of organic chemistry is reflected in its relevance to, and application within, the pharmaceutical industry. Thousands of organic molecules have to be synthesised and screened for activity as part of the drug discovery and development process. The industry is facing significant challenges, however, as drug development is often a lengthy and expensive process. In 2010, figures showed that the cost of developing a new commercial pharmaceutical was approximately US $1.8 billion.[1]

In light of the enormous costs associated with drug discovery, the industry is keen to optimise its approaches and operations. Organic synthesis can play a key role in facilitating this shift and to better understand how this could be brought about, it is important to consider the general properties and features of small molecule drugs. As the majority of drugs are orally administered, they must display high oral bioavailability for efficient absorption by carefully tuning the physicochemical properties of the active pharmaceutical ingredients.

Lipinski has devised a set of rules as a guide to ascertain whether a drug molecule is likely to have desirable physicochemical properties.[2] Out of 2,245 compounds chosen from the World Drug Index, 90% were found to obey Lipinski's rules,[3] which are the following:

- Log P < 5 (lipophilicity): the partition coefficient relating to the relative solubility of a molecule in an octanol/water mixture.

- No more than 10 hydrogen bond acceptor groups.
- No more than 5 hydrogen bond donor groups.
- MW < 500 g mol^{-1}.

The first three rules directly refer to the balance between water and fat solubility of a drug. Too little aqueous solubility results in slow absorption as well as slow uptake into the blood stream. On the other hand, low fat solubility reduces the ability of the molecule to permeate through the cellular lipid membrane to reach its target. Therefore, the right balance of water and fat solubility is required for a drug to be effective when administered orally.

According to Lipinski's rules, drug molecules should possess a molecular weight of < 500 g mol^{-1}.[3] It is generally found that organic compounds with a large molecular weight have problems permeating through the intestinal barrier and the blood brain barrier.[4] It is, therefore, important to maintain a low molecular weight. On the other hand, a very low molecular weight may result in both promiscuous, non-selective binding, as well as lower binding affinity due to the lack of specific binding contacts.

Further factors that could contribute to the oral bioavailability of a drug molecule, are its polar surface area and the number of rotatable bonds in the structure.[5] The polar surface area describes the overall surface sum of all the polar atoms (mainly oxygen and nitrogen). If this is too high, then the molecule may not penetrate through the cellular wall efficiently,[5,6] as well as having difficultly passing through the blood-brain barrier.[7] Finally, rotatable bonds

enhance the flexibility of the molecule, and it has been shown that more rotatable bonds can reduce the permeation rate of a drug.[5] In contrast, drugs with fewer than 10 rotatable bonds tend to have improved oral bioavailability profiles. In addition, a large number of rotatable bonds can incur an entropic penalty upon the binding of the molecule to its target.[8] This entropic loss decreases the affinity of the drug molecule for binding to the target receptor.

Lipinski's rule of 5 directly links to ADMET properties which are: absorption, distribution, metabolism, excretion and toxicity.[9] Absorption and distribution are determined by the correct balance of water soluble groups and fat soluble groups within the drug molecule. Metabolism concerns the breaking down of the drug so that it can be excreted from the body. A lipophilic molecule is more likely to be more readily metabolised in the liver, due to their affinity for metabolic enzymes,[10] potentially necessitating a larger dose, which increases the risk of toxic side effects.[11]

Another important consideration is the potency of the drug. A potent drug will have high specificity for a target, which effectively enables the use of a lower dosage of the active pharmaceutical ingredient. Drugs administered at a lower dosage have the potential to reduce their side effects and it has also been shown that potency has a positive effect on the binding affinity of certain drugs.[12,13]

If a drug molecule is chiral, then one enantiomer of the molecule is likely to exhibit more potent binding.[14] For example, racemic succinimides **1**-**3** and enantiomerically pure succinimides **4**-**6** were tested as potential antifungal agents (Figure 1).[15] It was found that enantiomerically pure succinimides displayed higher antifungal activity than their racemic counterparts, as shown by the enhancement ratio (the factor in which the antifungal activity had been increased using the enantiomerically pure succinimide), between the racemic and the enantiomerically pure succinimides.

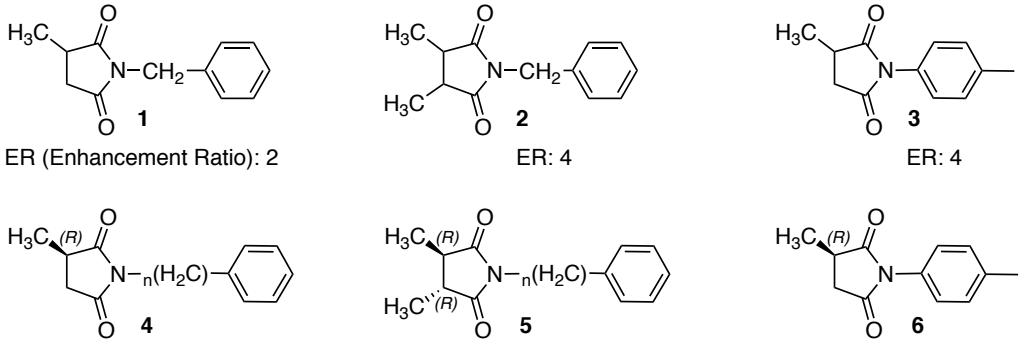


Figure 1: The enhancement ratio between chiral and racemic succinimides of the antifungal activity of Candida albicans.

A further example of the effect of chirality on drug activity is the tuberculosis drug ethambutol (**7**, Figure 2). The (*S*,*S*)-isomer **7** is 500 times more potent than the (*R*,*R*)-isomer **8** at binding to its target, and therefore, a significantly lower dose of the (*S*,*S*)-isomer is required to achieve the desired effect.[16]

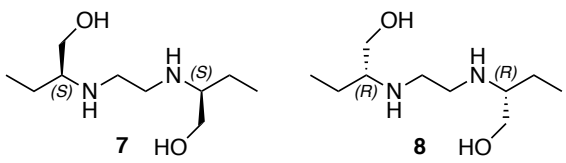


Figure 2: (*R,R*)- and (*S,S*)-ethambutol.

The factors described so far concern the general properties of potential drug-like molecules. However, to arrive at the point of the optimal, marketable drug molecule, extensive screening of a large number of compounds is required. This involves testing for activity against the drug target until a number of lead compounds, which show potency and some degree of selectivity for the given target, as well as exhibit desirable ADMET properties, are identified. These lead compounds then undergo extensive optimisation, which may eventually result in the development of a marketed drug. Typically, the molecular weight of a lead compound increases during development due to the addition of new functionality as a means of enhancing its potency and selectivity, minimising toxicity and maximising oral bioavailability. Therefore, given that the molecular weight of small molecule drugs is often < 500 g mol^{-1}, it is clear that the molecular weight of a lead compound undergoing development should be significantly lower, often < 300 g mol^{-1}.[17] Furthermore, introduction of additional structural complexity typically increases the lipophilicity of compounds during the lead optimisation process. As such, an optimal lead compound should possess a log P < 3 in order to ensure that the structure of the optimised drug molecule does not exceed the lipophilicity principles of a typical drug (log P < 5).[18]

Chemical space is another key area for study in drug research and development. This concept is defined as the space spanned by all possible known molecules or structures.[19] Compound screening libraries containing more varied structures have a greater ability to interrogate that chemical

space, which is important as only a small fraction of the vast array of chemical space has been explored to date.[19,20] Due to the tetrahedral nature of sp^3-hybridised carbon atoms, sp^3-rich compounds typically possess greater 3D complexity than aromatic, flat sp^2-rich molecules and, therefore, can potentially tap into untested areas of chemical space. This could lead to the identification of molecules that display interactions with new targets.[21]

The application of synthetic chemistry methodology has underpinned the creation of small molecules for drug discovery and development programmes. However, it is believed that the chemical methods available to synthetic chemists have had an inadvertently negative impact on the drug discovery processes by facilitating the construction of molecules with undesirable physicochemical properties.[21] This has led to a decline in the productivity of the pharmaceutical to the point where the number of new drugs approved per billion dollars spent has halved roughly every 9 years since 1950.[22] The main reason for this is the extensive use of similar chemical processes, which are highly effective at constructing sp^2-rich compounds (*vide infra,* section 4.1), which tend to be flat and more lipophilic. As a result, many screening libraries are over-populated with sp^2-rich compounds of limited structural diversity.[23] Indeed, several studies have shown that only 2.6% of commercially available building blocks are within a lead-like defined space,[24] and almost half of all known compounds only tap into 0.25% of the possible molecular frameworks.[25] This highlights the lack of chemical space explored by the

current synthetic chemistry methodologies in the creation of small molecules with lead-like properties.

Due to the overuse of chemical methods for the assembly of sp^2-rich molecules, thereby contributing to a decline in the productivity of the pharmaceutical industry,[22] there is now an increase in the demand for molecules with a higher degree of saturation (sp^3-rich). In addition to the observation that sp^3-rich compounds tend to be less lipophilic than sp^2-rich ones,[21] saturation can give rise not only to greater structural variation, but also stereoisomerism. The number of chiral centres in a molecule can correlate with the success of that compound in the transition from discovery through development to the active drug.[25] When dimethylpyridine (**9**) and dimethylpiperidine (**10**) are compared (Figure 3),[21] a clear difference in the ability to access chemical space by the possible isomers that can be formed with either molecule is apparent. Specifically, dimethylpyridine (**9**) is essentially an unsaturated, flat molecule with just five potential isomers and little structural complexity. In contrast, dimethylpiperidine (**10**), which has more sp^3 character, is a fully saturated molecule: the ring structure of **10** is not flat and comprises two chiral centres, enhancing its 3-dimensionality. As a result of the added chirality, the number of potential isomers of **10** is significantly increased compared to that of **9**. This enhancement of structural diversity, therefore, enables the exploration of greater areas of chemical space. The importance of sp^3 centres is also apparent when the total carbon count in lead and drug compounds is compared: in lead compounds, the average Fsp^3

(fraction of sp^3 carbon atoms) is 0.36, whereas in drug compounds, this number increases to 0.47.[21]

9 5 isomers $Fsp^3 = 0.29$

10 34 isomers $Fsp^3 = 1.00$

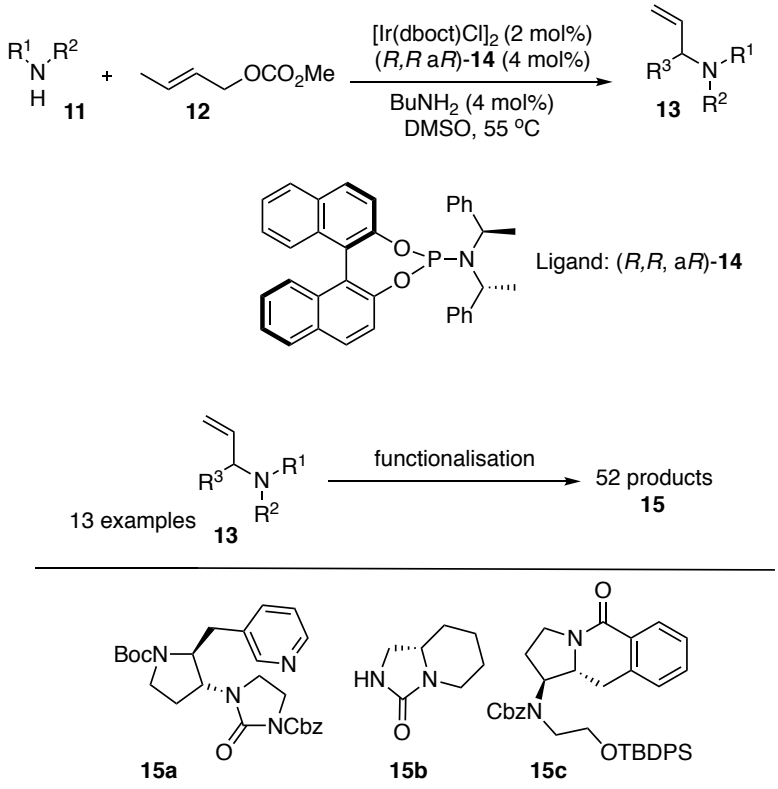
Figure 3: The effect of saturation on structural diversity.

To address the diminishing access to structurally novel lead molecules, the concept of lead-oriented synthesis has recently emerged.[24,26] Lead-oriented synthesis targets lead-like molecules with specific molecular properties, including a suitable molecular weight, polar surface area, number of hydrogen bond donors and acceptors, number of rotatable bonds and the amount of chemical space the molecule can explore.

As lead optimisation tends to increase the molecular weight and lipophilicity of the lead molecule, some parameters have been set to estimate whether a lead compound could successfully be developed to a drug molecule. Typically, log P plays an important role (log P < 3 for lead compounds), as well as the molecular weight (MW < 300). In fact, it was found that just 2.6% of 4.9 million commercially available compounds survive the filtering process based on these parameters.[24]

Nelson and co-workers devised a unified lead-oriented synthesis to produce over 50 molecular scaffolds (Scheme 1).[27] Starting from a choice of 10 amines

11, two allylic carbonates **12**, and using ligand **14**, over 50 molecules of type **15a**-**15c** were generated from amines of type **13**. Most of the products made had created had the right balance of molecular weight, lipophilicity, polarity and a sufficient amount of sp^3 character, all desirable properties for lead-like molecules, which could lead to the access of new areas of chemical space not accessible through previous methods.[28]



Scheme 1: Lead-oriented synthesis contributing to the synthesis of over 50 diverse molecular scaffolds.

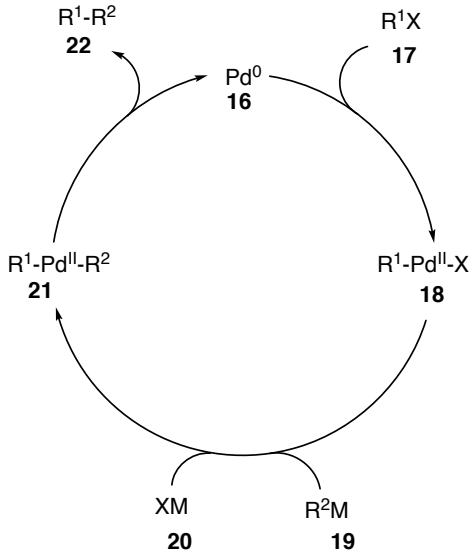
There is sufficient evidence to suggest that molecular properties of lead candidates directly affect the probability of successful development of a candidate to a marketed drug.[29] To achieve this, more efficient chemical processes for the synthesis of sp^3-rich structures must be sourced to access novel molecular frameworks with lead-like properties. However, before this

can be discussed, an overview of cross-coupling methodologies, which focus on sp^2-rich molecule synthesis, is warranted.

5.1. Catalytic Cross-Coupling Reactions

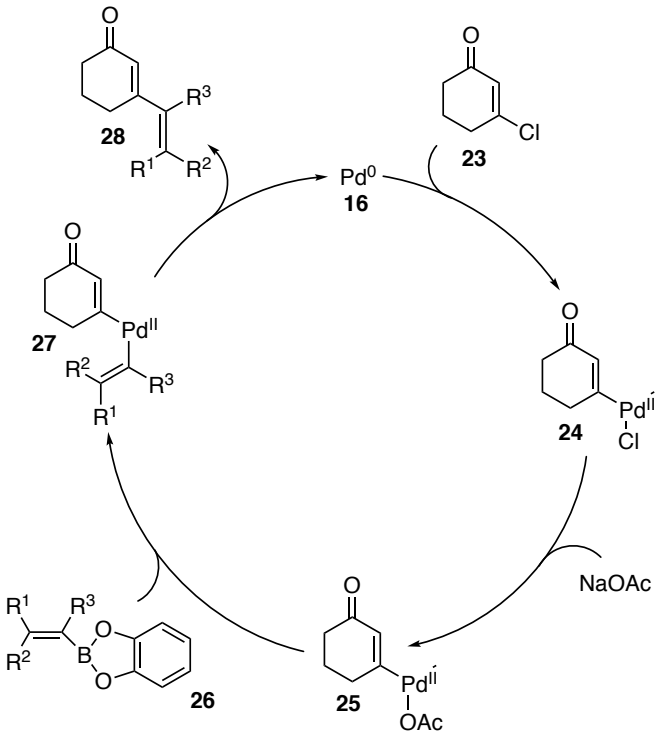
Catalytic cross-coupling reactions have allowed for significant advances in the synthesis of complex molecules by facilitating carbon-carbon bond formation. These processes have been efficiently utilised in the creation of polymers,[30] agrochemicals and pharmaceuticals.[31-33]

A typical sp^2-sp^2 cross-coupling reaction is mediated by a metal catalyst, most frequently palladium (Scheme 2). Mechanistically, palladium catalyst **16** undergoes oxidative addition to organohalide **17** to form organopalladium species **18**.[34] Transmetallation with a second coupling partner **19** displaces the halide from **18** to form **20** and palladium intermediate **21**. The resulting intermediate **21** undergoes reductive elimination to form coupled product **22** and in turn regenerates the catalyst.



Scheme 2: Mechanism of a typical palladium-catalysed cross-coupling reaction.

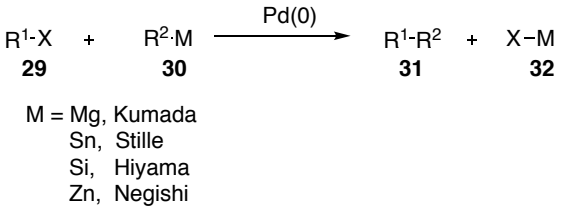
The first example of a palladium-catalysed cross-coupling reaction was reported in 1975 by Murahashi,[35] providing the basis for rapid development. An example of a well-known cross-coupling reaction heavily utilised in the pharmaceutical industry, is the Suzuki-Miyaura reaction, first reported by Suzuki and Miyaura in 1979 (Scheme 3).[34]



Scheme 3: Reaction mechanism of the Suzuki-Miyaura coupling.

This process has been used extensively to couple sp^2 centres together and requires a boronic acid or ester, and a halide as the coupling partners. Mechanistically, Pd^0 undergoes oxidative addition to organohalide **23** to form intermediate **24**, which reacts with a base, such as sodium acetate, to afford intermediate **25**. In addition, the base reacts with boronic acid/ester **26** to form a boronate species, which undergoes transmetallation with intermediate **25** to form **27**. Finally, reductive elimination occurs to form cross-coupled product **28** and regenerate the catalyst.

As well as the Suzuki-Miyaura coupling, other coupling partners have also found utility in this general process, all of which proceed *via* a similar reaction mechanism (Scheme 4). These include Kumada,[35] Stille,[36] Hiyama,[37] and Negishi cross-coupling reactions.[38]

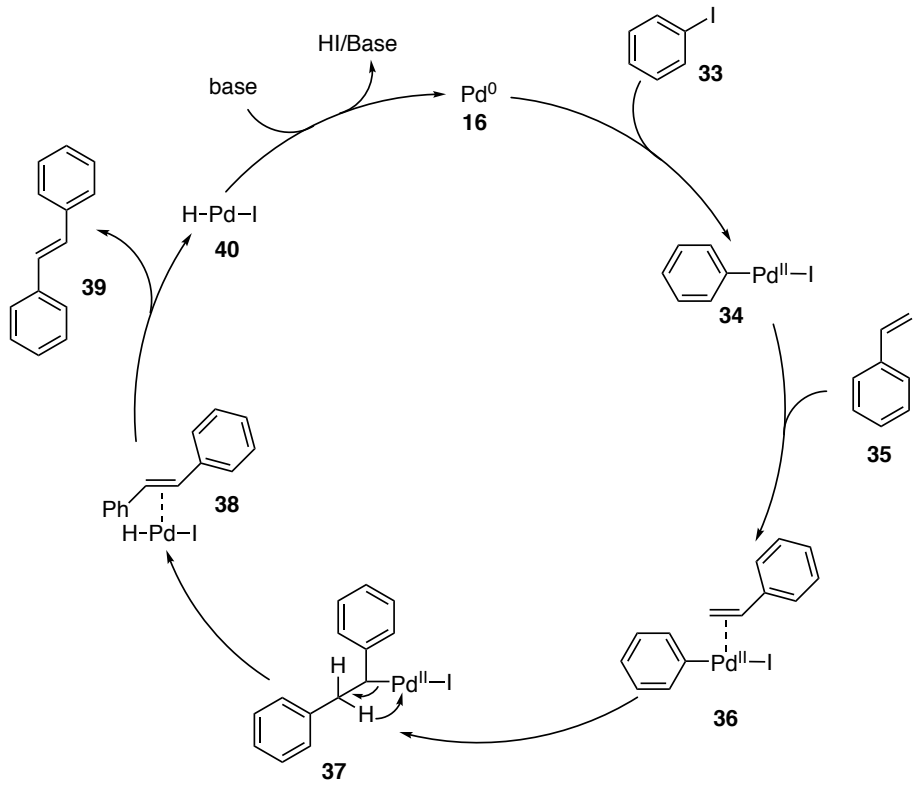


Scheme 4: Generality of the palladium-catalysed cross-coupling.

The primary reason why the Suzuki-Miyaura reaction is so popular stems from the fact that organoboron reagents are often commercially available, tend to be easy to make, many are relatively stable and the reaction itself is operationally straightforward.[34] In contrast, organotin reagents in Stille reactions are often toxic, and the separation of products from starting materials and by-products can be difficult.[39] Kumada couplings use Grignard reagents as one of the coupling partners, which are very moisture sensitive and can introduce practical complexities. The Hiyama coupling utilises silicon reagents, which are very stable, however, basic fluorides and harsh reaction conditions are required to cleave the silicon-carbon bond. As such, base-sensitive functionality may be affected by the addition of this activator. Negishi couplings use organozinc reagents, which are highly reactive. Therefore, the main drawback of the Negishi coupling is that zinc reagents have less functional group compatibility due to their high reactivity. In spite of this, Negishi couplings have been widely used for sp^2-sp^3 coupling.[40,41]

In addition to the aforementioned processes, the Heck reaction is similar to the above in that it allows for sp^2-sp^2 coupling of an organohalide as one of

the coupling partners, but the difference is that the second coupling partner is an unactivated alkene (Scheme 5).[42,43]

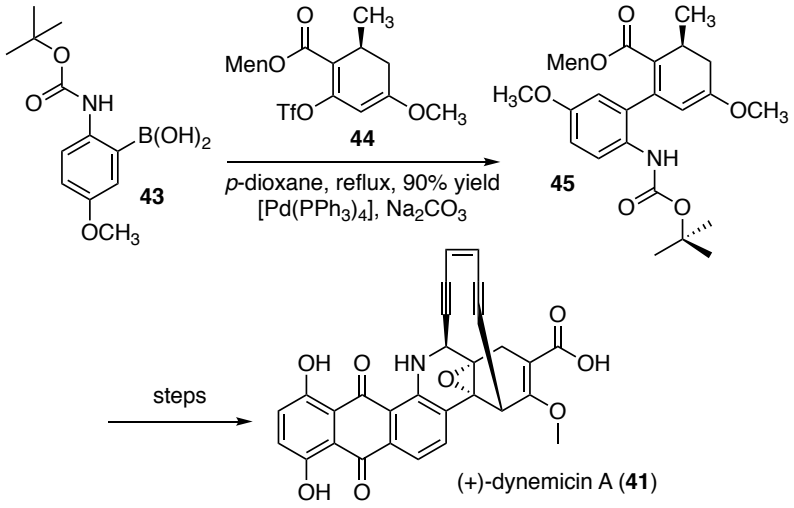


Scheme 5: General mechanism for the Heck reaction.

Mechanistically, palladium catalyst **16** oxidatively adds into the aryl-iodine bond in **33** to form intermediate **34**. The palladium centre in **34** then forms a π-complex with alkene **35** to give **36**, and undergoes carbopalladation in a *syn* fashion to form intermediate **37**. The next step is β-hydride elimination, which forms π-complex **38** from **37**, at which point the palladium catalyst dissociates from the alkene to release product **39**. The final step is the regeneration of Pd(0) catalyst **16** from **40** by means of a base.

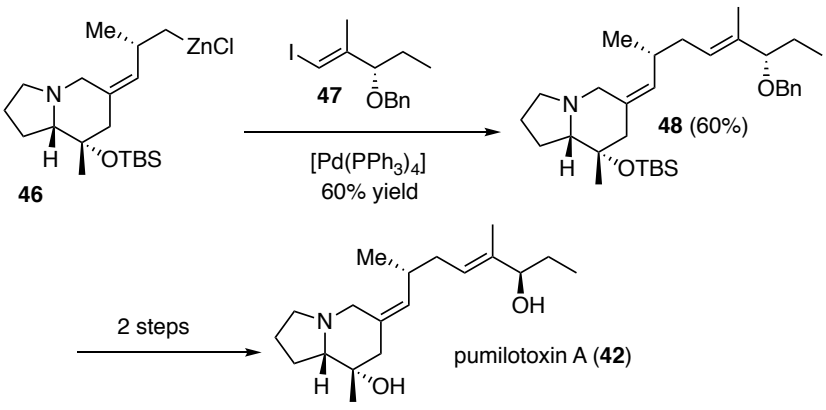
A number of pharmaceuticals and natural products have been accessed by utilising palladium-catalysed cross-coupling processes (Schemes 6 and 7),

such as an analogue of (+)-dynemicin **41**, an anticancer drug, and the natural product pumilotoxin A (**42**), a toxic component in the saliva of frogs.[44,45] The key step in the synthesis of the dynemicin analogue (**41**) is a Suzuki-Miyaura cross-coupling between aryl boronic acid **43** and triflate **44**, giving rise to cross-coupled product **45**, which was eventually transformed to product **41**.



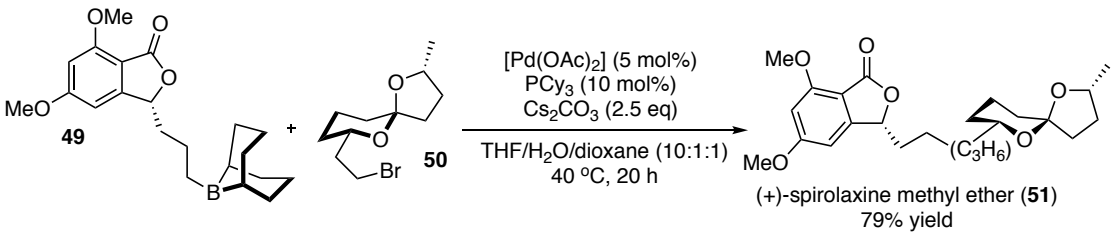
Scheme 6: The Suzuki-Miyaura cross-coupling in the synthesis of (+)-dynemicin (**41**).

In pumilotoxin A (**42**) synthesis, a Negishi coupling between highly functionalised **46** and **47** was performed to generate advanced intermediate **48**, which, in several steps, was converted to pumilotoxin A (**42**).



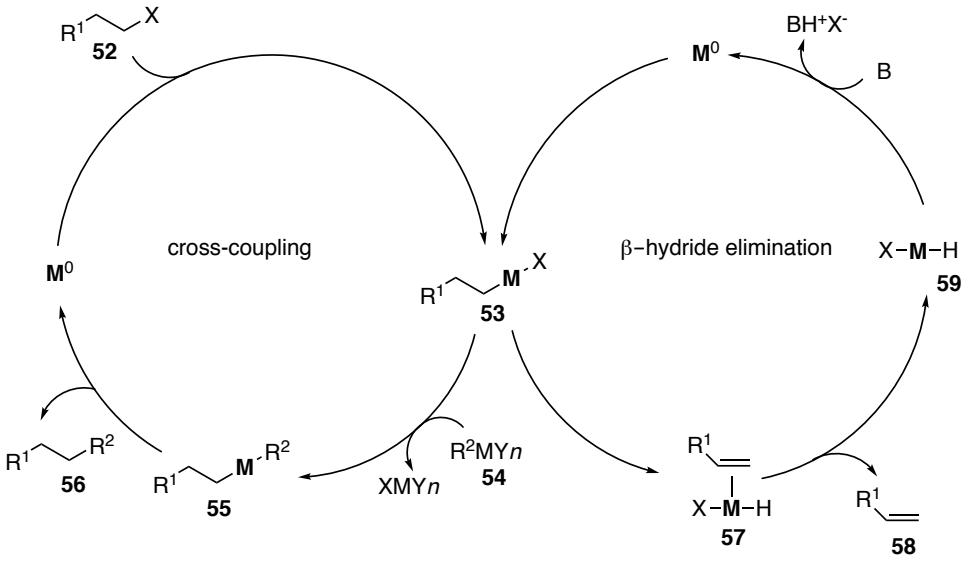
Scheme 7: Negishi coupling in pumilotoxin A (**42**) synthesis.

Indeed, the importance and broad application of cross-coupling reactions, mainly effective at the union of sp^2 carbon centres, has resulted in the Nobel Prize being awarded to Suzuki, Negishi and Heck in 2010.[46] However, given that sp^2-rich molecules are recognised to have a lower probability of being developed into a commercially viable pharmaceutical,[21] it is argued that the vast utility of these processes have unintentionally facilitated the academic and industrial synthesis of flat, lipophilic molecules, with negative consequences to the pharmaceutical industry.[23] It is, therefore, becoming apparent that new chemical methods that enable the coupling of molecules with greater sp^3 character are highly sought after to accelerate the synthesis of compounds that are less lipophilic and more structurally diverse. There has been some recent progress made towards extending sp^2-sp^2 coupling to the union of sp^3 centres.[47] For example, in 2007, Phillips and Keaton demonstrated a palladium-catalysed sp^3-sp^3 cross-coupling reaction, in the field of natural product synthesis (Scheme 8).[48] The synthesis of polyketide (+)-spirolaxine methyl ether (**51**), known to inhibit the growth of cholesterol, relies on a late stage alkyl-alkyl Suzuki-Miyaura cross-coupling reaction between borane **49** and alkyl halide **50**.



Scheme 8: Palladium-catalysed synthesis of spirolaxine methyl ether *via* an sp^3-sp^3 coupling process.

The fundamental obstacle to sp^3-sp^3 coupling is the competing reaction of β-hydride elimination, whereby an alkyl group bonded to the metal centre is converted to a metal hydride and an alkene.[49] As β-hydrogens are available for elimination in an sp^3-sp^3 coupling, β-hydride elimination is more likely to occur in these processes compared to the sp^2-sp^2 cross-coupling reactions (Scheme 9). More specifically, the metal catalyst oxidatively adds to the C–X bond of alkyl species **52** to form **53**. Transmetallation of **53** with metal species **54** then follows to give coupled intermediate **55**, before generating product **56** *via* reductive elimination. The competing β-hydride elimination reaction can also occur to generate complex **57** from **53**. This intermediate dissociates to form alkene **58** and complex **59**, while the base regenerates the catalyst.

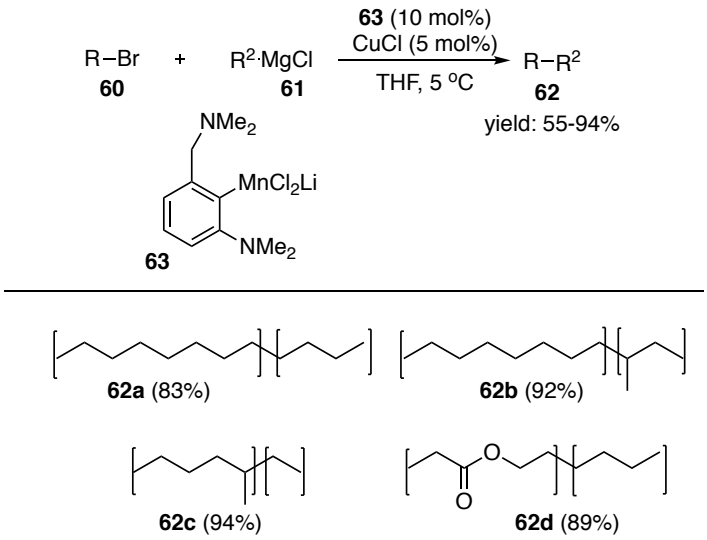


Scheme 9: sp^3-sp^3 cross-coupling vs β-hydride elimination mechanism.

There are strategies that can be employed to suppress β-hydride elimination. For example, it is possible to vary the ligand used for the cross-coupling reaction to inhibit the metal complex from adopting the geometry required for

β-hydride elimination. However, these methods have their limitations, as the nature of the metal coordination sphere under catalytic conditions is not always controllable or easily predictable. Therefore, it can often be challenging to deduce which ligands are more suitable for suppressing β-hydride elimination.[50]

The Kumada coupling has also been used extensively for sp^3-sp^3 coupling reactions,[51,52] utilising an alkyl Grignard reagent as the second coupling partner. In 1998, Donkervoort devised a method for sp^3-sp^3 coupling (Scheme 10), in which bromides **60** and Grignard reagents **61** were coupled with the aid of a manganese-based agent **63** and a copper catalyst, giving rise to coupled products **62** in 55-94% yields.[52] The yields were high when either straight chain alkyl or branched alkyl chains were used (**62a**-**62c**), and esters were also readily incorporated into the products (**62d**). Although the reaction is efficient at coupling sp^3-sp^3 centres together, the drawback of the reaction is the use of air sensitive and highly reactive Grignard reagents.



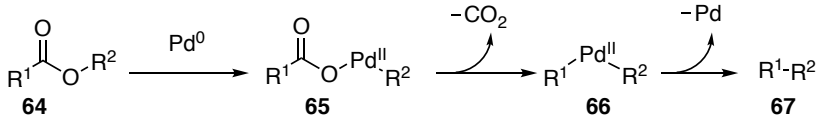
Scheme 10: sp^3-sp^3 coupling *via* a Kumada reaction.

While these reactions are efficient at forming C–C bonds, it is clear that functional group compatibility and competing side reactions can present obstacles for the broader development of the direct sp^3-sp^3 coupling. To overcome some of these difficulties, an alternative method for sp^3-sp^3 coupling, known as decarboxylative cross-coupling, has emerged. This type of reactivity is discussed in the next section.

5.2. Decarboxylative Cross-Coupling

The methods discussed so far involved the coupling of an organometallic species (M–R^2) and a halide (X–R^1) (*vide supra,* Scheme 2). To overcome some of the difficulties encountered previously with sp^3-sp^3 cross-coupling reactions, an efficient decarboxylative sp^3-sp^3 coupling process, which does not require the use of pre-functionalised coupling partners, was developed. In this reaction, a palladium(0) catalyst undergoes oxidative addition to ester species **64** to form **65**, which is followed by decarboxylation to provide

palladium(II) intermediate **66** (Scheme 11). Finally, reductive elimination forms coupled product **67**, in which a new $C(sp^3)$–$C(sp^3)$ bond had been formed.

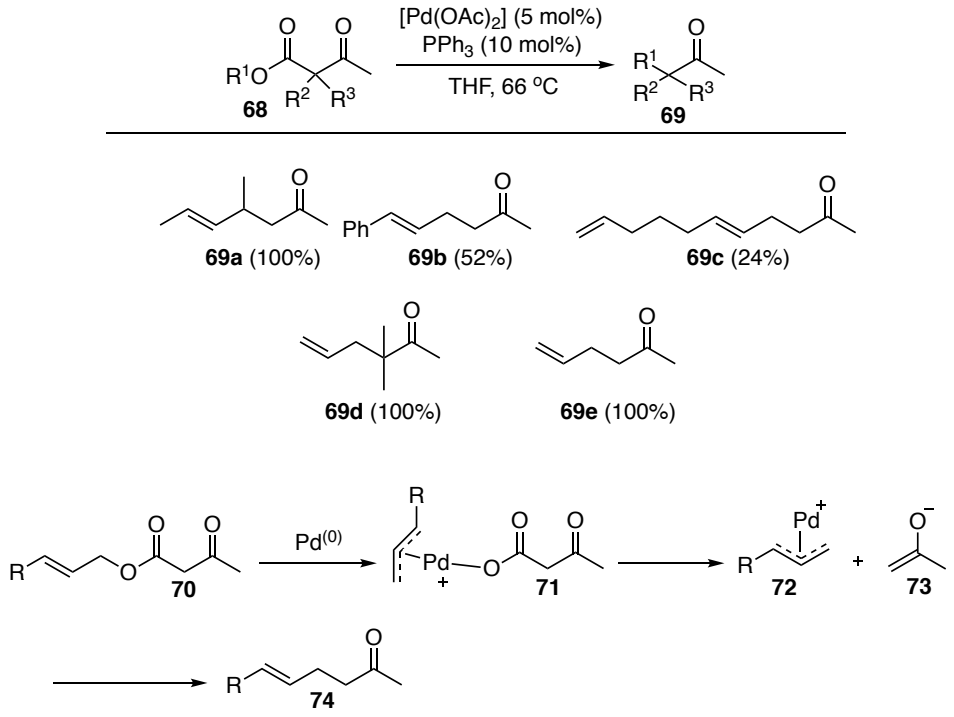


Scheme 11: General decarboxylative cross-coupling mechanism.

While the direct cross-coupling reactions required two coupling partners (*vide supra,* Scheme 2), this type of decarboxylative cross-coupling utilises only one coupling partner and the transmetallation step is replaced by decarboxylation; This removes the need for highly reactive or toxic coupling partners,[39] and the use of a strong base is no longer required.[34] The only waste product of the reaction is carbon dioxide, which is easily expelled from the reaction medium.

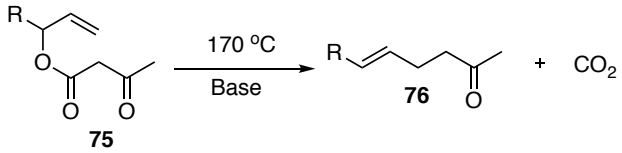
The most widely developed decarboxylative cross-coupling reaction is the palladium-catalysed allylic alkylation of enolates, first reported almost simultaneously by Tsuji,[53] and Saegusa.[54] In Tsuji's report, a number of allyl esters **68** were treated with a catalytic amount of palladium to form allylated ketones **69** (Scheme 12). Mechanistically, **70** undergoes oxidative addition with the palladium catalyst to form **71**, which is followed by decarboxylation to give rise to η^3-π-allylpalladium(II) intermediate **72** and enolate **73**, which may be covalently bonded to palladium or associated with **72** as a tight ion pair. The highly reactive enolate is then alkylated at the terminal carbon of the η^3-π-allylpalladium(II) species at the less hindered end to form the sp^3-sp^3 coupled product **74**. In this seminal report, the yields of the product were variable (**69a**-

69e, 24-100%),[53] with some substrates giving a low yield of **69** due to the formation of diallylated by-products.



Scheme 12: Palladium-catalysed decarboxylative allylic alkylation of ketone enolates.

This reaction is analogous to the Carroll rearrangement, in which substrate **75** is heated to 170 °C to form **76** (Scheme 13). [55,56]

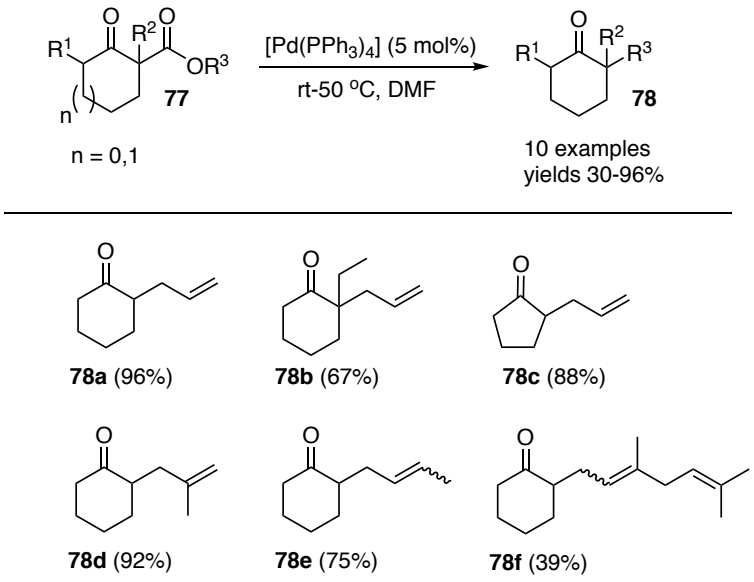


Scheme 13: The Carroll rearrangement.

The Carroll rearrangement uses harsher reaction conditions and requires a base. This highlights the superiority of the palladium-catalysed cross-coupling

reaction over the Carroll rearrangement, whereby the reaction conditions are significantly milder and the transformation is base-free.

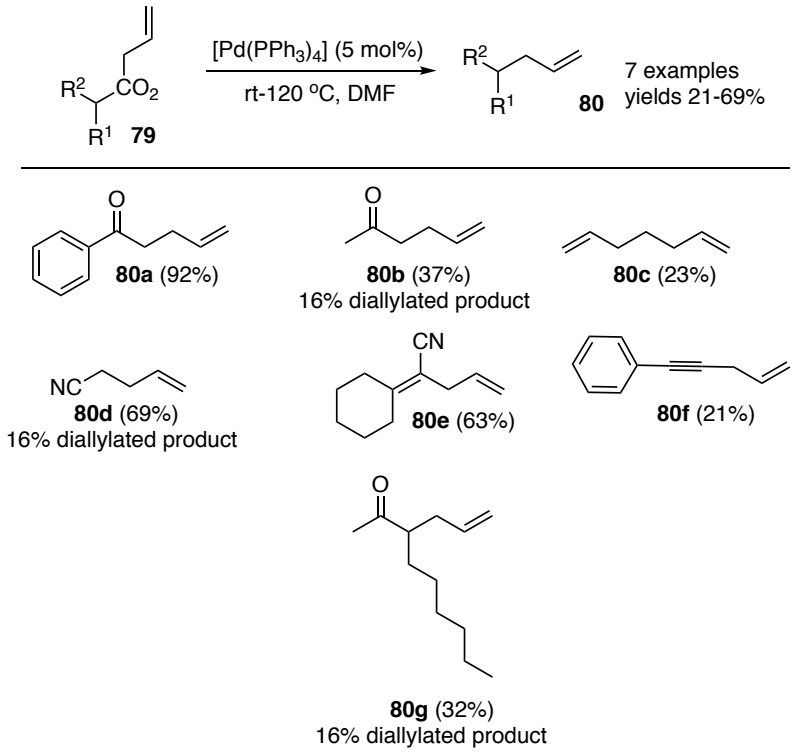
Around the same time, Saegusa reported the decarboxylative allylic alkylation of ketone enolates using β-keto esters of type **77** as substrates to form products **78a**-**78f** (Scheme 14).[54]



Scheme 14: Saegusa's decarboxylative allylic alkylation of cyclic ketones.

In this work, ketone products were obtained in varying yields and it was found that cyclic substrates were less prone to diallylation than the acyclic substrates (Scheme 15).[54] Despite only a couple of the cyclic products containing an all-carbon quaternary centre being reported (e.g. **78b**), there was no diallylation observed for any of the reactions involving cyclic ketones in which a tertiary centre had been constructed (**78a**, **78c-78f**). On the other hand, the acyclic substrates were less successful, and three out of the seven acyclic ketones, **80b**, **80d** and **80g**, underwent diallylation as a side reaction,

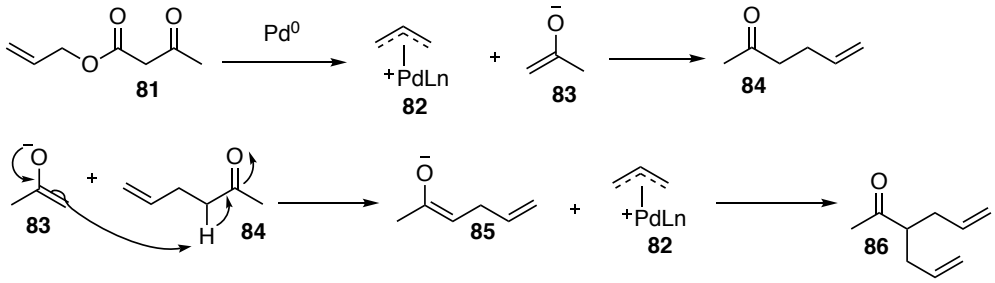
contributing to a reduced yield of the mono-allylated product. Despite **80a** being produced in a high yield, most of the linear based substrates gave yields lower than that of their cyclic counterparts (**80a**-**80f**).



Scheme 15: Saegusa's decarboxylative allylic alkylation of acyclic ketones.

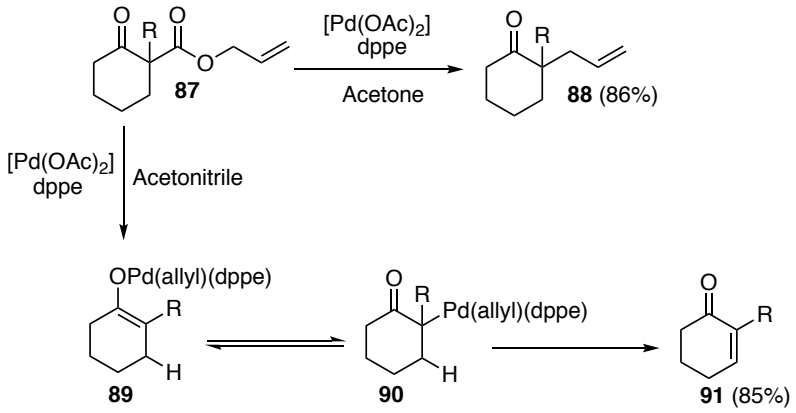
Concerning the mechanism of diallylation, it is postulated that following oxidative addition of the catalyst to **81**, decarboxylation generates η^3-π-allylpalladium(II) intermediate **82**, and enolate **83** addition to the terminal carbon of the η^3-π-allylpalladium(II) intermediate gives rise to product **84** (Scheme 16). However, the enolate generated *in situ* (**83**) can also deprotonate the α-position of ketone product **84**, thus creating a new enolate **85**, which can undergo a second allylic alkylation with η^3-π-allylpalladium(II) intermediate **82** to form diallylated product **86**.[54] Interestingly, while most of the

cyclic examples contained an α-proton in the product, and therefore, were susceptible to deprotonation (*vide supra*, Scheme 15), diallylation was not observed in any of the reactions.



Scheme 16: Mechanism of the diallylation side-reaction.

Tsuji has also reported work involving the conversion of β-keto esters **87** to β-unsaturated ketones **88** in good yields (Scheme 17).[57] It was found that one of two reaction pathways could be followed depending on the conditions used. With acetone as the solvent, the decarboxylative allylic alkylation process generated **88** from **87**. In contrast, using other aprotic solvents, such as acetonitrile, decarboxylation formed intermediate **89**, which is in equilibrium with carbon-palladium bonded complex **90**, poised to undergo β-hydride elimination to give cyclohexenone **91**.[57] This stands as further evidence that as described earlier (*vide supra*, Scheme 9), when β-hydrogens are available, β-hydride elimination can compete with the cross-coupling reaction.

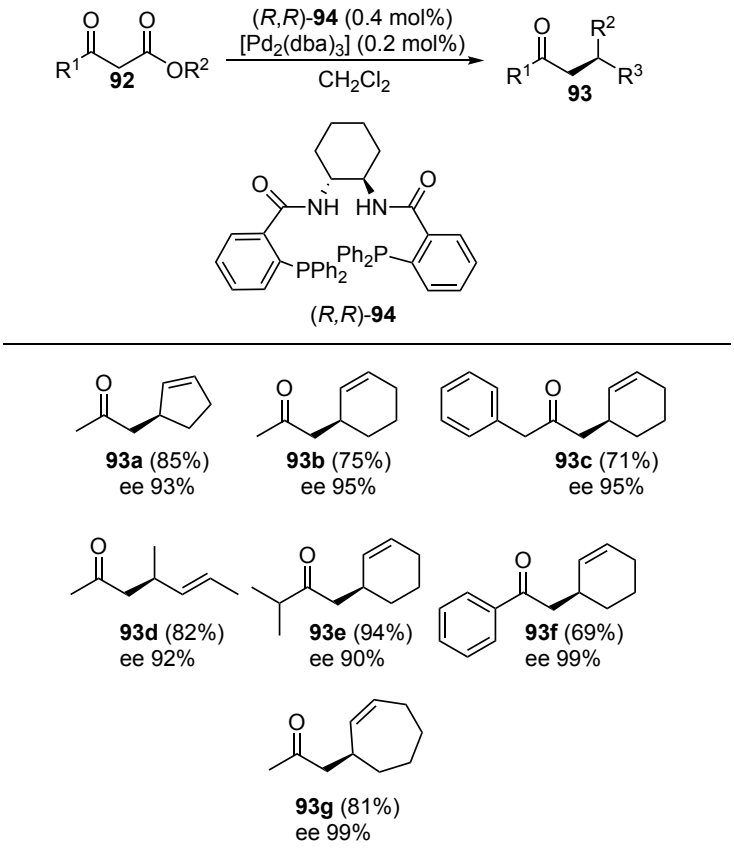


Scheme 17: Allylic alkylation vs β-hydride elimination.

Decarboxylative allylation has been expanded to other allylic derivatives, such as allyl enol carbonates.[58] Later, malonates were also successfully used: although the initial results were weak and required heating the reactions to above 100 °C,[59] 20 years later, Ito and coworkers drastically improved the yields of the decarboxylative allylic alkylation of malonates under mild reaction conditions.[60]

The versatility of the method has allowed facile access to compounds such as allylic amines,[61] vinyl azetidines,[62] and vinyl piperidines,[63] through the use of nitrogen-based nucleophiles such as allylic carbamates and vinyl oxazinanones. *O*-allylation has also been utilised, creating allyl ethers from allylic esters.[63] Finally, allyl selenides could be generated from allyl selenocarbonates.[64] Overall, these methods are effective at creating C–N, C–O and C–Se bonds, respectively, highlighting the generality and versatility of this process.

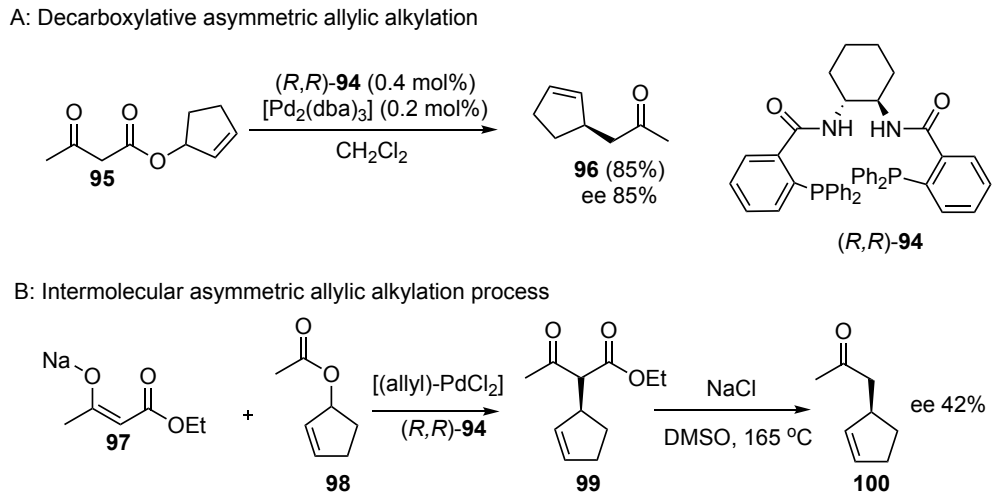
Significantly later, in 2004, the first asymmetric method for the decarboxylative allylic alkylation of ketone enolates was reported by Burger and Tunge (Scheme 18).[65] It was found that high levels of asymmetric induction could be obtained in the palladium-catalysed decarboxylative rearrangement of allyl-β-keto carboxylates **92** to **93** in the presence of Trost's chiral phosphine ligand (**94**).



Scheme 18: The first asymmetric decarboxylative allylic alkylation.

Tunge compared this method to the intermolecular asymmetric allylic alkylation process (Scheme 19).[66] In the first instance, cyclopentylacetate **95** was reacted under the developed decarboxylative allylic alkylation reaction

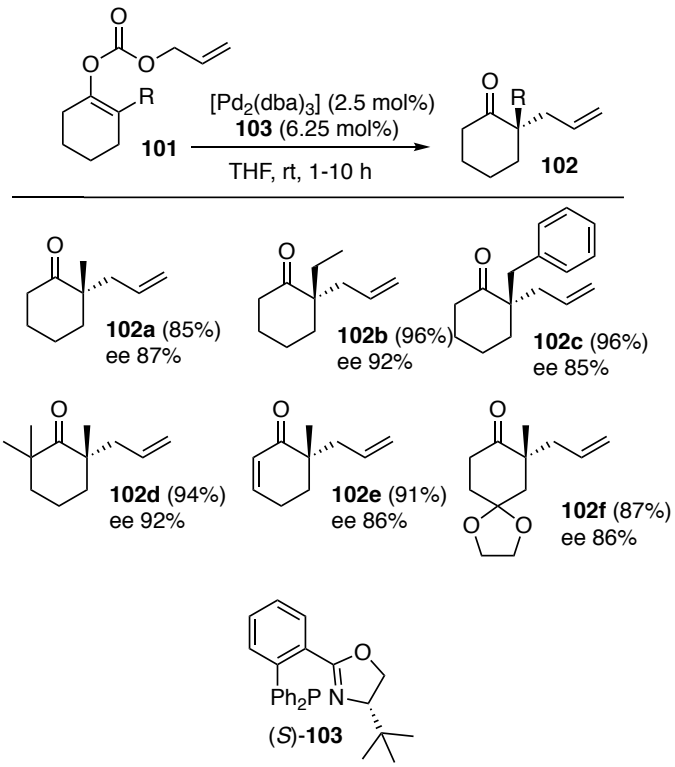
conditions to form **96**. The enantiomeric excess of **96** (85% ee) was then compared to that obtained in the intermolecular allylic alkylation reaction using sodium ethyl acetate **97** and allylic acetate **98** as the coupling partners. More specifically, product **100** was obtained *via* **99** in 42% ee following a Krapcho decarboxylation, highlighting that the level of enantioselectivity of the decarboxylative allylic alkylation approach is superior to that observed when using the intermolecular coupling variant.



Scheme 19: Decarboxylative vs intermolecular asymmetric allylic alkylation process.

In 2004, Stoltz and Behenna reported the first asymmetric decarboxylative allylic alkylation reaction to enable the formation of an all-carbon quaternary centre (Scheme 20).[67] Enol carbonates of type **101** underwent decarboxylation with a palladium catalyst and in the presence of chiral ligand **103**, afforded enantio-enriched allyl ketones of type **102** with good yields and enantioselectivities. Interestingly, the Trost ligand that had been successful for

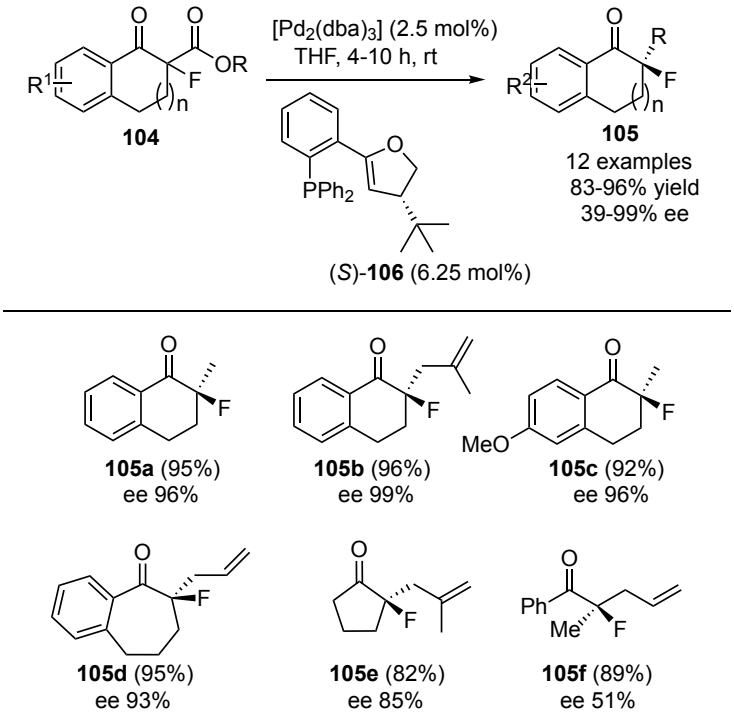
Tunge and Burger (*vide supra,* Scheme 18), gave no enantioselectivity in this reaction.



Scheme 20: Enantioselective decarboxylative allylation.

In 2005, Nakamura's group explored enantioselective decarboxylative allylic alkylation of α-fluoroketones.[68] It was found that the reaction of fluorinated allyl esters **104** in the presence of a source of palladium(0) and a chiral ligand (**106**) afforded products **105** in high yields and enantioselectivity (Scheme 21). Chiral phosphinooxazoline **106** was found to be the most efficient ligand, where the substitution on the oxazoline ring of **106** proved crucial to the observed enhancement of enantioselectivity, and it was observed that a large *tert*-butyl substituent was essential in obtaining high enantioselectivities of **105**. Using the optimised conditions, it was shown that 6-membered

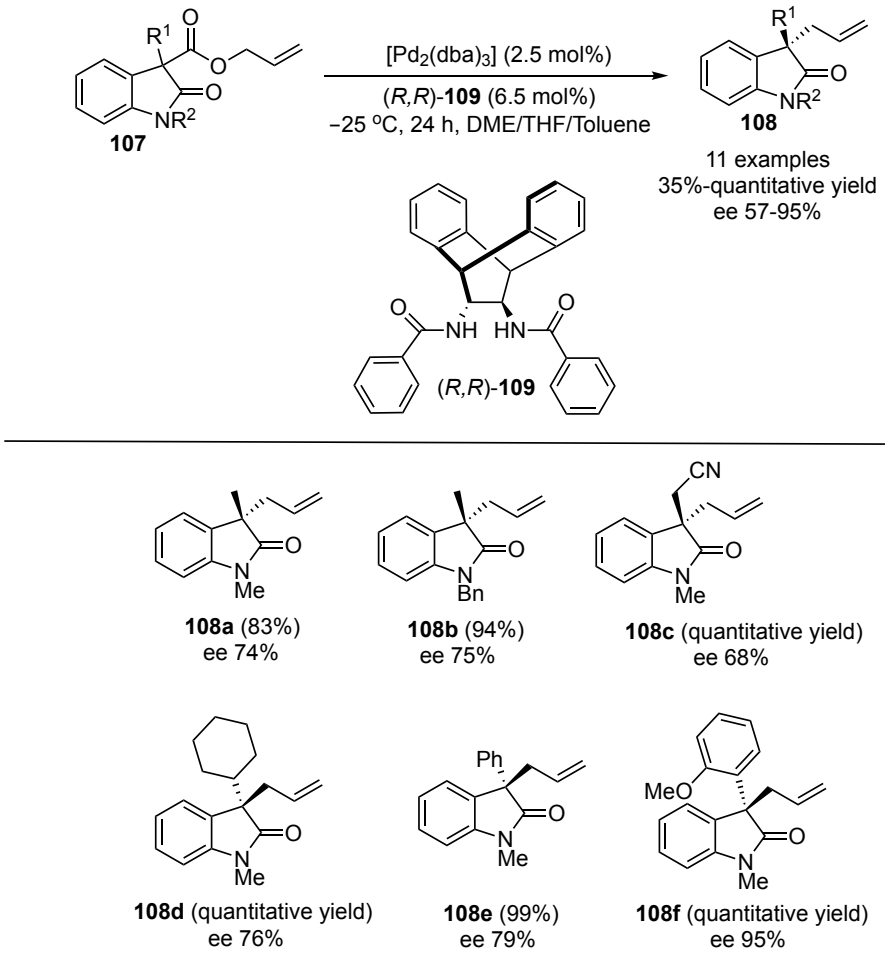
substrates gave the best enantioselectivity in this decarboxylative cross-coupling process, as shown by the enantioselectivity in the formation of products **105a**-**105d**.



Scheme 21: Chiral α-fluoroketone synthesis *via* decarboxylative allylic alkylation.

The fluorinated products obtained through this approach were particularly interesting from a medicinal chemistry perspective, as fluorine has unique properties that can alter the physical and chemical characteristics of drug molecules. For example, the presence of an electron withdrawing fluorine atom can reduce the pK_a of a molecule, which has been known to increase its oral bioavailability.[69] In addition, fluorination of certain functional groups can lead to either an increase or a decrease in lipophilicity, depending on the substituent that the fluorine molecule is attached to.[70]

In addition to ketone enolates, other carbonyl compounds can also be successfully employed in this reaction. For instance, in 2011 an asymmetric decarboxylative allylic alkylation of oxindoles was developed (Scheme 22).[71] In this case, enantio-enriched oxindoles, containing an all-carbon quaternary centre (**108**), were generated *via* an sp^3-sp^3 coupling process involving oxindoles of type **107**. Interestingly, using the same enantiomer of ligand **109**, the sense of enantioinduction varied depending on the size of the R substituent in **108**. It is thought that smaller groups direct the sterically bulky oxindole ring under the 'open flap' of the chiral ligand (**108a-c**), whilst a sterically bulky group overrides this effect and provides product **108** with the opposite stereochemical configuration in the allylic alkylation of oxindole enolates (**108d-108f**).[72]

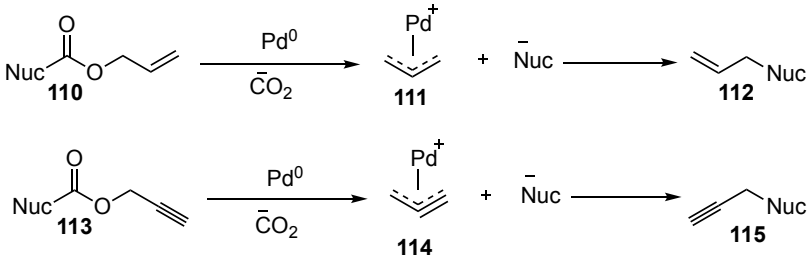


Scheme 22: Asymmetric decarboxylative allylic alkylation of oxindoles.

The enantioselective palladium-catalysed allylic alkylation process has been explored heavily, for example, in the synthesis of enantio-enriched α-tertiary hydroxyaldehydes, as well as allylated 2-acylimidazoles.[73,74] Notably, Trost disclosed the asymmetric allylic alkylation of cyclic vinylogous ester and thioesters, showing that a wide range of ester and thioesters could be successfully coupled in an enantioselective manner, creating products with a chiral all-carbon quaternary centre.[75]

5.3. Palladium-Catalysed Decarboxylative Cross-Coupling of Propargylic Electrophiles

So far, focus has been given to the decarboxylative allylic alkylation of nucleophiles with allylic electrophiles, whereby decarboxylation of allylic ester **110** forms η^3-π-allylpalladium(II) intermediate **111** and the nucleophile adds to the terminal carbon of η^3-π-allylpalladium(II) intermediate **111** to form **112** (Scheme 23). In this section, palladium-catalysed reactions of propargylic electrophiles, which have been studied less thoroughly, will be discussed. In this context, when a palladium catalyst oxidatively adds to propargylic electrophile **113**, decarboxylation leads to η^3-π-allenylpalladium(II) intermediate **114** (Scheme 23). The nucleophile generated *in situ* can then attack the η^3-π-allenylpalladium(II) species to form **115** in a propargylation, rather than an allylation, reaction.[76] However, this is not the only pathway that this reaction can take and the reactivity profile of propargylic electrophiles warrants a more detailed discussion.



Scheme 23: Decarboxylative allyl transfer vs propargyl group transfer.

Palladium-bound intermediate **114** differs from its allyl variant **111**. The metal centre can bind to the allyl motif *via* two η^1 modes or an η^3 mode (**116**, **117** and **111**, Figure 4), while the propargylic system can either form η^1-σ-propargylpalladium(II) intermediate **118**, η^1-σ-allenylpalladium(II) intermediate

119, or η^3-π-allenylpalladium(II) intermediate **114**. Studies have shown that the η^3-π-allyl bound species tends to be favoured in most cases for a decarboxylative allylic alkylation reaction.[77-79]

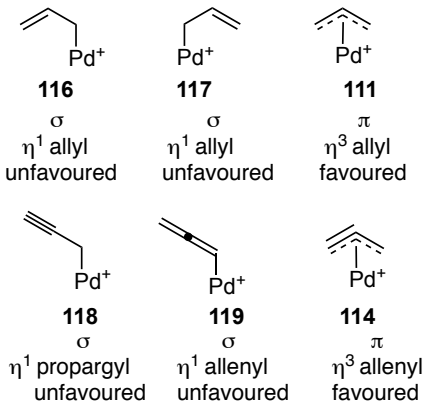
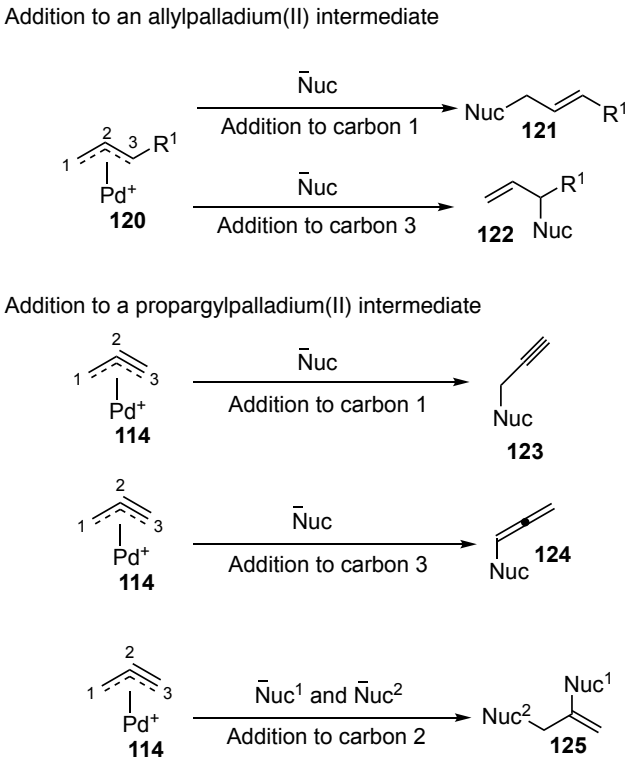


Figure 4: Structures of different palladium bound allyl and propargyl groups.

However, during propargyl group transfer, the intermediate formed (**114**, **118** or **119**) is not quite as well defined. In 1982, Keinan and Bosch predicted that the η^1-σ-propargylpalladium(II) and η^1-σ-allenylpalladium(II) intermediates **118** and **119**, respectively, would be more stable than η^3-π-allenylpalladium(II) species **114**.[80] However, further studies have shown that η^3-π-allenylpalladium(II) species **114** could be the preferred intermediate,[81] an observation that has been confirmed by X-ray crystallography.[82] As well as palladium, the η^3-π-allenyl-bound intermediates with other metals, such as iridium, rhenium and platinum, have also been isolated.[83,84]

Allyl and propargyl palladium cations also react differently with nucleophiles (Scheme 24). In the case of η^3-π-allylpalladium(II) intermediate **120**, the nucleophile attacks one of the terminal carbon atoms in **120** to form **121** or

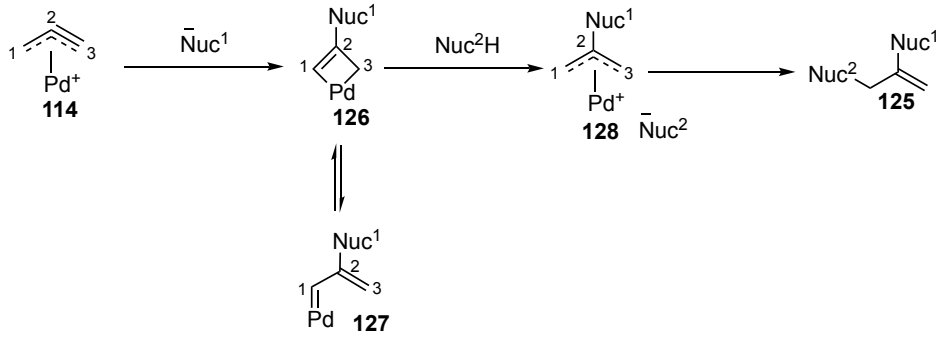
122. Typically, addition at the less substituted position (C-1) in **120** occurs due to steric effects.[85] In contrast, with η^3-π-allenylpalladium(II) systems, three reaction pathways are possible. Hard nucleophiles, such as unstabilised enolates, are more likely to attack at the terminal carbon atom 1 or 3 in **114** to form either alkyne **123** or allene **124**, respectively. Soft nucleophiles, such as stabilised enolates, are more likely to attack at the central carbon (carbon 2), which is followed by a second nucleophilic addition to form **125**.



Scheme 24: Modes of reactivity of allyl palladium and propargyl palladium intermediates.

Concerning the latter reactivity mode, when the first stable nucleophile attacks the central carbon atom of η^3-π-allenylpalladium(II) intermediate **114** (Scheme 25), it gives rise to putative palladacyclobutene intermediate **126** (which can also be viewed as palladium carbenoid **127**). Following protonation of the

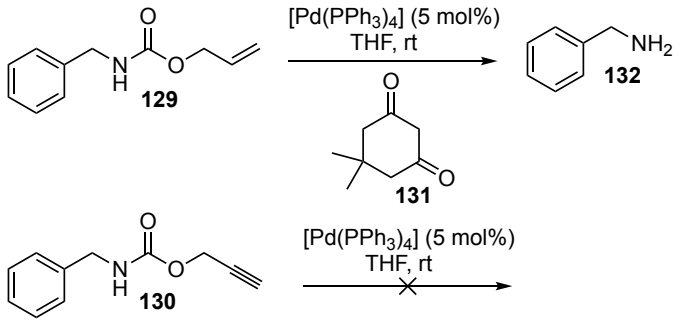
palladacycle **126** by the second nucleophile, η^3-π-allylpalladium(II) intermediate **128** is formed. In the final mechanistic step, nucleophilic addition to one of the terminal carbon atoms in **128** generates product **125** (Scheme 25). We can only speculate the structure of palladcyclobutene **126**, as there is a lack of empirical evidence to confirm its implication in the mechanism. It is possible that intermediate **126** is only transient and its formation is followed by immediate protonation to give η^3-π-allylpalladium(II) intermediate **127** in a synchronous manner.[82] However, given that the analogous metallacyclobutenes of rhenium, iridium and platinum have been isolated and characterised,[83,84] the existence of palladacyclobutene **126** in this mechanism cannot be ruled out.



Scheme 25: Palladium-catalysed reactions of soft nuclophiles with propargylic electrophiles.

The much lower extent of investigation of the palladium-mediated decarboxylative reactions of propargylic electrophiles as compared to allylic ones is likely to be due to the lower reactivity of the former with palladium (Scheme 26). A study comparing the deprotection of allyl groups and propargyl groups in the presence of dimedone (**131**) and [$Pd(PPh_3)_4$] found that, while the allyl carbonate **129** reacted to form amine **132** at room

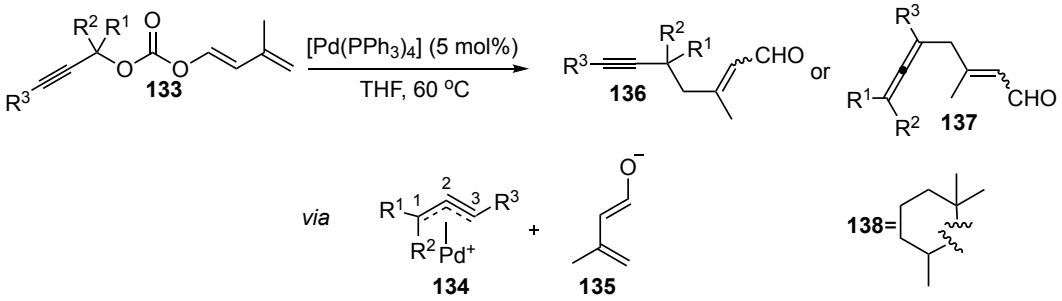
temperature, propargylic analogue **130** did not react and starting carbamate **130** was recovered.[86]



Scheme 26: Deprotection of allyl and propargyl carbonates.

Despite the reduced reactivity of propargylic electrophiles, significant progress has been made in this area over the past two decades. In 1994, Bienayme released a report on the decarboxylative propargylation and allenylation of aldehydes (Table 1).[87] Mechanistically, oxidative addition to **133** and decarboxylation forms the η^3-π-allenylpalladium(II) intermediate **134** along with an extended enolate **135**. Given the relatively unstabilised nature of enolate **135**, the reaction follows one of two pathways. The first is the addition of the enolate **135** to carbon atom 1 in **134** to form propargylated product **136**, while the second is addition to carbon atom 3 in **134** to form allenyl species **137**. Despite some evidence that the allenylation pathway would dominate for steric reasons, the main reason being that addition to the less hindered end of the η^3-π-allenylpalladium(II) intermediate forms the allenylated product,[88] the steric effects of substituents R^1, R^2 and R^3 were not clear cut in this study. While bulky groups on carbon atom 1 promoted attack at carbon atom 3 of η^3-allenylpalladium(II) intermediate **134** to form allenylated **137** (entry 3, Table 1),

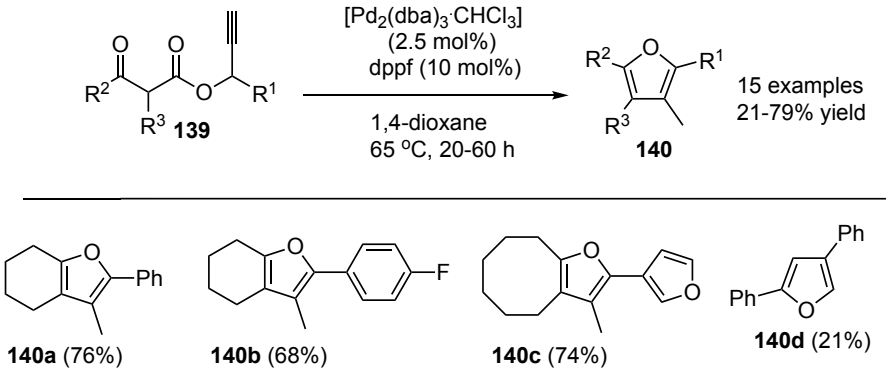
surprisingly, some bulky R^3 substitutents also promoted addition to carbon atom 3 in an allenylation, rather than a propargylation reaction (entry 4, Table 1). Propargylated aldehyde **136** was formed only when all the substituents were small (entries 1 and 2).



Entry	R^1	R^2	R^3	Combined yield (%)	Ratio **136/137**
1	Me	Me	H	59	64/36
2	H	H	H	64	100/0
3	**138**	**138**	H	69	0/100
4	Me	Me	Ph	90	0/100

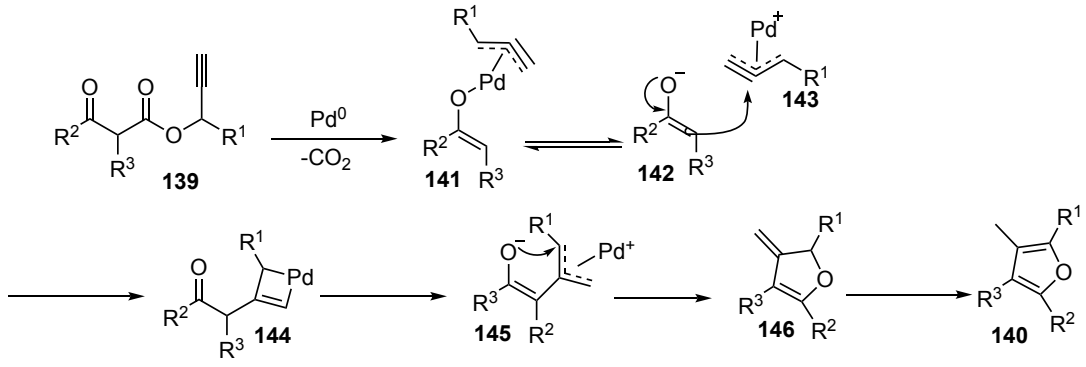
Table 1: Selected examples of decarboxylative propargylation and allenylation of aldehydes.

It was stated previously that, generally, unstabilised enolates would favour addition to the terminal positions of the η^3-π-allenylpalladium(II) intermediate to give either propargylated or allenylated products. However, this is not always the case. Yoshida *et al*. discovered that the analogous decarboxylative process with monosubstituted β-ketoester **139** resulted in nucleophilic addition of an unstabilised ketone enolate to the *central* carbon atom of the η^3-π-allenylpalladium(II) intermediate (Scheme 27).[89]



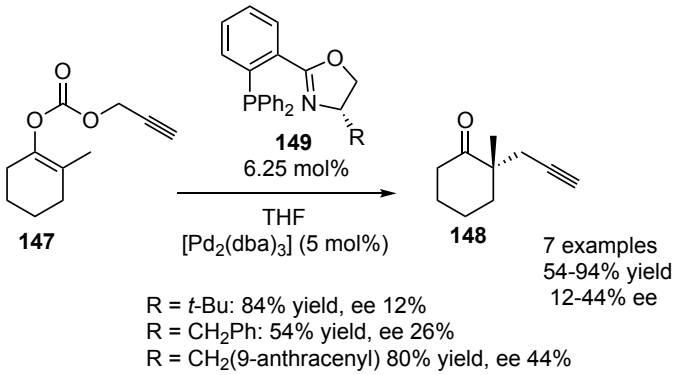
Scheme 27: Synthesis of tetrasubstitutued furans by palladium-catalysed decarboxylative cyclisation of propargyl β-ketoesters.

Upon oxidative addition to **139** and decarboxylation, η^3-π-allenylpalladium(II) intermediate **141** is formed, which may be in equilibrium with its ion pair **142** and **143** (Scheme 28). Nucleophilic attack of the ketone enolate at the central carbon atom of **143**, then leads to η^3-π-allylpalladium(II) intermediate **145** *via* protonation of putative palladacyclobutene **144**. Enolate **145** then undergoes intramolecular *O*-alkylation at the more substituted terminal carbon of the η^3-π-allylpalladium(II) intermediate to form **146** which isomerises to give substituted furan **140** (Scheme 28). Addition does not occur at the less-hindered terminal carbon atom of the η^3-π-allylpalladium(II), in contrast to the expected reaction pathway, whereby the allylic alkylation of the nucleophile takes place at the less hindered end of the unsymmetrical η^3-π-allylpalladium(II) intermediate.[85] This work demonstrates that the regioselectivity of enolate addition to the η^3-π-allenylpalladium(II) intermediate may not always be easily predicted, and it is shown later how different factors can affect the outcome as to what end of the the unsymmetrical η^3-π-allylpalladium(II) intermediate the nucleophile can add onto during the allylic alkylation step (*vide supra*, Scheme 34).



Scheme 28: Synthesis of tetrasubstitutued furans by the palladium-catalysed decarboxylative cyclisation of propargyl β-ketoesters.

It was only in 2011 that Stoltz devised the first asymmetric palladium-catalysed decarboxylative propargylation of ketone enolates (Scheme 29).[90] The reaction yielded ketone products **148** from **147**, albeit with moderate levels of enantioselectivity, despite the variation of the side-chain in ligand **149**. The reaction is significant as is renders a highly congested all-carbon quaternary centre in an enantio-enriched form.

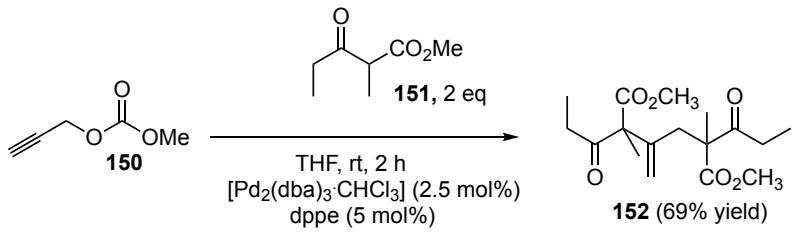


Scheme 29: Stoltz's asymmetric decarboxylative propargylation.

5.4. The Coupling of Soft Nucleophiles and Propargylic Electrophiles

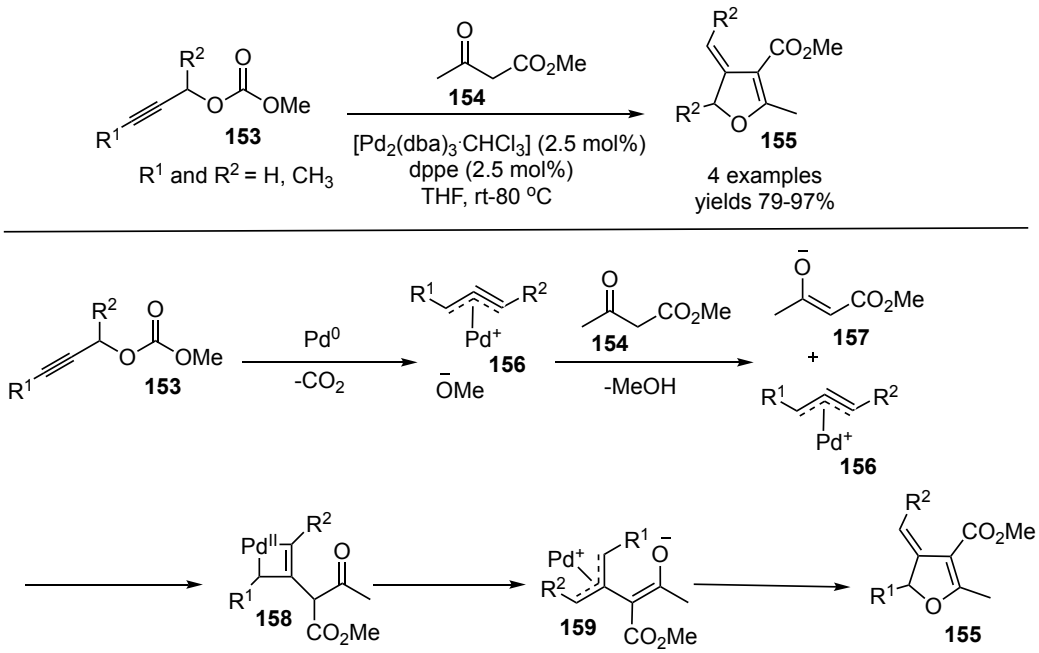
The examples discussed so far have focused on the reactivity of unstabilised enolates in, with some exceptions, decarboxylative propargylation and allenylation processes. In contrast, when a stabilised enolate is used as the nucleophile, the mechanism described in Scheme 28 is likely to be dominant, in which double nucleophilic addition, one at the central carbon atom and one at the terminal position of the propargylic electrophile, takes place (*vide supra*, Scheme 24). A few examples of the reactivity of propargylic electrophiles with soft nucleophiles in a direct manner, rather than a decarboxylative manner, are discussed next.

In 1985, Tsuji described a reaction of propargyl carbonate **150** with two equivalents of substituted β-ketoester **151** to form **152**. As the two nucleophiles are the same, there are no selectivity issues. This process enabled the formation of two new C–C bonds as well as the installation of two all-carbon quaternary centres (Scheme 30).[91] In this process, intramolecular cyclisation is not possible due to the formation of an all-carbon quaternary centre. As a consequence, two equivalents of β-ketoester **151** are required.



Scheme 30: Tsuji reaction scheme involving two equivalents of a soft nucleophile.

As well as performing a cross-coupling reaction using a stabilised enolate to form two C–C bonds in a single process, Tsuji reported a cyclisation process of propargyl carbonates **153** with methyl acetoacetate **154** to afford dihydrofurans **155**, in which a C–C and a C–O bond were created (Scheme 31).[91]



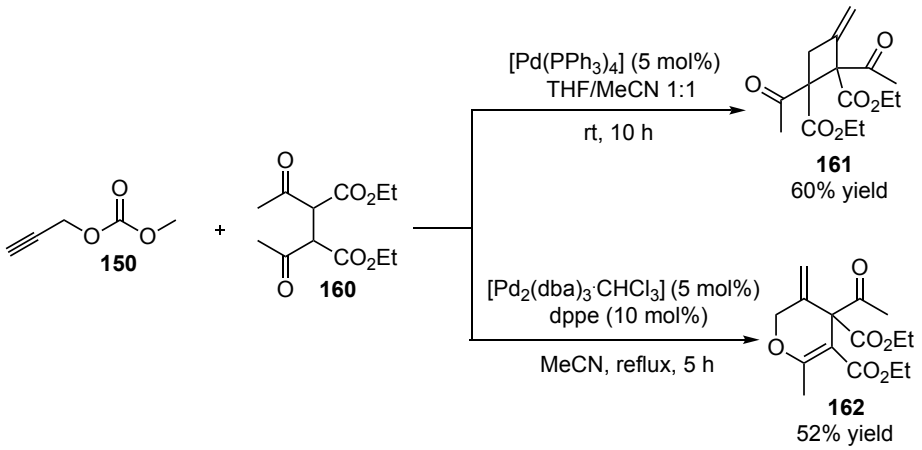
Scheme 31: Mechanism for the creation of a furan ring *via O*-alkylation.

The authors proposed a mechanism in which the palladium catalyst oxidatively adds to propargyl carbonate **153** to form η^3-π-allenylpalladium(II) unit **156** *via* decarboxylation. The methoxide anion thus formed deprotonates methyl acetoacetate **154** to form stabilised enolate **157**, which attacks η^3-π-allenylpalladium(II) intermediate **156** at the central carbon atom to generate palladacyclobutene **158**. Protonation of palladacyclobutene **158** forms enolate **159**. In the final step, intramolecular *O*-alkylation of the *in situ* generated nucleophile attacks the terminal carbon of the η^3-π-allylpalladium(II) system at

the more hindered end to afford dihydrofuran species **155**. In this reaction, the second nucleophile is revealed by means of deprotonation only after the first nucleophilic addition had taken place, and therefore, there are no issues with selectivity.

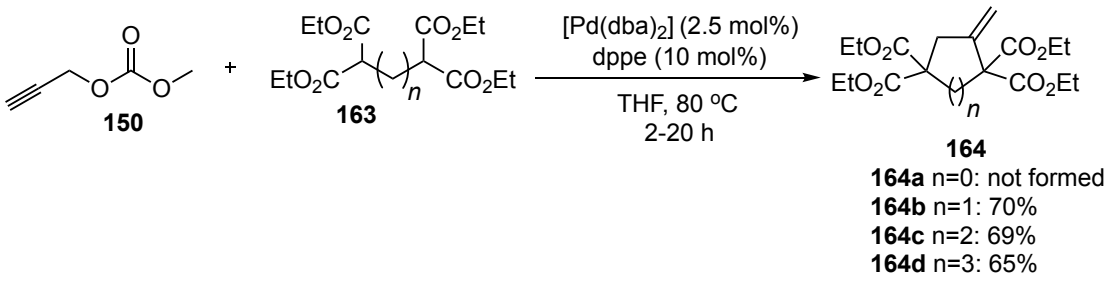
5.5. The Cyclisation of Symmetrical Bis-Nucleophiles with Propargylic Electrophiles

Given that soft nucleophiles undergo a double addition process in reactions with propargylic compounds, namely first at the central carbon atom, followed by addition at the terminal carbon atom, new cyclisation reactions emerged in which the two nucleophiles are tethered to a bis-nucleophile. In this context, Geng and Lu demonstrated how cyclic products could be obtained using symmetrical bis-nucleophile **160**, either *via C*-alkylation or *O*-alkylation, which depended on the conditions used (Scheme 32).[92] When a tetrahydrofuran/acetonitrile solvent was used with [$Pd(PPh_3)_4$] as the catalyst at room temperature, propargyl enol carbonate **150** underwent double nucleophilic addition with 2,3-diacetylsuccinate (**160**) to form kinetically controlled product **161**, which is remarkable considering a highly strained 4-membered ring had been generated. In contrast, with dppe as the ligand in refluxing acetonitrile, thermodynamic product **162** was formed *via O*-alkylation.



Scheme 32: Cyclisation with 2,3-diacetylsuccinate.

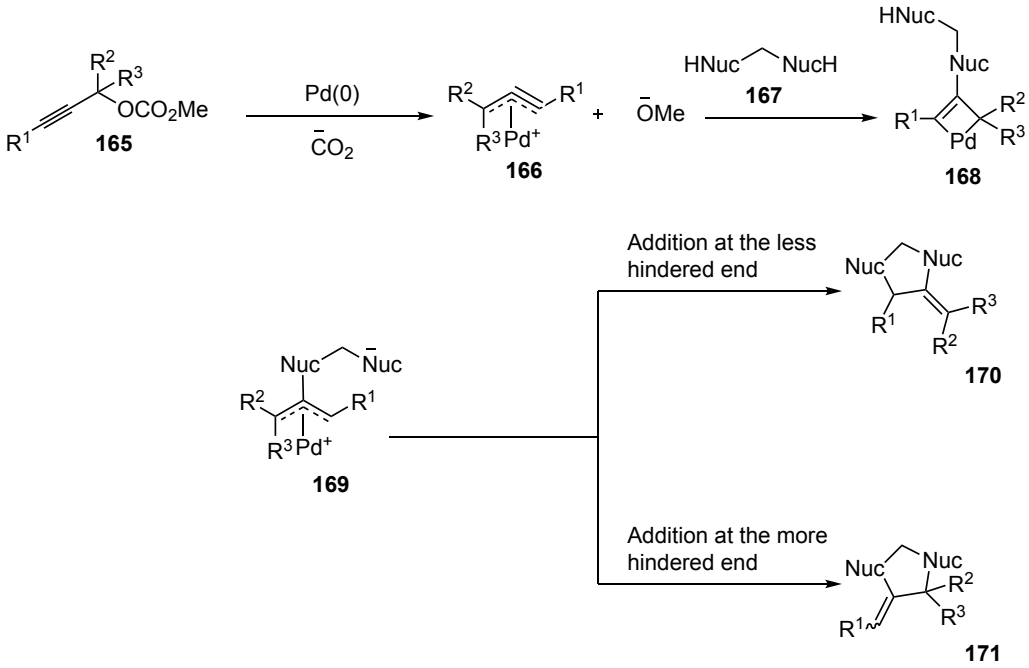
The authors then explored the use of malonate-based symmetrical bis-nucleophiles of type **163** to prevent *O*-alkylation from taking place and thus create carbocycles **164** of varying sizes (Scheme 33).[93] While cyclobutane ring **164a** did not form, more stable 5-7 membered ring products **164b**-**164d** were isolated in good yields. This process created two new C–C bonds and two all-carbon quaternary centres in a single step in **164**.



Scheme 33: Cyclisation with soft carbon bis-nucleophiles.

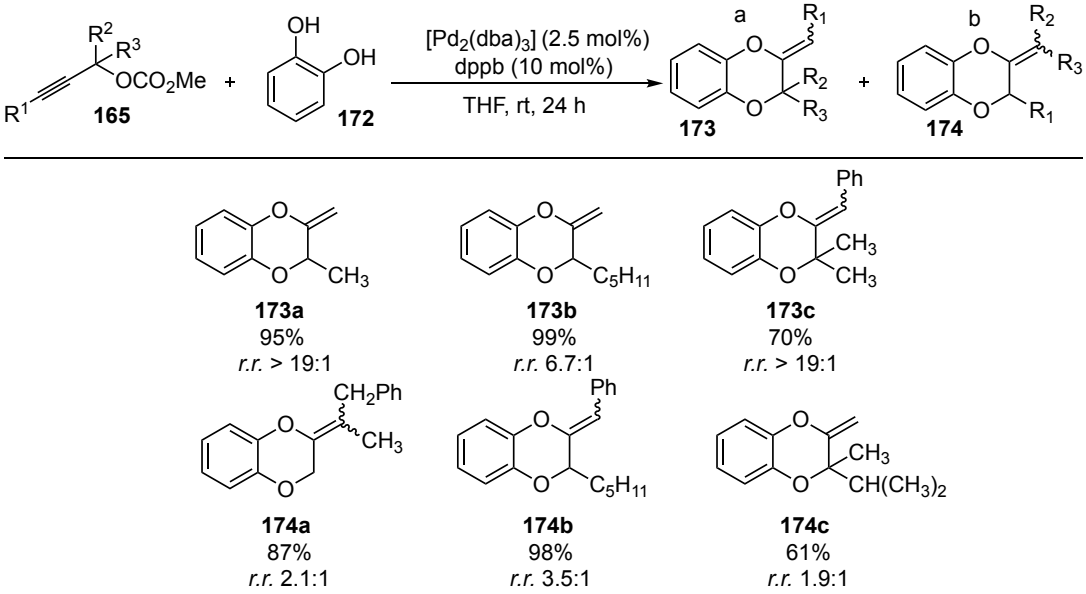
The previous two examples have utilised a simple, unsubstituted propargyl carbonate. However, selectivity issues arise if an unsymmetrical propargylic electrophile **165** is used (Scheme 34). Oxidative addition of palladium(0) to

165 would afford unsymmetrical η^3-π-allenylpalladium(II) intermediate **166** after decarboxylation. Addition of bis-nucleophile **167** to the central carbon atom of **166** would form putative palladacyclobutene **168**, which, after protonation by the second nucleophile, would generate the η^3-π-allylpalladium(II) intermediate **169**. Given that η^3-π-allylpalladium(II) intermediate **169** is no longer symmetrical, two products could potentially form, **170** or **171**, depending on whether the second nucleophilic addition takes place at the less or the more hindered end of the η^3-π-allylpalladium(II) motif.



Scheme 34: The mechanism of the addition of a bis-nucleophile to an unsymmetrical propargylic electrophile.

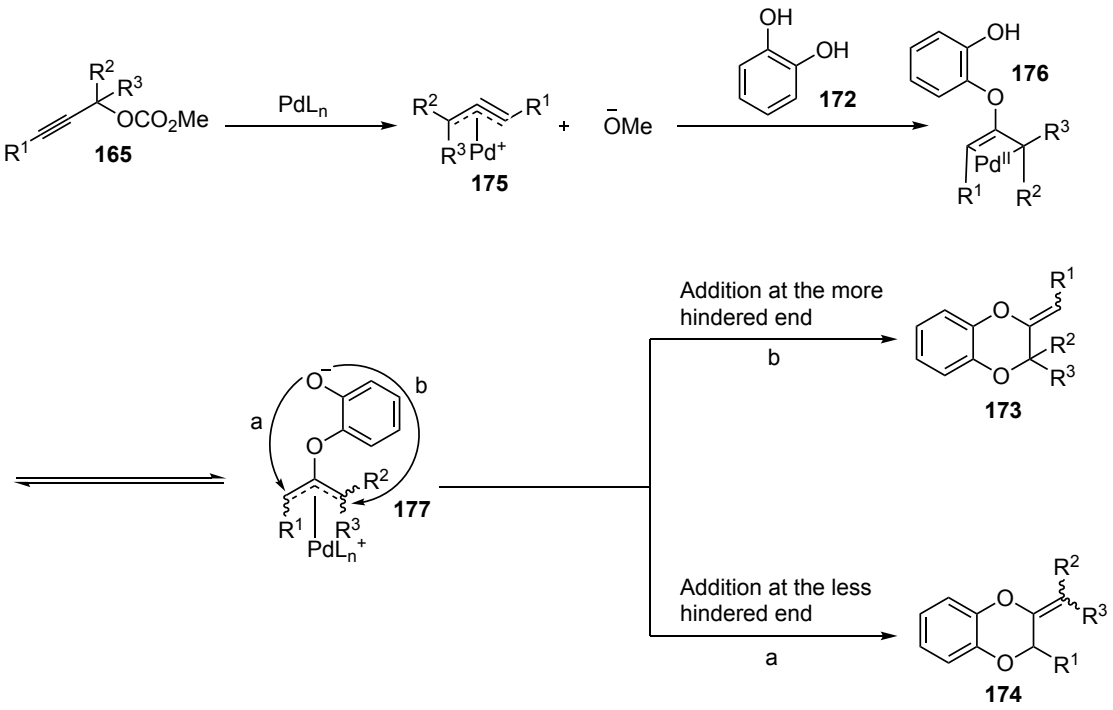
The similarity in acidity of phenols and 1,3-dicarbonyl compounds allowed Sinou and co-workers to explore the coupling of soft catechol bis-nucleophile **172** with an unsymmetrical propargyl enol carbonate **165**, to form either **173** or **174** (Scheme 35).[94]



Scheme 35: The palladium-catalysed synthesis of 2,3-dihydro-2-ylidene-1,4-benzodioxins.

Regarding the mechanism, following formation of η^3-π-propargylpalladium(II) intermediate **175**, catechol **172** adds to the central carbon atom of **175**, eventually forming intermediate **176** (Scheme 38).[94] Deprotonation of catechol **172** preceeds the second oxygen anion addition to either of the terminal carbon atoms of η^3-π-allylpalladium(II) intermediate **177** to form either product **173** or **174**. It was argued that the cationic η^3-π-allylpalladium(II) intermediate species **177** has a partial positive charge lying at the more substituted terminal carbon atom for electronic reasons. This means that the allylic alkylation step is most likely to occur at this position. This is opposite to the general observation that addition to η^3-π-allylpalladium(II) intermediates take place at the less substituted end of the allylic system due to steric effects.[84] Indeed, with smaller substituents, electronic effects dominate resulting in addition at the more hindered end (**173a**-**173c**, pathway b). However, when the substituents are larger, steric hindrance takes over the electronic effects and either addition at the more hindered end of the η^3-π-allylpalladium(II)

intermediate occurs with a lower regioselectivity, or the addition occurs at the less hindered end of the η^3-π-allylpalladium(II) intermediate (**174a**-**174c**, pathway a).

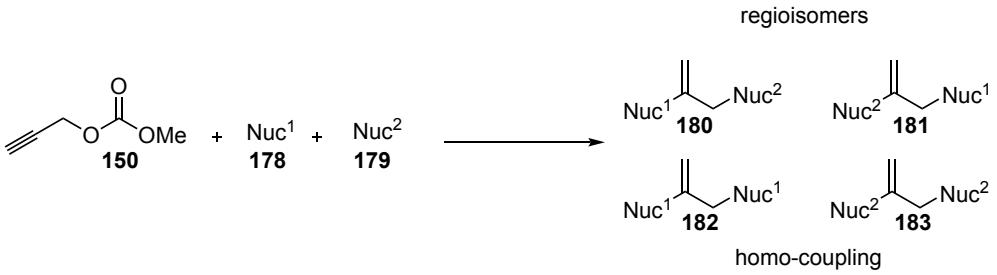


Scheme 36: The proposed mechanism for the palladium-catalysed synthesis of 2,3-dihydro-2-ylidene-1,4-benzodioxins.

5.6. The Control of Selectivity through Cyclisation Reactions of Propargylic Electrophiles with Soft Nucleophiles

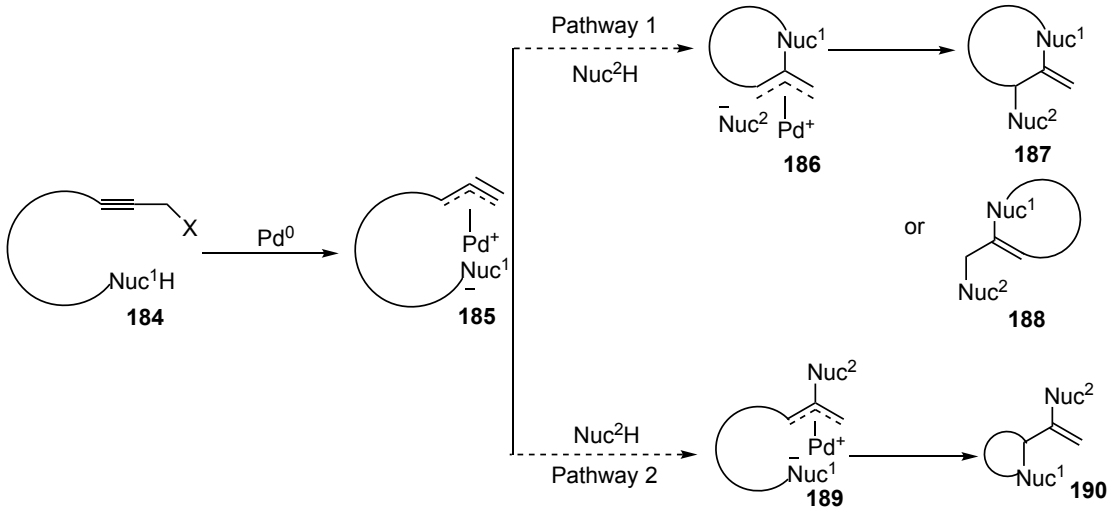
The above palladium-catalysed reactions of propargylic electrophiles with soft nucleophiles utilised symmetrical bis-nucleophiles with either symmetrical or unsymmetric propargylic electrophiles. The utility of this process can be significantly broadened if two different nucleophiles could be employed. However, regio- and chemoselectivity issues arise when reacting propargylic electrophile **150** with two different nucleophiles **178** and **179** (Scheme 37). Firstly, the challenge of regioselectivity must be addressed, whereby the order of addition of the nucleophiles must be controlled, as either products **180** or

181 are possible. Secondly, the homo-coupling of one of the nucleophiles, forming either **182** or **183**, needs to be prevented.



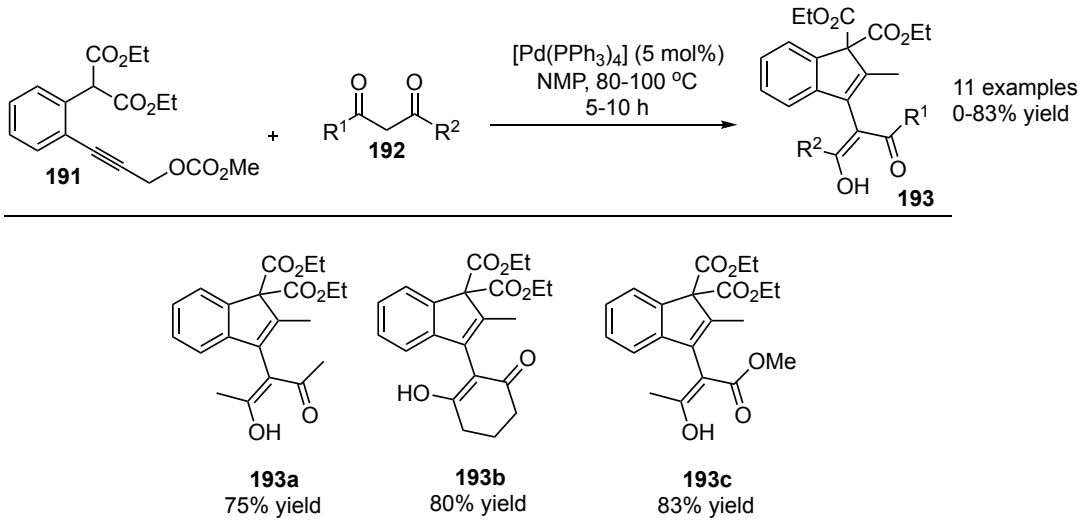
Scheme 37: The control of selectivity in reactions with soft nucleophiles.

One of the strategies to overcome the potential selectivity issues entails the tethering of one of the nucleophiles to the propargylic electrophile (Scheme 38). In this case, following oxidative addition to **184** and decarboxylation, addition of the tethered nucleophile to the central carbon of the η^3-π-allenylpalladium(II) intermediate **185** should be favoured over addition of the untethered nucleophile due to the intramolecular nature of the reaction, which is the entropically favoured addition. The second nucleophile should then add to one of the termini of the η^3-π-allylpalladium(II) complex **186** at the more or the less hindered end to yield product **187** or **188** (Pathway 1). The second pathway in which intermolecular nucleophilic attack occurs prior to intramolecular nucleophilic addition to give **190** *via* intermediate **189** would be less likely for entropic reasons (pathway 2).



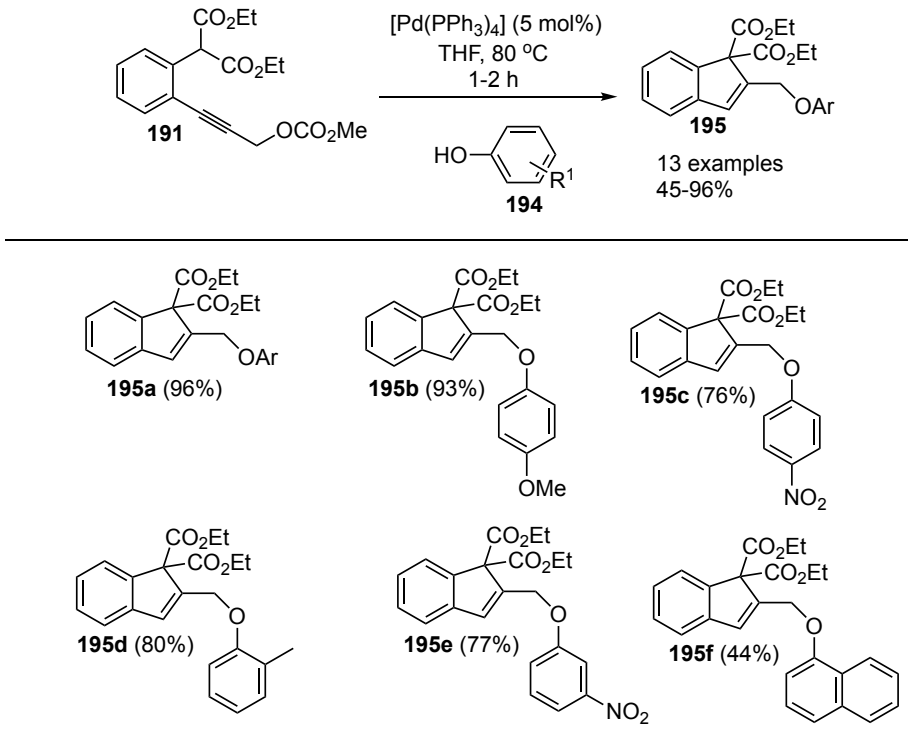
Scheme 38: Controlling the regioselectivity through the use of tethered nucleophiles.

In 2006, Guo and co-workers demonstrated that propargylic carbonates **191** appended with a malonate nucleophile could be coupled to 1,3-dicarbonyl compounds **192** to afford 2,3-disubstituted indenes **193** regioselectively (Scheme 39).[95] In this context, the alkenylation of the tethered diethyl malonate proceeds first due to the intramolecular nature of the reaction and installs an all-carbon quaternary centre in **193**. The intermolecular allylic alkylation of the enolate of **192** then follows, occurring almost exclusively at the more substituted benzylic position of the η^3-π-allylpalladium(II) intermediate due to electronic effects. While 1,3-diketones and β-ketoesters can be successfully used (**193a**-**193c**), malonates did not take part in the desired reaction.



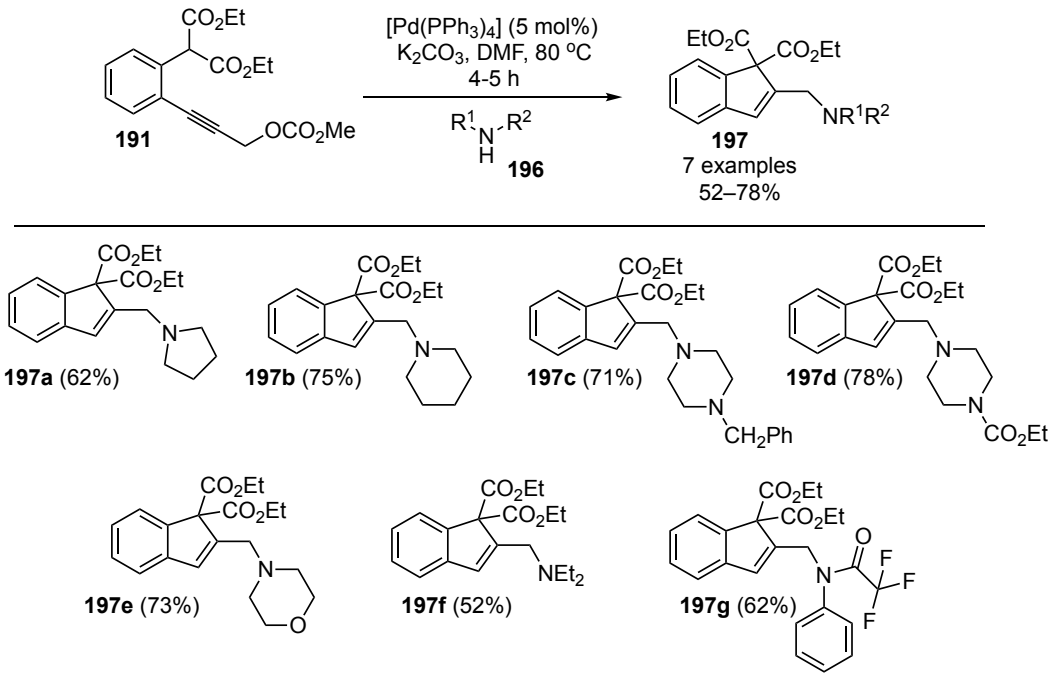
Scheme 39: Palladium-catalysed carboannulation using 1,3-dicarbonyls.

In 2007, Guo expanded the palladium-catalysed carboannulation process by using phenol nucleophiles (Scheme 40).[96] Propargylic electrophile **191** was successfully coupled with phenols **194** to afford products **195** with complete regioselectivity, but in contrast to using 1,3-dicarbonyls as the external nucleophile, the allylic alkylation step took place at the less substituted end of the η^3-π-allylpalladium(II) intermediate. The reaction was found to be amenable to both electron-rich and deficient phenols (**195a**-**195e**), however using α-napthol as the nucleophile dramatically reduced the yield (**195f**).



Scheme 40: Palladium-catalysed carboannulation using phenols.

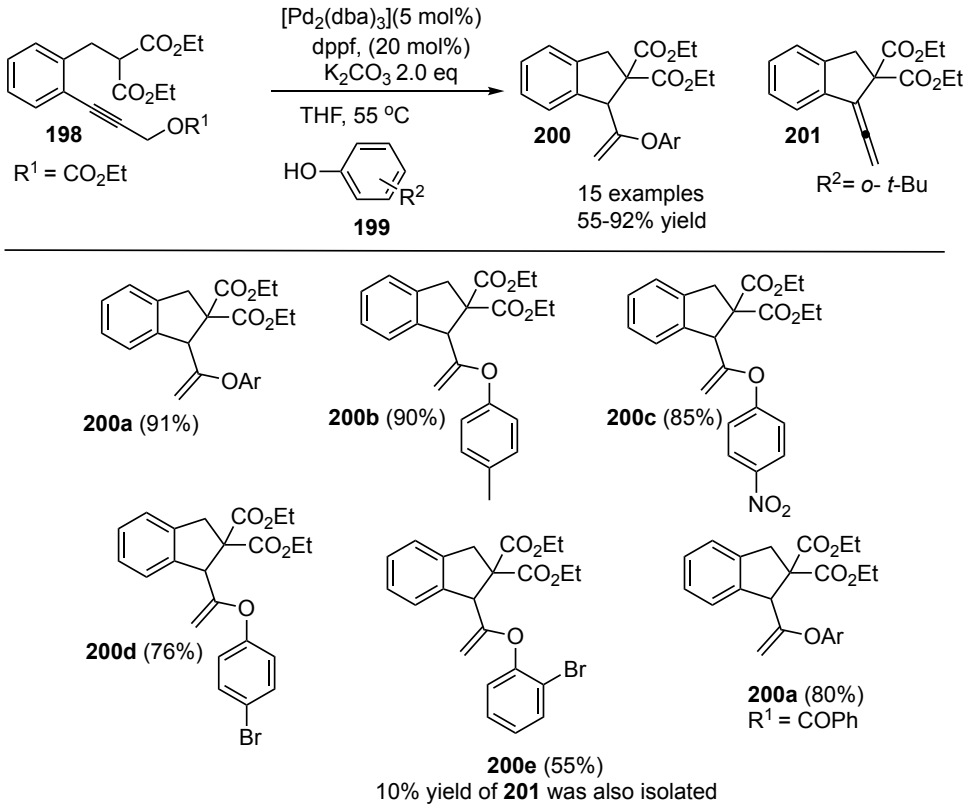
Similarly, the use of amines as the nucleophile gave rise to the desired products with full regiocontrol, in moderate to good yields (Scheme 41).[96] Each of these processes afforded a new all-carbon quaternary centre and two new bonds in **197** in a single step. Various secondary amines (**196**) could react with **191** to give the desired product **197a**-**197g** in moderate to good yields. Aryl secondary amine **196g**, also afforded its corresponding product **197g**, while linear secondary amine **196f** was successfully coupled with **191**, albeit the yield of **197f** was lower.



Scheme 41: Palladium-catalysed carboannulation with nitrogen nucleophiles.

In 2008, Guo published an intriguing report of a reaction between a similar propargylic electrophile **198** and phenols as the external nucleophile, in which the regioselectivity of the reaction had been reversed (Scheme 42).[97] In this case, the intermolecular *O*-alkylation of phenol **199** had occurred before the cyclisation to give product **200**. Most substituents afforded cyclic product **200** in excellent yields, however, when an *o*-^{t}Bu substituted phenol was used, the phenol was not incorporated, presumably due to steric effects, and the tethered nucleophile added to the terminal carbon atom of the η^3-π-allenylpalladium(II) intermediate to form exocyclic allene **201**. The authors postulated that the switch in regioselectivity was owing to the additional carbon atom in the carbon chain of **200**, which would have given rise to a six-membered, rather than a five-membered ring, after intramolecular alkenylation. As five-membered rings are formed faster than six-membered

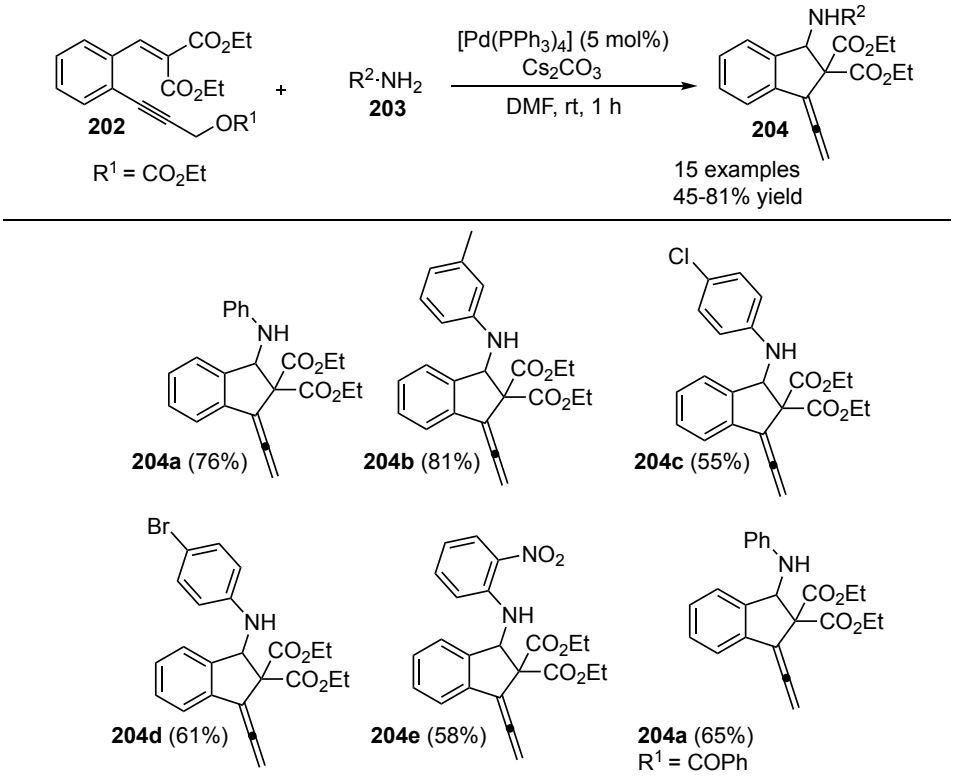
rings, it was suggested that this could be the driving force for the initial addition of the phenol nucleophile, leading to the eventual formation of five-membered ring product **200**. The reaction was successful, with electron-withdrawing and donating groups attached to the phenol ring (**200a**-**200e**), however the yields were lower when the substituent was moved from the *para* to the *ortho* position of the phenol ring (**200e**). Substrate **198b**, containing a phenyl propargyl carbonate, was also investigated and this gave product **200a** with a yield only slightly less than that with the ethyl propargyl carbonate electrophile.



Scheme 42: Reversal of regioselectivity in the cross-coupling of two nucleophiles.

It was also discovered that exocyclic allenes can be formed in moderate to excellent yields in the coupling of amines **203** with α,β-unsaturated malonates

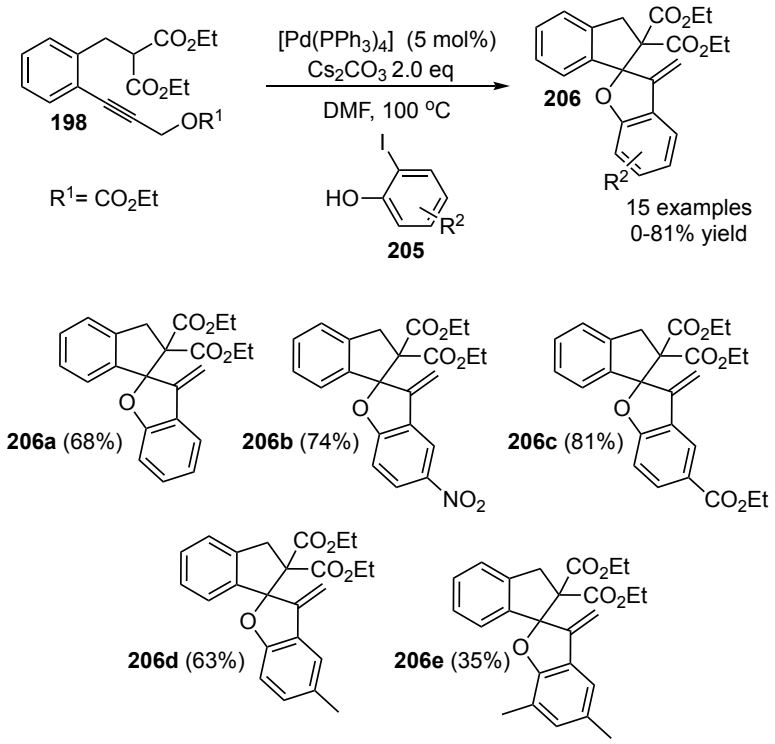
tethered to a propargyl carbonate in **202** (Scheme 43).[98] This was achieved by using a variety of tethered carbonates and amines to afford products **204a-204e** in moderate to excellent yields. In this process, Michael addition of amine **203** to **202** gives rise to an enolate, which undergoes an intramolecular cyclisation to generate allene **204**. As well as a high yield obtained of **204a** with aniline, both electron-withdrawing and donating anilines were successfully incorporated into the products (**204b-204e**). The reactions afforded a new all-carbon quaternary centre, as well as new C–C and C–N bonds in **204**.



Scheme 43: Tandem Michael addition/cyclisation.

Access to exocyclic allenes allowed the Liang group to exploit the reactivity of these products in a tandem double-cyclisation sequence to gain entry to unusual spirocyclic products **206** from **198** in the presence of 2-iodophenols

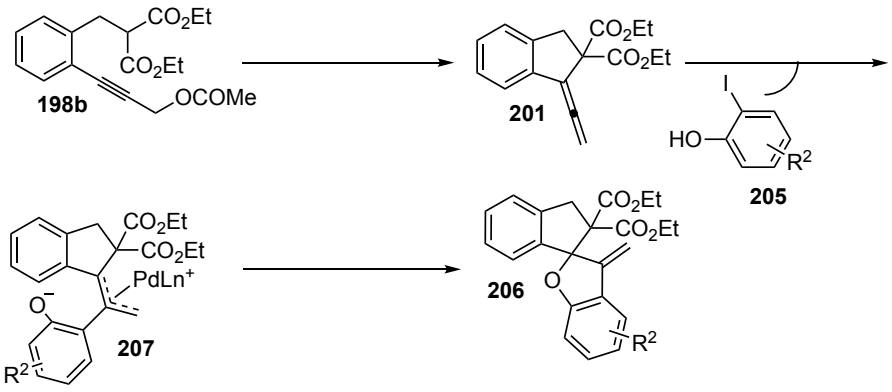
205 (Scheme 44).[99] While a good yield of **206a** was obtained, 2-iodophenols bearing an electron-withdrawing group in the *para* position resulted in an increase in the yield of the reaction (**206b** and **206c**), while electron-donating groups contributed to a decrease in yield (**206d**), a decrease even more substantial when two electron-donating groups were present (**206e**).



Scheme 44: Regioselective spirocyclisation reaction.

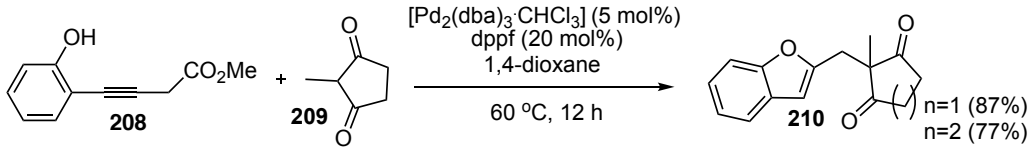
Liang and co-workers proposed a mechanism for the reaction (Scheme 45).[99] Following oxidative addition to propargylic electrophile **198b**, cyclisation forms exocyclic allene **201** as an intermediate. At this stage, oxidative addition of the palladium catalyst to 2-iodophenol **205** is followed by carbopalladation of **201**, giving rise to η^3-π-allylpalladium(II) intermediate **207**. The final cyclisation step at the more hindered end of the η^3-π-allylpalladium(II) electrophile then affords spirocycle **206**. The reaction is significant as during the enolate cyclisation

step, an all-carbon quaternary centre within a complex spirocyclic structure is formed.



Scheme 45: The proposed mechanism for the regioselective spirocyclisation reaction.

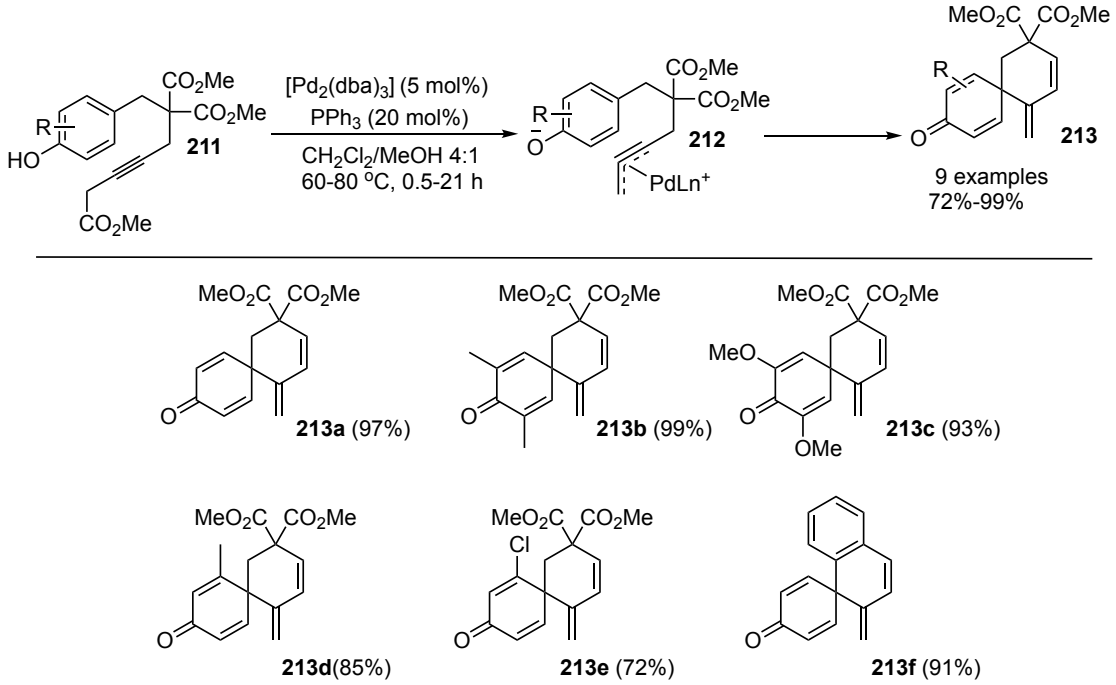
Yoshida *et al*. developed a palladium-catalysed cyclisation reaction of a propargylic carbonate tethered to a phenol (**208**) in the presence of a cyclic 1,3-diketone **209** for the synthesis of benzofurans **210**. In the usual way, the initial intramolecular cyclisation was followed by the regioselective addition of the enolate of diketone **209** at the less hindered site of the η^3-π-allylpalladium(II) intermediate, thus installing an all-carbon quaternary centre in **212** (Scheme 46).[100,101]



Scheme 46: Benzofuran synthesis with 1,3-dicarbonyl nucleophiles.

In 2013, Hamada and co-workers reported the first example of a dearomatisation of a phenol tethered to a propargyl carbonate *via* palladium catalysis (Scheme 47).[102] Starting with phenol **211**, oxidative addition

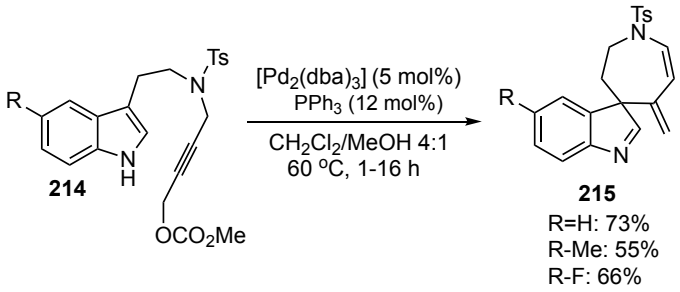
generates η^3-π-propargylpalladium(II) unit in **212**, which undergoes intramolecular spirocyclisation at the central carbon atom of the η^3-π-propargylpalladium(II) unit in **212** with concomitant dearomatisation and formation of an all-carbon quaternary centre. β-Hydride elimination then affords desired product **213**. As well as using phenol, *ortho*- and *meta*-substituted phenol derivatives were also effective substrates for the reaction (**213a**-**213e**), as well as phenyl-containing substrate **211f** which formed the corresponding product **213f** in 91% yield.



Scheme 47: Dearomatisation of phenols.

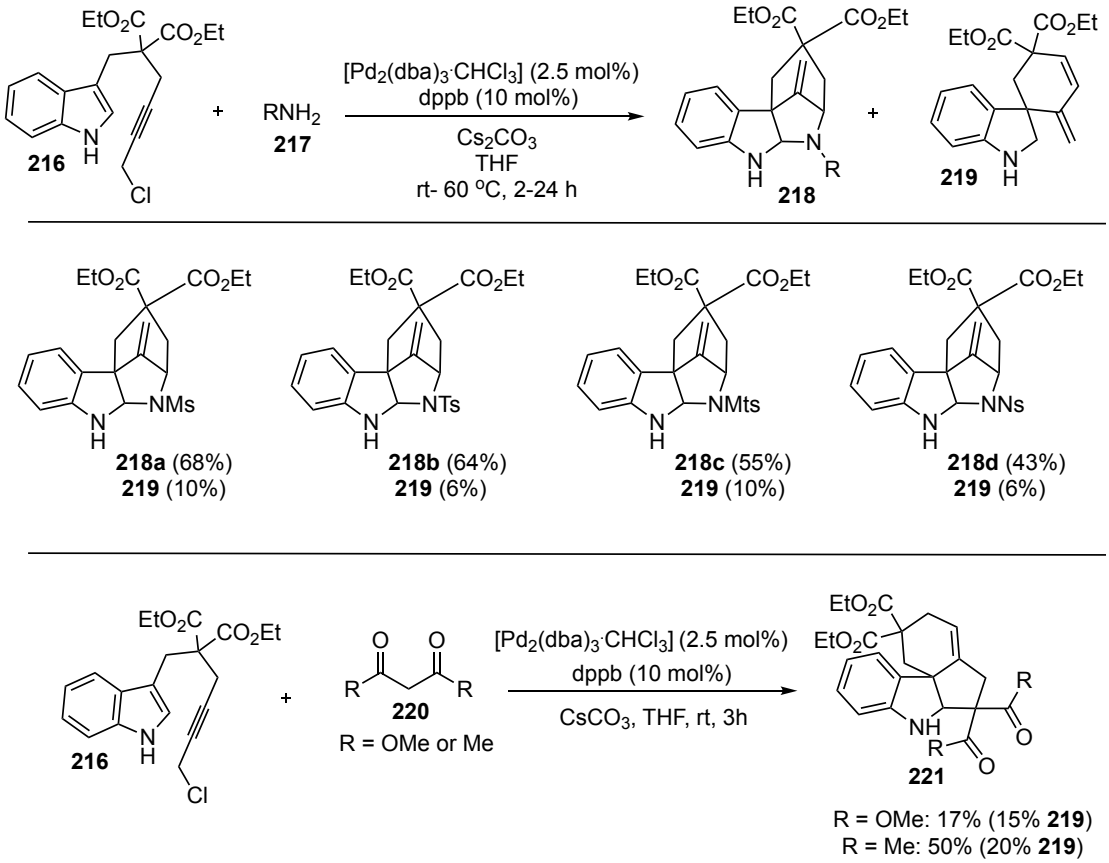
The authors also observed that the same reaction conditions could be applied to the dearomatisation reaction of indoles **214**, installing an all-carbon quaternary centre in spirocyclic indolenine products **215** (Scheme 48).[102] Overall, a range of tryptamines **214** were tested and the desired transformation resulted in the formation of spirocycles **215** in good yields. As

with the dearomatisation of phenols, a spirocyclic all-carbon quaternary centre had been constructed in the process.



Scheme 48: Dearomatisation of indoles.

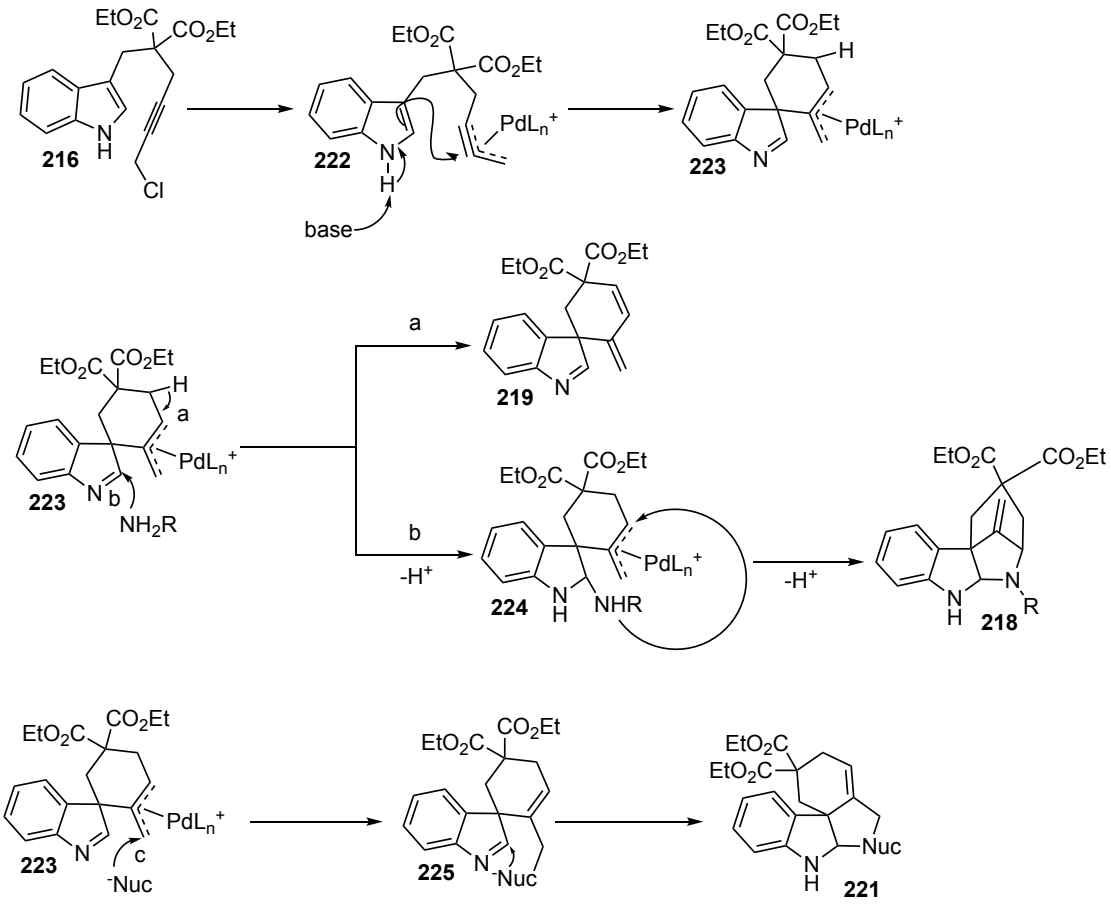
Ohno and co-wokers extended this method by utilising nitrogen and carbon nucleophiles **217** and **220** for the dearomatisation of indoles **216** (Scheme 49).[103] Using dppb as the bidentate phosphine ligand, tetracyclic products **218** were obtained along with a small amount of **219**, which arose from β-hydride elimination *via* the aforementioned pathway without incorporation of the aniline nucleophile. Sulfonamides **217a**-**217d** were generally good, producing **218a**-**218d** in moderate yields, even though a small amount of product **219** was observed in all cases. Benzylamine on the other hand, only gave a moderate yield of the β-hydride elimination product. When dimethyl malonate and acetylacetone nucleophiles **220** were used, product **221** was formed instead. Both products formed at least one new all-carbon quaternary centre.



Scheme 49: Dearomatisation of indoles in the presence of external nucleophiles.

To rationalise the formation of the observed products **218**, **219** and **221**, the authors proposed the following mechanism (Scheme 50). After oxidative addition to **216** and decarboxylation, intermediate **222** is formed. The intramolecular spirocyclisation of the indole functionality then occurs at the central carbon atom of η^3-π-propargylpalladium(II) intermediate **222**, installing an all-carbon quaternary centre in intermediate **223**. At this stage, β-hydride elimination can occur to give rise to **219** (path a). Alternatively, addition of the nitrogen nucleophile to the imine functionality in **223** affords intermediate **224** (path b). The intramolecular nucleophilic attack at the more substituted position of the η^3-π-allylpalladium(II) intermediate forms the second C–N bond in product **218**. In contrast, when dimethyl malonate or acetyl acetone is used

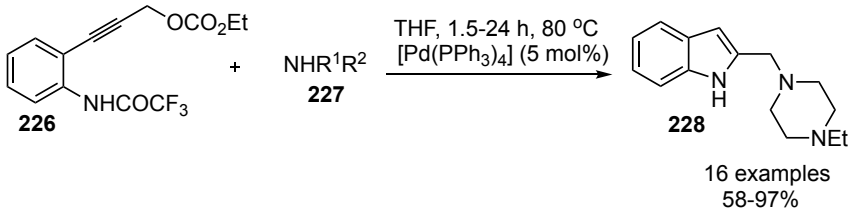
as the nucleophile, addition at the less hindered end of η^3-π-propargylpalladium(II) intermediate **223** is followed by cyclisation to the imine in **225** to form **221**. The authors postulated that owing to the larger steric bulk of the carbon nucleophiles, the neighbouring quaternary spirocyclic centre prohibits the initial attack at the sterically hindered imine carbon.



Scheme 50: Proposed mechanism for the palladium-catalysed dearomatisation of indoles in the presence of external nucleophiles.

The selective coupling of nucleophiles by means of tethering of one of the nucleophiles to the propargylic electrophile is very broad and not limited to the quaternary-centre generating processes. For example, in 2009, Cacchi and co-workers devised a method for the palladium-catalysed synthesis of 2-aminomethylindoles **228**, in which two new C–N bonds were formed (Scheme

51).[104] The process utilised two nitrogen-based nucleophiles, including an amine tethered to the propargylic electrophile in **226** for the intramolecular cyclisation, and an amine **227**, which undergoes the subsequent intermolecular allylic alkylation process to form **228**.

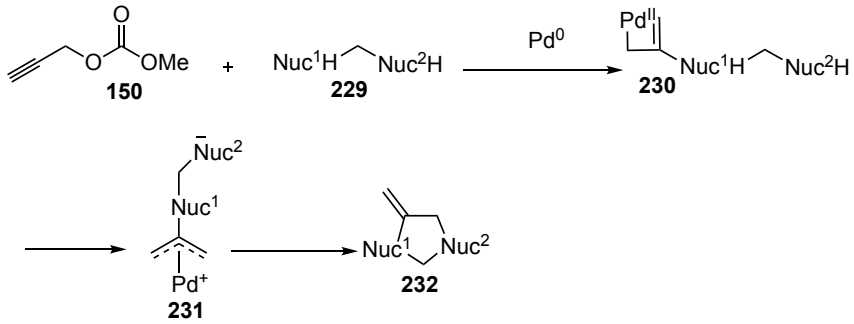


Scheme 51: Palladium-catalysed synthesis of 2-aminomethyl-, 2-vinyl and 2-alkylindoles.

This method has been expanded and applied to the synthesis of a range of novel heterocycles *via* the formation of new carbon-heteroatom bonds using a range of nitrogen based nucleophiles. This includes the synthesis of carbapenam,[105] and 2-oxazolidinones,[106] in which the palladium-catalysed cyclisation enabled the construction of new C–N bonds. Oxygen heterocycles could also be made through the palladium-catalysed cyclisation process, including furan derivatives, creating a new C–O bond.[107] Subsequently, methods using tethered systems that render unsymmetrical η^3-π-allenylpalladium(II) intermediates upon decarboxylation have also been successfully developed, such as that reported by Sinou *et al.,* which yielded a series of unsaturated dihydropyrans using an unsymmetrical propargylic electrophile.[108] Similarly, Cacchi and co-workers devised a method for the synthesis of 2-alkylindoles, which involved a palladium-catalysed cyclisation with an unsymmetrical propargylic electrophile, generating a new C–N bond in the process.[109]

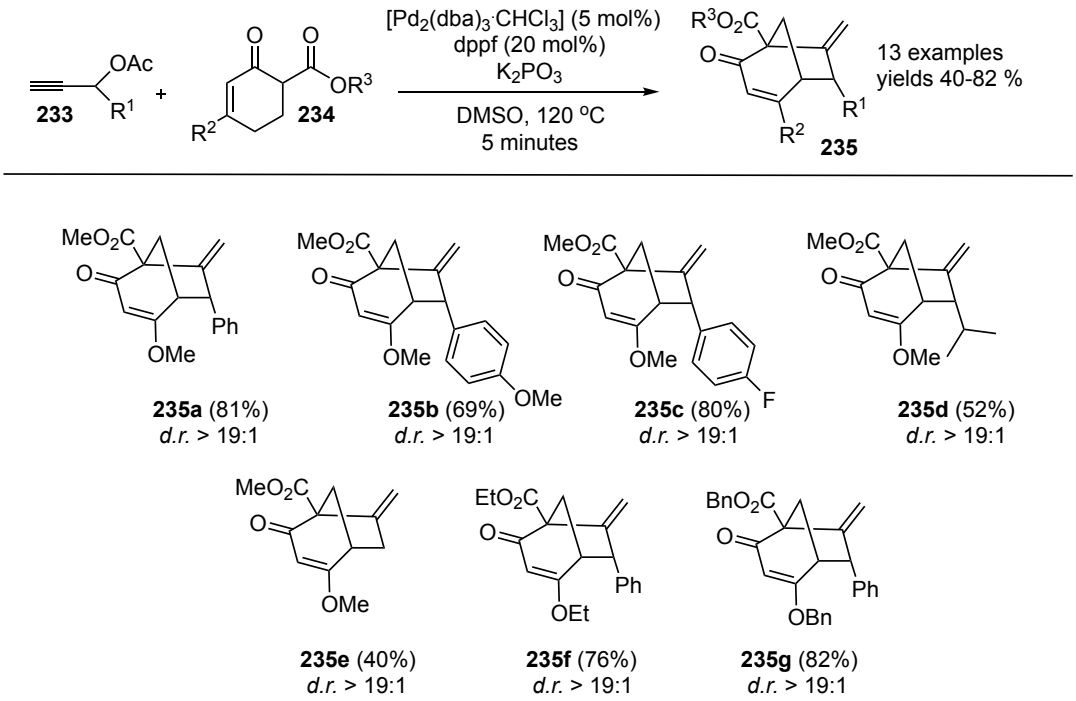
5.7. The Control of Selectivity through Cyclisation Reactions of Tethered Bis-Nucleophiles with Propargylic Electrophiles

The above examples concern the tethering of one of the nucleophiles to the propargylic electrophile to control the order of addition by exploiting the typically much faster rate of intramolecular cyclisation. The synthetic tools are effective at assembling novel building blocks *via* the rapid construction of new C–C, C–O and C–N bonds, as well as all-carbon quaternary centres, in a single step. A second widely used strategy to control the regioselectivity of nucleophilic addition is to tether the two nucleophiles, provided that one of the latent nucleophiles can be selectively deprotonated in the presence of the other due to a large difference in acidity (Scheme 52). For example, if Nuc^1H was significantly more acidic than Nuc^2H in bis-nucleophile **229**, then after oxidative addition and decarboxylation of propargylic electrophile **150**, Nuc^1H would be deprotonated by the methoxide anion. The resulting anion should then be more nucleophilic to undergo the first addition to the η^3-π-allenylpalladium(II) intermediate and generate palladacyclobutene **230**. At the same time, if the nucleophile is very acidic and results in the formation of a very stable anion, it may not be nucleophilic enough to undergo the first addition. Therefore, an appropriate balance between acidity and anion nucleophilicity must be achieved for a successful reaction. Subsequent protonation of **230** with Nuc^2H would give rise to the η^3-π-allylpalladium(II) intermediate **231**. The final intramolecular allylic alkylation of the second tethered nucleophile should afford cyclic product **232**.



Scheme 52: Control of selectivity in reactions with soft nucleophiles with unsymmetrical bis-nucleophiles.

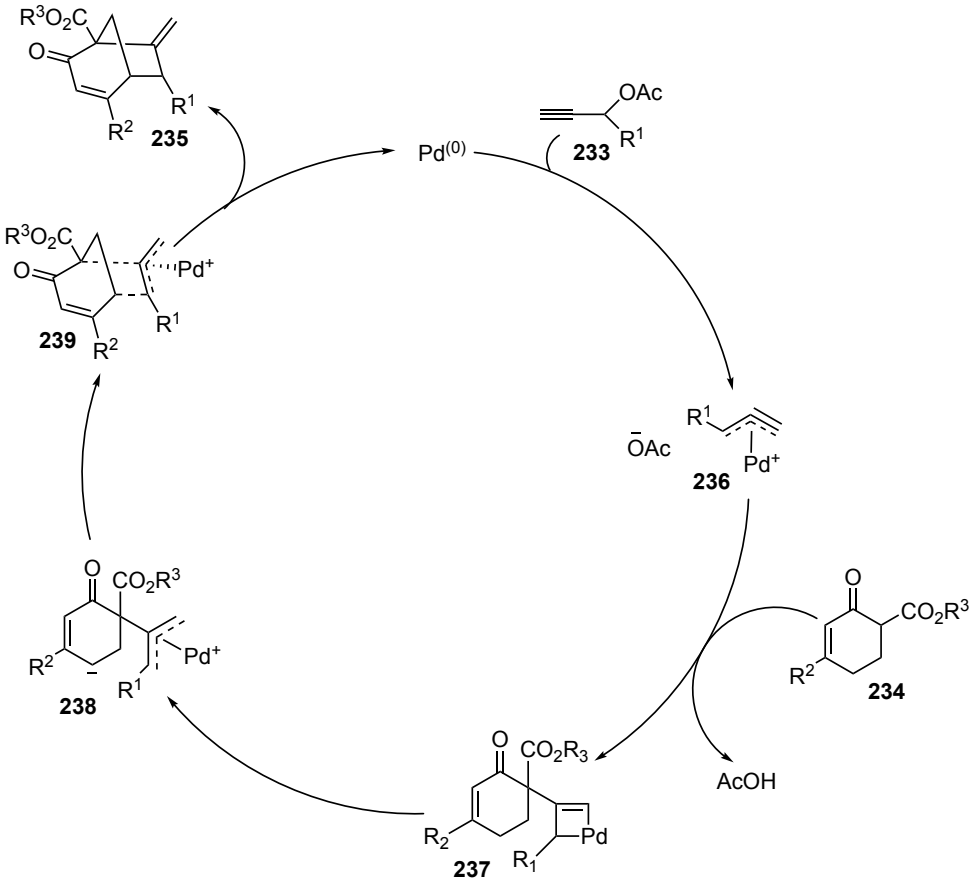
In 2011, Yoshida *et al.* utilised this strategy for the diastereoselective synthesis of bicyclo[3.2.1]octenone **235** from an unsymmetrical enone ester bis-nucleophile **234** in high yields and diastereoselectivity (Scheme 53).[110] 2-Oxocyclohex-3-enecarboxy-late **234** successfully reacted with a range of propargylic acetates **233a**-**233e** to give products **235a**-**235e** in moderate to high yields. Propargylic acetates containing aromatic groups, irrespective of whether they contained electron-withdrawing or donating substituents, gave good yields of product (**235a**-**235c**), while aliphatic propargylic electrophiles gave bicyclo[3.2.1]octenones **235d** and **235e** in poorer yields. Different 2-oxocyclohex-3-enecarboxylates **234** were reacted with **233**, giving good results (**235f** and **235g**), especially when using benzyl-substituted ester **234g**. All the reactions proceed with full diastereoselectivity.



Scheme 53: Diastereoselective synthesis of bicyclo[3.2.1]octenones.

In this process, two new C–C bonds, as well as an all-carbon quaternary centre, had been formed in a single step. In terms of the proposed mechanism of the reaction, the palladium catalyst reacts with propargylic acetate **233** to form η^3-π-allenylpalladium(II) intermediate complex **236** (Scheme 54). The acetate anion deprotonates **234** and the resulting stabilised enolate adds to the central carbon atom of intermediate **236** to form palladacyclobutene **237**. Protonation of palladacyclobutene **237** at the γ-position of the enone then gives rise to extended enolate **238**. Finally, *C*-alkylation of the extended enolate at the more hindered terminal carbon atom of the η^3-π-allylpalladium(II) intermediate, shown by its more favoured transition state **239**, proceeds with high regioselectivity to generate bicyclic product **235**. The observed order of addition is believed to result from the relative difference in

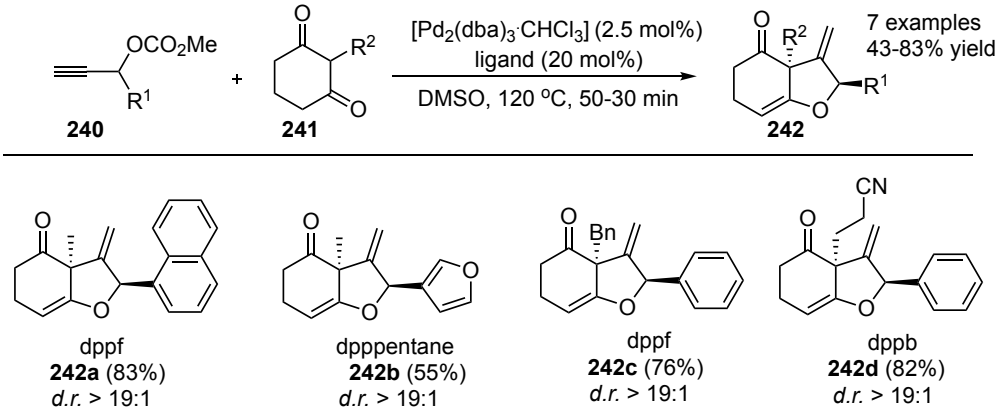
acidity of the two nucleophiles, with the β-ketoester proton being significantly more acidic than that at the γ-position of the enone.



Scheme 54: Mechanism for the diastereoselective synthesis of bicyclo[3.2.1]octenones.

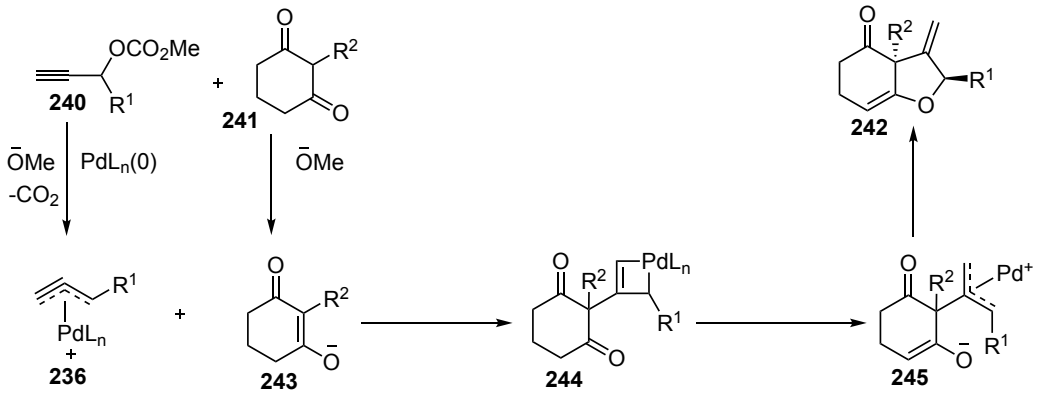
Yoshida *et al.* developed a method for the installation of quaternary carbon centres in the diastereoselective tetrahydrobenzofuranone **242** synthesis (Scheme 55),[111] in which *C*-alkenylation was followed by *O*-alkylation. In this work, a set of propargylic carbonates (**240**) were reacted with dimedone **241** under palladium catalysis to afford bicyclic products **242a-242d** with complete diastereoselectivity and simultaneous construction of an α-stereogenic quaternary all-carbon centre. A propargylic carbonate group with a 1-naphthyl substituent was able to react with 2-methyl-cyclohexane-1,3-dione **241a** to produce **242a** successfully in a high 83% yield. **240** also reacted with furan-

substituted **241b** to give **242b** in a moderate 55% yield. Meanwhile, benzyl- and 2-cyanoethyl-substituted substrates **241c** and **241d** reacted with **240** to deliver products **242c** and **242d** in 76% and 82% yields, respectively. All products were formed with full diastereoselectivity.



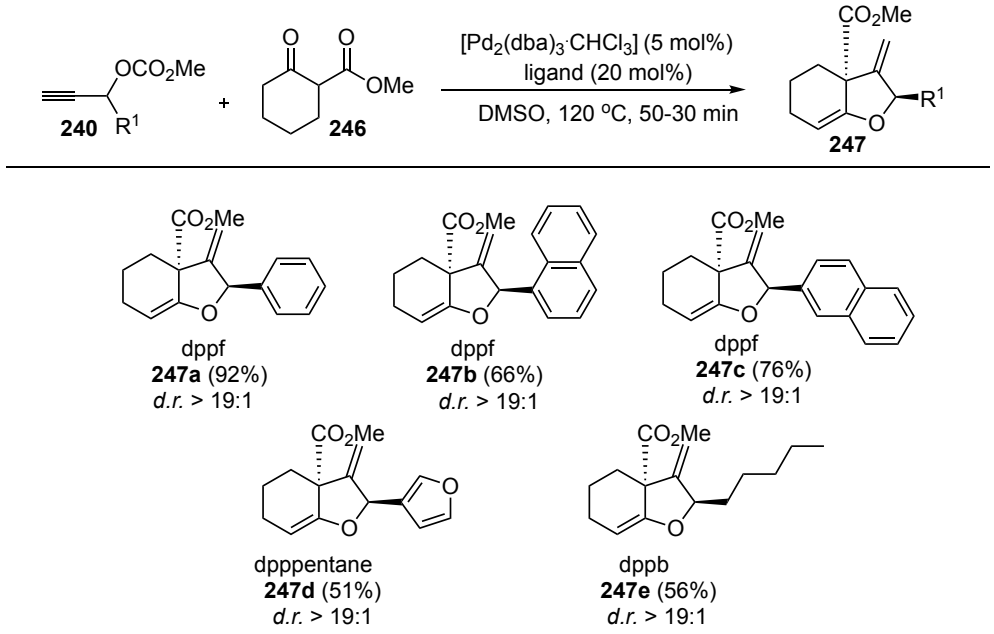
Scheme 55: Diastereoselective tetrahydrobenzofuranone synthesis.

The mechanism of the reaction is similar to that for the synthesis of bicyclo[3.2.1]octenones (Scheme 56). Specifically, the acidic proton of the 1,3-diketone functionality in **241** is removed by the methoxide anion formed upon decarboxylation of **240** to form η^3-π-allenylpalladium(II) intermediate **236** and stabilised enolate **243**. Upon addition of the stabilised enolate to the central carbon atom of the η^3-π-allenylpalladium(II) intermediate, palladacyclobutene **244** is formed. Deprotonation of the ketone then follows to generate enolate **245**, which undergoes intramolecular *O*-alkylation at the more substituted position to afford bicyclic product **242**.



Scheme 56: The mechanism for the diastereoselective tetrahydrobenzofuranone synthesis.

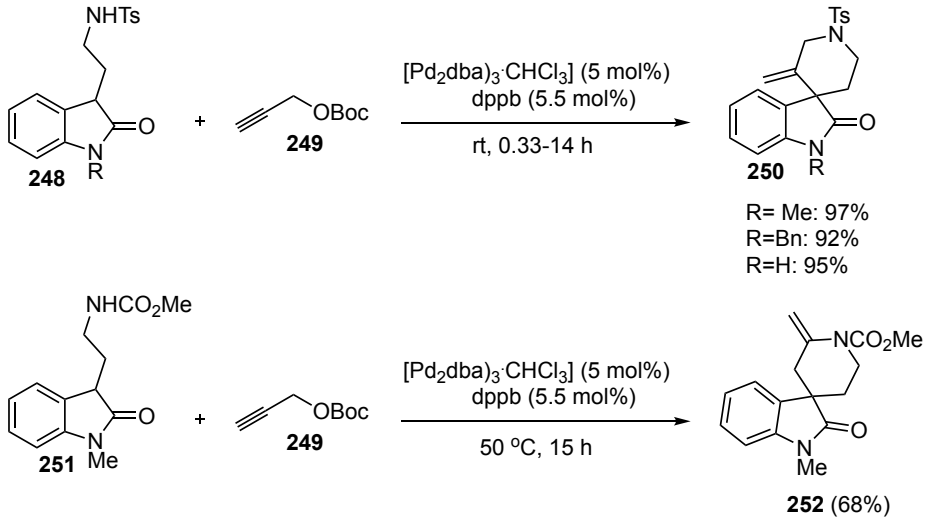
This method was subsequently extended to β-ketoesters **240** as bis-nucleophiles for the synthesis of bicyclic systems **246** with complete diastereoselectivity (Scheme 57).[112] Products **247a**-**247e**, appended with aryl and alkyl substituents, were all readily accessed by this method.



Scheme 57: Diastereoselective cyclisation of β-ketoesters.

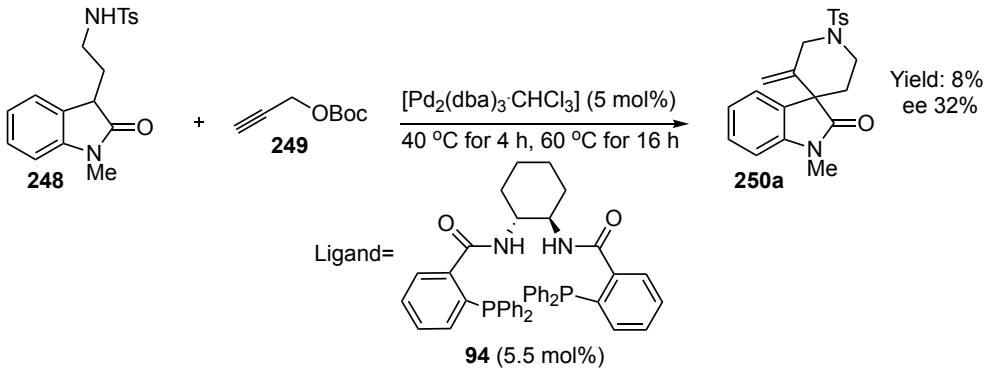
More recently, Rawal and co-workers developed a cyclisation reaction using oxindole substrates tethered to either a sulfonamide or an amide (Scheme

58).[113] Depending on the nature of the amide employed, spiro-oxindole **250**, or its regioisomer **252**, was obtained when reacted with propargylic electrophile **249**. In both cases, an all-carbon quaternary spirocentre had been installed. The authors suggested that the nucleophilicity of the tethered nucleophiles played a significant role in determining which reaction pathway is followed. For example, with a sulfonamide (**248**) as one of the nucleophiles, product **250** was formed, in which the oxindole enolate had undergone the first nucleophilic addition. In this case, it was postulated that although the sulfonamide functionality in **248** is likely to be more acidic, the nitrogen anion thus formed is also less nucleophilic due to the highly electron-withdrawing nature of the sulfonamide functionality. In contrast, product **252** was obtained in the case of tethered amide **251**, which is not as strongly electron-withdrawing, giving rise to a more nucleophilic nitrogen anion upon deprotonation and results in the initial addition of the amide functionality to afford the opposite regioisomer. (**252**).



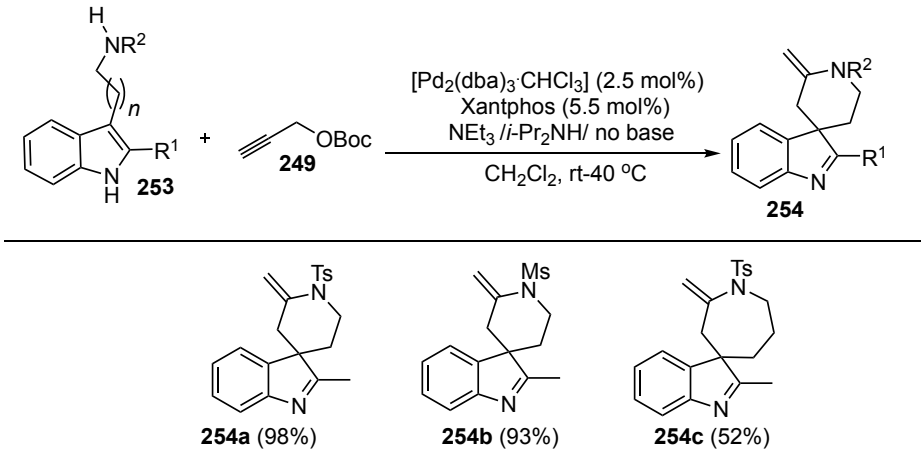
Scheme 58: Cyclisation of oxindole enolates.

Crucially, using a chiral Trost ligand **94**, spiro-oxindole **250a** could be generated enantioselectively (Scheme 59).[113] Although the yield of **250a** was poor and the enantioselectivity moderate, it is the only report to date of an enantioselective palladium-catalysed installation of an all-carbon quaternary centre *via* an alkenylation of a nucleophile with a propargylic electrophile.



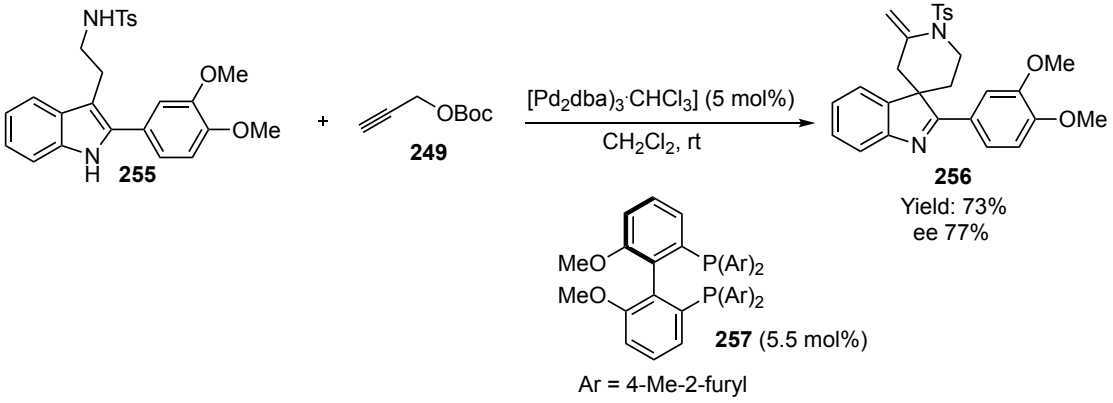
Scheme 59: Enantioselective cyclisation with an oxindole-sulfonamide bis-nucleophile.

The Rawal group extended this work to the dearomatisation of tryptamine derivatives **253** using propargylic electrophile **249** (Scheme 60).[114] After the nitrogen anion of the amine side-chain had undergone the initial attack, spirocyclisation took place to install the all-carbon quaternary centre in **254** with complete regioselectivity. Tosyltryptamine **253a** and methanesulfonamide **253b** performed well, giving products **254a** and **254b**, respectively, in excellent yields. *para*-Toluenesulfonamide **253c**, extended by one carbon atom, gave a significantly lower yield although the regioselectivity was still complete. The high regioselectivity was thought to be due to the high acidity of sulfonamides, yet the sense of selectivity was opposite to that observed with oxindole substrates (*vide supra*, Scheme 58).



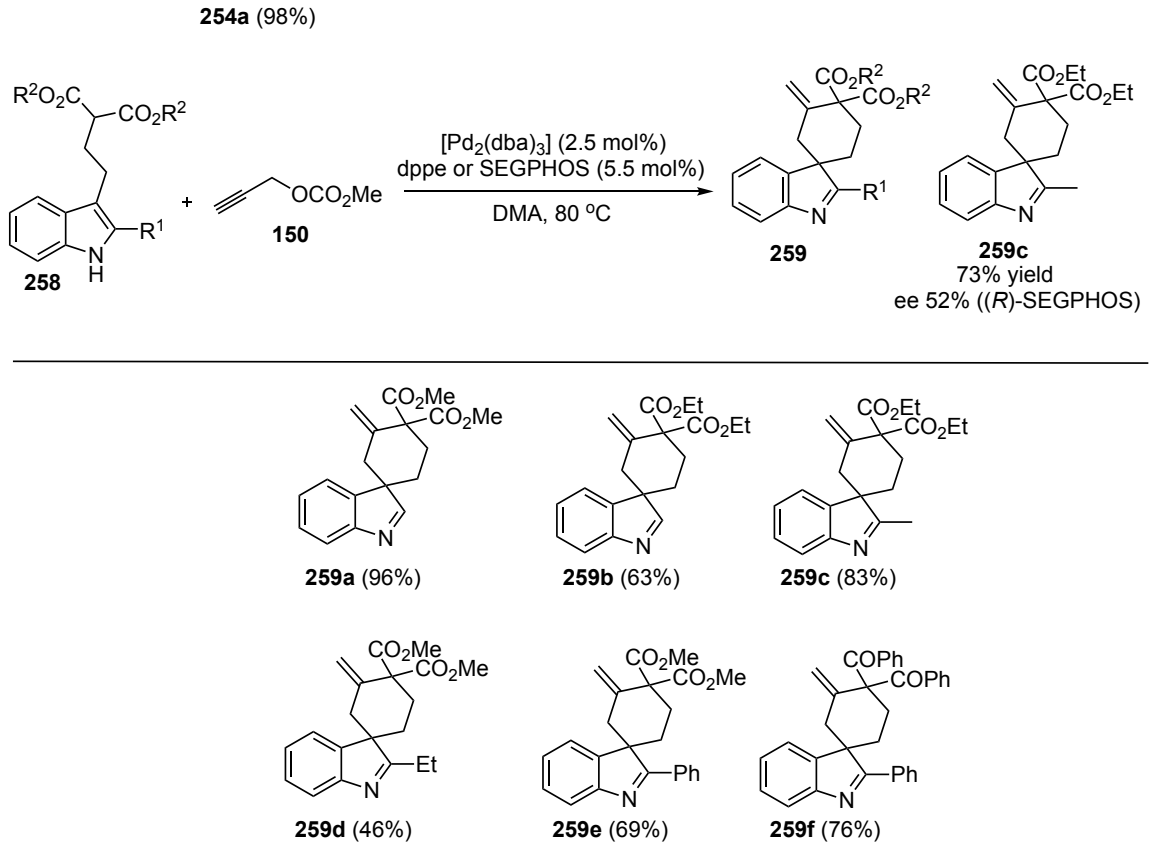
Scheme 60: Dearomatisation of tryptamine derivatives.

The authors also disclosed the use of chiral ligand **257** to install the all-carbon quaternary centre in **256** in an enantioselective manner. Using tryptamine **255** and propargyl carbonate **249**, spirocycle **256** was obtained in a high yield and enantioselectivity (Scheme 61).[113] In contrast to the previous example of a stereogenic all-carbon quaternary centre being formed in **250a** (*vide supra,* Scheme 59), the chiral centre in this case is generated *via* allylic alkylation.



Scheme 61: Investigation of chiral phosphine ligands for the indole spirocyclisation.

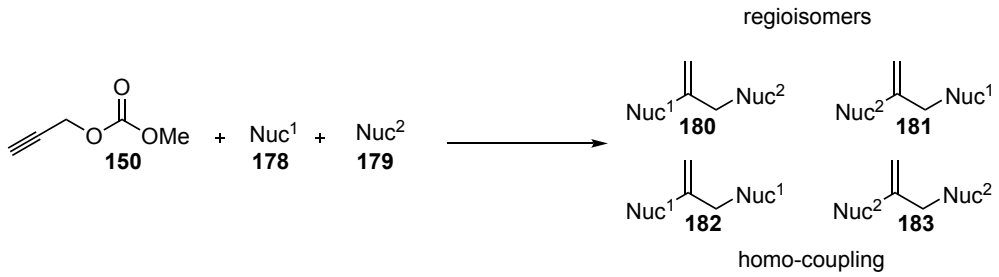
In an analogous process, You and co-workers found that the nitrogen nucleophile can be replaced by a malonate in **258**, giving rise to the installation of an all-carbon quaternary centre in spiroindolenines **259**, through coupling with propargylic electrophile **150,** with high regioselectivity (Scheme 62).[115] The control of the order of addition is derived from the fact that the malonate is a lot more acidic than the NH proton of the indole moiety, resulting in the deprotonation and alkenylation of the malonate functionality. Methyl, and ethyl ester side chains were successfully incorporated in product structures (**259a** and **259b**), and substitution at the 2 position of the indole was also tolerated (**259c**-**259f**). Very importantly, a quaternary all-carbon stereogenic centre in **259c** was installed with an ee of 52% in the allylic alkylation step using (*R*)-SEGPHOS as the ligand.



Scheme 62: Dearomatisation of indoles in the presence of tethered malonates.

5.8. The Coupling of Propargylic Electrophiles with Two Independent Nucleophiles

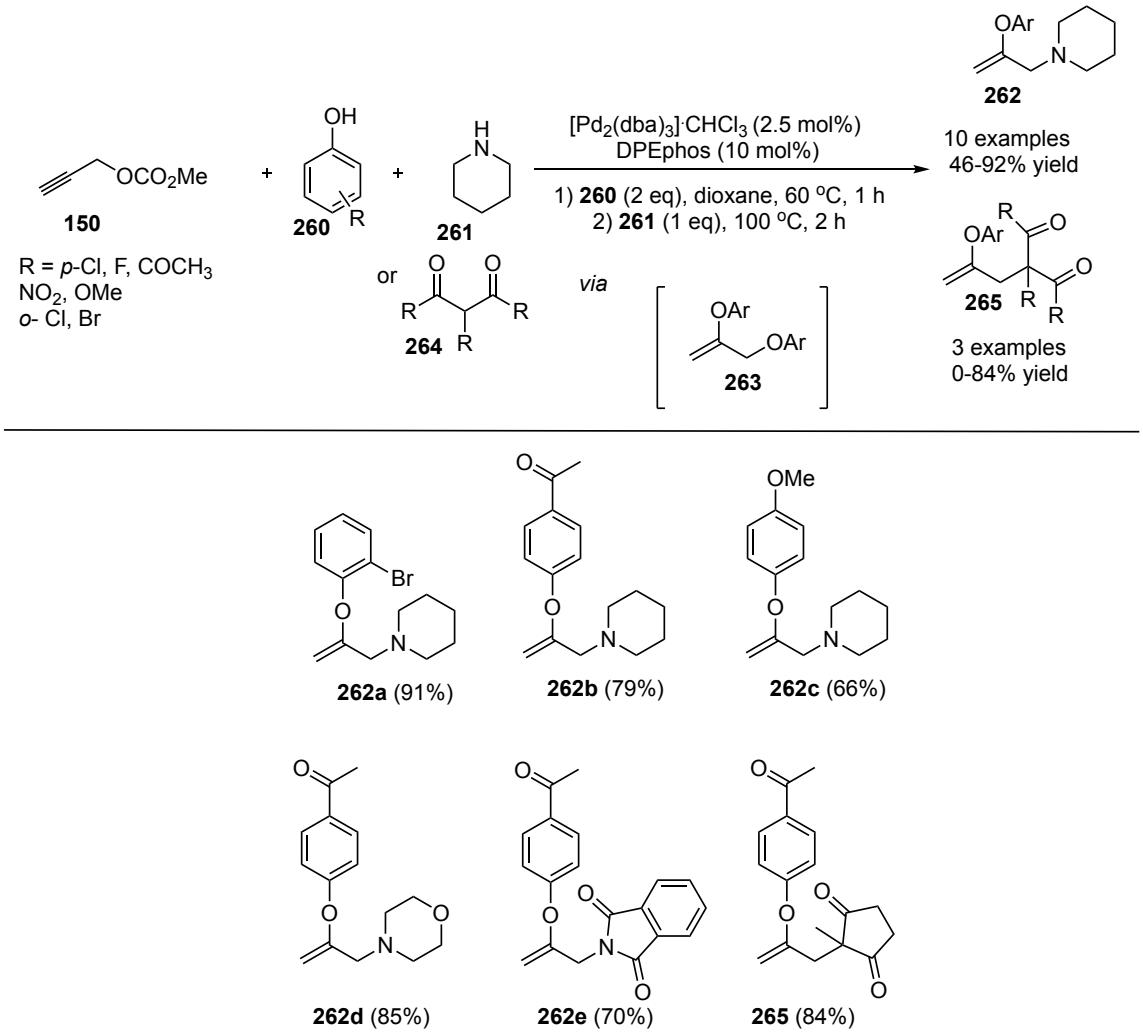
So far, regioselectivity issues have been controlled by using tethering strategies to control the order addition of nucleophiles. However, if two different nucleophiles **178** and **179** were to react in a purely intermolecular sense with propargylic electrophile **150**, the challenges associated with the cross-coupling reaction would be significantly more difficult to overcome. The order of addition of the two nucleophiles has to be controlled to form one regioisomer and not the other (**180** vs **181**), and the homo-coupling of each nucleophile leading to **182** or **183** must be prevented (Scheme 63).



Scheme 63: The control of selectivity with two soft nucleophiles.

In 2011, Nishioka disclosed a report of a palladium-catalysed three component reaction of methyl propargylcarbonate **150** with phenols and other nucleophiles (Scheme 64).[116] It was found that the regioselectivity (*i.e.* the order of addition) could be controlled if the nucleophiles were in a sequential manner rather than in a simultaneous manner. More specifically, after a one hour reaction time, two equivalents of phenol **260** with methyl propargyl carbonate **150**, amine **261** was added, affording products **262a**-**262e** in good yields. The authors postulated that two equivalents of phenol take part in this

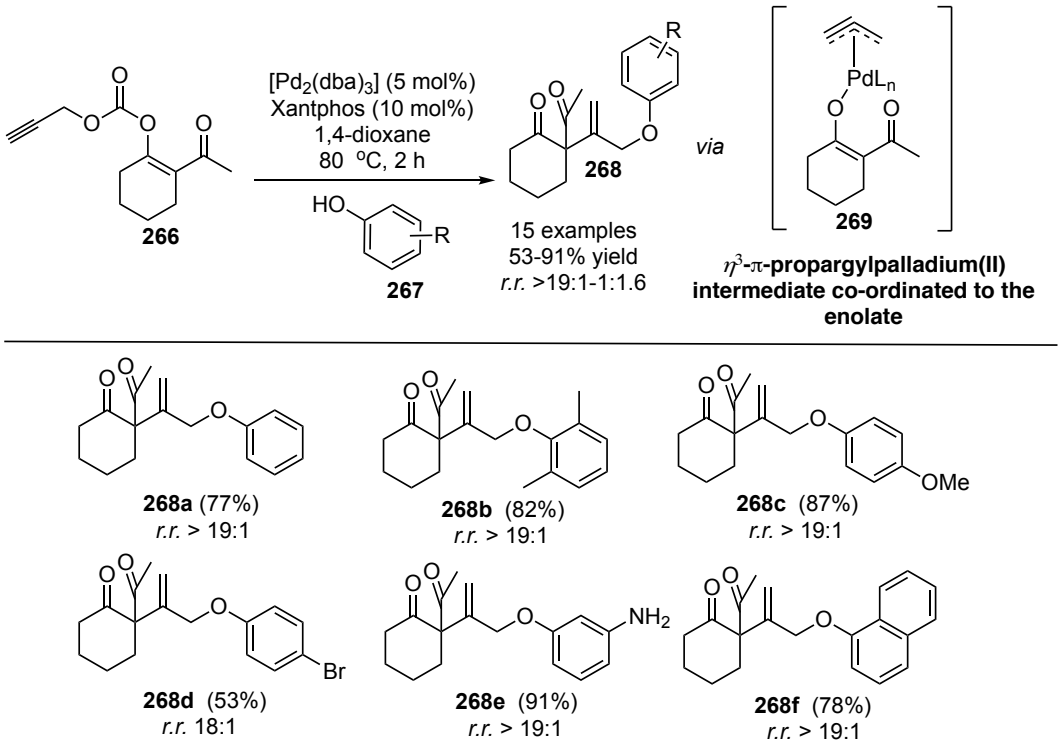
process, giving rise to the phenol homo-coupled product **263** as an intermediate of the reaction in the first instance. At the next stage, addition of piperidine (**261**) results in a palladium-catalysed substitution of phenol to afford the final product **262**. The nitrogen based nucleophile was also replaced with 1,3-dicarbonyl nucleophiles of type **264**, to afford product **265**.



Scheme 64: Selective nucleophile addition for the cross-coupling of two nucleophiles.

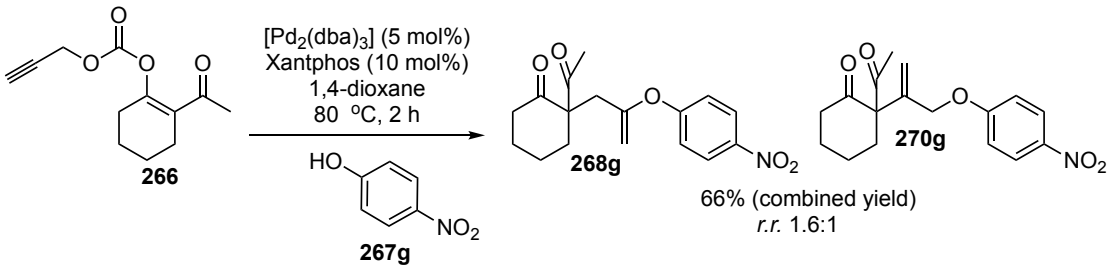
In 2013, our group disclosed the first selective intermolecular coupling reaction of two nucleophiles without the need to control the order of addition or use an excess of one of the coupling partners (Scheme 65).[117] In this process,

propargyl enol carbonates **266**, derived from a 1,3-dicarbonyl, were coupled to a range of phenols (**267a**-**267f**) in a decarboxylative manner to afford products **268a**-**268f** with high regioselectivity in which an all-carbon quaternary centre had been installed. Electron-rich phenols were shown to give products **268b**, **268c** and **268e** in high yields and regioselectivities, while electron-poor phenols were less effective, forming **268d** in a lower yield. Aniline-containing phenol was also effective, forming **268e**, while fused bicyclic phenols, such as naphthol, efficiently afforded product **268f** in a high yield and regioselectivity. It was postulated that the regioselectivity of the reaction was controlled due to the tight association of the η^3-π-allenylpalladium(II) intermediate with the enolate in **266** after the decarboxylation step (**269**). This makes the addition of the enolate to the central carbon of the η^3-π-allenylpalladium(II) intermediate highly favoured due to the essentially intramolecular nature of the process, which is only then followed by the allylic alkylation step of the phenol nucleophile **267**.



Scheme 65: Intermolecular coupling of 1,3-dicarbonyl compounds with phenols.

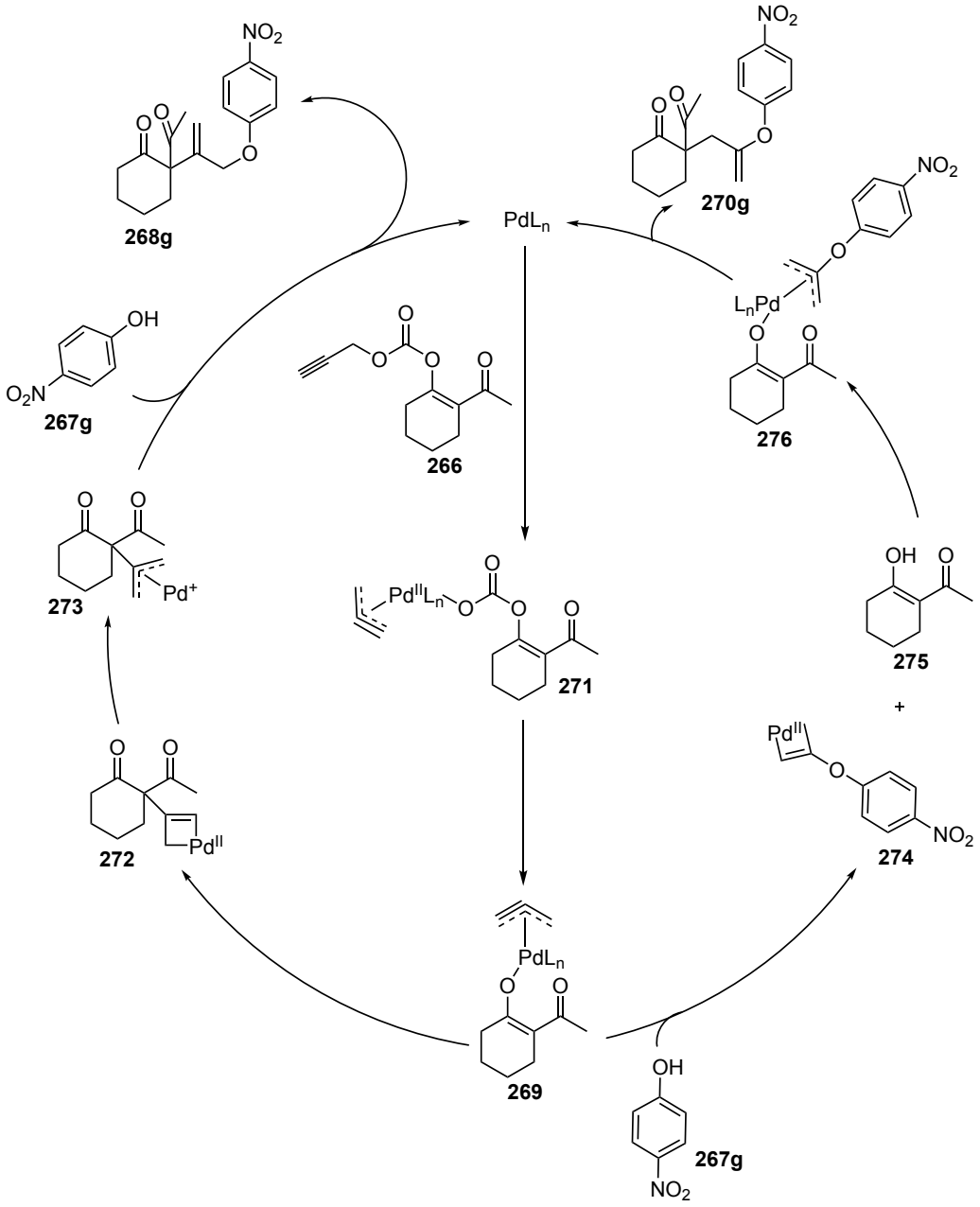
While the reaction was regioselective to form **268** in most cases, the use of an electron-poor, and therefore, more acidic phenol, such as **267g**, resulted in significantly diminished regioselectivity.



Scheme 66: Intermolecular coupling of a 1,3-dicarbonyl compound with an electron-poor phenol.

To explain these observations, the following reaction mechanism was proposed (Scheme 67). The palladium catalyst oxidatively adds to carbonate **266** to provide **271**. Decarboxylation then generates stabilised enolate **269**, which is believed to be associated with the η^3-π-allenylpalladium(II) cation. At

this point, two outcomes are possible. The first pathway, which is taken by the majority of the phenol nucleophiles, involves attack of the enolate at the central carbon atom of the η^3-π-allenylpalladium(II) intermediate to form palladacyclobutene **272**. Subsequent protonation of **272** with phenol **267** and addition of the phenolate anion to the terminal carbon atom of the η^3-π-allylpalladium(II) intermediate **273** gives rise to **268g** with high regiocontrol. regiocontrol. However, in the case of the more acidic *para*-nitro substituted phenol **267g**, protonation of the enolate occurs, resulting in the dissociation of the enol from the η^3-π-allenylpalladium(II) cation in **269**. As a consequence, the η^3-π-allenylpalladium(II) motif is attacked by the resulting phenolate anion to form palladacyclobutene **274**. Subsequent protonation of palladacyclobutene **274** with enol **275** gives rise to η^3-π-allylpalladium(II) intermediate **276**. In the final mechanistic step, allylic alkylation of the enolate affords the opposite regioisomer **270g**.



Scheme 67: Mechanism for the cross-coupling of a 1,3-dicarbonyl compound with a phenol.

This method enables the concomitant formation of C–C and C–O bonds and the creation of a new quaternary all-carbon centre *via* an sp^3-sp^2 coupling reaction. We were, therefore, keen to extend the utility of this reaction process to the coupling of a broader variety of nucleophiles, thus readily incorporating

carbon, oxygen and nitrogen functionality into the reaction, and paving the way to the general synthesis of sp^3-rich building blocks with potential application in drug discovery. The research objectives aimed at expanding this methodology are outlined in the next section.

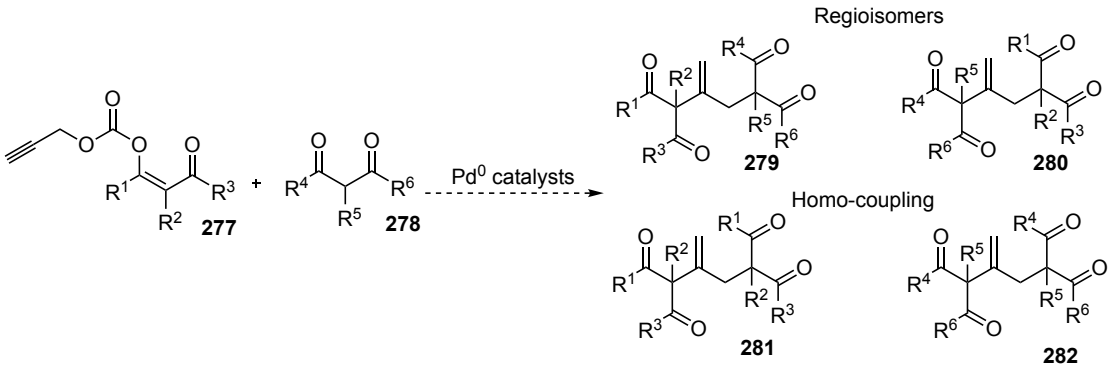
6. Research Project Objectives

This thesis comprises three main areas of study:

1. The development of a palladium-catalysed regio- and chemoselective cross-coupling reaction of enolates in the presence of propargylic electrophiles.
2. The development of an analogous palladium-catalysed regio- and chemoselective cross-coupling reaction of enolates with nitrogen heterocycles in the presence of propargylic electrophiles.
3. The development of enantioselective variants of the palladium-catalysed cross-coupling of nucleophiles in the presence of propargylic electrophiles.

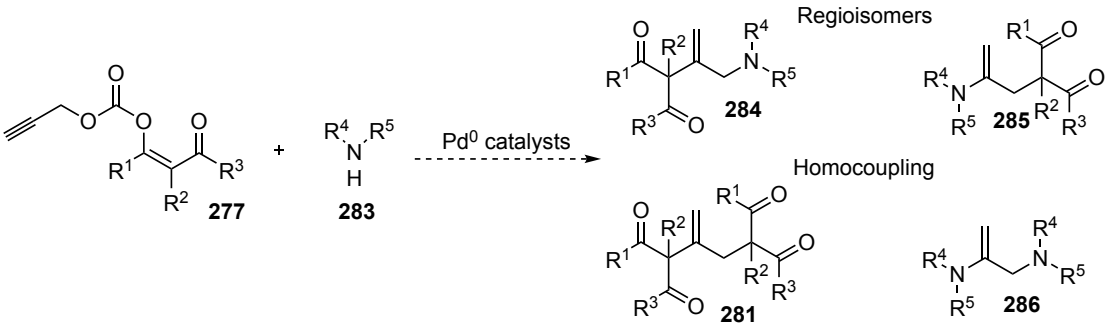
1: In light of the successful regioselective decarboxylative coupling of enolates and phenols with propargylic electrophiles (*vide supra*, Scheme 65),[116] we were interested in applying this approach to the selective coupling of two different *C*-nucleophiles, namely 1,3-dicarbonyls, with propargylic electrophiles in a chemo- and regioselective manner (Scheme 68). This would involve the coupling of an enolate appended to a propargylic electrophile in **277** with 1,3-dicarbonyl based nucleophile **278** to give **279**, whilst preventing the formation of regioisomer **280** and homo-coupled products **281** and **282**. Given the recent drive to develop methodologies that facilitate the synthesis of sp^3-rich molecules for drug discovery programmes,[21] this process would not only result in the formation of two C–C

bonds, but also install two congested all-carbon quaternary centres in **279** in a single operation.



Scheme 68: The proposed palladium-catalysed decarboxylative regio- and chemoselective coupling of two 1,3-dicarbonyl species.

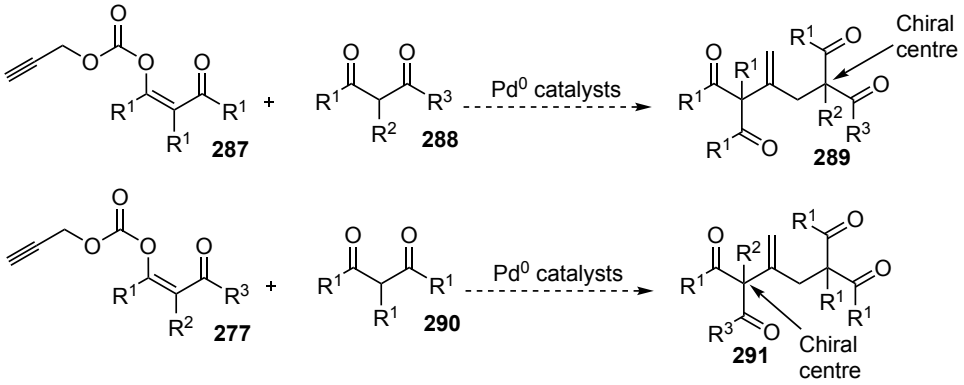
2: The incorporation of nitrogentated molecular motifs is particularly relevant towards increasing the polarity of compounds.[5] Therefore, we reasoned that the successful coupling of 1,3-dicarbonyl-derived nucleophiles with phenols could pave the way to the use of *N*-heterocycles as nucleophiles in place of phenols (Scheme 69). This process could lead to nitrogenated products of type **284** by the coupling of *N*-heterocycles **283** with 1,3-dicarbonyl compounds **277**, yet avoiding the formation of side products **285**, **281** and **286**. This would lead to the installation of new C–C and C–N bonds, as well as an all-carbon quaternary centre. There are, however, clear challenges in such a reaction. Firstly, analogous to the coupling of *C*-nucleophiles, the regio- and chemoselectivity of this process would need to be controlled. In addition, amines are significantly less acidic than phenols, which could exacerbate the aforementioned selectivity issues. If successful, this method would enable the incorporation of nitrogenated functionality products **284.**



Scheme 69: The proposed palladium-catalysed decarboxylative coupling of 1,3-dicarbonyl compounds with *N*-nucleophiles.

3: Finally, having developed catalytic routes to products **279** and **284** in racemic form, our ultimate goal in this research will be the enantioselective catalytic construction of all-carbon quaternary centres in these building blocks. Concerning the cross-coupling of 1,3-dicarbonyl-derived enolates with propargylic electrophiles, we envisage addressing two key areas of enantioselective catalysis (Scheme 70). The first area focuses on the enantioselective allylic alkylation. This approach would necessitate the use of a propargyl enol carbonate derived from an achiral 1,3-dicarbonyl substrate (**287**) in the presence of a non-symmetrical 1,3-dicarbonyl species **288**, which would give rise to enantio-enriched products **289** in the presence of a chiral palladium(0) catalyst. While there have been reports of successful enantioselective allylic alkylation reactions of nucleophiles with propargylic electrophiles in cyclisation processes (*vide supra*, Scheme 61),[115] the asymmetric allylic alkylation using propargylic electrophiles in an intermolecular sense remains unexplored. The second area of stereoselective catalysis we seek to explore is the induction of enantioselectivity at the alkenylation step of the mechanism. This requires the coupling of a prochiral

enol carbonate **277** with an achiral 1,3-dicarbonyl **290** to pave the way to the stereoselective construction of an all-carbon quaternary centre in **291** *via* alkenylation. The enantioselective palladium-catalysed alkenylation of nucleophiles with propargylic compounds has only been precedented in tethered systems, albeit with poor yields and low levels of enantioselectivity (*vide supra*, Scheme 59).[113]



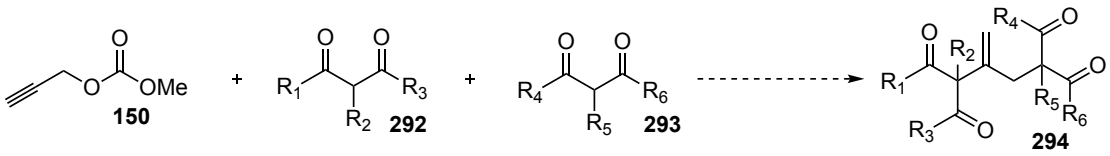
Scheme 70: The proposed enantioselective decarboxylative cross-coupling reactions.

However, all of these processes are likely to pose a number of challenges, since in addition to the induction of stereoselectivity, the simultaneous control of regio- and chemoselectivity, as well as reaction efficiency, will also be required. As such, suitable conditions, which can successfully balance the above control factors, would represent a remarkable achievement. The results from our work towards meeting these preliminary project aims are detailed in the next chapter.

7. Results and Discussion

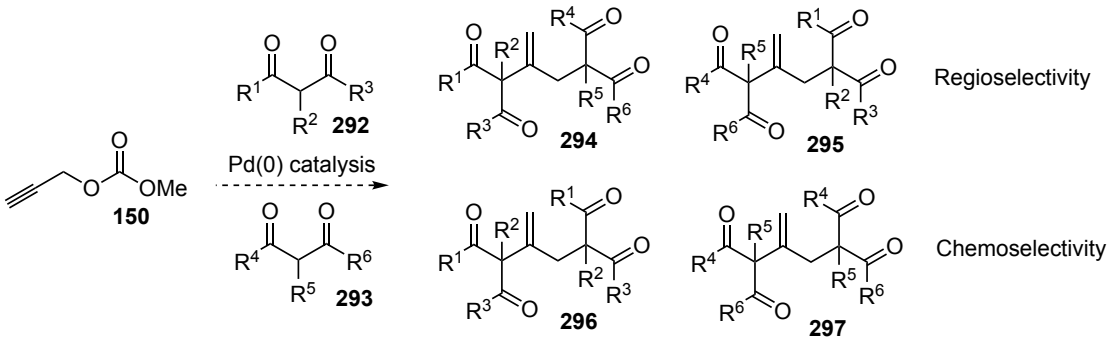
7.1. The Coupling of 1,3-Dicarbonyl Compounds: Initial Results

In the first stage of the project we sought to investigate the purely intermolecular catalytic coupling of 1,3-dicarbonyl substrates **292** and **293** in the presence of a propargylic electrophile **150** (Scheme 71). In such a reaction, two new C–C bonds and two all-carbon quaternary centres in **294** would be formed.



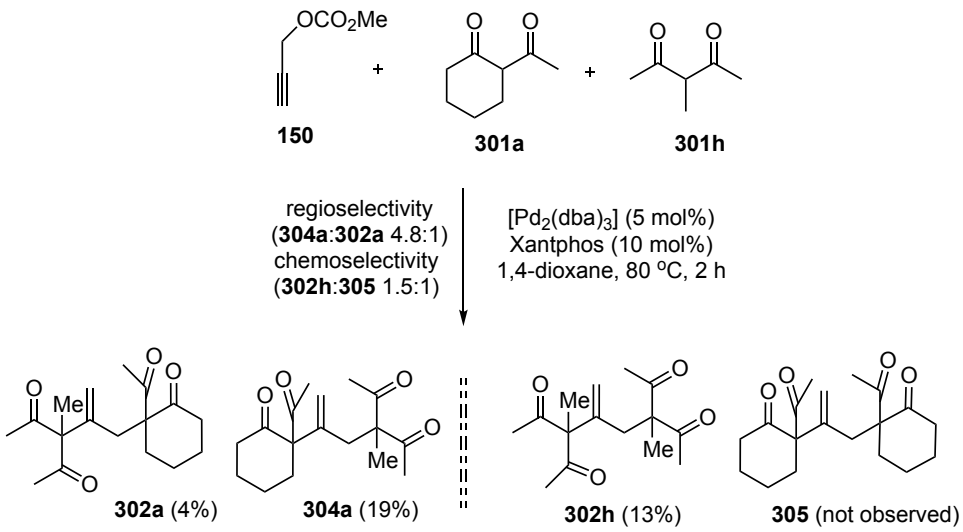
Scheme 71: The cross-coupling of two 1,3-dicarbonyl compounds with a propargyl enol carbonate.

The first challenge associated with the coupling of two soft carbon-based nucleophiles **292** and **293** in an intermolecular fashion was the control of regioselectivity (**294** vs **295**), which dictates the order of addition of nucleophiles (Scheme 72), and chemoselectivity, which could give rise to homo-coupled products **296** or **297**. Our ultimate aim was to develop conditions that could regioselectively create either regioisomer **294** or **295**, as required, whilst simultaneously avoiding any homo-coupling.



Scheme 72: Chemo- and regioselective coupling of enolates and 1,3-dicarbonyl compounds.

To test this idea, an intermolecular coupling reaction of two 1,3-diketone nucleophiles **301a** and **301h** with propargyl carbonate **150** in the presence of a source of Pd(0) and Xantphos as the ligand ligand was investigated (Scheme 73). Given the similarity in both acidity and reactivity of 1,3-diketones **301a** and **301h**, it was not surprising to discover that, out of the four possible products that could have been formed, three were isolated. Specifically, regioisomers **304a** and **302a** were obtained in a 4.8:1 ratio in 19% and 4% yield, respectively, whilst homo-coupled product **302h** was obtained in a 13% yield. This indicated that a purely intermolecular process was low yielding and gave poor control of regio- and chemoselectivity.

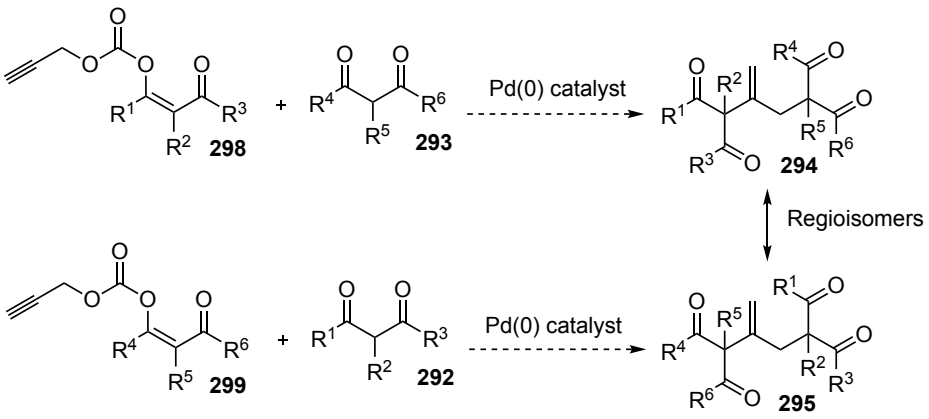


Scheme 73: Selectivity issues with the intermolecular coupling of two carbon-based nucleophiles.

7.1.1. Optimisation of Reaction Conditions

We, therefore, reasoned that higher levels of regio- and chemoselectivity could be bestowed upon the reaction by utilising a propargyl enol carbonate derived from the 1,3-dicarbonyl nucleophile. This has previously been shown to be successful when coupling 1,3-diketones **266** with phenols **267** to form products of type **268** (*vide supra,* Scheme 65).[117] It is believed that the reason behind the observed high levels of selectivity is due to the palladium catalyst being associated with the enolate following decarboxylation.

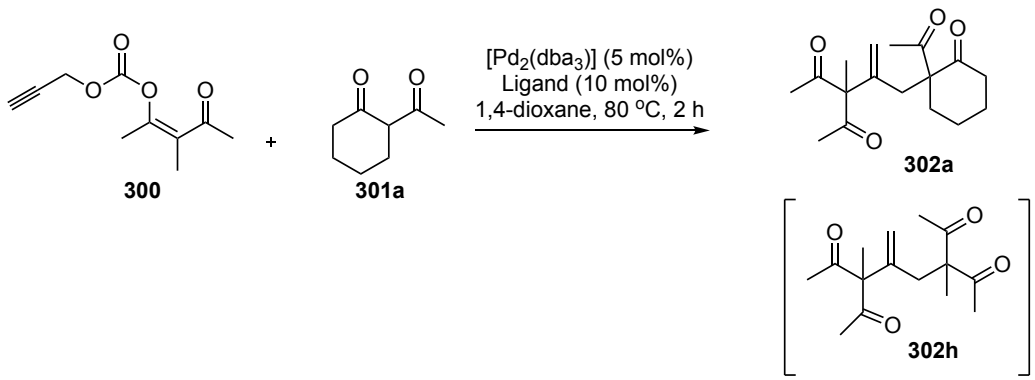
If this approach is applied to the use of two 1,3-diketones, the scrambling of enolates could potentially be prevented by utilising one of the 1,3-diketones as a propargyl enol carbonate (Scheme 74). In this way, enol carbonate **298** would undergo alkenylation with the η^3-π-propargylpalladium(II) complex. We reasoned that regioselectivity would be controlled by the association of the enolate following decarboxylation of **298** with the η^3-π-propargylpalladium(II) intermediate, essentially making the alkenylation step an intramolecular process (*vide supra,* Scheme 65). The external 1,3-dicarbonyl nucleophile **293** would then undergo the subsequent allylic alkylation to form **294**. In addition, by utilising propargyl enol carbonate **299** derived from **293** in the presence of 1,3-dicarbonyl **292**, regioisomer **295** could potentially be accessed, rendering the reaction regioswitchable depending on the judicious choice of the propargyl enol carbonate.



Scheme 74: The regioswitchable coupling of two 1,3-diketones.

Indeed, when propargyl enol carbonate **300**, derived from 3-methyl-2,4-pentanedione, was reacted with **301a** in the presence of a palladium(0) catalyst and Xantphos as the ligand, desired product **302a** was obtained with

complete regioselectivity, good chemoselectivity and in good yield (Table 2, entry 1). This result confirmed the superiority of using a pre-formed propargyl enol carbonate as one of the coupling partners, whereby the propargylic electrophile is temporarily tethered to one of the carbon based nucleophiles. The yield of **302a** was improved further when the ligand dppf was used (entry 2), and similarly good results were obtained with conventional [$Pd(PPh_3)_4$] as the catalyst (entry 3). Finally, the use of a large-bite-angle ligand DPEphos afforded **302a** in a high 85% yield with complete regioselectivity and good chemoselectivity (entry 4).

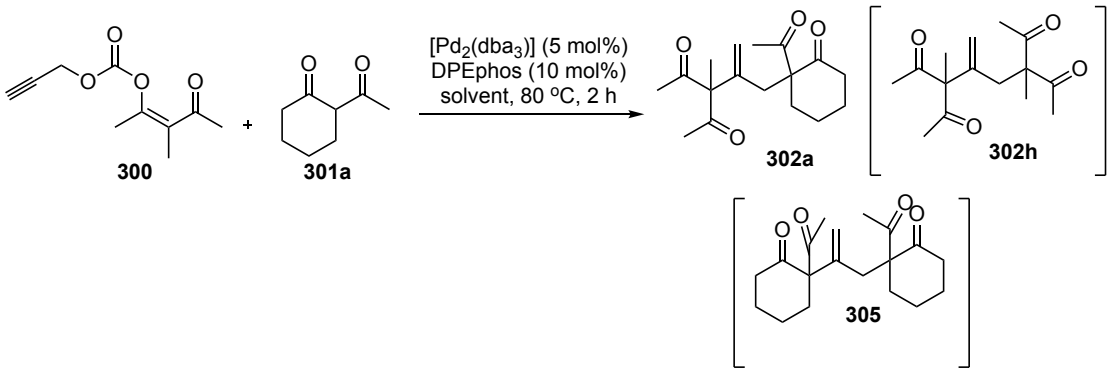


		Selectivity		
Entry	Ligand	Regio (**302a**:**304a**)[a]	Chemo (**302**:**302h**)[a]	Yield (**302**)[b]
1	Xantphos	> 19:1	5.9:1	59
2	dppf	> 19:1	6.4:1	73
3	PPh_3[c]	> 19:1	5.8:1	56
4	**DPEphos**	**> 19:1**	**6.1:1**	**85**

[a]Ratio determined by ^1H NMR spectroscopy. [b]Isolated yield of major isomer **302a**. [c][$Pd(PPh_3)_4$] was used in place of [$Pd_2(dba_3)$].

Table 2: Ligand screen.

Using DPEphos as the ligand, a solvent screen was performed next (Table 3). The use of polar and non-polar solvents, including toluene, acetonitrile, dimethylformamide and dichloromethane, reduced the chemoselectivity of the reaction and in some cases, dramatically eroded the yield of **302a**.



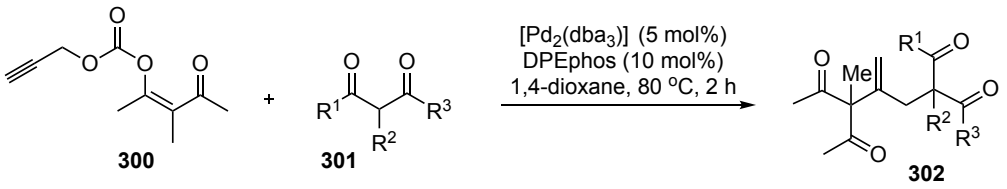
		Selectivity		
Entry	Solvent	Regio (**302a**:**304a**)[a]	Chemo (**302a**:**302h**:**305**)[a]	Yield (**302a**)[b]
1	Toluene	> 19:1	4.4:1:0	60
2	MeCN	> 19:1	1.4:1:1.4	31
3	DMF	> 19:1	1.6:1:1.6	26
4	CH_2Cl_2[c]	> 19:1	1.7:1:2.2	16
5	**Dioxane**	**> 19:1**	**6.1:1:0**	**85**

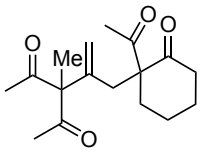
[a]Ratio determined by ^{1}H NMR spectroscopy. [b]Isolated yield of major isomer **302a**. [c]Reaction was run at 60 °C.

Table 3: Solvent screen.

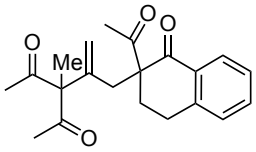
7.1.2. 1,3-Dicarbonyl Nucleophile Scope

Having identified the optimal reaction conditions, the reaction scope was investigated by coupling a range of 1,3-dicarbonyl compounds with linear enol carbonate **300** (Table 4).

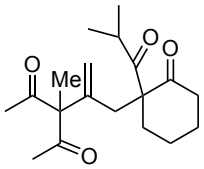




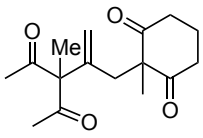
302a (85%)[a,b]
r.r. >19:1;
chemoselectivity 6.1:1[c]



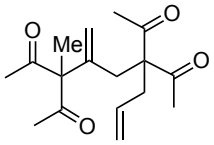
302b (79%)[e]
r.r. >19:1;
chemoselectivity 10:1.2[c]:1[d]



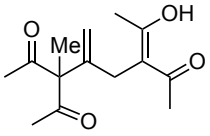
302c (47%)[f]
r.r. >19:1;
chemoselectivity 5.2:1.1[c]:1[d]



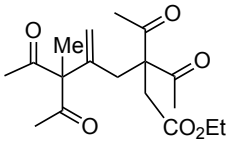
302d (27%)[g]
r.r. 1.3:1;
chemoselectivity:
6.2[d]:2.6:1.3:1[c]



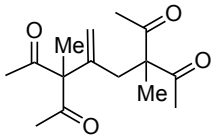
302e (70%)
r.r. >19:1;
chemoselectivity 4.6:1[c]



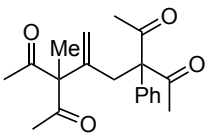
302f (56%)
r.r. and chemoselectivity *n.d.*



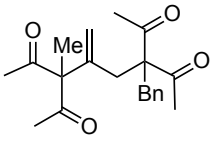
302g (60%)
r.r. >19:1;
chemoselectivity 10:1.2[c]:1[d]



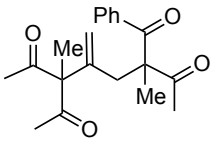
302h (74%)



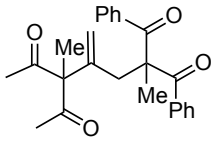
302i (36%)
*r.r. a*nd chemoselectivity n.d.



302j (73%)
r.r. >19:1;
chemoselectivity 6.9:1[c]



302k (54%)
r.r. >19:1;
chemoselectivity 4.6:1[c]



302l (No reaction)

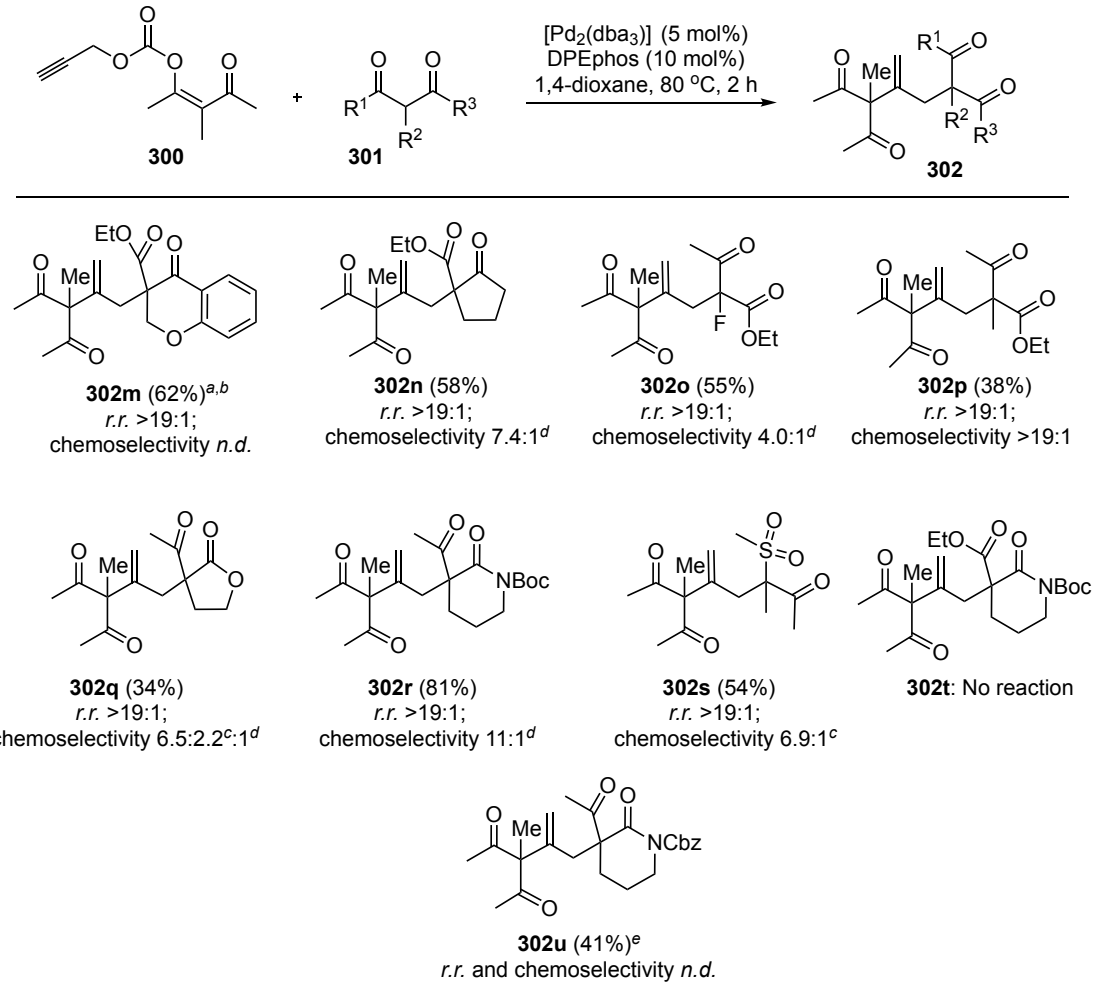
[a]All reactions were performed on a 0.24 mmol scale unless otherwise stated. [b]Isolated yields of major isomer **302**. [c]Homo-coupling of **300**. [d]Homo-coupling of **301**. [e]Reaction was run on a 0.12 mmol scale. [f]Reaction was run for 4 hours. [g]Homo-coupling of nucleophile **301d** was the main product isolated in 27% yield.

Table 4: 1,3-Dicarbonyl scope.

Cyclohexanone-based nucleophiles **301a** and **301b** were installed in products **302a** and **302b**, respectively, in high yields and with complete regioselectivity and high chemoselectivity. The *iso*-propyl-bearing product **302c** was obtained in a lower yield, which was caused by the reaction not proceeding to completion, even when reacted for longer periods of time. Unfortunately, diketone **301d** did not react to afford desired product **302d** and the homo-coupled product of **301d** was the major isomer isolated. It could be postulated

that the higher acidity of methyl-dimedone **301d** leads to the formation of a more stable anion following decarboxylation, which is able to diffuse from the η^3-π-propargylpalladium(II) complex, resulting in the erosion of selectivity. The use of acyclic diketones **301e-301g** provided the products **302e**-**302g** in high yields and regioselectivities, however, some homo-coupling accompanied the reactions in the synthesis of **302e** and **302g**. Phenyl- and benzyl-substituted acyclic diketones **301j** and **301k** were also incorporated in high yields and regioselectivities, whereas a poor yield of **302i** was obtained. Diphenyl-substituted 1,3-diketone **301l** did not react and the starting material was recovered. Long-range HMBC correlations were used to confirm the structure of the major regioisomer in all cases.

Having tested the reactivity of 1,3-diketones in the reaction, the use of other 1,3-dicarbonyl nucleophiles was investigated (Table 5). 1,3-Dicarbonyls that possess both ester and amide functionality are less acidic than 1,3-diketones and we sought to explore what impact this would have on the efficiency and selectivity of the reaction.



[a]All reactions were performed on a 0.24 mmol scale unless otherwise stated. [b]Isolated yields of major isomer **302**. [c]Homo-coupling of **300**. [d]Homo-coupling of **301**. [e]The reaction was performed on a 0.16 mmol scale. *n.d.* = not determined.

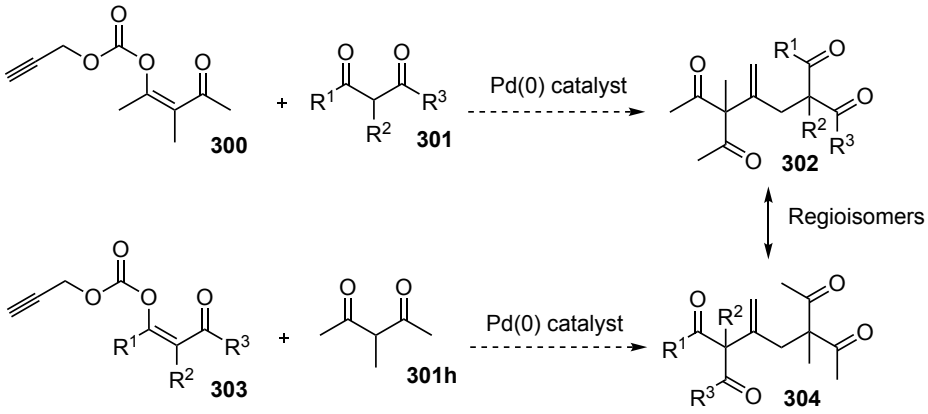
Table 5: 1,3-Dicarbonyl scope.

β-Keto esters **302m**, **302n** and fluorinated β-Keto ester **302o** were isolated in good yields and selectivities, whereas ester **301p** and β-keto lactone **301q** resulted in lower yields for **302p** and **302q**, despite the high regioselectivity. The scope was expanded to β-keto lactam and sulfone-containing compounds **301r** and **301s**; the β-keto-lactam nucleophile furnished product **302r** in a good yield and with full regioselectivity, however a small amount of the homo-coupled product of **302r** was observed. β-Ketosulfone product **302s** was synthesised in a moderate yield and with high regioselectivity, although a

minor amount of homo-coupled product **302h** was also formed. However, β-ester lactam nucleophile **301t** failed to couple with enol carbonate **300** and only starting material **301t** was recovered. Finally, Cbz protected β-keto lactam **301u** coupled with **300** to produce **302u** in a moderate yield.

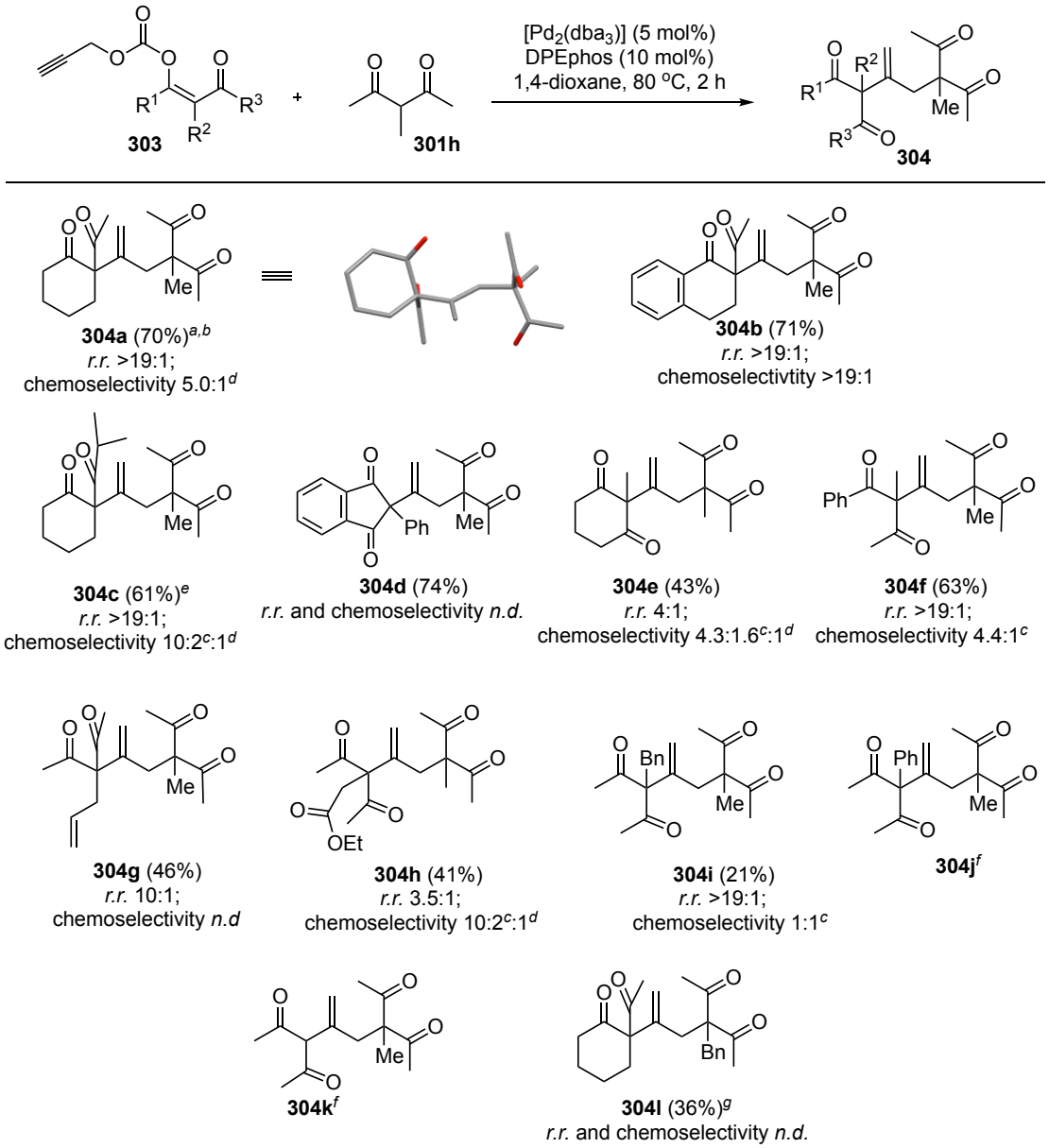
7.1.3. Propargyl Enol Carbonate Scope

Considering that the enolate generated *in situ* from propargyl enol carbonate **300** after decarboxylation is regioselectively alkenylated and the externally added partner **301** is allylated, we postulated that the regioselectivity of the reaction could be reversed by simply utilising a propargyl enol carbonate of the latter partner **303** and the neutral 1,3-dicarbonyl species **301h** derived from the former carbonate to create species **304** (Scheme 75).



Scheme 75: The regioswitchable coupling of two 1,3-carbonyl compounds.

To explore this idea, a set of propargyl enol carbonates derived from a range of 1,3-diketones were reacted with 3-methyl-2,4-pentanedione (**301h**) under the optimised reaction conditions (Table 6).



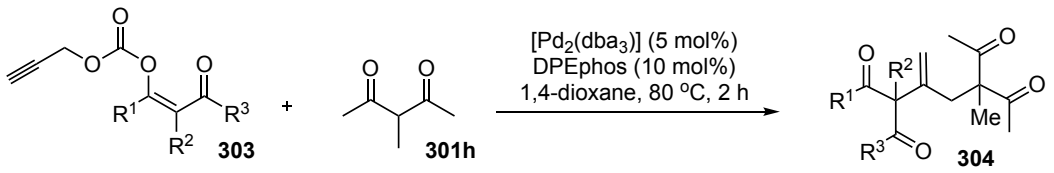
[a]All reactions were performed on a 0.24 mmol scale unless stated otherwise. [b]Isolated yields of major isomer **304**. [c]Homo-coupling of **303**. [d]Homo-coupling of **301h**. [e]Reaction was run for 4 hours. [f]A complex mixture of products was isolated. [g]The reaction was performed on a 0.16 mmol scale in THF at 60 °C for 2 hours. *n.d.* = not determined.

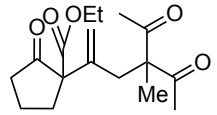
Table 6: Propargyl enol carbonate scope.

Pleasingly, the regioselectivity was high in most cases. Cyclohexanone-based carbonates **304a-304d** were isolated in good yields and, although the identity of the major regioisomer could be readily confirmed by long range HMBC analysis, a crystal structure of **304a** was also obtained, which conclusively

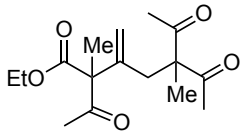
proved the sense of regioselectivity of the reaction. Dimedone-derived carbonate **303e** favoured the formation of the desired product **304e** over homo-coupling, albeit the yield was moderate. This observation was in contrast to the reaction when methyl-dimedone **301d** was used as the 1,3-dicarbonyl nucleophile (*vide supra*, Table 4), where homo-coupling was the major reaction pathway. Linear 1,3-diketone products **304f** and **304g** were formed in 63% and 46% yield, respectively, with product **304g** exhibited a lower regioselectivity. Unexpectedly, **304h** was produced with low regioselectivity, unlike the analogous coupling of carbonate **300** with ester-substituted 1,3-diketone **301g** (*vide supra*, Table 4). High regioselectivity was achieved with benzylated enol carbonate **303i**, to produce **304i**, however, the reaction was not chemoselective. Phenyl-substituted carbonate **303j** produced a complex mixture of products and the lack of desired reactivity may be attributed to the conjugated nature of the enolate formed following decarboxylation of carbonate **303j,** affecting its reactivity profile. Carbonate **303k**, derived from unsubstituted acetylacetone also led to the formation of a complex mixture of products. We reasoned that the presence of an acidic proton in **303k** enables **303k** to take part in further coupling reactions, resulting in the formation of by-products. Finally, **304l** was formed using tetrahydrofuran as the solvent rather than 1,4-dioxane.

To further probe the regioswitchable nature of the reaction, several carbonates, derived from 1,3-dicarbonyls other than 1,3-diketones, were reacted with 3-methyl-2,4-pentanedione (**301h**) (Table 7).

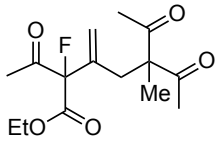




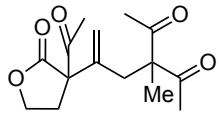
304m (58%)[a,b]
r.r >19:1;
chemoselectivity 10:2.0[d]:1[c]



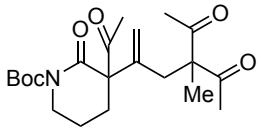
304n (42%)
r.r. >19:1;
chemoselectivity: 14:6.7[d]:1[c]



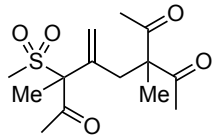
304o (35%)
r.r. >19:1;
chemoselectivity 18:10[c]:1[d]



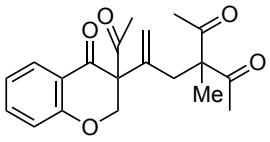
304p[e]



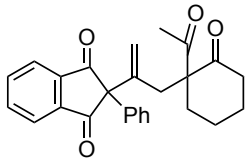
304q (53%)
r.r. >19:1;
chemoselectivity 7.8:1[c]



304r (21%)
r.r. >19:1;
chemoselectivity 5.0:1[d]



304s (32%)[f,g]
r.r. 3.2:1;
chemoselectivity *n.d.*



304t (33%)[f]
r.r. and chemoselectivity *n.d.*

[a]All reactions were performed on a 0.24 mmol scale unless stated otherwise. [b]Isolated yields of major isomer **304**. [c]Homo-coupling of **303**. [d]Homo-coupling of **301h**. [e]A complex mixture of products was observed. [f]The reaction was performed on a 0.16 mmol scale. [g]The reaction was performed in THF at 60 °C for 2 hours. *n.d.* = not determined.

Table 7: Enol carbonate scope.

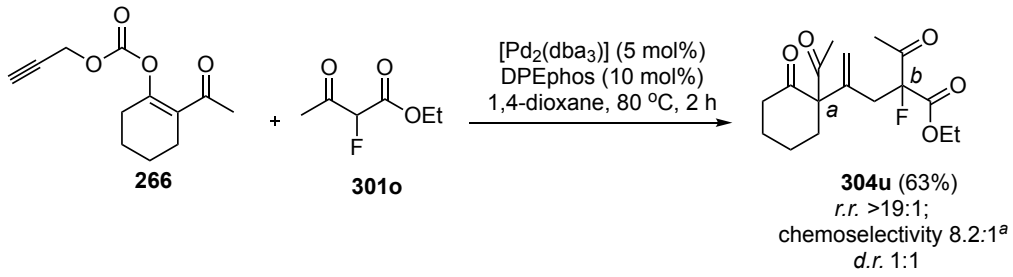
Enol carbonates **303m** and **303n**, derived from β-ketoesters **301m** and **301p**, produced products **304m** and **304n** with high regioselectivities and in moderate yields, with some homo-coupling observed by ^{1}H NMR analysis of product mixtures. Fluorinated **304o** was formed with high regioselectivity, but a low yield of 35%, presumably due to the electron-withdrawing nature of the fluorine atom, which decreases the nucleophilicity of the enolate formed after decarboxylation. Unfortunately, lactone **304p** could not be isolated and a

complex mixture of products was observed. β-keto lactam **304q** was successfully isolated in a good yield of 53%, whereas sulfone **304r** was formed with high regioselectivity, albeit in a low yield of 21%. Finally, **304s** and **304t** were formed in moderate yields under slightly different reaction conditions.

Overall, it has been possible to demonstrate the regioswitchable nature of the reaction by showing that, in most cases, high levels of regioselectivity were maintained irrespective of which coupling partner was utilised as the propargyl enol carbonate. However, despite the high regioselectivity, a number of reactions were low or moderately yielding, indicating that the reaction conditions originally optimised for the coupling of other 1,3-diketones with the propargyl enol carbonate of 3-methyl-2,4-pentanedione require further optimisation in order to enhance the efficiency of the coupling of other 1,3-dicarbonyl compounds. Nevertheless, the concept of a regioswitchable process has been developed in practice for the coupling of two 1,3-dicarbonyl compounds to form two new C–C bonds as well as two all-carbon quaternary centres.

Given that two new all-carbon quaternary centres are installed in the product of the coupling reaction, the use of two unsymmetrical coupling partners would give rise to the formation of two chiral centres in a single step. With this in mind, we reacted carbonate **266** with β-keto ester **301o**, giving rise to product **304u**, in which two chiral centres had been installed (Scheme 76). While the

regio- and chemoselectivity of the reaction was high and the yield of isolated **304u** was good, the overall process was not diastereoselective, and equal quantities of inseparable diastereoisomers were formed.



266 + **301o**

304u (63%)
r.r. >19:1;
chemoselectivity 8.2:1[a]
d.r. 1:1

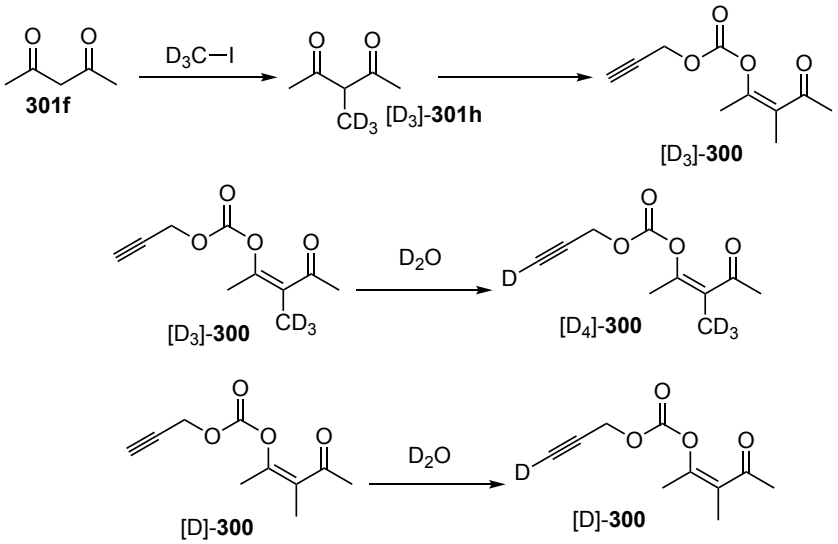
[a]Homo-coupling of **301o**.

Scheme 76: Diastereoselective coupling reaction.

Given that the stereogenic centres *a* and *b* in **304u** are three bonds away, the substituents on the chiral centre *a* do not appear to exert sufficient steric influence on the allylic alkylation step of the enolate of **301o**.

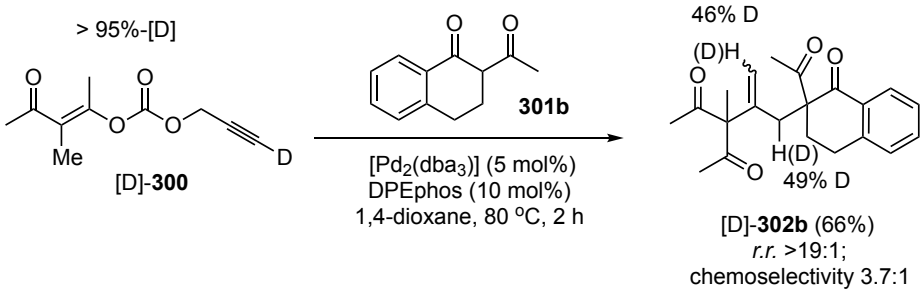
7.1.4. Mechanistic Studies

In order to gain an insight into the mechanism of the reaction, two deuterium-labelling studies were performed. This required the creation of deuterium-containing enol carbonates (Scheme 77). In the first instance, **301f** was reacted with d_3-Iodomethane to form [D_3]-**301h**. Then, through a literature procedure,[117] [D_3]-**300h** was made, followed by deuterium exchange of the propargylic proton to form [D_4]-**300h**. This same procedure was also used to create a single deuterated enol carbonate ([D]-**300h**).



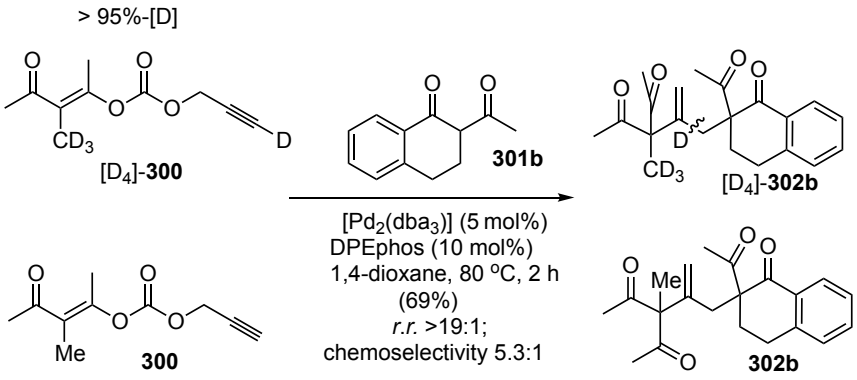
Scheme 77: The creation of deuterium based enol carbonates.

After the deuterium based enol carbonates were made, two experimental procedures were carried out. First, deuterated propargyl enol carbonate [D]-**300** was reacted with 1,3-diketone **301b** to form deuterated product [D]-**302b** (Scheme 78). The scrambling of the deuterium label was even across the vinylic and allylic position in [D]-**302b**. This supports the hypothesis that a symmetrical η^3-π-allylpalladium(II) intermediate is implicated in the mechanism.



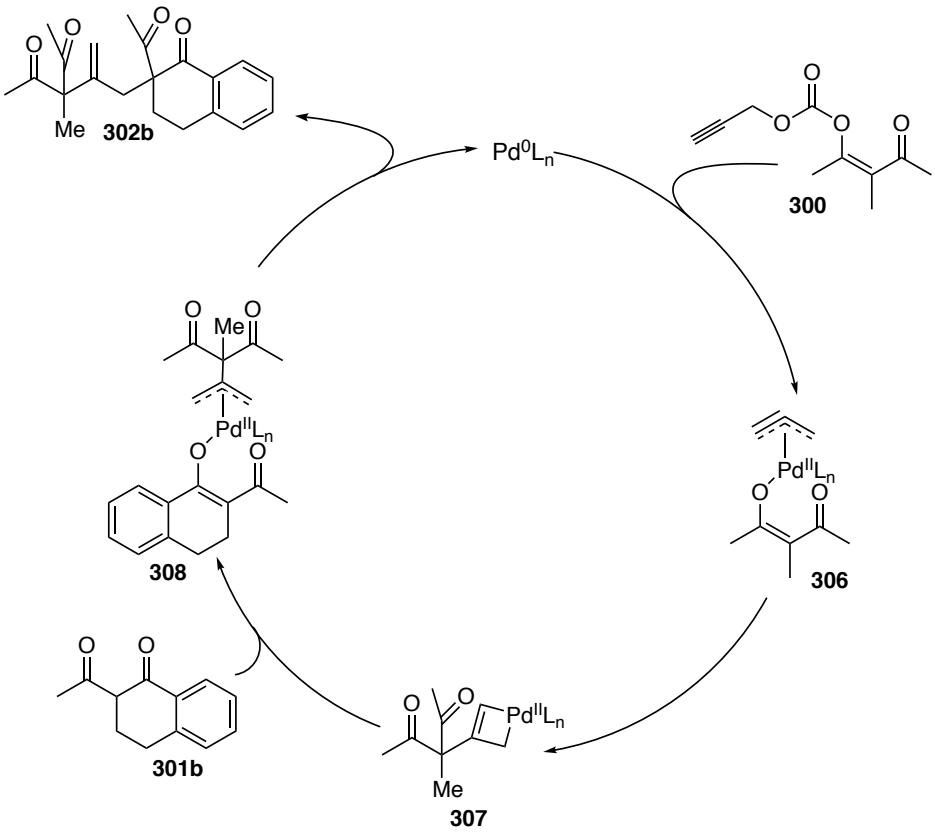
Scheme 78: Deuterium scrambling experiment.

In light of the high regioselectivities observed in the substrate scope investigation, it can be postulated that the enolate formed following decarboxylation remains coordinated to the η^3-π-propargylpalladium(II) complex. To test this hypothesis, an equimolar amount of [D_4]-**300** and non-deuterated **300** were reacted with nucleophile **301b** (Scheme 79). Mass spectrometry confirmed the presence of solely [D_4]-**302b** and **302b**, suggesting that there is no crossover of the enolates during the course of the reaction and this indicates a tight association of the enolate with the palladium centre following the decarboxylation step.



Scheme 79: Enolate crossover experiment.

With the results of the deuterated experiments obtained, a mechanism of the reaction can be postulated (Scheme 80).



Scheme 80: Proposed mechanism.

The palladium(0) catalyst undergoes oxidative addition to carbonate **300**, which, after decarboxylation, gives intermediate **306**. The strong association of the enolate with the palladium centre suggests an intramolecular inner-sphere addition mechanism of the enolate to the central carbon atom of the η^3-π-propargylpalladium(II) electrophile to form transient palladacyclobutene **307**, which determines the high regioselectivity of the reaction. Although several metallacyclobutenes of other transition metal have been isolated,[83,84] there is no experimental evidence for the implication of this intermediate in the mechanism. It is, therefore possible, that the nucleophilic addition of enolate **306** is followed by immediate protonation of **307** in a synchronous manner to give rise to enolate **308**. In the final mechanistic step, the η^3-π-

allylpalladium(II) intermediate in **307** undergoes nucleophilic addition with the enolate to afford product **302b** with complete regiocontrol and regenerates the palladium(0) catalyst.

Overall, the coupling of two 1,3-dicarbonyl compounds in our study has been generally successful, resulting in the installation of two all-carbon quaternary centres and the formation of two new C–C bonds in a single process. A mechanism for the reaction has also been deduced through deuterium-labelling studies.

7.1.5. The Coupling of 1,3-Dicarbonyl Compounds with Unstabilised Nucleophiles

The substrates investigated thus far have centred around stabilised enolates, namely those derived from 1,3-dicarbonyl compounds. To extend the utility of this methodology further, we sought to explore the reactivity of unstabilised nucleophiles, such as cyclohexanone **309a**, with a propargyl enol carbonate **300** (Table 8). If the reaction were to proceed *via* the previously postulated mechanism (*vide supra*, Scheme 79), then deprotonation of a much less acidic hydrogen atom would be required. Unfortunately, the reaction was unsuccessful: desired product **310a** was not formed and a complex mixture of products was observed instead. To enhance the acidity of the carbonyl functionality and attempt to facilitate enolate formation, we tested the following substrates: cyclohexenone **309b**, which has been precedented in an intramolecular version of the reaction (*vide supra*, Scheme 54),[110] an α-difluorinated ester **309c**, which is more acidic than a simple ester due to the

electron-withdrawing nature of fluorine, and furanone **309d**, which would give a more stable aromatic anion upon deprotonation than an enolate of a saturated lactone. It was then disappointing to discover that, in all three cases, only a complex mixture of products was observed.

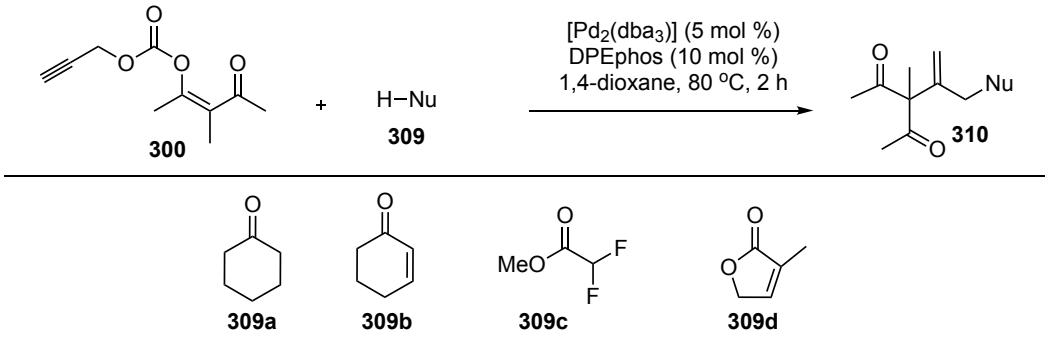
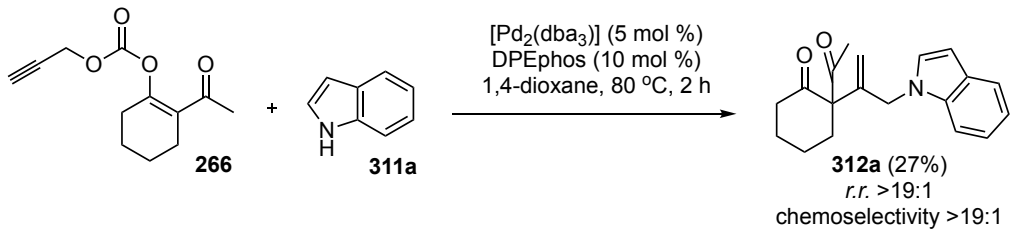


Table 8: The use of simple carbonyl compounds as nucleophiles.

However, we were encouraged to discover that indole (**311a**) was readily deprotonated and alkylated to afford **312a** in a modest yield but with complete regio- and chemoselectivity, using propargyl enol carbonate **266** (Scheme 81). Despite the aromatic nature of the indole anion, the acidity of indole **311a** (pK_a 18-20 in DMSO)[118] is even lower than that of ketones (pK_a 13-16) in DMSO,[119] and yet indole readily takes part in the reaction while simple carbonyl compounds do not. This was a remarkable result given that relatively acidic 1,3-dicarbonyl compounds are readily coupled, while less acidic simple carbonyls do not react.

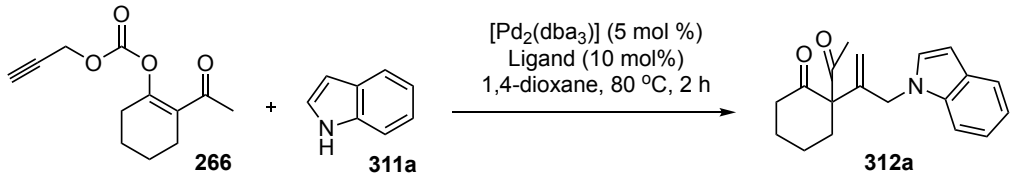


Scheme 81: The use of indole as a nucleophile.

Overall, this one-pot process installs one new C–C bond and one new C–N bond as well as an all-carbon quaternary centre in **312a** in a single step, with the initial result indicating that high levels of regio- and chemoselectivity are maintained. Inspired by the opportunity to utilise less acidic *N*-heterocyclic nucleophiles in the reaction, we set out to explore this idea further.

7.2.1. The Use of *N*-Heterocycles: Optimisation of Reaction Conditions

In the first instance, we tested the reactivity of propargyl enol carbonate **266**, derived from a 1,3-diketone, and indole (**311a**) in the presence of a palladium(0) catalyst and a phosphine ligand in 1,4-dioxane at 80 °C (Table 9). With the exception of dppe (entry 1), large-bite-angle ligands all afforded the desired coupled product **312a** (entries 2-3), however, significant quantities of unreacted starting indole **311a** were observed in the crude product mixtures. The best result was obtained with Xantphos as the ligand, which afforded a 1:2.0 ratio of **312a**:**311a** and a 32% isolated yield of **312a** (entry 4). We reasoned that the significantly lower acidity of indole **311a** as compared to that of 1,3-dicarbonyl compounds was responsible for only partial conversion. The use of palladium tetrakistriphenylphosphine led to the formation of product **312a**, albeit in a poor yield (entry 5). Remarkably, all the reactions proceeded with full regio- and chemoselectivity, even though the yields were low.



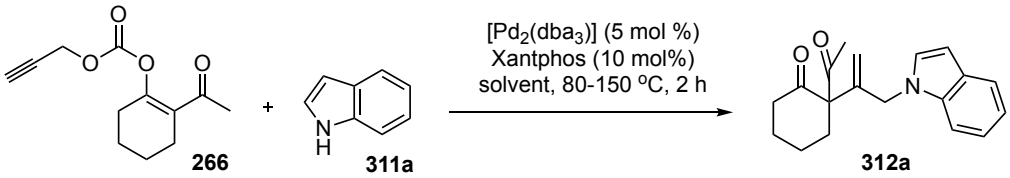
266 311a 312a

Entry	Ligand	Yield[b]	**312a**:**311a**[c]
1[a,e]	dppe	No reaction	-
2	dppf	28	1:2.1
3	DPEphos	27	1:2.3
4	Xantphos	32	1:2.0
5	$Pd(PPh_3)_4$[d]	13	1:4.7

[a]All reactions performed on a 0.24 mmol scale. [b]Yield of isolated **312a**. [c]Determined by ^1H NMR analysis of the crude product mixtures. [d]$[Pd(PPh_3)_4]$ was used in place of $[Pd_2(dba_3)]$.[e] The results were obtained through work of Danny Kitson.

Table 9: Ligand screen for the coupling of 1,3-dicarbonyls with indole.

With Xantphos as the chosen ligand, a solvent screen was performed (Table 10). At 80 °C, the solvent screen did not result in a significant improvement in reaction efficiency (entries 2-6). However, given that the reaction does not proceed to completion at 80 °C, as evidenced by the presence of unreacted indole, we wanted to explore whether deprotonation of indole prior to the alkylation step could be facilitated by increasing the temperature of the reaction. In this context, the reaction in toluene at 120 °C did in fact result in an increased yield of product **312a** of 55% (entry 7). Increasing the temperature to 150 °C in xylene as the solvent, however, did not produce further enhancement in yield (entry 8), and 120 °C was settled upon as optimal.



266 311a 312a

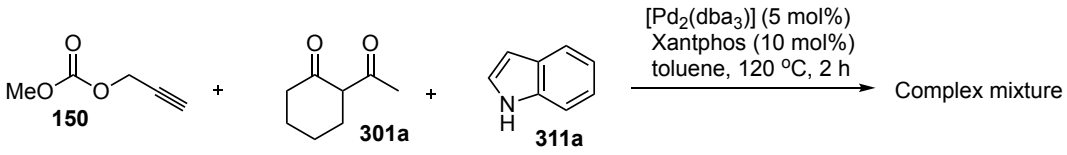
Entry	Solvent	Temperature (°C)	Yield (%)[b]	**312a:311a** ratio[c]
1[a]	1,4-dioxane	80	27	1:2.0
2	DMF	80	-	Complex mixture
3	MeCN	80	11	1:3.5
4	THF	80	24	1:1.8
5	CH_2Cl_2	80	35	1:1.9
6	toluene	80	37	1:0.8
7	**toluene**	**120**	**55**	**1:0.7**
8	xylene	150	32	1:0.8

[a]All reactions performed on a 0.24 mmol scale. [b]Yield of isolated **312a**. [c]Determined by ^{1}H NMR analysis of the crude product mixtures.

Table 10: Solvent screen for the coupling of 1,3-dicarbonyls with indole.

Overall the *N*-allylic alkylation of the indole (**311a**) was the dominant reaction and no *C*-alkylation products were observed. This is in contrast to the previously reported allylic alkylation of indoles with allylic electrophiles,[120] and the palladium-catalysed reaction of indoles with propargylic compounds where, due to the intramolecular arrangement of the reaction centres, the *C*-alkylation pathway dominates.[103]

Having demonstrated already with 1,3-dicarbonyls that an intermolecular coupling process leads to a mixture of products (*vide supra*, Scheme 73), we also tested the efficiency of the intermolecular coupling of indole (**311a**) in the presence of methyl propargyl carbonate **150** and 1,3-diketone **301a** (Scheme 82). This reaction led to poor mass recovery, a complex mixture of products and highlighted the requirement for a propargyl enol carbonate in order to efficiently control regio- and chemoselectivity.

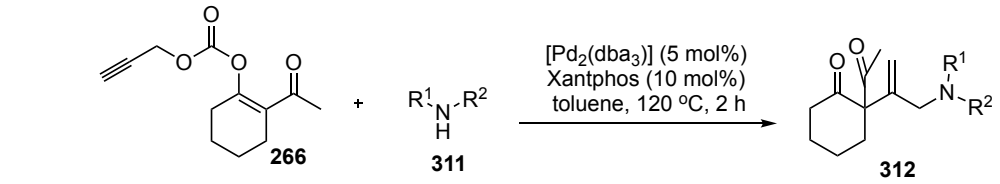


Scheme 82: Selectivity issues with the intermolecular coupling of a 1,3-diketone and indole.

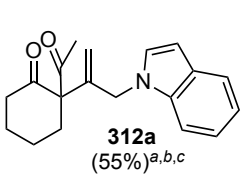
7.2.2. Indole Scope

To explore the scope of the reaction, a range of indoles was investigated under the optimised conditions (Table 11). Remarkably, all substrates were found to react with complete regio- and chemoselectivity. In addition to unsubstituted indole (**311a**), the presence of electron-withdrawing groups resulted in an increase in the yield in **312b**, presumably due to the higher acidity of the indole NH proton. Despite containing a 3-nitrile substituent, product **312c** was isolated in the same yield as that with unsubstituted indole **312a**. An electron-withdrawing ester side chain at the 2-position afforded **312d** in a 59% yield and its structure was conclusively proved by X-ray crystallography, thus confirming the regioselectivity of the reaction. The presence of electron-withdrawing substitutents on the benzene ring provided products **312e**-**312g** in moderate to good yields. Indoles containing electron-donating groups, however, gave significantly poorer yields of products **312h**

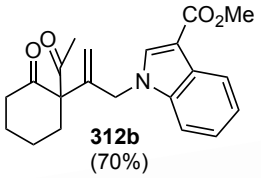
and **312i**. It is likely that the reduced acidity of the indole NH proton impacts negatively on the reaction efficiency, as indicated by the presence of significant quantities of unreacted indole. Finally, we were pleased to discover 7-azaindole and carbazole (**311j** and **311k**) also gave rise to products **312j** and **312k** in 73% and 53% yield, respectively.



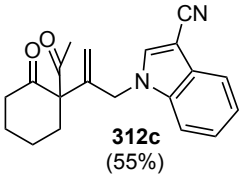
266 + **311** → **312**



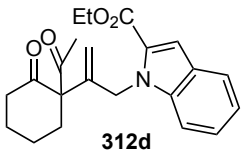
312a (55%)[a,b,c]



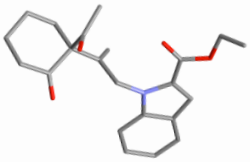
312b (70%)

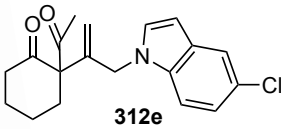


312c (55%)

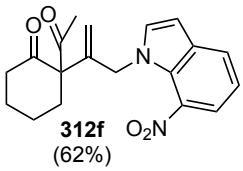


312d (59%)

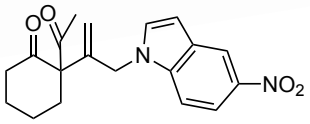




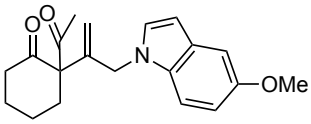
312e (52%)



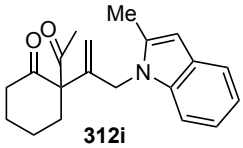
312f (62%)



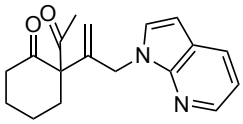
312g (62%)



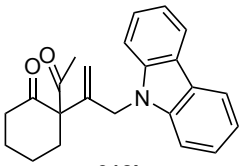
312h (27%)



312i (19%)



312j (73%)



312k (53%)

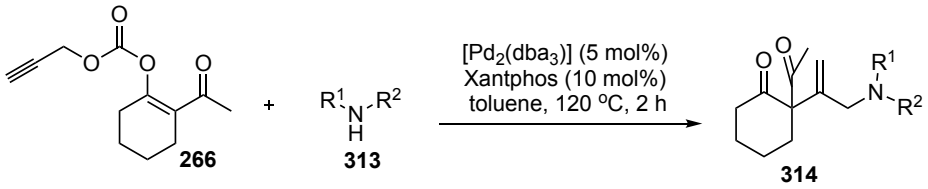
[a]All reactions were performed on a 0.24 mmol scale. [b]Yield of isolated **312**. [c]All reactions proceeded with full regio- and chemoselectivity as determined by ^{1}H NMR analysis of the crude product mixtures.

Table 11: Indole screen.

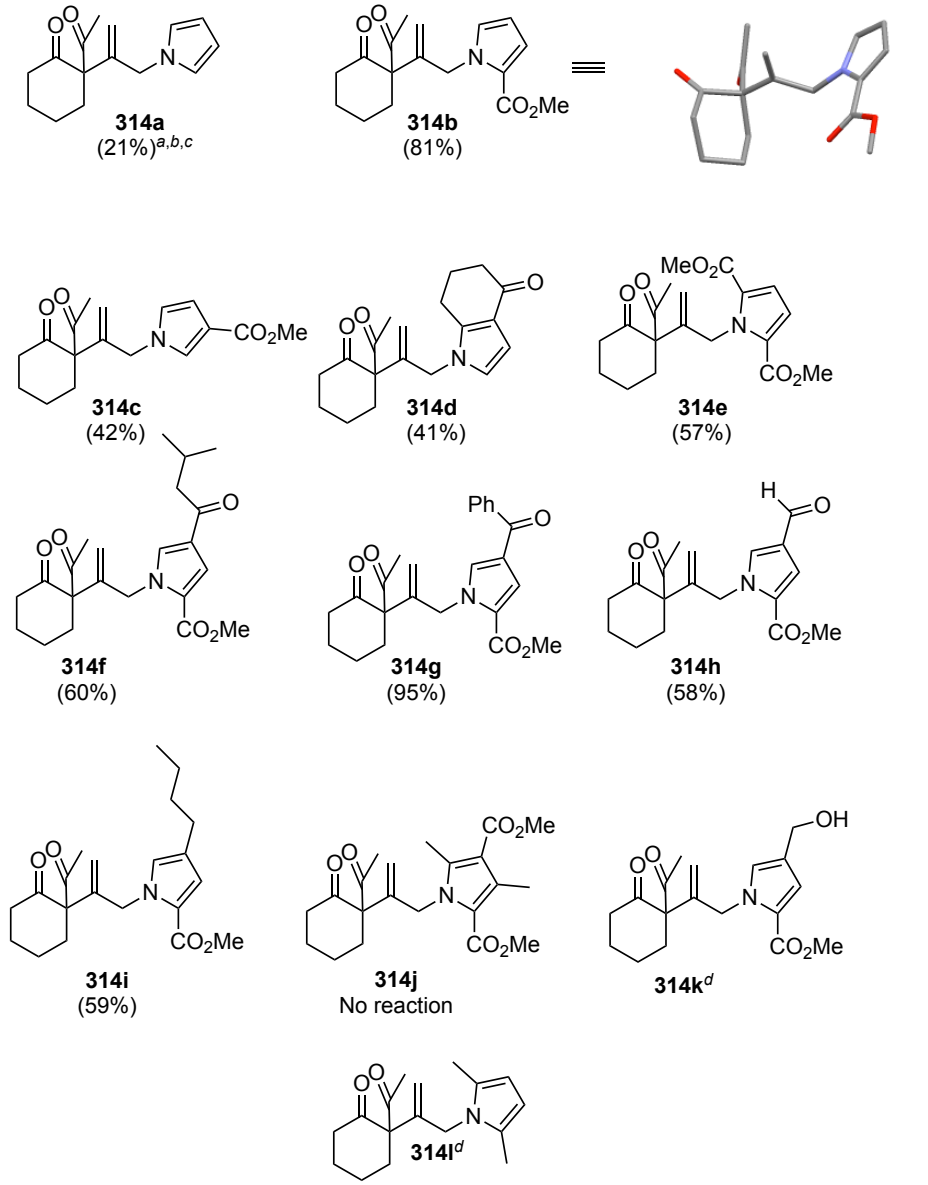
7.2.3. Pyrrole Scope

To the best of our knowledge there are no reports of palladium-catalysed cross-coupling reactions of pyrroles with propargylic compounds. Therefore, encouraged by the reactivity of indoles, our attention turned to the use of pyrroles as *N*-nucleophiles (Table 12). The requisite pyrroles were obtained from commercial sources or prepared *via* known methods (see the Experimental Section for more details). In all cases, where the desired products was obtained, the reactions proceeded with complete regio- and chemoselectivity. The use of pyrrole (**313a**) itself gave rise to **314a** with complete selectivity and no *C*-alkylation was observed. Pyrrole, however, was relatively unreactive, affording **314a** in a 21% yield, which is likely to be brought about due to the electron-rich nature of pyrrole (**313a**), making deprotonation less facile. The introduction of electron-withdrawing substituents at the 2-position of pyrrole drastically increased its reactivity, and **314b** was isolated in a significantly higher yield. The regioselectivity of the reaction was confirmed by the X-ray crystal structure of **314b**. The introduction of an electron-withdrawing substituent at the 3-position gave **314c** in a moderate yield, presumably due to the cross-conjugated nature of **313c**, albeit still higher than that with unsubstituted pyrrole **314a**. Similar results were obtained with a pyrrole fused with a 6-membered ketone (**334d**). The incorporation of two electron-withdrawing groups at the 2- and 5-position of pyrrole afforded a higher yield of **314e**, but surprisingly, it was not as high as that of **314b**, potentially due to steric hindrance exerted by the two ester substituents (**313e**). Further decoration of the pyrrole motif with electron-withdrawing

groups at the 2- and 4-positions offered moderate to excellent results (**314f-314h**). A mixture of electron-donating and -withdrawing substituents were also effective (**314i**). On the other hand, tetrasubstitution of the pyrrole nucleophile afforded no product (**314j**), presumably due to steric effects, whereas the incorporation of an alcohol functionality resulted in a complex mixture of products being formed (**314k**). It is plausible that, as the unprotected primary alcohol contains an acidic proton, competing side-reactions can occur. Finally, the use of an electron-rich 2,5-dimethyl also produced a complex mixture of products (**314l**).



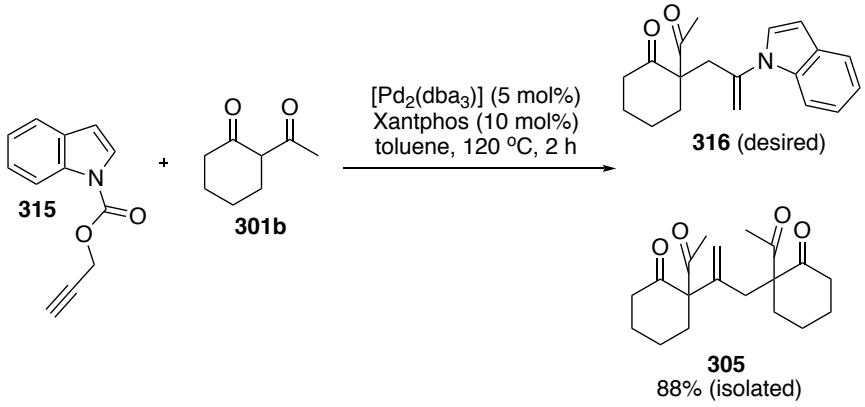
266 + **313** → **314**



[a]All reactions were performed on a 0.24 mmol scale. [b]Yield of isolated **314**. [c]All reactions obtained full regio- and chemoselectivity. [d]A complex mixture was observed.

Table 12: Pyrrole screen.

Having successfully coupled 1,3-diketone **266** with both indole and pyrrole substrates, we sought to test the regioswitchable nature of the reaction and investigate whether the opposite regioisomer **316** could be accessed by utilising a propargyl carbamate of indole **315** (Scheme 83). Instead of the desired product **316** being formed, homo-coupling of 1,3-diketone **301b** exclusively took place to afford **305** in an 88% yield. It is likely that, due to the large difference in acidity between indoles and 1,3-diketones, the indole anion generated after decarboxylation readily deprotonates 1,3-diketone **301b**, with the resulting enolate undergoing alkenylation with the η^3-π-propargylpalladium(II) intermediate. Subsequent allylic alkylation is also more facile with 1,3-diketone nucleophile **301b** due to its high acidity. Therefore, overall, homo-coupling of **301b** dominates.

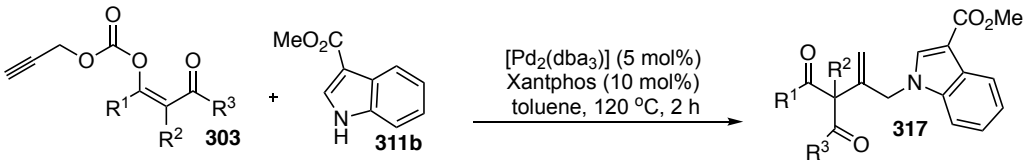


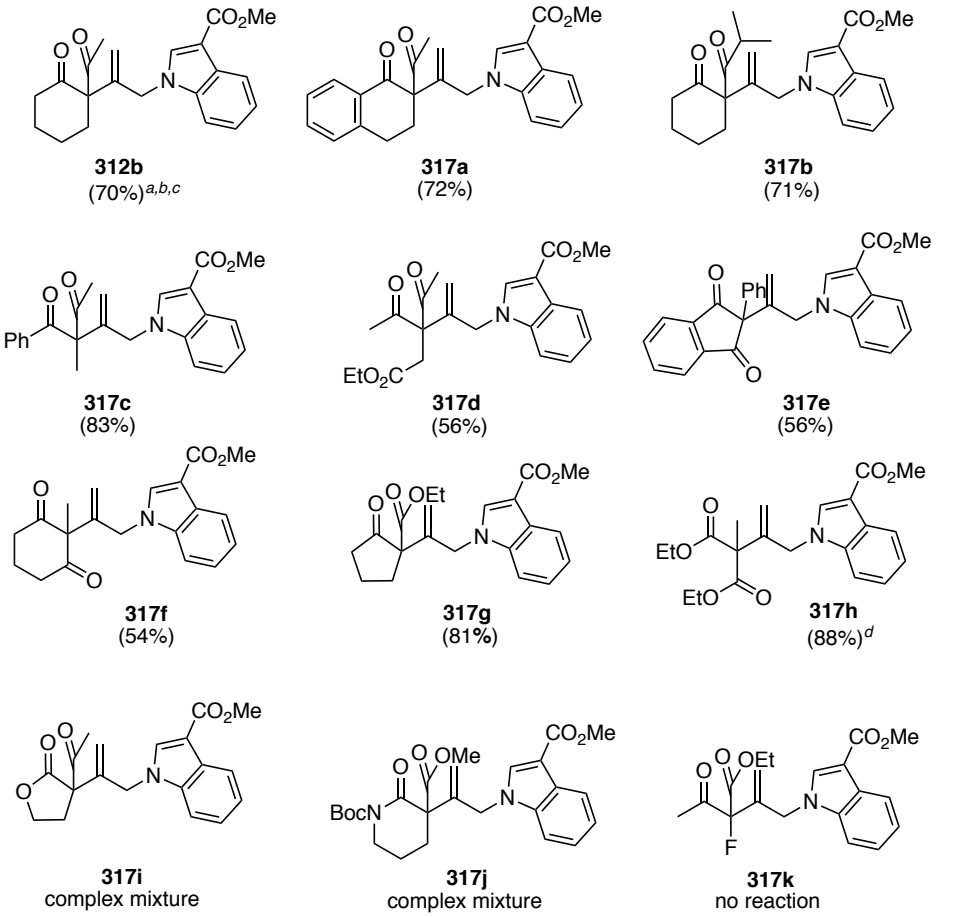
Scheme 83: Use of propargyl carbamate of indole.

7.2.4. Propargyl Enol Carbonate Scope with Indole and Pyrrole Nucleophiles.

Attention was then focused on studying the efficiency and selectivity of the coupling of a range of 1,3-dicarbonyl-derived nucleophiles with indole **311b**

(Table 13) and pyrrole **313b** (Table 14). A variety of 1,3-dicarbonyl-derived propargyl enol carbonates were first coupled with indole **311b** and again, we found the reactions proceeded with full regioselectivity and no homo-coupling of nucleophiles (Table 13). Cyclohexanone-based carbonates **303b** and **303c** produced **317a** and **317b** in good yields and complete selectivity. Similarly, the use of propargyl enol carbonates derived from both linear and cyclic 1,3-diketones readily generated products **317c-317f**. In addition to 1,3-diketones, β-ketoester **303m** was coupled with indole **311b** to afford product **317g** in a high yield of 81%. In an attempt to couple malonate **303t** with indole **311b**, homo-coupled indole side-product **317hb** was isolated in 88% yield (Figure 5). Finally, carbonates **303o**, **303p** and **303u** failed to react, with **303o** and **303u** producing complex mixtures, while the starting indole and the decarboxylated α-fluoro β-ketoester were recovered in the case of **303p**.





[a]All reactions were performed on a 0.24 mmol scale. [b]Yield of isolated **317**. [c]All reactions proceeded with full regio- and chemoselectivity. [d]Major product was homo-coupled indole **311b** (**317hb**).

Table 13: 1,3-Dicarbonyl enol propargyl carbonate scope with indole **311b**.

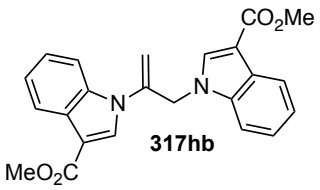
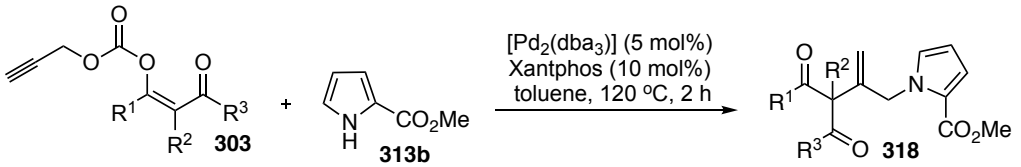


Figure 5: Homo-coupled product **317hb**.

Next, we set out to explore the coupling of pyrrole nucleophile **313b** with several propargyl enol carbonates (Table 14). In a similar fashion to reactions with indole nucleophiles, complete regio- and chemoselectivity was maintained when pyrrole **313b** was coupled with 1,3-dicarbonyl compounds. More specifically, cyclohexanone-containing 1,3-diketones and linear 1,3-diketones provided the desired products in good yields (**318a-318e**). Cyclic 1,3-diketones **318f** and **318g** were also isolated in high yields. The use of β-ketoesters and malonates afforded **318h** and **318i** in 55% and 61% yields, respectively, whereas β-ketolactone was coupled with pyrrole **313b** to give **318j** in a remarkably high 99% yield. Finally, it was encouraging to discover that ß-amidoesters were successfully incorporated, with desired product **318k** being produced in a 56% yield, whereas the α-fluorinated ß-ketoester **303p** failed to produce **318l** and instead, the starting material was recovered.



314b
(81%)[a,b,c]

318a
(66%)

318b
(55%)

318c
(60%)

318d
(55%)

318e
(74%)

318f
(85%)

318g
(72%)

318h
(55%)

318i
(61%)[d]

318j
(99%)

318k
(56%)

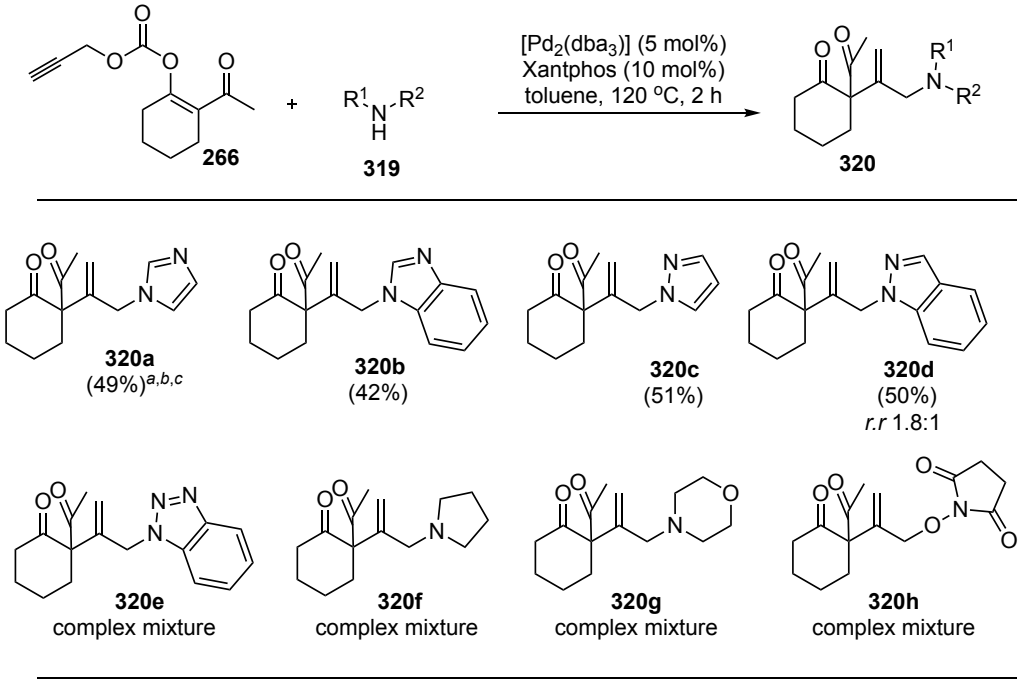
318l
no reaction

[a]All reactions were performed on a 0.24 mmol scale. [b]Yield of isolated **318**. [c]All reactions proceeded with full regio- and chemoselectivity. [d]The result was obtained through work of Danny Kitson.

Table 14: 1,3-Dicarbonyl propargyl enol carbonate screen. With pyrrole **313b**.

7.2.5. The Coupling of 1,3-D-icarbonyl Compounds with Other *N*-Heterocycles

Having demonstrated the successful use of indole and pyrrole nucleophiles in the reaction, we set out to extend the scope and generality of this process to other nitrogen nucleophiles. In this context, it was found that analogous aromatic *N*-heterocycles, namely imidazole, benzimidazole and pyrazole (**319a**-**319c**, Table 15), all afforded coupled products **320a**-**320c** in moderate yields but with complete regioselectivity. It was surprising to discover that indazole **319d** gave product **320d** in 50% yield with poor regioselectivity, which was in contrast to the consistently high regioselectivity of the reactions with other nitrogen-based nucleophiles. Benzotriazole **319e** failed to couple with enol carbonate **266** and a complex mixture of products was observed by ^{1}H NMR spectroscopy. We were particularly keen to incorporate aliphatic amines into our products, in order to generate molecular building blocks with more sp^3 character. Unlike unsaturated *N*-heterocycles, which generate an aromatic anion upon deprotonation, saturated amines are significantly less acidic and, thus, less likely to react *via* the usual reaction pathway. Indeed, saturated cyclic amines pyrrolidine (**319f**) and morpholine (**319g**) failed to afford the desired products **320f** and **320g** and only complex mixtures of products were isolated. The use of *N*-hydroxysuccinimide **319h** as a nucleophile was also unsuccessful.

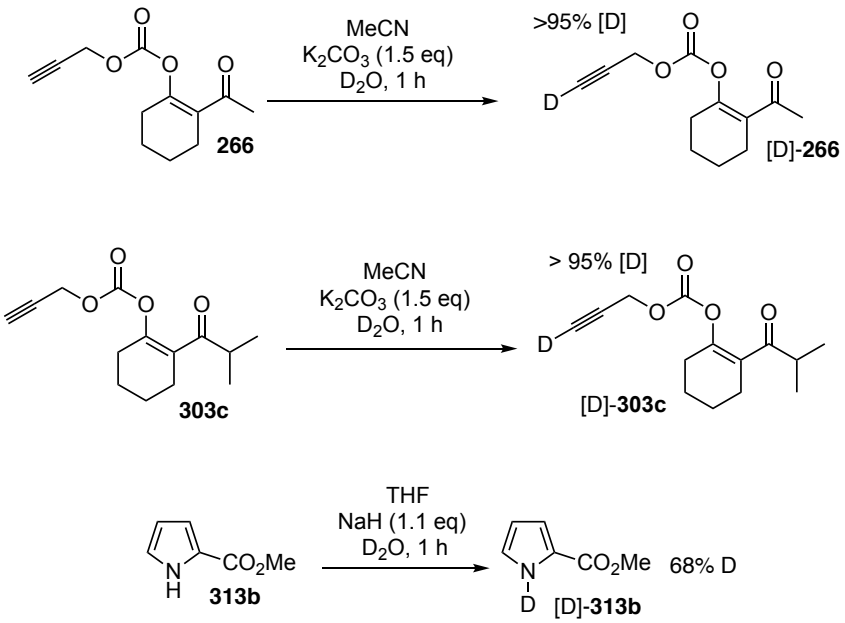


[a]All reactions were performed on a 0.24 mmol scale. [b]Yield of isolated **320**. [c]Unless otherwise stated, all reactions proceeded with full regio- and chemoselectivity

Table 15: Analgous *N*-heterocycle substrate scope.

7.2.6. Mechanistic Studies

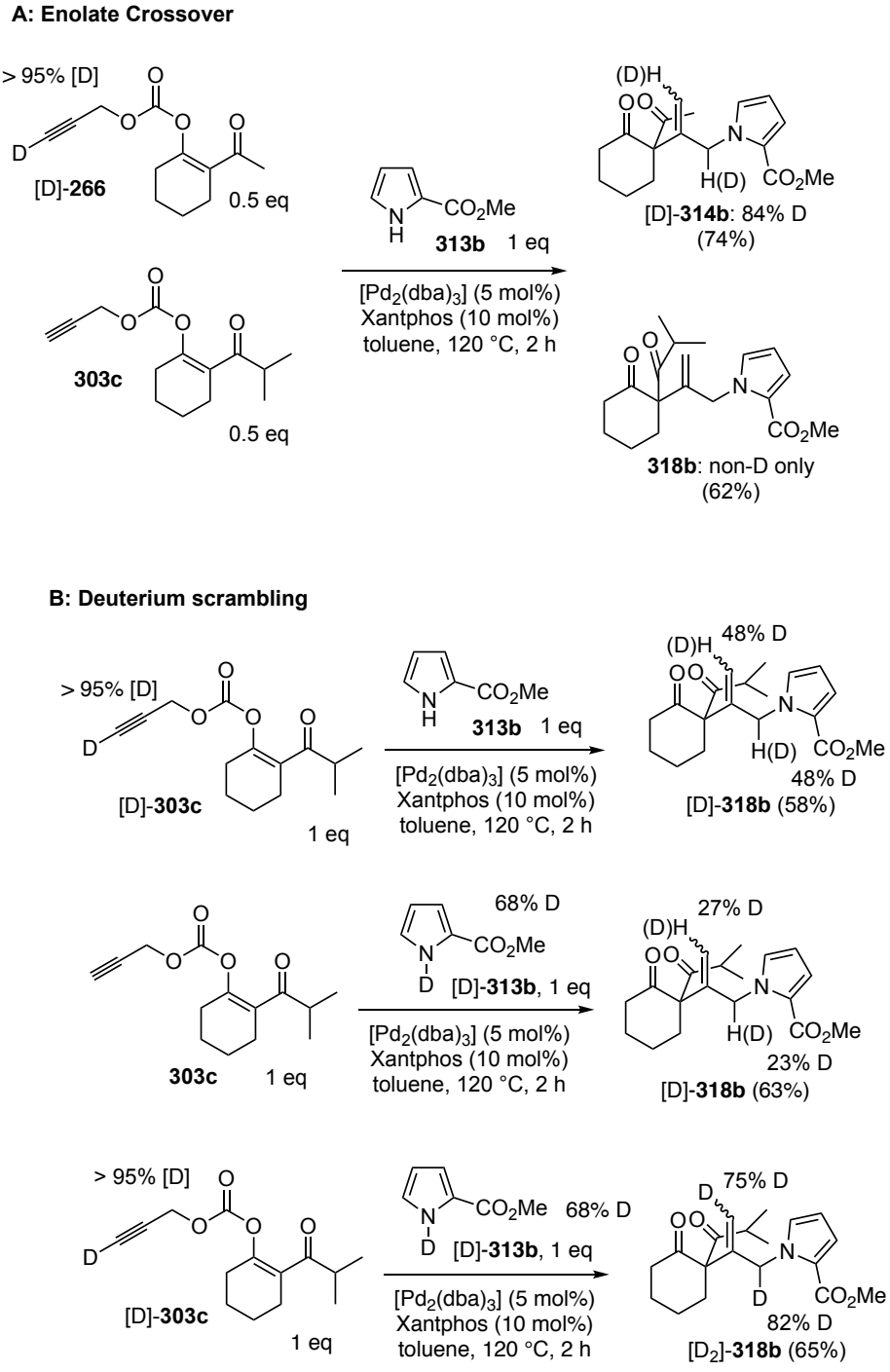
To gain a better understanding of the mechanism of the reaction between 1,3-dicarbonyl compounds and *N*-heterocyclic nucleophiles, as well as the origins of the displayed selectivity, several experiments were conducted. In a similar fashion to the deuterated enol carbonates made for the mechanistic studies for the coupling of the 1,3-dicarbonyl compounds (*vide supra,* Scheme 77), enol carbonates [D]-**266** and [D]-**303c** were made in a similar fashion (Scheme 84).[117] For the enolate scrambling experiments, pyrrole [D]-**313b** was also made, though a stronger base was used due to the increased pK_a of the pyrrole.



Scheme 84: The creation of deuterated substrates for the mechanistic studies.

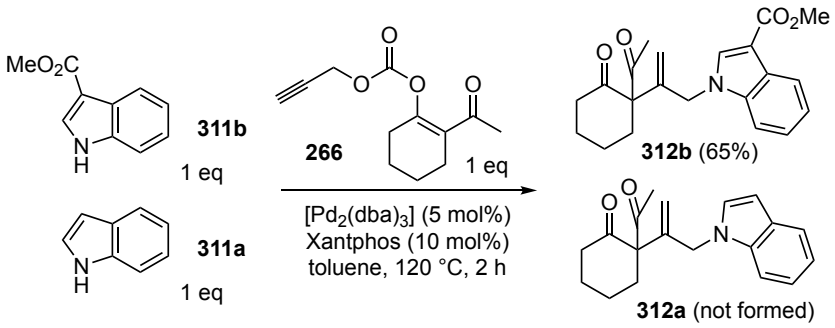
The first experiment conducted was an enolate crossover experiment (Schem e 85), in which two structurally similar propargyl enol carbonates [D]-**266** and **303c** were reacted with pyrrole **313b** and the products were isolated. ^{1}H NMR spectroscopy indicated 84% deuterium incorporation in [D]-**314b** and no deuterium incorporation in **318b**. This observation indicates that there is no enolate crossover in the reaction, suggesting that the η^3-π-propargylpalladium(II) intermediate formed after decarboxylation is tightly bound to the corresponding enolate. A deuterium scrambling experiment was also performed using [D]-**303c**, resulting in an even distribution of the deuterium labels at the allylic and vinylic positions in [D]-**318b**. Deuterium scrambling also occurred when non-deuterated **303c** was coupled with deuterated pyrrole [D]-**313b**. These results were further confirmed by the incorporation of two deuterium labels at the vinylic and allylic positions in

almost equal amounts in [D_2]-**318b**, when [D]-**303c** was coupled with [D]-**313b**. In light of these results, it is feasible to conclude that a nitrogen deprotonation step and a symmetrical π-allylpalladium(II) intermediate are implicated in the mechanism, analogous to the mechanism proposed for the coupling of 1,3-dicarbonyl compounds (*vide supra*, Scheme 80).



Scheme 85: Enolate crossover and deuterium scrambling experiments.

Finally, a competition experiment between indoles **311a** and **311b** was performed (Scheme 86), bearing in mind that indole **311b**, containing an ester side-chain at the 3-position, is more acidic than unsubstituted indole (**311a**). Although both indoles can take part in individual reactions with carbonate **266**, the combination of the two only afforded product **312b** and not **312a**. Therefore, it can be postulated that the acidity of the NH proton and thus, the rate of deprotonation, affects the overall rate of reaction. This conclusion is corroborated by the fact that the more acidic indoles and pyrroles in general give rise to higher yields of the coupled product (*vide supra,* Table 11).



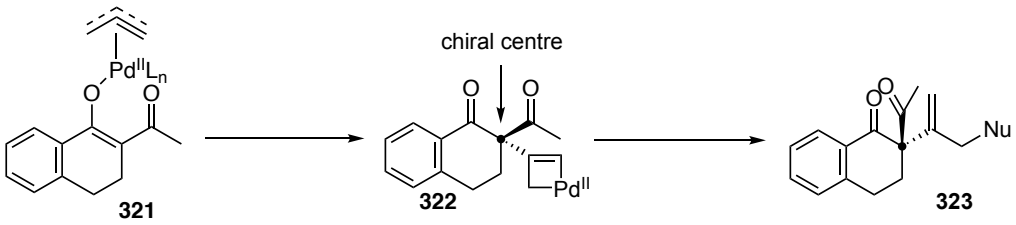
Scheme 86: Competition experiment: effect of acidity.

The results regarding the cross-coupling reaction of two 1,3-dicarbonyl compounds, as well as the cross-coupling reactions of 1,3-dicarbonyl compounds with *N*-heterocyclic nucleophiles were very positive. This palladium-catalysed cross-coupling reaction affords the desired products with high regio- and chemoselectivity in most cases, even when less acidic nitrogen nucleophiles are used. In addition, in the coupling of 1,3-dicarbonyl compounds, the reaction can be made regioswitchable by simply choosing an appropriate propargyl enol carbonate as one of the coupling partners. Using

deuterium-labelling and competition experiments, a mechanism of the reaction has been delineated. The flexibility of this process means that two new bonds can be made in a single step as well as one or two quaternary all-carbon centres, depending on the type of external nucleophile used.

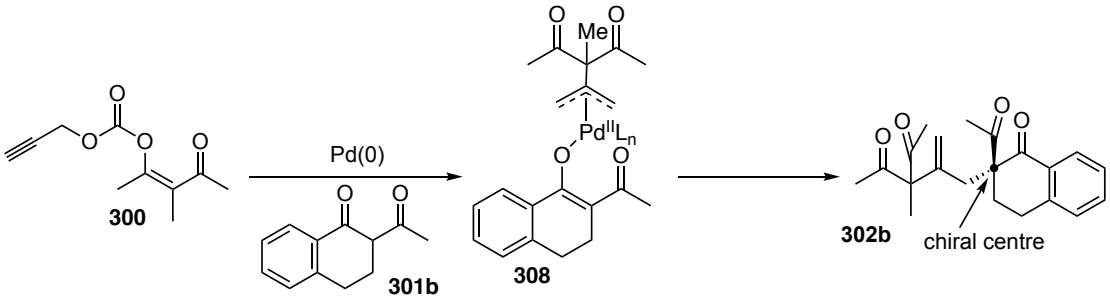
7.3. The Development of Enantioselective Coupling of Nucleophiles

Having successfully developed the coupling of 1,3-dicarbonyl-derived enolates with 1,3-dicarbonyl compounds and *N*-heterocycles in racemic form, focus was shifted to the development of enantioselective variants of the reaction. There are two stages of this process at which enantioselectivity could be imported. The first involves the enantioselective alkenylation of the enolate of the 1,3-dicarbonyl coupling partner (Scheme 87). Specifically, the all-carbon quaternary centre in **322** is introduced by the addition of the enolate at the central carbon atom of the η^3-π-propargylpalladium(II) intermediate in **321**. By using a pro-chiral propargyl enol carbonate and a chiral ligand for palladium, this step could be made to proceed enantioselectively, generating enantio-enriched product **323** following allylic alkylation of a nucleophile (Scheme 85). While the enantioselective alkenylation of nucleophiles with propargylic electrophiles has been precedented (*vide supra,* Scheme 60),[113] the reaction gave a poor yield and enantioselectivity. However, to the best of our knowledge, it is the only known process of an enantioselective palladium-catalysed alkenylation of an enolate in the presence of a second nucleophile and a propargylic electrophile to date.



Scheme 87: The enantioselective alkenylation.

The second chiral centre can be formed through the allylic alkylation of the external nucleophile (Scheme 88). By using propargyl enol carbonate **300**, derived from a symmetrical 1,3-dicarbonyl in the presence of prochiral 1,3-dicarbonyl **301b**, η^3-π-allylpalladium(II) intermediate **308** would be formed. With an appropriate chiral ligand for palladium, an enantioselective allylic alkylation could take place, generating an all-carbon quaternary centre in **302b** in an enantio-enriched form. There are several examples of an enantioselective palladium-catalysed allylic alkylation using propargylic electrophiles,[114] however, these are intramolecular processes, whereas the induction of enantioselectivity *via* allylic alkylation with propargylic electrophiles in an intermolecular sense is not known.



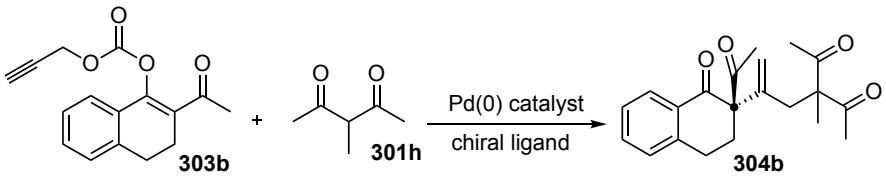
Scheme **88:** The enantioselective allylic alkylation.

Given the lack of success of a diastereoselective reaction, in which *two* chiral centres are formed (*vide supra,* Scheme 76), the development of an

enantioselective variant of such a process was likely to be formidable. Therefore, we sought to investigate each process separately. Notwithstanding, there were a number of difficult challenges that needed to be overcome. Indeed, there is a clear lack of examples of both the enantioselective alkenylation and allylic alkylation of nucleophiles with propargylic electrophiles, suggesting that the development of such processes is an ambitious task. More specifically, the use of a chiral ligand for palladium requires the control of not only the enantioselectivity, but also the regioselectivity and chemoselectivity, whilst maintaining the high yield of the reaction. The simultaneous control of all four of these factors in an intermolecular coupling reaction makes this endeavour both highly challenging and exciting.

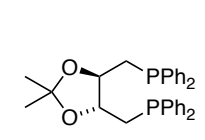
7.3.1. Enantioselective Alkenylation

We first focused on the alkenylation of prochiral propargyl enol carbonate **303b** in the presence of a symmetrical 1,3-dicarbonyl **301h** to generate a quaternary all-carbon centre in **304b** in enantio-enriched form *via* alkenylation (Scheme 89).

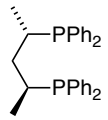


Scheme 89: Induction of enantioselectivity *via* the alkenylation step.

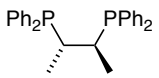
In the first instance, a screen of a broad range of chiral ligands for palladium was performed (Figures 6 and 7).



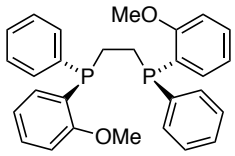
L1: (*R*,*R*)-DIOP



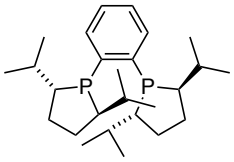
L2: (*S*,*S*)-BDPP



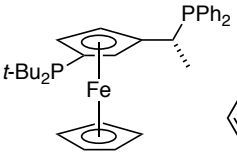
L3: (*S*,*S*)-Chiraphos



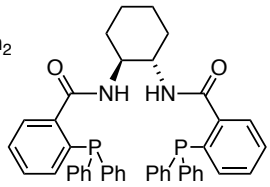
L4: (*R*,*R*)-DIPAMP



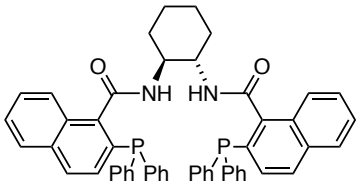
L5: (*R*,*R*)-i-Pr-DUPHOS



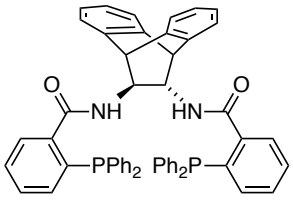
L6: (*R*)-JOSIPHOS



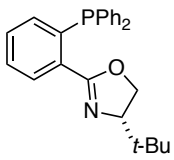
L7: (*S*,*S*)-DACH Phenyl Trost



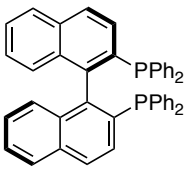
L8: (*S*,*S*)-DACH Naphthyl Trost



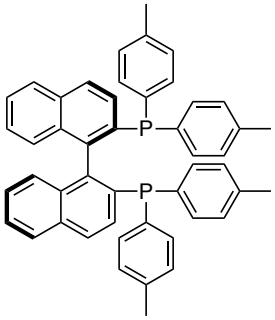
L9: (*S*,*S*)-ANDEN Phenyl Trost



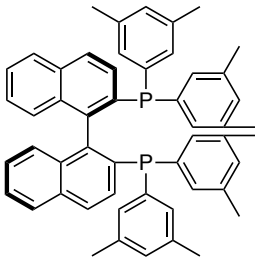
L10: (*S*)-*t*-Bu-PHOX



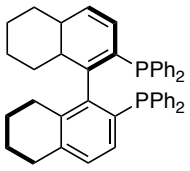
L11: (*R*)-BINAP



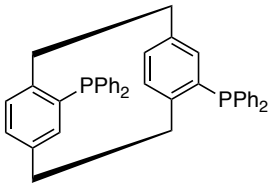
L12: (*R*)-Tol-BINAP



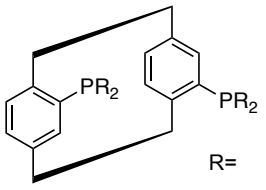
L13: (*R*)-DM-BINAP



L14: (*R*)-H_8-BINAP



L15: (*R*)-Phanephos



L16: (*R*)-Xylyl-Phanephos

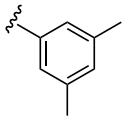
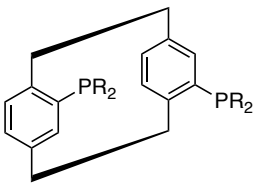
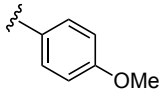


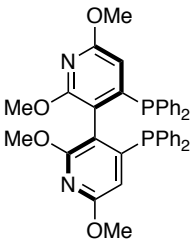
Figure 6: Chiral ligands part 1.



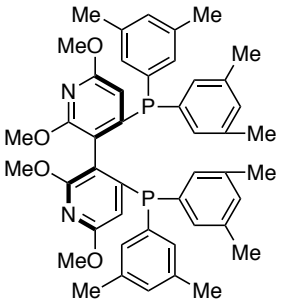
L17: (*S*)-Methoxyphenyl-Phanephos

R=

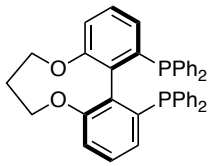




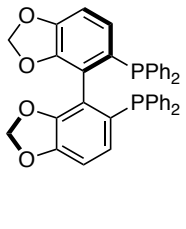
L18: (*R*)-P-PHOS



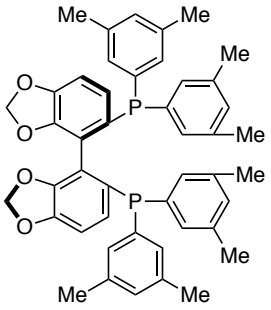
L19: (*R*)-Xylyl-P-PHOS



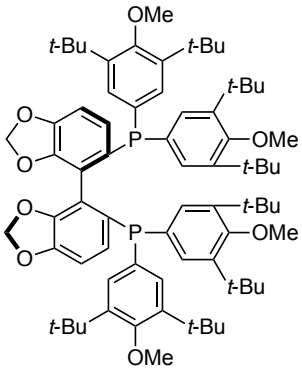
L20: (*R*)-C_3-TunePhos



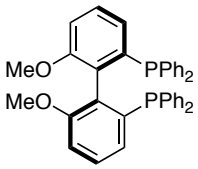
L21: (*R*)-SEGPHOS



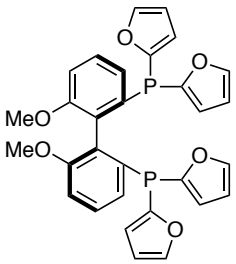
L22: (*R*)-DM-SEGPHOS



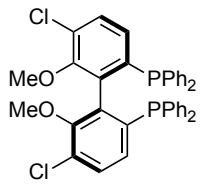
L23: (*R*)-DTBM-SEGPHOS



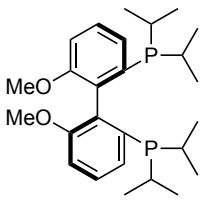
L24: (*R*)-(+)-MeO-BIPHEP



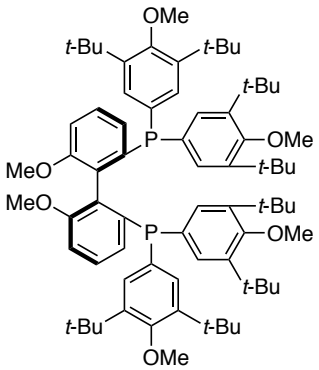
L25: (*R*)-OMe-2-furyl-BIPHEP



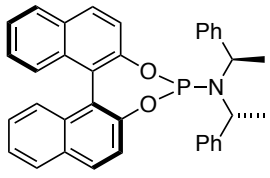
L26: (*R*)-(+)-Cl-MeO-BIPHEP



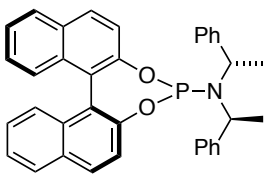
L27: (*R*)-OMe-*i*Pr-BIPHEP



L28: (*S*)-OMe-DTBM-BIPHEP



L29: (*S*,*R*,*R*)-Phosphoramidite

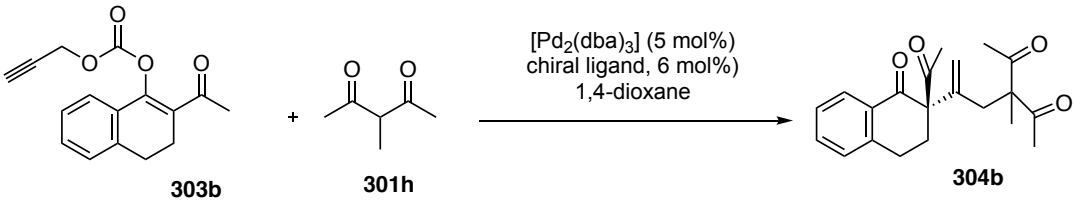


L30: (*S*,*S*,*S*)-Phosphoramidite

Figure 7: Chiral ligands part 2.

The majority of phosphine ligands with an alkyl backbone failed to push the reaction to completion (**L2**-**L4**), with the exception of (*R*,*R*)-DIOP (**L1**), which did invoke the desired reactivity, however, the yield and enantioselectivity was poor (**L1**, chemoselectivity: 7.5:1, regioselectivity: > 19:1, yield: 28%, ee: 5 %.). In addition, DUPHOS (**L5**) and JOSIPHOS (**L6**) failed to afford the product. Trost ligands and (*S*)-*t*-Bu-PHOX, particularly useful in the enantioselective allylic alkylation of enolates,[67] also did not afford the desired product (**L6**-**L10**).

While axially chiral (*R*)-BINAP afforded **304b**, albeit in a low yield and enantioselectivity (**L11**, entry 1, Table 16), the rest of the BINAP family were unsuccessful (**L12-14**, entries 2-4). The Phanephos ligand family (**L15**-**L17**) was noticeably more successful, producing **304b** with complete selectivity and in good yields, however, in all cases, the enantioselectivity was low (entries 5-7). Electron-rich (*R*)-P-PHOS (**L18**) gave a similar result (entry 8). The most enantioselective reaction was with (*R*)-Xylyl-P-Phos (**L19**) as the ligand, affording **304b** in a low yield, but with the highest enantioselectivity (19% ee, entry 9). (*R*)-C_3-Tunephos (**L20**) produced **304b** in a low yield and with lower enantioselectivity (entry 20). The low yields were associated with poorer selectivity, as well as the presence of starting material in the crude product mixtures.



303b **301h** **304b**

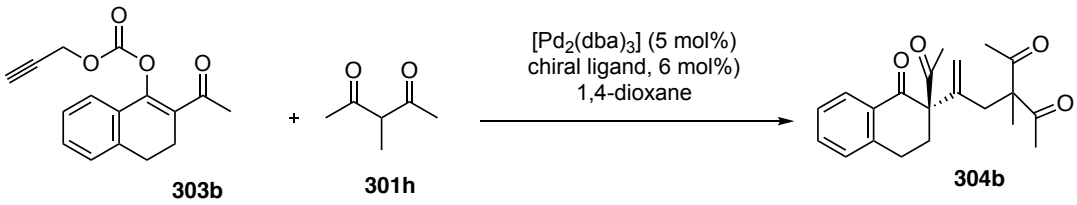
Entry	Ligand	Conditions	Chemo selectivity[a]	Regio selectivity[a]	Yield (%)[b]	ee (%)[c]	Product:S.M. ratio[a]
1	**L11**	RT, 16 h	9.5:2.2[d]:1[e]	> 19:1	11	5	-
2	**L12**	80 °C, 2 h,	-	-	-	-	-
3	**L13**	80 °C, 2 h	-	-	-	-	-
4	**L14**	80 °C, 2 h	-	-	-	-	-
5	**L15**	**RT, 16 h**	Full selectivity	**> 19:1**	**54**	**7**	**-**
6	**L16**	RT, 16 h	Full selectivity	> 19:1	62	–5	-
7	**L17**	RT, 16 h	Full selectivity	> 19:1	55	–2	-
8	**L18**	RT, 16 h	5.5:1.8[d]:1[e]	> 19:1	34	6	-
9	**L19**	**RT, 16 h**	**2.8:1[d]**	**> 19:1**	**17**	**19**	**1.9:1**
10	**L20**	80 °C, 2 h 120 °C, 2h	11:4.6[d]: 1[e]	> 19:1	13	13	-

[a]Determined by ^{1}H NMR analysis of the crude product mixtures. [b]Isolated yield. [c]The enantioselectivity was determined by chiral HPLC. [d]Homo-coupling of **303b**. [e]Homo-coupling of **301h**. S.M. = starting material.

Table 16: Ligand screen for enantioselective alkenylation.

Two of the three axially-chiral SEGPHOS ligands **L21** and **L22** gave rise to **304b** in 22% yield and 11% ee, and 28% and 15% ee, respectively (entries 1 and 2, Table 17), with one of the ligands of the SEGPHOS family failing to

push the reaction to completion (entries 1-3). The final set of ligands that successfully mediated the reaction was the BIPHEP family (**L24-L28**, entries 4-8). BIPHEP ligands had been previously successful in the enantioselective synthesis of spirocyclised oxindoles *via* alkenylation and allylic alkylation.[113] However, in the context of our intermolecular cross coupling reaction, while the yields were moderate, enantioselectivity remained low. Finally, the phosphoramidite ligand family, often successful in the iridium-catalysed enantioselective allylic alkylation reactions,[121] failed to push the reaction to completion, even when heated to 120 ^{o}C (**L29** and **L30,** entries 9 and10).



303b **301h** **304b**

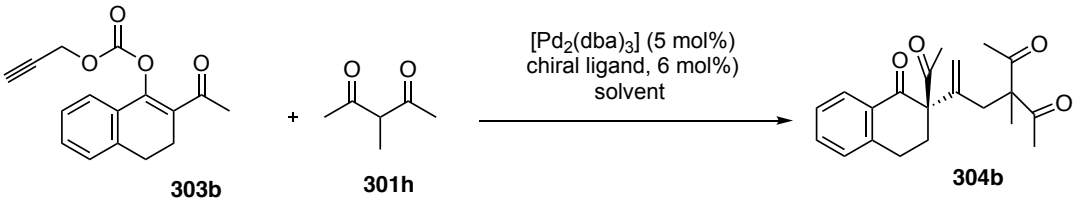
Entry	Ligand	Conditions	Chemo selectivity[a]	Regio selectivity[a]	Yield (%)[b]	ee (%)[c]	Product:S.M. ratio[a]
1	**L21**	RT, 16 h	2.2:1[d]	> 19:1	22	11	1.6:1
2	**L22**	60 °C, 16 h	8.2:1[d]	> 19:1	28	15	-
3	**L23**	-	-	-	-	-	-
4	**L24**	-	-	-	-	-	-
5	**L25**	60 °C, 16 h	Full selectivity	> 19:1	53	–3	6.1:1
6	**L26**	RT, 16 h	10:2[d]:1[e]	> 19:1	48	10	-
7	**L27**	RT, 16 h	1.4[d]:1.2[e]:1	> 19:1	11	–12	-
8	**L28**	80 °C, 2 h,	-	-	-	-	-
9	**L29**	80 °C, 2 h, 120 °C, 2h	-	-	-	-	-
10	**L30**	80 °C, 2 h	-	-	-	-	-

[a]Determined by ^{1}H NMR analysis of the crude product mixtures. [b]Isolated yield. [c]The enantioselectivity was determined by chiral HPLC. [d]Homo-coupling of **303b**. [e]Homo-coupling of **301h**. S.M. = starting material.

Table 17: Ligand screen for enantioselective alkenylation.

Overall, it was not possible to identify a ligand which afforded **304b** both in a good yield and with high regio-, chemoselectivity and enantioselectivity. Two ligands were selected for further optimisation: one gave a good yield of product (**L15**) and the other gave rise to higher enantioselectivity, but a poorer yield (**L19**). In this context, a solvent screen with each ligand was performed

(Table 18). Overall, six solvents were screened, from more polar solvents such as methyl *tert*-butyl ether, dimethoxyethane, tetrahydrofuran and diethyl ether, to non-polar solvents such as dichloromethane or toluene. Despite the vast array of solvents screened, the improvement of the results was not substantial. When using **L15** as the ligand, there were some small gains in enantioselectivity, for instance, using dichloromethane at 40 ^{o}C and tetrahydrofuran as the solvent at 60 ^{o}C for 2 hours may increase the enantioselectivity (entries 2 and 6, Table 19), however, the increase in enantioselectivity was not significant enough (in addition to a low yield being produced in respect to using dichloromethane). While using diethyl ether, dimethyoxethane and toluene increased the yield (entries 4, 5 and 7) there was no increase in enantioselectivity. Using **L19**, the reaction in dichloromethane resulted in product **304b** being formed with a higher enantioselectivity of 30% (entry 9), however the yield of **304b** was low (13%). Heating the reaction in 1,4-dioxane to 80 ^{o}C did not increase the enantioselectivity of the reaction, although it did increase the yield to 44% (entry 8). Reactions in dimethoxyethane, diethyl ether, methyl *tert*-butyl ether and toluene as solvents showed no improvement in enantioselectivity (entries 10, 11 and 12). The reaction in tetrahydrofuran with **L19** as the ligand resulted in an enhancement in enantioselectivity by 2%, as well as an increase in yield by 32% (entry 13). With these improved results, (*R*)-Xylyl-P-PHOS (**L19**) in THF at 60 ^{o}C for 2 hours were the chosen conditions for the subsequent substrate screen.



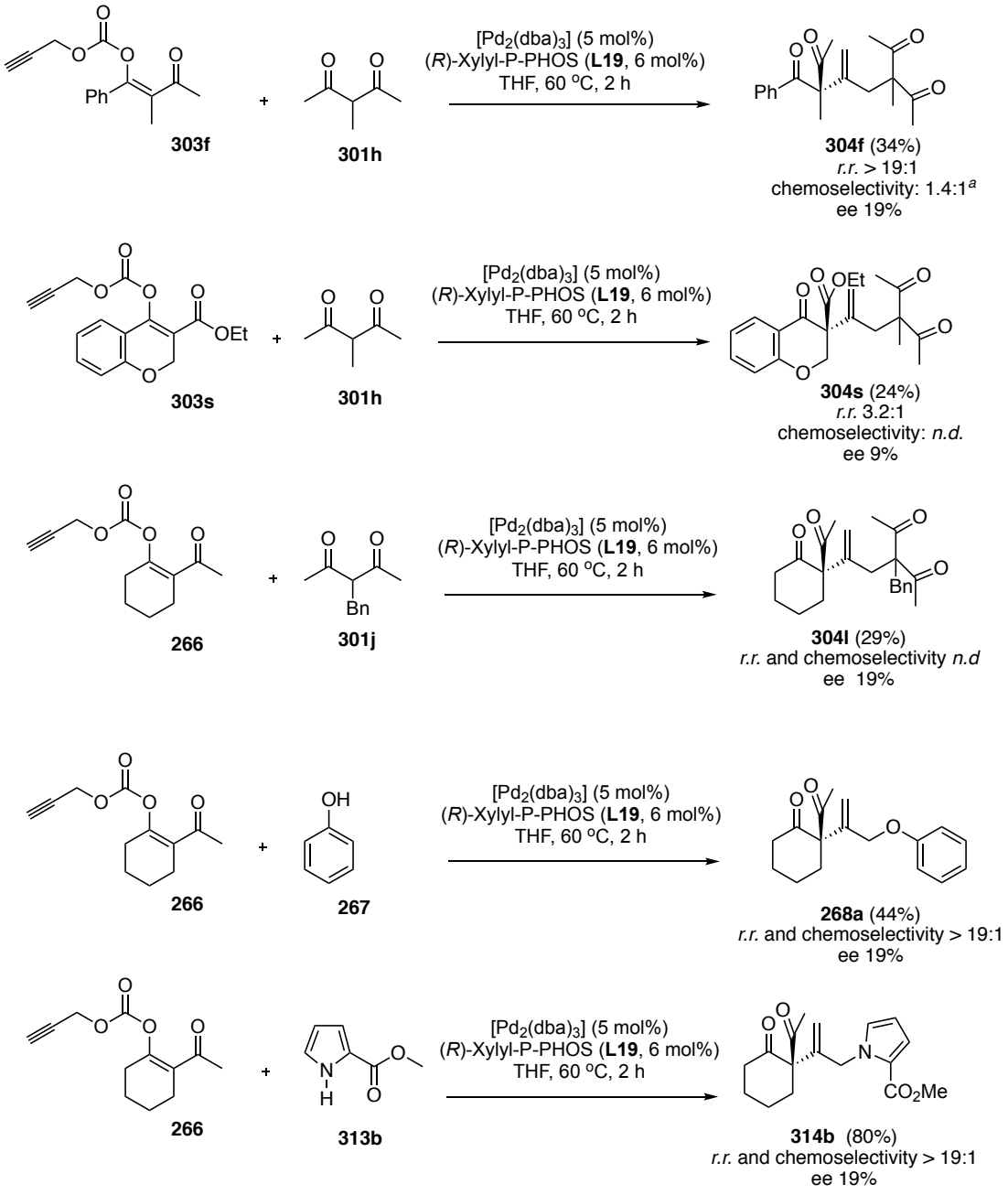
303b **301h** **304b**

Entry	Ligand	Solvent	Conditions	Chemo selectivity[a]	Regio selectivity[a]	Yield (%)[b]	ee (%)[c]
1	**L15**	1,4-Dioxane	RT, 16 h	Full Selectvity	> 19:1	54	7
2	**L15**	CH_2Cl_2	40 °C, 2 h	2.3:1.4[d]:1[e]	3.4:1	17	8
3	**L15**	DME	RT, 16 h	6.2:1.8[d]:1[e]	> 19:1	48	7
4	**L15**	Et_2O	RT, 16 h	Full selectivity	> 19:1	75	5
5	**L15**	MTBE	RT, 16 h	Full selectivity	> 19:1	73	4
6	**L15**	THF	RT, 16 h 60 °C, 2 h	Full selectivity	> 19:1	61	11
7	**L15**	Tol	RT, 16 h	Full selectivity	> 19:1	53	1
8	**L19**	1,4-Dioxane	80 °C, 2 h,	10:1.3[e]:1[d]	> 19:1	44	14
9	**L19**	CH_2Cl_2	40 °C, 2 h,	2.2:1.4[d]:1[e]	> 19:1	13	30
10	**L19**	DME	60 °C, 2 h,	10:3.6[d]:1[e]	> 19:1	37	11
11	**L19**	Et_2O	40 °C, 2 h,	3.6:1.3[c]:1[d]	> 19:1	42	11
12	**L19**	MTBE	80 °C, 2 h,	13:1.6[c]:1[d]	> 19:1	57	17
13	**L19**	**THF**	**60 °C, 2h**	**16:3.4[c]:1[d]**	**> 19:1**	**57**	**21**
14	**L19**	Tol	80 °C, 2h	16:3.4[c]:1[d]	> 19:1	51	7

[a]Determined by ^{1}H NMR analysis of the crude product mixtures. [b]Isolated yield. [c]The enantioselectivity was determined by chiral HPLC. [d]Homo-coupling of **303b**. [e]Homo-coupling of **301h**.

Table 18: Solvent screen for enantioselective alkenylation.

A substrate scope study was performed using the most effective conditions identified in the solvent screen (Scheme 90). When linear prochiral enol carbonate **303f** was coupled with 3-methyl-2,4-pentanedione (**301h**), **304f** was isolated in 34% yield and 19% ee, whereas the reaction of 4-chromanone-derived propargyl enol carbonate **303s** with **301h** afforded **304s** in 24% yield and 9% ee. Using 2-acetylcyclohexanone-derived carbonate **266** with linear 1,3-diketone **301j** afforded product **304l** in a poor yield and low enantioselectivity. Finally, the coupling of the same propargyl enol carbonate **266** with phenol and pyrrole nucleophiles **268** and **313b** afforded products **268** and **314b** in 44% and 80% yields, respectively, and with low enantioselectivity in both cases (19% ee).

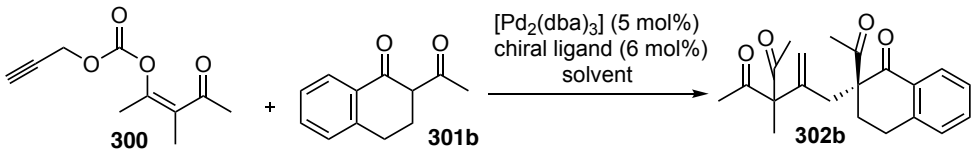


[a]Homo-coupling of the propargyl enol carbonate.

Scheme 90: Substrate scope of the enantioselective alkenylation.

7.3.2. The Enantioselective Allylic Alkylation

Following the attempted development of an enantioselective alkenylation reaction, attention was turned to the enantioselective allylic alkylation using a propargyl enol carbonate derived from an achiral 1,3-diketone, such as **300**, and a chiral external nucleophiles, such as **301b** (Scheme 91).

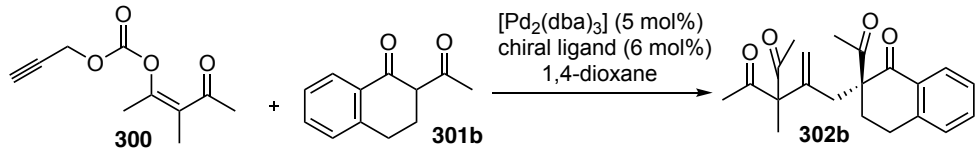


Scheme 91: Enantioselective allylic alkylation.

Using the same chiral ligands (*vide supra*, Figures 5 and 6), a comprehensive ligand screen was performed (Table 20). The first set of ligands **L1-L10** failed to afford desired product **302b**, with the exception of (*R*,*R*)-DIOP (**L1**), which gave rise to **302b** in a low 37% yield, a moderate 6:2.2:1 chemoselectivity, full regioselectivity and 10% ee.

Utilisation of the BINAP ligand **L11-L14** family led to an increase in the enantioselectivity of the allylic alkylation (Table 19, entries 1-4). (*R*)-Tol-BINAP (**L12**) gave particularly good results, namely 68% yield of **302b** and higher enantioselectivity (27% ee). Unexpectedly, (*R*)-DM-BINAP (**L13**), while giving rise to a good yield of **302b**, led to negligible enantioselectivity despite its structural similarity to (*R*)-Tol-BINAP (**L12**). Reactions with (*R*)-BINAP and (*R*)-H_8-BINAP (**L11** and **L14**) were both not as enantioselective as that with **L12**, and lower yielding. The Phanephos family afforded high yields of **302b**, but the enantioselectivity was low (**L15-L17**, entries 5-7). While (*R*)-P-PHOS (**L18**) led to an improvement in enantioselectivity (24% ee), the reaction with

(*R*)-Xylyl-P-PHOS (**L19**) was not enantioselective (entries 8-9). (*R*)-C_3-Tunephos (**L20**) produced **302b** with the highest enantioselectivity, however, the product was formed in a low yield (entry 10).



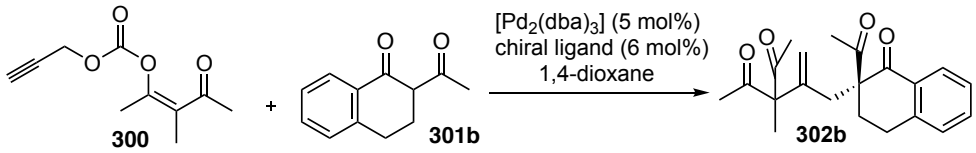
Entry	Ligand	Conditions	Chemo selectivity[a]	Regio selectivity[a]	Yield (%)[b]	ee (%)[c]	Product:S.M. ratio[a]
1	**L11**	RT, 16 h	5.3:1.4[e]:1[d]	13:1	40	11	-
2	**L12**	**RT, 16 h**	**7.9:1.3[e]:d[c]**	**> 19:1**	**68**	**27**	**-**
3	**L13**	RT, 16 h	5.9:1.4[e]:1[d]	> 19:1	49	1	-
4	**L14**	RT, 16 h	6.4:1.3[e]:d[c]	18:1	22	1	-
5	**L15**	RT, 16 h	12:1.1[e]:1[c]	> 19:1	62	13	
6	**L16**	RT, 16 h	Full selectivity	> 19:1	73	12	-
7	**L17**	RT, 16 h	Full selectivity	> 19:1	42	16	-
8	**L18**	RT, 16 h	6.3:1.3[e]:1[d]	>18:1	55	24	-
9	**L19**	RT, 16 h	5.4:1.7[d]:1[e]	14:1	31	2	-
10	**L20**	RT, 16 h	10:3.4[e]: 1[d]	> 19:1	37	34	2.8:1

[a]Determined by ^{1}H NMR analysis of the crude product mixtures. [b]Isolated yield. [c]The enantioselectivity was determined by chiral HPLC. [d]Homo-coupling of **300**. [e]Homo-coupling of **301b**. S.M. = starting material.

Table 19: Ligand screen for the enantioselective allylic alkylation.

The SEGPHOS family provided the best results regarding enantioselectivity (Table 20, entries 1-3). Although axially-chiral SEGPHOS ligand **L21** produced **302b** in a moderate yield, the enantioselectivity was higher. (*R*)-DM-

SEGPHOS (**L22**) gave a poor ee of **302b** (entry 2), whereas (*R)*-DTBM-SEGPHOS (**L23**) provided product **302b** with the best enantioselectivity (39%), albeit in a lower yield of 37% (entry 3). The BIPHEP family gave varying results (**L24-L28**, entries 4-8), and no improvement was observed with regards to the enantioselectivity as compared to (*R*)-DTBM-SEGPHOS (**L23**). Finally, the phosphoramidite family **L29-L30** failed to push the reaction to completion (entries 9-10).



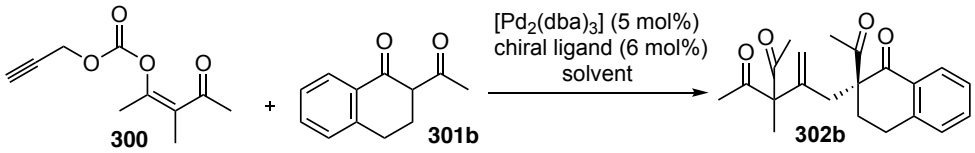
Entry	Ligand	Conditions	Chemo selectivity[a]	Regio selectivity[a]	Yield (%)[b]	ee (%)[c]	Product:S.M. ratio[a]
1	**L21**	RT, 16 h	8.5:2[e]:1[d]	14:1	48	32	7.1:1
2	**L22**	RT, 16 h	5.7:1.4[e]:1[d]	14:1	42	6	-
3	**L23**	**80 °C, 2 h**	**5.9:1.7[e]:1[d]**	**> 19:1**	**37**	**39**	**-**
4	**L24**	80 °C, 2 h	15:2.9[e]:1[d]	> 19:1	59	21	-
5	**L25**	RT, 16 h	11:1.5[e]:1[d]	> 19:1	39	–4	-
6	**L26**	RT, 16 h	Full selectivity	> 19:1	48	12	-
7	**L27**	80 °C, 2 h	Poor selectivity	> 19:1	17	10	-
8	**L28**	80 °C, 2 h	-	-	-	-	-
9	**L29**	80 °C, 2 h	-	-	-	-	-
10	**L30**	80 °C, 2 h	-	-	-	-	-

[a]Determined by ^{1}H NMR analysis of the crude product mixtures. [b]Isolated yield. [c]The enantioselectivity was determined by chiral HPLC. [d]Homo-coupling of **300**. [e]Homo-coupling of **301b**. S.M. = starting material.

Table 20: Ligand screen for the enantioselective allylic alkylation.

As a result of this study, two ligands were chosen for further reaction optimisation *via* a solvent screen: (*R*)-Tol-BINAP (**L12**) gave the highest yield of **302b** but the enantioselectivity was lower, and (*R*)-DTBM-SEGPHOS (**L23**), which produced **302b** with the highest enantioselectivity. In this context, we were unsuccessful in improving the levels of enantioselectivity while maintaining a high yield of product when screening the reaction with a number

of solvents using (*R*)-Tol-BINAP (**L12**) as the ligand (Table 21, entries 2-6). Similarly, the solvent screen using (*R*)-DTBM-SEGPHOS **L23** failed to afford product **302b** in a yield above 30% and produced only marginal improvements in enantioselectivity (entries 7-13). Attempts to lower the reaction temperature with **L23** as the ligand in a 1,4-dioxane solvent did not improve the enantioselectivity either (entries 8 and 9). Therefore, in both cases, 1,4-dioxane was chosen as the optimal solvent. Given that the enantioselectivity with **L23** as the ligand in 1,4-dioxane (39%) was only marginally higher than that obtained with **L12** (27% ee), but the yield was significantly lower (37% for **L23** vs 68% for **L12**), the remainder of this study centred around reactions with **L12** as the chiral ligand for palladium.

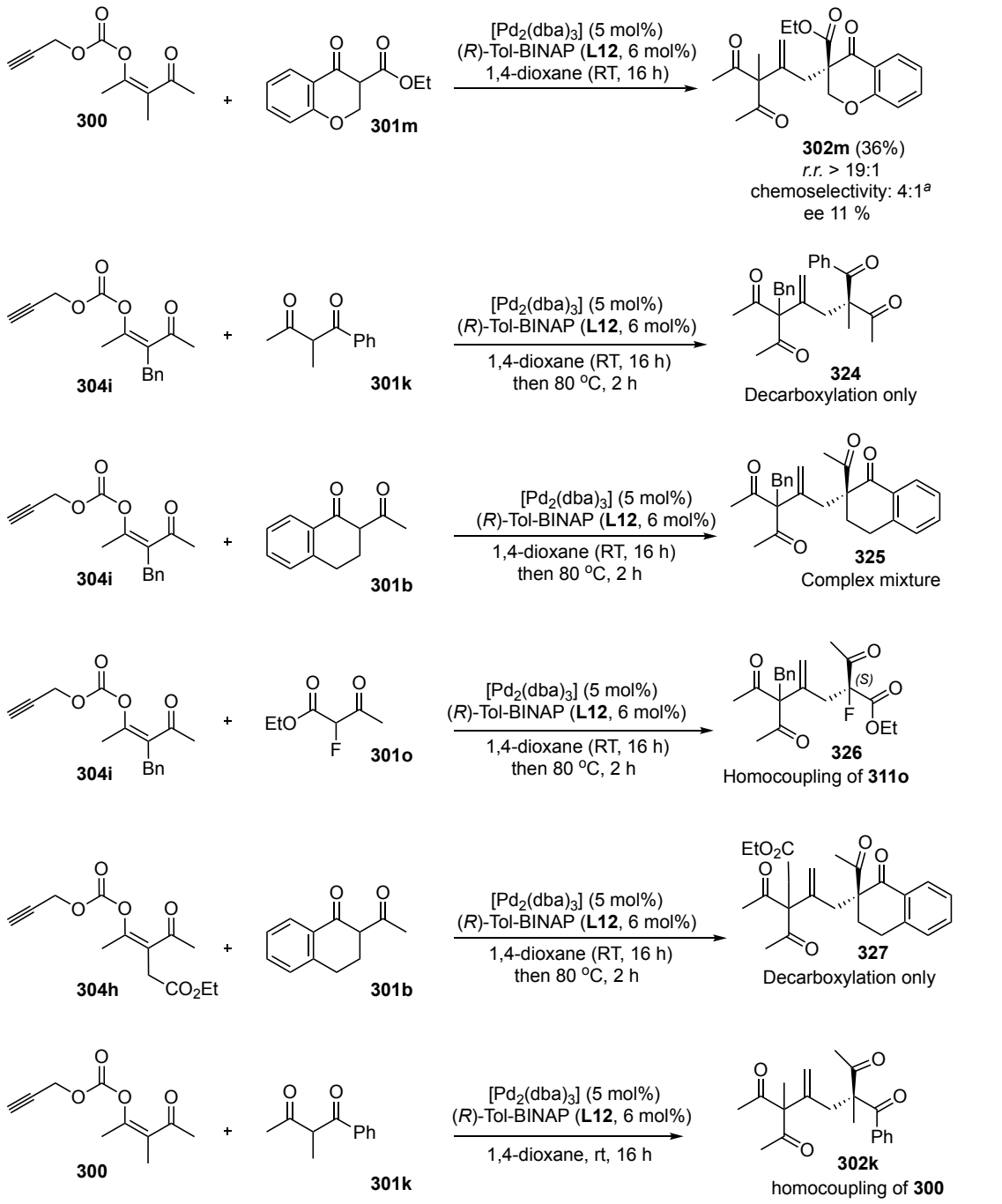


Entry	Ligand	Solvent	Conditions	Chemo[a]	Regio[a]	Yield (%)[b]	ee (%)[b]
1	**L12**	**1,4-dioxane**	**RT, 16 h**	**7.9:1.3[e]:1[d]**	**> 19:1**	**68**	**27**
2	**L12**	DME	RT, 16 h	2.5:4[e]:1[d]	1.5:1	13	23
3	**L12**	Et_2O	RT, 16 h	5.8:2.4[e]:1[d]	8.1:1	37	30
4	**L12**	MTBE	RT, 16 h	6.5:2.3[e]:1[d]	> 19:1	39	27
5	**L12**	THF	RT, 16 h then 40 °C, 2 h	1.7:2.0[e]:1[d]	1.4:1	18	24
6	**L12**	Toluene	RT, 16 h, then 40 °C, 2 h	4.9:1.6[e]:1[d]	> 19:1	46	31
7	**L23**	1,4-dioxane	80 °C, 2 h	5.9:1.7[e]:1[d]	> 19:1	37	39
8	**L23**	1,4-dioxane	60 °C, 2 h	6.4:1[d]	> 19:1	15	40
9	**L23**	1,4-dioxane	40 °C, 16 h	6.9:1.5[e]:1[d]	11:1	26	41
10	**L23**	Et_2O	40 °C, 2 h	6.3:1[e]	> 19:1	31	46
11	**L23**	MTBE	60 °C, 2 h	10:1[d]:1[e]	> 19:1	29	43
12	**L23**	THF	60 °C, 2 h	6.7:1.6[e]:1[d]	> 19:1	15	41
13	**L23**	Toluene	60 °C, 2 h	7:1.5[e]:1[d]	> 19:1	28	37

[a]Determined by ^{1}H NMR analysis of the crude product mixtures. [b]Isolated yield. [c]The enantioselectivity was determined by chiral HPLC. [d]Homo-coupling of **300**. [e]Homo-coupling of **301b**.

Table 21: Ligand screen for the enantioselective allylic alkylation.

In the final stage of this work, focus shifted to the extension of the substrate scope using **L12** as the ligand (Scheme 92). While propargyl enol carbonate **300** was successfully coupled with β-ketoester **301m** to afford **302m** in 42% yield and 11% ee, we were unable to isolate products **324-327** or **302k**, having screened several propargyl enol carbonates (**300**, **304i** and **304h**) and 1,3-dicarbonyl compounds (**301b**, **301k** and **301o**). In most cases, either decarboxylation took place but no desired coupling occured (**324**, and **327**), homo-coupling of one of the partners took place (**326** and **302k**), or a complex mixture of products was obtained (**325**). In light of these results with ligand **L12**, a further investigation of the substrates using **L23** as the chiral ligand is warranted.



[a]Homo-coupling of the propargyl enol carbonate.

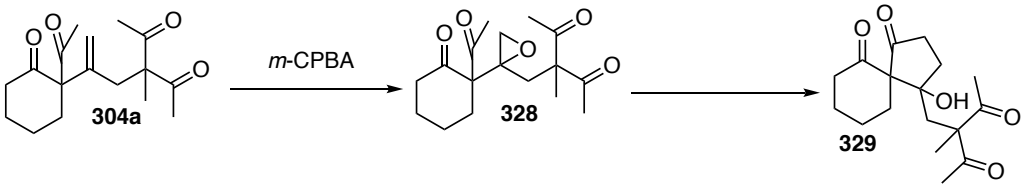
Scheme 92: Substrate scope for the enantioselective allylic alkylation.

Overall, this enantioselective catalysis study proved to be extremely challenging. Despite an extensive ligand screen and optimisation, both yields and enantioselectivities were relatively low. Unfortunately, the reaction

conditions used to obtain the best result for one substrate were not readily transferrable to others.

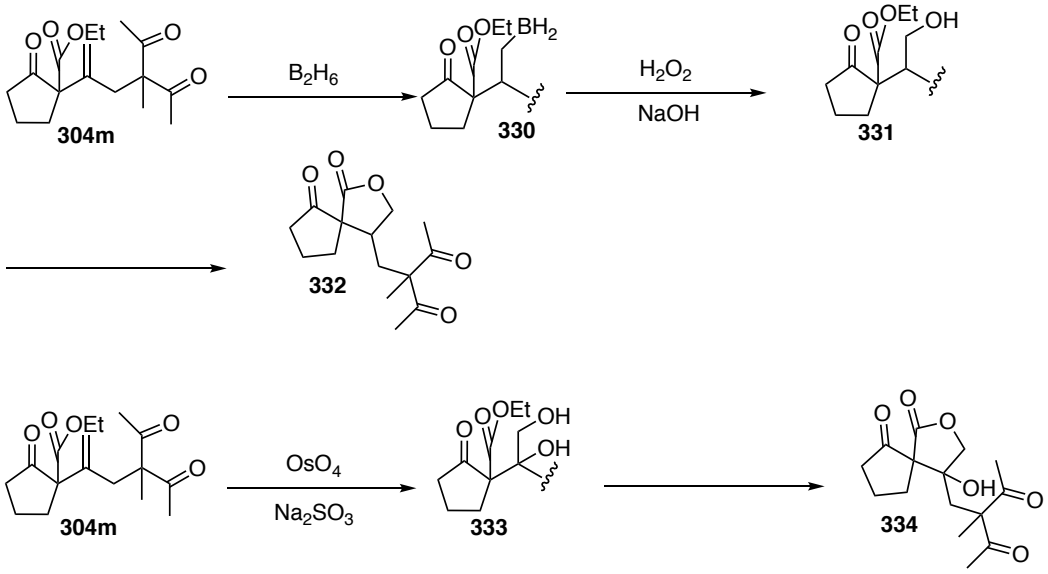
8. Future Work

Having successfully developed access to a range of products *via* the catalytic coupling of nucleophiles, further functionalisation of the cross-coupled products needs to be investigated. In particular, all of the building blocks obtained by this methodology contain a disubstituted alkene, which could be further derivatised to enable cyclisation reactions towards novel spirocyclic compounds. For example, the alkene in **304a** could be epoxidised to form **328**, and treated with a base to generate spirocycle **329** (Scheme 93).



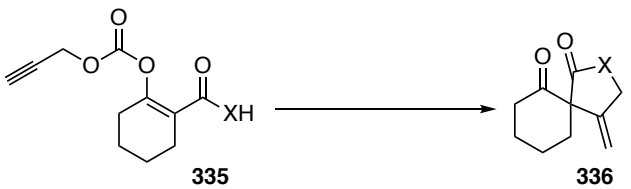
Scheme 93: Functionalisation of the double bond in **304a**.

The double bond created in β-ketoester **304m** can also be functionalised (Scheme 94). Hydroboration can lead to intermediates **330** and **331**, followed by cyclisation with the ester as the intramolecular electrophile to afford spirocyclic product **332**. Similarly, dihydroxylation of **304m** would form diol **333**, followed by intramolecular cyclisation to form **334**.



Scheme 94: Functionalisation of the double bond in **304a**.

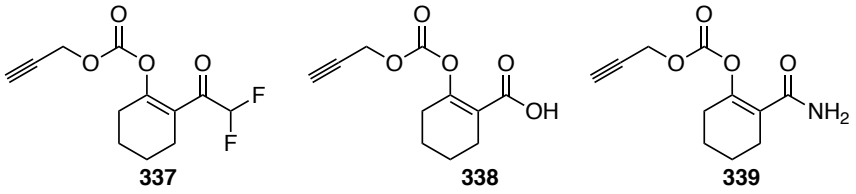
Having developed an intermolecular coupling reaction as part of this research, we aim to extend this work to an intramolecular process, paving the way to the direct synthesis of spirocyclic and fused bicyclic molecular structures in a single step. For example, by utilising enol carbonate **335**, containing an intramolecular nucleophile X, spirocyclic structures of type **336** could potentially be obtained, which contains an all-carbon quaternary centre (Scheme 95).



Scheme 95: Mechanism for spirocycle formation *via* an intramolecular decarboxylative cross-coupling reaction.

Indeed, we have already begun work in the area by designing substrates **337**-

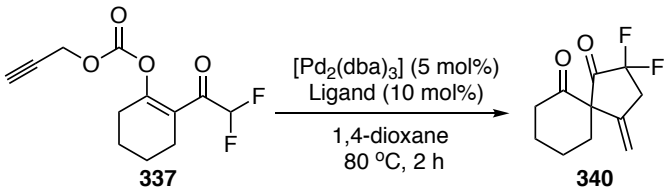
339 (Figure 8), each of which contains an appended nucleophilic side-chain once deprotonated: an acidic fluorinated ketone in **337**, a carboxylic acid in **338** and an amide in **339**.



337 **338** **339**

Figure 8: Propargyl enol carbonates for spirocycle formation.

Fluorinated enol carbonate **337** has already been prepared and the opportunity for spirocyclisation has been investigated by screening several ligands and solvents (Table 22). Unfortunately, we have been unable to obtain **340** thus far due to either lack of reactivity or decomposition. However, heteroatom-based substrates **338** and **339** are due to be tested.



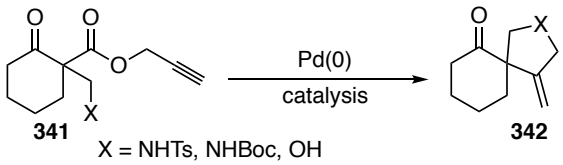
337 **340**

Entry	Ligand	Outcome
1	PCy_3	No reaction[a]
2	Dppe	No reaction[a]
3	$P(C_6F_5)_3$	No reaction[a]
4	BINAP	Decarboxylation only
5	SPhos	Decarboxylation only
6	dppm	Decarboxylation only
7	dppp	Decarboxylation only
8	dppf	Decomposition
9	*t*-Bu-Xantphos	Decomposition
10	DPEphos	Decomposition
11	Xantphos	Decomposition
12	$Pd(PPh_3)_4$[b]	Decomposition

[a]Reaction was performed at 120 °C; Oxidative addition occurred but no reaction beyond that step. [b]$[Pd(PPh_3)_4]$ was used in place of $[Pd_2(dba_3)]$.

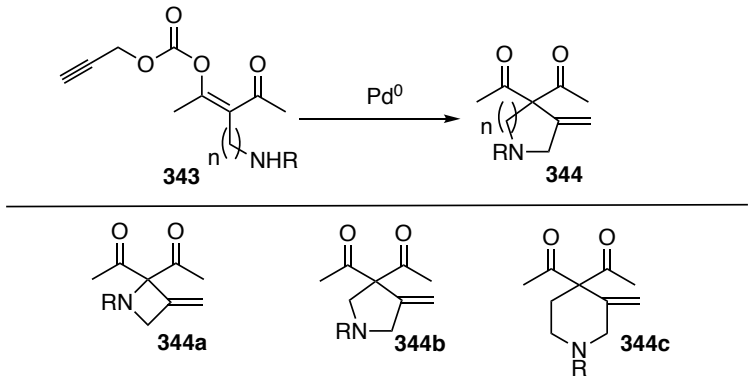
Table 22: Ligand screen for spirocyclic **340** formation.

Alternatively, propargyl enol carbonate of type **341** could be utilised which would give rise to oxygenated and nitrogenated spirocycles **342**, depending on the nucleophilic side-chain used (Scheme 96).



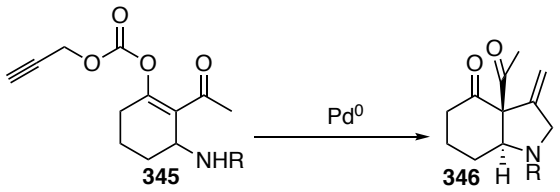
Scheme 96: Palladium-catalysed spirocyclisation with tethered nucleophiles.

The intramolecular coupling reaction also has the potential to lead to nitrogen heterocycles from linear substrates (Scheme 97). More specifically, by varying the nitrogen-bearing side-chain, all-carbon quaternary centre containing azetidines **344a**, pyrrolidines **344b** and piperidines **344c** could be accessed.



Scheme 97: Linear substrates for heterocycle synthesis.

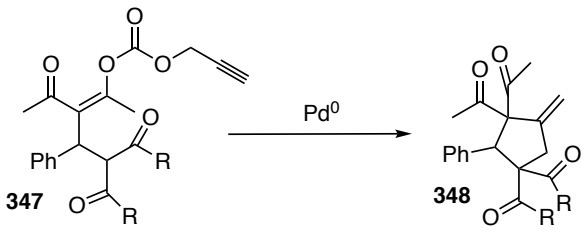
However, if the propargyl enol carbonate is derived from a 1,3-dicarbonyl containing a cyclic ketone, then *trans*-fused bicyclic products **346** could be obtained from **345** in this enolate/amine cyclisation reaction (Scheme 98).



Scheme 98: Palladium-catalysed synthesis of fused bicycles.

Similarly, by replacing the nitrogen containing side-chain with a carbon

nucleophile in **347**, obtained *via* a Michael process (Scheme 99), a tethered bis-nucleophile **348** would be accessed. A palladium-catalysed cyclisation of **347** would give rise to highly functionalised carbocycle **348**, which represents an intramolecular variant of the coupling reaction of 1,3-dicarbonyl compounds presented in this thesis.



Scheme 99: Palladium-catalysed synthesis of functionalised carbocycles.

Finally, the catalytic palladium-mediated reactions would enable us to explore the scope of generating the quaternary carbon centre in an enantioselective manner. Overall, the development of these processes will not only open up opportunities to explore untapped areas of 3D chemical space, but this will also provide access to polar and sp^3-rich building blocks, likely to be of interest to medicinal chemists.[2]

9. Conclusions

An intermolecular regio- and chemoselective decarboxylative palladium-catalysed coupling of two carbon nucleophiles, namely 1,3-dicarbonyl compounds, has been clearly demonstrated. The transformation generates two C–C bonds and two all-carbon quaternary centres in a single operation. The reaction is predictably regioswitchable, providing access to either of the two regioisomers of product depending on the choice of the propapgyl enol carbonate substrate (*vide supra,* Tables 4 and 6). In addition to 1,3-diketones, other 1,3-dicarbonyl compounds, such as β-ketoesters, lactones, lactams and sulfones have enabled the incorporation of oxygen, nitrogen and sulfur functionality. A mechanism of the reaction has been proposed based on deuterium labeling studies (*vide supra*, Scheme 79).

A decarboxylative palladium-catalysed coupling reaction of 1,3-dicarbonyl compounds with weakly acidic *N*-heterocycles under neutral conditions, which generates new C–C and C–N bonds and an all-carbon quaternary centre in a single step, has been developed. The broad scope of this transformation was demonstrated through the coupling of a variety of 1,3-dicarbonyl compounds with a range of indoles and pyrroles, as well as other *N*-heterocyclic substrates. In all cases, the reactions proceeded with full regio- and chemoselectivity, efficiently controlled by utilising a propargyl enol carbonate as one of the coupling partners. The reaction mechanism was deduced through deuterium-labelling studies, which is analogous to that of the coupling of two 1,3-dicarbonyl compounds.

The development of enantioselective alkenylation and allylic alkylation for the stereoselective construction of one of the two chiral all-carbon quaternary centres in the coupling of 1,3-dicarbonyl compounds with nucleophiles has been undertaken (*vide supra*, Scheme 87 and 89). In this context, a broad range of chiral ligands for palladium were screened. The enantioselective alkenylation afforded products in moderate yields and low ees. The enantioselective allylic alkylation was less successful: although one product was obtained with an ee of 40%, the yield was low and the reaction was not general across a range of substrates. There is a clear direction where the project can go next, with methods for the catalytic synthesis of novel cyclic and spirocyclic compounds already being developed in our laboratory.

10. Experimental Section

10.1. General Experimental Section

All reactions were performed under an argon atmosphere in oven-dried glassware. All solvents used were either purchased and kept over molecular sieves or passed through an activated alumina column. All other reagents and solvents were used as supplied and all aqueous reagents were saturated unless specified otherwise.

Thin layer chromatography (TLC) was carried out using pre-coated Fluka analytical silica gel on aluminium foils, with a fluorescent indicator (254 nm). Column chromatography was carried out using Fisher Silica 60 Å particle size. Petrol refers to the fraction of petroleum ether that boils between 40-60 ^{o}C. Visualisation of the TLC plates was done *via* staining with potassium permanganate or aqueous acidic ammonium molybdate (IV).

NMR spectra were recorded using a Bruker 400 and 300 MHz Ultra Shield Plus spectrometer and are reported as follows: chemical shift, δ_H (in parts per million, ppm), multiplicity, coupling constant, *J*, number of protons and assignment. Couplings are classed as singlet, s, doublet, d, triplet, t, quartet, q, quintet, quint, septet, sept, sextet, sext, broad, br, multiplet, m, or a combination of these. ^{13}C NMR spectra were recorded on the same instruments at 100 MHz and 75 MHz, respectively. Residual solvent $CHCl_3$ was referenced at 7.26 ppm for ^{1}H NMR spectra and the central signal of $CDCl_3$ was referenced to 77.0 ppm for ^{13}C NMR spectra. A range of NMR

techniques (DEPT-135, COSY, HMBC and HSQC) were used to aid the analysis of ^{1}H and ^{13}C spectra. For clarity in the NMR assignments, atoms are numbered in the experimental diagrams. This numbering does not correspond to IUPAC nomenclature.

IR spectroscopy analysis was performed on an Agilent Technologies Cary 630 FTIR spectrometer.

Accurate mass spectrometry was recorded using electron spray ionisation on Shimadzu HRMS LCMS-IT-TOF mass spectrometer at Lancaster University, Lancaster UK, or the EPSRC Finnigan MAT 95 XP instrument at the UK EPSRC National Mass Spectrometry facility, Swansea, UK.

Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected.

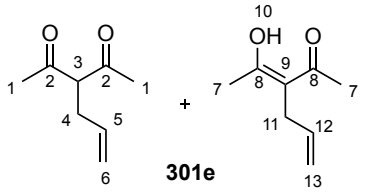
X-ray crystallography data was recorded using a Beamline I19 diffractometer AT the UK EPSRC National Crystallography Service at the University of Southampton or at Lancaster University, using an Agilent Supernova diffractor for single crystal X-ray diffraction.

HPLC analysis was performed using a Shimdazu NexeraX2 instrument and this was used to determine enantiomeric excesses.

10.2. Experimental Procedures.

10.2.1. Synthesis of 1,3-Dicarbonyl Compounds.

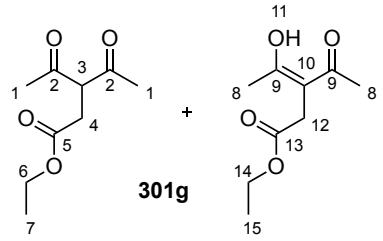
3-Allylpentane-2,4-dione (301e):



301e

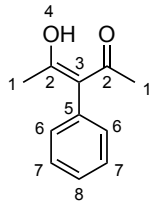
According to a literature procedure,[122] to a solution of acetylacetone (1.50 mL, 15.0 mmol) in acetone (20 mL) was added potassium carbonate (2.40 g, 18.0 mmol) portionwise. The suspension was stirred at room temperature for 15 minutes. Allyl bromide (1.55 mL, 18.0 mmol) was added dropwise. The mixture was heated to reflux at 80 °C for 18 hours. The mixture was filtered under reduced pressure and the filtrate was concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 99:1] afforded **301e** (355 mg, 17%) as a pale liquid. R_F 0.65 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2980, 1699 (C=O), 1597, 1418; δ_H (400 MHz, $CDCl_3$, 1.4:1 keto:enol tautomer, enol tautomer annotated by an asterisk) 16.68 (s, 1H*, **H10**), 5.86-5.75 (m, 1H*, **H12**), 5.72-5.61 (m, 1H, **H5**), 5.09-4.93 (m, 2H and 2H*, **H6** and **H13**), 3.70 (t, J = 7.5 Hz, 1H, **H3**), 2.95 (dt, J = 5.1, 1.9 Hz, 2H*, **H11**), 2.55 (tt, J = 7.1, 1.3 Hz, 2H, **H4**), 2.15 (s, 6H, **H1**), 2.06 (s, 6H*, **H7**); δ_C (100 MHz, $CDCl_3$, 1.4:1 keto:enol tautomer, enol tautomer annotated by an asterisk) 203.6 (**C2**), 191.4 (**C8***), 135.6 (**C12***), 134.0 (**C5**), 117.4 (**C13***), 114.8 (**C6**), 107.0 (**C9***), 67.9 (**C3**), 32.1 (**C4**), 31.1 (**C11***), 29.2 (**C1**), 22.8 (**C7***). Synthesis of this compound has been reported in the literature.[122]

Ethyl 3-acetyl-4-oxopentanoate (301g):



According to a literature procedure,[117] to a solution of acetylacetone (2.05 mL, 20.0 mmol) and ethyl bromoacetate (2.22 mL, 20.0 mmol) in dichloromethane (20 mL) was added solid potassium carbonate (2.76 g, 20.0 mmol). The mixture was stirred at room temperature for 72 hours. The reaction was quenched by addition of aq. HCl (1 N, 20 mL) and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 49:1-4:1] afforded **301g** (1.82 g, 48%) as a yellow oil. R_F 0.68 [Petrol:EtOAc 1:1]; ν_{max} (film)/cm^{-1} 2983, 1723 (C=O), 1701 (C=O), 1602; δ_H (400 MHz, $CDCl_3$, 1.9:1 keto:enol tautomer, enol tautomer annotated by an asterisk) 16.76 (s, 1H*, **H11**), 4.17-4.06 (m, 3H and 2H*, **H3**, **H6** and **H14**), 3.22 (s, 2H*, **H12**), 2.85 (d, *J* = 6.7 Hz, 2H, **H4**), 2.24 (s, 6H, **H1**), 2.13 (s, 6H*, **H8**), 1.27-1.19 (m, 3H and 3H*, **H7** and **H15**); δ_C (100 MHz, $CDCl_3$, 1.9:1 keto:enol tautomer, enol tautomer annotated by an asterisk) 202.4 (**C2**), 191.8 (**C9***), 171.4 (**C13***), 171.1 (**C5**), 104.3 (**C10***), 63.2 (**C3**), 61.1 (**C6**), 61.1 (**C14***), 33.3 (**C12***), 32.5 (**C4**), 29.5 (**C1**), 23.3 (**C8***), 14.1 (**C7**), 14.0 (**C15***); HRMS (ESI) Found: $[M+H]^+$, 187.0964. $C_9H_{14}O_4$ requires $[M+H]^+$, 187.0965. Data matches literature values.[117]

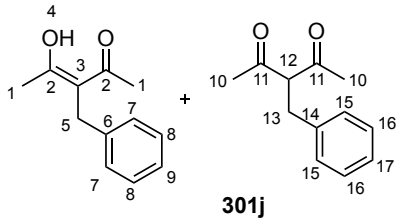
4-Hydroxy-3-phenylpent-3-en-2-one (301i):



301i

According to a literature procedure,[123] acetylacetone (3.08 mL, 30 mmol), iodobenzene (1.14 mL, 10 mmol), copper iodide (190 mg, 1 mmol), L-proline (230 mg, 2 mmol) and potassium carbonate (552 mg, 40 mmol) were dissolved in dimethylsulfoxide (40 mL) and the solution was heated to 90 °C for 18 hours. The reaction was quenched by the addition of aq. HCl (1 N, 50 mL). The mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were further washed with water (5 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 99:1] afforded **301i** (500 mg, 28%) as a light brown solid. R_F 0.55 [Petrol:EtOAc 4:1]; m.p. 57–59 °C; δ_H (400 MHz, $CDCl_3$) 16.6 (s, 1H, **H4**), 7.41-7.29 (m, 3H, **H7** and **H8**), 7.19-7.15 (m, 2H, **H6**), 1.88 (s, 6H, **H1**); δ_C (100 MHz, $CDCl_3$) 190.6 (**C2**), 136.9 (**C5**), 131.1 (**C6**), 128.8 (**C7**), 127.4 (**C8**), 115.2 (**C3**), 24.1 (**C1**); HRMS (ESI) Found: $[M+H]^+$, 177.0906. $C_{10}H_{12}O_4$ requires $[M+H]^+$, 177.0910. Synthesis of this compound has been reported in the literature.[123]

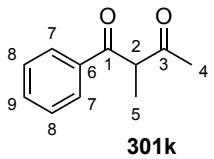
3-Benzylpentane-2,4-dione (301j):



301j

According to a literature procedure,[117] to a solution of acetylacetone (1.03 mL, 10.0 mmol) in acetone (8 mL) was added solid potassium carbonate (1.38 g, 10.0 mmol), followed by benzyl bromide (1.43 mL, 12.0 mmol). The mixture was heated to 65 °C for 18 hours. The solution was allowed to cool to room temperature and quenched with aq. HCl (1 N, 20 mL). The mixture was extracted with Et_2O (3 x 25 mL) and the combined organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:Et_2O 19:1-9:1] afforded **301j** (605 mg, 32%) as a colourless oil. R_F 0.50 [Petrol:Et_2O 4:1]; ν_{max} (film)/cm^{-1} 3062, 2948, 2924, 1723 (C=O), 1697 (C=O), 1600, 1494; δ_H (400 MHz, $CDCl_3$, 1:1 enol:keto tautomer, keto tautomer annoted by an asterisk) 16.84 (s, 1H, **H4**), 7.35-7.26 (m, 2H and 2H*, **H8** and **H16**), 7.25-7.20 (m, 1H and 1H*, **H9** and **H17**), 7.20-7.15 (m, 2H and 2H*, **H7** and **H15**), 4.03 (t, J = 7.7 Hz, 1H*, **H12**), 3.68 (s, 2H, **H5**), 3.17 (d, J = 7.6 Hz, 2H*, **H13**), 2.14 (s, 6H*, **H10**), 2.07 (s, 6H, **H1**); δ_C (100 MHz, $CDCl_3$, 1:1 enol:keto tautomer, keto tautomer annoted by an asterisk) 203.5 (**C11***), 191.9 (**C1**), 139.6 (**C6**), 137.9 (**C14***), 128.7 (**C16***), 128.6 (**C8**), 128.5 (**C15***), 127.3 (**C7**), 126.7 (**C17***), 126.2 (**C9**), 108.2 (**C3**), 69.8 (**C12***), 34.2 (**C13***), 32.8 (**C5**), 29.7 (**C10***), 23.2 (**C1**); HRMS (ESI) Found: $[M+H]^+$, 191.1058. $C_{12}H_{14}O_2$ requires $[M+H]^+$, 191.1067. Data matches literature values.[117]

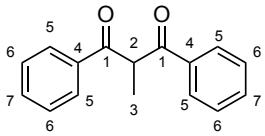
2-Methyl-1-phenylbutane-1,3-dione (301k):



301k

According to a literature procedure,[117] to a stirred suspension of 1-phenyl-1,3-butadione (1.62 g, 10.0 mmol) and potassium carbonate (3.04 g, 22.0 mmol) in acetone (40 mL) was added methyl iodide (623 µL, 10.0 mmol). The mixture was heated to reflux at 60 °C for 18 hours. After cooling to room temperature, the mixture was concentrated *in vacuo* to half the volume and quenched by addition of aq. HCl (1 N, 20 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1] afforded **301k** (1.00 g, 57%) as a yellow oil. R_F 0.44 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2927, 1718 (C=O), 1675 (C=O), 1597; δ_H (400 MHz, $CDCl_3$) 7.99-7.94 (m, 2H, **H7**), 7.62-7.56 (m, 1H, **H9**), 7.52-7.45 (m, 2H, **H8**), 4.48 (q, J = 7.4 Hz, 1H, **H2**), 2.15 (s, 3H, **H4**), 1.45 (dt, J = 7.0, 0.7 Hz, 3H, **H5**); δ_C (100 MHz, $CDCl_3$) 205.0 (**C3**), 197.3 (**C1**), 135.9 (**C6**), 133.7 (**C9**), 128.8 (**C7**), 128.6 (**C8**), 56.8 (**C2**), 27.8 (**C4**), 13.6 (**C5**); HRMS (ESI) Found: $[M+H]^+$, 177.0905. $C_{11}H_{12}O_2$ requires $[M+H]^+$, 177.0910. Data matches literature values.[117]

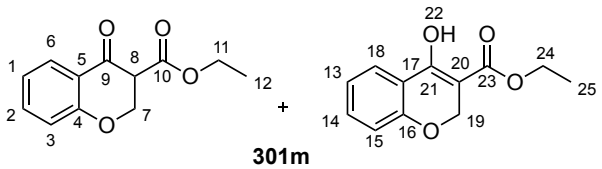
2-Methyl-1,3-diphenylpropane-1,3-dione (301l):



301l

According to a literature procedure,[124] to a suspension of 1,3-diphenyl-1,3-propanedione (1.12 g, 5.0 mmol) and potassium carbonate (1.03 g, 7.5 mmol) in dimethylformamide (5 mL) was added dropwise iodomethane (311 µL, 5 mmol) dropwise. The reaction was stirred at 60 °C for 5 hours. The solution was allowed to cool to room temperature and quenched by the addition of water (50 mL). The mixture was extracted with EtOAc (4 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1-9:1-5:1-3:1-1:1] afforded **301l** (281 mg, 24%) as a yellow solid. R_F 0.55 [Petrol:EtOAc 5:1]; m.p. 71–73 °C; ν_{max} (film)/cm^{-1} 2991, 2939, 1686 (C=O), 1664, 1593, 1578; δ_H (400 MHz, $CDCl_3$) 7.87-7.84 (m, 4H, **H5**), 7.44 (td, *J* = 7.5, 1.5 Hz, 2H, **H7**), 7.36-7.30 (m, 4H, **H6**), 5.20 (q, *J* = 7.1 Hz, 1H, **H2**), 1.49 (d, *J* = 6.9 Hz, 3H, **H3**); δ_C (100 MHz, $CDCl_3$) 197.1 (**C1**), 135.6 (**C4**), 133.4 (**C7**), 128.9 (**C6**), 128.4 (**C5**), 50.8 (**C2**), 14.3 (**C3**); HRMS (ESI) Found: $[M+Na]^+$, 239.1049. $C_{14}H_{16}O_2$ requires $[M+Na]^+$, 239.1043. Data matches literature values.[124]

Ethyl 4-oxochroman-3-carboxylate (301m):

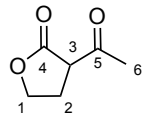


301m

According to a literature procedure,[125] to a solution of 4-chromanone (1 g, 6.80 mmol) in tetrahydrofuran (20 mL) cooled to –78 °C was added a solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 7.4 mL, 7.40 mmol) dropwise and the mixture was stirred at –78 °C for 30 minutes. Ethyl cyanoformate (0.8 mL, 8.0 mmol) in tetrahydrofuran (6 mL) was added dropwise and the reaction was stirred at –78 °C for 1 hour. The mixture was allowed to warm to room temperature and was quenched by the addition of aq. NH_4Cl (25 mL) and H_2O (25 mL). The mixture was extracted with Et_2O (3 x 25 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1] afforded **301m** (478 mg, 32%) as a white solid. R_F 0.76 [Petrol:EtOAc 5:1]; m.p 51–53 °C; ν_{max} (film)/cm^{-1} 2983, 2935, 1723 (C=O), 1679 (C=O), 1604, 1578, 1468; δ_H (400 MHz, $CDCl_3$, 2.1:1 keto:enol tautomer, enol tautomer annotated by an asterisk) 11.97 (s, 1H*, **H22**), 7.82 (dd, *J* = 7.8, 1.5, 0.7 Hz, 1H, **H6**), 7.56 (dd, *J* = 7.9, 1.9 Hz, 1H*, **H15**), 7.39 (ddd, *J* = 7.3, 1.8, 0.6 Hz, 1H, **H1**), 7.21 (ddd, *J* = 7.6, 1.8, 0.9 Hz, 1H*, **H13**), 6.98-6.92 (m, 1H, **H2**), 6.91-6.85 (m, 1H and 1H*, **H3** and **H14**), 6.77 (dd, *J* = 8.2, 0.9 Hz, 1H*, **H18**), 4.86 (s, 2H*, **H19**), 4.69 (dd, *J* = 11.6, 8.5 Hz, 1H, **H7a**), 4.54 (dd, *J* = 11.6, 4.8 Hz, 1H, **H7b**) 4.22-4.11 (m, 2H and 2H*, **H11** and **H24**), 3.66 (dd, *J* = 8.6, 4.7 Hz, 1H, **H8**), 1.25 (t, *J* = 7.5 Hz, 3H, **H12**), 1.19 (t,

J = 6.6 Hz, 3H*, **H25**); δ_C (100 MHz, $CDCl_3$, 2.1:1 keto:enol tautomer, enol tautomer shown by an asterisk) 186.7 (**C9**), 169.4 (**C23***), 166.9 (**C10**), 162.3 (**C16***), 161.0 (**C4**), 157.3 (**C21***), 136.0 (**C3**), 132.7 (**C15***), 127.2 (**C6**), 124.1 (**C13***), 121.4 (**C2**), 121.1 (**C14***), 120.2 (**C5**), 117.9 (**C17***), 117.5 (**C1**), 116.1 (**C18***), 91.6 (**C20***), 67.9 (**C7**), 63.4 (**C19***), 61.4 (**C11**), 60.4 (**C24***), 52.2 (**C8**), 13.9 (**C12***), 13.7 (**C25**); HRMS (ESI) Found: $[M+H]^+$, 221.0798. $C_{12}H_{12}O_4$ requires $[M+H]^+$, 221.0808. Synthesis of this compound has been reported in the literature.[125]

3-Acetyldihydrofuran-2(3*H*)-one (301q):

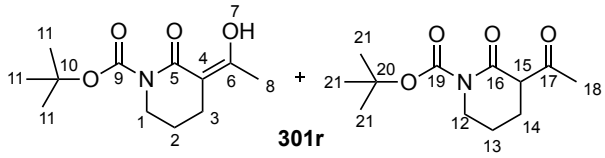


301q

According to a literature procedure,[117] to a stirred solution of γ-butyrolactone (384 µL, 5 mmol, 1.0 eq) in tetrahydrofuran (10 mL) cooled to –78 °C was added a solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 10.5 mL, 10.5 mmol, 2.1 eq) dropwise. The mixture was stirred at this temperature for 15 minutes. Acetic anhydride (471 µL, 5 mmol, 1.0 eq.) was added dropwise and the mixture was stirred at –78 °C for a further 1 hour. The reaction was quenched by addition of aq. HCl (1 N, 10 mL). The mixture was allowed to warm to room temperature and extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4;1-3:1] afforded **301q** (527 mg, 82%) as a green oil. R_F 0.55

[Petrol:EtOAc 3:1]; δ_H (400 MHz, $CDCl_3$, 10:1 keto:enol tautomer, resonances due to keto tautomer quoted) 4.39-4.22 (m, 2H, **H1**), 3.69-3.60 (m, 1H, **H3**), 2.74-2.62 (m, 1H, **H2a**), 2.39-2.35 (m, 3H, **H6**), 2.31-2.19 (m, 1H, **H2b**); δ_C (100 MHz, $CDCl_3$) 200.0 (**C5**), 172.9 (**C4**), 67.2 (**C1**), 52.8 (**C3**), 29.5 (**C6**), 23.6 (**C2**). Synthesis of this compound has been reported in the literature.[117]

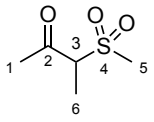
***tert*-Butyl-3-acetyl-2-oxopiperidine-1-carboxylate (301r):**



According to a literature procedure,[117] to a stirred solution of *N*-Boc-2-piperidone (995 mg, 5.0 mmol) in tetrahydrofuran (10 mL) cooled to –78 °C was added a solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 10.5 mL, 10.5 mmol) dropwise. The mixture was stirred at this temperature for 15 minutes. Acetic anhydride (471 µL, 5.0 mmol) was added dropwise and the mixture was stirred at –78 °C for a further 1 hour. The reaction was quenched by addition of aq. NH_4Cl (10 mL). The mixture was allowed to warm to room temperature and extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1] afforded **301r** (199 mg, 16%) as a yellow oil. R_F 0.36 [Petrol:EtOAc 1:1]; ν_{max} (film)/cm^{-1} 2978, 2931, 1716 (C=O), 1619; δ_H (400 MHz, $CDCl_3$, 1.9:1 enol:keto tautomer, keto tautomer annotated by an asterisk) 14.90 (s, 1H, **H7**), 3.64-3.60 (m, 2H and 2H*, **H1** and **H12**), 3.55 (t, *J*

= 6.7 Hz, 1H*, **H15**), 2.33 (t, *J* = 7.1 Hz, 2H, **H3**), 2.32 (s, 3H*, **H18**), 1.98 (s, 3H, **H8**), 1.93-1.72 (m, 2H and 4H*, **H2**, **H13** and **H14**), 1.51 (s, 9H, **H11**), 1.50 (s, 9H*, **H21**); δ_C (100 MHz, $CDCl_3$, 1.92:1 enol:keto tautomer annoted by an asterisk) 204.0 (**C17***), 175.2 (**C6**), 171.8 (**C5**), 168.4 (**C16***), 152.3 (**C19***), 152.1 (**C9**), 97.2 (**C4**), 83.3 (**C20***), 82.8 (**C10**), 57.8 (**C15***), 46.1 (**C1**), 45.9 (**C12***), 29.8 (**C18***), 28.0 (**C11**), 27.9 (**C21***), 23.8 (**C3**), 22.6 (**C14***), 22.4 (**C2**), 20.9 (**C13***), 19.5 (**C8**); HRMS (ESI) Found: $[M+H]^+$, 242.1391. $C_{12}H_{19}NO_4$ requires $[M+H]^+$, 242.1387. Data matches literature values.[117]

3-(Methylsulfonyl)butan-2-one (301s):

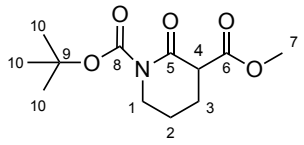


301s

According to a literature procedure,[126] to a solution of methane sulfonylacetone (1.0 g, 7.85 mmol) in acetone (30 mL) was added potassium carbonate (1.0 g, 7.85 mmol). Methyl iodide (458 µL, 7.85 mmol) was added dropwise and the mixture was stirred at room temperature for 2 hours. The reaction was quenched by addition of aq. HCl (1 N, 20 mL) and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 2:1] afforded **301s** (268 mg, 23%) as a colourless oil. R_F 0.20 [Petrol:EtOAc 1:1]; ν_{max} (film)/cm^{-1} 2935, 1716 (C=O), 1295 (S=O); δ_H (400 MHz, $CDCl_3$) 3.99 (q, *J* = 7.5 Hz, 1H, **H3**), 2.85 (d, *J* = 0.5 Hz, 3H, **H4**), 2.40 (s, 3H, **H1**), 1.56 (d, *J* = 6.9 Hz, 3H, **H5**); δ_C (100 MHz,

$CDCl_3$) 201.7 (**C2**), 69.1 (**C3**), 37.2 (**C4**), 30.8 (**C1**), 11.5 (**C5**). Synthesis of this compound has been reported in the literature.[126]

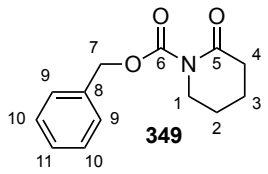
1-*tert*-Butyl 3-methyl 2-oxopiperidine-1,3-dicarboxylate (301t):



301t

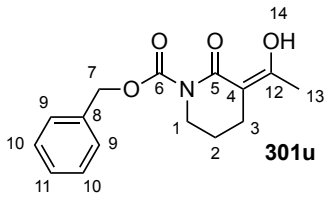
According to a literature procedure,[127] to a solution of 1-Boc-2-piperidone (997 mg, 5 mmol) in tetrahydrofuran (15 mL) cooled to –78 °C was added lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran solution, 6.5 mL, 6.5 mmol) and the reaction mixture was stirred at –78 °C for 1 hour. Methyl chloroformate (386 μL, 5 mmol) was added dropwise and the reaction mixture was stirred at –78 °C for 2 hours. The solution was allowed to warm to room temperature, poured into saturated aq. NH_4Cl (15 mL) and extracted with EtOAc (3 x 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **301t** (980 mg, 76%) as a clear oil. R_F 0.22 [Petrol:EtOAc 4:1]; δ_H (400 MHz, $CDCl_3$) 3.77 (s, 3H, **H10**), 3.71-3.69 (m, 2H, **H4**), 3.52 (dd, J = 8.9, 6.8 Hz, 1H, **H7**), 2.24-2.14 (m, 1H, **H5a**), 2.13-2.05 (m, 1H, **H5b**), 2.02-1.93 (m, 1H, **H6a**), 1.87-1.77 (m, 1H, **H6b**), 1.52 (s, 9H, **H1**); δ_C (100 MHz, $CDCl_3$) 170.4 (**C9**), 167.3 (**C8**), 152.6 (**C3**), 83.5 (**C2**), 52.6 (**C10**), 51.3 (**C7**), 45.8 (**C4**), 28.0 (**C1**), 24.2 (**C5**), 21.0 (**C6**); HRMS (ESI) Found: $[M+Na]^+$, 280.1160. $C_{12}H_{19}NO_5$ requires $[M+Na]^+$, 280.1155. Synthesis of this compound has been reported in the literature.[127]

Benzyl 2-oxopiperidine-1-carboxylate (349):



To a solution of δ-valerolactam (3.5 g, 35 mmol) in tetrahydrofuran (30 mL) and dimethylformamide (20 mL) at –50 °C was added sodium hydride (60 wt% in mineral oil, 1.55 g, 38.9 mmol) and the reaction was stirred at –50 °C for 45 minutes. Benzyl chloroformate (5.50 mL, 36.3 mmol) was added dropwise and the reaction mixture was stirred at –50 °C for 6 hours, then at room temperature for 16 hours. The reaction was quenched by the addition of aq. $NaHCO_3$ (30 mL) and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1-2:1] afforded **349** (2.0 g, 25%) as a pale yellow oil. R_F 0.30 [Petrol:EtOAc 2:1]; δ_H (400 MHz, $CDCl_3$) 7.46-7.41 (m, 2H, **H9**), 7.39-7.29 (m, 3H, **H10** and **H11**), 5.28 (s, 2H, **H7**), 3.79-3.70 (m, 2H, **H1**), 2.59-2.48 (m, 1H, **H4**), 1.88-1.80 (m, 4H, **H2** and **H3**); δ_C (400 MHz, $CDCl_3$) 171.2 (**C5**), 154.2 (**C6**), 135.4 (**C8**), 128.6 (**C10**), 128.3 (**C11**), 128.1 (**C9**), 68.5 (**C7**), 46.6 (**C1**), 34.9 (**C4**), 22.7 (**C2**), 20.4 (**C3**); HRMS (ESI) Found: $[M+H]^+$, 234.1118. $C_{13}H_{15}NO_3$ requires $[M+H]^+$, 234.1125. Synthesis of this compound has been reported in the literature.[128]

(*Z*)-Benzyl 3-(1-hydroxyethylidene)-2-oxopiperidine-1-carboxylate (301u):

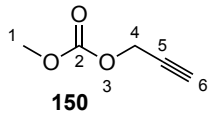


301u

To a solution of **349** (1.5 g, 6.9 mmol) in tetrahydrofuran (15 mL) cooled to –78 °C was added lithium bis(trimethylsilyl)amide (1M in tetrahydofuran, 14.5 mL, 14.5 mmol) and the reaction was stirred at –78 °C for 15 minutes. Acetic anhydride (0.650 mL, 6.9 mmol) was added dropwise and the reaction mixture was stirred at –78 °C for 2 hours. The reaction was quenched by the addition of NH_4Cl (20 mL) and then allowed to warm to room temperature. The mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1] afforded **301u** (500 mg, 27%) as a white solid. R_F 0.50 [Petrol:EtOAc 2:1]; m.p. 37–39 °C; ν_{max} (film)/cm^{-1} 2931, 1768, 1707 (C=O), 1679; δ_H (400 MHz, $CDCl_3$) 14.77 (s, 1H, **H14**), 7.46-7.40 (m, 2H, **H9**), 7.40-7.30 (m, 3H, **H10** and **H11**), 5.30-5.28 (m, 2H, **H7**), 3.73 (t, *J* = 5.8 Hz, 2H, **H1**), 2.40-2.34 (m, 2H, **H3**), 2.01 (s, 3H, **H13**), 1.90-1.81 (m, 2H, **H2**); δ_C (100 MHz, $CDCl_3$) 176.1 (**C12**), 171.6 (**C5**), 153.7 (**C6**), 135.5 (**C8**), 128.6 (**C10**), 128.3 (**C11**), 128.1 (**C9**), 97.3 (**C4**), 68.5 (**C7**), 46.3 (**C1**), 23.7 (**C3**), 22.4 (**C2**), 19.6 (**C13**); HRMS (ESI) Found: $[M+H]^+$, 276.1219. $C_{15}H_{17}NO_4$ requires $[M+H]^+$, 276.1230.

10.2.2 Synthesis of Propargyl Carbonates, Esters and Carbamates

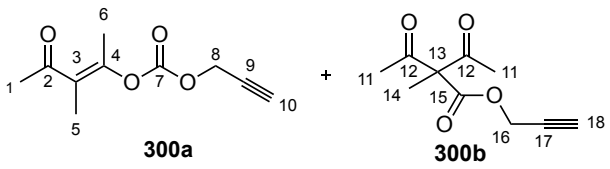
Methyl prop-2-ynyl carbonate (150):



150

According to a literature procedure,[129] a solution of propargyl alcohol (1 mL, 17 mmol) and pyridine (2.8 mL, 34 mmol) in diethyl ether (17 mL) was cooled to 0 °C. Methyl chloroformate (1.3 mL, 17 mmol) was added dropwise over 10 min. The mixture was stirred at room temperature for 15 hours, then quenched with aq. HCl (1 N, 20 mL) and extracted with Et_2O (3 x 20 mL). The organic phases were combined and washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 3:1] afforded **150** (300 mg, 15%) as a clear oil. δ_H (400 MHz, $CDCl_3$) 4.73 (d, J = 2.5 Hz, 2H, **H3**), 3.82 (s, 3H, **H1**), 2.52 (t, J = 2.4 Hz, 1H, **H5**). Synthesis of this compound has been reported in the literature.[129]

3-Methyl-4-oxopent-2-en-2-yl prop-2-ynyl carbonate (300a) and **prop-2-ynyl 2-acetyl-2-methyl-3-oxobutanoate (300b):**

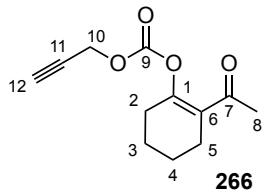


300a **300b**

According to a literature procedure,[117] a suspension of sodium hydride (60 wt% in mineral oil, 76 mg, 1.90 mmol) in tetrahydrofuran (10 mL) was cooled to 0 °C. A solution of 3-methylpentane-2,4-dione (201 µL, 1.73 mmol) in

tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (187 μL, 1.90 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was stirred at room temperature for 1 hour. The reaction was quenched with aq. HCl (1 N, 50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1] afforded an inseparable 5.3:1 mixture of carbonate **300a** and ester **300b** (250 mg, 74%) as a clear oil. R_F 0.21 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3281, 2973, 2148 (C≡C), 1757 (C=O), 1653 (C=O), 1555; δ_H (400 MHz, $CDCl_3$, resonances due to **310b** annotated by an asterisk) 4.80 (s, 2H*, **H16**), 4.79 (d, *J* = 2.5 Hz, 2H, **H8**), 2.56 (t, *J* = 2.4 Hz, 1H, **H10**), 2.52 (t, *J* = 2.6 Hz, 1H*, **H18**), 2.30 (s, 3H, **H1**), 2.26 (s, 6H*, **H11**), 2.08 (d, *J* = 0.8 Hz, 3H, **H6**), 1.83 (d, *J* = 1.0 Hz, 3H, **H5**), 1.61 (s, 3H*, **H14**); δ_C (100 MHz, $CDCl_3$ 5:1 carbonate/ester, resonances due to **310b** annotated by an asterisk) 201.5 (**C12***), 199.1 (**C2**), 168.2 (**C15***), 151.7 (**C7**), 150.5 (**C4**), 125.0 (**C3**), 76.3 (**C9**), 76.2 (**C10**), 75.8 (**C18***), 75.3 (**C17***), 72.7 (**C13***), 56.0 (**C8**), 53.2 (**C16***), 30.9 (**C1**), 27.6 (**C11***), 17.9 (**C6**), 17.3 (**C14***), 14.0 (**C5**); HRMS (ESI) Found: $[M+H]^+$, 197.0804. $C_{10}H_{12}O_4$ requires $[M+H]^+$, 197.0808. Data matches literature values.[117]

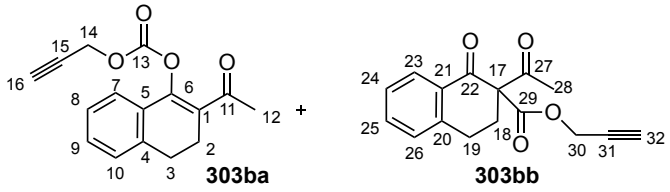
2-Acetylcyclohex-1-enyl prop-2-ynyl carbonate (266):



266

According to a literature procedure,[117] a suspension of sodium hydride (60 wt% in mineral oil, 440 mg, 11.0 mmol) int tetrahydrofuran (60 mL) was cooled to 0 °C. A solution of 2-acetylcyclohexanone (1.32 mL, 10.0 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (1.07 mL, 11.0 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was stirred at room temperature for 1 hour. The reaction was quenched with aq. HCl (1 N, 30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic fractions were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1] afforded **266** (1.96 g, 86%) as a clear oil. R_F 0.46 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3283, 2940, 2864, 2128 (C≡C), 1757 (C=O), 1695 (C=O), 1649; δ_H (400 MHz, $CDCl_3$) 4.80 (d, J = 2.4 Hz, 2H, **H10**), 2.56 (t, J = 2.4 Hz, 1H, **H12**), 2.40-2.33 (m, 4H, **H2** and **H5**), 2.30 (s, 3H, **H8**), 1.79-1.70 (m, 2H, **H3**), 1.68-1.58 (m, 2H, **H4**); δ_C (100 MHz, $CDCl_3$) 198.2 (**C7**), 154.2 (**C1**), 151.6 (**C9**), 126.3 (**C6**), 76.4 (**C11**), 76.2 (**C12**), 56.0 (**C10**), 30.8 (**C8**), 28.2 (**C2**), 24.8 (**C5**), 22.2 (**C3**), 21.5 (**C4**); HRMS (ESI) Found: $[M+H]^+$, 223.0964. $C_{12}H_{14}O_4$ requires $[M+H]^+$, 223.0965. Data matches literature values.[117]

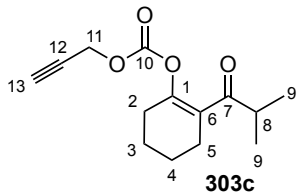
2-Acetyl-3,4-dihydronaphthalen-1-yl prop-2-ynyl carbonate (303ba) and **(1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene) ethyl prop-2-ynyl carbonate (303bb):**



According to a literature procedure,[117] a suspension of sodium hydride (60 wt% in mineral oil, 220 mg, 5.50 mmol) in tetrahydrofuran (40 mL) was cooled to 0 °C. A solution of 2-acetyltetralone (940 mg, 5.0 mmol) in tetrahydrofuran (2 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (540 µL, 5.50 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was stirred at room temperature for 1 hour. The reaction was quenched by the addition of aq. HCl (1 N, 25 mL) and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded an inseparable 7.7:1 mixture of carbonate **303ba** and ester **303bb** (1.18 g, 87%) as a pale solid. R_F 0.27 [Petrol:EtOAc 4:1]; m.p. 53–55 °C; ν_{max} (film) cm^{-1} 3278, 2940, 2840, 2569, 2137 (C≡C), 1755 (C=O), 1654, 1617, 1569; δ_H (400 MHz, $CDCl_3$, resonances due to **303bb** annotated by an asterisk) 8.08 (dd, *J* = 7.9, 1.3 Hz, 1H*, **H23**), 7.52 (td, *J* = 7.6, 1.5 Hz, 1H*, **H26**), 7.39 (d, *J* = 7.8 Hz, 1H, **H7**), 7.37-7.20 (m, 3H and 2H*, **H8**, **H9**, **H10**, **H24** and **H25**), 4.87 (d, *J* = 2.8 Hz, 2H, **H14**), 4.80 (d, *J* =

2.6 Hz, 2H*, **H30**), 2.99 (t, *J* = 6.4 Hz, 2H*, **H19**), 2.89 (t, *J* = 6.8 Hz, 2H, **H3**), 2.76-2.69 (m, 2H and 2H*, **H2** and **H18**), 2.62 (t, *J* = 2.5 Hz, 1H, **H16**), 2.51 (t, *J* = 2.5 Hz, 1H*, **H32**), 2.45 (s, 3H, **H12**), 2.37 (s, 3H*, **H28**); δ_C (100 MHz, $CDCl_3$, resonances due to **303bb** annotated by an asterisk) 200.3 (**C27***), 197.2 (**C11**), 191.5 (**C22***), 167.7 (**C29***), 151.7 (**C13**), 149.9 (**C6**), 142.8 (**C21***), 138.6 (**C5**), 134.2 (**C26***), 131.3 (**C20***), 130.4 (**C8**), 129.5 (**C4**), 128.8 (**C25***), 128.0 (**C23***), 127.6 (**C10**), 127.0 (**C24***), 126.8 (**C9**), 124.9 (**C1**), 123.1 (**C7**), 77.3 (**C31***), 76.4 (**C16**), 76.2 (**C15**), 75.7 (**C32***), 71.4 (**C17***), 56.3 (**C14**), 53.2 (**C30***), 30.5 (**C12**), 28.9 (**C18***), 28.6 (**C28***), 27.1 (**C3**), 25.5 (**C19***), 23.4 (**C2**); HRMS (ESI) Found: $[M+H]^+$, 271.0961. $C_{16}H_{14}O_4$ requires $[M+H]^+$, 271.0965. Synthesis of this compound has been reported in the literature.[117]

2-*iso*-Butyrylcyclohex-1-enyl prop-2-ynyl carbonate (303c):

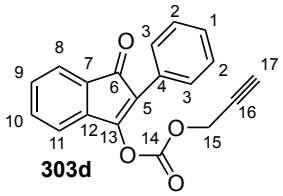


303c

According to a literature procedure,[117] a suspension of sodium hydride (60 wt% in mineral oil, 110 mg, 2.75 mmol) in tetrahydrofuran (20 mL) was cooled to 0 °C. A solution of 2-isobutyrylcyclohexanone (410 µL, 2.5 mmol) in tetrahydrofuran (4 mL) was added dropwise and the mixture was stirred at 0 °C for 15 minutes. Propargyl chloroformate (268 µL, 2.75 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was

stirred at room temperature for 1 hour. The reaction was quenched by the addition of aq. HCl (1 N, 25 mL) and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 49:1-19:1] afforded carbonate **303c** (384 mg, 61%) as a clear oil. R_F 0.56 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3242, 2939, 2868, 2122 (C≡C), 1757 (C=O), 1638; δ_H (400 MHz, $CDCl_3$) 4.66 (d, *J* = 2.6 Hz, 2H, **H11**), 2.83 (sept, *J* = 6.8 Hz, 1H, **H8**), 2.51 (t, *J* = 2.5 Hz, 1H, **H13**), 2.26-2.20 (m, 4H, **H2** and **H5**), 1.68-1.51 (m, 4H, **H3** and **H4**), 0.94 (d, *J* = 6.8 Hz, 6H, **H9**); δ_C (100 MHz, $CDCl_3$) 206.0 (**C7**), 151.4 (**C10**), 150.3 (**C1**), 125.7 (**C6**), 76.3 (**C13**), 75.9 (**C12**), 55.5 (**C11**), 38.8 (**C8**), 27.3 (**C2**), 25.4 (**C5**), 21.9 (**C4**), 21.3 (**C3**), 17.9 (**C9**); HRMS (ESI) Found: $[M+H]^+$, 251.1273. $C_{14}H_{18}O_4$ requires $[M+H]^+$, 251.1278. Data matches literature values.[117]

3-Oxo-2-phenylcyclopent-1-enyl prop-2-ynyl carbonate (303d):

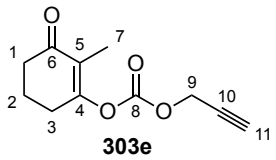


303d

According to a literature procedure,[117] a suspension of sodium hydride (60 wt% in mineral oil, 132 mg, 3.30 mmol) in tetrahydrofuran (20 mL) was cooled to 0 °C. A solution of 2-phenyl-1,3-indandione (666 mg, 3.0 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (323 µL, 3.30 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was

stirred at room temperature for 1 hour. The reaction was quenched with aq. HCl (1 N, 50 mL) and extracted with with EtOAc (3 x 50 mL). The combined organic fractions were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1] afforded **303d** (784 mg, 86%) as a bright orange solid. R_F 0.28 [Petrol:EtOAc 4:1]; m.p. 90–92 °C; ν_{max} (film)/cm^{-1} 3244, 2134 (C≡C), 1764 (C=O), 1716 (C=O); δ_H (400 MHz, $CDCl_3$) 7.60-7.52 (m, 2H, **H3**), 7.41 (d, *J* = 7.2 Hz, 1H, **H8**), 7.34-7.12 (m, 5H, **H1**, **H2**, **H9** and **H10**), 6.97 (d, *J* = 1.0 Hz, 1H, **H11**), 4.68 (d, *J* = 2.5 Hz, 2H, **H15**), 2.50 (t, *J* = 2.5 Hz, 1H, **H17**); δ_C (100 MHz, $CDCl_3$) 192.7 (**C6**), 162.8 (**C13**), 149.7 (**C14**), 138.7 (**C7**), 133.4 (**C9**), 130.0 (**C12**), 129.7 (**C10**), 128.6 (**C3**), 128.4 (**C2**), 128.4 (**C4**), 128.4 (**C1**), 122.6 (**C8**), 121.2 (**C5**), 119.0 (**C11**), 76.9 (**C16**), 75.7 (**C17**), 56.8 (**C15**). Data matches literature values.[117]

2-Methyl-3-oxocyclohex-1-enyl prop-2-ynyl carbonate (303e):

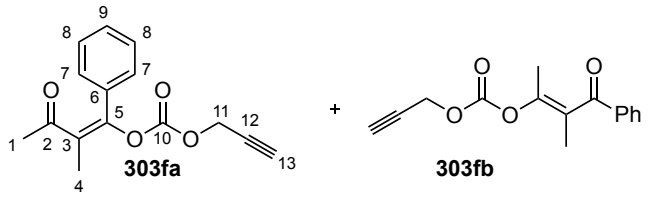


303e

According to a literature procedure,[117] to a suspension of 2-methyl-1,3-cyclohexadione (0.38 g, 3.0 mmol) in acetone (5 mL) was added potassium carbonate (0.83 g, 6.0 mmol). The mixture was cooled to 0 °C and stirred at this temperature for 15 minutes. Propargyl chloroformate (320 μL, 3.3 mmol) was added dropwise, the ice bath was removed and the mixture was stirred at room temperature for 16 hours. The reaction was quenched by the addition of

aq. HCl (1 N, 40 mL) and the mixture was extracted with EtOAc (3 x 40 mL). The combined organic phases were washed with aq. HCl (1 N, 2 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1] afforded **303e** (487 mg, 78%) as a yellow solid. R_F 0.70 [Petrol:EtOAc 4:1]; m.p. 43–45 °C; δ_H (400 MHz, $CDCl_3$) 4.69 (d, J = 2.5 Hz, 2H, **H9**), 2.56 (t, J = 2.8 Hz, 1H, **H11**), 2.52-2.46 (m, 2H, **H3**), 2.32 (t, J = 6.4 Hz, 2H, **H1**), 1.97-1.87 (m, 2H, **H2**), 1.57 (t, J = 1.8 Hz, 3H, **H7**); δ_C (100 MHz, $CDCl_3$) 198.7 (**C6**), 163.1 (**C4**), 150.1 (**C8**), 124.6 (**C5**), 76.3 (**C11**), 76.0 (**C10**), 56.0 (**C9**), 36.5 (**C1**), 27.9 (**C3**), 20.5 (**C2**), 8.0 (**C7**); HRMS (ESI) Found: $[M+H]^+$, 209.0817. $C_{11}H_{12}O_4$ requires $[M+H]^+$, 209.0808. Data matches literature values.[117]

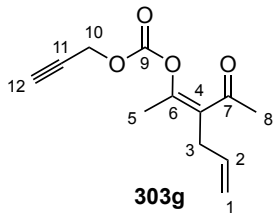
2-Methyl-3-oxo-1-phenylbut-1-enyl prop-2-ynyl carbonate (303fa) and **3-methyl-4-oxo-4-phenylbut-2-en-2-yl prop-2-ynyl carbonate (303fb):**



According to a literature procedure,[117] a suspension of sodium hydride (60 wt% in mineral oil, 240 mg, 6.0 mmol) in tetrahydrofuran (40 mL) was cooled to 0 °C. A solution of diketone **301k** (880 mg, 5.0 mmol) in tetrahydrofuran (3 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (590 µL, 6.0 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was stirred at room

temperature for 1 hour. The reaction was quenched by the addition of aq. HCl (1 N, 20 mL) and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1-15:1] afforded an inseparable 4.9:1 mixture of carbonates **303fa** and **303fb** (1.17 g, 90%) as a clear solid. R_F 0.20 [Petrol:EtOAc 9:1]; m.p. 54–56 °C; ν_{max} (film)/cm^{-1} 3255, 2126 (C≡C), 1759 (C=O), 1690 (C=O), 1595; δ_H (400 MHz, $CDCl_3$, resonances due to **303fa** quoted) 7.85-7.80 (m, 2H, **H7**), 7.55 (tt, *J* = 7.3, 2.0 Hz, 1H, **H9**), 7.47-7.38 (m, 2H, **H8**), 4.48 (d, *J* = 2.5 Hz, 2H, **H11**), 2.43 (t, *J* = 2.4 Hz, 1H, **H13**), 2.12 (q, *J* = 1.2 Hz, 3H, **H1**), 1.96 (q, *J* = 1.3 Hz, 3H, **H4**); δ_C (100 MHz, $CDCl_3$, resonances due to **303fa** quoted) 196.9 (**C2**), 151.6 (**C10**), 145.6 (**C5**), 136.8 (**C6**), 133.1 (**C9**), 128.8 (**C7**), 128.5 (**C8**), 123.9 (**C3**), 76.3 (**C12**), 75.9 (**C13**), 55.5 (**C11**), 16.1 (**C1**), 15.2 (**C4**); HRMS (ESI) Found: $[M+H]^+$, 259.0955. $C_{15}H_{14}O_4$ requires $[M+H]^+$, 259.0965. Synthesis of this compound has been reported in the literature.[117]

3-Acetylhexa-2,5-dien-2-yl prop-2-ynyl carbonate (303g):

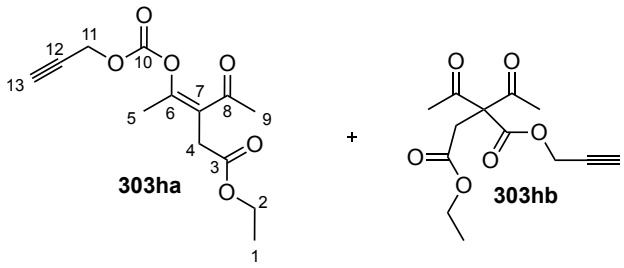


303g

A suspension of sodium hydride (60 wt% in mineral oil, 48.4 mg, 1.21 mmol) in tetrahydrofuran (7 mL) was cooled to 0 °C. A solution of diketone **301e** (154 mg, 1.10 mmol) in tetrahydrofuran (3 mL) was added dropwise and the

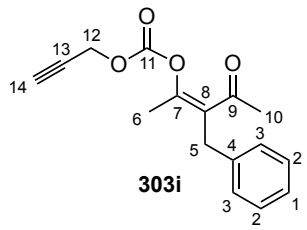
mixture was stirred at 0 °C for 15 minutes. Propargyl chloroformate (118 µL, 1.21 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was stirred at room temperature for 1 hour. The reaction was quenched by the addition of aq. HCl (1 N, 10 mL) and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 99:1] afforded **303g** (100 mg, 41%) as a light green oil. R_F 0.64 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3285, 2926, 2130 (C≡C), 1757 (C=O), 1649; δ_H (400 MHz, $CDCl_3$) 5.81-5.70 (m, 1H, **H2**), 5.09-5.01 (m, 2H, **H1**), 4.79 (d, *J* = 2.3 Hz, 2H, **H10**), 3.01 (d, *J* = 5.9 Hz, 2H, **H3**), 2.57 (t, *J* = 2.6 Hz, 1H, **H12**), 2.29 (s, 3H, **H8**), 2.08 (s, 3H, **H5**); δ_C (100 MHz, $CDCl_3$) 198.5 (**C7**), 152.1 (**C6**), 151.6 (**C9**), 133.8 (**C2**), 127.0 (**C4**), 115.9 (**C1**), 76.3 (**C12**), 75.8 (**C11**), 56.0 (**C10**), 32.0 (**C3**), 31.0 (**C8**), 17.7 (**C5**); HRMS (ESI) Found: $[M+H]^+$, 223.0967. $C_{12}H_{14}O_4$ requires $[M+H]^+$, 223.0965.

Ethyl-3-acetyl-4-((prop-2-ynyloxy)carbonyloxy)pent-3-enoate (303ha) and **4-ethyl 1-prop-2-ynyl 2,2-diacetylsuccinate (303hb):**



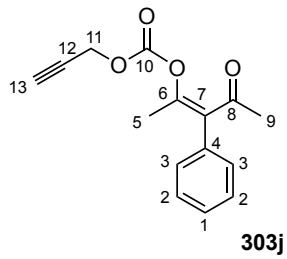
According to a literature procedure,[117] a suspension of sodium hydride (60 wt% in mineral oil, 130 mg, 3.26 mmol) in tetrahydrofuran (50 mL) was cooled to 0 °C. A solution of **301g** (550 mg, 2.96 mmol) in tetrahydrofuran (10 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (320 µL, 3.26 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was stirred at room temperature for 1 hour. The reaction was quenched by the addition of aq. HCl (1 N, 20 mL) and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-3:1] afforded an inseparable 4.3:1 mixture of carbonate **303ha** and ester **303hb** (681 mg, 86%) as a grey oil. R_F 0.77 [Petrol:EtOAc 1:1]; δ_H (400 MHz, $CDCl_3$, resonances due to **303ha** quoted $CDCl_3$) 4.78 (d, *J* = 2.5 Hz, 2H, **H11**), 4.09 (q, *J* = 7.2 Hz, 2H, **H2**), 3.29 (s, 2H, **H4**), 2.57 (t, *J* = 2.7 Hz, 1H, **H13**), 2.35 (s, 3H, **H9**), 2.11 (s, 3H, **H5**), 1.21 (t, *J* = 7.4 Hz, 3H, **H1**); δ_C (100 MHz, $CDCl_3$, resonances due to **303ha** quoted) 197.8 (**C8**), 170.1 (**C3**), 153.8 (**C6**), 151.2 (**C10**), 124.0 (**C7**), 76.5 (**C13**), 76.1 (**C12**), 61.0 (**C2**), 56.1 (**C11**), 34.0 (**C4**), 31.1 (**C9**), 18.2 (**C5**), 14.1 (**C1**); HRMS (ESI) Found: $[M+H]^+$, 269.1013. $C_{13}H_{16}O_6$ requires $[M+H]^+$, 269.1020. Data matches literature values.[117]

3-Benzyl-4-oxopent-2-en-2-yl prop-2-ynyl carbonate (303i):



According to a literature procedure,[117] a suspension of sodium hydride (60 wt% mineral oil, 116 mg, 2.90 mmol) in tetrahydrofuran (20 mL) was cooled to 0 °C. A solution of **301j** (500 mg, 2.64 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (282 µL, 2.90 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was stirred at room temperature for 1.5 hours. The reaction was quenched by the addition of aq. HCl (1 N, 30 mL) and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1] afforded **303i** (401 mg, 50%) as a clear oil. R_F 0.21 [Petrol:EtOAc 4:1]; δ_H (400 MHz, $CDCl_3$) 7.34-7.28 (m, 2H, **H2**), 7.25-7.19 (m, 3H, **H1** and **H3**), 4.85 (d, J = 2.5 Hz, 2H, **H12**), 3.70 (s, 2H, **H5**), 2.61 (t, J = 2.4 Hz, 1H, **H14**), 2.28 (s, 3H, **H10**), 2.18 (s, 3H, **H6**); δ_C (100 MHz, $CDCl_3$) 198.9 (**C9**), 152.0 (**C7**), 151.7 (**C11**), 138.0 (**C4**), 128.6 (**C2**), 128.5 (**C8**), 128.0 (**C3**), 126.4 (**C1**), 77.2 (**C13**), 76.3 (**C14**), 56.1 (**C12**), 33.8 (**C5**), 31.3 (**C10**), 18.0 (**C6**); HRMS (ESI) Found: $[M+H]^+$, 273.1125. $C_{16}H_{16}O_4$ requires $[M+H]^+$, 273.1121. Data matches literature values.[117]

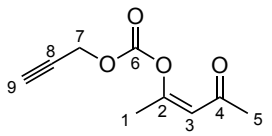
4-Oxo-3-phenylpent-2-en-2-yl prop-2-ynyl carbonate (303j):



303j

A suspension of sodium hydride (60 wt% in mineral oil, 74.8 mg, 1.87 mmol) in tetrahydrofuran (15 mL) was cooled to 0 °C. A solution of **301i** (300 mg, 1.70 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (182 µL, 1.87 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was stirred at room temperature for 1.5 hours. The reaction was quenched by the addition of aq. HCl (1 N, 10 mL) and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1] afforded **303j** (279 mg, 57%) as a green solid. R_F 0.16 [Petrol:EtOAc 2:1]; m.p. 46–48 °C; ν_{max} (film)/cm^{-1} 3270, 2989, 2126 (C≡C), 1763 (C=O), 1686 (C=O), 1612; δ_H (400 MHz, $CDCl_3$) 7.41-7.30 (m, 4H, **H2** and **H3**), 7.25-7.21 (m, 2H, **H1**), 4.81 (d, J = 2.8 Hz, 2H, **H11**), 2.58 (t, J = 2.1 Hz, 1H, **H13**), 2.11 (s, 3H, **H9**), 1.91 (s, 3H, **H5**); δ_C (100 MHz, $CDCl_3$) 198.2 (**C8**), 151.1 (**C10**), 150.7 (**C6**), 134.8 (**C4**), 131.1 (**C7**), 129.3 (**C3**), 128.8 (**C2**), 128.0 (**C1**), 76.4 (**C12**), 76.1 (**C13**), 55.9 (**C11**), 30.6 (**C9**), 18.4 (**C5**); HRMS (ESI) Found: $[M+H]^+$, 250.0962. $C_{15}H_{14}O_4$ requires $[M+H]^+$, 227.0965.

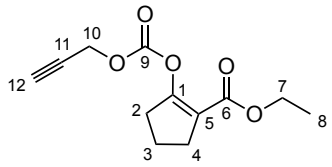
4-oxopent-2-en-2-yl prop-2-ynyl carbonate (303k):



303k

A suspension of sodium hydride (60 wt% in mineral oil, 98.0 mg, 2.45 mmol) in tetrahydrofuran (30 mL) was cooled to 0 °C. A solution of acetylacetone (222 µL, 2.22 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (239 µL, 2.45 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was stirred at room temperature for 1 hour. The reaction was quenched by the addition of aq. HCl (1 N, 15 mL) and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 1:1] afforded **303k** (334 mg, 84%) as a clear oil. R_F 0.23 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3278, 2130 (C≡C), 1761, 1701 (C=O), 1668 (C=O), 1630; δ_H (400 MHz, $CDCl_3$) 5.73 (s, 1H, **H3**), 4.67 (d, J = 2.5 Hz, 2H, **H7**), 2.54 (t, J = 2.5 Hz, 1H, **H9**), 2.05 (s, 3H, **H5**), 1.92 (s, 3H, **H1**); δ_C (100 MHz, $CDCl_3$) 194.8 (**C4**), 156.4 (**C2**), 150.2 (**C6**), 115.9 (**C3**), 76.2 (**C9**), 76.2 (**C8**), 55.7 (**C7**), 30.6 (**C5**), 20.5 (**C1**); HRMS (ESI) Found: $[M+H]^+$, 183.0650. $C_9H_{10}O_4$ requires $[M+H]^+$, 183.0652.

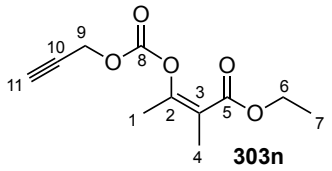
1-(2-Oxocyclopentylidene) ethyl prop-2-ynyl carbonate (303m):



303m

A suspension of sodium hydride (60 wt% in mineral oil, 660 mg, 16.50 mmol) in tetrahydrofuran (40 mL) was cooled to 0 °C. A solution of 2-acetylcyclopentanone (2.20 mL, 15.0 mmol) in tetrahydrofuran (2 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (1.61 mL, 16.50 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was stirred for 1 hour. The reaction was quenched by the addition of aq. HCl (1 N, 30 mL) and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1] afforded **303m** (2.61 g, 73%) as a pale solid. R_F 0.30 [Petrol:EtOAc 4:1]; m.p. 37–39 °C; ν_{max} (film)/cm^{-1} 3255, 2983, 2133 (C≡C), 1766 (C=O), 1697 (C=O), 1653; δ_H (400 MHz, $CDCl_3$) 4.78 (d, J = 2.4 Hz, 2H, **H10**), 4.15 (q, J = 7.2 Hz, 2H, **H7**), 2.68-2.60 (m, 4H, **H2** and **H4**), 2.55 (t, J = 2.5 Hz, 1H, **H12**), 1.94 (quint, J = 7.7 Hz, 2H, **H3**), 1.24 (t, J = 6.9 Hz, 3H, **H8**); δ_C (100 MHz, $CDCl_3$) 163.3 (**C6**), 158.1 (**C1**), 150.8 (**C9**), 118.8 (**C5**), 76.3 (**C12**), 76.1 (**C11**), 60.2 (**C7**), 56.0 (**C10**), 32.9 (**C2**), 29.3 (**C4**), 18.8 (**C3**), 14.0 (**C8**); HRMS (ESI) Found: $[M+H]^+$, 239.0915. $C_{12}H_{14}O_5$ requires $[M+H]^+$, 239.0914.

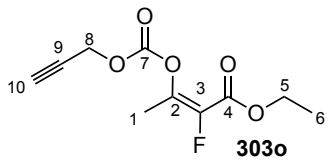
Ethyl 2-methyl-3-((prop-2-ynyloxy)carbonyloxy)but-2-enoate (303n):



303n

A suspension of sodium hydride (60 wt% in mineral oil, 92.3 mg, 2.31 mmol) in tetrahydrofuran (10 mL) was cooled to 0 °C. A solution of 2-methyl ethyl acetoacetate (300 µL, 2.1 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (225 µL, 2.31 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was stirred at room temperature for 1.5 hours. The reaction was quenched by the addition of aq. HCl (1 N, 20 mL) and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1] afforded **303n** (200 mg, 45%) as a clear oil. R_F 0.65 [Petrol:EtOAc 7:1]; ν_{max} (film)/cm^{-1} 3368, 2939, 2122 (C≡C), 1723 (C=O), 1686 (C=O), 1638; δ_H (400 MHz, $CDCl_3$) 4.79 (d, *J* = 2.4 Hz, 2H, **H9**), 4.18 (q, *J* = 7.3 Hz, 2H, **H6**), 2.55 (t, *J* = 2.4 Hz, 1H, **H11**), 2.05 (q, *J* = 1.2 Hz, 3H, **H1**), 1.90 (q, *J* = 1.2 Hz, 3H, **H4**), 1.27 (t, *J* = 6.8 Hz, 3H, **H7**); δ_C (100 MHz, $CDCl_3$) 166.2 (**C5**), 152.1 (**C8**), 151.3 (**C2**), 117.0 (**C3**), 76.6 (**C10**), 76.0 (**C11**), 60.9 (**C6**), 55.8 (**C9**), 18.1 (**C1**), 14.5 (**C4**), 14.0 (**C7**); HRMS (ESI) Found: $[M+H]^+$, 227.0916. $C_{11}H_4O_5$ requires $[M+H]^+$, 227.0914.

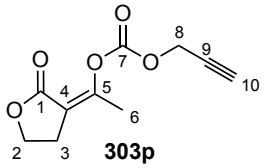
Ethyl 2-fluoro-3-((prop-2-ynyloxy)carbonyloxy) but-2-enoate (303o):



303o

A suspension of sodium hydride (60 wt% in mineral oil, 352 mg, 8.80 mmol) in tetrahydrofuran (30 mL) was cooled to 0 °C. A solution of 2-ethyl fluoroacetate (1.00 mL, 8.0 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (857 µL, 8.80 mmol) was added dropwise and the mixture was allowed to warm to temperature and was stirred at room temperature for 1.5 hours. The reaction was quenched by the addition of aq. HCl (1 N, 20 mL) and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1] afforded **303o** (1.2 g, 65%) as a clear oil. R_F 0.70 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3289, 2987, 2133 (C≡C), 1768, 1727 (C=O), 1686 (C=O); δ_H (400 MHz, $CDCl_3$) 4.79 (d, *J* = 2.4, 2H, **H8**), 4.26 (q, *J* = 7.2 Hz, 2H, **H5**), 2.57 (t, *J* = 2.2 Hz, 1H, **H10**), 2.10 (d, *J* = 5.9 Hz, 3H, **H1**), 1.29 (t, *J* = 7.3 Hz, 3H, **H6**); δ_C (100 MHz, $CDCl_3$) 158.9 (d, *J* = 31.5 Hz, **C4**), 151.4 (d, *J* = 3.9 Hz, **C7**), 145.1 (d, *J* = 30.8 Hz, **C2**), 143.7 (d, *J* = 235.1 Hz, **C3**), 76.3 (**C10**), 76.1 (**C9**), 61.7 (**C5**), 56.4 (**C8**), 15.3 (**C1**), 13.9 (**C6**); HRMS (ESI) Found: $[M+Na]^+$, 253.0471. $C_{10}H_{11}FO_5$ requires $[M+Na]^+$, 253.0483.

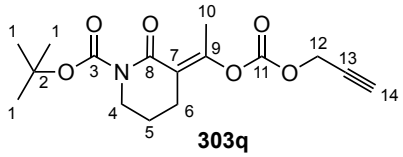
(*E*)-1-(2-Oxodihydrofuran-3(2*H*)-ylidene) ethyl prop-2-ynyl carbonate (303p):



303p

According to a literature procedure,[117] a suspension of sodium hydride (60 wt% in mineral oil, 103 mg, 2.58 mmol) in tetrahydrofuran (20 mL) was cooled to 0 °C. A solution of **301q** (220 mg, 1.72 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (185 µL, 1.89 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was stirred at room temperature for 1.5 hours. The reaction was quenched by the addition of aq. HCl (1 N, 20 mL) and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 3:1] afforded carbonate **303p** (201 mg, 55%) as a green oil. R_F 0.20 [Petrol:EtOAc 3:1]; δ_H (300 MHz, $CDCl_3$) 4.79 (d, *J* = 2.4 Hz, 2H, **H8**), 4.33 (t, *J* = 7.4 Hz, 2H, **H2**), 2.98 (tq, *J* = 7.6, 1.7 Hz, 2H, **H3**), 2.56 (t, *J* = 2.6 Hz, 1H, **H10**), 2.06 (t, *J* = 1.8 Hz, 3H, **H6**); δ_H (75 MHz, $CDCl_3$) 167.1 (**C1**), 153.0 (**C5**), 151.1 (**C7**), 113.3 (**C4**), 76.4 (**C9**), 76.1 (**C10**), 64.6 (**C2**), 56.1 (**C8**), 26.0 (**C3**), 19.5 (**C6**); HRMS (ESI) Found: $[M+H]^+$, 211.0613. $C_{10}H_{10}O_5$ requires $[M+H]^+$, 211.0601. Data matches literature values.[117]

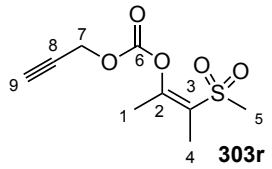
***tert*-Butyl-2-oxo-3-(1((prop-2-ynyloxy)carbonyloxy)ethylidene) piperidine-1-carboxylate (303q):**



303q

According to a literature procedure,[117] a suspension of sodium hydride (60 wt% in mineral oil, 26 mg, 0.65 mmol) in tetrahydrofuran (7 mL) was cooled to 0 °C. A solution of **301r** (130 mg, 0.54 mmol) in tetrahydrofuran (3 mL) was added dropwise and the mixture was stirred at 0 °C for 15 minutes. Propargyl chloroformate (59.0 μL, 0.60 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was stirred at room temperature for 1 hour. The reaction was quenched by the addition of aq. HCl (1 N, 10 mL) and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-5:1] afforded **303q** (121 mg, 69%) as a clear oil. R_F 0.40 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3268, 2980, 2128 (C≡C), 1759 (C=O), 1707 (C=O), 1638; δ_H (400 MHz, $CDCl_3$) 4.78 (d, *J* = 2.6 Hz, 2H, **H12**), 3.69-3.63 (m, 2H, **H4**), 2.57 (t, *J* = 2.4 Hz, 1H, **H14**), 2.46 (tq, *J* = 7.0, 2.0 Hz, 2H, **H6**), 2.36 (t, *J* = 1.8 Hz, 3H, **H10**), 1.85-1.77 (m, 2H, **H5**), 1.53 (s, 9H, **H1**); δ_C (100 MHz, $CDCl_3$) 165.2 (**C3**), 156.4 (**C9**), 152.4 (**C8**), 151.1 (**C11**), 120.7 (**C7**), 83.0 (**C2**), 76.3 (**C14**), 76.3 (**C13**), 56.0 (**C12**), 45.4 (**C4**), 28.0 (**C1**), 23.4 (**C6**), 21.7 (**C5**), 18.9 (**C10**); HRMS (ESI) Found: $[M+Na]^+$, 346.1258. $C_{16}H_{21}NO_6$ requires $[M+Na]^+$, 346.1261. Data matches literature values.[117]

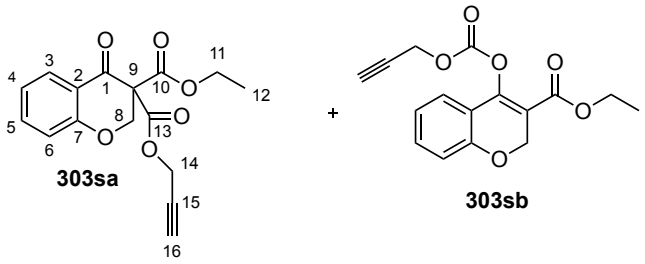
3-(Methylsulfonyl)but-2-en-2-yl prop-2-ynyl carbonate (303r):



303r

A suspension of sodium hydride (60 wt% in mineral oil, 30.4 mg, 0.76 mmol) in tetrahydrofuran (30 mL) was cooled to 0 °C. A solution of **301s** (104 mg, 0.69 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (74 µL, 0.76 mmol) was added dropwise and the mixture allowed to warm to room temperature and was stirred at room temperature for 1.5 hours. The reaction was quenched by the addition of aq. HCl (1 N, 10 mL) and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1-1:1] afforded **303r** (101 mg, 64%) as a white solid. R_F 0.10 [Petrol:EtOAc 1:1]; m.p. 75–77 °C; ν_{max} (film)/cm^{-1} 3293, 2929, 2137 (C≡C), 1763, 1668 (C=O); δ_H (300 MHz, $CDCl_3$) 4.78 (d, J = 2.7 Hz, 2H, **H7**), 2.99 (s, 3H, **H5**), 2.58 (t, J = 2.3 Hz, 1H, **H9**), 2.13 (q, J = 1.2 Hz, 3H, **H1**), 2.03 (q, J = 1.7 Hz, 3H, **H4**); δ_C (75 MHz, $CDCl_3$) 152.7 (**C2**), 150.8 (**C6**), 127.7 (**C3**), 76.4 (**C8**), 76.0 (**C9**), 56.3 (**C7**), 42.6 (**C5**), 18.3 (**C1**), 13.5 (**C4**); HRMS (ESI) Found: $[M+Na]^+$, 255.0291. $C_9H_{12}SO_5$ requires $[M+H]^+$, 255.0298.

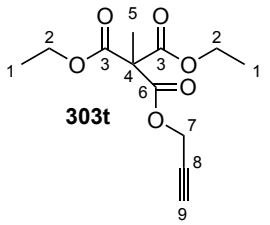
3-Ethyl 3-prop-2-ynyl 4-oxochroman-3,3-dicarboxylate (303sa) and **(*Z*)-ethoxy(4-oxochroman-3-ylidene)methyl prop-2-ynyl carbonate (303sb):**



To a suspension of sodium hydride (60 wt% in mineral oil, 48 mg, 1.20 mmol) in tetrahydrofuran (15 mL) was cooled to 0 °C. A solution of **301m** (240 mg, 1.09 mmol) in tetrahydrofuran (5 mL) was added dropwise and the reaction mixture was stirred at 0 °C 15 minutes. Propargyl chloroformate (117 µL, 1.20 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was stirred at room temperature for 1 hour. The reaction was quenched by the addition of aq. HCl (1 N, 20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1] afforded an inseparable mixture of **303sa** and **303sb** in a 3.6:1 ratio (231 mg, 70%) as a colourless oil. R_f 0.38 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3281, 2883, 2130, 1735 (C=O), 1695 (C=O); δ_H (400 MHz, $CDCl_3$, resonances due to **303sa** quoted) 7.96 (dd, *J* = 8.0, 1.7 Hz, 1H, **H3**), 7.51 (ddd, *J* = 9.0, 7.3, 1.9 Hz, 1H, **H4**), 7.08 (ddd, *J* = 8.1, 7.3, 1.1 Hz, 1H, **H5**), 6.98 (dd, *J* = 8.6, 0.8 Hz, 1H, **H6**), 4.93 (s, 2H, **H8**), 4.81 (d, *J* = 2.5 Hz, 2H, **H14**), 4.30 (q, *J* = 7.1 Hz, 1H, **H11a**), 4.30 (q, *J* = 7.2 Hz, 1H, **H11b**), 2.49 (t, *J* = 2.4 Hz, 1H, **H16**), 1.27 (t, *J* = 7.2 Hz, 3H, **H12**); δ_C (100 MHz, $CDCl_3$, resonances due to **313sa** quoted) 183.7 (**C1**), 164.7 (**C10**), 164.5 (**C13**), 160.7 (**C2**), 136.6 (**C4**), 128.1 (**C3**), 122.7 (**C5**), 119.9 (**C7**), 117.8 (**C4**), 76.3 (**C16**),

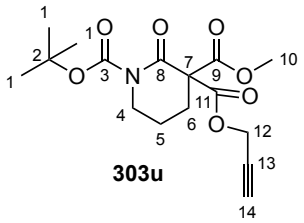
75.8 (**C15**), 65.1 (**C9**), 63.0 (**C11**), 53.8 (**C14**), 13.9 (**C12**); HRMS (ESI) Found: $[M+H]^+$, 303.0860. $C_{16}H_{14}O_6$ requires $[M+H]^+$, 303.0863.

1,1-Diethyl 1-prop-2-ynyl ethane-1,1,1-tricarboxylate(303t):



To a solution of diethyl methyl malonate (425 μL, 2.5 mmol) in tetrahydrofuran (20 mL) was added potassium *tert*-butoxide (313 mg, 3.13 mmol) and the mixture was stirred at room temperature for 10 minutes. Propargyl chloroformate (270 μL, 3.12 mmol) was added dropwise and the solution was stirred at room temperature for 90 minutes. The reaction was quenched with aq. HCl (1 N, 20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1] afforded **303t** (300 mg, 47%) as a clear oil. R_F 0.66 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3280, 2963, 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 4.73 (d, J = 2.5 Hz, 2H, **H7**), 4.22 (q, J = 7.1 Hz, 4H, **H2**), 2.47 (t, J = 2.5 Hz, 1H, **H9**), 1.69 (s, 3H, **H5**), 1.24 (t, J = 7.2 Hz, 6H, **H1**); δ_C (100 MHz, $CDCl_3$) 167.2 (**C3**), 166.9 (**C6**), 76.5 (**C9**), 75.4 (**C8**), 62.3 (**C2**), 61.7 (**C7**), 53.3 (**C4**), 18.6 (**C5**), 13.7 (**C1**); HRMS (ESI) Found: $[M+Na]^+$, 279.0818. $C_{12}H_{16}O_6$ requires $[M+Na]^+$, 279.0839.

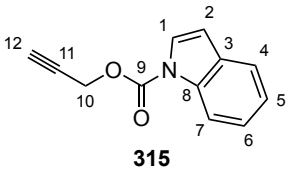
1-*tert*-Butyl 3-methyl 3-prop-2-ynyl 2-oxopiperidine-1,3,3-tricarboxylate (303u):



303u

A suspension of sodium hydride (60 wt in mineral oil%, 48.5 mg, 1.21 mmol) in tetrahydrofuran 10 mL) was cooled to 0 °C. A solution of **301t** (300 mg, 1.1 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (117 μL, 1.21 mmol) was added dropwise and the mixture was allowed to warm to room temperature and was stirred at room temperature for 1 hour. The reaction was quenched with the addition of aq. HCl (1 N, 20 mL) and extracted with EtOAc (3 x 25 mL). The combined organic fractions were washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1-3:1] afforded **303u** (211 mg, 57%) as a yellow oil. R_F 0.17 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3270, 2980, 1716 (C=O); δ_H (400 MHz, $CDCl_3$) 4.74 (dd, J = 4.9, 2.5 Hz, 2H, **H12**), 3.76 (s, 3H, **H10**), 3.50 (t, J = 6.9 Hz, 2H, **H4**), 2.48 (t, J = 2.3 Hz, 1H, **H14**), 2.47-2.44 (m, 2H, **H6**), 1.83-1.74 (m, 2H, **H5**), 1.45 (s, 9H, **H1**); δ_C (100 MHz, $CDCl_3$) 167.2 (**C9**), 166.5 (**C11**), 165.0 (**C8**), 152.4 (**C3**), 83.4 (**C2**), 76.4 (**C14**), 75.6 (**C13**), 65.6 (**C7**), 53.6 (**C12**), 53.3 (**C10**), 45.2 (**C4**), 28.1 (**C6**), 27.7 (**C1**), 19.2 (**C5**); HRMS (ESI) Found: $[M+Na]^+$, 362.1216. $C_{12}H_{21}NO_7$ requires $[M+Na]^+$, 362.1210.

Prop-2-ynyl 1*H*-indole-1-carboxylate (315):

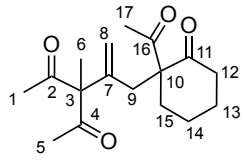


315

A suspension of sodium hydride (60 wt% in mineral oil, 110 mg, 2.75 mmol) in tetrahydrofuran 15 mL) was cooled to 0 °C. A solution of indole **301a** (296 mg, 2.5 mmol) in tetrahydrofuran (5 mL) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. Propargyl chloroformate (268 μL, 2.75 mmol) was added dropwise and the mixture was warmed to room temperature and stirred for 1 hour. The reaction was quenched with the addition of aq. HCl (1 N, 20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1] afforded **315** (130 mg, 26%) as a red/brown solid. R_F 0.35 [Petrol:EtOAc 4:1]; m.p. 48–51 °C; ν_{max} (film)/cm^{-1} 3281, 2137 (C≡C), 1712 (C=O), 1604; δ_H (400 MHz, $CDCl_3$) 8.10 (d, J = 7.9 Hz, 1H, **H1**), 7.49 (d, J = 3.8 Hz, 1H, **H4**), 7.45 (dt, J = 7.9, 1.1 Hz, 1H, **H7**), 7.26-7.21 (m, 1H, **H5**), 7.17-7.12 (m, 1H, **H6**), 6.50 (dd, J = 3.8, 0.7 Hz, 1H, **H2**), 4.89 (d, J = 2.5 Hz, 2H, **H10**), 2.49 (t, J = 2.5 Hz, 1H, **H12**); δ_C (100 MHz, $CDCl_3$) 150.0 (**C9**), 135.2 (**C3**), 130.3 (**C8**), 125.1 (**C4**), 124.6 (**C5**), 123.1 (**C6**), 121.0 (**C7**), 115.1 (**C1**), 108.6 (**C2**), 76.9 (**C12**), 76.0 (**C11**), 54.2 (**C10**). Synthesis of this compound has been reported in the literature.[130]

10.2.3. Palladium-Catalysed Alkenylation Reactions for the Coupling of Two 1,3-Dicarbonyl Compounds

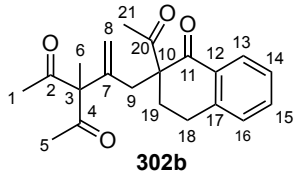
3-(3-(1-Acetyl-2-oxocyclohexyl)prop-1-en-2-yl)-3-methylpentane-2,4-dione (302a):



302a

Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and 2-acetylcyclohexanone (30 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded an inseparable mixture of **302a** and **302h** in an 8.8:1 ratio (66 mg, corresponding to 60 mg of **302a**, 85%, *r.r.* > 19:1) as a red solid. R_F 0.40 [Petrol:EtOAc 4:1]; m.p. 68–71 °C; ν_{max} (film)/cm^{-1} 3419, 2911, 2870, 1693 (C=O), 1644 (C=O), 1421; δ_H (400 MHz, $CDCl_3$) 5.02 (q, *J* = 1.4 Hz, 1H, **H8a**), 4.91 (q, *J* = 1.4 Hz, 1H, **H8b**), 2.59-2.37 (m, 6H, **H9**, **H12** and **H15**), 2.18 (s, 9H, **H1**, **H5** and **H17**), 1.75-1.62 (m, 4H, **H13** and **H14**), 1.55 (s, 3H, **H6**); δ_C (100 MHz, $CDCl_3$) 209.7 (**C2**), 208.3 (**C4**), 207.5 (**C11**), 207.5 (**C16**), 141.1 (**C7**), 116.8 (**C8**), 71.9 (**C3**), 67.1 (**C10**), 41.2 (**C12**), 36.2 (**C15**), 35.7 (**C9**), 27.2 (**C13**), 27.2 (**C1**), 27.0 (**C5**), 26.3 (**C17**), 21.8 (**C14**), 18.9 (**C6**); HRMS (ESI) Found: $[M+H]^+$, 293.1736. $C_{17}H_{24}O_4$ requires $[M+H]^+$, 293.1747.

3-(3-(2-Acetyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)prop-1-en-2-yl)-3-methylpentane-2,4-dione (302b):



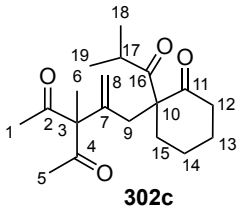
302b

Carbonate **300** (23.5 mg, 0.12 mmol), $Pd_2(dba)_3$ (5.5 mg, 0.006 mmol), DPEphos (6.5 mg, 0.012 mmol) and 2-acetyl-1-tetralone (26.7 mg, 0.12 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded an inseparable mixture of **302b** and **302h** in a 14:1 ratio (34.8 mg, corresponding to 32.3 mg of **302b**, 79%, *r.r.* > 19:1) as a red solid. R_F 0.33 [Petrol:EtOAc 4:1]; m.p. 82–84 °C; ν_{max} (film)/cm^{-1} 2976, 2931, 1702 (C=O), 1674 (C=O); δ_H (400 MHz, $CDCl_3$) 8.01 (dd, *J* = 7.9, 1.12 Hz, 1H, **H13**), 7.47 (td, *J* = 7.5, 1.4 Hz, 1H, **H14**), 7.30 (t, *J* = 8.2 Hz, 1H, **H15**), 7.20 (d, *J* = 7.8 Hz, 1H, **H16**), 5.04 (q, *J* = 1.2 Hz, 1H, **H8a**), 4.98 (q, *J* = 1.2 Hz, 1H, **H8b**), 3.12-3.01 (m, 1H, **H18a**), 2.92 (dt, *J* = 17.4, 5.0 Hz, 1H, **H18b**), 2.75 (dt, *J* = 17.1, 1.4 Hz, 1H, **H9a**), 2.56 (dt, *J* = 14.0, 5.0 Hz, 1H, **H19a**), 2.47 (dt, *J* = 17.2, 1.2 Hz, 1H, **H9b**), 2.38-2.26 (m, 1H, **H19b**), 2.20 (s, 3H, **H21**), 2.16 (s, 3H, **H1**), 2.16 (s, 3H, **H5**), 1.54 (s, 3H, **H6**); δ_C (100 MHz, $CDCl_3$) 207.2 (**C2**), 207.1 (**C4**), 206.8 (**C20**), 197.1 (**C11**), 143.3 (**C17**), 141.3 (**C7**), 134.0 (**C14**), 131.9 (**C12**), 128.8 (**C16**), 127.9 (**C13**), 126.8 (**C15**), 117.5 (**C8**), 72.0 (**C3**),

63.5 (**C10**), 36.0 (**C9**), 28.9 (**C19**), 27.2 (**C21**), 27.2 (**C1**), 27.1 (**C5**), 25.7 (**C18**), 18.7 (**C6**); HRMS (ESI) Found: $[M+Na]^+$, 363.1551. $C_{21}H_{24}O_4$ requires $[M+Na]^+$, 363.1554.

The formation of **302b** was also carried out under enantioselective conditions: Carbonate **300** (31.3 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), (*R*)-Tol-BINAP **L12** (6.5 mg, 0.0096 mmol) and 2-acetyltetralone (30 mg, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1 mL) was added and the sealed tube was stirred at room temperature for 16 hours, then concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **302b** (37 mg, 68% yield, *r.r.* > 19:1). Chiral HPLC: OD-H column, 1 mL/min, 9:1 Hexane:IPA, t_A (major) = 11.2 min, t_B (minor) = 12.9 min, 27% ee; $[\alpha]_D^{25}$ +1.4 (*c* 0.1, $CHCl_3$, 27% ee).

3-(3-(1-*iso*butyryl-2-oxocyclohexyl)prop-1-en-2-yl)-3-methylpentane-2,4-dione (302c):

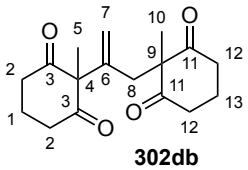


302c

Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and ethyl 2-methyl acetoacetate (34 μL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and

the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 4 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1] afforded **302c** (36 mg, 47%, *r.r.* > 19:1) a yellow solid. R_F 0.25 [Petrol:EtOAc 4:1]; m.p. 40–42 °C; ν_{max} (film)/cm^{-1} 2972, 2931, 2875, 1694 (C=O), 1641 (C=O); δ_H (400 MHz, $CDCl_3$) 5.02 (q, *J* = 1.2 Hz, 1H, **H8a**), 4.87 (q, *J* = 1.4 Hz, **H8b**), 3.01 (sept, *J* = 6.6 Hz, 1H, **H17**), 2.54-2.39 (m, 5H, **H9, H12** and **H15a**), 2.18 (s, 3H, **H1**), 2.17 (s, 3H, **H5**), 1.79-1.60 (m, 5H, **H13**, **H14** and **H15b**), 1.55 (s, 3H, **H6**), 1.10 (d, *J* = 7.1 Hz, 3H, **H18**), 0.98 (d, *J* = 6.2 Hz, 3H, **H19**); δ_C (100 MHz, $CDCl_3$) 214.8 (**C16**), 209.9 (**C11**), 207.6 (**C2**), 207.4 (**C4**), 141.4 (**C7**), 116.9 (**C8**), 71.9 (**C3**) 67.6 (**C10**), 41.5 (**C12**), 36.0 (**C17**), 35.7 (**C9**), 34.3 (**C15**), 27.2 (**C1**), 27.1 (**C5**), 27.1 (**C14**), 22.0 (**C13**), 21.0 (**C18**), 20.6 (**C19**), 18.8 (**C6**); HRMS (ESI) Found: $[M+H]^+$, 297.1684. $C_{16}H_{24}O_5$ requires $[M+H]^+$, 297.1697.

2,2'-(Prop-2-ene-1,2-diyl)bis(2-methylcyclohexane-1,3-dione (homo-coupled 302db):

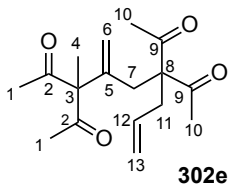


302db

Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol), and 2-methyl-1,3-cyclohexadione (30.2 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was

stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1] afforded an inseparable mixture of homo-coupled **301d** (**302db**), regioisomer **302**, minor isomer **304d** and **302h** in a 9:4:1.2:1 ratio (39 mg, corresponding to 20 mg of **302db,** 27%) as an orange solid. R_F 0.29 [Petrol:EtOAc 9-1:4:1]; m.p. 63–65 °C; ν_{max} (film)/cm^{-1} 3368, 2939, 1723 (C=O), 1686 (C=O), 1638; δ_H (400 MHz, $CDCl_3$, resonances due to **302db** quoted) 4.67 (q, *J* = 1.5 Hz, 1H, **H7a**), 4.11 (q, *J* = 1. 5 Hz, 1H, **H7b**), 2.96-2.87 (m, 2H, **H12a**), 2.84-2.75 (m, 2H, **H12b**), 2.72-2.57 (m, 3H, **H2a, Hb** and **H2c**), 2.54-2.50 (m, 1H, **H2d**), 2.48 (t, *J* = 1.5 Hz, 2H, **H8**), 2.18-2.13 (m, 2H, **H13**), 1.60-1.58 (m, 2H **H1**), 1.33-1.31 (m, 6H, **H5** and **H10**); δ_C (100 MHz, $CDCl_3$, resonances due to **302db** quoted) 209.1 (**C3**), 208.1 (**C11**), 144.9 (**C6**), 113.0 (**C7**), 73.5 (**C4**), 63.2 (**C9**), 38.7 (**C2**), 37.5 (**C12**), 36.0 (**C8**), 26.7 (**C5**), 17.5 (**C1**), 17.5 (**C10**), 17.4 (**C13**); For homo-coupled **302db**: HRMS (ESI) Found: $[M+H]^+$, 291.1580. $C_{17}H_{22}O_4$ requires $[M+H]^+$, 291.1591. For **302d**: HRMS (ESI) Found: $[M+H]^+$, 279.1580. $C_{16}H_{22}O_4$ requires $[M+H]^+$, 279.1591.

3,6-Diacetyl-6-allyl-3-methyl-4-methyleneoctane-2,7-dione (302e):

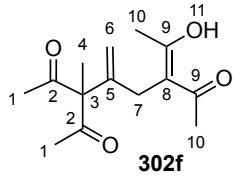


302e

Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and **301e** (33.6 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged

further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1] afforded an inseparable mixture of **302e** and **302h** in a 9.3:1 ratio (55 mg, corresponding to 49.4 mg of **302e**, 70%, *r.r.* > 19:1) as a pale yellow solid. R_F 0.33 [Petrol:EtOAc 9:1-4:1]; m.p. 64–66 °C; ν_{max} (film)/cm^{-1} 2981, 2926, 1694 (C=O), 1638 (C=O); δ_H (400 MHz, $CDCl_3$) 5.50-5.38 (m, 1H, **H12**), 5.11-5.04 (m, 2H, **H13**), 4.97 (q, *J* = 1.6 Hz, 1H, **H6a**), 4.87 (q, *J* = 1.8 Hz, 1H, **H6b**), 2.82 (dt, *J* = 7.3, 1.3 Hz, 2H, **H11**), 2.57 (t, *J* = 1.8 Hz, 2H, **H7**), 2.16 (s, 6H, **H1**), 2.14 (s, 6H, **H10**), 1.56 (s, 3H, **H4**); δ_C (100 MHz, $CDCl_3$) 207.0 (**C2**), 206.2 (**C9**), 141.9 (**C5**), 132.0 (**C12**), 119.4 (**C13**), 115.3 (**C6**), 71.9 (**C3**), 69.2 (**C8**), 35.5 (**C11**), 32.5 (**C7**), 27.1 (**C1**), 26.8 (**C10**), 18.9 (**C4**); HRMS (ESI) Found: $[M+H]^+$, 293.1736. $C_{17}H_{24}O_4$ requires $[M+H]^+$, 293.1747.

3-Acetyl-6-(1-hydroxyethylidene)-3-methyl-4-methyleneoctane-2,7-dione (302f):

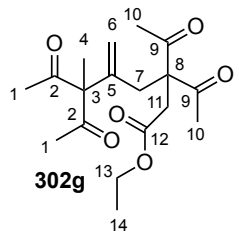


302f

Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and acetylacetone (25 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed

tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1] afforded an inseparable mixture of **302f** and **302h** in a 10:1 ratio (37 mg, corresponding to 33.6 mg **302f**, 56%, *r.r.* not determined) as a yellow solid. R_F 0.27 [Petrol:EtOAc 9:1-4:1]; m.p. 63–65 °C; ν_{max} (film)/cm^{-1} 2983, 2926, 1704 (C=O), 1639 (C=O), 1562; δ_H (400 MHz, $CDCl_3$) 16.88 (s, 1H, **H11**), 5.08 (t, *J* = 2.2 Hz, 1H, **H6a**), 5.01 (t, *J* = 1.9 Hz, 1H, **H6b**), 2.83 (t, *J* = 2.0 Hz, 2H, **H7**), 2.21 (s, 6H, **H1**), 2.06 (s, 6H, **H10**), 1.64 (s, 3H, **H4**); δ_C (100 MHz, $CDCl_3$) 207.1 (**C2**), 192.3 (**C9**), 144.5 (**C5**), 114.5 (**C6**), 106.0 (**C8**), 71.0 (**C3**), 30.7 (**C7**), 26.9 (**C1**), 22.7 (**C10**), 18.9 (**C4**); HRMS (ESI) Found: $[M+H]^+$, 253.1442. $C_{14}H_{20}O_4$ requires $[M+H]^+$, 253.1456.

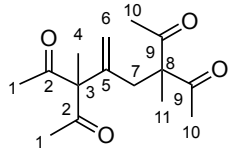
Ethyl 3,3,6-triacetyl-6-methyl-5-methylene-7-oxooctanoate (302g):



Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and **301g** (44.6 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash

column chromatography [Petrol:EtOAc 9:1-4:1] afforded an inseparable mixture of **302g**, homo-coupled **301g** and **302h** in a 11:1.2:1 ratio (59 mg, corresponding to 48.4 mg of **302g**, 60%, *r.r.* > 19:1) as an orange oil. R_F 0.38 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2992, 2967, 1700 (C=O), 1678 (C=O); δ_H (400 MHz, $CDCl_3$) 4.97 (q, *J* = 1.5 Hz, 1H, **H6a**), 4.77 (q, *J* = 1.7 Hz, 1H, **H6b**), 4.11 (q, *J* = 6.9 Hz, 2H, **H13**), 3.26 (s, 2H, **H11**), 2.82 (t, *J* = 1.7 Hz, 2H, **H7**), 2.16 (s, 6H, **H10**), 2.15 (s, 6H, **H1**), 1.57 (s, 3H, **H4**), 1.23 (t, *J* = 7.2 Hz, 3H, **H14**); δ_C (100 MHz, $CDCl_3$) 206.7 (**C2**), 204.9 (**C9**), 171.2 (**C12**), 142.4 (**C5**), 115.3 (**C6**), 71.9 (**C3**), 68.5 (**C8**), 61.0 (**C13**), 35.6 (**C11**), 33.2 (**C7**), 27.0 (**C1**), 26.0 (**C10**), 18.8 (**C4**), 14.0 (**C14**); HRMS (ESI) Found: $[M+H]^+$, 339.1789. $C_{18}H_{26}O_6$ requires $[M+H]^+$, 339.1802.

3,6-Diacetyl-3,6-dimethyl-4-methyleneoctane-2,7-dione (302h):

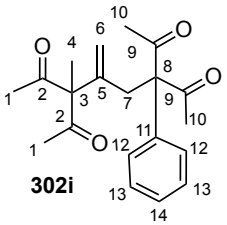


302h

Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11.0 mg, 0.012 mmol), DPEphos (13.1 mg, 0.020 mmol) and 3-methyl-2,4-pentanedione (28 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **302h** (47 mg, 74%) as a yellow solid. R_F 0.42 [Petrol:EtOAc 4:1];

m.p. 72–74 °C; ν_{max} (film)/cm^{-1} 3386, 2909, 1698 (C=O), 1652, 1426; δ_H (400 MHz, $CDCl_3$) 4.99 (q, *J* = 1.4 Hz, 1H, **H6a**), 4.83 (q, *J* = 1.3 Hz, 1H, **H6b**), 2.56 (t, *J* = 2.5 Hz, 2H, **H7**), 2.15 (s, 6H, **H1**), 2.13 (s, 6H, **H10**), 1.55 (s, 3H, **H4**), 1.42 (s, 3H, **H11**); δ_C (100 MHz, $CDCl_3$) 207.0 (**C2**), 207.0 (**C9**), 141.9 (**C5**), 115.7 (**C6**), 72.0 (**C3**) 66.0 (**C8**), 36.0 (**C7**), 27.1 (**C1**), 26.3 (**C10**), 18.8 (**C4**), 18.2 (**C11**); HRMS (ESI) Found: $[M+H]^+$, 267.1578. $C_{15}H_{22}O_4$ requires $[M+H]^+$, 267.1591.

3,6-Diacetyl-3-methyl-4-methylene-6-phenyloctane-2,7-dione (302i):

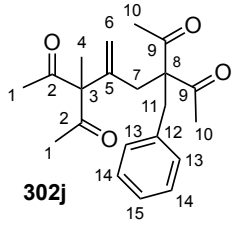


302i

Carbonate **300** (65.3 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and **301i** (42 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded an inseparable mixture of **302i** and **302h** in a 4.8:1 ratio (35 mg, corresponding to 28.2 mg of **302i**, 36%, *r.r.* > 19:1) as a red oil. R_F 0.22 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3058, 2983, 2926, 1692 (C=O), 1641 (C=O), 1500; δ_H (400 MHz, $CDCl_3$) 7.36-7.27 (m, 5H, **H12**, **H13** and **H14**), 5.08 (q, *J* = 1.7 Hz, 1H, **H6a**), 4.89 (q, *J* = 1.9 Hz, 1H, **H6b**), 3.03 (t, *J* = 2.0 Hz, 2H, **H7**), 2.21 (s, 6H, **H10**), 2.20 (s, 6H,

H1), 1.61 (s, 3H, **H4**); δ_C (100 MHz, $CDCl_3$) 207.5 (**C2**), 205.8 (**C9**), 141.1 (**C5**), 136.1 (**C11**), 129.0 (**C12**), 128.2 (**C14**), 128.0 (**C13**), 117.1 (**C6**), 72.8 (**C8**), 71.8 (**C3**), 35.2 (**C7**), 28.1 (**C1**), 27.0 (**C10**), 19.0 (**C4**); HRMS (ESI) Found: $[M+H]^+$, 329.1750. $C_{20}H_{24}O_4$ requires $[M+H]^+$, 329.1747.

3,6-Diacetyl-6-benzyl-3-methyl-4-methyleneoctane-2,7-dione (302j):

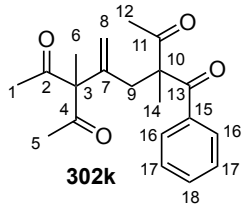


302j

Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and **301j** (44.6 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **302j** (60 mg, 73%, *r.r.* > 19:1) as a yellow oil. R_F 0.38 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3386, 2924, 2338, 1695 (C=O), 1638; δ_H (400 MHz, $CDCl_3$) 7.25-7.19 (m, 3H, **H14** and **H15**), 6.97-6.91 (m, 2H, **H13**), 5.02 (q, *J* = 1.8 Hz, 1H, **H6a**), 4.98 (q, *J* = 1.5 Hz, 1H, **H6b**), 3.40 (s, 2H, **H11**), 2.44 (t, *J* = 1.7 Hz, 2H, **H7**), 2.20 (s, 6H, **H10**), 2.10 (s, 6H, **H1**), 1.40 (s, 3H, **H4**); δ_C (100 MHz, $CDCl_3$) 206.9 (**C2**), 206.4 (**C9**), 142.1 (**C5**), 135.9 (**C12**), 129.5 (**C13**), 128.4 (**C15**), 127.2 (**C14**), 115.4 (**C6**), 71.8 (**C3**), 70.3 (**C8**), 37.4 (**C11**), 32.7 (**C7**), 27.3 (**C10**), 27.0 (**C1**),

18.6 (**C4**); HRMS (ESI) Found: $[M+H]^+$, 343.1888. $C_{21}H_{26}O_4$ requires $[M+H]^+$, 343.1904.

3-Acetyl-6-benzoyl-3,6-dimethyl-4-methyleneoctane-2,7-dione (302k):

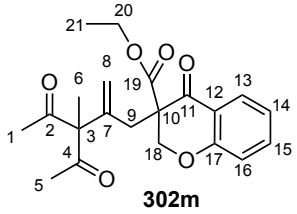


302k

Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and **301k** (42.3 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded an inseparable mixture of **302k** and **302h** in a 13:1 ratio (45 mg, corresponding to 42.7 mg of **302k**, 54%, *r.r.* > 19:1) as a red oil. R_F 0.31 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2987, 2928, 1762 (C=O), 1674 (C=O); δ_H (400 MHz, $CDCl_3$) 7.68-7.64 (m, 2H, **H16**), 7.50 (tt, *J* = 7.4, 2.0 Hz, 1H, **H18**), 7.41-7.35 (m, 2H, **H17**), 5.02 (q, *J* = 1.3 Hz, 1H, **H8a**), 4.93 (q, *J* = 1.2 Hz, 1H, **H8b**), 2.80 (dt, *J* = 18.3, 1.6 Hz, 1H, **H9a**), 2.70 (dt *J* = 18.3, 1.1 Hz, 1H, **H9b**), 2.13 (s, 3H, **H12**), 2.04 (s, 3H, **H1**), 1.88 (s, 3H, **H5**), 1.58 (s, 3H, **H14**), 1.40 (s, 3H, **H6**); δ_C (100 MHz, $CDCl_3$) 207.1 (**C11**), 206.9 (**C2**), 206.9 (**C4**), 200.1 (**C13**), 141.6 (**C7**), 136.4 (**C15**), 132.9 (**C18**), 128.6 (**C16**), 128.5 (**C17**), 116.7 (**C8**), 72.2 (**C3**), 64.6 (**C10**),

36.8 (**C9**), 26.8 (**C1** and **C5**), 26.4 (**C12**), 19.7 (**C14**), 18.5 (**C6**); HRMS (ESI) Found: $[M+Na]^+$, 351.1556. $C_{20}H_{24}O_4$ requires $[M+Na]^+$, 351.1567.

Ethyl 3-(3-acetyl-3-methyl-2-methylene-4-oxopentyl)-4-oxochroman-3-carboxylate (302m):



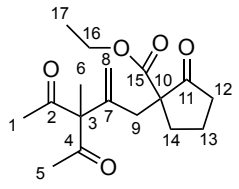
302m

Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and **301m** (53 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-5:1-4:1] afforded **302m** (55 mg, 62%, *r.r.* > 19:1) as a brown oil. R_F 0.42 [Petrol:EtOAc 5:1]; ν_{max} (film)/cm^{-1} 2982, 2117, 1695 (C=O), 1607, 1480; δ_H (400 MHz, $CDCl_3$) 7.88 (ddd, *J* = 7.9, 1.8, 0.4 Hz, 1H, **H16**), 7.47 (ddd, *J* = 8.4, 1.8, 0.5 Hz, 1H, **H15**), 7.05-7.00 (m, 1H, **H14**), 6.95 (dd, *J* = 8.4, 0.6 Hz, 1H, **H13**), 5.21 (q, *J* = 1.2 Hz, 1H, **H8a**), 5.09 (q, *J* = 0.5 Hz, 1H, **H8b**), 4.78 (d, *J* = 11.7 Hz, 1H, **H18a**), 4.67 (d, *J* = 12.1 Hz, 1H, **H18b**), 4.17 (qd, *J* = 7.2, 1.2 Hz, 2H, **H20**), 2.69 (d, *J* = 17.0 Hz, 1H, **H9a**), 2.49 (d, *J* = 16.8 Hz, 1H, **H9b**), 2.16 (s, 3H, **H1**), 2.15 (s, 3H, **H5**), 1.57 (s, 3H, **H6**), 1.18 (t, *J* = 6.9 Hz, 3H, **H21**); δ_C (100 MHz, $CDCl_3$) 207.2 (**C2**), 207.1 (**C4**), 189.6 (**C11**), 169.3 (**C19**), 160.8 (**C17**), 140.8 (**C7**), 136.2

(**C14**), 127.9 (**C16**), 121.8 (**C15**), 119.8 (**C12**), 118.5 (**C8**), 117.7 (**C13**), 71.9 (**C3**), 70.9 (**C18**), 62.0 (**C20**), 56.7 (**C10**), 31.8 (**C9**), 27.1 (**C1**), 27.0 (**C5**), 18.6 (**C6**), 13.8 (**C21**); HRMS (ESI) Found: $[M+H]^+$, 373.1629. $C_{21}H_{24}O_6$ requires $[M+H]^+$, 373.1646.

The formation of **302m** was also carried out under enantioselective conditions: Carbonate **300** (31.3 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol) (*R*)-Tol-BINAP **L12** (7.3 mg, 0.0096 mmol) and **301m** (35.2 mg, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1 mL) was added and the sealed tube was stirred at room temperature for 16 hours, then concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **302m** (21 mg, 35% yield, *r.r.* > 19:1). Chiral HPLC: OD-H column, 1 mL/min, 9:1 Hexane:IPA, t_A (major) = 10.1 min, t_B (minor) = 11.2 min, 11% ee; $[\alpha]_D^{25}$ +0.8 (*c* 0.1, $CHCl_3$, 11% ee).

Ethyl 1-(3-acetyl-3-methyl-2-methylene-4-oxopentyl)-2-oxocyclopentanecarboxylate (302n):

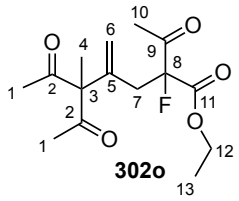


302n

Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.0120 mmol), DPEphos (13.1 mg, 0.024 mmol) and ethyl-2-oxocyclopentane carboxylate

(35 μL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **302n** (43 mg, 58%, *r.r.* > 19:1) as a yellow oil. R_F 0.35 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2982, 2110, 1752 (C=O), 1702 (C=O); δ_H (400 MHz, $CDCl_3$) 4.99 (q, *J* = 1.3 Hz, 1H, **H8a**), 4.98 (q, *J* = 1.4 Hz, 1H, **H8b**), 4.14 (q, *J* = 7.2 Hz, 1H, **H16a**), 4.14 (q, *J* = 7.2 Hz, 1H, **H16b**), 2.78-2.69 (m, 2H, **H9a** and **H14a**), 2.44-2.24 (m, 2H, **H12**), 2.16 (s, 3H, **H1**), 2.14 (s, 3H, **H5**), 2.10-1.88 (m, 4H, **H9b**, **H13** and **H14b**), 1.51 (s, 3H, **H6**), 1.21 (t, *J* = 7.0 Hz, 3H, **H17**); δ_C (100 MHz, $CDCl_3$) 213.5 (**C11**), 207.2 (**C2**), 207.2 (**C4**), 170.0 (**C15**), 142.6 (**C7**), 115.5 (**C8**), 71.5 (**C3**), 61.7 (**C16**), 59.6 (**C10**), 37.4 (**C12**), 36.3 (**C9**), 32.3 (**C14**), 27.3 (**C1**), 26.9 (**C5**), 19.6 (**C13**), 18.6 (**C6**), 13.9 (**C17**); HRMS (ESI) Found: $[M+Na]^+$, 331.1502. $C_{17}H_{24}O_5$ requires $[M+Na]^+$, 331.1516.

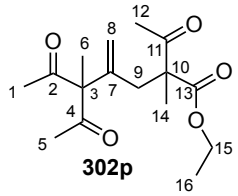
Ethyl 2,5-diacetyl-2-fluoro-5-methyl-4-methylene-6-oxoheptanoate (302o):



302o

Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and ethyl-2-fluoroacetoacetate (30 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **302o** (40 mg, 55%, *r.r.* > 19:1) as a yellow oil. R_F 0.39 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2987, 2933, 2341, 1762, 1736 (C=O), 1717 (C=O); δ_H (400 MHz, $CDCl_3$) 5.37 (s, 1H, **H6a**), 5.07 (s, 1H, **H6b**), 4.29-4.20 (m, 2H, **H12**), 2.97-2.74 (m, 2H, **H7**), 2.30 (d, *J* = 5.0 Hz, 3H, **H10**), 2.15 (s, 6H, **H1**), 1.52 (s, 3H, **H4**), 1.28 (t, *J* = 7.0 Hz, 3H, **H13**); δ_C (100 MHz, $CDCl_3$) 206.6 (**C2**), 201.0 (d, *J* = 27.5 Hz, **C9**), 165.6 (d, *J* = 25.4 Hz, **C11**), 139.8 (**C5**), 118.8 (**C6**), 99.8 (d, *J* = 197.1 Hz, **C8**), 71.7 (**C3**), 62.9 (**C12**), 35.1 (d, *J* = 21.8 Hz, **C7**), 27.0 (**C1a**), 26.9 (**C1b**), 25.5 (**C10**), 18.7 (**C4**), 13.9 (**C13**); HRMS (ESI) Found: $[M+H]^+$, 301.1451. $C_{15}H_{21}FO_5$ requires $[M+H]^+$, 301.1446.

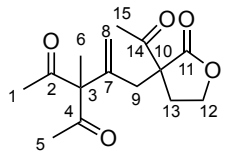
Ethyl 2,5-diacetyl-2,5-dimethyl-4-methylene-6-oxoheptanoate (302p):



302p

Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and ethyl 2-methyl acetoacetate (34 μL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **302p** (27 mg, 38%, *r.r.* > 19:1) as a black oil. R_F 0.29 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2983, 2931, 1701 (C=O), 1653 (C=O); δ_H (400 MHz, $CDCl_3$) 5.01-4.99 (m, 2H, **H8a** and **H8b**), 4.18 (q, *J* = 7.1 Hz, 1H, **H15a**), 4.18 (q, *J* = 7.1 Hz, 1H, **H15b**), 2.69 (dt, *J* = 18.1, 1.8 Hz, **H9a**), 2.49 (dt, *J* = 17.7, 1.5 Hz, **H9b**), 2.19 (s, 3H, **H12**), 2.11 (s, 3H, **H1**), 2.10 (s, 3H, **H5**), 1.43 (s, 3H, **H6**), 1.39 (s, 3H, **H14**), 1.19 (t, *J* = 7.2 Hz, 3H, **H16**); δ_C (100 MHz, $CDCl_3$) 207.2 (**C2**), 207.1 (**C4**), 205.0 (**C11**), 172.7 (**C13**), 142.4 (**C7**), 116.0 (**C8**), 72.0 (**C3**), 61.8 (**C15**), 58.7 (**C10**), 36.2 (**C9**), 27.3 (**C1**), 27.0 (**C5**), 26.0 (**C12**), 19.0 (**C14**), 18.6 (**C6**), 13.9 (**C16**); HRMS (ESI) Found: $[M+H]^+$, 297.1684. $C_{16}H_{24}O_5$ requires $[M+H]^+$, 297.1697.

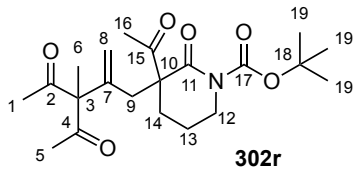
3-(3-(3-Acetyl-2-oxotetrahydrofuran-3-yl)prop-1-en-2-yl)-3-methylpentane-2,4-dione (302q):



302q

Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol), and **301q** (30.8 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded an inseparable mixture of **302q**, **302h** and homo-coupled **301q** in a 6.8:2.2:1 ratio (35 mg, corresponding to 23.0 mg of **302q**, 34%, *r.r.* > 19:1) as a yellow oil. R_F 0.15 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2981, 2924, 2855, 1759 (C=O), 1701 (C=O); δ_H (300 MHz, $CDCl_3$) 5.02 (q, *J* = 1.4 Hz, 1H, **H8a**), 4.89 (q, *J* = 1.8 Hz, 1H, **H8b**), 4.38-4.24 (m, 2H, **H12**), 3.13-3.00 (m, 2H, **H13**), 3.01 (dt, *J* = 18.2, 1.6 Hz, 1H, **H9a**), 2.43-2.33 (m, 1H, **H9b**), 2.36 (s, 3H, **H15**), 2.17 (s, 3H, **H1**), 2.16 (s, 3H, **H5**), 1.59 (s, 3H, **H6**); δ_C (75 MHz, $CDCl_3$) 206.6 (**C2**), 206.4 (**C4**), 203.3 (**C14**), 174.7 (**C11**), 142.1 (**C7**), 115.6 (**C8**), 66.9 (**C12**), 60.5 (**C10**), 37.7 (**C9**), 29.7 (**C13**), 27.0 (**C1**), 27.0 (**C5**), 25.7 (**C15**), 18.9 (**C6**); HRMS (ESI) Found: $[M+H]^+$, 281.1348. $C_{15}H_{20}O_5$ requires $[M+H]^+$, 281.1384.

***tert*-Butyl-3-acetyl-3-(3-acetyl-3-methyl-2-methylene-4-oxopentyl)-2-oxopiperidine-1-carboxylate (302r):**

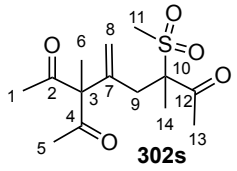


302r

Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and **301r** (58 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded an inseparable mixture of **302r** and homo-coupled **301r** in a 17:1 ratio (81 mg, corresponding to 76 mg of **302r**, 81%, *r.r.* > 19:1) as a red oil. R_F 0.30 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2980, 2933, 1768 (C=O), 1714 (C=O); δ_H (400 MHz, $CDCl_3$) 4.98 (q, *J* = 0.7 Hz, 1H, **H8a**), 4.95 (d, *J* = 1.0 Hz, 1H, **H8b**), 3.65-3.53 (m, 2H, **H12**), 2.78 (dt, *J* = 16.8, 1.6 Hz, 1H, **H9a**), 2.39-2.30 (m, 1H, **H9b**), 2.28-2.22 (m, 2H, **H14**), 2.24 (s, 3H, **H16**), 2.13 (s, 3H, **H1**), 2.11 (s, 3H, **H5**), 2.00-1.91 (m, 1H, **H13a**), 1.80-1.70 (m, 1H, **H13b**), 1.56 (s, 3H, **H6**), 1.47 (s, 9H, **H19**); δ_C (100 MHz, $CDCl_3$) 207.3 (**C2**), 207.1 (**C4**), 206.1 (**C15**), 171.6 (**C11**), 152.6 (**C17**), 141.3 (**C7**), 117.4 (**C8**), 83.1 (**C18**), 71.8 (**C3**), 62.5 (**C10**), 46.5 (**C12**), 37.4 (**C9**), 27.8 (**C19**), 27.3 (**C1**), 27.1 (**C14**), 26.9 (**C5**), 26.7 (**C16**), 20.6

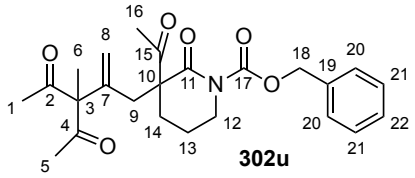
(**C13**), 18.7 (**C6**); HRMS (ESI) Found: $[M+Na]^+$, 416.2029. $C_{21}H_{31}NO_6$ requires $[M+Na]^+$, 416.2044.

3-Acetyl-3,6-dimethyl-4-methylene-6-(methylsulfonyl)octane-2,7-dione (302s):



Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and **301s** (36.0 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1] afforded **302s** (39 mg, 54%, *r.r.* > 19:1) as a dark yellow solid. R_F 0.15 [Petrol:EtOAc 4:1]; m.p. 89–92 °C; ν_{max} (film)/cm^{-1} 3006, 2931, 1701 (C=O), 1641; δ_H (400 MHz, $CDCl_3$) 5.05 (t, *J* = 1.2 Hz, 1 H, **H8a**), 4.83 (q, *J* = 1.6 Hz, 1H, **H8b**), 3.20 (d, *J* = 15.8 Hz, 1H, **H9a**), 2.80 (s, 3H, **H11**), 2.45 (s, 3H, **H13**), 2.45 (dd, *J* = 16.4, 1.1 Hz, 1H, **H9b**), 2.17 (s, 3H, **H1**), 2.13 (s, 3H, **H5**), 1.75 (s, 3H, **H14**), 1.60 (s, 3H, **H6**); δ_C (100 MHz, $CDCl_3$) 206.6 (**C2**), 206.5 (**C4**), 206.0 (**C12**), 140.5 (**C7**), 118.0 (**C8**), 74.6 (**C10**), 71.8 (**C3**), 35.4 (**C11**), 33.6 (**C9**), 28.8 (**C13**), 27.1 (**C1**), 27.0 (**C5**), 18.9 (**C14**), 14.5 (**C6**); HRMS (ESI) Found: $[M+H]^+$, 303.1250. $C_{14}H_{22}O_5S$ requires $[M+H]^+$, 303.1261.

Benzyl 3-acetyl-3-(4-acetyl-4-methyl-5-oxohex-1-en-2-yl)-2-oxopiperidine-1-carboxylate (302u):

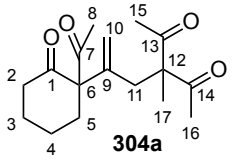


302u

Carbonate **300** (31.4 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), DPEphos (8.6 mg, 0.0160 mmol) and **301u** (44.3 mg, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Dioxane (1 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1-1:1] afforded **302u** (28 mg, 41%, *r.r.* not determined) as a colourless oil. R_F 0.10 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2950, 2109, 1770, 1697 (C=O); δ_H (400 MHz, $CDCl_3$) 7.42-7.30 (m, 5H, **H20, H21** and **H22**), 5.26 (s, 2H, **H18**), 5.02 (q, *J* = 0.8 Hz, 1H, **H8a**), 4.97 (q, *J* = 1.2 Hz, 1H, **H8b**), 3.73 (dd, *J* = 7.1, 5.1 Hz, 2H, **H14**), 2.84 (dt, *J* = 16.4, 1.1 Hz, 1H, **H9a**), 2.42-2.35 (m, 2H, **H9b** and **H13a**), 2.26 (s, 3H, **H16**), 2.16 (s, 3H, **H1**), 2.10 (s, 3H, **H5**), 2.04 (ddd, *J* = 15.5, 10.2, 5.3 Hz, 1H, **H13b**), 1.84-1.73 (m, 2H, **H14**), 1.62 (s, 3H, **H6**); δ_C (100 MHz, $CDCl_3$) 207.4 (**C2**), 207.2 (**C5**), 205.9 (**C15**), 171.6 (**C11**), 153.9 (**C17**), 141.2 (**C7**), 135.2 (**C19**), 128.5 (**C21**), 128.3 (**C22**), 128.0 (**C20**), 118.0 (**C8**), 71.7 (**C3**), 68.6 (**C18**), 62.8 (**C10**), 46.8 (**C12**), 37.5 (**C9**), 27.3 (**C1**), 27.1 (**C14**), 26.9 (**C5**), 26.7 (**C16**),

20.6 (**C13**), 18.7 (**C6**); HRMS (ESI) Found: $[M+H]^+$, 428.2071. $C_{24}H_{29}NO_6$ requires $[M+H]^+$, 428.2068.

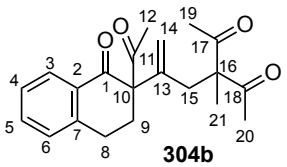
3-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-3-methylpentane-2,4-dione (304a):



304a

Carbonate **266** (53.3 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and 3-methyl-2,4-pentanedione **301h** (28 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **304a** (49 mg, 70%, *r.r.* > 19:1) as a yellow solid. R_F 0.38 [Petrol:EtOAc 4:1]; m.p. 55–58 °C; ν_{max} (film)/cm^{-1} 3389, 2933, 1699 (C=O); δ_H (400 MHz, $CDCl_3$) 4.97 (q, *J* = 1.3 Hz, 1H, **H10a**), 4.84 (q, *J* = 1.4 Hz, 1H, **H10b**), 2.54 (t, *J* = 1.5 Hz, 2H, **H11**), 2.49 (t, *J* = 7.0 Hz, 2H, **H2**), 2.31-2.21 (m, 1H, **H5a**), 2.14 (s, 6H, **H15** and **H16**), 2.13 (s, 3H, **H8**), 1.93-1.52 (m, 5H, **H3**, **H4** and **H5b**), 1.43 (s, 3H, **H17**); δ_C (100 MHz, $CDCl_3$) 209.3 (**C1**), 207.3 (**C13**), 207.3 (**C14**), 207.1 (**C7**), 141.2 (**C9**), 116.4 (**C10**), 73.9 (**C6**), 65.8 (**C12**), 41.0 (**C2**), 36.5 (**C11**), 32.9 (**C5**), 27.1 (**C3**), 26.7 (**C8**), 26.3 (**C15**), 26.3 (**C16**), 21.8 (**C4**), 18.3 (**C17**); HRMS (ESI) Found: $[M+H]^+$, 293.1749. $C_{17}H_{24}O_4$ requires $[M+H]^+$, 293.1782.

3-(2-(2-Acetyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)allyl)-3-methylpentane-2,4-dione (304b):

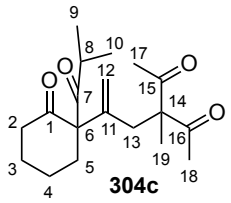


304b

Carbonate **303b** (64.8 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and 3-methyl-2,4-pentanedione **301h** (28 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **304b** (58 mg, 71%, *r.r.* > 19:1) as a yellow oil. R_F 0.34 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2929, 1698 (C=O), 1676 (C=O), 1599; δ_H (400 MHz, $CDCl_3$) 8.03 (dd, *J* = 8.0, 1.2 Hz, 1H, **H3**), 7.47 (td, *J* = 7.4, 1.5 Hz, 1H, **H4**), 7.31 (t, *J* = 8.0 Hz, 1H, **H5**), 7.20 (d, *J* = 7.9 Hz, 1H, **H6**), 4.88 (q, *J* = 1.2 Hz, 1H, **H14a**), 4.79 (q, *J* = 1.7 Hz, 1H, **H14b**), 3.01-2.88 (m, 2H, **H8**), 2.81 (dt, *J* = 18.4, 2.0 Hz, 1H, **H15a**), 2.63-2.44 (m, 3H, **H9** and **H15b**), 2.28 (s, 3H, **H12**), 2.15 (s, 3H, **H19**), 2.14 (s, 3H, **H20**), 1.47 (s, 3H, **H21**); δ_C (100 MHz, $CDCl_3$) 206.9 (**C17**), 206.8 (**C18**), 206.0 (**C11**), 196.4 (**C1**), 142.9 (**C2**), 140.5 (**C13**), 133.8 (**C4**), 132.1 (**C7**), 128.6 (**C6**), 127.8 (**C3**), 127.0 (**C5**), 116.9 (**C14**), 70.4 (**C10**), 66.1 (**C16**), 36.5 (**C15**), 29.3 (**C9**), 28.3 (**C12**), 26.3 (**C19** and **C20**), 25.8 (**C8**), 18.0 (**C21**); HRMS (ESI) Found: $[M+Na]^+$, 363.1568. $C_{21}H_{24}O_4$ requires $[M+Na]^+$, 363.1567.

The formation of **304b** was also carried out under enantioselective conditions: Carbonate **303b** (43.2 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol) (*R*)-Xylyl-P-PHOS **L19** (7.3 mg, 0.0096 mmol) and 3-methyl-2,4-pentanedione **301h** (0.019 µL, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Tetrahydrofuran (1 mL) was added and the sealed tube was stirred at 60 °C for 2 hours, then concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **304b** (30 mg, 57% yield, *r.r.* > 19:1). Chiral HPLC: AD-H column, 1 mL/min, 9:1 Hexane:IPA, t_A (minor) = 10.7 min, t_B (major) = 12.6 min, 21% ee; $[\alpha]_D^{25}$ –1.3 (*c* 0.1, $CHCl_3$, 21% ee).

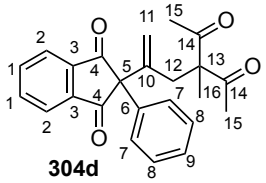
3-(2-(1-*iso*-Butyryl-2-oxocyclohexyl)allyl)-3-methylpentane-2,4-dione (304c):



Carbonate **303c** (60.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and 3-methyl-2,4-pentanedione **301h** (28 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 4 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1]

afforded product **304c** (47 mg, 61%, *r.r.* > 19:1) as a yellow solid. R_F 0.35 [4:1 Pet:EtOAc]; m.p. 82–84 °C; ν_{max} (film)/cm^{-1} 2968, 2935, 1694 (C=O), 1636; δ_H (400 MHz, $CDCl_3$) 4.93 (q, *J* = 1.5 Hz, 1H, **H12a**), 4.87 (q, *J* = 1.5 Hz, 1H, **H12b**), 2.92 (sept, *J* = 7.0 Hz, 1H, **H8**), 2.64 (dt, *J* = 18.5, 1.6 Hz, 1H, **H13a**), 2.56-2.43 (m, 3H, **H2** and **H13b**), 2.33-2.22 (m, 2H, **H5**), 2.17 (s, 3H, **H17**), 2.17 (s, 3H, **H18**), 1.92-1.81 (m, 2H, **H3**), 1.77-1.67 (m, 2H, **H4**), 1.48 (s, 3H, **H19**), 1.10 (d, *J* = 6.6 Hz, 3H, **H9**), 1.06 (d, *J* = 6.7 Hz, 3H, **H10**); δ_C (100 MHz, $CDCl_3$) 213.7 (**C7**), 209.9 (**C1**), 207.4 (**C15**), 207.3 (**C16**), 140.6 (**C11**), 116.2 (**C12**), 74.5 (**C6**), 66.0 (**C14**), 41.1 (**C2**), 37.2 (**C8**), 36.5 (**C13**), 32.4 (**C5**), 26.9 (**C3**), 26.4 (**C17**), 26.4 (**C18**), 21.8 (**C4**), 20.9 (**C9**), 20.5 (**C10**), 18.3 (**C19**); HRMS (ESI) Found: $[M+Na]^+$, 343.1872. $C_{19}H_{28}O_4$ requires $[M+Na]^+$, 343.1880.

2-(4-Acetyl-4-methyl-5-oxohex-1-en-2-yl)-2-phenyl-1H-indene-1,3(2*H*)-dione (304d):

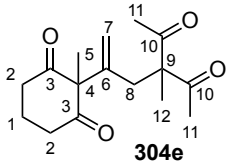


304d

Carbonate **303d** (73.0 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and 3-methyl-2,4-pentanedione **311h** (28 µL, 0.240 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and

concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **304d** (66 mg, 74%) as an orange oil. R_F 0.33 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2102, 1740 (C=O), 1699 (C=O), 1591; δ_H (400 MHz, $CDCl_3$) 8.08-8.02 (m, 2H, **H2**), 7.91-7.84 (m, 2H, **H1**), 7.45-7.39 (m, 2H, **H7**), 7.36-7.27 (m, 3H, **H8** and **H9**), 4.96 (q, *J* = 1.4 Hz, 1H, **H11a**), 4.92 (q, *J* = 1.2 Hz, 1H, **H11b**), 2.74 (t, *J* = 1.5 Hz, 2H, **H12**), 2.08 (s, 6H, **H15**), 1.42 (s, 3H, **H16**); δ_C (100 MHz, $CDCl_3$) 207.0 (**C14**), 199.0 (**C4**), 141.6 (**C10**), 141.2 (**C3**), 136.1 (**C1**), 134.6 (**C6**), 128.8 (**C8**), 128.4 (**C7**), 128.1 (**C9**), 123.9 (**C2**), 118.7 (**C11**), 69.8 (**C5**), 66.3 (**C13**), 36.3 (**C12**), 26.1 (**C15**), 17.8 (**C16**); HRMS (ESI) Found: $[M+Na]^+$, 397.1397. $C_{24}H_{22}O_4$ requires $[M+Na]^+$, 397.1410.

2-(4-Acetyl-4-methyl-5-oxohex-1-en-2-yl)-2-methylcyclohexane-1,3-dione (304e):

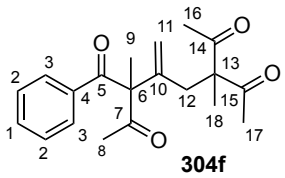


304e

Carbonate **303e** (50 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and 3-methyl-2,4-pentanedione **301h** (28 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1]

afforded product **304e** (29 mg, 43%, *r.r.* 4.0:1) as a yellow solid. R_F 0.31 [Petrol:EtOAc 4:1]; m.p. 42–44 °C; ν_{max} (film)/cm^{-1} 3382, 2994, 2950, 2942, 1722 (C=O), 1692 (C=O), 1634; δ_H (400 MHz, $CDCl_3$) 4.89 (q, *J* = 1.7 Hz, 1H, **H7a**), 4.73 (q, *J* = 1.7 Hz, **H7b**), 2.85-2.74 (m, 2H, **H2a**), 2.62-2.53 (m, 2H, **H2b**), 2.47 (t, *J* = 1.2 Hz, 2H, **H8**), 2.15-2.12 (m, 1H, **H1**), 2.10 (s, 6H, **H11**), 1.42 (s, 3H, **H12**), 1.31 (s, 3H, **H5**); δ_C (100 MHz, $CDCl_3$) 208.0 (**C3**), 206.6 (**C10**), 142.8 (**C6**), 114.8 (**C7**), 73.2 (**C4**), 65.9 (**C9**), 38.5 (**C2**), 36.2 (**C8**), 26.2 (**C11**), 18.9 (**C1**), 18.2 (**C12**), 17.4 (**C5**); HRMS (ESI) Found: $[M+H]^+$, 279.1585. $C_{16}H_{22}O_4$ requires $[M+H]^+$, 279.1591.

6-Acetyl-3-benzoyl-3,6-dimethyl-4-methyleneoctane-2,7-dione (304f):



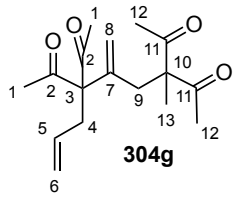
304f

Carbonate **303f** (61.9 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and 3-methyl-2,4-pentanedione **301h** (28 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded an inseparable mixture of **304f** and homocoupled **303f** in a 5.1:1 ratio (60 mg, corresponding to 49.5 mg of **304f**, 63%, *r.r.* > 19:1) as a red solid. R_F 0.26 [Petrol:EtOAc 4:1]; m.p. 73–76 °C; ν_{max} (film)/cm^{-1} 2976, 2928, 1717,

1698 (C=O), 1667 (C=O); δ_H (400 MHz, $CDCl_3$) 7.83-7.79 (m, 2H, **H3**), 7.50 (tt, *J* = 7.3, 1.9 Hz, 1H, **H1**), 7.41-7.35 (m, 2H, **H2**), 5.13 (q, *J* = 1.3 Hz, 1H, **H11a**), 4.87 (q, *J* = 1.6 Hz, 1H, **H11b**), 2.80 (dt, *J* = 18.3, 1.9 Hz, 1H, **H12a**), 2.61 (dt, *J* = 18.3, 1.6 Hz, 1H, **H12b**), 2.18 (s, 3H, **H8**), 2.14 (s, 3H, **H16**), 2.12 (s, 3H, **H17**), 1.68 (s, 3H, **H9**), 1.43 (s, 3H, **H18**); δ_C (100 MHz, $CDCl_3$) 207.2 (**C14**), 207.2 (**C15**), 206.2 (**C7**), 200.7 (**C5**), 143.0 (**C10**), 135.7 (**C4**), 132.9 (**C1**), 129.3 (**C3**), 128.3 (**C2**), 115.8 (**C11**), 70.3 (**C6**), 65.9 (**C13**), 36.7 (**C12**), 27.6 (**C8**), 26.3 (**C16**), 26.2 (**C17**), 20.9 (**C9**), 18.2 (**C18**); HRMS (ESI) Found: $[M+H]^+$, 329.1759. $C_{20}H_{24}O_4$ requires $[M+H]^+$, 329.1747.

The formation of **304f** was also carried out under enantioselective conditions: Carbonate **303f** (45,8 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol) (*R*)-Xylyl-P-PHOS **L12** (7.3 mg, 0.0096 mmol) and 3-methyl-2,4-pentanedione **301h** (0.019 µL, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Tetrahydrofuran (1 mL) was added and the sealed tube was stirred at 60 °C for 2 hours, then concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **304f** (18 mg, 34% yield, *r.r.* > 19:1). Chiral HPLC: OD-H column, 1 mL/min, 9:1 Hexane:IPA, t_A (major) = 7.7 min, t_B (minor) = 8.5 min, 19% ee; $[\alpha]_D^{25}$ +0.5 (*c* 0.1, $CHCl_3$, 19% ee).

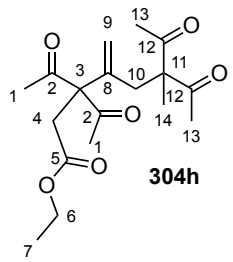
3,6-Diacetyl-3-allyl-6-methyl-4-methyleneoctane-2,7-dione (304g):



304g

Carbonate **303g** (53.2 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and 3-methyl-2,4-pentanedione **301h** (28 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded product **304g** (32 mg, 46%, *r.r.* 10:1) as a brown oil. R_F 0.34 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3386, 2924, 2835, 1694 (C=O); δ_H (400 MHz, $CDCl_3$) 5.67-5.55 (m, 1H, **H5**), 5.16-5.04 (m, 3H, **H6** and **H8a**), 4.90 (q, *J* = 1.8 Hz, 1H, **H8b**), 2.80 (dt, *J* = 7.0, 1.5 Hz, 2H, **H4**), 2.57 (t, *J* = 1.5 Hz, 2H, **H9**), 2.17 (s, 6H, **H1**), 2.13 (s, 6H, **H12**), 1.42 (s, 3H, **H13**); δ_C (100 MHz, $CDCl_3$) 206.8 (**C11**), 205.8 (**C2**), 140.6 (**C7**), 132.9 (**C5**), 118.8 (**C6**), 117.2 (**C8**), 76.8 (**C3**), 65.9 (**C10**), 36.0 (**C4**), 35.7 (**C9**), 27.8 (**C1**), 26.2 (**C12**), 18.2 (**C13**); HRMS (ESI) Found: $[M+H]^+$ 293.1741. $C_{17}H_{24}O_4$ requires $[M+H]^+$, 293.1747.

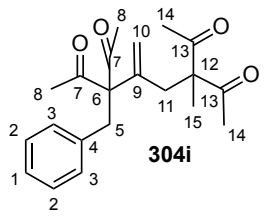
Ethyl 3,3,6-triacetyl-6-methyl-4-methylene-7-oxooctanoate (304h):



304h

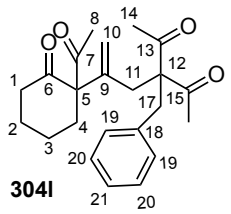
Carbonate **303h** (50 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol), and 3-methyl-2,4-pentanedione **301h** (28 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1] afforded an inseparable 16:1.2:1 mixture of **304h**, **302h** and **302g** (38 mg, corresponding to 33.5 mg of **304h**, 41%, *r.r.* 3.5:1) as a green oil. R_F 0.31 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2983, 2935, 1697 (C=O), 1638; δ_H (400 MHz, $CDCl_3$) 5.09 (q, *J* = 1.8 Hz, 1H, **H9a**), 4.87 (q, *J* = 1.9 Hz, 1H, **H9b**), 4.13 (q, *J* = 4.1 Hz, 2H, **H6**), 3.05 (s, 2H, **H4**), 2.54 (t, *J* = 1.6 Hz, 2H, **H10**), 2.25 (s, 6H, **H1**), 2.11 (s, 6H, **H13**), 1.40 (s, 3H, **H14**), 1.25 (t, *J* = 7.2 Hz, 3H, **H7**); δ_C (100 MHz, $CDCl_3$) 206.4 (**C12**), 204.8 (**C2**), 170.6 (**C5**), 140.2 (**C8**), 117.2 (**C9**), 73.5 (**C3**), 65.3 (**C11**), 61.2 (**C6**), 37.7 (**C4**), 36.0 (**C10**), 28.1 (**C1**), 26.2 (**C13**), 18.0 (**C14**), 14.0 (**C7**); HRMS (ESI) Found: $[M+Na]^+$, 361.1606. $C_{18}H_{26}O_6$ requires $[M+Na]^+$, 361.1622.

3,6-Diacetyl-3-benzyl-6-methyl-4-methyleneoctane-2,7-dione (304i):



Carbonate **303i** (65.3 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol), and 3-methyl-2,4-pentanedione **301h** (28 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded an inseparable mixture of **304i** and homocoupled **303i** in a 6.5:1 ratio (21 mg, corresponding to 17.5 mg of **304i**, 21%, *r.r.* > 19:1) as a yellow solid. R_F 0.37 [Petrol:EtOAc 4:1]; m.p. 70–72 °C; ν_{max} (film)/cm^{-1} 3384, 2993, 2927, 1692 (C=O), 1641, 1500; δ_H (400 MHz, $CDCl_3$) 7.24-7.17 (m, 3H, **H1** and **H2**), 7.06 (dd, *J* = 7.7, 1.5 Hz, 2H, **H3**), 5.18 (q, *J* = 1.4 Hz, 1H, **H10a**), 4.91 (q, *J* = 1.9 Hz, 1H, **H10b**), 3.47 (s, 2H, **H5**), 2.64 (t, *J* = 1.7 Hz, 2H, **H11**), 2.15 (s, 6H, **H8**), 2.11 (s, 6H, **H14**), 1.41 (s, 3H, **H15**); δ_C (100 MHz, $CDCl_3$) 206.9 (**C13**), 205.8 (**C7**), 141.2 (**C9**), 136.1 (**C4**), 129.7 (**C3**), 128.4 (**C2**), 127.0 (**C1**), 117.5 (**C10**), 78.0 (**C6**), 66.0 (**C12**), 37.8 (**C5**), 35.6 (**C11**), 28.4 (**C8**), 26.2 (**C14**), 18.0 (**C15**); HRMS (ESI) Found: $[M+H]^+$, 343.1898. $C_{21}H_{26}O_4$ requires $[M+H]^+$, 343.1904.

3-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-3-benzylpentane-2,4-dione (304l):

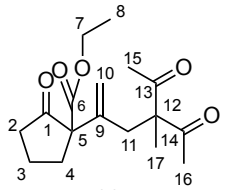


304l

Carbonate **266** (35.5 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), DPEphos (8.6 mg, 0.0160 mmol) and **301j** (30.4 mg, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Tetrahydrofuran (1 mL) was added and the sealed tube was added to an oil bath preheated to 60 °C. The mixture was stirred at 60 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **304l** (21 mg, 36%, *r.r.* not determined) as a colourless oil. R_F 0.44 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2942, 2206, 1694 (C=O); δ_H (400 MHz, $CDCl_3$) 7.25-7.19 (m, 3H, **H20** and **H21**), 6.99-6.93 (m, 2H, **H19**), 5.04 (q, *J* = 1.7 Hz, 1H, **H10a**), 4.97 (q, *J* = 1.5 Hz, 1H, **H10b**), 3.40 (dd, *J* = 19.3, 15.0 Hz, 2H, **H17**), 2.56 (dt, *J* = 19.1, 1.6 Hz, 1H, **H11a**), 2.52-2.36 (m, 3H, **H1** and **H11b**), 2.24 (s, 3H, **H14**), 2.22 (s, 3H, **H16**), 2.17-2.13 (m, 2H, **H4a**), 2.07 (s, 3H, **H8**), 2.07-2.00 (m, 1H, **H4b**), 1.90-1.80 (m, 1H, **H2a**), 1.77-1.66 (m, 1H, **H2b**), 1.57-1.46 (m, 2H, **H3**); δ_C (100 MHz, $CDCl_3$) 209.1 (**C6**), 207.4 (**C7**), 206.9 (**C13**), 206.6 (**C15**), 141.2 (**C9**), 135.9 (**C18**), 129.6 (**C19**), 128.4 (**C20**), 127.2 (**C12**), 115.8 (**C10**), 73.4 (**C5**), 70.2 (**C12**), 41.0 (**C11**), 38.0 (**C17**), 33.6 (**C1**), 33.0 (**C4**), 27.7 (**C14**), 27.4 (**C16**), 27.1 (**C2**), 26.7 (**C8**), 21.7 (**C3**); HRMS (ESI) Found: $[M+H]^+$, 369.2050. $C_{23}H_{28}O_4$ requires $[M+H]^+$, 369.2060.

The formation of **304l** was also carried out under enantioselective conditions: Carbonate **266** (35.5 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), (*R*)-Xylyl-P-PHOS **L19** (7.3 mg, 0.0096 mmol) and **301j** (30.4 mg, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Tetrahydrofuran (1 mL) was added and the sealed tube was stirred at 60 °C for 2 hours, then concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **304l** (17 mg, 29% yield, *r.r.* not determined). Chiral HPLC: AD-H column, 1 mL/min, 9:1 Hexane:IPA, t_A (minor) = 8.4 min, t_B (major) = 9.5 min, 19% ee; $[\alpha]_D^{25}$ +1.0 (*c* 0.1, $CHCl_3$, 19% ee).

Ethyl-1-(4-acetyl-4-methyl-5-oxohex-1-en-2-yl)-2-oxocyclopentanecarboxylate (304m):

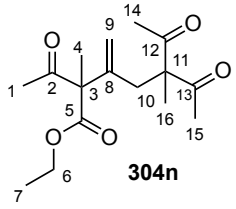


304m

Carbonate **303m** (57.2 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and 3-methyl-2,4-pentanedione **301h** (28 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and

concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded an inseparable mixture of **304m** and **302h** in a 17:1 ratio (45 mg, corresponding to 42.6 mg of **304m**, 58%, *r.r.* > 19:1) as a red oil. R_F 0.36 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3015, 2935, 1719 (C=O), 1698 (C=O); δ_H (400 MHz, $CDCl_3$) 4.99 (q, *J* = 1.2 Hz, 1H, **H10a**), 4.72 (q, *J* = 1.5 Hz, 1H, **H10b**), 4.17 (q, *J* = 7.2 Hz, 1H, **H7a**), 4.17 (q, *J* = 7.2 Hz, 1H, **H7b**), 2.81 (dt, *J* = 18.2, 1.4 Hz, 1H, **H11a**), 2.66 (dt, *J* = 17.9, 1.6 Hz, 1H, **H11b**), 2.57-2.49 (m, 1H, **H4a**), 2.37-2.24 (m, 3H, **H2** and **H4b**), 2.11 (s, 3H, **H15**), 2.10 (s, 3H, **H16**), 1.98-1.80 (m, 2H, **H3**), 1.41 (s, 3H, **H17**), 1.23 (t, *J* = 6.2 Hz, 3H, **H8**); δ_C (100 MHz, $CDCl_3$) 212.0 (**C1**), 207.1 (**C13**), 207.0 (**C14**), 170.2 (**C6**), 139.3 (**C9**), 114.7 (**C10**), 67.4 (**C5**), 66.2 (**C12**), 61.8 (**C7**), 37.7 (**C2**), 35.9 (**C11**), 33.2 (**C4**), 26.3 (**C15**), 26.1 (**C16**), 19.2 (**C3**), 17.8 (**C17**), 14.0 (**C8**); HRMS (ESI) Found: $[M+H]^+$, 309.1699. $C_{17}H_{24}O_5$ requires $[M+H]^+$, 309.1697.

Ethyl 2,5-diacetyl-2,5-dimethyl-3-methylene-6-oxoheptanoate (304n):

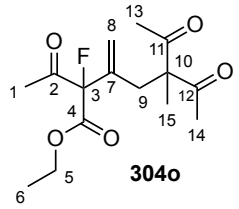


304n

Carbonate **303n** (54.3 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and 3-methyl-2,4-pentanedione **301h** (28 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and

concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded an inseparable mixture of **304n**, homocoupled **302h** and homocoupled **303n** in a 16:1.3:1 ratio (34 mg, corresponding to 30 mg of **304n**, 42%, *r.r.* > 19:1) as a yellow oil. R_F 0.35 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2935, 2873, 1694 (C=O), 1641, 1556; δ_H (400 MHz, $CDCl_3$) 5.00 (q, *J* = 1.2 Hz, 1H, **H9a**), 4.76 (q, *J* = 1.4 Hz, 1H, **H9b**), 4.21 (q, *J* = 7.1 Hz, 2H, **H6**), 2.70 (d, *J* = 6.2 Hz, 2H, **H10**), 2.21 (s, 3H, **H1**), 2.13 (s, 3H, **H14**), 2.12 (s, 3H, **H15**), 1.55 (s, 3H, **H4**), 1.43 (s, 3H, **H16**), 1.27 (t, *J* = 7.1 Hz, 3H, **H7**); δ_C (100 MHz, $CDCl_3$) 207.1 (**C12**), 206.9 (**C13**), 204.8 (**C2**), 171.4 (**C5**), 142.0 (**C8**), 114.7 (**C9**), 66.4 (**C3**), 66.3 (**C11**), 61.6 (**C6**), 36.1 (**C10**), 27.0 (**C1**), 26.3 (**C14**), 26.2 (**C15**), 19.9 (**C4**), 17.8 (**C16**), 14.0 (**C7**); HRMS (ESI) Found: $[M+Na]^+$, 349.1609. $C_{17}H_{26}O_6$ requires $[M+Na]^+$, 349.1622.

Ethyl 2,5-diacetyl-2-fluoro-5-methyl-3-methylene-6-oxoheptanoate (304o):

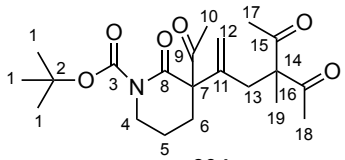


304o

Carbonate **303o** (55.2 mg, 0.240 mmol), $Pd_2(dba)_3$ (11 mg, 0.0120 mmol), DPEphos (13.1 mg, 0.024 mmol) and 3-methyl-2,4-pentanedione **301h** (28 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and

concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 8:1-5:1] afforded product **304o** (25 mg, 35%, *r.r.* > 19:1) as a clear oil. R_F 0.35 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2987, 2937, 1753, 1727 (C=O), 1697 (C=O); δ_H (400 MHz, $CDCl_3$) 5.33 (q, *J* = 0.7 Hz, 1H, **H8a**), 5.09 (sext, *J* = 1.6 Hz, 1H, **H8b**), 4.30 (q, *J* = 7.1 Hz, 2H, **H5**), 2.78 (s, 2H, **H9**), 2.30 (d, *J* = 4.8 Hz, 3H, **H1**), 2.12 (s, 6H, **H13** and **H14**), 1.38 (s, 3H, **H15**), 1.31 (t, *J* = 6.9 Hz, 3H, **H6**); δ_C (100 MHz, $CDCl_3$) 206.6 (**C11**), 206.5 (**C12**), 199.9 (d, *J* = 29.3 Hz, **C2**), 165.1 (d, *J* = 25.6 Hz, **C4**), 136.7 (d, *J* = 21.3 Hz, **C7**), 119.1 (d, *J* = 8.4 Hz, **C8**), 100.0 (d, *J* = 198.5 Hz, **C3**), 66.2 (**C10**), 62.9 (**C5**), 34.4 (d, *J* = 3.6 Hz, **C9**), 26.4 (**C13**), 26.4 (**C14**), 25.7 (**C1**), 17.9 (**C15**), 13.9 (**C6**); HRMS (ESI) Found: $[M+H]^+$, 301.1448. $C_{15}H_{21}FO_5$ requires $[M+H]^+$, 301.1446.

***tert*-Butyl 3-acetyl-3-(4-acetyl-4-methyl-5-oxohex-1-en-2-yl)-2-oxopiperidine-1-carboxylate (304q):**

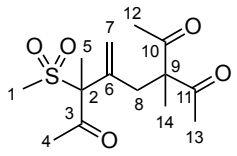


304q

Carbonate **303q** (77.6 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and 3-methyl-2,4-pentanedione **301h** (28 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1]

afforded **304q** (50 mg, 53%, *r.r.* > 19:1) as a red oil. R_F 0.31 (4:1 Petrol:EtOAc); ν_{max} (film)/cm^{-1} 2978, 2933, 1764, 1714 (C=O), 1695 (C=O), 1457; δ_H (400 MHz, $CDCl_3$) 4.98 (q, *J* = 1.2 Hz, 1H, **H12a**), 4.78 (q, *J* = 1.7 Hz, 1H, **H12b**), 3.67-3.53 (m, 2H, **H4**), 2.82 (dt, *J* = 18.2, 1.8 Hz, 1H, **H13a**), 2.49 (dt, *J* = 18.4, 1.9 Hz, 1H, **H13b**), 2.39-2.29 (m, 1H, **H5a**), 2.27 (s, 3H, **H10**), 2.15 (s, 3H, **H17**), 2.13 (s, 3H, **H18**), 2.07-1.99 (m, 1H, **H5b**), 1.83-1.74 (m, 2H, **H6**), 1.49 (s, 9H, **H1**), 1.46 (s, 3H, **H19**); δ_C (100 MHz, $CDCl_3$) 207.1 (**C15**), 206.8 (**C16**), 204.4 (**C9**), 170.6 (**C8**), 153.0 (**C3**), 142.0 (**C11**), 116.2 (**C12**), 83.3 (**C2**), 69.5 (**C7**), 66.2 (**C14**), 46.5 (**C4**), 36.1 (**C13**), 28.1 (**C5**), 28.1 (**C10**), 27.9 (**C1**), 26.4 (**C17**), 26.1 (**C18**), 19.6 (**C6**), 18.1 (**C19**); HRMS (ESI) Found: $[M+Na]^+$, 416.2049. $C_{21}H_{31}NO_6$ requires $[M+Na]^+$, 416.2044.

6-Acetyl-3,6-dimethyl-4-methylene-3-(methylsulfonyl)octane-2,7-dione (304r):

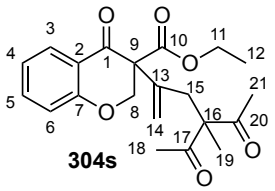


304r

Carbonate **303r** (55.7 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and 3-methyl-2,4-pentanedione **301h** (28 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-1:1]

afforded **304r** (15 mg, 21%, *r.r.* > 19:1) as a green oil. R_F 0.10 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2927, 2855, 1712 (C=O), 1695 (C=O), 1634; δ_H (400 MHz, $CDCl_3$) 5.23 (q, *J* = 1.6 Hz, 1H, **H7a**), 5.07 (q, *J* = 1.9 Hz, 1H, **H7b**), 3.07 (s, 3H, **H1**), 2.96-2.94 (m, 1H, **H8a**), 2.93-2.91 (m, 1H, **H8b**), 2.25 (s, 3H, **H4**), 2.18 (s, 3H, **H12**), 2.17 (s, 3H, **H13**), 1.86 (s, 3H, **H5**), 1.48 (s, 3H, **H14**); δ_C (100 MHz, $CDCl_3$) 207.1 (**C10**), 207.0 (**C11**), 202.7 (**C3**), 137.2 (**C6**), 121.1 (**C7**), 80.2 (**C2**), 65.7 (**C9**), 37.8 (**C1**), 35.7 (**C8**), 27.2 (**C4**), 26.7 (**C12**), 26.2 (**C13**), 18.9 (**C5**), 15.6 (**C14**); HRMS (ESI) Found: $[M+H]^+$, 303.0790. $C_{14}H_{22}SO_5$ requires $[M+H]^+$, 303.1261.

3-Ethyl 3-prop-2-ynyl 4-oxochroman-3,3-dicarboxylate (304s):



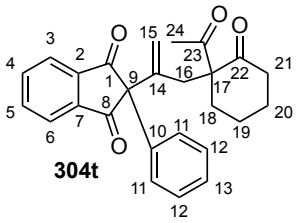
304s

Carbonate **303s** (48 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), DPEphos (8.6 mg, 0.0160 mmol) and 3-methyl-2,4-pentanedione **301h** (19 μL, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Tetrahydrofuran (1 mL) was added and the sealed tube was added to an oil bath preheated to 60 °C. The mixture was stirred at 60 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **304s** (19 mg, 32%, *r.r.* 2.3:1) as a clear oil. R_F 0.25 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2933, 1733, 1694 (C=O); δ_H (400 MHz, $CDCl_3$) 7.91 (dd,

J = 8.1, 1.8 Hz, 1H, **H3**), 7.47 (ddd, *J* = 9, 7.4, 2.0 Hz, 1H, **H4**), 7.04 (ddd, *J* = 8.1, 7.3, 1.0 Hz, 1H, **H5**), 6.93 (dd, *J* = 8.4, 0.8 Hz, 1H, **H6**), 4.94 (q, *J* = 1.2 Hz, 1H, **H14a**), 4.87 (q, *J* = 1.8 Hz, 1H, **H14b**), 4.88 (q, *J* = 17.6, Hz, 2H, **H11**), 2.86 (t, *J* = 1.8 Hz, 2H, **H15**), 2.13 (s, 6H, **H18** and **H21**), 1.47 (s, 3H, **H19**), 1.26 (t, *J* = 7.2 Hz, 3H, **H12**); δ_C (100 MHz, $CDCl_3$) 207.1 (**C17**), 206.9 (**C20**), 189.0 (**C1**), 168.1 (**C10**), 160.8 (**C13**), 137.1 (**C2**), 136.1 (**C4**), 127.9 (**C3**), 121.9 (**C5**), 120.2 (**C7**), 118.0 (**C14**), 117.5 (**C6**), 70.2 (**C8**), 66.5 (**C16**), 63.9 (**C9**), 62.2 (**C11**), 36.4 (**C15**), 26.3 (**C18**), 26.1 (**C21**), 17.7 (**C19**), 14.0 (**C12**); HRMS (ESI) Found: $[M+H]^+$, 373.1638. $C_{21}H_{24}O_6$ requires $[M+H]^+$, 373.1646.

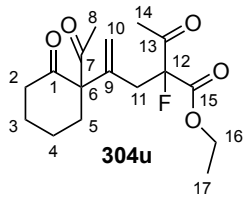
The formation of **304s** was also carried out under enantioselective conditions: Carbonate **303s** (48 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), (*R*)-Xylyl-P-PHOS **L19** (7.3 mg, 0.0096 mmol) and 3-methyl-2,4-pentanedione (0.019 µL, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Tetrahydrofuran (1 mL) was added and the sealed tube was stirred at 60 °C for 2 hours, then concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded chiral **304s** (14 mg, 24% yield, *r.r.* 3.2:1). Chiral HPLC: AD-H column, 1 mL/min, 9:1 Hexane:IPA, t_A (major) = 7.6 min, t_B (minor) = 10.0 min, 9% ee; $[\alpha]_D^{25}$ –0.3 (*c* 0.1, $CHCl_3$, 9% ee).

2-(3-(1-acetyl-2-oxocyclohexyl)prop-1-en-2-yl)-2-phenyl-1*H*-indene-1,3(2*H*)-dione (304t):



Carbonate **303d** (48.7 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), DPEphos (8.6 mg, 0.0160 mmol) and 2-acetylcyclohexanone (22 μL, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-dioxane (1 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1-9:1] afforded **304t** (21 mg, 33% *r.r.* not determined) as a colourless oil. R_F 0.35 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2939, 1697 (C=O); δ_H (400 MHz, $CDCl_3$) 8.05-7.98 (m, 2H, **H3** and **H6**), 7.89-7.82 (m, 2H, **H4** and **H5**), 7.42-7.37 (m, 2H, **H12**), 7.35-7.27 (m, 3H, **H11** and **H13**), 4.98 (q, *J* = 1.1 Hz, 1H, **H15a**), 4.96 (q, *J* = 1.0 Hz, 1H, **H15b**), 2.75 (dt, *J* = 18.1, 1.6 Hz, 1H, **H16a**), 2.57 (dt, *J* = 18.0, 1.4 Hz, 1H, **H16b**), 2.44-2.34 (m, 3H, **H20a** and **H21**), 2.06 (s, 3H, **H24**), 1.95-1.86 (m, 1H, **H19a**), 1.74-1.56 (m, 4H, **H18**, **H19b** and **H20b**); δ_C (100 MHz, $CDCl_3$) 209.7 (**C22**), 208.1 (**C23**), 199.2 (**C1**), 199.0 (**C8**), 141.2 (**C2**), 141.1 (**C7**), 140.7 (**C14**), 136.1 (**C3** and **C6**), 134.8 (**C10**), 128.7 (**C11**), 128.5 (**C12**), 128.0 (**C13**), 123.9 (**C4**), 123.9 (**C5**), 119.8 (**C15**), 69.7 (**C9**), 67.4 (**C17**), 41.1 (**C21**), 36.2 (**C16**), 34.5 (**C20**), 26.9 (**C19**), 26.2 (**C24**), 21.9 (**C18**); HRMS (ESI) Found: M+H]$^+$, 401.1731. $C_{26}H_{24}O_4$ requires [M+H]$^+$, 401.1747.

Ethyl 2-acetyl-4-(1-acetyl-2-oxocyclohexyl)-2-fluoropent-4-enoate (304u):

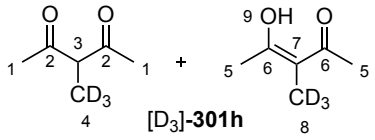


Carbonate **266** (53.3 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and ethyl 2-fluoroacetoacetate (30 μL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded an inseparable mixture of diastereoisomers of **304u** in a 1:1 ratio (49 mg, 63%, *r.r.* > 19:1) as a yellow oil. R_F 0.37 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2944, 2870, 1751, 1699 (C=O), 1640; δ_H (400 MHz, $CDCl_3$, resonances due to diastereoisomer **304ub** annotated by an asterisk) 5.37 (s, 1H and 1H*, **H10a** and **H10a**), 5.02 (d, *J* = 6.3 Hz, 1H and 1H*, **H10b** and **H10b**), 4.23 (q, *J* = 7.0 Hz, 2H and 2H*, **H16** and **H16**), 2.96-2.68 (m, 2H and 2H*, **H11** and **H11**), 2.58-2.35 (m, 2H and 2H*, **H2** and **H2**), 2.32-2.26 (m, 3H and 3H*, **H14** and **H14**), 2.27-2.21 (m, 1H and 1H*, **H5a** and **H5a**), 2.13 (s, 3H and 3H*, **H8** and **H8**), 2.11-2.01 (m, 1H and 1H*, **H5b** and **H5b**), 1.85-1.52 (m, 4H and 4H*, **H3**, **H4**, **H3** and **H4**), 1.26 (t, *J* = 7.2, Hz, 3H, **H17**) 1.25 (t, *J* = 7.2 Hz, 3H*, **H17**); δ_C (100 MHz, $CDCl_3$, resonances due to diastereoisomer

304ub annotated by an asterisk) 208.9 (**C1**), 208.7 (**C1***), 206.7 (**C7**), 206.5 (**C7***), 201.2 (d, *J* = 28.8 Hz, **C13**), 200.9 (d, *J* = 28.8 Hz, **C13***), 165.7 (d, *J* = 25.5 Hz, **C15**), 165.7 (d, *J* = 25.5 Hz, **C15***), 139.2 (d, *J* = 22.7 Hz, **C9**), 139.2 (d, *J* = 22.7 Hz, **C9***), 119.5 (d, *J* = 3.8 Hz, **C10**), 118.8 (d, *J* = 4.0 Hz, **C10***), 99.8 (d, *J* = 201.5 Hz, **C12**), 99.7 (d, *J* = 201.1 Hz, **C12***), 73.8 (**C6***), 73.4 (**C6**), 62.8 (**C16**), 62.8 (**C16***), 40.8 (**C2***), 40.8 (**C2**), 35.4 (d, *J* = 20.2 Hz, **C11**), 35.3 (d, *J* = 19.5 Hz, **C11***), 32.2 (**C5**), 32.2 (**C5***), 27.0 (**C3**), 26.9 (**C3***), 26.9 (**C8***), 26.7 (**C8**), 25.6 (**C14**), 25.4 (**C14***), 21.7* (**C4***), 21.7 (**C4**), 13.9 (**C17**), 13.8 (**C17***); HRMS (ESI) Found: $[M+H]^+$, 327.1604. $C_{17}H_{23}FO_5$ requires $[M+H]^+$, 327.1602.

10.2.4. Mechanistic Studies for the Coupling of 1,3-Dicarbonyl Compounds

d$_3$-3-Methyl 2,4-petanedione (D_3]-301h):

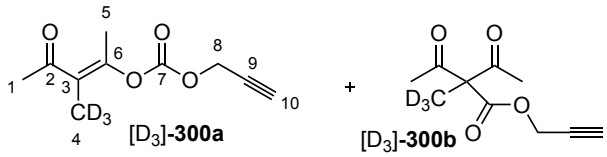


[D_3]-**301h**

To a solution of acetylacetone (1.02 mL, 10.0 mmol) in acetone (30 mL) was added potassium carbonate (1.38 g, 10.0 mmol). The mixture was stirred at room temperature for 15 minutes. *d*$_3$-Iodomethane (0.747 mL, 12.0 mmol) was added dropwise and the reaction was heated to reflux at 65 °C for 18 hours. The reaction was quenched with aq. HCl (1 N, 30 mL). The mixture was extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash

column chromatography [Petrol:EtOAc 19:1] afforded [D_3]-**301h** (200 mg, 17%) as a green liquid. Analysis by ^{1}H NMR spectroscopy indicated 98% deuterium incorportation. R_F 0.55 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2240, 1721, 1700 (C=O), 1611; δ_H (400 MHz, $CDCl_3$, 1.4:1 keto:enol tautomer, enol tautomer is annotated by an asterisk) 16.39 (s, 1H, **H9***), 3.62 (s, 1H, **H3**), 2.16 (s, 6H, **H1**), 2.08 (s, 6H, **H5***); δ_C (100 MHz, $CDCl_3$, 1.4:1 keto:enol tautomer, enol tautomer annotated by an asterisk) 205.1 (**C2**), 190.4 (**C6***), 104.6 (**C7***), 61.8 (**C3**), 28.6, (**C1**), 23.3 (**C5***), 12.7-11.5 (m, **C4** and **C8***). Synthesis of this compound has been reported in the literature.[131]

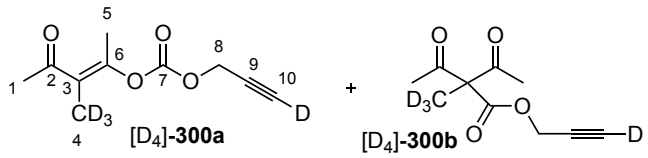
***d*$_3$-3-Methyl-4-oxopent-2-en-2-yl prop-2-ynyl carbonate ([D_3]-300a)** and ***d*$_3$-prop-2-ynyl 2-acetyl-2-methyl-3-oxobutanoate ([D_3]-300b):**



A suspension of sodium hydride (60 wt% in mineral oil, 56 mg, 1.40 mmol) in tetrahydrofuran (15 mL) was cooled to 0 °C. A solution of [D_3]-**301h** (150 mg, 1.28 mmol) in tetrahydrofuran (3 mL) was added dropwise and was stirred at 0 °C for 10 minutes. Propargyl chloroformate (136 µL, 1.40 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 1 hour. The reaction was quenched by the addition of aq. HCl (1 N, 10 mL) and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (15

mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1] afforded an inseparable mixture of carbonate [D_3]-**300a** and ester [D_3]-**300b** in a 5:1 ratio (120 mg, 47%) as a clear oil. R_F 0.21 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3285, 2130 (C≡C), 1991 (C-D), 1757 (C=O), 1668 (C=O), 1647; δ_H (400 MHz, $CDCl_3$, resonances due to [D_3]-**300a** quoted) 4.80 (d, *J* = 2.4 Hz, 2H, **H8**), 2.57 (t, *J* = 2.4 Hz, 1H, **H10**), 2.31 (s, 3H, **H1**), 2.09 (s, 3H, **H5**), resonance to due **H4** not observed; δ_C (100 MHz, $CDCl_3$, resonances due to [D_3]-**300a** quoted) 199.1 (**C2**), 151.7 (**C7**), 150.6 (**C6**), 124.9 (**C3**), 76.4 (**C9**), 76.2 (**C10**), 56.0 (**C8**), 30.9 (**C1**), 18.0 (**C5**), resonance due to **C4** not observed; HRMS (ESI) Found: $[M+H]^+$, 200.1004. $C_{10}H_9D_3O_4$ requires $[M+H]^+$, 200.0997.

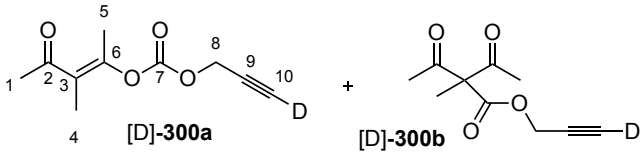
***d*$_4$-3-Methyl-4-oxopent-2-en-2-yl prop-2-ynyl carbonate ([D$_4$]-300a**) and ***d*$_4$-prop-2-ynyl 2-acetyl-2-methyl-3-oxobutanoate ([D$_4$]-300b):**



According to a literature procedure,[132] to a solution of [D_3]-**300** (45.7 mg, 0.23 mmol) in MeCN (4 mL) was added potassium carbonate (95.5 mg, 0.69 mmol) at room temperature and the suspension was stirred for 30 minutes. Deuterium oxide (0.61 mL) was added and the mixture was stirred at room temperature for 18 hours. The mixture was extracted with CH_2Cl_2 (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford an inseparable mixture of carbonate [D_4]-**300a** and ester [D_4]-**300b** in a 5:1 ratio (44.5 mg, 97%) as a

clear oil. Analysis by ^{1}H NMR spectroscopy indicated 96% deuterium incorporation. R_F 0.21 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3285, 2924, 2585, 2131 (C≡C), 1991 (C-D), 1760 (C=O), 1648; δ_H (400 MHz, $CDCl_3$, resonances due to [D_4]-**300a** quoted) 4.79 (s, 2H, **H8**), 2.30 (s, 3H, **H1**), 2.08 (s, 3H, **H5**); δ_C (100 MHz, $CDCl_3$, resonances due to [D_4]-**300a** quoted) 199.0 (**C2**), 151.7 (**C7**), 150.5 (**C6**), 124.9 (**C3**), 76.3 (t, *J* = 12.6 Hz, **C9**), 75.9 (t, *J* = 8.3 Hz, **C10**), 56.0 (**C8**), 30.9 (**C1**), 17.9 (**C5**), resonance due to **C4** was not observed; HRMS (ESI) Found: $[M+H]^+$ 201.1064. $C_{10}H_8D_4O_4$ requires $[M+H]^+$, 201.1059.

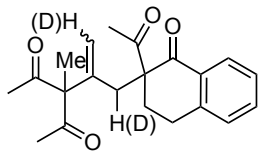
***d*$_1$-3-Methyl-4-oxopent-2-en-2-yl prop-2-ynyl carbonate ([D]-300a)** and ***d*$_4$-prop-2-ynyl 2-acetyl-2-methyl-3-oxobutanoate ([D]-300b):**



According to a literature procedure,[132] to a solution of propargyl carbonate **300** (144 mg, 0.730 mmol) in MeCN (8 mL) was added solid potassium carbonate (311 mg, 2.25 mmol). The suspension was stirred at room temperature for 30 min. Deuterium oxide (2 mL) was added *via* syringe and the solution was stirred at room temperature for 1 hour. The mixture was extracted with CH_2Cl_2 (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford an inseparable mixture of deuterated alkyne [D]-**300a** and ester [D]-**300b** in a 5.3:1 ratio (140 mg, 97%) as a pale yellow oil. Analysis by ^{1}H NMR spectroscopy indicated 97% deuterium incorporation. R_F 0.21 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2950, 2584, 1990 (C-D), 1757, 1709 (C=O), 1653; δ_H (400 MHz, $CDCl_3$,

resonances due to [D]-**300a** quoted) 4.74 (s, 2H, **H8**), 2.24 (s, 3H, **H1**), 2.03 (s, 3H, **H5**), 1.77 (s, 3H, **H4**); δ_C (100 MHz, $CDCl_3$, resonances due to [D]-**300a** quoted) 199.1 (**C2**), 151.7 (**C7**), 150.5 (**C6**), 125.0 (**C3**), 76.4 (t, *J* = 6.9 Hz, **C9**), 75.9 (t, *J* = 8.3 Hz, **C10**), 56.0 (**C8**), 30.9 (**C1**), 17.9 (**C5**), 14.0 (**C4**); HRMS (ESI) Found: $[M+Na]^+$ 220.0685. $C_{10}H_{11}DO_4$ requires $[M+Na]^+$, 220.0691.

d_1-3-(3-(2-Acetyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)prop-1-en-2-yl)-3-methylpentane-2,4-dione ([D]-302b):

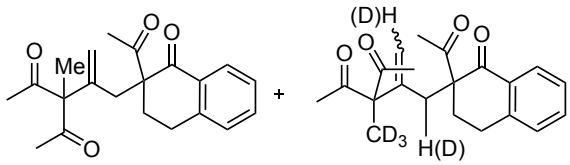


[D]-**312b**

[D]-**300** (47.3 mg, 0.24), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and 2-acetyl-1-tetralone (53.2 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded an inseparable mixture of [D]-**302b** and the homocoupled product of 2-acetyl-1-tetralone (**301b**) in a 10:1 ratio (60 mg, corresponding to 54 mg of [D]-**302b**, 66%, *r.r.* > 19:1) as a red oil. ^{1}H NMR analysis indicated 46% deuterium incorporation at the vinylic position and 49% deuterium incorporation at the allylic position. R_F 0.41

[Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2935, 1699 (C=O), 1671 (C=O), 1599; HRMS (ESI) Found: $[M+H]^+$, 342.1805. $C_{21}H_{23}DO_4$ requires $[M+H]^+$, 342.1810.

***d*$_4$-3-(3-(2-Acetyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)prop-1-en-2-yl)-3-methylpentane-2,4-dione** (**[D$_4$]-302b**) and **3-(3-(2-Acetyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)prop-1-en-2-yl)-3-methylpentane-2,4-dione (302b)**:

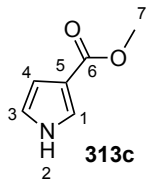


302b: non-D only [D$_4$]-**302b**: 95% D

Carbonate **300** (23.5mg, 0.12 mmol), carbonate [D$_4$]-**300** (24.0 mg, 0.12 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), DPEphos (13.1 mg, 0.024 mmol) and 2-acetyl-1-tetralone (53.2 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded a mixture of **302b** and [D$_4$]-**302b** (57 mg, 69 %, *r.r.* > 19:1) as a red oil. R_F 0.41 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2927, 1699 (C=O), 1671 (C=O), 1599; HRMS analysis indicated the presence **302b** and [D$_4$]-**302bb** only. HRMS (ESI) **302b**: Found: $[M+Na]^+$ 363.1559. $C_{21}H_{24}O_4$ requires $[M+Na]^+$, 363.1567; [D$_4$]-**302b**: Found: $[M+Na]^+$, 367.1813. $C_{21}H_{20}D_4O_4$ requires $[M+Na]^+$, 367.1818.

10.2.5. The Synthesis of Pyrroles

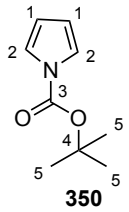
Methyl 1*H*-pyrrole-3-carboxylate (313c):



313c

According to a literature procedure,[133] to a suspension of potassium *tert*-butoxide (2.1 g, 18.7 mmol) in tetrahydrofuran (24 mL) was added dropwise a solution of *p*-toluenesulfonylmethyl isocyanide (3 g, 15.3 mmol) and methyl acrylate (1.25 mL, 14 mmol) in tetrahydrofuran (10 mL) over 30 minutes. The resulting mixture was stirred at room temperature for 2 hours. The reaction was quenched with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The organic phase was dried ($MgSO_4$), and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1] afforded **313c** (443 mg, 25%) as a brown solid. R_F 0.46 [Petrol:EtOAc 3:1]; m.p. 88–92 °C; ν_{max} (film)/cm^{-1} 3263 (N–H), 1664 (C=O), 1502; δ_H (400 MHz, $CDCl_3$) 9.27 (br s, 1H, **H2**) 7.43-7.39 (m, 1H, **H1**), 6.75-6.72 (m, 1H, **H4**), 6.65-6.61 (m, 1H, **H3**), 3.81 (s, 3H, **H7**); δ_C (100 MHz, $CDCl_3$) 165.9 (**C6**), 123.7 (**C1**), 119.0 (**C4**), 115.8 (**C5**), 109.5 (**C3**), 51.1 (**C7**); HRMS (ESI) Found: $[M+H]^+$, 126.0550. $C_6H_7NO_2$ requires $[M+H]^+$, 126.0550. Synthesis of this compound has been reported in the literature.[133]

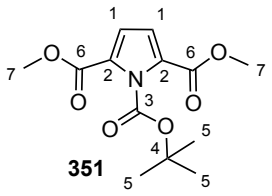
***tert*-Butyl 1*H*-pyrrole-1-carboxylate (350):**



350

According to a literature procedure,[134] to a solution of pyrrole (1 g, 15 mmol) in acetonitrile (20 mL) was added di-*tert* butyl dicarbonate (3.9 g, 18 mmol) and 4-dimethylaminopyridine(0.25 g, 4.5 mmol) at room temperature. The mixture was stirred at room temperature for 2.5 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography [Petrol:EtOAc 4:1], to give **350** (1.7 g, 70%) as a yellow oil. R_F 0.82 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2980, 1738 (C=O); δ_H (400 MHz, $CDCl_3$) 7.14 (t, *J* = 2.3 Hz, 2H, **H2**), 6.12 (t, *J* = 2.4 Hz, 2H, **H1**), 1.50 (s, 9H, **H5**); δ_C (100 MHz, $CDCl_3$) 148.8 (**C3**), 119.9 (**C2**), 117.7 (**C1**), 83.4 (**C4**), 27.8 (**C5**). Synthesis of this compound has been reported in the literature.[134]

***tert*-Butyl 2,5-dimethyl 1*H*-pyrrole-1,2,5-tricarboxylate (351):**

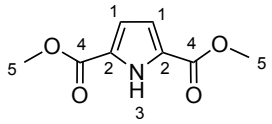


351

According to a literature procedure,[135] to a solution of 2,2,6,6-tetramethyl-piperidine (1.35 mL, 0.08 mol) in tetrahydrofuran (20 mL) under an atmosphere of argon at –78 °C was added *n*-butyllithium (1.6 M in hexanes, 5 mL, 8 mmol) dropwise *via* cannula. A solution of **350** (535 mg, 3.2 mmol) in tetrahydrofuran (5 mL) was then added dropwise *via* cannula. The reaction

mixture was stirred at –78 °C for 3 hours before being transferred dropwise *via* cannula into a stirred solution of methyl chloroformate (0.740 mL, 3.2 mmol) cooled to –78 °C. After 30 minutes the reaction was quenched by the addition of aq. NH_4Cl (10 mL) and allowed warmed to room temperature. Water (10 mL) was added and the mixture was extracted with Et_2O (4 x 20 mL). The combined organic layers were washed with aq. HCl (1 N, 20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated *in vauo*. Flash column chromatography [EtOAc:Petrol 1:4] afforded **351** (300 mg, 33%) as a pink solid. R_F 0.55 [Petrol:EtOAc 4:1]; m.p. 172–174 °C; ν_{max} (film)/cm^{-1} 2959, 1774 (C=O), 1705 (C=O), 1537; δ_H (400 MHz, $CDCl_3$) 6.83 (s, 2H, **H1**), 3.78 (s, 6H, **H7**), 1.66 (s, 9H, **H5**); δ_C (100 MHz, $CDCl_3$) 160.0 (**C6**), 148.8 (**C3**), 126.7 (**C2**), 115.9 (**C1**), 86.3 (**C4**), 52.0 (**C7**), 27.3 (**C5**); HRMS (ESI) Found: $[M+Na]^+$, 306.0946. $C_{13}H_{17}NO_6$ requires $[M+Na]^+$, 306.0948. Synthesis of this compound has been reported in the literature.[135]

Dimethyl 1*H*-pyrrole-2,5-dicarboxylate (313e):

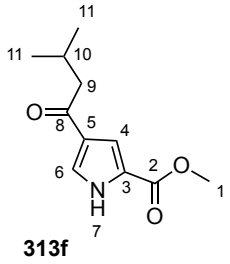


313e

According to a literature procedure,[134] to a solution of **351** (140 mg, 0.494 mmol) in dichloromethane (1.5 mL) cooled to 0 °C was added trifluoroaceticacid (0.5 mL) and the resulting mixture was stirred at room temperature for 2 hours. The mixture was diluted with EtOAc (5 mL) and washed with aq. Na_2CO_3 (5 mL) and H_2O (5 mL). The organic phase was dried

($MgSO_4$) and concentrated *in vacuo* to afford **313e** (85 mg, 95%) as a white solid. R_F 0.55 [Petrol:EtOAc 4:1]; m.p. 128–130 °C; ν_{max} (film)/cm^{-1} 3289 (N–H), 1709 (C=O), 1554; δ_H (400 MHz, $CDCl_3$) 9.77 (br s, 1H, **H3**), 6.87 (d, J = 2.6 Hz, 1H, **H1**), 3.89 (s, 3H, **H5**); δ_C (100 MHz, $CDCl_3$) 160.7 (**C4**), 126.0 (**C2**), 115.6 (**C1**), 52.0 (**C5**). Synthesis of this compound has been reported in the literature.[134]

Methyl 4-(3-methylbutanoyl)-1*H*-pyrrole-2-carboxylate (313f):

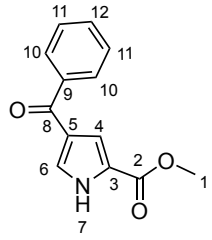


313f

According to a literature procedure,[136] to a solution of methyl-2-pyrrole carboxylate (300 mg, 2.4 mmol) and isovaleryl chloride (380 μL, 3.1 mmol) in dichloromethane (10 mL) cooled to 0 °C was added aluminium chloride (959 mg, 7.2 mmol). The mixture was stirred at room temperature for 18 hours. The solution was poured into ice-cold water (20 mL), then extracted with CH_2Cl_2 (2 x 20 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1] afforded **313f** (405 mg, 81%) as a yellow solid. R_F 0.12 [Petrol:EtOAc 4:1]; m.p. 111–114 °C; ν_{max} (film)/cm^{-1} 3192, 2953, 1697 (C=O), 1636 (C=O); δ_H (400 MHz, $CDCl_3$) 9.48 (br s, 1H, **H7**), 7.45 (dd, J = 3.2, 1.5 Hz, 1H, **H6**), 7.28 (dd, J = 2.4, 1.5 Hz, 1H, **H4**), 3.88 (s, 3H, **H1**), 2.62 (d, J = 7.1 Hz, 2H, **H9**), 2.26 (sept, J = 7.7 Hz, 1H, **H10**), 0.98 (d, J = 6.7 Hz, 6H, **H11**); δ_C (100 MHz, $CDCl_3$) 195.7 (**C8**), 161.4

(**C2**), 127.7 (**C5**), 126.0 (**C6**), 123.8 (**C3**), 114.8 (**C4**), 51.9 (**C1**), 48.8 (**C9**), 25.5 (**C10**), 22.8 (**C11**); HRMS (ESI) Found: $[M+H]^+$, 210.1097. $C_{11}H_{15}NO_3$ requires $[M+H]^+$, 210.1125. Synthesis of this compound has been reported in the literature.[136]

Methyl 4-benzoyl-1*H*-pyrrole-2-carboxylate (313g):

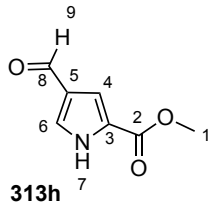


313g

According to a literature procedure,[136] to a solution of methyl-2-pyrrole carboxylate (300 mg, 2.4 mmol) and benzoyl chloride (361 μL, 3.1 mmol) in dichloromethane (10 mL) cooled to 0 °C was added aluminium chloride (959 mg, 7.2 mmol). The mixture was stirred at room temperature for 18 hours. The solution was poured into ice-cold water (20 mL), then extracted with dichloromethane (2 x 20 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1-1:1] afforded **313g** (398 mg, 72%) as a pink solid. R_F 0.16 [Petrol:EtOAc 3:1]; m.p. 147–149 °C; ν_{max} (film)/cm^{-1} 3352, 2950, 1716 (C=O), 1617, 1595; δ_H (400 MHz, $CDCl_3$) 10.57 (br s, 1H, **H7**), 7.87-7.81 (m, 2H, **H10**), 7.60-7.54 (m, 2H, **H6** and **H12**), 7.50-7.44 (m, 2H, **H11**) 7.37 (dd, J = 2.4, 1.7 Hz, 1H, **H4**), 3.88 (s, 3H, **H1**); δ_C (100 MHz, $CDCl_3$) 195.7 (**C8**), 161.4 (**C2**), 138.9 (**C9**), 128.9 (**C10**), 128.7 (**C12**), 128.3 (**C11**), 126.0 (**C6**), 125.6 (**C5**), 123.8 (**C3**), 114.8 (**C4**), 51.9 (**C1**); HRMS (ESI) Found: $[M-H]^-$, 228.0666. $C_{13}H_{11}NO_3$ requires

[M–H]$^-$, 228.0666. Synthesis of this compound has been reported in the literature.[136]

Methyl 4-formyl-1*H*-pyrrole-2-carboxylate (313h):

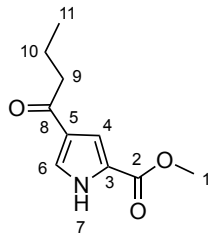


313h

According to a literature procedure,[137] a solution of phosphorus(III) oxychloride (1 mL) in dimethylformamide (0.862 mL) added at 0 °C, was warmed to room temperature and stirred for 30 minutes. Then a solution of methyl 1*H*-pyrrole-2-carboxylate (700 mg, 5.6 mmol) in dimethylformamide (1.6 mL) was added and reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 16 hours. The mixture was cooled to 0 ^{o}C and NaOH (4 N, 5 mL) was added slowly with stirring until pH 7 had been reached. The mixture was filtered and extracted with EtOAc (3 x 20 mL). The organic phases were combined and washed with water (20 mL), and brine (20 mL) then concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAC 4:1] afforded **313h** (200 mg, 26%) as a light red liquid. R_F 0.48 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2983, 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 10.13 (br s, 1H, **H7**), 9.67 (s, 1H, **H9**), 6.95-6.91 (m, 2H, **H4** and **H6**), 3.91 (s, 3H, **H1**); δ_C (100 MHz, $CDCl_3$) 180.4 (**C8**), 160.8 (**C2**), 134.5 (**C5**), 128.2 (**C3**), 119.7 (**C6**),

115.7 (**C4**), 52.2 (**C1**). Synthesis of this compound has been reported in the literature.[137]

Methyl 4-butyryl-1*H*-pyrrole-2-carboxylate (352):

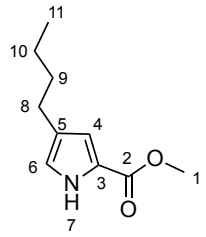


352

According to a literature procedure,[136] to a solution of methyl-2-pyrrole carboxylate (300 mg, 2.4 mmol) and butyryl chloride (324 μL, 3.1 mmol) in dichloromethane (10 mL) stirred at 0 °C was added aluminium chloride (959 mg, 7.2 mmol) and the solution was stirred at room temperature for 18 hours. The solution was poured into ice-cold water (20 mL), then extracted with dichloromethane (2 x 20 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1] afforded **352** (140 mg, 30%) as a beige solid. R_F 0.15 [Petrol:EtOAc 3:1]; m.p. 88–90 °C; ν_{max} (film)/cm^{-1} 3278 (N–H), 2955, 1697 (C=O), 1664 (C=O), 1559; δ_H (400 MHz, $CDCl_3$) 9.87 (br s, 1H, **H7**), 7.55 (dd, *J* = 3.1, 1.6 Hz, 1H, **H6**), 7.29 (dd, *J* = 2.5, 1.6 Hz, 1H, **H4**), 3.88 (s, 3H, **H1**), 2.74 (t, *J* = 7.3 Hz, 2H, **H9**), 1.73 (sext, *J* = 7.2 Hz, 2H, **H10**), 0.97 (t, *J* = 7.6 Hz, 3H, **H11**); δ_C (100 MHz, $CDCl_3$) 196.1 (**C8**), 161.4 (**C2**), 127.2 (**C5**), 126.2 (**C6**), 123.7 (**C3**), 114.9 (**C4**), 51.9 (**C1**), 41.7 (**C9**), 18.0 (**C10**), 13.9 (**C11**); HRMS (ESI) Found:

$[M–H]^-$, 194.0824. $C_{10}H_{13}NO_3$ requires $[M–H]^-$, 194.0823. Synthesis of this compound has been reported in the literature.[136]

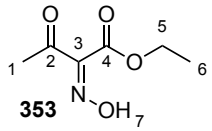
Methyl 4-butyl-1*H*-pyrrole-2-carboxylate (313i):



313i

According to a literature procedure,[136] to a solution of **352** (400 mg, 2.05 mmol) in trifluoroacetic acid (1.57 mL, 20.5 mmol) was added triethylsilane (0.654 mL, 4.1 mmol) and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with aq. $NaHCO_3$ (15 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1] afforded **313i** (149 mg, 40%) as a white solid. R_F 0.56 [Petrol:EtOAc 1:1]; m.p. 69–70 °C; ν_{max} (film)/cm^{-1} 3289 (N–H), 2924, 1677 (C=O); δ_H (400 MHz, $CDCl_3$) 9.16 (br s, 1H, **H7**), 6.77-6.73 (m, 2H, **H4** and **H6**), 3.83 (s, 3H, **H1**), 2.46 (t, J = 7.9 Hz, 2H, **H8**), 1.59-1.49 (m, 2H, **H9**), 1.35 (sext, J = 7.4 Hz, 2H, **H10**), 0.91 (t, J = 7.2 Hz, 3H, **H11**); δ_C (100 MHz, $CDCl_3$) 161.2 (**C2**), 126.7 (**C5**), 122.0 (**C3**), 120.8 (**C6**), 115.0 (**C4**), 51.3 (**C1**), 33.1 (**C9**), 26.3 (**C8**), 22.3 (**C10**), 13.9 (**C11**). Synthesis of this compound has been reported in the literature.[136]

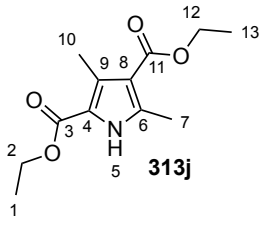
(*Z*)-Ethyl 2-(hydroxyimino)-3-oxobutanoate (353):



353

According to a literature procedure,[138] to a solution of ethyl acetoacetate (3.4 mL, 26.9 mmol) in glacial acetic acid cooled to 0 °C was added a solution of sodium nitrite (1.84 g, 26.7 mmol) in water (7 mL). The reaction was allowed to warm to room temperature and stirred at this temperature for 30 minutes. The reaction was quenched with water (30 mL) and extracted with EtOAc (2 x 25 mL). The organic layers were combined and washed with H_2O (20 mL) and aq. $NaHCO_3$ (20 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*, giving **353** (1.72 g, 40 %) as a pale yellow oil. R_F 0.10 [Petrol:EtOAc 4:1]; δ_H (400 MHz, $CDCl_3$) 8.81 (br s, 1H, **H7**), 4.39 (q, J = 7.4 Hz, 2H, **H5**), 2.41 (s, 3H, **H1**), 1.36 (t, J = 7.2 Hz, 3H, **H6**); δ_C (100 MHz, $CDCl_3$) 193.2 (**C2**), 161.2 (**C4**), 151.3 (**C3**), 62.4 (**C5**), 25.5 (**C1**), 14.0 (**C6**). Synthesis of this compound has been reported in the literature.[138]

Diethyl 3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylate (313j):

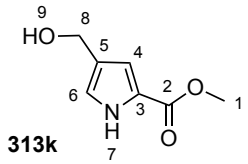


313j

According to a literature procedure,[139] a solution of **353** (0.840 g, 5 mmol), ethyl acetoacetate (0.840 mL, 7 mmol) and sodium acetate (1.18 g, 14.4 mmol) in glacial acetic acid (0.840 ml, 7 mmol) was heated to 60 °C. Zinc

powder (0.90 g, 13.8 mmol) was added portionwise over a period of 5 minutes and the reaction mixture was heated from 60 °C to 90 °C and stirred for 2 hours. The reaction mixture was allowed to cool slightly and poured into ice-cold water (50 mL). The precipitate was collected by vacuum filtration and solid washed with water (50 mL) and re-dissolved in hot methanol (50 mL). The product was then precipitated with water (50 mL), collected by filtration, and dried *in vacuo* to give **313j** (508 mg, 42 %) as a white solid. R_F 0.30 [Petrol:EtOAc 4:1]; m.p. 91–94 °C; δ_H (400 MHz, $CDCl_3$) 9.08 (br s, 1H, **H7**), 4.36-4.26 (m, 4H, **H2** and **H12**), 2.56 (s, 3H, **H7**), 2.51 (s, 3H, **H10**), 1.37 (t, *J* = 7.1 Hz, 1H, **H1**), 1.36 (t, *J* = 7.1 Hz, 1H, **H13**); δ_C (100 MHz, $CDCl_3$) 165.5 (**C3**), 161.7 (**C11**), 138.8 (**C4**), 130.9 (**C8**), 117.9 (**C6**), 113.6 (**C9**), 60.3 (**C2**), 59.5 (**C12**), 14.4 (**C7**), 14.4 (**C10**), 14.3 (**C1**), 12.0 (**C13**); HRMS (ESI) Found: $[M+H]^+$, 238.1075. $C_{12}H_{17}NO_4$ requires $[M+H]^+$, 238.1085.

Methyl 4-(hydroxymethyl)-1H-pyrrole-2-carboxylate (313k):



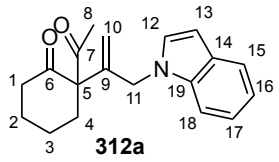
313k

According to a literature procedure,[140] to a solution of **313h** (95 mg, 0.63 mmol) in methanol (1 mL) was added sodium borohydride (24 mg, 0.63 mmol) and the solution was stirred at room temperature for 3 hours. The reaction mixture was quenched with water (2 mL) and extracted with Et_2O (2 x 5 mL). The combined organic phases were washed with water (5 mL), dried ($MgSO_4$)

and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 1:1] afforded **313k** (60 mg, 97%) as a pink oil. R_F 0.05 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3296 (O-H), 1671 (C=O), 1571; δ_H (400 MHz, $CDCl_3$) 10.09 (br s, 1H, **H7**), 6.83 (dd, J = 3.7, 2.5 Hz, 1H, **H4**), 6.12-6.09 (m, 1H, **H6**), 4.67 (s, 2H, **H8**), 3.84 (s, 3H, **H1**), 2.84 (br s, 1H, **H9**); δ_C (100 MHz, $CDCl_3$) 162.2 (**C2**), 137.1 (**C5**), 122.2 (**C3**), 116.0 (**C4**), 108.4 (**C6**), 57.8 (**C8**), 51.6 (**C1**); HRMS (ESI) Found: $[M–H]^–$, 154.0517. $C_7H_9NO_3$ requires $[M–H]^–$, 154.0510. Synthesis of this compound has been reported in the literature.[141]

10.2.6. Palladium Catalysed Alkenylation Reactions with *N*-Heterocycles

2-(3-(1*H*-Indol-1-yl)prop-1-en-2-yl)-2-acetylcyclohexanone (312a):

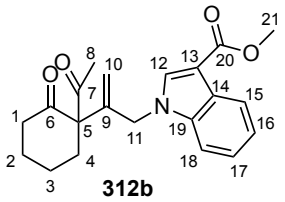


312a

Carbonate **266** (53.3 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and indole **311a** (28 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1-9:1] afforded **312a** (39 mg, 55%) as a yellow solid. R_F 0.52 [Petrol:EtOAc 4:1]; m.p. 94–96 °C; ν_{max} (film)/cm^{-1} 3386, 3089, 3056, 2946, 2858, 1709 (C=O), 1694, 1652, 1610,

1511; δ_H (400 MHz, $CDCl_3$) 7.63 (dt, *J* = 8.1, 1.1 Hz, 1H, **H15**), 7.36 (dq, *J* = 8.1, 0.8 Hz, 1H, **H18**), 7.23-7.17 (m, 1H, **H16**), 7.13-7.07 (m, 1H, **H17**), 7.06 (d, *J* = 3.2 Hz, 1H, **H12**), 6.54 (dd, *J* = 3.1, 0.9 Hz, 1H, **H13**), 4.99-4.98 (m, 1H, **H10a**), 4.85-4.79 (m, 1H, **H11a**), 4.63-4.57 (m, 2H, **H10b** and **H11b**), 2.55 (dd, *J* = 8.0, 5.9 Hz, 2H, **H1**), 2.48-2.41 (m, 1H, **H3a**), 2.22 (s, 3H, **H8**), 2.12-2.03 (m, 2H, **H3b**), 2.01-1.93 (m, 1H, **H2a**), 1.90-1.66 (m, 3H, **H2b** and **H4**); δ_C (100 MHz, $CDCl_3$) 208.8 (**C6**), 206.8 (**C7**), 142.3 (**C9**), 136.3 (**C14**), 128.6 (**C18**), 128.3 (**C19**), 121.8 (**C16**), 120.8 (**C15**), 119.5 (**C17**), 115.8 (**C10**), 109.7 (**C12**), 101.8 (**C13**), 72.2 (**C5**), 48.3 (**C11**), 41.1 (**C1**), 33.3 (**C3**), 27.0 (**C2**), 26.3 (**C8**), 22.0 (**C4**); HRMS (ESI) Found: $[M+H]^+$, 296.1650. $C_{19}H_{21}NO_2$ requires $[M+H]^+$, 296.1645.

Methyl 1-(2-(1-acetyl-2-oxocyclohexyl)allyl)-1*H*-indole-3-carboxylate (312b):

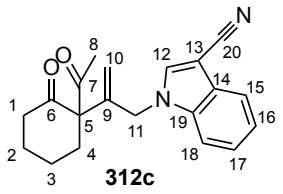


312b

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and methyl-indole-3-carboxylate **311b** (42 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-

4:1] afforded **312b** (59 mg, 70%) as a pale yellow solid. R_F 0.20 [Petrol:EtOAc 4:1]; m.p. 108–110 °C; ν_{max} (film)/cm^{-1} 2950, 1692 (C=O), 1528; δ_H (400 MHz, $CDCl_3$) 8.12-8.08 (m, 1H, **H17**), 7.71 (s, 1H, **H12**), 7.37-7.34 (m, 1H, **H15**), 7.23-7.17 (m, 2H, **H16** and **H18**), 4.95 (q, J = 0.6 Hz, 1H, **H10a**), 4.84-4.77 (m, 1H, **H11a**), 4.52-4.46 (m, 2H, **H10b** and **H11b**), 3.83 (s, 3H, **H21**), 2.56-2.45 (m, 2H, **H1**), 2.45-2.37 (m, 1H, **H4a**), 2.15 (s, 3H, **H8**), 2.02-1.88 (m, 2H, **H2a** and **H4b**), 1.84-1.55 (m, 3H, **H2b** and **H3**); δ_C (100 MHz, $CDCl_3$) 208.6 (**C6**), 206.8 (**C7**), 165.3 (**C20**), 141.5 (**C9**), 136.8 (**C19**), 135.0 (**C12**), 126.4 (**C14**), 123.1 (**C17**), 122.0 (**C16**), 121.6 (**C18**), 115.8 (**C10**), 110.5 (**C15**), 107.7 (**C13**), 72.2 (**C5**), 51.0 (**C21**), 48.9 (**C11**), 41.1 (**C1**), 33.5 (**C4**), 27.0 (**C2**), 26.2 (**C8**), 22.1 (**C3**); HRMS (ESI) Found: $[M+H]^+$, 354.1683. $C_{21}H_{23}NO_4$ requires $[M+H]^+$, 354.1700.

1-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-1H-indole-3-carbonitrile (312c):

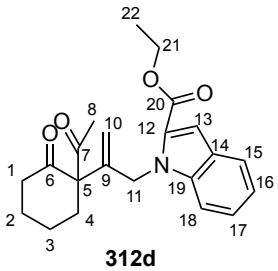


312c

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-cyanoindole (34.1 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **312c**

(43 mg, 55%) as a yellow solid. R_F 0.20 [Petrol:EtOAc 4:1]; m.p. 96–99 °C; ν_{max} (film)/cm^{-1} 3121, 2942, 2214 (C≡N), 1697 (C=O), 1645; δ_H (400 MHz, $CDCl_3$) 7.76-7.73 (m, 1H, **H15**), 7.60 (s, 1H, **H12**), 7.49 (dt, *J* = 8.1, 0.9 Hz, 1H, **H16**), 7.36-7.31 (m, 1H, **H18**), 7.30-7.26 (m, 1H, **H17**), 5.06 (q, *J* = 1.1 Hz, 1H, **H10a**), 4.90 (dt, *J* = 17.7, 1.3 Hz, 1H, **H11a**), 4.59-4.54 (m, 2H, **H10b** and **H11b**), 2.64-2.47 (m, 3H, **H1** and **H4a**), 2.22 (s, 3H, **H8**), 2.07-1.97 (m, 2H, **H2a** and **H4b**), 1.94-1.85 (m, 1H, **H3a**), 1.82-1.72 (m, 1H, **H2b**), 1.72-1.62 (m, 1H, **H3b**); δ_C (100 MHz, $CDCl_3$) 208.6 (**C6**), 206.8 (**C7**), 141.3 (**C9**), 135.7 (**C19**), 135.6 (**C12**), 127.6 (**C14**), 124.2 (**C18**), 122.3 (**C17**), 119.8 (**C15**), 115.9 (**C10**), 115.7 (**C13**), 111.1 (**C16**), 86.4 (**C20**), 72.2 (**C5**), 49.0 (**C11**), 41.1 (**C1**), 33.6 (**C4**), 26.8 (**C2**), 26.2 (**C8**), 22.1 (**C3**); HRMS (ESI) Found: $[M+H]^+$, 321.1541. $C_{20}H_{20}N_2O_2$ requires $[M+H]^+$, 321.1598.

Ethyl 1-(2-(1-acetyl-2-oxocyclohexyl)allyl)-1*H*-indole-2-carboxylate (312d):

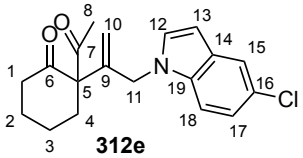


312d

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and ethyl-1*H*-2-indole carboxylate (45.4 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and

concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 29:1-19:1-9:1-4:1] afforded **312d** (52 mg, 59%) as a pale yellow solid. R_F 0.45 [Petrol:EtOAc 4:1]; m.p. 102–104 °C; ν_{max} (film)/cm^{-1} 2957, 1697 (C=O), 1649; δ_H (400 MHz, $CDCl_3$) 7.70-7.64 (m, 2H, **H15** and **H16**), 7.40-7.34 (m, 2H, **H13** and **H18**), 7.19-7.15 (m, 1H, **H17**), 5.19 (d, *J* = 18.1 Hz, 1H, **H11a**), 5.13 (d, *J* = 18.1 Hz, 1H, **H11b**), 4.32 (qd, *J* = 7.2, 1.0 Hz, 2H, **H10**), 4.20 (q, *J* = 1.2 Hz, 2H, **H21**), 2.61-2.56 (m, 2H, **H1**), 2.52-2.43 (m, 1H, **H3a**), 2.36 (s, 3H, **H8**), 2.27-2.18 (m, 1H, **H3b**), 2.02-1.91 (m, 2H, **H4**), 1.91-1.80 (m, 1H, **H2a**), 1.77-1.64 (m, 1H, **H2b**), 1.38 (t, *J* = 7.1 Hz, 3H, **H22**); δ_C (100 MHz, $CDCl_3$) 208.9 (**C6**), 207.3 (**C7**), 161.9 (**C20**), 140.5 (**C9**), 140.1 (**C19**), 127.2 (**C12**), 125.7 (**C14**), 125.5 (**C13**), 122.3 (**C15**), 120.9 (**C17**), 113.4 (**C10**), 111.4 (**C16**), 108.8 (**C18**), 72.0 (**C5**), 60.4 (**C21**), 46.7 (**C11**), 41.0 (**C1**), 33.4 (**C3**), 27.3 (**C4**), 26.2 (**C8**), 22.0 (**C2**), 14.3 (**C22**); HRMS (ESI) Found: $[M+H]^+$, 368.1847. $C_{22}H_{25}NO_4$ requires $[M+H]^+$, 368.1856.

Ethyl 1-(2-(1-acetyl-2-oxocyclohexyl)allyl)-1*H*-indole-2-carboxylate (312e):

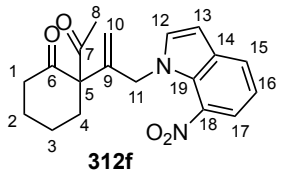


312e

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 5-chloro-1*H*-indole (36.3 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the

sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1-9:1] afforded **312e** (41 mg, 52%) as a brown solid. R_F 0.45 [Petrol:EtOAc 4:1]; m.p. 113–115 °C; ν_{max} (film)/cm^{-1} 2948, 1701 (C=O), 1643; δ_H (400 MHz, $CDCl_3$) 7.57 (dd, *J* = 2.1, 0.6 Hz, 1H, **H15**), 7.30 (dt, *J* = 8.8, 0.8 Hz, 1H, **H17**), 7.15 (dd, *J* = 8.7, 2.0 Hz, 1H, **H18**), 7.06 (d, *J* = 3.4 Hz, 1H, **H12**), 6.46 (dd, *J* = 3.2, 0.9 Hz, 1H, **H13**), 5.00-4.97 (m, 1H, **H10a**), 4.84-4.77 (m, 1H, **H11a**), 4.58-4.51 (m, 2H, **H10b** and **H11b**), 2.62-2.51 (m, 2H, **H1**), 2.49-2.41 (dddd, *J* = 14.4, 8.3, 5.5, 2.2 Hz, 1H, **H2a**), 2.20 (s, 3H, **H8**), 2.08-2.00 (m, 1H, **H2b**), 2.00-1.93 (m, 1H, **H4a**) 1.91-1.81 (m, 1H, **H4b**), 1.81-1.72 (m, 1H, **H3a**), 1.72-1.63 (m, 1H, **H3b**); δ_C (100 MHz, $CDCl_3$) 208.7 (**C6**), 206.8 (**C7**), 142.2 (**C9**), 134.7 (**C19**), 129.9 (**C12**), 129.4 (**C16**), 125.3 (**C14**), 122.1 (**C18**), 120.2 (**C15**), 115.7 (**C10**), 110.9 (**C17**), 101.5 (**C13**), 72.2 (**C5**), 48.7 (**C11**), 41.1 (**C1**), 33.5 (**C2**), 27.0 (**C4**), 26.3 (**C8**), 22.1 (**C3**); HRMS (ESI) Found: $[M+H]^+$, 330.1257. $C_{19}H_{20}NO_2Cl$ requires $[M+H]^+$, 330.1255.

2-Acetyl-2-(3-(7-nitro-1*H*-indol-1-yl)prop-1-en-2-yl)cyclohexanone (312f):

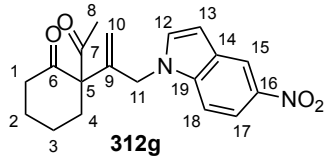


312f

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 7-nitro-1*H*-indole (38.9 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum

and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1-9:1-4:1] afforded **312f** (51 mg, 62%) as a brown/green solid. R_F 0.63 [Petrol:EtOAc 4:1]; m.p. 125–128 °C; ν_{max} (film)/cm^{-1} 2948, 1714 (C=O), 1694 (C=O), 1504; δ_H (400 MHz, $CDCl_3$) 7.88 (dd, *J* = 7.8, 1.0 Hz, 1H, **H15**), 7.81 (dd, *J* = 7.9, 1.1 Hz, 1H, **H17**), 7.27 (d, *J* = 3.4 Hz, 1H, **H12**), 7.14 (t, *J* = 7.9 Hz, 1H, **H16**), 6.70 (d, *J* = 3.4 Hz, 1H, **H13**), 4.97-4.91 (m, 1H, **H11a**), 4.87-4.81 (m, 2H, **H10a** and **H11b**), 4.31-4.29 (m, 1H, **H10b**), 2.55 (dd, *J* = 8.0, 5.9 Hz, 2H, **H1**), 2.50-2.42 (m, 1H, **H2a**), 2.23 (s, 3H, **H8**), 2.10-2.00 (m, 1H, **H2b**), 1.99-1.84 (m, 2H, **H4**), 1.82-1.73 (m, 1H, **H3a**),1.70-1.60 (m, 1H, **H3b**); δ_C (100 MHz, $CDCl_3$) 208.7 (**C6**), 207.3 (**C7**), 142.6 (**C9**), 136.7 (**C18**), 133.8 (**C19**), 133.6 (**C12**), 127.4 (**C15**), 127.0 (**C14**), 120.2 (**C17**), 118.7 (**C16**), 114.7 (**C10**), 103.7 (**C13**), 72.1 (**C5**), 51.8 (**C11**), 41.0 (**C1**), 33.3 (**C2**), 27.1 (**C4**), 26.5 (**C8**), 22.0 (**C3**); HRMS (ESI) Found: $[M+H]^+$, 341.1500. $C_{19}H_{20}N_2O_4$ requires $[M+H]^+$, 341.1496.

2-Acetyl-2-(3-(5-nitro-*1H*-indol-1-yl)prop-1-en-2-yl)cyclohexanone (312g):

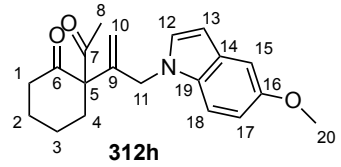


312g

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 5-nitroindole (38.9 mg, 0.24 mmol) were

added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1-9:1-4:1] afforded **312g** (51 mg, 62%) as an orange solid. R_F 0.22 [Petrol:EtOAc 4:1]; m.p. 120–122 °C; ν_{max} (film)/cm^{-1} 2927, 2111, 1709 (C=O), 1694 (C=O), 1511 (N-O); δ_H (400 MHz, $CDCl_3$) 8.57 (d, *J* = 2.1 Hz, 1H, **H15**), 8.11 (dd, *J* = 8.1, 2.1 Hz, 1H, **H17**), 7.46 (d, *J* = 9.0 Hz, 1H, **H18**), 7.21 (d, *J* = 3.2 Hz, 1H, **H12**), 6.71 (d, *J* = 3.2 Hz, 1H, **H13**), 5.04 (s, 1H, **H10a**), 4.90 (dt, *J* = 17.4, 1.5 Hz, 1H, **H11a**), 4.58 (dt, *J* = 17.5, 1.6 Hz, 1H, **H11b**), 4.54 (s, 1H, **H10b**), 2.64-2.47 (m, 3H, **H1** and **H4a**), 2.22 (s, 3H, **H8**), 2.09-1.98 (m, 2H, **H2a** and **H4b**), 1.95-1.86 (m, 1H, **H2b**), 1.83-1.63 (m, 2H, **H3**); δ_C (100 MHz, $CDCl_3$) 208.6 (**C6**), 205.8 (**C7**), 141.8 (**C9**), 141.8 (**C16**), 139.2 (**C19**), 131.9 (**C12**), 127.6 (**C14**), 118.1 (**C15**), 117.6 (**C17**), 115.6 (**C10**), 110.0 (**C18**), 104.5 (**C13**), 72.1 (**C5**), 49.0 (**C11**), 41.1 (**C1**), 33.6 (**C4**), 27.0 (**C2**), 26.2 (**C8**), 22.1 (**C3**); HRMS (ESI) Found: $[M+H]^+$, 341.1485. $C_{19}H_{20}N_2O_4$ requires $[M+H]^+$, 341.1496.

2-Acetyl-2-(3-(5-methoxy-1*H*-indol-1-yl)prop-1-en-2-yl)cyclohexanone (312h):

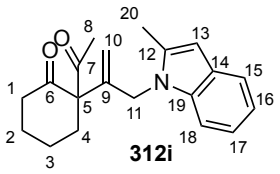


312h

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 5-methoxy-1*H*-indole (35.2 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 29:1-19:1-9:1-4:1] afforded **312h** (21 mg, 27%) as a red oil. R_F 0.25 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3121, 2942, 2214 (C≡N), 1697 (C=O), 1645; δ_H (400 MHz, $CDCl_3$) 7.26-7.23 (m, 1H, **H18**), 7.08 (d, *J* = 2.4 Hz, 1H, **H15**), 7.01 (d, *J* = 3.0 Hz, 1H, **H12**), 6.87 (dd, *J* = 8.9, 2.5 Hz, 1H, **H17**), 6.44 (dd, *J* = 3.1, 0.8 Hz, 1H, **H13**), 4.98 (t, *J* = 1.3 Hz, 1H, **H10a**), 4.78 (dt, *J* = 17.6, 1.6 Hz, 1H, **H11a**), 4.62 (t, *J* = 1.6 Hz, 1H, **H10b**), 4.55 (dt, *J* = 17.6, 1.6 Hz, 1H, **H11b**), 3.84 (s, 3H, **H20**), 2.55 (dd, *J* = 8.1, 6.4 Hz, 2H, **H1**), 2.47-2.39 (m, 1H, **H3a**), 2.20 (s, 3H, **H8**), 2.10-2.03 (m, 1H, **H3b**), 2.01-1.90 (m, 1H, **H4a**), 1.89-1.74 (m, 2H, **H2a** and **H4b**), 1.73-1.64 (m, 1H, **H2b**); δ_C (100 MHz, $CDCl_3$) 208.8 (**C6**), 206.8 (**C7**), 154.1 (**C16**), 142.5 (**C9**), 131.6 (**C19**), 129.1 (**C12**), 128.8 (**C14**), 115.8 (**C10**), 112.1 (**C17**), 110.6 (**C18**), 102.5 (**C15**), 101.4 (**C13**), 72.2 (**C5**), 55.8 (**C20**), 48.6 (**C11**), 41.1 (**C1**), 33.4 (**C3**), 27.0 (**C4**), 26.4 (**C8**), 22.1

(**C2**); HRMS (ESI) Found: $[M+H]^+$, 326.1747. $C_{20}H_{23}NO_3$ requires $[M+H]^+$, 326.1751.

2-Acetyl-2-(3-(2-methyl-1*H*-indol-1-yl)prop-1-en-2-yl)cyclohexanone (312i):

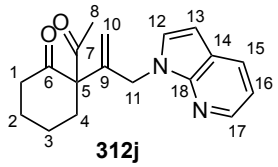


312i

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 2-methyl indole (31.4 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **312i** (14 mg, 19%) as a red oil. R_F 0.30 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2927, 1697 (C=O); δ_H (400 MHz, $CDCl_3$) 7.52 (d, J = 7.7 Hz, 1H, **H15**), 7.23 (d, J = 8.6 Hz, 1H, **H18**), 7.15-7.10 (m, 1H, **H17**), 7.08-7.04 (m, 1H, **H16**), 6.29 (s, 1H, **H13**), 4.92 (t, J = 1.5 Hz, 1H, **H10a**), 4.73 (dt, J = 19.0, 2.4 Hz, 1H, **H11a**), 4.47 (dt, J = 17.8, 1.7 Hz, 1H, **H11b**), 4.27 (t, J = 2.1 Hz, 1H, **H10b**), 2.62-2.55 (m, 2H, **H1**), 2.50-2.43 (m, 1H, **H2a**), 2.38 (s, 3H, **H20**), 2.30 (s, 3H, **H8**), 1.94-1.79 (m, 2H, **H2b** and **H4a**), 1.78-1.55 (m, 3H, **H3** and **H4b**); δ_C (100 MHz, $CDCl_3$) 208.7 (**C6**), 207.2 (**C7**), 141.7 (**C9**), 137.0 (**C19**), 136.7 (**C12**), 128.1 (**C14**),

120.7 (**C17**), 119.7 (**C15**), 119.5 (**C16**), 114.8 (**C10**), 109.1 (**C18**), 100.4 (**C13**), 72.1 (**C5**), 44.9 (**C11**), 41.1 (**C1**), 33.4 (**C2**), 27.1 (**C4**), 26.4 (**C8**), 22.2 (**C3**), 12.3 (**C20**); HRMS (ESI) Found: $[M+H]^+$, 310.1794. $C_{20}H_{23}NO_2$ requires $[M+H]^+$, 310.1802.

2-(3-(1*H*-Pyrrolo[2,3-b]pyridin-1-yl)prop-1-en-2-yl)-2-acetylcyclohexanone (312j):

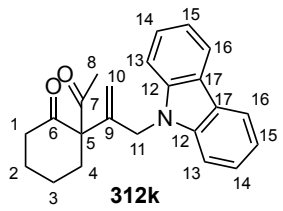


312j

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and azaindole (28.4 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **312j** (52 mg, 73%) as a brown solid. R_F 0.20 [Petrol:EtOAc 4:1]; m.p. 60–62 °C; ν_{max} (film)/cm^{-1} 2931, 1709 (C=O), 1695 (C=O), 1511; δ_H (400 MHz, $CDCl_3$) 8.27 (d, *J* = 4.8 Hz, 1.6 Hz, **H17**), 7.88 (dd, *J* = 7.9, 1.6 Hz, 1H, **H16**), 7.27 (d, *J* = 3.6 Hz, 1H, **H12**), 7.03 (dd, *J* = 7.8, 4.6 Hz, 1H, **H15**), 6.48 (d, *J* = 3.6 Hz, **H13**), 4.97 (t, *J* = 1.3 Hz, 1H, **H10a**), 4.84 (t, *J* = 1.4 Hz, 2H, **H11**), 4.68 (t, *J* = 1.6 Hz, 1H, **H10b**), 2.64-2.50 (m, 2H, **H1**), 2.44-2.36 (m, 1H, **H4a**), 2.27 (s,

3H, **H8**), 2.21-2.15 (m, 1H, **H4b**), 1.95-1.75 (m, 4H, **H2** and **H3**); δ_C (100 MHz, $CDCl_3$) 209.1 (**C6**), 207.2 (**C7**), 147.7 (**C18**), 143.1 (**C9**), 142.9 (**C17**), 128.7 (**C16**), 128.7 (**C12**), 120.2 (**C14**), 116.1 (**C10**), 115.8 (**C15**), 100.0 (**C13**), 72.4 (**C5**), 45.9 (**C11**), 41.0 (**C1**), 32.9 (**C4**), 27.1 (**C2**), 26.8 (**C8**), 21.8 (**C3**); HRMS (ESI) Found: $[M+H]^+$, 297.1588. $C_{18}H_{20}N_2O_2$ requires $[M+H]^+$, 297.1598.

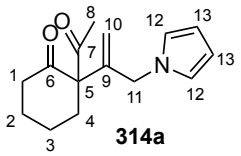
2-(3-(9H-Carbazol-9-yl)prop-1-en-2-yl)-2-acetylcyclohexanone (312k):



Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and carbazole (40.1 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Column chromatography [Petrol:EtOAc 9:1-4:1] afforded **312k** (44 mg, 53%) as an orange solid. R_F 0.30 [Petrol:EtOAc 4:1]; m.p. 105–107 °C; ν_{max} (film)/cm^{-1} 2942, 1701 (C=O), 1645; δ_H (400 MHz, $CDCl_3$) 8.11 (dt, *J* = 7.8, 0.9 Hz, 2H, **H13**), 7.46 (dd, *J* = 7.0, 1.1 Hz, 2H, **H16**), 7.40 (dt, *J* = 8.2, 0.8 Hz, 2H, **H14**), 7.25 (dd, *J* = 7.2, 1.2 Hz, 2H, **H15**), 4.98 (dt, *J* = 18.3, 1.7 Hz, 1H, **H11a**), 4.92 (t, *J* = 1.4 Hz, 1H, **H10a**), 4.70 (dt, *J* = 18.3, 1.9 Hz, 1H, **H11b**), 4.50 (t, *J* = 1.9 Hz, 1H, **H10b**), 2.67-2.61 (m, 2H, **H1**), 2.54-2.47 (m, 1H, **H3a**),

2.35 (s, 3H, **H8**), 2.25-2.16 (m, 1H, **H3b**), 2.06-1.90 (m, 2H, **H4**), 1.89-1.81 (m, 1H, **H2a**), 1.80-1.69 (m, 1H, **H2b**); δ_C (100 MHz, $CDCl_3$) 208.9 (**C6**), 207.3 (**C7**), 140.5 (**C12**), 140.1 (**C9**), 125.9 (**C16**), 122.9 (**C17**), 120.3 (**C13**), 119.2 (**C14**), 114.8 (**C10**), 108.8 (**C15**), 72.1 (**C5**), 45.0 (**C11**), 41.1 (**C1**), 33.5 (**C3**), 27.2 (**C4**), 26.5 (**C8**), 22.2 (**C2**); HRMS (ESI) Found: $[M+H]^+$, 346.1795. $C_{23}H_{23}NO_2$ requires $[M+H]^+$, 346.1802.

2-(3-(1*H*-Pyrrol-1-yl)prop-1-en-2-yl)-2-acetylcyclohexanone (314a):

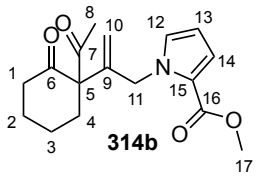


314a

Carbonate **266** (53.3 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and pyrrole (16.7 µL , 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1] afforded **314a** (12 mg, 21%) as a black solid. R_F 0.56 [Petrol:EtOAc 4:1]; m.p. 114–116 °C; ν_{max} (film)/cm^{-1} 3386, 3099, 3056, 2944, 2858, 1695 (C=O), 1511; δ_H (400 MHz, $CDCl_3$) 6.59 (t, *J* = 2.1 Hz, 2H, **H12**), 6.14 (t, *J* = 2.3 Hz, 2H, **H13**), 5.07 (t, *J* = 1.0 Hz, 1H, **H10a**), 4.92 (t, *J* = 1.5 Hz, 1H, **H10b**), 4.55 (dt, *J* = 16.5, 1.2 Hz, **H11a**), 4.36 (dt, *J* = 16.5, 1.2 Hz, 1H, **H11b**), 2.50 (dd, *J* = 8.0, 6.2 Hz, 2H, **H1**), 2.42-2.35 (m, 1H, **H3a**), 2.11 (s, 3H, **H8**), 2.03-1.88 (m, 2H, **H2a** and **H3b**), 1.83-1.70 (m, 2H, **H2b** and **H4a**), 1.68-1.61 (m, 1H, **H4b**); δ_C (100 MHz,

$CDCl_3$) 208.8 (**C6**), 206.8 (**C7**), 144.0 (**C9**), 121.5 (**C12**), 116.9 (**C10**), 108.4 (**C13**), 72.4 (**C5**), 51.7 (**C11**), 41.0 (**C1**), 33.1 (**C3**), 26.9 (**C2**), 26.7 (**C8**), 21.9 (**C4**); HRMS (ESI) Found: $[M+H]^+$, 246.1491. $C_{15}H_{19}NO_2$ requires $[M+H]^+$, 246.1489.

Methyl 1-(2-(1-acetyl-2-oxocyclohexyl)allyl)-1*H*-pyrrole-2-carboxylate (314b):



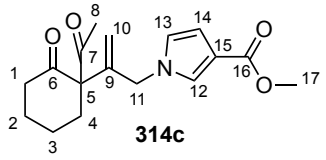
314b

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and methyl-1*H*-pyrrole-2-carboxylate (**313b**) (30 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **314b** (59 mg, 81%) as a yellow solid. R_F 0.43 [Petrol:EtOAc 4:1]; m.p. 104–106 °C; ν_{max} (film)/cm^{-1} 2946, 1716 (C=O), 1692 (C=O), 1643; δ_H (400 MHz, $CDCl_3$) 6.95 (dd, *J* = 4.1, 1.9 Hz, 1H, **H12**), 6.88 (dd, *J* = 2.5, 1.8 Hz, 1H, **H13**), 6.17 (dd, *J* = 3.9, 2.6 Hz, 1H, **H14**), 4.98-4.92 (m, 2H, **H10a** and **H11a**), 4.85 (dt, *J* = 16.7, 1.5 Hz, 1H, **H11b**), 4.39 (t, *J* = 1.7 Hz, 1H, **H10b**), 3.75 (s, 3H, **H17**), 2.63-2.47 (m, 2H, **H1**), 2.44-2.35 (m, 1H, **H2a**), 2.25 (s, 3H, **H8**), 2.15-2.07 (m, 1H, **H2b**), 1.96-1.75 (m, 3H, **H3a** and **H4**), 1.72-1.61 (m,

1H, **H3b**); δ_C (100 MHz, $CDCl_3$) 209.0 (**C6**), 207.3 (**C7**), 161.2 (**C16**), 143.9 (**C9**), 129.7 (**C13**), 121.8 (**C15**), 118.1 (**C12**), 114.2 (**C10**), 108.6 (**C14**), 72.1 (**C5**), 51.0 (**C17**), 50.2 (**C11**), 40.9 (**C1**), 33.0 (**C2**), 27.1 (**C4**), 26.6 (**C8**), 21.7 (**C3**); HRMS (ESI) Found: $[M+Na]^+$, 326.1348. $C_{17}H_{21}NO_4$ requires $[M+Na]^+$, 326.1363.

The formation of **314b** was also carried out under enantioselective conditions: Carbonate **266** (35.5 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), (*R*)-Xylyl-P-PHOS **L19** (7.3 mg, 0.0096 mmol) and methyl-1*H*-pyrrole-2-carboxylate **313b** (20 mg, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Tetrahydrofuran (1 mL) was added and the sealed tube was stirred at 60 °C for 2 hours, then concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **314b** (39 mg, 80% yield, *r.r.* > 19:1). Chiral HPLC: OD-H column, 1 mL/min, 19:1 Hexane:IPA, t_A (minor) = 8.7 min, t_B (major) = 9.1 min, 19% ee; $[\alpha]_D^{25}$ –0.5 (*c* 0.1, $CHCl_3$, 19% ee).

Methyl 1-(2-(1-Acetyl-2-oxocyclohexyl)allyl)-1*H*-pyrrole-3-carboxylate (314c):

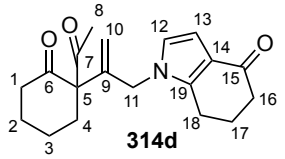


314c

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and **313c** (32 mg, 0.24 mmol) were added to

a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **314c** (30.5 mg, 42%) as a dark yellow solid. R_F 0.09 [Petrol:EtOAc 4:1]; m.p. 74–76 °C; ν_{max} (film)/cm^{-1} 2952, 1712 (C=O), 1694 (C=O); δ_H (400 MHz, $CDCl_3$) 7.23 (t, *J* = 2.0 Hz, 1H, **H14**), 6,57-6.52 (m, 2H, **H12** and **H13**), 5.11 (br s, 1H, **H10a**), 4.91 (t, *J* = 1.6 Hz, 1H, **H10b**), 4.56 (dt, *J* = 16.5, 1.3 Hz, 1H, **H11a**), 4.31 (dt, *J* = 16.3, 1.1 Hz, 1H, **H11b**), 3.77 (s, 3H, **H17**), 2.53-2.33 (m, 3H, **H1** and **H4a**), 2.10 (s, 3H, **H8**), 2.00-1.88 (m, 2H, **H2a** and **H4b**), 1.80-1.62 (m, 2H, **H2b** and **H3a**), 1.62-1.51 (m, 1H, **H3b**); δ_C (100 MHz, $CDCl_3$) 208.6 (**C7**), 206.7 (**C6**), 165.1 (**C16**), 143.1 (**C9**), 126.8 (**C14**), 122.7 (**C12**), 117.2 (**C10**), 116.1 (**C15**), 110.2 (**C13**), 72.3 (**C5**), 52.0 (**C11**), 51.0 (**C17**), 41.0 (**C1**), 33.3 (**C4**), 26.9 (**C2**), 26.1 (**C8**), 22.0 (**C3**); HRMS (ESI) Found: $[M+Na]^+$, 326.1348. $C_{17}H_{21}NO_4$ requires $[M+Na]^+$, 326.1363.

1-(2-(1-acetyl-2-oxocyclohexyl)allyl)-6,7-dihydro-1*H*-indol-4(5*H*)-one (314d):

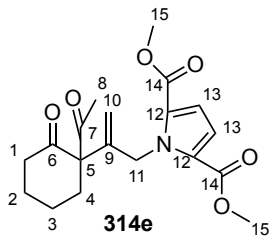


314d

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 1,5,6,7-tetraindole-4*H*-indol-4-one (32.4

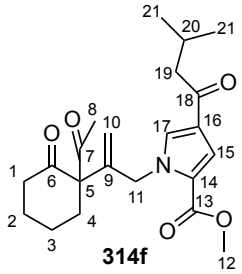
mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-3:1-1:1] afforded **314d** (31 mg, 41%) as a dark orange oil. R_F 0.10 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2939, 1697 (C=O), 1647; δ_H (400 MHz, $CDCl_3$) 6.56-6.48 (m, 2H, **H12** and **H13**), 5.08 (s, 1H, **H10a**), 4.60 (t, *J* = 1.4 Hz, 1H, **H10b**), 4.52 (dt, *J* = 17.5, 1.8 Hz, 1H, **H11a**), 4.23 (dt, *J* = 17.4, 1.5 Hz, 1H, **H11b**), 2.68 (t, *J* = 6.2 Hz, 2H, **H18**), 2.60-2.40 (m, 4H, **H4a**, **H16** and **H17a**), 2.17 (s, 3H, **H8**), 2.14-2.09 (m, 2H, **H1**), 2.04-1.93 (m, 2H, **H4b** and **H17b**), 1.91-1.70 (m, 4H, **H2** and **H3**); δ_C (100 MHz, $CDCl_3$) 208.5 (**C6**), 206.7 (**C7**), 194.2 (**C15**), 144.2 (**C19**), 142.5 (**C9**), 122.9 (**C12**), 120.9 (**C14**), 115.7 (**C10**), 105.9 (**C13**), 72.0 (**C5**), 48.9 (**C11**), 41.1 (**C16**), 37.7 (**C4**), 33.5 (**C17**), 27.0 (**C2**), 26.1 (**C8**), 23.7 (**C1**), 22.0 (**C3**), 21.4 (**C18**); HRMS (ESI) Found: $[M+Na]^+$, 336.1551. $C_{19}H_{23}NO_3$ requires $[M+Na]^+$, 336.1570.

Dimethyl 1-(2-(1-acetyl-2-oxocyclohexyl)allyl)-1*H*-pyrrole-2,5-dicarboxylate (314e):



Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and **313e** (44 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **314e** (49 mg, 57%) as a dark orange solid. R_F 0.29 [Petrol:EtOAc 4:1]; m.p. 144–146 °C; ν_{max} (film)/cm^{-1} 2946, 1727 (C=O), 1699 (C=O); δ_H (400 MHz, $CDCl_3$) 6.96 (s, 2H, **H13**), 5.61 (dt, *J* = 17.0, 2.0 Hz, 1H, **H11a**), 5.43 (dt, *J* = 16.9, 1.6 Hz, 1H, **H11b**), 4.84 (t, *J* = 1.8 Hz, 1H, **H10a**) 4.17 (t, *J* = 1.9 Hz, 1H, **H10b**), 3.82 (s, 6H, **H15**), 2.80-2.65 (m, 1H, **H4a**), 2.44-2.34 (m, 1H, **H4b**), 2.28 (s, 3H, **H8**), 2.31-2.26 (m, 2H, **H1**), 2.09-1.89 (m, 2H, **H2**), 1.86-1.70 (m, 2H, **H3**); δ_C (100 MHz, $CDCl_3$) 209.4 (**C6**), 206.6 (**C7**), 160.6 (**C14**), 144.1 (**C9**), 127.6 (**C12**), 117.0 (**C10**), 113.9 (**C13**), 72.2 (**C5**), 51.7 (**C15**), 47.9 (**C11**), 40.9 (**C4**), 32.5 (**C1**), 27.6 (**C3**), 27.1 (**C8**), 21.5 (**C2**); HRMS (ESI) Found: $[M+Na]^+$, 384.1406. $C_{19}H_{23}NO_6$ requires $[M+Na]^+$, 384.1418.

Methyl 1-(2-(1-acetyl-2-oxocyclohexyl)allyl)-4-(3-methylbutanoyl)-1*H*-pyrrole-2-carboxylate (314f):

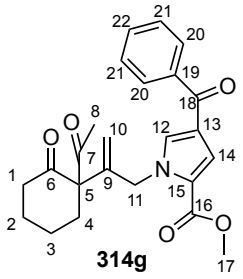


314f

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and **313f** (50.2 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **314f** (56 mg, 60%) as a light yellow solid. R_F 0.56 [Petrol:EtOAc 4:1]; m.p. 75–78 °C; ν_{max} (film)/cm^{-1} 3188, 2953, 1697 (C=O), 1636; δ_H (400 MHz, $CDCl_3$) 7.46 (d, *J* = 1.8 Hz, 1H, **H17**), 7.33 (d, *J* = 1.9 Hz, 1H, **H15**), 4.98-4.96 (m, 1H, **H10a**), 4.94-4.91 (m, 2H, **H11**), 4.42-4.39 (m, 1H, **H10b**), 3.77 (s, 3H, **H12**), 2.58 (d, *J* = 7.0 Hz, 2H, **H19**), 2.54 (dd, *J* = 8.2, 6.3 Hz, 2H, **H1**), 2.47-2.39 (m, 1H, **H4a**), 2.25 (s, 3H, **H8**), 2.26-2.19 (m, 1H, **H20**), 2.14-2.03 (m, 1H, **H4b**), 1.98-1.82 (m, 2H, **H2**), 1.84-1.73 (m, 2H, **H3a**), 1.70-1.58 (m, 1H, **H3b**), 0.94 (d, *J* = 6.4 Hz, 6H, **H21**); δ_C (100 MHz, $CDCl_3$) 208.8 (**C6**), 207.2 (**C7**), 195.3 (**C18**), 160.8 (**C13**), 143.2 (**C9**), 132.4 (**C17**), 125.3 (**C16**), 123.2 (**C14**), 117.7 (**C15**), 114.1 (**C10**), 72.0 (**C5**), 51.4 (**C12**), 50.8 (**C11**), 48.5 (**C19**), 41.0 (**C1**), 33.3

(**C4**), 27.1 (**C2**), 26.5 (**C20**), 25.4 (**C8**), 22.7 (**C21**), 21.9 (**C3**); HRMS (ESI) Found: $[M+Na]^+$, 410.1923. $C_{22}H_{29}NO_5$ requires $[M+Na]^+$, 410.1938.

Methyl 1-(2-(1-acetyl-2-oxocyclohexyl)allyl)-4-benzoyl-1*H*-pyrrole-2-carboxylate (314g):

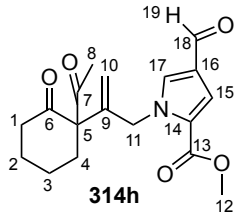


314g

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and **313g** (55 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 91-4:1] afforded **314g** (93 mg, 95%) as a red oil. R_F 0.22 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2950, 1701 (C=O), 1638; δ_H (400 MHz, $CDCl_3$) 7.85-7.80 (m, 2H, **H20**), 7.56 (tt, *J* = 7.3, 2.3 Hz, 1H, **H22**), 7.50-7.46 (m, 3H, **H14** and **H21**), 7.44 (d, *J* = 2.1 Hz, 1H, **H12**), 5.03-4.97 (m, 3H, **H10a** and **H11**), 4.49-4.47 (m, 1H, **H10b**), 3.80 (s, 3H, **H17**), 2.56 (dd, *J* = 7.8, 6.3 Hz, 2H, **H1**), 2.50-2.43 (m, 1H, **H4a**), 2.27 (s, 3H, **H8**), 2.14-2.05 (m, 1H, **H4b**), 2.00-1.87 (m, 2H, **H2**), 1.85-1.76 (m, 1H, **H3a**), 1.72-1.62 (m, 1H, **H3b**); δ_C (100 MHz, $CDCl_3$) 208.8 (**C6**), 207.1 (**C7**), 189.1

(**C18**), 160.9 (**C16**), 143.2 (**C9**), 139.0 (**C19**), 134.4 (**C14**), 131.9 (**C22**), 128.9 (**C20**), 128.4 (**C21**), 123.6 (**C13**), 123.3 (**C15**), 119.6 (**C12**), 114.2 (**C10**), 72.1 (**C5**), 51.5 (**C17**), 51.0 (**C11**), 41.0 (**C1**), 33.4 (**C4**), 27.1 (**C2**), 26.5 (**C8**), 21.9 (**C3**); HRMS (ESI) Found: $[M+Na]^+$, 430.1609. $C_{24}H_{25}NO_5$ requires $[M+Na]^+$, 430.1625.

Methyl 1-(2-(1-acetyl-2-oxocyclohexyl)allyl)-4-formyl-1*H*-pyrrole-2-carboxylate (314h):

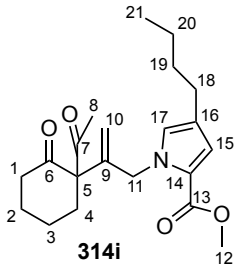


314h

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and **313h** (37 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **314h** (46 mg, 58%) as an orange solid. R_F 0.19 [Petrol:EtOAc 4:1]; m.p. 96–99 °C; ν_{max} (film)/cm^{-1} 2953, 1720 (C=O), 1697 (C=O), 1668, 1518; δ_H (400 MHz, $CDCl_3$) 9.75 (s, 1H, **H19**), 7.00 (d, J = 4.2 Hz, 1H, **H15**), 6.96 (d, J = 4.4 Hz, 1H, **H17**), 5.49 (dt, J = 17.3, 2.2 Hz, 1H, **H11a**), 5.35 (dt, J = 17.3, 2.0 Hz, 1H, **H11b**), 4.89-4.87 (m, 1H, **H10a**), 4.19-4.17 (m, 1H, **H10b**), 3.83 (s, 3H, **H12**), 2.73-2.64 (m, 1H, **H1a**), 2.47-2.38 (m, 1H, **H1b**), 2.29 (s, 3H, **H8**), 2.36-2.20 (m,

2H, **H4**), 2.07-1.96 (m, 1H, **H2a**), 1.96-1.87 (m, 1H, **H2b**), 1.86-1.79 (m, 1H, **H3a**), 1.79-1.69 (m, 1H, **H3b**); δ_C (100 MHz, $CDCl_3$) 209.2 (**C6**), 207.8 (**C7**), 181.0 (**C18**), 160.6 (**C13**), 143.7 (**C9**), 135.3 (**C16**), 129.0 (**C14**), 121.3 (**C17**), 117.5 (**C15**), 113.8 (**C10**), 72.1 (**C5**), 51.9 (**C12**), 48.1 (**C11**), 40.9 (**C1**), 32.7 (**C4**), 27.4 (**C2**), 27.0 (**C8**), 21.5 (**C3**); HRMS (ESI) Found: $[M+K]^+$, 370.1062. $C_{18}H_{21}NO_5$ requires $[M+K]^+$, 370.1051.

Methyl-1-(2-(1-acetyl-2-oxocyclohexyl)allyl)-4-butyl-1*H*-pyrrole-2-carboxylate (314i):

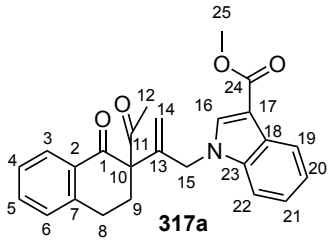


314i

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and **313i** (43.4 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **314i** (51 mg, 59%) as a yellow oil. R_F 0.51 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2927, 1697 (C=O); δ_H (400 MHz, $CDCl_3$) 6.79 (d, J = 1.9 Hz, 1H, **H15**), 6.68 (d, J = 1.9 Hz, 1H, **H17**), 4.94-4.86 (m, 2H, **H10a** and **H11a**), 4.81-4.75 (m, 1H, **H11b**), 4.43

(t, *J* = 2.2 Hz, 1H, **H10b**), 3.75 (s, 3H, **H12**), 2.65-2.48 (m, 2H, **H1**), 2.42 (t, *J* = 8.1 Hz, 1H, **H18**), 2.45-2.38 (m, 1H, **H4a**), 2.26 (s, 3H, **H8**), 2.17-2.08 (m, 1H, **H4b**), 1.94-1.78 (m, 3H, **H2** and **H3a**), 1.75-1.60 (m, 1H, **H3b**), 1.52 (sept, *J* = 7.7 Hz, 2H, **H19**), 1.33 (sext, *J* = 7.7 Hz, 2H, **H20**), 0.90 (t, *J* = 7.2 Hz, 3H, **H21**); δ_C (100 MHz, $CDCl_3$) 209.2 (**C6**), 207.4 (**C7**), 161.2 (**C13**), 144.1 (**C9**), 127.8 (**C17**), 124.8 (**C14**), 121.3 (**C16**), 117.7 (**C15**), 114.2 (**C10**), 72.1 (**C5**), 50.9 (**C12**), 50.0 (**C11**), 41.0 (**C18**), 33.0 (**C1**), 33.0 (**C4**), 27.2 (**C2**), 26.8 (**C8**), 26.2 (**C19**), 22.7 (**C20**), 21.8 (**C3**), 13.9 (**C21**); HRMS (ESI) Found: $[M+Na]^+$, 382.1993. $C_{21}H_{29}NO_4$ requires $[M+Na]^+$, 382.1989.

Methyl-1-(2-(2-acetyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)allyl)-1*H*-indole-3-carboxylate (317a):

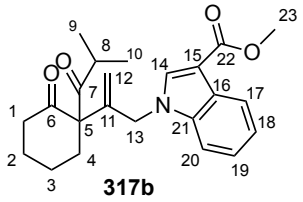


317a

Carbonate **303b** (64.8 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-methyl-indole-carboxylate (**311b**) (42 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-

4:1] afforded **317a** (69 mg, 72%) as a yellow solid. R_F 0.24 [Petrol:EtOAc 4:1]; m.p.149–152 °C; ν_{max} (film)/cm^{-1} 2946, 1697 (C=O), 1533; δ_H (400 MHz, $CDCl_3$) 8.17-8.12 (m, 1H, **H21**), 8.04 (dd, *J* = 8.1, 1.3 Hz, 1H, **H3**), 7.76 (s, 1H, **H16**), 7.52 (td, *J* = 7.5, 1.4 Hz, 1H, **H4**), 7.42-7.38 (m, 1H, **H5**), 7.33 (t, *J* = 7.8 Hz, 1H, **H20**), 7.29-7.22 (m, 3H, **H6**, **H19** and **H22**), 4.98 (q, *J* = 1.3 Hz, 1H, **H14a**), 4.83 (t, *J* = 1.7 Hz, 2H, **H15**), 4.52 (q, *J* = 0.9 Hz, 1H, **H14b**), 3.89 (s, 3H, **H25**), 3.11-2.96 (m, 2H, **H8**), 2.70 (ddd, *J* = 14.3, 7.3, 6.1 Hz, 1H, **H9a**), 2.43 (ddd, *J* = 14.0, 7.0, 5.1 Hz, 1H, **H9b**), 2.31 (s, 3H, **H12**); δ_C (100 MHz, $CDCl_3$) 204.8 (**C11**), 195.7 (**C1**), 165.3 (**C24**), 142.8 (**C2**), 140.7 (**C13**), 136.8 (**C23**), 134.9 (**C16**), 134.2 (**C4**), 131.7 (**C7**), 128.8 (**C6**), 128.0 (**C3**), 127.1 (**C20**), 126.4 (**C18**), 123.2 (**C22**), 122.1 (**C19**), 121.6 (**C21**), 116.5 (**C14**), 110.4 (**C5**), 107.7 (**C17**), 68.4 (**C10**), 50.9 (**C25**), 49.1 (**C15**), 29.7 (**C9**), 27.7 (**C12**), 25.8 (**C8**); HRMS (ESI) Found: $[M+H]^+$, 384.1565. $C_{25}H_{21}NO_3$ requires $[M+H]^+$, 384.1594.

Methyl-1-(2-(1-*iso*butyryl-2-oxocyclohexyl)allyl)-1*H*-indole-3-carboxylate (317b):

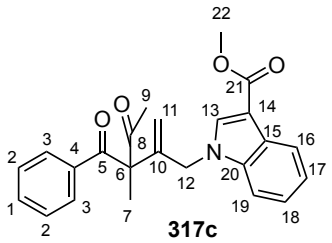


317b

Carbonate **303c** (60 mg, 0.240 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-methyl-indole-carboxylate (**311b**) (42 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted

with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **327b** (65 mg, 71%) as a pale yellow solid. R_F 0.20 [Petrol:EtOAc 4:1]; m.p. 81–83 °C; ν_{max} (film)/cm^{-1} 2950, 1758, 1723 (C=O), 1684 (C=O); δ_H (400 MHz, $CDCl_3$) 8.20-8.15 (m, 1H, **H18**), 7.78 (s, 1H, **H20**), 7.52-7.46 (m, 1H, **H15**), 7.32-7.25 (m, 2H, **H16** and **H17**), 4.97 (q, *J* = 1.0 Hz, 1H, **H12a**), 4.77 (dt, *J* = 17.6, 1.5 Hz, 1H, **H13a**), 4.62 (dt, *J* = 17.5 Hz, 1.6 Hz, 1H, **H13b**), 4.54-4.52 (m, 1H, **H12b**), 3.91 (s, 3H, **H23**), 3.04 (sept, *J* = 6.7 Hz, 1H, **H8**), 2.54 (t, *J* = 6.5 Hz, 2H, **H1**), 2.51-2.44 (m, 1H, **H4a**), 2.14-2.05 (m, 1H, **H4b**), 1.98-1.74 (m, 4H, **H2** and **H3**), 1.19 (d, *J* = 6.5 Hz, 3H, **H9**), 1.14 (d, *J* = 6.7 Hz, 3H, **H10**); δ_C (100 MHz, $CDCl_3$) 213.1 (**C7**), 209.0 (**C6**), 165.3 (**C22**), 141.1 (**C11**), 136.9 (**C14**), 134.9 (**C20**), 126.3 (**C19**), 123.1 (**C16**), 122.0 (**C17**), 121.5 (**C18**), 115.8 (**C12**), 110.6 (**C15**), 107.7 (**C21**), 72.5 (**C5**), 50.9 (**C23**), 49.0 (**C13**), 41.1 (**C1**), 37.1 (**C8**), 32.9 (**C4**), 26.6 (**C2**), 22.0 (**C3**), 21.2 (**C9**), 20.5 (**C10**); HRMS (ESI) Found: $[M+H]^+$, 370.1629. $C_{21}H_{23}NO_5$ requires $[M+H]^+$, 370.1649.

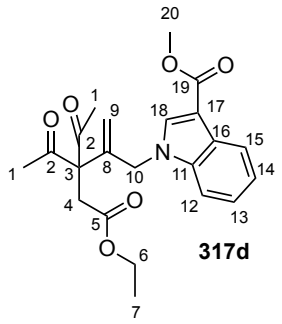
Methyl 1-(3-benzoyl-3-methyl-2-methylene-4-oxopentyl)-1*H*-indole-3-carboxylate (317c):



317c

Carbonate **303f** (61.9 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-methyl-indole-carboxylate (**311b**) (42 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **317c** (78 mg, 83%) as an orange oil. R_F 0.24 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2948, 1697 (C=O), 1677 (C=O), 1533; δ_H (400 MHz, $CDCl_3$) 8.18-8.13 (m, 1H, **H17**), 7.91-7.85 (m, 2H, **H3**), 7.77 (s, 1H, **H13**), 7.58 (tt, *J* = 7.6, 1.4 Hz, 1H, **H1**), 7.47 (t, *J* = 7.9 Hz, 2H, **H2**), 7.43-7.39 (m, 1H, **H18**), 7.30-7.22 (m, 2H, **H16** and **H19**), 5.11 (s, 1H, **H11a**), 4.92 (d, *J* = 17.9 Hz, 1H, **H12a**), 4.79 (d, *J* = 17.9 Hz, 1H, **H12b**), 4.55 (s, 1H, **H11b**), 3.90 (s, 3H, **H22**), 2.24 (s, 3H, **H9**), 1.80 (s, 3H, **H7**); δ_C (100 MHz, $CDCl_3$) 206.1 (**C8**), 199.6 (**C5**), 165.4 (**C21**), 143.6 (**C10**), 136.8 (**C20**), 135.5 (**C4**), 135.1 (**C13**), 133.4 (**C1**), 129.1 (**C3**), 128.7 (**C2**), 126.4 (**C15**), 123.1 (**C16**), 122.0 (**C19**), 121.6 (**C17**), 115.0 (**C11**), 110.5 (**C18**), 107.6 (**C14**), 68.5 (**C6**), 51.9 (**C22**), 49.1 (**C12**), 27.5 (**C9**), 21.0 (**C7**); HRMS (ESI) Found: $[M+H]^+$, 390.1675. $C_{24}H_{23}NO_4$ requires $[M+H]^+$, 390.1670.

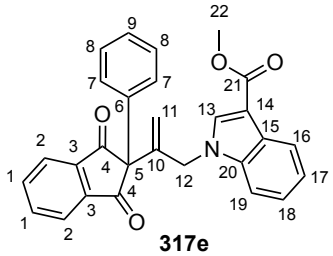
Methyl 1-(3,3-diacetyl-5-ethoxy-2-methylene-5-oxopentyl)-1*H*-indole-3-carboxylate (317d):



Carbonate **303h** (61 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and methyl-indole-3-carboxylate (**311b**) (42 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **317d** (54 mg, 56%) as an orange solid. R_F 0.10 [Petrol:EtOAc 4:1]; m.p. 104–107 °C; ν_{max} (film)/cm^{-1} 2935, 1716 (C=O), 1692 (C=O), 1531; δ_H (400 MHz, $CDCl_3$) 8.13-8.08 (m, 1H, **H13**), 7.68 (s, 1H, **H18**), 7.24-7.16 (m, 3H, **H12, H14** and **H15**), 4.89 (q, *J* = 1.4 Hz, 1H, **H9a**), 4.81 (t, *J* = 1.7 Hz, 2H, **H10**), 4.45 (q, *J* = 1.9 Hz, 1H, **H9b**), 4.13 (q, *J* = 7.1 Hz, 2H, **H6**), 3.84 (s, 3H, **H20**), 3.14 (s, 2H, **H4**), 2.22 (s, 6H, **H1**), 1.22 (t, *J* = 7.3 Hz, 3H, **H7**); δ_C (100 MHz, $CDCl_3$) 203.6 (**C2**), 170.8 (**C5**), 165.3 (**C19**), 141.7 (**C8**), 136.6 (**C11**), 134.8 (**C18**), 126.4 (**C16**), 123.2 (**C13**), 122.1 (**C14**), 121.8 (**C12**), 117.0 (**C9**), 110.0 (**C15**), 108.0 (**C17**), 72.3 (**C3**), 61.5 (**C6**), 51.0 (**C20**), 48.7

(**C10**), 39.6 (**C4**), 27.6 (**C1**), 14.0 (**C7**); HRMS (ESI) Found: $[M+Na]^+$, 422.1580. $C_{22}H_{25}NO_6$ requires $[M+Na]^+$, 422.1574.

Methyl-1-(2-(1,3-dioxo-2-phenyl-2,3-dihydro-1*H*-inden-2-yl)allyl)-1*H*-indole-3-carboxylate (317e):

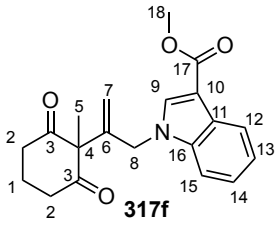


317e

Carbonate **303d** (73.0 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-methyl-indole-carboxylate (**311b**) (42 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **317e** (59 mg, 56%) as a dark orange oil. R_F 0.40 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2946, 1697 (C=O); δ_H (400 MHz, $CDCl_3$) 8.09-8.02 (m, 1H, **H17**), 8.00-7.96 (m, 2H, **H2**), 7.87-7.83 (m, 2H, **H1**), 7.65 (s, 1H, **H13**), 7.51-7.47 (m, 2H, **H8**), 7.41-7.36 (m, 3H, **H7** and **H9**), 7.24-7.18 (m, 3H, **H16, H18** and **H19**), 4.99 (q, *J* = 0.7 Hz, 1H, **H11a**), 4.78 (t, *J* = 1.6 Hz, 2H, **H12**), 4.64 (q, *J* = 0.7 Hz, 1H, **H11b**), 3.80 (s, 3H, **H22**); δ_C (100 MHz, $CDCl_3$) 198.3 (**C4**), 165.2 (**C21**), 141.2 (**C10**), 140.7 (**C3**), 136.6 (**C6**), 136.3 (**C1**), 135.1

(**C13**), 134.3 (**C20**), 129.1 (**C8**), 128.4 (**C9**), 128.2 (**C7**), 126.4 (**C15**), 124.0 (**C2**), 123.0 (**C16**), 122.0 (**C18**), 121.4 (**C19**), 117.9 (**C11**), 110.3 (**C17**), 107.7 (**C14**), 66.6 (**C5**), 50.9 (**C22**), 48.9 (**C12**); HRMS (ESI) Found: $[M+H]^+$, 436.1534. $C_{28}H_{21}NO_4$ requires $[M+H]^+$, 436.1543.

Methyl 1-(2-(1-methyl-2,6-dioxocyclohexyl)allyl)-1*H*-indole-3-carboxylate (317f):

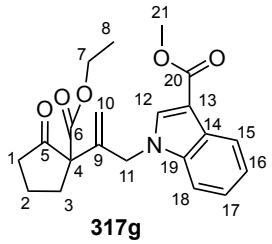


317f

Carbonate **303e** (49 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-methyl-indole-carboxylate (**311b**) (42 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **317f** (44 mg, 54%) as a yellow oil. R_F 0.12 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2946, 1692 (C=O), 1533; δ_H (400 MHz, $CDCl_3$) 8.17-8.11 (m, 1H, **H13**), 7.72 (s, 1H, **H9**), 7.29-7.19 (m, 3H, **H12**, **H14** and **H15**), 4.97 (q, J = 1.4 Hz, 1H, **H7a**), 4.62 (q, J = 1.9 Hz, 1H, **H7b**), 4.56 (t, J = 1.3 Hz, 2H, **H8**), 3.88 (s, 3H, **H18**), 2.70-2.57 (m, 4H, **H2**), 1.99-1.82 (m, 2H, **H1**), 1.51 (s, 3H, **H5**); δ_C (100 MHz, $CDCl_3$) 207.5 (**C3**), 165.2 (**C17**), 142.3 (**C6**), 136.7 (**C16**), 135.0 (**C9**), 126.4 (**C11**), 123.2 (**C12**), 122.3 (**C14**), 121.7 (**C13**), 115.8 (**C7**), 110.2 (**C15**), 108.8 (**C10**), 70.3 (**C4**), 51.1 (**C18**), 48.5 (**C8**), 38.4 (**C2**), 19.9

(**C1**), 17.4 (**C5**); HRMS (ESI) Found: $[M+H]^+$, 340.1537. $C_{20}H_{21}NO_4$ requires $[M+H]^+$, 340.1543.

Methyl 1-(2-(1-(ethoxycarbonyl)-2-oxocyclopentyl)allyl)-1*H*-indole-3-carboxylate (317g):

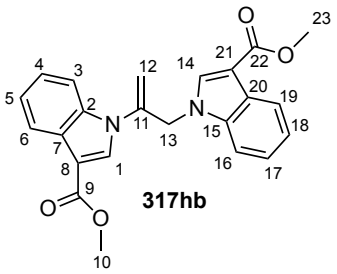


317g

Carbonate **303m** (57.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-methyl-indole-carboxylate (**311b**) (42 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **317g** (72 mg, 81%) as a red oil. R_F 0.19 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2940, 1695 (C=O), 1533; δ_H (400 MHz, $CDCl_3$) 8.13-8.07 (m, 1H, **H16**), 7.72 (s, 1H, **H12**), 7.32-7.26 (m, 1H, **H17**), 7.21-7.15 (m, 2H, **H15** and **H18**), 5.03 (br s, 1H, **H10a**), 4.95 (dt, *J* = 17.4, 1.5 Hz, 1H, **H11a**), 4.79 (dt, *J* = 17.2, 1.5 Hz, 1H, **H11b**), 4.50-4.47 (m, 1H, **H10b**), 4.10 (q, *J* = 7.2 Hz, 2H, **H7**), 3.82 (s, 3H, **H21**), 2.53-2.37 (m, 2H, **H1a** and **H3a**), 2.33-2.21 (m, 2H, **H1b** and **H3b**), 1.99-1.81 (m, 2H, **H2**), 1.20 (t, *J* = 6.8 Hz, 3H, **H8**); δ_C (100 MHz, $CDCl_3$) 211.8 (**C5**), 170.1 (**C6**), 165.4 (**C20**), 139.3 (**C9**), 136.8 (**C19**),

135.1 (**C12**), 126.4 (**C14**), 123.0 (**C15**), 122.0 (**C18**), 121.5 (**C16**), 114.9 (**C10**), 110.5 (**C17**), 107.5 (**C13**), 64.4 (**C4**), 62.1 (**C7**), 50.9 (**C21**), 48.7 (**C11**), 37.9 (**C3**), 33.7 (**C1**), 19.5 (**C2**), 14.0 (**C8**); HRMS (ESI) Found: $[M+H]^+$, 382.2007. $C_{23}H_{27}NO_4$ requires $[M+H]^+$, 382.2013.

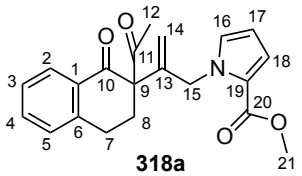
Dimethyl 1,1'-(prop-2-ene-1,2-diyl)bis(1*H*-indole-3-carboxylate) (317hb):



Carbonate **303t** (61.7 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-methyl-indole-carboxylate (**311b**) (42 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **317hb** (35 mg, 88%) as an orange solid. R_F 0.08 [Petrol:EtOAc 4:1]; m.p. 135–137 °C; ν_{max} (film)/cm^{-1} 2946, 1705 (C=O), 1654; δ_H (400 MHz, $CDCl_3$) 8.23-8.17 (m, 2H, **H6** and **H19**), 7.76 (s, 1H, **H1**), 7.76 (s, 1H, **H14**), 7.47-7.42 (m, 1H, **H16**), 7.35-7.28 (m, 5H, **H3**, **H4**, **H5**, **H17** and **H18**), 5.51 (q, *J* = 0.9 Hz, 1H, **H12a**), 5.19 (q, *J* = 1.5 Hz, 1H, **H12b**), 5.12 (t, *J* = 1.1 Hz, 2H, **H13**), 3.91 (s, 3H, **H23**), 3.91 (s, 3H, **H10**); δ_C (100 MHz, $CDCl_3$) 165.1 (**C9**),

165.0 (**C22**), 139.1 (**C11**), 136.4 (**C15**), 136.3 (**C6**), 134.2 (**C7**), 132.3 (**C14**), 126.7 (**C1**), 126.6 (**C20**), 123.8 (**C4**), 123.5 (**C17**), 122.7 (**C3**), 122.4 (**C18**), 122.1 (**C2**), 122.0 (**C19**), 113.7 (**C12**), 110.8 (**C16**), 109.7 (**C5**), 109.6 (**C8**), 108.6 (**C21**), 51.2 (**C10**), 51.1 (**C23**), 49.6 (**C13**); HRMS (ESI) Found: $[M+Na]^+$, 411.1295. $C_{23}H_{20}NO_2$ requires $[M+Na]^+$, 411.1315.

Methyl-1-(2-(2-acetyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)allyl)-1*H*-pyrrole-2-carboxylate (318a):

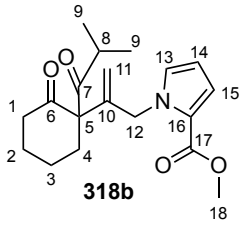


318a

Carbonate **303b** (64.8 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-methyl-1*H*-2-pyrrole carboxylate (**313b**) (30 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **318a** (56 mg, 66%) as a pale yellow solid. R_F 0.60 [Petrol:EtOAc 4:1]; m.p. 92–95 °C; ν_{max} (film)/cm^{-1} 2939, 1694 (C=O); δ_H (400 MHz, $CDCl_3$) 8.06 (dd, *J* = 7.9, 1.3 Hz, 1H, **H2**), 7.49 (td, *J* = 7.5, 1.5 Hz, 1H, **H3**), 7.32 (tt, *J* = 8.0, 0.6 Hz, 1H, **H4**), 7.24 (d, *J* = 8.1 Hz, 1H, **H5**), 6.96 (dd, *J* = 4.1, 2.0 Hz, 1H, **H16**), 6.88 (dd, *J* = 2.5, 1.8 Hz, 1H, **H18**), 6.18 (dd, *J* = 4.0, 2.7 Hz, 1H,

H17), 5.30-5.23 (m, 1H, **H15a**), 4.87 (t, *J* = 1.6 Hz, 1H, **H14a**), 4.84-4.83 (m, 1H, **H15b**), 4.38-4.36 (m, 1H, **H14b**), 3.76 (s, 3H, **H21**), 3.15 (ddd, *J* = 17.0, 9.9, 4.9 Hz, 1H, **H7a**), 3.01 (ddd, *J* = 17.5, 5.9, 4.7 Hz, 1H, **H7b**), 2.70-2.61 (m, 1H, **H8a**), 2.48 (ddd, *J* = 14.2, 6.5, 4.6 Hz, 1H, **H8b**), 2.37 (s, 3H, **H12**); δ_C (100 MHz, $CDCl_3$) 205.8 (**C10**), 195.9 (**C11**), 161.2 (**C20**), 143.5 (**C1**), 143.3 (**C13**), 133.9 (**C3**), 132.0 (**C6**), 129.7 (**C18**), 128.8 (**C5**), 127.9 (**C2**), 126.9 (**C4**), 122.0 (**C19**), 118.2 (**C16**), 115.0 (**C14**), 108.8 (**C17**), 68.6 (**C9**), 51.1 (**C21**), 50.3 (**C15**), 29.3 (**C7**), 28.1 (**C12**), 25.7 (**C8**); HRMS (ESI) Found: $[M+K]^+$, 390.1105. $C_{21}H_{21}NO_4$ requires $[M+K]^+$, 390.1102.

Methyl 1-(2-(1-*iso*butyryl-2-oxocyclohexyl)allyl)-1*H*-pyrrole-2-carboxylate (318b):

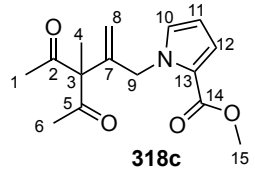


318b

Carbonate **303c** (60 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and methyl-1*H*-2-pyrrole carboxylate (**313b**) (30 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1] afforded **318b** (44 mg, 55%) as an orange oil. R_F 0.70 [Petrol:EtOAc 4:1];

ν_{max} (film)/cm^{-1} 2946, 1697 (C=O); δ_H (400 MHz, $CDCl_3$) 6.96 (dd, *J* = 4.0, 1.8 Hz, 1H, **H13**), 6.90 (dd, *J* = 2.5, 1.9 Hz, 1H, **H15**), 6.17 (dd, *J* = 3.9, 2.6 Hz, 1H, **H14**), 5.12 (dt, *J* = 17.1, 1.9 Hz, 1H, **H12a**), 4.88-4.86 (m, 1H, **H11a**), 4.68 (d, *J* = 17.0, 1.5 Hz, 1H, **H12b**), 4.41 (t, *J* = 1.9 Hz, 1H, **H11b**), 3.77 (s, 3H, **H18**), 3.0 (sept, *J* = 6.3 Hz, 1H, **H8**), 2.74-2.64 (m, 1H, **H1a**), 2.47-2.39 (m, 1H, **H1b**), 2.36-2.29 (m, 1H, **H4a**), 2.26-2.17 (m, 1H, **H4b**), 2.01-1.90 (m, 2H, **H3**), 1.86-1.73 (m, 2H, **H2**), 1.13 (d, *J* = 6.8 Hz, 3H, **H9a**), 1.09 (d, *J* =6.8 Hz, 3H, **H9b**); δ_C (100 MHz, $CDCl_3$) 213.3 (**C6**), 209.8 (**C7**), 161.2 (**C17**), 143.2 (**C10**), 129.7 (**C15**), 122.0 (**C16**), 118.1 (**C13**), 114.7 (**C11**), 108.7 (**C14**), 72.7 (**C5**), 51.0 (**C18**), 50.2 (**C12**), 41.1 (**C1**), 37.4 (**C8**), 33.3 (**C4**), 28.9 (**C3**), 21.5 (**C2**), 20.8 (**C9**); HRMS (ESI) Found: $[M+Na]^+$, 354.1660. $C_{19}H_{25}NO_4$ requires $[M+Na]^+$, 354.1676.

Methyl 1-(3-acetyl-3-methyl-2-methylene-4-oxopentyl)-1*H*-pyrrole-3-carboxylate (318c):

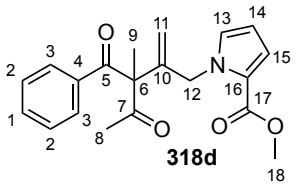


318c

Carbonate **300** (47.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-methyl-1*H*-2-carboxylate (**313b**) (30 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature

and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **318c** (40 mg, 60%) as a yellow solid. R_F 0.22 [Petrol:EtOAc 4:1]; m.p. 58–61 °C; ν_{max} (film)/cm^{-1} 2991, 1716 (C=O), 1692 (C=O), 1531; δ_H (400 MHz, $CDCl_3$) 6.96 (dd, *J* = 4.0, 1.8 Hz, 1H, **H10**), 6.86 (dd, *J* = 2.5, 1.8 Hz, 1H, **H12**), 6.18 (dd, *J* = 3.9, 2.5 Hz, 1H, **H11**), 4.95-4.92 (m, 1H, **H8a**), 4.89 (t, *J* = 1.6 Hz, 2H, **H9**), 4.38 (dt, *J* = 1.9, 0.6 Hz, 1H, **H8b**), 3.76 (s, 3H, **H15**), 2.23 (s, 6H, **H1** and **H6**), 1.64 (s, 3H, **H4**); δ_C (100 MHz, $CDCl_3$) 206.9 (**C2** and **C5**), 161.2 (**C14**), 144.3 (**C7**), 129.7 (**C12**), 121.8 (**C13**), 118.2 (**C10**), 113.9 (**C8**), 108.6 (**C11**), 70.1 (**C3**), 51.0 (**C15**), 50.0 (**C9**), 27.0 (**C1** and **C6**), 18.4 (**C4**); HRMS (ESI) Found: $[M+Na]^+$, 300.1192. $C_{15}H_{29}NO_4$ requires $[M+Na]^+$, 300.1206.

Methyl-1-(3-benzoyl-3-methyl-2-methylene-4-oxopentyl)-1*H*-pyrrole-2-carboxylate (318d):

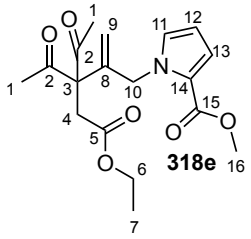


318d

Carbonate **303f** (62 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-methyl-1*H*-2-pyrrole carboxylate (**313b**) (30 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-

4:1] afforded **318d** (45 mg, 55%) as a pale yellow solid. R_F 0.75 [Petrol:EtOAc 4:1]; m.p. 91–93 °C; ν_{max} (film)/cm^{-1} 2948, 1707 (C=O), 1654; δ_H (400 MHz, $CDCl_3$) 7.95-7.92 (m, 2H, **H3**), 7.53 (tt, *J* = 7.5, 2.1 Hz, 1H, **H1**), 7.45-7.40 (m, 2H, **H2**), 6.98 (dd, *J* = 4.1, 1.9 Hz, 1H, **H13**), 6.87 (dd, *J* = 2.5, 1.9 Hz, 1H, **H15**), 6.19 (dd, *J* = 3.9, 2.6 Hz, 1H, **H14**), 5.24 (dt, *J* = 17.0, 2.4 Hz, 1H, **H12a**), 4.98-4.91 (m, 2H, **H11a** and **H12b**), 4.39-4.35 (m, 1H, **H11b**), 3.79 (s, 3H, **H18**), 2.25 (s, 3H, **H8**), 1.79 (s, 3H, **H9**); δ_C (100 MHz, $CDCl_3$) 206.1 (**C7**), 200.3 (**C5**), 161.3 (**C17**), 145.6 (**C10**), 135.3 (**C4**), 132.9 (**C1**), 129.9 (**C3**), 129.7 (**C15**), 128.3 (**C2**), 122.0 (**C16**), 118.2 (**C13**), 114.5 (**C11**), 108.7 (**C14**), 68.7 (**C6**), 51.0 (**C18**), 50.2 (**C12**), 27.4 (**C8**), 20.5 (**C9**); HRMS (ESI) Found: $[M+Na]^+$, 362.1339. $C_{20}H_{21}NO_4$ requires $[M+Na]^+$, 362.1363.

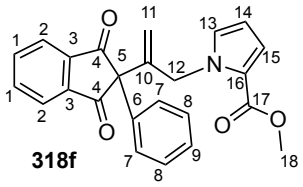
Methyl 1-(3,3-diacetyl-5-ethoxy-2-methylene-5-oxopentyl)-1*H*-pyrrole-2-carboxylate (318e):



Carbonate **303h** (61 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-methyl-1*H*-2-carboxylate (**313b**) (30 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature

and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **318e** (62 mg, 74%) as a red oil. R_F 0.15 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2952, 1733 (C=O), 1701 (C=O), 1533; δ_H (400 MHz, $CDCl_3$) 6.96 (dd, *J* = 4.0, 1.8 Hz, 1H, **H11**), 6.76 (dd, *J* = 2.6, 1.8 Hz, 1H, **H13**), 6.17 (dd, *J* = 4.0, 2.6 Hz, 1H, **H12**), 4.98 (q, *J* = 1.7 Hz, 1H, **H9a**), 4.87 (t, *J* = 1.9 Hz, 2H, **H10**), 4.36-4.32 (m, 1H, **H9b**), 4.15 (q, *J* = 7.3 Hz, 2H, **H6**), 3.75 (s, 3H, **H16**), 3.19 (s, 2H, **H4**), 2.30 (s, 6H, **H1**), 1,26 (t, *J* = 7.2 Hz, 3H, **H7**); δ_C (100 MHz, $CDCl_3$) 204.5 (**C2**), 170.8 (**C5**), 161.1 (**C15**), 142.7 (**C8**), 129.3 (**C13**), 121.7 (**C14**), 118.3 (**C11**), 115.3 (**C9**), 108.8 (**C12**), 71.6 (**C3**), 61.1 (**C6**), 51.0 (**C16**), 50.0 (**C10**), 37.4 (**C4**), 27.8 (**C1**), 14.0 (**C7**); HRMS (ESI) Found: $[M+Na]^+$, 372.1416. $C_{18}H_{23}NO_6$ requires $[M+Na]^+$, 372.1418.

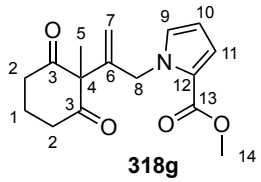
Methyl-1-(2-(1,3-dioxo-2-phenyl-2,3-dihydro-1*H*-inden-2-yl)allyl)-1H-pyrrole-2-carboxylate (318f):



Carbonate **303d** (73 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-methyl-1*H*-2-pyrrole carboxylate (**313b**) (30 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature

and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **318f** (79 mg, 85%) as an orange oil. R_F 0.40 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2948, 1699 (C=O), 1593; δ_H (400 MHz, $CDCl_3$) 8.03 (dd, *J* = 5.7, 3.1 Hz, 2H, **H2**), 7.89-7.83 (m, 2H, **H1**), 7.49-7.45 (m, 2H, **H8**), 7.39-7.34 (m, 2H, **H7**), 7.30 (tt, *J* = 7.2, 2.4 Hz, 1H, **H9**), 6.87 (dd, *J* = 4.0, 1.9 Hz, 1H, **H13**), 6.67 (dd, *J* = 2.6, 1.9 Hz, 1H, **H15**), 6.07 (dd, *J* = 3.9, 2.6 Hz, 1H, **H14**), 5.07 (t, *J* = 1.5 Hz, 2H, **H12**), 5.02 (t, *J* = 1.5 Hz, 1H, **H11a**), 4.59 (t, *J* = 1.8 Hz, 1H, **H11b**), 3.75 (s, 3H, **H18**); δ_C (100 MHz, $CDCl_3$) 198.4 (**C4**), 161.0 (**C17**), 143.4 (**C10**), 140.9 (**C3**), 136.1 (**C1**), 134.6 (**C6**), 129.3 (**C15**), 128.8 (**C8**), 128.4 (**C7**), 128.2 (**C9**), 124.0 (**C2**), 122.4 (**C16**), 118.0 (**C13**), 116.5 (**C11**), 108.6 (**C14**), 67.1 (**C5**), 51.0 (**C18**), 50.2 (**C12**); HRMS (ESI) Found: $[M+Na]^+$, 408.1186. $C_{24}H_{19}NO_4$ requires $[M+Na]^+$, 408.1206.

Methyl-1-(2-(1-methyl-2,6-dioxocyclohexyl)allyl)-1*H*-pyrrole-2-carboxylate (318g):

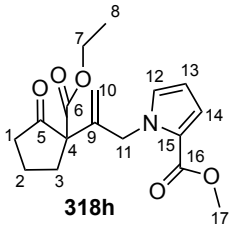


318g

Carbonate **303e** (49 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-methyl-1*H*-2-pyrrole carboxylate (**313b**) (30 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature

and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **318g** (50 mg, 72%) as a yellow solid. R_F 0.41 [Petrol:EtOAc 4:1]; m.p. 84–87 °C; ν_{max} (film)/cm^{-1} 2939, 1725 (C=O), 1690 (C=O); δ_H (400 MHz, $CDCl_3$) 6.96 (dd, *J* = 4.0, 1.8 Hz, 1H, **H9**), 6.73 (dd, *J* = 2.6, 1.8 Hz, 1H, **H11**), 6.17 (dd, *J* = 4.0, 2.6 Hz, 1H, **H10**), 4.79 (t, *J* = 1.8 Hz, 2H, **H8**), 4.77-4.75 (m, 1H, **H7a**), 4.21 (dt, *J* = 2.7, 0.8 Hz, 1H, **H7b**), 3.77 (s, 3H, **H14**), 3.03-2.94 (m, 2H, **H2a**), 2.62-2.53 (m, 2H, **H2b**), 2.27-2.18 (m, 1H, **H1a**), 1.81-1.69 (m, 1H, **H1b**), 1.42 (s, 3H, **H5**); δ_C (100 MHz, $CDCl_3$) 207.7 (**C3**), 161.1 (**C13**), 145.7 (**C6**), 129.4 (**C9**), 121.9 (**C11**), 118.3 (**C12**), 112.5 (**C7**), 108.8 (**C10**), 71.3 (**C4**), 51.1 (**C14**), 49.7 (**C8**), 39.7 (**C2**), 18.2 (**C5**), 17.6 (**C1**); HRMS (ESI) Found: $[M+Na]^+$, 312.1204. $C_{16}H_{19}NO_4$ requires $[M+Na]^+$, 312.1206.

Methyl 1-(2-(1-(ethoxycarbonyl)-2-oxocyclopentyl)allyl)-1*H*-pyrrole-2-carboxylate (318h):

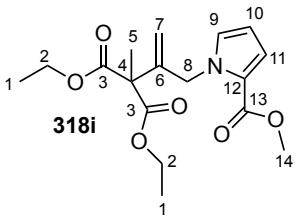


318h

Carbonate **303m** (57.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-methyl-1*H*-2-pyrrole carboxylate (**313b**) (30 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-

4:1] afforded **318h** (42 mg, 55%) as an orange oil. R_F 0.35 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2978, 1750 (C=O), 1701 (C=O); δ_H (400 MHz, $CDCl_3$) 6.95 (dd, *J* = 4.0, 1.7 Hz, 1H, **H12**), 6.84 (d, *J* = 2.8, 2.1 Hz, 1H, **H14**), 6.16 (dd, *J* = 4.1, 2.7 Hz, 1H, **H13**), 5.20 (dt, *J* = 16.9, 1.4 Hz, 1H, **H11a**), 4.90-4.95 (m, 2H, **H10a** and **H11b**), 4.34 (t, *J* = 1.6 Hz, 1H, **H10b**), 4.21-4.12 (m, 2H, **H7**), 3.76 (s, 3H, **H17**), 2.64-2.54 (m, 1H, **H1a**), 2.45-2.35 (m, 3H, **H1b** and **H3**), 2.05-1.93 (m, 2H, **H2**), 1.29 (t, *J* = 7.3 Hz, 1H, **H8**); δ_C (100 MHz, $CDCl_3$) 212.1 (**C5**), 170.0 (**C6**), 161.2 (**C16**), 142.0 (**C9**), 129.7 (**C14**), 121.9 (**C15**), 118.1 (**C12**), 113.1 (**C10**), 108.4 (**C13**), 65.1 (**C4**), 61.9 (**C7**), 51.0 (**C17**), 50.1 (**C11**), 37.8 (**C3**), 33.3 (**C1**), 19.4 (**C2**), 14.0 (**C8**); HRMS (ESI) Found: $[M+Na]^+$, 342.1284. $C_{17}H_{21}NO_5$ requires $[M+Na]^+$, 342.1312.

Diethyl-2-(3-(2-(methoxycarbonyl)-1*H*-pyrrol-1-yl)prop-1-en-2-yl)-2-methylmalonate (318i):

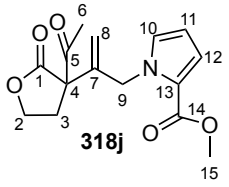


318i

Ester **303t** (61.7 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and methyl-1*H*-2-pyrrole carboxylate (**313b**) (30 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and

concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19:1-9:1] afforded **318i** (49 mg, 61%) as a clear oil. R_F 0.60 [Petrol:EtOAc 19:1]; ν_{max} (film)/cm^{-1} 2983, 1727 (C=O), 1705 (C=O); δ_H (400 MHz, $CDCl_3$) 6.95 (dd, *J* = 4.0, 1.8 Hz, 1H, **H9**), 6.88 (dd, *J* = 2.6, 2.0 Hz, 1H, **H11**), 6.17 (dd, *J* = 3.9, 2.6 Hz, 1H, **H10**), 5.18 (t, *J* = 1.6 Hz, 2H, **H8**), 5.03 (t, *J* = 1.6 Hz, 1H, **H7a**), 4.34 (t, *J* = 1.9 Hz, 1H, **H7b**), 4.25 (q, *J* = 7.0 Hz, 4H, **H2**), 3.77 (s, 3H, **H14**), 1.69 (s, 3H, **H5**), 1.30 (t, *J* = 7.1 Hz, 6H, **H1**); δ_C (100 MHz, $CDCl_3$) 170.6 (**C3**), 161.2 (**C13**), 144.2 (**C6**), 129.5 (**C11**), 122.2 (**C9**), 117.9 (**C12**), 112.9 (**C7**), 108.5 (**C10**), 61.7 (**C2**), 58.5 (**C4**), 51.0 (**C14**), 50.1 (**C8**), 20.8 (**C5**), 14.0 (**C1**); HRMS (ESI) Found: $[M+Na]^+$, 360.1407. $C_{17}H_{23}NO_6$ requires $[M+Na]^+$, 360.1418.

Methyl 1-(2-(3-acetyl-2-oxotetrahydrofuran-3-yl)allyl)-1*H*-pyrrole-2-carboxylate (318j):

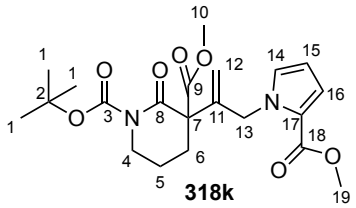


318j

Carbonate **303p** (50.5 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and methyl-1*H*-2-pyrrole carboxylate (**313b**) (30 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature

and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **318j** (69 mg, 99%) as a brown oil. R_F 0.67 [Petrol:EtOAc 2:1]; ν_{max} (film)/cm^{-1} 2922, 1761 (C=O), 1701 (C=O), 1533; δ_H (400 MHz, $CDCl_3$) 6.98 (dd, *J* = 4.0, 1.8 Hz, 1H, **H10**), 6.81 (dd, *J* = 2.6, 1.9 Hz, 1H, **H12**), 6.19 (dd, *J* = 3.9, 2.6 Hz, 1H, **H11**), 5.24-5.22 (m, 1H, **H8a**), 5.06 (dt, *J* = 17.0, 1.8 Hz, 1H, **H9a**), 4.83 (dt, *J* = 16.9, 1.7 Hz, 1H, **H9b**), 4.47-4.45 (m, 1H, **H8b**), 4.30 (ddd, *J* = 13.1, 7.9, 5.2 Hz, 1H, **H2a**), 4.25-4.18 (m, 1H, **H2b**), 3.76 (s, 3H, **H15**), 3.04 (ddd, *J* = 13.2, 7.2, 5.3 Hz, 1H, **H3a**), 2.53-2.45 (m, 1H, **H3b**), 2.41 (s, 3H, **H6**); δ_C (100 MHz, $CDCl_3$) 200.6 (**C5**), 173.0 (**C1**), 161.2 (**C14**), 141.5 (**C7**), 129.6 (**C12**), 121.7 (**C13**), 118.6 (**C10**), 114.8 (**C8**), 108.8 (**C11**), 66.1 (**C2**), 65.7 (**C4**), 51.1 (**C15**), 50.1 (**C9**), 30.2 (**C3**), 25.7 (**C6**); HRMS (ESI) Found: $[M+Na]^+$, 314.0986. $C_{15}H_{17}NO_5$ requires $[M+Na]^+$, 314.0999.

1-*tert*-Butyl-3-methyl-3-(3-(2-(methoxycarbonyl)-1*H*-pyrrol-1-yl)prop-1-en-2-yl)-2-oxopiperidine-1,3-dicarboxylate (318k):

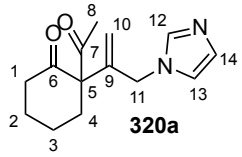


318k

Carbonate **303r** (81 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and methyl-1*H*-2-pyrrole carboxylate (**313b**) (30 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The

mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 4:1] afforded **318k** (57 mg, 56%) as a light brown oil. R_F 0.12 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2953, 1701 (C=O), 1533; δ_H (400 MHz, $CDCl_3$) 6.96 (dd, *J* = 4.0, 1.8 Hz, 1H, **H15**), 6.93 (dd, *J* = 2.6, 1.9 Hz, 1H, **H16**), 6.17 (dd, *J* = 3.9, 2.6 Hz, 1H, **H14**), 5.26 (dt, *J* = 17.0, 2.0 Hz, 1H, **H13a**), 5.04-5.02 (m, 1H, **H12a**), 4.91 (dt, *J* = 16.7, 1.4 Hz, 1H, **H13b**), 4.39-4.38 (m, 1H, **H12b**), 3.80 (s, 3H, **H19**), 3.76 (s, 3H, **H10**), 3.72-3.65 (m, 2H, **H4**), 2.53-2.43 (m, 1H, **H6a**), 2.27 (ddd, *J* = 13.2, 6.1, 3.9 Hz, 1H, **H6b**), 2.02-1.86 (m, 2H, **H5**); δ_C (100 MHz, $CDCl_3$) 170.7 (**C8**), 169.1 (**C9**), 161.3 (**C18**), 153.1 (**C3**), 143.2 (**C11**), 130.0 (**C15**), 121.8 (**C17**), 118.1 (**C14**), 114.2 (**C12**), 108.6 (**C16**), 83.3 (**C2**), 62.3 (**C7**), 53.0 (**C19**), 51.0 (**C10**), 49.9 (**C13**), 46.2 (**C4**), 28.6 (**C6**), 27.9 (**C1**), 19.0 (**C5**); HRMS (ESI) Found: $[M+Na]^+$, 443.1771. $C_{21}H_{28}N_2O_7$ requires $[M+Na]^+$, 443.1789.

2-(3-(1*H*-Imidazol-1-yl)prop-1-en-2-yl)-2-acetylcyclohexanone (320a):

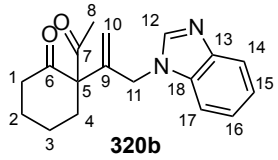


320a

Carbonate **266** (53.3 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and imidazole (16.3 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube

was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [EtOAc:EtOAc + 1% Et_3N] afforded **320a** (29 mg, 49%) as an orange solid. R_F 0.23 [EtOAc]; m.p. 92–94 °C; ν_{max} (film)/cm^{-1} 3386, 3117, 2946, 2924, 2873, 1695 (C=O), 1641, 1507; δ_H (400 MHz, $CDCl_3$) 7.43 (t, *J* = 1.1 Hz, 1H, **H13**), 7.03 (t, *J* = 1.2 Hz, **H14**), 6.87 (t, *J* = 1.3 Hz, 1H, **H12**), 5.14 (q, *J* = 0.8 Hz, 1H, **H10a**), 4.92-4.91 (m, 1H, **H10b**), 4.61 (dt, *J* = 16.6, 1.1 Hz, 1H, **H11a**), 4.36 (dt, *J* = 16.8, 1.1 Hz, 1H, **H11b**), 2.56-2.40 (m, 3H, **H1** and **H4a**), 2.10 (s, 3H, **H8**), 2.0-1.91 (m, 2H, **H2a** and **H4b**), 1.87-1.78 (m, 1H, **H3a**), 1.77-1.66 (m, 1H, **H2b**), 1.64-1.54 (m, 1H, **H3b**); δ_C (100 MHz, $CDCl_3$) 208.5 (**C6**), 207.6 (**C7**), 142.8 (**C9**), 137.9 (**C13**), 129.5 (**C14**), 119.6 (**C12**), 117.1 (**C10**), 72.3 (**C5**), 48.7 (**C11**), 41.0 (**C1**), 33.4 (**C4**), 26.8 (**C2**), 26.0 (**C8**), 21.9 (**C3**); HRMS (ESI) Found: $[M+H]^+$, 247.1441. $C_{14}H_{18}N_2O_2$ requires $[M+H]^+$, 247.1441.

2-(3-(1*H*-Benzo[d]imidazol-1-yl)prop-1-en-2-yl)-2-acetylcyclohexanone (320b):

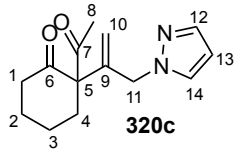


320b

Carbonate **266** (53.3 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and benzimidazole (28.3 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at

120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [EtOAc + 1% Et_3N] afforded **320b** (30 mg, 42%) as an orange solid. R_F 0.10 [Petrol:EtOAc 1:1]; m.p. 90–92 °C; ν_{max} (film)/cm^{-1} 3093, 2958, 2942, 2860, 1697 (C=O), 1645, 1615; δ_H (400 MHz, $CDCl_3$) 7.89 (s, 1H, **H12**), 7.82-7.78 (m, 1H, **H14**), 7.50-7.45 (m, 1H, **H15**), 7.33-7.26 (m, 2H, **H16** and **H17**), 5.07 (q, *J* = 1.2 Hz, 1H, **H10a**), 4.91 (dt, *J* = 17.5, 1.5 Hz, 1H, **H11a**), 4.69 (q, *J* = 0.8 Hz, 1H, **H10b**), 4.60 (dt, *J* = 17.5, 1.6 Hz, 1H, **H11b**), 2.64-2.48 (m, 3H, **H1** and **H4a**), 2.23 (s, 3H, **H8**), 2.09-1.97 (m, 2H, **H2a** and **H4b**), 1.93-1.86 (m, 1H, **H3a**), 1.83-1.73 (m, 1H, **H2b**), 1.73-1.60 (m, 1H, **H3b**); δ_C (100 MHz, $CDCl_3$) 208.5 (**C6**), 206.7 (**C7**), 143.7 (**C12**), 143.5 (**C18**), 141.3 (**C9**), 133.9 (**C13**), 123.3 (**C15**), 122.2 (**C16**), 120.2 (**C14**), 115.9 (**C10**), 110.2 (**C17**), 72.2 (**C5**), 46.7 (**C11**), 41.1 (**C1**), 33.6 (**C4**), 26.9 (**C2**), 26.2 (**C8**), 22.1 (**C3**); HRMS (ESI) Found: $[M+H]^+$, 297.1598. $C_{18}H_{20}N_2O_2$ requires $[M+H]^+$, 297.1598.

2-(3-(1*H*-Pyrazol-1-yl)prop-1-en-2-yl)-2-acetylcyclohexanone (320c):

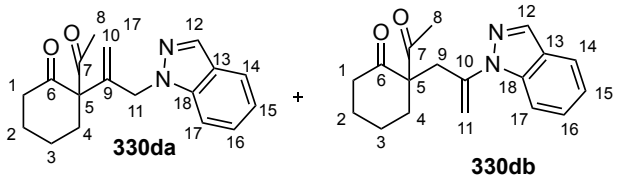


320c

Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and pyrazole (16.3 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube

was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 1:1 + 1% Et_3N-EtOAc + 1% Et_3N] afforded **320c** (30 mg, 51%) as a yellow solid. R_F 0.14 [Petrol:EtOAc 1:1]; m.p. 61–63 °C; ν_{max} (film)/cm^{-1} 2935, 1699 (C=O), 1558; δ_H (400 MHz, $CDCl_3$) 7.50 (dd, *J* = 1.8, 0.5 Hz, 1H, **H14**), 7.41 (dd, *J* = 2.5, 0.6 Hz, 1H, **H12**), 6.25 (t, *J* = 2.1 Hz, 1H, **H13**), 5.12 (t, *J* = 0.9 Hz, 1H, **H10a**), 4.97 (t, *J* = 1.5 Hz, 1H, **H10b**), 4.81 (dt, *J* = 16.3, 1.2 Hz, 1H, **H11a**), 4.66 (dt, *J* = 16.3, 1.1 Hz, 1H, **H11b**), 2.51 (dd, *J* = 7.7, 6.0 Hz, 2H, **H1**), 2.44-2.36 (m, 1H, **H4a**), 2.12 (s, 3H, **H8**), 2.06-1.98 (m, 1H, **H4b**), 1.96-1.87 (m, 1H, **H2a**), 1.86-1.68 (m, 2H, **H2b** and **H3a**), 1.67-1.55 (m, 1H, **H3b**); δ_C (100 MHz, $CDCl_3$) 208.9 (**C6**), 207.0 (**C7**), 142.6 (**C9**), 139.6 (**C14**), 130.5 (**C12**), 117.9 (**C10**), 105.9 (**C13**), 72.3 (**C5**), 54.1 (**C11**), 41.0 (**C1**), 33.1 (**C4**), 26.9 (**C2**), 26.3 (**C8**), 21.8 (**C3**); HRMS (ESI) Found: $[M+Na]^+$, 269.1267. $C_{14}H_{18}N_2O_2$ requires $[M+Na]^+$, 269.1261.

2-(3-(1*H*-indazol-1-yl)prop-1-en-2-yl)-2-acetylcyclohexanone and **2-(2-(1*H*-indazol-1-yl)allyl)-2-acetylcyclohexanone (320da** and **320db):**

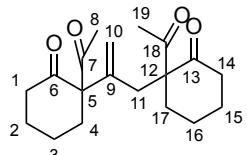


Carbonate **266** (53.1 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and indazole (28.3 mg, 0.24 mmol) were

added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 1:1 + 1% Et_3N-EtOAc +1% Et_3N] afforded an inseparable 1.8:1 mixture of **320da** and **320db** (35.5 mg, 50%) as a yellow solid. R_F 0.25 [Petrol:EtOAc 1:1]; m.p. 66–68 °C; ν_{max} (film)/cm^{-1} 2944, 1701 (C=O), 1643; δ_H (400 MHz, $CDCl_3$, resonances due to the **320db** annotated by an asterisk) 8.02 (d, *J* = 1.0 Hz, 1H, **H12**), 7.99 (dd, *J* = 1.0 Hz, 1H*, **H12**), 7.74-7.69 (m, 1H, **H17**), 7.74-7.69 (m, 1H*, **H17**), 7.64 (dt, *J* = 8.5, 1.0 Hz, 1H*, **H15**), 7.57 (dd, *J* = 8.6, 1.0 HZ, 1H, **H15**), 7.41-7.36 (m, 1H, **H16**), 7.29-7.23 (m, 1H*, **H16**), 7.17-7.12 (m, 1H, **H14**), 7.09-7.04 (m, 1H*, **H14**), 5.15 (s, 1H*, **H11a**), 5.12-5.05 (m, 1H, **H10a**), 5.12-5.05 (m, 1H*, **H9a**), 5.02 (s, 1H, **H11a**), 4.98-4.93 (m, 1H*, **H11b**), 4.90-4.84 (m, 1H*, **H9b**), 4.87 (dt, *J* = 17.3, 1.5 Hz, 1H, **H11b**), 4.61 (t, *J* = 1.8 Hz, 1H, **H10b**), 2.57 (dd, *J* = 7.9, 6.3 Hz, 2H, **H1**), 2.56-2.51 (m, 2H*, **H1**), 2.48-2.40 (m, 1H*, **H3a**), 2.47-2.40 (m, 1H, **H3a**), 2.19 (s, 3H, **H8**), 2.16-2.10 (m, 1H, **H3b**), 2.16 (s, 3H*, **H8**), 2.07-1.99 (m, 1H*, **H3b**), 1.99-1.91 (m, 1H, **H4a**), 1.99-1.91 (m, 1H*, **H4a**), 1.90-1.74 (m, 2H, **H2a** and **H4b**), 1.89-1.73 (m, 2H*, **H2a** and **H4b**), 1.75-1.55 (m, 1H, **H2b**), 1.75-1.55 (m, 1H*, **H2b**); δ_C (100 MHz, $CDCl_3$, resonances due to the **320db** annotated by an asterisk) 208.9 (**C6**), 208.8 (**C6***), 207.0 (**C7**), 207.0 (**C7***), 148.9 (**C10***), 142.0 (**C18***), 141.8 (**C9**), 139.2 (**C18**), 133.6 (**C12**), 126.6 (**C16**), 126.0 (**C16***), 124.1 (**C12***), 124.0 (**C13**), 122.0 (**C13***), 121.9 (**C14***), 120.9 (**C17**), 120.8 (**C15**), 120.2 (**C15***), 118.0 (**C11***), 117.4

(**C17***), 116.3 (**C10**), 109.7 (**C14**), 72.5 (**C5***), 72.2 (**C5**), 55.5 (**C9***), 51.1 (**C11**), 41.0 (**C1**), 41.0 (**C1***), 33.2 (**C3**), 33.2 (**C3***), 27.0 (**C4**), 26.9 (**C4***), 26.3 (**C8**), 26.3 (**C8***), 21.9 (**C2**), 21.9 (**C2***); HRMS (ESI) Found: $[M+Na]^+$, 319.1414. $C_{18}H_{20}N_2O_2$ requires $[M+Na]^+$, 319.1417.

2,2'-(Prop-2-ene-1,3-diyl)bis(2-acetylcyclohexan-1-one) (305):



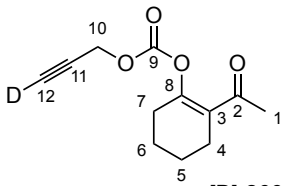
305

Carbonate **315** (48mg, 0.24 mmol) $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 2-acetylcyclohexanone (31 µL, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded **305** (32 mg, 88%) as a 1.2:1 mixutre of diastereoisomers rather than the desired cross-coupled product **316**. R_F 0.32 [Petrol:EtOAc 4:1]; m.p. 123–126 ^oC; ν_{max} (film)/cm^{-1} 2931, 2848, 1697 (C=O); δ_H (400 MHz, $CDCl_3$, resonances due to the the diastereoisomer of **305b** annotated by an asterisk) 5.03-4.99 (m, 1H and 1H*, **H10a** and **H10a***), 4.93 (s, 1H and 1H*, **H10b** and **H10b***), 2.68-2.24 (m, 8H and 8H*, **H1, H4**, **H11** and **H14, H1***, **H4***, **H11*** and **H14***), 2.22, 2.19 and 2.18 (s, 6H and 6H* **H8** and **H19**, **H8*** and **H19***), 2.14-2.06 (m, 1H and

1H* **H17a** and **H17a***), 2.00-1.82 (m, 2H and 2H*, **H2a** and **H2a* H17b** and **H17b***), 1.78-1.54 (m, 7H and 7H*, **H2b, H3**, **H15**, **H16** and **H2b***, **H3***, **H15*** and **H16***); δ_C (100 MHz, $CDCl_3$, resonances due to the the diastereoisomer of **305b** annotated by an asterisk) 210.0 (**C1***), 209.9 (**C1**), 209.8 (**C13***), 209.7 (**C13**), 209.1 (**C7**), 209.1 (**C7***), 208.3 (**C14**), 207.9 (**C14***), 140.6 (**C9***), 140.3 (**C9**), 117.3 (**C10**), 117.0 (**C10***), 73.9 (**C5**), 73.8 (**C5***), 67.0 (**C12**), 66.9 (**C12***), 41.3 (**C1***), 41.0 (**C1**), 41.0 (**C14***), 41.0 (**C14**), 37.1 (**C11**), 36.6 (**C11***), 36.2 (**C4**), 35.3 (**C4***), 33.3 (**C17***), 33.1 (**C17**), 27.5 (**C3***), 27.4 (**C3**), 27.2 (**C16**), 27.1 (**C16***), 26.7 (**C8**), 26.6 (**C8***), 26.5 (**C19**), 26.3 (**C19***), 21.9 (**C15***), 21.8 (**C15**), 21.8 (**C2**), 21.7 (**C2***); HRMS (ESI) Found: $[M+H]^+$, 319.1906. $C_{19}H_{26}O_4$ requires $[M+H]^+$, 319.1904.

10.2.7. Mechanistic Studies

***d*$_1$-2-Acetylcyclohex-1-enyl prop-2-ynyl carbonate ([D]-266):**

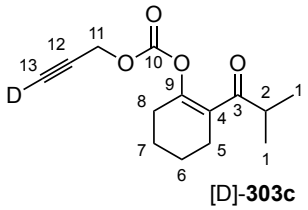


[D]-**266**

According to a literature procedure,[117] to a solution of propargyl carbonate (333 mg, 1.5 mmol) in acetonitrile (8 mL) was added solid potassium carbonate (310 mg, 2.25 mmol). The suspension was stirred at room temperature for 30 minutes. Deuterium oxide (2 mL) was added *via* syringe and the solution was stirred at room temperature for 1 hour. The mixture was extracted with CH_2Cl_2 (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford deuterated alkyne [D]-**266** (300 mg, 90%) as a pale yellow oil. Analysis

by ^{1}H NMR spectroscopy indicated 97% deuterium incorporation. ν_{max} (film)/cm^{-1} 2940, 1988 (C–D), 1757 (C=O), 1649; δ_H (400 MHz, $CDCl_3$) 4.78 (s, 2H, **H10**), 2.37-2.31 (m, 4H, **H4** and **H7**), 2.28 (s, 3H, **H1**), 1.77-1.59 (m, 4H, **H5** and **H6**). HRMS (ESI) Found: $[M+Na]^+$, 246.0844. $C_{12}H_{13}DO_2$ requires $[M+Na]^+$, 246.0847. Synthesis of this compound has been reported in the literature.[117]

***d*$_1$-2-*iso*-Butyrylcyclohex-1-en-1-yl-Prop-2-yn-1-yl-3 ([D]-303c):**

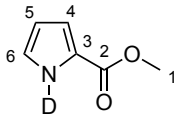


[D]-**303c**

To a solution of propargyl carbonate **303c** (203 mg, 0.81 mmol) in acetonitrile (8 mL) was added solid potassium carbonate (167 mg, 1.20 mmol). The suspension was stirred at room temperature for 30 minutes. Deuterium oxide (2 mL) was added *via* syringe and the mixture was stirred at room temperature for 1 hour. The mixture was extracted with CH_2Cl_2 (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford deuterated alkyne [D]-**303c** (170 mg, 83%) as a pale yellow oil. Analysis by ^{1}H NMR spectroscopy indicated 96% deuterium incorporation. R_F 0.54 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2935, 2564, 1975 (C–D), 1793, 1692 (C=O); δ_H (400 MHz, $CDCl_3$) 4.78 (s, 2H, **H11**), 2.93 (sept, J = 7.0 Hz, 1H, **H2**), 2.41-2.31 (m, 4H, **H5** and **H8**), 1.80-1.64 (m, 4H, **H6** and **H7**), 1.07 (d, J = 6.9 Hz, 6H, **H1**); δ_C (100 MHz, $CDCl_3$) 206.6 (**C3**), 151.8 (**C10**), 150.6 (**C9**), 76.2 (**C12**), 76.0 (**C13**), 55.9 (**C11**), 39.1 (**C2**), 27.6 (**C5**),

25.7 (**C8**), 22.2 (**C7**), 21.7 (**C6**), 18.3 (**C1**); HRMS (ESI) Found: $[M+Na]^+$, 274.1153. $C_{14}H_{17}DO_4$ requires $[M+Na]^+$, 274.1160.

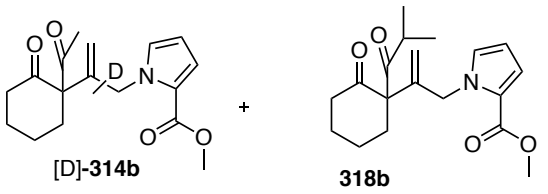
d$_1$-Methyl 1*H*-pyrrole-2-carboxylate-1 ([D]-313b):



[D]-**313b**

A suspension of sodium hydride (60 wt % in mineral oil, 70 mg, 1.75 mmol) in tetrahydrofuran (10 mL) was cooled to 0 °C. A solution of pyrrole **313b** (200 mg, 1.6 mmol) in tetrahydrofuran (5 mL) was added dropwise, and the mixture was stirred at 0 °C for 30 min. Deuterium oxide (2 mL) was added dropwise, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (10 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford [D]-**313b** (152 mg, 76%) as a purple solid. Analysis by ^{1}H NMR spectroscopy indicated 68% deuterium incorporation. R_F 0.60 [Petrol:EtOAc 4:1]; m.p. 74–77 °C; ν_{max} (film)/cm^{-1} 3287, 2924, 2458 (N–D), 1668, 1530; δ_H (400 MHz, $CDCl_3$) 9.09 (br s, 0.32H, **H7**), 6.96 (dd, *J* = 2.7, 1.5 Hz, 1H, **H5**), 6.92 (dd, *J* = 3.7, 1.5 Hz, 1H, **H6**), 6.27 (dd, *J* = 3.7, 2.6 Hz, 1H, **H4**), 3.86 (s, 3H, **H1**); δ_C (75 MHz, $CDCl_3$) 161. (**C2**), 122.8 (**C6**) 122.6 (**C3**), 115.2 (**C6**), 110.4 (**C4**), 51.4 (**C1**).

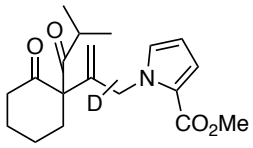
***d*$_1$-Methyl-1-(2-(1-acetyl-2-oxocyclohexyl)allyl)-1*H*-pyrrole-2-carboxylate** and **Methyl-1-(2-(1-*iso*butyryl-2-oxocyclohexyl)allyl)-1*H*-pyrrole-2-carboxylate ([D]-314b** and **318b):**



[D]-**314b** **318b**

[D]-**266** (26.8 mg, 0.12 mmol), carbonate **303c** (30 mg, 0.12 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol), Xantphos (13.9 mg, 0.024 mmol) and 3-methyl-2-pyrrole-1*H*-carboxylate (**313b**) (30 mg, 0.24 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1-4:1] afforded [D]-**314b** (27 mg, 74%) and **318b** (24.5 mg 62%). [D]-**314b**: ν_{max} (film)/cm^{-1} 2946, 1694 (C=O), 1531; HRMS (ESI) Found: $[M+Na]^+$, 327.1425. $C_{17}H_2DNO_4$ requires $[M+Na]^+$, 327.1426. **318b**: HRMS (ESI) Found: $[M+Na]^+$, 354.1666. $C_{19}H_{25}NO_4$ requires $[M+Na]^+$, 354.1676.

d_1-Methyl 1-(2-(1-*iso*butyryl-2-oxocyclohexyl)allyl)-1*H*-pyrrole-2-carboxylate ([D]-318b):



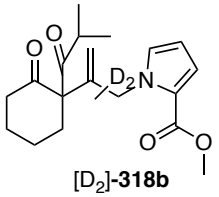
[D]-**318b**

Deuterated carbonate [D]-**303c** (60 mg, 0.24 mmol), pyrrole (**313b**) (30 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol) and Xantphos (13.9 mg, 0.024 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1–4:1] afforded [D]-**318b** (46 mg, 58%). Analysis by ^{1}H NMR spectroscopy indicated 48% deuterium incorporation at the vinylic position and 48% at the allylic position. HRMS (ESI) Found: $[M+Na]^+$, 355.1727. $C_{19}H_{24}DNO_4$ requires $[M+Na]^+$, 355.1739.

[D]-**318b** was also obtained by the reaction of carbonate **303c** (60 mg, 0.24 mmol) with deuterated pyrrole [D]-**313b** (30 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol) and Xantphos (13.9 mg, 0.024 mmol), which were added to a dried tube under argon. Toluene (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 120 °C. The mixture was stirred at 120 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*.

Flash column chromatography [Petrol:EtOAc 9:1–4:1] afforded [D]-**318b** (50 mg, 63%). Analysis by ^{1}H NMR spectroscopy indicated 27% deuterium incorporation at the vinylic position and 23% at the allylic position. HRMS (ESI) Found: $[M+Na]^+$, 355.1752. $C_{19}H_{24}DNO_4$ requies $[M+Na]^+$, 355.1739.

d$_2$-Methyl 1-(2-(1-Isobutyryl-2-oxocyclohexyl)allyl)-1*H*-pyrrole-2-carboxylate ([D$_2$]-318b)

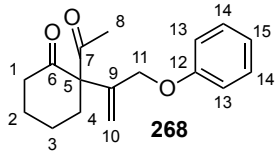


[D$_2$]-**318b**

Deuterated carbonate [D]-**303c** (60 mg, 0.24 mmol), pyrrole [D]-**313b** (30 mg, 0.24 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol) and Xantphos (13.9 mg, 0.024 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. 1,4-Dioxane (1.5 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo.* Flash column chromatography [Petrol:EtOAc 9:1–4:1] afforded [D$_2$]-**318b** (52 mg, 65%). Analysis by ^{1}H NMR spectroscopy indicated 75% deuterium incorporation at the vinylic position and 82% at the allylic position. HRMS (ESI) Found: $[M+Na]^+$, 356.1790. $C_{19}H_{23}D_2NO_4$ requires $[M+Na]^+$, 356.1801.

10.2.8. Synthesis of Compounds for Enantioselective Structures

2-Acetyl-2-(3-phenoxyprop-1-en-2-yl)cyclohexanone (268):

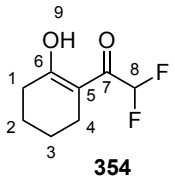


Carbonate **266** (35.5 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), Xantphos (9.2 mg, 0.0160 mmol) and phenol (15 mg, 0.16 mmol) were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Dioxane (1 mL) was added and the sealed tube was added to an oil bath preheated to 80 °C. The mixture was stirred at 80 °C for 2 hours, then cooled to room temperature and concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 9:1] afforded **268** (41 mg, 71%, *r.r.* > 19:1) as a colourless oil. R_F 0.40 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2939, 2111, 1697 (C=O), 1597; δ_H (400 MHz, $CDCl_3$) 7.31-7.25 (m, 2H, **H14**), 6.96 (tt, *J* = 7.4 Hz, 1H, **H15**), 6.91-6.86 (m, 2H, **H13**), 5.68 (t, *J* = 1.2 Hz, 1H, **H10a**), 5.23 (s, 1H, **H10b**), 4.58 (dt, *J* = 12.3, 1.0 Hz, 1H, **H11a**), 4.48 (dd, *J* = 12.2, 0.8 Hz, 1H, **H11b**), 2.67-2.59 (m, 1H, **H1a**), 2.55-2.48 (m, 1H, **H1b**), 2.46-2.39 (m, 1H, **H4a**), 2.26 (s, 3H, **H8**), 2.15-2.07 (m, 1H, **H4b**),1.93-1.82 (m, 2H, **H2**), 1.82-1.66 (m, 2H, **H3**); δ_C (100 MHz, $CDCl_3$) 209.1 (**C6**), 206.7 (**C7**), 158.2 (**C12**), 142.2 (**C9**), 129.5 (**C14**), 121.2 (**C15**), 119.4 (**C10**), 114.6 (**C13**), 71.6 (**C5**), 69.2 (**C11**), 40.8 (**C1**), 32.4 (**C4**), 27.3 (**C8**), 27.1 (**C2**), 21.8 (**C3**); HRMS (ESI) Found: $[M+H]^+$, 273.1475. $C_{17}H_{20}O_3$ requires $[M+H]^+$, 273.1485. Synthesis of this compound has been reported in the literature.[117]

The formation of **268** was also carried out under enantioselective conditions: Carbonate **266** (35.5 mg, 0.16 mmol), $Pd_2(dba)_3$ (7.3 mg, 0.008 mmol), (*R*)-Xylyl-P-PHOS **L19** (7.3 mg, 0.0096 mmol) and phenol (15 mg, 0.16 mmol), were added to a dried tube under argon. The tube was fitted with a septum and purged further with argon. Tetrahydrofuran (1 mL) was added and the sealed tube was stirred at 60 °C for 2 hours, then concentrated *in vacuo*. Flash column chromatography [Petrol:EtOAc 19;1-9:1] afforded **268** (19 mg, 44% yield, *r.r.* > 19:1). Chiral HPLC: AD-H column, 1 mL/min, 9:1 Hexane:IPA, t_A (major) = 6.0 min, t_B (minor) = 6.5 min, 19% ee. $[\alpha]_D^{25}$ +0.8 (*c* 0.1, $CHCl_3$, 19% ee).

10.2.9. Synthesis of Compounds for Intramolecular Cyclisation Studies

2,2-Difluoro-1-(2-hydroxycyclohex-1-enyl)ethanone (354):

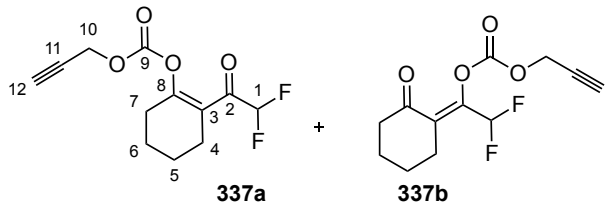


354

To a suspension of sodium hydride (60 wt% mineral oil, 440 mg, 11 mmol) in tetrahydrofuran (25 mL) was added a solution of cyclohexanone (1.03 mL, 10 mmol) in tetrahydrofuran (10 mL) dropwise and the mixture was stirred at room temperature temperature for 75 minutes. The reaction was cooled to 0 ^oC and methyl difluoroacetate (0.97 mL, 11 mmol) was added dropwise over a period of 15 minutes and the reaction mixture was warmed to room temperature and stirred at that temperature for 24 hours. The reaction was

quenched by the addition of aq. NH_4Cl (30 mL) and aq. HCl (1 N, 30 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Petrol:Et_2O 199:1] afforded **354** (401 mg, 50%) as a clear oil. R_F 0.72 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 2942, 1572 (C=O); δ_H (400 MHz, $CDCl_3$) 15.25 (s, 1H, **H9**), 6.06 (t, J = 52.3 Hz, 1H, **H8**), 2.48-2.43 (m, 4H, **H1** and **H4**), 1.80-1.71 (m, 4H, **H2** and **H3**); δ_C (100 MHz, $CDCl_3$) 188.8 (**C6**), 184.1 (J = 22.7 Hz, **C7**), 110.2 (J = 240.7 Hz, **C8**), 105.8 (**C5**), 31.8 (**C1**), 22.2 (**C4**), 21.6 (**C2**), 20.9 (**C3**); HRMS (ESI) Found: $[M+H]^+$, 177.0719. $C_{18}H_{11}F_2O_6$ requires $[M+Na]^+$, 177.0722. Synthesis of this compound has been reported in the literature.[142]

2-(2,2-Difluoroacetyl)cyclohex-1-enyl prop-2-ynyl carbonate (337a) and **(*Z*)-2,2-Difluoro-1-(2-oxocyclohexylidene)ethyl prop-2-ynyl carbonate (337b):**



337a **337b**

To a solution of **354** (120 mg, 0.68 mmol) in tetrahydrofuran (13 mL) was added potassium *tert*-butoxide (83 mg, 0.75 mmol). Propargyl chloroformate (0.073 mL, 0.75 mmol) was added dropwise upon stirring and the reaction mixture was stirred at room temperature for 18 hours. The reaction was quenched with aqueous NH_4Cl (30 mL) and aq. HCl (1 N, 30 mL), and the

mixture was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford an inseparable mixture of **337a** and **337b** (134 mg, 76% yield) as a yellow solid. R_F 0.71 [Petrol:EtOAc 4:1]; ν_{max} (film)/cm^{-1} 3257, 2950, 2125 (C≡C), 1769, 1646 (C=O); δ_H (400 MHz, $CDCl_3$, resonances due to **337a** quoted) 6.20 (t, *J* = 52.7 Hz, 1H, **H1**), 4.81 (d, *J* = 1.6 Hz, 2H, **H10**), 2.59 (t, *J* = 2.4 Hz, 2H, **H12**), 2.54-2.50 (m, 2H, **H7**), 2.42-2.39 (m, 2H, **H4**), 1.81-1.75 (M, 2H, **H6**), 1.72-1.65 (m, 2H, **H5**); δ_C (100 MHz, $CDCl_3$, resonances due to **337a** quoted) 187.2 (*J* = 22.5 Hz, **C2**), 159.1 (**C8**), 150.8 (**C9**), 122.5 (**C3**), 109.4 (*J* = 242.3 Hz, **C1**), 76.5 (**C12**), 75.9 (**C11**) 56.4 (**C10**), 28.3 (**C7**), 23.8 (**C4**), 21.8 (**C6**) 21.1 (**C5**); HRMS (ESI) Found: $[M+NH_4]^+$, 276.1044. $C_{12}H_{12}F_2O_4$ requires $[M+NH_4]^+$, 276.1042.

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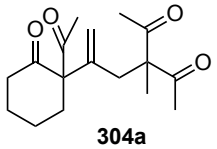
12. Appendices

12.1.1. Crystal Structure of 304a.

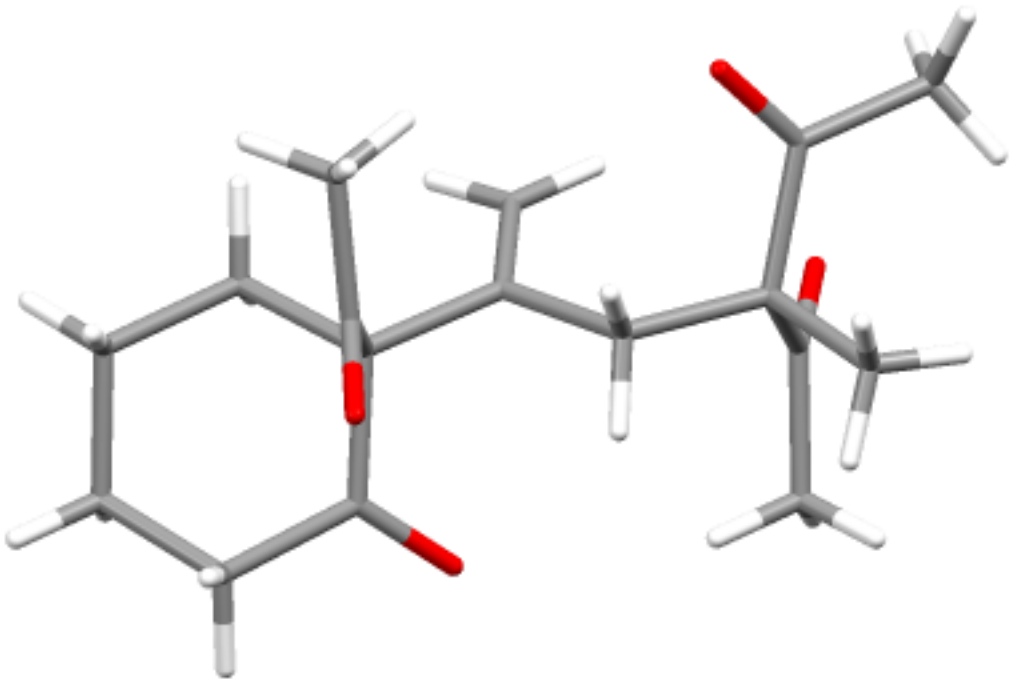


304a

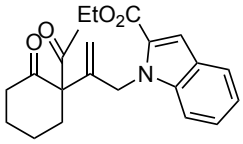
314a (CCDC 1411246).

Identification code	**2015ncs0412a**
Empirical formula	$C_{17}H_{24}O_4$
Formula weight	292.36
Temperature	100(2) K
Wavelength	0.6889 Å
Crystal system	Monoclinic
Space group	*P*21/*n*
Unit cell dimensions	a = 6.0924(2) Å α = 90°
	b = 27.0824(6) Å β = 97.770(2)°
	c = 9.3335(2) Å γ = 90°
Volume	1525.86(7) Å^3
Z	4 0.083 mm^{-1}
Density (calculated)	1.273 Mg / m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	632.0
Crystal	Chip; colourless
Crystal size	0.03 × 0.03 × 0.01 mm^3
θ range for data collection	2.256 – 31.788°
Index ranges	$-9 \le h \le 9$, $-40 \le k \le 41$, $-14 \le l \le 13$
Reflections collected	30947
Independent reflections	5401 [R_{int} = 0.0605]
Completeness to θ = 24.415°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	1.00000 and 0.81133
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5401 / 0 / 194
Goodness-of-fit on F^2	1.035

Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0486, *wR2* = 0.1144
R indices (all data)	*R1* = 0.0674, *wR2* = 0.1282
Extinction coefficient	n/a
Largest diff. peak and hole	0.464 and −0.347 e Å^{-3}



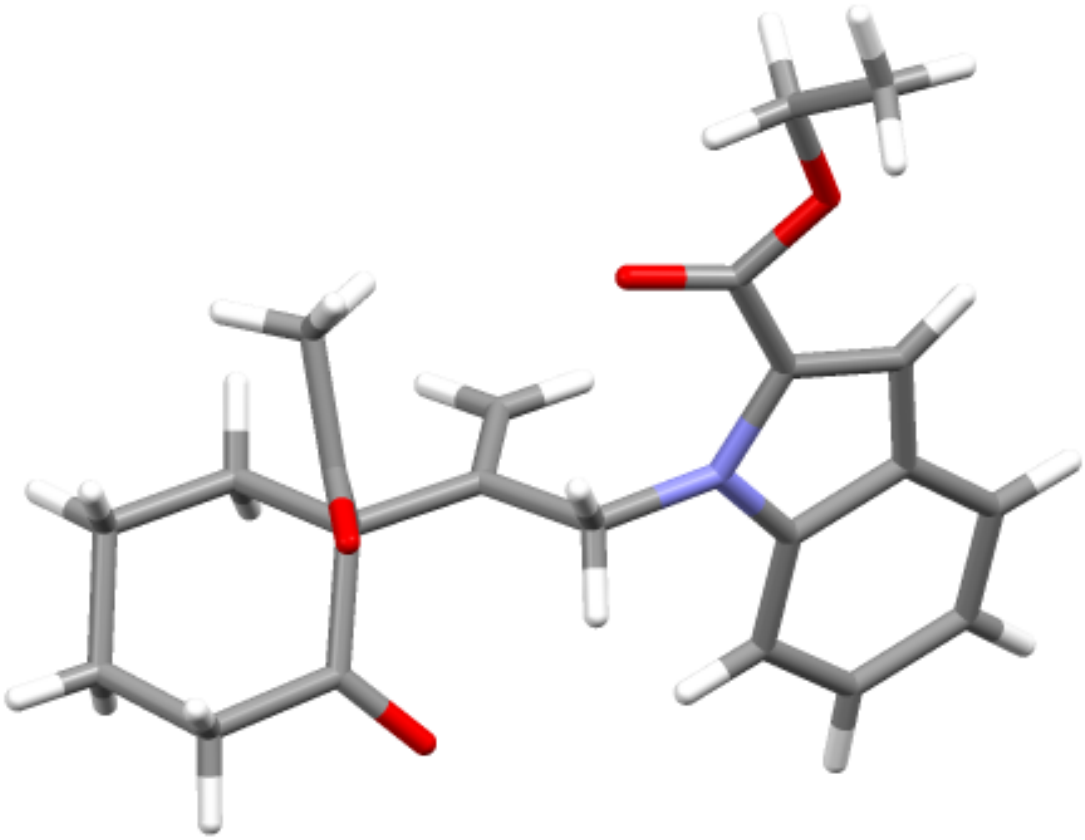
12.1.2. Crystal Structure of 312d



312d

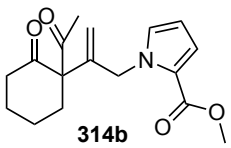
322d (CCDC 1443121)

Identification code	**VF101**
Empirical formula	$C_{22}H_{25}NO_4$
Formula weight	367.43
Temperature/K	179.98(10)
Crystal system	triclinic
Space group	P-1
a/Å	7.6750(3)
b/Å	10.0757(4)
c/Å	12.4531(5)
α/°	87.781(3)
β/°	84.683(3)
γ/°	82.145(3)
Volume/Å^3	949.54(6)
Z	2
ρ_{calc} g/cm^3	1.285
μ/mm^{-1}	0.713
F(000)	392.0
Crystal size/mm^3	0.341 × 0.294 × 0.251
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.132 to 154.874
Index ranges	-9 ≤ h ≤ 9, -12 ≤ k ≤ 12, -15 ≤ l ≤ 15
Reflections collected	23526
Independent reflections	3986 [R_{int} = 0.0212, R_{sigma} = 0.0113]
Data/restraints/parameters	3986/12/265
Goodness-of-fit on F^2	1.048
Final R indexes [I>=2σ (I)]	R_1 = 0.0416, wR_2 = 0.1085
Final R indexes [all data]	R_1 = 0.0433, wR_2 = 0.1101
Largest diff. peak/hole / e Å^{-3}	0.25/-0.32



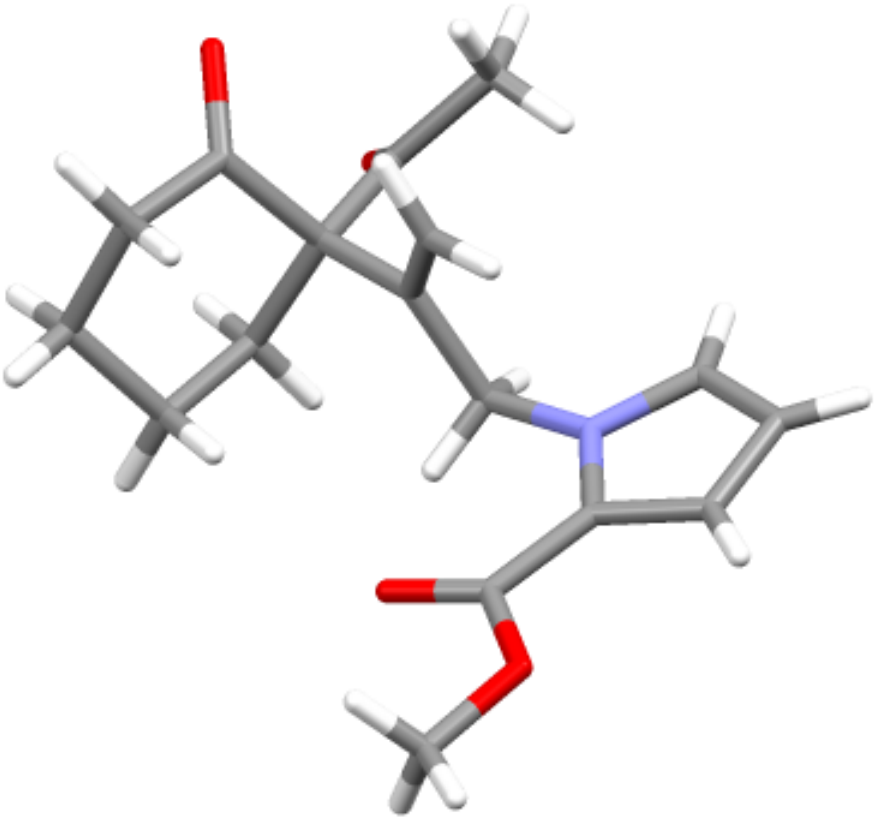
12.1.3. Crystal structure of 314b

324b (CCDC 1443120)



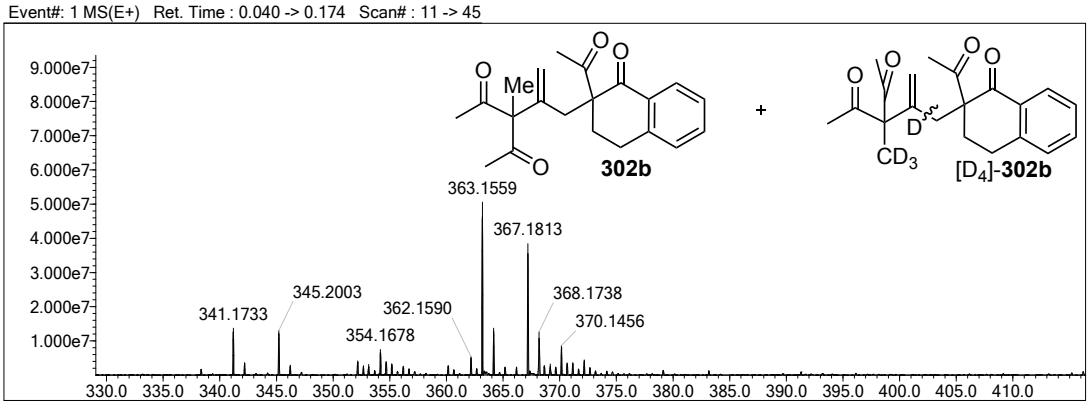
314b

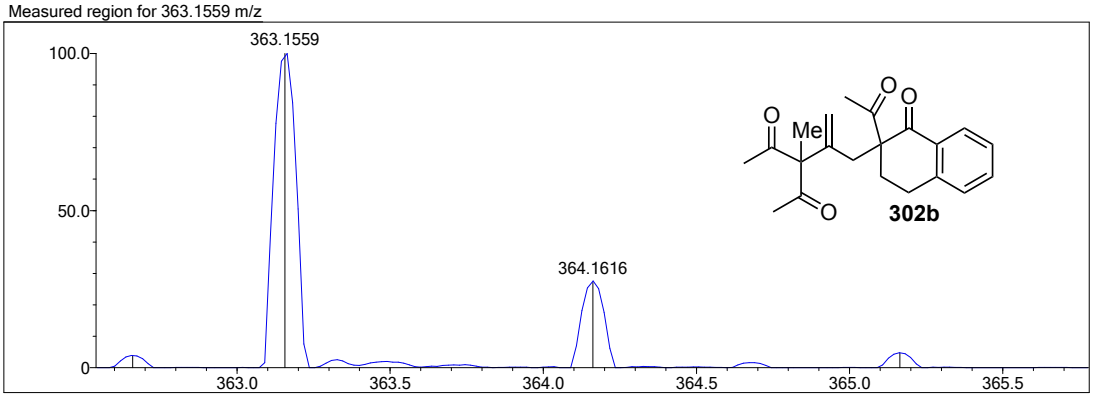
Identification code	**VF100**
Empirical formula	$C_{17}H_{21}NO_4$
Formula weight	303.35
Temperature/K	99.9(2)
Crystal system	triclinic
Space group	P-1
a/Å	6.7520(2)
b/Å	8.3609(2)
c/Å	13.8172(3)
α/°	85.356(2)
β/°	85.858(2)
γ/°	80.981(2)
Volume/Å^3	766.44(4)
Z	2
ρ_{calc} g/cm^3	1.314
μ/mm^{-1}	0.765
F(000)	324.0
Crystal size/mm^3	? × ? × ?
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.74 to 147.794
Index ranges	-8 ≤ h ≤ 8, -9 ≤ k ≤ 10, -17 ≤ l ≤ 17
Reflections collected	11458
Independent reflections	3051 [R_{int} = 0.0197, R_{sigma} = 0.0144]
Data/restraints/parameters	3051/0/209
Goodness-of-fit on F^2	1.037
Final R indexes [I>=2σ (I)]	R_1 = 0.0332, wR_2 = 0.0853
Final R indexes [all data]	R_1 = 0.0343, wR_2 = 0.0861
Largest diff. peak/hole / e Å^{-3}	0.31/-0.30

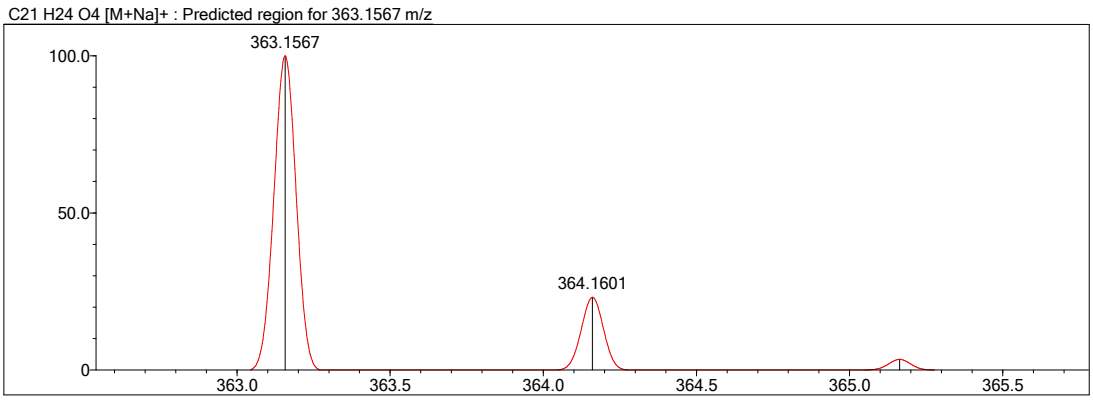


12.2. Mass Spectrometry Data

A: Enolate crossover experiment with [D_4]-**300** and **301b**

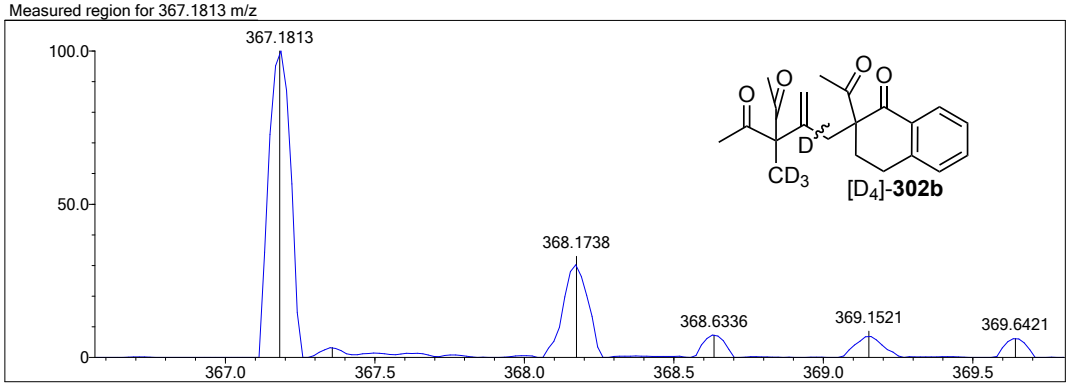




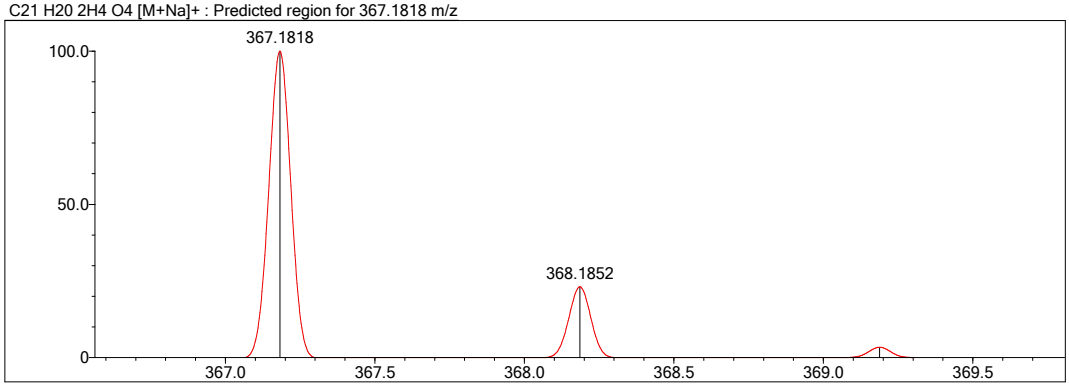


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
5	90.92	C21 H24 O4	[M+Na]+	363.1559	363.1567	-0.8	-2.20	93.74	10.0

Measured region for 367.1813 m/z

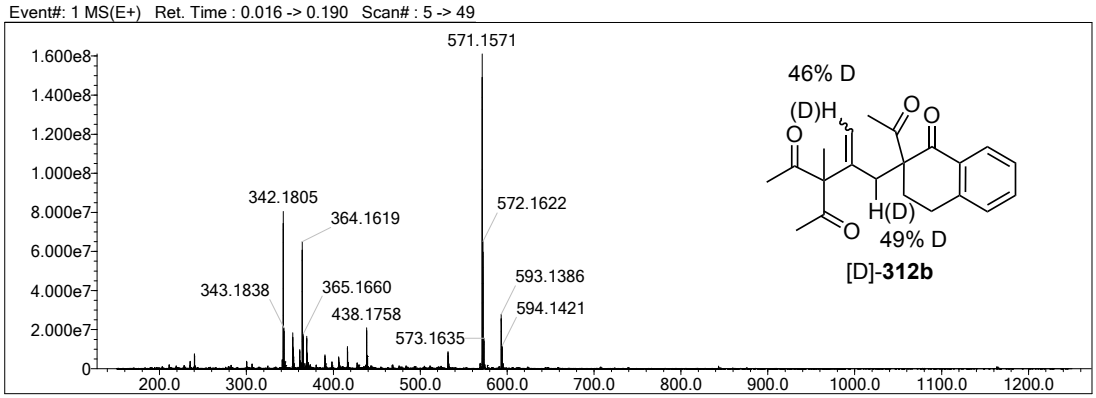


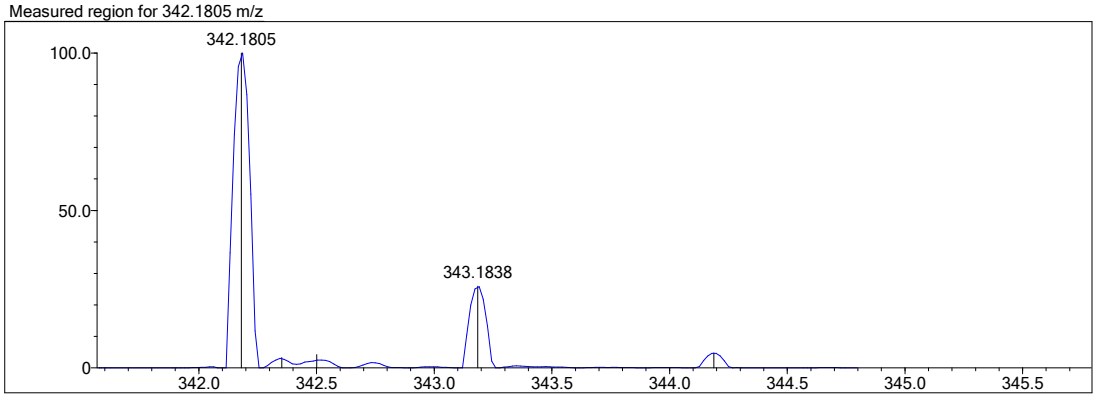
C21 H20 2H4 O4 [M+Na]+ : Predicted region for 367.1818 m/z

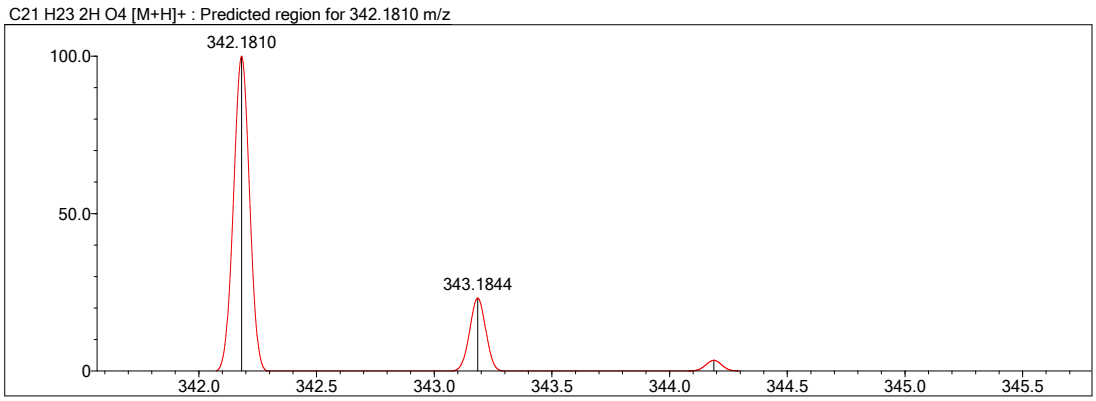


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	62.36	C21 H20 2H4 O4	[M+Na]+	367.1813	367.1818	-0.5	-1.36	62.93	10.0

B. Deuterium scrambling experiment with [D]-**300** and **30 1b**.

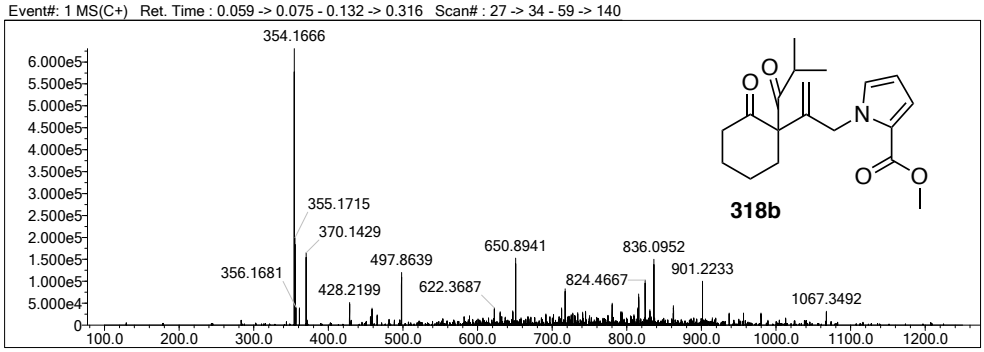


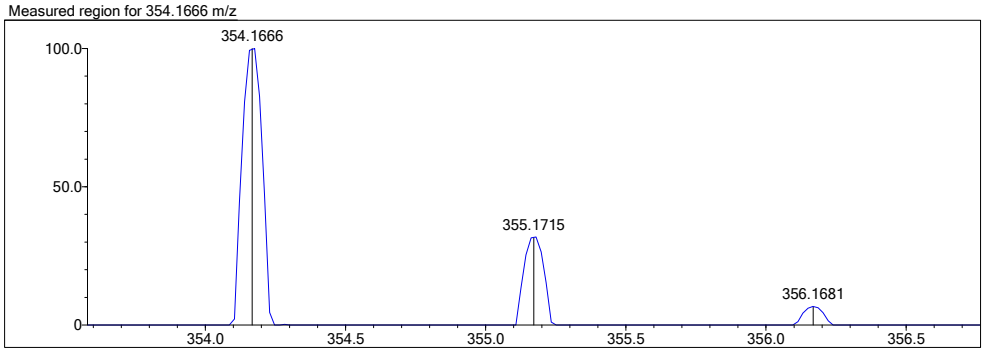


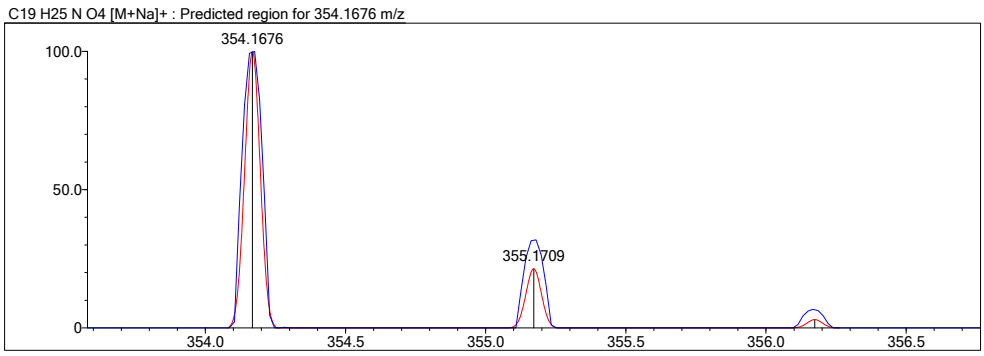


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	98.85	C21 H23 2H O4	[M+H]+	342.1805	342.1810	-0.5	-1.46	100.00	10.0

C: Enolate crossover experiment with [D]-**266** and **303c** with **313b**.

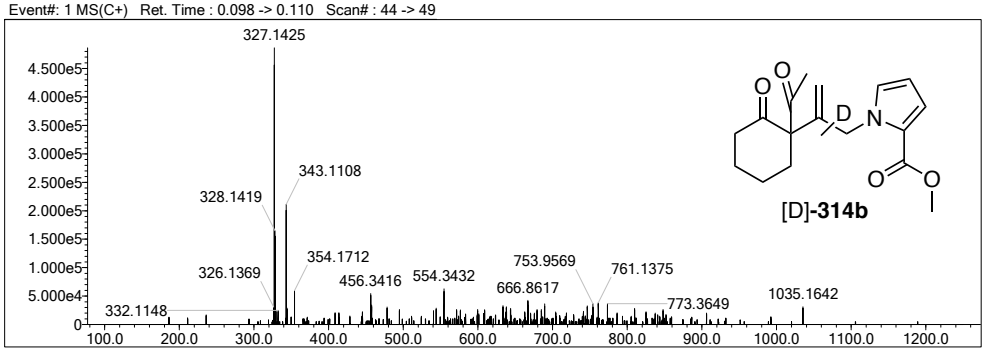




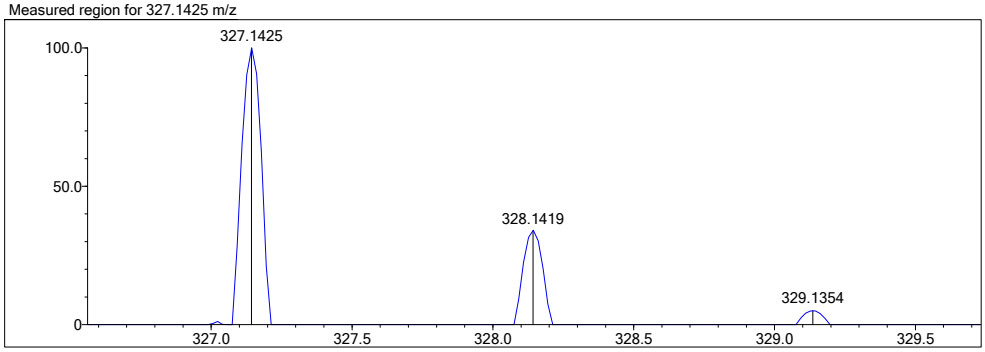


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	71.06	C19 H25 N O4	[M+Na]+	354.1666	354.1676	-1.0	-2.82	74.45	8.0

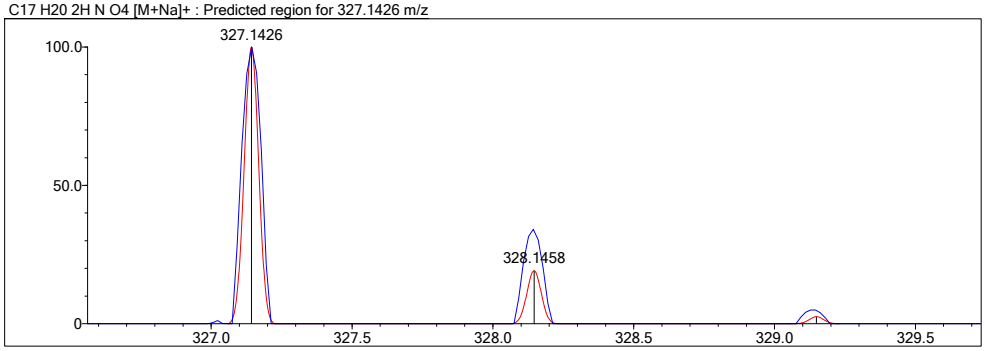
Event#: 1 MS(C+) Ret. Time : 0.098 -> 0.110 Scan# : 44 -> 49



Measured region for 327.1425 m/z

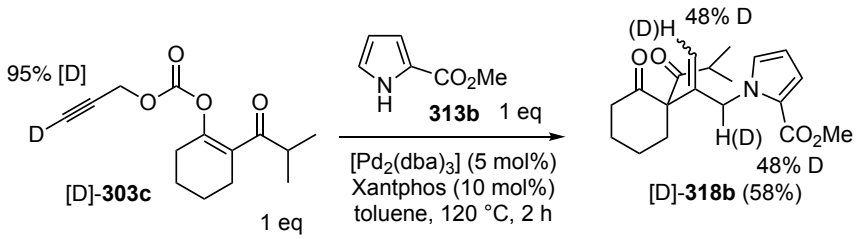


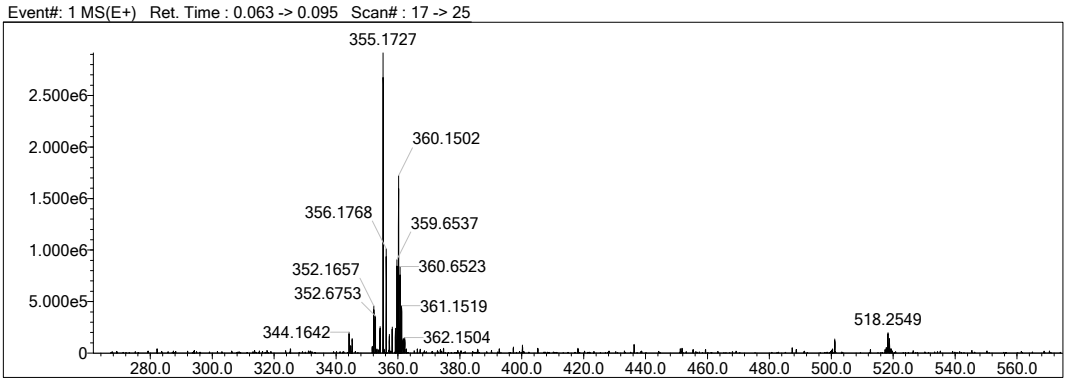
C17 H20 2H N O4 [M+Na]+ : Predicted region for 327.1426 m/z

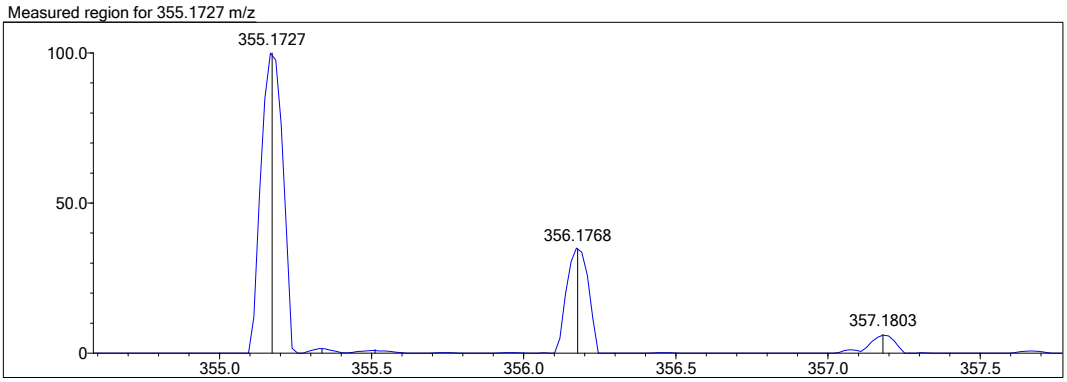


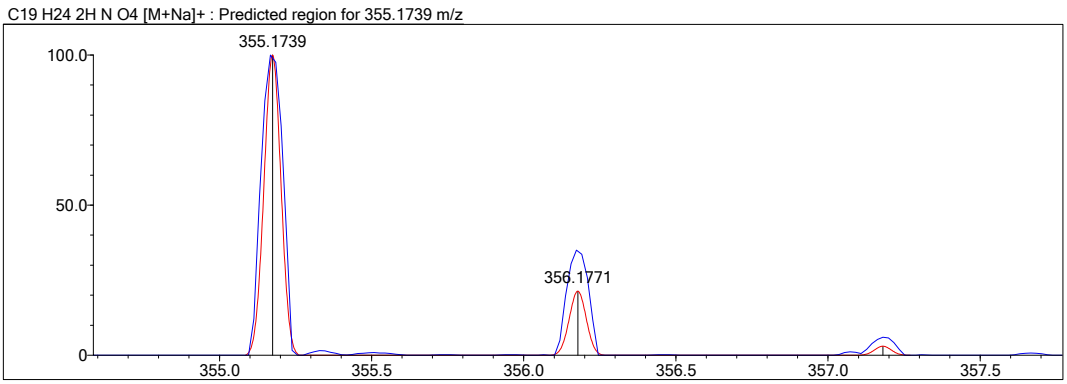
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	50.30	C17 H20 2H N O4	[M+Na]+	327.1425	327.1426	-0.1	-0.31	50.30	8.0

D: Deuterium scrambling experiment with **[**D]-**303c** and **313b**.



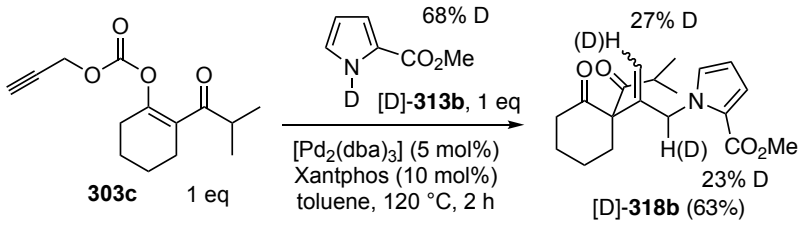


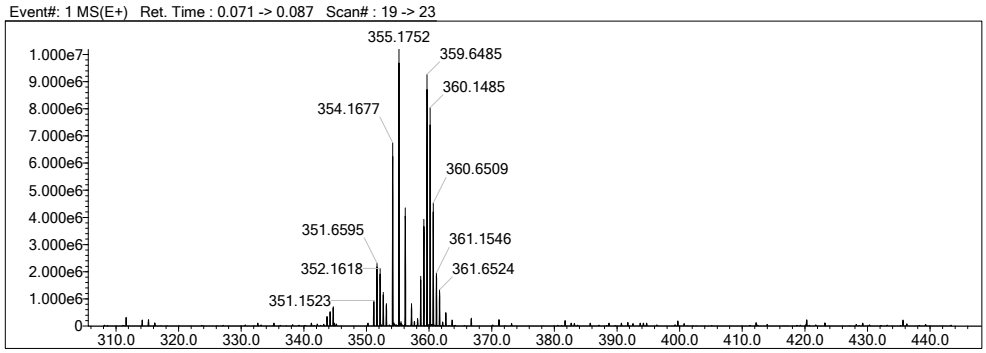


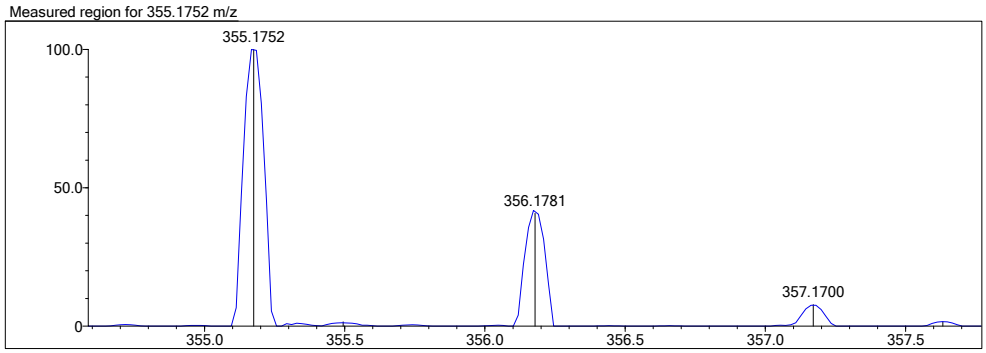


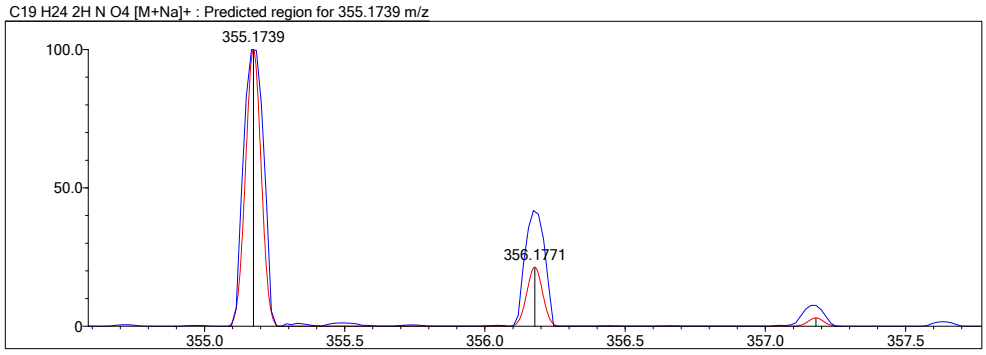
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	66.88	C19 H24 2H N O4	[M+Na]+	355.1727	355.1739	-1.2	-3.38	71.11	8.0

E: Deuterium Scrambling experiment with **303c** and [D]-**313b**.



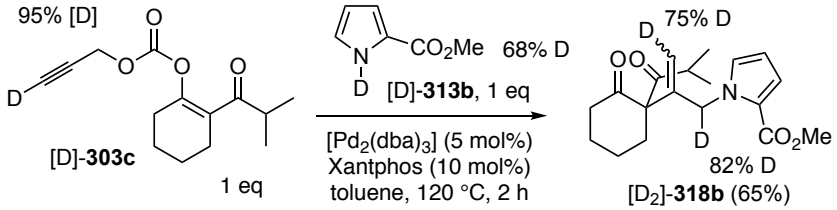


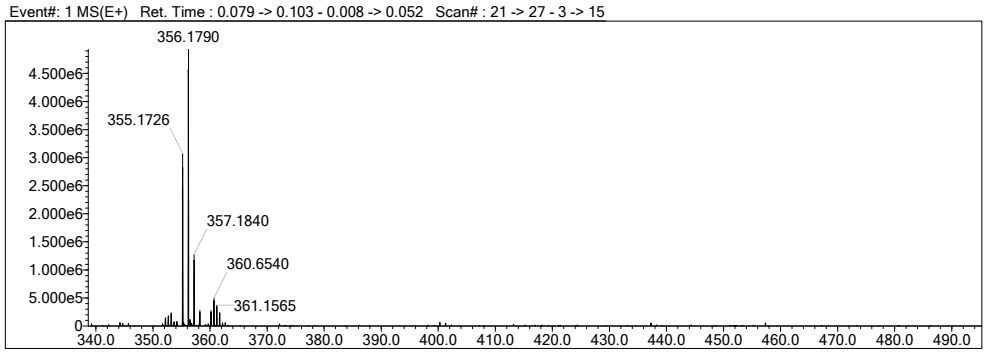


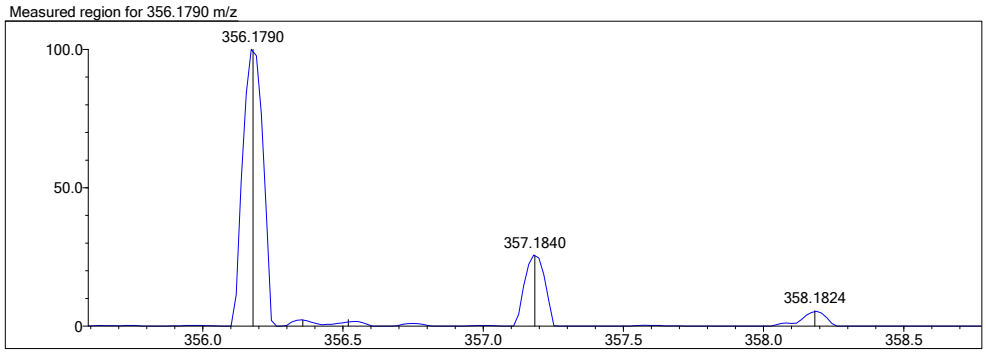


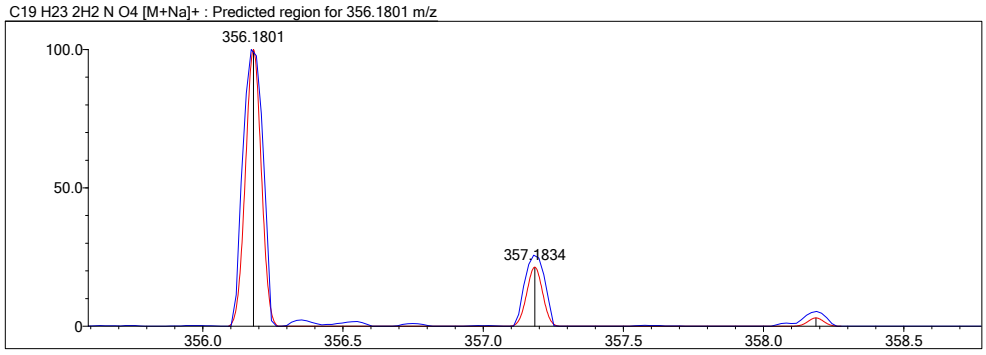
Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	51.21	C19 H24 2H N O4	[M+Na]+	355.1752	355.1739	1.3	3.66	54.86	8.0

F: Deuterium Scrambling experiment with [D]-**303c** and [D]-**313b**.







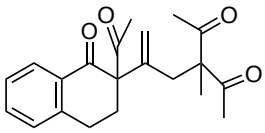


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	84.86	C19 H23 2H2 N O4	[M+Na]+	356.1790	356.1801	-1.1	-3.09	89.54	8.0

12.3. Chiral HPLC Traces

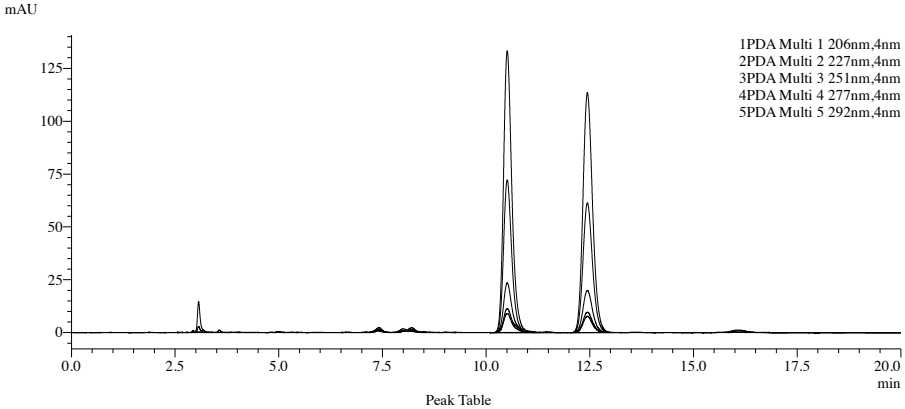
Lancaster University Department of Chemistry - HPLC Analysis

Sample Name	: MK341-f g i l
Sample ID	: MK341 f g i l analysis002
Data File	: mk 341 002.lcd
Batch File	: mk341 first set.lcb
Vial#	: 2
Injection Volume	: 2
Method File	: Method1.lcm
Date Acquired	: 29/06/2016 09:45:59
Date Processed	: 29/06/2016 11:40:22



304b

Chromatogram
MK341-f g i l mk 341 002.lcd



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
MK181-Race1	1	10.509	1879695	50.513	S
MK181-Race2	2	12.442	1841541	49.487	
	Total		3721237	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
MK181-Race1	1	10.509	339584	51.341	
MK181-Race2	2	12.442	321844	48.659	
	Total		661429	100.000	

PDA Ch3 251nm

Name	Peak#	Ret. Time	Area	Area%	Mark
MK181-Race1	1	10.509	1003488	50.296	
MK181-Race2	2	12.442	991693	49.704	
	Total		1995181	100.000	

PDA Ch4 277nm

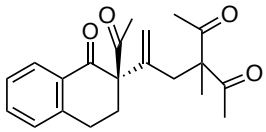
Name	Peak#	Ret. Time	Area	Area%	Mark
MK181-Race1	1	10.509	133344	51.791	
MK181-Race2	2	12.442	124123	48.209	
	Total		257467	100.000	

PDA Ch5 292nm

Name	Peak#	Ret. Time	Area	Area%	Mark
MK181-Race1	1	10.509	178546	53.402	
MK181-Race2	2	12.442	155800	46.598	
	Total		334346	100.000	

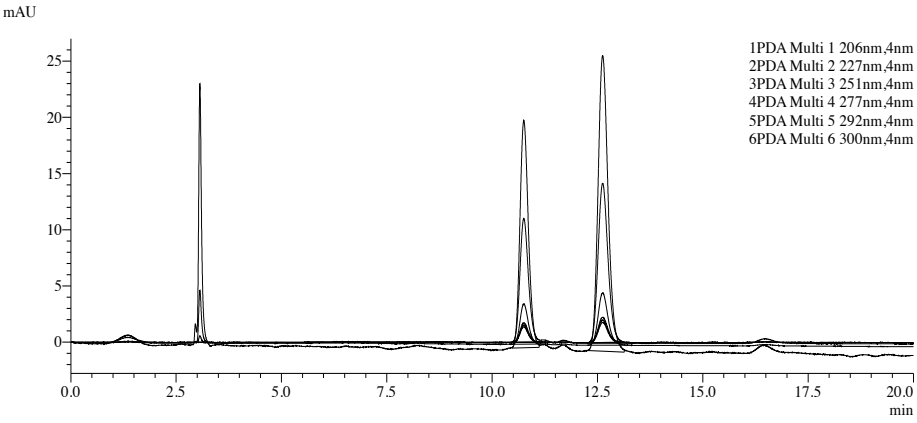
Lancaster University Department of Chemistry - HPLC Analysis

Sample Name	: mk344-THF
Sample ID	: mk344-THF
Data File	: mk344-THF.lcd
Batch File	: mk341 solvent screen.lcb
Vial#	: 7
Injection Volume	: 2
Method File	: Method1.lcm
Date Acquired	: 04/10/2016 13:51:53
Date Processed	: 05/10/2016 10:11:27



304b
ee 21%

Chromatogram
mk344-THF mk344-THF.lcd



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.753	282161	39.148	M
	2	12.624	438596	60.852	M
	Total		720757	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.752	49320	38.931	
	2	12.624	77363	61.069	
	Total		126683	100.000	

PDA Ch3 251nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.752	156672	39.802	
	2	12.624	236952	60.198	
	Total		393624	100.000	

PDA Ch4 277nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.752	19078	39.226	
	2	12.625	29559	60.774	
	Total		48638	100.000	

PDA Ch5 292nm

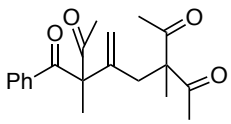
Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.753	23973	39.405	
	2	12.624	36864	60.595	
	Total		60836	100.000	

PDA Ch6 300nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.752	21362	39.306	
	2	12.625	32986	60.694	
	Total		54348	100.000	

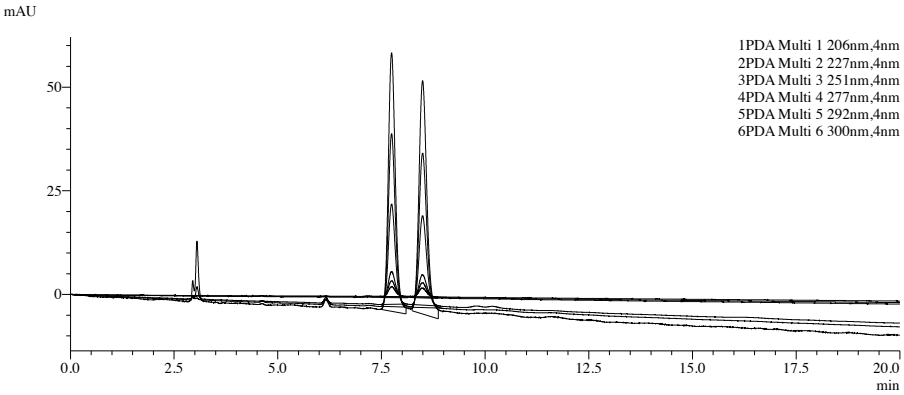
Lancaster University Department of Chemistry - HPLC Analysis

Sample Name	: MK184-1-ODH
Sample ID	: MK184-1-ODH
Data File	: mk184-1-ODH.lcd
Batch File	: MK199 and MK349.lcb
Vial#	: 5
Injection Volume	: 2
Method File	: Method1.lcm
Date Acquired	: 16/12/2016 12:16:07
Date Processed	: 16/12/2016 13:06:38



304f

Chromatogram
MK184-1-ODH mk184-1-ODH.lcd



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.744	741784	49.428	M
	2	8.492	758940	50.572	M
	Total		1500724	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.744	279891	50.349	
	2	8.492	276015	49.651	
	Total		555907	100.000	

PDA Ch3 251nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.744	485794	50.159	
	2	8.492	482718	49.841	V
	Total		968512	100.000	

PDA Ch4 277nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.744	75852	50.701	M
	2	8.491	73756	49.299	M
	Total		149607	100.000	

PDA Ch5 292nm

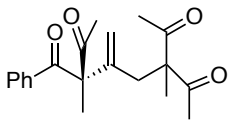
Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.746	48362	51.448	M
	2	8.490	45639	48.552	M
	Total		94001	100.000	

PDA Ch6 300nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.747	29675	51.695	M
	2	8.487	27728	48.305	M
	Total		57403	100.000	

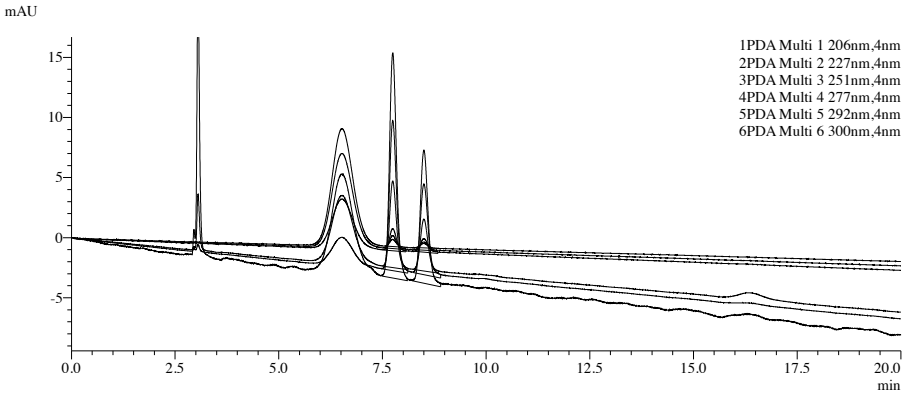
Lancaster University Department of Chemistry - HPLC Analysis

Sample Name	: MK352-ODH
Sample ID	: MK352-ODH
Data File	: MK352-ODH.lcd
Batch File	: MK199 and MK349.lcb
Vial#	: 7
Injection Volume	: 2
Method File	: Method1.lcm
Date Acquired	: 16/12/2016 12:56:49
Date Processed	: 16/12/2016 17:03:07



304f
ee 19%

Chromatogram
MK352-ODH MK352-ODH.lcd



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.749	224357	60.280	M
	2	8.500	147832	39.720	M
	Total		372188	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.748	86367	59.816	M
	2	8.500	58020	40.184	M
	Total		144387	100.000	

PDA Ch3 251nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.748	150443	59.457	M
	2	8.500	102584	40.543	M
	Total		253027	100.000	

PDA Ch4 277nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.748	22989	59.216	M
	2	8.499	15833	40.784	M
	Total		38822	100.000	

PDA Ch5 292nm

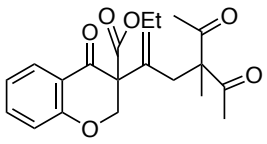
Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.748	12751	58.457	M
	2	8.498	9062	41.543	M
	Total		21812	100.000	

PDA Ch6 300nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.746	6764	60.235	
	2	8.494	4465	39.765	
	Total		11229	100.000	

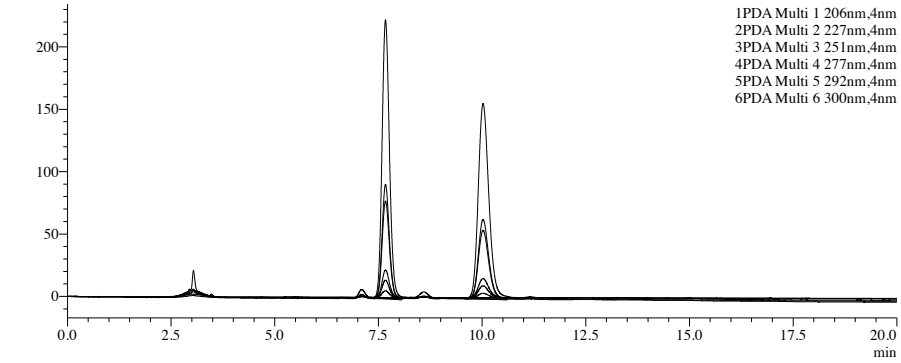
Lancaster University Department of Chemistry - HPLC Analysis

Sample Name	: MK354 racemate
Sample ID	: MK354 racemate
Data File	: mk354 racemate.lcd
Batch File	: MK199 and MK349.lcb
Vial#	: 4
Injection Volume	: 2
Method File	: Method1.lcm
Date Acquired	: 23/11/2016 12:15:41
Date Processed	: 16/12/2016 13:49:34



304s

Chromatogram
MK354 racemate mk354 racemate.lcd



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.670	2783502	49.787	M
	2	10.023	2807310	50.213	M
	Total		5590812	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.670	969827	49.735	M
	2	10.023	980155	50.265	M
	Total		1949982	100.000	

PDA Ch3 251nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.670	1134748	50.312	M
	2	10.023	1120653	49.688	M
	Total		2255401	100.000	

PDA Ch4 277nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.668	67485	51.181	M
	2	10.022	64370	48.819	M
	Total		131855	100.000	

PDA Ch5 292nm

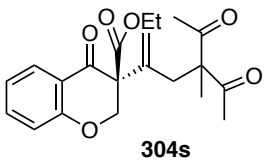
Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.669	172278	50.841	M
	2	10.023	166575	49.159	M
	Total		338853	100.000	

PDA Ch6 300nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.670	274749	50.178	M
	2	10.022	272804	49.822	M
	Total		547552	100.000	

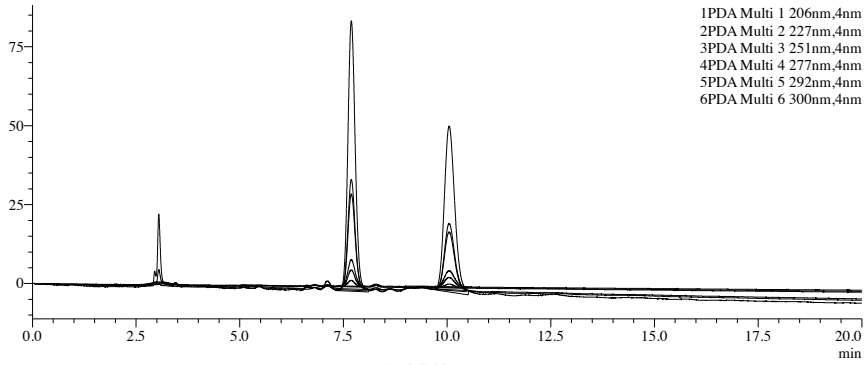
Lancaster University Department of Chemistry - HPLC Analysis

Sample Name	: mk352
Sample ID	: mk352
Data File	: mk354 enantioselective.lcd
Batch File	: MK199 and MK349.lcb
Vial#	: 5
Injection Volume	: 2
Method File	: Method1.lcm
Date Acquired	: 22/11/2016 12:50:25
Date Processed	: 16/12/2016 17:05:53



304s
ee 9%

Chromatogram
mk352 mk354 enantioselective.lcd



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.690	1064349	53.482	M
	2	10.049	925754	46.518	M
	Total		1990103	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.690	370860	54.216	M
	2	10.049	313186	45.784	
	Total		684047	100.000	

PDA Ch3 251nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.690	439152	54.436	M
	2	10.049	367585	45.564	M
	Total		806737	100.000	

PDA Ch4 277nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.686	27445	55.319	M
	2	10.047	22167	44.681	M
	Total		49612	100.000	

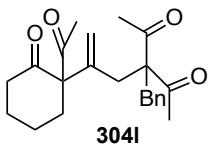
PDA Ch5 292nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.689	67276	54.178	M
	2	10.048	56899	45.822	M
	Total		124176	100.000	

PDA Ch6 300nm

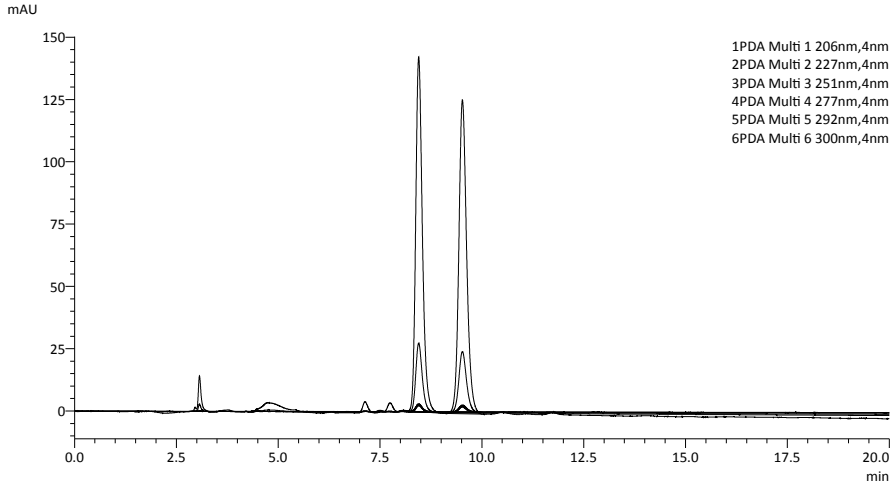
Name	Peak#	Ret. Time	Area	Area%	Mark
	1	7.690	105322	54.338	M
	2	10.049	88506	45.662	M
	Total		193829	100.000	

Sample Name : MK353-ADH a
Sample ID : MK353-ADH a
Data File : MK353 ADH a.lcd
Batch File : MK199 and MK349.lcb
Vial# : 5
Injecti **o**n Volume : 2
Method File : Method1.lcm
Date Acquired : 24/11/2016 13:36:23
Date Processed : 09/12/2016 10:02:49



304l

Chromatogram
MK353-ADH a MK353 ADH a.lcd



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.449	1621618	49.114	
	2	9.523	1680143	50.886	
	Total		3301761	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.449	314681	48.749	M
	2	9.522	330831	51.251	M
	Total		645512	100.000	

PDA Ch3 251nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.450	30532	49.308	M
	2	9.519	31388	50.692	M
	Total		61920	100.000	

PDA Ch4 277nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.451	28859	49.260	M
	2	9.522	29726	50.740	M
	Total		58584	100.000	

PDA Ch5 292nm

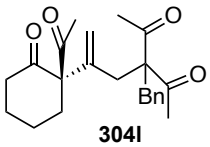
Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.448	36854	50.307	M
	2	9.523	36404	49.693	M
	Total		73258	100.000	

PDA Ch6 300nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.448	36501	50.773	V
	2	9.523	35390	49.227	
	Total		71890	100.000	

Lancaster University Department of Chemistry - HPLC Analysis

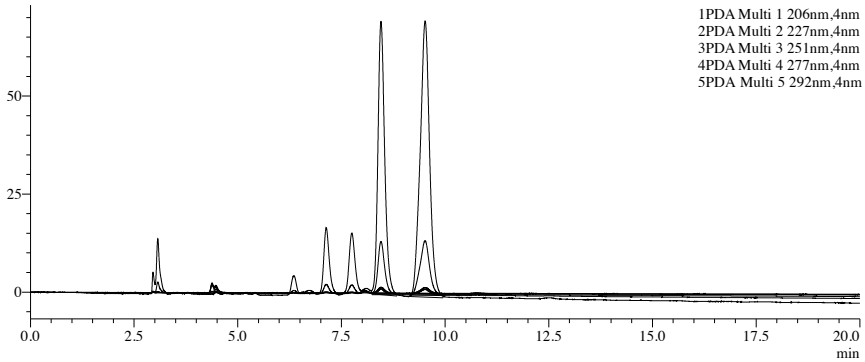
Sample Name	: MK353-ADH b
Sample ID	: MK353-ADH b
Data File	: MK353 ADH b.lcd
Batch File	: MK199 and MK349.lcb
Vial#	: 6
Injection Volume	: 2
Method File	: Method1.lcm
Date Acquired	: 24/11/2016 13:56:46
Date Processed	: 16/12/2016 13:59:23



304l
ee 19%

Chromatogram
MK353-ADH b MK353 ADH b.lcd

mAU



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.454	794274	41.519	M
	2	9.518	1118766	58.481	M
	Total		1913040	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.454	155793	40.824	M
	2	9.516	225827	59.176	M
	Total		381620	100.000	

PDA Ch3 251nm

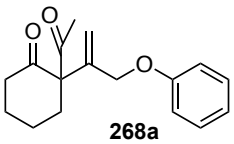
Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.454	13736	40.306	M
	2	9.516	20343	59.694	M
	Total		34079	100.000	

PDA Ch4 277nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.454	12932	40.748	M
	2	9.520	18805	59.252	M
	Total		31737	100.000	

PDA Ch5 292nm

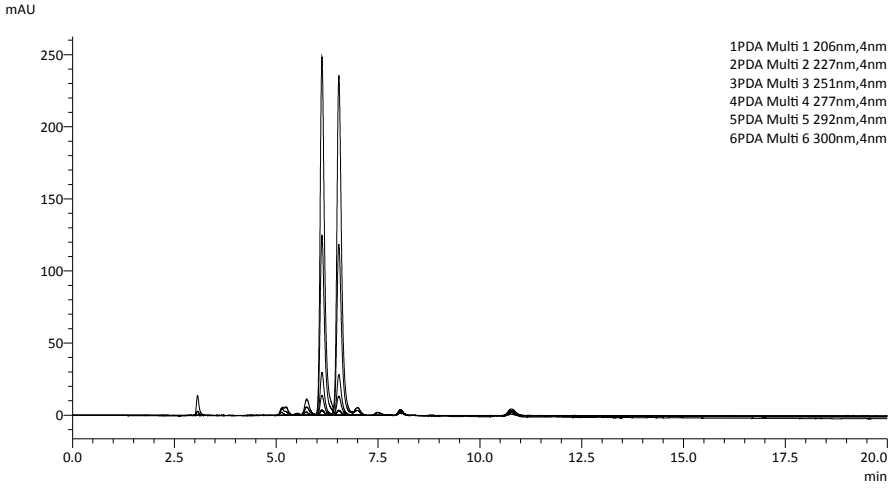
Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.454	17262	41.972	M
	2	9.519	23865	58.028	M
	Total		41127	100.000	



268a

Sample Name	: MK355 racemate ADH
Sample ID	: mk355 racemate ADH
Data File	: mk355 racemate ADH.lcd
Batch File	: MK199 and MK349.lcb
Vial#	: 7
Injecti **o**n Volume	: 2
Method File	: Method1.lcm
Date Acquired	: 24/11/2016 14:17:09
Date Processed	: 09/12/2016 12:45:31

Chromatogram
MK355 racemate ADH mk355 racemate ADH.lcd



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	6.124	1911074	50.011	V
	2	6.539	1910263	49.989	V
	Total		3821337	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	6.124	958280	49.726	V
	2	6.539	968851	50.274	V
	Total		1927131	100.000	

PDA Ch3 251nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	6.124	102017	48.813	M
	2	6.537	106980	51.187	M
	Total		208997	100.000	

PDA Ch4 277nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	6.124	224549	50.330	V
	2	6.539	221609	49.670	V
	Total		446158	100.000	

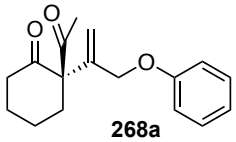
PDA Ch5 292nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	6.124	28543	48.847	M
	2	6.539	29890	51.153	M
	Total		58433	100.000	

PDA Ch6 300nm

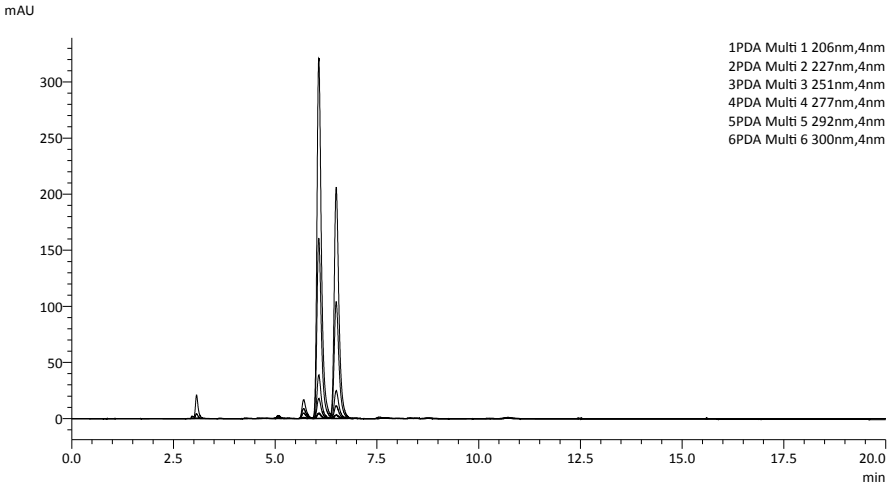
Name	Peak#	Ret. Time	Area	Area%	Mark
	1	6.124	25914	49.462	
	2	6.539	26478	50.538	V
	Total		52391	100.000	

Sample Name	: MK355 chiral ADH
Sample ID	: MK355 chiral ADH
Data File	: mk355 Chiral ADH.lcd
Batch File	: MK199 and MK349.lcb
Vial#	: 5
Injecti **o**n Volume	: 2
Method File	: Method1.lcm
Date Acquired	: 09/12/2016 13:14:53
Date Processed	: 23/05/2017 17:21:25



268a
ee 19%

Chromatogram
MK355 chiral ADH mk355 Chiral ADH.lcd



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	6.072	2438765	59.447	V
	2	6.500	1663670	40.553	V
	Total		4102435	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	6.072	1230586	59.289	V
	2	6.500	844981	40.711	V
	Total		2075566	100.000	

PDA Ch3 251nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	6.072	134181	59.230	
	2	6.500	92362	40.770	M
	Total		226544	100.000	

PDA Ch4 277nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	6.072	292930	59.567	V
	2	6.500	198832	40.433	V
	Total		491763	100.000	

PDA Ch5 292nm

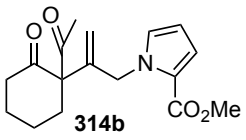
Name	Peak#	Ret. Time	Area	Area%	Mark
	1	6.072	38564	58.690	M
	2	6.500	27143	41.310	M
	Total		65707	100.000	

PDA Ch6 300nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	6.072	34038	59.467	
	2	6.500	23200	40.533	V
	Total		57239	100.000	

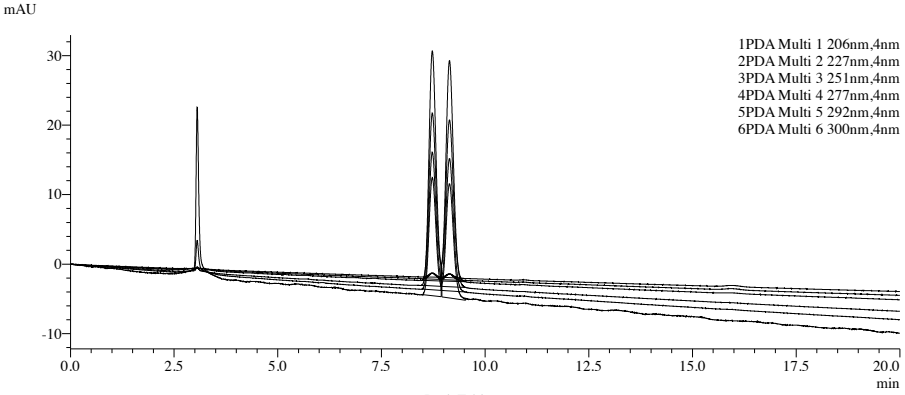
Lancaster University Department of Chemistry - HPLC Analysis

Sample Name	: MK253-2-ODH
Sample ID	: MK253-2-ODH
Data File	: MK253-2-ODH less polar.lcd
Batch File	: MK199 and MK349.lcb
Vial#	: 3
Injection Volume	: 2
Method File	: Method2.lcm
Date Acquired	: 16/12/2016 16:08:48
Date Processed	: 21/12/2016 17:40:13



314b

Chromatogram
MK253-2-ODH MK253-2-ODH less polar.lcd



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.726	203110	48.889	M
	2	9.140	212339	51.111	M
	Total		415448	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.726	237089	49.280	
	2	9.140	244017	50.720	V
	Total		481107	100.000	

PDA Ch3 251nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.726	405966	49.214	
	2	9.141	418934	50.786	V
	Total		824900	100.000	

PDA Ch4 277nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.726	290131	49.237	
	2	9.141	299123	50.763	V
	Total		589253	100.000	

PDA Ch5 292nm

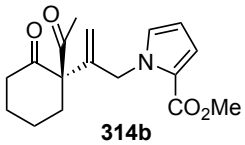
Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.725	10638	48.913	M
	2	9.137	11110	51.087	M
	Total		21748	100.000	

PDA Ch6 300nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.729	6381	49.662	
	2	9.139	6468	50.338	
	Total		12849	100.000	

Lancaster University Department of Chemistry - HPLC Analysis

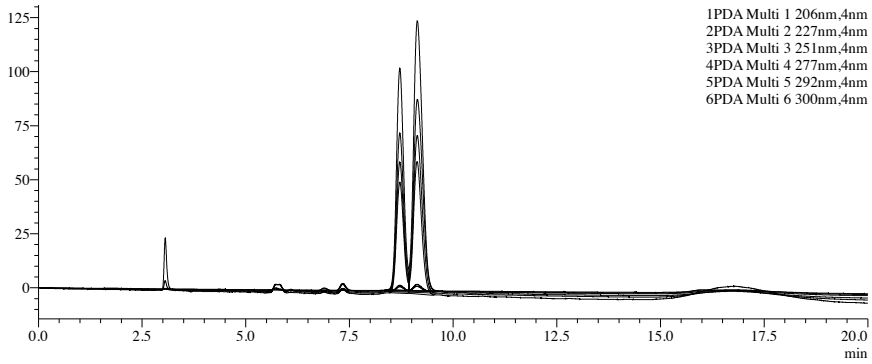
Sample Name	: MK368-ODH
Sample ID	: MK368-ODH
Data File	: mk368-ODH less polar.lcd
Batch File	: MK199 and MK349.lcb
Vial#	: 4
Injection Volume	: 2
Method File	: Method2.lcm
Date Acquired	: 16/12/2016 16:29:09
Date Processed	: 21/12/2016 17:38:48



314b
ee 19%

Chromatogram
MK368-ODH mk368-ODH less polar.lcd

mAU



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.715	611667	42.207	M
	2	9.132	837541	57.793	M
	Total		1449209	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.715	721261	40.745	
	2	9.135	1048934	59.255	V
	Total		1770195	100.000	

PDA Ch3 251nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.715	1236073	40.007	
	2	9.137	1853602	59.993	V
	Total		3089675	100.000	

PDA Ch4 277nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.715	889939	39.749	
	2	9.139	1348986	60.251	V
	Total		2238925	100.000	

PDA Ch5 292nm

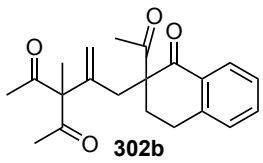
Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.716	31302	39.917	M
	2	9.131	47115	60.083	M
	Total		78416	100.000	

PDA Ch6 300nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	8.714	21008	42.028	M
	2	9.128	28978	57.972	M
	Total		49987	100.000	

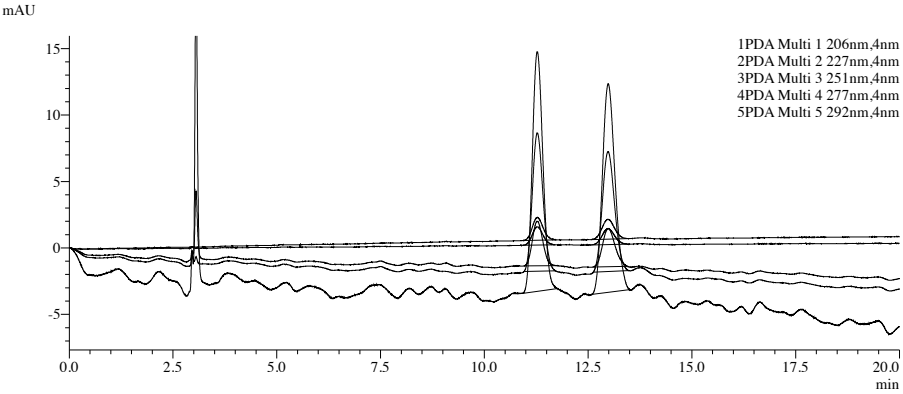
Lancaster University Department of Chemistry - HPLC Analysis

Sample Name	: MK342 part 1
Sample ID	: MK342 part 2
Data File	: MK342 race 002.lcd
Batch File	: mk342 part 1.lcb
Vial#	: 2
Injection Volume	: 2
Method File	: Method1.lcm
Date Acquired	: 26/08/2016 18:08:41
Date Processed	: 30/08/2016 14:58:37



302b

Chromatogram
MK342 part 1 MK342 race 002.lcd



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	11.276	320678	48.994	M
	2	12.984	333851	51.006	M
	Total		654529	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	11.276	58809	49.286	M
	2	12.987	60512	50.714	M
	Total		119321	100.000	

PDA Ch3 251nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	11.276	186261	49.923	
	2	12.981	186835	50.077	
	Total		373096	100.000	

PDA Ch4 277nm

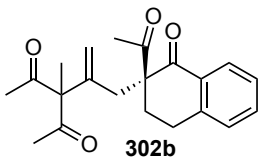
Name	Peak#	Ret. Time	Area	Area%	Mark
	1	11.281	24696	49.650	M
	2	12.980	25044	50.350	M
	Total		49740	100.000	

PDA Ch5 292nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	11.280	31280	50.145	M
	2	12.979	31099	49.855	M
	Total		62379	100.000	

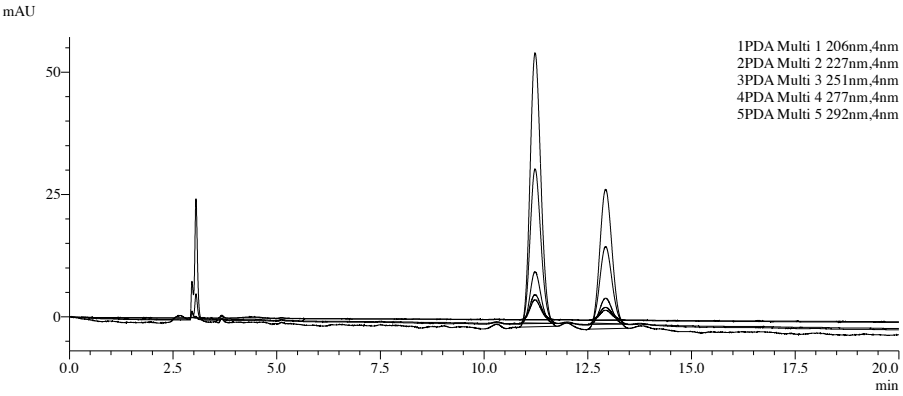
Lancaster University Department of Chemistry - HPLC Analysis

Sample Name	: MK342 part 1
Sample ID	: MK342 part 15
Data File	: MK342 dd.lcd
Batch File	: mk342 part 1.lcb
Vial#	: 15
Injection Volume	: 2
Method File	: Method1.lcm
Date Acquired	: 26/08/2016 22:33:18
Date Processed	: 30/08/2016 14:18:35



302b
ee 27%

Chromatogram
MK342 part 1 MK342 dd.lcd



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	11.230	1021222	62.946	
	2	12.930	601144	37.054	
	Total		1622366	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	11.229	188069	64.206	
	2	12.931	104847	35.794	
	Total		292916	100.000	

PDA Ch3 251nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	11.229	575906	63.607	
	2	12.930	329505	36.393	
	Total		905411	100.000	

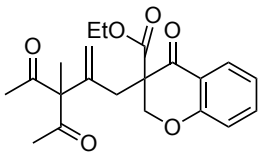
PDA Ch4 277nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	11.230	74681	63.806	M
	2	12.927	42364	36.194	M
	Total		117044	100.000	

PDA Ch5 292nm

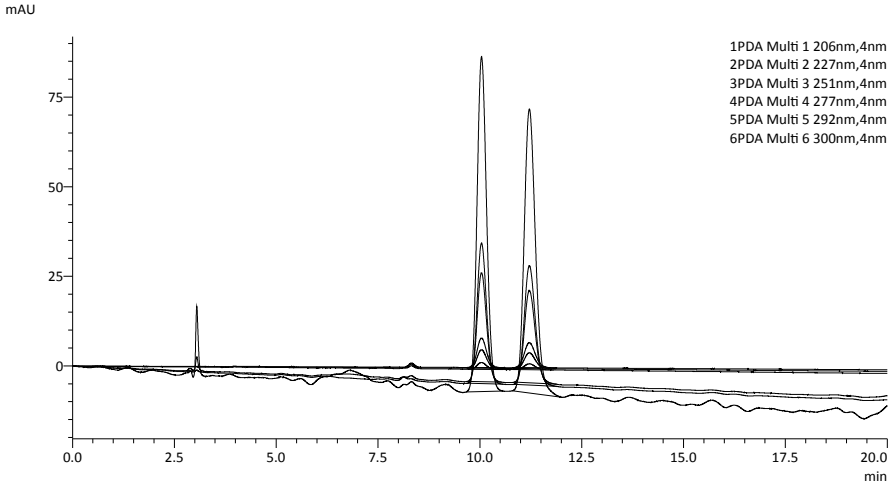
Name	Peak#	Ret. Time	Area	Area%	Mark
	1	11.230	92188	63.866	M
	2	12.930	52158	36.134	M
	Total		144346	100.000	

Sample Name	: MK199
Sample ID	: MK199
Data File	: mk199.lcd
Batch File	: MK199 and MK349.lcb
Vial#	: 2
Injecti **o**n Volume	: 2
Method File	: Method1.lcm
Date Acquired	: 21/11/2016 16:11:33
Date Processed	: 14/06/2017 09:44:31



302m

Chromatogram
MK199 mk199.lcd



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.041	1537279	49.854	
	2	11.216	1546288	50.146	
	Total		3083567	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.041	498732	50.085	
	2	11.215	497042	49.915	
	Total		995775	100.000	

PDA Ch3 251nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.041	642026	50.119	
	2	11.215	638975	49.881	
	Total		1281002	100.000	

PDA Ch4 277nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.040	31339	49.765	
	2	11.216	31635	50.235	
	Total		62974	100.000	

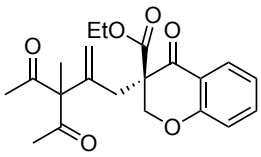
PDA Ch5 292nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.041	84937	50.021	
	2	11.216	84865	49.979	
	Total		169802	100.000	

PDA Ch6 300nm

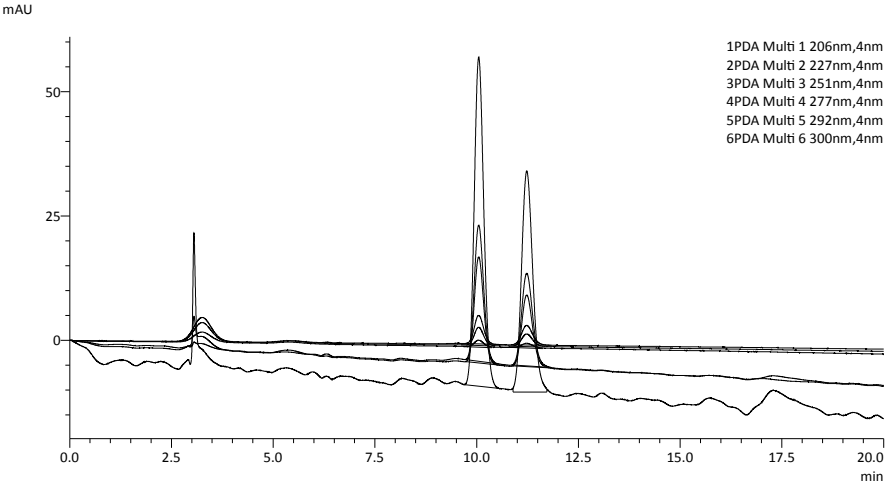
Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.040	134602	50.116	
	2	11.215	133978	49.884	
	Total		268579	100.000	

Sample Name	: MK349
Sample ID	: MK349
Data File	: mk349.lcd
Batch File	: MK199 and MK349.lcb
Vial#	: 3
Injecti ɑ Volume	: 2
Method File	: Method1.lcm
Date Acquired	: 21/11/2016 16:31:54
Date Processed	: 23/05/2017 17:27:00



302m
ee 11%

Chromatogram
MK349 mk349.lcd



Peak Table

PDA Ch1 206nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.051	1088451	55.748	
	2	11.232	864001	44.252	M
	Total		1952452	100.000	

PDA Ch2 227nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.050	347209	55.752	
	2	11.231	275569	44.248	
	Total		622778	100.000	

PDA Ch3 251nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.050	443651	55.354	
	2	11.231	357833	44.646	
	Total		801484	100.000	

PDA Ch4 277nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.050	24672	55.714	M
	2	11.227	19611	44.286	M
	Total		44283	100.000	

PDA Ch5 292nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.049	60815	54.788	M
	2	11.228	50186	45.212	M
	Total		111001	100.000	

PDA Ch6 300nm

Name	Peak#	Ret. Time	Area	Area%	Mark
	1	10.050	92622	55.164	
	2	11.230	75281	44.836	
	Total		167904	100.000	