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Palladium-Catalysed Enolate Arylation in the Synthesis of Aromatic Heterocycles and Substituted Pyruvates

BY

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Declaration

This thesis and the work described herein is entirely my own, except where the help of co-workers is acknowledged or where reference is made to a published source or thesis.

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Abstract

Palladium-Catalysed Enolate Arylation in the Synthesis of Aromatic Heterocycles and Substituted Pyruvates

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Chapter 1. Introduction

A literature background on the early development of the Pd-catalysed cross-coupling reactions and the later discovery of the enolate arylation reaction is presented. In the second part, the literature on pyruvate chemistry is explored, focusing on enantioselective transformations and the synthesis of α-arylated pyruvate derivatives. The final part presents reported protocols on the synthesis of β-carboline, isoquinoline and indole esters, from the classical approaches to the more recent methodologies based on metal catalysed transformations.

Chapter 2. Results and Discussion

2.1 A study towards the synthesis of substituted amino-pyridines *via* 6π-electrocyclisation of 1-azatrienes is presented. The aspects impacting the efficiency of the cyclisation reaction are discussed using the experimental data collected and kinetic experiments published by other groups.

2.2 A synthetic methodology for the synthesis of substituted β-carbolines from 3-bromoindoles and commercially available ketones *via* Pd-catalysed enolate arylation is discussed. The α-functionalisation of the keto-indole intermediate with electrophiles provided access to C4-functionalised β-carbolines. The one-pot protocol for this sequence was also developed.

2.3 A protected pyruvate equivalent that allows the α-arylation and α-arylation/alkylation reactions to be carried out at the methyl group *via* Pd-catalysed enolate arylation is presented. The deprotection of the OBO moiety allows the formation mono and multiply α-functionalised pyruvates.

2.4 The synthesis of isoquinoline, β-carboline and indole esters *via* Pd-catalysed enolate arylation of the OBO-protected pyruvate equivalent developed in this thesis is demonstrated. The functionalisation of these heterocycles *via* α-alkylation of the aryl-ketone intermediates is also discussed and some examples synthesised to validate the methodology.

Abbreviations and Acronyms

Å	Ångström
Ac	Acetate
Amphos	Di-tert-butyl(4-dimethylaminophenyl)phosphine
Ar	Aryl
B	Base
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
b.p.	Boiling point
Boc	tert-Butyloxycarbonyl
bpy	2,2'-Bipyridine
br.	Broad
Bu	Butyl
cm^{-1}	Wavenumber
cod	1,5-Cyclooctadiene
COSY	Correlated spectroscopy
Cy	Cyclohexyl
d	Doublet
d.r.	Diastereomeric ratio
DAST	Diethylaminosulfur trifluoride
DavePhos	2-Dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
1,2-DCB	1,2-Dichlorobenzene
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless enhancement by polarisation transfer

DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	N,N-Dimethylformamide
DMP	Dess–Martin Periodinane
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dtbpf	1,1'-Bis(di-tert-butylphosphino)ferrocene
E^+	Generic electrophile
EDC·HCl	(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
en route	During the course of (Latin)
eq	Equivalent(s)
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron-withdrawing group
g	Gram
h	Hour(s)
HIV	Human Immunodeficiency virus
HMBC	Heteronuclear multiple-bond correlation
HMDS	Hexamethyldisilazide
HOBt	Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
i	Iso
in situ	In position (Latin)
in vacuo	In a vacuum (Latin)
IR	Infrared
IUPAC	International union of pure and applied chemistry
J	Scalar coupling constant

K_a	Acid dissociation constant
L	Generic ligand
LDA	Lithium diisopropylamide
Lit.	Literature report
LUMO	Lowest Unoccupied Molecular Orbital
[M]	Generic metal
M	Molar
m	Multiplet
m	meta
M	Mega
m.p.	Melting point
m/z	Mass to charge ratio
Me	Methyl
μL	Microlitre(s)
μW	Microwave irradiation
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
mol%	Molar percent
MS	Molecular sieves
Ms	Methanesulfonyl
n	Normal
naph	Naphthyl
NBS	N-Bromosuccinimide
NHC	N-Heterocyclic carbene
nm	Nanometre(s)
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser effect
Nu	Generic nucleophile

[O]	Generic oxidant
o	ortho
OBO	4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl
°C	Degrees Celsius
p	para
PG	Protecting group
pH	–log[Ka]
Ph	Phenyl
PIDA	Phenyliodine diacetate
pin	Pinacolato
Piv	Pivaloyl
pK_a	–log[Ka]
ppm	Parts per million
ppy	2-Phenylpyridine
Pr	Propyl
pTSA	p-toluenesulfonic acid
Py	Pyridyl
q	Quartet
QPhos	1,2,3,4,5-Pentaphenyl-1'-(di-tert-butylphosphino)ferrocene
R	Generic alkyl group
RT	Room temperature
s	Singlet
sec	Secondary
S_N2	Bimolecular nucleophilic substitution
T	Temperature
t	Triplet
T3P®	Propylphosphonic anhydride solution
TBAB	Tetrabutylammonium bromide
TBAT	Tetrabutylammonium difluorotriphenylsilicate

TBHP	tert-Butyl hydroperoxide
TBS	tert-Butyldimethylsilyl
tert/*t*	Tertiary
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
tol-BINAP	2,2'-Bis(di-p-tolylphosphino)-1,1'-binaphtyl
Ts	p-Toluenesulfonyl
ν	Resonant frequency
via	By way of (Latin)
ν_{max}	Absorption maximum
vs	Versus
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Chapter 1: Introduction

1.1. Palladium-catalysed enolate arylation

1.1.1 Palladium cross-coupling reaction

Chemical reactions capable of forging new C–C bonds are at the centre of synthetic organic chemistry, drawing the attention of chemists since the early days of this science. In this context, metal-catalysed cross-coupling reactions are among the most versatile means of building complex carbon backbones in an efficient way while at the same tolerating a range of chemical functionalities.

The development of the field can be traced back to Ullman's discovery of the homodimerisation of 2-bromonitrobenzene in the presence of copper, a $C(sp^2)$–$C(sp^2)$ bond-forming transformation.[1] The next fundamental step was provided by Meerwein in 1939 with the development of a copper(II)-catalysed coupling of aryldiazonium salts with alkenes[2] and Kharasch, in 1943, with the cobalt-catalysed coupling of vinyl bromides with arylmagnesium bromides.[3] These reports represent the earliest examples of the coupling of two different partners relying on a catalytic amount of metal.

Two decades later, inspired by the Wacker process,[4] Heck investigated the behaviour of *β*-hydrogen-free organopalladium compounds, leading to the development of palladium-catalysed cross-coupling reactions between organomercurial compounds and alkenes.[5,6] This concept was improved in subsequent years and what is now known as the Mizoroki-Heck reaction emerged.[7,8,9] An aryl group (originating from an aryl halide or pseudohalide) is coupled to an alkene in a catalytic transformation orchestrated by the metal centre. A Pd(0) species inserts into an aryl-halide bond in a process called oxidative addition, generating a Pd(II) complex. Carbopalladation of the alkene forms a new Pd(II) intermediate that after *β*-hydride elimination forges the new C–C bond. A base then regenerates the original Pd(0) species, completing the cycle (**Figure 1**).

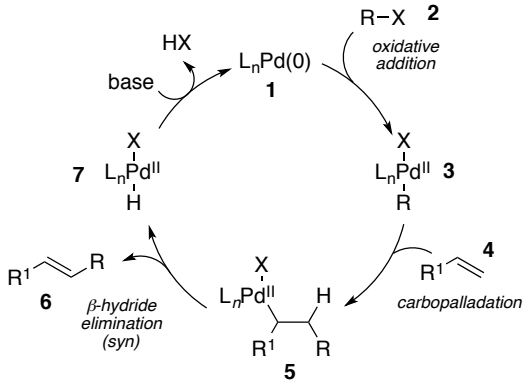


Figure 1. Mizoroki-Heck reaction catalytic cycle.

The intense work in the field in the following years led to the development of a myriad of palladium-catalysed cross-coupling reactions in which different versions of organometallic reagents are coupled with aryl halides and pseudohalides in a slightly modified catalytic cycle. In this cycle, the aryl group is transferred to the Pd(II) intermediate during the transmetalation step. Reductive elimination follows, creating a C–C bond and regenerating the Pd(0) active species (**Figure 2**).

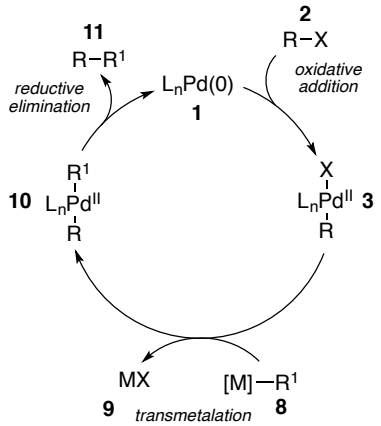


Figure 2. General catalytic cycle for Pd-catalysed cross-coupling reactions.

Figure 3 summarises some of the most important versions of this concept and their corresponding organometallic substrates: Corriu-Kumada coupling (Grignard reagents),[10,11] Sonogashira coupling (Cu(I) acetylides),[12] Negishi coupling (organoaluminium and organozinc reagents),[13,14] Stille coupling (organotin reagents),[15,16] Suzuki-Miyaura (organoboranes)[17] and Hiyama coupling (organosilanes).[18]

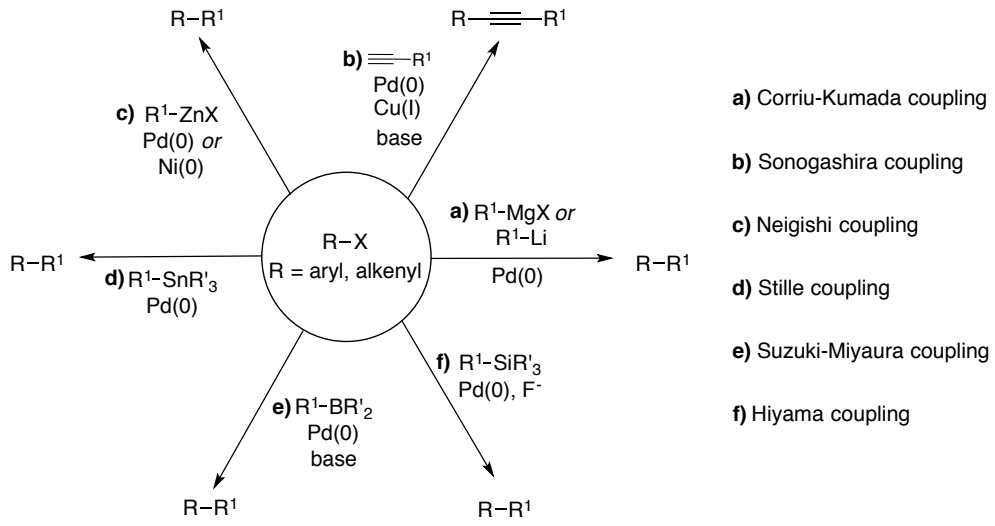


Figure 3: Summary of Pd-catalysed cross-coupling reactions.

The scope for this reaction was expanded beyond the formation of C–C bonds with the development of a protocol to build C–N bonds, the Buchwald-Hartwig amination.[19,20] Other carbon-heteroatom protocols such as C–S[21,22] and C–O[23,24] couplings were also established, making the palladium-catalysed cross-coupling reaction a fundamental tool in organic synthesis.[25,26]

1.1.2 Earliest examples of enolate arylation

The formal construction of a $C(sp^2)$–$C(sp^3)$ bond in the alpha position of ketones has been explored in the literature for years. Prior to the development of a catalytic methodology, several approaches were proposed albeit suffering from major setbacks such as use of stoichiometric amounts of toxic organometallic reagents[27,28,29] or the need to use pre-functionalised ketones.[30,31,32]

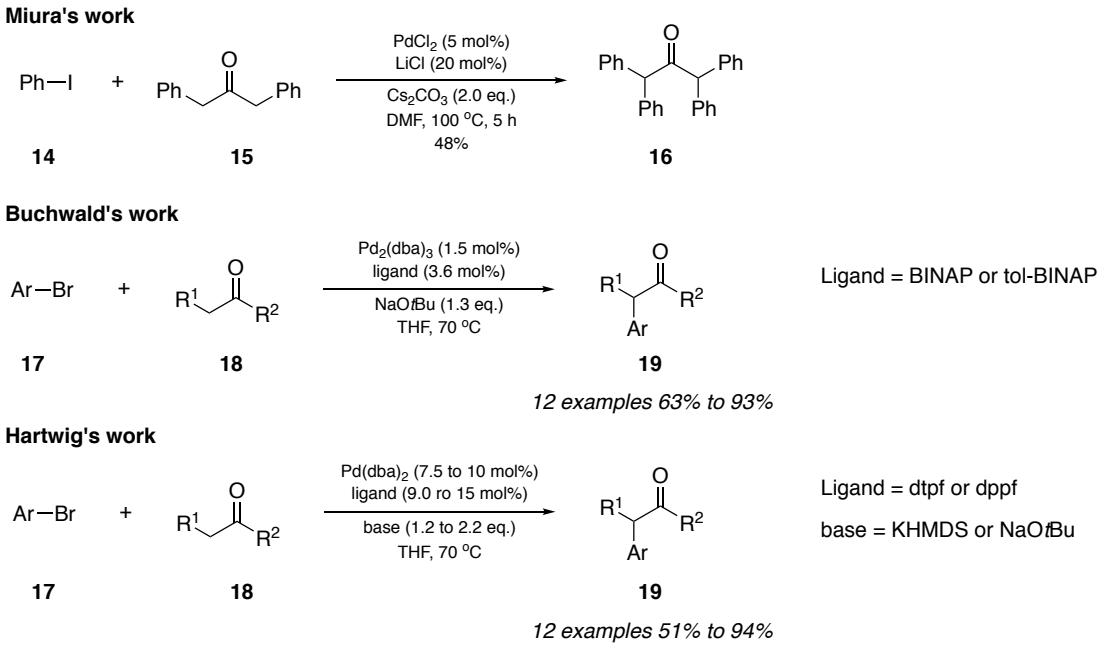
The first example of a palladium-catalysed α-arylation of a ketone emerged in 1997 when Natsume and co-workers reported the intramolecular α-arylation of a methyl ketone with aryl triflates in the synthesis of fused hetereocyclic pharmacophores (**Scheme 1**).[33]

12
X = O, S or CH

13

Scheme 1. Intramolecular α-arylation of **12**.

Shortly thereafter, Miura,[34,35] Buchwald,[36] Hartwig[37] and co-workers concomitantly introduced conditions to allow the intermolecular α-arylation of ketones using a choice of palladium and, in the two latter cases, also a phosphine ligand (**Scheme 2**). Buchwald reported the initial discovery as a by-product found during the study of the Pd-catalysed *O*-arylation of alcohols, Hartwig isolated the α-arylated ketone by-product while investigating Pd-catalysed aminations in acetone while Miura found one example of enolate arylation in the context of a study involving mono- and diarylation of 2-phenylphenols.



Scheme 2. Early examples of intermolecular Pd-catalysed α-arylation of ketones.

The proposed mechanism for this transformation involves the oxidative addition of Pd(0) to aryl bromide forming a Pd(II) complex **20** followed by ligand substitution with the metal

enolate affording Pd(II) complex **23**. Reductive elimination then liberates α-aryl ketone **19** and regenerates the catalytic active Pd(0) species (**Figure 4**).

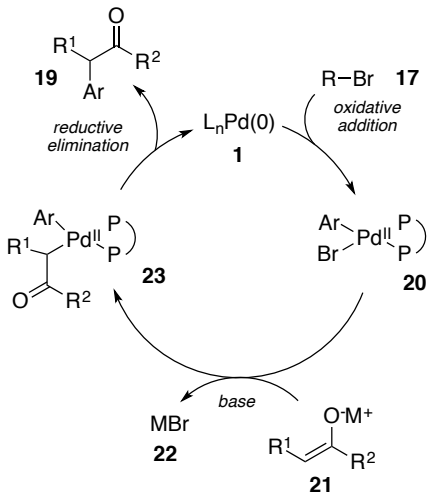
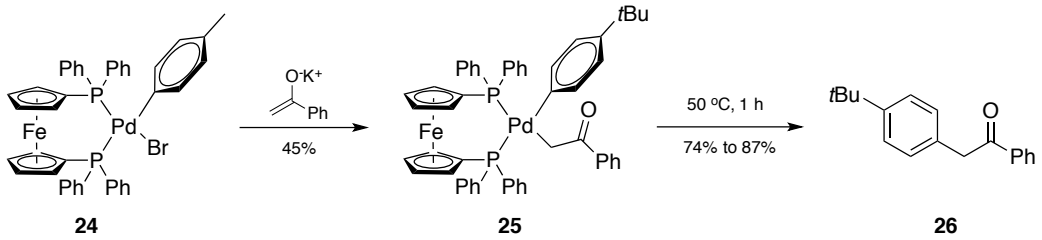


Figure 4. Proposed mechanism for the Pd-catalysed α-arylation of ketones.

Hartwig observed that Pd(II) complex **24** cleanly generated a new complex characterised by $^{31}P\{^{1}H\}$ and ^{1}H NMR spectroscopy as being **25**. ^{1}H NMR spectroscopy showed a signal at δ 3.40 corresponding to the ketone methylene protons as a virtual triplet (J_{HP} = 10.7 Hz), coupling to two different phosphine ligands, indicating that the enolate is C–bound to the palladium centre. Moreover, complex **25** was completely consumed after 1 h at 50 °C, affording aryl-ketone **26** (**Scheme 3**).



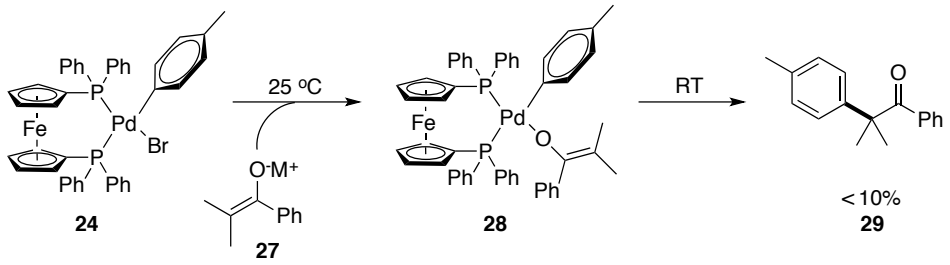
Scheme 3. Mechanistic studies of Pd(II) intermediates.

1.1.3 Catalyst/ligand system

In order to elucidate the role of the ligand in the catalytic cycle, Hartwig conducted a systematic screening[38] of different catalytic systems considering some premises: 1) oxidative addition as well as reductive elimination involve both low-coordinate Pd(0) intermediates which means that steric effects should increase the energy of the more stable high coordinate species, facilitating reductive elimination and product formation;[39,40] 2) alkylphosphines are normally more resistant toward P–C cleavage than arylphosphines, which increases catalyst turnover number;[41,42] 3) chelation should prevent β-hydride elimination.[43,44]

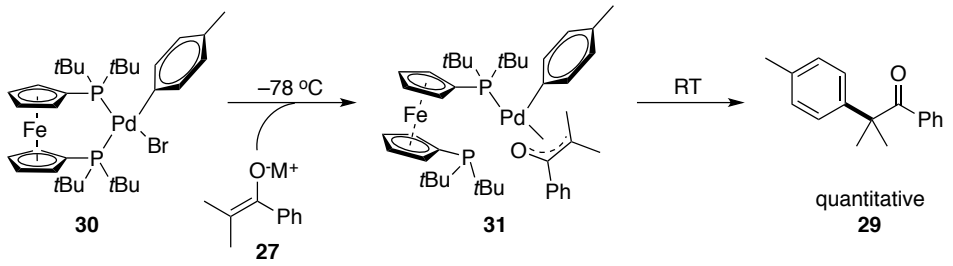
Following these ideas, dtbpf showed high activity with both bromo- and chloroarenes, the latter at only 70 °C, and turnover numbers of 20,000 were obtained.

In order to evaluate the role of chelation, arylpalladium complex **24** was reacted with isobutyrophenone enolate **27**. Spectroscopic data showed that *O*-bound palladium complex **28** was formed. This species reacted at RT delivering <10% of product **29** along with biaryl by-products (**Scheme 4**).



Scheme 4. Mechanistic studies with Pd complex **24**.

On the other hand, the more sterically bulky arylpalladium complex **31** was formed at –78 °C in contact with enolate **27**. $^{31}P\{^{1}H\}$ showed two singlets at 24.8 and 57.2 ppm in a 1:1 ratio, typical regions for coordinated and uncoordinated ligands, suggesting that complex **31** is bound to the metal by only one phosphorous atom. Complex **31** cleanly underwent reductive elimination to give product **29** in quantitative yield at RT. Due to spectroscopic difficulties, the geometry and hapticity of the enolate in the complex **31** could not be determined (**Scheme 5**).[38]



Scheme 5. Mechanistic studies with Pd complex **30**.

These observations suggested that sterically hindered monophosphines can be effective catalysts for enolate arylation chemistry and, indeed, commercially available P(*t*Bu)$_3$ and PCy$_3$ proved effective in this transformation. These results show that the selectivity for reductive elimination over β-hydride elimination might be driven by sheer steric hindrance.[38]

Buchwald corroborated these observations demonstrating that a series of electron-rich biaryl monodentate molecules could be active ligands for the α-arylation of ketones (**Figure 5**).

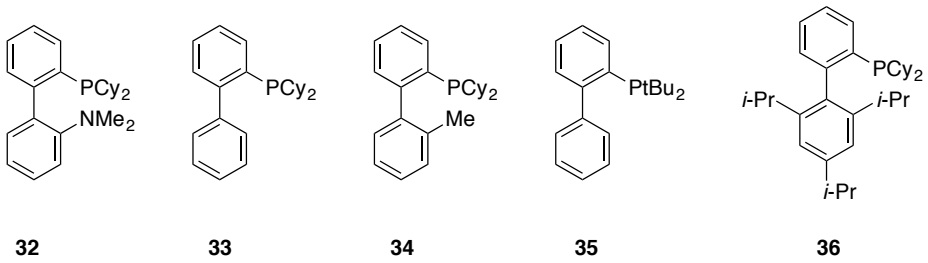


Figure 5. Buchwald's biaryl ligands.

A series of substrates were tolerated under the reaction conditions studied and aryl bromides as well as aryl chlorides were competent coupling partners.[45]

1.1.4 α-Arylation scope

The application of this chemistry is not limited to the α-arylation of ketones. Several different methodologies were developed to construct C(sp^3)–C(sp^2) bonds by taking advantage of acidic C–H bonds next to a variety of functional groups.

The cross-coupling of silyl enol ethers with aryl halides, for example, demonstrates some advantages when compared to the aforementioned ketone α-arylation: greater functional group compatibility due to the reduced basicity of the system and the possibility to perform the coupling at the more hindered site of ketones with two enolisable positions.[46] Some protocols initially involved the use of stoichiometric organotin reagents as a means of generating stannyl enolates prior to the transmetalation step in the catalytic cycle,[47] however, a series of tin-free protocols relying on a combination of different metal fluorides were later developed. **Table 1** shows one of these examples. The cause of the synergistic effect observed when using a combination of different metal fluorides was, nevertheless, unclear to the authors of the study.[46]

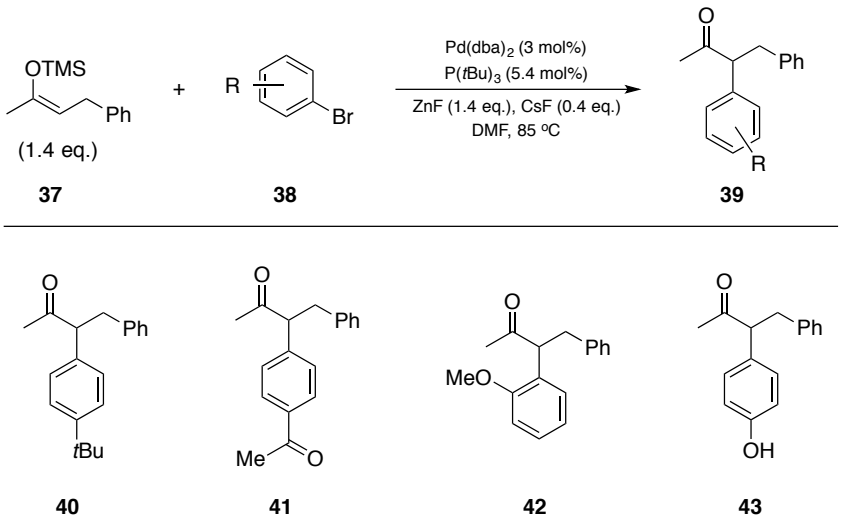


Table 1. Pd-catalysed α-arylation of silyl enol ether **37**.

Despite the predisposition for aldehydes to undergo unwanted aldol condensation under basic conditions, Miura and co-workers overcame this side reaction and proposed the first intermolecular Pd-catalysed α-arylation reaction employing a $Pd(OAc)_2/P(tBu_3)_3$ catalytic system in dioxane.[48] Years later, Buchwald developed a more general and mild protocol, exploring conditions in which the aldol reaction would be reversible,[49,50] by means of avoiding the dehydration of the intermediate that typically occurs at high temperatures. The proposed methodology tolerated a wider range of substrates and at the same time relied on lower catalyst loadings and substrate equivalents. This α-arylation protocol could also be carried out using aryl chlorides as well as bromides as coupling partners in comparable yields. (**Table 2**).[51]

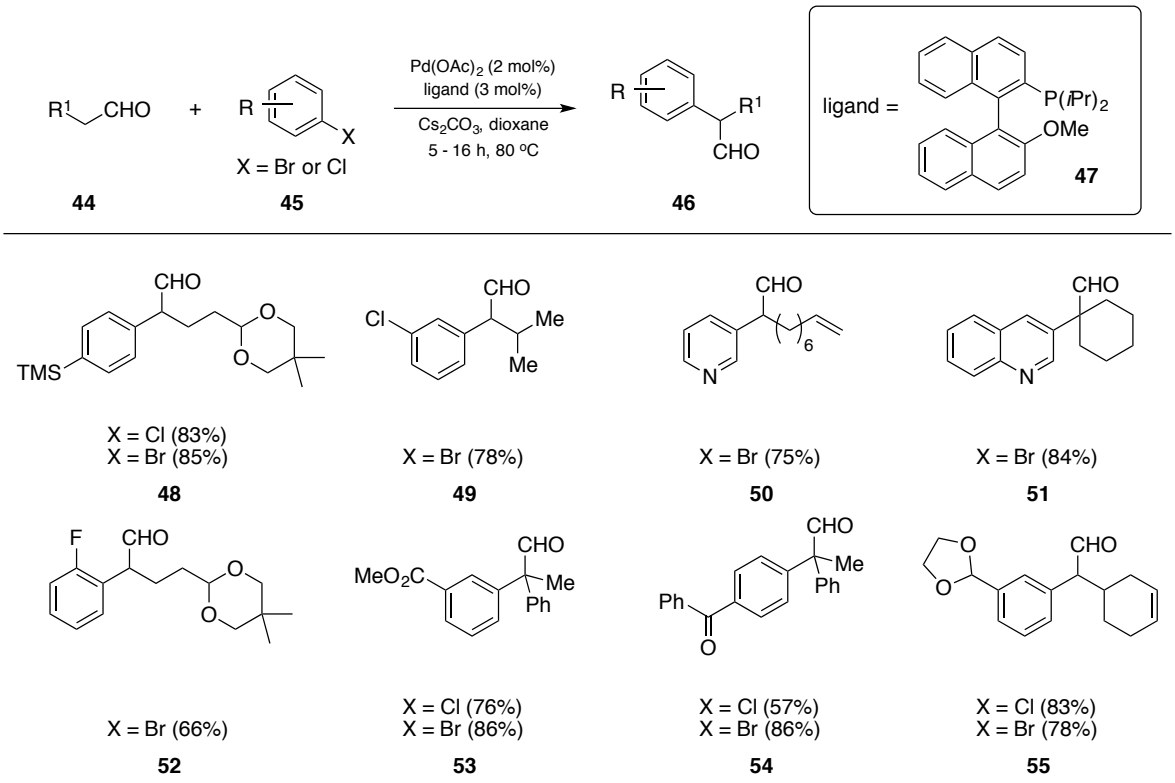
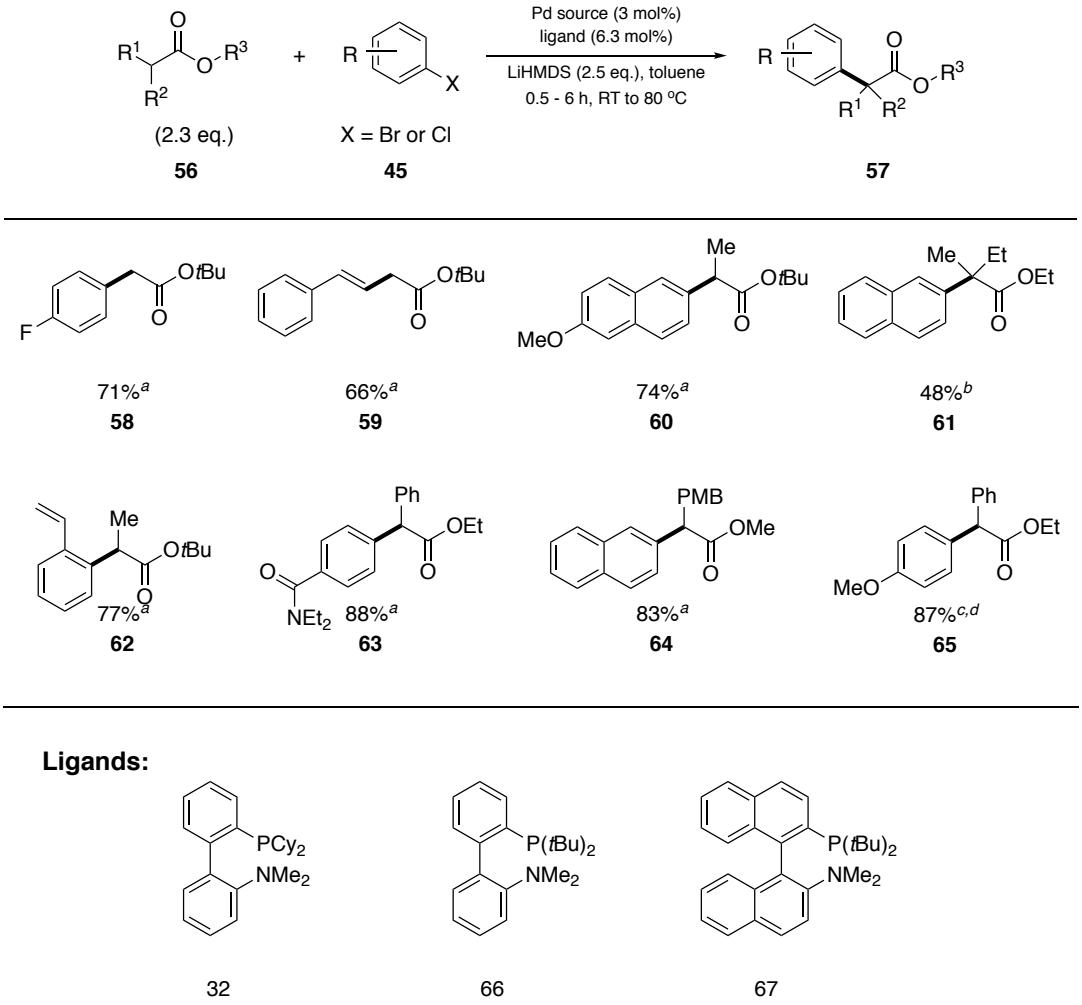


Table 2. Pd-catalysed α-arylation of aldehydes with aryl halides.

Esters were also studied as coupling substrates in this reaction. Despite the lack of regioselectivity problems linked to this functional group, their lower reactivity and the potential to undergo Claisen condensation can pose problems for the clean formation of α-aryl esters under basic conditions. Buchwald found that a series of bulky electron-rich biaryl phosphines and the use of LiHMDS could deliver the transformation in good yields, despite the need for an excess of the ester starting material in order to account for the formation of condensation by-products. A variety of α-arylated esters were successfully synthesised under these conditions. *tert*-Butyl, ethyl and methyl esters were tolerated, as well as acetates, propionates and α-α-disubstituted esters. Aryl bromides and chlorides were also active as coupling partners. **Table 3** shows 8 representative examples of the α-arylated products obtained following this protocol.[52]



Ligands:

32 66 67

Table 3. Representative scope for the α-arylation of esters. [a] Ligand **32**, [b] ligand **67** and [c] ligand **66**. [d] aryl chloride used as coupling partner.

Amides, a related carbonyl substrate, pose more complex challenges associated with the conditions required for α-arylation to occur. Stronger bases are required, which limits the scope of the aryl halide to electron-neutral or electron-rich rings and at the same time leads to catalyst decomposition, requiring higher loadings of palladium. Hartwig proposed the use of *in situ* generated zinc amide enolates, which could be made by adding *sec*-BuLi[53,54] at –78 °C, followed by $ZnCl_2$ at RT. The Reformatsky reagent then cleanly arylated at mild temperatures, allowing a series of α-arylated amides in good yields (**Table 4**).[55]

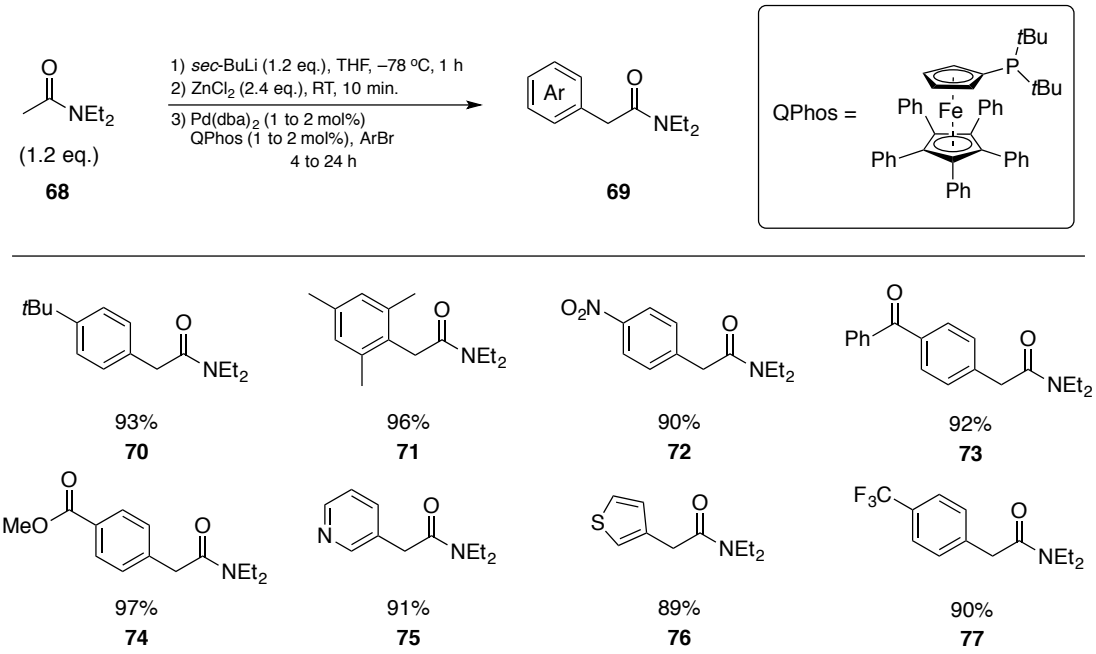


Table 4. One-pot α-arylation of amides *via* zinc amide enolate.

Other methodologies avoiding the formation of organozinc intermediate have been developed, however, the formation of diarylated products is a constant problem to overcome.[56,57]

Finally, it is important to mention that Pd-catalysed α-arylation protocols are not limited to the functional groups described above. Some other acidic functionalities have been subject to related procedures in literature, such as ketimines,[58] lactones,[59] nitriles,[60] nitroalkanes,[61] sulfoximines[62] and sulfones.[63]

1.1.5 Enantioselective α-arylation of carbonyl compounds

Following Buchwald's initial work on the α-arylation of ketones employing a $Pd_2(dba)_3$/BINAP catalytic system (**Scheme 2**),[36] investigations were focused on the development of an enantioselective version of this transformation. The initial attempts to form tertiary stereocentres using a similar protocol failed, which led the group to focus on the formation of quaternary centres using 2-methyl-α-tetralones as starting material. This report showed the feasibility of an enantioselective ketone α-arylation, albeit employing harsh conditions and high catalyst loadings.[64] Years later, the same group developed a mild methodology to carry out

enantioselective α-arylation reactions on 2-alkylcyclopentanones. 5-*N*-methyl-anilino-methy-ene was chosen as a blocking group to avoid competitive side reactions; this could easily be removed by acidic hydrolysis followed by retro-Claisen reaction.[65] A combination of a low catalyst loading with newly developed binaphthyl ligands at RT provided mild reaction conditions that allowed the installation of aryl groups in good yields and reasonable to excellent enantiomeric excess (**Table 5**).[66]

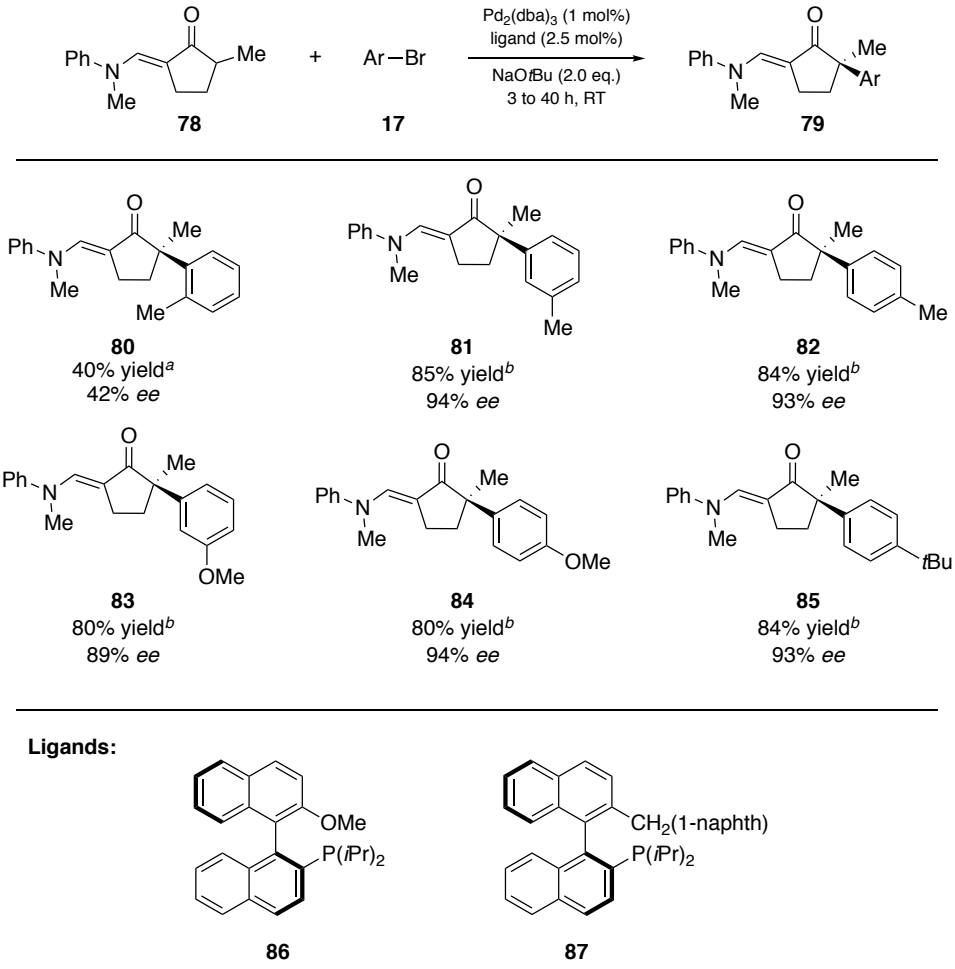


Table 5. Scope for the enantioselective α-arylation of α-protected-2-methyl-cyclopentanones. [a] Ligand = **86**; [b] ligand = **87**.

The fact that α-arylated ketones are more acidic than the ketone starting material dramatically limits the formation of tertiary chiral centres under the basic conditions required for the Pd-catalysed α-arylation reaction as base-labile stereocentres are likely to undergo racemisation in the presence of alkali metal enolates.[67] Based on these assumptions, Hartwig

and co-workers proposed the diastereoselective arylation of silyl enolates derived from Evans' chiral auxiliaries.[68] They started from the premise that trimethylsilyl ketene acetals undergo Lewis-acid promoted aldol reaction[69] and found that weakly basic zinc additives promoted the Pd-catalysed α-arylation reaction in good diasteriomeric ratios without racemisation of the products (**Table 6**). They credit the requirement for different reaction temperatures when ZnF_2 or $Zn(OtBu)_2$ were used as additives to differences in solubility.

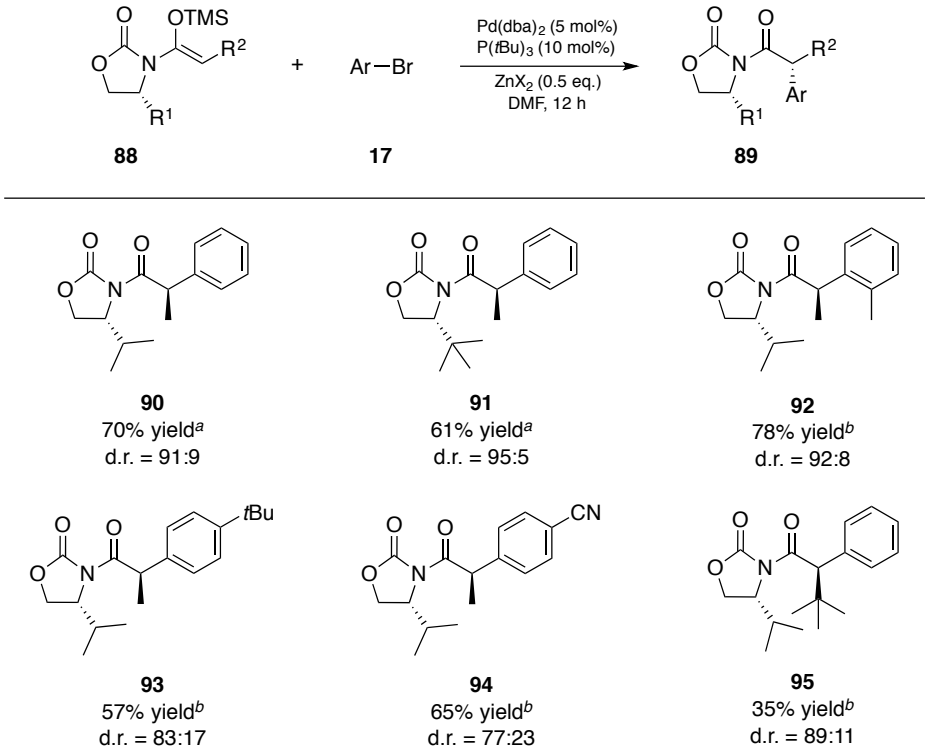


Table 6. Scope for the diastereoselective α-arylation of silyl enolates derived from Evans' chiral auxiliaries. [a] $ZnX_2 = Zn(OtBu)_2$, temperature = RT; [b] $ZnX_2 = ZnF_2$, temperature = 80 °C.

The final challenge in the field was the formation of tertiary α-centres avoiding both racemisation and double arylation. Building on the precedent shown in **Table 6**, Zhou reasoned that the use of weakly basic activators could prevent the deprotonation of the arylated products allowing catalyst control of stereochemistry. They found that *O*-trimethylsilyl ketene acetals derived from *tert*-butyl propionate and aryl triflates (more active in this type of couplings)[70] in conjunction with LiOAc as activator and a monophosphine as ligand allowed the enantioselective installation of aryl groups in good yields and *ee* (**Table 7**).[71]

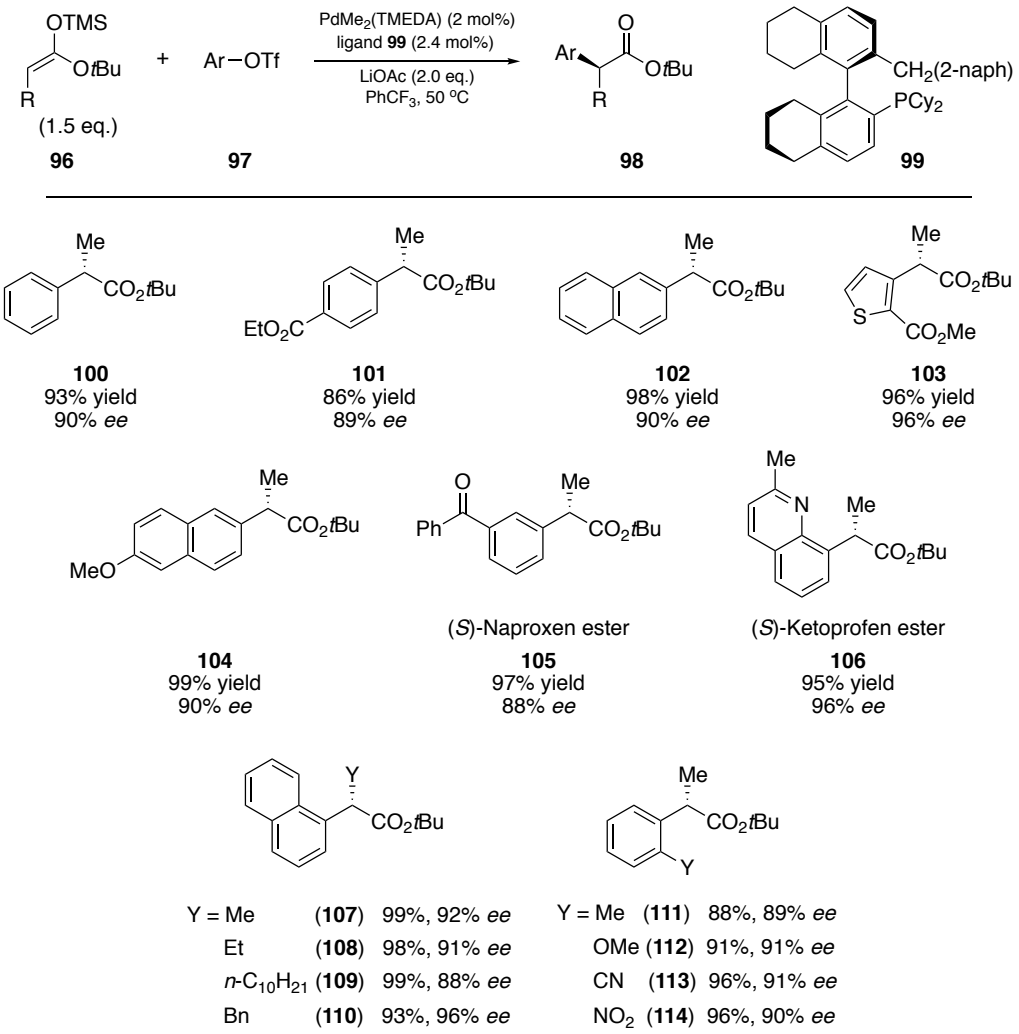


Table 7. Scope for the enantioselective α-arylation of ester enolates.

It was pointed out that the size of the alkyl group in the acetal had a major influence on the *ee* observed with the *tert*-butyl giving the best results. Likewise, the geometry of the enolate impacted the outcome of the reaction, with (*Z*)-isomer giving poor *ee*, which indicates that LiOAc was not forming a lithium enolate that would rapidly equilibrate between the two geometric isomers.[71]

The proposed mechanism is depicted in **Figure 6**. After oxidative addition, a palladium cationic species **116** is formed. Binding of acetate to palladium intermediate **117** allows the transfer of the enolate from silicon to palladium *via* a bridged structure **119**. Finally, reductive elimination releases enantioenriched product **122** and regenerates the active Pd(0) species (**Figure 6**).

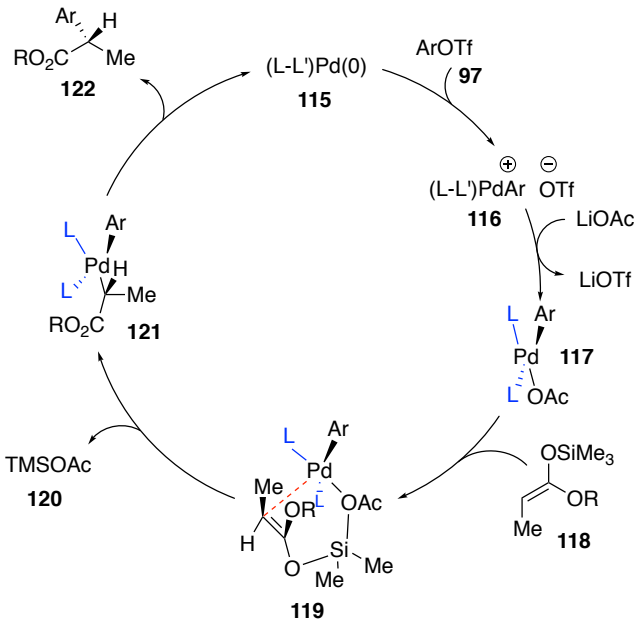


Figure 6. Proposed catalytic cycle for the enantioselective α-arylation of ester enolates.

The examples shown in this chapter attest to the versatility of the Pd-catalysed α-arylation reaction for the functionalisation of a variety of acidic C-H bonds. The selection of functional groups allowed in the arylic moiety coupled in the process and the number of substrates involved in these reactions, make this chemistry fundamental in the making of C–C bonds.

1.2. Pyruvate derivatives in organic synthesis

1.2.1. Pyruvate synthons

Pyruvate derivatives are attractive small molecules in organic synthesis due to their dense number of functional groups and inherent ambident reactivity: they have the potential to react both as nucleophiles and electrophiles under specific conditions.

The general structure incorporates a d^2 synthon and two a^1 synthons (**Figure 7**).

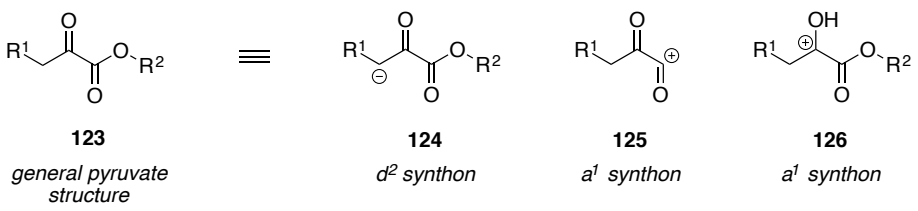
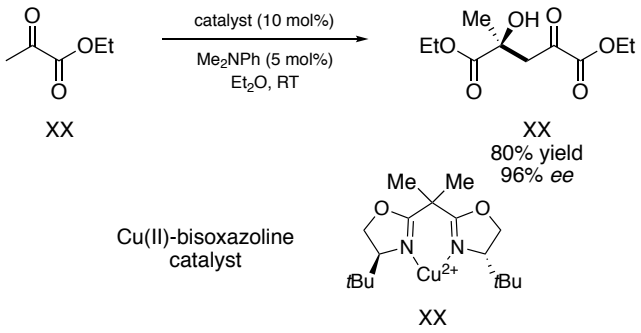


Figure 7. Representation of d^2 and a^1 synthons derived from pyruvates.

By controlling the reactivity of these molecules, one can incorporate this relatively small fragment in a sequence of transformations capable of considerably increasing structural complexity after only a few steps. Therefore, it is expected that the selective activation of pyruvates is the focal point of its chemistry and the key to benefiting from both of its reactivities.

1.2.2. First stereoselective transformations

In 2000, Jørgensen and co-workers reported the first successful stereoselective transformation involving a pyruvate. In this publication, a chiral Lewis acid based on a Cu(II)-bisoxazoline complex mimics the action of pyruvate-dependent aldolases[72] in the enantioselective homo-aldol reaction of ethyl pyruvate (**Scheme 6**).[73]



Scheme 6. Stereoselective homo-aldol reaction of ethyl pyruvate **127**.

Chiral catalyst **129** generated and stabilised the enol form of **127**, controlling the stereochemistry of this addition.

1.2.3. Mannich-type reactions

Relying on a similar catalytic system, the same group later reported the first Mannich reaction involving pyruvate derivatives and *N*-tosyl-α-imino esters, in which these substrates react in a diastereo- and enantioselective fashion, allowing the formation of *syn* products (**Table 8**).[74]

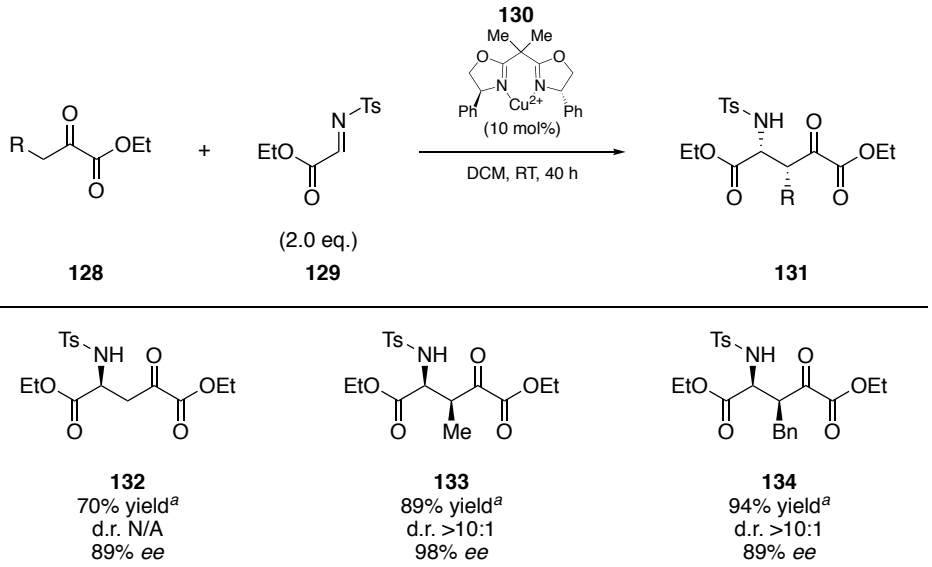


Table 8. Mannich reaction between pyruvates **128** and *N*-tosyl-α-imino esters **129**.

Taking advantage of the electrophilic character of the ester moiety, upon treatment with L-selectride and *p*TSA, highly functionalised enantiomerically pure lactones were accessed in good yields (**Scheme 7**).

Scheme 7. Synthesis of enantiomerically pure lactones from 1,5-diesters **131**.

The presence of an *N*-tosyl group in the product is, however, not desirable from a synthetic point of view as the required deprotection is not trivial.

Exploring this drawback, Shibasaki and co-workers developed an asymmetric *syn* Mannich-type reaction between α-keto anilides and various *N*-thiophenesulfonyl imines.[75] Relying on a La/Li bimetallic catalyst, a greater variety of γ-amino amides were synthesised in good yields and selectivities (**Table 9**).[76]

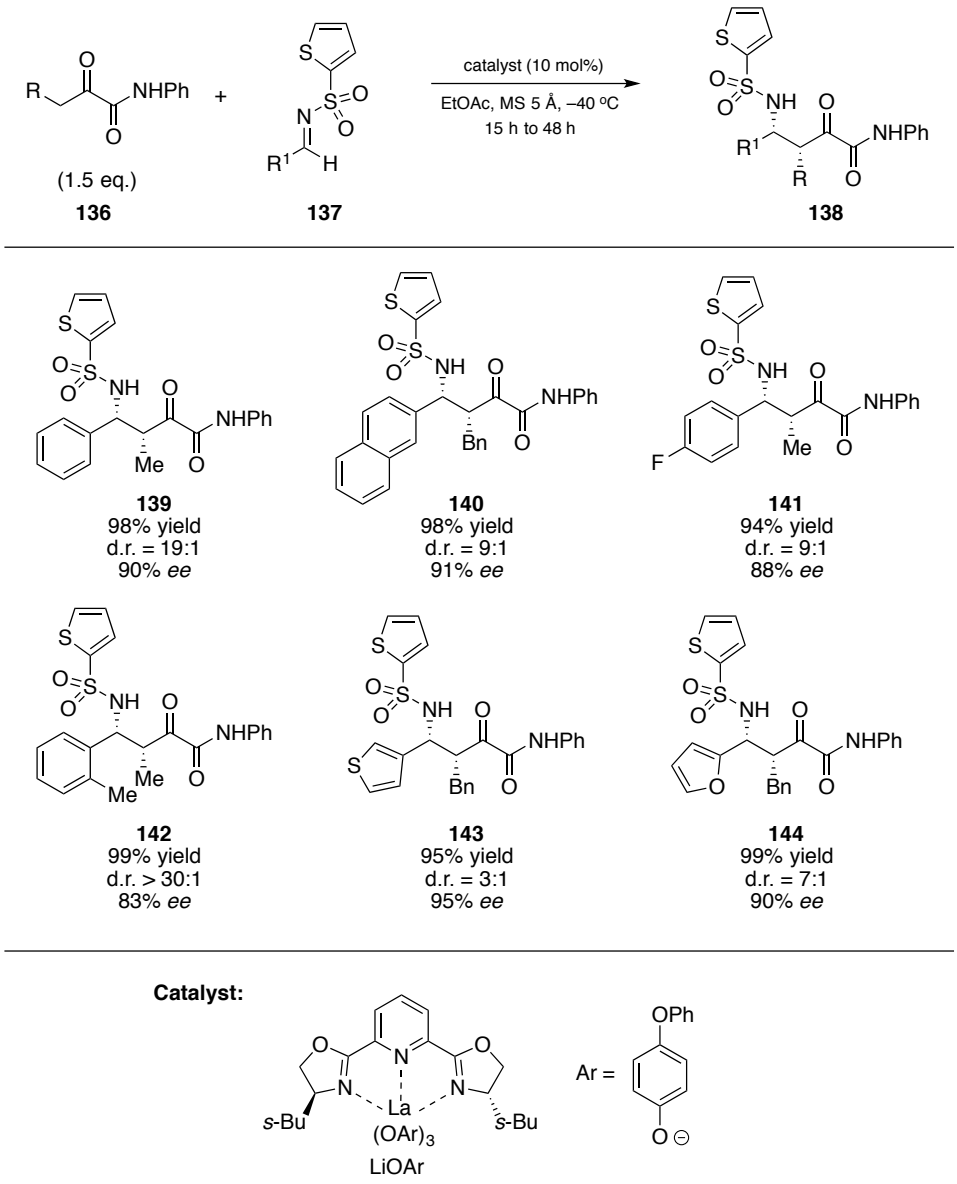


Table 9. The *syn*-Mannich reaction between α-ketoanilides and *N*-thiophenesulfonyl imines.

The same group later published a complementary methodology presenting an *anti*-selective asymmetric Mannich-type reaction. The reaction of α-ketoanilides and *o*-nitrobenzenesulfonyl (*o*-Ns) imines was catalysed by a biphenyldiamine-based dinucleating Schiff base (**153**) and delivered *anti*-γ-amino-amides in good yields (**Table 10**).[77]

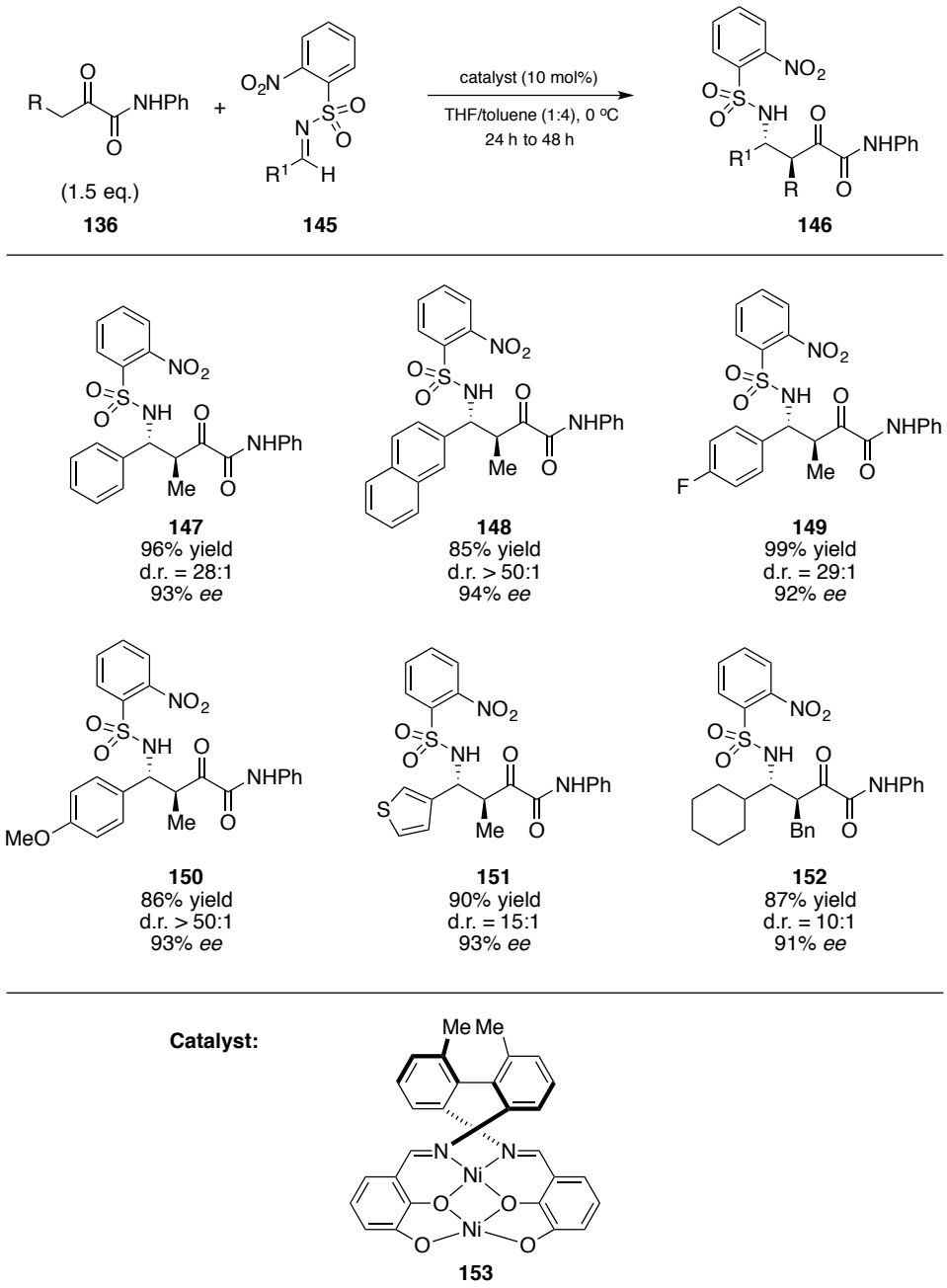


Table 10. Representative examples of the *anti*-Mannich reaction between α-ketoanilides and *o*-nitrobenzenesulfonyl imines.

1.2.4. Conjugate addition to nitroalkenes

In 2010, Sodeoka and co-workers published the first report of a diastereo- and enantioselective conjugate addition of pyruvates to nitroalkenes. A nickel complex combined with a structurally

simple chiral diamine ligand delivered a series of *anti*-Michael adducts in good yields and selectivities requiring a low catalyst loading (**Table 11**).[78]

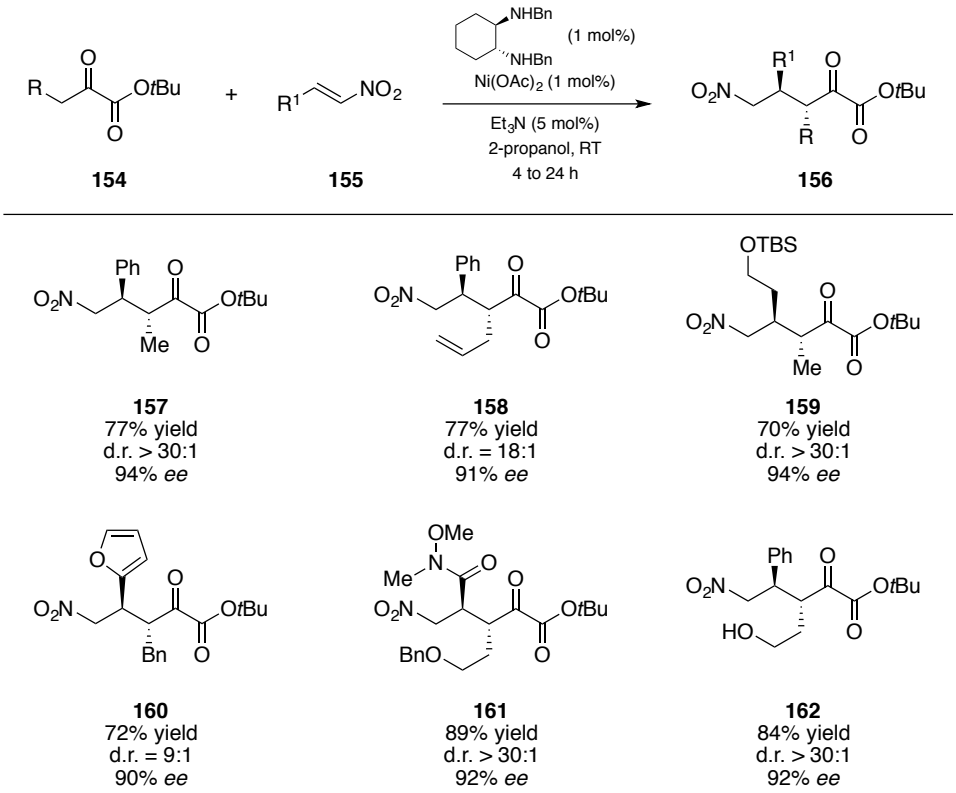


Table 11. Representative examples of *anti*-conjugate addition of pyruvates **154** to nitroalkenes.

Shibasaki and co-workers later described a complementary *syn* selective version of this transformation employing the previously active dinuclear nickel catalyst **153**[77] and α-ketoanilides as nucleophiles.[79]

In a different approach to this reaction, Rodriguez and co-workers disclosed a diastereo- and enantioselective *anti*-conjugate addition of α-ketoanilides to nitroalkenes, employing an ingenious bifunctional amino thiourea organocatalyst. This metal-free protocol allowed the formation of a good range of Michael adducts in high yields and excellent selectivities (**Table 12**).[80]

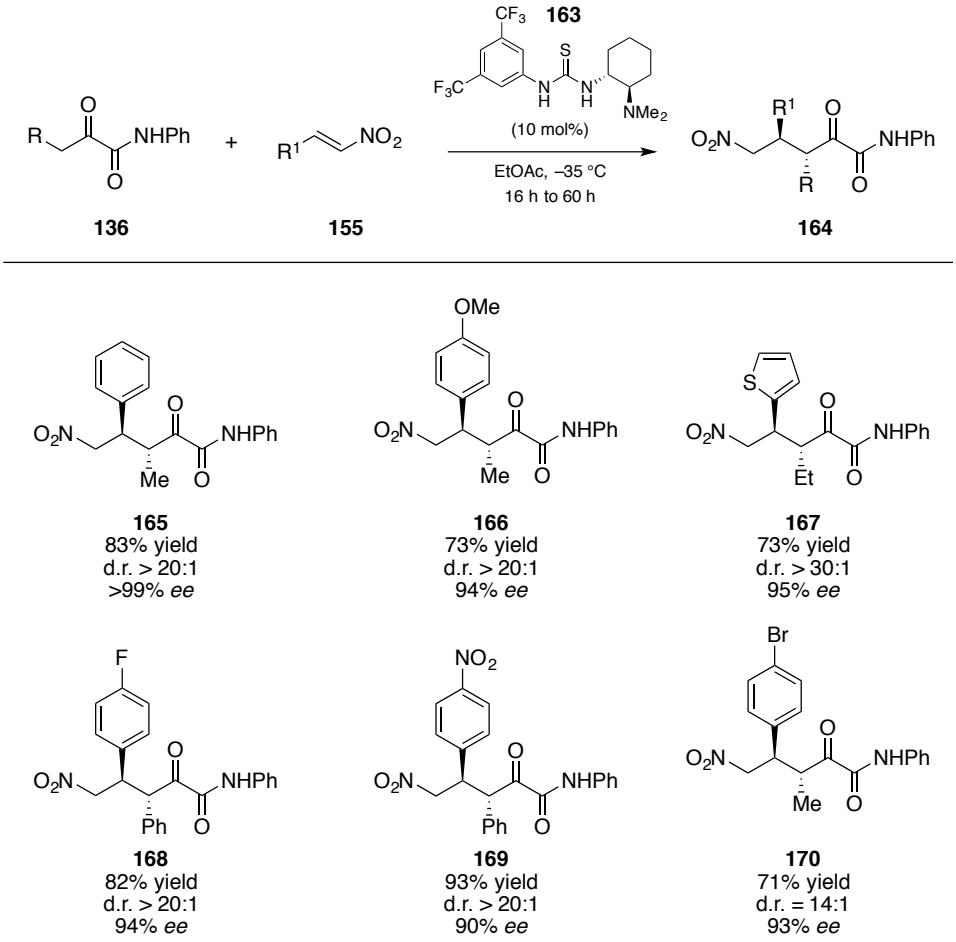
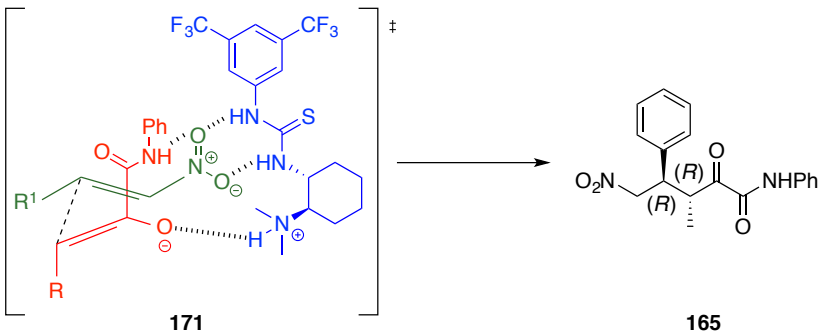


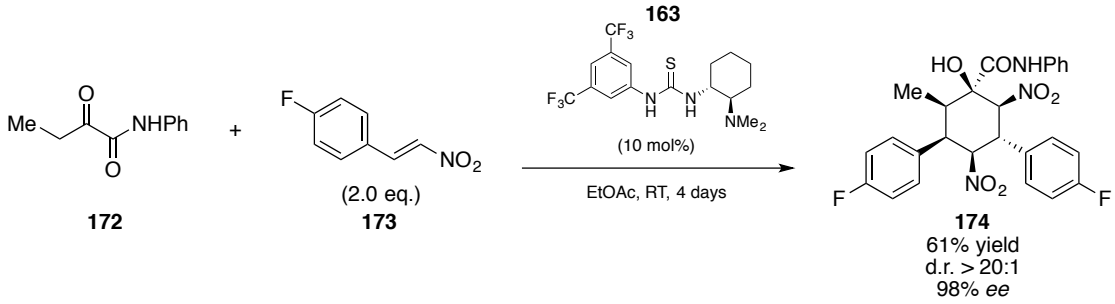
Table 12. Organocatalysed *anti*-Mannich reaction between α-ketoanilides and nitroalkenes.

The authors proposed an electrophilic activation of the nitroalkene *via* a bidentate hydrogen bond interaction and concomitant protonation of the tertiary amine basic centre. This conformation allows a preferential approach from the *Si* face of the (*Z*)-enolate on the *Re* face of the nitroalkane (**Scheme 8**).[80]



Scheme 8. Proposed transition state for the Michael addition.

In order to demonstrate the applicability of this transformation, the group used this organocatalysed reaction to build a densely functionalised cyclohexane ring (**174**) in remarkably high *ee* in a Michael-Michael-Henry cascade reaction (**Scheme 9**).



Scheme 9. Enantioselective synthesis of hexasubstituted cyclohexane **174** *via* an asymmetric Michael-Michael-Henry cascade reaction.

1.2.5. Aldol reactions

Aldol reactions involving pyruvate derivatives are widely explored as a tool to construct complex heterocyclic structures in sequential reactions, attesting to the utility of the previously discussed ambident reactivity of these molecules.

The cross-aldol reaction between pyruvic acids and various aldehydes catalysed by a proline-derived organocatalyst allowed the enantioselective synthesis of a series of isotetronic acid derivatives. The yields obtained range from poor to good, with aldehydes bearing electron-donating groups showing low reactivity (**Table 13**).[81]

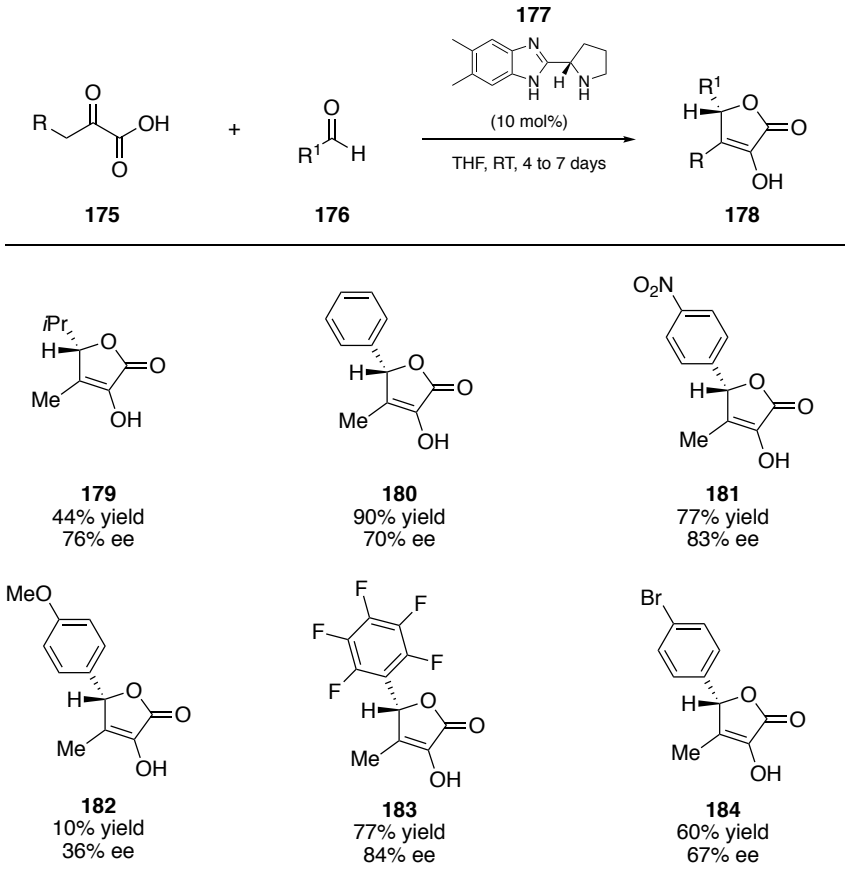


Table 13. Enantioselective synthesis of isotetronic acid derivatives *via* an aldol reaction.

The authors suggested a chair-like transition state in which the benzimidazole ring is protonated by the carboxylic acid and the aldehyde is activated by hydrogen bonding interactions (**Figure 8**).

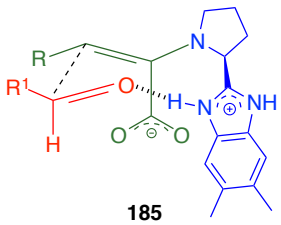
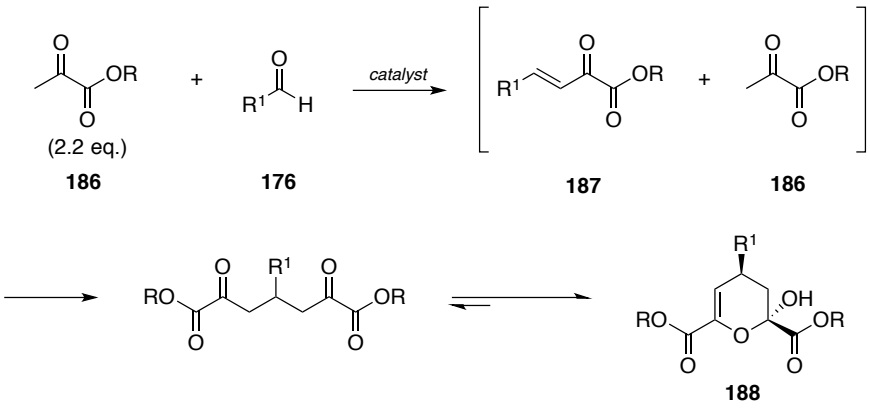


Figure 8. Proposed transition state for the Michael addition.

Likewise, Tanaka and co-workers explored this reaction to develop a one-pot synthesis of dihydropyrans.[82] A sequential transformation starting with the aldol formation of a

β,*γ*-unsaturated *α*-ketoester (**187**) followed by Michael addition-cyclisation delivered dihydropyrans with the general structure **188** (**Scheme 10**).



Scheme 10. Overview of dihydropyran formation from pyruvates and aldehydes.

The conditions screened identified (*S*)-*β*-proline as a very active catalyst for the cross-aldol reaction. The amino acid in combination with acetonitrile at RT allowed the formation of a series of substituted dihydropyrans (**Table 14**).

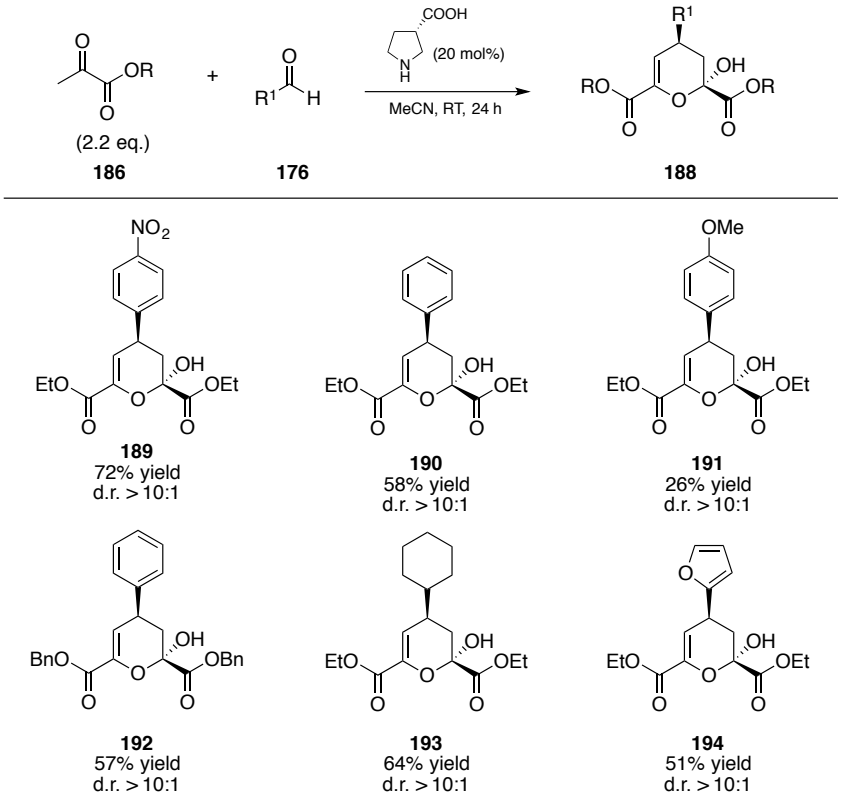
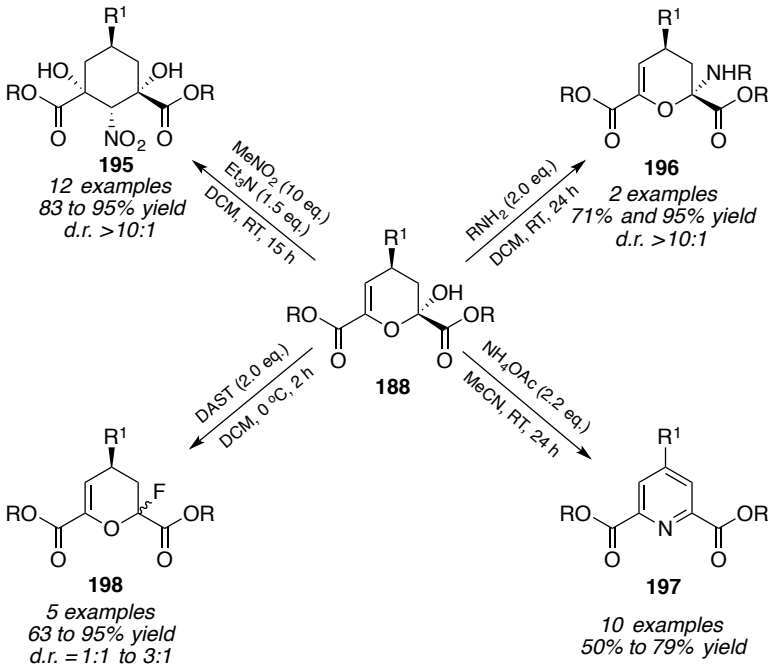


Table 14. Representative examples the (*S*)-*β*-proline catalysed synthesis of dihydropyrans.

The dihydropyrans were all mostly formed as single diastereomers (d.r. > 10:1) and the relative stereochemistry was determined by X-ray crystallography.

Taking advantage of the partial α-ketoester character of these products, the authors investigated simple chemical derivatisations that allowed the formation of a series of highly functionalised cyclohexanes and heterocycles (**Scheme 11**).



Scheme 11. Derivatisation of dihydropyran **188**.

1.2.6. Synthesis of aryl-pyruvates and aryl-pyruvic acids

The construction of $C(sp^3)$–$C(sp^2)$ bonds at the α-centre of pyruvates constitutes a transformation fundamentally different from the ones described above, which can be attested by the variety of approaches attempted in the past decades.

The first general procedure was described in 1966 by Horner and Renth. Condensation of ethyl dimethyl-glycinate (**199**) (and related compounds) with aromatic aldehydes generated ethyl acrylate intermediates (**201**), which are readily hydrolysed by aqueous HCl to furnish aryl-pyruvates (**202**) (**Table 15**).[83]

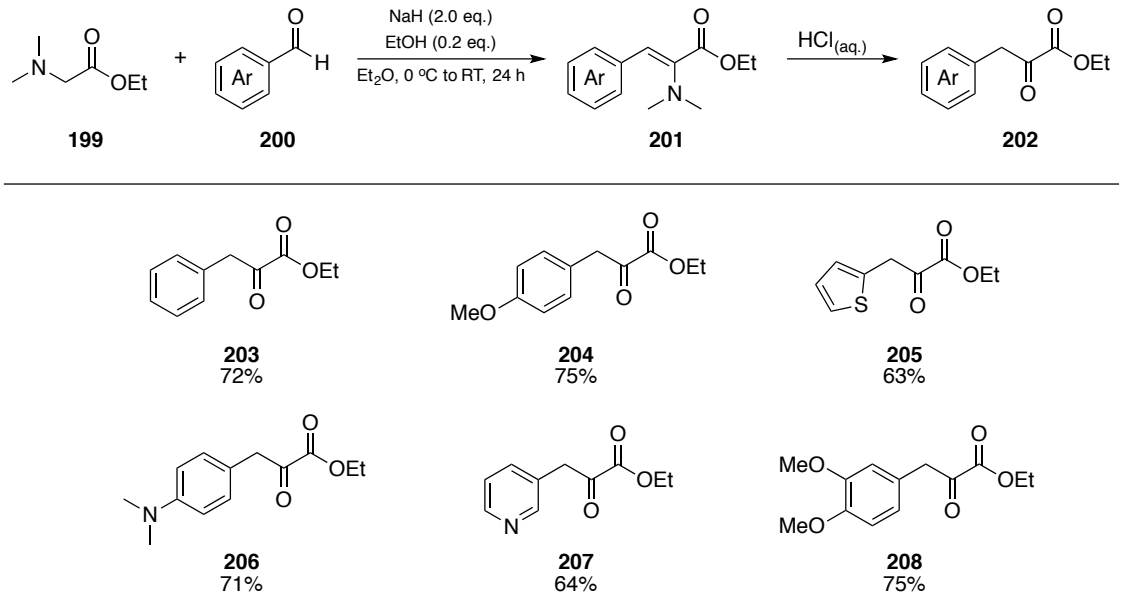


Table 15. Scope for the synthesis of aryl-pyruvates *via* condensation of ethyl dimethyl-glycinate with aromatic aldehydes. Yields given over 2 steps.

A related condensation-hydrolysis protocol was proposed decades later in the context of the synthesis of (±)-*β*-aryllactic acid derivatives. 4-Benzylideneoxazol-5(4*H*)-ones (**211**) were accessed *via* condensation of benzaldehydes with *N*-acetyl glycines (**209**), followed by acid-catalysed hydrolysis and general deprotection. Acrylic acid intermediates **212** were isolated and subjected to harsher hydrolysis conditions to furnish aryl-pyruvic acid derivatives (**Table 16**).[84]

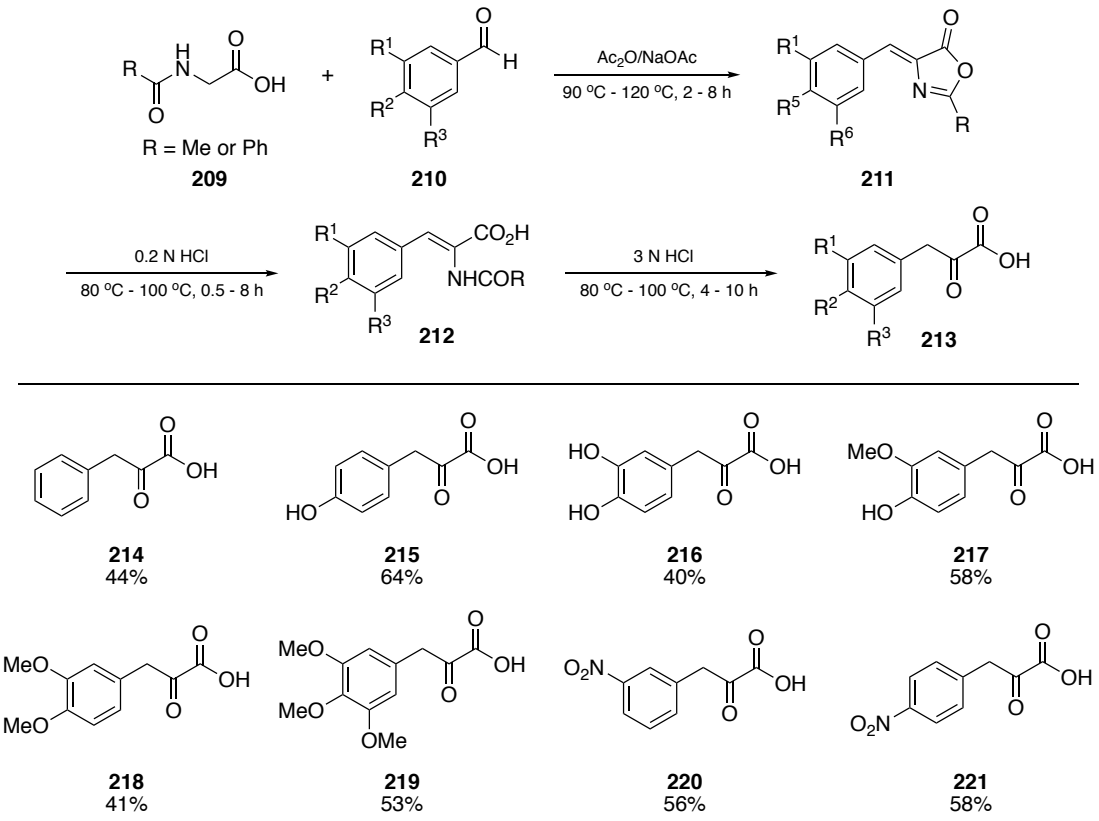


Table 16. Scope for the synthesis of aryl-pyruvates *via* 4-Benzylideneoxazol-5(4*H*)-one intermediates **211**. Yields given over 3 steps.

In 2015 Koo and co-workers reported the synthesis of aryl-pyruvates *via* catalytic oxidative deacetylation of acetoacetic esters *en route* to indoles. Addition of NaH to ethyl acetoacetate generated a stabilised carbanion *in situ* which was quenched upon addition of *ortho*-nitrobenzyl bromides. The intermediate **223** was then oxidised under air[85,86,87] in the presence of catalytic amounts of $Mn(OAc)_2$ and $CoCl_2$ (**Table 17**).[88]

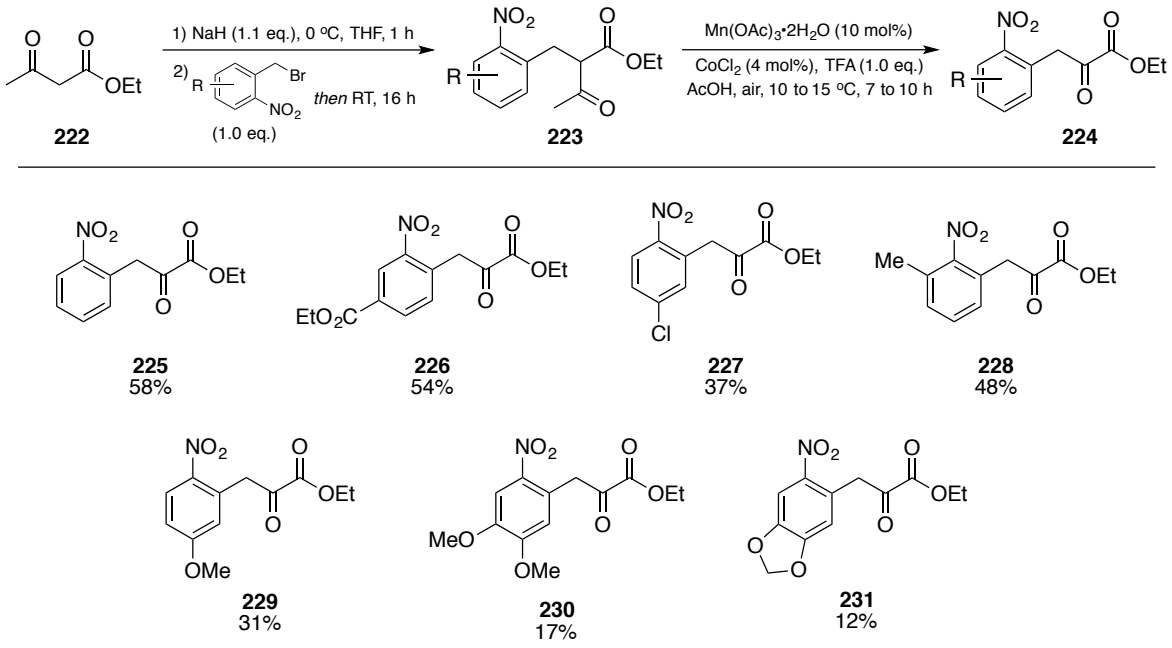


Table 17. Scope for the synthesis of aryl-pyruvates *via* catalytic oxidative deacetylation of acetoacetic esters.

In another oxidative approach to pyruvates, Yao and co-workers described the oxidation of a series of *β*-ketonitriles with PIDA. They found that 2 equivalents of the oxidant were capable of delivering the oxidised products in good yields. Moreover, the addition of nucleophiles permitted the formation of different esters and amides under slightly modified reaction conditions (**Table 18**).[89]

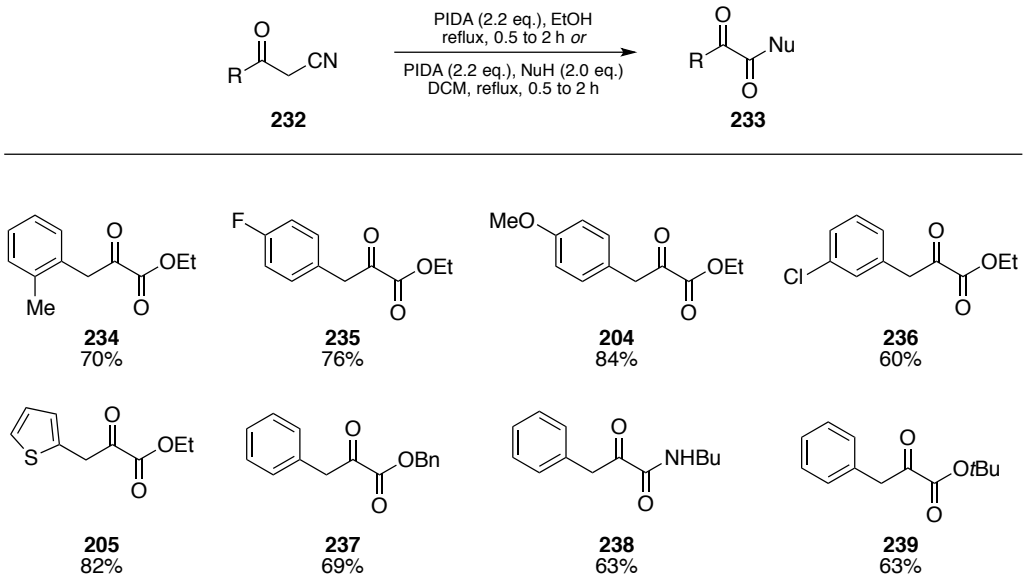
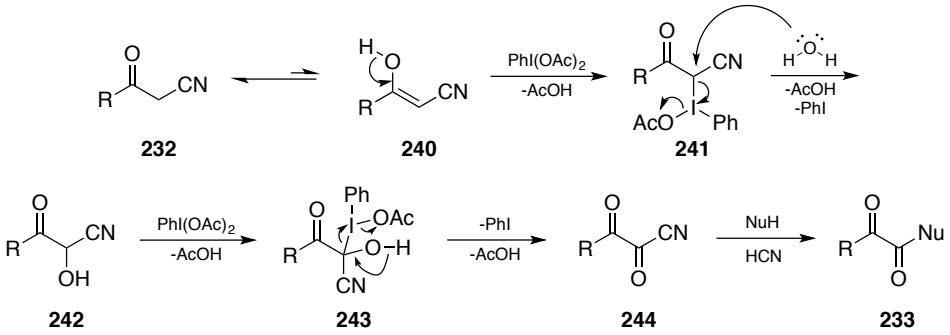


Table 18. Representative examples of the oxidation of *β*-ketonitriles with PIDA.

The proposed mechanism involves the addition of PIDA to the enol tautomer of substrate **232**. α-hydroxy-α-cyano-ketone **242** is formed after addition of water and release of iodobenzene and acetic acid. Addition of a second molecule of PIDA and loss of one equivalent of iodobenzene and acetic acid generates cyanide **244**, which then affords pyruvate derivatives upon reaction with a nucleophile and release of HCN (**Scheme 12**).



Scheme 12. Proposed oxidative mechanism for the synthesis of pyruvate derivatives from β-ketonitriles.

Some impressive work published recently by Johnson and co-workers tackled the enolate α-arylation of α-alkyl-pyruvates by relying on the hindered *tert*-butyl ester moiety and K_2CO_3 as a mild base, avoiding unwanted hydrolysis of the starting material.[90] α-Aryl-α-alkyl-pyruvates were synthesised in excellent yields and a variety of aryl bromides were tolerated in this catalytic protocol (**Table 19**).[91]

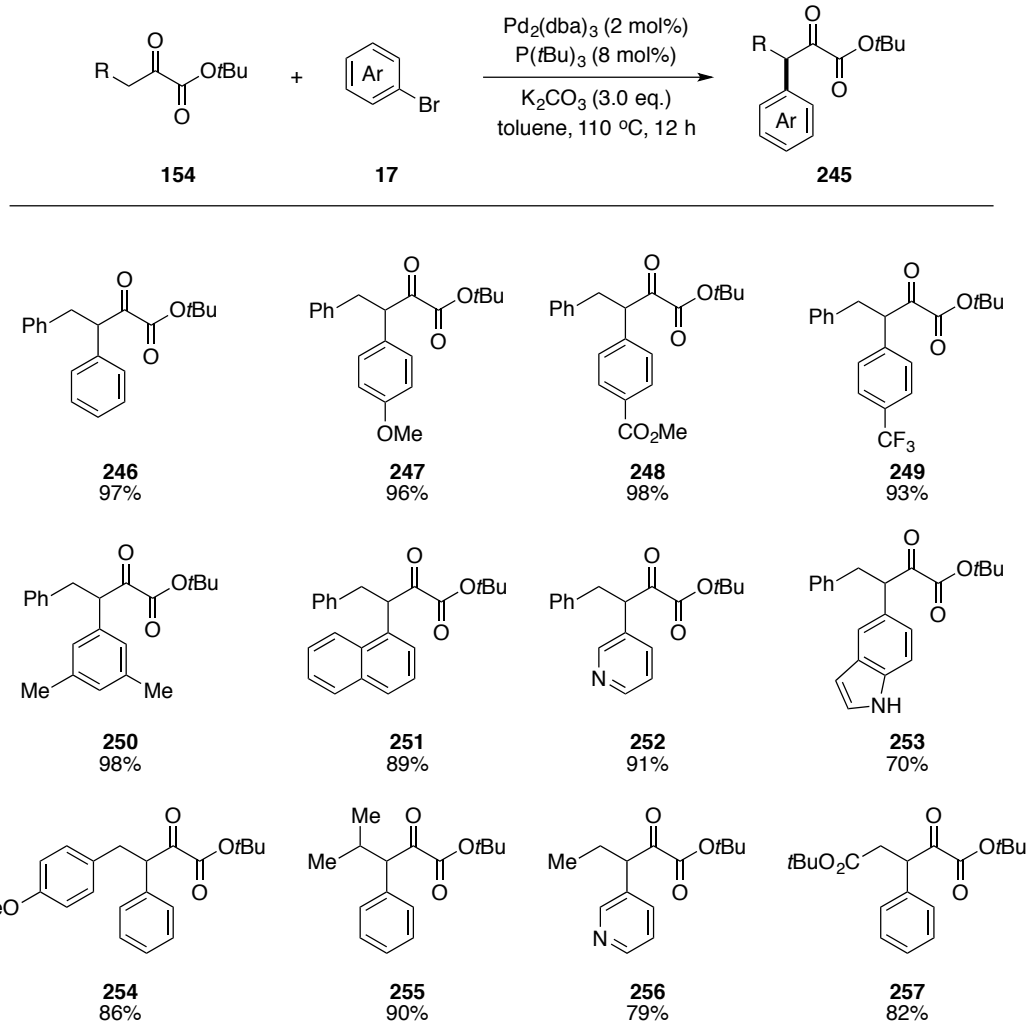


Table 19. Scope for the Pd-catalysed α-arylation of α-alkyl-pyruvates.

This protocol, as the first metal-catalysed direct coupling of an aryl electrophile and a pyruvate, greatly advanced the field of pyruvate chemistry, representing the most efficient and versatile route to α-aryl-pyruvates currently published.

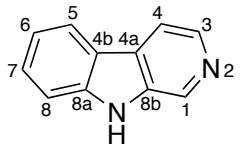
The transformations involving pyruvates and pyruvate derivatives presented in this chapter illustrate only part of the advancements in the field in the past years. Additional methodologies not discussed in detail involve: α-fluorination,[92] asymmetric Nazarov cyclisation,[93] asymmetric Claisen rearrangement,[94] α-amination[95,96] and [3+2] cycloaddition.[97]

1.3. Synthesis of heterocyclic aromatic esters

During the course of our studies towards the synthesis of substituted pyruvates *via* Pd-catalysed enolate arylation of a protected pyruvate equivalent (**Chapter 2.3**), the application of this small molecule in the *de novo* synthesis of heterocyclic aromatic esters emerged as potentially useful. This chapter will explore some of the literature precedents for the synthesis of these molecules as well as their importance as part of bioactive natural products and pharmaceuticals.

1.3.1 β-Carbolines

β-Carboline (IUPAC name: 9*H*-pyrido[3,4-b]indole) is a 14-π–electron nitrogen-containing heterocyclic aromatic compound comprising three fused rings, also known as norharmane (**Figure 9**).[98] The NH group is relatively acidic (pK_a = 14.5) and can be easily deprotonated by strong bases.[99]



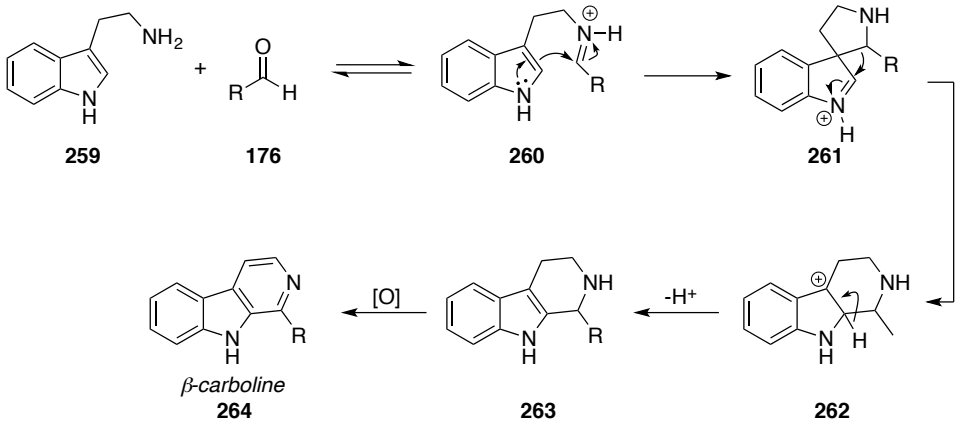
β-carboline
258

Figure 9. β-carboline structure and numbering.

The tricyclic structure of β-carbolines constitute an important *N*-heterocyclic aromatic core present in natural products and bioactive molecules.[100,101] This activity arises from its affinity towards a variety of different receptors in the central nervous system such as 5-hydroxy serotonin receptors,[102] monoamine oxidase[103] and benzodiazepine receptors.[104,105] In the view of these pharmacological properties, efficient methodologies for the synthesis of β-carbolines have been pursued over the years.

The most widely explored route to β-carbolines relies on the Pictet–Spengler reaction[106] as a means of constructing the heterocyclic pyridine ring skeleton from tryptophan derivatives **259** and aldehydes **176**.[107] After the condensation of **259** with **176**, a cascade of intramolecular

transformations delivers tetrahydro-*β*-carboline **263** which then forms *β*-carbolines upon oxidation, a route analogous to the biosynthetic pathway of naturally-occurring *β*-carbolines (**Scheme 13**).[108]



Scheme 13. Pictet–Spengler reaction in the *β*-carboline synthesis.

Relying on this sequence, *β*-carbolines have been synthesised from tetrahydro-*β*-carboline precursors under several different oxidative conditions. Hypervalent iodine reagents perform this transformation under mild conditions delivering *β*-carbolines in high yields, as published by Alarifi, Waters and co-workers (**Table 20**).[109,110]

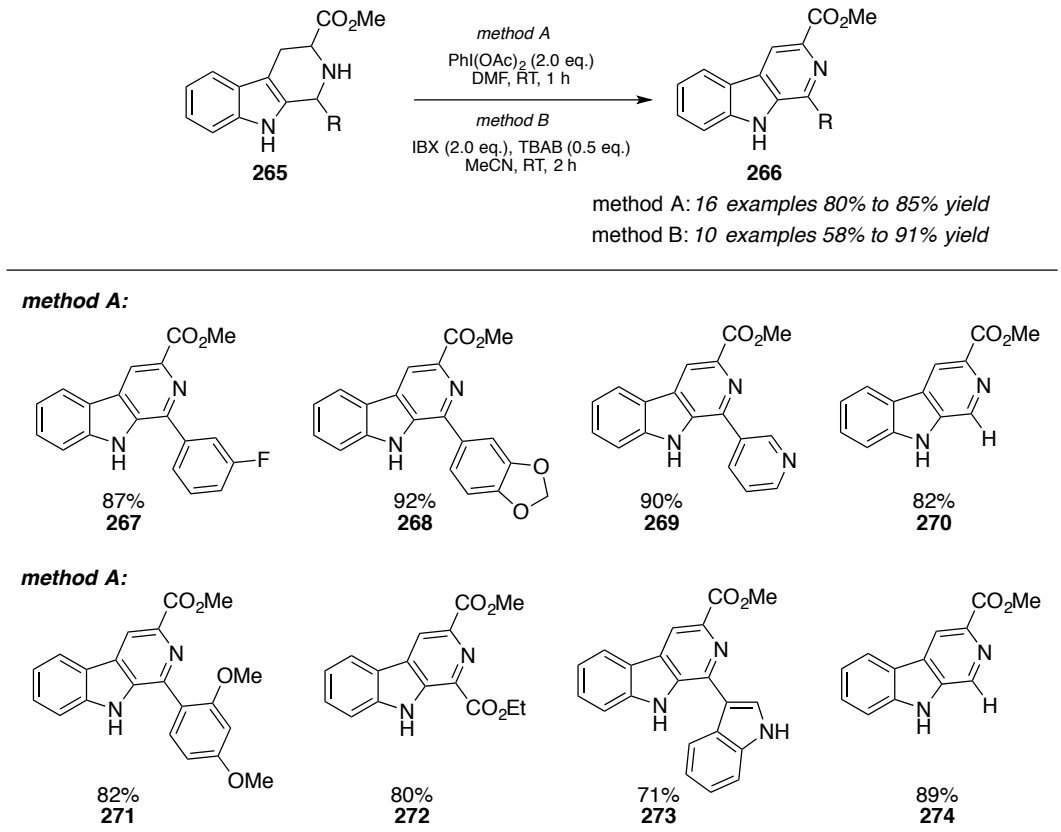


Table 20. Oxidation of tetrahydro-*β*-carbolines by hypervalent iodine reagents.

Some other oxidative agents have been reported for this transformation and include sulfur,[111] SeO_2,[112] MnO_2,[113] chloranil[114] and DDQ.[115]

In a similar approach carried out in one pot, Batra and co-workers described a protocol employing substoichiometric amounts of iodine in DMSO. Alkynes were used as aldehyde precursors, which upon oxidation allowed the formation of 2-oxoaldehydes *in situ*. Condensation of these building blocks with tryptophan esters delivered tetrahydro-*β*-carbolines, readily oxidised to 1-keto-*β*-carbolines in one pot (**Table 21**).[116]

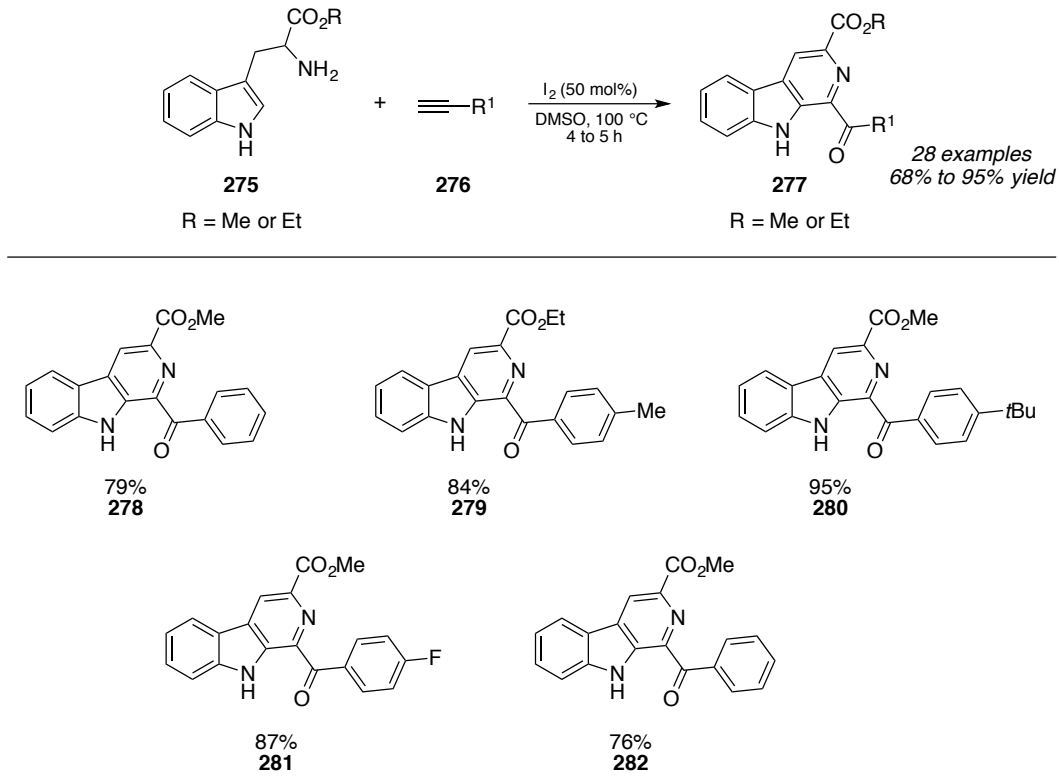


Table 21. Batra's *β*-carboline synthesis.

Despite the prevalence in the literature of the Pictet–Spengler reaction in the synthesis of *β*-carbolines, other methodologies have also been explored with different degrees of success. Larock and co-workers reported in 2001 an annulative approach to *β*-carbolines. In this publication, a Pd-catalysed annulation of internal alkynes with *tert*-butylimines of *N*-substituted 3-iodoindole-2-carboxaldehydes permitted the construction of a variety of substituted *β*-carbolines. Three examples (and two regioisomers) of *β*-carboline esters were reported (**Table 22**).[117,118]

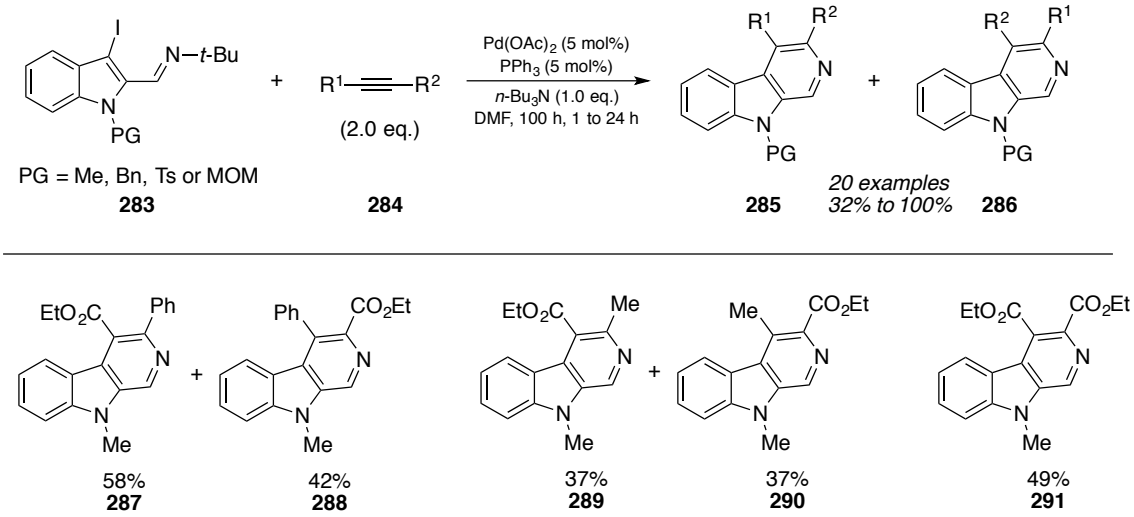


Table 22. Larock's annulative synthesis of substituted *β*-carbolines.

The proposed mechanism starts with the oxidative addition of Pd(0) to the imine **283** to form complex **292**. Carbopalladation with an internal alkyne **284** generates the vinylic intermediate **293** which then displaces iodide and forms the ionic palladacycle **294**. Reductive elimination regenerates the active Pd(0) species and eliminates *tert*-butyl carbolinium salt **295** which, driven by steric interaction between R^2 and the *tert*-butyl group[119] releases isobutylene and allows the formation of *β*-carboline product **285** (**Figure 10**).

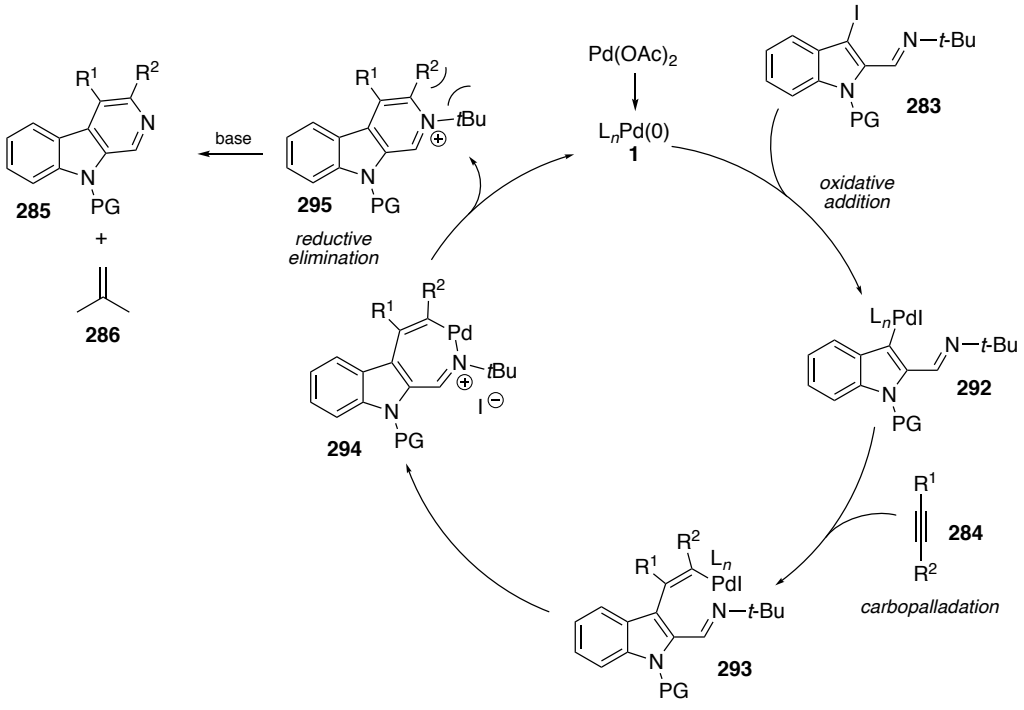


Figure 10. Proposed mechanism for the Pd-catalysed annulative synthesis of *β*-carbolines.

Despite the simplicity of this procedure, the poor regiocontrol over this reaction diminishes its synthetic attractiveness. Years later Jiao and co-workers developed a C–H activation version of this annulative transformation, however, poor regioselectivity was again a problem.[120]

In 2011, Witulski and co-workers reported a methodology based on the Ru-catalysed [2+2+2] cycloaddition[121] of yne-ynamides with methylcyanoformate to deliver *β*- and *γ*-carbolines. This protocol successfully allowed *β*-carboline esters to be formed in moderate to good yields (**Table 23**).[122]

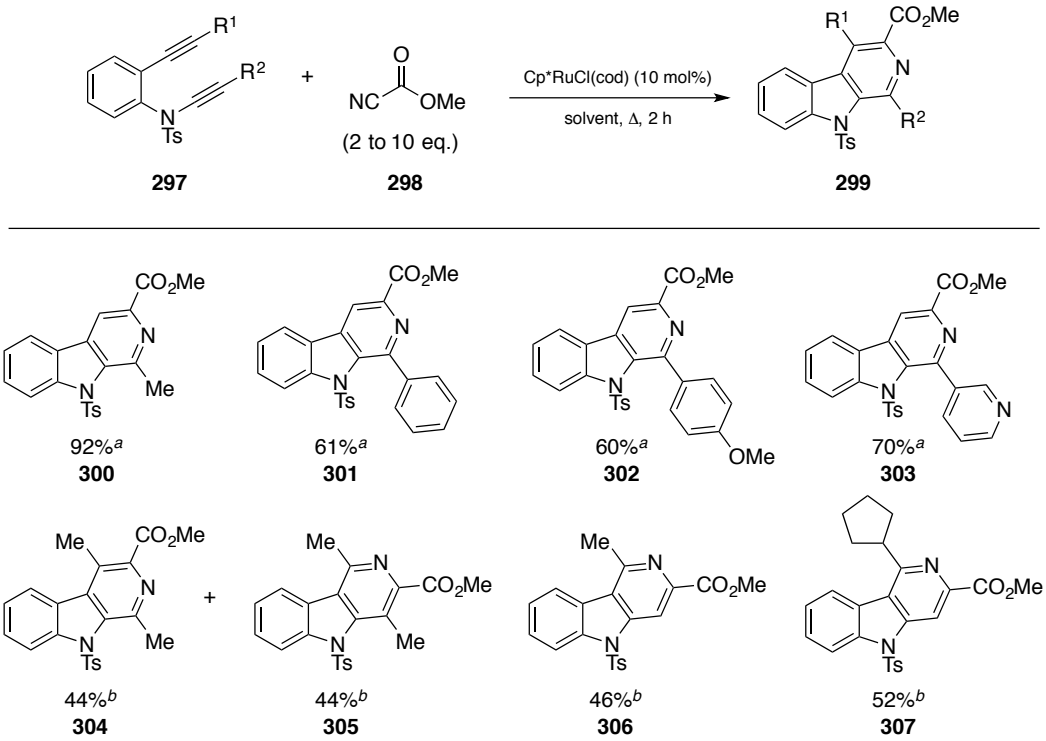
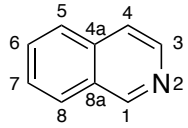


Table 23. Scope for the synthesis of *β*- and *γ*-carbolines *via* Ru-catalysed [2+2+2] cycloadditions of yne-ynamides with methylcyanoformate. [a] Temperature = 35 °C; [b] temperature = 120 °C.

Depending on R^1 and R^2 in the substrate **297**, however, poor regiocontrol was also observed. *β*-Carbolines were exclusively obtained when R^1 = H, whereas *γ*-carbolines were isolated when R^2 = H. When $R^1 = R^2$, mixtures of both regioisomers were observed in equal amounts. These results indicate that steric factors dictate the regiocontrol of the [2+2+2] cycloaddition, observation in consonance with other reports.[123,124]

1.3.2 Isoquinolines

Isoquinoline is a 10-π–electron benzopyridine in which the benzene ring is fused to the 3- and 4-positions of the pyridine ring. The compound structure and IUPAC numbering are shown in **Figure 11**.

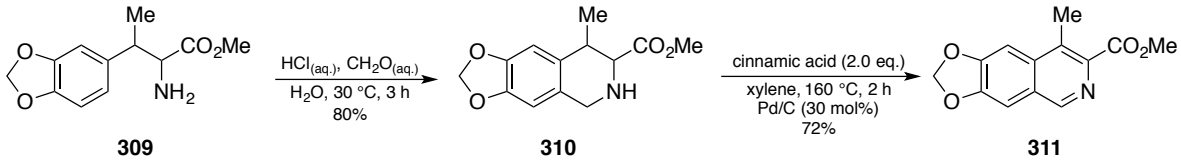


isoquinoline
308

Figure 11. Isoquinoline structure and numbering.

This aromatic heterocycle is a ubiquitous core in molecules of interest, especially bioactive naturally-occurring structures, such as papaverine, an important vasodilator;[125] trabectedin, an anti-tumor drug[126] or the peripheral benzodiazepine receptor binder PK-11195.[127] Due to the attractive bioactivity of isoquinoline derivatives, many syntheses have been developed up to this date and some will be discussed in some detail in this chapter.

Similarly to *β*-carbolines, isoquinolines can also be synthesised *via* the Pictet–Spengler reaction. Phenylalanine derivatives replace tryptophan in the sequence to allow the formation of tetrahydroisoquinolines which then can be subjected to oxidative conditions to furnish isoquinolines. Takagi and Uyeo utilised this sequence to obtain isoquinoline **311**. Phenylalanine derivative **309** was subjected to Pictet-Spengler conditions with aqueous formaldehyde to deliver tetrahydroisoquinoline intermediate **310**. Pd-catalysed oxidation then furnished isoquinoline **311 (Scheme 13)**.



309 **310** **311**

Scheme 13. Takagi and Uyeo isoquinoline synthesis *via* Pictet-Spengler reaction.

In 2008, Stoltz and co-workers reported a general methodology to synthesise substituted isoquinolines *via* a benzyne intermediate. Addition of a fluoride source to silyl aryl triflates triggers the formation of benzynes which are then attacked by enamides to generate anion **314**. This anion then undergoes dehydrative aromatisation to furnish substituted isoquinolines (**Table 24**).[128]

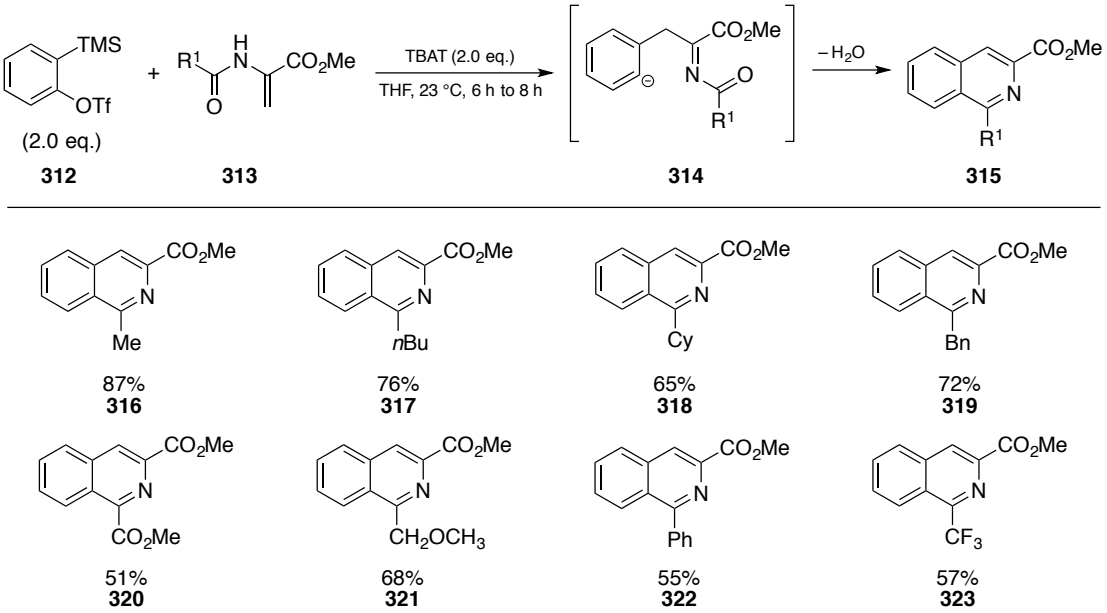


Table 24. Stoltz's isoquinoline synthesis.

This methodology showed good versatility for the installation of different substituents at C1, however, no C4-substituted isoquinoline esters were presented in this publication.

In 2012, Wu and co-workers published a protocol for the synthesis of isoquinoline esters *via* a silver catalysed reaction of 2-alkynylbenzaldehydes with 2-isocyanoacetate (**Table 25**).[129]

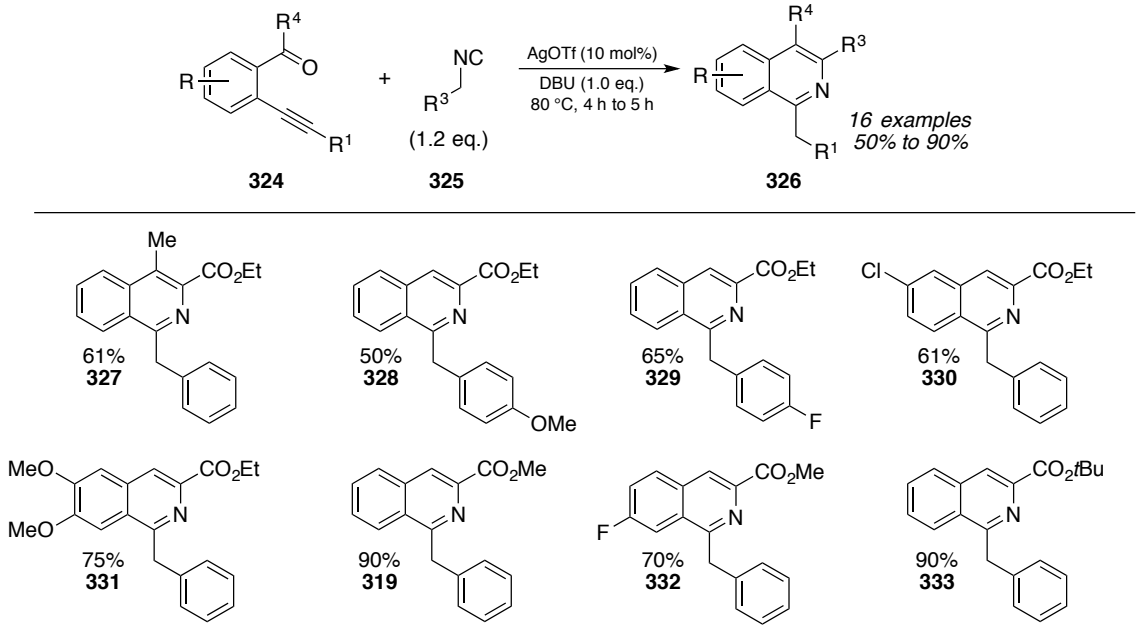
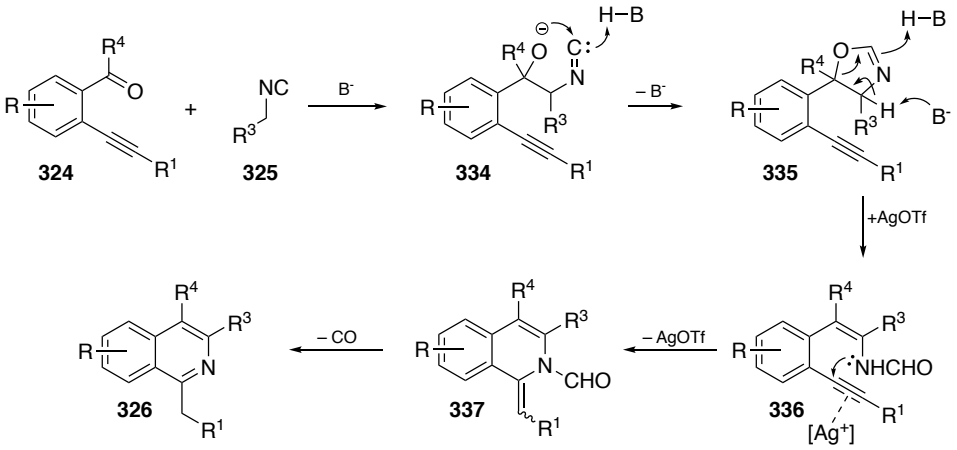


Table 25. Wu's Ag^+ catalysed synthesis of substituted isoquinolines.

The authors proposed that deprotonated isocyanoacetate **325** attacks the carbonyl moiety in **324** to deliver intermediate **334**. The alkoxide generated then attacks the isocyanide fragment to form oxazole **335**, which rearranges to give enamide **336**.[130,131] Activation of the alkyne moiety by Ag^+ triggers a 6-*exo*-dig cyclisation that delivers isoquinoline **326** with the loss of carbon monoxide (**Scheme 14**).[132]



Scheme 14. Proposed mechanism for the synthesis of isoquinolines *via* isocyanoacetate condensation and silver catalysed cyclisation.

Exploring a different approach to isoquinolines, Yu and co-workers published a methodology relying on the visible-light promoted somophilic insertion of vinyl isocyanides with diaryliodonium salts,[133] a competent aryl radical precursor.[134,135] Vinyl isocyanides were prepared *via* condensation of aryl ketones/aldehydes with isocyanides.[136]

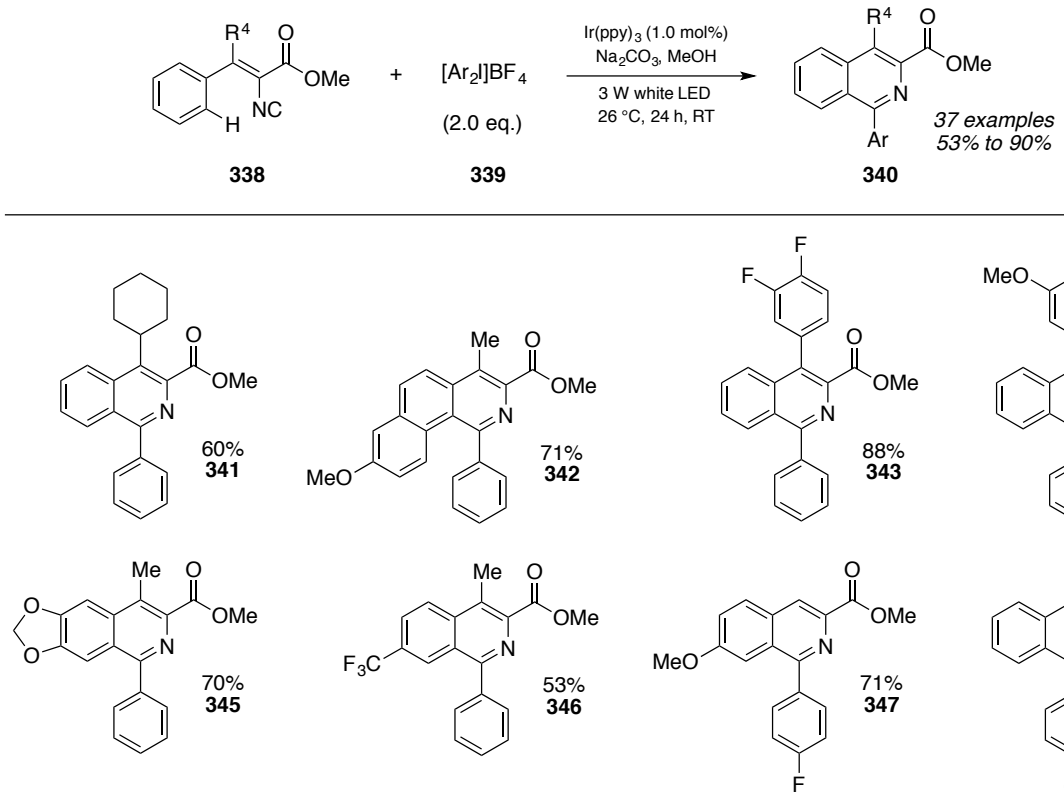


Table 26. Representative scope for the Yu's visible-light promoted isoquinoline synthesis.

The proposed mechanism starts with the formation of the excited species $Ir^{III}(ppy)_3^*$ **350** by visible light irradiation. This complex is then quenched by the diaryliodonium salt, generating the catalyst oxidised form, $Ir^{IV}(ppy)_3^+$ **352** and the aryl radical **351**. Addition of this radical to vinyl isocyanide **338** delivers the imidoyl radical **353**, which then undergoes intramolecular homolytic aromatic substitution to form radical intermediate **354**. Oxidation by $Ir^{IV}(ppy)_3^+$ gives the cationic intermediate **355** and regenerates the active catalyst $Ir^{III}(ppy)_3$. Deprotonation of **355** finally allows the formation of isoquinoline **340** (**Figure 12**).

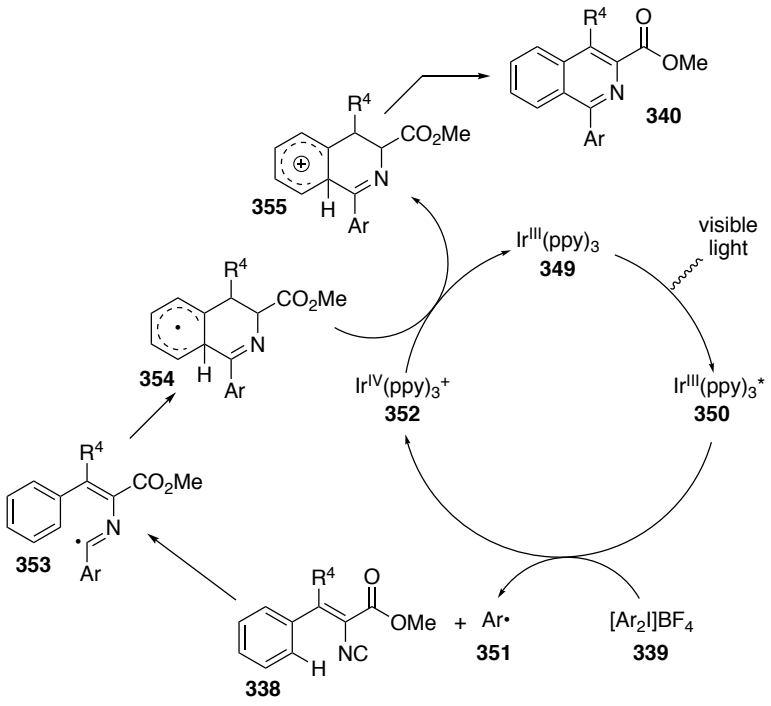


Figure 12. Proposed mechanism for Yu's visible-light promoted isoquinoline synthesis.

This methodology demonstrates several desirable features: low catalyst loading, mild temperatures, broad scope and easy access to all positions in the isoquinoline skeleton.

Recently, a variation of this sequence has been published by She and co-workers in which α-oxo radicals are generated by photoredox catalysis and added to the isocyanide moiety which then follows the pathway shown in **Figure 12** to deliver substituted isoquinolines (**Table 27**).[137]

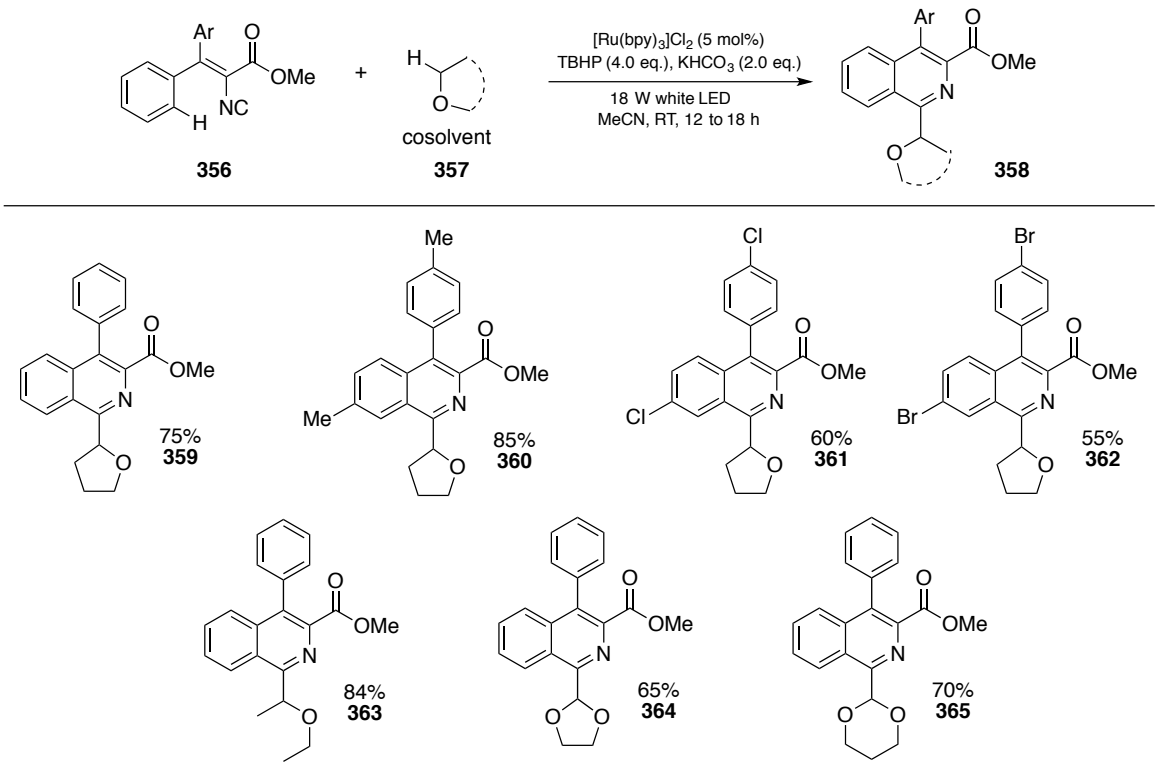


Table 27. Scope for She's visible-light promoted isoquinoline synthesis.

1.3.3 Indoles

Benzopyrrole, more commonly known as indole, is a 10-π–electron heterocyclic aromatic compound comprising a benzene ring fused to the 2- and 3- positions of the pyrrole ring (**Figure 13**).[138] The NH group can be protected under basic conditions given its mild acidity (pKa = 16.7).[99]

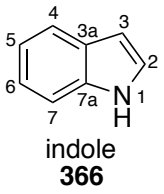
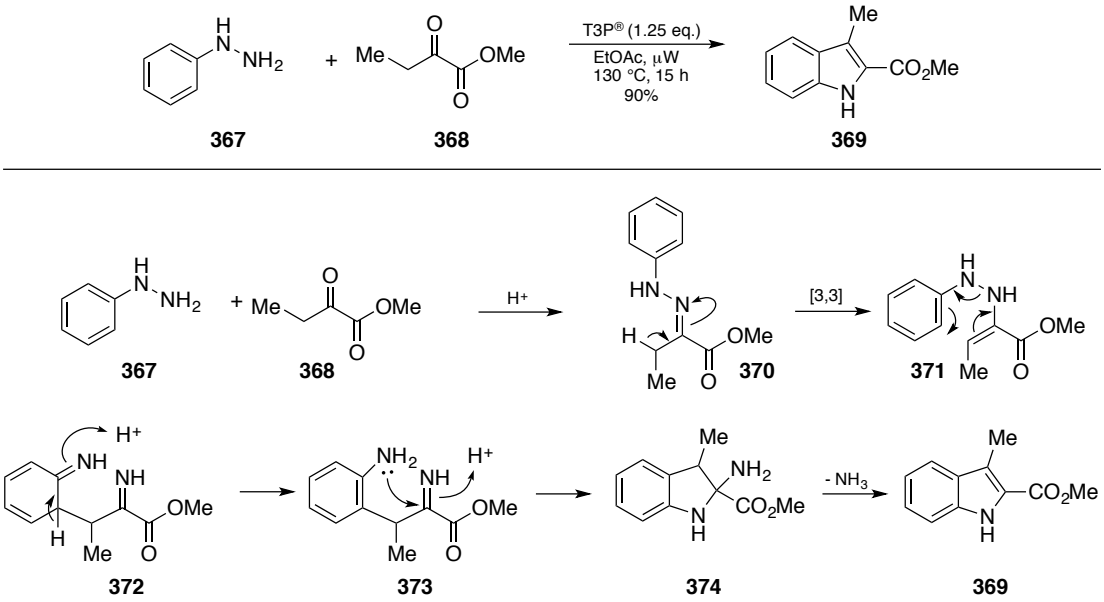


Figure 13. Indole structure and numbering.

This structure is found in a variety of alkaloid natural products. Eudistomin K and L, isolated from Caribbean tunicate *Eudistoma olivaceum* demonstrated antiviral activity;[139,140] Nortopsentins A, B and C, isolated from the sponge *Spongosorites ruetzleri*, exhibited

antifungal activity[141] while Halocyamine A, obtained from the solitary ascidian *Halocynthia roretzi* showed antimicrobial activity.[142] The indole unit is also present in the structure of psychoactive molecules such as lysergic acid[143] and psilocybin, found in psychedelic mushrooms,[144] both considered drugs of abuse.

The Fischer indole synthesis is one of the earliest reported routes to indoles, with the original publication dating back to 1883.[145,146] This reaction is known for its reliability and it is remarkable that it is still one of the preferred methods to make indoles.[147,148] The methodology also allows the installation of an ester group at C2, a subject explored in this chapter.[148] The first step is the formation of imine **370** from a phenylhydrazone **367** and pyruvate **368**. Tautomerisation followed by a rearrangement forms a C–C bond and breaks a N–N bond, delivering diimine **372**. Rearomatisation and intramolecular attack gives aminal **374** which then loses NH_3 to aromatise the indole unit and form isoquinoline **369** (**Scheme 15**).[149]



Scheme 15. Mechanism for Fischer's indole synthesis of indole **369**.

In 2009, Ding and co-workers reported a copper-catalysed methodology to synthesise 2,3-disubstituted indole 2-carboxylic acid esters *via* a condensation/coupling/deformylation cascade with 2-halo-keto-arenes and ethyl isocyanoacetate. With an increase in temperature from 50 °C to 80 °C the authors were also able to use aryl chlorides, which are normally poorly reactive towards ligand-free Cu-catalysed Ullmann-type reactions (**Table 28**).[150]

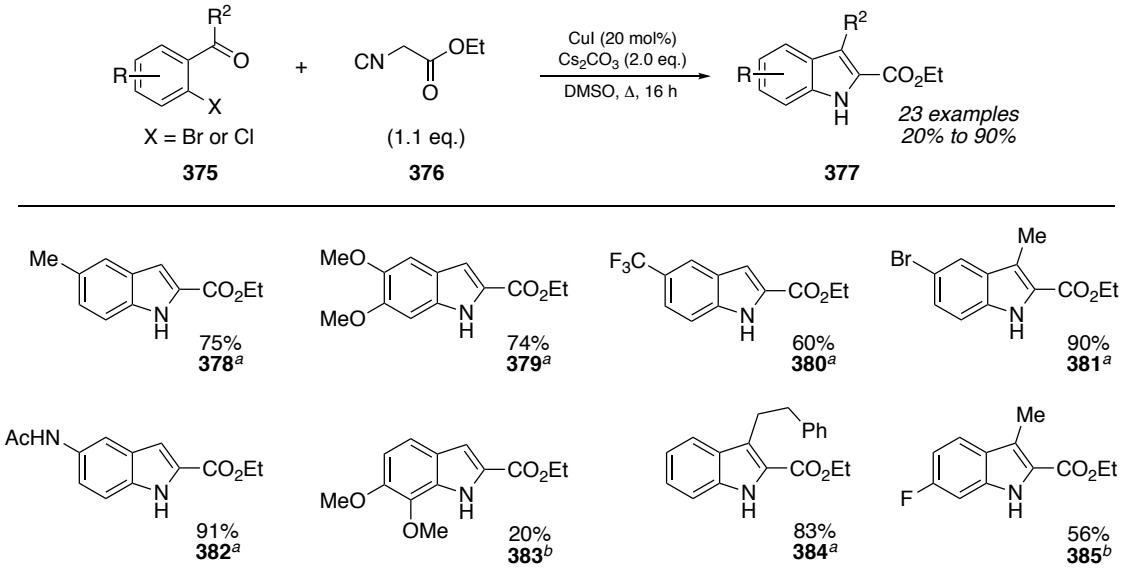


Table 28. Representative scope for Ding's Cu-catalysed indole synthesis. [a] X = Br, temperature = 50 °X; [b] X = Cl, temperature = 80 °C.

Ukita and co-workers explored Rh-carbenoid chemistry to develop a protocol towards indole 2-carboxylic acid esters. Rh-catalysed insertion of α-diazophosphonate **387** to an aniline N–H bond gives intermediate **388**, which under basic conditions generates a stable phosphonate ylide that smoothly undergoes intramolecular Horner–Wadsworth–Emmons reaction at RT to furnish substituted indole 2-carboxylic acid esters in good yields (**Table 29**).[151]

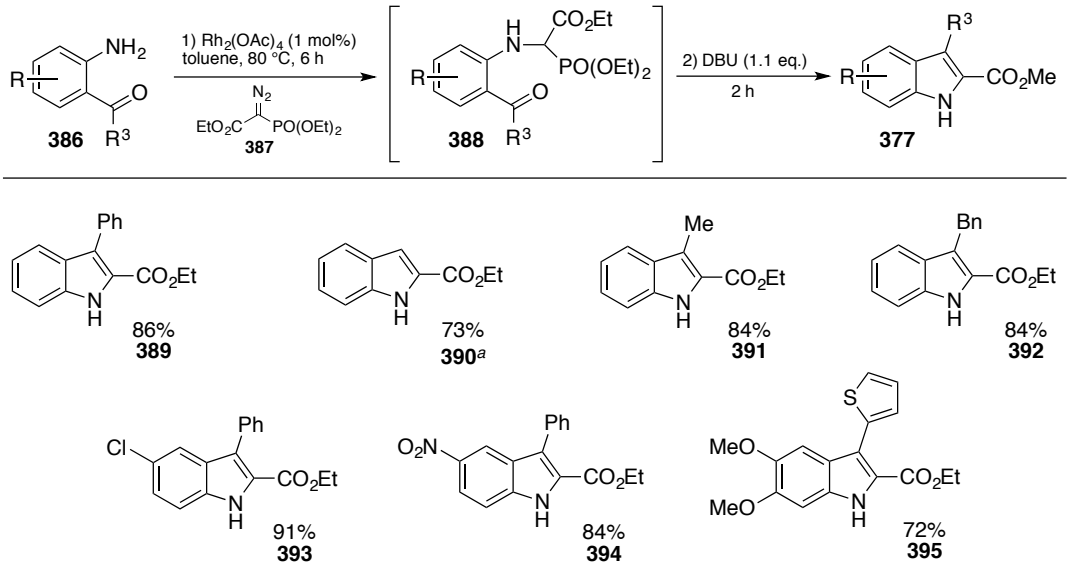
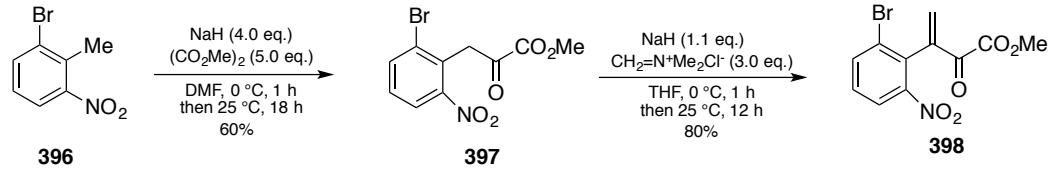


Table 29. Ukita's synthesis of substituted indole 2-carboxylic acid esters *via* Rh-catalysed carbenoid insertion.

In an approach to 3-substituted indole carboxylic acid esters in the context of their studies towards the synthesis of the antibiotic nocathiacin I,[152] Nicolau and co-workers reported a reductive annulation procedure from α,β-unsaturated ketoesters. This substrate was obtained in two steps from bromo-nitro-arene **396** (**Scheme 16**).[153]



Scheme 16. Synthesis of α,β-unsaturated ketoester **398**.

Addition of $SnCl_2 \cdot H_2O$ reduces the nitro moiety which then immediately cyclises to give α,β-unsaturated nitrone **399**. Addition of silyl enol ethers functionalise C2, allowing a variety of 3-substituted-*N*-hydroxy-indole-2-carboxylic acid esters (**Table 30**).

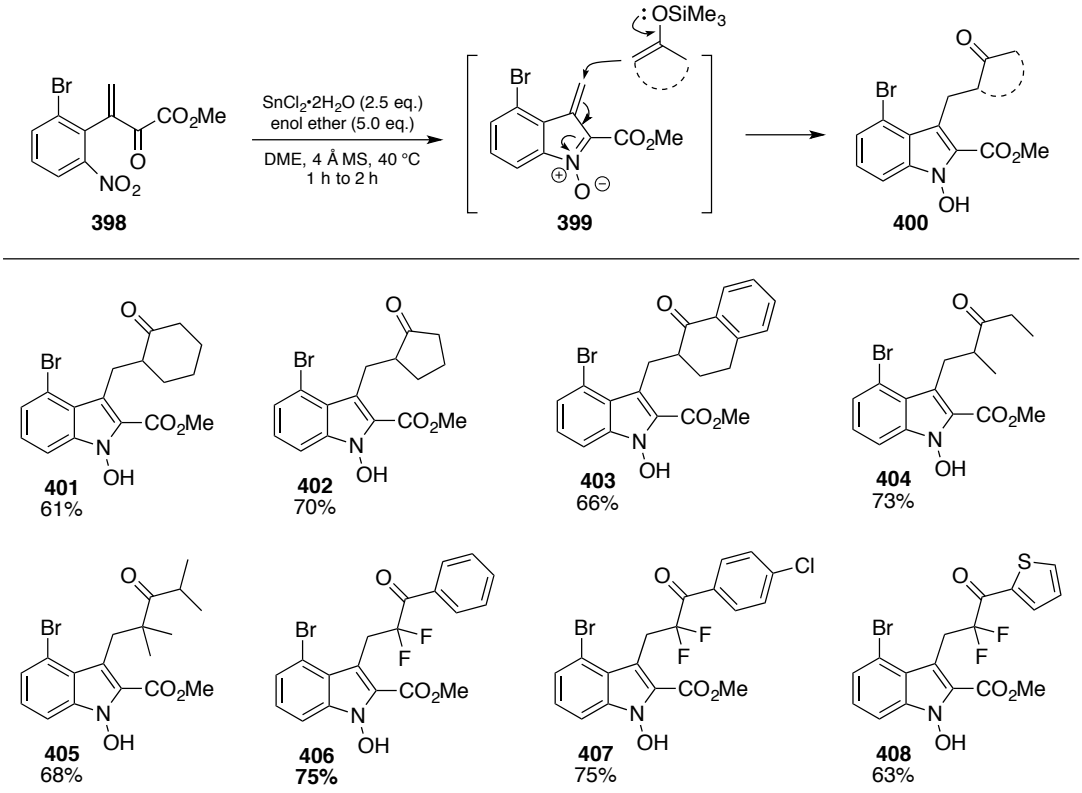


Table 30. Synthesis of 3-substituted-*N*-hydroxy-indole-2-carboxylic acid esters *via* reductive annulation/silyl enol ether addition sequence.

The authors also investigated the addition of activated silicon and tin nucleophiles (*e.g.* allyl silane and stannanes) to the intermediate **399**. Again, this allowed the installation of a diverse collection of functional groups such as methoxy and unsaturated carbon fragments (**Table 31**).

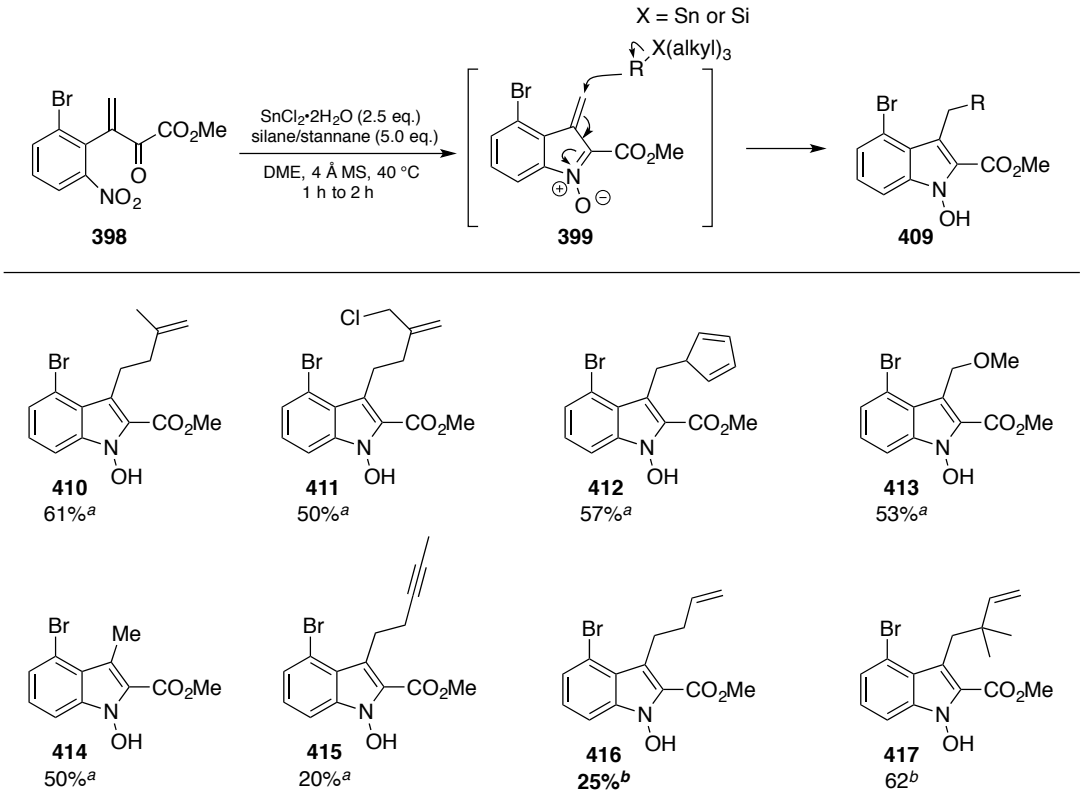


Table 31. Synthesis of 3-substituted-*N*-hydroxy-indole-2-carboxylic acid esters *via* reductive annulation/tin and silicon activated nucleophile addition sequence. [a] X = silicon [b] X = tin.

Sulfur, oxygen and nitrogen nucleophiles were also successfully used in this transformation as well as different bromo-nitro-arenes. These findings were reported as a separate work by the same group.[154]

Marinelli and co-workers developed an alternative protocol to 3-alkenyl-indole-2-carboxylic acid esters relying on a 5-*exo*-dig intramolecular annulation[155] of anionic alkynyl-aniline intermediates **420**.[156] followed by the loss of ethyl carbonate. This intermediate is generated *via* alkylation of aniline **418** with α-iodoacetophenone **419**. This approach permitted the introduction of a versatile internal or terminal olefin moiety at C3. Substitutions in the benzocyclic ring were also tolerated and the indole products were obtained in moderate to good yields (**Table 32**).

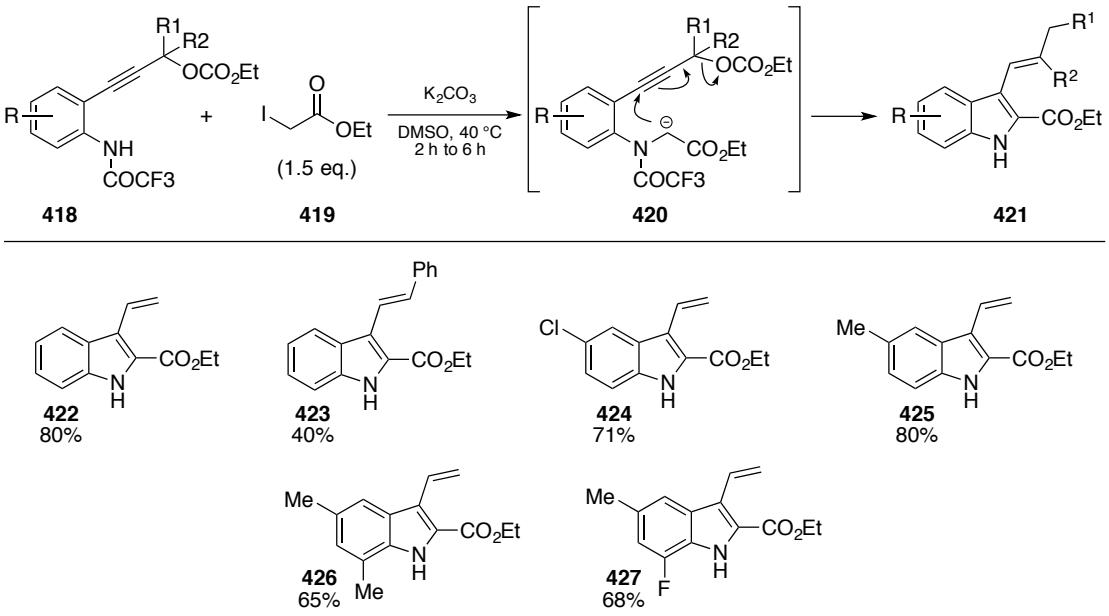
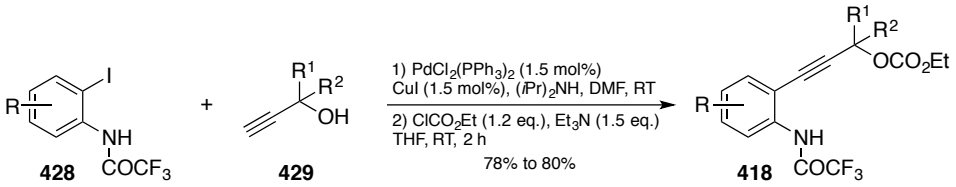


Table 32. Marinelli's synthesis of 3-alkenyl-indole-2-carboxylic acid esters *via* 5-*exo*-dig annulation.

The substrates **418** were obtained *via* Sonogashira cross coupling between iodoanlines **428** and substituted propargylic alcohols **429** followed by the addition of ethyl chloroformate in a telescoped sequence (**Scheme 17**).



Scheme 17. Synthetic route to alkynyl-anilines **418**.

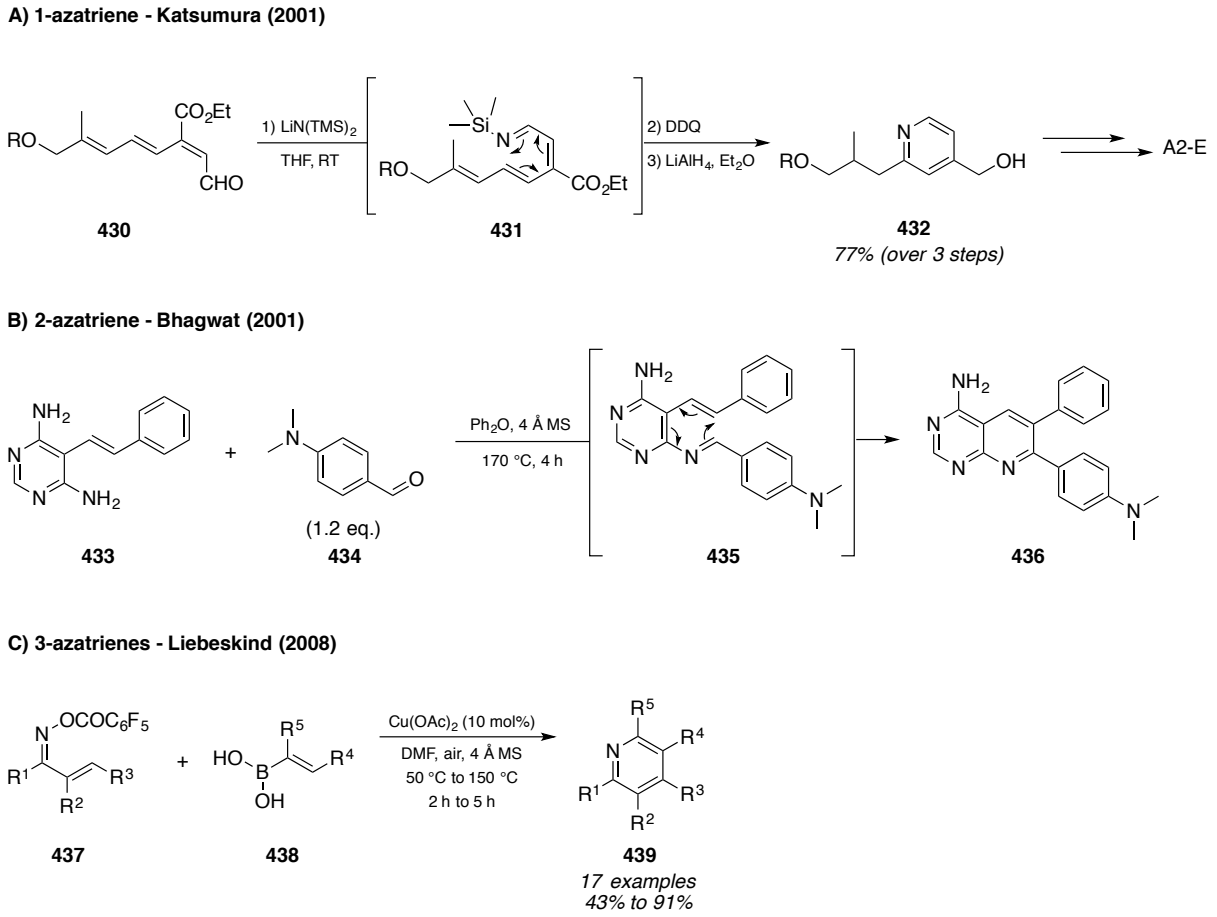
This chapter presented a short selection of methodologies towards the synthesis of substituted indole 2-carboxylic acid esters. It is important to mention that while there is a vast number of routes to substituted indoles described in the literature, only a limited share of these include the formation of 3-substituted-indole-2-carboxylic acid esters, subject under scrutiny in this thesis.[157,158]

Chapter 2: Results and Discussion

2.1. Synthesis of substituted pyridines *via* electrocyclisation

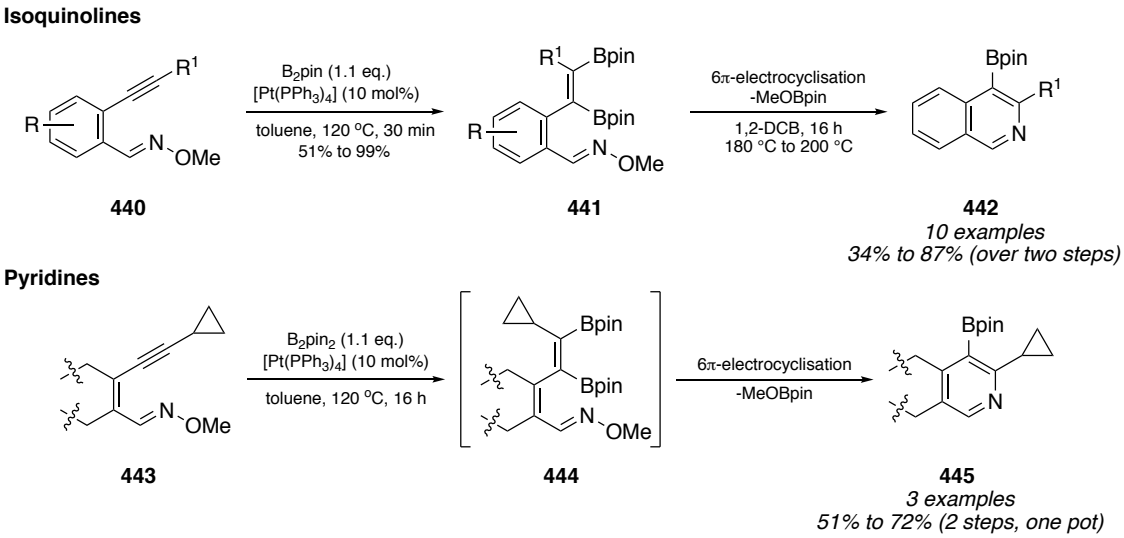
Among heterocyclic aromatic compounds, pyridines are of special interest in synthetic methodology. This structure is extensively found in natural products,[159,160] biologically active compounds,[161,162] functionalised materials[163,164] and ligands for transition metals.[165] The construction of pyridine rings bearing complex substitution patterns have been extensively described in the literature and several ingenious approaches have proved effective towards this goal. Some methodologies involve the condensation of π-nucleophiles with amides,[166] ring expansion of 2-allyl-*2H*-azirines[167] and addition of alkynes to azazirconacycles.[168]

Thermal electrocyclisations of 1-, 2- and 3-azatrienes have also been reported in the literature as a means to rapidly access pyridines and pyridine derivatives. Katsumura and co-workers published a detailed kinetic study on the 6π-electrocyclisation of 1-azatrienes in the formation of dihydropyridines, which includes the synthesis of the pyridine core of A2-E,[169] a fluorophore connected to age-related decline of eye cells[170] **(Scheme 18A)**.[171] Bhagwat and co-workers reported the synthesis of the pyridine derivative **436** in the context of the study of a series of nitrogen-containing heterocycles as non-nucleoside adenosine kinase inhibitor. The key step, a 6π-electrocyclisation of 2-azatriene **435**, proceeds at 170 °C in diphenyl ether (**Scheme 18B**).[172] Liebeskind and co-workers described a versatile methodology for the modular construction of fully substituted pyridines relying on a one-pot reaction cascade comprising of a new copper-catalysed C–N cross-coupling of alkenyl boronic acids **438** and oxime *O*-carboxylates **437**, 6π-electrocyclisation of the 3-azatriene intermediate and aerobic oxidation follow to deliver fully substituted pyridines (**Scheme 18C**).[173]



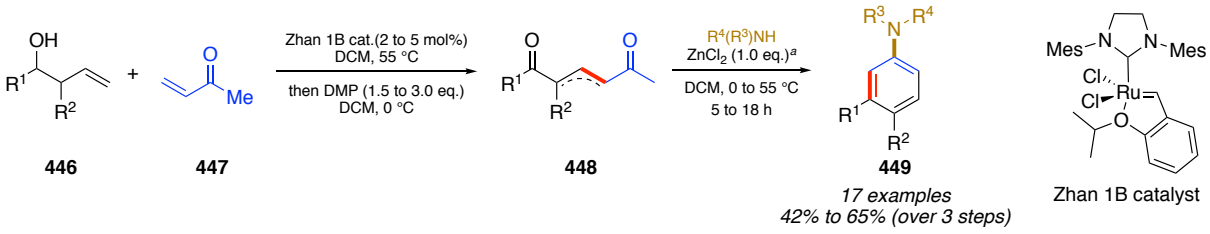
Scheme 18. Literature precedents for the 6π-electrocyclisation of 1-, 2- and 3-azatrienes.

In a recent report, Harrity and co-workers also utilised 1-azatrienes as intermediates *en route* to pyridine boronic acid derivatives. In this ingenious sequence, the Pt-catalysed diborylation of yne-ene-oximes gave easy access to a series of 1-azatrienes **441**, which then underwent 6π-electrocyclisation to allow borylated isoquinolines **442**. When this procedure was applied to aliphatic yne-ene-oximes, however, the authors were not able to isolate the 1-azatriene intermediate as the reaction conditions for the alkyne diborylation smoothly furnished pyridines **445** in one-pot (**Scheme 19**).[174]



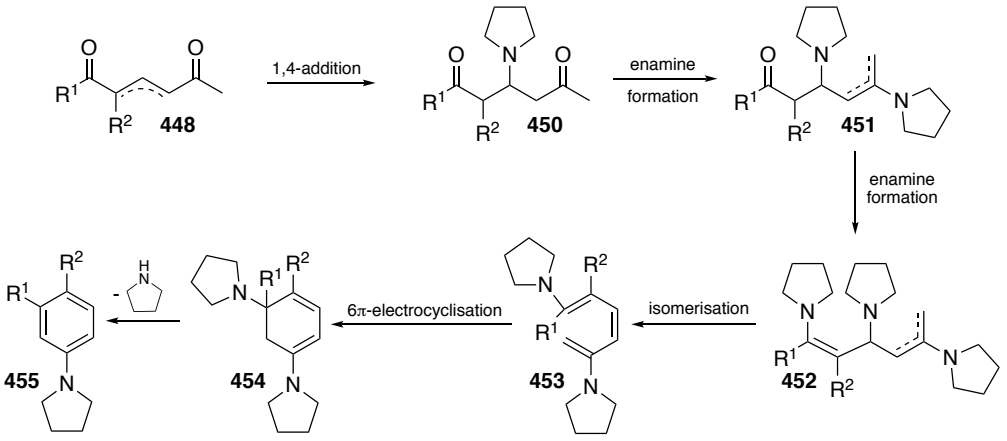
Scheme 19. Harrity's synthesis of isoquinolines and pyridines *via* 6π-electrocyclisation of 1-azatrienes.

Previous work in the Donohoe group had reported a facile *de novo* synthesis of aryl amines from methyl vinyl ketone and homoallylic alcohols relying on the ruthenium-catalysed cross metathesis reaction as key C–C bond forming step, followed by oxidation in one-pot to deliver 1,5-unsaturated dicarbonyl compounds **448**. This intermediate smoothly cyclised *via* an electrocyclisation to deliver the aromatic products upon addition of amines and $ZnCl_2$ in some cases (**Figure 20**).[175]



Scheme 20. Synthesis of amines *via* Ru-catalysed cross metathesis. [a] Lewis acid additive used in one example.

The proposed mechanism starts with the amine (*e.g.* pyrrolidine) 1,4-addition to the double bond in **448**. A second equivalent of amine may form enamine **451** and a third equivalent of amine generates the bisenamine **452**. Isomerisation of the double bond and elimination of pyrrolidine generates 1,3,5-triene **453** which then undergoes 6π-electrocyclisation to form diene **454**. Finally, elimination of pyrrolidine allows the formation of aryl amines **451** (**Scheme 21**).

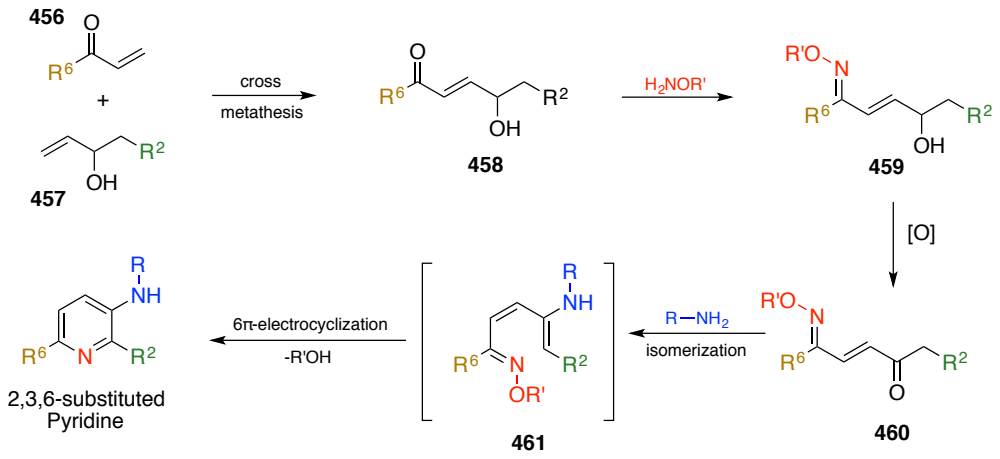


Scheme 21.[175] Proposed mechanism for the formation of aryl amines *via* 6π-electrocyclisation. Amine = pyrrolidine.

Based on this precedent and the reported methodologies for 6π-electrocyclisation of 1-azatrienes, a new methodology to access 3-amino-pyridines was then pursued.

2.1.1 Strategy overview

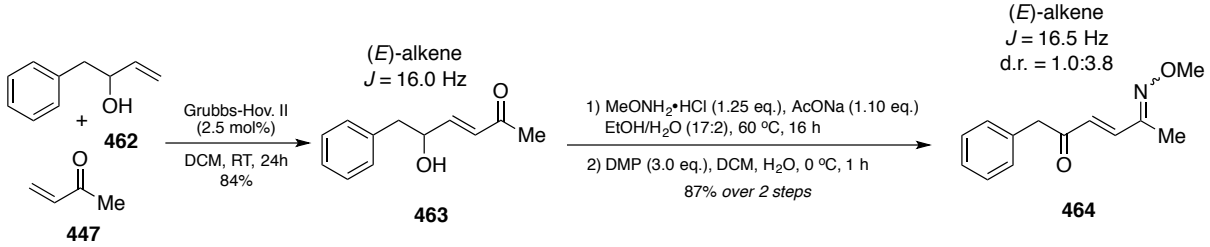
Inspired by the sequence shown in **Scheme 21**, a new route to 3-amino-pyridines was designed. Ruthenium-catalysed cross metathesis[176] of vinyl ketones **456** with homoallylic alcohols **457** would generate hydroxy-ketones **458**. Addition of *O*-alkyl hydroxylamines followed by oxidation of the alcohol moiety would give access to key substrate **460**. It was anticipated that treatment of **460** with amines would form 1-azatrienes **461** after isomerisation, which would then undergo 6π-electrocyclisation, eliminating ROH and furnishing 2,3,6-aminopyridines. (**Scheme 22**).



Scheme 22. Proposed route to the synthesis of 2,3,6-trisubstituted amino-pyridines.

2.1.2 Cyclisation conditions

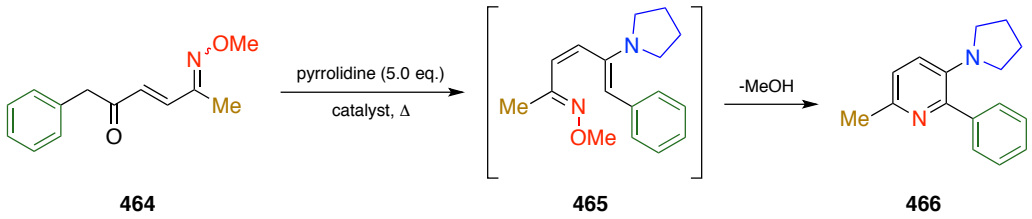
In order to investigate this sequence, oxime **464** was synthesised following the route in **Scheme 23**. Cross metathesis of methyl vinyl ketone **447** with homoallylic alcohol **462** allowed hydroxy-ketone **463**, identified by the presence of a pair of doublets at 6.81 and 6.28 ppm (J = 16.0 Hz), indicating the formation of an internal *E*-alkene exclusively. Treatment of **463** with methoxyamine, followed by oxidation with Dess-Martin periodinane (DMP) allowed the formation of keto-oxime **464** in 87% yield as a mixture of diastereoisomes (d.r. = 1.0:3.8). The identity of the product **464** was attested by the presence of a singlet at 3.70 ppm, corresponding to the methylene protons in **464** (**Scheme 23**).



Scheme 23. Synthetic route to *O*-methoxy oxime **464**.

With compound **464** in hand, electrocyclisation conditions were screened. Pyrrolidine (5.0 eq.) was chosen as model amine due to the positive results obtained in a related project in the group.[175] From the beginning, it was clear that the reaction would require high temperatures to

proceed, regardless of the presence of Lewis acid (entries 1 and 2). Addition of Brønsted acid and higher temperature afforded pyridine **466** in low yield (entry 3). Pyridine **466** was identified by a pair of doublets in the ^{1}H NMR spectrum at 7.10 and 6.98 ppm (J = 8.3 Hz), indicative of the presence of a 2,3,6-trisubstituted pyridine. A solvent and catalyst screening was carried out in order to find milder conditions for the electrocyclisation, however, this failed to improve the yield (entries 4 to 7). Solvents with higher boiling points produced better results, as they allowed the reaction to proceed at higher temperatures. Finally, HCl at 160 °C (entry 8) was the best combination with pyridine **466** being isolated in 25% yield. Microwave heating was also attempted in order to shorten the reaction time and avoid decomposition of the starting material, however, the increase in yield was negligible (entries 10 and 11) (**Table 33**).



464 **465** **466**

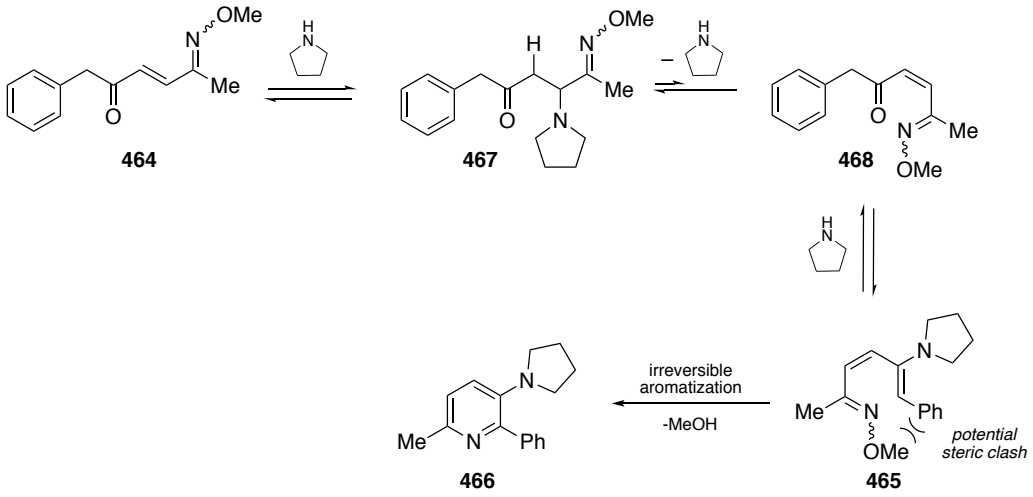
entry	solvent	catalyst (mol%)	T (°C)	yield **466** (%)
1	DCM	-	60	0
2	DCM	$ZnCl_2$ (100)	60	0
3	1,2-DCB	TsOH (15)	160	12
4	toluene	TsOH (15)	100	5
5	2-propanol	TsOH (15)	80	0
6	toluene	HCl (200)	100	5
7	toluene	$ZnCl_2$ (100)	100	0
8	1,2-DCB	HCl (15)	160	25
9	1,2-DCB	$ZnCl_2$ (100)	150	11
10[a]	*n*-butanol	HCl (15)	130	25
11[a]	1,2-DCB	HCl (15)	160	27

Table 33. Conditions screened for the 6π-electrocyclisation of **464**. [a] Microwave heating.

2.1.3 Cyclisation troubleshooting

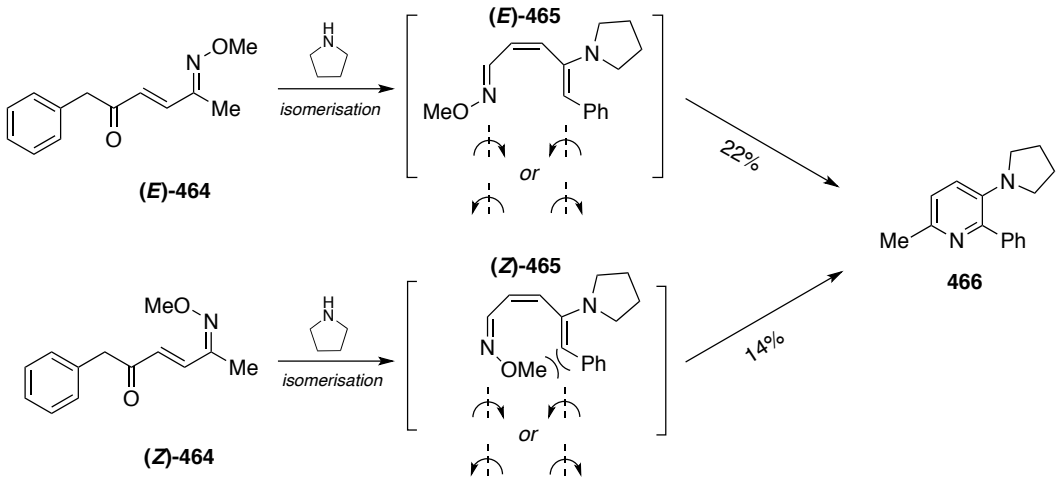
Based on these results, our attention was then focused again on the sequence described in **Scheme 22** in order to identify potential problems in those individual reaction steps.

In the formation of the compound **464**, a mixture of oxime geometric isomers was obtained (**Scheme 23**). It was then speculated that these two molecules could present different reactivities towards the isomerisation of the internal olefin moiety from *E* to *Z*, step necessary prior to the 6π-electrocylisation.[177] A reasonable pathway to explain the geometry switch is the reversible addition/elimination of pyrrolidine to the double bond, followed by irreversible aromatisation (**Scheme 24**).



Scheme 24. Proposed bond isomerisation mechanism.

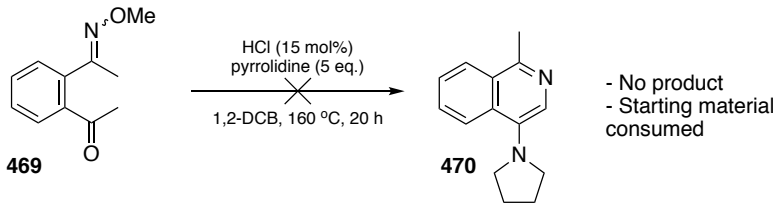
The steric clash between the methoxy and phenyl moieties in **(*Z*)-465** intermediate, could potentially preclude its formation, leading to overall low reaction yields. After careful chromatographic separation, both geometric isomers of **464** were identified by nOe and it was shown that the major isomer was **(*E*)-464**. These molecules were separately subjected to the best conditions found in **Table 33** (entry 8) and both allowed the formation of pyridine **466** (**(*E*)-464** = 22%, **(*Z*)-464** = 14%) (**Scheme 25**). The formation of product from **(*Z*)-464** demonstrates that this substrate can still form intermediate **(*Z*)-465**. The difference in yields suggests that the *O*-methoxy oxime geometry has some influence on the formation of the (*Z*)-alkene intermediate **(*Z*)-465**, however, it does not shut down the reaction.



Scheme 25. Disrotatory 6π-electrocyclisation of **(*E*)-465** and **(*Z*)-465**.

It is interesting to notice, however, that once intermediates **(*E*)-465** and **(*Z*)-465** are formed, the 6π-electrocyclisation of **(*Z*)-465** should be more facile when compared to **(*E*)-465** due to the disrotatory nature of this process. **(*Z*)-465** proceeds through a less congested *anti* transition state when compared to the *syn* transition state expected for **(*E*)-465**.[178]

In order to further test the influence of the alkene isomerisation in the reaction, *O*-methyl oxime **469** containing an obligatory *Z*-double bond was synthesised and subjected to the cyclisation conditions. Unfortunately, this substrate did not produce the desired isoquinoline **470** and the starting material was completely decomposed after 20 h (**Scheme 26**).



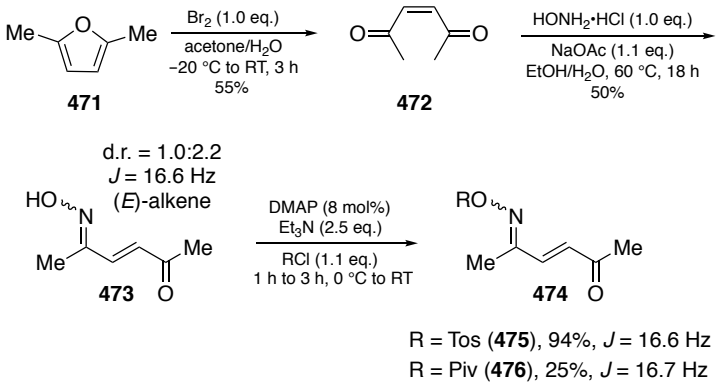
Scheme 26. *O*-methyl oxime **469** test reaction.

Despite the different nature of the starting material **469** when compared to **464**, this result suggests that the isomerisation is not a major barrier to the overall process and the mechanism proposed in **Scheme 24** should operate well. Moreover, there are precedents in the literature

for the formation of both pyridines and isoquinolines under similar conditions *via* 6π-electrocyclisation mechanism (**Scheme 19**).[174]

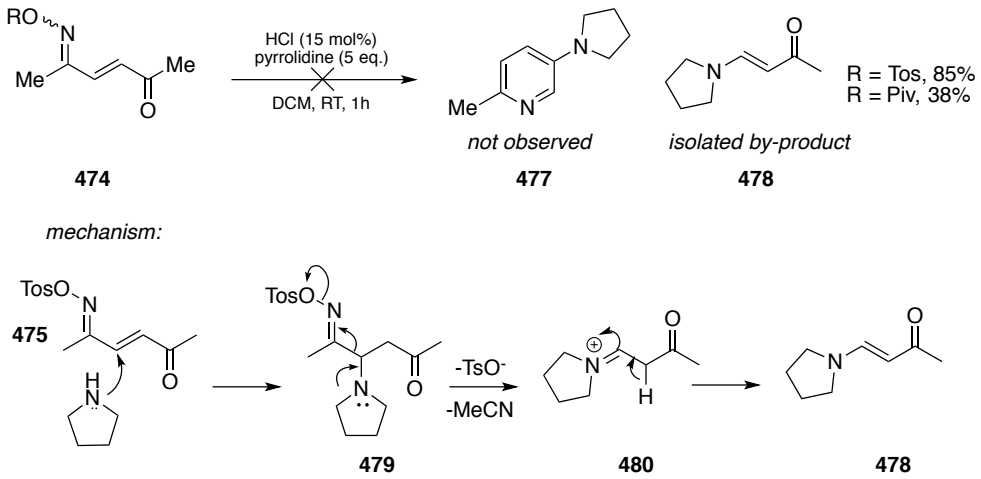
The influence of water (eliminated in the course of the formation of enamine **465**) or methanol (eliminated during aromatisation) on the reaction outcome was then investigated to search for product formation inhibition. Two control experiments were carried out: addition of five equivalents of methanol and saturation of the reaction solvent, 1,2-DCB, with water. These experiments afforded pyridine **466** in 35% and 15% yield, respectively, discarding a possible influence of these nucleophiles on the reaction outcome. The slight increase in the reaction yield observed when five equivalents of methanol were added is believed to have been originated from experimental error due to the scale in which these reactions were carried out rather than any positive influence in the reaction sequence.

The next experiment was designed to evaluate the leaving group released during aromatisation. Two different *O*-substituted oximes containing better leaving groups were synthesised in a shorter route *via* symmetrical intermediate **472** (**Scheme 27**).



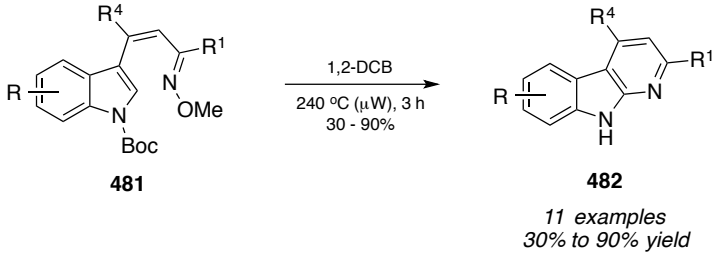
Scheme 27. Synthesis of oximes **475** and **476** from 2,3-dimethyl furan.

Interestingly, when submitted to the standard cyclisation conditions, by-product **478** was isolated instead of the desired pyridine **477** at RT, showing a limitation for their use in our system. A plausible mechanism involves the addition of pyrrolidine to the double bond, followed by elimination of MeCN and tosylate (**Scheme 28**).



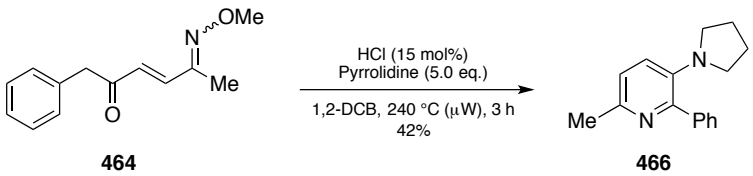
Scheme 28. *β*-Amino-ketone **478** by-product formation and proposed mechanism.

After testing four different hypotheses, it was reasonable to conclude that the limiting factor slowing down the reaction was the energy barrier imposed by the electrocyclisation step itself. Moody and co-workers[179] have published a related route to carbolines employing an analogous 6π-electrocyclisation step. It was shown that very high temperatures were necessary to afford the cyclic products, suggesting a high-energy barrier (**Scheme 29**).



Scheme 29.[179] Synthesis of carbolines from *O*-methyl oximes *via* 6π-electrocyclisation.

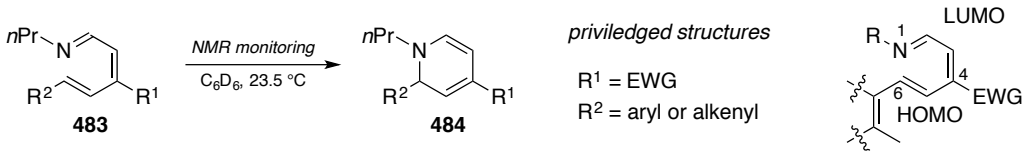
Moody's reaction conditions were then applied to the cyclisation of *O*-methyl oxime **464**, resulting in an improvement in yield from 25% to 42% (**Scheme 30**). However, this result was still not synthetically attractive; neverthless, it fits in the range of yields reported by Moody (**Scheme 29**).



464 **466**

Scheme 30. 6π-electrocyclisation of **464** following Moody's procedure.

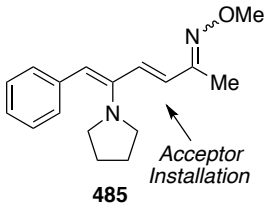
Focusing on the improvement of reaction yields, an alternative to reach a lower energy barrier was pursued. Katsumura and co-workers have published a detailed kinetic and computational study of the 6π-electrocyclisation reaction of substituted 1-azatrienes. In their system, they found both experimentally and computationally that an acceleration in the reaction rates is obtained when R^1 = EWG and R^2 = aryl or alkenyl (**Scheme 31**). Whereas the aryl/alkenyl moiety was found by calculations to raise the energy of the HOMO in these molecules, the presence of an EWG proved fundamental to lower the energy of the LUMO, significantly narrowing the energy gap between them. Their calculations also suggested that the HOMO electron density is arranged between C5–C6 while the LUMO electron density is positioned between C1–C4 (**Scheme 31**).[171,180]



483 **484**

Scheme 31. 6π-electrocyclisation of **483** in C_6D_6 for NMR kinetic studies.

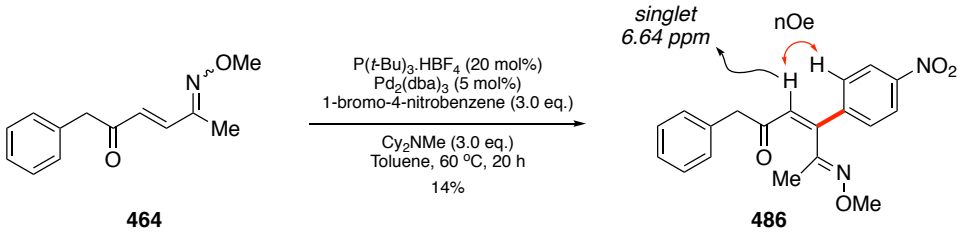
In order to evaluate this concept in our system, we presumed that an electron-withdrawing group should be installed either at the *α*- or *β*-position of the amino-oxime **485** (**Figure 14**).



485

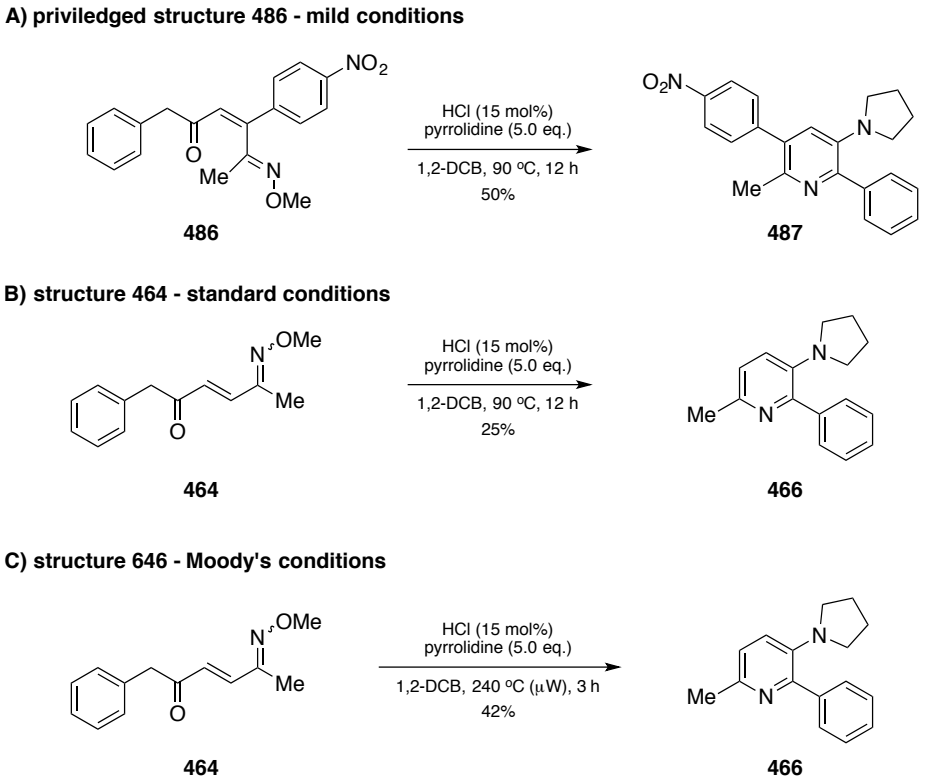
Figure 14. Structure of amino-oxime **485** and required position for the installation of an EWG.

Keto-oxime **464** was then subjected to a Heck cross-coupling procedure with 1-bromo-4-nitrobenzene in order to obtain a product resembling the privileged structure shown in **Scheme 31**. A single regioisomer was successfully isolated from the reaction mixture in low yield and its identity was confirmed by a singlet at 6.64 ppm in the ^{1}H spectrum corresponding to the alkenyl proton. The regiochemistry of the arylation was determined by HMBC experiment and the geometry of the double bond was elucidated by nOe experiments (**Scheme 32**).



Scheme 32. Pd-catalysed Heck arylation of compound **464**.

To attest the increased reactivity towards 6π-electrocyclisation of compound **486**, it was then subjected to the standard cyclisation conditions at lower temperatures and it was found by TLC analysis that 90 °C was sufficient to generate pyridine product **487**. Moreover, substrate **486** rendered a cleaner reaction in comparison with the cyclisation of **464**, affording product **487** in 50% yield. This result is higher yielding than substrate **464** at 160 °C (25%) (**Scheme 33B**) and at 240 °C with microwave heating (42%) (**Scheme 33C**).



486 **487** **464** **466** **464** **466**

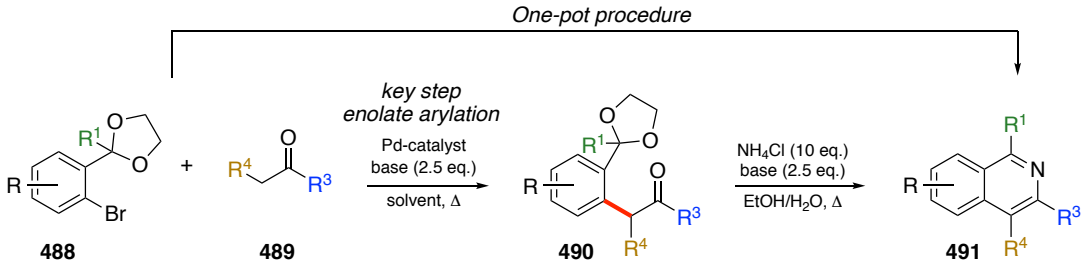
Scheme 33. Facilitated cyclisation of **486** in comparison with **464**.

This result and the literature precedents discussed in this chapter strongly suggest that the low yields observed for the 6π-electrocyclisation of compound **464** were due to the high energy barrier for this transformation. Unfortunately, the original proposed sequence (**Scheme 22**) could not be easily adapted to accommodate the introduction of an EWG at the oxime's α-position *via* Heck reaction, as attested by the low yield obtained in the reaction depicted in **Scheme 32**. A second option to install an EWG at the α-position of compound **464** would involve the use α-substituted vinyl ketones in the route described in **Scheme 22** but, unfortunately, these substrates are inert towards cross metathesis conditions.[176] The conclusions reached about the 6π-electrocyclisation energy barrier and the unfeasibility of an easy installation of an EWG in the reaction substrates led us to discontinue the investigations at this point and pursue a different project that will be discussed in the next chapters.

2.2 Synthesis of *β*-carbolines *via* the enolate arylation reaction

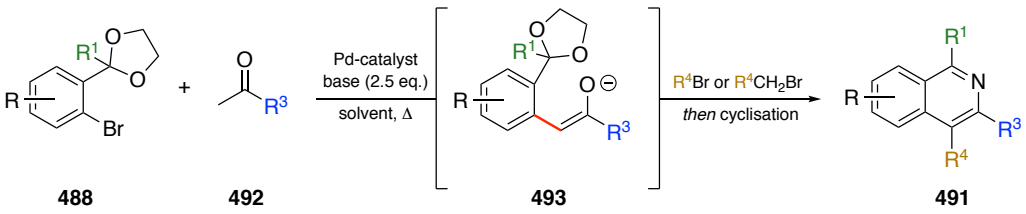
2.2.1 Synthesis of isoquinolines in the Donohoe group

Over recent years, the Donohoe group have explored the use of Pd-catalysed α-arylation and α-alkenylation reactions for the *de novo* construction of substituted aromatic heterocyclic compounds. The synthesis of isoquinolines was pursued in a series of papers published from 2012 to 2016.[181,182,183,184] The α-arylation reaction was designed to build the C–C bond linking the carbocyclic and pyridine rings. The acetal moiety provided a masked carbonyl that upon exposure to acid and a nitrogen source, delivered substituted isoquinolines in good yields both stepwise or in one-pot. Ammonium chloride was effective in most cases as both a source of acid to effect the acetal deprotection and the source of nitrogen required for cyclisation (**Scheme 34**).



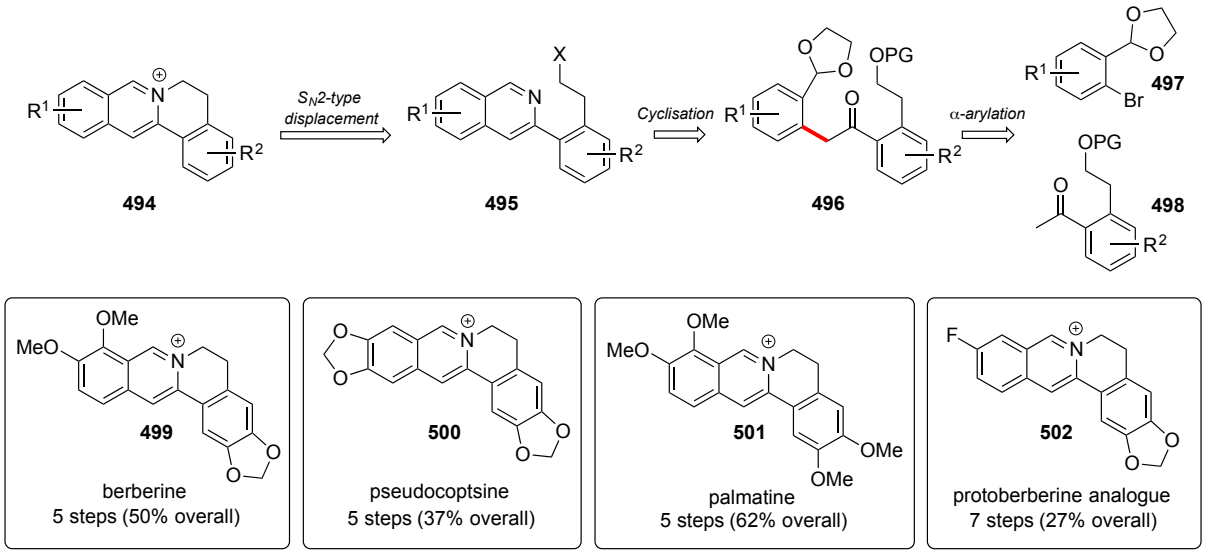
Scheme 34. General concept for the Pd-catalysed synthesis of substituted isoquinolines.

The original idea was then expanded by taking advantage of the acidic nature of intermediate **490**. The difference in pK_a between **489** and the starting material **489** at the ketone alpha position (*i.e.* acetophenone pK_a = 24.7;[185] phenylacetophenone pK_a = 17.7[186]) means that the enolate arylation reaction needs at least two equivalents of base to guarantee full deprotonation and avoid diarylation of **490**.[187,188] Two different approaches to C4 functionalisation were explored: the addition of electrophiles to deliver α-alkylated ketones and the addition of a second aryl bromide to deliver α,α-diarylated ketones through a second enolate arylation. Both methodologies installed a variety of groups at C4, a position not easily functionalised in isoquinolines (**Scheme 35**).[189]



Scheme 35. One-pot functionalisation of intermediate **493** with aryl bromides or electrophiles.

To show the applicability of this methodology, the protoberberine family of alkaloids was synthesised using this approach to construct the isoquinoline core. The main target, berberine **499**, was obtained in 50% in 5 steps, a large improvement over the previously reported synthesis.[190] Good yields of isoquinolines were also obtained with other members of the protoberberine family and a fluorinated analogue, by changing the coupling partners used in the key C–C bond forming α-arylation reaction, proving the modularity of the methodology (**Scheme 36**).

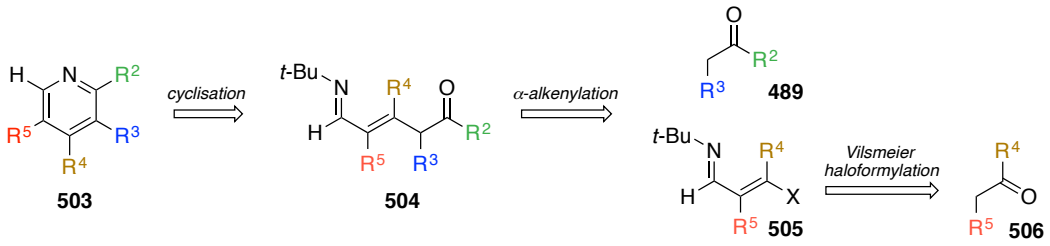


Scheme 36. Retrosynthetic analysis of the protoberberine skeleton and related protoberberines synthesised. PG = protecting group.

2.2.2 Synthesis of pyridines in the Donohoe group

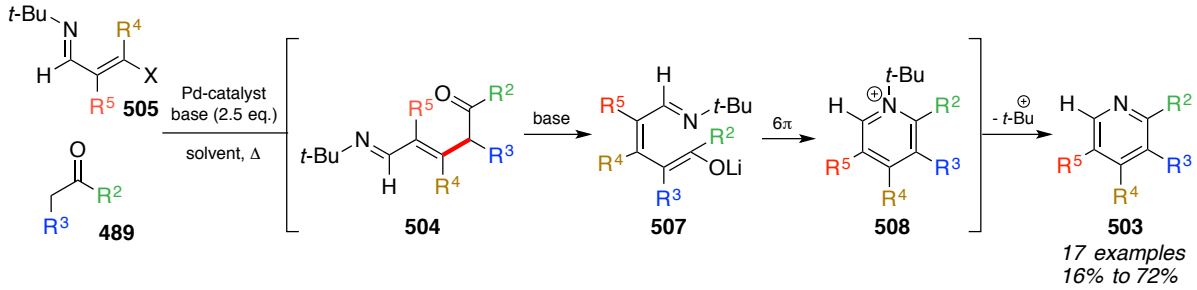
In related work regarding the α-alkenylation of ketones, the Pd-catalysed enolate vinylation was employed in the synthesis of tetrasubstituted pyridines. The coupling of a ketone enolate with α,β-unsaturated *tert*-butylimines delivered nitrogen-containing masked 1,5-dicarbonyl

compounds which then readily cyclised to form pyridines. The *tert*-butylimine starting materials were obtained *via* Vilsmeier haloformylation of commercially available ketones (**Scheme 37**).[191]



Scheme 37. Pd-catalysed α-alkenylation approach to pyridines.

After enolate vinylation, the acyclic intermediate **504** was not isolated as it reacted *in situ* to deliver pyridines at the temperature required for the α-alkenylation reaction to take place. In the proposed mechanism, the intermediate **504** is immediately converted to its lithium enolate, given the excess base present in the reaction, which in turn can undergo a 6π-electrocyclisation with loss of Li_2O.[192] The pyridinium salt **508** then loses a *tert*-butyl cation to deliver the pyridine product (**Scheme 38**).

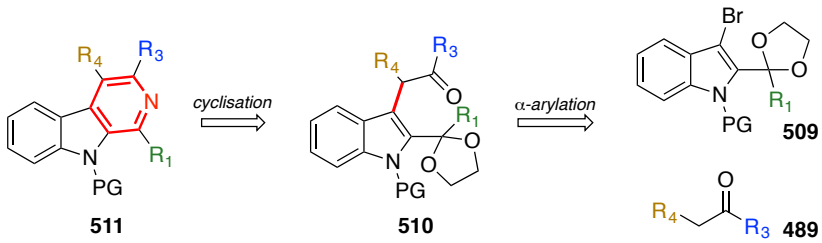


Scheme 38. Proposed cyclisation mechanism.

2.2.3 Retrosynthesis of β-carbolines and starting material synthesis

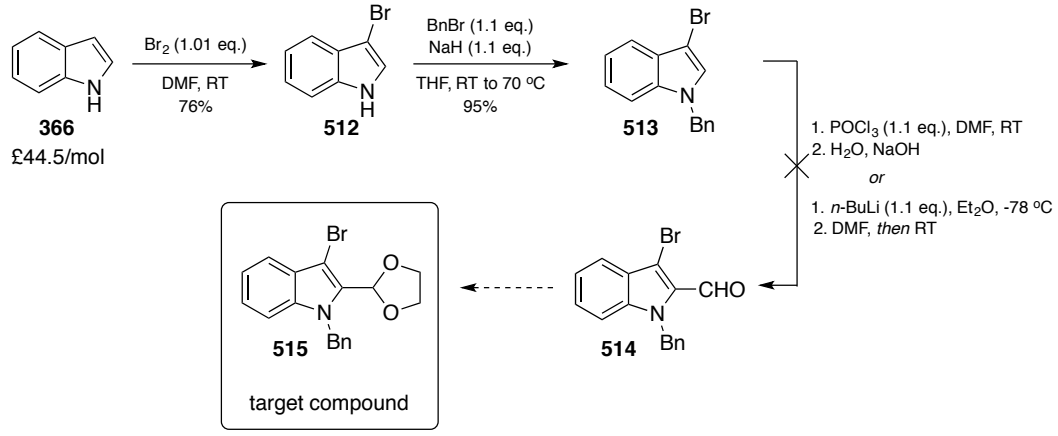
Inspired by the success of the synthesis of isoquinolines and the versatility of the methods developed, it was decided to test a similar approach to the construction of the more complex β-carboline core *via* an enolate arylation reaction. The pyridine ring in the β-carboline would be formed by the cyclisation of keto-indoles **510** with a protected carbonyl strategically positioned to deliver the imine required for the transformation. This intermediate, in turn, could

be obtained *via* arylation of different ketones with 3-bromoindoles in the key C–C bond formation step (**Scheme 39**).



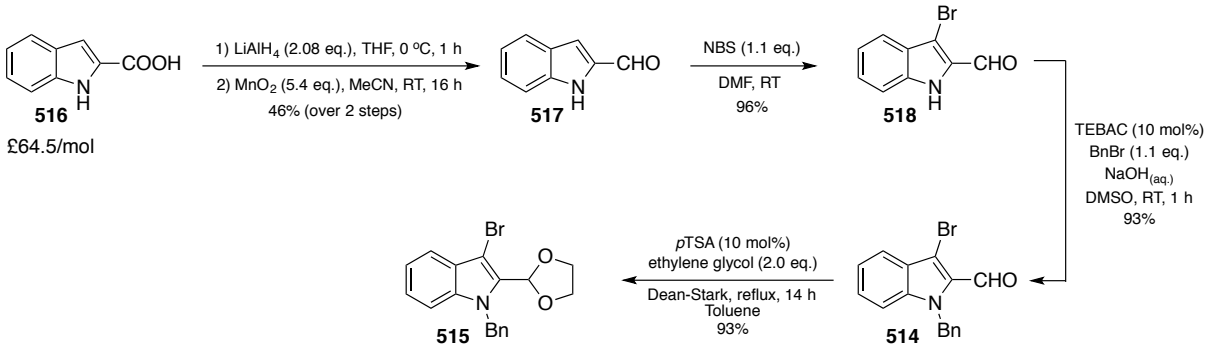
Scheme 39. Retrosynthetic analysis of the β-carboline synthesis.

In order to test the feasibility of this idea, a model 3-bromoindole substrate had to be synthesised. Compound **515** was chosen for the initial screenings as it is the simplest version of the general bromoindole skeleton **509** (**Scheme 39**). A benzyl group was chosen due to its stability towards the basic conditions required for the α-arylation reaction and also its ease of removal under orthogonal conditions.[193] The first route to **515** attempted was based on indole **366**, a cheap and readily available material (**Scheme 40**). The first step was the bromination of C3 following a literature procedure.[194] The nitrogen was then deprotonated with NaH and benzyl-protected with benzyl bromide. Two different approaches were then tested for the formylation at the C2 position. First, the Vilsmeier-Haack reaction was attempted, but unfortunately no product **514** was formed. The crude ^{1}H NMR spectrum showed that starting material remained along with a complex mixture of by-products. Taking advantage of the accessibility of the C2 hydrogen, a second approach was designed focusing on the lithiation of **513** followed by addition of DMF at –78 °C. Again, this sequence also failed to produce **514** and only starting material was recovered. It is possible that a stronger base was required at this temperature, as suggested by other indole C2-functionalisation procedures.[195,196]



Scheme 40. Proposed synthetic route to **515** based on indole. Price supplied by Fluorochem (on 6th July 2017).

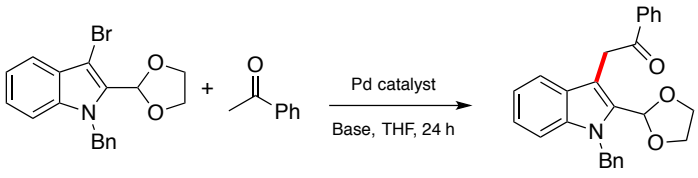
In parallel to the route depicted in **Scheme 40**, a second sequence based on indole-2-carboxylic acid was also explored. Just like the previous starting material, **516** is also cheap and commercially available. This molecule can be converted to **517** in two steps. Bromination at C3 was easily achieved using NBS in DMF[197] and the *N*-benzylation was carried out under phase transfer catalysis (PTC) *via* an adapted literature procedure[198] that delivered **514** in 93% yield under mild conditions. The acetal protection of the aldehyde was cleanly accomplished with ethylene glycol and catalytic acid in toluene under reflux in a Dean–Stark apparatus, delivering the target 3-bromoindole **515** in 93% yield (**Scheme 41**). The identity of **515** was confirmed by a singlet at 6.21 ppm corresponding to the methine proton in the acetal moiety.



Scheme 41. Synthetic route to 3-bromoindole **515**. Price supplied by Fluorochem (on 6th July 2017).

2.2.4 Exploring conditions for the α-arylation reaction

With compound **515** in hand, the Pd-catalysed α-arylation step was investigated using acetophenone as model ketone (**Table 34**). Considering the scope, versatility and robustness shown by the use of Pd(dtbpf)Cl_2 in combination with NaO*t*Bu in THF at 70 °C in the synthesis of isoquinoline previously reported in our group,[182] it was decided to choose those conditions as a starting point. Two equivalents of the ketone were initially used in an attempt to maximise the conversion of 3-bromoindole **515**, a more valuable substrate. The product **520** was isolated in encouraging 45% yield along with a complex mixture of by-products, with no indication of starting material remains by ^{1}H NMR analysis of the crude material (**Table 34**, entry 1). The identity of ketone-indole **520** was confirmed by the presence of a singlet at 4.65 ppm, corresponding to the methylene protons at the ketone alpha-position. In order to avoid the formation of by-products, the reaction was carried out at 50 °C (entry 2). This modification allowed a small increase in yield from 45% to 52% (entry 2). Pleasingly, when the base was replaced by LiHMDS, previously very effective in a related project.[187] **520** was isolated in 93% yield (entry 3). Further modification showed that lower catalyst loadings and/or ketone equivalents still delivers **520** in good yields (entries 4, 5 and 6). Moreover, the reaction also proceeds at room temperature in reasonable yield (entry 7).[199]



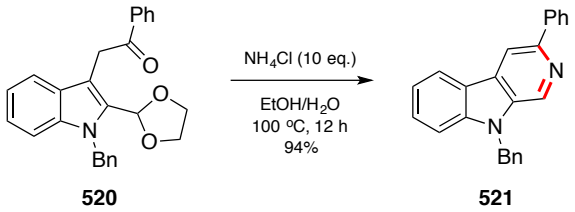
515 **519** **520**

entry	catalyst (mol %)	ketone (eq.)	base (2.5 eq.)	T (ºC)	yield **520** (%)
1	Pd(dtbf)Cl_2 (5.0)	2	NaOtBu	70	45
2	Pd(dtbf)Cl_2 (5.0)	2	NaOtBu	50	52
3	Pd(dtbf)Cl_2 (5.0)	2	LiHMDS	50	93
4	Pd(dtbf)Cl_2 (5.0)	1.2	LiHMDS	50	80
5	Pd(dtbf)Cl_2 (2.5)	2	LiHMDS	50	86
6	Pd(dtbf)Cl_2 (2.5)	1.2	LiHMDS	50	70
7	Pd(dtbf)Cl_2 (5.0)	2	LiHMDS	RT	66

Table 34. Optimisation studies for the Pd-catalysed α-arylation of acetophenone.

2.2.5 Cyclisation and benzyl deprotection

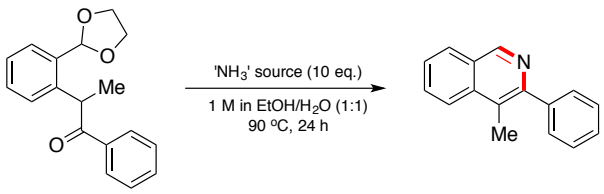
Compound **520** was then subjected to cyclisation conditions with NH_4Cl (10 eq.) in a mixture of EtOH and water (3:1) to furnish *β*-carboline **521** in excellent yield (**Scheme 42**). The identity of **521** was confirmed by ^1H NMR analysis, which showed the presence of two singlets at 8.82 and 8.33 ppm corresponding to the C1 and C4 protons, respectively.



520 **521**

Scheme 42. Formation of *β*-carboline **521** *via* thermal cyclisation of **520**.

It has been shown by Ben Pilgrim, a previous member of the group, that the pH plays a pivotal role in this type of transformation. A screening of different ammonia sources revealed that the pH obtained with a NH_4Cl solution in $EtOH/H_2O$ (1:1) gives the best compromise between acetal deprotection and imine formation, carrying out the cyclisation of **522** in 84% yield (**Table 35**).[200]

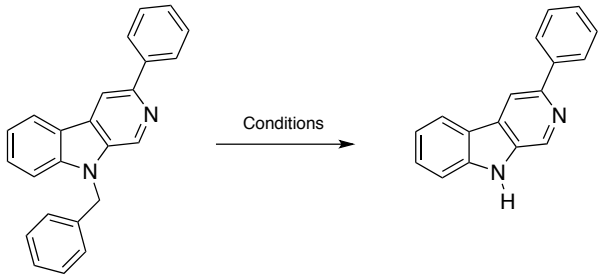


522 **523**

entry	'NH$_3$ source'	pH at RT	yield **523** (%)
1	NH_4OH	12.0	0
2	NH_4HCO_3	9.0	0
3	NH_4OAc	7.0	0
4	$(NH_4)_2SO_4$	5.5	63
5	NH_4Cl	5.0	84
6	NH_4Cl/HCl	3.0	81
7	NH_4Cl/HCl	1.0	79

Table 35.[200] Screening of different ammonia sources for the conversion of **522** to isoquinoline **523**.

Next, the deprotection of the benzyl group was investigated under different conditions. First, mild Pd-catalysed hydrogenolysis was attempted with no success: no reaction was observed and the starting material was recovered intact (**Table 36**, entries 1 and 2).[201] A literature procedure for the *N*-debenzylation aromatic heterocycles under an O_2 atmosphere again did not deliver *β*-carboline **524** nor consumed the starting material (entry 3).[202] Finally, it was discovered that $AlCl_3$ cleanly reacted with *N*-protected *β*-carboline **521** to afford **524** in 88% yield (entry 4).[203,204] The identity of *β*-carboline **524** was confirmed by the presence of a broad singlet at 11.69 ppm, corresponding to the hydrogen connected to the nitrogen in the carboline central ring.



521 **524**

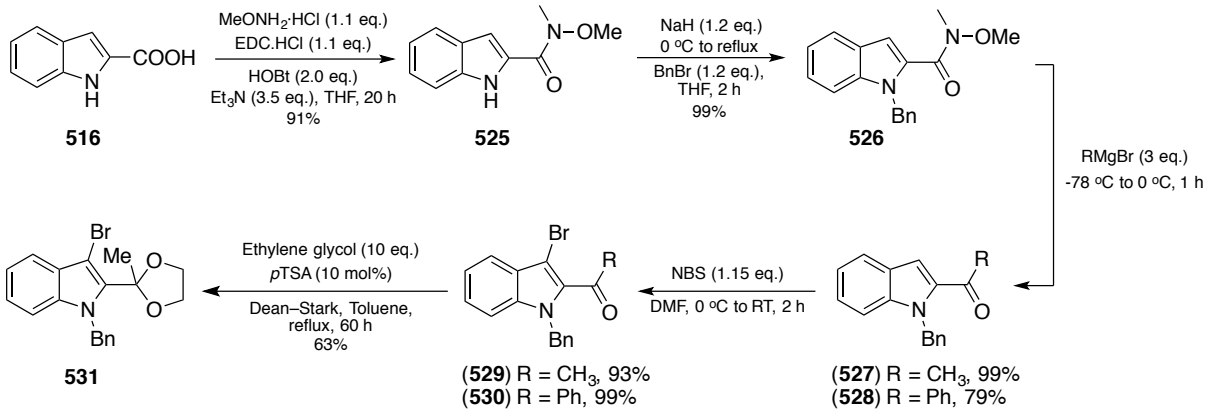
entry	conditions	solvent	T (°C)	yield **524** (%)
1	H_2, Pd/C	EtOH	RT	0
2	H_2, Pd/C, $AcOH_{(cat.)}$	EtOH	45 °C	0
3	O_2, KO*t*Bu	DMSO	RT	0
4	$AlCl_3$	Toluene	RT	88%

Table 36. Reaction conditions for the *N*-debenzylation of **521**.

2.2.6 Accessing the *β*-carboline C1 and C4 positions

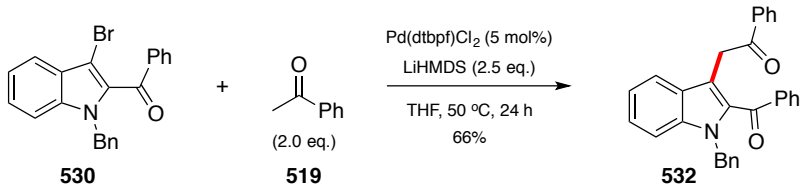
With the *α*-arylation of acetophenone **519** with 3-bromoindole **515**, cyclisation of intermediate **520** and deprotection of *β*-carboline **521** accomplished, variation of the substitution pattern in the pyridine ring was examined starting at C1. In order to access this position, a different bromoindole had to be synthesised. Starting again from commercially available indole-2-carboxylic acid **516**, Weinreb amide **525** was obtained in 91% yield. The addition of HOBt increased the reaction rate and in its absence, only traces of the product were obtained after

20 h at RT.[149] The *N*-benzylation of **525** proceeded in 99%, followed by Grignard reagent addition at –78 °C and quenching of the organometallic intermediate at 0 °C to afford methyl and phenyl ketones **527** and **528** in good yields.[205,206] Bromination of the electron-rich C3 position afforded bromoindoles **529** and **530** in very good yields and, finally, acid-catalysed acetal protection with ethylene glycol delivered **531** in 63% yield (**Scheme 43**). The identity of **531** was confirmed by ^{1}H NMR analysis by the presence of two sets of multiplets at 3.95 – 3.83 and 3.65 – 3.53 ranges, corresponding to the methylene protons in the ketal moiety. A singlet at 1.60 ppm corresponding to the methyl fragment was also present in this spectrum.



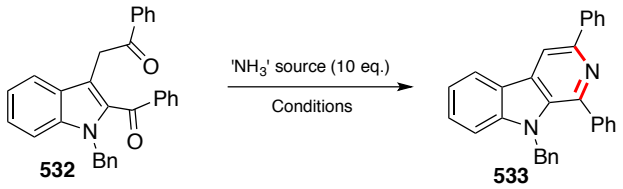
Scheme 43. Synthetic route to bromoindoles **530** and **531**.

The acetal protection reaction proved very sensitive to the size of R (**Scheme 43**). Whereas **515** could be synthesised in 93% after 14 h (**Scheme 41**), **531** was only obtained in 63% after 60 h, requiring 10 equivalents of ethylene glycol. Phenyl ketone **530** was completely unreactive under the same conditions. Taking this observation into account, it was speculated that given ketone **530** was unreactive towards acetalisation, it would also be inert towards any aldol side reactions likely to occur under α-arylation conditions (this was the reason why the carbonyl group had to be protected in the first place). Avoiding this protection step could not only allow the installation of larger groups at C1, but also reduce the number of steps in the sequence. Therefore, unprotected substrate **530** was then subjected to the conditions shown in **Table 34** and, pleasingly, diketo-indole **532** was successfully isolated in 66% (**Scheme 44**).



Scheme 44. α-Arylation of bromoindole **530** with acetophenone.

Diketone **532** was then subjected to basic cyclisation conditions since the acetal moiety was no longer present in the substrate. Basic ammonia sources were tested briefly: NH_4OH failed to produce β-carboline **533**, whereas NH_3 in MeOH furnished **533** in 35%. At this point it was hypothesised that due to the extra hindrance provided by the phenyl group, the activation energy to cyclisation would be higher than before and therefore higher temperatures were required. Indeed, the usual source, NH_4Cl, allowed the formation of **533** in 85% at 110 °C (**Table 37**). The identity of **533** was confirmed by the presence of only one singlet (8.48 ppm) in the aromatic region of the ^{1}H NMR spectrum, corresponding to the hydrogen at C4.



entry	conditions	solvent	T (°C)	yield **533** (%)
1	NH_4OH	EtOH/H_2O	100	0
2	NH_3 in MeOH	EtOH/H_2O	100	35
3	NH_4Cl	EtOH/H_2O DMF	110	85

Table 37. Cyclisation conditions for ketone **532**.

Finally, utilising different commercially available ketones and the prepared bromoindoles as starting materials, it was shown that this new methodology allowed the installation of substituents at every position on the heterocyclic pyridine ring of the carboline skeleton (**Table 38**). The typical aromatic singlets in the ^{1}H NMR spectra for compounds **521**, **536**, **537** and **533** were observed at 8.82 and 8.33 ppm (compound **521**, C1 and C4 protons, respectively),

8.82 ppm (compound **536**, C1 proton), 8.31 ppm (compound **537**, C4 proton) and 8.48 ppm (compound **533**, C4 proton).

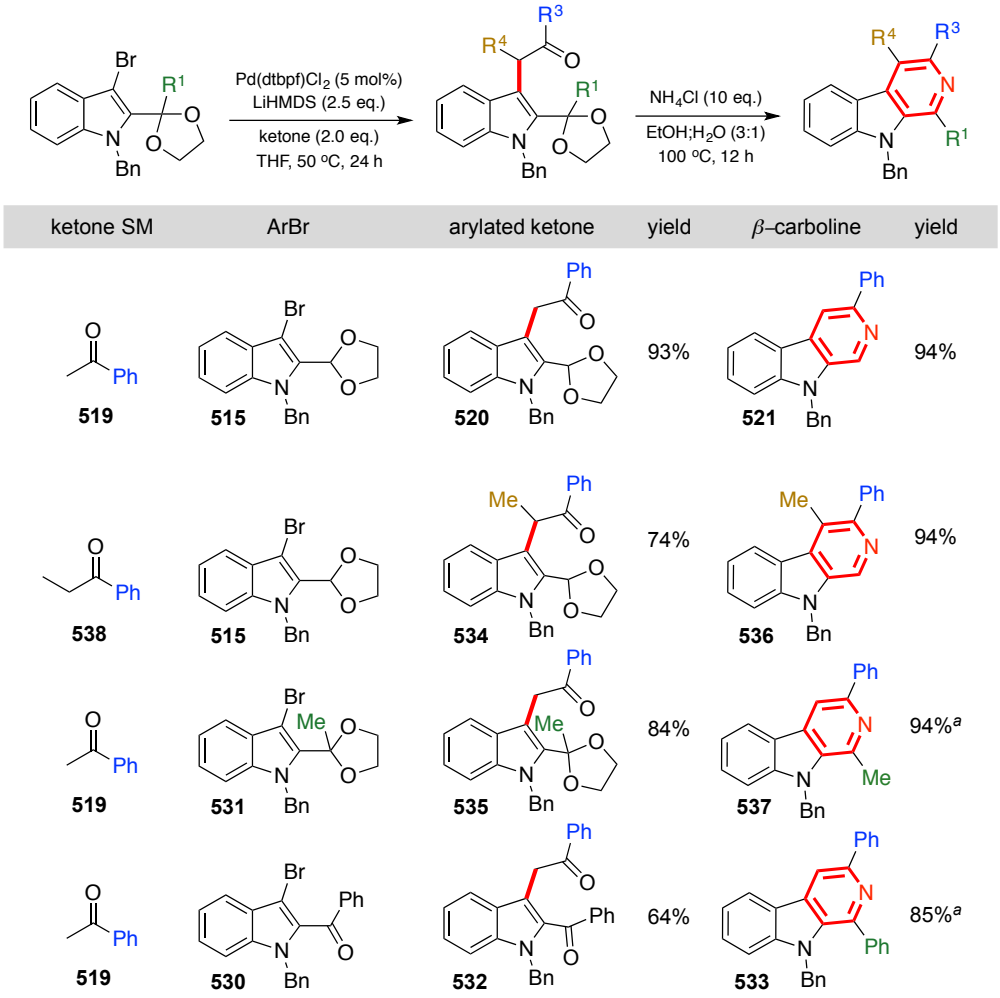
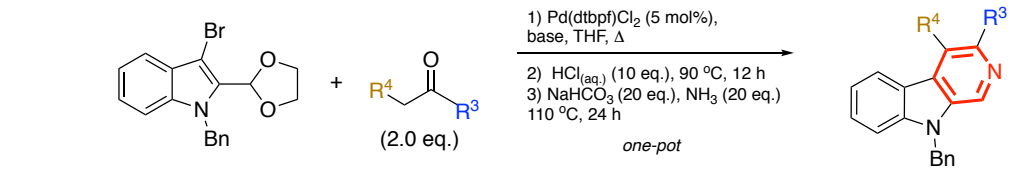


Table 38. Scope for the formation of *β*-carbolines. [a] Cyclisation conducted at 110 °C using EtOH/H_2O/DMF (3:1:2) as solvent.

2.2.7 One-pot synthesis of substituted *β*-carbolines

Using the examples shown in **Table 38** as a proof of concept, a one-pot protocol was developed. Initially, the normal arylation conditions were used in the first step, followed by the direct addition of $HCl_{(aq)}$ to simultaneously quench the excess base and deprotect the acetal moiety. Sodium bicarbonate was then added to basify the reaction medium and a solution of NH_3 in methanol provided the nitrogen source required for the cyclisation. This deprotection/cyclisation sequence provided better results in one pot when compared to the use

of a NH_4Cl solution in $EtOH/H_2O$. Pleasingly, carboline **521** was obtained in 68% yield, a slightly less efficient process than the stepwise synthesis shown in **Table 38** (stepwise yield = 88% over two steps). However, as the ketone substrate was changed from acetophenone to 3,3-dimethyl-2-butanone **541** and isovalerophenone **543**, low yields of the corresponding *β*-carboline products were observed (**542** and **544** in **Table 39** with 34% and 42%, respectively). In each case, the crude ^1H NMR spectrum suggested that bromoindole **515** was not being fully consumed in the arylation step as the aldehyde peak at 10.11 ppm corresponding to the deprotected indole starting material (compound **514**) was observed. A change in the base from LiHMDS to NaO*t*Bu and an increase in the reaction temperature from 50 °C to 75 °C allowed better results over a wider range of commercially available ketones and the *β*-carbolines presented in **Table 39** were isolated in good yields. All *β*-carbolines showed one or two singlets in the ^1H NMR spectra (depending whether or not substitutes at C4) between 8.00 and 9.00 ppm. These peaks corresponded to the C1 and C4 hydrogens in these molecules.



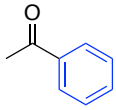
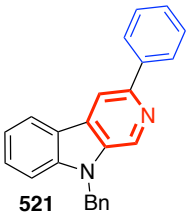
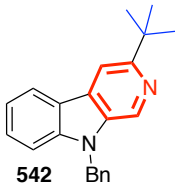
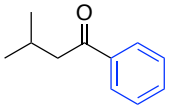
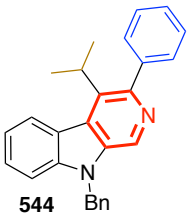
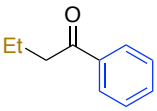
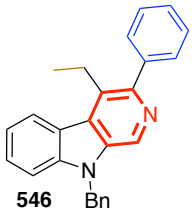
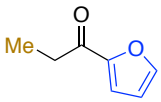
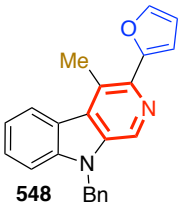
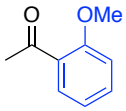
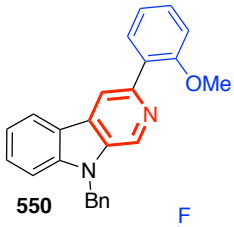
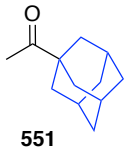
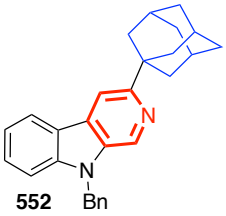
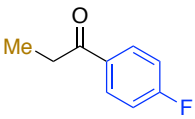
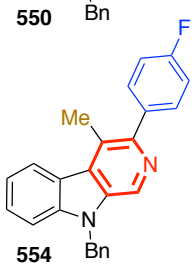
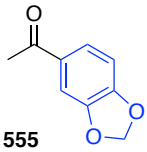
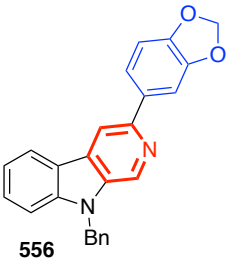
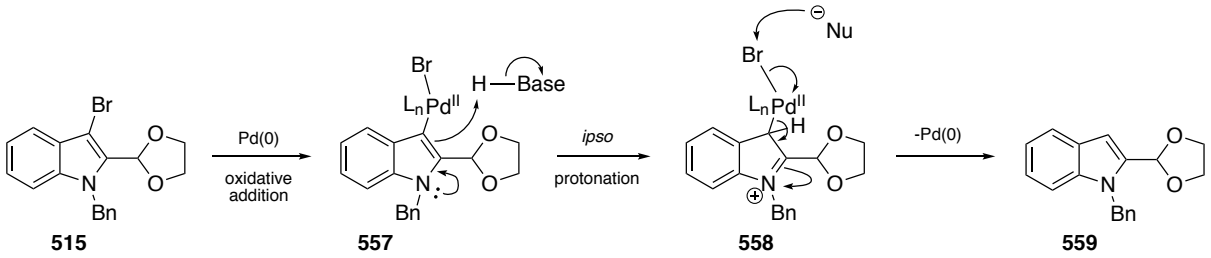
ketone	β-carboline	yield	ketone	β-carboline	yield
 **519**	 **521**	68%[a]	 **541**	 **542**	34%[a] 53%[b]
 **543**	 **544**	42%[a] 73%[b]	 **545**	 **546**	68%[b]
 **547**	 **548**	75%[b]	 **549**	 **550**	74%[b]
 **551**	 **552**	61%[b]	 **553**	 **554**	52%[b]
 **555**	 **556**	61%[b]			

Table 39. One-pot synthesis of β-carbolines from 3-bromoindole **515** and commercially available ketones. [a] LiHMDS as base, 50 °C; [b] NaO*t*Bu as base, 75 °C.

The developed methodology tolerated a variety of groups: electron-donating (**550** and **556**) and electron-withdrawing (**554**) aryl substituents, simple (**542**, **544** and **546**) and bulky alkyl group (**542**) and a heterocyclic aromatic ring (**548**).

Interestingly, in some cases a by-product was isolated in low yields and characterised as the debrominated indole **559**. A similar debromination process has already been observed in the Donohoe group and a proposed mechanism involves the *ipso* protonation of the electron-rich indole **557** once bound to palladium, followed by a nucleophile-assisted reduction of Pd(II) to deliver debrominated indole **559**.[207] The Pd-catalysed dehalogenation of aryl halides is a process that has been extensively described in the literature[208,209,210] with reports also including heterocyclic aromatic compounds.[211,212]



Scheme 45.[207] Proposed mechanism for the Pd-catalysed debromination of **515**.

Some commercially available ketones tested under the one-pot conditions shown in **Table 40** were either unreactive or delivered the corresponding β-carbolines in only trace amounts with the α-arylation step being the problematic one as, again, an aldehyde peak at 10.11 ppm corresponding to the deprotected indole starting material (compound **514**) was observed in the ^{1}H NMR spectrum of the crude material isolated from these reactions. Some substituents not tolerated were: pyrrolyl, cyclic alkyl, pyridyl, anilinyl, nitryl, cyclopropyl, ester, nitrile, alkenyl and acetal (**Table 40**). Nitrogen-containing compounds such as **560**, **564** and **565** could deactivate the palladium catalyst *via* coordination and inhibit the α-arylation reaction,[213] while electron-deficient ketones (**567**, **568** and **569**) could potentially participate in facile self-condensation reactions.

It was found later (**Chapter 2.3**) that solid NaO*t*Bu gave variable results when repeating specific α-arylation reactions, with some transformations failing to be replicated. The use of a commercially available 2 M solution of NaO*t*Bu in THF solved this problem in that instance. It is possible that the substitution of solid NaO*t*Bu by the commercially available 2 M in THF

could have been beneficial in the synthesis of β-carbolines as well, increasing the observed yields.

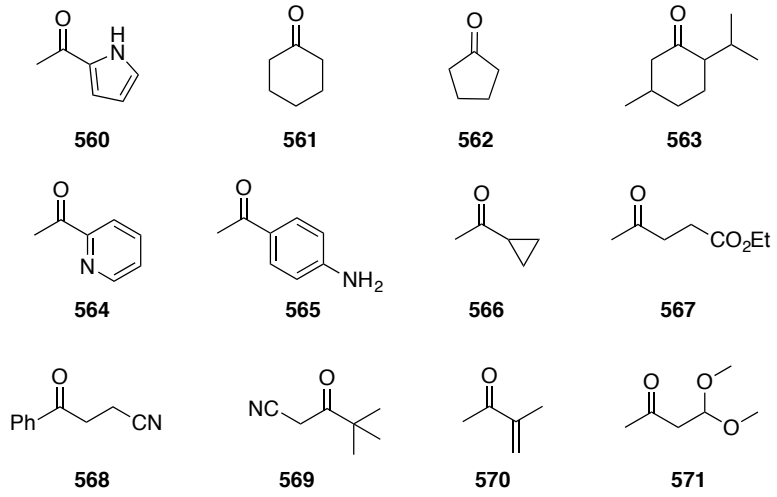


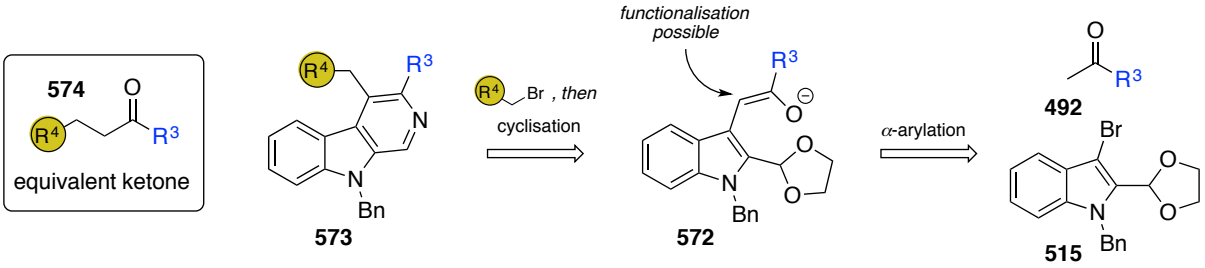
Table 40. Unreactive ketones in the one-pot synthesis of β-carbolines.

2.2.8 *In situ* functionalisation with electrophiles: exploring C4 variations

Next the *in situ* functionalisation of the arylated ketone was investigated. This idea would allow us to trap the enolate intermediate formed after the α-arylation reaction *via* the addition of electrophiles. After cyclisation, this would lead to the formation of 4-substituted β-carbolines. Functionalisation at this position in the aromatic compound itself is not particularly facile. Some of the few approaches published involve *ortho*-lithiation directed by a carboxamide installed at C3 followed by the addition of electrophiles,[214,215] iodination of C4 followed by Heck coupling[216] or *ortho*-magnesiation, also directed by a carboxamide at C3.[217] All of these reactions require organometallic reagents and the presence of a directing group to guide the functionalisation, which cannot be easily removed after the transformation.

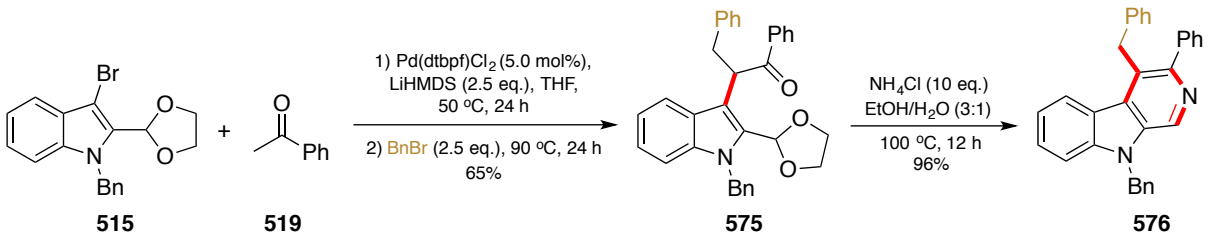
Inspired by the previous work on isoquinolines (**Scheme 35**), it was envisioned that C4 functionalisation would be possible with the electrophile quenching of the enolate intermediate formed *in situ* immediately after the α-arylation. The alkylated compound would then cyclise under standard conditions to furnish C4-functionalised β-carbolines. Moreover, the overall transformation, starting from a simple methyl ketone, would be equivalent to the direct α-arylation and cyclisation of a more complex ketone **574** that would be not commercially

available or not compatible with the reaction conditions. In some cases, this strategy can also solve problems with the regioselectivity of the ketone deprotonation (*e.g.* the use of 3-hexanone vs 2-butanone + EtI addition) (**Scheme 46**).



Scheme 46. Strategy for the C4 functionalisation of *β*-carbolines using electrophiles.

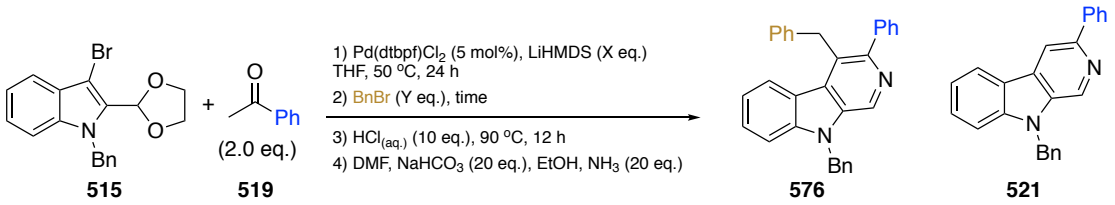
To test this concept, bromoindole **515** was subjected to the standard *α*-arylation conditions followed by the addition of 2.5 equivalents of benzyl bromide and further heating. The alkylated ketone **575** was obtained in 65% and no dialkylation was observed. The intermediate **575** was then subjected to cyclisation conditions to furnish *β*-carboline **576** in an excellent yield of 96% (**Scheme 47**). Ketone **575** was identified by the presence of two diastereotopic hydrogens at 3.99 and 3.59 ppm in the ^{1}H NMR spectrum, corresponding to the benzylic *β*-hydrogens of ketone **575**. *β*-Carboline **576** showed in its ^{1}H NMR spectrum a characteristic singlet at 8.95 ppm, corresponding to the hydrogen at C1 and also a singlet at 4.68 ppm, corresponding to the benzylic protons connected to C4.



Scheme 47. C4 functionalisation of *β*-carboline **576** *via* enolate quench with benzyl bromide.

Next the feasibility of a one-pot arylation and cyclisation procedure was investigated. It was clear from our first reactions that the alkylation would be the most challenging step as

C4-unfunctionalised *β*-carboline **521** was also isolated along with the desired product. The crude NMR ratio of the product **576** and by-product **521** could be easily established comparing both benzylic protons present in their protecting groups. The addition of more equivalents of benzyl bromide showed no change in the NMR ratio between these carbolines (entry 2). When the reaction was conducted at room temperature, the ratio of unfunctionalised by-product increased, as expected (entries 3 and 4). Extended reaction times at 50 ºC and 90 ºC with 4.0 and 2.5 equivalents of benzyl bromide also failed to eliminate **521** nor significantly reduce it (entries 5 to 9). Finally, it was speculated that the excess ketone left from the first step could be consuming the electrophile added, so it was kept at only 1.2 equivalents with 1.5 equivalents of base, but this also failed to eliminate **521** (entry 10) (**Table 41**).



entry	BnBr (eq.)	base (eq.)	time (h)	T (ºC)	^{1}H NMR ratio yield **576** **576**	**521**	(%)
1	2.5	2.5	24	90	1.0	0.27	60
2	4.0	2.5	24	90	1.0	0.27	53
3	2.5	2.5	24	RT	1.0	1.0	-
4	4.0	2.5	24	RT	1.0	0.39	-
5	2.5	2.5	48	50	1.0	0.33	-
6	4.0	2.5	48	50	1.0	0.27	-
7	2.5	2.5	48	90	1.0	0.22	60
8	4.0	2.5	48	90	1.0	0.18	61
9	2.5	5.0	48	90	1.0	0.56	-
10[a]	2.5	1.5	48	90	1.0	1.1	-

Table 41. Screening of reaction conditions for the one-pot synthesis of **576**. [a] 1.1 eq. of ketone added.

The formation of by-product **521** in this one-pot procedure attests that the enolate alkylation (step 2) was not complete. This problem is believed to be caused by a difficult deprotonation step with LiHMDS due to steric effects. This hypothesis is supported by the fact that a ketone (compound **612**) with a structure similar to **520** was fully deprotonated and *α*-alkylated with

three different electrophiles when LiHMDS was replaced with NaH as the base of choice (see **Chapter 2.4.2**).

The results compiled in Table **41** show that the keto-indole alkylation is faster at higher temperatures (entries 1 and 2), which favours the access of the hindered base to the ketone intermediate methylene protons. The concentration of benzyl bromide added seems to be irrelevant to the outcome of the reaction, which again agrees with the formation of the enolate being the slow step (entries 2, 4, 6 and 8).

Despite this problem, the best yield obtained for this reaction (61%) was still very good considering this is a four-component one-pot transformation. Moreover, as previously mentioned, this sequence can be particularly useful when: 1) the 'equivalent ketone' generated by the added electrophile is not commercially available; 2) the 'equivalent ketone' generated by the added electrophile possesses two distinct enolisable and sterically similar set of hydrogens or 3) the 'equivalent ketone' generated by the added electrophile is incompatible with the Pd-catalysed α-arylation reaction conditions (*e.g.* β-carboline **581** would require ketone **582** as starting material, a substrate that could potentially undergo competitive Pd-catalysed Heck reaction with bromoindole **515** in the first step).

The scope for this one-pot reaction was then explored with different electrophiles and five different C4-substituted β-carbolines were obtained in reasonable yields (**Table 42**). These products were identified by the presence of the characteristic aromatic singlets between 8.50 and 9.01 ppm corresponding to the hydrogens at C1 in the ^{1}H NMR spectrum. The methylene protons in the C4 substituents were also observed as singlets in the ^{1}H NMR spectra between 4.47 and 4.84 ppm for compounds **576**, **578** and **579** and as a multiplet between 3.92 and 3.84 ppm for β-carboline **581**. The hydrogens from the methyl group in **580** produced a characteristic singlet at 2.91 ppm in the ^{1}H NMR spectrum.

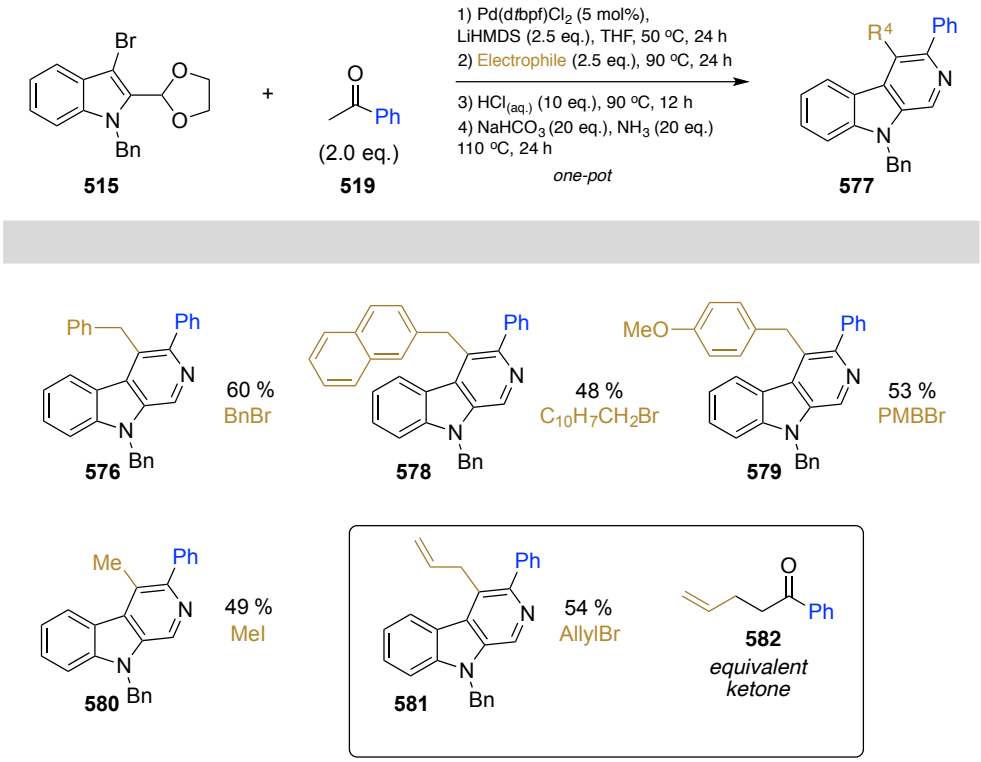


Table 42. Four-component one-pot synthesis of C4-substituted *β*-carbolines.

The methodology discussed in this chapter presents an efficient route to substituted *β*-carbolines. The one-pot procedure allowed easy access to these compounds with ease and in reasonable yields and a variety of different substituents (both electronically and sterically) were tolerated in this transformation. The addition of electrophiles following the *α*-arylation step in one-pot allowed the installation of different substituents at C4 in reasonable to good yields, adding great versatility to this methodology.

2.2.9 *β*-carbolines in Nature: the C3 carbonyl

With two different one-pot procedures established, attention was then focused on concise pathways to natural product targets employing the developed sequence. A search revealed that most of the bioactive *β*-carboline natural products isolated bear a carbonyl-containing group at C3. Some illustrative examples are lavendamycin,[218] metacarboline C,[219] dichotomine C,[220] marinacarboline C,[221] dragmacidonamine B[222] and stolonine C.[223]

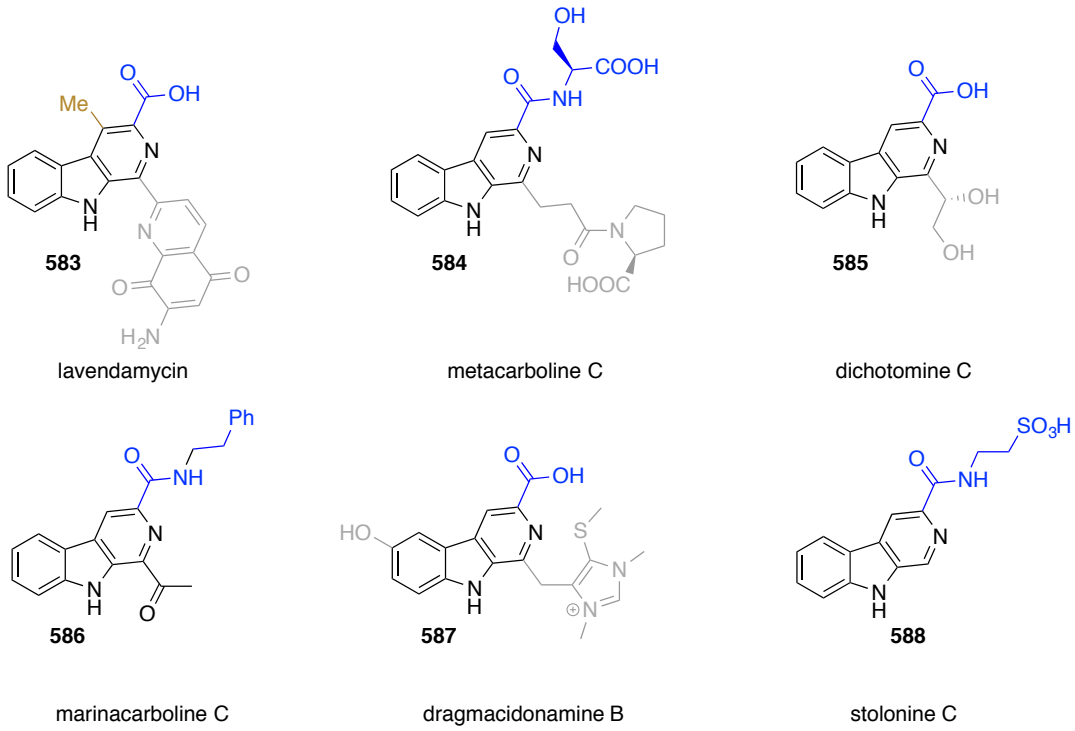
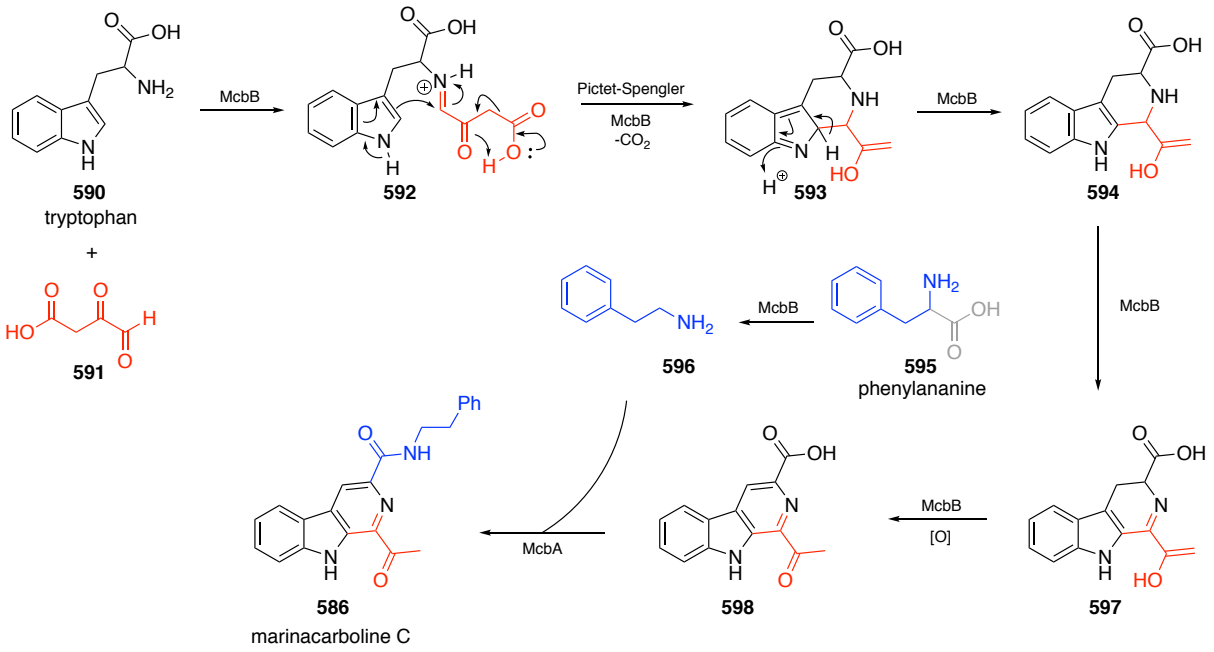


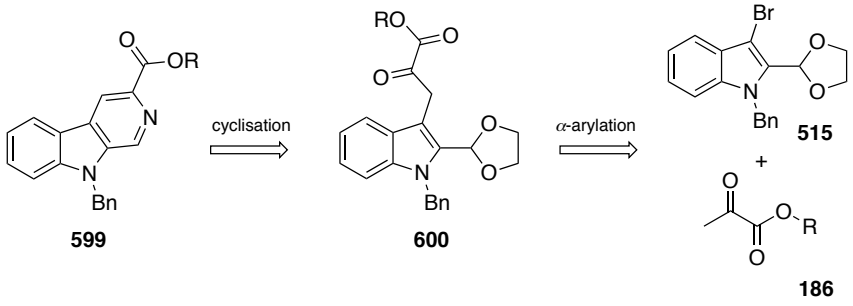
Figure 15. Illustrative examples of bioactive *β*-carboline-derived natural products.

The reason behind this pattern is the biosynthetic origin of most *β*-carboline natural products: the amino acid tryptophan **590**.[224,225] Scheme **48** illustrates the biosynthesis of marinacarboline C **586** from three building blocks: tryptophan **590**, oxaloacetaldehyde **591** and phenylalanine **595**. Enzymes McbA, B and C were found to be the enzymes operating this process, which starts with the formation of imine **592**, followed by Pictet–Spenger condensation with concomitant decarboxylation. Oxidation of **597** and coupling with amine **596** delivers the product marinacarboline C **586**.[226]



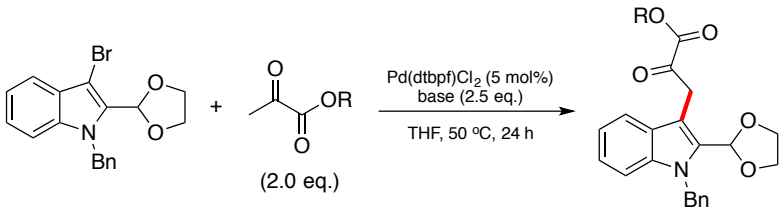
Scheme 48.[226] Biosynthesis of marinacarboline C, as elucidated by Ju and co-workers.

In order to install these groups at C3 utilising our methodology, a pyruvate enolate derivative would need to be arylated by bromoindole **515** (**Scheme 49**).



Scheme 49. Retrosynthetic analysis of β-carboline **599**.

After screening conditions for α-arylation reactions involving pyruvate derivatives, it became clear that these substrates were not compatible with a basic reaction medium. The reactions tested completely failed to give the product **600**, regardless of the base used (**Table 43**).

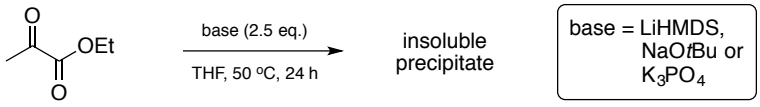


515 **186** **600**

entry	base	R	yield **600** (%)
1	LiHMDS	H	0
2	LiHMDS	Et	0
3	NaO*t*Bu	Et	0
4	K_3PO_4	Et	0

Table 43. Attempted α-arylation of **186** with bromoindole **515**.

Control experiments showed that when ethyl pyruvate **127** was subjected to the same reaction conditions in the absence of the palladium catalyst and bromoindole **515**, the starting material formed a viscous gel-like precipitate almost instantly and no starting material was recovered.



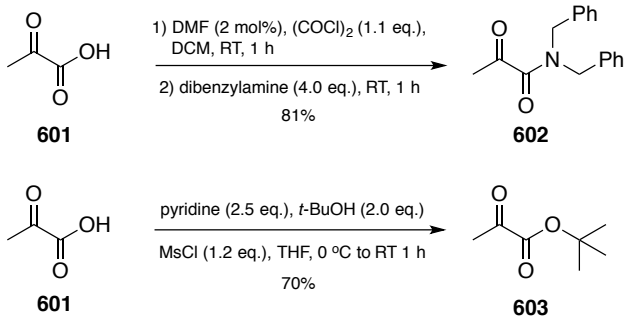
127

Scheme 50. Control experiments showing the decomposition of **127** under basic conditions.

The probable origin of this decomposition is the ambident reactivity of pyruvates under basic conditions. The nucleophilic end of one molecule can attack the electrophilic moiety of a second molecule in a chain reaction that could lead to polymerisation.[227]

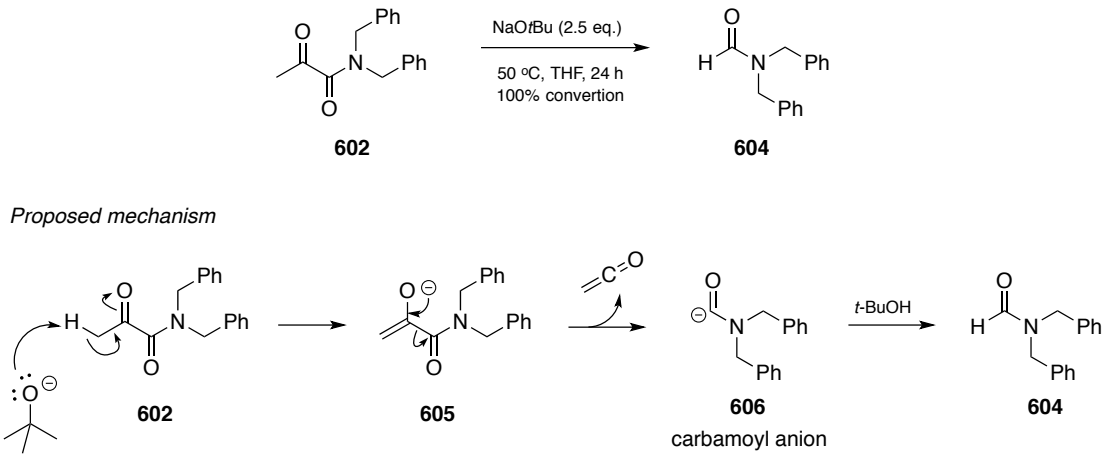
2.2.10 Pyruvate equivalents as coupling partners: β-carboline ester synthesis

Considering these results, it was then decided to investigate alternatives to ethyl pyruvate **127** in which the electrophilic end of the molecule would be either masked or hindered in order to avoid nucleophilic attack. For this purpose, α-keto amides **602** and *tert*-butyl pyruvate **603** were synthesised (**Scheme 51**).



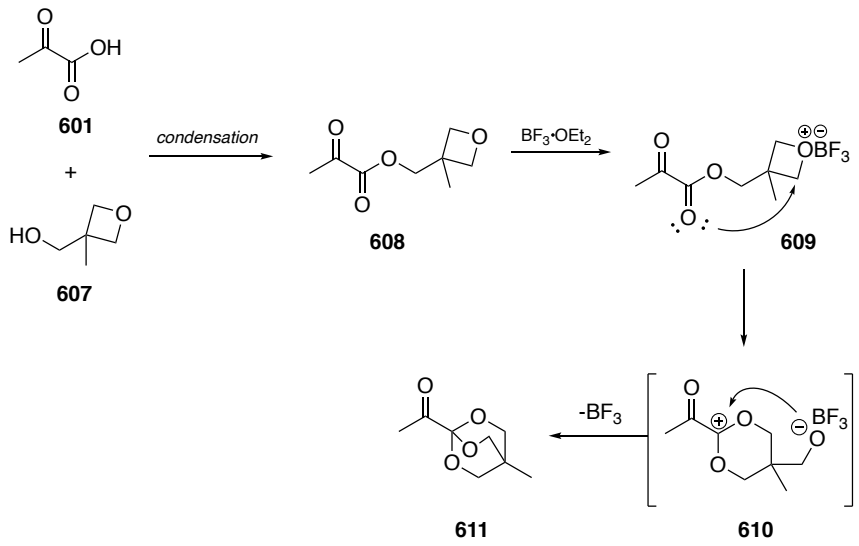
Scheme 51. Synthesis of α-ketoamide **602** and *tert*-butyl pyruvate **603**.

The first candidate, *tert*-butyl pyruvate failed to react with 3-bromoindole **515** under the α-arylation conditions and bromoindole **515** was recovered intact. Interestingly, when α-ketoamide **602** was subjected to α-arylation conditions, no coupling reaction was observed. Instead, **602** was decomposed to give *N*,*N*-dibenzylformamide **604**. A control experiment carried out with NaO*t*Bu and THF showed that compound **602** is unstable under strongly basic conditions. Bases of similar strength (*e.g.* LDA) led to the same outcome, whereas milder ones, such as Et_3N or proton sponge did not react with the substrate and the α-ketoamide **602** was recovered intact. Although the mechanism is not entirely clear, it was speculated that the enolate form of **602** might be unstable and collapse to give a ketene and the carbamoyl anion **606**, which could, in turn, be protonated by *t*-BuOH formed in the first step to give formamide **604** as by-product (**Scheme 52**). Carbamoyl anions generated from the deprotonation of formamides are known in the literature and have been explored as useful synthetic intermediates.[228]



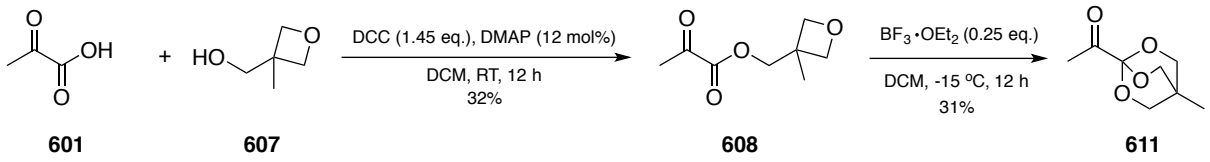
Scheme 51. α-ketoamide **602** decomposition under basic conditions and proposed mechanism.

The unsuitability of **602** and **603** as coupling partners under the α-arylation reaction conditions suggested that a more robust protecting group had to be chosen. An orthoester was investigated next in the form of oxabicyclo[2.2.2]octyl orthoester, OBO.[229] This protecting group is formed *via* rearrangement of a oxetanyl ester **608**, which can be generated by the condensation of a carboxylic acid with commercially available 3-hydroxymethyl-3-methyloxetane **607**. **Scheme 53** shows the mechanism for pyruvic acid.



Scheme 53. Mechanism of formation of methyl-OBO ketone **611**.

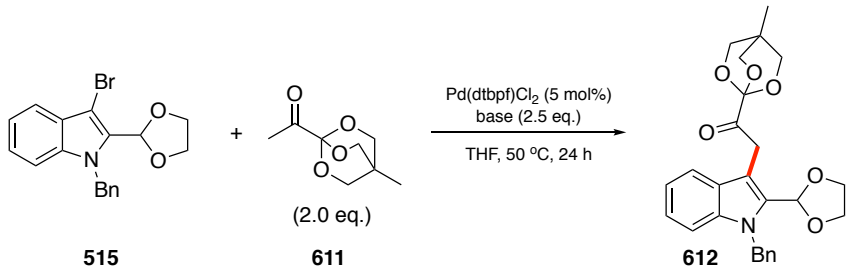
The synthesis of methyl-OBO ketone was then attempted. First the condensation of pyruvic acid and 3-hydroxymethyl-3-methyloxetane **607** was performed with DCC and DMAP. Pleasingly, the BF_3-catalysed rearrangement of **608** then furnished the novel methyl-OBO ketone **611**, albeit in low yield (**Scheme 54**). The identity of **611** was confirmed by the presence of three singlets at 3.76, 2.00 and 0.63 ppm in the ^{1}H NMR spectrum, corresponding to the methylene hydrogens, the ketone methyl group and the methyl group in the OBO moiety, respectively. The identity of oxetanyl ester **608** was confirmed by the presence of two dublets at 4.52 and 4.43 (J = 6.1 Hz) corresponding to the two distinct pairs of hydrogens in the oxetane ring.



601 **607** **608** **611**

Scheme 54. Synthetic sequence to **611** from pyruvic acid **601**.

Next, the α-arylation of bromoindole **515** with methyl OBO ketone was examined. Pleasingly, NaO*t*Bu allowed the formation of arylated OBO-ketone **612** in 91% yield (**Table 44**).

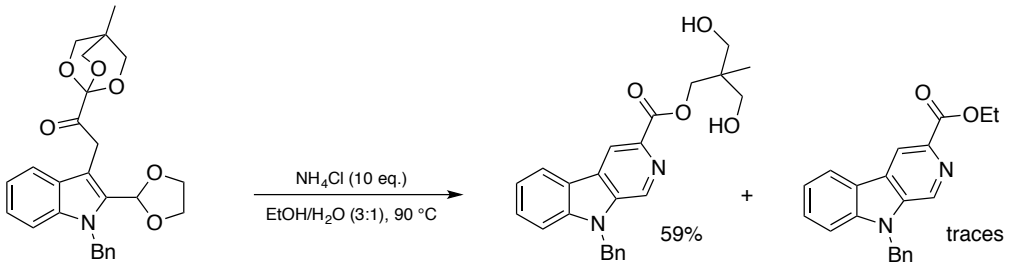


515 **611** **612**

entry	base	conversion (%)	yield **612** (%)
1	K_3PO_4	0	0
2	LiHMDS	58	44
3	NaO*t*Bu	100	91

Table 44. Base screening for the α-arylation of bromoindole **515** with methyl-OBO ketone **611**.

Finally, with keto-indole **612** obtained in high yield, the cyclisation/deprotection sequence was carried out under the standard conditions. However, the major isolated product was ester **613**, intermediate *en route* to the desired β-carboline **614**, which was identified in trace amounts (**Scheme 55**).



612 **613** **614**

Scheme 55. Cyclisation of keto-indole **612** under standard conditions.

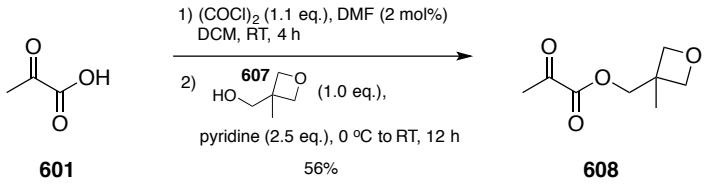
Given this encouraging precedent, optimisation studies for the formation of β-carboline **614** from methyl-OBO-ketone **611** in good yields will be discussed in detail in **Chapter 2.4.2**, which will focus more generally on the use of methyl-OBO-ketone **611** in the synthesis of heterocyclic aromatic esters.

2.3 Synthesis of α-functionalised pyruvates

2.3.1 Screening of the conditions for the esterification of pyruvic acid

The preliminary result shown in **Table 44** demonstrated the efficiency of methyl-OBO ketone **611** as an effective pyruvate equivalent that can operate at high pH values, however, its formation depicted in **Scheme 54** was still not practical due to the low yields obtained, so a new approach to **611** was sought.

The esterification of pyruvic acid **601** was then attempted *via* the formation of its corresponding acyl chloride, followed by the addition of the commercially available alcohol **607** and pyridine in one pot (**Scheme 56**).[230]



Scheme 56. Formation of ester **608** from pyruvic acid **601**.

Despite the considerable increase in efficiency observed with this method (from 32% to 56% yield), it was still unclear why higher yields were not being obtained. The formation of the intermediate, pyruvoyl chloride, should not be problematic given it was also generated in the synthesis of α-ketoamide **602**, which proceeded in 81% yield over two steps (**Scheme 51**). Moreover, no obvious by-product could be spotted in the crude ^{1}H NMR spectrum after workup (**Figure 16**).

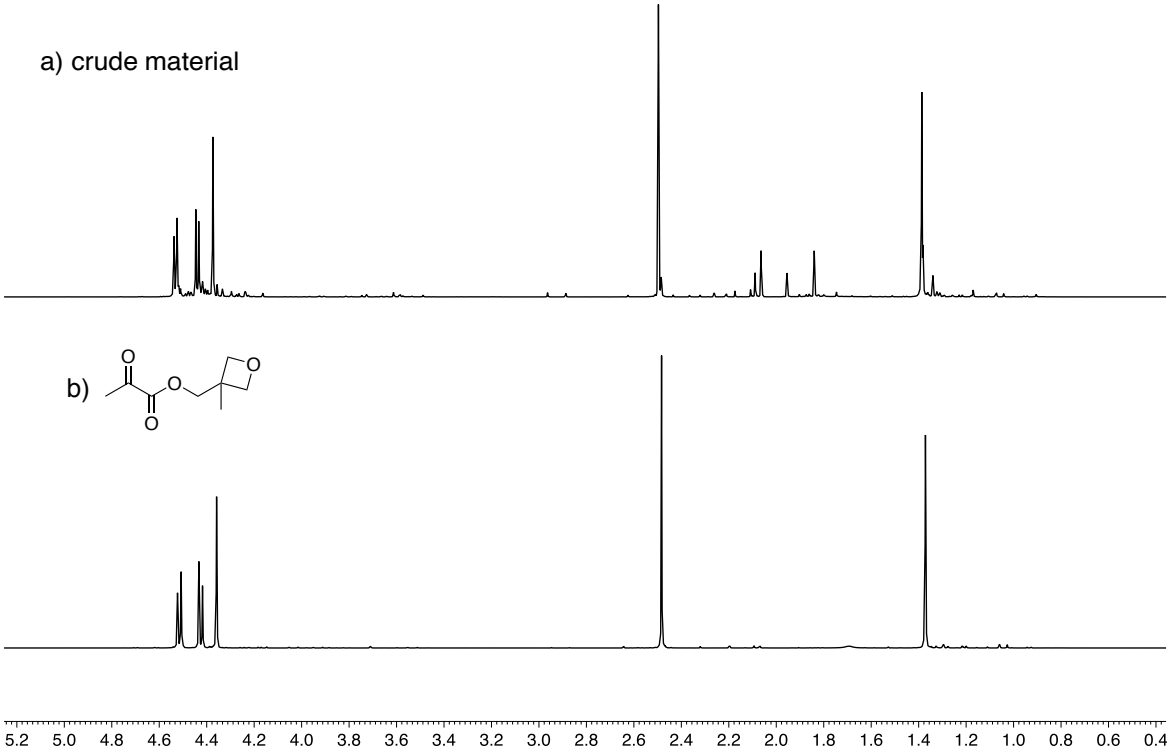


Figure 16. a) Crude ^{1}H NMR spectrum of the reaction shown in Scheme **56**. b) ^{1}H NMR spectrum of a pure sample of ester **608**.

The reaction course was then monitored by an infrared probe in order to assess how fast the acyl chloride intermediate **615** was being consumed upon addition of a mixture of pyridine and alcohol **607**. Acyl chloride **615**, oxetanyl ester **608** and pyruvic acid **601** were monitored at 873 cm^{-1}, 1486 cm^{-1} and 1346 cm^{-1}, respectively. Oxalyl chloride was added over 45 minutes at 0 °C and then reacted at RT for 3 h. The reaction profile in **Figure 17** shows that the formation of the acyl chloride **615** starts as the addition is stopped and the mixture is warmed to RT. After 3 h, the reactor content was cooled to 0 °C and a mixture of pyridine and alcohol **607** was added over 30 mins. As shown by the reaction profile, the intermediate **615** was immediately consumed, forming the product **608** which was stable under the reaction conditions for more than 10 h.

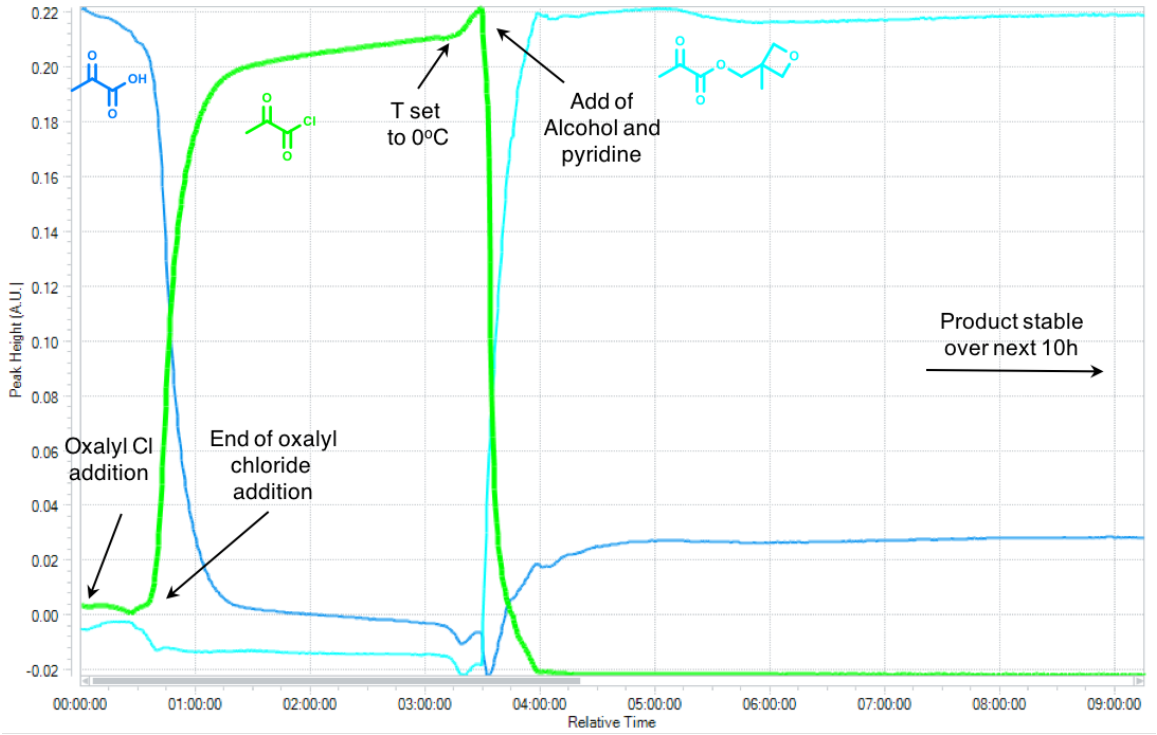
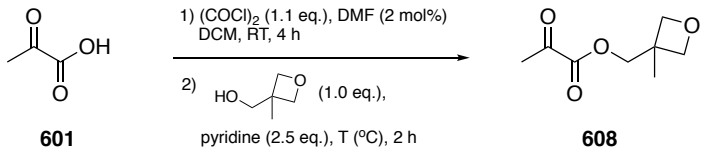


Figure 17. Reaction profile for the esterification of pyruvic acid with alcohol **607**.

Considering the high reactivity observed for intermediate **615**, it was then decided to screen lower temperatures for the addition of the alcohol **607** solution in pyridine with the expectation this could render a cleaner esterification. Indeed, **Table 45** shows that the temperature plays a fundamental role during this addition and –40 °C was optimal to deliver oxetanyl ester **608** in 77% over two steps.



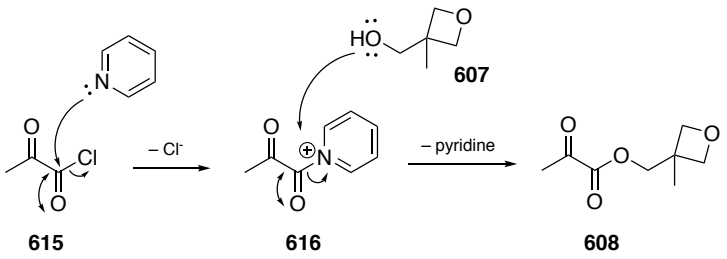
601 **608**

entry	temperature (ºC)	yield **608** (%)
1	0	56
2	–40	71
3	–40 to RT	77
4	–78	62

Table 45. Temperature screening for the addition of alcohol **607** and pyridine to intermediate **615**.

In contrast to the formation of α-ketoamides already discussed, in which an excess of a secondary amine acts as nucleophile and base (**Scheme 51**, **Chapter 2.2.10**), a less nucleophilic alcohol is the coupling partner in the reaction screened in **Table 45**. The mechanism should involve pyridine acting as a nucleophilic catalyst to form the more reactive acyl pyridinium ion intermediate **616** from pyruvoyl chloride **615**, which is then attacked by alcohol **607** to form oxetanyl ester **608** (**Scheme 57**).

The intemediate **616** bears a positive charge next to an electron-poor carbonyl, which could potentially make this molecule unstable at higher temperatures. It is noteworthy that even a simple α-ketoamide such as **602** is unstable under relatively mild conditions (**Scheme 51**), therefore making the assumption of the instability of **616** plausible.

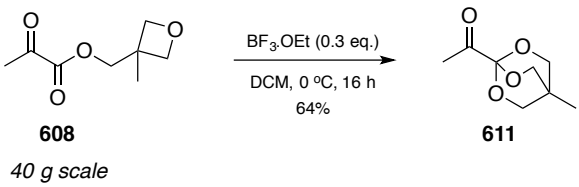


Scheme 57. Proposed mechanism for the esterification of **615**.

With the modification of the temperature in place, the reaction proceeded in good yields even at 100 g scale. The product could be isolated by reduced vacuum distillation, eliminating the need for expensive and laborious chromatographic methods.

2.3.2 Oxetane rearrangement: synthesis of methyl-OBO-ketone

Next, the rearrangement of oxenatyl ester **608** was studied under a range of temperatures and it was observed that 0 °C was optimal to convert 100% of the starting material while avoiding extensive decomposition of the product **611**. Unfortunately, despite efforts, the isolated yield of **611** was consistently between 50% and 60%. However, the transformation showed good reliability, especially at large scale (**Scheme 58**).



Scheme 58. Synthesis of methyl-OBO-ketone **611**.

Moreover, the product could be isolated after a simple filtration through a plug of silica followed by crystallisation from methyl-*tert*-butyl ether (MTBE). The methyl-OBO-ketone **611** obtained was a non-hygroscopic and bench-stable crystalline solid, which also facilitates its use and storage (**Figure 18**).

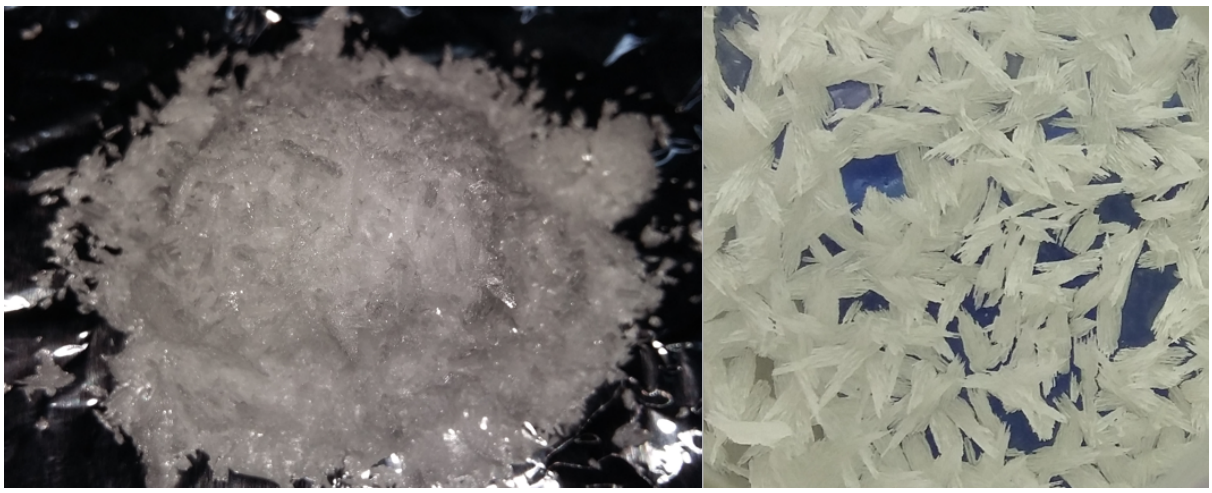
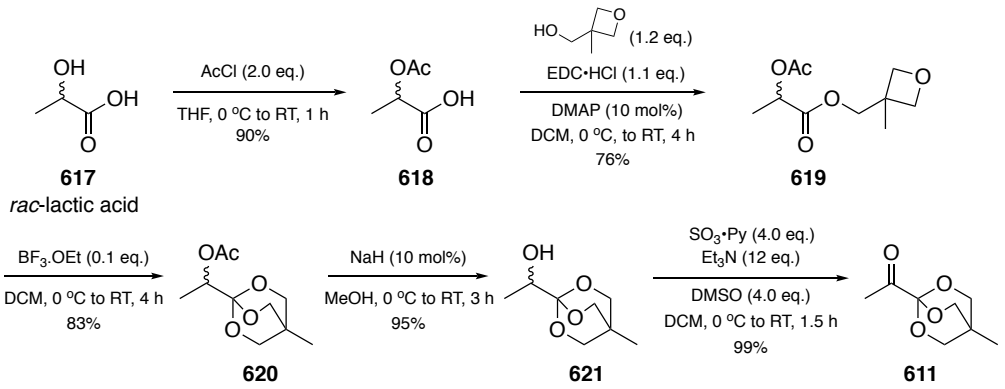


Figure 18. Methyl-OBO-ketone as obtained after crystallisation from MTBE.

It is noteworthy that the yields obtained in OBO-forming reactions in the literature vary in the range 50-65%[231,232,233] to 80-90%[234,235,236] in most of the cases.

It is important to mention that shortly before the writing of this thesis began, Makino and co-workers published an alternative route to methyl-OBO-ketone **611** from *rac*-lactatic acid.[237] In their publication the group explored stereoselective aldol reactions involving **611**, focusing on the synthesis of sialic acid derivatives. In their proposed synthesis, **611** was obtained in 53% over five steps, requiring five chromatographic separations. These steps include one protection/deprotection sequence and one change in oxidation state. Moreover, the synthesis is

less atom efficient as it requires stoichiometric amounts of EDC·HCl in the second step, four equivalents of oxidizing agent and twelve equivalents of base in the final step (**Scheme 59**).



Scheme 59. Makino's synthesis of **611** from *rac*-lactatic acid.

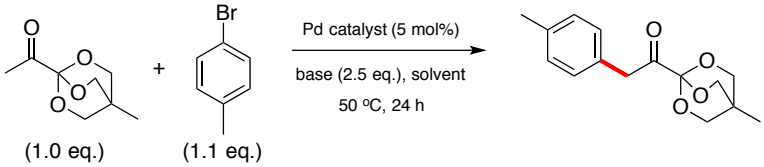
In contrast, the synthesis developed in our group afforded **611** in 49% yield over three steps (two steps in one pot), requiring only one chromatographic separation or, alternatively, **611** could be isolated in 44% at multi-gram scale relying only on one vacuum distillation and one crystallisation.

2.3.3 α-Arylation of methyl-OBO-ketone: condition screening

With a practical and scalable synthesis of **611** established, it was then decided to explore the full potential of this molecule as a general coupling partner towards the enolate arylation reaction, aiming to make it an entry to mono and multiply α-functionalised pyruvates.

The screening of conditions described in **Table 46** was carried out by Christopher Hall, a fellow group member and former Part II student in the Donohoe group.[238]

To accomplish this task, 4-methylbromobenzene was initially chosen as model aryl halide and a variety of palladium catalysts, solvents, bases and temperatures were screened (**Table 46**).



(1.0 eq.) **611** (1.1 eq.) **622** **623**

entry	catalyst	Solvent	base	conversion[a] (%)	yield **623** (%)
1	Pd(QPhos)(crotyl)Cl	THF	NaO*t*Bu	100	40
2	Pd(QPhos)(allyl)Cl	THF	NaO*t*Bu	90	-
3	$Pd(Amphos)_2$	THF	NaO*t*Bu	0	-
4	Pd(Amphos)(allyl)Cl	THF	NaO*t*Bu	0	-
5	$Pd(PPh_3)_2(PhCH_2)Cl$	THF	NaO*t*Bu	0	-
6	$[Pd(NHC)(naphtoquinone)]_2$	THF	NaO*t*Bu	0	-
5	$Pd(cod)Cl_2$	THF	NaO*t*Bu	70	52
8	$Pd(dtbpf)Cl_2$	THF	NaO*t*Bu	100	85
9[b]	$Pd(dtbpf)Cl_2$	THF	NaO*t*Bu	0	0
10	$Pd(dtbpf)Cl_2$	Toluene	NaO*t*Bu	87	39
11	$Pd(dtbpf)Cl_2$	DCE	NaO*t*Bu	58	51
12	$Pd(dtbpf)Cl_2$	Dioxane	NaO*t*Bu	87	44
13	$Pd(dtbpf)Cl_2$	THF	LiHMDS	0	0
14	$Pd(dtbpf)Cl_2$	THF	Cs_2CO_3	95	14

Table 46.[238] Optimisation of the α-arylation of **611**. [a] Conversion based on the crude ^{1}H NMR spectra [b] Reaction run at 75 °C.

Preformed palladium complexes were chosen for their well-defined structure and air stability when compared to the more common choice of *in situ* formation of the catalytic species upon addition of a palladium source and a ligand of choice. Furthermore, it has been demonstrated that preformed catalysts show superior results when compared with some mixtures formed *in situ* in the context of Pd-catalysed arylation reactions: in a report by Colacot and co-workers, $Pd(dtbpf)Cl_2$ showed higher activity when compared to a 1:1 mixture of $Pd_2(dba)_3$ and dtbpf towards the enolate arylation reaction.[188] In a different study involving Pd-catalysed C-N bond forming reactions, it was found in mixtures of $Pd_2(dba)_3$ and Xantphos, that the metal/ligand ratio dramatically influences the activity of the catalyst.[239] The observations suggest that thermodynamically stable 18-electron species (PdL_2) might be formed and may not equilibrate

back to the reactive 14-electron species (PdL) required in the catalytic cycle.[240] The structures of the catalysts screened in **Table 46** (entries 1 to 8) are shown in **Figure 18**.

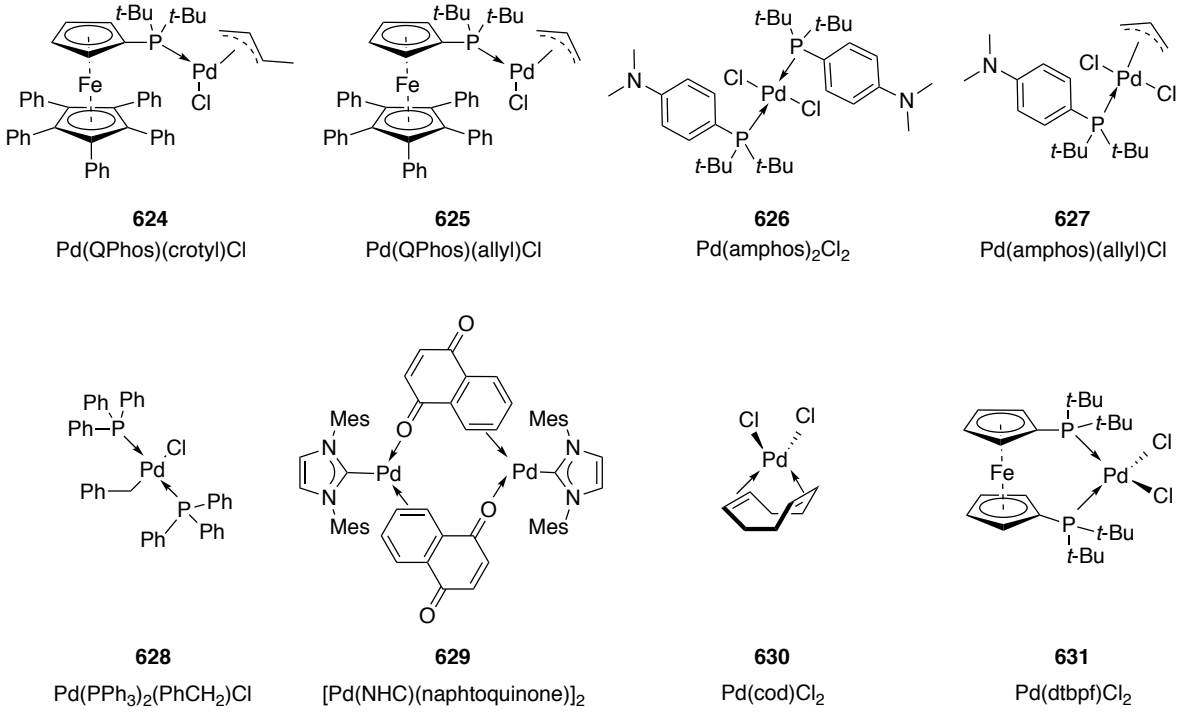


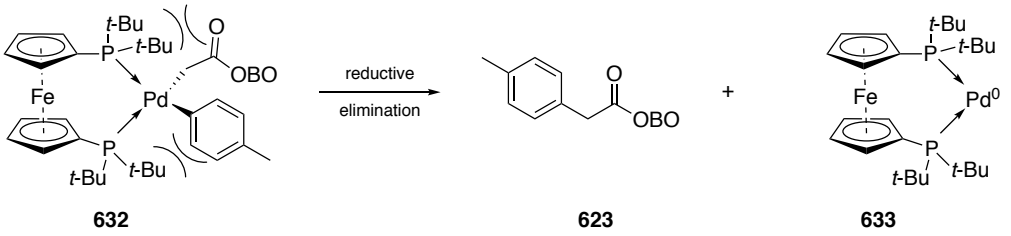
Figure 18.[238] Structures of the screened palladium catalysts.

The first two palladium complexes tested, Pd(QPhos)(crotyl)Cl and Pd(QPhos)(allyl)Cl gave 100% and 90% conversion of the starting material **611**, however, product **623** was obtained in only 40% isolated yield with Pd(QPhos)(crotyl)Cl (entry 1). $Pd(Amphos)_2$, Pd(Amphos)(allyl)Cl, $Pd(PPh_3)_2(PhCH_2)Cl$ and $[Pd(NHC)(naphthoquinone)]_2$ were inactive and no conversion of the starting material **611** was observed (entries 3 to 6). $Pd(cod)Cl_2$ gave 70% conversion and 52% isolated yield while $Pd(dtbpf)Cl_2$ proved to be the most active catalyst tested, allowing the product **623** in 85% yield (entry 8).

The identity of the aryl-OBO-ketone **623** was confirmed by the presence of a singlet at 3.95 ppm in the ^1H NMR spectrum, corresponding to the ketone methylene hydrogens and a second singlet at 2.33 ppm, corresponding to the aromatic methyl group.

The trend observed in **Table 46** (entries 1 to 8) suggests that steric bulk favours the formation of product. This observation was expected as bulky ligands facilitate the reductive elimination,

the rate determining step in the catalytic cycle, by releasing strain to regenerate the Pd(0) species and forming the key C–C bond, yielding product **623** (**Scheme 60**).[38]



632 **623** **633**

Scheme 60.[234] Strain relief during reductive elimination.

Bidentate ligands also favour the reductive elimination process by forcing the coupling partners to reside in a *cis* configuration, required for reductive elimination.[39,40] Pd(dtbpf)Cl_2 (entry 8), the most active catalyst tested possesses a bidentate bulky phosphine ligand with a large bite angle, favouring the reductive elimination of intermediate **632** *via* two different, but complementary phenomena.

With the preferred catalyst established for this reaction, a change in temperature from 50 °C to 75 °C failed to deliver **623**, yielding instead the diarylated product (entry 9). Various other solvents (toluene, DCE and dioxane) did not have a beneficial effect on the reaction yields (entries 10 to 12) and, finally, Cs_2CO_3 as base delivered **623** in only 14% (entry 14), while LiHMDS did not afford any product **623** (entry 13). It is important to mention that a commercially available 2 M solution of NaO*t*Bu in THF was used as base in **Table 46** where indicated as well as in all experiments described beyond this point. Although solid NaO*t*Bu gave satisfactory results in most of the cases where tested, the yields were consistently lower and in some cases, depending on the batch of the base, it completely shut down the reaction. These observations are not entirely surprising given the hygroscopic nature of this base and the fact it was handled outside a glovebox.

2.3.4 α-Arylation of methyl-OBO-ketone: scope screening

The optimal conditions were then applied to a wide variety of aryl bromides (**Table 47**).

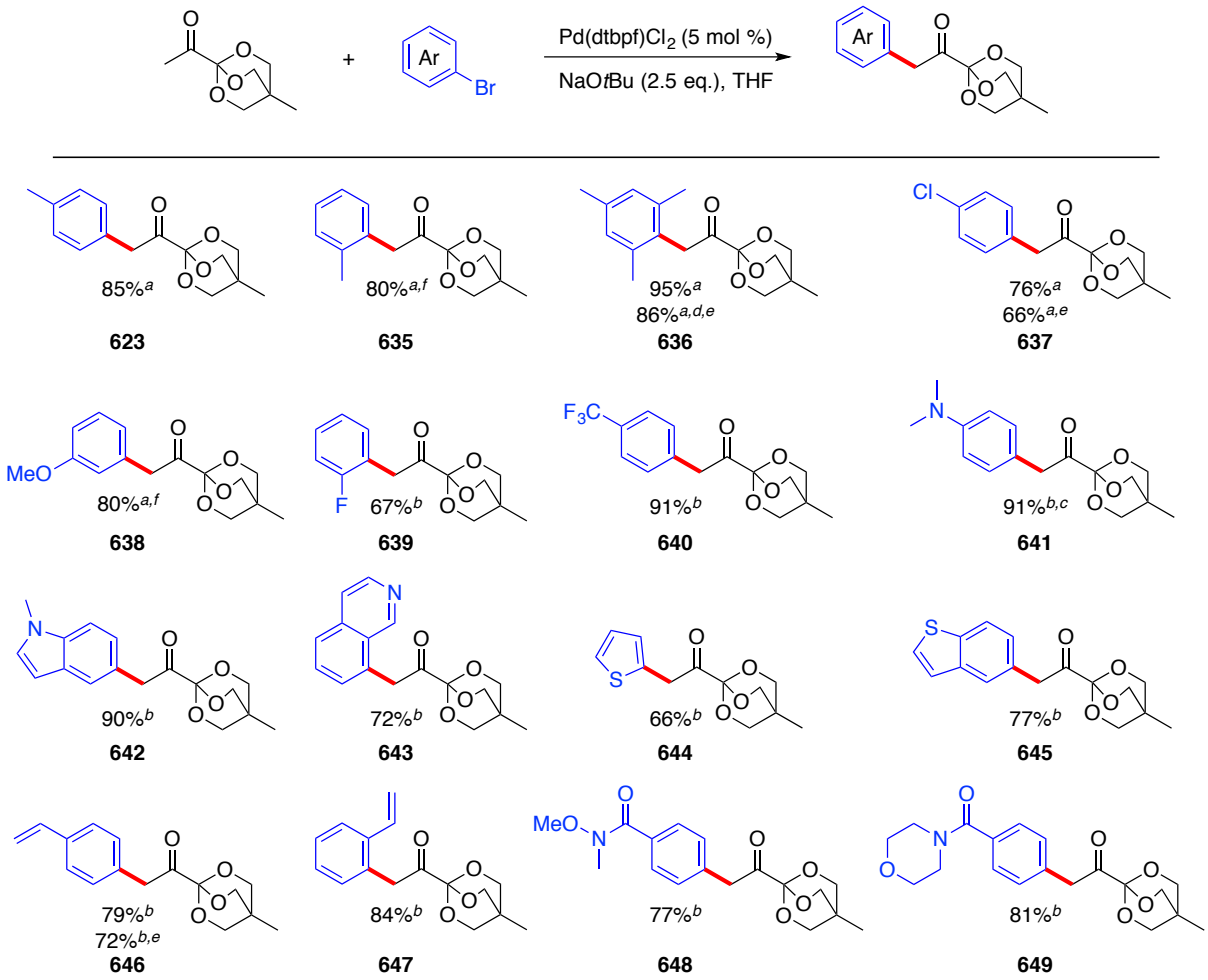


Table 47. Scope of the methyl-OBO-ketone mono-arylation reaction with aryl bromides. [a] Conditions: methyl-OBO-ketone (1.0 eq.), aryl bromide (1.1 eq.), 50 °C, 24 h; [b] conditions: methyl-OBO-ketone (1.5 eq.), aryl bromide (1.0 eq.), 70 °C, 24 h; [c] reaction temperature 50 °C; [d] gram-scale reaction, 2 mol% catalyst loading; [e] crude material purified by crystallisation; [f] Compound synthesised by Christopher Hall.[238]

The α-arylation reaction demonstrated great tolerance to a variety of aryl groups. Substitution at all positions of the phenyl ring was tolerated (**623**, **635** and **636**). Rings containing electron-withdrawing and electron-donating substituents were equally well coupled (**636**, **638**, **639**, **640** and **641**). Heterocyclic aromatic bromides were coupled in good yields (**642**, **643**, **644** and **645**) as well as *N*-substituted amides (**648** and **649**), which did not hydrolise under the reaction conditions. Surprisingly, styryl-bromides also tolerated the catalytic amount of palladium in the reaction and were coupled with **611** in good yields (**646** and **647**). Compound **637** shows that the reaction is selective towards aryl bromides in the presence of aryl chlorides at 50 °C, which leaves a useful handle for further coupling reactions (*e.g.* Suzuki and Sonogashira couplings,[241]

C–N amination,[242] etc.). Similar observation can be made regarding Weinreb amide **648** or styrenes **646** and **647**, which can also be subjected to a great variety of functionalisations.

Aryl chlorides were also successfully coupled under the same reaction conditions, a desirable feature from a financial point of view given the lower cost of these substrates when compared to aryl bromides (**Table 48**).

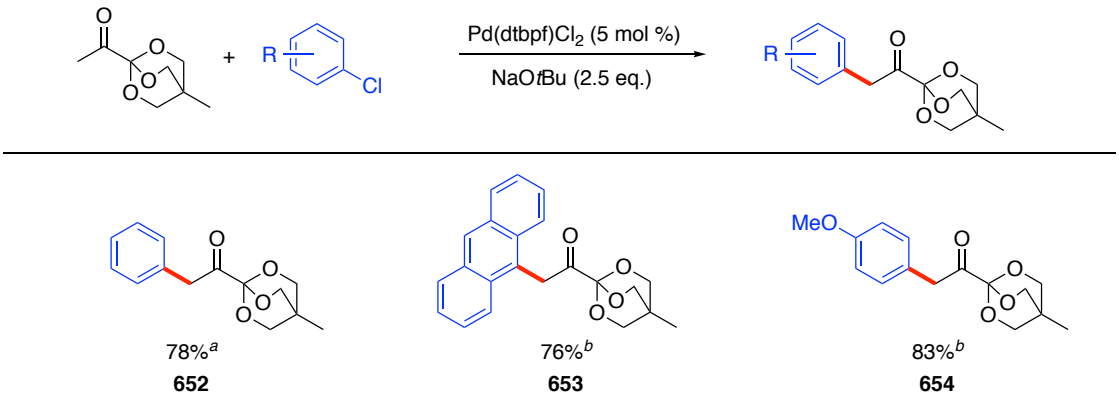


Table 48. Scope of the methyl-OBO-ketone mono-arylation reaction with aryl chlorides. [a] Conditions: methyl-OBO-ketone (1.0 eq.), aryl chloride (1.1 eq.), 50 °C, 24 h; [b] conditions: methyl-OBO-ketone (1.5 eq.), aryl chloride (1.0 eq.), 70 °C, 24 h.

The compounds shown in **Table 47** and **Table 48** were identified by their characteristic singlets between 5.10 and 3.50 ppm in the ^{1}H NMR spectra corresponding to the ketone methylene hydrogens.

Similar to methyl-OBO-ketone **611**, all the products shown in **Table 47** and **Table 48** are crystalline solids. This characteristic was explored as compounds **637** and **646** were isolated in comparable yields relying only on a single crystallisation. Likewise, compound **636** was synthesised in gram-scale requiring only 2 mol% catalyst and, again, relying on a single crystallisation as the sole purification method. These results suggest that this protocol could be a strong candidate for scaled-up processes.

It is important to mention that some substituents were not tolerated or delivered the product in only trace amounts: nitrile (**655**), unsubstituted amide (**656**), pyridine (**658** and **659**), alkyne (**660**), vinyl bromide (**661**), ester (**662**), carboxylic acid (**663**) and aliphatic alcohol (**664**) (**Table 49**).

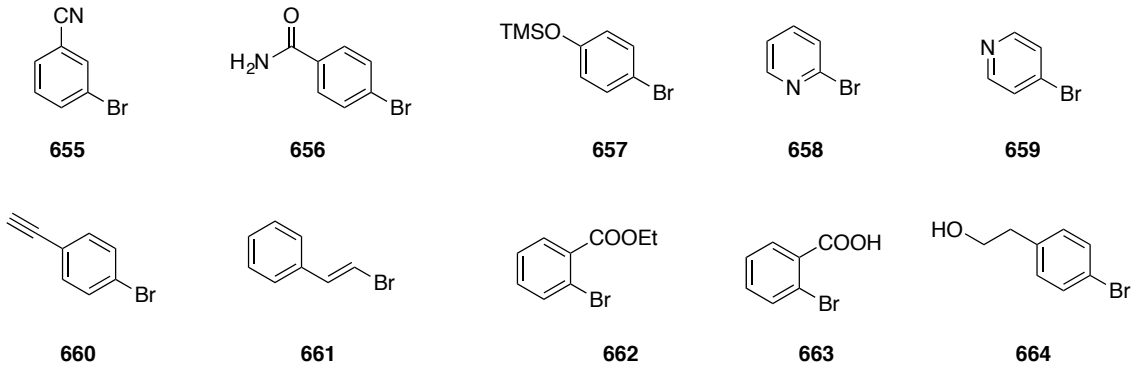
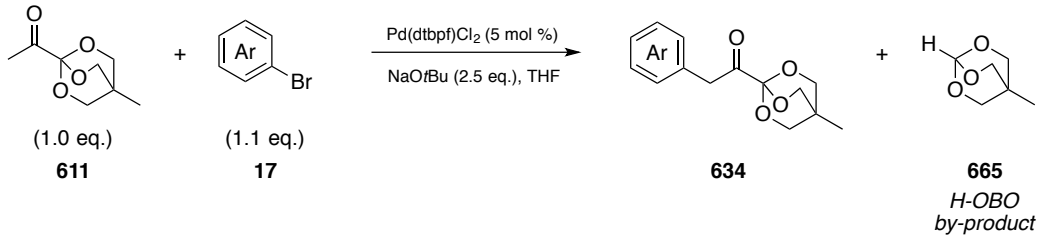


Table 49. Unreactive aryl bromides towards α-arylation of methyl-OBO-ketone **611**.

The set of conditions presented in entry 8 (**Table 46**) was used for the α-arylation involving some of the aryl halides in **Table 47** and **Table 48**. The excess of aryl halide facilitated the chromatographic separation of the products as the methyl-OBO-ketone starting material **611** and the arylated products containing only hydrocarbon substituents had nearly the same polarity. These aryl halides delivered their corresponding products shown in **Table 47** and **Table 48** in good yields. However, for some other examples, the same conditions led to low starting material (aryl halide) conversions. With an increase in temperature from 50 °C to 70 °C, the conversion of **611** was increased, however, in some cases, decomposition of methyl-OBO-ketone **611** was observed with the formation of by-product H-OBO **665**, therefore leading again to low yields. In some cases, as much as 50% of methyl-OBO-ketone **611** was converted to H-OBO **665**, as observed in the crude ^{1}H NMR spectrum (**Scheme 61**).



Scheme 61. Formation of H-OBO **665** by-product.

With these observations in mind, a second set of conditions was established: a higher temperature (70 °C) and an excess of starting material **611** (1.5 equivalents) were then used. This modification allowed a great expansion in the scope of aryl halides coupled to **611** in good to excellent yields (**Table 47** and **Table 48**).

2.3.5 α,α-Diarylation of methyl-OBO-ketone

In light of the diarylation of **611** observed in **Table 46** (entry 9), it was envisaged that the formation of diarylated methyl-OBO-ketones may be extendable to different aryl halides provided the reaction temperature was high enough to allow the formation of a more congested Pd(II) intermediate prior to reductive elimination (**Figure 19**) and an excess of aryl halide was present.[243,244]

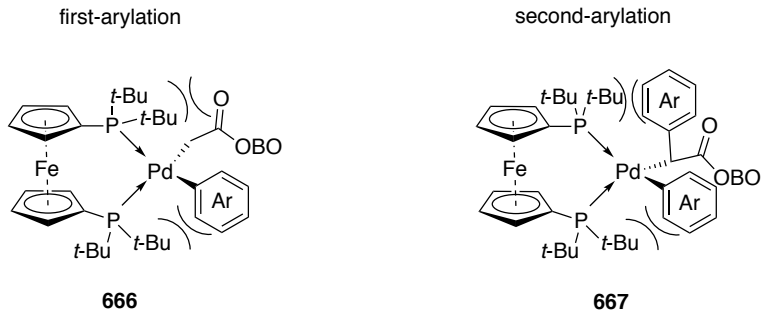


Figure 19. Comparison of the tetracoordinated Pd(II) intermediate during the first and second enolate arylation.

Pleasingly, with an increase in the reaction temperature to 80 °C, accompanied by the presence of three equivalents of the aryl halide coupling partner, diarylated OBO-ketones **670** and **671** were isolated in 81% and 73%, respectively (**Table 50**).

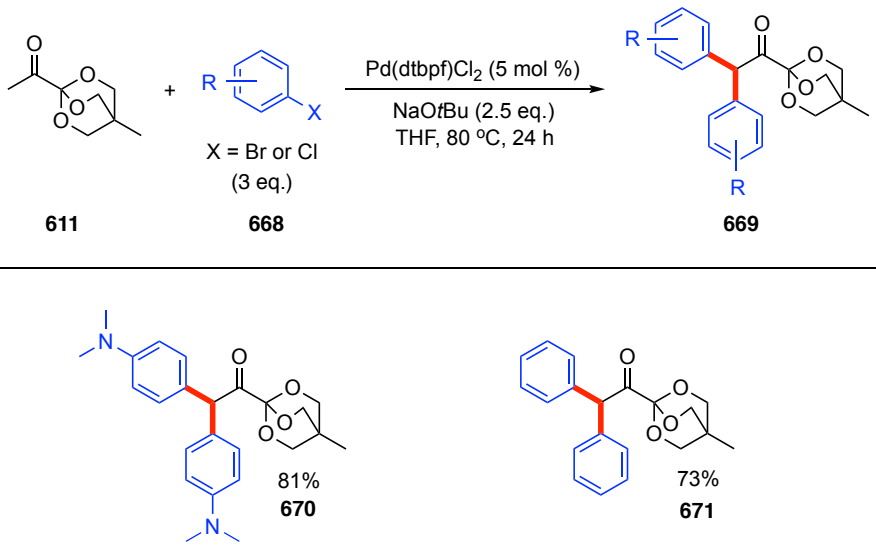


Table 50. α,α-Diarylation of methyl-OBO-ketone **671**.

The strong dependence of the outcome of the α-arylation reaction on the temperature suggested that α,α-heterodiarylation of methyl-OBO-ketone **611** should be possible. The first C–C bond formation would occur at 50 °C, which is insufficient to allow the formation of intermediate **667**, hence the diarylated product. The addition of an excess of a second aryl halide and an increase in temperature would follow, allowing the formation of a second C–C bond in an overall transformation that would deliver a tertiary α-centre containing two distinct aryl groups. Gratifyingly, this strategy proved to be successful and α,α-heterodiarylated ketones **673** and **674** were obtained in 67% and 71% yield, respectively (**Table 51**). The compounds shown in **Table 50** and **Table 51** were identified by their characteristic singlets between 6.00 and 5.50 ppm in the ^{1}H NMR spectra corresponding to the methine hydrogens in the α,α-diarylated ketone products.

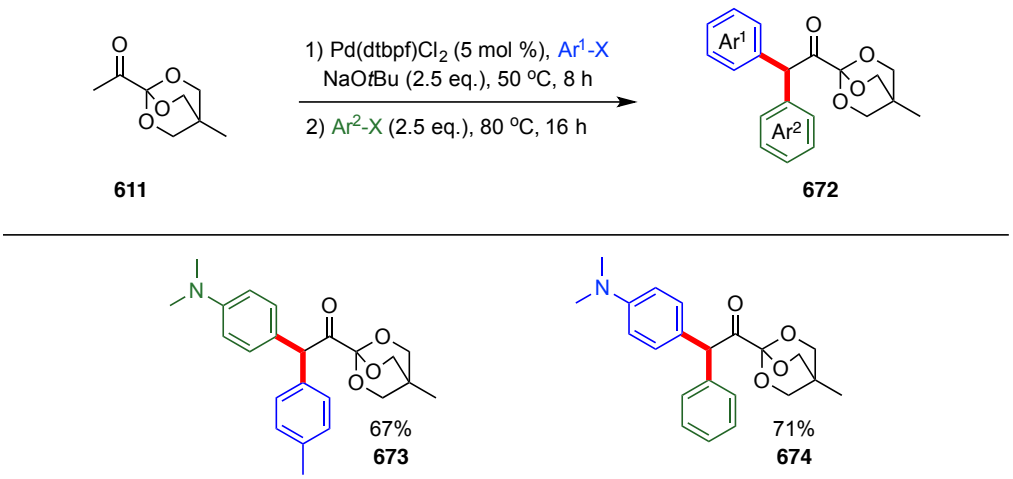


Table 51. Heterodiarylation of methyl-OBO-ketone **611**.

Perhaps as expected, not all aryl halides that cleanly mono-arylated methyl-OBO-ketone **611** (**Table 47** and **Table 48**) could diarylate this substrate. As prerequisites, the aryl halide must be reactive at lower temperatures (*i.e.* 50 °C) and cannot have significant steric bulk at the *ortho* position: for example bromomesitylene despite being the most active aryl halide tested towards monoarylation of methyl-OBO-ketone **611** (**Table 47**), completely failed to deliver any diarylated product when subjected to the reaction conditions in **Table 50**. Presumably, the Pd(II) intermediate **667** is too congested to be formed in this instance.

2.3.6 One-pot α-functionalisation of arylated OBO-ketones

Next the α-alkylation of arylated OBO-ketones was investigated as a complementary means of constructing tertiary α-centres. As previously discussed in **Chapter 2.2.8**, the α-arylation reaction requires at least two equivalents of base to cleanly deliver the mono-arylated product given this molecule is more acidic than the methyl-ketone starting material. The product is then present as its enolate in solution, which can be readily α-alkylated in one-pot by simply adding an electrophile.

This concept was applied in a one-pot α-arylation/α-alkylation sequence using methyl-OBO-ketone **611** as substrate. Gratifyingly, this protocol successfully allowed the installation of a variety of different groups: alkyl (**618** and **683**), allyl (**684**, **685**, and **686**), bromo-vinyl (**677**), acetophenyl (**682**), acetyl (**679**) and propargyl (**680**). Furthermore, some of these groups can operate as useful handles for further functionalisation such as cross-coupling reactions on **677** or hydrofunctionalisations[245] on **680**, **684**, **685** and **686**. Compound **682**, a 1,4-dicarbonyl compound formed in one pot, is of special interest as this structure is an entry to pyrroles,[246] furans[247] and thiophenes,[248] approach currently being explored by a fellow group member. At higher temperatures, an excess of an electrophile and base alkylated the α-centre twice, generating a quaternary centre (**685**). A careful control of the reaction temperature and the amount of electrophile added also allowed the installation of two distinct groups at the α-centre (**686**) (**Table 52**). The identity of the α-alkyated aryl-OBO-ketones obtained was confirmed by the presence of two diastereotopic hydrogens between 5.00 and 1.70 ppm in the ^{1}H NMR spectra corresponding to the methylene hydrogens at the β-position of the ketones. Compound **678** was identified by the characteristic doublet at 1.39 ppm (J = 7.0 Hz) in the ^{1}H NMR spectrum, corresponding to the methyl group installed in the α-alkylation step.

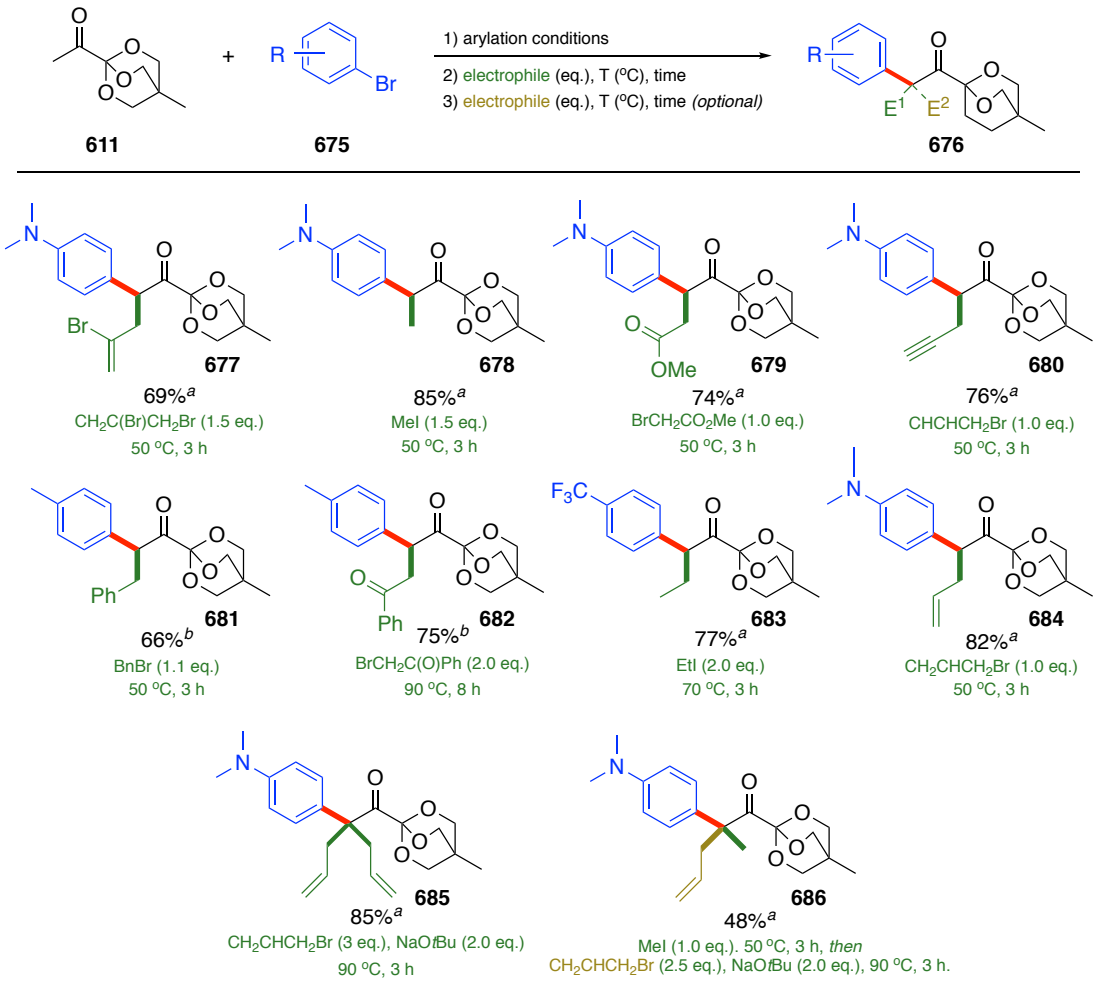
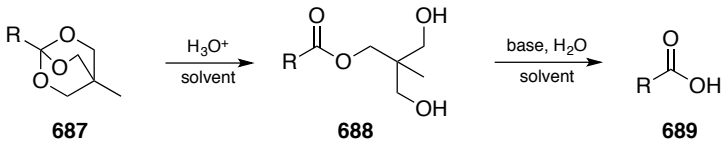


Table 52. One-pot α-arylation/α-alkylation of methyl-OBO ketone **611**. [a] Arylation conditions: methyl-OBO-ketone (1.5 eq.), aryl bromide (1.0 eq.), 70 °C, 24 h; [b] arylation conditions: methyl-OBO-ketone (1.0 eq.), aryl bromide (1.1 eq.), 70 °C, 24 h.

2.3.7 Deprotection of the OBO moiety: accessing pyruvic acids

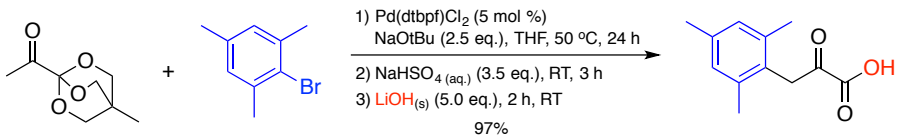
With the ability to construct a diverse collection of mono-, di- and tri-substituted OBO ketones established, the next step was the development of a general methodology to deprotect the OBO moiety in order to reveal the valuable substituted pyruvates. The formation of pyruvic acid was the first procedure explored following a two-step well-established literature procedure.[249] In the first step a source of mild aqueous acid (*e.g.* $NaHSO_4$) hydrolyses the orthoester cage structure to form ester **688**. Saponification of this intermediate gives then the corresponding carboxylic acid (**Scheme 62**).



687 **688** **689**

Scheme 62. Two-step OBO deprotection sequence.

It was then decided to test the concept of a three-step one-pot sequence: α-arylation, acidic orthoester hydrolysis and basic ester hydrolysis. Taking advantage of the carboxylic acid moiety, it was envisaged that a basic aqueous workup followed by pH adjustment to pH 1 and an extraction with an organic solvent would allow the separation of the pyruvic acid in good purity. Indeed, when this sequence was applied to 2-bromomesitylene **690** and methyl-OBO-ketone **611**, the pyruvic acid **691** was isolated in excellent yield and in remarkable purity, as showed by the crude ^{1}H NMR spectrum (**Scheme 63** and **Figure 20**).



(1.0 eq.) **611** (1.1 eq.) **690** **691**

Scheme 63. One-pot synthesis of pyruvic acid **691**.

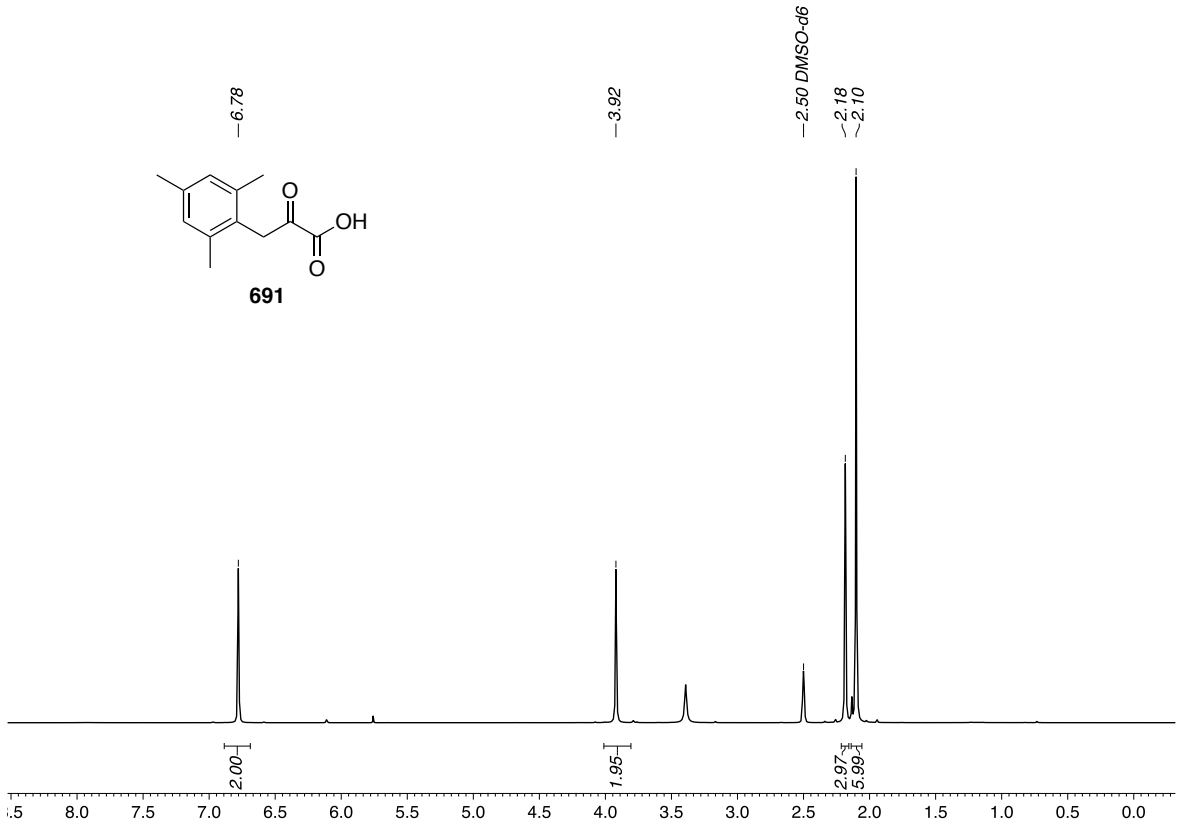


Figure 20. Crude ^{1}H NMR spectrum of **691** in DMSO-d_6.

The crude ^{1}H NMR spectrum clearly shows all the peaks expected for the product **691** along with some extra small singlets between 6.5 and 5.5 ppm and between 2.5 and 2.0 ppm. After a literature search, it was found that aryl-pyruvic acids and pyruvates normally exist as a mixture of their ketone and enol tautomers. The ratio between these two forms is mostly influenced by the electronic nature of the phenyl ring: electron-withdrawing groups at the *ortho*-position favour the keto tautomer over the enol[250] as these groups prevent the sharing of electronic density observed in the extended π-system found in the enol tautomer. It can be speculated that steric factors (two *ortho* methyl groups in compound **691**) can also influence the formation of the keto form, as observed in the example in **Figure 20**. The enol form of this compound requires the aryl ring to be aligned with the alcohol moiety in order to benefit from the electron delocalisation of the π-system. This configuration displays some steric clash between the *ortho* methyl group and the alcohol moiety, therefore shifting the equilibrium towards the formation of the ketone tautomer. An in-depth analysis of the NMR spectra of compound **691**, especially

the ^{13}C and the HSQC spectra, revealed that the extra peaks observed in **Figure 20** indeed belong to the enol form of **691**.

When the same procedure was attempted on *p*-bromotoluene a disappointing result emerged: despite a good mass recovery, the product obtained was not completely clean (**Figure 21**).

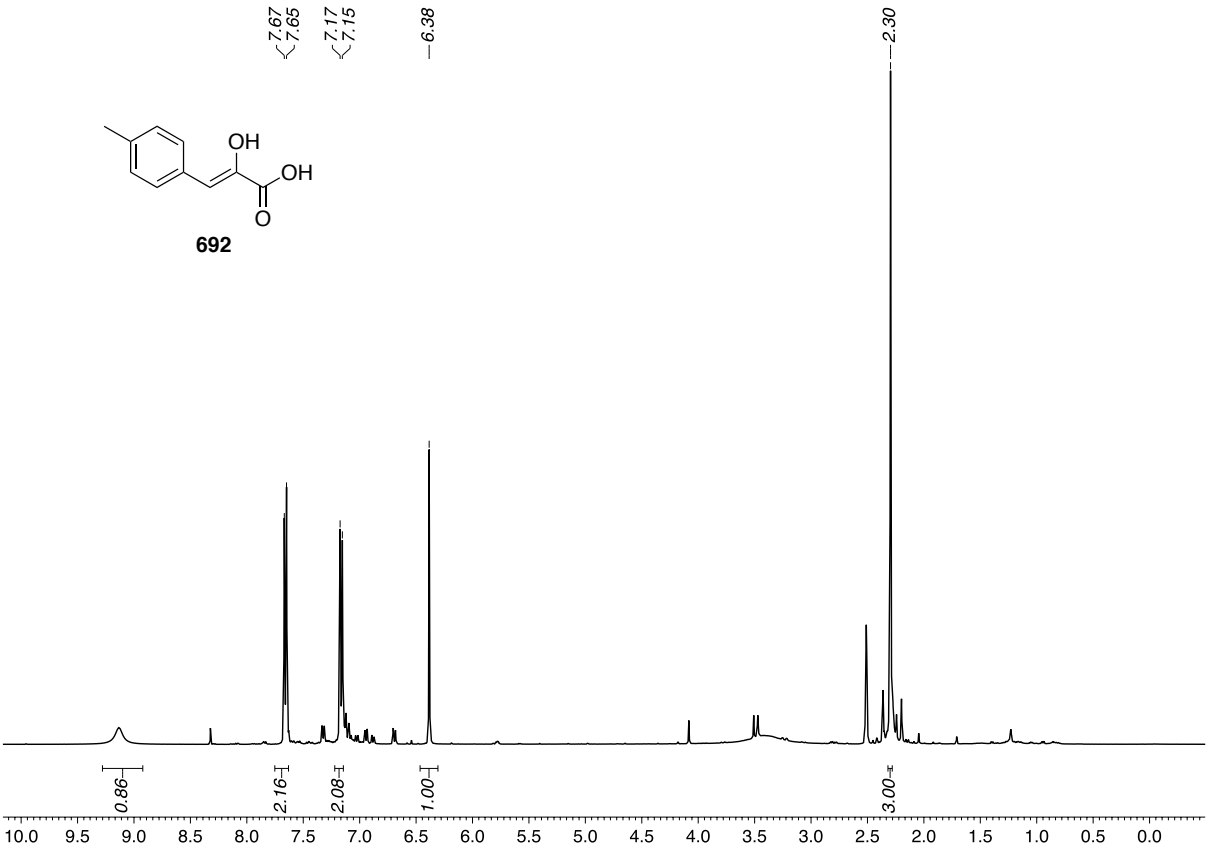


Figure 21. Crude ^{1}H NMR spectrum of pyruvic acid **692** in $CDCl_3$.

Worse results were obtained when different aryl bromides (1-bromonaphthalene, 1-bromo-4-cholobenzene and 5-bromo-1-methylindole) were subjected to the same reaction conditions. The crude compounds could not be purified to a satisfactory standard by chromatographic methods due to the equally high polarity of the products and the impurities formed.

From the ^{1}H NMR spectrum in **Figure 21**, however, it was possible to observe that the absence of two methyl substituents at the *ortho* position of **692** caused a massive shift in the keto/enol equilibrium favouring almost completely the enol form, when compared to **691**, despite their similar electronic nature. This agrees with the assumption of steric clash between the *ortho*-methyl groups and the OH in the enol form of compound **691**.

From the aryl halides tested, 1-bromo-4-chlorobenzene delivered the most impure product when subjected to the α-arylation/deprotection one-pot sequence described above, therefore it was then decided to breakdown this procedure, subjecting the arylated OBO-ketone **637** to similar deprotection conditions. This experiment showed that the impurities observed in the crude ^{1}H NMR spectrum originated during the deprotection step rather than being carried through from the α-arylation reaction (**Figure 22**).

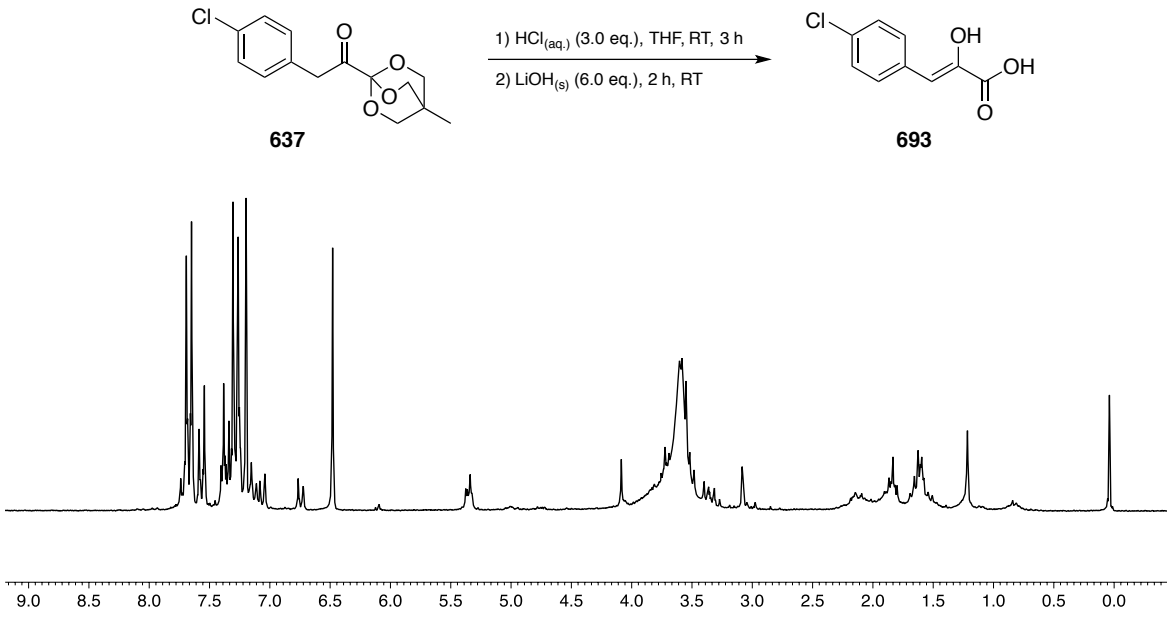
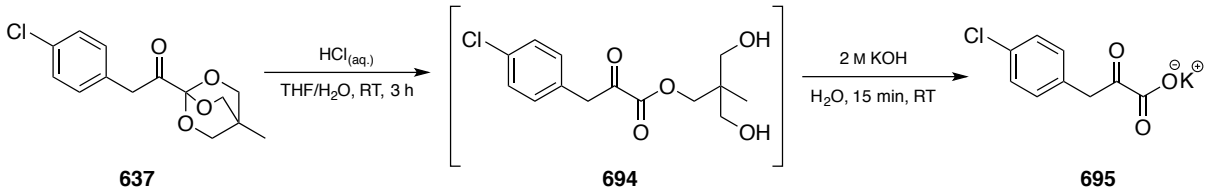


Figure 22. Crude ^{1}H NMR spectrum of the attempted deprotection of **637** in $CDCl_3$.

Based on the results obtained, it was hypothesised that parallel reactions such as self-condensation could be taking place during the hydrolysis step, most likely with the diol intermediate **694**. This would explain why sterically hindered pyruvic acid **691** was cleanly isolated, while **692** was not. With this observations in mind, a change in the deprotection procedure was tested: after all the starting material was consumed upon the addition of $HCl_{(aq.)}$, most of the solvent in the mixture was evaporated and then the residue was added dropwise to an aqueous 2 M KOH solution to carry out a fast saponification of the ester intermediate **694** and the formation of the potassium pyruvic salt **695** (the former procedure involved the addition of 6.0 eq. of solid LiOH to the THF/aqueous acid solution, see **Figure 22**) (**Scheme 63**).



Scheme 63. Adapted procedure for the deprotection of compound **637**.

The idea behind this modification was that once the diol intermediate **694** was in contact with an aqueous solution of a strong base, the hydrolysis would immediately take place forming a pyruvic salt in water that should be less prone to side reactions. **Figure 23** shows the crude ^{1}H NMR spectrum for pyruvic acid **693** obtained under these conditions.

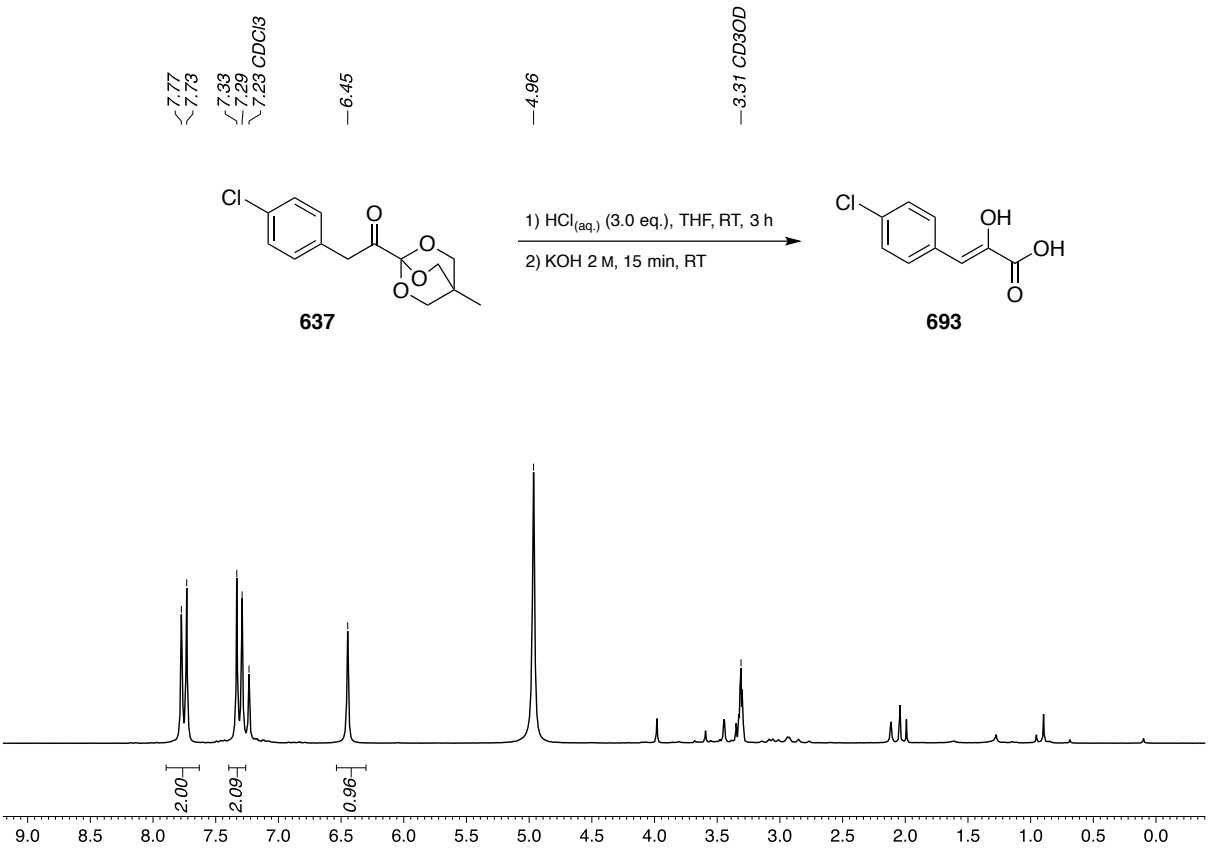


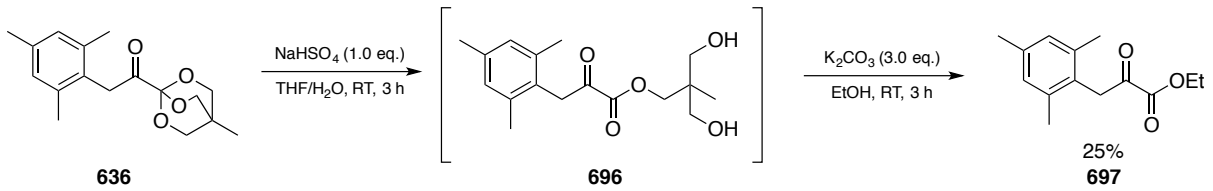
Figure 23. Crude ^{1}H NMR spectrum for the deprotection of **637**. Sample dissolved in a mixture of $CD_3OD/CDCl_3$.

Figure 23 shows a significant improvement in the purity of the material obtained under the modified deprotection conditions, however, it was still unsatisfactory and chromatographic separations were also not an option, as previously discussed. It was then decided to explore the

formation of pyruvates from OBO ketones as an alternative to the pyruvic acid synthesis attempted.

2.3.8 Deprotection of the OBO moiety: accessing pyruvates

The first approach to access ethyl pyruvates involved a two-step sequence: acid-catalysed hydrolysis of the OBO moiety followed by transesterification of intermediate **696** by potassium ethoxide generated *in situ* (**Scheme 64**).[251]

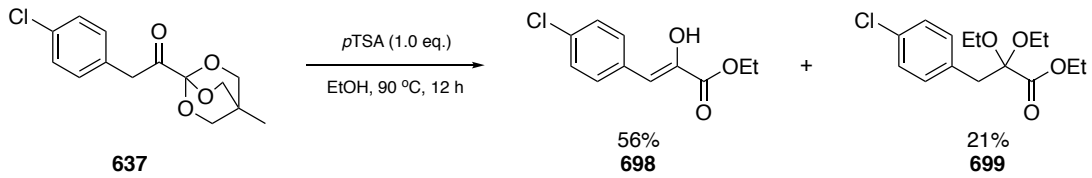


636 **696** **697**

Scheme 64. Deprotection sequence of aryl-OBO-ketone **636**.

Pyruvate **697** was isolated in only 25% yield after a low mass recovery upon workup, which could have been caused by the hydrolysis of the intermediate **696** by adventitious water present in small amounts in the solvent and/or remaining from the first step. Although not isolated before the transesterification, diol **696** was extracted from the reaction mixture, dried over $MgSO_4$, filtered and concentrated in a rotary evaporator and the resulting solid was further dried under high-vacuum for two hours. Despite these precautions, it is likely that some water was carried through the sequence and could have hydrolysed **696** and **697**. Moreover, the hydrolysis reaction under basic conditions is irreversible once the pyruvic salt is formed, consuming the intermediate **696** as well as the product **697** as this side reaction takes place.

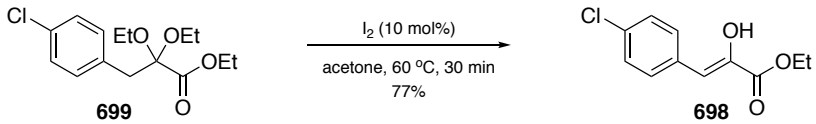
Next, the acid-catalysed opening of OBO moiety followed by acidic hydrolysis of the diol intermediate **694** was examined on aryl-OBO-ketone **637**. The aryl pyruvate **698** could be isolated in 56% yield, showing the feasibility of this procedure. Unfortunately, acetal **699** was also isolated as by-product (**Scheme 65**). The structure of **699** was confirmed by a characteristic diastereotopic multiplet from 3.70 to 3.48 ppm of relative intensity four in the ^1H NMR spectrum corresponding to the methylene hydrogens in the acetal moiety.



Scheme 65. Acid-catalysed deprotection of aryl-OBO-ketone **637**.

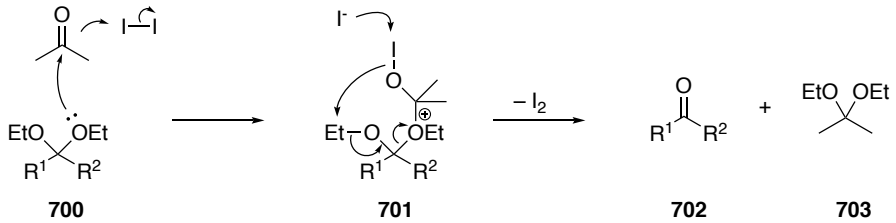
Attempts to deprotect acetal **699** in an acidic THF/H_2O mixture failed at temperatures below 70 °C. Higher temperatures effected the acetal deprotection, nevertheless, ester hydrolysis was also observed.

An alternative literature method, however, allowed acetal deprotection in good yield. This procedure employs catalytic I_2 and acetone as solvent (**Scheme 66**).[252]



Scheme 66. I_2-catalysed deprotection of acetal **699**.

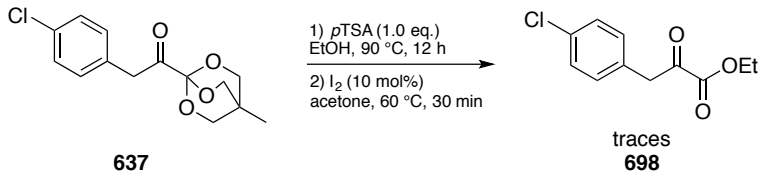
The authors proposed a mechanism which involves a substrate exchange pathway rather than hydrolysis (they found that anhydrous acetone accelerates the reaction rates). They suggest that iodine coordinates to the carbonyl group in acetone which is then attacked by one of the oxygen atoms present in the acetal, forming the oxonium intermediate **701**. Iodide then initiates the migration of the ethyl group which in turn yields ketone **702**, acetal **703** and regenerates I_2 (**Scheme 67**).



Scheme 67. Potential mechanism for the I_2-catalysed acetal deprotection.

Unfortunately, when this protocol was applied directly to the crude material of the acid-catalysed deprotection of **637**, only small amounts of product **698** were obtained along with a

complex mixture of by-products, making this sequence of no use without the introduction of a chromatographic purification between steps 1 and 2 (**Scheme 68**).



Scheme 68. Attempted deprotection sequence of compound **637**.

Finally, in order to limit the undesired acetalisation of the ketone moiety, it was decided to closely monitor the reaction course by TLC, limiting the reaction time and temperature to the minimum necessary to observe product formation.

Following this precaution, a variety of aryl-OBO-ketones were successfully deprotected yielding aryl-pyruvates in good yields (**Table 53**).

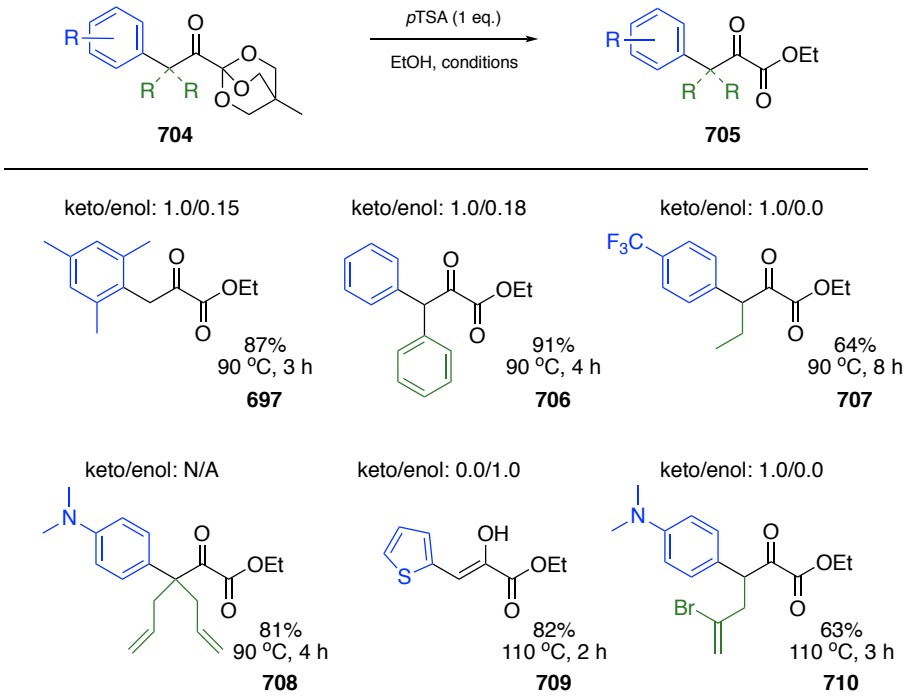


Table 53. Scope for the deprotection of aryl-OBO-ketones. Products are drawn as the major tautomer.

Pleasingly, the reaction conditions were tolerated by electron-withdrawing and electron-donating groups (**707** and **708**) as well as by a heteroaromatic substituent (**709**). The presence

of tertiary or quaternary centres in the alpha position did not affect the reaction outcome and compounds **706**, **707**, **708** and **710** were synthesised in good yields. Pleasingly, allylic groups and a vinyl bromide moiety were not affected by the acidic conditions of the reaction and **708** and **710** were isolated in 81% and 63%, respectively.

As expected, electron-donating thiophene favoured the enol form of **709** with no traces of the keto form observed. This could be attested by different means: 1) the peak at 6.48 ppm in the ^{1}NMR spectrum was easily assigned as the hydroxy group by HSQC analysis; 2) the ^{13}C NMR spectrum shows no signal around 200 ppm; 3) the infrared spectrum shows a broad absorption peak at 3385 cm^{-1}, corresponding to the expected OH stretch and 4) only one stretch corresponding to the α,β-unsaturated ester moiety was observed in the carbonyl region of the IR spectrum at 1684 cm^{-1} (**Figure 24**).

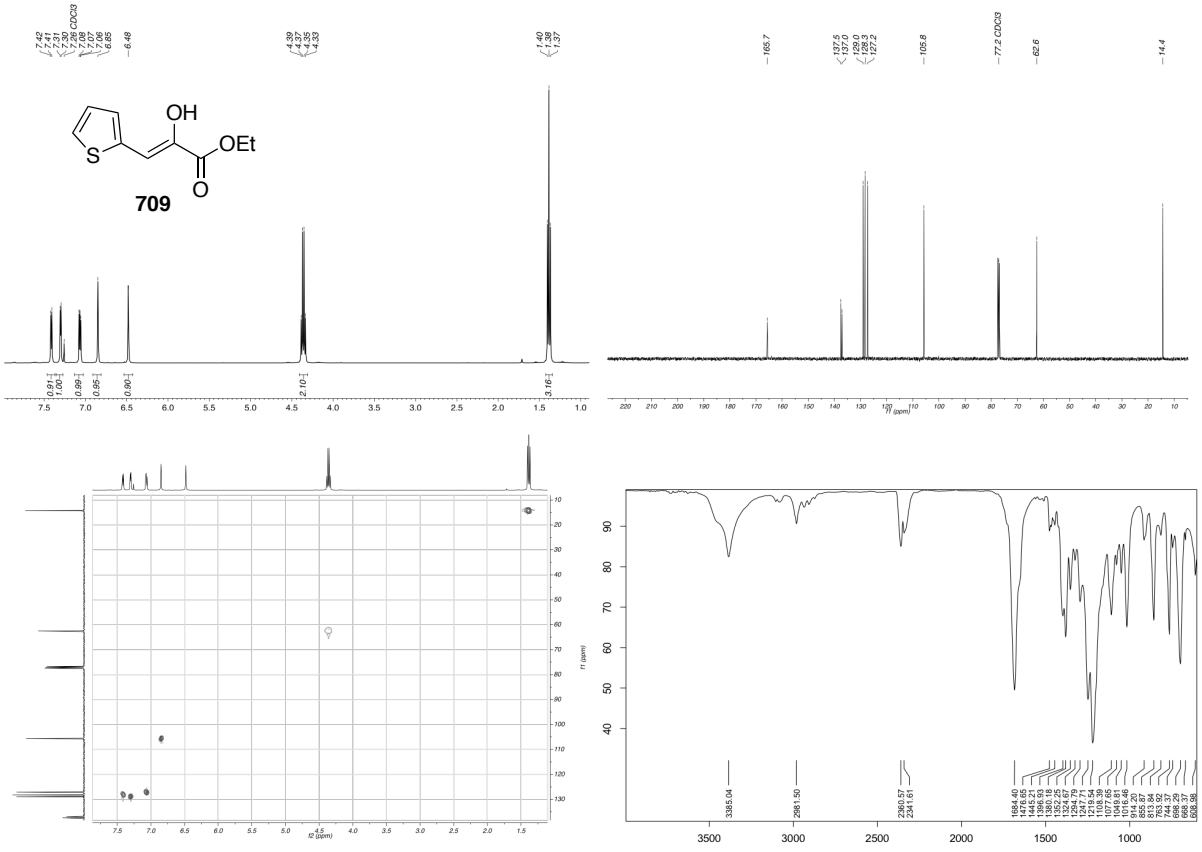


Figure 24. ^{1}H NMR, ^{13}C NMR, infrared and HSQC spectra of compound **709**.

α-Substituted aryl-pyruvates were observed as 100% keto tautomers in $CDCl_3$ regardless of the electronic nature of the aryl ring, observation in agreement with several examples reported in the literature.[91] The peaks at 191.7 and 193.0 in the ^{13}C spectra of **710** and **707**, respectively, attested the presence of the keto form of these compounds.

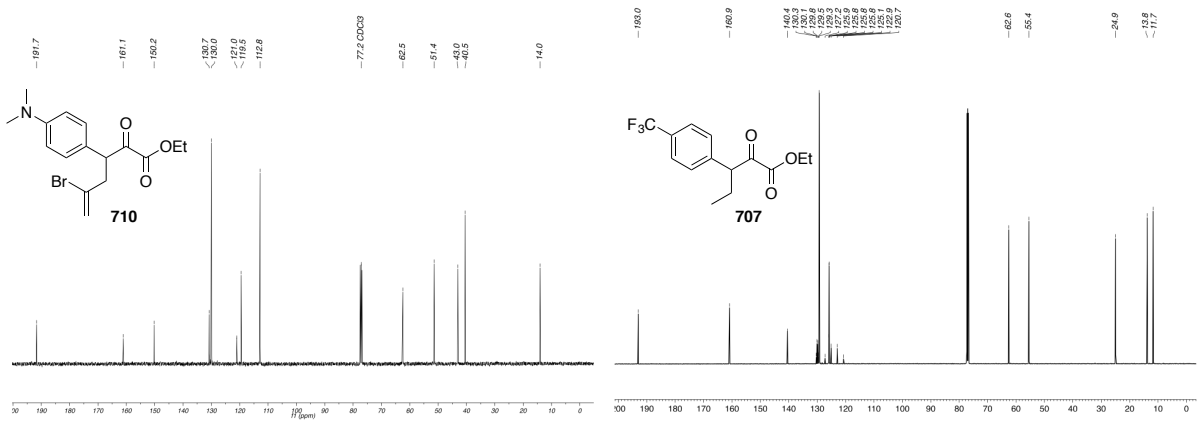


Figure 25. ^{13}C NMR spectra of compounds **710** and **707**.

Remarkably, compound **706**, despite the presence of a tertiary α-centre, is present in the $CDCl_3$ solution as 15% enol tautomer. This observation can be explained by the extended π-system allowed by this isomer, which involves two aromatic rings. **Figure 26** shows the ^{1}H NMR of compound **706** in which the presence of a mixture of tautomers is clear by the pair of quartets at 4.24 and 4.02 and a pair of triplets at 0.86 and 1.24 ppm.

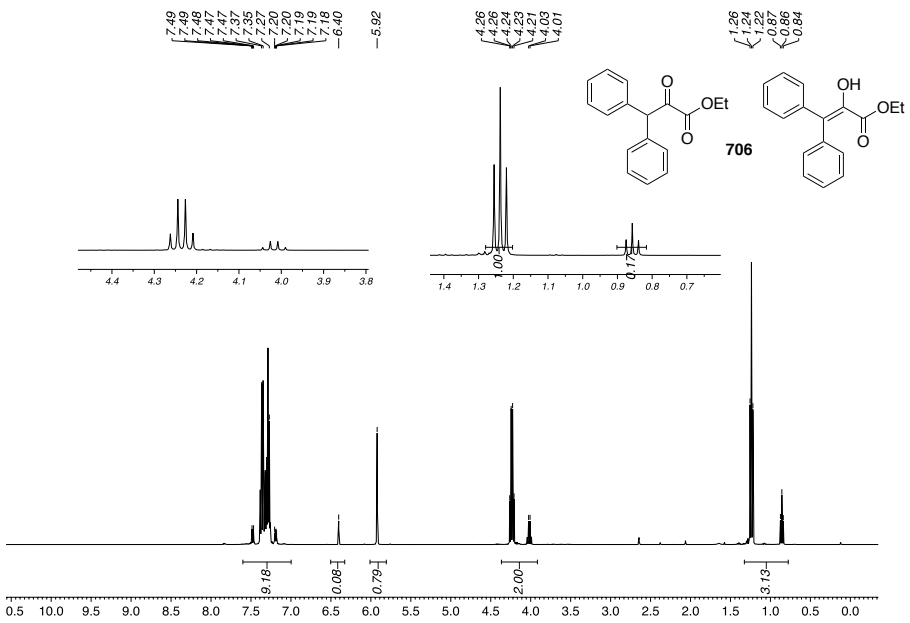


Figure 26. ^{1}H NMR spectrum of compound **706**.

From the aryl-OBO-ketones subjected to the deprotection conditions shown in **Table 53**, only molecules containing styryl substituents were not tolerated, resulting in a complex mixture of compounds after ten minutes at 90 °C. Activation of the olefin followed by the addition of a nucleophile such as ethanol was probably operative.[253]

2.3.9 TBS protected pyruvates: storing unstable aryl-pyruvates

With some substrates, the expected aryl-pyruvates were isolated in good yields, however, these molecules partially decomposed after some hours and completely decomposed over a week. In order to demonstrate the stability of these molecule under the conditions described for OBO deprotection, the freshly formed crude aryl-pyruvates were subjected to TBS protection conditions, forming the silyl enol ethers shown in **Table 54** in moderate to good yields. It is important to mention that these three TBS-protected molecules (**712**, **713** and **714**) were stable on silica and were not decomposed even after one week dissolved in $CDCl_3$. This approach could be used not only to illustrate the OBO-deprotection methodology, but also as a synthetic tool to synthesise and store inherently unstable aryl-pyruvates. Only one isomer of each of the

enols **712**, **713** and **714** was observed in the NMR experiments, however, their geometry was not determined (**Table 54**).

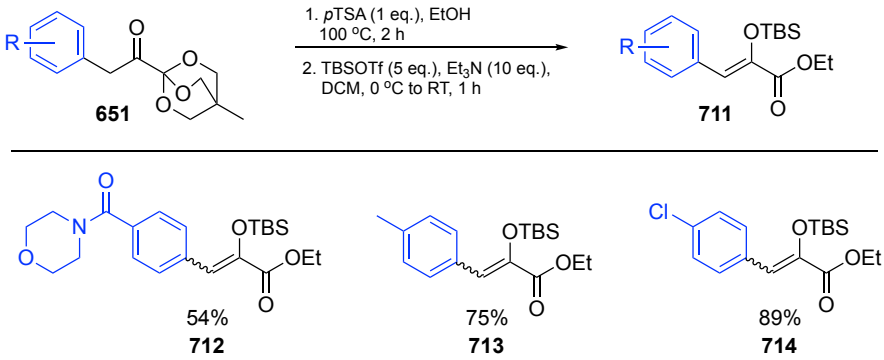
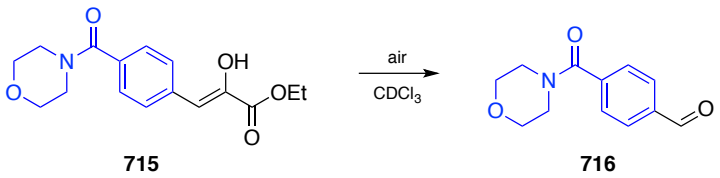


Table 54. Deprotection/TBS protection sequence of aryl-OBO-ketones.

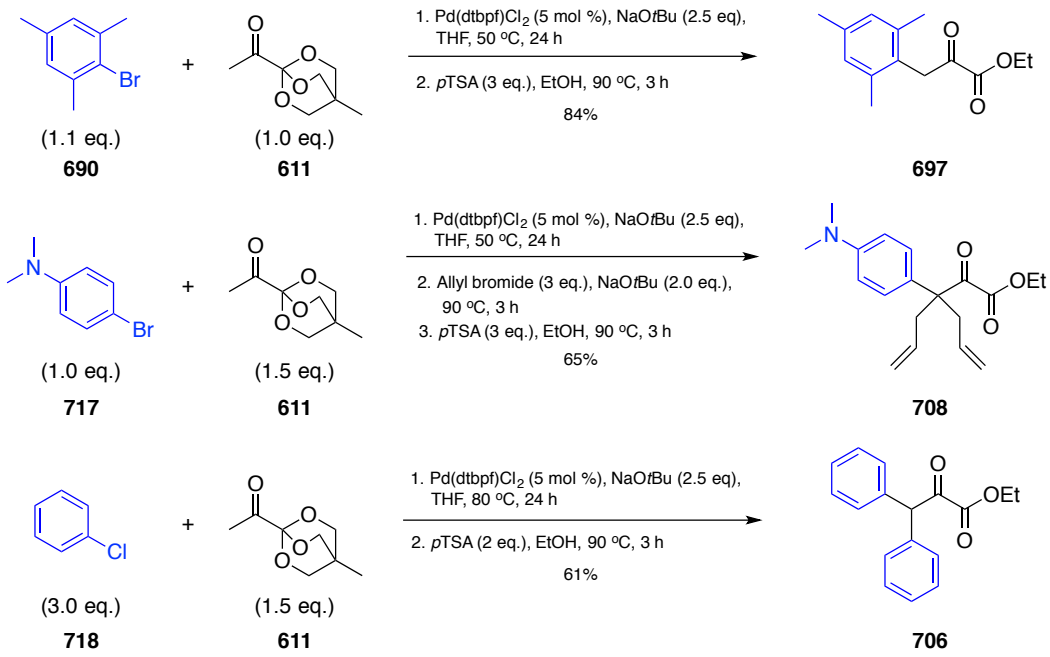
One of the decomposition products of **715** was isolated in 14% yield and identified as the aromatic aldehyde **716**, presumably originated from the oxidation of **715** by air (**Scheme 69**). The presence of a characteristic singlet at 10.05 ppm in the ^{1}H NMR spectrum attested to the presence of this by-product.



Scheme 69. Decomposition of pyruvate **715**.

2.3.10 One-pot synthesis of α-functionalised aryl-pyruvates

In order to extend the applicability of the present methodology, aryl-pyruvates were synthesised directly from aryl halides, methyl-OBO ketone **611** and electrophiles in one pot (**Scheme 70**).



Scheme 70. One-pot synthesis of aryl-pyruvates and α-functionalised-aryl-pyruvates from aryl halides and methyl-OBO-ketone **611**.

These results showed that the yields obtained were comparable with those of the stepwise synthesis. The operational simplicity of this sequence could greatly facilitate the scale-up of this methodology. The examples in **Scheme 70** were chosen to be representative of the classes of pyruvates shown in **Table 53**.

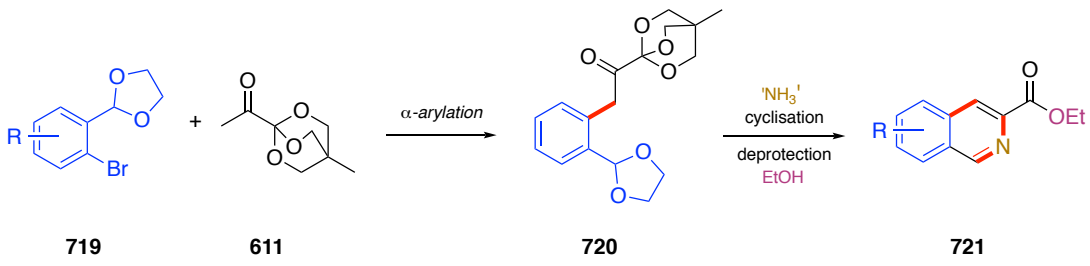
2.4 The synthesis of heterocyclic aromatic esters

Building on the original problem that led to the development of the methyl-OBO-ketone molecule (*i.e.* installation of an ester moiety at the C3 position of a *β*-carboline structure, **Scheme 49**) and the literature precedents described in **Chapter 2.2.9**, it was then decided to investigate further the use of methyl-OBO-ketone **611** in the formation of different heterocyclic aromatic esters, as well as its use in *β*-carboline synthesis.

2.4.1 Isoquinolines

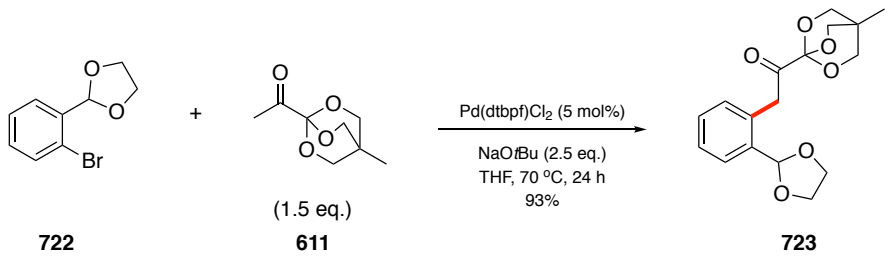
The established Donohoe synthesis of isoquinolines discussed in **Chapter 2.2.1** was the first methodology investigated. It was thought that methyl-OBO-ketone **611** could potentially deliver C3-ester-substituted isoquinolines, expanding the repertoire of this chemistry.

The overall transformation is depicted in **Scheme 71** and would involve methyl-OBO-ketone *α*-arylation as first step, followed by acetal deprotection, cyclisation and OBO deprotection. Ammonium chloride, the preferred nitrogen source for this methodology (**Table 35**, **Chapter 2.2.5**) should effect the acetal deprotection and at the same time deliver the nitrogen required for the pyridine ring construction.



Scheme 71. Overall sequence for the synthesis of isoquinoline esters from methyl-OBO-ketones and aryl bromides.

As the first step, methyl-OBO-ketone **611** and aryl bromide **719** were subjected to the enolate arylation conditions previously described (**Chapter 2.2.4**) in order to test the feasibility of this key C–C bond formation step with aryl-acetals. Gratifyingly, the cross-coupling reaction proceeded smoothly, yielding aryl-OBO-ketone **723** in 93% (**Scheme 72**).

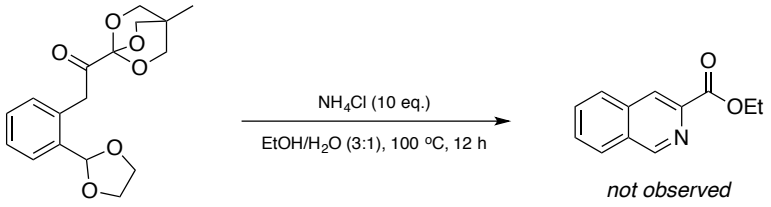


722 **611** **723**

Scheme 72. α-Arylation of methyl-OBO-ketone **611** with aryl bromide **722**.

The α-arylation reaction shown in **Scheme 72** also delivered **723** in 94% yield using 1.1 equivalents of aryl bromide **722** and 1.0 equivalents of methyl-OBO-ketone **611** instead, which could be useful for large-scale reactions, considering the cost of both materials.

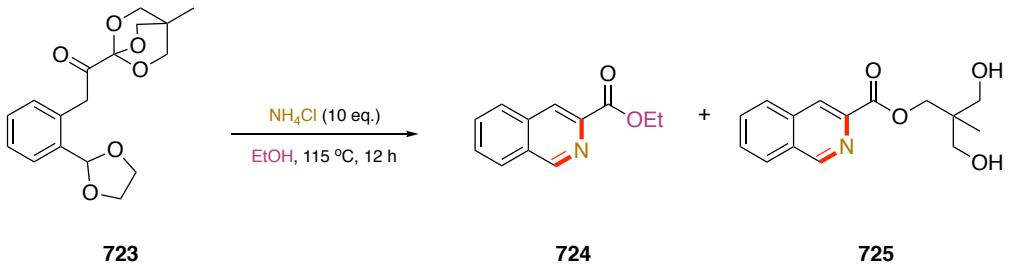
Compound **723** was then subjected to the cyclisation conditions previously described.[184] Unfortunately, a complex mixture of products emerged from the reaction with no desired product observed (**Scheme 73**).



723 **724**

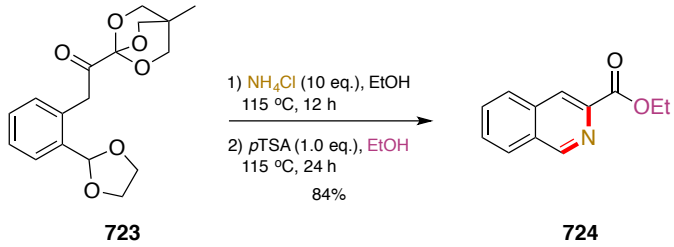
Scheme 73. Attempted cyclisation of **723**.

Control experiments showed that the presence of large amounts of water (3:1 mixture with ethanol) was precluding the formation of isoquinoline ester **724**, potentially due to unwanted hydrolysis of the product **724** and the intermediate diol **725**. A screening of the crude ^{1}H NMR spectra from small-scale reactions showed that commercial grade ethanol and an increase in temperature cleanly delivered a mixture two compounds presenting a pair of aromatic singlets each (9.30 and 8.58 ppm; 9.32 and 8.58 ppm) corresponding to C1 and C4 hydrogens in the isoquinoline structure of esters **724** and **725** (**Scheme 74**). When extra dry ethanol was used, extra spots were observed by TLC, which disappeared upon the addition of a few droplets of water and further heating at 115 °C, suggesting the formation of ethyl acetals under anhydrous conditions.



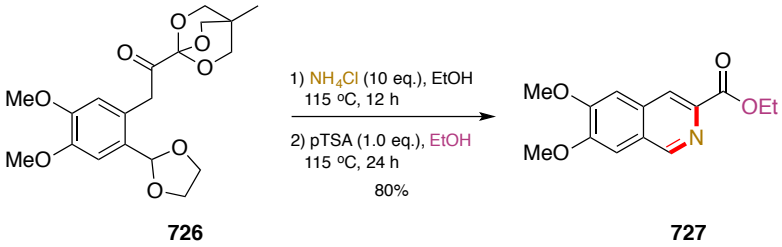
Scheme 74. Formation of isoquinolines **724** and **725** by thermal cyclisation.

The formation of isoquinoline ester **725** showed that the final transesterification step was sluggish when catalysed by NH_4Cl. An extra transesterification step catalysed by *p*TSA was then introduced, which permitted the isolation of isoquinoline **724** in 85% yield (**Scheme 75**). Unfortunately, the addition of *p*TSA immediately after the cyclisation in one-pot did not deliver product **724** in comparable yields and a workup between these two steps proved necessary.



Scheme 75. Synthesis of isoquinoline **724** from acetal **723**.

This procedure was then repeated with an electron-rich substrate (**726**), which cleanly delivered isoquinoline **727** in 80% yield (**Scheme 76**).



Scheme 76. Synthesis of isoquinoline **727** from acetal **726**.

The α-alkylation of acetal **723** was then investigated. The addition of 1.5 equivalents of Na*t*OBu and 1.05 equivalents of benzyl bromide to compound **723** in THF at RT did not deliver

any alkylated product **730**. At 50 °C, some alkylation was observed, nonetheless the reaction was sluggish. At 70 °C, all the starting material was finally consumed, as observed by TLC, and the product **730** was isolated in 74% yield. The procedure was repeated with methyl iodide which also successfully alkylated aryl-OBO-ketone **729** in 67% (**Table 55**). Compound **729** was identified by the presence of a quartet at 4.75 (J = 6.9 Hz), while compound **730** was identified by the presence of a doublet of doublets at 5.01 (J = 8.4 and 5.0 Hz) in its ^{1}H NMR spectra, both signals corresponding to their respective methine protons.

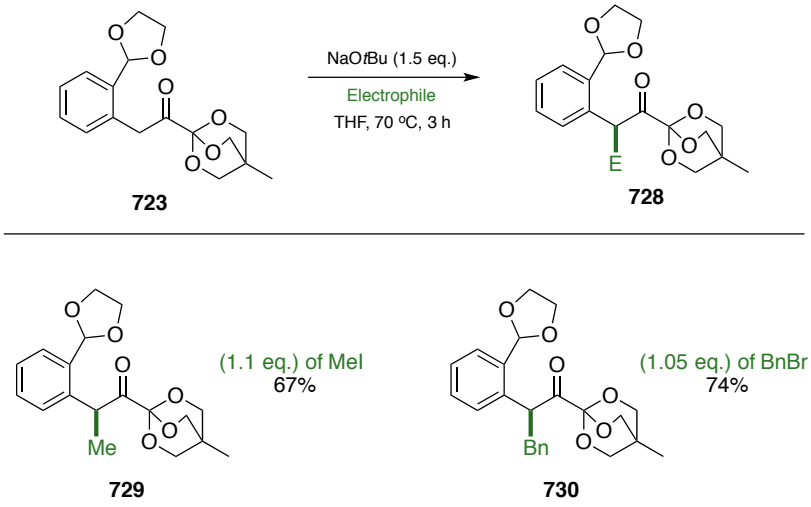
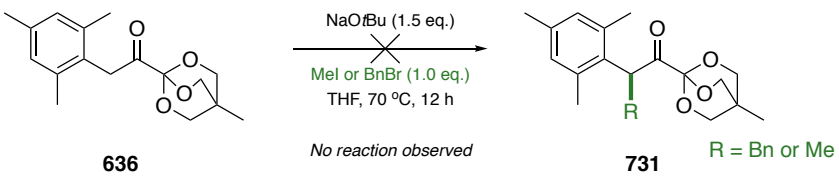


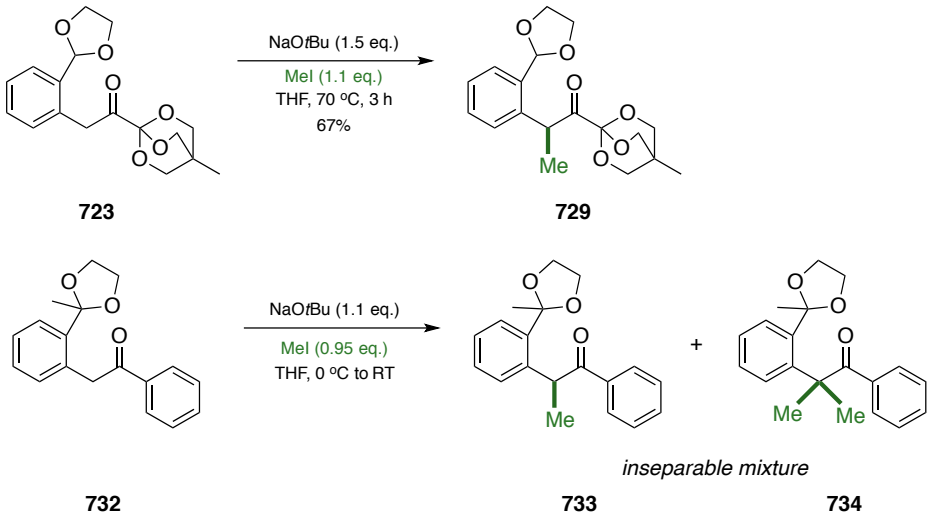
Table 55. α-Alkylation of aryl-OBO-ketone **723**.

There are two main factors influencing this α-functionalisation: the acetal positioned at the *ortho* position and the bulky nature of the OBO moiety. *Ortho*-substituted rings dramatically slow the reaction rates and, depending on the size of the group or the presence of a second *ortho*-substituent, it can shut down the reaction. Compound **636**, for example, was completely inert towards α-functionalisation under the reaction conditions described in **Chapter 2.3.6**. (**Scheme 77**).



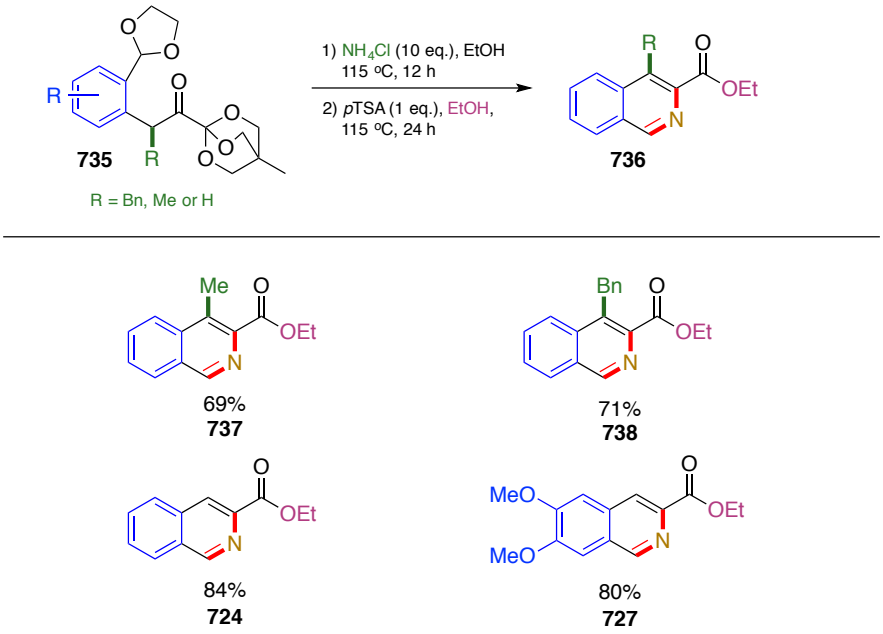
Scheme 77. Failed α-alkylation of compound **636**.

The OBO moiety also impacts the reaction rates. A comparison with α-alkylation studies conducted previously in the Donohoe group clearly demonstrates the difference.[200] While ketone **723** required 70 °C to form the α-alkylated product **729**, ketone **732** was reactive enough to yield an inseparable mixture of products at 0 °C under similar reaction conditions. (**Scheme 78**).



Scheme 78. α-Methylation of ketones **723** and **732**.

Finally, the cyclisation conditions were then applied to **729** and **730**, yielding C4-substituted isoquinolines **737** and **738** in 69% and 71%, respectively. **Table 56** shows a summary of the isoquinolines synthesised following the procedures described in this chapter. Isoquinolines **738** and **737** were identified by the presence of aromatic singlets at 9.25 ppm and 9.15 ppm in their ^{1}H NMR spectra, respectively, corresponding to the C1 hydrogen and compounds **724** and **727** were identified by the presence of a pair of aromatic singlets between 8.40 and 9.50 ppm in their ^{1}H NMR spectra, corresponding to C1 and C4 hydrogens



Scheme 56. Scope for the formation of isoquinoline esters.

With small alterations to the original procedure, four representative isoquinolines were synthesised in good yields, adding to the scope of the existing methodology the possibility to introduce a new and useful functionality at C3. Phenanthriviridone[254] and aaptamine[255] are two illustrative examples of natural products whose synthesis could benefit from the methodology described herein.

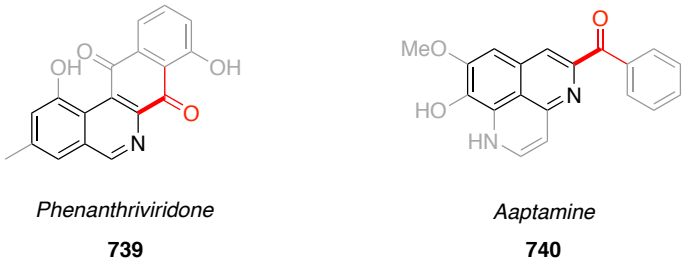


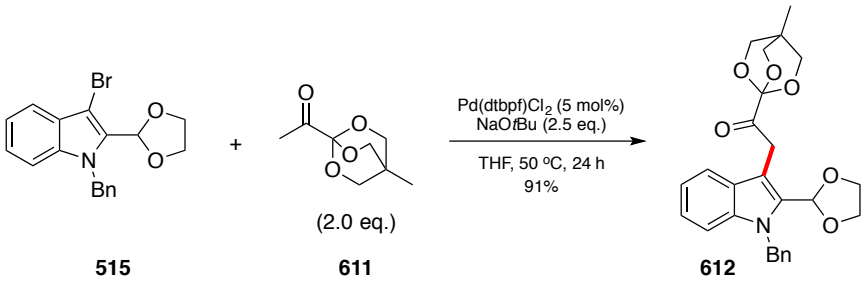
Figure 27. Natural products phenanthriviridone and aaptamine.

2.4.2 *β*-Carbolines

The synthesis of C3-ester-substituted *β*-carbolines discussed in **Chapter 2.2** was the original problem that led to the development of the methyl-OBO-ketone molecule. After exploring the

pyruvate chemistry described in **Chapter 2.3**, the synthesis of substituted *β*-carbolines was revisited.

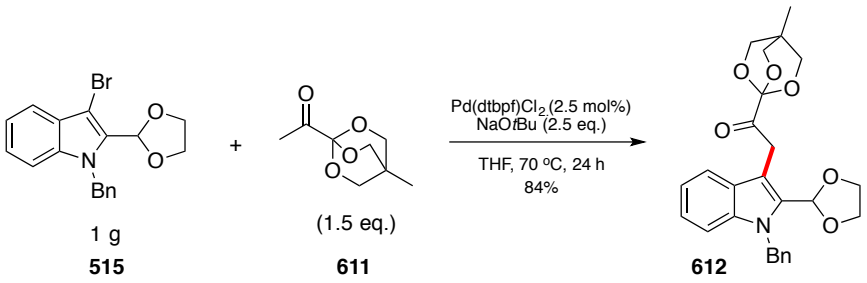
The keto-indole required as starting material for the formation of *β*-carboline esters was initially synthesised in 91%, following the quick base screening previously described (**Scheme 79**).



515 **611** **612**

Scheme 79. Synthesis of keto-indole **612**.

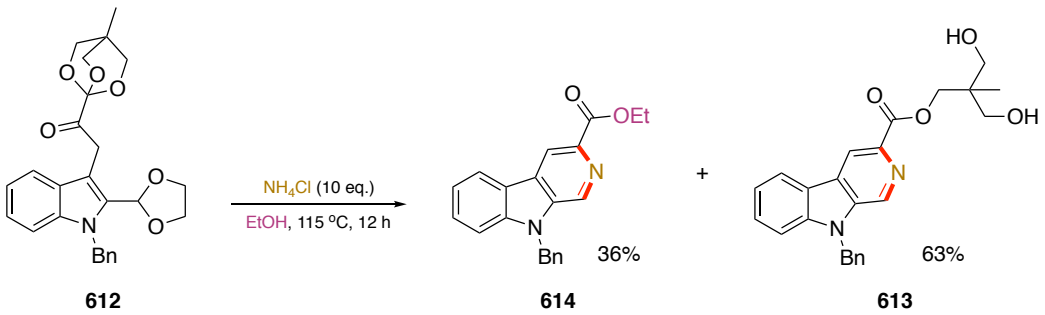
Product **612** was still delivered in 84% in a gram-scale reaction with a reduction in catalyst loading and methyl-OBO-ketone equivalents, showing the scalability of this process (**Scheme 80**).



1 g
515 **611** **612**

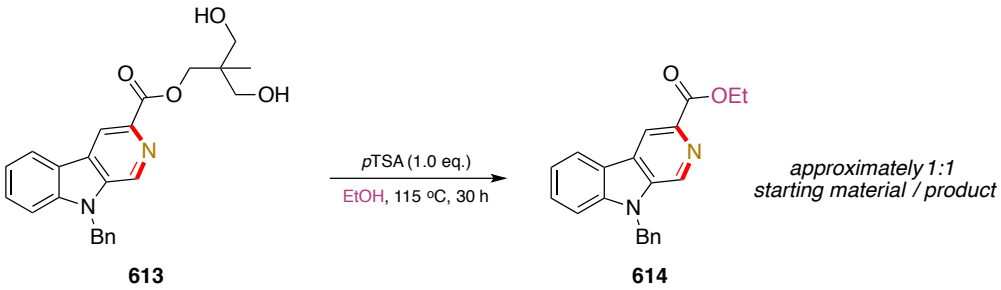
Scheme 80. Gram-scale synthesis of keto-indole **612**.

Building on the observations made in the course of the isoquinoline project described above, the same procedure with pure ethanol as solvent was attempted for the cyclisation of keto-indole **612**. The cyclisation occurred smoothly in high yield, generating a mixture of esters **613** and **614**, as expected (**Scheme 81**). Both *β*-carbolines were identified by their characteristic singlets between 8.90 and 9.20 ppm in the ^{1}H NMR spectra, corresponding to C1 and C4 aromatic hydrogens.



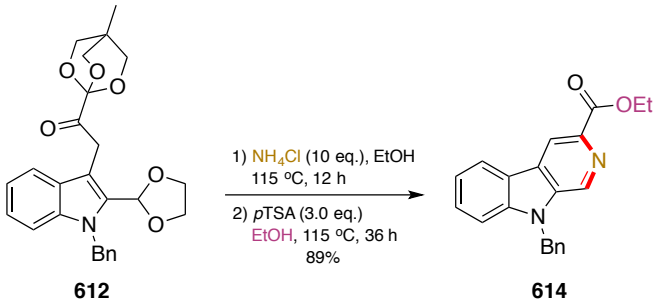
Scheme 81. Synthesis of esters **613** and **614** *via* thermal cyclisation of **612**.

In order to carry out the transesterification of ester **613**, it was subjected to the reaction conditions established for isoquinolines in **Chapter 2.4.1**. However, after 30 h at 115 °C, a TLC analysis showed approximately a 1:1 ratio of starting material and product (**Scheme 82**).



Scheme 82. Attempted acid-catalysed transesterification of ester **613**.

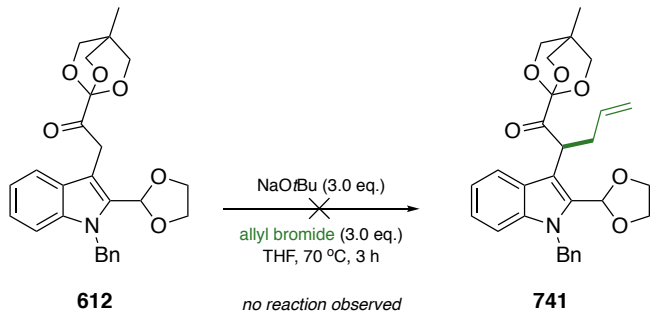
Based on the result obtained, it was hypothesised that the nitrogen on the heterocyclic pyridine ring of the carboline skeleton could be slowing the acid catalysed transesterification reaction, as it is expected to be more basic than the nitrogen present in the isoquinoline structure. In fact, there is a difference of about 1 pK_a unit between isoquinoline[256] and *N*-methyl-*β*-carboline,[257] a difference that can be extrapolated to the systems under scrutiny, given their structural similarity. To test this supposition, three equivalents of *p*TSA were added while keeping the same reaction conditions for this step and, in fact, *β*-carboline **614** was isolated in 89% and no traces of **613** were identified in the crude ^{1}H NMR spectrum (**Scheme 83**).



612 **614**

Scheme 83. Synthesis of **614** *via* thermal cyclisation of **612**.

With a reliable cyclisation procedure established, the α-functionalisation of ketone **612** was then investigated. The α-alkylation of keto-indoles such as **612** is a disfavoured process given the steric hindrance around the ketone alpha protons discussed in **Chapter 2.2.8**. In the case of compound **612**, this effect was expected to be even more pronounced, as the OBO moiety present in this case produces extra hindrance around the reactive site, precluding the approach of the base. Indeed, even harsh conditions completely failed to α-functionalise **612** (**Scheme 84**).



612 **741**

Scheme 84. Attempted α-functionalisation of OBO-ketone **612**.

With these observations experimentally checked, sodium hydride replaced NaO*t*Bu as base, which could easily deprotonate the ketone's α-position. In fact, at high temperatures (*i.e.* 50 °C to 70 °C), the reaction gave a mixture of compounds. Mass spectroscopy analysis indicated the formation of di-alkyated products, possibly α,α-dialkylated or *N*,*O*-dialkylated ketones. Gratifyingly, when the reaction was kept at 0 °C and slowly allowed to warm to room temperature, α-alkylated products were cleanly formed and isolated in high yields (**Table 57**). Compounds **741** and **744** were identified by the presence of two diastereotopic hydrogens

between 3.70 and 2.70 ppm in the ^{1}H NMR spectra, corresponding to the methylene protons at the β-position of these ketones. Compound **743** displayed a characteristic doublet at 1.63 ppm (J = 7.1 Hz), corresponding to the methyl group installed at the ketone α-position.

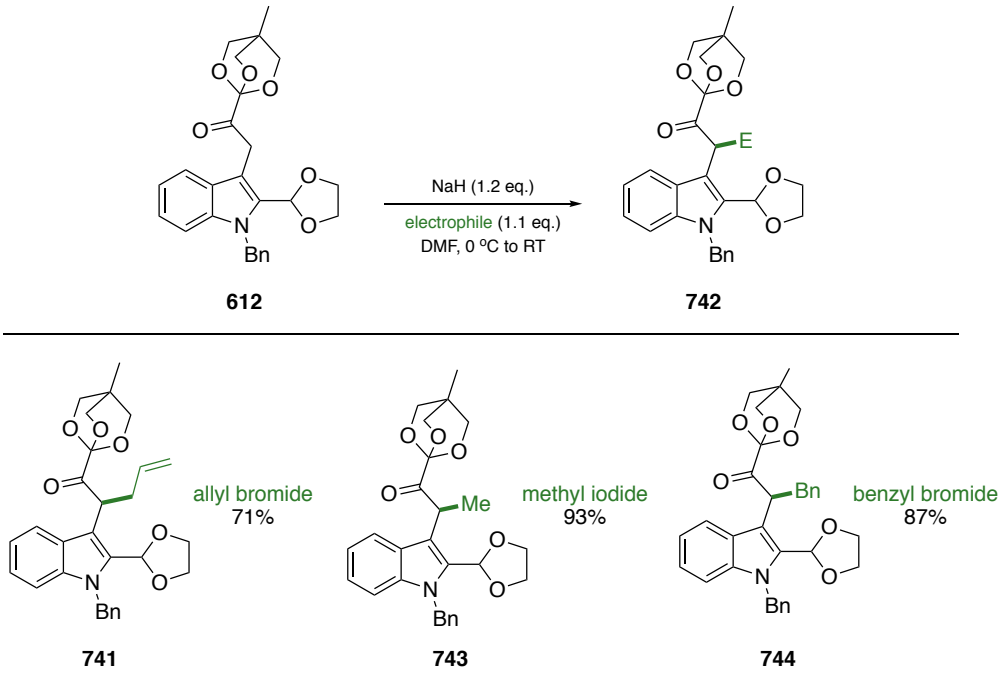


Table 57. Scope for the α-alkylation of keto-indole **612**.

Compounds **741** and **743** were then subjected to the cyclisation conditions and delivered β-carbolines **748** and **747** in good yields. **Table 58** shows a summary of the β-carbolines esters synthesised under the conditions described in this chapter. C4 substituted ketones **747** and **748** showed only one aromatic singlet each at 8.76 and 8.83 ppm in the ^{1}H NMR spectra, corresponding to the C1 hydrogens.

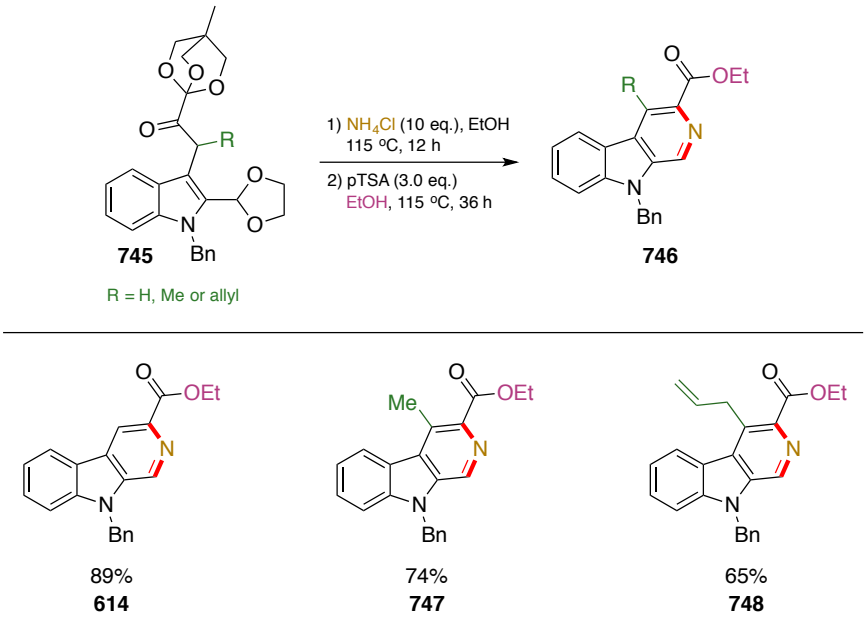
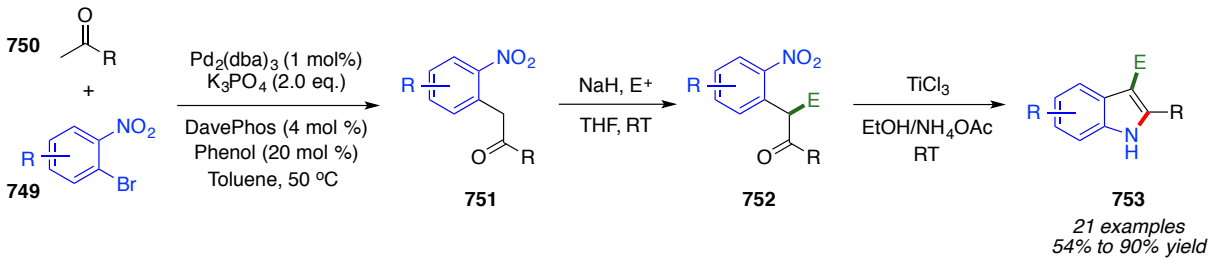


Table 58. Scope for the formation of *β*-carboline esters.

It is important to notice that structures shown in **Table 58** are of great importance in the synthesis of natural products, as discussed in **Chapter 2.2.9**. Compound **747**, for example, contains the carboline core of lavendamycin, an important bioactive molecule found in soil bacteria.[218]

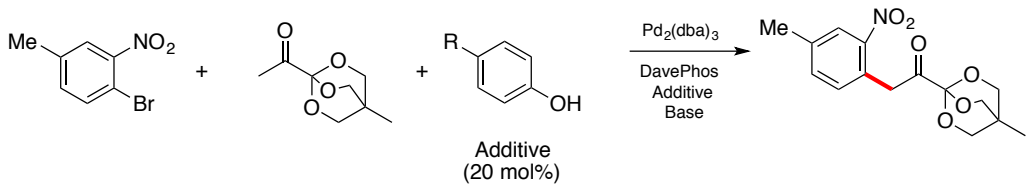
2.4.3 Indoles

In the course of the synthesis of ester-substituted heterocyclic aromatic compounds, indoles were the next class of compounds examined. Buchwald's indole synthesis *via* Pd-catalysed coupling of nitro-bromo-arenes to ketones worked as a starting point for the synthesis of indole esters. This was the first report of nitro-arenes participating in an enolate arylation reaction (**Scheme 85**).[258]



Scheme 85.[258] Buchwald's indole synthesis.

In order to screen conditions for the coupling of methyl-OBO-ketone **611** with bromo-nitro-arenes, 2-bromo-4-methyl-nitrobenzene **754** was chosen as model substrate and subjected to the reaction conditions described by Buchwald. This protocol delivered product **756** in encouraging 28% and 37% conversion (entry 1). Variations in the base (NaO*t*Bu and Cs_2CO_3) were deleterious to the reaction (entries 2 and 3). Replacement of 4-methoxyphenol by phenol as additive increased the conversion from 37% to 47% (entry 4). Doubling the catalyst loading increased the conversion to only 60%, affording **756** in 48% isolated yield (entry 5). Increasing the equivalents of methyl-OBO-ketone practically did not change the conversion observed (entries 6 and 7). When the reaction temperature was raised to 80 °C, however, full conversion was observed, but only 56% isolated yield was obtained. Finally, a switch in the excess reagent delivered the product **756** in 91% yield (**Table 59**). Compound **756** was identified by the presence of a singlet at 4.36 ppm in the ^{1}H NMR spectrum, corresponding to the methylene hydrogens at the ketone α-position.



754 **611** **755** **756**

Entry	**611** (eq.)	**754** (eq.)	$Pd_2(dba)_3$ (mol%)	DavePhos (mol%)	Additive (R)	T (°C)	Base (2.0 eq.)	Convertion (%)	yield **756** (%)
1	1.1	1.0	1	4	OMe	50	K_2CO_3	37	28
2	1.1	1.0	1	4	OMe	50	NaO*t*Bu	0	-
3	1.1	1.0	1	4	OMe	50	Cs_2CO_3	7	-
4	1.1	1.0	1	4	H	50	K_2CO_3	47	-
5	1.1	1.0	2	8	H	50	K_2CO_3	60	48
6	2.0	1.0	1	4	H	50	K_2CO_3	63	-
7	2.0	1.0	2	8	H	50	K_2CO_3	66	-
8	1.1	1.0	1	4	H	80	K_2CO_3	100	56
9	1.0	2.0	1	4	H	80	K_2CO_3	100	91

Table 59. Screening of reaction conditions for the α-arylation of methyl-OBO-ketone **611**.

Interestingly, the removal of the phenol additive shuts down the reaction shown in **Table 59**. The authors offer two possible explanations for the phenomenon: they hypothesise that a palladium phenoxide intermediate **757** might stabilise an otherwise unstable electron-poor intermediate, avoiding catalyst decomposition (**Figure 28A**).[259] Alternatively, they suggest that phenoxide **759** could operate as base in the deprotonation of the ketone, while palladium complex **758** serves as Lewis acid (**Figure 28B**).

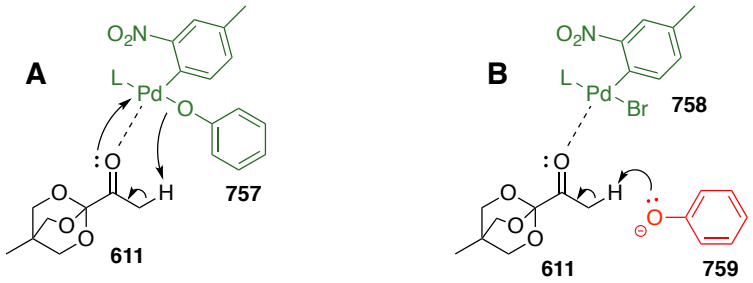


Figure 28. Proposed roles for phenol in the cross-coupling cycle.

The optimal set of conditions found in **Table 59** were then applied in a larger-scale reaction to the same substrate **754** and 1-bromo-4-methoxy-2-nitrobenzene, yielding nitroaryl-OBO-ketones **756** and **761** in good yields (**Table 60**).

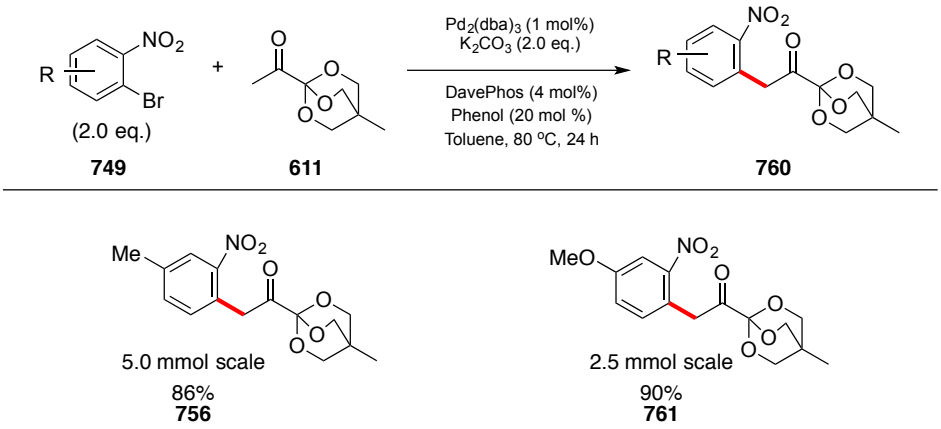
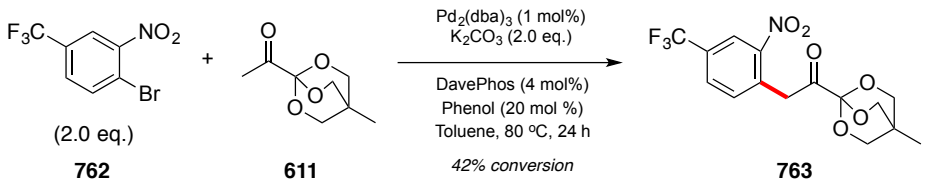


Table 60. Synthesis of OBO-ketones **756** and **761**.

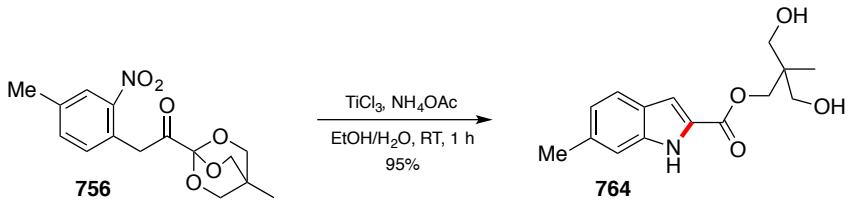
When a more electron-deficient aryl-halide was subjected to these reaction conditions, however, only 42% conversion was observed in the crude ^{1}H NMR spectrum (**Scheme 86**).



Scheme 86. α-Arylation of methyl-OBO-ketone **611** with aryl halide **762**.

A potential explanation for the observed low conversion might be related to the role of phenol in stabilising the palladium intermediate shown in **Figure 28A**, as the electron density moving from the metal centre to the aryl substituent should be more accentuated in this case. This could possibly be counterbalanced by adding a more electron-rich phenol such as 4-methoxyphenol, screened in **Table 59**. Unfortunately, this additive was not tested for this substrate.

With compounds **756** and **761** in hand, the reductive cyclisation was then performed under Buchwald's conditions. Due to the acidic nature of the commercially available solution of $TiCl_3$ used as reducing agent, the OBO orthoester moiety was also partially deprotected *in situ*, yielding indole **764** in 95% yield (**Scheme 87**). The identity of indole **764** was confirmed by the presence of two singlets at 6.85 and 6.76 ppm ^{1}H NMR spectrum corresponding to C3 and C7 hydrogens.



Scheme 87. Reductive cyclisation of nitroaryl-OBO-ketone **756**.

An acid-catalysed transesterification step was then added to the sequence and compounds **756** and **761** allowed indoles **766** and **767** to be isolated in 93% and 85% yield, respectively (**Table 61**).

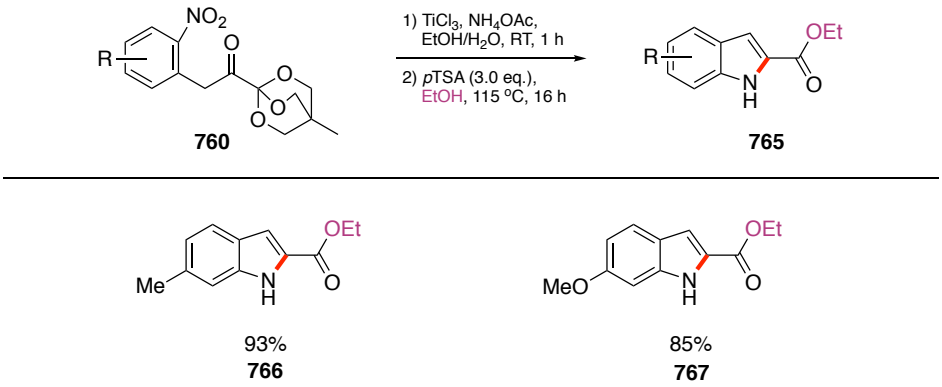


Table 61. Synthesis of indoles **766** and **767** from nitroaryl-OBO-ketones.

Next, the α-alkylation of compounds **756** and **761** was attempted. Building on the observations made for the α-alkylation of keto-indole **612**, the same approach was reproduced here with great success. Both ketones were cleanly functionalised in excellent yields (**Table 62**). The identity of the α-alkylated ketones **769** and **770** was attested by the presence of a quartet at 4.89 ppm (J = 6.9 Hz) and a doublet of doublets at 5.22 ppm (J = 8.1 and 6.7 Hz) in the ^{1}H NMR spectra, respectively. These peaks correspond to the methine hydrogens in each structure.

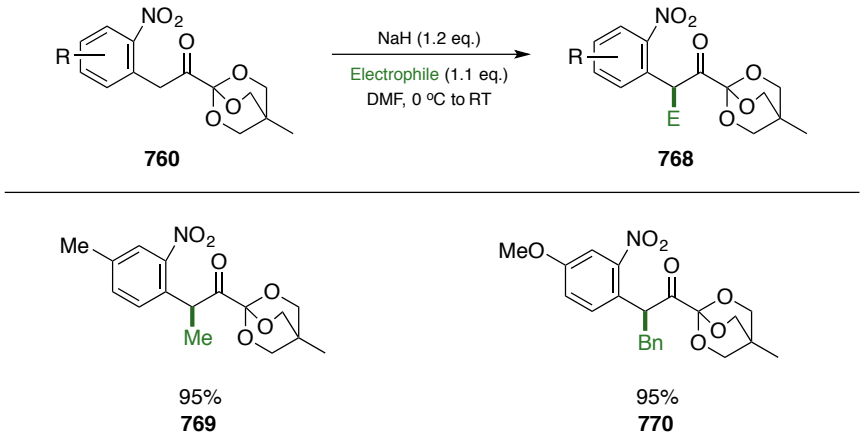


Table 62. Scope for the α-alkylation of nitroaryl-OBO-ketones.

These compounds were then subjected to the reductive cyclisation/transesterification sequence, delivering indoles **773** and **774** in good yields. **Table 63** shows a summary of the indole-esters synthesised under the conditions described in this chapter.

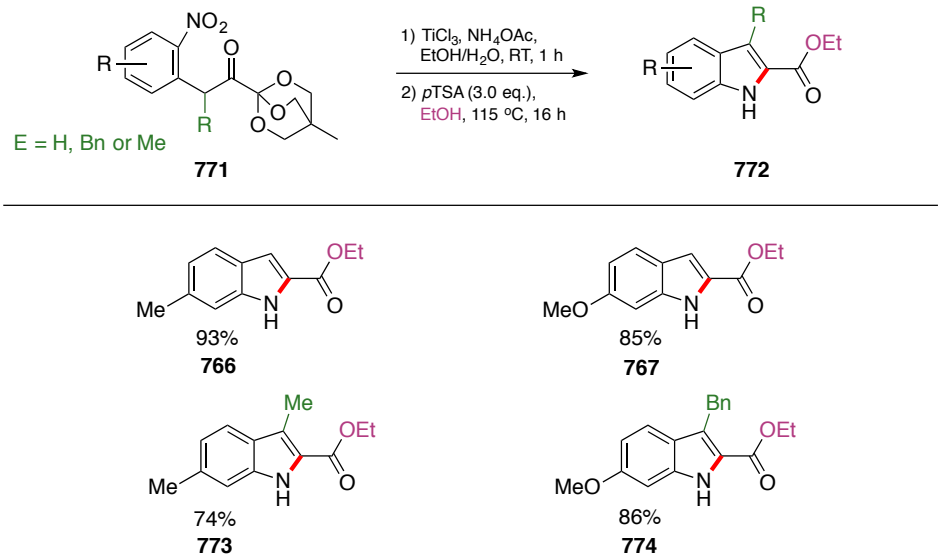


Table 63. Scope for the synthesis of indole esters.

Figure 29 shows two illustrative structures that could potentially be synthesised following the described methodology. Delavirdine, a reverse transcriptase inhibitor used for the treatment of HIV[260] and crooksidine, an alkaloid natural product extracted from *Haplophyton crooksii*, a perennial shrub.[261]

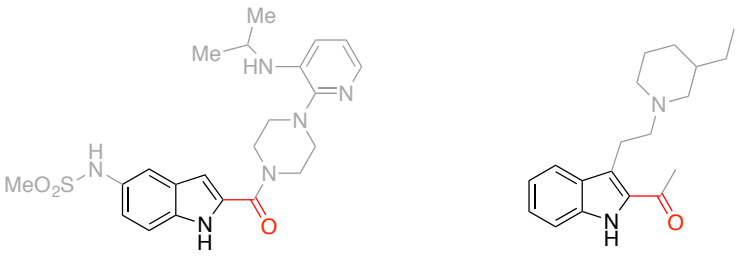
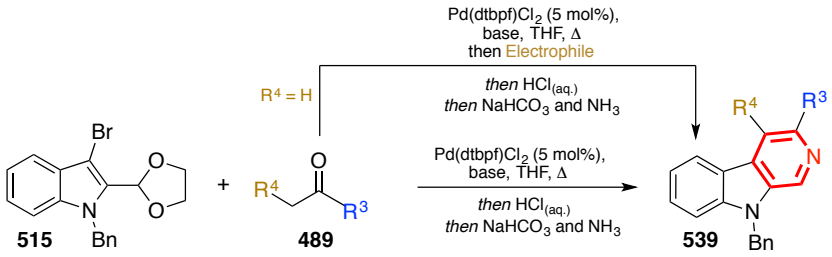


Figure 29. Natural products phenanthriviridone and aaptamine.

Chapter 3: Conclusions

3. Conclusions

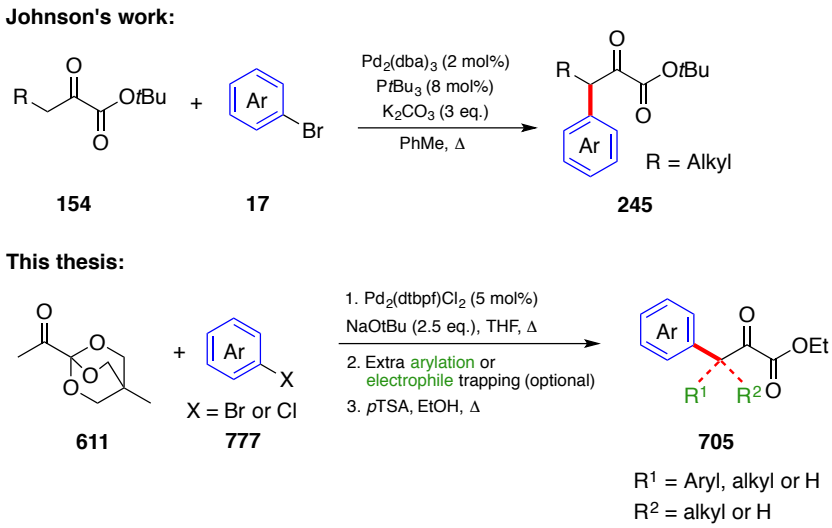
In **Chapter 2.2**, a one-pot procedure for the synthesis of substituted *β*-carbolines was described. This sequence allowed the formation of a variety of substituted *β*-carboline structures from commercially available ketones and 3-bromoindole **515**. The introduction of electrophiles immediately after the enolate arylation step proved successful in *α*-functionalising the ketone intermediate **520**, giving access to C4-substituted *β*-carbolines from simple methyl ketones (**Scheme 88**).



Scheme 88. One-pot *β*-carboline synthesis *via* enolate arylation.

This protocol demonstrated some advantages compared to the methodologies described in **Chapter 1.3.1**. The widely explored synthesis of *β*-carbolines *via* the Pictet–Spengler reaction (**Scheme 13**), for example, does not allow the formation of C4-functionalised *β*-carbolines because tryptophan derivatives, which are not easily functionalised, are the substrates of choice for this methodology.[106] Larock's and Witulski's work, on the other hand, demonstrated poor regioselectivity for similar product structures (**Table 22** and **Table 23**). The first methodology obtained almost an equimolar mixture of *β*-carboline regioisomers, while the latter found that the formation of *β*- or *γ*-carbolines was strongly influenced by the substrate and in some cases a mixture of both regioisomers was obtained. The one-pot protocol with enolate quench described in this thesis addresses this issue, as the C4 substituent is introduced after the enolate arylation occurs, allowing the formation of a single C4-functionalised regioisomer (**Table 42**). The synthesis of aryl pyruvates discussed in **Chapter 2.3** described the formation of mono and multiply *α*-functionalised pyruvates in good yields (**Table 53**). These results can be compared to Johnson's synthesis of aryl-pyruvates discussed in **Chapter 1.2.6**, the most versatile

approach published to date[91] which, differently from this work, allowed only the formation of α-alkyl-α-aryl-pyruvates (**Scheme 89** and **Table 19**).

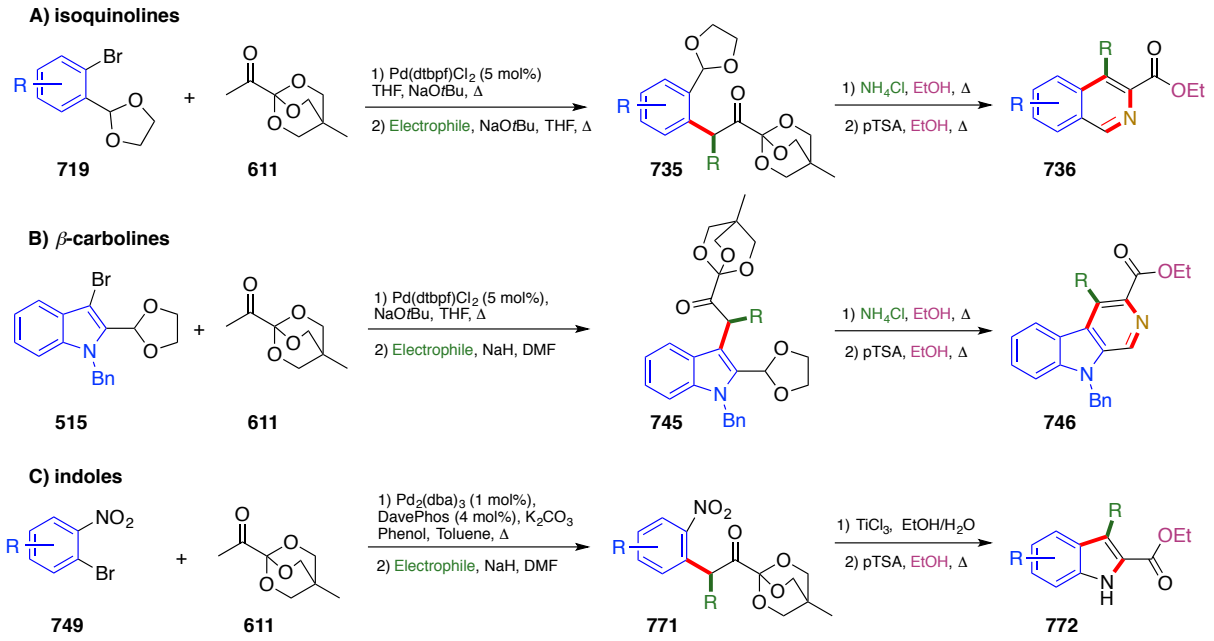


Scheme 89. Johnson's synthesis of arylated pyruvates compared to the work described in this thesis.

Moreover, to the best of our knowledge, our methodology is the first general protocol to allow the synthesis of aryl-pyruvates bearing an α-quaternary centre. Other methodologies discussed in **Chapter 1.2.6** also do not allow the α-functionalisation of aryl-pyruvates and each have their own limitations.

Furthermore, the aryl-OBO-ketones obtained demonstrated great stability, ease of purification and scalability (**Table 47**). These features along with the one-pot synthesis of aryl pyruvates (**Scheme 70**) make this methodology attractive for several synthetic applications, including scaled-up processes.

Finally, the synthesis of isoquinolines, β-carbolines and indole esters *via* enolate arylation of methyl-OBO-ketone **611** was described in **Chapter 2.4**. The use of pyruvate equivalent **611** allowed the rapid construction of heterocyclic aromatic esters following adapted literature procedures.[184,258] Enolate chemistry permitted the α-functionalisation of the aryl-OBO-ketone intermediates which then cyclised to give C4-substituted isoquinolines and β-carbolines and C3-substituted indoles (**Scheme 90**).



Scheme 90. Synthesis of heterocyclic aromatic esters *via* enolate arylation of methyl-OBO-ketone **611**.

The modularity of these sequences allowed the construction of highly substituted heterocycles, which are not easily accessed through most of the literature methodologies available (**Chapter 1.3**). *β*-carboline **747**, which contains the carboline core present in the natural product lavendamycin, was easily obtained *via* the sequence shown in **Scheme 90B** employing MeI as electrophile. The classic approach to *β*-carbolines *via* the Pictet–Spengler reaction, for example, cannot deliver this substitution pattern, which can be attested by some of the reported total syntheses of this natural product.[262,263] Similarly, the indole synthesis shown in **Scheme 90C** adds a new sequence to prepare 3-substituted indole-2-carboxylic acid esters, which are scarce among the vast literature focused on the synthesis of indoles.[157]

Finally, the use of Pd-catalysed enolate arylation of methyl-OBO-ketone **611** in the synthesis of heterocyclic aromatic esters may not limited to isoquinolines, *β*-carbolines and indoles. Further applications are currently being investigated in the Donohoe group, especially the formation of 5-membered-ring heterocycles.

Chapter 4: Experimental

General Methods

Solvents were dried over 4 A molecular sieves. Dry ethanol used for OBO deprotection experiments was purified following a literature procedure.[264] All reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics or Fluorochem and used without further purification. All reactions requiring dry equipment were carried out using glassware flame-dried under vacuum. Flash column chromatography was performed using Merck Kieselgel 60 (0.040 – 0.063 mm) silica gel following the established literature method.[265] Thin layer chromatography was performed on Merck Kieselgel 60 F_{254} 0.25 mm pre-coated aluminum-backed plates. Product spots were visualized under UV light (λ_{max} = 254 nm) and/or by staining with vanillin, phosphomolybdic acid or basic potassium permanganate solutions. Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AVII400, AVIII400, or AVII500 instruments at 400 MHz or 500 MHz for ^{1}H NMR, 101 MHz or 126 MHz for ^{13}C NMR and 377 MHz for ^{19}F NMR. ^{13}C NMR spectra were recorded with broadband proton decoupling and ^{19}F NMR spectra were recorded without broadband proton decoupling. Chemical shifts, δ, are reported relative to residual solvent peaks and quoted in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H and to the nearest 0.1 ppm for ^{13}C and ^{19}F. Coupling constants, *J*, are quoted to the nearest 0.1 Hz. Assignments were made on DEPT, COSY, HSQC, HMBC and nOe experiments. High-resolution mass spectra were acquired using electrospray ionisation (ESI) as ionization source and were recorded on a Thermo Exactive orbitrap spectrometer equipped with a Waters Equity LC system. Infrared spectra (IR) were obtained from evaporated films using a Bruker Tensor 27 spectrometer, equipped with a Pike Miracle Attenuated Total Reflectance (ATR) sampling accessory. Absorption is quoted in wavenumbers (cm^{-1}) for the range 3500 – 600 cm^{-1}. Melting points (m.p.) were obtained by using a Lecia VMTG heated-stage microscope with a Testo 720 thermometer and are uncorrected. Compound names were generated by the software ChemDraw Professional 15.1.

General procedure A: α-arylation of ketones.

A fresh solution of LiHMDS was prepared in a dry vial by adding sequentially dry THF (2.0 mL), HMDS (80 μL, 0.38 mmol, 2.5 eq.) and a 2.5 M solution of *n*BuLi (0.15 mL, 0.38 mmol, 2.5 eq.) at –78 °C for 10 mins. The ketone (0.31 mmol, 2.0 eq.) was then added at 0 °C and stirred for 15 mins. In a second dry vial were added bromoindole (0.15 mmol, 1.0 eq.) and Pd(dtbpf)Cl_2 (5 mg, 8 μmol, 5 mol%). The vial was sealed and flushed with argon for 5 mins. The freshly formed enolate solution was then transferred *via* syringe to the vial and the mixture was stirred at 50 °C for 24 h. The reaction was cooled down to RT, filtered through a plug of silica using EtOAc as eluent and concentrated *in vacuo*. The crude product was purified by flash column chromatography as indicated.

General procedure B: cyclisation of α-arylated ketones.

To a reaction flask were added the α-arylated ketone (4.15 mmol, 1.0 eq.) and aqueous 1 M $NH_4Cl_{(aq.)}$ (4.1 mL, 10 eq.) in EtOH/H_2O (3:1). The mixture was stirred at 90 °C for 12 h. Solid NH_4HCO_3 (6.97 g, 83.0 mmol, 20 eq.) was then slowly added and the solution was stirred at 90 °C for 3 h. The crude product was concentrated *in vacuo* then re-dissolved in pure EtOAc and mixed with water. The layers were separated and the aqueous layer was extracted twice with EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography as indicated.

General procedure C: bromination of keto-indoles

To a dry reaction flask were added the appropriate ketone (5.45 mmol, 1.0 eq.) and DMF (3.9 mL). A 1.6 M solution of NBS (1.11 g, 6.27 mmol, 1.15 eq.) in DMF was added over 30 mins at 0 °C and the resulting mixture was then stirred at RT for 2 h. Distilled water was added and the resulting slurry was extracted three times with EtOAc. The organic extracts were combined and washed five times with water, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography as indicated.

General procedure D: one-pot synthesis of *β*-carbolines.

To a dry vial were added bromoindole **1** (110 mg, 307 μmol, 1.0 eq.), Pd(dtbpf)Cl_2 (10 mg, 15 μmol, 5 mol%) and NaO*t*Bu (74 mg, 0.77 mmol, 2.5 eq.). The flask was flushed with argon for 5 mins and then dry THF (4.0 mL) and the corresponding ketone (0.61 mmol, 2.0 eq.) were added sequentially and stirred for 24 h at 75 °C. After cooling to RT, 1 M $HCl_{(aq.)}$ (10 eq.) was added and the mixture was stirred for 12 h at 90 °C. After cooling to RT, DMF (2.0 mL), EtOH (4.0 mL), solid $NaHCO_3$ (516 mg, 6.14, 20 eq.) and 7 M NH_3 in MeOH (0.88 mL, 6.1 mmol, 20 eq.) were added and the mixture was stirred at 110 °C for 24 h. The crude product was concentrated *in vacuo* and then re-dissolved in pure EtOAc and mixed with water. The mixture was separated and the aqueous layer was extracted twice with EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography as indicated.

General procedure E: one-pot synthesis of *β*-carboline with addition of electrophiles.

A fresh solution of LiHMDS was prepared in a dry vial by adding sequentially dry THF (4 mL), HMDS (0.16 mL, 0.77 mmol, 2.5 eq.) and a 2.5 M solution of *n*BuLi (0.31 mL, 0.77 mmol, 2.5 eq.) and stirring at –78 °C for 10 mins. Acetophenone (72 μL, 0.61 mmol, 2.0 eq.) was then added at 0 °C and stirred for 15 mins. In a second dry vial were added bromoindole **1** (110 mg, 307 μmol, 1.0 eq.) and Pd(dtbpf)Cl_2 (10 mg, 15 μmol, 5 mol%). The flask was flushed with argon for 5 mins. The freshly formed enolate solution was then transferred *via* syringe to the flask and the mixture was stirred at 50 °C for 24 h. After cooling to RT, the appropriate electrophile (0.77 mmol, 2.5 eq.) was added and the mixture was stirred at 90 °C for 24 h. After cooling to RT, 1 M $HCl_{(aq.)}$ (3.1 mL, 10 eq.) was added and the mixture was stirred for 12 h at 90 °C. After cooling to RT, DMF (2 mL), EtOH (4 mL), $NaHCO_3$ (516 mg, 6.14 mmol, 20 eq.,) and 7 M NH_3 in MeOH (0.88 mL, 6.1 mmol, 20 eq.) were added and the mixture was stirred at 110 °C for 24 h. The crude product was concentrated *in vacuo*, re-dissolved in EtOAc and mixed with water. The aqueous layer was separated and extracted twice with EtOAc. The

organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solids were purified by flash column chromatography as indicated.

General procedure F: α-arylation of methyl-OBO ketones.

To a flame-dried vial capped with a rubber septum were added methyl-OBO ketone (100 mg, 0.58 mmol, 1.0 eq.), the corresponding aryl halide (0.64 mmol, 1.1 eq.) if solid and Pd(dtbpf)Cl_2 (19 mg, 29 μmol, 5 mol%). The rubber septum was replaced by an aluminium cap and then THF (5.1 mL), the aryl halide (0.64 mmol, 1.1 eq.) if liquid, and 2 M NaO*t*Bu in THF (0.72 mL, 1.45 mmol, 2.5 eq.) were added *via* syringe. The vial was flushed with argon for 5 mins and heated at 50 °C for 24 h. The resulting mixture was filtered through a plug of silica, concentrated *in vacuo* and purified as indicated.

General procedure G: α-arylation of methyl-OBO ketones.

To a flame-dried vial capped with a rubber septum were added methyl-OBO ketone (100 mg, 058 mmol, 1.5 eq.), the corresponding aryl halide (0.39 mmol, 1.0 eq.) if solid and Pd(dtbpf)Cl_2 (13 mg, 19 μmol, 5 mol%). The rubber septum was replaced by an aluminium cap and then THF (5.3 mL), the aryl halide (0.39 mmol, 1.0 eq.) if liquid and 2 M NaO*t*Bu in THF (0.49 mL, 0.98 mmol, 2.5 eq.) were added *via* syringe. The vial was flushed with argon for 5 mins then heated at 70 °C for 24 h. The resulting mixture was filtered through a plug of silica using EtOAc as eluent, concentrated *in vacuo* and purified as indicated.

General procedure H: α,α-diarylation of methyl-OBO ketones.

To a flame-dried vial capped with a rubber septum were added methyl-OBO ketone (100 mg, 0.58 mmol, 1.0 eq.), the corresponding aryl halide (1.74 mmol, 3.0 eq.) if solid and Pd(dtbpf)Cl_2 (19 mg, 29 μmol, 5 mol%). The rubber septum was replaced by an aluminium cap and then THF (5.1 mL), the aryl halide (1.74 mmol, 3.0 eq.) if liquid and 2 M NaO*t*Bu in THF (0.72 mL, 1.45 mmol, 2.5 eq.) were added *via* syringe. The vial was flushed with argon for 5 mins and heated at 80 °C for 24 h. The resulting mixture was filtered through a plug of silica using EtOAc as eluent, concentrated *in vacuo* and purified as indicated.

General procedure I: α,α-heterodiarylation of methyl-OBO ketones.

The indicated aryl halide was subjected to the indicated α-arylation general procedure for 8 h, followed by the addition of the second aryl halide (2.5 eq.). The mixture was heated at 80 °C for 16 h and then cooled to RT, filtered through a plug of silica using EtOAc as eluent, concentrated *in vacuo* and purified as indicated.

General procedure J: one-pot α-arylation of methyl-OBO ketones followed by the addition of electrophiles.

The indicated aryl halide was subjected to the indicated α-arylation general procedure, followed by the addition of the indicated amount of electrophile for the indicated time (the consumption of the arylated methyl-OBO ketone intermediate was closely monitored by TLC). Once the intermediate was completely consumed, the mixture was cooled to RT, filtered through a plug of silica using EtOAc as eluent, concentrated *in vacuo* and purified as indicated.

General procedure K: synthesis of ethyl pyruvates.

To a flame-dried vial were added *p*-toluenesulfonic acid (1.0 eq.), the corresponding OBO-protected pyruvate (1.0 eq.) and dry EtOH (0.1 M to the OBO-protected pyruvate). The vial was sealed, flushed with argon for 5 mins and stirred at the indicated temperature for the indicated time. After cooling down to RT, $NaHCO_3$ (2.0 eq.) was added and the mixture was concentrated *in vacuo*. The crude product was purified by flash column chromatography as indicated.

General procedure L: synthesis of TBS-protected ethyl pyruvates.

To a flame-dried vial were added *p*-toluenesulfonic acid (1.0 eq.), dry EtOH (0.1 M to the OBO-protected pyruvate) and the corresponding OBO-protected pyruvate (1.0 eq.). The vial was sealed, flushed with argon for 5 mins and stirred at 100 °C for 2 h. After cooling down, $NaHCO_3$ (2.0 eq.) was added and the reaction mixture was concentrated *in vacuo*. The crude material was then re-dissolved in DCM and mixed with distilled water. The mixture was separated and the aqueous layer was extracted 3 times with DCM and the organic extracts were combined,

dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was dissolved in dry DCM (0.1 M to the OBO-protected pyruvate), transferred to a flame-dried vial and cooled to 0 °C. Dry Et_3N (10 eq.) was added, followed by the slow addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (5.0 eq.). The reaction mixture was then allowed to warm to RT and stirred for 1 h. The solvent was evaporated and the crude product was purified by flash column chromatography as indicated.

General procedure M: cyclisation of aryl-OBO-ketone acetals.

Step 1: To a vial were added NH_4Cl (160 mg, 3.0 mmol, 10.0 eq.), the indicated acetal (0.3 mmol, 1.0 eq.) and EtOH (3.0 mL, 0.1 M). The mixture was stirred at 110 °C for 12 h. After cooling down to RT, the crude material was concentrated *in vacuo*, passed through a short silica column using EtOAc as eluent and concentrated again.

Step 2: the crude material was dissolved in dry EtOH (3.0 mL, 0.1 M) and transferred *via* syringe to a flamed-dried vial containing *p*-toluenesulfonic acid (153 mg, 0.9 mmol, 3.0 eq.) and stirred at 115 °C until all the intermediate was completely consumed, as indicated by TLC. After cooling down to RT, the reaction was neutralised with solid $NaHCO_3$ (151 mg, 1.8 mmol, 6.0 eq.) and concentrated *in vacuo*. The crude material was re-dissolved in DCM and washed with water. The mixture was separated and the aqueous layer was extracted with DCM 3 times. The organic layers were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash column chromatography as indicated.

General procedure N: reductive cyclisation of nitro-aryl OBO-ketones.

Step 1: To a vial were added an aqueous solution of $TiCl_3$ (16.5 eq.), NH_4OAc (6.6 M, 4.5 mL) and EtOH (1.5 mL). The vial was capped with a rubber septum and purged with argon for 5 mins. A solution of the indicated aryl OBO-ketone (0.30 mmol, 1.0 eq.) dissolved in EtOH (4.5 mL) was added dropwise and stirred at RT for 1 h. The mixture was extracted with DCM 3 times, dried over $MgSO_4$ and concentrated *in vacuo*.

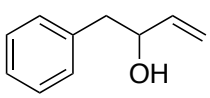
Step 2: the crude material was dissolved in dry EtOH (3.0 mL) and added *via* syringe to a flame-dried vial containing *p*-toluenesulfonic acid (156 mg, 0.90 mmol, 3.0 eq.) and stirred at 115 °C until all the intermediate was completely consumed as indicated by TLC. After cooling down

to RT, the reaction was neutralized with solid $NaHCO_3$ (151 mg, 1.80 mmol, 6.0 eq.) and concentrated *in vacuo*. The crude material was re-dissolved in DCM and washed with water. The mixture was separated and the aqueous layer was extracted with DCM 3 times. The organic layers were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash column chromatography as indicated.

General procedure O: α-alkylation of aryl OBO-ketones using NaH and DMF.

To a flame-dried vial capped with a rubber septum were added the indicated aryl OBO-ketone (0.60 mmol, 1.0 eq.) and electrophile (0.66 mmol, 1.1 eq.). The rubber septum was replaced by an aluminium cap and dry DMF (3.0 mL) was added. The mixture was stirred at 0 °C for 10 mins, followed by the addition of NaH (60% in mineral oil, 29 mg, 0.72 mmol, 1.2 eq.). The reaction was stirred for 15 mins at 0 °C after which the ice was removed from the cooling bath and the cold water was allowed to warm to RT over 2 h. The reaction was quenched with saturated $NH_4Cl_{(aq.)}$ and extracted three times with DCM. The organic layers were combined and washed with water 5 times, dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash column chromatography, as indicated.

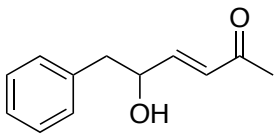
1-Phenylbut-3-en-2-ol (462)



To a dry reaction flask were added a solution of 1 M vinylmagnesium bromide (47 mL, 47 mmol, 1.5 eq.) and THF (125 mL). Phenylacetaldehyde (3.5 mL, 31 mmol, 1.0 eq.) was slowly added at 0 °C and the mixture was stirred for 1 hour and then allowed to warm to room temperature and stirred for 1 h. The reaction was then quenched with saturated $NH_4Cl_{(aq.)}$ (100 mL) and the aqueous phase was extracted three times with DCM. The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash-column chromatography using petrol/EtOAc (10%) as eluent, affording allylic alcohol **462** (3.56 g, 77%) as a light green oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.45 – 7.22 (5H, m, 5 × HC_{Ar}), 5.98 (1H, ddd, J = 17.2, 10.5, 5.8 Hz, CHCHCH$_2$), 5.29 (1H, dt, J = 17.2, 1.4 Hz, CHCH_{trans}CH$_{cis}$), 5.18 (1H, dt, J = 10.5, 1.3 Hz, CHCH$_{trans}$CH_{cis}), 4.42 – 4.32 (1H, m, CHOH), 2.92 (1H, dd, J = 13.6 Hz, 5.4 Hz, PhCH_aH$_b$), 2.85 (1H, dd, J = 13.5, 7.7 Hz, PhCH$_a$$H_b$), 2.06 (1H, s, O$H$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 140.2 (CHCHCH$_2$), 137.8 (C_{Ar}), 129.6, 128.5, 126.6 (3 × HC_{Ar}), 114.9 (CHCHCH$_2$), 73.7 (CHOH), 43.9 (PhCH$_2$). Spectroscopic data are consistent with those previously reported.[266]

5-Hydroxy-6-phenylhex-3-en-2-one (463)

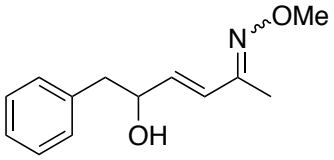


To a dry reaction flask were added Hoveyda-Grubbs II catalyst (126 mg, 0.20 mmol, 2.5 mol%), DCM (40 mL), 1-phenylbut-3-en-2-ol **462** (1.20 g, 8.10 mmol, 1.0 eq.) and but-3-en-2-one (3.4 mL, 41 mmol, 5.0 eq.). The flask was then purged with argon for 5 min and the mixture was stirred at RT for 24 h. The resulting mixture was then concentrated *in vacuo* and the residue was purified by flash-column chromatography using petrol/EtOAc (40%) as eluent, affording ketone **463** (1.29 g, 84%) as a colourless oil.

IR: ν_{max} (thin film) 3331, 2788, 1742, 1669, 1630, 1151, 1108, 1040, 986, 700 cm^{-1}. **HRMS**: calculated for $C_{12}H_{14}O_2Na$, 213.0886 $[M+Na]^+$, found m/z 213.0890, Δ = –1.8 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.37 – 7.20 (5H, m, 5 × HC_{Ar}), 6.81 (1H, dd, J = 16.0, 4.7 Hz, CHCHC(O)), 6.28 (1H, dd, J = 16.0, 1.8 Hz, CHCHC(O)), 4.58 – 4.50 (1H, m, CHOH), 2.94 (1H, dd, J = 13.6, 8.1 Hz, PhCH_aH$_b$), 2.85 (1H, dd, J = 13.6, 8.1 Hz, PhCH$_a$$H_b$), 2.68 (1H, d,

J = 4.3 Hz, O*H*), 2.25 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 198.9 (*C*(O)), 148.1 (*C*HCHC(O)), 136.9 (C_{Ar}), 129.5 (HC_{Ar}), 129.2 (CH*C*HC(O)), 128.7 (HC_{Ar}), 126.9 (HC_{Ar}), 71.8 (*C*HOH), 43.3 (Ph*C*H_2), 27.4 (*C*H_3).

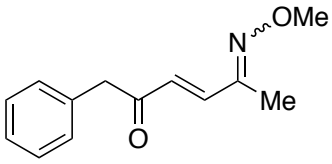
5-Hydroxy-6-phenylhex-3-en-2-one *O*-methyl oxime (E-1)



To a reaction flask were added hydroxy-vinyl-ketone **463** (900 mg, 4.73 mmol, 1.0 eq.), sodium acetate trihydrate (804 mg, 5.91 mmol, 1.25 eq.), methoxyamine hydrochloride (592 mg, 7.09 mmol, 1.5 eq.), ethanol (34 mL) and water (4.0 mL). The reation was stirred at RT for 1 h and then extracted three times with DCM. The resulting organic phases were combine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash-column chromatography using petrol/EtOAc (20%) as eluent, affording *O*-methyl-oxime **E-1** (1.04 g, 99%) as a colorless oil and a mixture of *E* and *Z* *O*-methyl oxime diastereoisomers (d.r.: 1.0:1.5).

IR: ν_{max} (thin film) 3373, 3065, 3028, 2938, 2909, 1588, 1399, 1075, 1046, 915, 750, 707, 697 cm^{-1}. **HRMS**: calculated for $C_{13}H_{17}NO_2Na$, 242.1151 $[M+Na]^+$, found *m/z* 242.1156, Δ = –2.0 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) (Diastereoisomer A) δ_H: 7.40 – 7.20 (5H, m, 5 × HC_{Ar}), 6.33 (1H, dd, *J* = 16.1, 1.2 Hz, CHC*H*C(N)), 6.10 (1H, dd, *J* = 16.1, 6.1 Hz, C*H*CHC(N)), 4.52 – 4.44 (1H, m, C*H*OH), 3.91 (3H, s, OCH_3), 2.92 (1H, dd, *J* = 13.5, 4.9 Hz, PhC$H_a$$H_b$), 2.84 (1H, dd, *J* = 13.5, 8.2 Hz, PhH$_a$$H_b$), 1.95 (3H, s, CC$H_3$), 1.88 (1H, d, *J* = 3.8 Hz, O*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) (Diastereoisomer A) δ_C: 154.9 (*C*(N)), 137.4 (C_{Ar}), 136.3 (*C*HCHC(N)), 129.5, 128.6 (2 × HC_{Ar}), 127.8 (CH*C*HC(N)), 126.7 (HC_{Ar}), 73.0 (C*H*OH), 61.8 (OCH_3), 43.9 (Ph*C*H_2), 10.1 (*C*H_3). **^{1}H NMR** (400 MHz, $CDCl_3$) (Diastereoisomer B) δ_H: 7.40 – 7.20 (5H, m, 5 × HC_{Ar}), 7.00 (1H, dd, *J* = 16.3, 1.4 Hz, CHC*H*C(N)), 6.20 (1H, dd, *J* = 16.3, 5.9 Hz, C*H*CHC(N)), 4.52 – 4.44 (1H, m, C*H*OH), 3.87 (3H, s, OCH_3), 2.94 (1H, dd, *J* = 13.6, 4.9 Hz, PhC$H_a$$H_b$), 2.84 (1H, dd, *J* = 13.6, 8.3 Hz, PhCH$_a$$H_b$), 1.99 (3H, s, CC$H_3$), 1.90 (1H, d, *J* = 4.0 Hz, O*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) (Diastereoisomer B) δ_C: 151.8 (*C*(N)), 140.2 (*C*HCHC(N)), 137.4 (C_{Ar}), 129.5, 128.6, 126.7 (3 × HC_{Ar}), 119.3 (CH*C*HC(N)), 72.9 (*C*HOH), 61.5 (OCH$_3$), 43.8 (Ph*C*H_2), 16.9 (CCH$_3$).

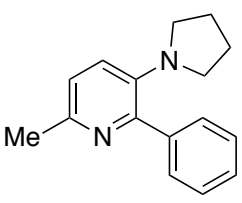
5-(Methoxyimino)-1-phenylhex-3-en-2-one (464)



To a reaction flask were added hydroxy-vinyl-methyl oxime **E-1** (1.04 g, 4.73 mmol, 1.0 eq.), DCM (47 mL) and water (0.5 mL). DMP (6.02 g, 14.2 mmol, 3.0 eq.) was then added at 0 °C and the reaction was allowed to warm to RT and stirred for 3 h. The resulting mixture was filtered under vacuum and washed with water. The aqueous layer was extracted three times with DCM and the resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash-column chromatography using petrol/EtOAc (20%) as eluent, affording keto-oxime **464** (900 mg, 88%) as a light green oil and a mixture of *E* and *Z O*-methyl oxime diastereoisomers (d.r.:1.0:3.8).

IR: ν_{max} (thin film) 3029, 2938, 2820, 1686, 1661, 1607, 1496, 1325, 1248, 1046, 976, 932, 843, 703 cm^{-1}. **HRMS**: calculated for $C_{13}H_{16}NO_2$, 218.1176 $[M+H]^+$, found *m/z* 218.1170, Δ = –2.6 ppm. **^{1}H NMR** (400 MHz, C_6D_6) (***E*-464**) δ_H: 7.40 (1H, d, *J* = 16.4 Hz, C*H*CHC(N)), 7.25 – 7.06 (5H, m, 5 × *H*C_{Ar}), 6.25 (1H, d, *J* = 16.4 Hz, CHC*H*C(N)), 3.80 (3H, s, OCH_3), 3.60 (2H, s, PhCH_2), 1.64 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, C_6D_6) (***E*-464**) δ_C: 195.7 (*C*(O)), 154.0 (*C*(N)), 139.8 (*C*HCHC(N)), 134.6 (C_{Ar}), 129.5 (HC_{Ar}), 129.3 (CH*C*HC(N)), 128.6, 126.8 (2 × *H*C_{Ar}), 62.1 (O*C*H$_3$), 47.3 (Ph*C*H$_2$), 9.6 (C*C*H$_3$). **^{1}H NMR** (400 MHz, C_6D_6) (***Z*-464**) δ_H: 8.01 (1H, d, *J* = 16.5 Hz, C*H*CHC(N)), 7.25 – 7.08 (5H, m, 5 × *H*C_{Ar}), 6.15 (1H, d, *J* = 16.5 Hz, CHC*H*C(N)), 3.80 (3H, s, OCH_3), 3.56 (2H, s, PhCH_2), 1.68 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, C_6D_6); (***Z*-464**) δ_C: 196.4 (*C*(O)), 150.3 (*C*(N)), 134.3 (C_{Ar}), 131.2 (CH*C*HC(N)), 129.5 (HC_{Ar}), 128.8 (*C*HCHC(N)), 128.6, 126.9 (2 × HC_{Ar}), 61.7 (O*C*H$_3$), 47.5 (Ph*C*H$_2$), 16.1 (C*C*H$_3$).

6-Methyl-2-phenyl-3-(pyrrolidin-1-yl)pyridine (466)

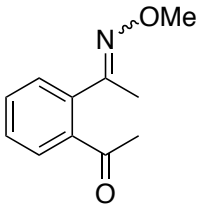


To a flame-dried vial capped with a rubber septum were added *O*-methyl oxime **464** (50 mg, 0.23 mmol, 1.0 eq.), pyrrolidine (96 µL, 1.15 mmol, 5.0 eq.), 4 M HCl solution in dioxane (9 µL, 37 µmol, 15 mol%) and 1,2-dichlorobenzene (2.3 mL). The rubber septum was replaced by an aluminium cap and the vial was flushed with argon for 5 mins and then heated at 240 °C for

3 h. The resulting mixture was washed with water and the aqueous layer was extracted three times with DCM. The resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash-column chromatography using petrol/EtOAc (20%), affording pyridine **466** (23 mg, 42%) as a light brown oil.

IR: ν_{max} (thin film) 2964, 1558, 1458, 1436, 1320, 1240, 1149, 1053, 814, 745, 696 cm^{-1}. **HRMS**: calculated for $C_{16}H_{19}N_2$, 239.1543 $[M+H]^+$, found *m/z* 239.1550, Δ = –3.2 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.67 – 7.62 (2H, m, 2 × *H*C_{Ar}), 7.40 – 7.25 (3H, m, 3 × *H*C_{Ar}), 7.10 (1H, d, *J* = 8.3 Hz, *H*C_{Ar}), 6.97 (1H, d, *J* = 8.3 Hz, *H*C_{Ar}), 2.90 – 2.84 (4H, m, N(C*H*$_2$)$_2$(CH$_2$)$_2$), 2.51 (3H, s, C*H*$_3$), 1.79 – 1.74 (4H, m, N(CH$_2$)$_2$(C*H*$_2$)$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 147.2, 147.0, 142.3, 142.1 (4 × *C*$_{Ar}$), 128.9, 128.0, 127.2, 122.3, 121.5 (5 × H*C*$_{Ar}$), 50.9 (N(*C*H$_2$)$_2$(CH$_2$)$_2$), 25.3 (N(CH$_2$)$_2$(*C*H$_2$)$_2$), 23.4 (*C*H$_3$).

1-(2-(1-(Methoxyimino)ethyl)phenyl)ethan-1-one (469)

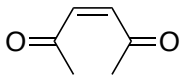


To a reaction flask were added 1,2-diacetylbenzene (100 mg, 0.61 mmol, 1.05 eq.), methoxyamine hydrochloride (48 mg, 0.57 mmol, 1.0 eq.), sodium acetate trihydrate (93 mg, 0.68 mmol, 1.2 eq.), ethanol (4.4 mL) and water (0.5 mL). The reaction was stirred at room temperature for 1 hour and then the resulting mixture was washed with water. The aqueous layer was extracted three times with DCM and the resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash-column chromatography using petrol/EtOAc (20%) as eluent, affording the keto-oxime **469** (89 mg, 81%) as a light pink oil and a mixture of *E* and *Z O*-methyl oxime diastereoisomers (d.r.: 1.0:4.5).

IR: ν_{max} (thin film) 2937, 1687, 1433, 1355, 1253, 1043, 956, 891, 761 cm^{-1}. **HRMS**: calculated for $C_{11}H_{13}NO_2Na$, 214.0838 $[M+Na]^+$, found *m/z* 214.0842, Δ = –1.8 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) (diastereoisomer A) δ_H: 7.58 – 7.37 (4H, m, 4 × *H*C_{Ar}), 3.94 (3H, s, OC*H*$_3$), 2.47 (3H, s, C*H*$_3$C(O)), 2.19 (3H, s, C*H*$_3$C(N)). **^{13}C NMR** (101 MHz, $CDCl_3$) (diastereoisomer A) δ_C: 202.0 (*C*(O)), 155.8 (*C*(N)), 139.6, 136.1 (2 × *C*$_{Ar}$), 130.9, 128.7, 128.6, 128.2 (4 × H*C*$_{Ar}$), 61.8 (O*C*H$_3$), 29.7 (*C*H$_3$C(O)), 15.3 (*C*H$_3$C(N)). **^{1}H NMR** (400 MHz, $CDCl_3$) (diastereoisomer B) δ_H: 7.70 (1H, dd, *J* = 7.7, 0.9 Hz, *H*C_{Ar}), 7.58 – 7.37 (2H, m, 2 × *H*C_{Ar}), 7.17 (1H, dd, *J* = 7.6,

0.8 Hz, *H*C_{Ar}), 3.72 (3H, s, OC*H*$_3$), 2.54 (3H, s, C*H*$_3$C(O)), 2.23 (3H, s, C*H*$_3$C(N)). **^{13}C NMR** (101 MHz, $CDCl_3$) (diastereoisomer B) δ_C: 199.3 (*C*(O), 155.7 (*C*(N)), 137.4, 134.9 (2 × C_{Ar}), 131.7, 128.3, 128.0, 127.3 (4 × *H*C_{Ar}), 61.3 (O*C*H$_3$), 27.6 (*C*H$_3$C(O)), 21.7 (*C*H$_3$C(N)).

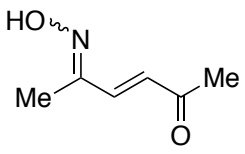
Hex-3-ene-2,5-dione (472)



To a reaction flask were added 2,5-dimethylfuran (6.50 mL, 61.1 mmol, 1.0 eq.) and a 2:1 mixture of acetone/water (75 mL). The mixture was cooled to –20 °C and bromine (9.76 g, 61.1 mmol, 1.0 eq.) was added dropwise under vigorous stirring for 40 minutes. The reaction was then allowed to warm to RT and stirred for 3 h. The resulting mixture was washed with a saturated solution of $NaHCO_{3(aq.)}$ (80 mL) and the aqueous layer was extracted three times with Et_2O. The resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash-column chromatography using petrol/EtOAc (40%), affording diketone **472** (3.75 g, 55%) as a brown solid.

m.p.: 73 – 75 °C. **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H: 6.79 (2H, s, 2 × C*H*C(O)), 2.38 (6H, s, 2 × C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 198.5 (*C*(O)), 137.9 (*C*HC(O)), 28.0 (*C*H$_3$). Spectroscopic data and m.p. are consistent with those previously reported.[267,268]

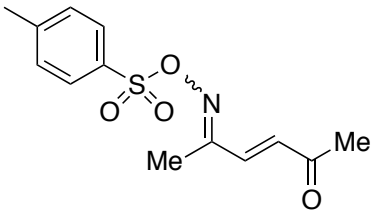
5-(Hydroxyimino)hex-3-en-2-one (473)



To a reaction flask were added hex-3-ene-2,5-dione **472** (580 mg, 5.17 mmol, 1.0 eq.), hydroxylamine hydrochloride (359 mg, 5.17 mmol, 1.0 eq.), sodium acetate trihydrate (774 mg, 5.69 mmol, 1.1 eq.), ethanol (37 mL) and water (4.4 mL). The reaction was heated to 60 °C for 18 h and then allowed to cool to RT. The resulting mixture was washed with water and the aqueous layer was extracted three times with DCM. The resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash-column chromatography using petrol/EtOAc (40%) as eluent, affording the keto-oxime **473** (329 mg, 50%) as a pale yellow solid and a mixture of *E* and *Z* oxime diastereoisomers (d.r.: 1.0:2.2).

^{1}H NMR (400 MHz, $CDCl_3$) (diastereoisomer A) δ_H: 9.74 (1H, br. s, O*H*), 7.18 (1H, d, *J* = 16.6 Hz, CH_a), 6.44 (1H, d, *J* = 16.6 Hz, CH_b), 2.37 (3H, s, CH_3C(O)), 2.07 (3H, s, CH_3C(N)). **^{13}C NMR** (101 MHz, $CDCl_3$) (diastereoisomer A) δ_C: 198.8 (*C*(O)), 155.7 (*C*(N)), 140.6 (*C*H_a), 131.3 (*C*H_b), 27.2 (*C*H_3C(O)), 9.7 (*C*H_3C(N)). **^{1}H NMR** (400 MHz, $CDCl_3$) (diastereoisomer B) δ_H: 9.74 (1H, br. s, O*H*), 7.85 (1H, d, *J* = 16.8 Hz, CH_a), 6.40 (1H, d, *J* = 16.8 Hz, CH_b), 2.41 (3H, s, CH_3C(O)), 2.09 (3H, s, CH_3C(N)). **^{13}C NMR** (101 MHz, $CDCl_3$) (diastereoisomer B) δ_C: 199.6 (*C*(O)), 152.1 (*C*(N)), 133.5 (*C*H_a), 129.3 (*C*H_b), 27.1 (CH_3C(O)), 16.7 (CH_3C(N)). Spectroscopic data are consistent with those previously reported.[269]

5((Tosyloxy)imino)hex-3-en-2-one (475)

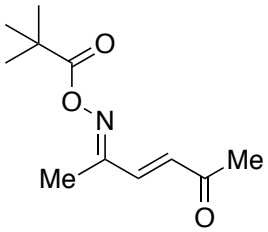


To a dry reaction flask were added 5-(hydroxyimino)hex-3-en-2-one **473** (120 mg, 0.94 mmol, 1.0 eq.), DMAP (10 mg, 82 μmol, 9 mol%), triethylamine (0.37 mL, 2.7 mmol, 2.8 eq.) and dry DCM (20 mL). Tosyl chloride (161 μL, 1.18 mmol, 1.25 eq.) was then slowly added at 0 °C and the mixture was stirred at RT for 3 h. The reaction was quenched with saturated $NaHCO_{3(aq.)}$ (20 mL) and the aqueous phase was extracted three times with DCM. The resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash-column chromatography using petrol/EtOAc (20%) as eluent, affording *O*-tosyloxime **475** (235 mg, 94%) as a light brown oil and a mixture of *E* and *Z O*-tosyloxime diastereoisomers (d.r.: 1.0:2.7).

IR: ν_{max} (thin film) 2925, 1700, 1680, 1371, 1308, 1253, 1191, 1177, 733, 665 cm^{-1}. **HRMS**: calculated for $C_{13}H_{15}NO_4Na$, 304.0614 $[M+Na]^+$, found *m/z* 304.0622, Δ = –2.6 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) (diastereoisomer A) δ_H: 7.92 – 7.86 (2H, m, 2 × *H*C$_{Ar}$), 7.40 – 7.33 (2H, m, 2 × *H*C$_{Ar}$), 7.03 (1H, d, *J* = 16.6 Hz, C*H*C(O)), 6.51 (1H, d, *J* = 16.6 Hz, C*H*C(N)), 2.46 (3H, s, CH_3Ph), 2.33 (3H, s, CH_3C(O)), 2.12 (3H, s, CH_3C(N)). **^{13}C NMR** (101 MHz, $CDCl_3$) (diastereoisomer A) δ_C: 197.4 (*C*(O)), 162.1 (*C*(N)), 145.5 (*C*$_{Ar}$), 137.3 (*C*HC(O)), 135.0 (*C*HC(N)), 129.8 (H*C*$_{Ar}$), 129.7 (*C*$_{Ar}$), 129.0 (H*C*$_{Ar}$), 27.5 (*C*H_3C(O)), 21.8 (*C*H_3Ph), 11.7 (*C*H_3C(N)). **^{1}H NMR** (400 MHz, $CDCl_3$) (diastereoisomer B) δ_H: 7.92 – 7.86 (2H, m, 2 × *H*C$_{Ar}$), 7.55 (1H, d, *J* = 16.6 Hz, C*H*C(O)), 7.40 – 7.33 (2H, m, 2 × *H*C$_{Ar}$), 6.43 (1H, d, *J* = 16.6 Hz,

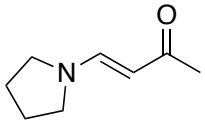
C*H*C(N)), 2.46 (3H, s, C*H*$_3$Ph), 2.39 (3H, s, C*H*$_3$C(O)), 2.10 (3H, s, C*H*$_3$C(N)). **^{13}C NMR** (101 MHz, $CDCl_3$) (diastereoisomer B) δ_C: 198.1 (*C*(O)), 159.1 (*C*(N)), 145.5 (C_{Ar}), 136.8 (*C*HC(N)), 129.8 (HC_{Ar}), 129.7 (C_{Ar}), 129.0 (HC_{Ar}), 128.1 (*C*HC(O)), 27.5 (C*H*$_3$C(O)), 21.8 (*C*H$_3$Ph), 11.9 (*C*H$_3$C(N)).

5-((Pivaloyloxy)imino)hex-3-en-2-one (476)



To a dry reaction flask were added 5-(hydroxyimino)hex-3-en-2-one **473** (300 mg, 2.67 mmol, 1.0 eq.), DMAP (26 mg, 0.21 mmol, 8 mol%), triethylamine (0.93 mL, 6.7 mmol, 2.5 eq.) and DCM (38 mL). Pivaloyl chloride (0.49 mL, 4.00 mmol, 1.5 eq.) was then added dropwise at 0 °C over 15 minutes. The mixture was stirred at room temperature for 1 hour and then quenched with a saturated solution of $NaHCO_{3(aq.)}$ (20 mL). The aqueous phase was extracted three times with DCM and the resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash-column chromatography using petrol/EtOAc (40%) as eluent, affording keto-oxime **476** (139 mg, 25%) as a light yellow solid. **m.p.**: 44 – 46 °C**. IR**: ν_{max} (thin film) 2975, 1765, 1671, 1368, 1245, 1088, 1022, 980, 924, 909, 790, 755 cm^{-1}. **HRMS**: calculated for $C_{11}H_{17}NO_3Na$, 234.1101 $[M+Na]^+$, found *m/z* 234.1102, Δ = –0.6 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.32 (1H, d, *J* = 16.7 Hz, C*H*C(O)), 6.55 (1H, d, *J* = 16.7 Hz, C*H*C(N)), 2.38 (3H, s, C*H*$_3$C(O)), 2.19 (3H, s, C*H*$_3$C(N)), 1.33 (9H, s, (C*H*$_3$)$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 198.0 (*C*(O)), 174.6 (*C*O$_2$), 161.5 (*C*(N)), 139.0 (*C*HC(O)), 134.9 (*C*HC(N)), 38.8 (*C*(CH$_3$)$_3$), 27.1 (C(*C*H$_3$)$_3$), 26.8 (*C*H$_3$C(O)), 11.7 (*C*H$_3$C(N)).

4-(pyrrolidin-1-yl)but-3-en-2-one (478)

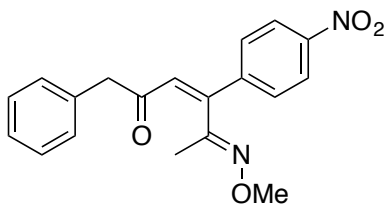


To a flame-dried vial capped with a rubber septum were added *O*-tosyl oxime **475** (90 mg, 0.32 mmol, 1.0 eq.), pyrrolidine (131 µL, 1.60 mmol, 5.0 eq.), 4 M HCl solution in dioxane (12 µL, 48 µmol, 15 mol%) and DCM (3.2 mL). The rubber septum was replaced by an aluminium cap and the vial was flushed with argon for 5 mins and stirred at RT for 1 h. The resulting mixture was washed with water and the aqueous layer was extracted three times with DCM. The resulting organic phases were

combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash-column chromatography using acetone as eluent, affording ketone **478** (38 mg, 85%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.64 (1H, d, J = 12.7 Hz, CH_a), 4.98 (1H, d, J = 12.8 Hz, CH_b), 3.50 – 3.03 (4H, m, 2 × CH_2), 2.07 (3H, s, CH_3C(O)), 2.02 – 1.81 (4H, m, 2 × CH_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 195.1 (*C*(O)), 148.5 (*C*H), 97.4 (*C*H, br.), 52.1 (*C*H_2), 46.8 (*C*H_2), 25.3 (*C*H_3). Spectroscopic data are consistent with those previously reported.[270]

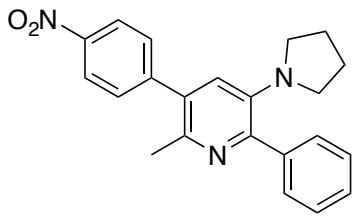
5-(Methoxyimino)-4-(4-nitrophenyl)-1-phenylhex-3-en-2-one (486)



To a flame-dried vial capped with a rubber septum were added *O*-methyl oxime **464** (300 mg, 1.38 mmol), $Pd_2(dba)_3$ (63 mg, 69 μmol, 5 mol%), P(*t*-Bu)$_3$·HBF_4 (80 mg, 0.28 mmol, 20 mol%), *N*-cyclohexyl-*N*-methylcyclohexanamine (0.88 mL, 4.14 mmol, 3.0 eq.) and dry toluene (14 mL). The rubber septum was replaced by an aluminium cap and the vial was purged with argon for 5 min. The reaction was then stirred at 85 °C for 20 h and the resulting mixture was washed with water after cooling to RT. The aqueous layer was extracted three times with DCM and the resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash-column chromatography using petrol/EtOAc (20%) as eluent, affording an impure material that was purified again by flash-column chromatography using DCM as eluent, affording keto-oxime **486** (66 mg, 14%) as an orange oil.

IR: ν_{max} (thin film) 1692, 1593, 1517, 1343, 1046, 849, 732, 696 cm^{-1}. **HRMS**: calculated for $C_{19}H_{19}N_2O_4$, 339.1339 $[M+H]^+$, found *m/z* 339.1335, Δ = –1.33 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.23 – 8.19 (2H, m, 2 × *H*C$_{Ar}$), 7.59 – 7.54 (2H, m, 2 × *H*C$_{Ar}$), 7.40 – 7.22 (5H, m, 5 × *H*C$_{Ar}$), 6.64 (1H, s, C*H*C(O)), 3.93 (3H, s, OCH_3), 3.89 (2H, s, PhCH_2), 1.98 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 197.1 (*C*(O)), 154.7 (*C*(N)), 148.4, 146.7 (2 × *C*$_{Ar}$), 143.2 (*C*C(N)), 133.6 (*C*$_{Ar}$), 129.6 (H*C*$_{Ar}$), 129.0 (*C*HC(O)), 128.8, 128.5, 127.3, 124.0 (4 × H*C*$_{Ar}$), 62.1 (O*C*H$_3$), 50.7 (Ph*C*H$_2$), 15.6 (C*C*H$_3$).

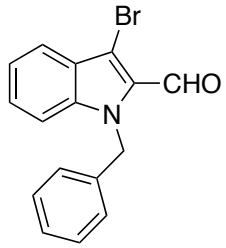
2-Methyl-3-(4-nitrophenyl)-6-phenyl-5-(pyrrolidin-1-yl)pyridine (487)



To a flame-dried vial capped with a rubber septum were added *O*-methyl oxime **486** (60 mg, 0.18 mmol, 1.0 eq.), pyrrolidine (74 μL, 0.89 mmol, 5.0 eq.), 4 M HCl solution in dioxane (7 μL, 27 μmol, 15 mol%) and dry 1,2-dichlorobenzene (1.8 mL). The rubber septum was replaced by an aluminium cap and the reaction was stirred at 90 °C for 5 h. The resulting mixture was washed with water and the aqueous layer was extracted three times with DCM. The resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash-column chromatography using petrol/EtOAc (20%) as eluent, affording pyridine **487** (32 mg, 50%) as an orange solid.

m.p.: 208 – 210 °C. **IR**: ν_{max} (thin film) 2922, 1596, 1514, 1439, 1338, 1246, 1167, 1027, 896, 867, 739, 697 cm^{-1}. **HRMS**: calculated for $C_{22}H_{22}N_3O_2$, 360.1706 $[M+H]^+$, found *m/z* 360.1702, Δ = –1.17 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.34 – 8.30 (2H, m, 2 × HC_{Ar}), 7.72 – 7.66 (2H, m, 2 × HC_{Ar}), 7.62 – 7.55 (2H, m, 2 × HC_{Ar}), 7.45 – 7.38 (2H, m, 2 × HC_{Ar}), 7.36 – 7.30 (1H, m, HC_{Ar}), 7.00 (1H, s, CC*H*C), 3.00 – 2.90 (4H, m, N(CH_2)$_2$(CH_2)$_2$), 2.45 (3H, s, CH_3), 1.85 – 1.75 (4H, m, N(CH_2)$_2$(CH_2)$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 147.7, 147.1, 146.9, 143.6, 142.3, 141.7, 132.9 (7 × C_{Ar}), 130.1, 128.8, 128.1, 127.6, 123.6 (5 × HC_{Ar}), 122.5 (C*C*HC), 51.0 (N(CH_2)$_2$(CH_2)$_2$), 25.4 (N(CH_2)$_2$(CH_2)$_2$), 22.3 (CH_3).

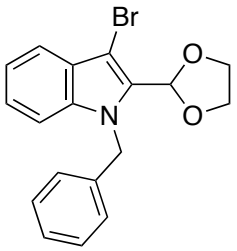
1-Benzyl-3-bromo-1*H*-indole-2-carbaldehyde (514)



To a reaction flask were added 3-bromo-1*H*-indole-2-carbaldehyde **518** (200 mg, 0.89 mmol, 1.0 eq.), benzyltriethylammonium chloride (20 mg, 89 μmol, 10 mol%), benzyl bromide (117 μL, 0.98 mmol, 1.1 eq.), 6.5 M NaOH (0.72 mL) and DMSO (1.5 mL). The reaction was stirred at RT for 1 h and then mixed with distilled water. The mixture was extracted with DCM three times. The organic extracts were combined and washed with distilled water six times. The resulting organic fraction was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography using pentane/EtOAc (5%) as eluent to afford bromo-indole **514** (260 mg, 93%) as a yellow solid.

m.p.: 84 – 86 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 10.11 (1H, s, C*H*O), 7.70 (1H, d, *J* = 8.1 Hz, *H*C_{Ar}), 7.43 – 7.32 (2H, m, 2 × *H*C_{Ar}), 7.26 – 7.17 (4H, m, 4 × *H*C_{Ar}), 7.10 – 7.04 (2H, m, 2 × *H*C_{Ar}), 5.79 (2H, s, PhC*H*$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 182.4 (*C*HO), 139.3, 137.4, 129.6 (3 × *C*$_{Ar}$), 128.8, 128.5, 127.6, 126.7 (4 × H*C*$_{Ar}$), 126.5 (*C*$_{Ar}$), 122.0, 121.8, 111.3 (3 × H*C*$_{Ar}$), 107.2 (*C*$_{Ar}$), 48.1 (Ph*C*H$_2$). Analytical data are consistent with those previously reported.[272]

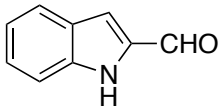
1-Benzyl-3-bromo-2-(1,3-dioxolan-2-yl)-1*H*-indole (515).



To a dry reaction flask connected to a Dean–Stark apparatus were added 1-benzyl-3-bromo-1*H*-indole-2-carbaldehyde **514** (330 mg, 1.05 mmol), ethylene glycol (116 μL, 2.09 mmol, 2.0 eq.), *p*-toluenesulfonic acid monohydrate (20 mg, 105 μmol, 10 mol%) and toluene (10 mL). The resulting mixture was heated at reflux for 14 h and then cooled to RT and quenched with saturated $NaHCO_{3(aq.)}$. The layers were separated and the aqueous layer was extracted twice with EtOAc, the organic extracts combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography using petroleum ether/EtOAc (10%) as eluent, affording bromo-indole **515** (350 mg, 93%) as a yellow solid.

m.p.: 64 – 67 °C. **IR**: ν_{max} (thin film) 3315, 1664, 1611, 1454, 1349, 1249, 1119, 861, 741, 722 cm^{-1}. **HRMS**: calculated for $C_{18}H_{17}{}^{79}BrNO_2$, 358.0437 $[M+H]^+$, found *m/z* 358.0438, Δ = 0.20 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.62 – 7.55 (1H, m, *H*C_{Ar}), 7.30 – 7.00 (8H, m, 8 × *H*C_{Ar}), 6.21 (1H, s, C*H*(OR)$_2$), 5.46 (2H, s, PhC*H*$_2$R), 4.06 – 3.86 (4H, m, (OC*H*$_2$)$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 137.9, 137.4, 129.3 (3 × *C*$_{Ar}$), 128.6 (H*C*$_{Ar}$), 127.3 (H*C*$_{Ar}$), 126.7 (C$_{Ar}$), 126.3, 124.3, 120.7, 120.0, 110.6 (5 × H*C*$_{Ar}$), 98.7 (*C*H(OR)$_2$), 94.5 (*C*(3)), 65.2 ((O*C*H$_2$)$_2$), 48.5 (Ph*C*H$_2$).

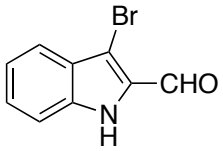
1*H*-Indole-2-carbaldehyde (517).



To a dry reaction flask were added 1*H*-indole-2-carboxylic acid 98% **516** (4.00 g, 24.3 mmol, 1.0 eq.) and dry THF (40 mL). $LiAlH_4$ (1.92 g, 50.6 mmol, 2.08 eq.) was added over 1 h at 0 °C and the mixture was stirred at RT for 30 mins. The reaction was then slowly and carefully quenched with distilled water at 0 °C. The resulting slurry was filtered and extracted three times with DCM. The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was transferred to a flask containing MeCN (100 mL) and MnO_2 (11.5 g, 132 mmol, 5.4 eq.) and was stirred at RT for 16 h. The mixture was filtered and the solvent evaporated. The crude material was purified by flash column chromatography using pentane/EtOAc (40%) as eluent, affording aldehyde **517** (1.61 g, 46%) as a yellow solid.

m.p.: 133 – 136 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 9.87 (1H, s, C*H*O), 9.60 (1H, s, N*H*), 7.76 (1H, d, J = 8.1 Hz, *H*C_{Ar}), 7.50 (1H, d, J = 8.4 Hz, *H*C_{Ar}), 7.41 (1H, t, J = 7.6 Hz, *H*C_{Ar}), 7.30 (1H, s, C*H*CCHO), 7.19 (1H, t, J = 7.5 Hz, *H*C_{Ar}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 182.4 (*C*HO), 138.3, 136.1 (2 × C_{Ar}), 127.5 (HC_{Ar}), 127.4 (C_{Ar}), 123.5, 121.4 (2 × HC_{Ar}), 115.2 (*C*HCCHO), 112.7 (HC_{Ar}). Analytical data are consistent with those previously reported.[271]

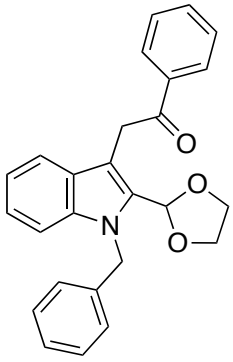
3-Bromo-1*H*-indole-2-carbaldehyde (518)



To a dry reaction flask were added 1*H*-indole-2-carbaldehyde **517** (200 mg, 1.38 mmol, 1.0 eq.) and dry DMF (1.0 mL). A solution of *N*-bromosuccinimide (269 mg, 1.51 mmol, 1.1 eq.) in DMF (1.0 mL) was then added dropwise at 0 °C. The mixture was stirred at RT for 2 h then distilled water (23 mL) was added, forming a precipitate that was filtered, washed with water and dried under vacuum, affording 3-bromoindole **518** as an off-white solid (296 mg, 96%).

m.p.: 187 – 189 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 9.99 (1H, s, C*H*O), 9.53 (1H, s, N*H*), 7.71 (1H, d, J = 8.2 Hz, *H*C_{Ar}), 7.48 – 7.40 (2H, m, 2 × *H*C_{Ar}), 7.29 – 7.22 (1H, m, *H*C_{Ar}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 181.4 (*C*HO), 137.0, 131.6 (2 × C_{Ar}), 128.6 (*H*C_{Ar}), 127.3 (C_{Ar}), 122.1, 121.6, 112.9 (3 × HC_{Ar}), 104.5 (C_{Ar}). Spectroscopic data are consistent with those previously reported.[272]

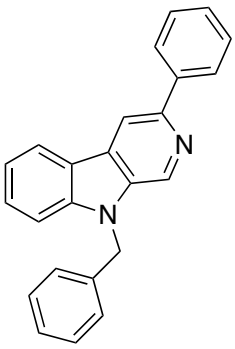
2-(1-Benzyl-2-(1,3-dioxolan-2-yl)-1*H*-indol-3-yl)-1-phenylethan-1-one (520).



Acetophenone (36 μL, 0.31 mmol, 2.0 eq.) was subjected to general procedure A and purified by flash column chromatography using petroleum ether/EtOAc (20%) as eluent, affording keto-indole **520** (57 mg, 93%) as a brown solid.

m.p.: 100 – 102 °C. **IR**: ν_{max} (thin film) 3368, 3060, 2925, 1613, 1533, 1349, 1213, 1182, 1082, 745 cm^{-1}. **HRMS**: calculated for $C_{26}H_{24}NO_3$, 398.1751 $[M+H]^+$, found *m/z* 398.1750, Δ = –0.30 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.15 – 8.10 (2H, m, 2 × *H*C_{Ar}), 7.63 – 7.54 (2H, m, 2 × *H*C_{Ar}), 7.48 (2H, t, *J* = 7.4 Hz, 2 × *H*C_{Ar}), 7.33 – 7.03 (9H, m, 9 × *H*C_{Ar}), 6.13 (1H, s, C*H*$(OR)_2$), 5.54 (1H, s, PhC*H*$_2$), 4.65 (2H, s, C*H*$_2$C(O)), 4.05 – 3.90 (4H, m, (OC*H*$_2)_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 196.7 (C(O)), 137.1, 136.4, 135.9 (3 × *C*$_{Ar}$), 131.8 (H*C*$_{Ar}$), 129.8 (*C*$_{Ar}$), 127.5, 127.5, 127.4 (3 × H*C*$_{Ar}$), 126.6 (*C*$_{Ar}$), 126.0, 125.0, 121.9, 118.7, 118.2, 109.0 (6 × H*C*$_{Ar}$), 108.2 (*C*$_{Ar}$), 97.9 (*C*H$(OR)_2$), 63.9 ((O*C*H$_2)_2$), 46.7 (R*C*H$_2$Ph), 34.0 (*C*H$_2$C(O)).

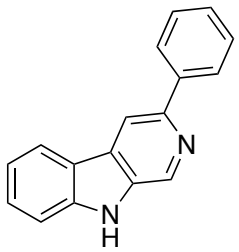
9-Benzyl-3-phenyl-9*H*-pyrido[3,4-b]indole (521)



Indole **520** (1.65 g, 4.15 mmol, 1.0 eq.) was subjected to general procedure B and purified by flash column chromatography using petroleum ether/EtOAc (10%) as eluent, affording *β*-carboline **521** (1.30 g, 94%) as a light brown solid.

m.p.: 143 – 146 °C. **IR**: ν_{max} (thin film) 3059, 3030, 1460, 733, 694 cm^{-1}. **HRMS**: calculated for $C_{24}H_{19}N_2$, 335.1543 $[M+H]^+$, found *m/z* 335.1535, Δ = –2.3 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.82 (1H, s, C(1)), 8.33 (1H, s, C(4)), 8.13 (1H, d, *J* = 7.8 Hz, *H*C_{Ar}), 8.08 (2H, d, *J* = 7.5 Hz, *H*C_{Ar}), 7.55 – 7.43 (3H, m, 3 × *H*C_{Ar}), 7.40 – 7.31 (2H, m, 2 × *H*C_{Ar}), 7.30 – 7.15 (4H, m, 4 × *H*C_{Ar}), 7.14 – 7.05 (2H, m, 2 × *H*C_{Ar}), 5.41 (2H, s, PhC*H*$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 147.9, 141.9, 140.6, 136.5, 136.0 (5 × *C*$_{Ar}$), 131.9 (H*C*(1)), 129.8 (*C*$_{Ar}$), 129.0, 128.8, 128.6, 127.9, 127.8, 126.9, 126.7, 122.0 (8 × H*C*$_{Ar}$), 121.7 (*C*$_{Ar}$), 120.0, 111.4, 109.9 (3 × H*C*$_{Ar}$), 47.0 (Ph*C*H$_2$Ar). Spectroscopic data are consistent with those previously reported.[273]

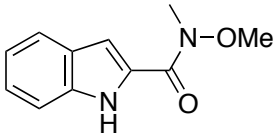
3-Phenyl-9*H*-pyrido[3,4-b]indole (524).



To a dry reaction flask were added freshly sublimed $AlCl_3$ (287 mg, 2.15 mmol, 6.0 eq.) and toluene (1.8 mL). A solution of *β*-carboline **521** (120 mg, 359 μmol) in toluene (1.8 mL) was added at 0 °C over 10 mins and stirred at RT for 2 h. The resulting mixture was quenched with saturated $NaHCO_3$ and the aqueous layer extracted twice with EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solids were purified by flash column chromatography using $CHCl_3$/MeOH (5%) as eluent, affording *β*-carboline **524** (71 mg, 88%) as a white solid.

m.p.: 226 - 229 °C. **IR**: ν_{max} (thin film) 3125, 3018, 2923, 2755, 1137, 738, 696 cm^{-1}. **HRMS**: calculated for $C_{17}H_{13}N_2$, 245.1073 $[M+H]^+$, found *m/z* 245.1073, Δ = –0.10 ppm. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 11.69 (1H, s, N*H*), 9.00 (1H, s, *H*C(1)), 8.77 (1H, s, *H*C(4)), 8.36 (1H, d, *J* = 7.9 Hz, *H*C_{Ar}), 8.22 (2H, ddd, *J* = 8.3, 1.2, 1.0 Hz, 2 × *H*C_{Ar}), 7.66 – 7.60 (1H, m, *H*C_{Ar}), 7.58 (1H, dd, *J* = 6.9, 1.2 Hz, *H*C_{Ar}), 7.54 – 7.48 (2H, m, 2 × *H*C_{Ar}), 7.41 – 7.35 (1H, m, *H*C_{Ar}), 7.28 (1H, ddd, *J* = 8.0, 6.9, 1.0 Hz, *H*C_{Ar}). **^{13}C NMR** (101 MHz, DMSO-d_6) δ_C: 146.0, 141.6, 140.6, 135.9 (4 × C_{Ar}) , 134.0 (H*C*(1)), 129.3 (C_{Ar}), 129.1, 128.7, 127.9, 126.6 122.5, (5 × HC_{Ar}), 121.5 (C_{Ar}), 119.8, 112.5 (2 × HC_{Ar}), 111.6 (H*C*(4)). ^{1}H NMR data are consistent with those previously reported.[274]

***N*-Methoxy-*N*-methyl-1*H*-indole-2-carboxamide (525)**

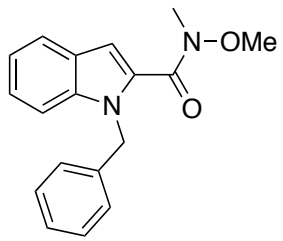


To a dry reaction flask were added 1*H*-indole-2-carboxylic acid **516** (5.00 g, 30.1 mmol, 1.0 eq.), *N*,*O*-dimethylhydroxylamine hydrochloride (3.23 g, 33.1 mmol, 1.1 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (11.5 g, 60.2 mmol, 2.0 eq.), hydroxybenzotriazole (8.13 g, 60.2 mmol, 2.0 eq.) and dry THF (250 mL). The reaction was cooled to 0 °C and then dry triethylamine (14.7 mL, 105 mmol, 3.5 eq.) was added dropwise. The resulting mixture was stirred at RT for 20 h. The resulting mixture was washed with distilled water and then extracted three times with DCM. The organic extracts were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was purified by flash

column chromatography, using pentane/EtOAc (40%) as eluent to afford indole **525** (5.6 g, 91%) as a white solid.

m.p.: 132 – 135 °C. **IR**: ν_{max} (thin film) 3271, 1604, 1525, 1344, 1264, 731, 703 cm^{-1}. **HRMS:** calculated for $C_{11}H_{13}N_2O_2$, 205.0971 $[M+H]^+$, found *m/z* 205.0973, Δ = 0.70 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 9.49 (1H, s, N*H*), 7.71 (1H, dd, *J* = 8.1, 0.9 Hz, *H*C_{Ar}), 7.45 (1H, dd, *J* = 8.3, 0.9 Hz, *H*C_{Ar}), 7.31 (1H, ddd, *J* = 8.3, 7.0, 1.1 Hz, *H*C_{Ar}), 7.25 (1H, dd, *J* = 2.1, 1.0 Hz, C*H*CC(O)), 7.14 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, *H*C_{Ar}), 3.86 (3H, s, OCH_3), 3.45 (3H, s, NCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 161.8 (*C*(O)), 135.9, 128.4, 128.1 (3 × C_{Ar}), 125.0, 122.7, 120.6, 111.9, 108.1 (5 × HC_{Ar}), 61.5 (OCH_3), 33.4 (NCH_3). m.p. and spectroscopic data are consistent with those previously reported.[275]

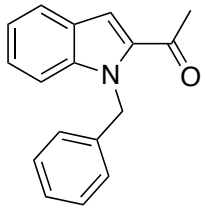
1-Benzyl-*N*-methoxy-*N*-methyl-1*H*-indole-2-carboxamide (526).



To a dry reaction flask equipped with a reflux condenser were added indole 525**6** (12.0 g, 58.7 mmol, 1.0 eq.) and dry THF (590 mL). NaH (60% in mineral oil, 2.82 g, 70.5 mmol, 1.2 eq.) was added slowly at 0 °C over 10 mins and the resulting mixture was heated at reflux for 30 mins. After cooling to RT, benzyl bromide (8.4 mL, 70 mmol, 1.2 eq.) was added and the solution was heated at reflux for 2 h and then cooled to 0 °C, when it was quenched using $NH_4Cl_{(aq.)}$. The aqueous layer was extracted twice with EtOAc and the organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography using petroleum ether/EtOAc (20%) as eluent, affording *N*-protected indole **526** (17.1 g, 99%) as a white solid.

m.p.: 34 – 37 °C. **IR**: ν_{max} (thin film) 3060, 3030, 2931, 1632, 1453, 739 cm^{-1}. **HRMS:** calculated for $C_{18}H_{19}N_2O_2$, 295.1441 $[M+H]^+$, found *m/z* 295.1440, Δ = –0.41 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.79 – 7.40 (1H, m, *H*C_{Ar}), 7.44 (1H, dd, *J* = 8.4, 0.8 Hz, *H*C_{Ar}), 7.33 (1H, ddd, *J* = 8.3, 7.0, 1.2 Hz, *H*C_{Ar}), 7.31 – 7.19 (5H, m, 6 × *H*C_{Ar}), 7.13 (2H, d, *J* = 6.6 Hz, 2 × *H*C_{Ar}), 5.77 (2H, s, PhCH_2), 3.53 (3H, s, OCH_3), 3.34 (3H, s, NCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 162.8 (*C*(O)), 138.6, 138.4, 129.6 (3 × C_{Ar}), 128.6, 127.3, 126.8 (3 × HC_{Ar}), 126.7 (C_{Ar}), 124.4, 122.3, 120.6, 110.6, 108.1 (5 × HC_{Ar}), 61.2 (OCH_3), 47.9 (CH_2Ph), 33.9 (NCH_3).

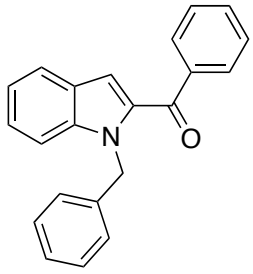
1-(1-Benzyl-1*H*-indol-2-yl)ethan-1-one (527).



To a dry reaction flask were Weinreb amide **526** (2.00 g, 6.79 mmol, 1.0 eq.) and dry THF (68 mL, 0.1 M). A 3 M solution methylmagnesium bromide (6.8 mL, 20 mmol, 3.0 eq.) was slowly added over 30 mins at –78 °C and then allowed to stir at 0 °C for 1 h. The mixture was then quenched at 0 °C with $NH_4Cl_{(aq.)}$. The aqueous layer was extracted twice with EtOAc, then the organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography using petroleum ether/EtOAc (20%) as eluent, affording indole **527** (1.68 g, 99%) as a white solid.

m.p.: 125 – 126 °C. **IR**: ν_{max} (thin film) 3061, 3031, 2924, 1657, 725 cm^{-1}. **HRMS:** calculated for $C_{17}H_{16}NO$, 250.1226 $[M+H]^+$, found *m/z* 250.1230, Δ = 1.50 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.81 – 7.77 (1H, m, *H*C_{Ar}), 7.45 – 7.36 (3H, m, 3 × *H*C_{Ar}), 7.32 – 7.20 (4H, m, 4 × *H*C_{Ar}), 7.14 – 7.08 (2H, m, 2 × *H*C_{Ar}), 5.91 (2H, s, NC*H*$_2$Ph), 2.66 (s, 3H, C(O)C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 191.3 (*C*(O)), 140.0, 138.4, 134.4 (3 × *C*$_{Ar}$), 128.5, 127.1, 126.5, 126.3 (4 × H*C*$_{Ar}$), 126.0 (*C*$_{Ar}$), 123.0, 121.1, 113.0, 111.0 (4 × H*C*$_{Ar}$), 48.2 (Ph*C*H$_2$N), 28.1 (C(O)*C*H$_3$). ^{1}H NMR data are consistent with those previously reported.[276]

(1-Benzyl-1*H*-indol-2-yl)(phenyl)methanone (**528**).

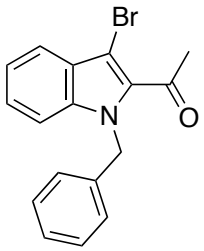


To a dry reaction flask were Weinreb amide **526** (3.00 g, 10.2 mmol, 1.0 eq.) and dry THF (100 mL, 0.1 M). A 3 M solution methylmagnesium bromide (10.2 mL, 30.3 mmol, 3.0 eq.) was slowly added over 30 mins at –78 °C and then allowed to stir at 0 °C for 1 h. The mixture was then quenched at 0 °C with $NH_4Cl_{(aq.)}$. The aqueous layer was extracted twice with EtOAc, then the organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography using petroleum ether/EtOAc (20%) as eluent, affording indole **528** (2.51 g, 79%) as a white solid.

m.p.: 107 – 110 °C. **IR**: ν_{max} (thin film) 3060, 3030, 2923, 1633, 718, 694 cm^{-1}. **HRMS**: calculated for $C_{22}H_{17}ONNa$, 334.1202 $[M+Na]^+$, found *m/z* 334.1202, Δ = –0.02 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.95 – 7.90 (2H, m, 2 × *H*C_{Ar}), 7.73 (1H, d, *J* = 8.0, *H*C_{Ar}), 7.65 – 7.58

(1H, m, HC_{Ar}), 7.54 – 7.48 (2H, m, 2 × HC_{Ar}), 7.44 (1H, dd, J = 8.5, 0.7 Hz, HC_{Ar}), 7.38 (1H, ddd, J = 8.4, 6.9, 1.1 Hz, HC_{Ar}), 7.31 – 7.18 (4H, m, 4 × HC_{Ar}), 7.18 – 7.14 (2H, m, 2 × HC_{Ar}), 7.12 (1H, d, J = 0.6 Hz, C(3)), 5.91 (2H, s, PhCH_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 188.6 (C(O)), 140.2, 139.4, 138.4, 134.7 (4 × C_{Ar}), 132.2, 129.8, 128.6, 128.2, 127.2, 126.6, 126.2 (7 × HC_{Ar}), 126.1 (C_{Ar}), 123.1,121.1,115.8, 111.1 (4 × HC_{Ar}), 48.1 (PhCH$_2$R). ^{1}H data are consistente with those previously reported.[277]

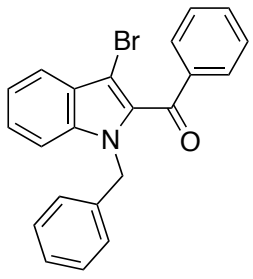
1-(1-Benzyl-3-bromo-1*H*-indol-2-yl)ethan-1-one (**529**).



Indole **527** (1.36 g, 5.45 mmol, 1.0 eq.) was subjected to general procedure C and purified by flash column chromatography using petroleum ether/EtOAc (5%) as eluent, affording indole **529** (1.66 g, 93%) as a white solid.

m.p.: 118 – 120 °C. **IR**: ν_{max} (thin film) 3061, 3032, 2921, 1651, 1450, 1348, 1321, 726 cm^{-1}. **HRMS**: calculated for $C_{17}H_{15}NOBr$, 328.0331 $[M+H]^+$, found m/z 328.0335, Δ = 0.99 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.80 – 7.74 (1H, m, HC_{Ar}), 7.43 – 7.39 (2H, m, 2 × HC_{Ar}), 7.32 – 7.22 (4H, m, 4 × HC_{Ar}), 7.08 – 7.03 (2H, m, 2 × HC_{Ar}), 5.80 (2H, s, PhCH_2N), 2.83 (3H, s, C(O)CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 192.0 (C(O)), 138.4, 138.0, 132.6 (3 × C_{Ar}), 128.6, 127.3, 127.1 (3 × HC_{Ar}), 126.8 (C_{Ar}), 126.3, 121.9, 121.8, 111.0 (4 × HC_{Ar}), 100.0 (C_{Ar}), 48.9 (PhCH$_2$N), 31.9 (C(O)CH$_3$).

(1-Benzyl-3-bromo-1*H*-indol-2-yl)(phenyl)methanone (**530**).

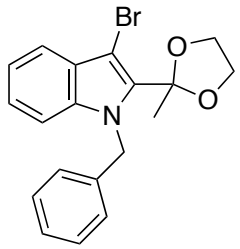


Indole **528** (1.30 g, 4.17 mmol, 1.0 eq.) was subjected to general procedure C and purified by flash column chromatography using petroleum ether/EtOAc (20%) as eluent, affording bromo-indole **530** (1.62 g, 99%) as a white solid.

m.p.: 87 – 89 °C. **IR**: ν_{max} (thin film) 3060, 3030, 1651, 1348, 1098, 954, 722, 692 cm^{-1}. **HRMS**: calculated for $C_{22}H_{17}NOBr$, 390.0488 $[M+H]^+$, found m/z 390.0496, Δ = 2.02 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.82 – 7.78 (2H, m, 2 × HC_{Ar}), 7.68 (1H, d, J = 8.0 Hz, HC_{Ar}), 7.62 – 7.56 (1H, m, HC_{Ar}), 7.46 – 7.34 (4H, m, 4 × HC_{Ar}), 7.27 (1H, ddd, J =

8.0, 6.6, 1.3 Hz, *H*C_{Ar}), 7.24 – 7.14 (3H, m, 3 × *H*C_{Ar}), 7.08 – 7.03 (2H, m, *H*C_{Ar}), 5.60 (2H, s, PhC*H*$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 189.4 (*C*(O)), 138.0, 138.0, 137.5, 133.5 (4 × *C*$_{Ar}$), 133.3, 130.2, 128.7, 128.5, 127.6 (5 × H*C*$_{Ar}$), 126.8 (C_{Ar}), 126.7, 126.2, 121.6, 121.3, 110.9 (5 × H*C*$_{Ar}$), 98.1 (*C*$_{Ar}$), 48.3 (Ph*C*H$_2$R).

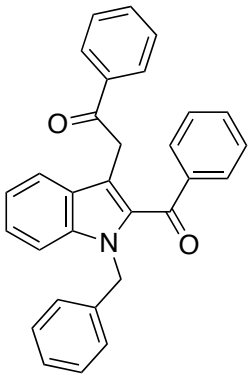
1-Benzyl-3-bromo-2-(2-methyl-1,3-dioxolan-2-yl)-1*H*-indole (531).



To a dry reaction flask connected to a Dean–Stark apparatus were added bromo-indole **529** (3.00 g, 9.14 mmol), ethylene glycol (5.1 mL, 91 mmol, 10 eq.), *p*-toluenesulfonic acid monohydrate (175 mg, 914 μmol, 10 mol%) and toluene (91 mL). The resulting mixture was heated at 120 °C for 60 h and then cooled to RT and quenched with $NaHCO_{3(aq.)}$. The aqueous layer was extracted twice with EtOAc, the organic extracts combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography using petroleum ether/$CHCl_3$ (45%), affording bromo-indole **531** (2.14 g, 63%) as a white solid.

m.p.: 89 – 90 °C. **IR**: ν_{max} (thin film) 3031, 2990, 2892, 1662, 1219, 1030 cm^{-1}. **HRMS**: calculated for $C_{19}H_{18}NO_2Br$, 372.0594 $[M+H]^+$, found *m/z* 372.0593, Δ = –0.19 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.59 – 7.53 (1H, m, *H*C_{Ar}), 7.20 – 7.05 (6H, m, 6 × *H*C_{Ar}), 7.85 – 6.79 (2H, m, 2 × *H*C_{Ar}), 5.60 (2H, s, PhC*H*$_2$), 3.95 – 3.83 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 3.65 – 3.53 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$), 1.60 (3H, s, CC*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 138.4, 137.1, 135.4 (3 × *C*$_{Ar}$), 128.6 (H*C*$_{Ar}$), 127.4 (*C*$_{Ar}$), 127.0, 125.7, 123.6, 120.7, 119.8, 110.3 (6 × H*C*$_{Ar}$), 106.4 (*C*CH$_3$), 89.6 (*C*$_{Ar}$), 64.6 (O*C*H$_2$)$_2$), 48.6 (Ph*C*H$_2$), 26.4 (C*C*H$_3$).

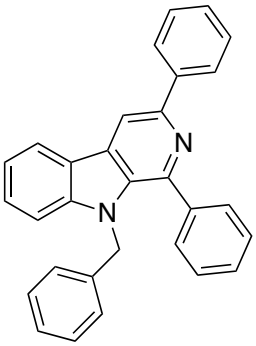
2-(2-Benzoyl-1-benzyl-1*H*-indol-3-yl)-1-phenylethan-1-one (**532**).



Indole **530** (2.48 g, 6.36 mmol, 1.0 eq.) and acetophenone (1.48 mL, 12.7 mmol, 2.0 eq.) were subjected to general procedure A, affording keto-indole **532** (1.75 g, 64%) as a yellow solid.

m.p.: 132 - 134 °C. **IR:** ν_{max} (thin film) 3059, 3030, 1689, 1637, 1449, 1345, 1226, 1212, 745, 729 cm^{-1}. **HRMS**: calculated for $C_{30}H_{23}NO_2Na$, 452.1621 $[M+Na]^+$, found *m/z* 452.1618, Δ = –0.59 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.78 (2H, ddd, *J* = 8.0, 1.3, 0.9 Hz, 2 × *H*C_{Ar}), 7.74 – 7.69 (2H, m, 2 × *H*C_{Ar}), 7.58 (1H, d, *J* = 8.0 Hz, *H*C_{Ar}), 7.54 – 7.48 (1H, m, *H*C_{Ar}), 7.43 – 7.13 (11H, m, 11 × *H*C_{Ar}), 7.05 – 7.00 (2H, m, 2 × *H*C_{Ar}), 5.59 (2H, s, PhC*H*$_2$Ar), 4.26 (2H, s, C*H*$_2$C(O)). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 196.4, 190.2 (2 × *C*(O)), 139.6, 138.8, 138.0, 136.6, 134.5 (5 × *C*$_{Ar}$), 133.0, 132.8, 129.4, 128.6, 128.6, 128.5, 128.1 (7 × H*C*$_{Ar}$), 127.5 (*C*$_{Ar}$), 127.3, 126.5, 125.6, 121.1, 120.9 (5 × H*C*$_{Ar}$), 116.1 (*C*$_{Ar}$), 110.9 (H*C*$_{Ar}$), 48.1 (Ph*C*H$_2$), 36.0 (*C*H$_2$C(O)).

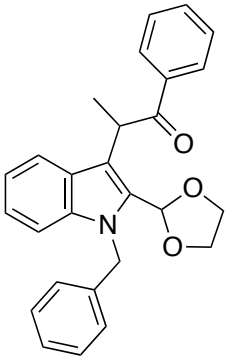
9-Benzyl-1,3-diphenyl-9*H*-pyrido[3,4-b]indole (**533**).



Indole **532** (75 mg, 0.17 mmol, 1.0 eq.) was subjected to general procedure B and purified by flash column chromatography using petroleum ether/EtOAc (10%) as eluent, affording *β*-carboline **533** (61 mg, 85%) as a yellow solid. A mixture of EtOH/H_2O/DMF (3:1:2) was used as solvent and the temperature was kept at 110 °C for this cyclisation.

m.p.: 170 – 174 °C. **IR**: ν_{max} (thin film) 3058, 3031, 1468, 1450, 737, 694 cm^{-1}. **HRMS:** calculated for $C_{30}H_{23}N_2$, 411.1856 $[M+H]^+$, found *m/z* 411.1845, Δ = –2.57 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.48 (1H, s, *H*C(4)), 8.30 (1H, ddd, *J* = 7.8, 1.2, 0.8 Hz, *H*C_{Ar}), 8.23 – 8.18 (2H, m, 2 × *H*C_{Ar}), 7.58 – 7.47 (5H, m, 5 × *H*C_{Ar}), 7.45 – 7.30 (6H, m, 6 × *H*C_{Ar}), 7.20 – 7.10 (3H, m, 3 × *H*C_{Ar}), 6.68 – 6.62 (2H, m, 2 × *H*C_{Ar}), 5.25 (2H, s, PhC*H*$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 147.1, 144.0, 143.2, 140.3, 139.9, 137.1, 134.0, 131.8 (8 × *C*$_{Ar}$), 129.6, 128.7, 128.6, 128.4, 128.3, 128.0, 127.8, 127.1, 127.0, 125.8 (10 × H*C*$_{Ar}$), 122.0 (*C*$_{Ar}$), 121.6, 120.3 (2 × H*C*$_{Ar}$), 110.8 (*C*(3)), 110.2 (H*C*$_{Ar}$), 48.2 (Ph*C*H$_2$).

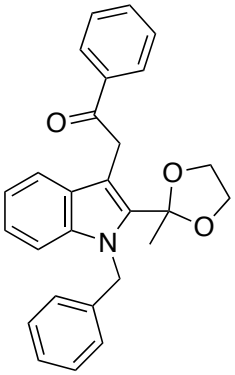
2-(1-Benzyl-2-(1,3-dioxolan-2-yl)-1*H*-indol-3-yl)-1-phenylpropan-1-one (**534**).



Propiophenone (41 μL, 0.31 mmol, 2.0 eq.) was subjected to general procedure A and purified by flash column chromatography using petroleum ether/EtOAc (20%) as eluent, affording keto-indole **534** (47 mg, 74%) as a yellow solid.

m.p.: 159 – 164 °C. **IR**: ν_{max} (thin film) 3061, 2974, 2930, 2890, 1680, 1424, 1134, 1079, 745 cm^{-1}. **HRMS**: calculated for $C_{27}H_{26}NO_3$, 412.1907 $[M+H]^+$, found *m/z* 412.1920, Δ = 3.0 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.01 (2H, d, *J* = 7.40 Hz, 2 × *H*C_{Ar}), 7.64 (1H, d, *J* = 7.6 Hz, *H*C_{Ar}), 7.34 (1H, t, *J* = 7.4 Hz, *H*C_{Ar}), 7.24 (2H, t, *J* = 7.4 Hz, 2 × *H*C_{Ar}), 7.21 – 7.13 (3H, m, 3 × *H*C_{Ar}), 7.08 – 6.99 (3H, m, 3 × *H*C_{Ar}), 6.90 – 6.84 (2H, m, 2 × *H*C_{Ar}), 6.18 (1H, s, C*H*$(OR)_2$), 5.42 (1H, s, PhCH_aH_b), 5.41 (1H, s, PhCH_aH_b), 5.15 (1H, q, *J* = 6.8 Hz, C*H*CH_3), 4.12 – 3.92 (4H, m, (OC$H_2)_2$), 1.66 (3H, d, CH_3CH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 201.1 (*C*(O)), 138.1, 137.6, 137.0 (3 × C_{Ar}), 132.4, 128.8 (2 × HC_{Ar}), 128.7 (C_{Ar}), 128.6, 128.2, 127.1, 125.9 (4 × HC_{Ar}), 125.8 (C_{Ar}), 123.1, 120.2, 119.9 (3 × HC_{Ar}), 116.7 (C_{Ar}), 110.1 (HC_{Ar}), 98.6 (*C*H$(OR_2)_2$), 65.2 ($C_aH_2C_bH_2$), 65.0 ($C_aH_2C_bH_2$), 47.7 (Ph*C*H_2), 39.8 (*C*HCH_3), 18.0 (CH*C*H_3).

2-(1-Benzyl-2-(2-methyl-1,3-dioxolan-2-yl)-1*H*-indol-3-yl)-1-phenylethan-1-one (**535**).

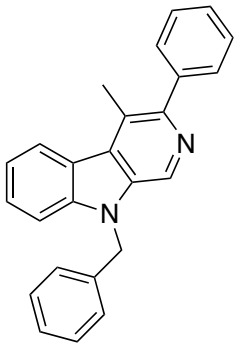


Acetophenone (34 μL, 0.29 mmol, 2.0 eq.) and 3-bromoindole **531** (54 mg, 0.15 mmol, 1.0 eq.) were subjected to general procedure A and purified by flash column chromatography using petroleum ether/EtOAc (10%) as eluent, affording keto-indole **535** (50 mg, 84%) as an off-white solid.

m.p.: 128 – 131 °C. **IR**: ν_{max} (thin film) 3058, 3029, 2989, 2891, 1691, 1197, 1466, 1449, 1342, 1197, 742 cm^{-1}. **HRMS**: calculated for $C_{27}H_{25}NO_3Na$, 434.1727 $[M+Na]^+$, found *m/z* 434.1727, Δ = 0.08 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.15 – 8.11 (2H, m, 2 × *H*C_{Ar}), 7.63 – 7.56 (1H, m, *H*C_{Ar}), 7.55 – 7.46 (3H, m, 3 × *H*C_{Ar}), 7.30 – 7.12 (6H, m, 6 × *H*C_{Ar}), 6.98 – 6.93 (2H, m, 2 × *H*$C_{Ar)}$, 5.67 (2H, s, PhCH_2), 4.72 (2H, s, ArCH_2C(O)), 3.88 – 3.80 (2H, m, CH_aH_bCH_aH_b), 3.68 – 3.62 (2H, m, CH_aH_bCH_aH_b),

1.65 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 198.2 (*C*(O)), 139.0, 137.5, 137.4, 136.6 (4 × C_{Ar}), 132.8, 128.6, 128.5 (3 × HC_{Ar}), 128.4 (C_{Ar}), 128.3, 126.7, 125.8 , 122.5, 119.8, 118.6, 110.3 (7 × HC_{Ar}), 107.3, 106.8 (C_{Ar} and CCH_3), 64.8 ($OCH_2)_2$), 48.0 (PhCH_2), 35.2 (CH_2C(O)), 27.2 (CCH_3).

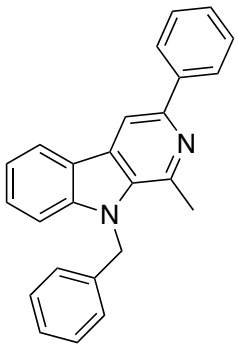
9-Benzyl-4-methyl-3-phenyl-9*H*-pyrido[3,4-b]indole (536).



Indole **534** (63 mg, 0.15 mmol, 1.0 eq.) was subjected to general procedure B and purified by flash column chromatography using petroleum ether/EtOAc (20%) as eluent, affording *β*-carboline **536** (50 mg, 94%) as a yellow solid.

m.p.: 164 – 167 °C. **IR**: ν_{max} (thin film) 3055, 3030, 2924, 1454, 737, 701 cm^{-1}. **HRMS:** calculated for $C_{25}H_{21}N_2$, 349.1699 $[M+H]^+$, found *m/z* 349.1695, Δ = –1.3 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.82 (1H, s, *H*C(1)), 8.33 (1H, d, *J* = 8.0 Hz, *H*C_{Ar}), 7.65 – 7.60 (2H, m, 2 × *H*C_{Ar}), 7.59 (1H, ddd, *J* = 8.3, 7.1, 1.2 Hz, *H*C_{Ar}), 7.54 – 7.47 (3H, m, 3 × *H*C_{Ar}), 7.45 – 7.39 (1H, m, *H*C_{Ar}), 7.34 (1H, t, *J* = 8.0 Hz, *H*C(6)), 7.32 – 7.25 (3H, m, 3 × *H*C_{Ar}), 7.22 – 7.17 (2H, m, 2 × *H*C_{Ar}), 5.58 (2H, s, PhCH_2R), 2.91 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 149.2, 141.7, 141.2, 136.6, 135.6 (5 × C_{Ar}), 130.0, 129.3 (2 × HC_{Ar}), 129.0 (*C*(1)), 128.4 (C_{Ar}), 128.1, 127.8, 127.8, 127.2, 126.6 (5 × HC_{Ar}), 124.9 (C_{Ar}), 124.2 (*C*(5)), 122.4 (C_{Ar}), 119.9 (*C*(6)), 109.6 (HC_{Ar}), 46.9 (PhCH_2), 17.6 (CH_3).

9-Benzyl-1-methyl-3-phenyl-9*H*-pyrido[3,4-b]indole (537).

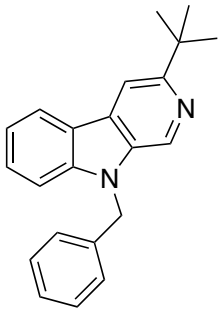


Indole **535** (35 mg, 85 μmol, 1.0 eq.) was subjected to general procedure B and purified by flash column chromatography using petroleum ether/EtOAc (20%) as eluent, affording *β*-carboline **537** (28 mg, 94%) as a brown solid. A mixture of EtOH/H_2O/DMF (3:1:2) was used as solvent and the temperature was kept at 110 °C for this cyclisation.

m.p.: 127 – 129 °C. **IR**: ν_{max} (thin film) 3060, 3030, 1472, 734, 694 cm^{-1}. **HRMS**: calculated for $C_{25}H_{21}N_2$, 349.1699 $[M+H]^+$, found *m/z* 349.1694, Δ = –1.41 ppm. **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 8.31 (1H, s, *H*C(4)), 8.22 (1H, d, *J* = 7.7 Hz, *H*C_{Ar}), 8.16 – 8.12

(2H, m, 2 × *H*C_{Ar}), 7.56 – 7.48 (3H, m, 3 × *H*C_{Ar}), 7.41 – 7.35 (2H, m, 2 × *H*C_{Ar}), 7.34 – 7.22 (4H, m, 5 × *H*C_{Ar}), 7.05 – 7.00 (2H, m, 2 × *H*C_{Ar}), 5.81 (2H, s, PhC*H*$_2$), 2.95 (3H, s, C*H*$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C: 145.9, 141.3, 140.2, 139.4, 137.0, 133.9, 129.2 (7 × *C*$_{Ar}$), 127.9, 127.6, 127.3, 126.5, 126.5, 125.7, 124.4 (7 × H*C*$_{Ar}$), 120.7 (*C*$_{Ar}$), 120.4, 119.0, 108.9 (3 × H*C*$_{Ar}$), 108.5 (*C*(4)), 47.2 (Ph*C*H$_2$), 22.4 (*C*H$_3$).

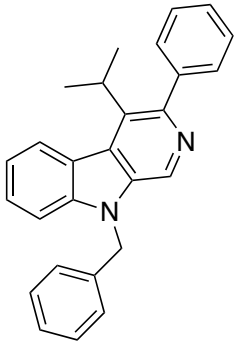
9-Benzyl-3-(*tert*-butyl)-9*H*-pyrido[3,4-b]indole (542).



3,3-Dimethyl-2-butanone (76 μL, 0.61 mmol, 2.0 eq.) was subjected to general procedure D and purified by flash column chromatography using pentane/EtOAc (10%) as eluent, affording *β*-carboline **542** (51 mg, 53%) as a brown solid.

m.p.: 132 – 134 °C. **IR**: ν_{max} (thin film) 3030, 2956, 2864, 1468, 740, 698 cm^{-1}. **HRMS**: calculated for $C_{22}H_{23}N_2$, 315.1856 $[M+H]^+$, found *m/z* 315.1853, Δ = –0.86 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.82 (1H, d, *J* = 0.9 Hz, *H*C(1)), 8.19 (1H, d, *J* = 7.8 Hz, *H*C_{Ar}), 8.19 (1H, d, *J* = 0.9 Hz, *H*C(4)), 7.55 (1H, ddd, *J* = 8.3, 7.1, 1.2 Hz, *H*C_{Ar}), 7.43 (1H, d, *J* = 8.3 Hz, *H*C_{Ar}), 7.32 – 7.18 (6H, m, 6 × *H*C_{Ar}), 5.53 (2H, s, PhC*H*$_2$N), 1.51 (9H, s, (C*H*$_3$)$_3$C). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 159.0, 141.8, 136.7, 135.0 (4 × *C*$_{Ar}$), 130.8 (*C*(1)), 129.3 (*C*$_{Ar}$), 128.9, 128.2, 127.8, 126.7, 121.8 (5 × H*C*$_{Ar}$), 121.6 (*C*$_{Ar}$), 119.6, 109.6 (2 × H*C*$_{Ar}$), 109.4 ((*C*4)), 47.1 (Ph*C*H$_2$), 37.2 ((CH$_3$)$_3$*C*), 30.9 ((*C*H$_3$)$_3$C).

9-Benzyl-4-isopropyl-3-phenyl-9*H*-pyrido[3,4-b]indole (544).

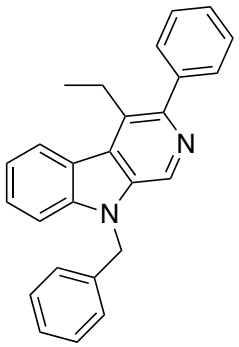


Isovalerophenone (103 μL, 614 μmol, 2.0 eq.) was subjected to general procedure D and purified by flash column chromatography using pentane/EtOAc (20%) as eluent, affording *β*-carboline **544** (84 mg, 73%) as a brown solid.

m.p.: 170 – 171 °C. **IR**: ν_{max} (thin film) 3055, 3030, 2990, 2958, 2929, 2872, 1439, 741, 701 cm^{-1}. **HRMS**: calculated for $C_{27}H_{25}N_2$, 377.2012 $[M+H]^+$, found *m/z* 377.2014, Δ = 0.42 ppm. **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 8.89 (1H, s, *H*C(1)), 7.62 – 7.53 (3H, m, 3 × *H*C_{Ar}), 7.46 – 7.37 (4H, m, 4 × *H*C_{Ar}), 7.33 – 7.23 (5H, m, 5 ×

HC_{Ar}), 6.95 (1H, dd, *J* = 8.0, 6.9 Hz, *H*C_{Ar}), 6.83 (1H, d, *J* = 8.0 Hz, *H*C_{Ar}) 5.53 (2H, s, PhC*H*$_2$N), 3.18 (1H, sept., *J* = 6.8 Hz, C*H*$(CH_3)_2$), 1.29 (6H, d, *J* = 6.8 Hz, CH(C*H*$_3$)$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 153.9, 141.8, 138.6, 136.7, 134.9 (5 × *C*$_{Ar}$), 130.9, 129.3, 128.9, 128.9 (4 × H*C*$_{Ar}$), 128.9, 128.8 (2 × *C*$_{Ar}$), 127.8, 127.8, 127.8, 126.8, 123.5 (5 × H*C*$_{Ar}$), 121.6 (*C*$_{Ar}$), 119.4, 109.3 (2 × H*C*$_{Ar}$), 47.0 (Ph*C*H$_2$), 30.9 (CH(*C*H$_3$)$_2$), 23.2 (*C*H(CH$_3$)$_2$).

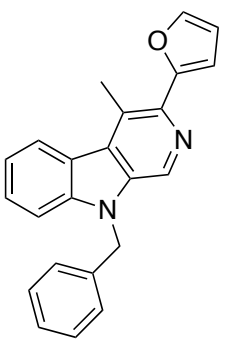
9-Benzyl-4-ethyl-3-phenyl-9*H*-pyrido[3,4-b]indole (546)



Butyrophenone (89 μL, 0.61 mmol, 2.0 eq.) was subjected to general procedure D and purified by flash column chromatography using pentane/EtOAc (20%) as eluent, affording *β*-carboline **546** (76 mg, 68%) as a brown solid.

m.p.: 136 – 138 °C. **IR**: ν_{max} (thin film) 3056, 2969, 2933, 2873, 1441, 730, 700 cm^{-1}. **HRMS:** calculated for $C_{26}H_{23}N_2$, 363.1856 $[M+H]^+$, found *m*/*z* 363.1853, Δ = –0.75 ppm. **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 8.81 (1H, s, *C*(1)), 8.28 (1H, d, *J* = 8.0 Hz, *H*C_{Ar}), 7.61 – 7.55 (3H, m, 3 × *H*C_{Ar}), 7.52 – 7.46 (3H, m, 3 × *H*C_{Ar}), 7.44 – 7.39 (1H, m, *H*C_{Ar}), 7.35 (1H, ddd, *J* = 8.0, 7.1, 1.0 Hz, *H*C_{Ar}), 7.32 – 7.26 (3H, m, 3 × *H*C_{Ar}), 7.24 – 7.20 (2H, m, 2 × *H*C_{Ar}), 5.60 (2H, s, PhC*H*$_2$), 3.26 (2H, q, *J* = 7.5 Hz, C*H*$_2$CH$_3$), 1.44 (3H, t, *J* = 7.5 Hz, CH$_2$C*H*$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C: 149.1, 141.7, 141.5, 136.6, 136.2 131.2 (6 × *C*$_{Ar}$), 129.5 (*C*(1)), 129.4, 129.0, 128.1, 127.8, 127.8 (5 × H*C*$_{Ar}$), 127.4 (*C*$_{Ar}$), 127.2, 126.6, 124.2 (3 × H*C*$_{Ar}$), 121.5 (*C*$_{Ar}$), 120.1, 109.7 (2 × H*C*$_{Ar}$), 46.9 (Ph*C*H$_2$N), 23.4 (*C*H$_2$CH$_3$), 14.5 (CH$_2$*C*H$_3$).

9-Benzyl-3-(furan-2-yl)-4-methyl-9*H*-pyrido[3,4-b]indole (548).

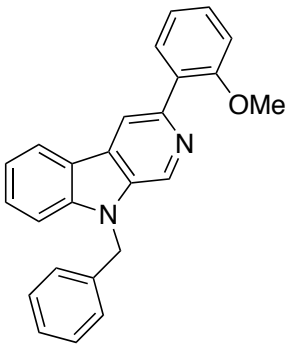


1-(2-Furyl)-1-propanone (76 mg, 0.61 mmol, 2.0 eq.) was subjected to general procedure D and purified by flash column chromatography using pentane/EtOAc (20%) as eluent, affording *β*-carboline **548** (78 mg, 75%) as a brown solid.

m.p.: 156 – 159 °C. **IR**: ν_{max} (thin film) 3141, 2918, 1488, 1301, 733, 696 cm^{-1}. **HRMS**: calculated for $C_{23}H_{19}N_2O$, 339.1492 $[M+H]^+$, found *m*/*z*

339.1488, Δ = –1.05 ppm. **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 8.63 (1H, s, *H*C(1)), 8.19 (1H, d, *J* = 8.0 Hz, *H*C_{Ar}), 7.50 (1H, dd, *J* = 1.9, 0.7 Hz, OC*H*), 7.44 (1H, ddd, *J* = 8.2, 7.2, 1.1 Hz, *H*C_{Ar}), 7.33 (1H, d, *J* = 8.3 Hz, *H*C_{Ar}), 7.20 (1H, ddd, *J* = 8.0, 7.3, 0.6 Hz, *H*C_{Ar}), 7.16 – 7.09 (3H, m, 3 × *H*C_{Ar}), 7.03 – 6.99 (2H, m, 2 × *H*C_{Ar}), 6.67 (1H, dd, *J* = 3.3, 0.7 Hz, OCC*H*), 6.46 (1H, dd, *J* = 3.3, 1.9 Hz, OCHC*H*), 5.39 (2H, s, PhCH_2), 2.89 (3H, s, CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C: 154.1 (*C*$_{Ar}$), 142.2 (*H*C_{Ar}), 141.6, 139.1, 136.4, 135.3 (4 × *C*$_{Ar}$), 129.6 (*C*(1)), 128.9 (H*C*$_{Ar}$), 128.3 (*C*$_{Ar}$), 127.8, 127.8, 126.5 (3 × H*C*$_{Ar}$), 125.4 (*C*$_{Ar}$), 124.2 (H*C*$_{Ar}$), 122.4 (*C*$_{Ar}$), 120.1, 111.2, 109.7, 109.6 (4 × H*C*$_{Ar}$), 46.8 (Ph*C*H$_2$), 16.8 (*C*H$_3$).

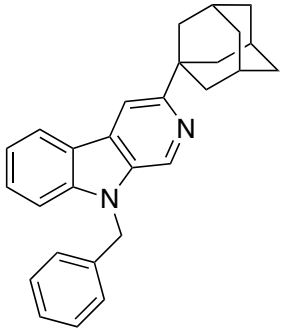
9-Benzyl-3-(2-methoxyphenyl)-9*H*-pyrido[3,4-b]indole (550)



2-Methoxyacetophenone (85 μL, 0.61 mmol, 2.0 eq.) was subjected to general procedure D and purified by flash column chromatography using pentane/EtOAc (20%) as eluent, affording *β*-carboline **550** (83 mg, 74%) as a yellow solid.

m.p.: 95 – 97 °C. **IR**: ν_{max} (thin film) 3030, 2935, 2834, 1491, 727, 700 cm^{-1}. **HRMS**: calculated for $C_{25}H_{21}N_2O$, 365.1648 $[M+H]^+$, found *m/z* 365.1646, Δ = –0.54 ppm. **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 8.94 (1H, d, *J* = 1.0 Hz, *H*C(1)), 8.51 (1H, d, *J* = 1.0 Hz, *H*C(4)), 8.22 (1H, ddd, *J* = 7.8, 1.2, 0.7 Hz, *H*C_{Ar}), 7.84, (1H, dd, *J* = 7.6, 1.8 Hz, *H*C_{Ar}), 7.57 (1H, ddd, *J* = 8.3, 7.1, 1.2 Hz, *H*C_{Ar}), 7.46 – 7.42 (1H, m, *H*C_{Ar}), 7.38 (1H, ddd, *J* = 8.3, 7.4, 1.8 Hz, *H*C_{Ar}), 7.34 – 7.18 (6H, m, 6 × *H*C_{Ar}), 7.14 – 7.09 (1H, m, *H*C_{Ar}), 7.06 (1H, dd, *J* = 8.3, 1.0 Hz, *H*C_{Ar}), 5.58 (2H, s, PhCH_2N), 3.91 (3H, s, CH_3O). **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C: 156.8, 146.0, 141.8, 136.6, 135.7 (5 × *C*$_{Ar}$), 131.6 (H*C*$_{Ar}$), 131.5 (*C*(1)), 130.2, 129.0 (2 × *C*$_{Ar}$), 128.9, 128.9, 128.4, 127.8, 126.7, 122.0 (6 × H*C*$_{Ar}$), 121.7 (*C*$_{Ar}$), 121.1, 119.8 (2 × H*C*$_{Ar}$), 115.9 (*C*(4)), 111.5, 109.7 (2 × H*C*$_{Ar}$), 55.8 (*C*H$_3$O), 47.0 (PhCH_2).

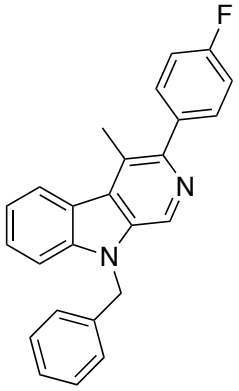
3-(Adamantan-1-yl)-9-benzyl-9*H*-pyrido[3,4-b]indole (552).



1-Adamantyl-methyl ketone (109 mg, 614 μmol, 2.0 eq.) was subjected to general procedure D and purified by flash column chromatography using pentane/EtOAc (10%) as eluent, affording *β*-carboline **552** (73 mg, 61%) as a brown solid.

m.p.: 241 – 243 °C. **IR**: ν_{max} (thin film) 2901, 2846, 1464, 1452, 738, 698 cm^{-1}. **HRMS**: calculated for $C_{28}H_{29}N_2$, 393.2325 $[M+H]^+$, found *m/z* 393.2326, Δ = 0.12 ppm. **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 8.82 (1H, d, *J* = 1.0 Hz, *H*C(1)), 8.17 (1H, d, *J* = 7.8 Hz, *H*C_{Ar}), 7.96 (1H, d, *J* = 1.0 Hz, *H*C(4)), 7.54 (1H, ddd, *J* = 8.3, 7.2, 1.1 Hz, *H*C_{Ar}), 7.43 (1H, d, *J* = 8.3 Hz, *H*C_{Ar}), 7.30 – 7.23 (4H, m, 4 × *H*C_{Ar}), 7.22 – 7.18 (2H, m, 2 × *H*C_{Ar}), 5.53 (2H, s, PhCH_2N), 2.19 – 2.15 (3H, m, 3 × C*H*), 2.14 (6H, d, *J* = 2.9 Hz, 3 × CCH_2CH), 1.84 (6H, t, *J* = 3.1 Hz, 3 × CH_2). **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C: 158.0, 140.7, 135.7, 134.0 (4 × C_{Ar}), 129.9 (*C*(1)), 128.3 (C_{Ar}), 127.8, 127.1, 126.7, 125.7, 120.7 (5 × HC_{Ar}), 120.6 (C_{Ar}), 118.5 (HC_{Ar}), 108.5 (*C*(4)), 108.2 (*H*C_{Ar}), 46.0 (PhCH_2), 41.6 (RC(*C*H_2)$_3$), 37.6 (R*C*(CH$_2$)$_3$), 35.9 (*C*H_2), 28.0 (*C*H).

9-Benzyl-3-(4-fluorophenyl)-4-methyl-9*H*-pyrido[3,4-b]indole (554).

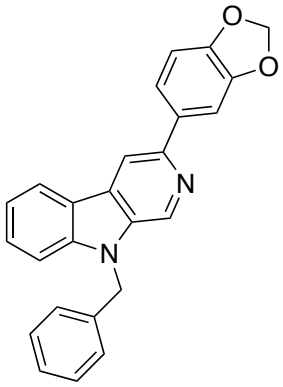


4'-Fluoroacetophenone (75 μL, 0.61 mmol, 2.0 eq.) was subjected to general procedure D and purified by flash column chromatography using pentane/EtOAc (20%) as eluent affording *β*-carboline **554** (58 mg, 52%) as a brown solid.

m.p.: 183 - 185 °C. IR: ν_{max} (thin film) 3056, 1455 1219, 731, 699 cm^{-1}. **HRMS:** calculated for $C_{25}H_{19}FN_2$, 367.1605 $[M+H]^+$, found *m/z* 367.1603, Δ = –0.45 ppm. **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 8.78 (1H, s, *H*C(1)), 8.32 (1H, d, *J* = 7.8 Hz, *H*C_{Ar}), 7.62 – 7.54 (3H, m, 3 × *H*C_{Ar}), 7.49 (1H, d, *J* = 8.2 Hz, *H*C_{Ar}), 7.35 (1H, t, *J* = 7.6 Hz, *H*C_{Ar}), 7.37 – 7.24 (3H, m, 3 × *H*C_{Ar}), 7.21 – 7.14 (4H, m, 4 × *H*C_{Ar}), 5.59 (2H, s, PhCH_2N), 2.89 (3H, s, CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C: 161.2 (d, *J* = 246 Hz, *C*F), 147.0, 140.6 (2 × C_{Ar}), 136.1 (d, *J* = 3.3 Hz, *C*CHCHCF), 135.4, 134.6 (2 × C_{Ar}) 130.5 (d, *J* = 8.1 Hz, *C*HCF), 128.2 (HC_{Ar}), 127.9 (H*C*(1)), 127.4 (C_{Ar}), 126.8 (d, *J* =

6.2 Hz, *C*HCHF), 125.5 (HC_{Ar}), 123.8 (C_{Ar}), 123.1 (HC_{Ar}), 121.2 (C_{Ar}), 118.9, 114.0, 113.8, 108.6 (4 × HC_{Ar}), 45.8 (Ph*C*H$_2$), 16.5 (*C*H$_3$). **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F: –115.4 (tt, *J* = 8.8, 5.5 Hz, C*F*).

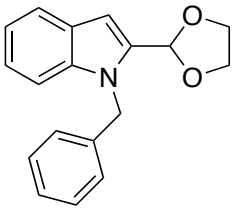
3-(Benzo[*d*][1,3]dioxol-5-yl)-9-benzyl-9*H*-pyrido[3,4-*b*]indole (556).



3',4'-(Methylenedioxy)acetophenone (101 mg, 614 μmol, 2.0 eq.) was subjected to general procedure D and purified by flash column chromatography using pentane/EtOAc (10%) as eluent, affording *β*-carboline **556** (71 mg, 61%) as a brown solid.

m.p.: 152 – 155 °C. **IR**: ν_{max} (thin film) 2890, 1459, 725 cm^{-1}. **HRMS**: calculated for $C_{25}H_{19}N_2O_2$, 379.1441 $[M+H]^+$, found *m/z* 379.1435, Δ = –1.53 ppm. **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 8.84 (1H, d, *J* = 0.9 Hz, *H*C(1)), 8.30 (1H, d, *J* = 0.9 Hz, *H*C(4)), 8.20 (1H, d, *J* = 7.8 Hz, *H*C_{Ar}), 7.64 – 7.54 (3H, m, 3 × *H*C_{Ar}), 7.43 (1H, d, *J* = 8.3 Hz, *H*C_{Ar}), 7.34 – 7.22 (4H, m, 4 × *H*C_{Ar}), 7.20 – 7.16 (2H, m, 2 × *H*C_{Ar}), 6.94 (1H, d, *J* = 8.1 Hz, *H*C_{Ar}), 6.01 (2H, s, O_2C*H*$_2$), 5.54 (2H, s, PhC*H*$_2$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C: 148.2, 147.5, 147.5, 141.9, 136.5, 135.8, 135.1 (7 × C_{Ar}), 131.6 (H*C*(1)), 129.8 (C_{Ar}), 129.0, 128.6, 127.9, 126.6, 121.9 (5 × HC_{Ar}), 121.6 (C_{Ar}), 120.4, 120.0 (2 × HC_{Ar}), 110.8 (H*C*(4)), 109.8, 108.5, 107.4 (3 × HC_{Ar}), 101.2 (O*C*H$_2$), 47.0 (PhC*H*$_2$).

1-benzyl-2-(1,3-dioxolan-2-yl)-1*H*-indole (559)

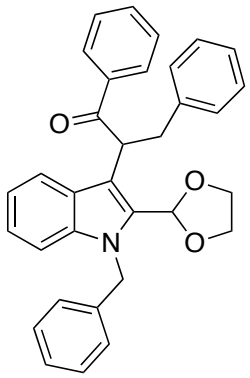


Propiophenone (41 μL, 0.31 mmol, 2.0 eq.) was subjected to general procedure A and purified by flash column chromatography using petroleum ether/EtOAc (20%) as eluent, affording by-product **559** (5 mg, 5%) as a brown oil.

IR: ν_{max} (thin film) 3030, 1665, 1611, 1495, 1452, 1411, 1322, 1274, 1153, 907, 840, 722, 694 cm^{-1}. **HRMS**: calculated for $C_{18}H_{18}NO_2$, 280.1332 $[M+H]^+$, found *m/z* 280.1334, Δ = 0.56 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.63 (1H, d, *J* = 7.7 Hz, *H*C_{Ar}), 7.30 – 7.00 (8H, m, 8 × *H*C_{Ar}), 6.71 (1H, s, NCC*H*), 6.04 (1H, s, C*H*(OR)$_2$), 5.47 (2H, 2, PhC*H*$_2$), 4.10 – 3.93 (4H, m, (OC*H*$_2$)$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 138.3, 138.1, 135.7 (3 × C_{Ar}), 128.7, 127.3 (2 × HC_{Ar}), 127.2

(C_{Ar}), 126.3, 122.6, 121.3, 120.0, 110.1 (5 × HC_{Ar}), 102.6 (NC*C*H), 99.2(*C*H(OR)$_2$), 65.1 ((OCH_2)$_2$), 47.7 (PhCH$_2$).

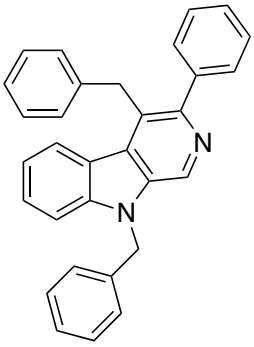
2-(1-benzyl-2-(1,3-dioxolan-2-yl)-1*H*-indol-3-yl)-1,3-diphenylpropan-1-one (575).



A fresh solution of LiHMDS was prepared in a dry vial adding sequentially dry THF (7.3 mL), HMDS (290 μL, 1.39 mmol, 2.5 eq.), a 2.5 M solution of *n*BuLi (558 μL, 1.39 mmol, 2.5 eq.) and stirring at –78 °C for 10 mins. Acetophenone (130 μL, 1.07 mmol, 2.0 eq.) was then added at 0 °C and stirred for 15 mins. In a second dry vial were added bromo-indole **515** (200 mg, 558 μmol) and Pd(dtbpf)Cl$_2$ (18 mg, 28 μmol, 5 mol%). The flask was sealed, evacuated and backfilled with argon twice. The freshly formed enolate solution was then transferred *via* syringe to the flask. The mixture was stirred at 50 °C for 24 h in an oil bath. After cooling to RT, benzyl bromide (166 μL, 1.39 mmol, 2.5 eq.) was added and the mixture was stirred at 90 °C for 24 h. After cooling to RT, the resulting mixture was filtered through a plug of silica using EtOAc as eluent and concentrated *in vacuo*. The crude product was purified by flash column chromatography using petroleum ether/EtOAc (10%) as eluent, affording keto-indole **575** (177 mg, 65%) as a brown solid.

m.p.: 134 – 135 °C. **IR**: ν_{max} (thin film) 3060, 3027, 2924, 1679, 13445, 1083, 1026, 742, 697 cm^{-1}. **HRMS**: calculated for $C_{33}H_{30}NO_3$, 488.2220 $[M+H]^+$, found *m/z* 488.2219, Δ = –0.14 ppm. **^{1}H NMR** (400 MHz, C_6D_6) δ_H: 8.24 (2H, ddd, *J* = 8.2, 1.9, 1.5 Hz, *H*C$_{Ar}$), 8.05 (1H, d, *J* = 8.05 Hz, *H*C$_{Ar}$), 7.17 – 7.14 (1H, m, *H*C$_{Ar}$), 7.12 – 6.89 (12H, m, *H*C$_{Ar}$), 6.86 (1H, d, *J* = 8.2 Hz, *H*C$_{Ar}$), 6.72 (2H, ddd, *J* = 7.6, 1.9, 1.3 Hz, 2 × *H*CAr), 5.92 (1H, s, C*H*(OR)$_2$), 5.39 (1H, dd, *J* = 8.4, 6.0 Hz, CH$_2$C*H*C(O)), 5.15 (1H, d, *J* = 17.1 Hz, PhCH_aH$_b$), 5.09 (1H, d, *J* = 17.1 Hz, PhCH$_a$$H_b$), 3.99 (1H, dd, *J* = 13.5, 6.0 Hz, PhCH_aH$_b$CH), 3.59 (1H, dd, *J* = 13.5, 8.4 Hz, PhCH$_a$CH_bCH), 3.36-3.13 (4H, m, (OCH_2)$_2$). **^{13}C NMR** (101 MHz, C_6D_6) δ_C: 198.9 (*C*(O)), 140.8, 138.3, 137.6, 137.3 (4 × C_{Ar}), 132.0 (HC_{Ar}), 129.9, (C_{Ar}), 129.4, 128.8, 128.3, 128.0, 128.0, 126.7 (6 × HC_{Ar}), 126.3 (C_{Ar}), 125.9, 125.8, 123.1, 120.5, 120.3 (5 × HC_{Ar}), 113.9 (C_{Ar}), 110.3 (HC_{Ar}), 99.5 (*C*H(OR)$_2$), 64.6 (O$_2$$C_aH_2C_bH_2$), 64.3 (O$_2C_aH_2$$C_bH_2$), 48.0 (CH$_2$*C*HC(O)), 47.5 (PhCH$_2$Ar), 38.2 (*C*H$_2$CHC(O))

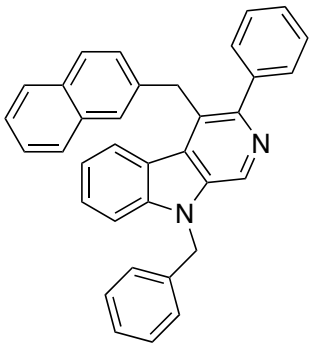
4,9-Dibenzyl-3-phenyl-9*H*-pyrido[3,4-b]indole (576).



Indole **575** (90 mg, 0.18 mmol, 1.0 eq.) was subjected to general procedure B and purified by flash column chromatography using pentane/EtOAc (10%) as eluent, affording **576** (75 mg, 96%) as an off-white solid. Alternatively, acetophenone (72 μL, 0.61 mmol, 2.0 eq.) and benzyl bromide (90 μL, 0.77 mmol, 2.5 eq.) were subjected to general procedure E, affording *β*-carboline **576** (78 mg, 60%) as an off-white solid.

m.p.: 201 - 204 °C. **IR**: ν_{max} (thin film) 3056, 3026, 1448, 740, 728, 699 cm^{-1}. **HRMS**: calculated for $C_{31}H_{25}N_2$, 425.2012 $[M+H]^+$, found *m/z* 425.2010, Δ = –0.48 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.95 (1H, s, *H*C(1)), 7.89 (1H, d, *J* = 8.0 Hz, *H*C_{Ar}), 7.55 – 7.44 (4H, m, 4 × *H*C_{Ar}), 7.42 – 7.10 (14H, m, 14 × *H*C_{Ar}), 5.64 (2H, s, PhC*H*$_2$N), 4.68 (2H, s, PhC*H*$_2$Ar). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 150.3, 141.8, 141.0, 139.7, 136.5, 136.0 (6 × *C*$_{Ar}$), 130.3 (H*C*(1)), 129.5, 129.0 (2 × H*C*$_{Ar}$), 128.9 (*C*$_{Ar}$), 128.7, 128.2, 128.0, 128.0, 127.9, 127.4, 126.7, 126.1 (8 × H*C*$_{Ar}$), 126.0 (*C*$_{Ar}$), 124.4 (H*C*$_{Ar}$), 121.5 (*C*$_{Ar}$), 120.1, 109.6 (2 × H*C*$_{Ar}$), 47.0 (Ph*C*H$_2$N), 36.4 (Ph*C*H$_2$Ar).

9-Benzyl-4-(naphthalen-2-ylmethyl)-3-phenyl-9*H*-pyrido[3,4-b]indole (578).

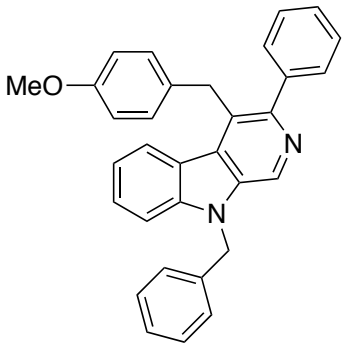


Acetophenone (72 μL, 0.61 mmol, 2.0 eq.) and 2-(bromomethyl)naphthalene (170 mg, 768 μmol, 2.5 eq.) were subjected to general procedure E and purified by flash column chromatography using pentane/EtOAc (10%) as eluent,, affording *β*-carboline 578 (70 mg, 48%) as a brown solid.

m.p.: 181 – 183 °C. **IR**: ν_{max} (thin film) 3052, 1419, 1335, 1221, 734, 699 cm^{-1}. **HRMS**: calculated for $C_{35}H_{27}N_2$, 475.2169 $[M+H]^+$, found *m/z* 475.2164, Δ = –0.91 ppm. **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 9.01 (1H, s, *H*C(1)), 7.88 (1H, d, *J* = 8.1 Hz, *H*C_{Ar}), 7.85 – 7.81 (2H, m, 2 × *H*C_{Ar}), 7.61 (1H, d, *J* = 7.8 Hz, *H*C_{Ar}), 7.57 – 7.52 (2H, m, 2 × *H*C_{Ar}), 7.51 – 7.46 (3H, m, 3 × *H*C_{Ar}), 7.45 – 7.25 (11H, m, 11 × *H*C_{Ar}), 7.09 – 7.03 (1H, m, *H*C_{Ar}),

5.66 (2H, s, PhCH_2N), 4.84 (2H, s, $C_{10}H_7CH_2$Ar). **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C: 150.3, 141.9, 140.9, 137.4, 136.5, 136.1, 133.8, 132.2 (8 × C_{Ar}), 130.5 (*C*(1)), 129.5, 129.0 (2 × HC_{Ar}), 129.0 (C_{Ar}), 128.5, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 127.0, 126.7, 126.3, 126.0 (11 × HC_{Ar}), 125.8 (C_{Ar}), 125.4, 124.4 (2 × HC_{Ar}), 121.5 (C_{Ar}), 120.5, 109.6 (2 × HC_{Ar}), 47.1 (PhCH_2N), 36.8 ($C_{10}H_7CH_2$Ar).

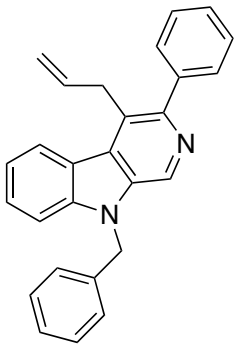
9-Benzyl-4-(4-methoxybenzyl)-3-phenyl-9*H*-pyrido[3,4-b]indole (579).



Acetophenone (72 μL, 0.61 mmol, 2.0 eq.) and 4-methoxybenzyl bromide (110 μL, 768 μmol, 2.5 eq.) were subjected to general procedure E and purified by flash column chromatography using pentane/EtOAc (10%) as eluent, affording *β*-carboline **579** (74 mg, 53%) as a yellow solid.

m.p.: 208 – 209 °C. **IR**: ν_{max} (thin film) 3058, 2932, 2835, 1244, 735, 699 cm^{-1}. **HRMS:** calculated for $C_{32}H_{27}N_2O$, 455.2118 $[M+H]^+$, found *m/z* 455.2116, Δ = –0.46 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.80 (1H, s, *H*C(1)) , 7.78 (1H, d, *J* = 8.0 Hz, HC_{Ar}), 7.42 – 7.30 (4H, m, 4 × HC_{Ar}), 7.28 – 7.08 (8H, m, 8 × HC_{Ar}), 7.05 – 6.98 (1H, m, HC_{Ar}), 6.94 (2H, d, *J* = 8.6 Hz, 2 × HC_{Ar}), 6.70 – 6.65 (2H, m, 2 × HC_{Ar}), 5.49 (2H, s, PhCH_2N), 4.47 (2H, s, PMBCH_2Ar), 3.63 (3H, s, CH_3O). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 157.9, 150.2, 141.8, 141.0, 136.5, 136.0, 131.7 (7 × C_{Ar}), 130.3 (*C*(1)), 129.5, 129.1, 129.0 (3 × HC_{Ar}), 128.9 (C_{Ar}), 128.0, 128.0, 127.9, 127.4, 126.7 (5 × HC_{Ar}), 126.4 (C_{Ar}), 124.5 (HC_{Ar}), 121.5 (C_{Ar}), 120.1, 114.1, 109.6 (3 × HC_{Ar}), 55.2 (CH_3O), 47.0 (PhCH_2N), 35.6 (PMBCH_2Ar).

4-Allyl-9-benzyl-3-phenyl-9*H*-pyrido[3,4-b]indole (581).

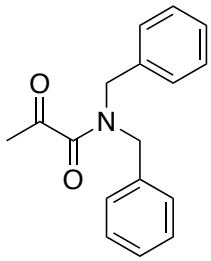


Acetophenone (72 μL, 0.61 mmol, 2.0 eq.) and allyl bromide (66 μL, 0.77 mmol, 2.5 eq.) were subjected to general procedure E and purified by flash column chromatography using pentane/EtOAc (10%) as eluent, affording *β*-carboline **581** (62 mg, 54%) as an off-white solid.

m.p.: 156 – 158 °C. **IR**: ν_{max} (thin film) 3056, 2926, 1487, 739, 700 cm^{-1}. **HRMS:** calculated for $C_{27}H_{23}N_2$, 375.1856 $[M+H]^+$, found *m/z* 375.1855,

Δ = –0.16 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.75 (1H, s, *H*C(1)), 8.09 (1H, d, *J* = 8.0 Hz, *H*C_{Ar}), 7.52 (2H, d, *J* = 7.0 Hz, 2 × *H*C_{Ar}), 7.44 (1H, t, *J* = 7.5 Hz, *H*C_{Ar}), 7.39 – 7.25 (4H, m, 4 × *H*C_{Ar}), 7.23 – 7.05 (6H, m, 6 × *H*C_{Ar}), 6.23 – 6.10 (1H, m, $ArCH_2CHCH_2$), 5.48 (2H, s, $PhCH_2N$), 5.08 (1H, dd, *J* = 10.3, 1.3 Hz, $CH_{cis}H_{trans}CHAr$), 4.87 (1H, dd, *J* = 17.4, 1.3 Hz, $CH_{cis}H_{trans}CHAr$), 3.92-3.84 (2H, m, $ArCH_2CHCH_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 149.8, 141.8, 141.1, 136.5, 135.9 (5 × C_{Ar}), 135.6 ($ArCH_2CHCH_2$), 130.0, 129.5, 129.0 (3 × HC_{Ar}), 128.4 (C_{Ar}), 128.0, 128.0, 127.9, 127.4, 126.6 (5 × HC_{Ar}), 125.9 (C_{Ar}), 124.6 (HC_{Ar}), 121.4 (C_{Ar}), 120.0 (HC_{Ar}), 116.8 ($ArCH_2CHCH_2$), 109.7 (HC_{Ar}), 47.0 ($PhCH_2N$), 34.5 ($ArCH_2CHCH_2$).

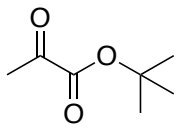
***N*,*N*-Dibenzyl-2-oxopropanamide (602)**



To a flame-dried flask were added pyruvic acid (1.0 mL, 14 mmol, 1.0 eq.), DMF (22 μL, 0.28 mmol, 2.0 mol%) and dry DCM (29 mL) then oxalyl chloride (1.4 mL, 15.8 mmol, 1.1 eq.) was added at RT over 1 h and then the reaction mixture was stirred for 3 h. After cooling the mixture to 0 °C, dibenzylamine (11 mL, 58 mmol, 4.0 eq.) was added over 30 mins and the mixture was then slowly warmed to RT and stirred for 1 h. The reaction was quenched with 3 M $HCl_{(aq.)}$ (14 mL, 3.0 eq.) and the layers were separated. The aqueous layer was extracted with DCM three times. The organic extracts were combined and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography using pentane/EtOAc (10%) as eluent, affording *a*-ketoamide **602** (3.10 g, 81%) as a yellow solid.

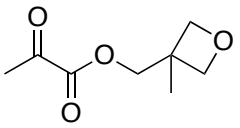
m.p.: 42 – 43 °C. **IR**: ν_{max} (thin film) 1714, 1637, 1152, 697 cm^{-1}. **HRMS**: calculated for $C_{17}H_{17}NO_2Na$, 290.1151 $[M+Na]^+$, found *m/z* 290.1153, Δ = 0.40 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.40 – 7.29 (6H, m, 6 × *H*C_{Ar}), 7.27 – 7.19 (4H, m, 4 × *H*C_{Ar}), 4.56 (2H, s, Ph^1CH_2N), 4.41 (2H, s, Ph^2CH_2N), 2.40 (3H, s, $CH_3C(O)$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 198.6 (*C*(O)), 167.5 (*C*(O)N), 135.9, 135.6 (2 × C_{Ar}), 129.0, 128.9, 128.6, 128.2, 128.0, 127.9 (6 × HC_{Ar}), 50.0 (Ph^2CH_2N), 47.3 (Ph^1CH_2N), 27.9 (CH_3).

***tert*-Butyl 2-oxopropanoate (603)**



To a flame-dried flask were added pyruvic acid (1.0 mL, 14 mmol), pyridine (2.9 mL, 36 mmol, 2.5 eq.), *tert*-butanol (2.7 mL, 29 mmol, 2.0 eq.) and dry THF (14 mL). The mixture was cooled to 0 °C and mesyl chloride (1.3 mL, 17 mmol, 1.2 eq.) added over 1 h, warmed to RT and stirred for 18 h. The reaction was then quenched with water and extracted three times with DCM. The organic extracts were combined and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography using pentane/EtOAc (6%) as eluent, affording pyruvate **603** (1.48 g, 70%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.41 (3H, s, CH_3), 1.54 (9H, s, C(CH_3)$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 191.0 (*C*(O)), 161.5 (*C*O_2), 85.9 (*C*$(CH_3)_3$), 27.1 (C(*C*H_3)$_3$), 23.2 (*C*H_3). Spectroscopic data are consistent with those previously reported.[278,279]

(3-Methyloxetan-3-yl)methyl 2-oxopropanoate (608)

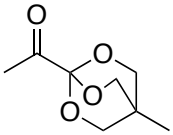


To a flame-dried flask were added pyruvic acid (1.0 mL, 14 mmol, 1.0 eq.), DMF (22 μL, 0.29 mmol, 2 mol%) and dry DCM (29 mL). Oxalyl chloride (1.3 mL, 16 mmol, 1.1 eq.) was added at RT over 1 h and then the reaction mixture was stirred for another 3 h. After cooling the mixture to –40 °C, a solution of 3-methyl-3-oxetanemethanol (1.4 mL, 14 mmol, 1.0 eq.) in pyridine (2.9 mL, 36 mmol, 2.5 eq.) was added over 30 mins and then slowly warmed to RT and stirred for 1 h. The reaction was finally quenched and extracted with 3 M HCl (14 mL, 3 eq.) and the aqueous layer extracted with DCM three times. The organic extracts were combined and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography using pentane/EtOAc (30%) as eluent, affording ester **608** (1.91 g, 77%) as a colourless oil. Alternatively, when performed at a 288 mmol scale, the crude product was distilled under reduced pressure (b.p. = 79 °C, 4.0 mbar), affording ester **608** (28.6 g, 69%).

IR: ν_{max} (thin film) 2934, 2874, 1730, 1702, 1134, 977, 754 cm^{-1}. **HRMS**: calculated for $C_8H_{13}O_4$, 173.0808 $[M+H]^+$, found *m/z* 173.0809, Δ = 0.14 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 4.52 (2H, d, *J* = 6.1 Hz, CH_aH$_b$OCH_aH$_b$), 4.43 (2H, d, *J* = 6.1 Hz, CH$_a$$H_bOCH_a$$H_b$), 4.36 (2H, s, CO_2CH_2C), 2.48 (3H, s, CH_3C(O)), 1.37 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$)

δ_C: 191.1 (CH_3C(O)), 160.7 (C(O)CO_2), 79.2 (CH_2OCH_2), 70.4 (OCH_2C), 39.1 (CCH_3), 26.8 (CH_3C(O)), 20.9 (CCH_3).

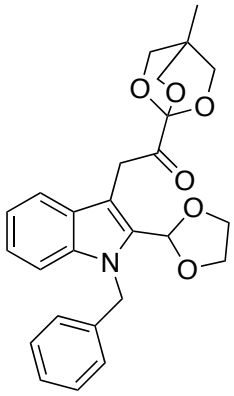
1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (611)



To a flame-dried flask were added (3-methyloxetan-3-yl)methyl-2-oxopropanoate **608** (40.0 g, 232 mmol) and dry DCM (500 mL). The mixture was cooled to 0 °C and $BF_3{\cdot}OEt_2$ (8.6 mL, 70 mmol, 0.3 eq.) added over 10 mins and stirred at 0 °C for 16 h. The reaction was quenched with Et_3N (9.7 mL, 70 mmol, 0.3 eq.), concentrated *in vacuo* and the resulting crude oil was filtered through a plug of silica using DCM as eluent. The crude solid was then crystallised from methyl *tert*-butyl ether to afford methyl-OBO-ketone **611** as a white crystal (25.5 g, 64%).

m.p.: 112 – 113 °C. **IR**: ν_{max} (thin film) 1734, 979, 638 cm^{-1}. **HRMS**: calculated for $C_8H_{13}O_4$, 173.0808 $[M+H]^+$, found *m/z* 173.0809, Δ = 0.65 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.76 (6H, s, 3 × OCH_2), 2.00 (3H, s, CH_3C(O)), 0.63 (3H, s, CH_3C). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 196.0 (*C*(O)), 102.8 (CO_3), 72.5 (OCH_2), 30.3 (CH_3C), 24.0 (CH_3C(O)), 13.5 (CH_3C). Analytical data are consistent with those previously reported.[237]

2-(1-Benzyl-2-(1,3-dioxolan-2-yl)-1*H*-indol-3-yl)-1-(4-methyl-2,6,7-trioxa-bicyclo-[2.2.2]-octan-1-yl)ethan-1-one (612)

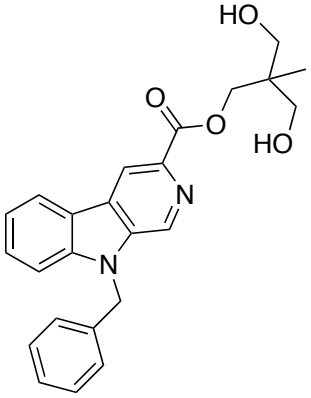


1-Benzyl-3-bromo-2-(1,3-dioxolan-2-yl)-1*H*-indole **515** (1 g, 2.79 mmol, 1.0 eq.) was subjected to general procedure G using 2.5 mol% of $Pd(dtbpf)Cl_2$ catalyst and purified by flash column chromatography using pentane/EtOAc (50%) as eluent, affording keto-indole **612** (1.05 g, 84%) as a brown solid.

M.p.: 135 – 137 °C. **IR**: ν_{max} (thin film) 3474, 2940, 2883, 1751, 1076, 735 cm^{-1}. **HRMS**: calculated for $C_{26}H_{28}NO_6$, 450.1911 $[M+H]^+$, found *m/z* 450.1909, Δ = –0.4 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.50 (1H, d, *J* = 7.9 Hz, HC_{Ar}), 7.28 – 7.02 (8H, m, 8 × HC_{Ar}), 6.06 (1H, s, $CH(OR)_2$), 5.50 (2H, s, $PhCH_2$), 4.32 (2H, s, CH_2C(O)), 4.05 (6H, s, 3 × OCH_2), 4.02 – 3.88 (4H, m, $(OCH_2)_2$), 0.87 (3H, s, CCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 195.7 (*C*(O)), 138.4, 137.4, 131.7 (3 × C_{Ar}), 128.6 (HC_{Ar}), 127.9 (C_{Ar}), 127.1, 126.2, 122.9, 119.7, 119.4, 110.0 (6 × HC_{Ar}), 107.9 (C_{Ar}), 104.0 (CO_3), 99.0 (CH(OR)$_2$), 73.2 (OCH$_2$), 65.0 ((OCH$_2$)$_2$), 47.8 (PhCH$_2$), 32.9 (CH$_2$C(O)), 31.0 (CCH$_3$), 14.4 (CCH$_3$).

3-Hydroxy-2-(hydroxymethyl)-2-methylpropyl 9-benzyl-9*H*-pyrido[3,4-b]-indole-3-carboxylate (613)

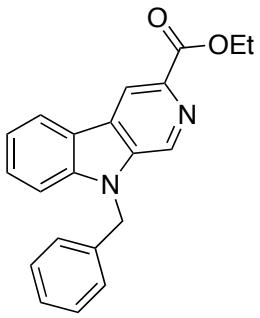


To a flame-dried vial capped with a rubber septum were added methyl-OBO ketone **611** (200 mg, 1.16 mmol, 2.0 eq.), 1-benzyl-3-bromo-2-(1,3-dioxolan-2-yl)-1*H*-indole (208 mg, 0.58 mmol, 1.0 eq.) and Pd(dtbpf)Cl_2 (19 mg, 29 μmol, 5 mol%). The rubber septum was replaced by an aluminium cap and then dry THF (5.1 mL) and 2 M NaO*t*Bu in THF (0.73 mL, 1.45 mmol) were added *via* syringe. The vial was flushed with argon for 5 mins then stirred at 70 °C for 24 h. After cooling to RT, the resulting mixture was filtered through a plug of silica using EtOAc as eluent and concentrated *in vacuo*. The crude material was dissolved in EtOH (5.8 mL), transferred *via* syringe to a vial containing NH_4Cl (310 mg, 58.0 mmol, 10.0 eq.) and stirred at 110 °C for 12 h. After cooling down, the mixture was concentrated *in vacuo* and purified by flash column chromatography using pentane/EtOAc (50% to 100%) as eluent, affording *β*-carboline **613** (138 mg, 59%) as a brown solid.

m.p.: 104 – 107 °C. **IR**: ν_{max} (thin film) 3357, 2990, 2930, 1683, 1200, 1054, 690 cm^{-1}. **HRMS**: calculated for $C_{24}H_{25}N_2O_4$, 405.1809 $[M+H]^+$, found *m/z* 405.1808, Δ = –0.09 ppm. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 9.20 (1H, s, *H*C(1)), 8.93 (1H, s, *H*C(4)), 8.47 (1H, d, *J* = 7.8 Hz, *H*C_{Ar}), 7.82 (1H, d, *J* = 8.3 Hz, *H*C_{Ar}), 7.65 (1H, ddd, *J* = 8.6, 7.1, 1.6 Hz, *H*C_{Ar}), 7.37 (1H, ddd, *J* = 7.9, 7.2, 0.8 Hz, *H*C_{Ar}), 7.31 – 7.20 (5H, m, 5 × *H*C_{Ar}), 5.84 (2H, s, PhCH_2), 4.60 (2H, t, *J* = 5.4 Hz, 2 × OH), 4.21 (2H, s, CO_2CH_2), 3.48 –3.39 (4H, m, 2 × CH_2OH), 0.94 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ_C: 165.5 (*C*(O)), 141.3, 137.6, 137.5, 137.1 (4 × C_{Ar}), 132.8 (*C*(1)), 129.1, 128.8, 127.7 (3 × HC_{Ar}), 127.6 (C_{Ar}), 127.0, 122.5, 120.9 (3 × HC_{Ar}), 120.7 (C_{Ar}),

117.4 (*C*(4)), 111.0 (H*C*$_{Ar}$), 67.0 (O*C*H$_2$), 63.7 (*C*H$_2$OH), 46.2 (Ph*C*H$_2$), 41.0 (*C*CH$_3$), 16.8 (C*C*H$_3$).

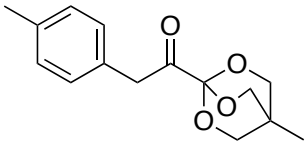
Ethyl 9-benzyl-9*H*-pyrido[3,4-b]indole-3-carboxylate (614)



OBO-ketone **612** (135 mg, 0.30 mmol, 1.0 eq.) was subjected to general procedure M and purified by flash column chromatography using pentane/EtOAc (40%) as eluent, affording *β*-carboline **614** (88 mg, 89%) as a light brown solid.

m.p.: 124 – 126 °C. **IR**: ν_{max} (thin film) 3062, 3029, 2993, 1721, 1267, 1216, 1028, 749, 722 cm^{-1}. **HRMS**: calculated for $C_{21}H_{19}N_2O_2$, 331.1441 [M+H]$^+$, found *m/z* 331.1440, Δ = –0.19 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.91 – 8.87 (2H, m, *H*C(1) + HC(4)), 8.22 (1H, d, *J* = 7.8 Hz, *H*C$_{Ar}$), 7.59 (1H, ddd, *J* = 8.3, 7.2, 1.2 Hz, *H*C$_{Ar}$), 7.48 (1H, d, *J* = 8.1 Hz, *H*C$_{Ar}$), 7.36 (1H, ddd, *J* = 8.0, 7.1, 0.9 Hz, *H*C$_{Ar}$), 7.29 – 7.21 (3H, m, 3 × *H*C$_{Ar}$), 7.16 – 7.10 (2H, m, 2 × *H*C$_{Ar}$), 5.59 (2H, s, PhC*H*$_2$), 4.53 (2H, q, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 1.48 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 166.2 (*C*(O)), 141.8, 138.1, 138.0, 135.8 (4 × *C*$_{Ar}$), 132.1 (*C*(1)), 129.1, 129.1 (2 × H*C*$_{Ar}$), 128.8 (*C*$_{Ar}$), 128.1, 126.6, 122.2 (2 × H*C*$_{Ar}$), 121.6 (*C*$_{Ar}$), 121.0 (H*C*$_{Ar}$), 117.8 (*C*(4)), 110.2 (H*C*$_{Ar}$), 61.7 (O*C*H$_2$CH$_3$), 47.3 (Ph*C*H$_2$), 14.6 (OCH$_2$*C*H$_3$). Analytical data are consistent with those previously reported[280,281]

1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-(*p*-tolyl)ethan-1-one (623)

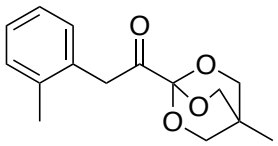


4-Bromotoluene (109 mg, 0.64 mmol, 1.1 eq.) was subjected to general procedure F and purified by flash column chromatography using toluene/MeCN (7%) as eluent, affording OBO-ketone **623** (130 mg, 85%) as a brown solid.

m.p.: 166 – 168 °C. **IR**: ν_{max} (thin film) 2881, 1755, 1033, 994 cm^{-1}. **HRMS**: calculated for $C_{15}H_{19}O_4$, 263.1278 [M+H]$^+$, found *m/z* 263.1278, Δ = 0.20 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.13 (2H, d, *J* = 8.1 Hz, *H*C$_{Ar}$), 7.07 (2H, d, *J* = 8.2 Hz, *H*C$_{Ar}$), 4.02 (6H, s, 3 × OC*H*$_2$), 3.95 (2H, s, C*H*$_2$C(O)), 2.33 (3H, s, C*H*$_3$Ph), 0.85 (3H, s, CC*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C:

195.9 (*C*(O)), 136.4, 130.3 (2 × C_{Ar}), 129.8, 129.1 (2 × HC_{Ar}), 103.8 (*C*O_3), 73.1 (O*C*H_2), 42.7 (*C*H_2C(O)), 30.9 (*C*CH_3), 21.1 (*C*H_3Ph), 14.2 (C*C*H_3).

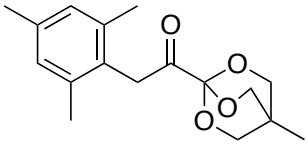
1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-(*o*-tolyl)ethan-1-one (635)



2-Bromotoluene (109 mg, 0.64 mmol, 1.1 eq.) was subjected to general procedure F and purified by flash column chromatography using pentane/EtOAc (30%) as eluent, affording OBO-ketone **635** (122 mg, 80%) as needle-like white crystals.

m.p.: 110 – 112 °C. **IR**: ν_{max} (thin film) 3441, 2970, 2883, 1742, 1252, 1188, 1122, 1094, 1038, 1013 cm^{-1}. **HRMS**: calculated for $C_{15}H_{19}O_4$, 263.1278 $[M+H]^+$, found *m/z* 263.1279, Δ = 0.40 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.20 – 7.05 (4H, m, 4 × *H*C_{Ar}), 4.04 (6H, s, 3 × O*C*H_2), 4.00 (2H, s, *C*H_2C(O)), 2.19 (3H, s, PhC*H*$_3$), 0.87 (3H, s, CC*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 195.5 (*C*(O)), 137.4, 132.3 (2 × C_{Ar}), 130.8, 130.2, 127.4, 126.0 (4 × HC_{Ar}), 103.8 (*C*O_3), 73.2 (O*C*H_2), 41.6 (*C*H_2C(O)), 31.0 (*C*CH_3), 19.6 (*C*H_3Ph), 14.3 (C*C*H_3). Spectroscopic data obtained by Christopher Hall.[238]

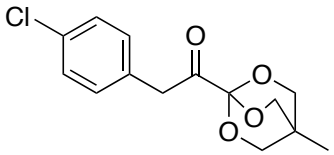
2-Mesityl-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (636).



2-Bromomesitylene (98 μL, 0.64 mmol, 1.1 eq.) was subjected to general procedure F and purified by flash column chromatography using heptane/EtOAc (30%) as eluent, affording OBO-ketone **636** (167 mg, 95%) as an off-white solid. Alternatively, 2-bromomesitylene (980 μL, 6.40 mmol, 1.1 eq.) was subjected to general procedure F with 2 mol% (76 mg) catalyst. The crude material was crystallised from EtOH, affording OBO-ketone **636** (1.45 g, 86%).

m.p.: 170 – 174 °C. **IR**: ν_{max} (thin film) 2971, 2888, 1739, 1623, 1195, 1071, 1049, 974, 946 cm^{-1}. **HRMS**: calculated for $C_{17}H_{23}O_4$, 291.1591 $[M+H]^+$, found *m/z* 291.1591, Δ = 0.04 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 6.86 (2H, s, 2 × *H*C_{Ar}), 4.06 (6H, s, 3 × O*C*H_2), 4.03 (2H, s, *C*H_2C(O)), 2.27 (3H, s, *C*H_3Ar), 2.16 (6H, s, 2 × *C*H_3Ar), 0.88 (3H, s, CC*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 195.5 (*C*(O)), 137.2, 136.5 (2 × C_{Ar}), 128.7 (*H*C_{Ar}), 128.0 (C_{Ar}), 103.9 (*C*O_3), 73.2 (O*C*H_2), 37.7 (*C*H_2C(O)), 30.9 (CH_3*C*), 21.0 (*C*H_3Ar), 20.1 (*C*H_3Ar), 14.3 (*C*H_3).

2-(4-Chlorophenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (637)

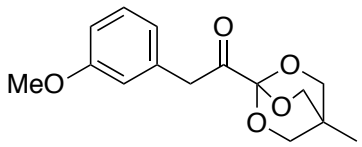


1-Bromo-4-chlorobenzene (122 mg, 0.64 mmol, 1.1 eq.) was subjected to general procedure F and purified by flash column chromatography using toluene/MeCN (7%) as eluent, affording OBO-ketone **637** (125 mg, 76%) as a white solid.

Alternatively, the crude material could also be crystallized from metyl *tert*-butyl ether to afford the product **637** in 66% (109 mg, 66%).

m.p.: 145 – 149 °C. **IR**: ν_{max} (thin film) 2967, 2879, 1726, 1272, 1172, 1092, 1015 cm^{-1}. **HRMS**: calculated for $C_{14}H_{16}O_4Cl$, 283.0732 $[M+H]^+$, found *m/z* 283.0731, Δ = –0.04 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.27 (2H, d, *J* = 8.2 Hz, HC_{Ar}), 7.11 (2H, d, *J* = 8.1 Hz, HC_{Ar}), 4.01 (6H, s, 3 × OCH_2), 3.94 (2H, $CH_2C(O)$), 0.85 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 195.4 (*C*(O)), 132.8, 131.9 (2 × C_{Ar}), 131.3, 128.5 (2 × HC_{Ar}), 103.7 (CO_3), 73.1 (OCH_2), 42.4 ($CH_2C(O)$), 30.9 (CCH_3), 14.1 (CH_3).

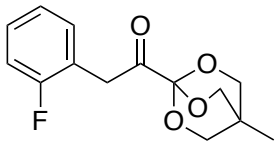
2-(3-methoxyphenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (638)



1-Bromo-3-methoxybenzene (120 mg, 0.64 mmol, 1.1 eq.) was subjected to general procedure F and purified by flash column chromatography using pentane/EtOAc (30%) as eluent, affording OBO-ketone **638** (128 mg, 80%) as pale orange flakes.

m.p.: 145 – 149 °C. **IR**: ν_{max} (thin film) 2941, 2883, 1752, 1256, 1076, 1050, 1036, 999 cm^{-1}. **HRMS**: calculated for $C_{15}H_{18}O_5Na$, 301.1046 $[M+Na]^+$, found *m/z* 301.1046, Δ = 0.0 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.21 (1H, t, *J* = 7.6 Hz, HC_{Ar}), 6.81 – 6.71 (3H, m, 3 × HC_{Ar}), 4.02 (6H, s, 3 × OCH_2), 3.95 (2H, s, $CH_2C(O)$), 3.77 (3H, s, OCH_3), 0.87 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 195.6 (*C*(O)), 159.6, 134.9 (2 × C_{Ar}), 129.4, 122.4, 115.5, 112.7 (4 × HC_{Ar}), 103.8 (CO_3), 73.2 (OCH_2), 55.3 (OCH_3), 43.2 ($CH_2C(O)$), 31.0 (CCH_3), 14.3 (CCH_3). Spectroscopic data obtained by Christopher Hall.[238]

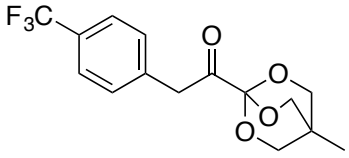
2-(2-Fluorophenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (639)



1-Bromo-2-fluorobenzene (42 μL, 0.39 mmol, 1.0 eq.) was subjected to general procedure G and purified by flash column chromatography using DCM as eluent, affording OBO-ketone **639** (69 mg, 67%) as a brown solid.

m.p.: 85 – 89 °C. **IR**: ν_{max} (thin film) 2970, 2889, 1753, 1074, 1045, 1028, 991, 761 cm^{-1}. **HRMS:** calculated for $C_{14}H_{16}FO_4$, 267.1027 $[M+H]^+$, found *m/z* 267.1027, Δ = 0.15 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.28 – 7.20 (1H, m, HC_{Ar}), 7.15 (1H, dd, *J* = 7.5, 2.0 Hz, HC_{Ar}), 7.10 – 6.99 (2H, m, 2 × HC_{Ar}), 4.03 (8H, s, $CH_2C(O)$) + 3 × OCH_2), 0.86 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 194.5 (*C*(O)), 161.3 (d, *J* = 246 Hz, *C*F), 132.0 (d, *J* = 4.8 Hz, HC_{Ar}), 129.0 (d, *J* = 7.9 Hz, HC_{Ar}), 124.0 (d, *J* = 3.5 Hz, HC_{Ar}), 120.8 (d, *J* = 16.7 Hz, FC*C*), 115.3 (d, *J* = 21.5 Hz, FC*C*H), 103.8 (CO_3), 73.2 (OCH_2), 36.9 ($CH_2C(O)$), 31.0 (CH_3C), 14.3 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F: –116.9 – –117.1 (1F, m, C*F*).

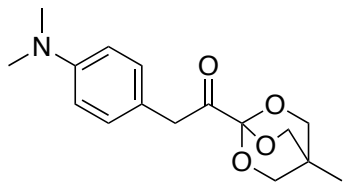
1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-(4-(trifluoromethyl)-phenyl)-ethan-1-one (640)



4-Bromobenzotrifluoride (54 μL, 0.39 mmol, 1.0 eq.) was subjected to general procedure G and purified by flash column chromatography using $CHCl_3$ as eluent, affording OBO-ketone **640** (111 mg, 91%) as a white solid.

m.p.: 63 – 65 °C. **IR**: ν_{max} (thin film) 2967, 2889, 1757, 1325, 1108, 995, 741 cm^{-1}. **HRMS**: calculated for $C_{15}H_{16}O_4F_3$, 317.0995 $[M+H]^+$, found *m/z* 317.0996, Δ = 0.19 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.55 (2H, d, *J* = 8.2 Hz, 2 × CF_3CCH), 7.29 (2H, d, *J* = 8.2 Hz, 2 × CH_2CCH), 4.02 (2H, s, $CH_2C(O)$), 4.02 (6H, s, 3 × OCH_2), 0.85 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 195.0 (*C*(O)), 137.6 ($CCH_2C(O)$), 130.4 ($F_3CCCHCH$), 129.2 (q, *J* = 32.4 Hz, F_3CC), 125.3 (q, *J* = 4.0 Hz, CF_3CCH), 124.3 (q, *J* = 270 Hz, CF_3), 103.8 (CO_3), 73.2 (OCH_2), 42.9 ($CH_2C(O)$), 31.0 (CH_3C), 14.2 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F: –62.45 (3F, s, CF_3).

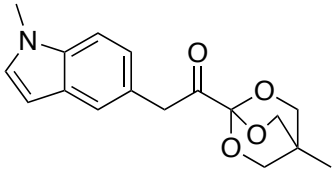
2-(4-(Dimethylamino)phenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (641)



4-Bromo-*N,N*-dimethylaniline (77 mg, 0.39 mmol, 1.0 eq.) was subjected to general procedure G at 50 °C and purified by flash column chromatography using $CHCl_3$/MeOH (1%) as eluent, affording OBO-ketone **641** (103 mg, 91%) as an off-white solid.

m.p.: 166 – 169 °C. **IR**: ν_{max} (thin film) 2959, 2884, 1751, 1524, 1029, 998, 975, 946, 806, 781 cm^{-1}. **HRMS:** calculated for $C_{16}H_{22}NO_4$, 292.1543 $[M+H]^+$, found *m/z* 292.1542, Δ = –0.61 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.08 – 7.02 (2H, m, 2 × HC_{Ar}), 6.72 – 6.67 (2H, m, 2 × HC_{Ar}), 4.01 (6H, s, 3 × OCH_2), 3.89 (2H, s, $CH_2C(O)$), 2.92 (6H, s, $N(CH_3)_2$), 0.85 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 196.4 ($C(O)$), 149.6 (C_{Ar}), 130.5 (HC_{Ar}), 121.1 (C_{Ar}), 112.8 (HC_{Ar}), 103.8 (CO_3), 73.1 (OCH_2), 42.2 ($CH_2C(O)$), 40.7 ($N(CH_3)_2$), 30.9 (CCH_3), 14.2 (CCH_3).

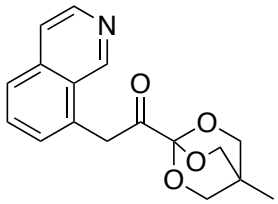
2-(1-Methyl-1*H*-indol-5-yl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (642)



5-Bromo-1-methylindole (81 mg, 0.39 mmol, 1.0 eq.) was subjected to general procedure G and purified by flash column chromatography using DCM as eluent, affording OBO-ketone **642** (105 mg, 90%) as a light red solid.

m.p.: 175 – 178 °C. **IR**: ν_{max} (thin film) 2939, 2881, 1749, 1074, 1047, 1034, 993, 749, 721, 672 cm^{-1}. **HRMS**: calculated for $C_{17}H_{20}NO_4$, 302.1387 $[M+H]^+$, found *m/z* 302.1388, Δ = 0.36 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.44 (1H, s, HC_{Ar}), 7.27 (1H, d, *J* = 8.4 Hz, HC_{Ar}), 7.05 (1H, d, *J* = 8.4 Hz, HC_{Ar}), 7.02 (1H, d, *J* = 3.2 Hz, HC_{Ar}), 6.43 (1H, s, *J* = 3.4 Hz, HC_{Ar}), 4.10 (2H, s, $CH_2C(O)$), 4.03 (6H, s, 3 × OCH_2), 3.74 (3H, s, NCH_3), 0.85 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 196.6 ($C(O)$), 135.9 (C_{Ar}), 129.1 (HC_{Ar}), 128.7, 124.0 (2 × C_{Ar}), 123.5, 122.0, 109.2 (3 × HC_{Ar}), 103.9 (CO_3), 100.7 (HC_{Ar}), 73.1 (OCH_2), 43.3 ($CH_2C(O)$), 32.9 (NCH_3), 30.9 (CH_3C), 14.2 (CCH_3).

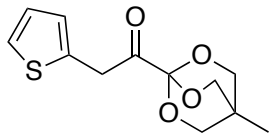
2-(Isoquinolin-8-yl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-ethan-1-one (643)



8-Bromoisoquinoline (81 mg, 0.39 mmol, 1.0 eq.) was subjected to general procedure G and purified by flash column chromatography using DCM/MeOH (5%) as eluent, affording OBO-ketone **643** (84 mg, 72%) as a brown solid.

m.p.: 105 – 108 °C. **IR**: ν_{max} (thin film) 2940, 2883, 1751, 1076, 1048, 1034, 991, 839, 726 cm^{-1}. **HRMS:** calculated for $C_{17}H_{18}NO_4$, 300.1230 $[M+H]^+$, found *m/z* 300.1231, Δ = 0.24 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 9.27 (1H, s, NC*H*C), 8.50 (1H, d, *J* = 5.6 Hz, *H*C_{Ar}), 7.71 (1H, d, *J* = 8.3 Hz, *H*C_{Ar}), 7.62 – 7.55 (2H, m, 2 × *H*C_{Ar}), 7.37 (1H, d, *J* = 7.0 Hz, *H*C_{Ar}), 4.48 (2H, s, C*H*$_2$C(O)), 4.05 (6H, s, 3 × OC*H*$_2$), 0.85 (3H, s, C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 195.1 (*C*(O)), 149.4 (N*C*HC), 142.9 (H*C*$_{Ar}$), 136.3, 131.3 (2 × *C*$_{Ar}$), 130.0, 130.0 (2 × H*C*$_{Ar}$), 127.3 (*C*$_{Ar}$), 126.5, 120.9 (2 × H*C*$_{Ar}$), 103.9 (*C*O_3), 73.3 (O*C*H$_2$), 40.2 (*C*H$_2$C(O)), 31.1 (CH$_3$*C*), 14.2 (*C*H$_3$).

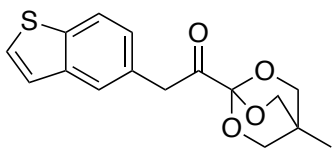
1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-(thiophen-2-yl)ethan-1-one (644)



2-Bromothiophene (37 μL, 0.39 mmol, 1.0 eq.) was subjected to general procedure G and purified by flash column chromatography using DCM as eluent, affording OBO-ketone **644** (65 mg, 66%) as a light yellow solid.

m.p.: 104 – 107 °C. **IR**: ν_{max} (thin film) 2966, 2889, 1756, 1044, 1029, 990, 928, 715 cm^{-1}. **HRMS:** calculated for $C_{12}H_{14}O_4SNa$ 277.0505 $[M+Na]^+$, found *m/z* 277.0505, Δ = 0.02 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.21 (1H, dd, *J* = 5.1, 1.2 Hz, SC*H*), 6.96 (1H, dd, *J* = 5.1, 3.5 Hz, SCHC*H*), 6.91 – 6.88 (1H, m, SCC*H*), 4.19 (2H, s, C*H*$_2$C(O)), 4.03 (6H, s, 3 × OC*H*$_2$), 0.87 (3H, s, C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 194.3 (*C*(O)), 134.2 (S*C*CH), 127.3 (SC*C*H), 126.9 (SCH*C*H), 125.1 (S*C*H), 103.8 (*C*O_3), 73.2 (O*C*H$_2$), 37.2 (*C*H$_2$C(O)), 31.0 (CH$_3$*C*), 14.3 (*C*H$_3$).

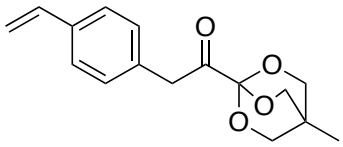
2-(Benzo[b]thiophen-5-yl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (645)



5-Bromo-1-benzothiophene (83 mg, 0.39 mmol, 1.0 eq.) was subjected to general procedure G and purified by flash column chromatography using DCM/MeOH (0.5%) as eluent, affording OBO-ketone **645** (91 mg, 77%) as a yellow solid.

m.p.: 90 – 92 °C. **IR**: ν_{max} (thin film) 3484, 2938, 2882, 1746, 1046 cm^{-1}. **HRMS**: calculated for $C_{16}H_{17}O_4{}^{32}S$, 305.0842 $[M+H]^+$, found *m/z* 305.0843, Δ = 0.17 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.73 (1H, d, *J* = 8.3 Hz, SC*H*), 7.56 (1H, d, *J* = 2.0 Hz, CC*H*C)), 7.33 (1H, d, *J* = 5.4 Hz, *H*C_{Ar}), 7.20 (1H, dd, *J* = 8.3, 0.6 Hz, *H*CAr), 7.09 (1H, dd, *J* = 8.3, 2.0 Hz, SCHC*H*), 4.10 (2H, s, CH_2C(O)), 4.04 (6H, s, 3 × OCH_2), 0.87 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 196.0 (*C*(O)), 140.0, 138.5, 129.5 (3 × C_{Ar}), 126.7 (HC_{Ar}), 126.4 (SCH*C*H), 124.9 (CH_2CCHC), 123.8 (HC_{Ar}), 122.5 (S*C*H), 103.9 (CO_3), 73.3 (OCH_2), 43.1 (CH_2C(O)), 31.1 (CH_3C), 14.3 (CH_3).

1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-(4-vinylphenyl)ethan-1-one (646)

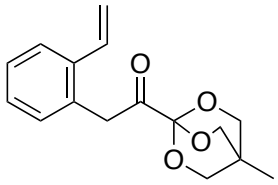


4-Bromostyrene (51 µL, 0.39 mmol, 1.0 eq.) was subjected to general procedure G and purified by flash column chromatography using toluene/MeCN (7%) as eluent, affording OBO-ketone **646** (85 mg, 79%) as a brown solid.

Alternatively, 4-bromostyrene (106 mg, 0.58 mmol) was subjected the same general procedure and the crude material was crystallised from EtOH, affording OBO-ketone **646** (115 mg, 72%).

m.p.: 135 – 139 °C. **IR**: ν_{max} (thin film) 2935, 2882, 1751, 1075, 1049, 993, 715 cm^{-1}. **HRMS:** calculated for $C_{16}H_{19}O_4$, 275.1277 $[M+H]^+$, found *m/z* 275.1278, Δ = –0.25 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.35 (2H, d, *J* = 8.1 Hz, *H*C_{Ar}), 7.14 (2H, d, *J* = 8.2 Hz, *H*C_{Ar}), 6.69 (1H, dd, *J* = 17.6, 10.9 Hz, CH_2CH), 5.72 (1H, d, *J* = 17.6 Hz, CHC$H_{trans}$$H_{cis}$), 5.21 (1H, d, *J* = 10.9 Hz, $CHCH_{trans}H_{cis}$), 4.02 (6H, s, 3 × OCH_2), 3.97 (2H, s, CH_2C(O)), 0.86 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 195.7 (*C*(O)), 136.7 (*C*HCH_2), 136.3, 133.0 (2 × C_{Ar}), 130.1, 126.3 (2 × HC_{Ar}), 113.7 ($CHCH_2$), 103.8 (CO_3), 73.2 (OCH_2), 43.0 (CH_2C(O)), 31.0 (CH_3C), 14.3 (CH_3).

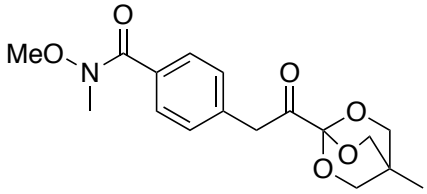
1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-(2-vinylphenyl)ethan-1-one (647)



2-Bromostyrene (49 μL, 0.39 mmol, 1.0 eq.) was subjected to general procedure G and purified by flash column chromatography using toluene/MeCN (7%) as eluent, affording OBO-ketone **647** (89 mg, 84%) as a brown solid.

m.p.: 122 – 123 °C. **IR**: ν_{max} (thin film) 2938, 2882, 1751, 1074, 1048, 1035, 991, 772, 719 cm^{-1}. **HRMS:** calculated for $C_{16}H_{18}O_4Na$, 297.1097 $[M+Na]^+$, found *m/z* 297.1096, Δ = –0.27 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.52 (1H, dd, *J* = 7.5, 1.9 Hz, *H*C_{Ar}), 7.29 – 7.18 (2H, m, 2 × *H*C_{Ar}), 7.09 (1H, dd, *J* = 7.3, 2.0 Hz, *H*C_{Ar}), 6.75 (1H, dd, *J* = 17.3, 10.9 Hz, CH_2CH), 5.62 (1H, dd, *J* = 17.3, 1.8 Hz, CH_aH_bCH), 5.28 (1H, dd, *J* = 10.9, 1.7 Hz, CH_aH_bCH), 4.07 (2H, s, $CH_2C(O)$), 4.04 (6H, s, 3 × OCH_2), 0.87 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 195.3 (*C*(O)), 137.7 (*C*$_{Ar}$), 134.4 (CH_2CH), 131.2 (H*C*$_{Ar}$), 131.2 (*C*$_{Ar}$), 127.8, 127.6, 125.9 (3 × H*C*$_{Ar}$), 116.3 (CH_2CH), 103.8 (CO_3), 73.2 (OCH_2), 41.2 ($CH_2C(O)$), 31.0 (CH_3C), 14.3 (CH_3).

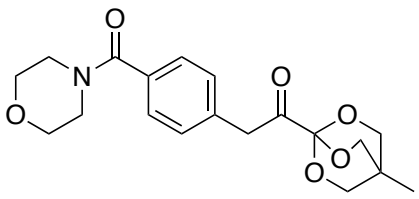
N-Methoxy-N-methyl-4-(2-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-oxoethyl)benzamide (648)



4-Bromo-*N*-methoxy-*N*-methylbenzamide (94 mg, 0.39 mmol, 1.0 eq.) was subjected to general procedure G and purified by flash column chromatography using Et_2O as eluent, affording OBO-ketone **648** (100 mg, 77%) as a white solid.

m.p.: 69 – 72 °C. **IR**: ν_{max} (thin film) 2936, 2884, 1752, 1636, 1076, 1049, 910, 726 cm^{-1}. **HRMS**: calculated for $C_{17}H_{22}NO_6$, 336.1442 $[M+H]^+$, found *m/z* 336.1437, Δ = –1.30 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.58 (2H, d, *J* = 7.8 Hz, 2 × *H*C_{Ar}), 7.17 (2H, d, *J* = 7.8 Hz, 2 × *H*C_{Ar}), 3.97 (6H, s, 3 × OCH_2), 3.96 (2H, s, $CH_2C(O)$), 3.51 (3H, s, OCH_3), 3.29 (3H, s, NCH_3), 0.81 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 195.2 (*C*(O)), 169.6 (*C*(O)N), 136.2, 132.5 (2 × *C*$_{Ar}$), 129.5, 128.3 (2 × H*C*$_{Ar}$), 103.6 (CO_3), 73.1 (OCH_2), 61.0 (OCH_3), 42.9 ($CH_2C(O)$), 33.9 (NCH_3), 30.9 (CCH_3), 14.1 (CCH_3).

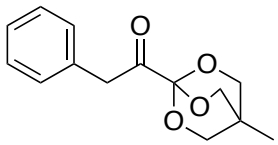
1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-(4-(morpholine-4-carbonyl)phenyl)-ethan-1-one (649).



(4-Bromophenyl)(morpholino)methanone (105 mg, 0.39 mmol, 1.0 eq.) was subjected to general procedure G and purified by flash column chromatography using EtOAc as eluent, affording OBO-ketone **649** (113 mg, 81%) as a white solid.

m.p.: 138 – 140 °C. **IR**: ν_{max} (thin film) 3390, 2962, 2930, 2888, 1748, 1625, 1455, 1027, 991, 972, 938 cm^{-1}. **HRMS**: calculated for $C_{19}H_{24}NO_6$, 362.1598 $[M+H]^+$, found *m/z* 362.1597, Δ = –0.23 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.33 (2H, d, *J* = 8.2 Hz, 2 × *H*C_{Ar}), 7.21 (2H, d, *J* = 8.1 Hz, 2 × *H*C_{Ar}), 4.02 (6H, s, 3 × O*C*H_2), 3.98 (2H, s, *C*H_2C(O)), 3.85 – 3.35 (8H, m, 2 × O*C*H_2*C*H_2N), 0.86 (3H, s, *C*H_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 195.2 (CH_2*C*(O)), 170.3 (*C*(O)N), 135.4, 133.8 (2 × C_{Ar}), 130.1, 127.3 (2 × HC_{Ar}), 103.7 (*C*O_3), 73.2 (O*C*H_2), 66.9 (2 × O*C*H_2), 48.3 ($C_a$$H_2NC_b$$H_2$, br.), 42.9 (*C*$H_2$C(O)), 42.6 ($C_a$$H_2$N*C*$_b$$H_2$, br.), 31.0 ($CH_3$*C*), 14.2 (*C*$H_3$).

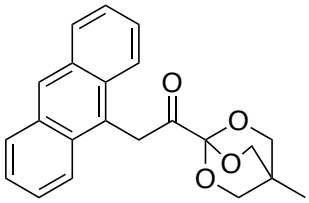
1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-phenylethan-1-one (652).



Chlorobenzene (65 μL, 0.64 mmol, 1.1 eq.) was subjected to general procedure F and purified by flash column chromatography using heptane/EtOAc (30%) as eluent, affording OBO-ketone **652** (113 mg, 78%) as a white solid.

m.p.: 118 – 120 °C. **IR**: ν_{max} (thin film) 2890, 1752, 1076, 1046, 1029, 992, 726 cm^{-1}. **HRMS**: calculated for $C_{14}H_{17}O_4$, 249.1121 $[M+H]^+$, found *m/z* 249.1123, Δ = 0.58 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.42 – 7.20 (5H, m, 5 × *H*C_{Ar}), 4.08 (6H, s, 3 × O*C*H_2), 4.05 (2H, s, *C*H_2C(O)), 0.91 (3H, s, *C*H_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 195.7 (*C*(O)), 133.4 (C_{Ar}), 129.9, 128.4, 126.9 (3 × HC_{Ar}), 103.7 (*C*O_3), 73.1 (O*C*H_2), 43.1 (*C*H_2C(O)), 30.9 (CH_3*C*), 14.2 (*C*H_3).

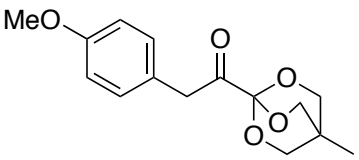
2-(Anthracen-9-yl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (653)



9-Chloroanthracene (82 mg, 0.39 mmol, 1.0 eq.) was subjected to general procedure G and purified by flash column chromatography using toluene/MeCN (7%) as eluent, affording OBO-ketone **653** (103 mg, 76%) as a yellow solid.

m.p.: 180 – 183 °C. **IR**: ν_{max} (thin film) 3056, 2938, 2882, 1752, 1058, 1032, 990, 729 cm^{-1}. **HRMS**: calculated for $C_{22}H_{21}O_4$, 349.1434 $[M+H]^+$, found *m/z* 349.1438, Δ = 0.95 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.44 (1H, s, $C_{Ar}HC_{Ar}C_{Ar}$), 8.08 (2H, d, *J* = 8.8 Hz, 2 × HC_{Ar}), 8.02 (2H, d, *J* = 8.2 Hz, 2 × HC_{Ar}), 7.56 – 7.44 (4H, m, 4 × HC_{Ar}), 5.05 (2H, s, $CH_2C(O)$), 4.07 (6H, s, 3 × OCH_2), 0.77 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 195.3 (*C*(O)), 131.5, 130.9 (2 × C_{Ar}), 129.2 (HC_{Ar}), 127.3 ($C_{Ar}HC_{Ar}C_{Ar}$), 126.1 (HC_{Ar}), 125.9 (C_{Ar}), 124.9, 124.3 (2 × HC_{Ar}), 104.1 (CO_3), 73.3 (OCH_2), 36.5 ($CH_2C(O)$), 30.9 (CCH_3), 14.1 (CCH_3).

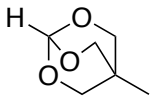
2-(4-methoxyphenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (654)



1-Chloromethoxybenzene (55 mg, 0.39 mmol, 1.0 eq.) was subjected to general procedure G and purified by flash column chromatography using toluene/MeCN (5%) as eluent, affording OBO-ketone **654** (89 mg, 83%) as a yellow solid.

m.p.: 154 – 156 °C. **IR**: ν_{max} (thin film) 2969, 2885, 1754, 1515, 1247, 1077, 1047, 1033, 999 cm^{-1}. **HRMS**: calculated for $C_{15}H_{18}O_5Na$, 301.1046 $[M+Na]^+$, found *m/z* 301.1048, Δ = 0.50 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.09 (2H, d, *J* = 8.7 Hz, 2 × HC_{Ar}), 6.84 (2H, d, *J* = 8.7 Hz, 2 × HC_{Ar}), 4.02 (6H, s, 3 × OCH_2), 3.91 (2H, s, $CH_2C(O)$), 3.78 (3H, s, OCH_3), 0.87 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 196.1 (*C*(O)), 158.6 (C_{Ar}), 131.0 (HC_{Ar}), 125.4 (C_{Ar}), 114.0 (HC_{Ar}), 103.8 (CO_3), 73.2 (OCH_2), 55.3 (OCH_3), 42.4 ($CH_2C(O)$), 31.0 (CCH_3), 14.4 (CCH_3). Spectroscopic data obtained by Christopher Hall.[238]

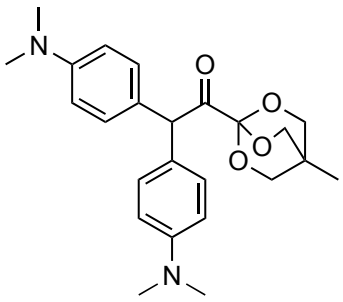
4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (665)



4-Bromopyridine (61 μL, 0.64 mmol, 1.1 eq.) was subjected to general procedure F and purified by flash column chromatography using pentane/EtOAc (30%) as eluent, affording by-product **665** (39 mg, 52%) as a white solid.

m.p.: 95 – 99 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 5.54 (1 H, s, HCO_3), 3.89 (6 H, s, 3 × OCH_2), 0.81 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, CDCl3) δ_C: 101.7 (HCO_3), 72.0 (OCH_2), 30.6 (CCH_3), 15.0 (CH_3). Spectroscopic and melting point data were consistent with those previously reported.[282] Spectroscopic data obtained by Christopher Hall.[238]

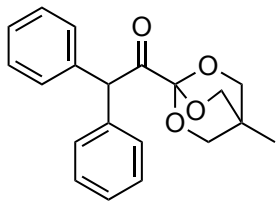
2,2-Bis(4-(dimethylamino)phenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]-octan-1-yl)-ethan-1-one (670)



4-Bromo-*N*,*N*-dimethylaniline (349 mg, 1.74 mmol, 3.0 eq.) was subjected to general procedure H and purified by flash column chromatography using pentane/EtOAc (30% to 45%) as eluent, affording OBO-ketone **670** (193 mg, 81%) as a white solid.

m.p.: 202 – 205 °C. **IR**: ν_{max} (thin film) 2980, 2881, 2784, 1745, 1612, 1560, 1071, 1037, 997, 790 cm^{-1}. **HRMS:** calculated for $C_{24}H_{31}N_2O_4$, 411.2278 $[M+H]^+$, found *m/z* 411.2266, Δ = –3.09 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.14 (4H, d, *J* = 8.7 Hz, 4 × HC_{Ar}), 6.67 (4H, d, *J* = 8.7 Hz, 4 × HC_{Ar}), 5.61 (1H, s, ArC*H*Ar), 3.98 (6H, s, 3 × OCH_2), 2.91 (12H, s, 2 × $N(CH_3)_2$), 0.81 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 197.4 (*C*(O)), 149.4 (C_{Ar}), 129.6 (HC_{Ar}), 127.3 (C_{Ar}), 112.6 (HC_{Ar}), 104.2 (CO_3), 73.1 (OCH_2), 54.8 (Ar*C*HAr), 40.7 ($N(CH_3)_2$), 31.0 (CH_3C), 14.3 (CH_3).

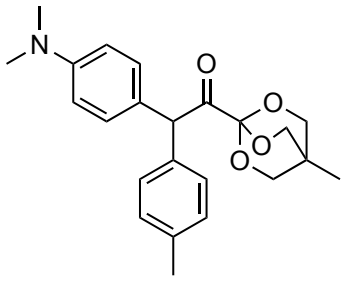
1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2,2-diphenylethan-1-one (671)



Chlorobenzene (176 μL, 1.74 mmol, 3.0 eq.) was subjected to general procedure H and purified by flash column chromatography using pentane/EtOAc (30%) as eluent, affording OBO-ketone **671** (137 mg, 73%) as a white solid.

m.p.: 112 – 113 °C. **IR**: ν_{max} (thin film) 2884, 1745, 996, 906, 727, 697 cm^{-1}. **HRMS:** calculated for $C_{20}H_{21}O_4$, 325.1434 $[M+H]^+$, found *m/z* 325.1433, Δ = –0.29 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.33 – 7.20 (10H, m, 10 × HC_{Ar}), 5.81 (1H, s, PhC*H*Ph), 3.98 (6H, s, 3 × OCH_2), 0.81 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 196.5 (*C*(O)), 138.6 (C_{Ar}), 129.1, 128.5, 127.0 (3 × HC_{Ar}), 104.2 (CO_3), 73.2 (OCH_2), 56.7 (Ph*C*HPh), 31.1 (CH_3C), 14.2 (CH_3).

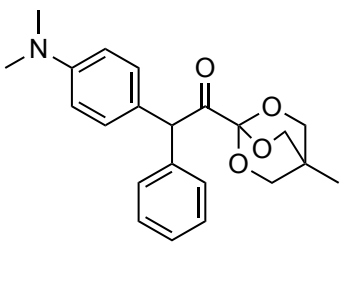
2-(4-(Dimethylamino)phenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-(*p*-tolyl)ethan-1-one (673)



4-Methyl-bromobenzene (109 mg, 0.64 mmol, 1.1 eq.) was subjected to general procedure F, followed by the addition of 4-bromo-*N*,*N*-dimethylaniline (290 mg, 1.45 mmol, 2.5 eq.) according to general procedure I. The resulting solid was purified by flash column chromatography using pentane/EtOAc (30%) as eluent, affording OBO-ketone **673** (149 mg, 67%) as a white solid.

m.p.: 184 – 187 °C. **IR**: ν_{max} (thin film) 2980, 2971, 2885, 1740, 1614, 1521, 1068, 1049, 1035, 1005, 776, 714 cm^{-1}. **HRMS:** calculated for $C_{23}H_{28}NO_4$, 382.2013 $[M+H]^+$, found *m/z* 382.2009, Δ = –0.98 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.16 – 7.06 (6H, m, 6 × HC_{Ar}), 6.69 – 6.64 (2H, m, 2 × HC_{Ar}), 5.65 (1H, s, Ar^1CHAr^2), 3.98 (6H, s, 3 × OCH_2), 2.91 (6H, s, $N(CH_3)_2$), 2.30 (3H, s, $PhCH_3$), 0.82 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 197.1 (*C*(O)), 149.6, 136.6, 136.3 (3 × C_{Ar}), 129.7, 129.1, 128.8 (3 × HC_{Ar}), 126.5 (C_{Ar}), 112.6 (HC_{Ar}), 104.3 (CO_3), 73.2 (OCH_2), 55.4 (Ar^1CHAr^2), 40.7 ($N(CH_3)_2$), 31.1 (CCH_3), 21.1 ($PhCH_3$), 14.4 (CCH_3).

2-(4-(Dimethylamino)phenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-phenylethan-1-one (674)

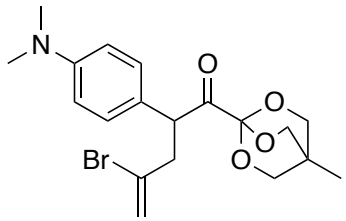


4-Bromo-*N*,*N*-dimethylaniline (116 mg, 0.58 mmol, 1.0 eq.) was subjected to general procedure G, followed by the addition of chlorobenzene (147 µL, 1.45 mmol, 2.5 eq.) according to general procedure I. The resulting solid was purified by flash column

chromatography using pentane/EtOAc (30%) as eluent, affording OBO-ketone **674** (151 mg, 71%) as a white solid.

m.p.: 136 – 138 °C. **IR**: ν_{max} (thin film) 2961, 2881, 1746, 1611, 1518, 1070, 1035, 1002, 725, 696 cm^{-1}. **HRMS:** calculated for $C_{22}H_{26}NO_4$, 368.1856 $[M+H]^+$, found *m/z* 368.1856, Δ = 0.01 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.31 – 7.17 (5H, m, 5 × *H*C_{Ar}), 7.16 – 7.11 (2H, m, 2 × *H*C_{Ar}), 6.69 – 6.64 (2H, m, 2 × *H*C_{Ar}), 5.69 (1H, s, Ar^1C*H*Ar^2), 3.98 (6H, 3 × O*C*H_2), 2.92 (6H, s, N(*C*H_3)$_2$), 0.82 (3H, s, *C*H_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 197.0 (*C*(O)), 149.6, 139.6 (2 × C_{Ar}), 129.8, 129.0, 128.3, 126.7 (4 × HC_{Ar}), 126.1 (C_{Ar}), 112.6 (HC_{Ar}), 104.2 (*C*O_3), 73.2 (O*C*H_2), 55.8 (Ar^1*C*HAr^2), 40.6 (N(*C*H_3)$_2$), 31.1 (*C*CH_3), 14.3 (C*C*H_3).

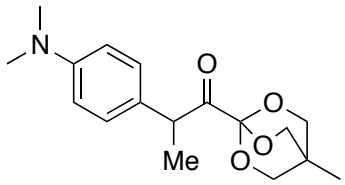
4-Bromo-2-(4-(dimethylamino)phenyl)-1-(4-methyl-2,6,7-trioxabicyclo-[2.2.2]octan-1-yl)pent-4-en-1-one (677)



4-Bromo-*N*,*N*-dimethylaniline (116 mg, 0.58 mmol, 1.0 eq.) was subjected to general procedure G, followed by the addition of 2,3-dibromopropene (90 μL, 0.87 mmol, 1.5 eq.), reacted at 50 °C for 3 h following general procedure J and was purified by flash column chromatography using toluene/MeCN (2% to 5%) as eluent, affording OBO-ketone **677** (165 mg, 69%) as a light red solid.

m.p.: 89 – 92 °C. **IR**: ν_{max} (thin film) 2936, 2882, 1745, 1612, 1520, 1349, 1325, 1125, 1066, 1031, 987, 947 cm^{-1}. **HRMS:** calculated for $C_{19}H_{25}NO_4Br$, 410.0961 $[M+H]^+$, found *m/z* 410.0959, Δ = –0.71 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.11 – 7.06 (2H, m, 2 × *H*C_{Ar}), 6.66 – 6.60 (2H, m, 2 × *H*C_{Ar}), 5.46 – 5.43 (1H, m, C*H*$_a$CH$_b$CBr), 5.29 (1H, d, *J* = 2.0 Hz, CH$_a$*H*$_b$CBr), 4.57 (1H, t, *J* = 7.3 Hz, C*H*CH_2), 3.93 (6H, s, 3 × O*C*H_2), 3.09 (1H, ddd, *J* = 14.8, 7.0, 1.0 Hz, CHC*H*$_a$H$_b$CBr), 2.91 (6H, s, N(*C*H_3)$_2$), 2.76 (1H, ddd, *J* = 14.8, 7.7, 0.8 Hz, CHCH$_a$*H*$_b$CBr), 0.80 (3H, s, *C*H_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 197.2 (*C*(O)), 149.7 (C_{Ar}), 131.0 (*C*Br), 129.5 (HC_{Ar}), 124.1 (C_{Ar}), 119.1 (*C*H_2CBr), 112.5 (HC_{Ar}), 104.0 (*C*O_3), 73.1 (O*C*H_2), 49.5 (*C*HCH_2), 44.8 (CH*C*H_2), 40.6 (N(*C*H_3)$_2$), 31.0 (*C*CH_3), 14.3 (C*C*H_3).

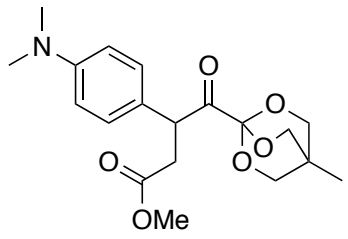
2-(4-(Dimethylamino)phenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)propan-1-one (678)



4-Bromo-*N*,*N*-dimethylaniline (116 mg, 0.58 mmol, 1.0 eq.) was subjected to general procedure G, followed by the addition of methyl iodide (54 μL, 0.87 mmol, 1.5 eq.), reacted at 50 °C for 3 h following general procedure J and was purified by flash column chromatography using toluene/MeCN (5%) as eluent, affording OBO-ketone **678** (151 mg, 85%) as a white solid.

m.p.: 116 – 118 °C. **IR**: ν_{max} (thin film) 2933, 2880, 2802, 1742, 1613, 1519, 1032, 1004, 948, 821 cm^{-1}. **HRMS**: calculated for $C_{17}H_{24}NO_4$, 306.1700 $[M+H]^+$, found *m/z* 306.1698, Δ = –0.50 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.17 – 7.12 (2H, m, 2 × *H*C_{Ar}), 6.69 – 6.64 (2H, m, 2 × *H*C_{Ar}), 4.30 (1H, q, *J* = 7.0 Hz, C*H*CH_3), 3.95 (6H, s, 3 × OCH_2), 2.91 (6H, s, N(CH_3)$_2$), 1.39 (3H, d, *J* = 7.0 Hz, CHCH_3), 0.82 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 199.5 (*C*(O)), 149.6 (*C*$_{Ar}$), 128.9 (H*C*$_{Ar}$), 127.9 (*C*$_{Ar}$), 112.7 (H*C*$_{Ar}$), 104.2 (*C*O_3), 73.1 (O*C*H_2), 45.0 (*C*HCH_3), 40.8 (N(*C*H_3)$_2$), 31.0 (*C*CH_3), 19.1 (CH*C*H_3), 14.4 (C*C*H_3).

Methyl 3-(4-(dimethylamino)phenyl)-4-(4-methyl-2,6,7-trioxabicyclo-[2.2.2]-octan-1-yl)-4-oxobutanoate (679)

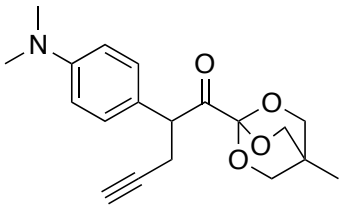


4-Bromo-*N*,*N*-dimethylaniline (77 mg, 0.39 mmol, 1.0 eq.) was subjected to general procedure G, followed by the addition of methyl bromoacetate (37 μL, 0.39 mmol, 1.0 eq.), reacted at 50 °C for 3 h following general procedure J and was purified by flash column chromatography using pentane/EtOAc (50%) as eluent, affording OBO-ketone **679** (104 mg, 74%) as a brown solid.

m.p.: 110 – 112 °C. **IR**: ν_{max} (thin film) 2950, 2882, 1734, 1612, 1520, 1033, 1002 cm^{-1}. **HRMS:** calculated for $C_{19}H_{26}NO_6$, 364.1755 $[M+H]^+$, found *m/z* 364.1750, Δ = –1.22 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.10 – 7.05 (2H, m, 2 × *H*C_{Ar}), 6.65 – 6.60 (2H, m, 2 × *H*C_{Ar}), 4.66 (1H, dd, *J* = 8.9, 6.4 Hz, C*H*CH_2), 3.91 (6H, s, 3 × OCH_2), 3.59 (3H, s, OCH_3), 3.09 (1H, dd, *J* = 16.7, 8.9 Hz, C$H_a$$H_b$$CO_2$Me), 2.91 (6H, s, N($CH_3$)$_2$), 2.62 (1H, dd, *J* = 16.7, 6.4 Hz, C$H_a$$H_b$$CO_2$Me), 0.79 (3H, s, C$CH_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 197.5 (*C*(O)), 172.2

(CO_2), 149.8 (C_{Ar}), 129.3 (HC_{Ar}), 124.1 (C_{Ar}), 112.6 (HC_{Ar}), 104.1 (CO_3), 73.1 (OCH_2), 51.8 (OCH_3), 47.2 ($CHCH_2$), 40.6 ($N(CH_3)_2$), 37.9 ($CHCH_2$), 30.9 (CCH_3), 14.3 (CCH_3).

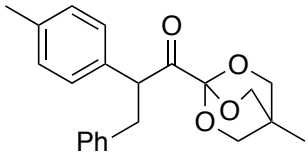
2-(4-(Dimethylamino)phenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)pent-4-yn-1-one (680)



4-Bromo-*N*,*N*-dimethylaniline (116 mg, 0.58 mmol, 1.0 eq.) was subjected to general procedure G, followed by the addition of propargyl bromide 80% in toluene (63 μL, 0.58 mmol, 1.0 eq.), reacted at 50 °C for 3 h following general procedure J and was purified by flash column chromatography using toluene/MeCN (5% to 10%) as eluent, affording OBO-ketone **680** (146 mg, 76%) as a light red solid.

m.p.: 111 – 113 °C. **IR**: ν_{max} (thin film) 3282, 2881, 2810, 1729, 1611, 1523, 1072, 1029, 1004, 984, 794, 671, 647 cm^{-1}. **HRMS**: calculated for $C_{19}H_{24}NO_4$, 330.1700 $[M+H]^+$, found *m/z* 330.1699, Δ = –0.28 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.13 – 7.08 (2H, m, 2 × HC_{Ar}), 6.67 – 6.62 (2H, m, 2 × HC_{Ar}), 4.38 (1H, dd, *J* = 8.2, 7.1 Hz, $CHCH_2$), 3.92 (6H, s, 3 × OCH_2), 2.92 (6H, s, $N(CH_3)_2$), 2.79 (1H, ddd, *J* = 16.8, 7.0, 2.6 Hz, $CHCH_aH_b$), 2.57 (1H, ddd, *J* = 16.8, 8.3, 2.7 Hz, $CHCH_aH_b$), 1.89 (1H, t, *J* = 2.6 Hz, CH_2CCH), 0.80 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 197.0 (C(O)), 149.8 (C_{Ar}), 129.2 (HC_{Ar}), 124.2 (C_{Ar}), 112.5 (HC_{Ar}), 104.0 (CO_3), 82.1 (CHC), 73.1 (OCH_2), 69.5 ($CHCCH_2$), 50.3 ($CHCH_2$), 40.5 ($N(CH_3)_2$), 31.0 (CCH_3), 23.0 ($CHCH_2$), 14.3 (CH_3).

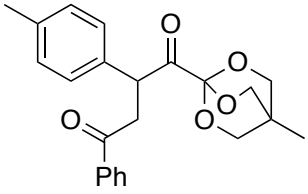
1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-3-phenyl-2-(*p*-tolyl)-propan-1-one (681)



4-Methyl-bromobenzene (109 mg, 0.64 mmol, 1.1 eq.) was subjected to general procedure F, followed by the addition of benzyl bromide (76 μL, 0.64 mmol, 1.1 eq.), reacted at 50 °C for 3 h following general procedure J and was purified by flash column chromatography using pentane/EtOAc (20%) as eluent, affording OBO-ketone **681** (136 mg, 66%) as an off-white solid.

m.p.: 136 – 139 °C. **IR**: ν_{max} (thin film) 2933, 2881, 1742, 1074, 1053, 1031, 1000, 986, 748, 698 cm^{-1}. **HRMS**: calculated for $C_{22}H_{25}O_4$, 353.1747 $[M+H]^+$, found *m/z* 353.1747, Δ = –0.15 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.21 – 7.00 (9H, m, 9 × HC_{Ar}), 4.51 (1H, dd, *J* = 8.7, 6.2 Hz, C*H*C(O)), 3.90 (6H, s, 3 × OCH_2), 3.34 (1H, dd, *J* = 13.8, 6.5 Hz, CHCH_aH$_b$), 2.98 (1H, dd, *J* = 13.8, 8.6 Hz, CHCH$_a$$H_b$), 2.29 (3H, s, C$H_3$Ph), 0.79 (3H, s, CC$H_3$) . **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 198.0 (*C*(O)), 139.4, 136.5, 134.6 (3 × C_{Ar}), 129.2, 129.1, 128.7, 128.1, 126.0 (5 × HC_{Ar}), 104.0 (CO_3), 73.0 (OCH_2), 53.5 (*C*HCH$_2$), 39.7 (CH*C*H$_2$), 30.9 (*C*CH$_3$), 21.2 (*C*H$_3$Ph), 14.3 (C*C*H$_3$).

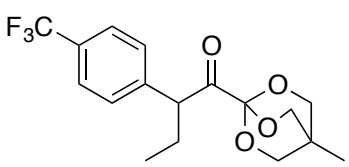
1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-4-phenyl-2-(*p*-tolyl)-butane-1,4-dione (682)



4-Methyl-bromobenzene (109 mg, 0.64 mmol, 1.1 eq.) was subjected to general procedure F, followed by the addition of bromoacetophenone (231 mg, 1.16 mmol, 2.0 eq.), reacted at 80 °C for 8 h following general procedure J and was purified by flash column chromatography using pentane/EtOAc (30%) as eluent, affording OBO-ketone **682** (165 mg, 75%) as a brown solid.

m.p.: 116 – 118 °C. **IR**: ν_{max} (thin film) 2936, 2881, 1741, 1686, 1069, 1034, 996, 754, 691 cm^{-1}. **HRMS**: calculated for $C_{23}H_{25}O_5$, 381.1696 $[M+H]^+$, found *m/z* 381.1695, Δ = –0.49 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.96 – 7.91 (2H, m, 2 × HC_{Ar}), 7.55 – 7.49 (1H, m, HC_{Ar}), 7.44 – 7.37 (2H, m, 2 × HC_{Ar}), 7.17 (2H, d, *J* = 8.1 Hz, 2 × HC_{Ar}), 7.10 (2H, d, *J* = 8.2 Hz, 2 × HC_{Ar}), 4.96 (1H, dd, *J* = 9.2, 5.0 Hz, C*H*CH$_2$), 3.95 (6H, s, 3 × OCH_2), 3.87 (1H, dd, *J* = 18.1, 9.2 Hz, CHCH_aH$_b$), 3.31 (1H, dd, *J* = 18.1, 5.0 Hz, CHCH$_a$$H_b$), 2.31 (3H, s, C$H_3$Ph), 0.80 (3H, s, C$H_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 197.7(C_a(O)), 197.2 (C_bC(O)), 136.8, 136.4, 134.3 (3 × C_{Ar}), 133.1, 129.3, 128.5, 128.5, 128.2 (5 × HC_{Ar}), 104.1 (CO_3), 73.0 (OCH_2), 46.8 (*C*HCH$_2$), 43.2 (CH*C*H$_2$), 30.9 (*C*CH$_3$), 21.1 (*C*H$_3$Ph), 14.3 (C*C*H$_3$).

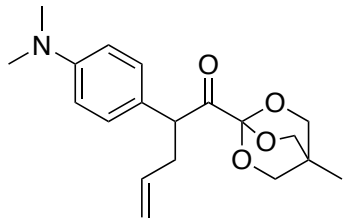
1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-(4-(trifluoromethyl)-phenyl)butan-1-one (683)



4-Bromobenzotrifluoride (81 μL, 0.58 mmol, 1.0 eq.) was subjected to general procedure G, followed by the addition of ethyl iodide (93 μL, 1.16 mmol, 2.0 eq.), reacted at 70 °C for 3 h following general procedure J and was purified by flash column chromatography using toluene/MeCN (3%) as eluent, affording OBO-ketone **683** (153 mg, 77%) as a white solid.

m.p.: 85 – 86 °C. **IR**: ν_{max} (thin film) 2968, 2882, 1746, 1323, 1163, 1067, 1048, 1034, 993 cm^{-1}. **HRMS:** calculated for $C_{17}H_{20}F_3O_4$, 345.1308 $[M+H]^+$, found *m/z* 345.1309, Δ = 0.11 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.52 (2H, d, *J* = 8.3 Hz, 2 × *H*C_{Ar}), 7.37 (2H, d, *J* = 8.3 Hz, 2 × *H*C_{Ar}), 4.22 (1H, t, *J* = 7.5 Hz, C*H*C(O)), 3.93 (6H, s, 3 × OC*H*$_2$), 2.12 – 1.98 (1H, m, C*H*$_a$H$_b$CH$_3$), 1.79 – 1.66 (1H, m, CH$_a$*H*$_b$CH$_3$), 0.81 (3H, s, CC*H*$_3$), 0.81 (3H, t, *J* = 7.3 Hz, CH$_2$C*H*$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C: 198.0 (*C*(O)), 142.6 (CHC(O)), 129.1 (q, *J* = 31.7 Hz, F$_3$C*C*), 129.0 (H*C*$_{Ar}$C$_{Ar}$CH), 125.3 (q, *J* = 3.8 Hz, F$_3$CC*C*H), 124.3 (q, *J* = 271.9 Hz, *C*F$_3$), 104.0 (*C*O$_3$), 73.1 (O*C*H$_2$), 53.6 (*C*HC(O)), 31.1 (*C*CH$_3$), 27.2 (*C*H$_2$CH$_3$), 14.3 (C*C*H$_3$), 12.1 (CH$_2$*C*H$_3$). **^{19}F NMR** (377 MHz, $CDCl_3$) δ_F: –62.6 (3F, s, C*F*$_3$).

2-(4-(Dimethylamino)phenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)pent-4-en-1-one (684)

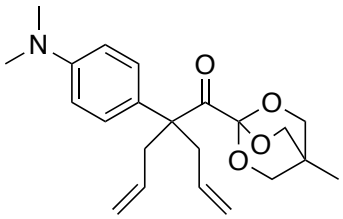


4-Bromo-*N*,*N*-dimethylaniline (116 mg, 0.58 mmol, 1.0 eq.) was subjected to general procedure G, followed by the addition of allyl bromide (50 μL, 0.58 mmol, 1.0 eq.), reacted at 50 °C for 3 h following general procedure J and was purified by flash column chromatography using toluene/MeCN (2% to 5%) as eluent, affording OBO-ketone **684** (158 mg, 82%) as an off-white solid.

m.p.: 86 – 88 °C. **IR**: ν_{max} (thin film) 2935, 2880, 1740, 1612, 1519, 1347, 1075, 1051, 1033, 990 cm^{-1}. **HRMS**: calculated for $C_{19}H_{26}NO4$, 332.1856 $[M+H]^+$, found *m/z* 332.1854, Δ = –0.72 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.14 – 7.08 (2H, m, 2 × *H*C_{Ar}), 6.68 – 6.62 (2H, m, 2 × *H*C_{Ar}), 5.70 – 5.58 (1H, m, CH$_2$C*H*CH$_2$), 5.02 (1H, dd, *J* = 17.1, 1.8 Hz, C*H*$_a$H$_b$CH),

4.93 (1H, dd, J = 10.2, 1.8 Hz, CH_aH_bCH), 4.23 (1H, t, J = 7.6 Hz, $CHC(O)$), 3.93 (6H, 3 × OCH_2), 2.91 (6H, s, $N(CH_3)_2$), 2.78 – 2.68 (1H, m, $CH_aH_bCHC(O)$), 2.49 – 2.38 (1H, m, $CH_aH_bCHC(O)$), 0.80 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 198.1 ($C(O)$), 149.6 (C_{Ar}), 136.0 (CH_2CHCH_2), 129.3 (HC_{Ar}), 125.4 (C_{Ar}), 116.5 ($CH_2CHCH_2C(O)$), 112.6 (HC_{Ar}), 104.0 (CO_3), 73.0 (OCH_2), 50.8 ($CHC(O)$), 40.6 ($N(CH_3)_2$), 37.9 ($C(O)CH$), 30.9 (CCH_3), 14.3 (CCH_3).

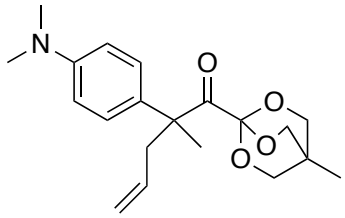
2-Allyl-2-(4-(dimethylamino)phenyl)-1-(4-methyl-2,6,7-trioxabicyclo-[2.2.2]octan-1-yl)pent-4-en-1-one (685)



4-Bromo-*N*,*N*-dimethylaniline (116 mg, 0.58 mmol, 1.0 eq.) was subjected to general procedure G, followed by the addition of allyl bromide (151 µL, 1.74 mmol, 3.0 eq.) and 2 M NaO*t*Bu in THF (0.58 mL, 2.0 eq.). The mixture was reacted at 80 °C for 3 h following general procedure J and was purified by flash column chromatography using toluene/MeCN (7%) as eluent, affording OBO-ketone **685** (183 mg, 85%) as a white solid.

m.p.: 140 – 142 °C. **IR**: ν_{max} (thin film) 2964, 2931, 2881, 1720, 1615, 1521, 1258, 1027, 1001, 654 cm^{-1}. **HRMS:** calculated for $C_{22}H_{30}NO_4$, 372.2169 $[M+H]^+$, found m/z 372.2170, Δ = 0.12 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.04 – 6.99 (2H, m, 2 × HC_{Ar}), 6.68 – 6.62 (2H, m, 2 × HC_{Ar}), 5.54 – 5.40 (2H, m, 2 × CH_2CH), 5.05 – 4.96 (4H, m, 2 × CH_2CHCH_2C), 3.78 (6H, s, 3 × OCH_2), 3.01 (2H, dd, J = 14.0, 7.2 Hz, 2 × CCH_aH_b), 2.93 (6H, s, $N(CH_3)_2$), 2.66 (2H, dd, J = 14.0, 7.2 Hz, 2 × CCH_aH_b), 0.72 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 199.4 ($C(O)$), 149.0 (C_{Ar}), 134.4 ($CHCH_2$), 128.0 (HC_{Ar}), 127.9 (C_{Ar}), 118.1 (CH_2CHCH_2C), 112.2 (HC_{Ar}), 104.9 (CO_3), 72.7 (OCH_2), 56.2 ($CC(O)$), 40.7 ($N(CH_3)_2$), 37.8 (CCH_2), 30.7 (CCH_3), 14.4 (CCH_3).

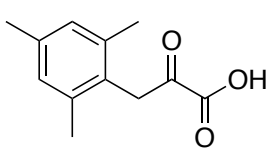
2-(4-(Dimethylamino)phenyl)-2-methyl-1-(4-methyl-2,6,7-trioxabicyclo-[2.2.2]octan-1-yl)pent-4-en-1-one (686)



4-Bromo-*N*,*N*-dimethylaniline (116 mg, 0.58 mmol, 1.0 eq.) was subjected to general procedure G, followed by the addition of methyl iodide (36 μL, 0.58 mmol, 1.0 eq.) and was reacted at 50 °C for 3 h following general procedure J. Allyl bromide (126 μL, 1.45 mmol, 2.5 eq.) and 2 M NaO*t*Bu in THF (0.58 mL, 1.16 mmol) were then added and the mixture was reacted at 80 °C for 3 h. The crude material was purified by flash column chromatography using pentane/EtOAc (20% to 30%) as eluent, affording OBO-ketone **686** (96 mg, 48%) as a white solid.

m.p.: 134 – 137 °C. **IR**: ν_{max} (thin film) 2928, 2876, 1721, 1639, 1521, 1030, 998, 918, 814, 737 cm^{-1}. **HRMS**: calculated for $C_{20}H_{28}NO_4$, 346.2013 $[M+H]^+$, found *m/z* 346.2008, Δ = –1.38 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.10 – 7.05 (2H, m, 2 × HC_{Ar}), 6.68 – 6.63 (2H, m, 2 × HC_{Ar}), 5.57 – 5.44 (1H, m, CH_2CHCH_2CH), 5.06 – 4.92 (2H, m, CH_2CHCH_2CH), 3.82 (6H, s, 3 × OCH_2), 2.92 (6H, s, $N(CH_3)_2$), 2.83 (1H, dd, *J* = 13.8, 7.3 Hz, CCH_aH_b), 2.57 (1H, dd, *J* = 13.8, 7.2 Hz, CCH_aH_b), 1.58 (3H, s, $CH_3CC(O)$), 0.75 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 199.3 (*C*(O)), 149.0 (C_{Ar}), 135.1 (CH_2CHCH_2CH), 129.5 (C_{Ar}), 127.5 (HC_{Ar}), 117.7 (CH_2CHCH_2CH), 112.3 (HC_{Ar}), 104.7 (CO_3), 72.7 (OCH_2), 52.7 (*C*C(O)), 44.4 ($CH_2CC(O)$), 40.7 ($N(CH_3)_2$), 30.8 (CCH_3), 20.8 ($C(O)CCH_3$), 14.4 (CCH_3).

3-Mesityl-2-oxopropanoic acid (691)

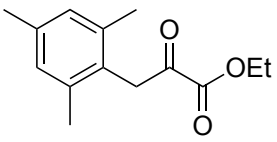


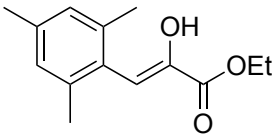
2-Bromomesitylene (98 μL, 0.64 mmol, 1.1 eq.) was subjected to general procedure F without chromatographic purification. To the crude product was added a solution of $NaHSO_4$ (244 mg, 2.03 mmol, 3.5 eq.) in water (1 mL) and the mixture was stirred at RT for 3 h. Solid LiOH (69 mg, 2.9 mmol, 5.0 eq.) was then added and the mixture was stirred at RT for 2 h. The reaction was diluted with DCM and extracted three times with 1 M NaOH (3 × 10 mL). The aqueous layers were combined, the pH adjusted to 1 using 3 M HCl and the resulting cloudy solution was

extracted three times with DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford pyruvic acid **691** (116 mg, 97%) as a white solid.

m.p.: 115 – 117 °C. **IR**: ν_{max} (thin film) 3463, 2917, 2850, 1723, 1485, 1446, 1309, 1248, 1055, 844, 683 cm^{-1}. **HRMS**: calculated for $C_{12}H_{13}O_3$, 205.0870 $[M-H]^-$, found *m/z* 205.0867, Δ = –1.40 ppm. **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H: 6.78 (2H, s, 2 × HC_{Ar}), 3.92 (2H, s, $CH_2C(O)$), 2.18 (3H, s, $ArCH_3$), 2.10 (6H, s, 2 × $ArCH_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 203.2 (*C*(O)), 168.3 (*C*OOH), 136.6, 134.8, 129.8 (3 × C_{Ar}), 128.2 (HC_{Ar}), 40.1 ($CH_2C(O)$), 20.6 ($ArCH_3$), 19.9 ($ArCH_3$).

Ethyl 3-mesityl-2-oxopropanoate (697)





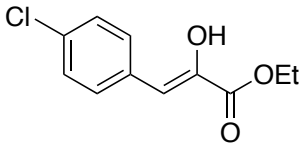
OBO-ketone **636** (87 mg, 0.30 mmol, 1.0 eq.) was subjected to general procedure K, heated for 3 h at 90 ºC and purified by flash column chromatography using pentane/EtOAc (5%) as eluent, affording pyruvate **697** (61 mg, 87%) as a colourless oil. The product exists as a mixture of the ketone and enol isomers (87:13).

Alternatively, to a flame-dried vial capped with a rubber septum were added methyl-OBO ketone (103 mg, 0.60 mmol, 1.0 eq.) and $Pd(dtbpf)Cl_2$ (20 mg, 30 μmol, 5 mol%). The rubber septum was replaced by an aluminium cap and then THF (5.3 mL), 2-bromomesitylene (101 μL, 0.66 mmol, 1.1 eq.), and 2 M NaO*t*Bu in THF (0.75 mL, 1.50 mmol, 2.5 eq.) were added *via* syringe. The vial was flushed with argon for 5 mins and then heated at 50 °C for 24 h. The cap was removed and the solvent evaporated *in vacuo*. EtOH (6.0 mL) and *p*-toluenesulfonic acid (310 mg, 1.80 mmol, 3.0 eq.) were added to the same vial, which was capped again and heated at 90 °C for 3 h. After cooling down to RT, $NaHCO_3$ (101 mg, 1.20 mmol, 2.0 eq.) was added and the mixture was concentrated *in vacuo*. The crude product was purified by flash column chromatography using pentane/EtOAc (5%) as eluent, affording pyruvate **697** (118 mg, 84%) as a colourless oil [mixture of the ketone and enol isomers (87:13)].

IR: ν_{max} (thin film) 3390, 2980, 1725, 1262, 1052, 851 cm^{-1}. **HRMS**: calculated for $C_{14}H_{19}O_3$, 235.1329 $[M+H]^+$, found *m/z* 235.1330, Δ = 0.59 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) *keto*

tautomer δ_H: 6.89 (2H, s, 2 × HC_{Ar}), 4.33 (2H, q, J = 7.2 Hz, OCH_2CH_3), 4.17 (2H, s, $CH_2C(O)$), 2.28 (3H, s, $ArCH_3$), 2.21 (6H, 2 × $ArCH_3$), 1.35 (3H, t, J = 7.2 Hz, OCH_2CH_3). *enol tautomer* δ_H: 6.90 (2H, s, 2 × HC_{Ar}), 6.61 (1H, s, CHCOH), 5.91 (1H, s, OH), 4.39 (2H, q, J = 7.1 Hz, OCH_2CH_3), 2.29 (3H, s, $ArCH_3$), 2.25 (6H, s, 2 × $ArCH_3$), 1.42 (3H, t, J = 7.1 Hz, OCH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) *keto tautomer* δ_C: 192.5 (C(O)), 165.5 (CO_2), 137.2, 137.1 (2 × C_{Ar}), 129.1 (HC_{Ar}), 126.9 (C_{Ar}), 62.6 (OCH_2CH_3), 40.4 ($CH_2C(O)$), 21.0 ($ArCH_3$), 20.3 ($ArCH_3$), 14.1 (OCH_2CH_3). *enol tautomer* δ_C: 165.5 (CO_2), 139.4, 137.3, 136.6, 130.3 (3 × C_{Ar} + COH)), 128.3 (HC_{Ar}), 110.2 (CHCOH), 62.2 (OCH_2CH_3), 21.1 (ArC_aH_3), 20.5 (ArC_bH_3), 14.4 (OCH_2CH_3).

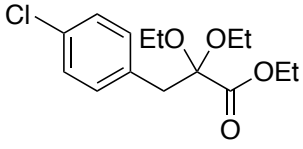
Ethyl 3-(4-chlorophenyl)-2-hydroxyacrylate (698)



OBO-ketone **637** (86 mg, 0.30 mmol, 1.0 eq.) was subjected to general procedure K heated for 12 h at 90 ºC and purified by flash column chromatography using pentane/EtOAc (5%) as eluent, affording pyruvate **698** (38 mg, 56%) as a colourless oil.

IR: ν_{max} (thin film) 2978, 2931, 2898, 1750, 1492, 1390, 1191, 1116, 1079, 1055, 1015, 774 cm^{-1}. **HRMS**: calculated for $C_{11}H_{12}O_3$ 227.0469 $[M+H]^+$, found m/z 227.0471, Δ = 0.89 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.64 – 7.60 (2H, m, 2 × HC_{Ar}), 7.27 – 7.23 (2H, m, 2 × HC_{Ar}), 6.48 (1H, s, OH), 6.39 (1H, s, CHCOH), 4.29 (2H, q, J = 7.2 Hz, OCH_2CH_3), 1.32 (3H, t, J = 7.2 Hz, OCH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 166.0 (CO_2), 139.6, 133.6, 132.6 (2 × C_{Ar} + COH), 131.1, 128.7 (2 × HC_{Ar}), 109.5 (CHCOH), 62.8 (OCH_2CH_3), 14.3 (OCH_2CH_3).

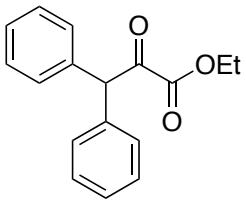
Ethyl 3-(4-chlorophenyl)-2,2-diethoxypropanoate (699)



OBO-ketone **637** (86 mg, 0.30 mmol, 1.0 eq.) was subjected to general procedure K heated for 12 h at 90 ºC and purified by flash column chromatography using pentane/EtOAc (5%) as eluent, affording by-product acetal **699** (19 mg, 21%) as a colourless oil.

IR: ν_{max} (thin film) 2978, 2933, 2897, 1749, 1492, 1443, 1391, 1191, 1116, 1078, 1053, 1015, 713 cm^{-1}. **HRMS**: calculated for $C_{15}H_{21}O_4ClNa$ 323.1021 $[M+H]^+$, found *m/z* 323.1016, Δ = –1.34 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.19 (2H, d, *J* = 8.2 Hz, 2 × *H*C_{Ar}), 7.12 (2H, d, *J* = 8.2 Hz, 2 × *H*C_{Ar}), 4.03 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 3.70 – 3.49 (4H, m, $C(OCH_2CH_3)_2$), 3.14 (2H, s, $ArCH_2$), 1.24 (6H, t, *J* = 7.1 Hz, $C(OCH_2CH_3)_2$), 1.09 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C:168.6 (CO_2), 133.4, 132.7 (2 × C_{Ar}), 131.2, 128.3 (2 × HC_{Ar}), 102.0 ($C(OCH_2CH_3)_2$), 61.3 ($CO_2CH_2CH_3$), 58.1 ($C(OCH_2CH_3)_2$), 40.2 ($ArCH_2$), 15.2 ($C(OCH_2CH_3)_2$), 14.1 ($CO_2CH_2CH_3$).

Ethyl 2-oxo-3,3-diphenylpropanoate (706)



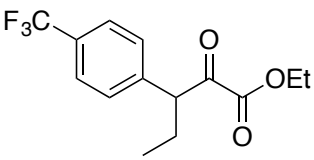
OBO-ketone **671** (97 mg, 0.3 mmol, 1.0 eq.) was subjected to general procedure K heated for 4 h at 90 °C and purified by flash column chromatography using pentane/EtOAc (7%) as eluent, affording pyruvate **706** (73 mg, 91%) as a colourless oil. The product exists as a mixture of ketone and enol isomers (85%/15%).

Alternatively, to a flame-dried vial capped with a rubber septum were added methyl-OBO ketone (103 mg, 0.60 mmol, 1.0 eq.) and $Pd(dtbpf)Cl_2$ (20 mg, 30 μmol, 5 mol%). The rubber septum was replaced by an aluminium cap and then THF (5.3 mL), chlorobenzene (183 μL, 1.80 mmol, 3.0 eq.), and 2 M NaO*t*Bu in THF (0.75 mL, 1.50 mmol, 2.5 eq.) were added *via* syringe. The vial was flushed with argon for 5 mins and then heated at 80 °C for 24 h. The cap was removed and the solvent evaporated *in vacuo*. EtOH (6.0 mL) and *p*-toluenesulfonic acid (206 mg, 1.20 mmol, 2.0 eq.) were added to the same vial, which was capped again and heated at 90 °C for 4 h. After cooling down to RT, $NaHCO_3$ (101 mg, 1.20 mmol, 2.0 eq.) was added and the mixture was concentrated *in vacuo*. The crude product was purified by flash column chromatography using pentane/EtOAc (5%) as eluent, affording product pyruvate **706** (98 mg, 61%) as a colourless oil [mixture of ketone and enol isomers (85%/15%)].

IR: ν_{max} (thin film) 3029, 2983, 1727, 1253, 1055, 698 cm^{-1}. **HRMS**: calculated for $C_{17}H_{17}O_3$, 269.1172 $[M+H]^+$, found *m/z* 269.1174, Δ = 0.67 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) *keto*

tautomer δ_H: 7.40 – 7.25 (10H, m, 10 × *H*C_{Ar}) 5.92 (1H, s, Ph_2CH), 4.24 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 1.24 (3H, t, *J* = 7.1 Hz, OCH_2CH_3). *enol tautomer* δ_H: 7.50 – 7.45 (2H, m, 2 × *H*C_{Ar}), 7.40 – 7.25 (6H, m, 6 × *H*C_{Ar}), 7.21 – 7.17 (2H, m, 2 × *H*C_{Ar}), 6.40 (1H, s, OH), 4.02 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 0.86 (3H, t, *J* = 7.2 Hz, OCH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) *keto tautomer* δ_C: 192.0 (*C*(O)), 161.5 (*C*O_2), 136.4 (*C*$_{Ar}$), 129.3, 128.9, 127.8 (3 × H*C*$_{Ar}$), 62.7 (OCH_2CH_3), 59.3 (*C*HC(O)), 13.9 (OCH_2CH_3). *enol tautomer* δ_C: 166.7 (*C*O_2), 140.3, 138.8, 137.1 (2 × *C*$_{Ar}$ + *C*COH), 130.1, 130.1, 128.0, 127.8, 127.7, 127.1 (6 × H*C*$_{Ar}$), 62.1 (OCH_2CH_3), 13.3 (OCH_2CH_3).

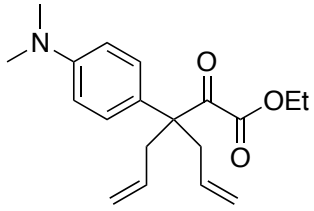
Ethyl 2-oxo-3-(4-(trifluoromethyl)phenyl)pentanoate (707)



OBO-ketone **683** (103 mg, 0.3 mmol, 1.0 eq.) was subjected to general procedure K for 8 h at 90 °C and purified by flash column chromatography using pentane/Et_2O (5%) as eluent, affording pyruvate **707** (55 mg, 64%) as a colourless oil.

IR: ν_{max} (thin film) 2970, 2937, 2879, 2849, 1730, 1325, 1165, 1125, 1068, 1049 cm^{-1}. **HRMS**: calculated for $C_{14}H_{16}F_3O_3$, 289.1046 $[M+H]^+$, found *m/z* 289.1048, Δ = 0.56 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.59 (2H, d, *J* = 8.3 Hz, 2 × *H*C_{Ar}), 7.35 (2H, d, *J* = 8.2 Hz, *H*C_{Ar}), 4.38 (1H, dd, *J* = 8.3, 6.5 Hz, C*H*C(O)), 4.26 – 4.14 (2H, m, OCH_2CH_3), 2.18 – 2.06 (1H, m, $CH_aH_bCH_3$), 1.85 – 1.73 (1H, m, $CH_aH_bCH_3$), 1.25 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.87 (3H, t, *J* = 7.4 Hz, CH_2CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C: 193.0 (*C*(O)), 160.9 (*C*O_2), 140.4 (*C*$_{Ar}$), 129.9 (q, *J* = 32.7 Hz, *C*CF_3), 129.3 ($F_3CCCHCH$), 125.8 (q, *J* = 4.3 Hz, F_3CCCH), 124.0 (q, *J* = 272.2 Hz, *C*F_3), 62.6 (OCH_2CH_3), 55.4 (*C*HC(O)), 24.9 (CH_2CH_3), 13.8 (OCH_2CH_3), 11.7 (CH_2CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F: –62.6 (3F, s, CF_3).

Ethyl 3-allyl-3-(4-(dimethylamino)phenyl)-2-oxohex-5-enoate (708)

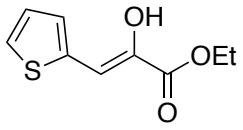


OBO-ketone **685** (111 mg, 0.3 mmol, 1.0 eq.) was subjected to general procedure K for 4 h at 90 °C and purified by flash column chromatography using toluene as eluent, affording pyruvate **708** (77 mg, 81%) as a yellow solid.

Alternatively, to a flame-dried vial capped with a rubber septum were added methyl-OBO ketone (155 mg, 0.90 mmol, 1.5 eq.), Pd(dtbpf)Cl_2 (20 mg, 30 μmol, 5 mol%) and 4-bromo-*N*,*N*-dimethylaniline (120 mg, 0.60 mmol, 1.0 eq.). The rubber septum was replaced by an aluminium cap and then THF (5.3 mL) and 2 M NaO*t*Bu in THF (0.75 mL, 1.50 mmol, 2.5 eq.) were added *via* syringe. The vial was flushed with argon for 5 mins and then heated at 50 °C for 24 h. Allyl bromide (156 μL, 1.80 mmol, 3.0 eq.) and 2 M NaO*t*Bu in THF (0.60 mL, 1.20 mmol, 2.0 eq.) were then added sequentially and the mixture was heated at 90 °C for 3 h. The cap was removed and the solvent evaporated *in vacuo*. EtOH (6.0 mL) and *p*-toluenesulfonic acid (310 mg, 1.80 mmol, 3.0 eq.) were added to the same vial, which was capped again and heated at 90 °C for 3 h. After cooling down to RT, $NaHCO_3$ (101 mg, 1.20 mmol, 2.0 eq.) was added and the mixture was concentrated *in vacuo*. The crude product was purified by flash column chromatography using pentane/EtOAc (5%) as eluent, affording product pyruvate **708** (124 mg, 65%) as a yellow solid.

m.p.: 53 – 56 °C. **IR**: ν_{max} (thin film) 3077, 2922, 2804, 1731, 1714, 1611, 1521, 1065, 918, 844 cm^{-1}. **HRMS**: calculated for $C_{19}H_{26}NO_3$, 316.1907 $[M+H]^+$, found *m/z* 316.1910, Δ = 0.92 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.05 (2H, d, *J* = 8.9 Hz, 2 × *H*C_{Ar}), 6.69 (2H, d, *J* = 8.9 Hz, 2 × *H*C_{Ar}), 5.57 – 5.44 (2H, m, 2 × C*H*CH_2), 5.12 – 5.03 (4H, m, 2 × C*H*$_2$CHCH_2C), 4.06 (2H, q, *J* = 7.1 Hz, OC*H*$_2$$CH_3$), 3.02 (2H, dd, *J* = 14.1, 8.2 Hz, CC*H*$_a$$H_b$), 2.94 (6H, s, N(C*H*$_3$)$_2$), 2.71 (2H, dd, *J* = 14.1, 6.5 Hz, CCH_aH_b), 1.11 (3H, t, *J* = 7.1 Hz, OCH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 196.5 (*C*(O)), 162.1 (*C*O_2), 149.7 (C_{Ar}), 133.1 (*C*HCH_2), 127.8 (H*C*$_{Ar}$), 125.7 (*C*$_{Ar}$), 118.9 (*C*H_2CHCH$_2$C), 112.5 (H*C*$_{Ar}$), 61.5 (O*C*$H_2$$CH_3$), 56.0 (*C*C(O)), 40.4 (N(*C*H_3)$_2$), 37.2 (C*C*H_2), 13.8 (OCH_2*C*H_3).

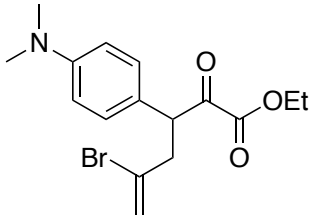
Ethyl 2-hydroxy-3-(thiophen-2-yl)acrylate (709)



OBO-ketone **644** (76 mg, 0.3 mmol, 1.0 eq.) was subjected to general procedure K for 2 h at 110 °C and purified by flash column chromatography using pentane/EtOAc (10%) as eluent, affording enol **709** (49 mg, 82%) as an off-white solid.

m.p.: 58 – 60 °C. **IR**: ν_{max} (thin film) 3385, 2981, 1684, 1247, 1219, 1108, 1016, 855, 763, 668 cm^{-1}. **HRMS**: calculated for $C_9H_{11}O_3S$ 199.0423 $[M+H]^+$, found *m/z* 199.0426, Δ = 1.23 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.41 (1H, d, *J* = 5.0 Hz, *H*C_{Ar}), 7.30 (1H, d, *J* = 3.7 Hz, *H*C_{Ar}), 7.07 (1H, dd, *J* = 5.1, 3.7 Hz, SCHC*H*), 6.85 (1H, s, C*H*COH), 6.48 (1H, d, *J* = 1.2 Hz, O*H*), 4.36 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 1.38 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 165.7 (*C*O_2), 137.5, 137.0 (*C*$_{Ar}$ + *C*OH), 129.0, 128.3 (2 × H*C*$_{Ar}$), 127.2 (SH*C*H), 105.8 (*C*HCOH), 62.6 (O*C*H$_2$CH$_3$), 14.4 (OCH$_2$*C*H$_3$). Spectroscopic data are consistent with those previously reported.[283]

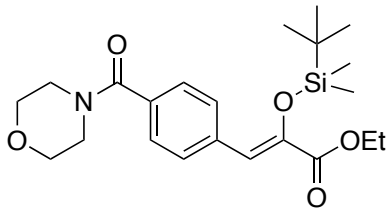
Ethyl 5-bromo-3-(4-(dimethylamino)phenyl)-2-oxohex-5-enoate (710)



OBO-ketone **677** (123 mg, 0.3 mmol, 1.0 eq.) was subjected to general procedure K and purified by flash column chromatography using pentane/EtOAc (5%) as eluent, affording pyruvate **710** (67 mg, 63%) as a colourless oil.

IR: ν_{max} (thin film) 2984, 2904, 2805, 1923, 1610, 1520, 1354, 1165, 1076, 1028, 812 cm^{-1}. **HRMS**: calculated for $C_{16}H_{21}NO_3{}^{79}Br$, 354.0699 $[M+H]^+$, found *m/z* 354.0701, Δ = 0.47 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 6.99 (2H, d, *J* = 8.9 Hz, 2 × *H*C_{Ar}), 6.58 (2H, d, *J* = 8.8 Hz, 2 × *H*C_{Ar}), 5.48 (1H, s, C*H*$_a$H$_b$C(Br)CH$_2$C), 5.34 (1H, d, *J* = 2.2 Hz, CH$_a$C(Br)CH$_2$C), 4.75 (1H, t, *J* = 7.3 Hz, C*H*C(O)), 4.25 – 4.12 (2H, m, OC*H*$_2$CH$_3$), 3.17 (1H, dd, *J* = 14.8, 6.8 Hz, CHC*H*$_a$H$_b$), 2.93 (6H, s, 3 × OC*H*$_2$), 2.80 (1H, dd, *J* = 14.8, 7.8 Hz, CHCH$_a$*H*$_b$), 1.24 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 191.7 (*C*(O)), 161.1 (*C*O_2), 150.2, 130.7 (2 × *C*$_{Ar}$), 130.0 (H*C*$_{Ar}$), 121.0 (*C*Br), 119.5 (*C*H$_2$C(Br)CH$_2$C), 112.8 (H*C*$_{Ar}$), 62.5 (O*C*H$_2$CH$_3$), 51.4 (*C*HC(O)), 43.0 (CH*C*H$_2$), 40.5 (N(*C*H$_3$)$_2$), 14.0 (OCH$_2$*C*H$_3$).

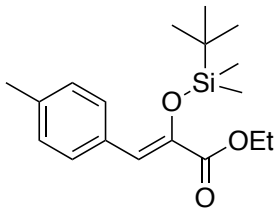
Ethyl 2-((*tert*-butyldimethylsilyl)oxy)-3-(4-(morpholine-4-carbonyl)-phenyl)acrylate (712)



OBO-ketone **649** (108 mg, 0.3 mmol, 1.0 eq.) was subjected to general procedure L and purified by flash column chromatography using pentane/Et_2O (60%) as eluent, affording silyl enol ether **712** (68 mg, 54%) as a colourless oil.

IR: ν_{max} (thin film) 2957, 2930, 2857, 1718, 1633, 1250, 1114, 837, 784 cm^{-1}. **HRMS**: calculated for $C_{22}H_{34}NO_5Si$, 420.2201 $[M+H]^+$, found *m/z* 420.2194, Δ = –1.63 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.71 (2H, d, *J* = 8.3 Hz, 2 × HC_{Ar}), 7.36 (2H, d, *J* = 8.3 Hz, 2 × HC_{Ar}), 6.81 (1H, s, C*H*CO), 4.27 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.85 – 3.35 (8H, m, 2 × OCH_2CH_2N), 1.35 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 0.91 (9H, s, $C(CH_3)_3$), 0.12 (6H, s, $Si(CH_3)_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 170.2 (*C*(O)N), 165.3 (CO_2), 141.8, 136.0, 134.4 (*C*OSi + 2 × C_{Ar}), 129.8, 127.1 (2 × HC_{Ar}), 117.5 (*C*HCO), 67.0 (($OCH_2)_2$), 61.6 (OCH_2CH_3), 48.3 (NC_aH_2), 42.6 (NC_bH_2), 25.9 ($C(CH_3)_3$), 18.7 ($C(CH_3)_3$), 14.4 (OCH_2CH_3), -3.8 ($Si(CH_3)_2$).

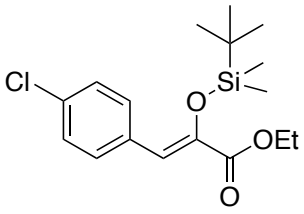
Ethyl 2-((*tert*-butyldimethylsilyl)oxy)-3-(p-tolyl)acrylate (713)



OBO-ketone **623** (79 mg, 0.3 mmol, 1.0 eq.) was subjected to general procedure L and purified by flash column chromatography using pentane/Et_2O (1%) as eluent, affording silyl enol ether **713** (72 mg, 75%) as a colourless oil.

IR: ν_{max} (thin film) 2955, 2929, 2858, 1717, 1632, 1252, 1122, 812, 783 cm^{-1}. **HRMS**: calculated for $C_{18}H_{29}O_3Si$, 321.1880 $[M+H]^+$, found *m/z* 321.1880, Δ = –0.09 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.60 (2H, d, *J* = 8.3 Hz, 2 × HC_{Ar}), 7.14 (2H, d, *J* = 8.3 Hz, 2 × HC_{Ar}), 6.84 (1H, s, C*H*CO), 4.27 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 2.35 (3H, s, $PhCH_3$), 1.36 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.96 (9H, s, $C(CH_3)_3$), 0.13 (6H, s, $Si(CH_3)_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 165.8 (CO_2), 140.1, 138.2, 131.4 (*C*OSi + 2 × C_{Ar}), 129.9, 129.0 (2 × HC_{Ar}), 119.2 (*C*HCO), 61.4 (OCH_2CH_3), 26.0 ($C(CH_3)_3$), 21.6 ($PhCH_3$), 18.7 ($C(CH_3)_3$), 14.5 (OCH_2CH_3), –3.7 ($Si(CH_3)_2$).

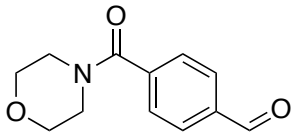
Ethyl 2-((*tert*-butyldimethylsilyl)oxy)-3-(4-chlorophenyl)acrylate (714)



OBO-ketone **637** (85 mg, 0.3 mmol, 1.0 eq.) was subjected to general procedure L and purified by flash column chromatography using pentane/Et_2O (1%) as eluent, affording silyl enol ether **714** (91 mg, 89%) as a colourless oil.

IR: ν_{max} (thin film) 2955, 2931, 2858, 1720, 1632, 1251, 1129, 824, 784 cm^{-1}. **HRMS**: calculated for $C_{17}{}^{35}ClH_{26}O_3Si$, 341.1334 $[M+H]^+$, found *m/z* 341.1335, Δ = 0.17 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.62 (2H, d, *J* = 8.7 Hz, 2 × *H*C_{Ar}), 7.30 (2H, d, *J* = 8.7 Hz, 2 × *H*C_{Ar}), 6.80 (1H, s, C*H*CO), 4.27 (2H, q, *J* = 7.2 Hz, OC*H*$_2$$CH_3$), 1.36 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.94 (9H, s, C(CH_3)$_3$), 0.13 (6H, s, Si(CH_3)$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 165.4 (*C*O_2), 141.2, 133.7, 132.8 (*C*OSi + 2 × *C*$_{Ar}$), 131.1, 128.5 (2 × H*C*$_{Ar}$), 117.6 (*C*HCO), 61.6 (OCH_2CH_3), 25.9 (C(*C*H_3)$_3$), 18.7 (*C*(CH_3)$_3$), 14.4 (OCH_2CH_3), –3.7 (Si(*C*H_3)$_2$).

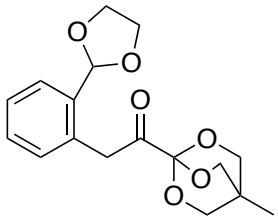
4-(Morpholine-4-carbonyl)benzaldehyde (716)



OBO-ketone **649** (108 mg, 0.3 mmol, 1.0 eq.) was subjected to general procedure K for 2 h at 100 °C and purified by flash column chromatography using EtOAc as eluent. The product obtained decomposed over 1 week and the by-product was purified by flash column chromatography using EtOAc as eluent, affording aldehyde **716** (9 mg, 14%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 10.05 (1H, s, C*H*O), 7.97 – 7.92 (2H, m, 2 × *H*C_{Ar}), 7.59 – 7.54 (2H, m, 2 × *H*C_{Ar}), 3.85 – 3.70 (4H, m, 2 × C*H*$_2$), 3.70 – 3.55 (2H, m, C*H*$_2$), 3.45 – 3.30 (2H, m, C*H*$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 191.5 (*C*HO), 169.2 (*C*(O)N), 141.1, 137.2 (2 × *C*$_{Ar}$), 130.1, 127.8 (2 × H*C*$_{Ar}$), 67.0 (*C*H_2). Spectroscopic data are consistent with those previously reported.[284]

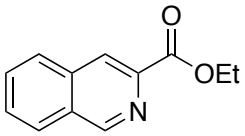
2-(2-(1,3-Dioxolan-2-yl)phenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]-octan-1-yl)ethan-1-one (723)



2-(2-Bromophenyl)-1,3-dioxolane (89 mg, 0.39 mmol, 1.0 eq.) was subjected to general procedure G and purified by flash column chromatography using pentane/EtOAc (35%) as eluent, affording OBO-ketone **723** (116 mg, 93%) as a brown solid.

m.p.: 86 – 87 °C. **IR**: ν_{max} (thin film) 2943, 2883, 1751, 1073, 1049, 993, 723 cm^{-1}. **HRMS**: calculated for $C_{17}H_{21}O_6$, 321.1333 $[M+H]^+$, found *m/z* 321.1335, Δ = 0.87 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.56 – 7.51 (1H, m, HC_{Ar}), 7.33 – 7.24 (2H, m, 2 × HC_{Ar}), 7.14 –7.08 (1H, m, HC_{Ar}), 5.80 (1H, s, $CH(OR)_2$), 4.18 (2H, s, $CH_2C(O)$) 4.10 – 3.90 (4H, m, $(OCH_2)_2$), 4.01 (6H, s, 3 × OCH_2), 0.83 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 195.4 (*C*(O)), 136.2, 132.3 (2 × C_{Ar}), 131.7, 129.0, 127.1, 126.7 (4 × HC_{Ar}), 103.7 (CO_3), 102.4 ($CH(OR)_2$), 73.1 (OCH_2), 65.0 ($CH(OR)_2$), 40.6 ($CH_2C(O)$), 30.9 (CH_3C), 14.2 (CH_3).

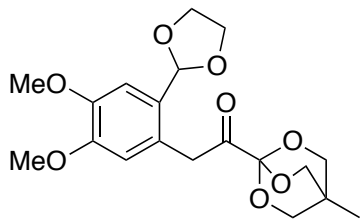
Ethyl isoquinoline-3-carboxylate (724)



OBO-ketone **723** (96 mg, 0.30 mmol, 1.0 eq.) was subjected to general procedure M and purified by flash column chromatography using pentane/EtOAc (40%) as eluent, affording isoquinoline **724** (51 mg, 84%) as a light brown solid.

m.p.: 43 – 45 °C. **IR**: ν_{max} (thin film) 2975, 2880, 1710, 1280, 1150, 750 cm^{-1}. **HRMS**: calculated for $C_{12}H_{12}NO_2$, 202.0863 $[M+H]^+$, found *m/z* 202.0862, Δ = –0.14 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 9.33 (1H, s, *H*C(1)), 8.58 (1H, s, *H*C(4)), 8.04 (1H, d, *J* = 7.8 Hz, HC_{Ar}), 7.95 (1H, d, *J* = 7.9 Hz, HC_{Ar}), 7.70 –7.80 (2H, m, 2 × HC_{Ar}), 4.52 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 1.47 (3H, t, *J* = 7.2 Hz, OCH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 165.9 (*C*(O)), 152.8 (*C*(1)), 141.9, 135.5 (2 × C_{Ar}), 131.2 (HC_{Ar}), 130.0 (C_{Ar}), 129.6, 128.1, 127.8 (3 × HC_{Ar}), 124.0 (*C*(4)), 62.0 (OCH_2CH_3), 14.6 (OCH_2CH_3). Spectroscopic data are consistent with those previously reported.[285]

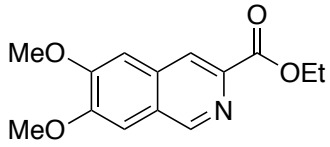
2-(2-(1,3-Dioxolan-2-yl)-4,5-dimethoxyphenyl)-1-(4-methyl-2,6,7-trioxa-bicyclo-[2.2.2]octan-1-yl)ethan-1-one (726)



2-(2-bromo-4,5-dimethoxyphenyl)-1,3-dioxolane (191 mg, 0.66 mmol, 1.1 eq.) was subjected to general procedure G and purified by flash column chromatography using pentane/EtOAc (50%) as eluent, affording OBO-ketone **726** (205 mg, 90%) as a brown solid.

m.p.: 100 – 103 °C. **IR**: ν_{max} (thin film) 2939, 2883, 1751, 1518, 1268, 1121, 1075, 1034, 1004, 750 cm^{-1}. **HRMS**: calculated for $C_{19}H_{25}O_8$, 381.1544 $[M+H]^+$, found *m/z* 381.1542, Δ = –0.58 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.01 (1H, s, HC_{Ar}), 6.53 (1H, s, HC_{Ar}), 5.63 (1H, s, $CH(OR)_2$), 4.03 (2H, s, $CH_2C(O)$), 4.00 – 3.83 (4H, m, $(OCH_2)_2$), 3.92 (6H, s, 3 × OCH_2), 3.79 (3H, s, OC_aH_3), 3.74 (3H, s, OC_bCH_3), 0.74 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 195.4 ($C(O)$), 148.7, 147.4, 128.1, 124.4 (4 × C_{Ar}), 114.2, 109.5 (2 × HC_{Ar}), 103.4 (CO_3), 101.7 ($CH(OR)_2$), 72.8 (OCH_2), 64.7 ($(OCH_2)_2$), 55.6 (OC_aH_3), 55.6 (OC_bH_3), 39.7 ($CH_2C(O)$), 30.5 (CCH_3), 13.8 (CCH_3).

Ethyl 6,7-dimethoxyisoquinoline-3-carboxylate (727)

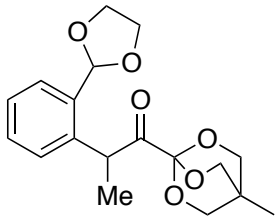


OBO-ketone **726** (114 mg, 0.30 mmol, 1.0 eq.) was subjected to general procedure M and purified by flash column chromatography using pentane/EtOAc (70%) as eluent, affording isoquinoline **727** (63 mg, 80%) as a light brown solid.

m.p.: 178 – 181 °C. **IR**: ν_{max} (thin film) 3069, 2980, 2834, 1703, 1504, 1408, 1245, 1148, 1104, 1006, 861 cm^{-1}. **HRMS**: calculated for $C_{14}H_{16}NO_4$, 262.1074 $[M+H]^+$, found *m/z* 262.1072, Δ = –0.86 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 9.10 (1H, s, $HC(1)$), 8.42 (1H, s, $HC(4)$), 7.24 (1H, s, HC_{Ar}), 7.16 (1H, s, HC_{Ar}), 4.48 (2H, q, J = 7.2 Hz, OCH_2CH_3), 4.03 (3H, s, OC_aH_3), 4.02 (3H, s, OC_bH_3), 1.45 (3H, t, J = 7.2 Hz, OCH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 166.1 (C(O)), 153.5, 152.1 (2 × C_{Ar}), 150.0 ($C(1)$), 140.8, 132.2, 126.4 (3 × C_{Ar}), 122.7 ($C(4)$), 105.9,

105.5 (2 × HC_{Ar}), 61.7 (O$CH_2$$CH_3$), 56.3 (O$C_a$$H_3$), 56.3 (O$C_b$$H_3$), 14.6 (OC$H_2$$CH_3$). Analytical data are consistent with those previously reported.[285,286]

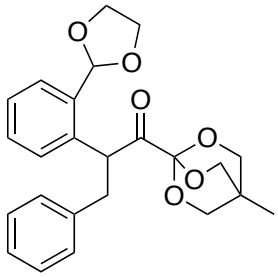
2-(2-(1,3-Dioxolan-2-yl)phenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]-octan-1-yl)-propan-1-one (729)



To a flame-dried vial capped with a rubber septum was added OBO-ketone **723** (250 mg, 0.78 mmol, 1.0 eq.). The rubber septum was replaced by an aluminium cap and then dry THF (7.2 mL), 2 M NaO*t*Bu in THF (0.59 mL, 1.2 mmol, 1.5 eq.) and methyl iodide (53 μL, 0.86 mmol, 1.1 eq.) were added sequentially *via* syringe. The vial was flushed with argon for 5 mins and then heated at 70 °C for 3 h. The resulting mixture was filtered through a plug of silica using EtOAc as eluent, concentrated *in vacuo* and purified by flash column chromatography using pentane/EtOAc (40%) as eluent, affording OBO-ketone **729** (175 mg, 67%) as a brown solid.

m.p.: 130 – 132 °C. **IR**: ν_{max} (thin film) 2946, 2887, 2824, 1740, 1113, 1056, 1046, 930, 747 cm^{-1}. **HRMS**: calculated for $C_{18}H_{23}O_6$, 335.1489 $[M+H]^+$, found *m/z* 335.1489, Δ = 0.03 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.55 (1H, d, *J* = 7.4 Hz, *H*C_{Ar}), 7.31 – 7.18 (3H, m, 3 × *H*C_{Ar}), 6.22 (1H, s, C*H*$(OR)_2$), 4.75 (1H, q, *J* = 6.9 Hz, C*H*CH_3), 4.20 – 3.99 (4H, m, $(OCH_2)_2$), 3.88 (6H, s, 3 × OCH_2), 1.40 (3H, d, *J* = 6.9 Hz, CH_3CH), 0.78 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 198.9 (*C*(O)), 138.7, 135.2 (2 × C_{Ar}), 129.1, 127.7, 126.7, 126.0 (4 × HC_{Ar}), 104.0 (CO_3), 101.7 (C*H*$(OR)_2$), 73.0 (OCH_2), 65.4 (O$C_a$$H_2$$C_b$$H_2$O), 65.1 (O$C_a$$H_2$$C_b$$H_2$O), 41.5 ($CH_3$*C*H), 30.9 (*C*$CH_3$), 19.2 (*C*$H_3$CH), 14.3 (C*C*$H_3$).

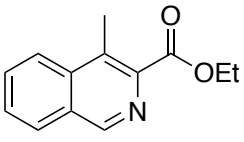
2-(2-(1,3-Dioxolan-2-yl)phenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]-octan-1-yl)-3-phenylpropan-1-one (730)



To a flame-dried vial capped with a rubber septum was added OBO-ketone **723** (100 mg, 0.31 mmol, 1.0 eq.). The rubber septum was replaced by an aluminium cap and then dry THF (2.9 mL), 2 M NaO*t*Bu in THF (234 μL, 1.5 eq.) and benzyl bromide (41 μL, 0.34 mmol, 1.1 eq.) were added sequentially *via* syringe. The vial was flushed with argon for 5 mins and then heated at 70 °C for 3 h. The resulting mixture was filtered through a plug of silica using EtOAc as eluent, concentrated *in vacuo* and purified by flash column chromatography using pentane/EtOAc (50%) as eluent, affording OBO-ketone **730** (95 mg, 74%) as a brown solid.

m.p.: 170 – 173 °C. **IR**: ν_{max} (thin film) 2980, 2884, 1748, 1072, 1062, 1029, 992, 943, 746, 726, 694 cm^{-1}. **HRMS:** calculated for $C_{24}H_{27}O_6$, 411.1802 $[M+H]^+$, found *m/z* 411.1802, Δ = –0.10 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.57 (1H, d, *J* = 7.5 Hz, *H*C_{Ar}), 7.34 – 7.11 (8H, m, 8 × *H*C_{Ar}), 6.20 (1H, s, C*H*$(OR)_2$), 5.01 (1H, dd, *J* = 9.4, 5.0 Hz, C*H*C(O)), 4.19 – 3.89 (4H, m, $(OCH_2)_2$), 3.81 (6H, s, 3 × OCH_2), 3.41 (1H, dd, *J* = 13.7, 9.3 Hz, $PhCH_aH_b$), 2.92 (1H, dd, *J* = 13.7, 5.0 Hz, $PhCH_aH_b$), 0.73 (3H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 197.5 (*C*(O)), 139.8, 137.0, 135.7 (3 × C_{Ar}), 129.3, 129.0, 128.1, 127.8, 126.8, 126.1, 126.0 (7 × HC_{Ar}), 103.7 (CO_3), 101.7 (C*H*$(OR)_2$), 72.9 (OCH_2), 65.3 ($OC_aH_2C_bH_2O$), 64.7 ($OC_aH_2C_bH_2O$), 49.2 (*C*HC(O)), 39.5 (CH_2Ph), 30.8(CCH_3), 14.1 (CH_3).

Ethyl 4-methylisoquinoline-3-carboxylate (737)

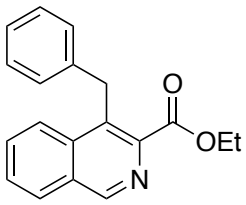


OBO-ketone **729** (100 mg, 0.30 mmol, 1.0 eq.) was subjected to general procedure M and purified by flash column chromatography using pentane/EtOAc (40%) as eluent, affording isoquinoline **737** (45 mg, 69%) as a yellow oil.

IR: ν_{max} (thin film) 2980, 1714, 1284, 1250, 1220, 1054, 768, 751 cm^{-1}. **HRMS**: calculated for $C_{13}H_{14}NO_2$, 216.1019 $[M+H]^+$, found *m/z* 216.1018, Δ = –0.67 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 9.15 (1H, s, *H*C(1)), 8.13 (1H, d, *J* = 8.6 Hz, *H*C_{Ar}), 7.99 (1H, dd, *J* = 8.1, 1.2 Hz,

*H*C$_{Ar}$), 7.79 (1H, ddd, *J* = 8.7, 6.8, 1.8 Hz, *H*C$_{Ar}$), 7.68 (1H, ddd, *J* = 8.0, 6.9, 1.1 Hz, *H*C$_{Ar}$), 4.51 (2H, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 2.87 (3H, s, ArC*H*$_3$), 1.46 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C: 167.6 (*C*(O)), 150.5 (*C*(1)), 141.7, 136.0 (2 × *C*$_{Ar}$), 131.0 (H*C*$_{Ar}$), 130.0, 128.9 (2 × *C*$_{Ar}$), 128.5, 128.2, 124.3 (3 × H*C*$_{Ar}$), 61.8 (O*C*H$_2$CH$_3$), 14.5 (OCH$_2$*C*H$_3$), 14.4 (Ar*C*H$_3$).

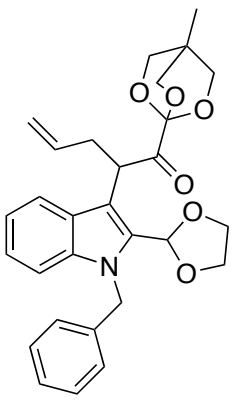
Ethyl 4-benzylisoquinoline-3-carboxylate (738)



OBO-ketone **730** (123 mg, 0.30 mmol, 1.0 eq.) was subjected to general procedure M and purified by flash column chromatography using pentane/EtOAc (40%) as eluent, affording isoquinoline **738** (62 mg, 71%) as an off-white solid.

m.p.: 118 – 120 °C. **IR**: ν_{max} (thin film) 3080, 3027, 2985, 1708, 1291, 1248, 1200, 1064, 789, 774, 693, 676 cm^{-1}. **HRMS**: calculated for $C_{19}H_{18}NO_2$, 292.1332 $[M+H]^+$, found *m/z* 292.1332, Δ = 0.01 ppm. **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H: 9.25 (1H, s, *H*C(1)), 8.98 – 8.10 (2H, m, 2 × *H*C$_{Ar}$), 7.71 – 7.62 (2H, m, 2 × *H*C$_{Ar}$), 7.25 – 7.11 (5H, m, 5 × *H*C$_{Ar}$), 4.77 (2H, s, PhC*H*$_2$), 4.46 (2H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 1.37 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C: 167.4 (*C*(O)), 151.5 (*C*(1)), 142.9, 139.9, 135.8, 131.4 (4 × *C*$_{Ar}$), 131.3 (H*C*$_{Ar}$), 129.4 (*C*$_{Ar}$), 128.6, 128.6, 128.4, 128.4, 126.2, 125.0 (6 × H*C*$_{Ar}$), 62.0 (O*C*H$_2$CH$_3$), 33.8 (Ph*C*H$_2$), 14.4 (OCH$_2$*C*H$_3$).

2-(1-Benzyl-2-(1,3-dioxolan-2-yl)-1*H*-indol-3-yl)-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]-octan-1-yl)pent-4-en-1-one (741)

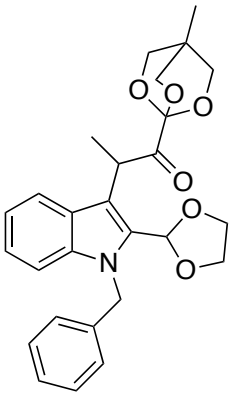


OBO-ketone **612** (270 mg, 0.60 mmol, 1.0 eq.) and allyl bromide were subjected to general procedure O and purified by flash column chromatography using DCM/MeOH (1%) as eluent, affording keto-indole **741** (209 mg, 71%) as a white solid.

m.p.: 177 – 180 °C. **IR**: ν_{max} (thin film) 2936, 2881, 1741, 1496, 1344, 1077, 988, 953, 910, 730 cm^{-1}. **HRMS**: calculated for $C_{29}H_{32}NO_6$, 490.2224 $[M+H]^+$, found *m/z* 490.2221, Δ = –0.69 ppm. **^{1}H NMR** (400

MHz, $CDCl_3$) δ_H: 7.77 – 7.72 (1H, m, HC_{Ar}), 7.26 – 7.16 (3H, m, 3 × HC_{Ar}), 7.11 – 6.96 (5H, m, 5 × HC_{Ar}), 6.25 (1H, s, $CH(OR)_2$), 5.80 – 5.66 (1H, m, CH_2CHCH_2CH), 5.55 (1H, d, J = 17.0 Hz, $PhCH_aH_b$), 5.49 (1H, d, J = 17.0 Hz, $PhCH_aH_b$), 5.05 (1H, dd, J = 17.1, 2.1 Hz, $CH_{trans}H_{cis}CH$), 4.97 (1H, dd, J = 10.2, 2.1 Hz, $CH_{trans}H_{cis}CH$), 4.74 (1H, t, J = 7.6 Hz, $CHC(O)$), 4.10 – 3.95 (4H, m, $(OCH_2)_2$), 3.87 (6H, s, 3 × OCH_2), 3.10 – 3.00 (1H, m, $CHCH_aH_bCH$), 2.80 – 2.70 (1H, m, $CHCH_aH_bCH$), 0.76 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 196.6 ($C(O)$), 138.7, 137.6 (2 × C_{Ar}), 135.9 (CH_2CHCH_2CH), 130.0 (C_{Ar}), 128.3, 126.8 (2 × HC_{Ar}), 126.2 (C_{Ar}), 126.0, 122.8, 121.0, 119.7 (4 × HC_{Ar}), 116.5 (CH_2CHCH_2CH), 112.6 (C_{Ar}), 110.2 (HC_{Ar}), 104.0 (CO_3), 98.4 ($CH(OR)_2$), 72.9 (OCH_2), 65.0 (OCH_2CH_2O), 64.9 (OCH_2CH_2O), 48.0 ($PhCH_2$), 43.5 ($CHC(O)$), 34.8 ($CHCH_2CH$), 30.8 (CCH_3), 14.3 (CCH_3).

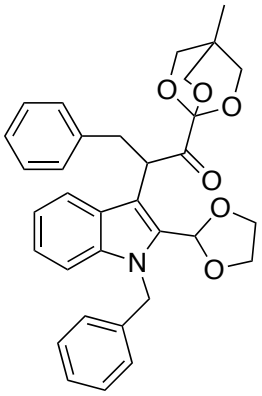
2-(1-Benzyl-2-(1,3-dioxolan-2-yl)-1*H*-indol-3-yl)-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2-]octan-1-yl)propan-1-one (743)



OBO-ketone **612** (270 mg, 0.60 mmol, 1.0 eq.) and methyl iodide were subjected to general procedure O and purified by flash column chromatography using DCM/MeOH (1%) as eluent, affording keto-indole **743** (259 mg, 93%) as a white solid.

m.p.: 182 – 184 °C. **IR**: ν_{max} (thin film) 2935, 2880, 1740, 1075, 1031, 989, 908, 726 cm^{-1}. **HRMS**: calculated for $C_{27}H_{30}NO_6$, 464.2068 $[M+H]^+$, found m/z 464.2066, Δ = –0.28 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.76 – 7.71 (1H, m, HC_{Ar}), 7.26 – 7.17 (3H, m, 3 × HC_{Ar}), 7.12 – 7.01 (5H, m, 5 × HC_{Ar}), 6.27 (1H, s, $CH(OR)_2$), 5.56 (1H, d, J = 17.0 Hz, $PhCH_aH_b$), 5.48 (1H, d, J = 17.0 Hz, $PhCH_aH_b$), 4.82 (1H, q, J = 7.1 Hz, $CHCH_3$), 4.12 – 3.95 (4H, m, $(OCH_2)_2$), 3.86 (6H, s, 3 × OCH_2), 1.63 (3H, d, J = 7.1 Hz, $CHCH_3$), 0.76 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 197.9 ($C(O)$), 138.7, 137.6, 129.2 (3 × C_{Ar}), 128.3, 126.7 (2 × HC_{Ar}), 126.1 (C_{Ar}), 126.0, 122.8, 120.9, 119.5 (4 × HC_{Ar}), 114.8 (C_{Ar}), 110.1 (HC_{Ar}), 104.0 (CO_3), 98.4 ($CH(OR)_2$), 72.8 (OCH_2), 64.9 (OCH_2CH_2O), 64.9 (OCH_2CH_2O), 47.9 ($PhCH_2$), 37.8 ($CHC(O)$), 30.7 (CCH_3), 16.8 ($CHCH_3$), 14.2 (CCH_3).

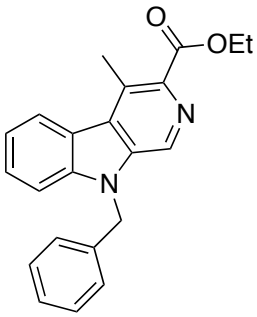
2-(1-Benzyl-2-(1,3-dioxolan-2-yl)-1*H*-indol-3-yl)-1-(4-methyl-2,6,7-trioxabi-cyclo[2.2.2]-octan-1-yl)-3-phenylpropan-1-one (744)



OBO-ketone **612** (270 mg, 0.60 mmol, 1.0 eq.) and benzyl bromide were subjected to general procedure O and purified by flash column chromatography using pentane/EtOAc (50%) as eluent, affording keto-indole **744** (282 mg, 87%) as a white solid.

m.p.: 85 – 87 °C. **IR**: ν_{max} (thin film) 2966, 2882, 1740, 1345, 1077, 1059, 1031, 988, 732, 697 cm^{-1}. **HRMS**: calculated for $C_{33}H_{34}NO_6$, 540.2381 $[M+H]^+$, found *m/z* 540.2375, Δ = –0.95 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.86 – 7.80 (1H, m, *H*C_{Ar}), 7.27 – 7.04 (11H, m, 11 × *H*C_{Ar}), 6.96 – 6.91 (2H, m, 2 × *H*C_{Ar}), 6.08 (1H, s, C*H*$(OR)_2$), 5.49 (2H, s, PhCH_2), 4.98 (1H, dd, *J* = 8.4, 6.5 Hz, C*H*C(O)), 3.98 – 3.87 (4H, m, $(OCH_2)_2$), 3.86 (6H, s, 3 × OCH_2), 3.64 (1H, dd, *J* = 13.8, 6.4 Hz, $CHCH_aH_b$), 3.33 (1H, dd, *J* = 13.7, 8.4 Hz, $CHCH_aH_b$), 0.76 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 196.9 (*C*(O)), 140.0, 138.6, 137.4, 130.4 (4 × C_{Ar}), 129.0, 128.2, 128.0, 126.7 (4 × HC_{Ar}), 126.3 (C_{Ar}), 126.0, 125.9, 122.7, 121.0, 119.7 (5 × HC_{Ar}), 112.2 (C_{Ar}), 110.1 (HC_{Ar}), 103.9 (*C*O_3), 98.4 (*C*H$(OR)_2$), 72.8 (OCH_2), 64.8 ($OC_aH_2C_bH_2O$), 64.7 ($OC_aH_2C_bH_2O$), 47.9 (Ph*C*H_2), 45.8 (*C*HC(O)), 36.5 (CH*C*H_2), 30.7 (*C*CH_3), 14.2 (C*C*H_3).

Ethyl 9-benzyl-4-methyl-9*H*-pyrido[3,4-b]indole-3-carboxylate (747)

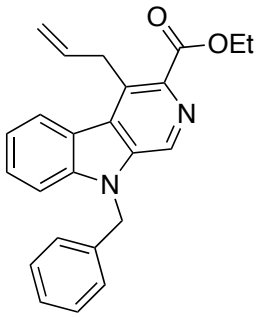


OBO-ketone **743** (139 mg, 0.30 mmol, 1.0 eq.) was subjected to general procedure M and purified by flash column chromatography using pentane/EtOAc (40%) as eluent, affording *β*-carboline **747** (76 mg, 74%) as a light brown solid.

m.p.: 116 – 118 °C. **IR**: ν_{max} (thin film) 3031, 2979, 2933, 1709, 1368, 1332, 1273, 1220, 1075, 747, 730, 699 cm^{-1}. **HRMS**: calculated for $C_{22}H_{21}N_2O_2$, 345.1597 $[M+H]^+$, found *m/z* 345.1593, Δ = –1.40 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.76 (1H, s, *H*C(1)), 8.34 (1H, d, *J* = 7.8 Hz, *H*C_{Ar}), 7.59 (1H, ddd, *J* = 8.3, 7.2, 1.2 Hz, *H*C_{Ar}), 7.49 (1H, d, *J* = 8.1 Hz, *H*C_{Ar}), 7.36 (1H, ddd, *J* = 8.1, 7.2, 1.2 Hz, *H*C_{Ar}), 7.27 – 7.21 (3H, m, 3 × *H*C_{Ar}), 7.13 – 7.08 (2H, m, 2 × *H*C_{Ar}), 5.56 (2H, s, PhCH_2), 4.51 (2H, q, *J* =

7.2 Hz, OCH_2CH$_3$), 3.15 (3H, s, ArCH_3), 1.48 (3H, t, J = 7.1 Hz, OCH$_2$CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 167.3 (*C*(O)), 141.5, 137.9, 137.0, 136.0, 131.4 (5 × C_{Ar}), 129.6 (*C*(1)), 129.1 (HC_{Ar}), 129.0 (C_{Ar}), 128.2, 128.1, 126.6, 124.4 (4 × HC_{Ar}), 122.4 (C_{Ar}), 120.8, 110.0 (2 × HC_{Ar}), 61.5 (OCH$_2$CH$_3$), 47.0 (PhCH$_2$), 16.7 (ArCH$_3$), 14.6 (OCH$_2$$CH_3$).

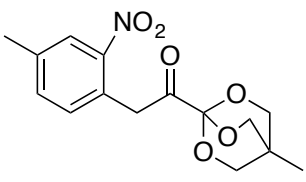
Ethyl 4-allyl-9-benzyl-9*H*-pyrido[3,4-b]indole-3-carboxylate (748)



OBO-ketone **741** (147 mg, 0.30 mmol, 1.0 eq.) was subjected to general procedure O and purified by flash column chromatography using toluene/MeCN (10%) as eluent, affording *β*-carboline **748** (72 mg, 65%) as a light brown solid.

m.p.: 82 – 85 °C. **IR**: ν_{max} (thin film) 2980, 2928, 1712, 1453, 1388, 1368, 1334, 1272, 1236, 736 cm^{-1}. **HRMS**: calculated for $C_{24}H_{23}N_2O_2$, 371.1754 $[M+H]^+$, found *m/z* 371, 1767, Δ = 3.56 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.83 (1H, s, *C*(1)), 8.30 (1H, d, J = 7.9 Hz, *H*C_{Ar}), 7.60 (1H, ddd, J = 8.4, 7.0, 1.4 Hz, *H*C_{Ar}), 7.52 (1H, d, J = 7.7 Hz, *H*C_{Ar}), 7.37 (1H, ddd, J = 8.1, 7.1, 1.1 Hz, *H*C_{Ar}), 7.29 – 7.23 (3H, m, 3 × *H*C_{Ar}), 7.17 – 7.12 (2H, m, 2 × *H*C_{Ar}), 6.30 – 6.18 (1H, m, CH$_2$C*H*), 5.61 (2H, s, PhCH_2), 5.16 – 5.04 (2H, m, CH_2CHCH$_2$Ar), 4.49 (2H, q, J = 7.1 Hz, OCH_2CH$_3$), 4.45 – 4.40 (2H, m, ArCH_2CH), 1.46 (3H, t, J = 7.2 Hz, OCH$_2$CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 167.0 (*C*(O)), 141.8, 138.0, 137.4, 136.0 (4 × C_{Ar}), 135.0 (CH$_2$*C*H), 132.6 (C_{Ar}), 130.2, 129.1, 128.5 (3 × HC_{Ar}), 128.2 (C_{Ar}), 128.2, 126.6, 124.6 (3 × HC_{Ar}), 121.6 (C_{Ar}), 121.0 (HC_{Ar}), 116.5 (*C*H$_2$CHCH$_2$Ar), 110.1 (HC_{Ar}), 61.6 (OCH$_2$CH$_3$), 47.1 (PhCH$_2$), 33.5 (ArCH$_2$CH), 14.6 (OCH$_2$$CH_3$).

2-(4-methyl-2-nitrophenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (756)

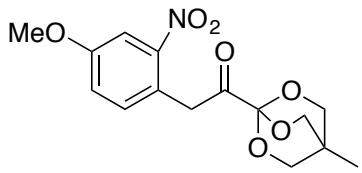


To a flame-dried vial capped with a rubber septum were added methyl-OBO ketone **611** (861 mg, 5.0 mmol, 1.0 eq.), 1-bromo-4-methyl-2-nitrobenzene (2.16 g, 10.0 mmol, 2.0 eq.), $Pd_2(dba)_3$ (46 mg, 50 μmol, 1 mol%), DavePhos (79 mg, 0.20 mmol, 4 mol%), K_2CO_3 (1.38 g, 10.0 mmol,

2.0 eq.) and phenol (20 mol%). The rubber septum was replaced by an aluminium cap and dry toluene (2.5 M) was added *via* syringe. The vial was flushed with argon for 5 mins and heated at 80 °C for 24 h. The resulting mixture was filtered through a plug of silica using EtOAc as eluent, concentrated *in vacuo* and purified by flash column chromatography using pentane/EtOAc (20%) as eluent, affording OBO-ketone **756** (1.32 g, 86%) as a yellow solid.

m.p.: 175 – 177 °C. **IR**: ν_{max} (thin film) 2933, 2879, 1723, 1613, 1521, 1350, 1076, 1032, 999, 909, 817, 739 cm^{-1}. **HRMS**: calculated for $C_{15}H_{18}NO_6$, 308.1129 $[M+H]^+$, found *m/z* 308.1127, Δ = –0.63 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.89 (1H, s, CC*H*C), 7.35 (1H, d, *J* = 7.8 Hz, *H*C_{Ar}), 7.12 (1H, d, *J* = 7.7 Hz, *H*C_{Ar}), 4.36 (2H, s, CH_2C(O)), 4.03 (6H, s, 3 × OCH_2), 2.40 (3H, s, ArCH_3), 0.87 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 194.0 (*C*(O)), 148.9 (*C*NO_2), 139.0 (*C*$_{Ar}$), 134.3, 133.3 (2 × H*C*$_{Ar}$), 126.2 (*C*$_{Ar}$), 125.6 (C*C*HC), 103.7 (*C*O_3), 73.3 (O*C*H_2), 42.0 (*C*H_2C(O)), 31.0 (*C*CH_3), 20.9 (Ar*C*H_3), 14.3 (C*C*H_3).

2-(4-Methoxy-2-nitrophenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (761)

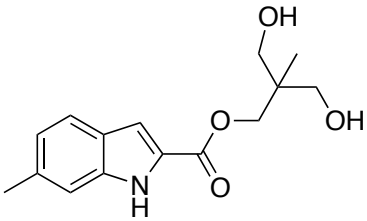


To a flame-dried vial capped with a rubber septum were added methyl-OBO ketone **611** (431 mg, 2.5 mmol, 1.0 eq.), 1-bromo-4-methoxy-2-nitrobenzene (1.16 g, 5.0 mmol, 2 eq.), $Pd_2(dba)_3$ (23 mg, 25 μmol, 1 mol%), DavePhos (40 mg, 0.10 mmol, 4 mol%), K_2CO_3 (0.70 g, 5.0 mmol, 2.0 eq.) and phenol (94 mg, 1.0 mmol, 20 mol%). The rubber septum was replaced by an aluminium cap and dry toluene (1.25 M) was added *via* syringe. The vial was flushed with argon for 5 mins and heated at 80 °C for 24 h. The resulting mixture was filtered through a plug of silica using EtOAc as eluent, concentrated *in vacuo* and purified by flash column chromatography using pentane/EtOAc (40%) as eluent, affording OBO-ketone **761** (727 mg, 90%) as a yellow solid.

m.p.: 152 – 154 °C. **IR**: ν_{max} (thin film) 2940, 2883, 1753, 1528, 1347, 1247, 1075, 1047, 1033, 993, 729 cm^{-1}. **HRMS**: calculated for $C_{15}H_{18}NO_7$, 324.1078 $[M+H]^+$, found *m/z* 324.1078, Δ = 0.22 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.60 (1H, d, *J* = 2.7 Hz, CC*H*C), 7.13 (1H, d, *J* = 8.6 Hz, CH_2CC*H*CH), 7.08 (1H, dd, *J* = 8.5, 2.6 Hz, CH_2CCHC*H*), 4.33 (2H, s, CH_2C(O)),

4.02 (6H, s, 3 × OCH_2), 3.83 (3H, s, OCH_3), 0.86 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 194.2 (*C*(O)), 159.3, 149.6 (2 × C_{Ar}), 134.2 (CH_2CCHCH), 121.1 (C_{Ar}), 120.0 (CH_2CCHCH), 110.0 (C*C*HC), 103.7 (CO_3), 73.2 (OCH_2), 55.9 (OCH_3), 41.7 (CH_2C(O)), 31.0 (CCH_3), 14.2 (CCH_3).

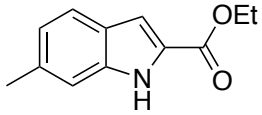
3-Hydroxy-2-(hydroxymethyl)-2-methylpropyl 6-methyl-1*H*-indole-2-carboxylate (764)



OBO-ketone **756** (85 mg, 0.28 mmol, 1.0 eq.) was subjected to *step 1* of general procedure N and purified by flash column chromatography using pentane/EtOAc (80%) as eluent, affording indole **764** (73 mg, 95%) as a white solid.

m.p.: 125 – 127 °C. **IR**: ν_{max} (thin film) 3368, 2920, 2881, 1685, 1520, 1317, 1207, 1035, 827, 792, 765, 741 cm^{-1}. **HRMS**: calculated for $C_{15}H_{20}NO_4$, 278.1387 $[M+H]^+$, found *m/z* 278.1387, Δ = 0.06 ppm. **^{1}H NMR** (400 MHz, MeOD/$CDCl_3$) δ_H: 7.11 (1H, d, *J* = 8.3 Hz, *H*C_{Ar}), 6.85 (1H, s, *H*C_{Ar}), 6.76 (1H, s, *H*C_{Ar}), 6.53 (1H, d, *J* = 8.3 Hz, *H*C_{Ar}), 3.89 (2H, s, CO_2CH_2), 3.19 (4H, s, 2 × CH_2OH), 2.04 (3H, s, ArCH_3), 0.61 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, MeOD/$CDCl_3$) δ_C: 162.1 (*C*(O)), 137.7, 134.6, 126.0, 124.7 (4 × C_{Ar}), 121.9, 121.1, 111.1, 108.0 (4 × HC_{Ar}), 65.7 (CO_2CH_2), 64.3 (CH_2OH), 40.6 (CO_2CH_2C), 20.8 (ArCH_3), 15.5 (CCH_3).

Ethyl 6-methyl-1*H*-indole-2-carboxylate (766)

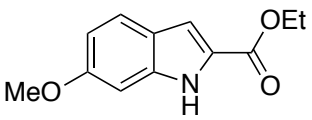


OBO-ketone **756** (92 mg, 0.30 mmol, 1.0 eq.) was subjected to general procedure N and purified by flash column chromatography using pentane/EtOAc (10%) as eluent, affording indole **766** (57 mg, 93%) as a white solid.

m.p.: 122 – 123 °C. **IR**: ν_{max} (thin film) 3308, 1684, 1522, 1327, 1250, 1206, 1021, 824, 773, 745 cm^{-1}. **HRMS**: calculated for $C_{12}H_{14}NO_2$, 204.1019 $[M+H]^+$, found *m/z* 204.1021, Δ = 1.01 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.94 (1H, s, N*H*), 7.57 (1H, d, *J* = 8.2 Hz, *H*C_{Ar}), 7.22 – 7.18 (2H, m, 2 × *H*C_{Ar}), 7.00 (1H, dd, *J* = 8.2, 1.5 Hz, *H*C_{Ar}), 4.42 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 2.48 (3H, s, ArCH_3), 1.42 (3H, t, *J* = 7.2 Hz, OCH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 162.2 (*C*(O)), 137.4, 135.7, 127.0, 125.5 (4 × C_{Ar}), 123.0, 122.3, 111.6, 108.8 (4 ×

HC_{Ar}), 61.1 (OCH_2CH_3), 22.1 ($ArCH_3$), 14.6 (OCH_2CH_3). Analytical data are consistent with those previously reported.[287,288]

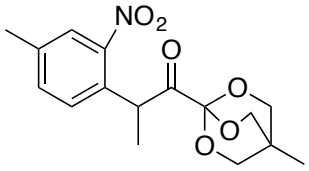
Ethyl 6-methoxy-1*H*-indole-2-carboxylate (767)



OBO-ketone **761** (97 mg, 0.30 mmol, 1.0 eq.) was subjected to general procedure N and purified by flash column chromatography using pentane/EtOAc (15%) as eluent, affording indole **767** (56 mg, 85%) as a white solid.

m.p.: 133 – 135 °C. **IR**: ν_{max} (thin film) 3317, 1677, 1626, 1253, 1196, 1023, 822, 767, 735 cm^{-1}. **HRMS**: calculated for $C_{12}H_{14}NO_3$, 220.0968 $[M+H]^+$, found *m/z* 220.0970, Δ = 0.82 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 9.22 (1H, s, N*H*), 7.55 (1H, d, *J* = 8.6 Hz, HC_{Ar}), 7.18 (1H, d, *J* = 2.3 Hz, HC_{Ar}), 6.86 – 6.81 (2H, m, 2 × HC_{Ar}), 4.42 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.85 (3H, s, OCH_3), 1.42 (3H, t, *J* = 7.1 Hz, OCH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 162.3 (*C*(O)), 158.9, 138.2, 126.5 (3 × C_{Ar}), 123.4 (HC_{Ar}), 121.9 (C_{Ar}), 112.4, 109.1, 93.8 (3 × HC_{Ar}), 60.9 (OCH_2CH_3), 55.5 (OCH_3), 14.5 (OCH_2CH_3). m.p. and spectroscopic data are consistent with those previously reported.[289]

2-(4-methyl-2-nitrophenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)propan-1-one (769)

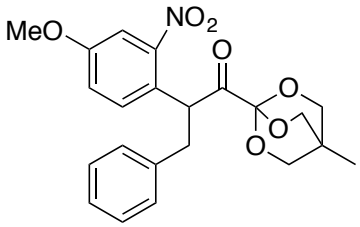


OBO-ketone **756** (184 mg, 0.60 mmol, 1.0 eq.) and methyl iodide were subjected to general procedure O and purified by flash column chromatography using pentane/EtOAc (20%) as eluent, affording OBO-ketone **769** (184 mg, 95%) as a yellow solid.

m.p.: 126 – 128 °C. **IR**: ν_{max} (thin film) 2937, 2882, 1748, 1527, 1354, 1032, 988, 946, 748 cm^{-1}. **HRMS**: calculated for $C_{16}H_{20}NO_6$, 322.1285 $[M+H]^+$, found *m/z* 322.1284, Δ = –0.20 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.54 (1H, s, $C_{Ar}HC_{Ar}C_{Ar}$), 7.28 (1H, d, *J* = 8.2 Hz, HC_{Ar}), 7.20 (1H, d, *J* = 8.0 Hz, HC_{Ar}), 4.89 (1H, q, *J* = 6.9 Hz, C*H*C(O)), 3.81 (6H, s, 3 × OCH_2), 2.36 (3H, s, $ArCH_3$), 1.44 (3H, d, *J* = 6.8 Hz, $CHCH_3$), 0.75 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 197.5 (*C*(O)), 149.8, 138.0 (2 × C_{Ar}), 133.4 (HC_{Ar}), 130.8 (C_{Ar}), 129.2 (HC_{Ar}), 124.6

($C_{Ar}HC_{Ar}C_{Ar}$), 103.8 (CO_3), 73.0 (OCH_2), 40.4 ($CHC(O)$), 30.9 (CCH_3), 20.8 ($ArCH_3$), 17.3 ($CHCH_3$), 14.1 (CCH_3).

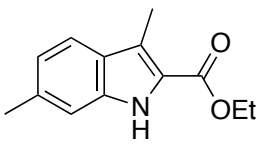
2-(4-Methoxy-2-nitrophenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-3-phenyl-propan-1-one (770)



OBO-ketone **761** (194 mg, 0.60 mmol, 1.0 eq.) and benzyl bromide were subjected to general procedure O and purified by flash column chromatography using pentane/EtOAc (40%) as eluent, affording OBO-ketone **770** (235 mg, 95%) as a yellow solid.

m.p.: 123 – 125 °C. **IR**: ν_{max} (thin film) 2937, 2883, 1747, 1529, 1356, 1251, 1030, 1001, 910, 729, 699 cm^{-1}. **HRMS**: calculated for $C_{22}H_{24}NO_7$, 414.1547 $[M+H]^+$, found *m/z* 414.1548, Δ = 0.14 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.33 (1H, d, *J* = 8.7 Hz, MeOCCHC*H*), 7.23 (1H, d, *J* = 3.4 Hz, $C_{Ar}HC_{Ar}C_{Ar}$), 7.20 – 7.09 (5H, m, 5 × HC_{Ar}), 7.04 (1H, dd, *J* = 8.8, 3.4 Hz, MeOCC*H*CH), 5.22 (1H, dd, *J* = 8.1, 6.7 Hz, C*H*C(O)), 3.78 (3H, s, OCH_3), 3.78 (6H, s, 3 × OCH_2), 3.41 (1H, dd, *J* = 13.9, 8.3 Hz, $CHCH_aH_b$), 3.03 (1H, dd, *J* = 13.9, 6.7 Hz, $CHCH_aH_b$), 0.72 (3H, s, CCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 196.3 (C(O)), 158.5, 150.7, 138.3 (3 × C_{Ar}), 130.4 (MeOCCH*C*H), 129.2, 128.1, 126.2 (3 × HC_{Ar}), 123.5 (C_{Ar}), 118.7 (MeOC*C*HCH), 109.5 ($C_{Ar}HC_{Ar}C_{Ar}$), 103.6 (CO_3), 72.9 (OCH_2), 55.7 (OCH_3), 46.8 ($CHC(O)$), 37.8 ($CHCH_2$), 30.7 (CCH_3), 14.0 (CCH_3).

Ethyl 3,6-dimethyl-1*H*-indole-2-carboxylate (773)

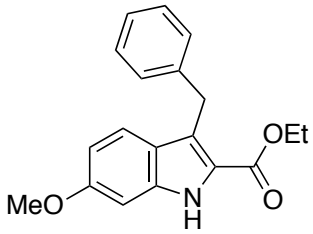


OBO-ketone **769** (96 mg, 0.30 mmol, 1.0 eq.) was subjected to general procedure N and purified by flash column chromatography using $CHCl_3$ as eluent, affording indole **773** (48 mg, 74%) as a white solid.

m.p.: 129 – 131 °C. **IR**: ν_{max} (thin film) 3315, 2975, 1676, 1327, 1266, 797, 776 cm^{-1}. **HRMS**: calculated for $C_{13}H_{16}NO_2$, 218.1176 $[M+H]^+$, found *m/z* 218.1177, Δ = 0.62 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.56 (1H, s, N*H*), 7.54 (1H, d, *J* = 8.1 Hz, HC_{Ar}), 7.14 (1H, s, C*H*C(4)), 6.98 (1H, dd, *J* = 8.3, 1.5 Hz, *H*CAr), 4.41 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 2.59 (3H, s, $ArCH_3$), 2.47

(3H, s, NCCH_3), 1.43 (3H, t, J = 7.1 Hz, OCH_2CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C: 162.9 (C(O)), 136.4, 135.9, 126.7, 123.0 (4 × C_{Ar}), 122.1 (HC_{Ar}), 120.5 (C(4)), 120.4 (C_{Ar}), 111.4 (HC_{Ar}), 60.7 (OCH_2CH_3), 22.1 ($ArCH_3$, benzocyclic), 14.6 (OCH_2CH_3), 10.1 ($ArCH_3$).

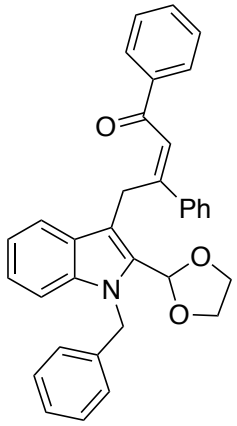
Ethyl 3-benzyl-6-methoxy-1*H*-indole-2-carboxylate (774)



OBO-ketone **770** (124 mg, 0.30 mmol, 1.0 eq.) was subjected to general procedure N and purified by flash column chromatography using pentane/EtOAc (10%) as eluent, affording indole **774** (80 mg, 86%) as a white solid.

m.p.: 142 – 145 °C. **IR**: ν_{max} (thin film) 3330, 2980, 2835, 1672, 1247, 1027, 950, 669 cm^{-1}. **HRMS**: calculated for $C_{19}H_{20}NO_3$, 310.1438 $[M+H]^+$, found m/z 310.1438, Δ = 0.00 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 8.89 (1H, s, NH), 7.48 (1H, d, J = 8.7 Hz, HC_{Ar}), 7.31 – 7.21 (4H, m, 4 × HC_{Ar}), 7.19 – 7.13 (1H, m, HC_{Ar}), 6.82 – 6.75 (2H, m, 2 × HC_{Ar}), 4.49 (2H, s, $PhCH_2$), 4.41 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.84 (3H, s, OCH_3), 1.38 (3H, t, J = 7.2 Hz, OCH_2CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 162.5 (C(O)), 159.1, 141.1, 137.1 (3 × C_{Ar}), 128.4, 128.3, 125.8 (3 × HC_{Ar}), 123.1, 122.6, 122.6 (3 × C_{Ar}), 122.1, 111.7, 93.6 (3 × HC_{Ar}), 60.7 (OCH_2CH_3), 55.5 (OCH_3), 30.7 ($PhCH_2$), 14.5 (OCH_2CH_3).

4-(1-Benzyl-2-(1,3-dioxolan-2-yl)-1*H*-indol-3-yl)-1,3-diphenylbut-2-en-1-one (S1)



A fresh solution of LiHMDS was prepared in a dry vial by adding sequentially dry THF (2.0 mL), HMDS (83 μL, 0.38 mmol, 2.5 eq.) and a 2.5 M solution of *n*BuLi (0.15 mL, 0.38 mmol, 2.5 eq.) at –78 °C for 10 mins. Acetophenone (36 μL, 0.31 mmol, 2.0 eq.) was then added at 0 °C and stirred for 15 mins. In a second dry vial were added bromoindole **520** (55 mg, 0.15 mmol, 1.0 eq.) and Pd(amphos)Cl_2 (5 mg, 8 μmol, 5 mol%). The vial was sealed and flushed with argon for 5 mins. The freshly formed enolate solution was then transferred *via* syringe to the vial and the mixture was stirred at 50 °C for 24 h. The reaction was cooled down to RT, filtered through a plug of silica using EtOAc as eluent and concentrated *in vacuo*. The crude product was purified by flash column

chromatography using DCM as eluent, affording keto-indole by-product **S1** (15 mg, 20%) as a brown oil.

IR: ν_{max} (thin film) 3059, 2922, 1685, 1597, 1495, 1447, 1351, 1329, 1210, 1076, 744, 692 cm^{-1}. **HRMS**: calculated for $C_{34}H_{29}NO_3Na$, 522.2040 $[M+Na]^+$, found *m/z* 522.2037, Δ = –0.56 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.87 – 7.82 (2H, m, 2 × *H*C_{Ar}), 7.59 – 7.46 (4H, m, 4 × *H*C_{Ar}), 7.39 – 7.32 (4H, m, 4 × *H*C_{Ar}), 7.30 – 7.07 (10H, m, 10 × *H*C_{Ar} + C*H*C(O)), 6.00 (1H, s, C*H*$(OR)_2$), 5.48 (2H, s, CH_2Ph), 4.42 (2H, s, CH_2CPh), 3.88 – 3.72 (4H, m, (OCH_2)$_2$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C: 197.9 (*C*(O)), 141.6, 138.8, 138.2, 137.7, 137.1 (4 × C_{Ar} + CH_2*C*Ph), 132.8 (HC_{Ar}), 129.9 (C_{Ar}), 128.5, 128.4, 128.4, 128.0, 127.4 (5 × HC_{Ar}), 127.1 (C_{Ar}), 127.0, 126.4, 126.1, 123.4, 122.4, 120.2, 120.0 (6 × HC_{Ar} + *C*HC(O)), 115.5 (C_{Ar}), 110.4 (HC_{Ar}), 98.3 (C*H*$(OR)_2$), 64.6 ((O*C*H_2)$_2$), 48.3 (*C*H_2Ph), 41.8 (*C*H_2CPh).

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