A Radical-Polar Crossover Approach to Interrupted [2+2] Cycloaddition *via* the Triplet state

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Declaration

This dissertation describes work carried out in the Chemistry Research Laboratory at the University of Oxford between September 2022 to March 2026. The dissertation is a product of my own work and includes some results obtained through collaboration where specifically indicated in the text.



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List of Abbreviations

°C	degree Celsius
Ac	acetyl
Boc	tert-butyloxycarbonyl
bpy	2,2′-bipyridine
Bu	butyl
CH_2Cl_2	dichloromethane
CV	cyclic voltammetry
d	doublet
d.r	diastereomeric ratio
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCVC	dry column vacuum chromatography
DFT	density functional theory
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
e.e	enantiomeric excess
e.r	enantiomeric ratio
EnT	energy transfer
equiv.	equivalent
ESI	electrospray ionisation
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron-withdrawing group

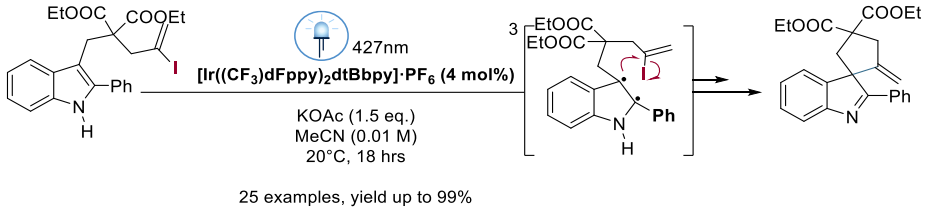
FTIR	Fourier transform infrared spectroscopy
HBPin	pinacolborane
HMDS	hexamethyldisilazane
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	Hertz
hr	hour
IC	internal conversion
INT	intermediate
ISC	intersystem crossing
J	coupling constant
k	rate constant
L	litre
L*	chiral ligand
LC	ligand centred
LED	light-emitting diode
LRMS	low-resolution mass spectrometry
m	multiplet
M	moles per litre
m	milli-
m-	meta-
max	maximum
MC	metal centred
Me	methyl

MeCN	acetonitrile
MeOH	methanol
min	minute
MLCT	metal-to-ligand charge transfer
MO	molecular orbital
Moc	methoxycarbonyl
mol	mole
NBO	natural bond orbital
NEt_3	Triethylamine
NEVPT	N-electron valence state perturbation theory
NMR	nuclear magnetic resonance
NuY	nucleophile
o-	ortho-
ox	oxidation
p-	para-
PC	photocatalyst
Ph	phenyl
ppy	2-phenylpyridine
quant.	quantitative
q	quartet
red	reduction
RPC	radical-polar crossover
s	singlet
sat.	saturated
SCE	saturated calomel electrode

SET	single-electron transfer
SHE	standard hydrogen electrode
t	triplet
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	N, N, N', N'-tetramethylethylenediamine
TMS	trimethylsilyl group
TosMIC	tosylmethyl isocyanide
TPPO	triphenylphosphine oxide
TS	transition state
Ts	toluenesulfonyl
TTET	triplet-triplet energy transfer
UV	ultraviolet
ν	absorbances
w/w	weight by weight
WBO	Wiberg bond order

Abstract

Photochemical [2+2] cycloadditions provide an efficient pathway for constructing strained cyclic frameworks, but the reactivity of the corresponding excited-state intermediates is generally directed towards conventional cyclobutane formation. This work examines whether the reactivity of a triplet-sensitised 2-phenylindole system can be diverted through incorporation of a redox shuttle, thereby interrupting the usual [2+2] pathway and enabling a triplet-state radical-polar crossover (RPC) process.



A series of redox-shuttle-containing 2-phenylindole substrates was designed and synthesised. A practical route to the target substrates was established. Under visible-light irradiation in the presence of an iridium photocatalyst, these substrates underwent cyclisation to afford 3-spiroindole products in good to excellent yields, while no conventional [2+2] cycloaddition product was observed under the standard conditions. The transformation showed broad substrate scope, tolerating halogen, electron-donating, electron-neutral and strongly electron-withdrawing substituents. Across the series examined, steric effects appeared to exert a greater influence on reaction efficiency than electronic effects.

Attempts to trap the iminium intermediate directly in one pot were unsuccessful, although hydrogenation of the cyclised products proceeded efficiently. Mechanistic studies were consistent with a triplet-state RPC pathway rather than the photoredox pathways. Taken together, these results show that the triplet-state radical-polar crossover can provide a useful methodology for redirecting the excited-state reactivity of 2-phenylindole systems and offer access to a range of spiroindole architectures.

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1. Introduction to photocatalysis

1.1 Photochemistry

Photochemistry is the study of chemical reactions initiated by the absorption of light,[1] in which electronic excitation enables reactivity that is not accessible from the ground state. Photoexcitation alters the electronic structure of a molecule, thereby modifying its bond strengths, spin state, and redox properties.[2] As a result, photochemical processes can facilitate transformations such as pericyclic reactions, isomerisations, and redox reactions.[3, 4]

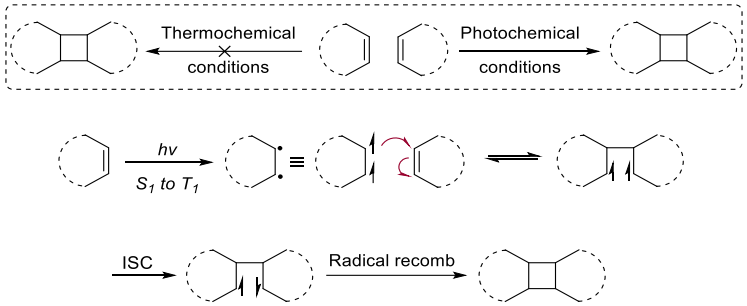


Figure 1. Photochemistry enables thermally forbidden reactions.

A well-established example is the [2+2] cycloaddition, which is thermally forbidden according to the Woodward–Hoffmann rules due to symmetry constraints between the interacting orbitals.[5] Under photochemical conditions, however, excitation of an alkene promotes an electron from a π to a π* orbital, enabling productive symmetry and allowing the cycloaddition to proceed. In a typical triplet-state pathway, one alkene is promoted to the singlet excited state and undergoes intersystem crossing (ISC) to the triplet state, stepwise C-C bond formation, intersystem crossing (ISC), and radical recombination to give a cyclobutane product (*Figure* 1).[6]

This distinctive reactivity has made photochemical [2+2] cycloaddition a widely used platform in synthesis[7-9] At the same time, it raises an interesting question: whether the reactivity of the corresponding excited-state intermediates can be diverted before cyclobutane formation occurs. Addressing this question forms the basis of the work described in this thesis.

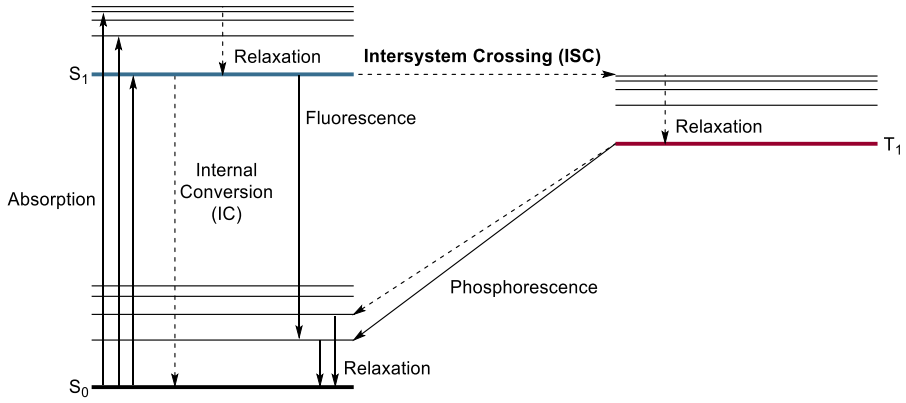


Figure 2. Jablonski diagram of typical photochemical process

The formation and behaviour of excited states can be described using a Jablonski diagram (*Figure* 2). Upon absorption of light, a molecule is promoted from the ground state (S_0) to a singlet excited state (S_1), which typically undergoes rapid relaxation *via* internal conversion (IC) or fluorescence.[10] Alternatively, intersystem crossing (ISC) can occur to generate a triplet excited state (T_1), which generally has a longer lifetime due to spin-forbidden relaxation.[11] These longer-lived triplet states are particularly important in synthetic photochemistry, as they enable bimolecular processes such as energy transfer.[3]

1.2 Photocatalysis

Although direct photoexcitation can enable access to excited-state reactivity, it often requires high-energy UV light, which can lead to poor chemoselectivity, limited functional group tolerance, and reduced synthetic applicability.[12] To address these limitations, visible-light photocatalysis has emerged as a powerful alternative, in which a photocatalyst absorbs light and transfers energy or electrons to a substrate under milder conditions.[3]

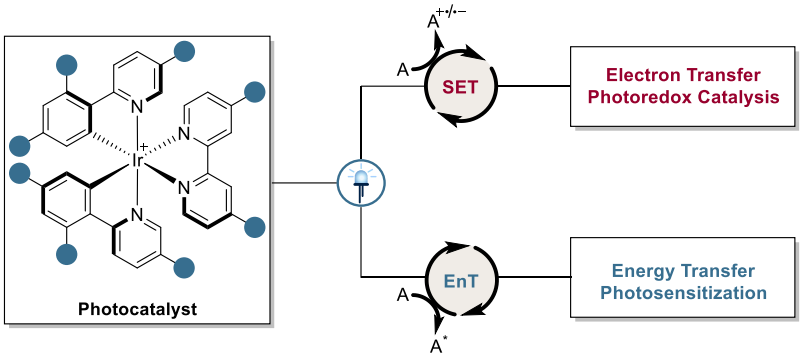


Figure 3. General definition of photocatalysis: Electron transfer photoredox catalysis involves a change of oxidation state, whereas energy transfer photosensitization does not.

Two fundamental activation modes are commonly distinguished: energy transfer (EnT) and photoredox catalysis (*Figure* 3).[3, 13] In energy-transfer processes, the photocatalyst transfers its excited-state energy to the substrate without changing oxidation state, typically *via* triplet-triplet energy transfer. In contrast, photoredox processes involve single-electron transfer (SET), generating radical intermediates through oxidation or reduction of the substrate. Distinguishing between these pathways is central to understanding the reactivity of photocatalytic systems, including those examined in this thesis.

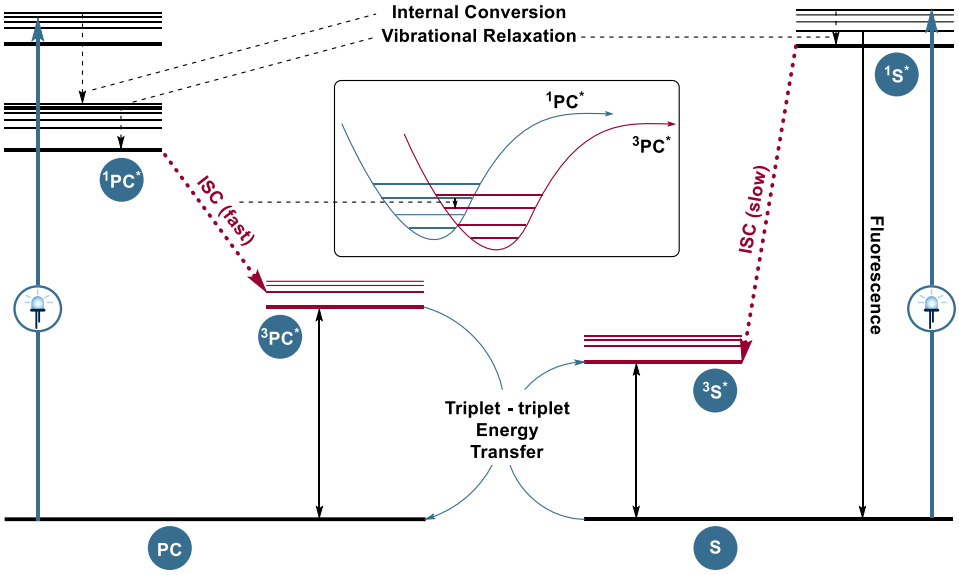


Figure 4. Jablonski diagram shows the mechanism of a typical energy transfer (EnT). Diagram in the centre represent the ISC between 2 vibrational states of singlet excited state and triplet excited state

To illustrate a general energy-transfer (EnT) mechanism (*Figure* 4), the photocatalyst absorbs a photon, promoting one electron from the ground state (PC) to the singlet excited state ($^1PC^*$). It can then decay to the ground state *via* internal conversion or fluorescence. Alternatively, it undergoes intersystem crossing (ISC) to transition to the triplet state ($^3PC^*$). Notably, intersystem crossing occurs between two energetically close vibrational states of singlet excited state and triplet excited state. The resulting excited photocatalyst can promote a substrate to the triplet state. This process is referred to as triplet-triplet energy transfer (TTET).[14, 15]

Since most energy-transfer acceptors do not directly absorb visible light, a non-radiative process is required to facilitate the mechanism of energy transfer (EnT).[16] Two mechanisms have been proposed to account for non-radiative energy transfer, which refer to coulombic interactions (Förster energy transfer) and exchange interactions (Dexter energy transfer).[17]

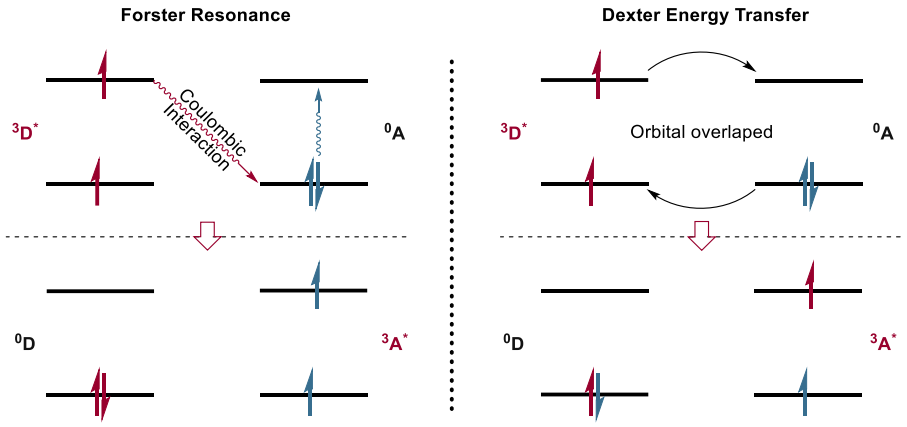


Figure 5. Förster and Dexter EnT process

Förster energy transfer describes a transmitter-antenna process in which energy is transferred through dipole-dipole coupling (*Figure* 5). The excited state of Donor ($^3D^*$) induces a dipole in the ground state of the acceptor (^0A), which results in an electronic oscillation of the acceptor (^0A). The relaxation of the donor with a concurrent excitation of the acceptor leads to the desired electron transition.[18] This mechanism involves two individual spin reversal

processes, which violates Wigner's spin conservation rules, and therefore, cannot describe EnT process in solution.[19]

In energy-transfer photocatalysis, the excited photocatalyst promotes the substrate to its triplet excited state. This process is most commonly described in terms of Dexter energy transfer (*Figure* 5), which involves simultaneous electron exchange between donor and acceptor.[20] The description of Dexter energy transfer is shown:

$$k_{\mathrm{EnT}} = K \cdot J \cdot \mathrm{e}^{-\frac{2R_{\mathrm{DA}}}{\mathrm{L}}} \qquad (1)$$

K is a parameter that takes into account the steric repulsion between donor and acceptor. *J* is an integral that represents the spectral overlap between the emission of the donor and the absorption of acceptor. In *Figure 6(A)*, where f_D is the normalized emission spectrum of the donor (phosphorescence spectrum) and ε_A is the normalized absorption spectrum of the acceptor (singlet to triplet). However, it is challenging to determine *J* experimentally in many cases since singlet to triplet absorption of the acceptor is difficult to measure.[17, 20] The magnitude of *J* however is positively correlated to ΔE_T, the energy difference between the triplet states of the acceptor and the donor ($\Delta E_T = E_T(A) - E_T(D)$). The simplified diagram is shown in *Figure 6(B)*.[21]

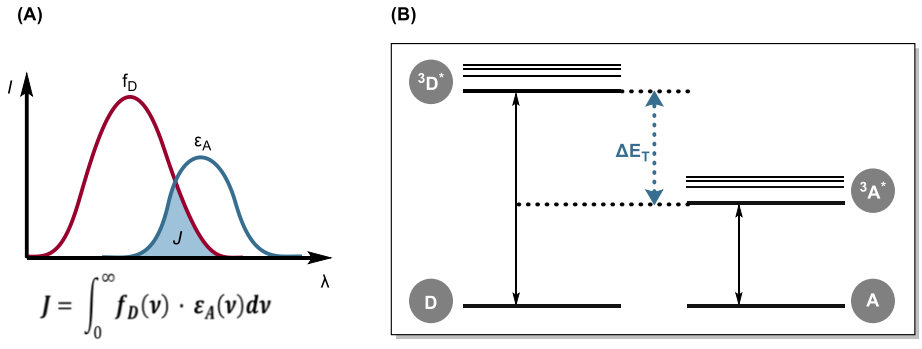


Figure 6. (A) Normalized absorption and emission overlap integral between donor and acceptor. (B) Simplified Jablonski diagram to represent the triplet-state energy difference between donor and acceptor

$\Delta E_T < 0$, a large number of EnT transitions are possible, resulting in a large number of possible $^3A^*$ stage and therefore a large J value. Consequently, the rate of EnT is large. By contrast, if $\Delta E_T > 0$, coupled transition only exists through vibrational or rotational levels of donor $^3D^*$. Since the overlap integral J is dependent on thermal population or vibrational or rotational state, it requires a longer donor triplet lifetime.

R_{DA}/L is a measure of distance between donor and acceptor which has a significant effect on the rate of energy transfer, as this mechanism requires a significant orbital overlap between donor and acceptor. In simpler terms, the donor and acceptor must come into physical contact.[22]

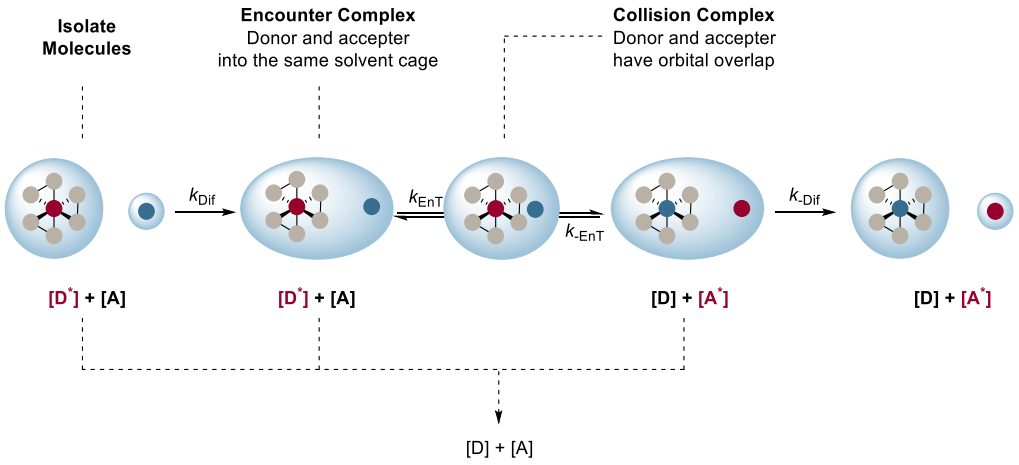


Figure 7. Simplified molecular diffusion process in solution.

The kinetics of the EnT process in solution can be divided into five stages. As illustrated in *Figure 7*, first, excited donor (D^*) and the ground state acceptor (A) form encounter complex *via* diffusion in the same solvent cage. The orbitals of donor (D^*) and acceptor (A) overlap to promote a Dexter EnT. Donor is quenched back to the ground state and acceptor is excited to the triplet state. Dissociation of the encounter complex releases the ground-state donor and the excited-state acceptor as separate molecules. While $k_{EnT} >> k_{Dif}$, the overall rate k_{obs} depends on diffusion rate k_{Dif}. By contrast, while $k_{EnT} << k_{Dif}$,the overall rate k_{obs} depends on energy transfer rate k_{EnT}. The k_{Dif} is solvent dependent, therefore, the solvent effect is also significant for energy transfer process.[17, 23]

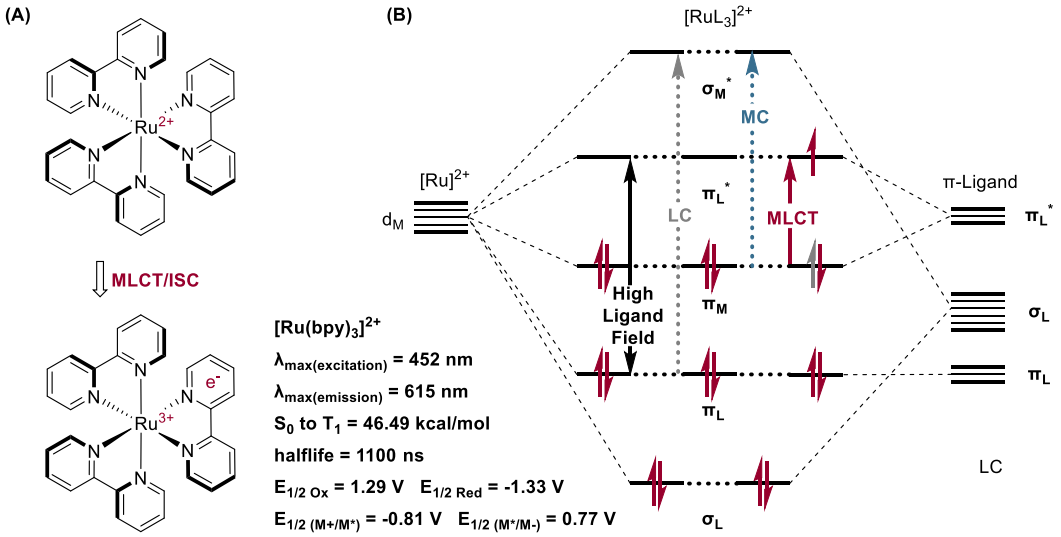


Figure 8. (A) Photophysical Properties and the simplified MLCT of $[Ru(bpy)_3]^{2+}$. (B) MO of typical $[RuL_3]^{2+}$ (involved with CT band)

Figure 8(B) shows a representative molecular orbital (MO) diagram for a Ruthenium-based complex with a high ligand field (low spin). A high field complex implies that the anti-bonding orbitals of the ligands (π_L^*) have lower energy than the anti-orbitals of the metal (σ_M^*). Multiple electronic transitions can happen between each orbital. An electron transfer from a HOMO orbital (π_M) to an anti-bonding orbital of a ligand (π_L^*) is referred to as metal-to-ligand charge-transfer (MLCT).[24,25] Since electrons exchanging between a donor and an acceptor is required for Dexter Energy transfer, MLCT induces one electron to the "shell" of the photocatalyst which is essential for Dexter EnT to facilely happen (*Figure 8(A)*). Moreover, the redox properties are altered upon MLCT excitation. Excited $[Ru(bpy)_3]^{2+}$ exhibits both a stronger oxidation potential and a stronger reduction potential than the ground state (MLCT transforms a redox inert substance to a redox active substance), which is essential for single-electron photoredox catalysis.[26]

An electron transfer from a ligand-centered π orbital to a ligand-centered antibonding orbital is referred to as a ligand-centered (LC) transition. As *Figure 9(A)* shows for absorption and emission spectra of $[Ru(bpy)_3]^{2+}$, this process generally requires more energy (e.g., UV

light).[27] Previous studies have shown that the LC state can relax spontaneously to the MLCT state.[28]

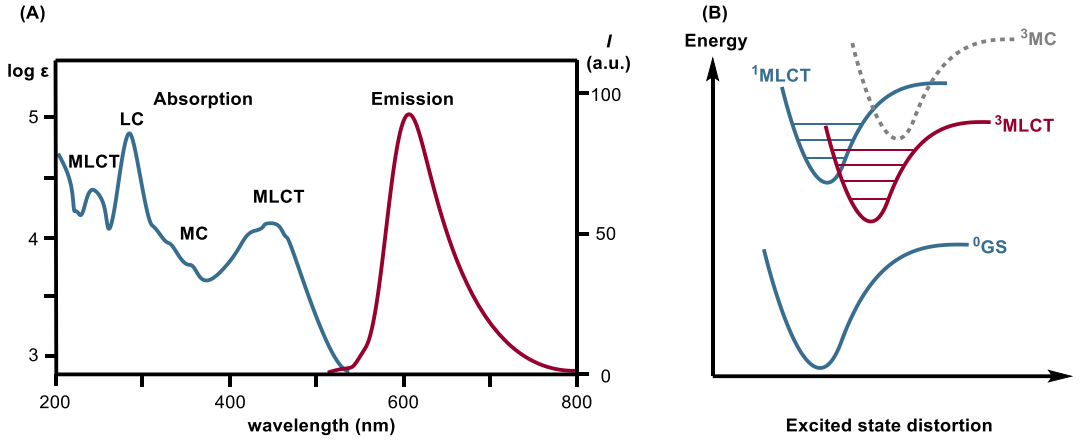


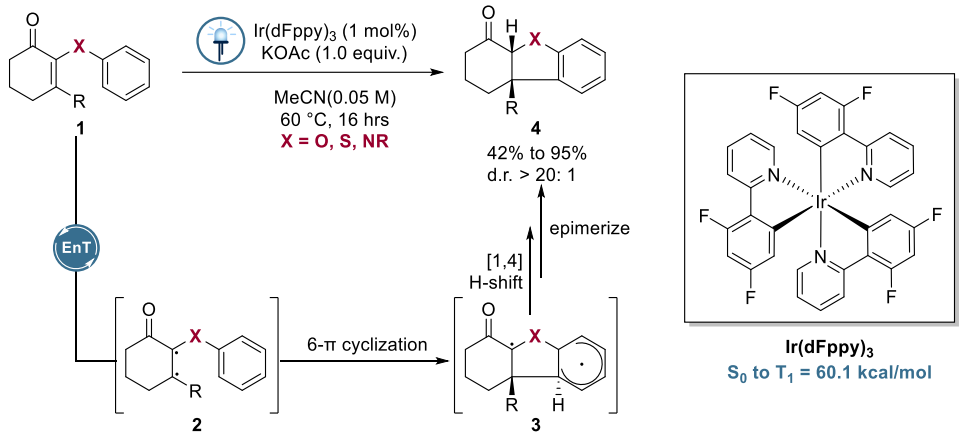
Figure 9. (A) Absorption and emission spectrum of $[Ru(bpy)_3]^{2+}$. (B) Simplified energy diagram to represent excited state quenching of a typical high ligand field strength photocatalyst.

Excitation of an electron from a metal-centered HOMO (π_M) to a metal-centered antibonding orbital (σ_M^*) is referred to as a metal-centered (MC) transition. In a high-field complex, the energy required to access the MC state is significantly higher than that required for metal-to-ligand charge transfer (MLCT). Therefore, quenching of the ^{3}MLCT state does not proceed through a MC state (*Figure 9(B)*),[25, 29] which is one of the primary reasons why high-field complexes are particularly well suited as photocatalysts. By contrast, the behaviours of low field complexes will be addressed in a later section. Notably, the quantum yields associated with the transitions discussed above are generally low (e.g., the quantum yield of MLCT is low ($[Ru(bpy)_3]Cl_2$: Φ =9.5% in MeCN)).[30] Several competing deactivation pathways, including internal conversion and fluorescence, can also occur.[27]

1.2.1 Examples of Energy Transfer Catalysis

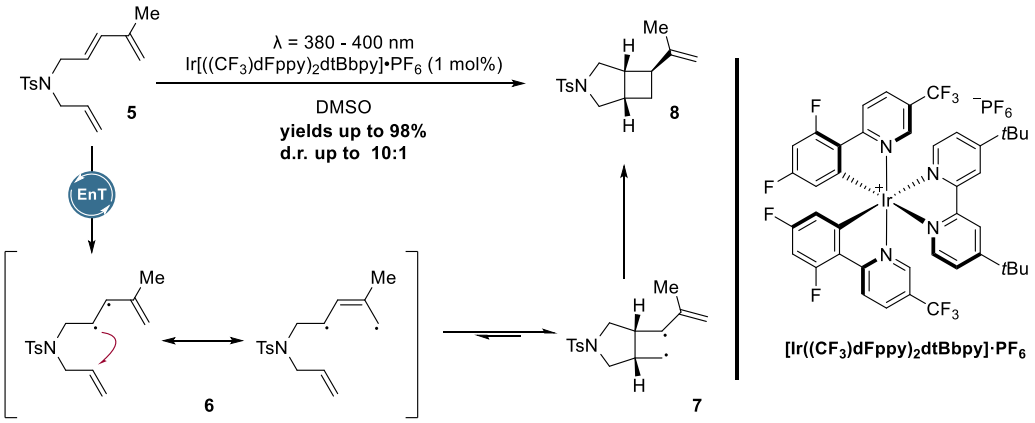
In 2017, the Smith group reported a triplet-state-mediated 6π heterocyclization of cyclohexanone (*Scheme* 1).[31] The triplet energy of $Ir(dFppy)_3$ is 60.1 kcal/mol (S_0 to T_1), which is well matched to the triplet energy of the substrate (58.2 kcal/mol determined by DFT). Upon

photoexcitation and EnT, the alkene moiety of cyclohexanone **1** is promoted to the triplet state, followed by a 6π cyclization to generate intermediate **3**.



Scheme 1. 6π heterocyclization of cyclohexanone by Smith's group

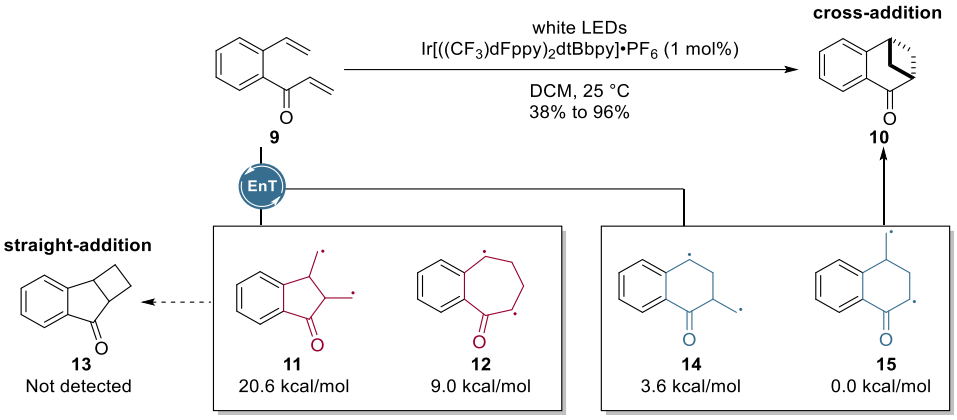
The resulting diradical intermediate is stabilized by conjugation. Subsequently, a [1,4]-hydrogen shift occurs, followed by epimerization of proton to afford the desired product. This Ir-based photocatalytic system enables the formation of fused dihydrobenzofurans, dihydroindolines, and dihydrobenzothiophenes in moderate to excellent yields and diastereoselectivity.



Scheme 2. Intramolecular [2+2] cycloaddition of 1,3-dienes via the triplet state by Yoon's group

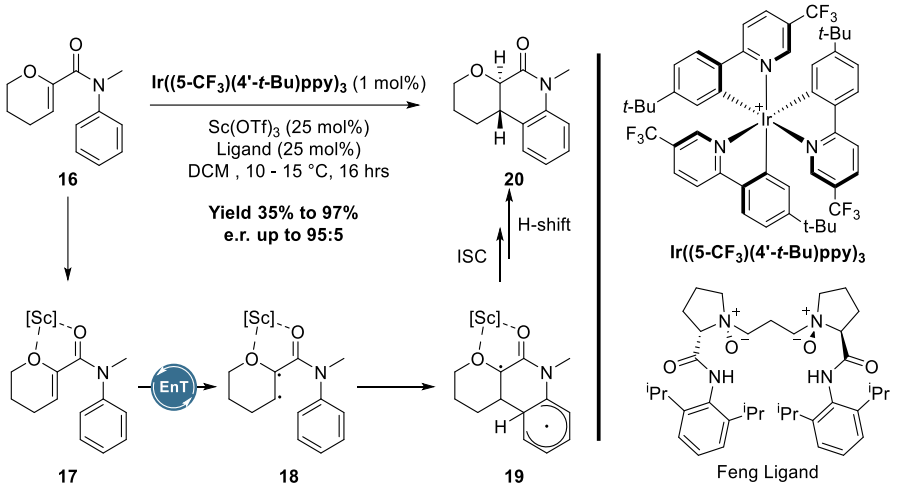
In 2014, Yoon's group reported a visible-light-mediated [2+2] cycloaddition of 1,3-dienes. Upon photoexcitation, the 1,3-diene **5** undergoes a stepwise [2+2] cycloaddition,

ultimately affording the desired cyclobutane product **8** in excellent yield and good diastereoselectivity (*Scheme 2*).[32]



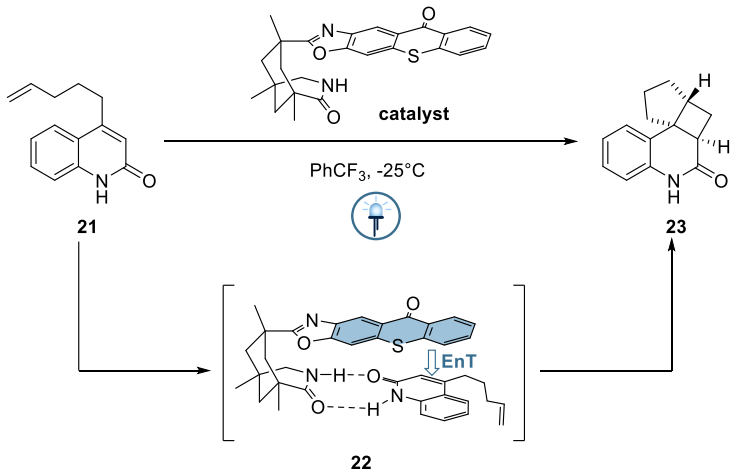
Scheme 3. Crossed intramolecular [2+2] cycloaddition via the triplet state by Kwon's group

Visible-light-mediated photocatalysis has been used for "crossed" [2+2] cycloadditions. A study published in 2017 by Kwon and coworkers demonstrated that dienones **9** could be used to generate bridged cyclobutanes **10**, demonstrating that dienones **9** first can undergo 6-*exo-trig* cyclization to generate desired bridged cyclobutane **10**. By contrast, the 5-*exo-trig* intermediate **11** and the 7-*endo-trig* intermediate **12** are significantly higher in energy (calculated by DFT). Consequently, straight-addition product **13** was not detected (*Scheme 3*).[33]



Scheme 4. Visible-light-mediated EnT for the enantioselective 6π cyclization of acrylanilides by Smith's group

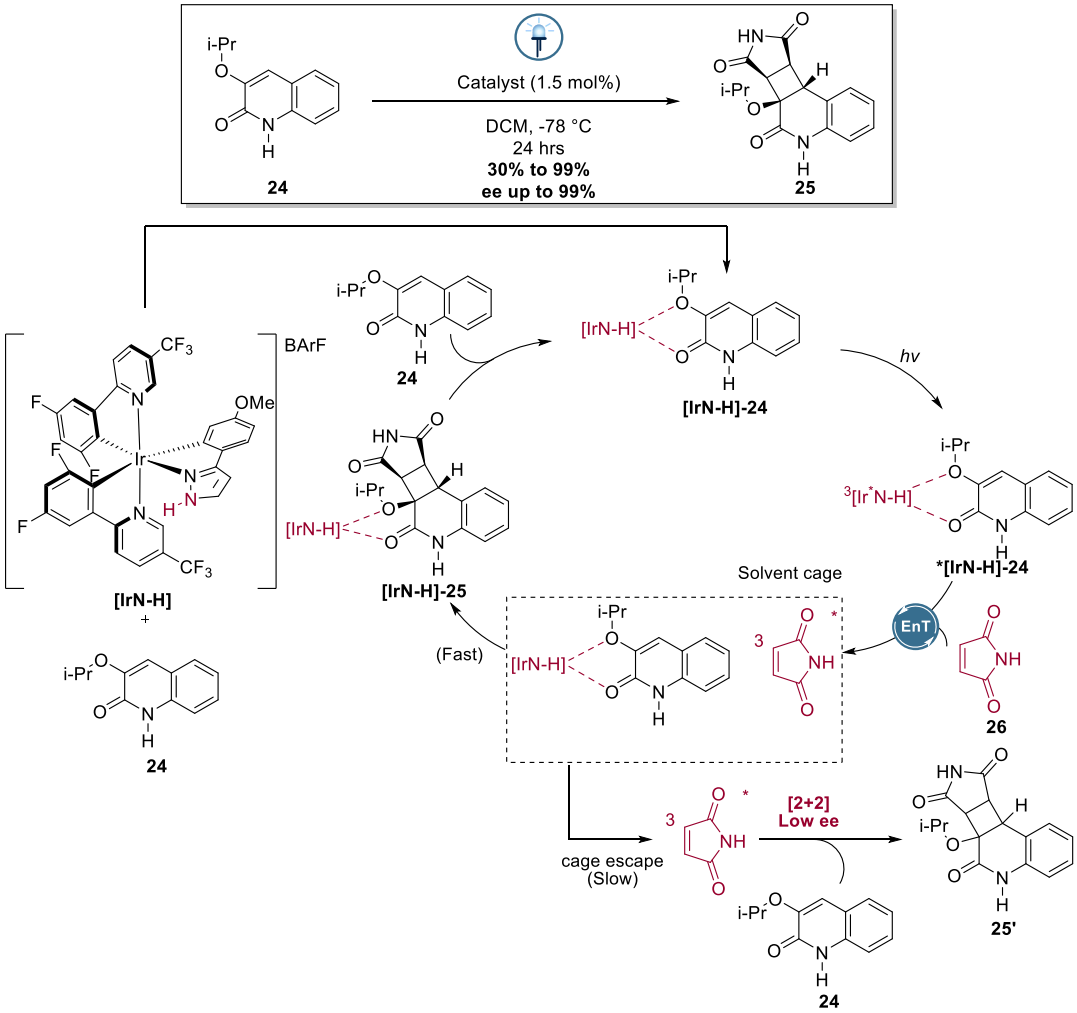
Recently, Smith's group demonstrated an enantioselective 6π cyclization of acrylanilides **16** to the corresponding cyclized product **20** in excellent yields and enantioselectivity (*Scheme* 4).[34] The acrylanilide substrate **16** first coordinates to a chiral Feng ligand-scandium complex, in which the Lewis-acidic metal center significantly lowers the triplet energy required for excitation of the substrate. Subsequent energy transfer from the photocatalyst promotes the bound chromophore to the triplet state, followed by a 6π cyclization to generate intermediate **19**. Finally, intersystem crossing and a hydrogen shift occur, delivering the desired product **20** with high enantioselectivity.



Scheme 5. Enantioselective [2+2] cycloaddition of quinolones via the triplet state.

In 2014, Bach and co-workers reported a strategy enabling the first enantioselective [2+2] cycloaddition *via* visible-light-mediated EnT photocatalysis (*Scheme 5*). In this study, a thioxanthone-based photocatalyst was employed to afford enantioenriched cyclobutanes **23** from quinolone **21**. The photocatalyst serves a dual role: it mediates energy transfer (EnT) and simultaneously binds the substrate through hydrogen-bonding interactions to exert enantioselective control. Initially, the catalyst associates with substrate **21** *via* hydrogen bonding and promotes substrate to the triplet state *via* π-π stacking interactions. Then, an enantioselective [2+2] cycloaddition occurs, affording the desired product in excellent yield and enantioselectivity.[35]

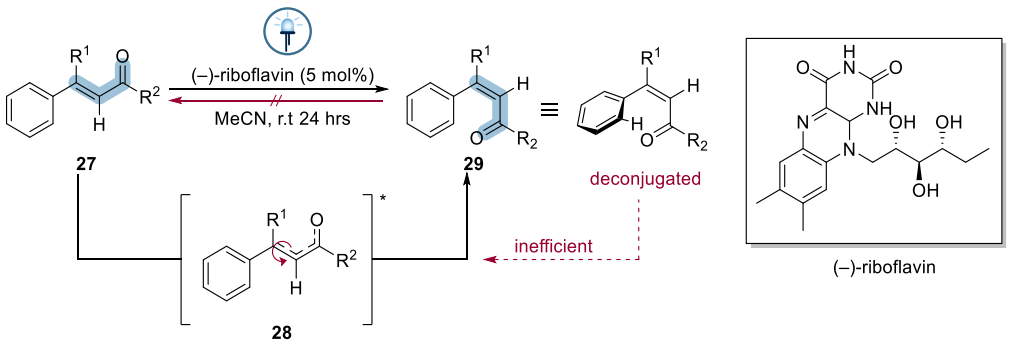
In 2019, Yoon and coworker reported a strategy for controlling the enantioselectivity of intermolecular [2+2] cycloadditions, as illustrated in *Scheme 6*. In this work, a modified Ir-based chiral photocatalyst was designed to bind with substrate **24** through hydrogen bond interactions. The resulting complex **[IrN-H]-24** was excited to the triplet state and can be regarded as the active photocatalytic species. At this stage, when substrate **26** approaches to the complex **[IrN-H]-24**, it promotes substrate **26** to the triplet state.[36]



Scheme 6. Triplet rebound strategy for intermolecular enantioselective [2+2] cycloaddition by Yoon's group.

Consequently, a highly enantioselective [2+2] cycloaddition occurs to generate the desired product **25**, as both the complex and the excited substrate **26** remain within the same solvent cage. This mechanistic pathway is referred to as triplet-rebound. By comparison, a fraction of the excited substrate **26** may escape from solvent cage, leading to a background

[2+2] cycloaddition with low enantioselectivity. However, when the concentration of **24** is significantly lower than that of **26**, the enantioselectivity of the reaction increases. A possible explanation is that **26** undergoes rapid dimerization under low concentrations of **24**. More recently, Yoon and co-workers have extended this strategy to enantioselective Paternò-Büchi reactions.[37]

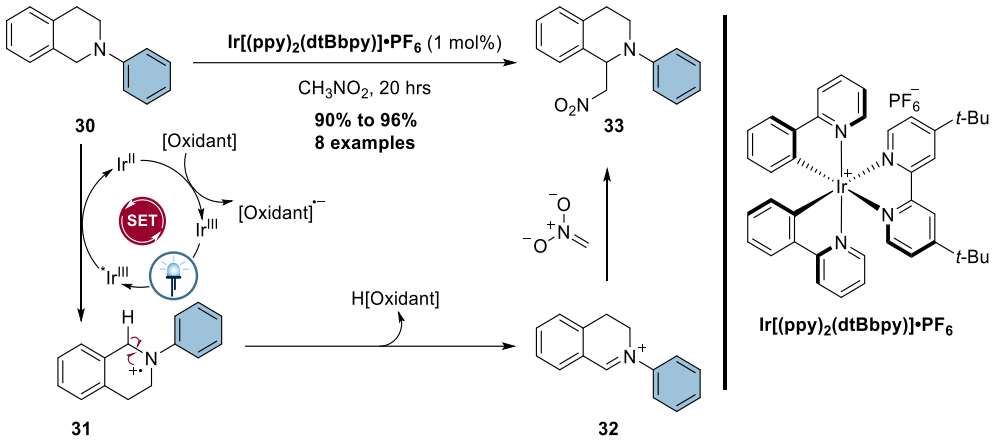


Scheme 7. E/Z isomerization of styrenyl alkenes by Gilmour and coworkers

In 2015, Gilmour and coworkers reported a highly selective E-to-Z photoisomerization of olefins **27**. This strategy relies on the incorporation of alkyl substituents on the alkene, as shown in *Scheme 7*. The *E*-configured substrate **27** can be repeatedly reactivated due to its efficient interaction with the enantioenriched photocatalyst **(-)-riboflavin**. In contrast, the desired product **29** cannot efficiently reactivate due to deconjugation between the twisted π-system and the photosensitizer. This reduced electronic conjugation leads to a weaker interaction with **(-)-riboflavin**, suppressing further excitation and ultimately resulting in high *E/Z* selectivity.[38]

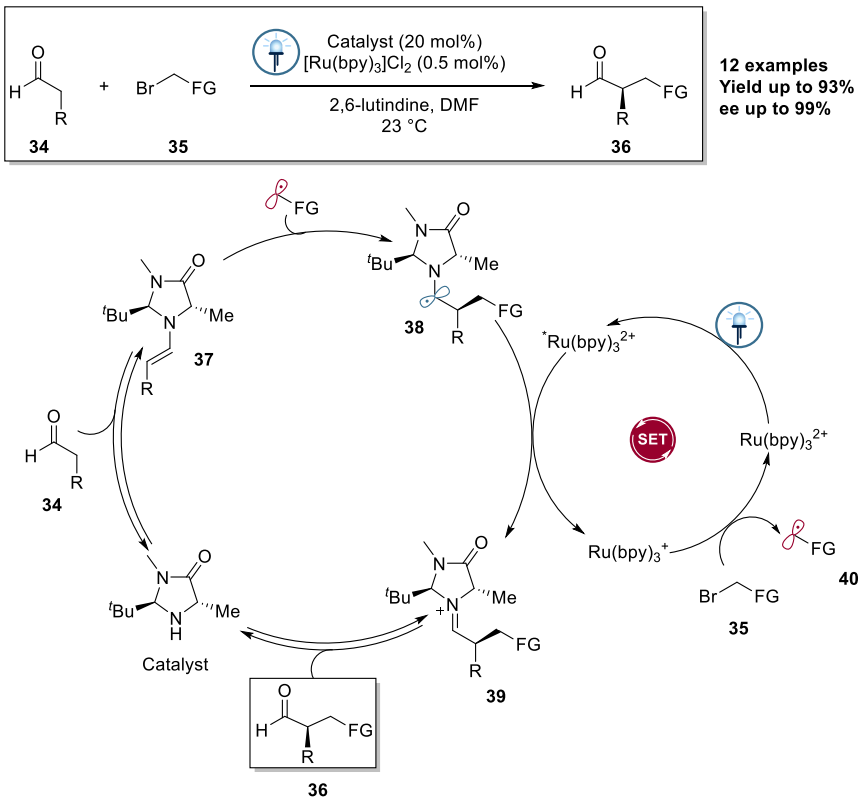
1.2.2 Examples of SET Photocatalysis

Apart from the examples of the triplet-state energy transfer photosensitization mentioned above, single-electron transfer photocatalysis is also important for understanding photocatalysis.



Scheme 8. Visible-light-mediated photoredox of aze-Henry reaction by Stephenson and coworkers

In 2010, Stephenson and coworkers reported visible-light-mediated photoredox aza-Henry reactions *via* C-H functionalization (*Scheme 8*). In this study, the excited photocatalyst undergoes reductive quenching by an amine **30**, resulting in an amine radical **31**, followed by an α-amino C-H abstraction and the formation of an α-amino radical. Consequently, a nucleophile traps the resulting imine to afford the desired product **33** in excellent yield.[39]



Scheme 9. Dual catalysis of asymmetric alkylation of aldehydes via photoredox by MacMillan and coworkers

MacMillan and coworkers reported a dual organophotoredox catalysis process for asymmetric alkylation of aldehydes (*Scheme 9*). In this study, an enantioenriched organic catalyst is employed to associate with the aldehyde **34** to form enantioenriched intermediate **37**. Then, a functionalized alkyl radical **40** attacks **37** resulting intermediate **38**. Following by a reductive quenching of the photocatalyst to generate desired intermediate **39**, eventually, the desired product is released in excellent yield and enantioselectivity. To close redox cycle, the metal-based photocatalyst is oxidised by alkyl bromide **35**.[40]

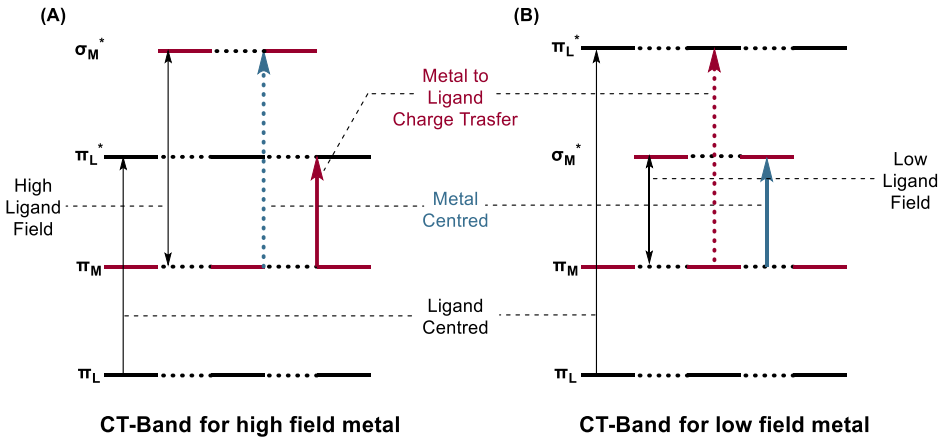


Figure 10. (A) Charge Transfer Band for high field complex. (B) charge Transfer Band for low field complex

The choice of photocatalyst plays a critical role in determining reactivity. Ruthenium- and iridium-based complexes are widely employed due to their favourable photophysical properties, including strong absorption in the visible region, long-lived triplet excited states, and tunable redox potentials.[26]

These properties arise primarily from metal-to-ligand charge transfer (MLCT) excited states, which can participate in both energy-transfer and photoredox processes.[29] In high-field complexes, the MLCT state is energetically well separated from metal-centred (MC) states, reducing non-radiative deactivation and enabling efficient bimolecular reactivity (*Figure 10(A)* and *Figure* 11*(A)*). Although ketone-based photocatalysts such as thioxanthones have been

widely explored, their limited redox window often requires bespoke catalyst synthesis for different substrate scaffolds.[13, 41]

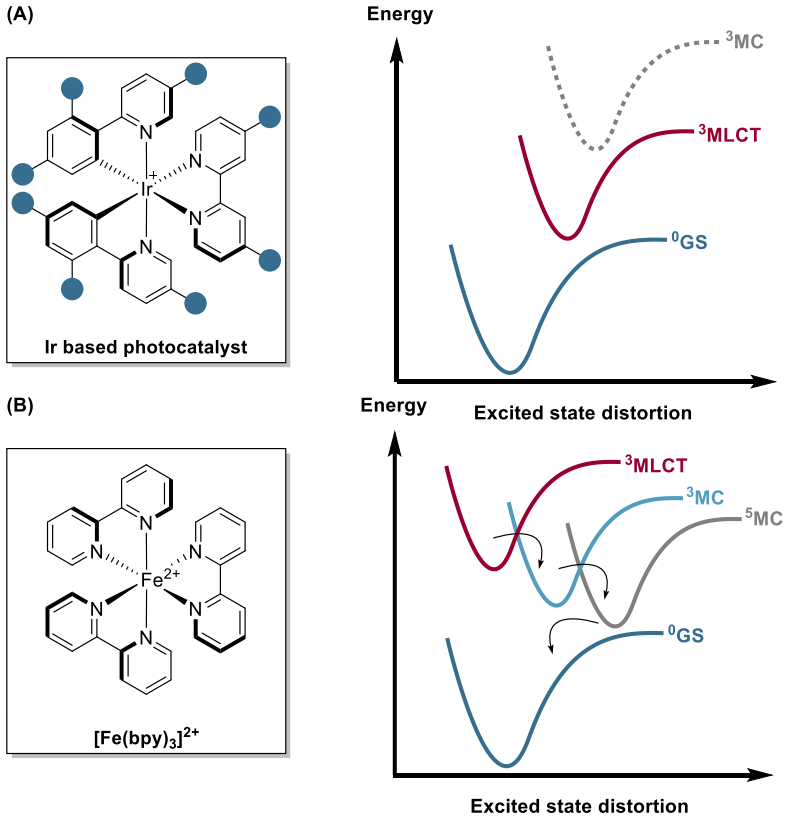


Figure 11. (A) Simplified energy diagram for the Ir-based photocatalyst representing quenching for MLCT. (B) simplified energy diagram for $[Fe(bpy)_3]^{2+}$ representing quenching for MLCT

More recently, there has been increasing interest in the use of first-row transition metal photocatalysts, motivated by considerations of cost and sustainability which are leading to the more practical application in pharmaceutical chemistry.[42] However, their application is often limited by short excited-state lifetimes resulting from rapid deactivation *via* low-lying MC states (*Figure 10(B) and Figure 10(B)*).[43, 44]

As illustrated in *Figure 12*, the relationship between the ligand field strength and the triplet-state lifetime can be rationalised using Marcus theory.[45] The parameter $\Delta G°$ represents the Gibbs free energy change associated with excitation to the ^{3}MLCT state and is commonly referred to as the driving force. The reorganisation energy (λ) is the energy required to reach the equilibrium geometry of the product state at the potential energy surface of the reactant

state and is approximately constant within a given series of complexes. The activation free energy (ΔG*) depends on both ΔG° and λ, and is directly related to the rate of excited-state decay, and hence the triplet-state lifetime.[46, 47]

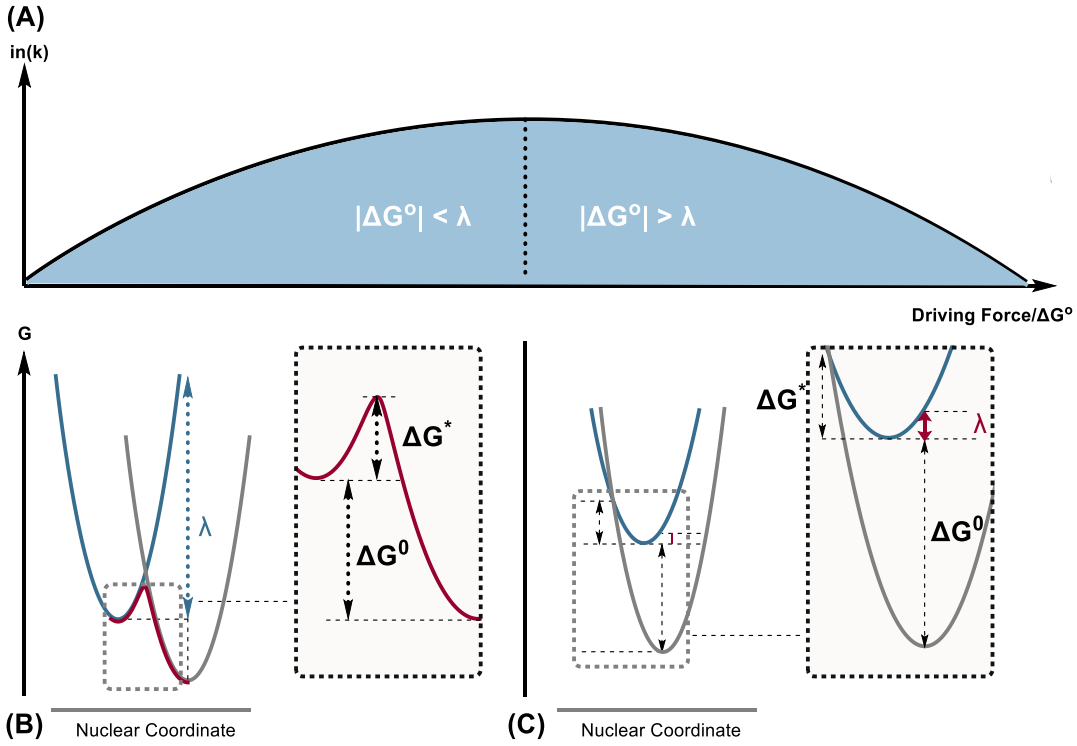
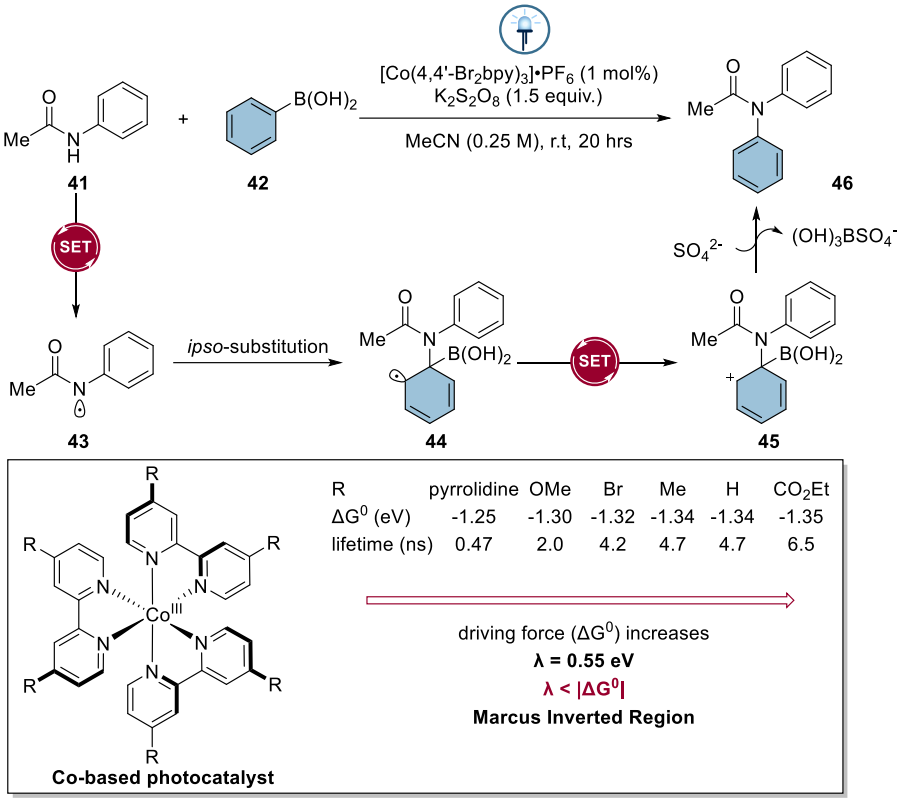


Figure 12. (A) Marcus Theory for correlation of driving force and decay rate. When $|\Delta G^o| < \lambda$, referred to as normal region. When $|\Delta G^o| > \lambda$, referred to as inverted region. (B) Energy surface for normal region complex. (C) Energy surface for inverted region complex.

In the normal region, defined by $|\Delta G^o| < \lambda$, an increase in the driving force ($|\Delta G^o|$), leads to a decrease in activation free energy (ΔG^*). Consequently, the triplet-state lifetime decreases. By contrast, in the inverted region, as described $|\Delta G^o| > \lambda$, when the driving force ($|\Delta G^o|$) decreases, the activation free energy (ΔG^*) increases, thereby, leading to an increasing of the triplet-state lifetime. Strategies to access longer-lived excited states, including operation in the Marcus inverted region, have therefore been explored to expand the scope of photocatalysis.[46, 48]

In 2023, MacMillan and co-workers reported a systematic investigation of the Marcus inverted region in first-row transition-metal-based photocatalysis. In this study, a series of cobalt-based complexes was examined to access the Marcus inverted region by altering the substituted group on the ligand of $[Co(bpy)_3]^{3+}$.[45]



Scheme 10. The Co-based photocatalyst to promote C(sp^2)-N coupling reaction by MacMillan and coworkers

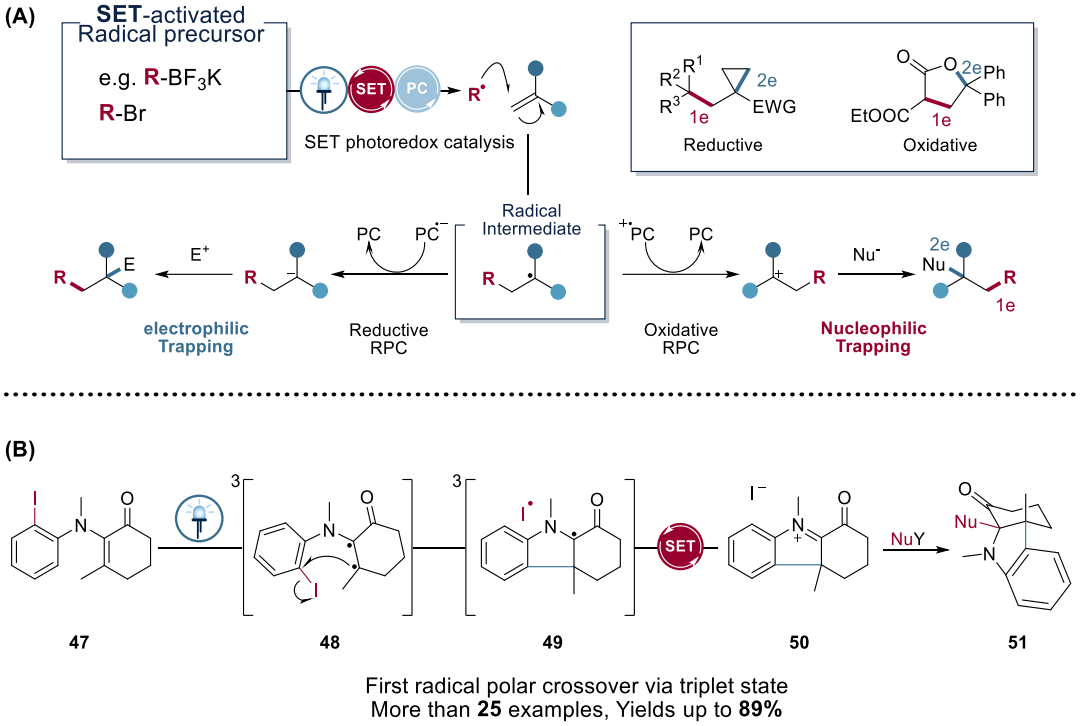
As illustrated in *Scheme 10*, an increase of lifetime is shown when driving force ($|\Delta G^o|$) increases. The resulting photocatalyst was employed to perform a C(sp^2)-N coupling reaction. Initially, aryl amide **43** is generated by a reductive single-electron transfer of excited Co-based catalyst. This is followed by an *ipso*-substitution with aryl boronic acid **42** to form intermediate **44**. Subsequent single-electron transfer and rearomatization ultimately afford the desired product **46**. Notably, this transformation proceeds inefficiently with commonly used photoredox catalysts such as $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$, 4-CzIPN and $[Ru(bpz)_3]PF_6$. However, this series of catalysts showed excellent performance for single-electron transfer photoredox catalysis, the relatively low lifetime still limited it to be employed as an EnT

photocatalyst (The lifetime is 500 times lower than the commonly used Ir-based photocatalysts).[45]

2. A Radical-Polar Crossover Approach to Interrupted [2+2] Cycloaddition *via* the Triplet State

2.1 Introduction to the Triplet State Radical-polar Crossover

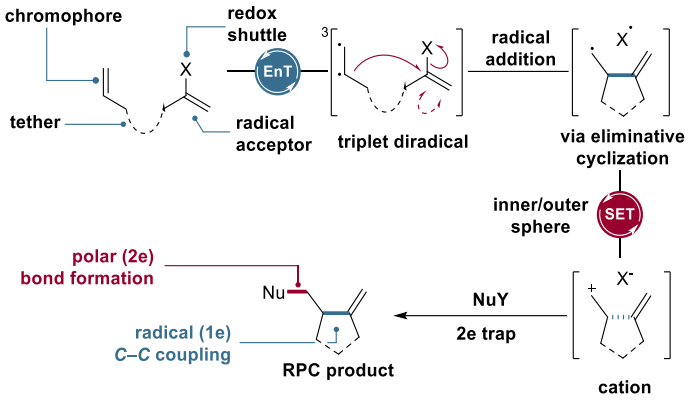
As illustrated in *Scheme 11(A)*, a classic radical-polar crossover (RPC) event commences with the generation of a carbon-centred radical by an excited state photocatalyst. The resulting radical attacks a radical acceptor which can either undergo a single-electron oxidation[49] or a single-electron reduction[50, 51] to generate an ionic intermediate. This ionic intermediate then engages into two-electron reactions to form diverse products, enabling a broad range of synthetically valuable transformations.[52-54]



Scheme 11. (A)Mechanism of SET-mediated radical-polar crossover. (B)A triplet-state radical-polar crossover developed by the Smith's group.

More recently, our group identified an alternative pathway for radical-polar crossover processes. In this study, we employed an alkene as a chromophore rather than a radical acceptor.[55] As shown in *Scheme 11(B)*, *N*-aryl enaminones **47** are promoted to the triplet excited state *via* direct photoexcitation, followed by a regioselective *ipso*-substitution at the C-I bond, affording the cyclized intermediate **49**. Subsequently, **49** undergoes single-electron

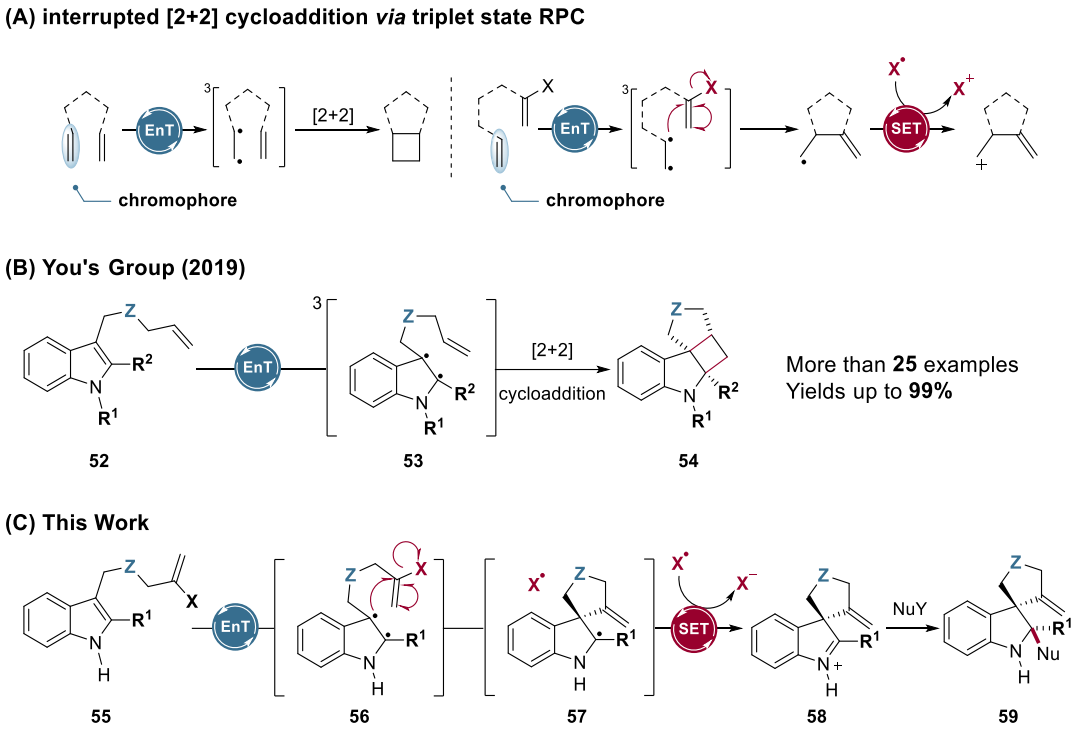
transfer to generate the iminium cation **50**, which is trapped by a nucleophile to afford the desired product **51** in excellent yields.



Scheme 12. Mechanism to represent the triplet-state radical-polar crossover.

Owing to the distinctive features of this transformation, namely, the use of an alkene as the chromophore rather than as a radical acceptor, and initiation of the reaction through a triplet-state pathway, the process is classified as the triplet-state radical-polar crossover (the triplet-state RPC) to distinguish it from a SET-mediated radical-polar crossover (*Scheme 12*).

This strategy can be extended to other existing reactions. [2+2] cycloadditions are among the most extensively studied transformations in photocatalysis. It is therefore of interest to determine whether their intrinsic reactivity can be diverted to access alternative reaction pathways. As illustrated in *Scheme 13(A)*, we hypothesized that installation of a redox shuttle on the radical acceptor could interrupt a conventional [2+2] cycloaddition by diverting the reaction through the triplet-state radical-polar (RPC) crossover pathway.



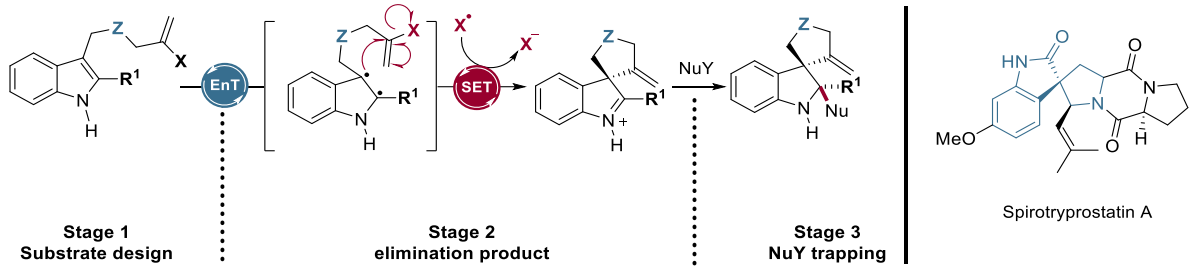
Scheme 13.(A)Hypothesis of interrupted [2+2] cycloaddition via the triplet-state radical-polar crossover. (B)Visible light mediated [2+2] cycloaddition to 2-phenylindolesystem by You and coworkers. (C)This work: A radical-polar crossover approach to interrupted [2+2] cycloaddition to 2-phenylindole system via the triplet state.

In 2019, You's group reported an intramolecular [2+2] cycloaddition of 2-phenylindole system **52**. In this study, indole **52** is promoted to the triplet state by the excited photocatalyst. Subsequently, a stepwise [2+2] cycloaddition proceeds to furnish cyclobutene-fused spiroindolines **54** in excellent yields. This work demonstrates the efficiency and synthetic utility of triplet-sensitized [2+2] cycloadditions, while also highlighting their well-defined reaction trajectory (*Scheme 13(B)*).[56]

Building on this work, as illustrated in *Scheme 13(C)*, we proposed an interrupted [2+2] cycloaddition pathway based on a 2-phenylindole substrate **55**. We hypothesized that installation of a redox shuttle on the alkene moiety would divert the reaction pathway, switching the outcome from cyclobutane-fused spiroindolines to spiroindolines **59**. To be more general, rather than undergoing a conventional [2+2] cycloaddition, the system proceeds through the triplet-state radical-polar crossover pathway.

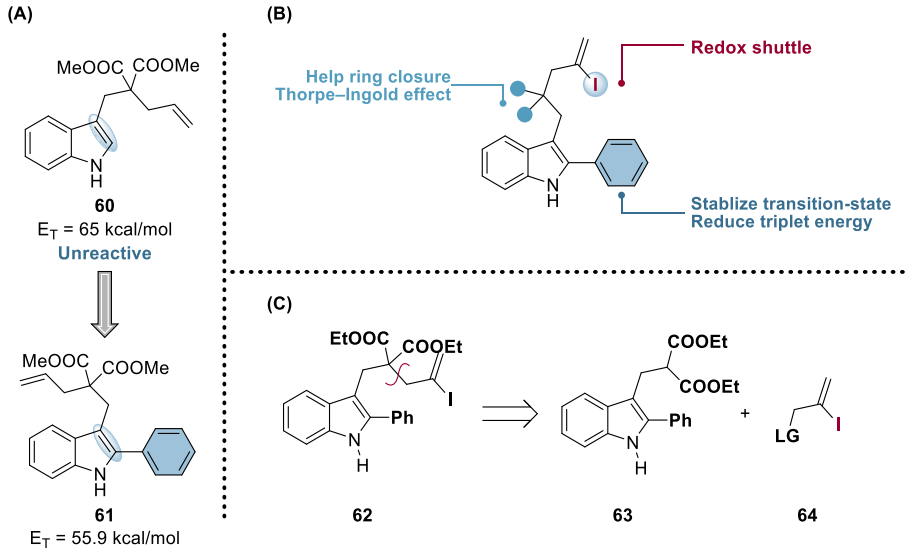
2.2 Reaction design and substrate synthesis

The motivation for this study stems from the significant value of spiroindole-containing natural products. For instance, as illustrated in *Scheme 14*, Spirotryprostatin A exhibits inhibitory activity against mammalian cell cycle progression at the G2/M phase, suggesting its potential as a lead compound for the identification of drug candidates.[57] This study was developed in three stages: substrate design, validation of the interrupted photocyclisation hypothesis, and subsequent product derivatisation.



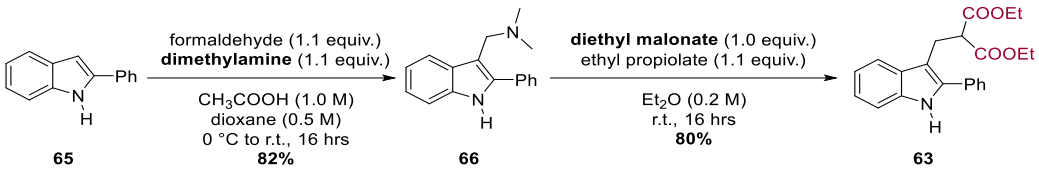
Scheme 14. Plan for the project and spiroindole-contained natural product

As shown in *Scheme 15(A)*, You and co-workers demonstrated that introduction of a phenyl group at the C2 position of the indole moiety significantly lowers the triplet energy of the substrate. Specifically, incorporation of the phenyl substituent decreases the triplet energy from 65 kcal/mol in **60** to 55.9 kcal/mol in **61**.[56] This substituent effect is therefore crucial for enabling efficient triplet excitation in this class of substrates.



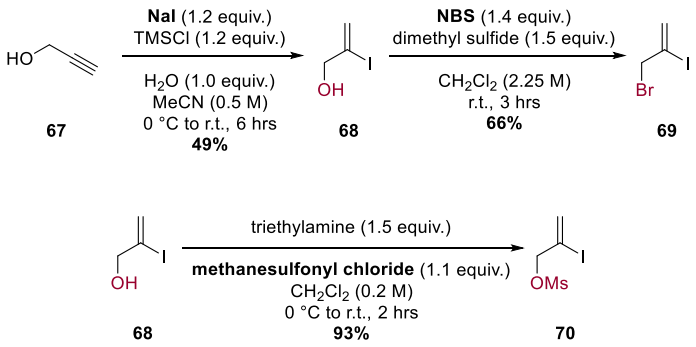
Scheme 15. (A)Importance of substitution with a phenyl group in this study. (B)Substrate design. (C)Retrosynthesis of the substrate

In addition, the malonate group on the linker facilitates ring closure *via* the Thorpe-Ingold effect.[58] Based on our previous studies, iodine was selected as the redox shuttle, as it has proven effective in promoting related transformations (*Scheme 15(B)*).[55] The initial target substrate **62** is depicted in *Scheme 15(C)*. Based on retrosynthetic analysis, diester-substituted indole **63** and vinyl iodide **64** were identified as key fragments for the synthesis of the target substrate **62**.



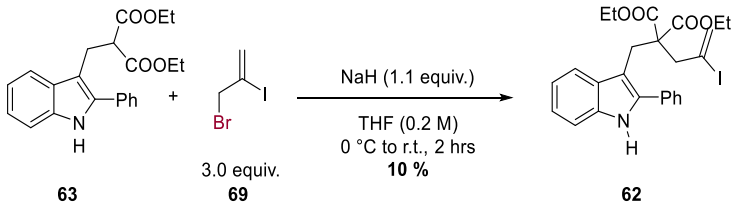
*Scheme 16. Synthesis toward precursor **63***

As outlined in *Scheme 16*, indole **63** was synthesized from 2-phenylindole **65**. Treatment of **65** with formaldehyde and dimethylamine afforded **66** *via* a Mannich reaction in 82% yield. Subsequently, a retro-Michael reaction was initiated by ethyl propiolate, followed by a Michael addition of diethyl malonate to furnish the target intermediate **63** in 80% yield.[56, 59, 60]



Scheme 17. Synthesis of vinyl-iodides

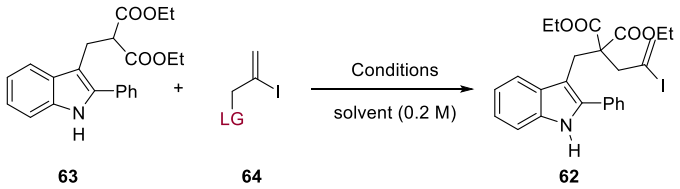
As shown in *Scheme 17*, vinyl iodide **69** was obtained in two steps from alkynyl **67**. An electrophilic iodination of alkyne **67** by treatment with sodium iodide and TMSCl generated vinyl iodide **68** in 49% yield.[61] Subsequently, bromination afforded target vinyl-iodide **69** in 66% yield.[62] Alternatively, vinyl-iodide **70** can be generated from vinyl-iodide **68** through a mesylation in a yield of 93%.[63]



*Scheme 18. Nucleophilic substitution approach to substrate **62** by using NaH as base*

The first attempt to access target substrate **62** from fragments **63** and **69** gave only 10% yield (*Scheme 18*). Subsequent attempts to optimise the reaction conditions are summarised in *Table 1*.

Table 1. Reaction optimisation for direct nucleophilic substitution approach

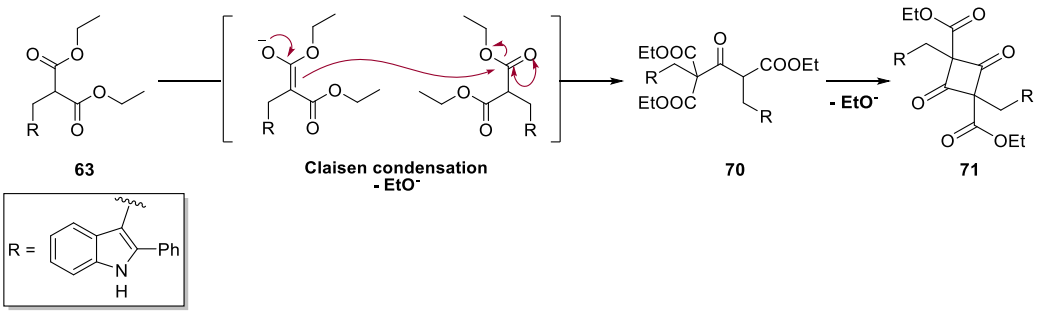


Entry	Base	Equiv.	Solvent	Temperature	Yield	LG
1	NaH	1.1	THF	0 to r.t	10%	-Br

2	NaH	1.1	THF	0 to r.t	10%	-OMs
3	NaH	1.1	THF	0 to r.t to reflux	~ 20%	-OMs
4	NaOEt	1.1	THF	r.t	10%	-Br
5	KOH	1.5	Acetone	r.t	< 5%	-Br
6	Cs_2CO_3	3	Acetone	r.t	< 5%	-Br
7	Cs_2CO_3	3	Acetone	reflux	20%	-Br
8	Cs_2CO_3	3	Acetone	reflux	27%	-OMs
9	Cs_2CO_3	3	MeCN	reflux	31%	-OMs

Note: yields were determined by quantitative NMR

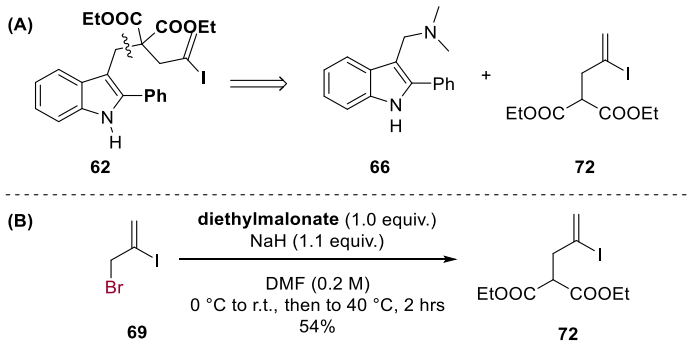
Replacement of the leaving group from bromide (-Br) to mesylate (-OMs) had no effect on the reaction yields under the initial conditions (Entries 1 & 2). Increasing the reaction temperature led to an improvement in yield to approximately 20% (Entry 3). However, changing the base at room temperature did not improve the yield (Entries 4 to 6). Higher temperature, use of a mesylate leaving group, and replacement of acetone with MeCN each provided incremental improvement in yield up to 31% (Entry 7 to 9). However, the yield remained too low for practical further development of the project.



*Scheme 19. Proposed mechanism of the dimerisation of **63** via Claisen condensation*

With further investigation, we isolated the major product **71** when employing NaH as the base, as shown in *Scheme 19*. Comparison of the crude ^{1}H-NMR spectra from all optimisation experiments indicated that this compound was the major product under conditions with a strong

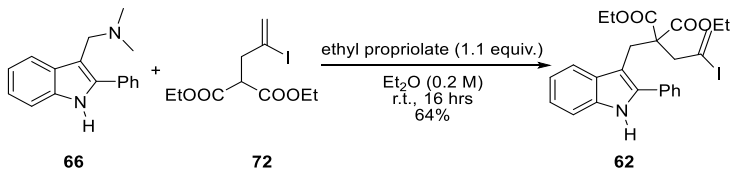
base (Entry 1 to 4). We therefore hypothesized that the vinyl iodide used in this reaction was insufficiently electrophilic to compete effectively with the Claisen condensation pathway. Therefore, we reconsidered the retrosynthetic design to develop a more viable synthetic route to the target substrate.



*Scheme 20. (A)Retrosynthesis of **62** through retro-Michael addition approach. (B)Synthesis of **72**.*

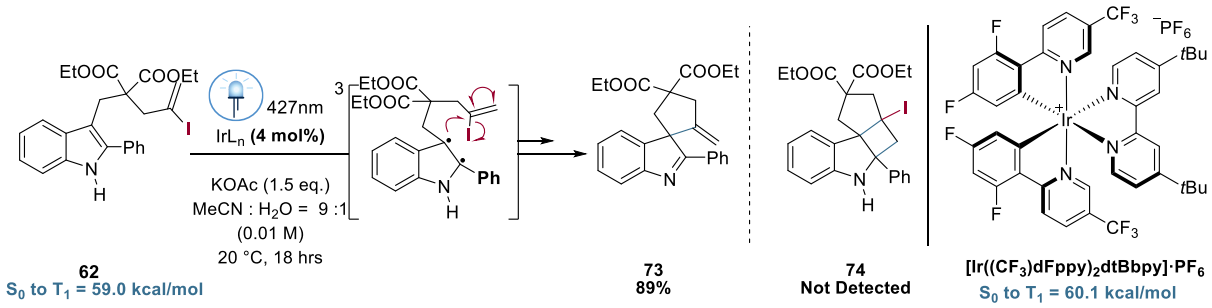
The synthesis of indole **63** is based on a sequence involving a retro-Michael reaction followed by a Michael addition. One possible approach is to integrate this transformation with the subsequent step, as illustrated in *Scheme 20(A)*. Indole **66** and malonate-derived vinyl iodide **72** were identified as alternative key fragments for the synthesis of the target substrate **62**.

Malonate-derived vinyl iodide **72** was synthesized according to a reported procedure from **69** affording the product in 54% yield (*Scheme 20(B)*).[64]



*Scheme 21. retro-Michael addition approach toward substrate **62**.*

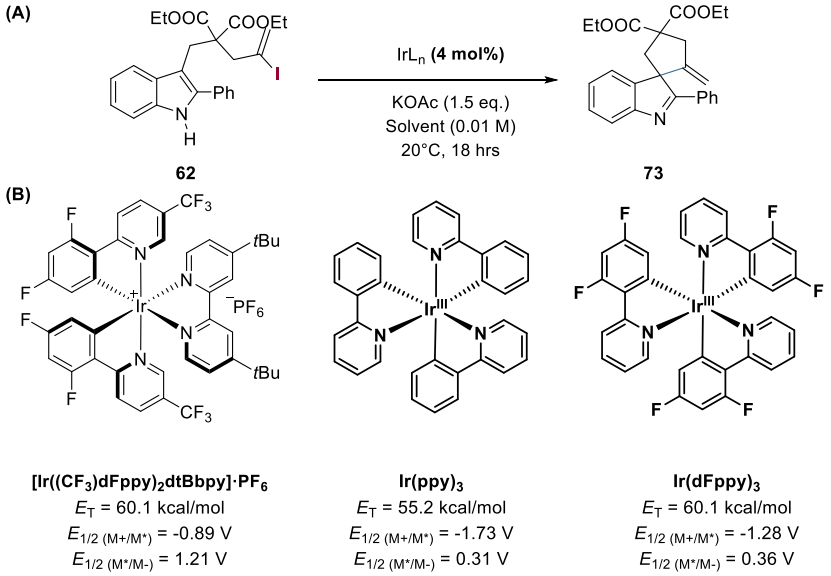
The desired product **62** was synthesized with key fragments indole **66** and malonate-derived vinyl iodide **72** in the presence of ethyl propiolate, affording the desired product in 64% yield (*Scheme 21*).[65] Notably, the desired product **62** was found to be unstable during purification on silica gel. Further details are provided in the Experimental Section.



*Scheme 22. Photochemical study of substrate **62**.*

The triplet energy of substrate **62** was calculated to be 59.0 kcal/mol by DFT (calculations performed by Dr Mihai V Popescu). This value is well matched with the triplet energy of $[Ir((CF_3)dFppy)_2dtBbpy]PF_6$, indicating that energy transfer from the photocatalyst to the substrate is feasible.[26] Substrate **62** was treated with 4 mol% of the photocatalyst in the presence of KOAc in MeCN and water,[55] affording the desired RPC product **73** in 89% yield. Notably, no [2+2] cycloaddition product was detected under the reaction conditions. This result supports the hypothesis that installation of the redox shuttle successfully diverts the conventional [2+2] pathway toward a triplet-state RPC process (*Scheme 22*).

Table 2. Control experiments and optimisation of the photochemical reaction.



Entry	Photocatalyst	Solvent	Conv. [%]	Yield [%]
1	$[Ir((CF_3)dFppy)_2dtBbpy]\cdot PF_6$	MeCN/H_2O 9:1	>95	89
2	$[Ir((CF_3)dFppy)_2dtBbpy]\cdot PF_6$	MeCN	>95	96
3	-	MeCN/H_2O 9:1	18	18
4[a]	$[Ir((CF_3)dFppy)_2dtBbpy]\cdot PF_6$	MeCN/H_2O 9:1	0	0
5	$Ir(ppy)_3$	MeCN/H_2O 9:1	68	68
6	$Ir(dFppy)_3$	MeCN	>95	87
7	$[Ir((CF_3)dFppy)_2dtBbpy]\cdot PF_6$	CH_2Cl_2	>95	89

Note: yields were determined by quantitative NMR except Entry 1 & 2
(a) Reaction performed in the dark.

Further control experiments and optimisation studies were conducted, as summarized in *Table 2*. Removal of the polar additive (H_2O) led to a slight improvement in yield to 96% (*Entry 2*). In contrast, removal of the photocatalyst resulted in a significant decrease in yield to 18% (*Entry 3*). Given that the emission profile of the light source partially extends into the UV region, direct excitation of the substrate may account for the formation of product in 18% yield. Nevertheless, this result indicates that the photocatalytic pathway is likely to be the dominant pathway under the standard conditions.

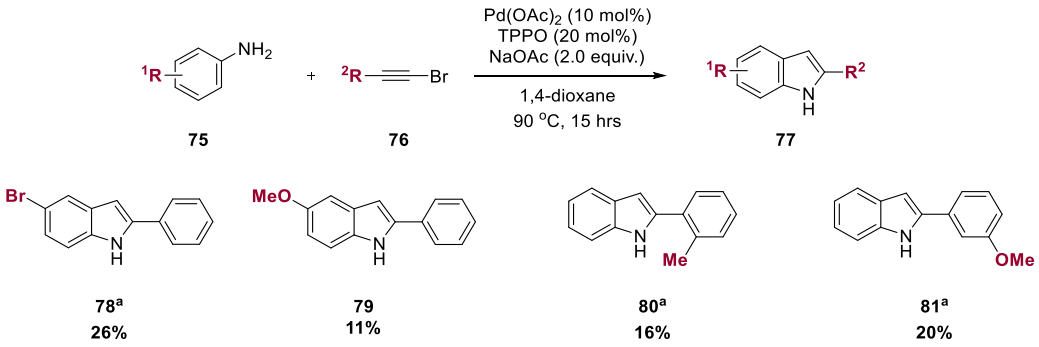
In the absence of light, no reaction was observed (*Entry 4*). When a photocatalyst with a relatively lower triplet energy was employed, the yield decreased to 68% (*Entry 5*). Furthermore, comparable results were obtained when using $Ir(dFppy)_3$ or when the solvent was changed to CH_2Cl_2 (*Entry 6 & 7*).

In summary, a general synthetic strategy was established for the preparation of the desired substrates. This platform enabled subsequent photochemical investigations, which proved consistent with the objectives of this study. We next turned our attention to exploring the reaction scope.

2.3 Substrate scope

2.3.1 Indole synthesis

The synthesis of 2-phenylindole derivatives has been well documented in the literature. However, attempts to directly construct 2-phenylindole derivatives *via* cross-coupling of indoles with phenyl halides were unsuccessful.[66] We therefore considered a palladium-catalysed annulation strategy, in which anilines react with bromoalkynes to afford the desired 2-phenylindole framework (*Scheme* 23).[67]

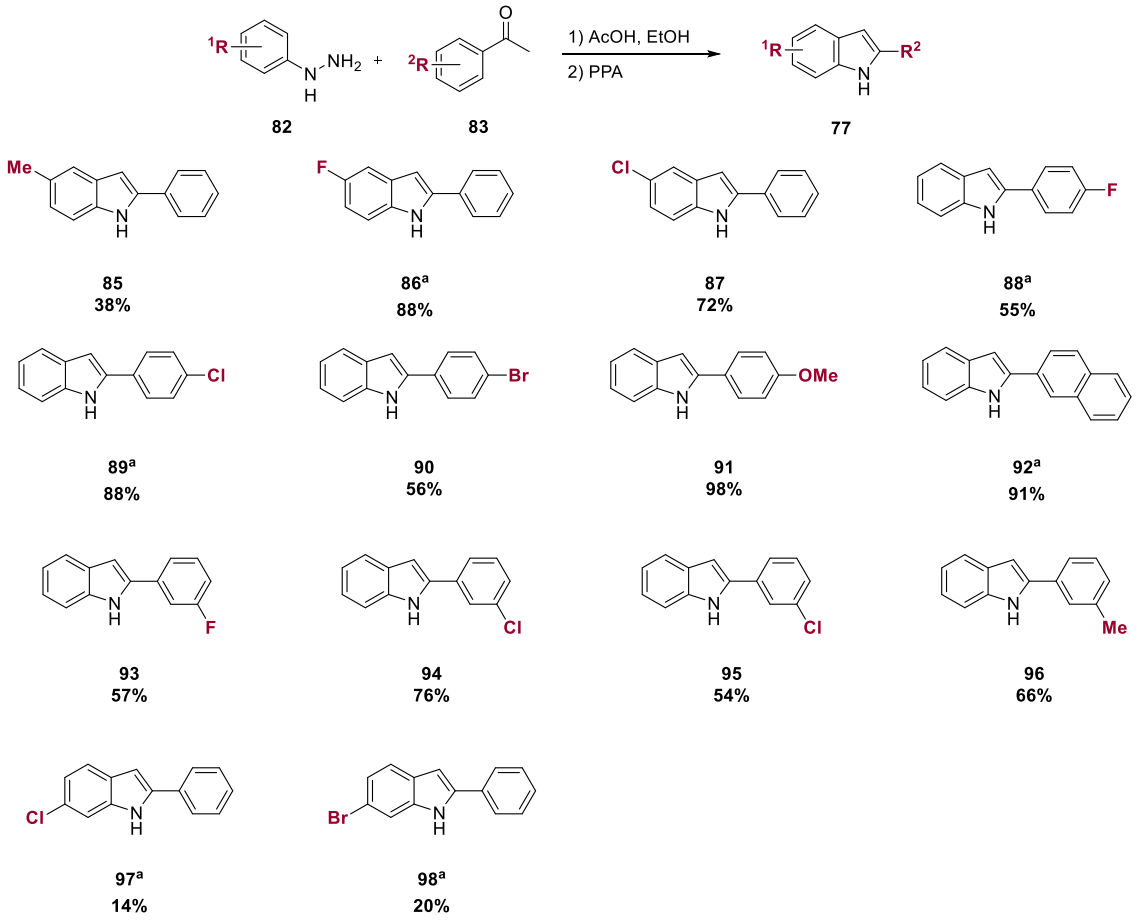


Scheme 23. Palladium-catalysed strategy of synthesis 2-phenylindole derivatives. (a)Synthesised by Niklas L Østergaard

This strategy proved inefficient when the reaction was conducted on a larger scale (e.g., 10 mmol). Aniline **75** initially underwent nucleophilic addition to bromoalkyne **76**. Subsequent treatment with catalytic $Pd(OAc)_2$ and TPPO afforded the intermediate, followed by an intramolecular C-H functionalisation to furnish the desired 2-phenylindole framework.

Under these conditions, 5-bromo-2-phenylindole **78** was obtained in 26% yield, 5-methoxy-2-phenylindole **79** in 11% yield, 2-(*o*-tolyl)-indole **80** in 16% yield, and 2-(*m*-methoxyphenyl)-indole **81** in 20% yield. Although the target substrates could be accessed using this approach, the consistently low yields limited its practicality for further development. Accordingly, a more practical and scalable route to the 2-phenylindole series was required. Given the well-established efficiency of Fischer indole synthesis in constructing substituted

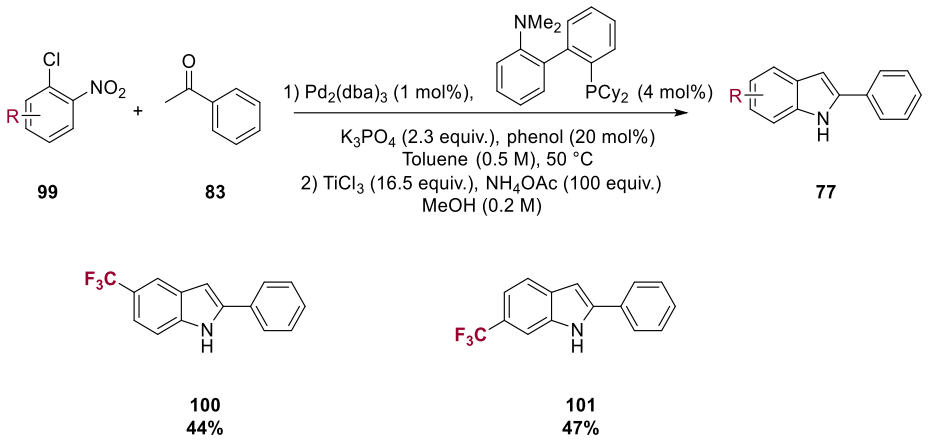
indole frameworks, we turned to this method as an alternative strategy for the preparation of 2-phenylindole derivatives (*Scheme 24*).[68-71]



Scheme 24. Fischer indole synthesis approach. (a)synthesised by Callan J Maloney

Phenylhydrazine **82** was condensed with acetophenone **83** under acidic conditions to form the corresponding hydrazone intermediate. Subsequent treatment with polyphosphoric acid (PPA) promoted cyclization to afford the desired 2-phenylindole derivatives.

Across the 18 derivatives prepared, yields ranged from 14% to 98%. The Fischer indole protocol exhibited good functional group tolerance toward halogen and methoxy substituents. In comparison to the palladium-catalysed annulation approach, the Fischer indole synthesis proved more reliable and operationally straightforward for the preparation of 2-phenylindole derivatives.



Scheme 25. Buchwald indole synthesis approach.

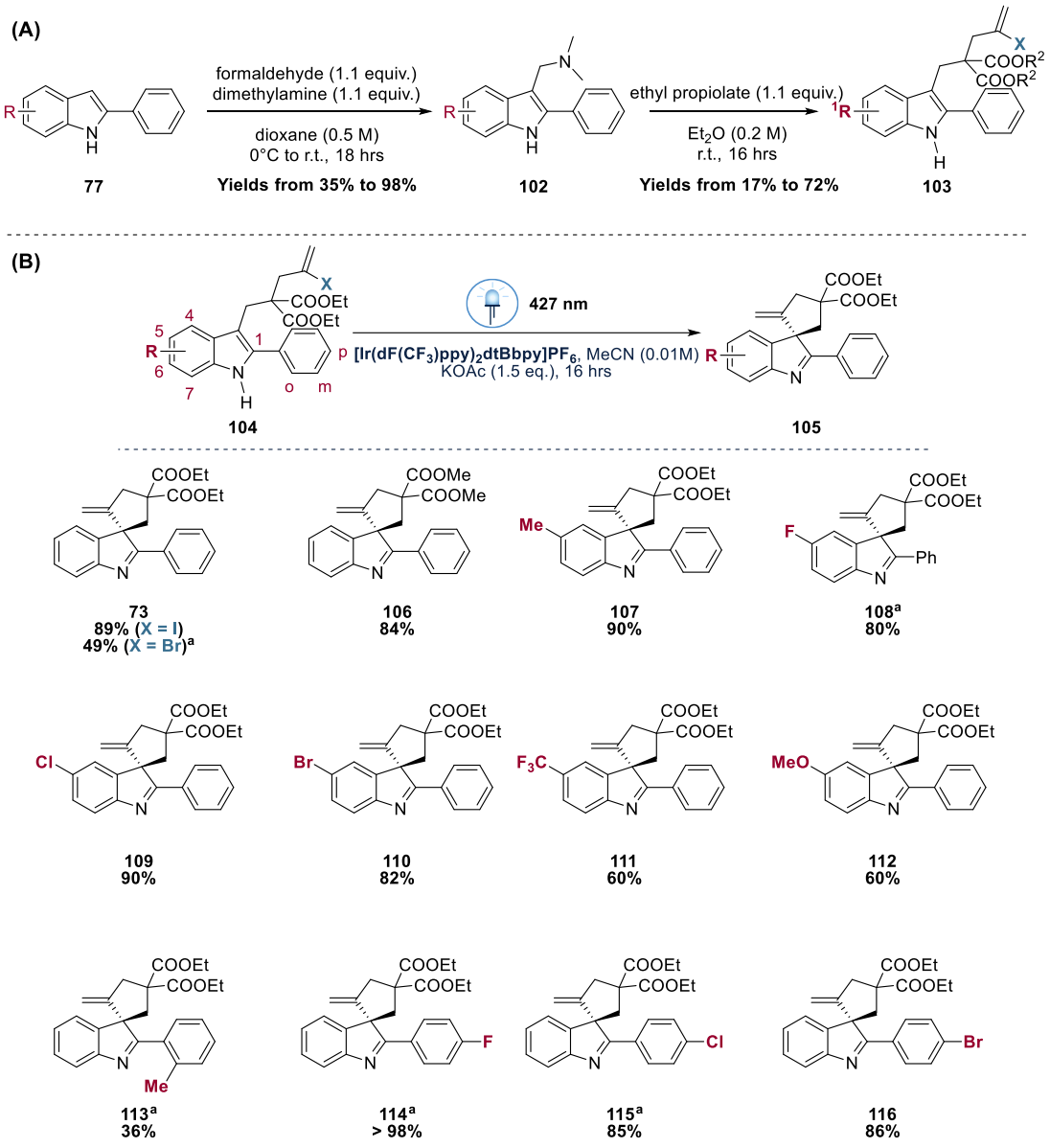
However, the Fischer indole synthesis exhibited limited efficiency when strongly electron-withdrawing groups, such as -CF_3, were present on the hydrazine component. To enable the incorporation of such substituents, we therefore turned to the Buchwald indole synthesis as an alternative strategy as shown in *Scheme 25*. By contrast, the Buchwald indole synthesis is more tolerant of electron-deficient substrates, offering a practical route to 2-phenylindole derivatives bearing strongly electron-withdrawing groups.[72] In the Buchwald indole synthesis, a chloro-substituted nitrobenzene **99** was coupled with acetophenone **83**. Subsequently the treatment with $TiCl_3$ reduced the nitro group, thereby generating the desired 2-phenylindole derivatives. Using this approach, 5-(trifluoromethyl)-2-phenylindole **100** and 6-(trifluoromethyl)-2-phenylindole **101** were obtained in yields of 44% and 47%, respectively.

In summary, the Fischer indole synthesis and the Buchwald indole synthesis were employed as complementary strategies for accessing 2-phenylindole derivatives. While the Fischer protocol proved suitable for a range of substrates (specifically halogen substituted, electron neutral group substituted 2-phenylindoles), the Buchwald approach enabled the incorporation of strongly electron-withdrawing substituents.

2.3.2 Scope of Substituents on the Indole Core

The target substrates were synthesized in two steps. First, gramine derivatives **102** were prepared from 2-phenylindole derivatives **77** *via* a Mannich reaction. Across all examined gramine derivatives, the yields ranged from 35% to 98%.[56, 59, 73] Subsequently, the target substrates were obtained through a retro-Michael/Michael addition sequence, the yields ranged from 17% to 72% (*Scheme 26*).

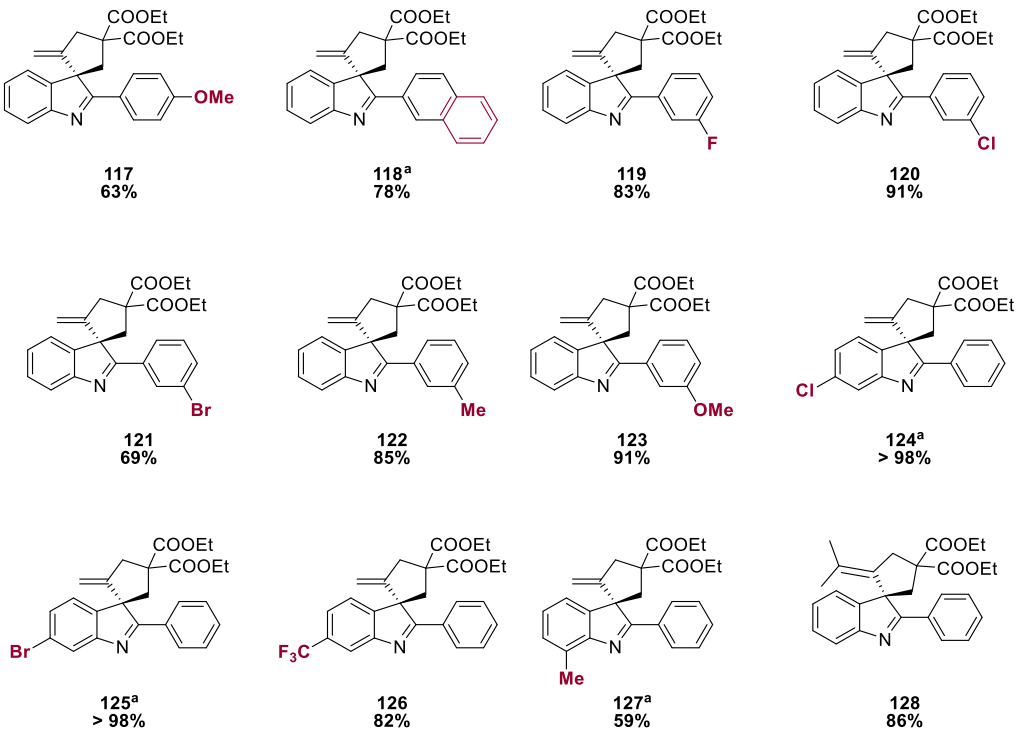
As illustrated in *Scheme 27* and *Scheme* 28, the photochemical RPC reaction proceeds in moderate to excellent yields across a range of substituted 2-phenylindole derivatives, demonstrating good functional group tolerance under the optimized photochemical conditions. Substrates bearing halogen substituents (-Cl, -Br, -F) on either the phenyl ring or the indole core were well tolerated, typically affording the corresponding cyclized products in moderate to excellent yields. This suggests that the reaction is relatively insensitive to the modest electronic perturbations introduced by halogen substituents.



Scheme 27. (A)Substrate synthesis. (B)Reaction scope. (a)Synthesised by Callan J Maloney and Niklas L Østergaard

Methoxy- and methyl-substituted substrates also underwent smooth cyclization. *Para*- and *meta*-methoxy derivatives provided moderate to good yields (63% and 91%, **117** and **123**), indicating that electron-donating groups do not significantly disrupt the reaction pathway. However, when substitution occurred at more sterically congested positions, a decrease in yield was observed (e.g., *ortho*-position of phenyl ring, **113**), implying that steric factors may play a more significant role than electronic effects. A plausible explanation is that, in the transition state, the phenyl ring must adopt a coplanar arrangement with the indole core to enable effective

conjugation and stabilization of the diradical intermediate. Increased steric hindrance, such as a methyl substituent at the ortho-position of the phenyl ring, may disrupt this planar geometry, thereby destabilize the transition state of cyclization and reduce the reaction efficiency.



Scheme 28. continuation of reaction scope. (a)Synthesised by Callan J Maloney

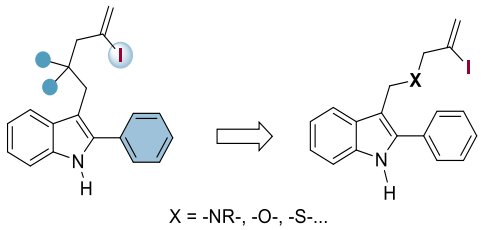
Substrates containing strong electron-withdrawing substituents such as CF_3 were compatible with the reaction, although in some cases the yields were slightly reduced (**111** & **126**, ~60-80%). This trend further suggests that while the reaction tolerates electron-deficient systems, a strongly electron-withdrawing substituent may influence radical reactivity or triplet-energy matching. Furthermore, substitution at the 6-position of the indole (**107** to **112**) ring was generally tolerated with moderate to high yields.

Overall, the reaction exhibits broad functional group tolerance and is largely controlled by steric effects rather than electronic factors. Electron-donating and moderately electron-

withdrawing substituents performed well, while increased steric hindrance near the cyclization site tended to reduce efficiency.

2.3.3 Examination of *O*-Linked and *N*-Linked Substrates

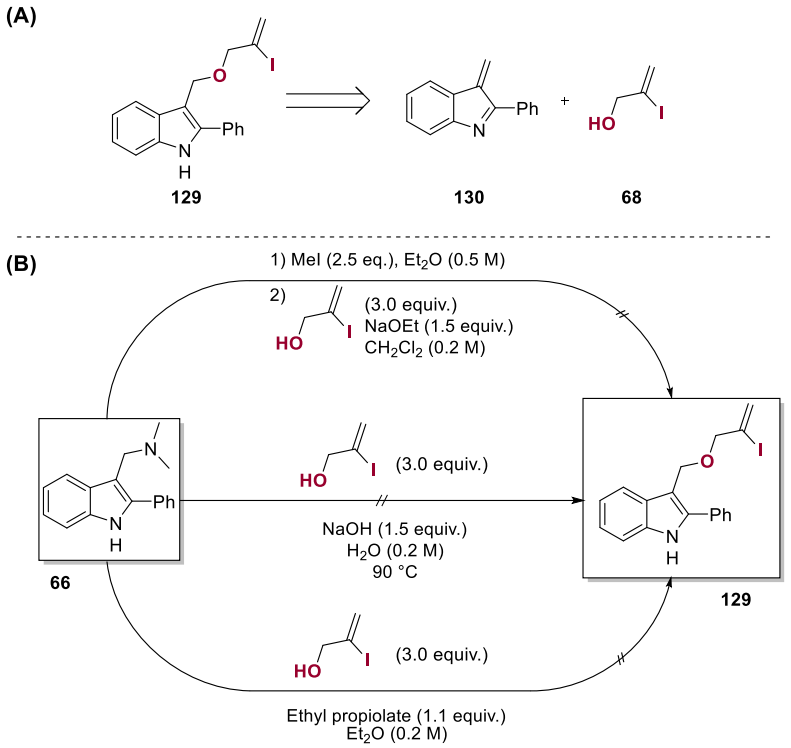
In addition to varying substitution on the indole core and the leaving group, we investigated the effect of linker identity on the reaction outcome.



Scheme 29. Variation of the linking atom

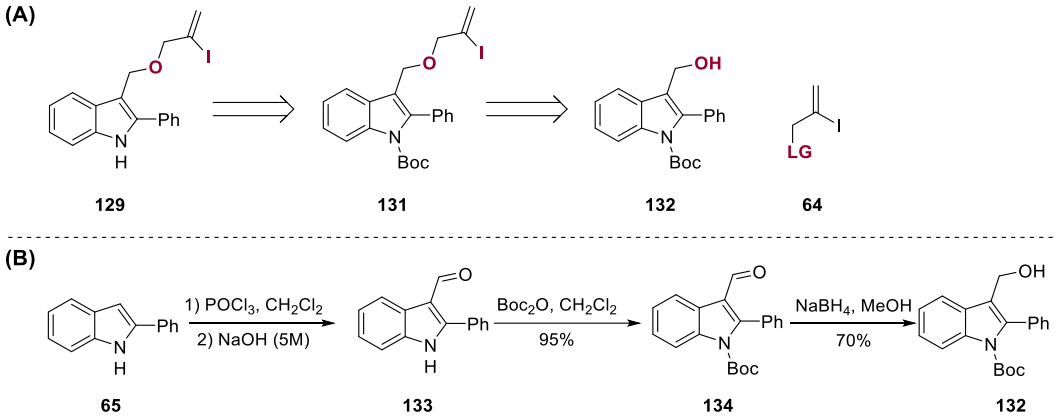
As illustrated in *Scheme 29*, it was of interest to determine whether the reaction would proceed upon replacing the malonate moiety with oxygen-, nitrogen-, or sulfur- linkers to access more spiro-cyclic cores

As shown in *Scheme 30(A)*, the first strategy employed for the synthesis of the oxygen-linked substrate **129** involved a retro-Michael/Michael addition sequence. As shown in *Scheme 30(B)*, gramine **66** was first treated with methyl iodide to generate the corresponding ammonium salt, which was anticipated to serve as a leaving group and thereby form the desired Michael acceptor.[74] The resulting intermediate was then expected to engage with vinyl iodide **68** to afford the target product. However, no reaction was observed under these conditions.



*Scheme 30. (A) Retrosynthesis of **129** via a retro-Michael/Michael addition strategy. (B) Approaches to the synthesis of **129**.*

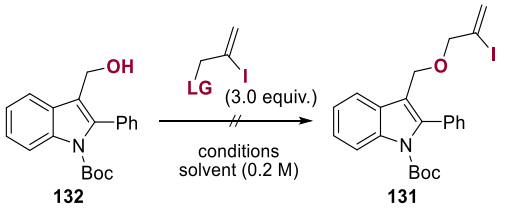
A more direct approach was subsequently attempted by heating gramine **66** in water at 90 °C. Previous reports have indicated that this method can effectively generate the corresponding Michael acceptor.[75] However, under these conditions, decomposition was observed. In addition, we attempted to apply the same strategy used for the formation of **63** (*Scheme 16*) by treating gramine **66** with ethyl propiolate. However, this strategy also proved unsuccessful.



*Scheme 31. (A) Retrosynthesis of **129** via direct nucleophilic substitution. (B) Synthesis of precursor **132**.*

The second strategy involved the use of Boc-protected hydroxymethyl indole **132**, which was intended to react with vinyl iodide **64**. The Boc protecting group was introduced to suppress rapid retro-Michael addition, which was anticipated to occur upon installation of a hydroxymethyl substituent on the indole core (*Scheme 31(A)*). Indole **132** was synthesized in three steps. First, indole-3-carbaldehyde **133** was obtained from 2-phenylindole **65** *via* a Vilsmeier-Haack reaction. The resulting aldehyde **133** was then protected with Boc_2O to afford **134** in 95% yield. Finally, reduction of the protected aldehyde **134** with $NaBH_4$ furnished the desired hydroxymethyl indole **132** (*Scheme 31(B)*).[76]

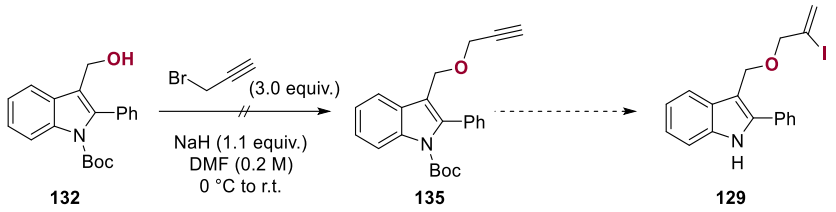
*Table 3. Reaction optimization of the nucleophilic substitution between **132** and vinyl iodide.*



Entry	Base	Solvent	Leaving group	Temperature	Additive
1	Cs_2CO_3 (3.0 equiv.)	MeCN	Br/OMs	Reflux	-
2	NEt_3 (3.0 equiv.)	CH_2Cl_2	Br	r.t.	-
3	$NaHCO_3$ (3.0 equiv.)	Acetone	Br	Reflux	NaI (3.0 equiv.)
4	NaH (1.1 equiv.)	DMF	Br	0 °C to r.t.	-
5	KO^tBu (1.2 equiv.)	THF	Br	0 °C to r.t.	-

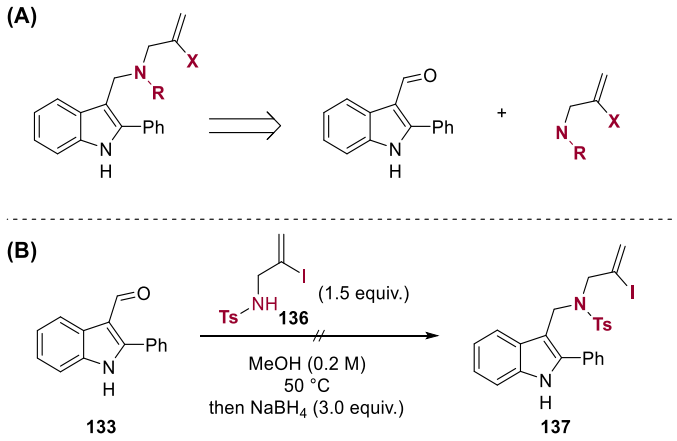
To facilitate the subsequent nucleophilic substitution, five sets of reaction conditions were examined, as summarized in *Table 3*. These included the use of Cs_2CO_3 under reflux (Entry 1), an organic base such as NEt_3 (Entry 2), Finkelstein conditions (Entry 3), and stronger bases including NaH and KO^tBu (Entries 4 and 5). Despite these efforts, no desired product was detected under any of the tested conditions and starting material was recovered. These

observations suggest that the electrophile is insufficiently activated to undergo efficient nucleophilic substitution under the tested conditions.



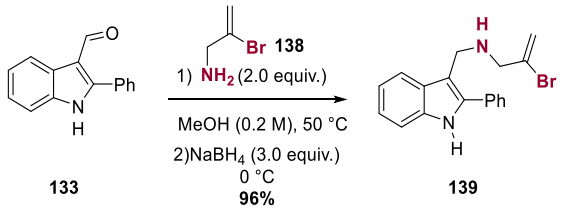
*Scheme 32. Synthetic route to **129** using 3-bromoprop-1-yne*

As shown in *Scheme 32*, we further explored the use of 3-bromoprop-1-yne as the electrophile, followed by an iodination step to generate the desired product **129**. However, no desired product was detected under these conditions. Taken together, these results suggested that further efforts toward *O*-linked substrates were unlikely to be productive. Consequently, our focus was redirected to the development of nitrogen-linked substrates.



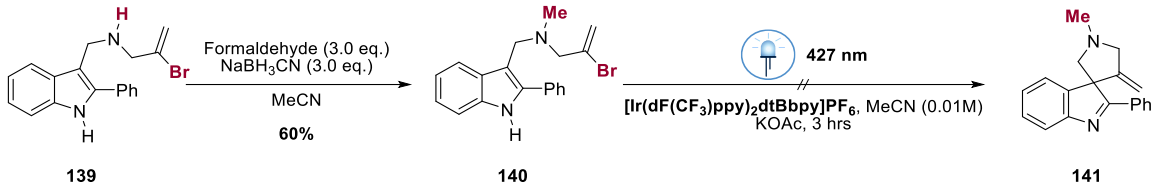
Scheme 33. (A)retrosynthesis of N-linked substrates through reductive amination. (B)reductive amination of a Ts-protected amine.

As outlined in *Scheme 33*, aldehyde **133** was anticipated to undergo reductive amination with protected vinyl iodide **136** to afford substrate **137**. However, no desired product was detected under these conditions. Possible reason can be addressed to the lack of nucleophilicity of amine **136**.



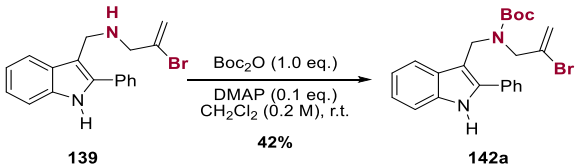
*Scheme 34. Reductive amination using **138**.*

As illustrated in *Scheme 34*, an unprotected amine **138** was subsequently employed to react with aldehyde **133**. Under these conditions, treatment with $NaBH_4$ afforded the desired intermediate **139** in 96% yield.



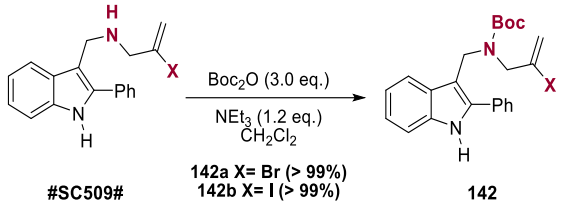
*Scheme 35. Methyl protection of **139** and photoreaction of **140**.*

As shown in *Scheme 35*, the methyl-protected substrate **140** was obtained in 60% yield under reductive amination conditions using formaldehyde and $NaBH_3CN$. However, subsequent photochemical study did not observe the desired cyclized product **141**. Notably, complete degradation of the photocatalyst was observed by ^{19}F-NMR under these conditions likely as a result of a photoredox process between catalyst and substrate taking place.[26] To reduce the redox activity of the substrate, an electron-withdrawing protecting group was considered necessary.[77].



*Scheme 36. Boc-protection of **139** by using DMAP*

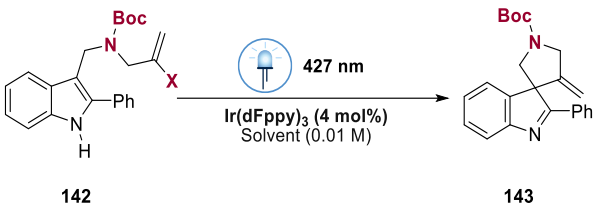
As shown in *Scheme 36*, substrate **139** was protected using Boc_2O in the presence of catalytic DMAP, affording **142a** in only 42% yield. This reduced efficiency was attributed to poor regioselectivity under these conditions, as partial protection occurred at the indole nitrogen rather than the amine.



*Scheme 37. Regioselective Boc-protection of **139**.*

Replacement of DMAP with triethylamine afforded the desired product **142a** in quantitative yield (*Scheme 37*). The improvement in yield was attributed to the decreasing of activation ability of triethyl amine compared to DMAP, which likely minimized competitive Boc protection at the indole nitrogen and thereby enhanced regioselectivity.

Table 4. Observations and optimisation of the photochemical reaction for N-linked substrates



Entry	X	Solvent	Base	Temperature	t (h)	Yield
1	Br	MeCN	KOAc (1.5 equiv.)	r.t.	3 hrs	54%
2	Br	CH_2Cl_2	KOAc (1.5 equiv.)	r.t.	3 hrs	45%
3	Br	CH_2Cl_2	Cs_2CO_3 (3.0 equiv.)	r.t.	3 hrs	60%
4	Br	CH_2Cl_2	Cs_2CO_3 (3.0 equiv.)	r.t.	16 hrs	0%
5	Br	CH_2Cl_2	Cs_2CO_3 (3.0 equiv.)	-20 °C	16 hrs	66%
6	I	CH_2Cl_2	Cs_2CO_3 (3.0 equiv.)	-20 °C	16 hrs	66%

We next examined whether the nitrogen-linked variant would be compatible with the established photochemical conditions (*Table 4*). Ir(dFppy)$_3$ was initially employed as the photocatalyst due to its low reduction potential comparing to Ir[((CF$_3$)dFppy)$_2$dtBbpy]PF$_6$ (more details are in *Table 6*), with MeCN as the solvent and KOAc as the base, under irradiation with a 427 nm lamp for 3 h. Under these conditions, the desired product was obtained in 54%

yield (Entry 1). During the reaction, substrate **142a** was found to exhibit limited solubility in MeCN, and starting material and product were found to be inseparable chromatographically. Based on these observations, MeCN was replaced with CH_2Cl_2 since substrate **142a** has higher solubility in CH_2Cl_2, but a slightly lower yield of the desired product was obtained (Entry 2). Moreover, the reaction still did not go to completion.

Bases were subsequently screened for this transformation, with Cs_2CO_3 affording the desired product in 60% yield (Entry 3). However, the reaction did not reach completion, which continued to complicate purification.

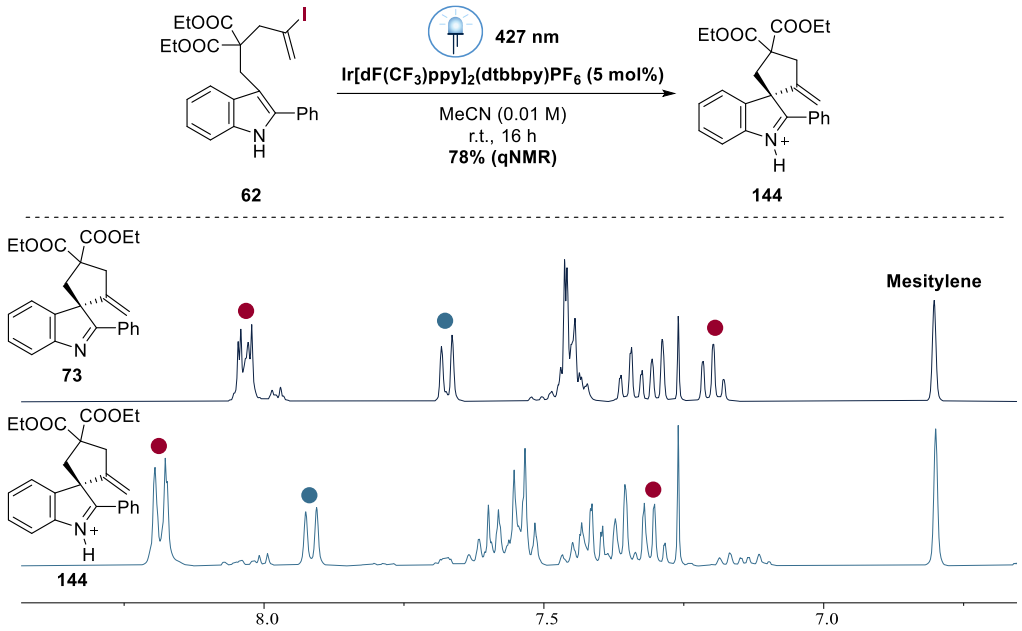
Extending the reaction time from 3 h to 16 h resulted in complete consumption of the starting material; however, no desired product was detected under these conditions (Entry 4). To investigate this observation further, both of the isolated product and the substrate were irradiated at room temperature for 16 hrs. In addition, the substrate was heated at 40 °C for 4 days. Under prolonged irradiation, the product underwent complete decomposition. The substrate remained stable under light irradiation but exhibited approximately 20% decomposition under thermal conditions.

To balance product stability with reaction completion and to facilitate isolation, the reaction was repeated at −20 °C. Under these conditions, full conversion was achieved, and the desired cyclized product **143** was isolated in 66% yield (Entry 5). Similarly, the vinyl iodide analogue exhibited comparable reactivity under the same conditions (Entry 6).

In summary, optimization studies revealed that base selection and reaction temperature significantly influenced the reaction outcome. Lowering the reaction temperature to −20 °C slowed product decomposition, enabling full conversion and isolation of the desired cyclized product in moderate yield.

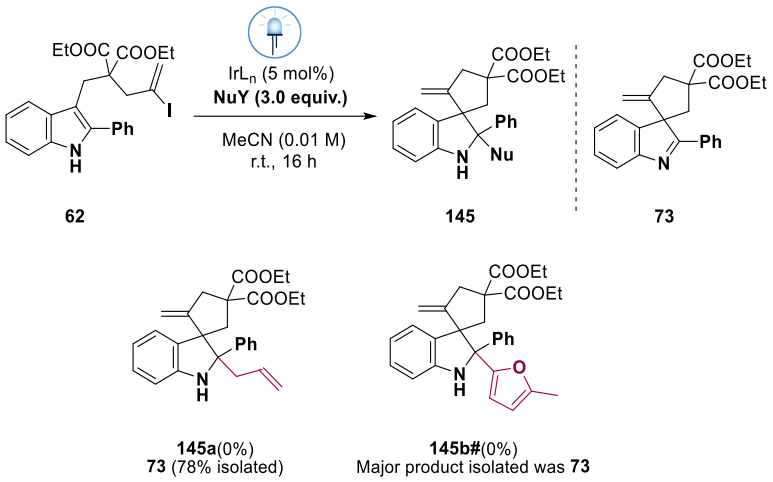
2.4 Product Transformations

After demonstrating that the radical-polar crossover strategy can interrupt the conventional [2+2] cycloaddition pathway, we subsequently attempted to explore whether the imine moiety in the cyclized product could serve as a platform for further functionalization. Our initial approach focused on trapping the imine intermediate in situ within the same reaction vessel during the photochemical process (One-pot trapping).



Scheme 38. Observation of iminium cation 144 under base-free conditions.

As illustrated in *Scheme 38*, KOAc was omitted from the standard reaction conditions. Analysis of the crude ^{1}H-NMR spectrum revealed noticeable differences in the aromatic region relative to the spectrum of product **73**. This observation suggests that the iminium cation **144** may be formed in the absence of base. To further investigate this possibility, nucleophiles were introduced under these modified conditions (removed base) to evaluate whether the iminium intermediate **144** could be trapped.



Scheme 39. One-pot trapping approaches.

As summarized in *Scheme 39*, allyltrimethylsilane and 2-methylfuran were introduced as potential trapping nucleophiles. However, no desired trapped products were detected. In both cases, the major product remained **73**. A plausible explanation is that the resulting iminium ion is not sufficiently electrophilic to undergo efficient nucleophilic trapping under these conditions.

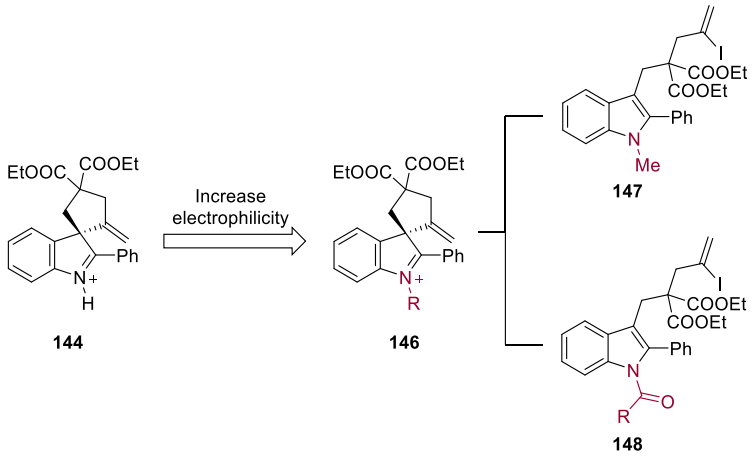
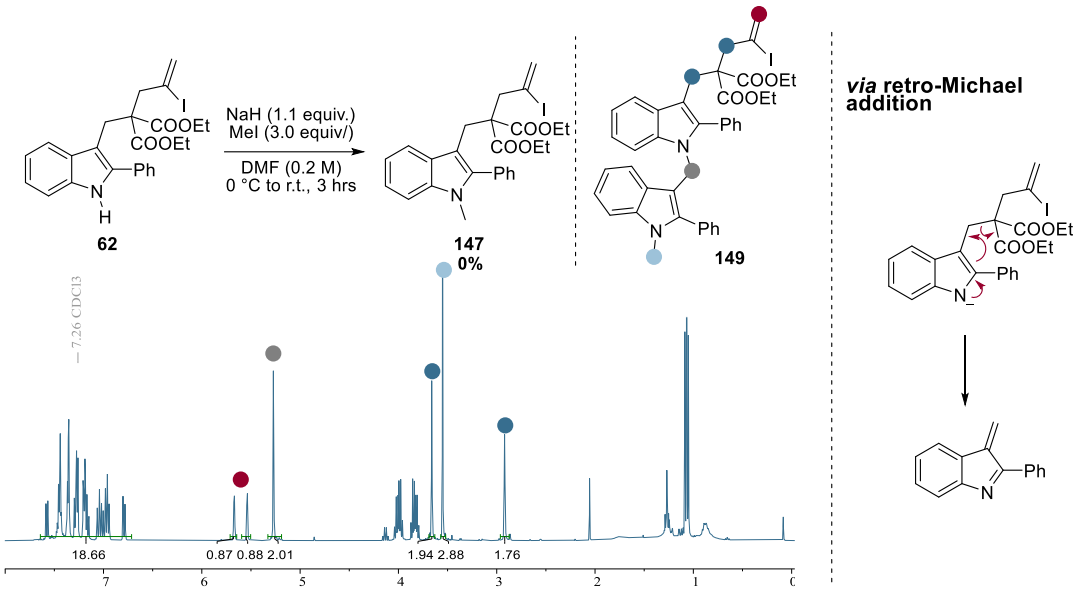


Figure 13. Increase the electrophilicity of substrates.

The iminium intermediate **144** may undergo deprotonation at the indole nitrogen, leading to a decrease in electrophilicity. To enhance the electrophilicity of the iminium species, protection of the indole nitrogen was introduced, as in the modified intermediate **146** (*Figure 13*).

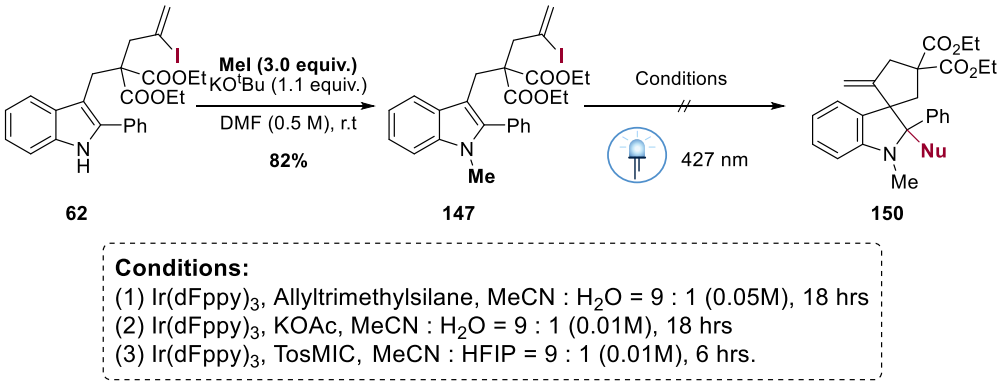
Our strategy was to employ substrates such as **147** and **148** as photochemical substrates. In the first case, introduction of an electron-neutral substituent (e.g., a methyl group) was expected to enhance the reactivity of the resulting iminium intermediate relative to **144**. If this modified substrate remained competent for triplet-state energy transfer, the more electrophilic iminium species could potentially be intercepted by an external nucleophile. Notably, installation of a methyl group on the indole core may also increase the triplet energy (the hindrance between the methyl-group and phenyl-group could destabilize the formation of diradicals),[59] which could influence the efficiency of energy transfer. In the second design, protection of the indole nitrogen with a carbonyl-containing group was anticipated to lower the triplet energy by induce effect relative to the standard substrate **62**.[59]



*Scheme 40. Unexpected outcome during methyl Protection of **62***

As shown in *Scheme 40*, the initial approach to synthesize the methyl-protected substrate **147** involved the use of NaH as the base. Following deprotonation, methyl iodide was added. However, no desired product was observed, instead substrate **62** rapidly underwent retro-Michael addition. The resulting Michael acceptor was subsequently attacked by another deprotonated indole species, leading to the formation of a di-indole intermediate. Followed by a methylation to afford **149**. Analysis of the ^{1}H-NMR spectrum of isolated product supported

this structural assignment (No further characterisation was undertaken). To suppress retro-Michael addition, a milder base was considered necessary.

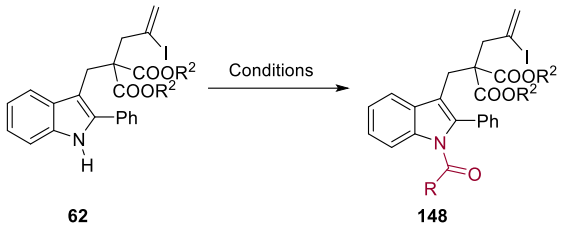


*Scheme 41. Methyl-protection of **62** and one-pot trapping attempts of **147***

In the second approach, KO^{t}Bu was employed as the base. Under the conditions shown in *Scheme 41*, the methyl-protected substrate **147** was isolated in 82% yield. This substrate was subsequently subjected to the photochemical conditions in the presence of nucleophiles, including allyltrimethylsilane, water, and TosMIC. However, no desired trapping products were detected, and complex mixtures were obtained instead.

One possible explanation for the lack of reactivity is that methyl-protected 2-phenylindoles possess substantially higher triplet energies than their unprotected counterparts, rendering triplet-state energy transfer inefficient under the conditions employed.[59]

Table 5. Reaction optimization for acetylation of 62.

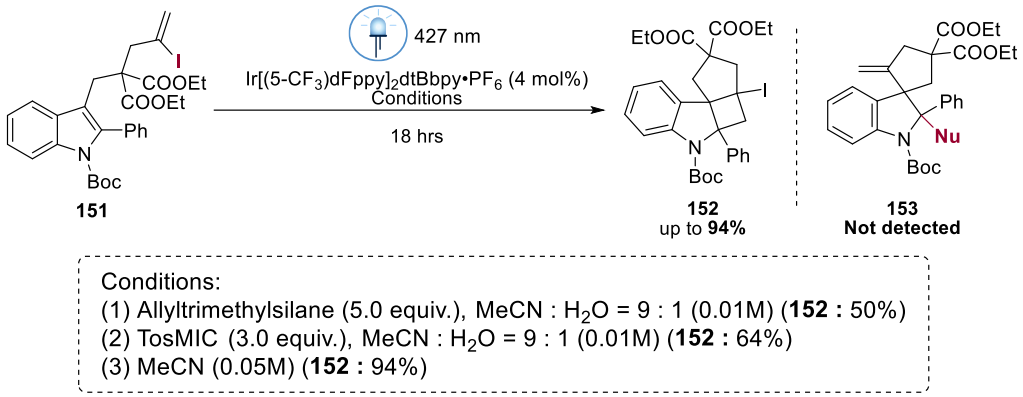


62 148

Entry	Carbonyl source	Base	Solvent	Catalyst	Yields
1	Ac_2O (1.5 equiv.)	NEt_3 (2.5 equiv.)	CH_2Cl_2 (0.1 M)	DMAP (0.1 equiv.)	0%
2	AcCl (3.0 equiv.)	NaOH (5.0 equiv.)	CH_2Cl_2 (0.125 M)	TBAHS (0.1 equiv.)	0%
3	AcCl (3.0 equiv.)	KO^{t}Bu (1.5 equiv.)	DMF (0.1 M)	-	0%
4	$(CF_3CO)_2O$ (1.5 equiv.)	K_2CO_3 (3.0 equiv.)	DMF (0.1 M)	-	0%
5	$(CF_3CO)_2O$ (1.5 equiv.)	Cs_2CO_3 (3.0 equiv.)	MeCN (0.1 M)	-	0%
6	Ac_2O (0.2 M)	-	-	DMAP (1.0 equiv.)	0%
7	$(CF_3CO)_2O$ (0.2 M)	-	-	DMAP (1.0 equiv.)	0%
8	Boc_2O (1.5 equiv.)	-	CH_2Cl_2 (0.2 M)	DMAP (1.0 equiv.)	> 98%

We subsequently attempted to synthesize the carbonyl-protected substrate **148**. As summarized in *Table 5*, a range of carbonyl-protection conditions was examined for substrate **62**. Initially, acetic anhydride was employed as the carbonyl source in the presence of catalytic DMAP and triethylamine as the base; however, no desired product was observed (Entry 1). Acetyl chloride was subsequently tested under phase-transfer conditions, but this approach also failed to afford the target compound (Entry 2). Switching to a stronger base, KO^{t}Bu, likewise resulted in no product formation (Entry 3). Two additional conditions utilizing trifluoroacetic anhydride as the carbonyl source were explored, yet both proved unsuccessful (Entries 4 & 5). The reactions were also conducted in neat acetic anhydride and neat

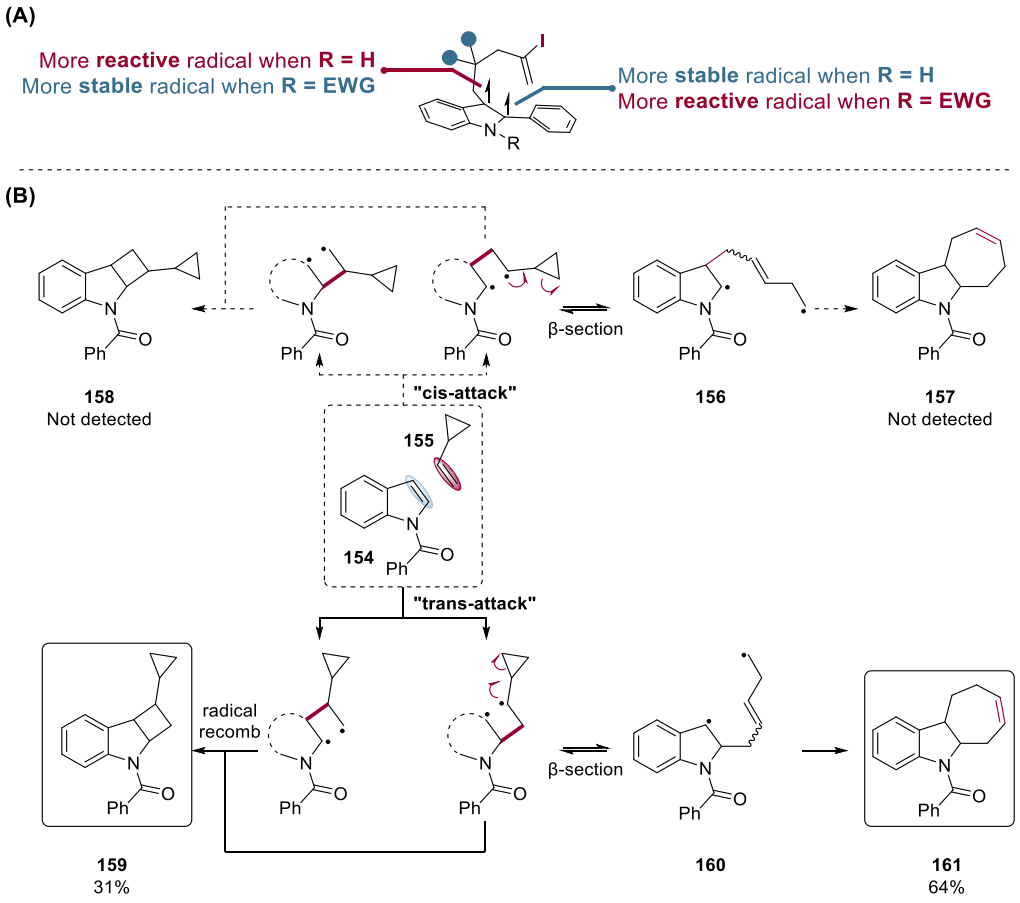
trifluoroacetic anhydride; however, no desired products were detected (Entries 6 & 7). Finally, use of Boc_2O in the presence of 1.0 equivalent of DMAP successfully delivered the desired protected product in quantitative yield (Entry 8).



Scheme 42. Observations of photoreaction of Boc-protected substrate 151.

The Boc-protected substrate **151** was subsequently subjected to photochemical evaluation. As illustrated in *Scheme 42*, in the presence of allyltrimethylsilane or TosMIC, no trapped products were detected. Instead, the major product in both cases was the [2+2] cycloaddition product **152**. When **151** was examined under the standard photochemical conditions, the [2+2] cyclized product was obtained in 94% yield.

To rationalize the differing reactivity observed relative to the unprotected substrate **62**, a working hypothesis concerning the relative reactivity of the two radical centers was proposed (*Scheme 43(A)*). In the absence of *N*-protection, the lone pair on the indole nitrogen can stabilize the adjacent radical through conjugation, rendering this radical less reactive. Consequently, the benzyl radical (C3-centered radical) is expected to exhibit higher reactivity. In contrast, when the indole nitrogen is protected with an electron-withdrawing group (e.g., a carbonyl group), the nitrogen lone pair is conjugated with the protecting group. This modification alters the electronic distribution, making the C2-centered radical relatively more reactive than that at C3.

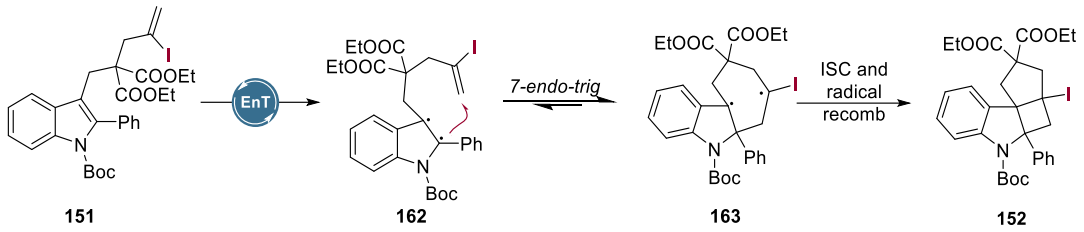


Scheme 43.(A)Hypothesis for the difference in reactivity between C1-centered radical and C2-centered radical when R group is varied. (B)Radical clock experiment to verify radical reactivity when R is electron-withdrawing group from Weedon and coworkers in 1991.[78]

To support the relative reactivity of the two radical centers in a protected indole system **154**, a radical clock experiment was reported in 1991.[78] In this study, indole **154** was reacted with vinylcyclopropane, which served as a radical clock. Four possible initial attack pathways *via* [2+2] cycloaddition were considered. If a cis-attack pathway had occurred, it would have produced the [2+2] product **158** and the β-scission product **157**; however, neither was detected (*Scheme 43(B)*). Instead, a trans-attack pathway was observed, affording the [2+2] cyclized product **159** in 31% yield. This [2+2] intermediate could then undergo two possible pathways depending on whether the radical at the C1 position was reactive. Notably, 64% of the β-scission product **161** was formed. Formation of **161** is consistent only with the pathway

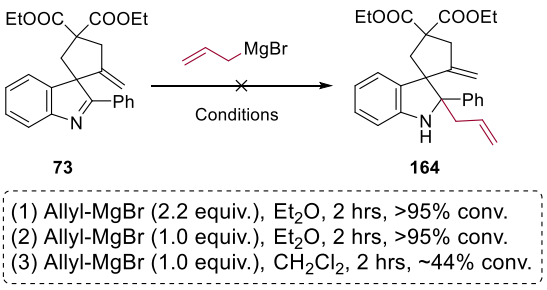
in which the C1-centered radical is more reactive, leading to intermediate **160**, followed by radical recombination.

Overall, this radical clock experiment supports the proposal that, upon carbonyl protection of the indole nitrogen, the radical at the C1 position becomes the more reactive center.



*Scheme 44. Proposed mechanism for Boc-protected substrate **151** under photochemical conditions*

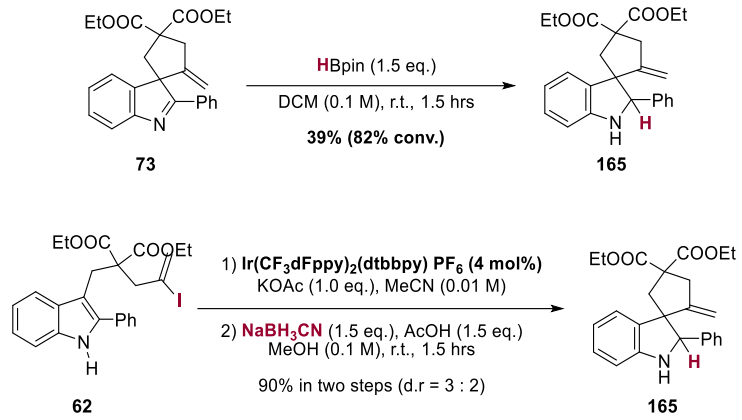
Based on this hypothesis, a plausible mechanism for the Boc-protected substrate is proposed, as depicted in *Scheme 44*. Substrate **151** is first promoted to its triplet excited state *via* energy transfer. Subsequently, a 7-endo-trig cyclization occurs to generate intermediate **163**. Finally, radical recombination furnishes the [2+2] cycloaddition product **152**. This mechanistic proposal is consistent with the enhanced reactivity of the C1-centered radical upon Boc protection of the indole nitrogen. By suppressing conjugative stabilization from the nitrogen lone pair, the electronic distribution is altered in a manner that favours *7-endo-trig* cyclization, thereby promoting formation of the [2+2] cycloaddition product.



Scheme 45. Stepwise trapping attempts by using Grignard reagent.

We further sought to examine whether a stepwise nucleophilic substitution strategy could be employed to further diversify the reactivity for the cyclized product. As summarized in

Scheme 45, cyclized product **73** was treated with a Grignard reagent. However, no desired product was detected, and a complex mixture was obtained under these conditions. A plausible explanation is that the Grignard reagent preferentially reacted with the malonate moiety rather than engaging in the intended transformation.



*Scheme 46. Hydrogenation of cyclised product **73** using HBPin or $NaBH_3CN$*

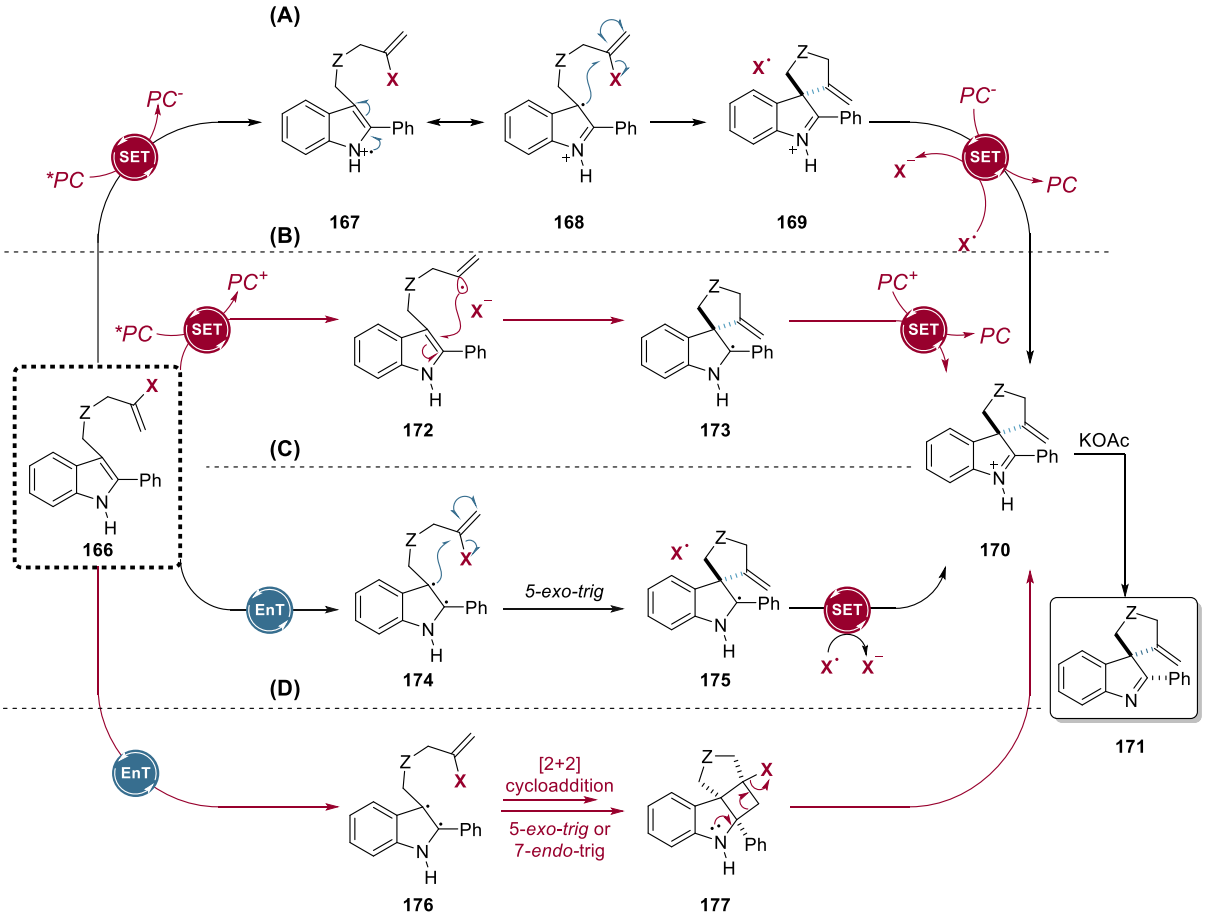
One possible explanation of why Grignard approaches didn't work is that steric hindrance at the iminium center may shut down nucleophilic addition, so we hypothesized that the use of hydride (H^-) source can be advantageous (*Scheme 46*). Initial experiments using HBPin as the hydride source afforded the hydrogenated product **165** in 39% yield. Subsequently, $NaBH_3CN$ was employed as an alternative hydride donor, starting from substrate **62**, which furnished **165** in 90% yield over two steps.

In summary, a series of nucleophilic substitution attempts were conducted to further functionalize the imine intermediate. However, trapping with various carbon- and heteroatom-based nucleophiles was unsuccessful. These outcomes suggest that the iminium center exhibits limited electrophilicity and/or is sterically hindered under the applied conditions. Notably, hydrogenation proved feasible, affording the corresponding product in moderate to high yield depending on the hydride source. This result indicates that while steric and electronic factors

restrict reactions with bulkier nucleophiles, smaller nucleophiles such as hydride remain capable of engaging the iminium intermediate.

2.5 Mechanistic study

To elucidate the mechanism of the key transformation, four possible pathways were considered: oxidative photocatalysis, reductive photocatalysis, the triplet-state radical-polar crossover (RPC), and the [2+2] cycloaddition pathway. Each pathway was evaluated based on experimental observations.



Scheme 47. Proposed Mechanistic Pathways: (A)Oxidative Photocatalytic Pathway; (B)Reductive Photocatalytic Pathway; (C)Triplet-State RPC Pathway; (D)Alternative [2+2]/Fragmentation Pathway.

As illustrated in *Scheme 47(A)*, the oxidative photocatalytic pathway can be described as follows. The indole core of substrate **166** is oxidized by the photocatalyst to generate an *N*-

centered radical cation. Subsequently, **168** undergoes intramolecular addition to the vinyl iodide moiety, leading to displacement of an iodine radical and formation of the cyclized intermediate **169**. Finally, the iodine radical oxidizes the reduced photocatalyst (PC^{-}), thereby completing the catalytic cycle.

As illustrated in *Scheme 47(B)*, the reductive photocatalytic pathway proceeds *via* reduction of the vinyl iodide moiety by the photocatalyst, generating a vinyl radical. This radical then undergoes intramolecular 5-*exo*-*trig* cyclization onto the indole core to afford the cyclized intermediate **173**. Subsequently, the radical intermediate **173** may reduce the oxidized photocatalyst (PC^{+}), thereby completing the catalytic cycle.

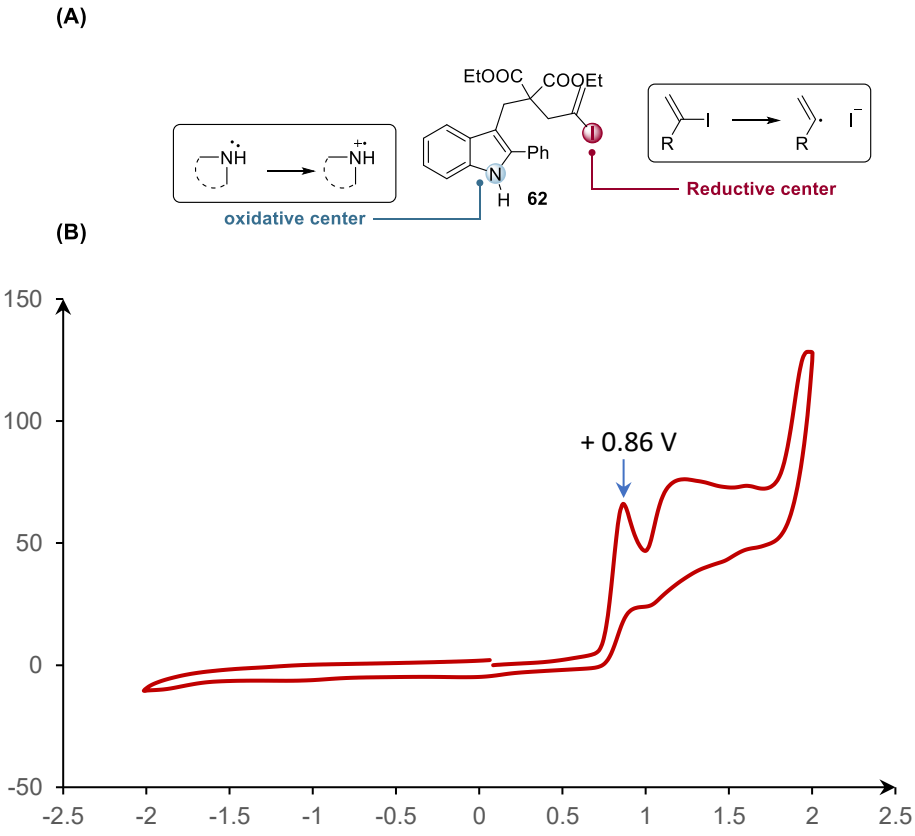


Figure 14. Reference electrode Ag/$AgNO_3$ (0.1 M in MeCN) with $E_{ref\ vs\ SHE}$ = +0.36 V [79]

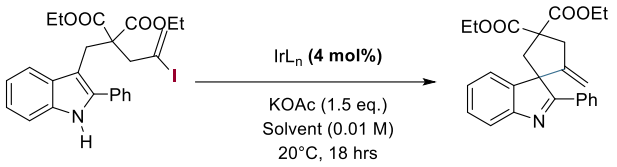
The reduction potential of **62** was determined to be +0.86 by CV with a reference Ag/$AgNO_3$ electrode. No reduction peak was detected within the applied potential window

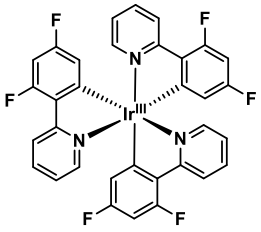
(−2.0 to 2.0 V). These results suggest that the reductive photocatalytic pathway is unlikely to operate under the reaction conditions (*Scheme 47(B)*).

$$E_{vs.SCE} = E_{measure} + (E_{ref\ vs.SHE} - 0.241\ V) \quad (2)$$

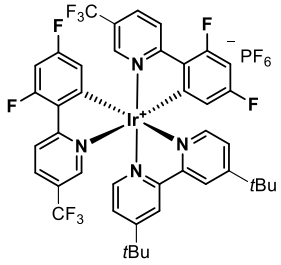
To enable comparison with literature data, the measured oxidation potential was converted to the saturated calomel electrode (SCE) scale. As shown in Equation 2, the oxidation potential of substrate **62** corresponds to +0.979 V *vs SCE*.[80]

Table 6. Control experiments.





Ir(dFppy)$_3$
S_0 to T_1 = 60.1 kcal/mol
$E_{1/2}$ (M^+/M^*) = **-1.28 V** *vs SCE*.
$E_{1/2}$ (M^*/M^-) = 0.36 V *vs SCE*.



Ir[((5-CF$_3$)dFppy)$_2$dtBbpy]PF$_6$
S_0 to T_1 = 60.1 kcal/mol
$E_{1/2}$ (M^+/M^*) = **-0.89 V** *vs SCE*.
$E_{1/2}$ (M^*/M^-) = 1.21 V *vs SCE*.

Entry	Photocatalyst	Solvent	Conv. [%]	Yield [%]
1	[Ir((CF$_3$)dFppy)$_2$dtBbpy]·PF$_6$	MeCN/H$_2$O 9:1	>95	89
2	Ir(dFppy)$_3$	MeCN	>95	87
3	-	MeCN/H$_2$O 9:1	18	18

As summarized in *Table 7*, when [Ir((CF$_3$)dFppy)$_2$dtBbpy]·PF$_6$ was employed as the photocatalyst (Entry 1), an oxidative photocatalytic pathway (*Scheme 48(A)*) appears thermodynamically feasible, as the excited-state reduction potential of the photocatalyst

($E_{½}(M^*/M^-)$ = 1.21 V *vs SCE*) exceeds the oxidation potential of substrate **62** ($E_{½}$ ox = + 0.979 V *vs SCE)*.

However, when $Ir(dFppy)_3$ was used as the photocatalyst (Entry 2), the reaction outcome remained essentially unchanged, despite its significantly lower excited-state reduction potential ($E_{½}(M^*/M^-)$ = +0.36 V *vs SCE*), which is insufficient to oxidize the indole core. Furthermore, even if oxidation of the indole were possible with $[Ir((CF_3)dFppy)_2dtBbpy]\cdot PF_6$, there is insufficient evidence to support closure of the catalytic cycle without an external oxidant. In particular, the iodine radical is not sufficiently reducing to regenerate the photocatalyst, as indicated by its reduction potential ($E^0(I^{\bullet}/I^-)$ = + 0.986 *vs SCE* in MeCN), compared with the reduction potential of the photocatalyst ($E_{½\ Ox}$ = + 1.69).[26, 81] Additionally, the reaction still afforded 18% of the desired product in the absence of a photocatalyst (Entry 3). Taken together, these observations suggest that the reaction is more likely to proceed *via* a triplet-state pathway rather than through a redox-mediated mechanism.

For the triplet-state pathways, as illustrated in *Scheme 47(C)* and *47(D)*, the radical-polar crossover (RPC) pathway is the proposed productive route. However, an alternative pathway may also lead to the same product, proceeding initially *via* a [2+2] cycloaddition through either a 5-*exo-trig* or 7-*endo-trig* cyclization. The resulting [2+2] intermediate may subsequently undergo fragmentation to afford the desired product **170**.

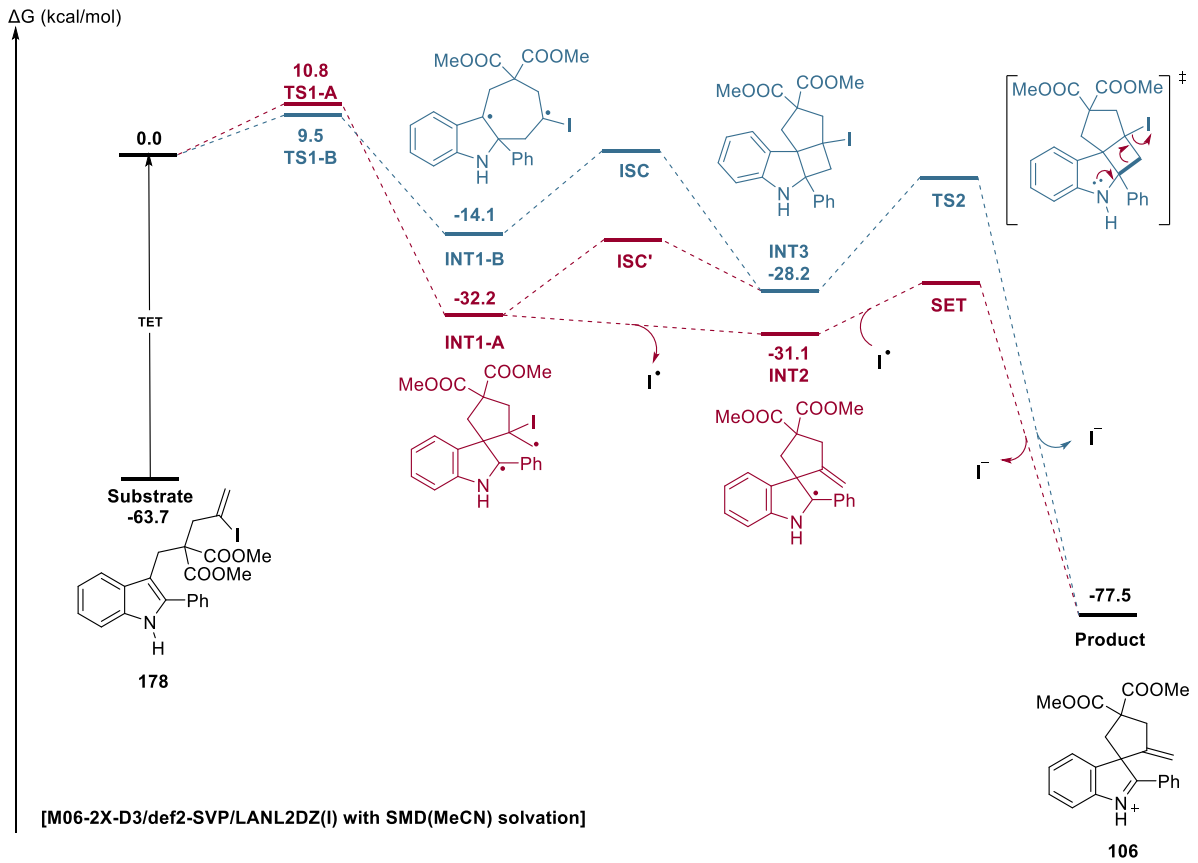


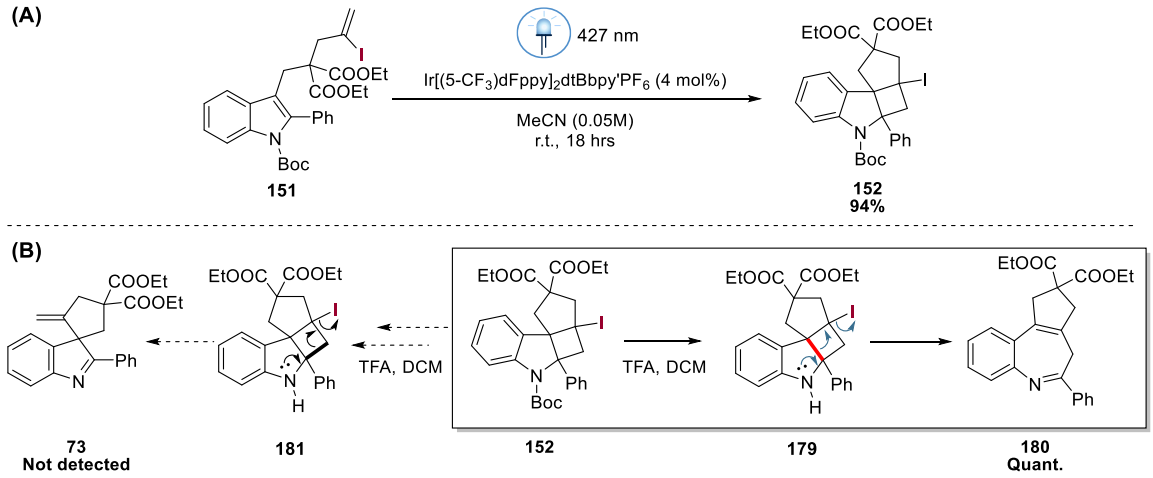
Figure 15. DFT study performed by William Hughes

The computational study conducted by William Hughes is presented in *Figure 15*. In this analysis, the calculated triplet energy of the substrate **178** was 63.7 kcal/mol. The resulting excited-state substrate can proceed *via* either the [2+2] cycloaddition pathway or the triplet-state radical-polar crossover (RPC) pathway, with comparable transition-state energies (**TS1-A**, 10.8 kcal/mol; **TS1-B**, 9.5 kcal/mol). The **TS1-B** pathway leads to intermediate **INT1-B** *via* a 7-*endo-trig* cyclization, with a Gibbs free energy of -14.1 kcal/mol. Subsequently, intersystem crossing (ISC) occurs, enabling radical recombination to afford the [2+2] cycloaddition intermediate **INT3**. This intermediate can then undergo fragmentation to furnish the target product **106**.

Alternatively, the 5-*exo-trig* pathway leads to intermediate **INT1-A** (-32.2 kcal·mol^{-1}), which can follow two possible pathways. It may undergo radical recombination to generate the [2+2] cycloaddition intermediate **INT3** or proceed *via ipso*-substitution to displace an iodine

radical, forming the radical intermediate **INT2**. Subsequently, the iodine radical can oxidize **INT2**, thereby furnishing the desired product **106**.

Based on the DFT results, the 7-*endo-trig* pathway is predicted to be slightly more favorable than the 5-*exo-trig* pathway, corresponding to the [2+2] cycloaddition route or radical-polar crossover (RPC) pathway. However, experimental observations indicate that the [2+2] pathway is unlikely to operate under the reaction conditions.



Scheme 49. (A) Unexpected Boc-protected [2+2] product observed during the one-pot trapping experiment. (B)Fragmentation of Boc-protected [2+2] product.

As illustrated in *Scheme 50*, during the one-pot trapping experiments, the Boc-protected [2+2] cycloaddition product **152** was isolated. This intermediate was therefore subjected to deprotection with TFA to evaluate whether it could undergo fragmentation to furnish the desired product **73**. Upon treatment with TFA, the Boc-protected [2+2] product **151** was quantitatively converted into the seven-membered ring product **180**, with no formation of **73** observed. This result indicates that the cyclobutane intermediate **181** is unlikely to undergo fragmentation to yield **73**, but instead preferentially undergoes ring expansion. Consequently, the [2+2] pathway is unlikely to be operative under the reaction conditions.

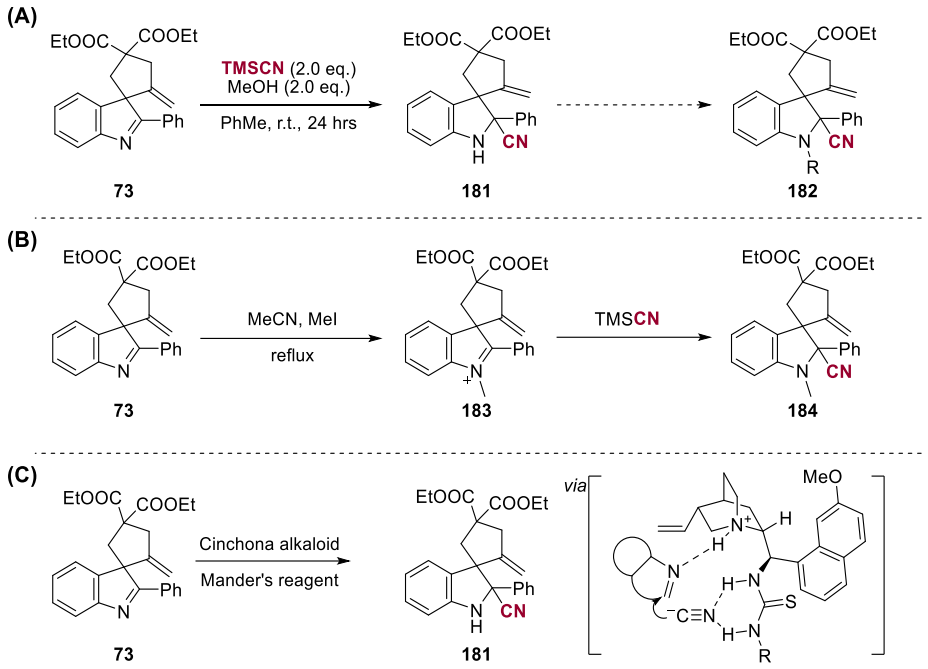
In conclusion, the key transformation is most consistent with the triplet-state radical-polar crossover (RPC) mechanism. Control experiments and electrochemical measurements

support the triplet-state pathway and exclude photoredox-mediated processes. DFT calculations suggest that the reaction may proceed *via* a 7-*endo*-*trig* pathway to form a [2+2] intermediate, followed by fragmentation to deliver the desired product. However, experimental evidence from the ring-expansion studies indicates that fragmentation does not proceed through this pathway but instead follows an alternative route.

Overall, this chapter shows that triplet-state radical-polar crossover can be used to interrupt the reactivity of a photochemical [2+2] cycloaddition manifold in 2-phenylindole systems. In doing so, it provides access to structurally diverse spiroindole architectures and establishes a conceptual basis for further development of this strategy.

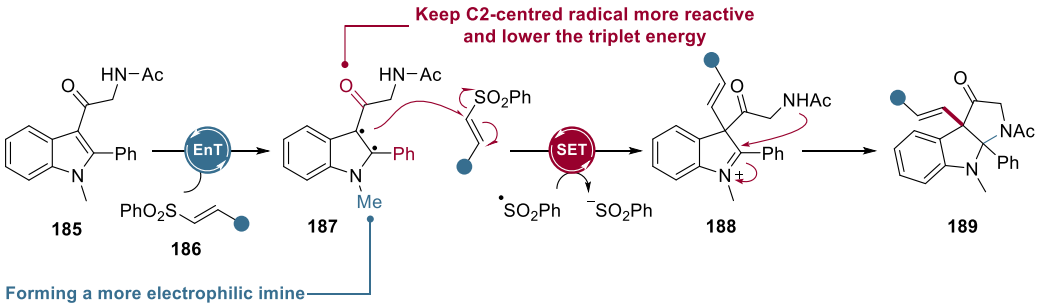
2.6 Future work

For further product diversification, as shown in *Scheme 51(A)*, substrate **73** was treated with TMSCN in MeOH. However, attempts to isolate the product were unsuccessful, as decomposition occurred during column chromatography. It is possible that direct protection or derivatization of the crude reaction mixture, without prior purification, may help to prevent decomposition and enable isolation of the desired product. An alternative strategy to achieve this transformation would involve prior introduction of a methyl substituent. The resulting intermediate **183** could then be treated with TMSCN under the same conditions. Installation of the methyl group is expected to enhance the electrophilicity of **73**, which may facilitate nucleophilic addition and improve the overall yield (*Scheme 51(B)*).



Scheme 51. (A)Stepwise trapping with TMSCN. (2)Strategy to pre-protect the imine to increase nucleophilicity. (C)Strategy to use a Cinchona alkaloid derivative to deliver the CN⁻ enantioselectively.

Previous studies have demonstrated that spiroindoles can be trapped enantioselectively through treatment with chiral Cinchona alkaloid derivative in combination with Mander's reagent, as illustrated in *Scheme 51(C)*. This approach may therefore represent an attractive strategy for further exploration.[82]

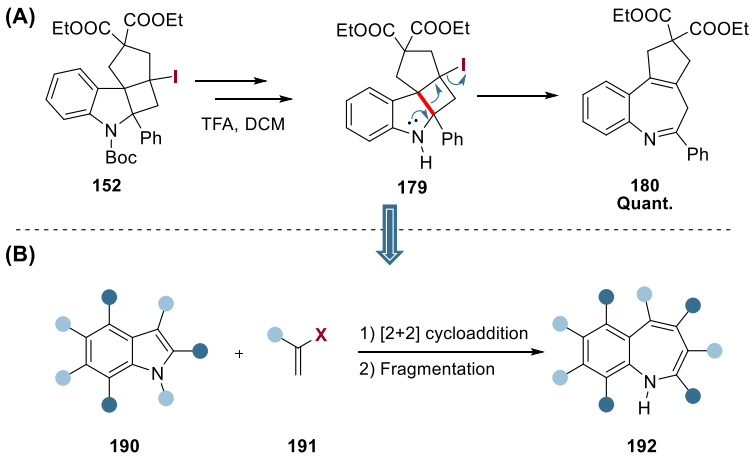


Scheme 52. Intermolecule the triplet-state radical-polar crossover (RPC) of 2-phenylindole derivatives.

With further development of the triplet-state radical-polar crossover concept, an intermolecular variant of this reaction could be explored. As illustrated in *Scheme 52*, a modified 2-phenylindole derivative **188** may serve as a suitable platform. In this design, the phenyl substituent, together with the ketone at the C2 position, is intended to lower the triplet

energy of the substrate. The ketone moiety may also influence regioselectivity, as its resonance stabilisation effect is expected to render the C2-centered radical more reactive than the C1-centered radical. Furthermore, installation of a methyl substituent could enhance the electrophilicity of the subsequent iminium intermediate.

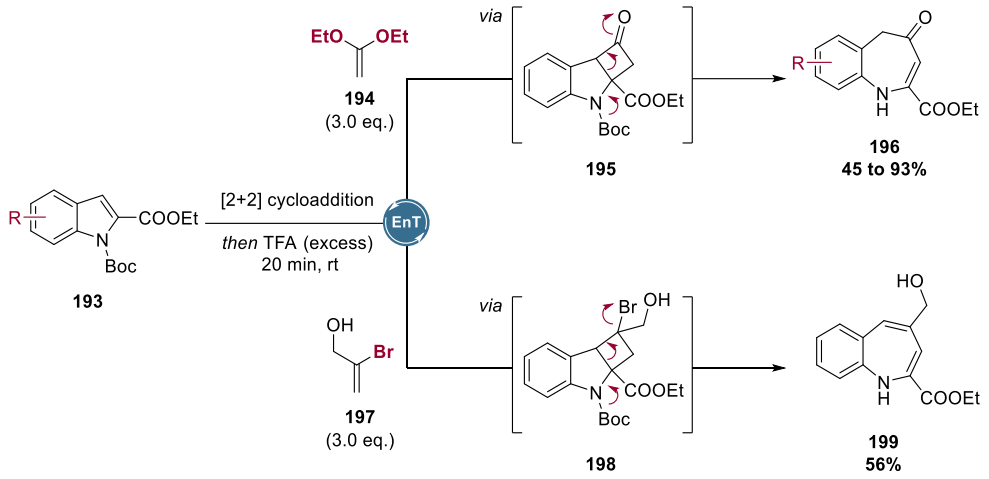
In the proposed pathway, the triplet intermediate **187** is expected to engage with a radical acceptor, in this case a sulfonyl alkene **186**.[83] This transformation would generate a sulfonyl radical and, consequently, oxidize the intermediate to form the iminium species **188**. The resulting iminium intermediate **189** could then undergo intramolecular nucleophilic attack by the amine to furnish the cyclized product.



Scheme 53. (A)Fragemation of 152 (B)Intermolecular [2+2] cycloaddition followed by a fagmentation to make benzazepines.

In our previous studies, as illustrated in *Scheme 53(A)*, the [2+2] cycloaddition product **152** was found to undergo fragmentation to furnish a benzazepine derivative **180**. It would therefore be interesting to extend this transformation to an intermolecular variant, as proposed in *Scheme 53(B)*, which could potentially enable broader access to benzazepine derivatives. The synthesis of benzazepines has historically been challenging and often requires multistep substrate modification, such as strategies involving intramolecular Heck reactions, double Tsuji-Trost reactions, or [3+3] cycloadditions. These approaches typically suffer from complex substrate design and limited substrate scope. In contrast, our proposal involves the

straightforward combination of indoles **190** and vinyl halides **191**, providing a potentially more direct route to benzazepine scaffolds. A key advantage of this strategy lies in its tunability, as both the indole and alkene components can be readily modified to expand structural diversity.



Scheme 54. Intermolecular [2+2] cycloaddition followed by a fagmentation to make benzazepines developed by Valentin Veselinov and Dr Anton Möllerke.

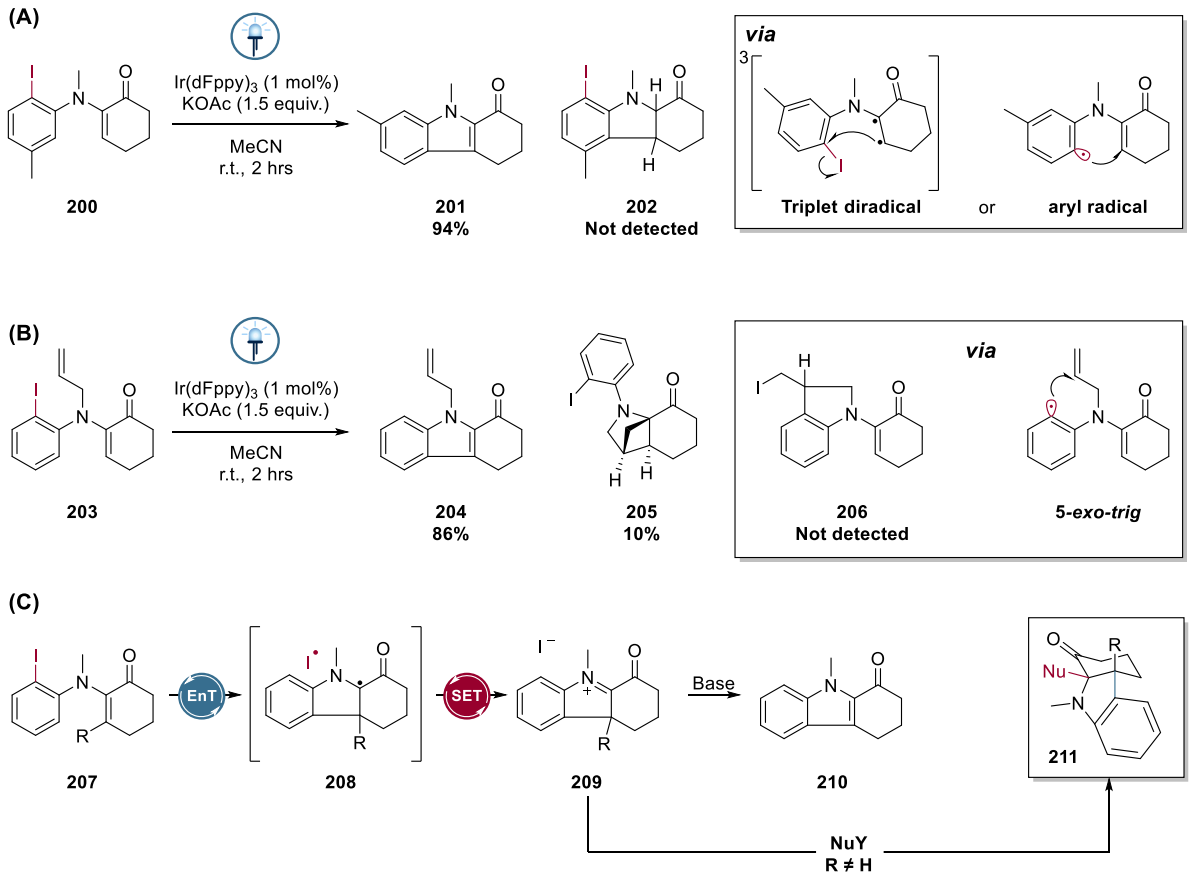
For the excellent work has been done by Valentin Veselinov and Dr Anton using the original idea described in *Scheme 55*, key results were achieved as illustrated in *Scheme 54*. In this study, 2-esterindole **193** was reacted with vinyl bromide **197** *via* a [2+2] cycloaddition. Subsequent treatment with TFA afforded benzazepine **199** in 56% yield. Moreover, application of a De Mayo-type fragmentation enabled further access to benzazepine derivatives. Treatment of 2-esterindole **193** with **194** furnished benzazepines **196** in yields ranging from 45% to 93% across more than 30 examples.

In summary, future investigations may focus on broadening the synthetic potential of the triplet-state radical-polar crossover platform. Key directions include the development of intermolecular variants, expansion toward benzazepine and related scaffolds, and further exploration of post-functionalization strategies of the iminium intermediates.

3. A Radical-polar Crossover Approach to Complex Nitrogen Heterocycles *via* the Triplet State

3.1 Previous work and project aim

In our previous study, as shown in *Scheme 56(A)*, an unexpected outcome was observed when substrate **200** was employed. Instead of affording the anticipated 6π cyclisation product **202**, the reaction yielded an eliminative product **201**. This product may arise *via* two possible pathways: a triplet diradical pathway (RPC pathway) or an aryl radical pathway (photoredox pathway).



Scheme 56. Previous works (A)Regioselective study. (B)Radical clock experiment. (C)Reactions design.

To probe the mechanism, a radical clock experiment was conducted (*Scheme 56(B)*). Upon blue-light irradiation, substrate **203** afforded the radical-polar crossover product **204** in 86% yield, together with a [2+2] cycloaddition product **205** in 10% yield. If the reaction were to proceed *via* an aryl radical intermediate under photoredox conditions, the resulting aryl

radical would be rapidly intercepted by the allyl group to generate product **206**. However, this product was not detected, indicating that a photoredox pathway is unlikely to operate.

The proposed mechanism is outlined in *Scheme 56(C)*. Consistent with the radical-polar-crossover pathway discussed in Chapter 2.1, formation of the iminium cation **209** is proposed. When R = H, this intermediate may undergo elimination to furnish product **210**. Alternatively, the imine cation can be intercepted by a nucleophile.[55]

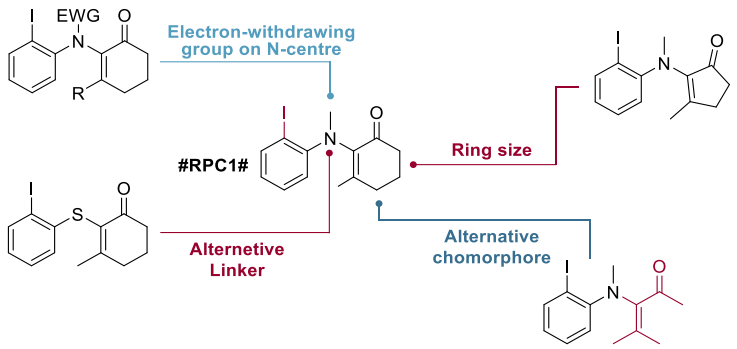


Figure 16. This work: project aims.

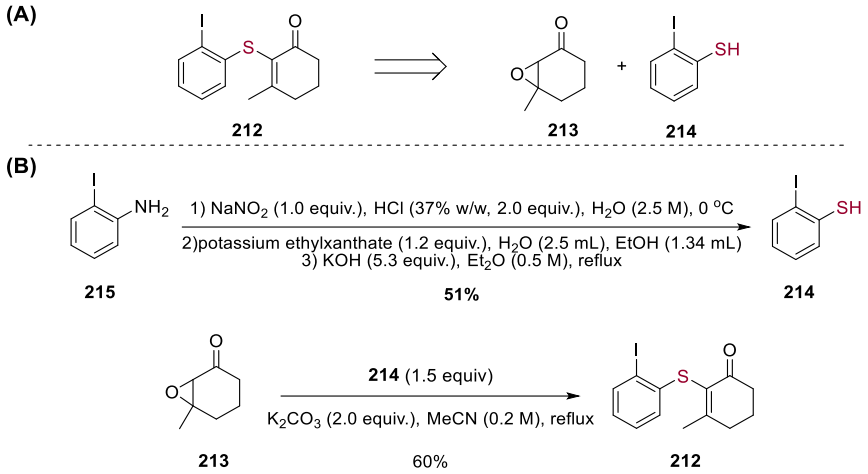
This project represents a continuation of the work described in *Scheme 11(B)* and *Scheme 56*. Building upon the previously established reaction framework, the present study aims to systematically investigate the influence of structural modifications to the reaction outcome. Specifically, the effects of varying the chromophore, altering the ring size, employing alternative linkers, and introducing electron-withdrawing groups at nitrogen were examined to determine their impact on the system (*Figure 16*).

3.2 Results and discussion

3.2.1 Examination of the S-linked Substrate

In our previous study, we demonstrated that *O*-linked substrates do not undergo the radical-polar crossover pathway.[31] It was therefore of interest to examine whether S-linked substrates would exhibit reactivity comparable to that of the *N*-linked analogues. In comparison

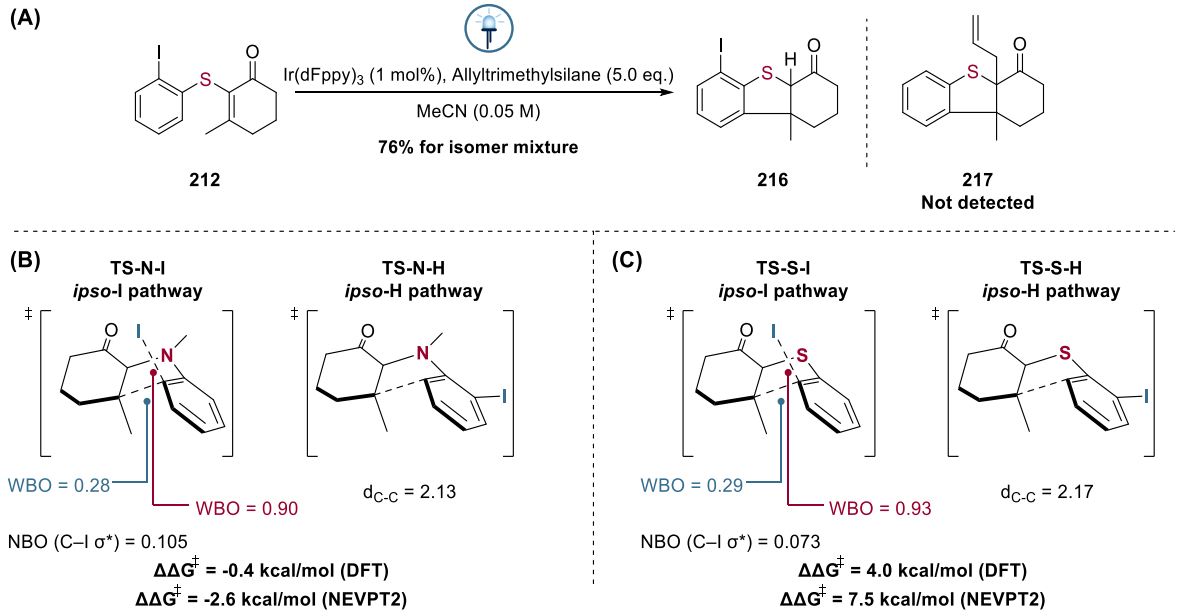
with oxygen, sulfur possesses larger and more polarizable orbitals and displays a stronger electron-donating character, which may contribute to stabilization of the corresponding transition state in S-linked systems.



*Scheme 57. (A)Retrosynthesis of **212**. (B)reaction outcome for synthesis **212***

As shown in *Scheme 57*, the thiol precursor **214** was prepared from aniline **215** *via* a diazotization-substitution sequence.[84] Specifically, aniline **215** was subjected to diazotization with $NaNO_2$ to generate the corresponding diazonium salt, which was subsequently trapped with potassium ethyl xanthate. Subsequent hydrolysis afforded the desired product **214** in 51% yield. Compound **212** was obtained by treating epoxide **213** with 2-iodobenzenethiol **214** under basic conditions.

With the S-linked substrate in hand, photochemical studies were subsequently undertaken. Substrate **212** was irradiated under blue light in the presence of 1 mol% of the photocatalyst and 5 equivalents of allyltrimethylsilane. As shown in *Scheme 58*, the reaction afforded the 6π cyclisation product **216** in 76% yield, and no radical-polar crossover product **217** was detected.



Scheme 58. (A)Photochemical study of substrate 212. (B)DFT comparison of the N-Linked and S-Linked substrates.

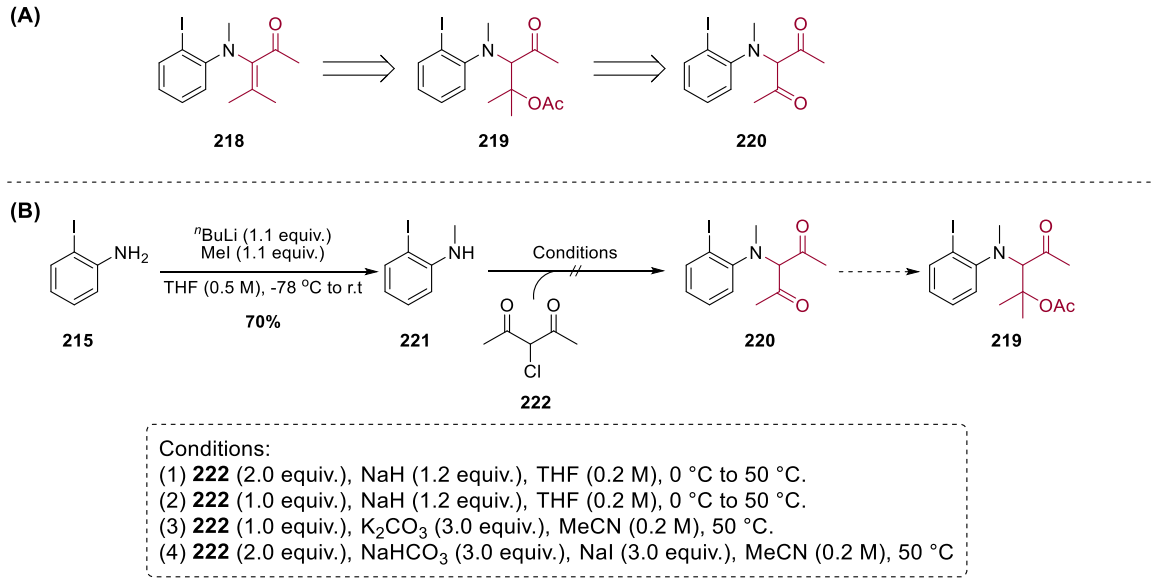
To rationalize the lack of reactivity observed for the S-linked substrate, further computational work was performed by Dr Mihai V. Popescu. The computational results indicate that, for the S-linked system, the *ipso*-H pathway (6π cyclisation) is energetically favoured over the ipso-I pathway, with a $\Delta\Delta G^{\ddagger}$ of 7.5 kcal/mol. In contrast, the N-linked substrate preferentially undergoes the ipso-I pathway ($\Delta\Delta G^{\ddagger}$ = -2.6 kcal/mol).

Comparison of the corresponding transition states shows that the Wiberg bond order (WBO) associated with the C-I and C-C bonds are similar for both substrates along the radical-polar crossover pathway. However, natural bond orbital (NBO) analysis shows that the antibonding σ*(C-I) orbital in the S-linked transition state possesses lower electron density than that in the N-linked analogue. More specifically, these results suggest that, in the N-linked substrate, delocalization from the linking heteroatom into the σ*(C-I) orbital during C-C bond formation provides additional stabilization of the transition state compared with the S-linked system (*Scheme 58*).

3.2.2 Examination of Alternative Chromophores and Ring Sizes

The investigation of chromophore structural variation focused on two principal aspects: modification of ring size and replacement of the cyclic framework with an acyclic chromophore. These studies were undertaken to evaluate the structural tolerance of the triplet-state radical-polar crossover (RPC) system.

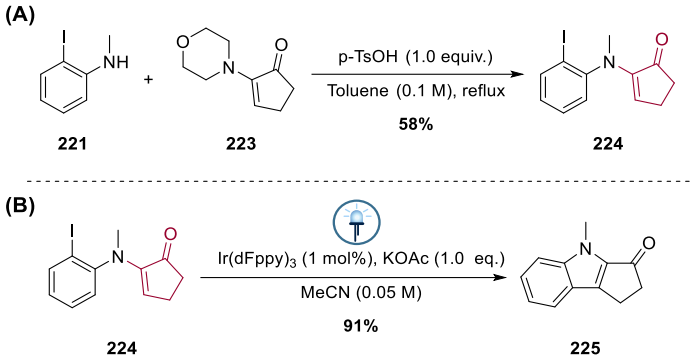
In our previous study, the chromophore was derived from a cyclic system, such as cyclohex-2-en-1-one. It was therefore of interest to investigate whether the reaction would proceed similarly with acyclic chromophores, for example 4-methylpent-3-en-2-one. To this end, substrate **218** was designed and synthesized from precursor **220**. This sequence involved methylation of the ketone to furnish **219**, followed by an elimination step to afford the desired product.



*Scheme 59. (A)Retrosynthesis toward **218**. (B)Synthetic route to **219***

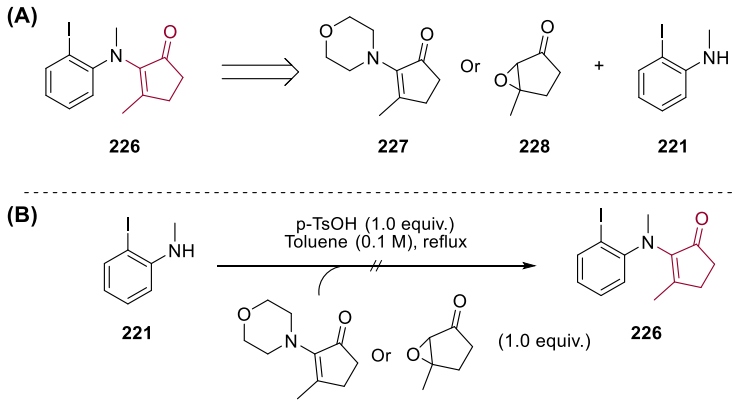
Methylaniline **221** was prepared from aniline **215**. However, subsequent attempts to synthesize precursor **220** proved unsuccessful (*Scheme 59*). Treatment of methylaniline **221** with 3-chloropentane-2,4-dione **222** in the presence of a strong base such as NaH did not afford the desired product, instead resulting in a complex mixture. The use of a weaker base, such as

K_2CO_3, likewise failed to deliver the target compound. Furthermore, no desired product was observed under Finkelstein conditions.



*Scheme 60. (A)Synthesis of **224**. (B)Photochem-study on **224**.*

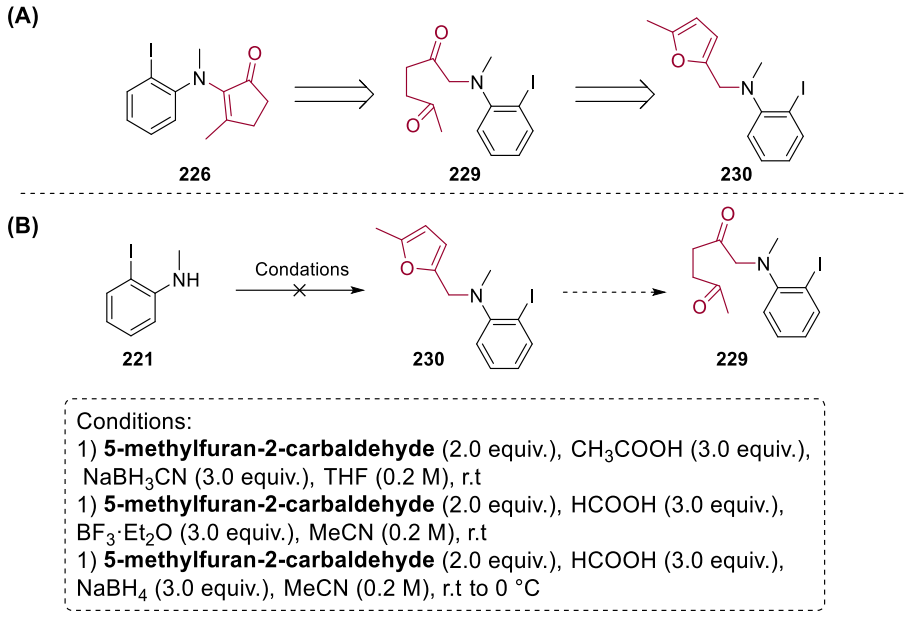
The next objective of this project was to investigate the effect of ring size on the reaction outcome as illustrated in *Scheme 60*. The β-H substrate **224** was prepared from methylaniline **221** and **223** under condensation conditions. Subsequent photochemical irradiation afforded the cyclised product **225** in 91% yield.



*Scheme 61. (A)Initial retrosynthesis of **226**. (B)Reaction outcome.*

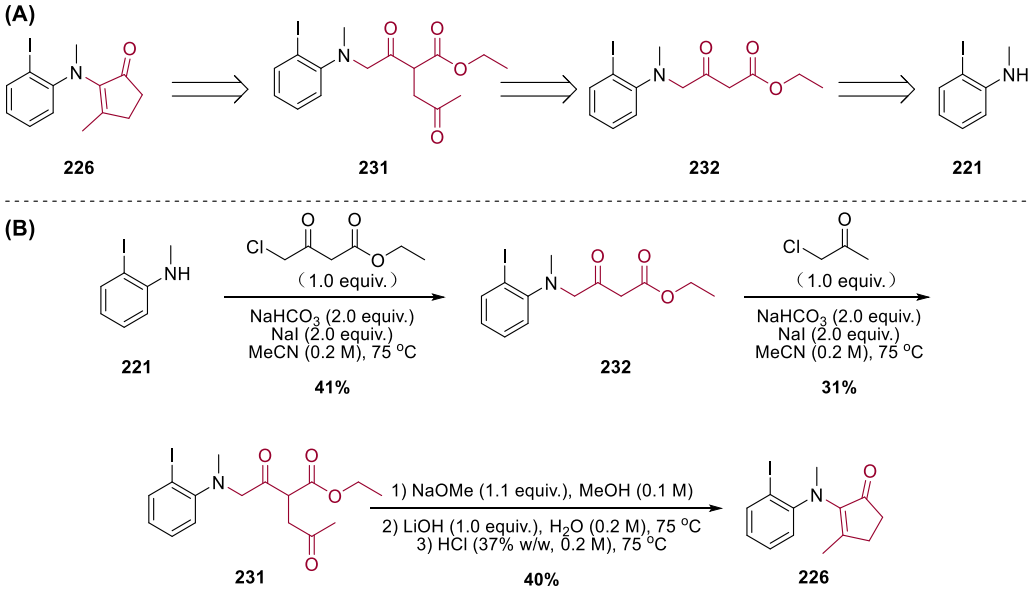
As described in *Scheme 61*, the following stage of the study aimed to determine whether the β-methyl substrate **226** could undergo the triplet-state radical-polar crossover pathway with efficiency comparable to that observed for the six-membered ring system. An initial strategy to access the β-methyl substrate involved condensation of methylaniline **221** with either epoxide **228** or morpholine **227**. However, under the attempted condensation conditions, no formation of the desired product was observed. The possible reason could be addressed to the

lack of electrophilicity of the more sterically hindered iminium intermediate formed upon protonation of **227** or more hindered epoxide **228** is more difficult to be opened.



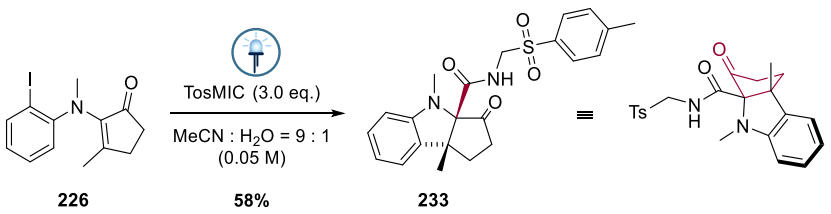
*Scheme 62. (B)2nd retrosynthesis of **226**. (B)Reaction outcome for 1st step*

As shown in *Scheme 62*, a subsequent strategy to access the β-methyl substrate **226** involved the preparation of intermediate **230**, which was envisaged to undergo oxidative ring opening to afford **229**, followed by an aldol condensation to generate the desired product. However, the synthesis of precursor **230** proved challenging. Three reductive amination protocols were examined, employing $NaBH_3CN$, a Lewis acid-mediated system, and $NaBH_4$, respectively. The possible reason could still be the lack of nucleophilicity of methylaniline **221**.



Scheme 63. (A)3rd retrosynthesis of ***226****. (B)Reaction outcomes*

A subsequent approach involved a more elaborate synthetic strategy. The design for accessing the key intermediate **231** was based on two sequential nucleophilic substitution reactions starting from methylaniline **221**. The first substitution was directed at the aniline nitrogen, whereas the second was intended to occur at the malonate center (*Scheme* 63*(A)*). Two sequential nucleophilic substitutions leading to the key intermediate **231** were successfully accomplished under Finkelstein conditions, affording the corresponding products in 41% and 31% yield, respectively. The final step toward the β-methyl substrate **226** involved an aldol condensation followed by decarboxylation to obtain desired product **226** in 40% yield (*Scheme* 63*(B)*).



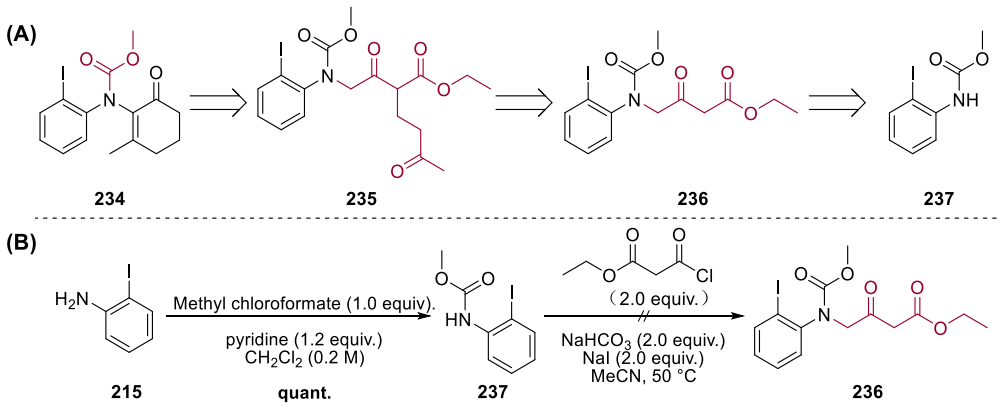
Scheme 64. Photochemical study of ***226****.*

The subsequent photochemical reaction was carried out under blue light irradiation in the presence of 3 equivalents of TosMIC. The desired radical-polar crossover product **233** was obtained in 58% yield. This result indicates that contraction of the six-membered chromophore

to a smaller ring system did not significantly reduce the reactivity, which gives some flexibility in the geometric requirements of the chromophore (*Scheme 64*).

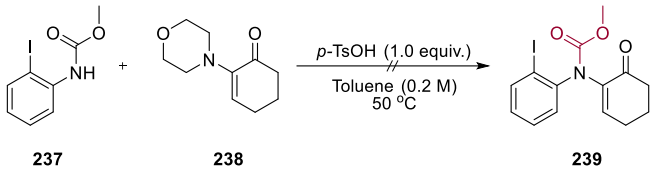
3.2.3 Effect of Introducing an Electron-Withdrawing Group at the Nitrogen Center

Based on the DFT analysis presented in *Scheme 58*, delocalization from the nitrogen center into the antibonding σ^*(C-I) orbital was identified as a key stabilizing factor in this transformation. Introduction of an electron-withdrawing group at the nitrogen center was therefore proposed as a means of experimentally probing this computational finding. It was hypothesized that decreasing the electron density at nitrogen would affect the competition between the radical-polar crossover pathway and the 6π cyclisation pathway.



*Scheme 65. (A)Retrosynthesis of **234**. (B)Reactions outcomes.*

Application of the same aldol strategy employed for the synthesis of **226** to access the β-methyl substrate **234** proved unsuccessful (*Scheme 65*). Carbamate **237** was obtained in quantitative yield from aniline **215** under acetylation conditions. However, the subsequent Finkelstein reaction did not proceed as expected. Although characteristic signals corresponding to the desired intermediate were observed in the crude ^{1}H-NMR spectrum, the compound decomposed during purification on silica gel.

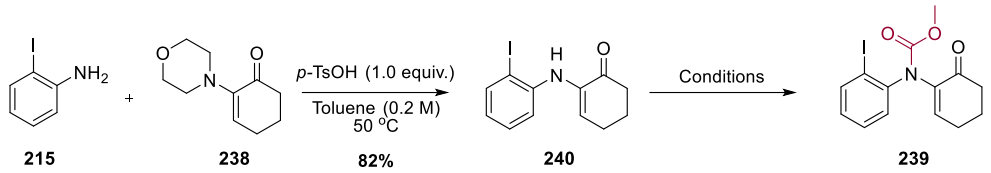


*Scheme 66. Approach of direct condensation to synthesise **239**.*

A subsequent strategy aimed to access the β-H substrate **239**. Carbamate **237** was subjected to condensation with morpholine **238** under the attempted reaction conditions. However, as shown in *Scheme 66*, no reaction was observed. This outcome may be attributed to the diminished nucleophilicity of carbamate **237**.

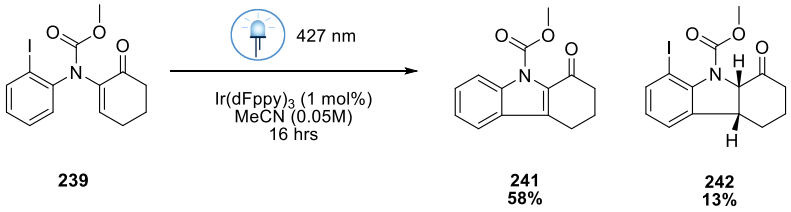
A revised strategy involved performing the condensation step prior to acetylation. The condensation was achieved by reacting aniline **215** with morpholine **238**, affording the desired intermediate **240** in 82% yield. The subsequent acetylation studies are summarised in *Table 8*. Treatment of **240** with Moc_2O in the presence of a catalytic amount of DMAP resulted in no observable reaction (Entry 1). Similarly, the use of DBU as base failed to promote conversion (Entry 2). Switching the carbonyl source to methyl chloroformate under DBU conditions also proved ineffective (Entry 3). This lack of reactivity may be attributed to the insufficient nucleophilicity of intermediate **240**. Consequently, pre-deprotonation of the intermediate was considered necessary to facilitate acetylation. Upon treatment with 3 equivalents of methyl cyanoformate and 1.2 equivalents of LiHMDS, the desired β-H substrate **239** was obtained in 28% yield (Entry 4). However, a further attempt to improve the yield by increasing the amount of base was unsuccessful and led to the formation of a complex mixture (Entry 5).

Table 8. Approaches of condensation before protection.



Entry	Carbonyl source	Base	Catalyst	Solvent	Temperature	Result
1	Moc_2O (1.0 equiv.)		DMAP (0.1 equiv.)	CH_2Cl_2 (0.2 M)	r.t.	No Reactions
2	Moc_2O (1.0 equiv.)	DBU (1.0 equiv.)		CH_2Cl_2 (0.2 M)	r.t.	No Reactions
3	Methyl chloroformate (1.5 equiv.)	DBU (1.5 equiv.)		CH_2Cl_2 (0.2 M)	r.t.	No Reactions
4	Methyl cyanoformate (3.0 equiv.)	LiHMDS (1.2 equiv.)		THF (0.2 M)	%-78 °C to r.t	28%
5	Methyl cyanoformate (3.0 equiv.)	LiHMDS (3.0 equiv.)		THF (0.2 M)	%-78 °C to r.t	complex mixture

With the β-H substrate **239** in hand, photochemical studies were undertaken. Substrate **239** was subjected to 1 mol% of the photocatalyst in MeCN under continuous irradiation for 16 hrs.



*Scheme 67. (A)Photochemcial study of **EX12***

The radical-polar crossover product **241** was obtained in 58% yield. Additionally, the 6π cyclisation product **242** was isolated in 13% yield. Analysis by ^{1}H-NOESY NMR spectroscopy confirmed that **242** was formed as the cis isomer (*Scheme 67*). The product ratio of **241** to **242** was approximately 4:1, indicating that the radical-polar crossover pathway remains favourable under this condition. These findings demonstrate that decreasing the electron density at the

nitrogen centre promotes increased competition between the radical-polar crossover and 6π cyclisation pathways. Experimentally, this observation supports the proposal that delocalization from nitrogen into the antibonding σ*(C-I) orbital is a key factor in stabilizing the transition state of the radical-polar crossover pathway.

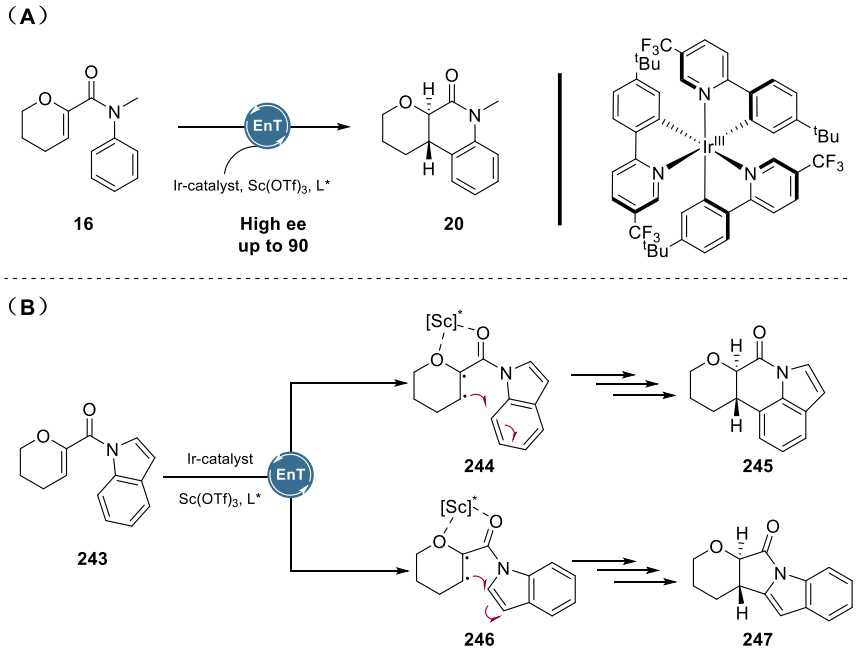
In summary, comparative investigations indicate that *N*-linked substrates preferentially undergo the RPC pathway, whereas S-linked substrate favours 6π cyclisation. DFT analysis identified delocalization from nitrogen into σ*(C-I) as a key stabilizing interaction in the RPC transition state. Variation of chromophore ring size demonstrated that moderate structural modification is tolerated without significant loss of RPC efficiency.

Electronic modulation at the nitrogen centre further confirmed the mechanism. The decreasing of electron density at nitrogen centre increased competition between the radical-polar crossover and 6π cyclisation pathways. Overall, the results indicate the critical role of delocalisation effect of heteroatom in stabilising transition state of radical-polar crossover pathway.

4. Catalytic Enantioselective 6π Photocyclization of *N*-Acylated Indoles

4.1 Background and Project Aim

In our group's previous work, a triplet energy transfer strategy was applied to enable the enantioselective 6π-cyclization of system **16** (*Scheme 68(A)*).[34] In that study, **16** was subjected to an Ir-based photocatalyst in the presence of $Sc(OTf)_3$ and a chiral Feng ligand, affording the cyclized product **20** in high yield and with excellent enantioselectivity. Moreover, $Sc(OTf)_3$ was shown to effectively lower the triplet energy of the substrate.

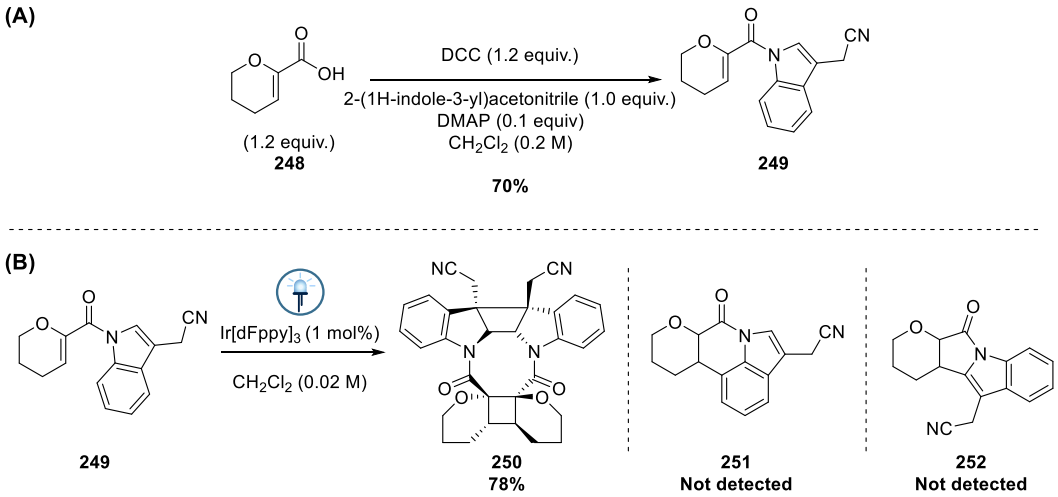


Scheme 68. (A)Previous work in the group. (B)This work: catalytic enantioselective 6π-photocyclization of N-acylated indoles

In this work, *N*-acylated indole **243** was investigated as a substrate for enantioselective 6π photocyclization. According to our mechanistic proposal (*Scheme 68(B)*), excitation of **243** to its triplet state enables two potential intramolecular cyclization pathways: 6π cyclization onto the benzene ring of the indole framework (at the C7 position) or onto the C2 position of the indole core. The objective of this study was to examine the regioselectivity of this transformation, to explore the possibility of modulating regioselectivity through reaction conditions, and ultimately to develop an enantioselective variant of the process.

4.2 Results and discussion

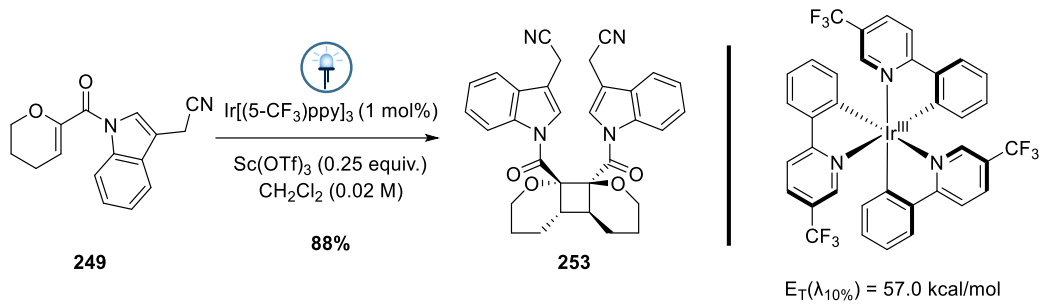
The initial attempt to synthesize the target substrate involved coupling acid **248** using DCC in the presence of a catalytic amount of DMAP. However, this approach proved unsuccessful when indole was employed as the nucleophilic partner. An alternative strategy, utilizing 2-(1H-indol-3-yl)acetonitrile, successfully afforded the desired product **249** in 70% yield (*Scheme 69(A)*).



*Scheme 69. (A)Synthesis route of **249**. (B)Photochemical study of **249** with Ir(dFppy)₃.*

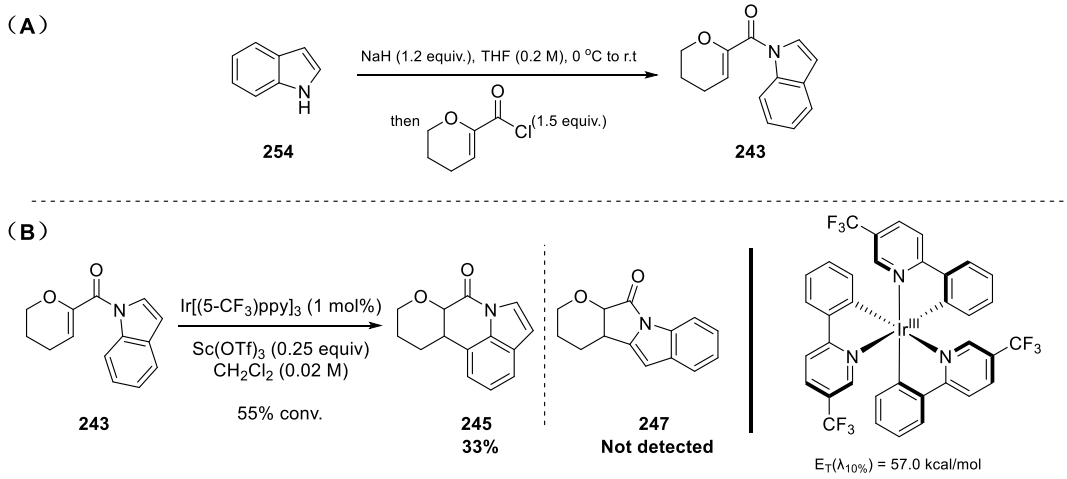
Further photochemical investigation of **249** was conducted using Ir(dFppy)₃ ($E_T(\lambda_{10\%})$ = 63.1 kcal/mol) as the photocatalyst. Under these conditions, the reaction afforded the double [2+2] dimer **250** in 78% yield, while no intramolecular cyclization products (**251** or **252**) were detected (*Scheme 69(B)*)

To further examine the reaction outcome, as shown in *Scheme 70*, a photocatalyst with a lower triplet energy ($E_T(\lambda_{10\%})$ = 57.0 kcal/mol) was employed. In addition, to lower the triplet energy of substrate, $Sc(OTf)_3$ was employed in this reaction. Under these conditions, the reaction selectively afforded the single [2+2] cycloaddition product in 88% yield.



*Scheme 70. Photochemical study of **249** with Ir[(5-CF₃)ppy]₃.*

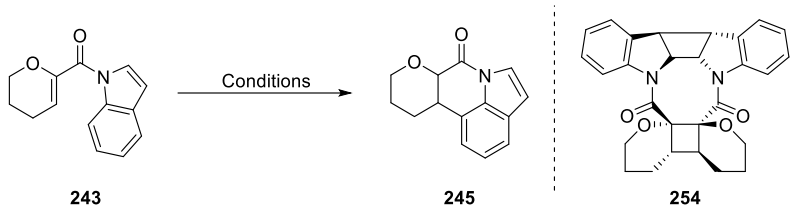
A possible explanation for this outcome is that the 3-MeCN substituent sterically inhibits the 6π cyclization pathway, particularly toward formation of **252**. Consequently, the next objective was the synthesis of substrate **243** to further evaluate the proposed reactivity.



*Scheme 71. (A)Synthesis route of **243**. (B) Photochemical study of **243** with Ir[(5-CF₃)ppy]₃.*

Substrate **243** can be afforded by pre-deprotonation of indole **254**, then treating with acid chloride. The first photochemical investigation was conducted with Ir[(5-CF_3)ppy]$_3$ and Sc(OTf)$_3$. The reaction resulted in cyclized product **245** in 33% yield. However, no **247** was detected (*Scheme 71*).

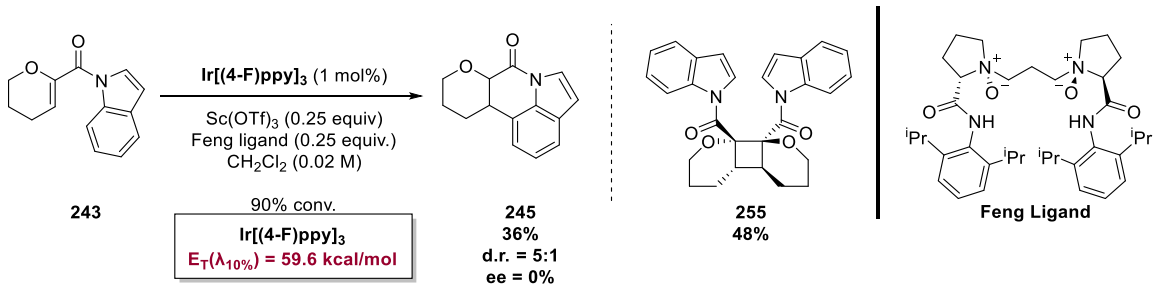
*Table 9. Optimisation of photoreaction of **243**.*



Entry	Photocatalyst	Lewis acid	Conv.	**245**	**254**	d.r
1	$Ir[(5\text{-}CF_3)ppy]_3$	$Sc(OTf)_3$	55%	33%	0%	59:41
2	$Ir(ppy)_3$	$Sc(OTf)_3$	26%	14%	0%	7:6
3	$Ir[dFppy]_3$	$Sc(OTf)_3$	100%	42%	55%	14:1
4	$Ir[dFppy]_3$	-	100%	<20%	64%	-

Further investigations of the racemic reaction are summarised in *Table 9*. Switching the photocatalyst to $Ir(ppy)_3$ led to reduced conversion and a lower isolated yield (Entry 2). When a higher triplet-energy photocatalyst, $Ir(dFppy)_3$ ($E_T(\lambda_{10\%})$ = 63.1 kcal/mol), was employed in the presence of $Sc(OTf)_3$, formation of the double [2+2] dimer **254** was observed; nevertheless, the cyclized product **245** was still obtained in 42% yield. In contrast, conducting the reaction with $Ir(dFppy)_3$ in the absence of the Lewis acid increased the yield of the double [2+2] dimer **254** and markedly decreased formation of **245**.

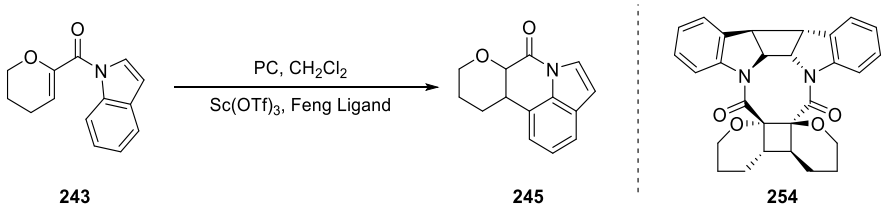
Taken together, these results suggest that production of the cyclized product **245** is strongly dependent on the Lewis acid. A plausible rationale is that the Lewis acid coordination lowers the effective triplet energy of the substrate, thereby promoting intramolecular 6π cyclization. However, the competition between 6π cyclization and [2+2] dimerization still suggests that [2+2] is more favourable.



*Scheme 72. Photochemical study on **243** with Ir[(4-F)ppy]₃.*

As shown in *Scheme 72*, use of a chiral Feng ligand in combination with [Ir(4-F)ppy]₃ afforded the cyclized product **245** in 36% yield with a 5:1 d.r. However, subsequent chiral HPLC analysis revealed that the major diastereomer was obtained with essentially no enantioenrichment (≈1:1 e.r.), indicating that the transformation is not enantioselective under these conditions. This outcome is consistent with inefficient coordination among the Lewis acid, the Feng ligand, and the substrate. In addition, the single [2+2] dimer **255** was formed in 48% yield. The formation of the single [2+2] product **255** further implies that the triplet sensitization required for excitation of the indole component demands an energy input exceeding 59.6 kcal/mol (*Scheme* 72).

Table 10. Enantioselective conditions optimisation.



243 245 254

Entry	Photocatalyst	Conv.	**245**	**254**	e.r trans(cis)
1	$Ir[(5\text{-}CF_3)ppy]_3$	<5%	0	0	-
2	$Ir[dFppy]_3$	100	42	51	53:47(62:38)
3	$Ir[(5\text{-}CF_3,4'\text{-}tBu)ppy]_3$	<5%	0	0	-
4	$Ir(ppy)_3$	<10%	<5%	<5%	-
5	$Ir[(p\text{-}^tBu)ppy]_3$	<10%	<5%	<5%	-
6	$Ir[dF(CF_3)ppy]_2(MeCN)_2PF_6$	<10%	<5%	<5%	-
7	FlvPic	<10%	<5%	<5%	-

Further investigations of the enantioselective variant are summarised in *Table 10*. When $Ir[(5\text{-}CF_3)ppy]_3$ was employed as the photocatalyst in the presence of the Feng ligand (Entry 1), no conversion was observed. By contrast, in the absence of the Feng ligand the same system delivered the cyclized product **245** in 33% yield, suggesting that the Lewis acid-Feng ligand complex is sufficiently stable but does not engage effectively with the substrate. As a consequence, the triplet energy of the substrate is unlikely to be lowered, thereby suppressing productive reactivity under these conditions.

When $Ir(dFppy)_3$ was used as the photocatalyst (Entry 2), the outcome was broadly comparable to that obtained without the Feng ligand, affording **245** in 42% yield alongside 51% of the double [2+2] dimer **254**. Additional attempts to improve the enantioselective reaction by varying the photocatalyst were unsuccessful.

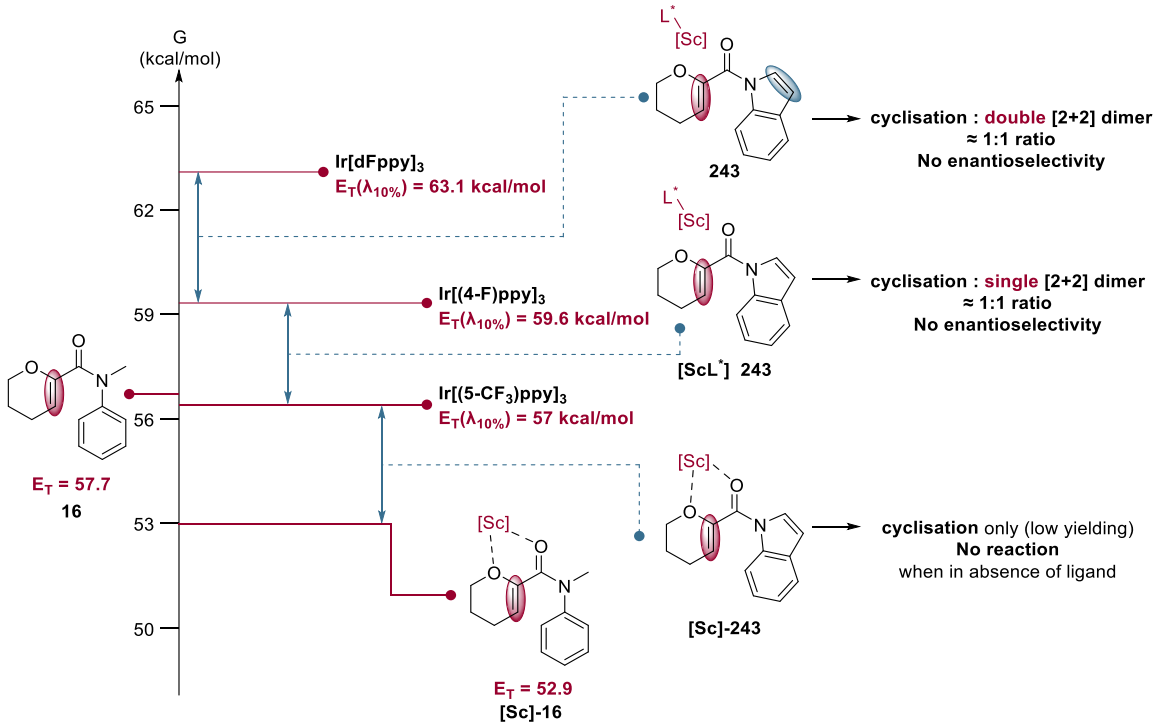


Figure 17. Information based on the project progress.

The principal findings of this project are summarised in *Figure 17*. The calculated triplet energy of the Lewis acid-coordinated substrate, **[Sc]-16**, was 52.9 kcal/mol. Experimentally, irradiation of substrate **243** with Ir[(5-CF_3)ppy]$_3$ led exclusively to the cyclized product **245** in the presence of the Lewis acid, whereas no reactivity was observed in its absence. This behaviour is consistent with **243** possessing a triplet energy comparable to that of **16** (DFT calculated as 57.7 kcal/mol), such that the Lewis acid coordination is required to lower the effective triplet energy into a range accessible to the photocatalyst. Notably, these results also suggest that strong substrate-Lewis acid coordination disfavors dimerization: under Ir[(5-CF_3)ppy]$_3$/Sc(OTf)$_3$ conditions, no single [2+2] dimer was detected.

When treated with [Ir(4-F)ppy]$_3$ as the photocatalyst in the present of Lewis acid and Feng ligand, single [2+2] dimer **255** was observed. This further could be explained as the Lewis acid-Feng ligand complex did not coordinate with substrate which promoted [2+2] dimerization. The further investigation verified this assumption. When treated with Ir(dFppy)$_3$ as the photocatalyst, no matter in the present of Lewis acid and Feng ligand or not, it results in

both cyclized product **245** and double [2+2] dimer **254**. Since the triplet energy of the photocatalyst is high enough to promote 6π cyclization without the Lewis acid, the 6π cyclization and dimerization are competing.

When $[Ir(4\text{-}F)ppy]_3$ was employed as the photocatalyst in the presence of both the Lewis acid and the Feng ligand, formation of the single [2+2] dimer **255** was observed. This outcome can be rationalised by inefficient engagement of the substrate with the Lewis acid-Feng ligand complex, such that substrate activation is not achieved and intermolecular [2+2] dimerization becomes competitive. Subsequent experiments were consistent with this interpretation. By contrast, when $Ir(dFppy)_3$ was used as the photocatalyst, both the cyclized product **245** and the double [2+2] dimer **254** were formed irrespective of whether the Lewis acid and Feng ligand were present. Given the higher triplet energy of $Ir(dFppy)_3$, sensitization of the indole core in the substrate can occur without the Lewis acid coordination; consequently, intramolecular 6π cyclization and intermolecular dimerization proceed in competition.

4.3 Project Summary

Overall, these results highlight that achieving enantioselectivity will require a reaction design in which the substrate is tightly bound within a Lewis acid-Feng ligand complex while triplet sensitization is sufficiently selective to suppress competing intermolecular [2+2] dimerization.

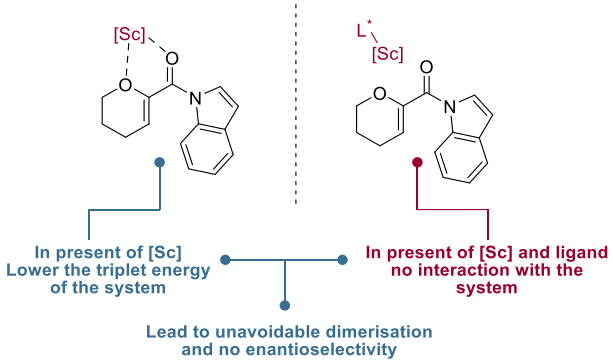
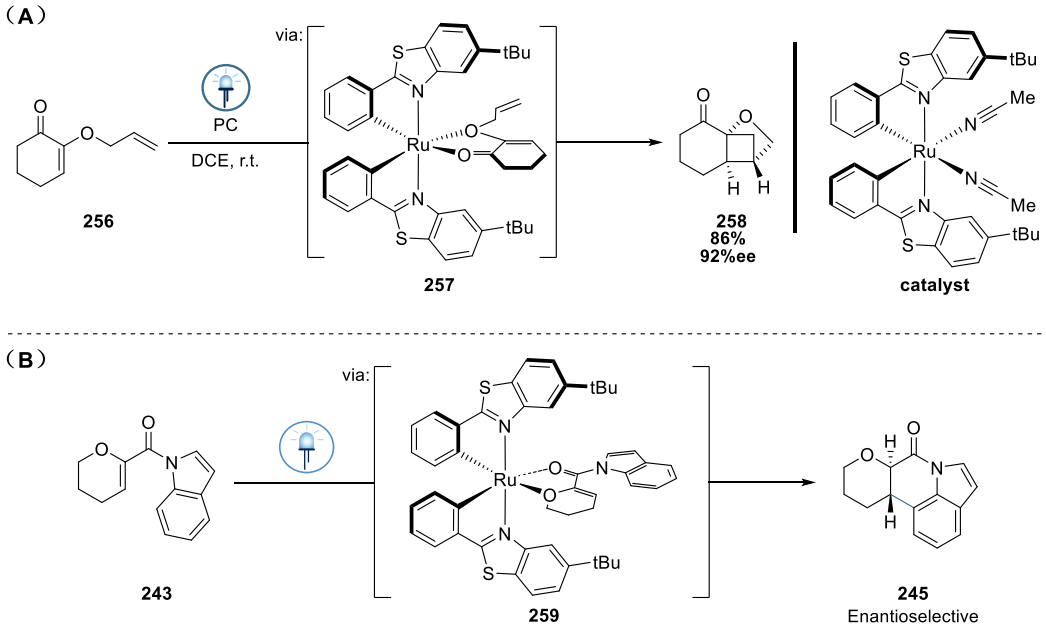


Figure 18. Summary of the project.

Improved enantioselectivity might, in principle, be achieved through further ligand optimisation. However, given the time already invested, none of the primary objectives of this project were met. Moreover, indiscriminate ligand screening was considered unjustified, as our results indicate that competitive [2+2] dimerization is difficult to suppress under the current reaction manifold. Accordingly, the project was discontinued. Nevertheless, these studies provided useful insight into the triplet-energy requirements of *N*-acylated indoles, as inferred from the reaction outcomes obtained across the catalyst and the Lewis acid survey.



Scheme 73. An alternative approach toward enantioselective reaction by applying a enantioenriched photocatalyst.

An alternative approach to asymmetric induction may involve the use of a chiral photocatalyst, as illustrated in *Scheme 73(A)*. In the reported study, substrate **256** forms a

coordinated intermediate **257**, which undergoes intramolecular [2+2] cycloaddition upon direct photoactivation, delivering the product in high yield with excellent enantioselectivity.[85] By analogy, applying a similar catalytic platform to N-acylated indoles may provide a viable route to enantioselective 6π cyclization.

Experimental Details and Characterisation

General Information

Compound names and atom numbers

Systematic names for all compounds were generated in ChemDraw Professional (version 25); the atom-numbering scheme used for NMR assignment is *arbitrary* and does not follow any particular convention.

Reaction conditions

Flame-dried or oven dried glassware was used for reactions requiring moisture-sensitive reagent. Room temperature refers to 20-25 °C. Temperatures of 0 °C were obtained using an ice/water bath. Temperatures of −78 °C were obtained using a dry ice/acetone bath. Reflux and heating conditions were obtained using a Drysyn® heating block or an oil bath equipped with a thermometer where the reported temperature refers to the temperature of the Drysyn® block or oil bath.

Solvents, reagents

Anhydrous MeCN and CH_2Cl_2 was obtained using an MBraun SPS-5 solvent purifier. Water was purified using a PURELAB Chorus 1 Complete system. Other solvents and reagents were used directly as received froma commercial suppliers or prepared according to literature procedures as specified.

Chromatography

Flash column chromatography was performed on Geduran Si 60 for column chromatography (40-63 μm particle size) or Millipore Aluminium oxide 90 standardised for column chromotographic adsorption analysis according to Brockmann (basic, activity stage I). Thin-layer chromatography was performed on Supelco TLC Silica gel 60 F_{254} or Alugram Alox N / UV_{254} pre-coated (0.2 mm) aluminium plates. Visualisation was achieved under ultraviolet

(UV) light (λ_{max} = 254 nm) or by staining with aqueous potassium permanganate or ethanolic vanillin solutions.

NMR Spectroscopy

NMR spectra were recorded on Bruker Avance spectrometers at room temperature in the deuterated solvent stated and are referenced to the residual non-deuterated solvent peak. Chemical shifts are quoted in ppm with signal splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), hept. (heptet), and multiplet (m). The abbreviation br. denotes broad. Coupling constants, J, are measured to the nearest 0.1 Hz and are presented as observed. Mnova (version 15) was used for processing, assigning and viewing NMR data.

Mass Spectrometry

Accurate masses (HRMS) were performed on an ACQUITY I-Class PLUS UPLC System (Waters, Milford, MA, USA) coupled to an ACQUITY RDa mass spectrometer (Waters, Milford, MA, USA) equipped with an ESI probe.

Infrared spectroscopy

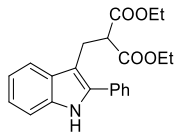
Fourier transform infrared (FTIR) spectra were recorded as thin films on a Tensor 27 FTIR spectrometer equipped with a diamond attenuated total reflectance (ATR) absorption module. Only selected maximum absorbances (ν_{max}) of the most intense peaks are reported (cm^{-1}).

Photoreactor

The photochemical equipment set up used paper cassettes and instruments equipped with Kessil® PR160L 427 nm lamps or PR160 440 nm LED lamps as light source. A water jacket cooling bath or nitrogen colling were equipped inside to maintain room temperature.

Precursors

diethyl 2-((2-phenyl-1H-indol-3-yl)methyl)malonate, 63



According to the procedure of You:[56] A 200 mL round bottom flask equipped with a magnetic stirring bar was added with **66** (2.75 g, 11.0 mmol, 1.1 equiv.) in Et_2O (50.0 mL). Dimethyl malonate (1.5 mL, 10.0 mmol, 1.0 equiv.) was added. Then ethyl propiolate (1.1 mL, 11.0 mmol, 1.1 equiv.) was added quickly. The reaction mixture was stirred overnight at room temperature. The mixture was quenched with water (20 mL) then was extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over $MgSO_4$, and the solvent was removed under vacuum. The concentrated crude product was purified by column chromatography (silica gel, CH_2Cl_2: pentane = 1: 1) to give the desired product as a pale yellow solid (2.92g, 80%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (1H, s), 7.65 (1H, d, *J* = 7.8 Hz), 7.62 – 7.55 (2H, m), 7.46 (2H, t, *J* = 7.6 Hz), 7.41 – 7.36 (1H, m), 7.36 – 7.30 (1H, m), 7.26 – 7.09 (2H, m), 4.01 (3H, qq, *J* = 10.8, 7.1 Hz), 3.77 (1H, t, *J* = 7.7 Hz), 3.61 (2H, d, *J* = 7.4 Hz), 1.09 (6H, t, *J* = 7.1 Hz)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.2, 135.8, 135.4, 133.0, 128.8, 128.1, 127.9, 122.4, 119.8, 119.1, 110.9, 108.7, 61.3, 52.7, 24.0, 13.9

All data are in accordance with those in literature.[56]

2-iodoprop-2-en-1-ol, 68



According to the procedure of Burton[61]*:* A 500 mL round bottom flask equipped with a stirring bar was charged with sodium iodide (14.38 g, 96.0 mmol, 1.2 equiv.) in MeCN (160.0 mL). The reaction was cooled to 0 °C. Trimethylsilyl chloride (12.2 mL, 96.0 mmol, 1.2 equiv.) was added slowly and reaction mixture was stirred for 15 mins at this temperature. H_2O (0.9 mL, 24.0 mmol, 1.0 equiv.) was added and followed by the addition of propargyl alcohol (4.6 mL, 80.0 mmol, 1.0 equiv.) dropwise. The reaction mixture was warmed up to room temperature and stirred for 6 hrs. sat. $NaHCO_3$ solution (200 mL) was added to the reaction, and the aqueous phase was extracted with Et_2O three times. The combined organics were washed with NaOH (1.0 M, 500 mL) and sat. $Na_2S_2O_3$ solution (500 mL). After the washing, the mixture was dried over $MgSO_4$, and the solvent was removed under vacuum. The residue was purified by flash column chromatography (silica gel, Et_2O: pentane = 1: 10) to afford 2-iodoprop-2-en-1-ol **68** as a pink oil (7.17g, 39.2 mmol, 49%)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.43 - 6.35 (1H, m), 5.88 - 5.81 (1H, m), 4.16 (2H, t, J = 1.5 Hz), 2.40 - 2.32 (1H, m,)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 124.5, 110.5, 71.0

All data are in accordance with those in literature.[61]

3-bromo-2-iodoprop-1-ene, 69



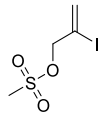
According to the procedure of Aggarwal[62]*:* NBS (11.2 g, 63.0 mmol, 1.4 equiv.) was dissolved in DCM (16.0 mL). The reaction was cooled to -20 °C, and Me_2S (4.9 mL, 67.0 mmol, 1.5 equiv.) was added dropwise. The reaction was stirred for 20 mins at this temperature before a solution of 2-iodoprop-2-en-1-ol **68** (8.24 g, 45.0 mmol, 1.0 equiv.) in DCM (4.0 mL) was added. The result mixture was warmed up to room temperature and stirring for 3 hrs. After the reaction was completed, pentane (20.0 mL) was added to dilute the reaction. Then the reaction was poured into ice cold water (ca., 15 mL). The organic phase was washed with brine then dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, 100% pentane) to afford the desired product (7.41 g, 29.7 mmol, 66%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.45 (1H, dt, *J* = 2.0, 1.3 Hz), 5.88 (1H, dd, *J* = 2.0, 0.6 Hz), 4.22 (2H, dd, *J* = 1.3, 0.6 Hz)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 129.8, 102.9, 41.4

All data are in accordance with those in literature.[62]

2-iodoallyl methanesulfonate, 70



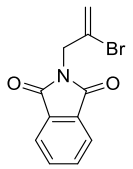
According to the procedure of Ollivier:[63] A solution of 2-iodoprop-2-en-1-ol **68** (0.99 g, 5.4 mmol, 1.0 equiv.)in CH_2Cl_2 (13.5 mL, 0.4 M)was cooled to 0 °C and triethylamine (1.13 mL, 8.1 mmol, 1.5 equiv.) was added under argon atmosphere. Methanesulfonyl chloride (0.47 mL, 6.0 mmol, 1.1 equiv.) was added dropwise over 5 mins and the reaction was stirred at 0 °C for 2 hrs. After the reaction complete, the mixture was quenched with water (30 mL). The aqueous phase was extracted with Et_2O (3 x 20 mL) and then washed with sat.NH_4Cl solution (30 mL), brine (30 mL), and dried with $MgSO_4$. The solvent was removed under reduced pressure. The product was purified by flash column chromatography (silica gel, EtOAc: pentane = 1: 5) to yield a pale red oil (1.30 g, 93%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.52 (1H, dt, J = 2.1, 1.5 Hz), 6.04 (1H, dt, J = 2.0, 0.9 Hz), 4.77 (2H, dd, J = 1.5, 0.9 Hz), 3.08 (3H, s)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 129.6, 99.2, 75.5, 38.6

All data are in accordance with those in literature.[63]

2-(2-bromoallyl)isoindoline-1,3-dione, S1



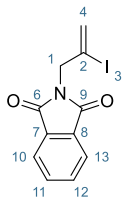
According to the procedure of Liu:[86] Potassium phthalimide (5.56 g, 30.0 mmol,1.2 equiv.) was added in to a solution of 2,3-dibromoprop-1-ene (5.00 g, 25.0 mmol,1.0 equiv.) in DMF (50.0 mL) at room temperature. The resulting mixture was stirred for 18 hrs at this temperature until a brown precipitate was formed. CH_2Cl_2 (50 mL) was added to the mixture, and the mixture was poured into H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2 three times. The combined organic was then washed with NaOH solution (0.2 M, 50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatographic (silica gel, 50% EtOAc in pentane) to give the desired product 2-(2-bromoallyl)isoindoline-1,3-dione **S1** in 90% (6.0 g, 22.5 mmol) yield as an off-white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 - 7.82 (2H, m), 7.80 - 7.69 (2H, m), 5.84 (1H, dd, *J* = 2.3, 1.1 Hz), 5.62 (1H, dd, *J* = 2.4, 0.9 Hz), 4.54 (2H, q, *J* = 1.0 Hz)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 167.5, 134.4, 132.0, 126.3, 123.8, 119.2, 45.4

All data are in accordance with those in literature.[86]

2-(2-iodoallyl)isoindoline-1,3-dione, S2



According to the procedure of Liu:[86] Potassium phthalimide (4.46 g, 24.0 mmol,1.2 equiv.) was added in to a solution of 3-bromo-2-iodoprop-1-ene **69** (4.94 g, 20.0 mmol,1.0 equiv.) in DMF (44.0 mL) at room temperature. The resulting mixture was stirred for 18 hrs at this temperature until a brown precipitate was formed. CH_2Cl_2 (50.0 mL) was added to the mixture, and the mixture was poured into H_2O (50.0 mL). The aqueous was extracted with CH_2Cl_2 three times. The combined organic was then washed with NaOH solution (0.2 M, 50.0 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatographic (silica gel, 50% EtOAc in pentane) to give the desired product 2-(2-iodoallyl)isoindoline-1,3-dione **S2** in a yield of 82% (5.14 g, 16.4 mmol) as an off-white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (2H, dd, *J* = 5.5, 3.1 Hz, H-10, H-13), 7.80 - 7.71 (2H, m, H-11, H-12), 6.29 (1H, q, *J* = 1.6 Hz, 4'), 5.91 (1H, dt, *J* = 2.3, 1.2 Hz, 4''), 4.53 (2H, t, *J* = 1.4 Hz, H-1)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 167.4 (C-6, C-9), 134.4 (C-11, C-12), 132.0 (C-7, C-8), 127.6 (C-4), 123.8 (C-10, C-13), 102.3 (C-2), 49.1 (C-1)

HRMS (ESI) *m/z* calcd. for $C_{11}H_9INO_2$ $[M+H]^+$: 313.9673; found: 313.9664

2-bromoprop-2-en-1-amine, 138



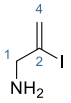
According to the procedure of Bach:[87] Hydrazine monohydrate (0.8 mL, 16.0 mmol, 2.0 equiv.) was added in to a suspension of 2-(2-bromoallyl)isoindoline-1,3-dione **S1** (2.13 g, 8.0 mmol, 1.0 equiv.) in ethanol (28.0 mL). The result mixture was heated to reflux for 1 hr. A HCl solution (2.0 M, 24.0 mL) was added to the reaction and heated for one more hour. The reaction mixture was cooled to 0 °C and phthalic hydrazide was removed under filtration. The ethanol was removed under vacuum, and the solid residue was redissolved in a NaOH solution (2.0 M, 40.0 mL). The solution was extracted with Et_2O three times, and the combined organic phase was dried over $MgSO_4$. The solvent was removed under reduced pressure to give 2-bromoprop-2-en-1-amine **138** in 68% yield as a yellow oil (737 mg, 5.4 mmol).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80 – 5.73 (1H, m), 5.49 – 5.43 (1H, m), 3.46 (3H, dd, J = 2.1, 1.1 Hz)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 136.8, 115.2, 51.1

All data are in accordance with those in literature.[88]

2-iodoprop-2-en-1-amine, S3



According to the procedure of Bach:[87] Hydrazine monohydrate (0.8 mL, 16.0 mmol, 2.0 equiv.) was added in to a suspension of 2-(2-iodoallyl)isoindoline-1,3-dione **S2** (2.50 g, 8.0 mmol, 1.0 equiv.) in ethanol (28.0 mL). The result mixture was heated to reflux for 1 hr. A HCl solution (2.0 M, 24.0 mL) was added to the reaction and heated for 1 more hr. The reaction mixture was cooled to 0 °C and phthalic hydrazide was removed under filtration. The ethanol was removed under vacuum, and the solid residue was redissolved in a NaOH solution (2.0 M, 40.0 mL). The solution was extracted with Et_2O three times, and the combined organic phase was dried over $MgSO_4$. The solvent was removed under reduced pressure to give 2- iodoprop-2-en-1-amine **S3** in 63% (917 mg, 5.01 mmol) yield as a pink oil.

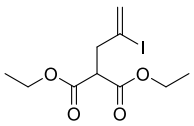
^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.20 (1H, q, *J* = 1.6 Hz, 4'), 5.74 (1H, dt, *J* = 1.8, 0.9 Hz, 4''), 3.41 - 3.36 (2H, m, H-1)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 124.0 (C-4), 115.8 (C-2), 54.8 (C-1)

HRMS (ESI) *m/z* calcd. for C_3H_7IN $[M+H]^+$: 183.9618; found: 183.9637.

FTIR (neat) ν/cm^{-1} = 1620, 1432, 903, 662, 642

diethyl 2-(2-iodoallyl)malonate, 72



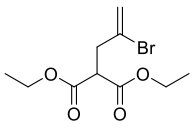
According to the procedure of Brian:[89] Diethyl malonate (1.7 mL, 11.3 mmol, 1.0 equiv.) was added in to a suspension of NaH (60% w/w dispersion in mineral oil) (500 mg, 12.5 mmol, 1.1 equiv.) in DMF (57.0 mL) at 0 °C. The reaction mixture was heated to 50 °C and stirred for 1 hr. Then The solution was cooled to 0 °C and 3-bromo-2-iodoprop-1-ene **69** (2.8 g, 11.3 mmol, 1.0 equiv.) was added dropwise over 15 mins. Then the reaction was heated to 40 °C. After one hour, the reaction was quenched with sat. NH_4Cl solution and the aqueous phase was extracted with Et_2O three times. The combined organics were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc: pentane = 1: 40) to give the desired product as colourless oil (2.07 g, 6.1 mmol, 54%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.12 (1H, q, *J* = 1.3 Hz), 5.76 (1H, d, *J* = 1.7 Hz), 4.26 - 4.13 (4H, m), 3.7 (1H, t, *J* = 7.5 Hz), 2.97 (2H, ddd, *J* = 7.6, 1.3, 0.5 Hz), 1.27 (6H, t, *J* = 7.2 Hz)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 168.1, 128.8, 105.8, 61.8, 51.7, 44.3, 14.2

All data are in accordance with those in literature.[90]

diethyl 2-(2-bromoallyl)malonate, S4



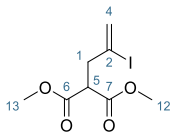
According to the procedure of Brian:[89] Diethyl malonate (1.7 mL, 11.3 mmol, 1.0 equiv.) was added in to a suspension of NaH (60% w/w dispersion in mineral oil) (500 mg, 12.5 mmol, 1.1 equiv.) in DMF (57.0 mL) at 0 °C. The reaction mixture was heated to 50 °C and stirred for 1 hr. The solution was cooled to 0 °C and 2,3-dibromoprop-1-ene (1.4 mL, 11.3 mmol, 1.0 equiv.) was added dropwise over 15 mins. Then the reaction was heated to 40 °C. After one hour, the reaction was quenched with sat. NH_4Cl solution and the aqueous phase was extracted with Et_2O three times. The combined organics were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc: pentane = 1 : 20) to give the desired product as colourless oil (1.4 g, 5.2 mmol, 44%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.76 – 5.64 (1H, m), 5.48 (1H, d, *J* = 1.9 Hz), 4.21 (4H, qd, *J* = 7.2, 1.1 Hz), 3.78 (1H, t, *J* = 7.5 Hz), 3.02 (2H, dd, *J* = 7.5, 1.1 Hz), 1.27 (6H, t, *J* = 7.1 Hz)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 168.3, 129.6, 119.8, 61.9, 50.8, 40.5, 14.2

All data are in accordance with those in literature.[91]

dimethyl 2-(2-iodoallyl)malonate, S5



According to the procedure of Brian:[89] Dimethyl malonate (0.46 mL, 4.0 mmol, 1.0 equiv.) was added in to a suspension of NaH (60% w/w dispersion in mineral oil) (176 mg, 4.4 mmol, 1.1 equiv.) in DMF (20.0 mL) at 0 °C. The reaction mixture was heated to 50 °C and stirred for 1 hr. Then The solution was cooled to 0 °C and 2-iodoallyl methanesulfonate **70** (1.05 g, 4 mmol, 1.0 equiv.) was added dropwise over 15 mins. Then the reaction was heated to 40 °C. After one hour, the reaction was quenched with sat. NH_4Cl solution and the aqueous phase was extracted with Et_2O three times. The combined organics were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc: pentane = 1: 40) to give the desired product as colourless oil (268 mg, 0.9 mmol, 22%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.13 (1H, q, *J* = 1.3 Hz, 4''), 5.79 – 5.73 (1H, m, 4'), 3.85 – 3.68 (7H, m, H-5, H-12, H-13), 2.98 (2H, ddd, *J* = 7.6, 1.3, 0.6 Hz, H-1)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 168.52 (C-6, C-7), 129.03 (C-4), 105.58 (C-2), 52.90 (C-12, C-13), 51.49 (C-5), 44.42 (C-1)

HRMS (ESI) m/z calcd. for $C_8H_{12}IO_4$ $[M+H]^+$: 298.9775; found: 298.9766

FTIR (neat) ν/cm^{-1} = 2955, 1738, 1677, 1610, 1437, 1342, 1239, 1155, 1093, 1027, 912, 650

2-iodo-3-methylbut-2-en-1-ol, S6



According to the procedure of Cai:[92] To a solution of 3-methylbut-2-enal (2.9 mL, 30.0 mmol, 1.0 equiv.) in a 1:1 mixture of THF and Water (100.0 mL). K_2CO_3 (5.0 g, 36.0 mmol, 1.2 equiv.), I_2 (11.42 g, 45.0 mmol, 1.5 equiv.) and DMAP (735 mg, 6.0 mmol, 0.2 equiv.) were added. The reaction was stirred for 3 hrs before diluted with EtOAc and washed with sat.$Na_2S_2O_3$ (ca., 50 mL). and HCl (ca., 50 mL, 1 M). The mixture was extracted with EtOAc for three times and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the intermediate was used in next step without further purification.

The resulting intermediate was dissolved in 15 mL MeOH. Then, $NaBH_4$ (1.70 g, 45.0 mmol, 1.5 equiv.) was added in portions at 0 °C. After the reaction completed, the mixture was quenched with HCl (ca., 10 mL, 1.0 M) and was extracted with EtOAc for three times. The combined organics were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified through flash column chromatography on silica gel to obtain the desired product **S6** as yellow oil (800 mg, 3.8 mmol, 12.6% in 2 steps).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.35 (2H, d, *J* = 6.1 Hz), 1.97 (3H, s), 1.93 (3H, s)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 140.6, 102.5, 68.0, 31.7, 20.0

All data are in accordance with those in literature.[93]

1-bromo-2-iodo-3-methylbut-2-ene, S7



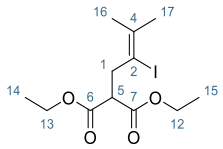
According to the procedure of Cai:[92] To a solution of **S6** (800 mg, 4 mmol, 1.0 equiv.) in Et_2O (8.0 mL, 0.5 M). PBr_3 (190 μL, 2.0 mmol, 0.5 equiv.) was added at 0 °C. The reaction was stirred at this temperature for 30 mins and stirred at room temperature for 30 more mins. The reaction was quenched with brine and then was extracted with Et_2O three times. The combined organics were washed with sat.$NaHCO_3$ and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was pure enough for next step (895 mg, 3.26 mmol, 81%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (2H, s), 4.76 (3H, s), 4.69 (3H, s)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 144.8, 94.2, 41.9, 31.9, 19.5

All data are in accordance with those in literature.[92]

diethyl 2-(2-iodo-3-methylbut-2-en-1-yl)malonate, S8



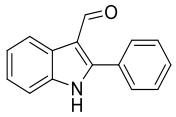
According to the procedure of Brian:[89] Diethyl malonate (0.46 mL, 3.0 mmol, 1.0 equiv.) was added in to a suspension of NaH (60% w/w dispersion in mineral oil) (144 mg, 3.3 mmol, 1.1 equiv.) in DMF (20.0 mL) at 0 °C. The reaction mixture was heated to 50 °C and stirred for 1 hr. Then The solution was cooled to 0 °C and 1-bromo-2-iodo-3-methylbut-2-ene **S7** (822 mg, 3 mmol, 1.0 equiv.) was added dropwise over 15 mins. Then the reaction was heated to 40 °C. After 1 hr, the reaction was quenched with sat. NH_4Cl solution and the aqueous phase was extracted with Et_2O three times. The combined organics were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, EtOAc: pentane = 1: 40) to give the desired product as colourless oil (354 mg, 1.0 mmol, 33%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.18 (4H, qd, *J* = 7.2, 2.9 Hz, 12", 13'), 3.84 (1H, t, *J* = 7.6 Hz, H-5), 3.15 – 3.06 (2H, m, H-1), 1.92 (3H, d, *J* = 1.1 Hz, H-16), 1.87 (3H, s, H-17), 1.26 (6H, t, *J* = 7.1 Hz, H-14, H-15)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 168.7 (C-6, C-7), 140.0 (C-4), 97.2 (C-2), 61.5 (C-12, C-13), 52.1 (C-5), 40.2 (C-1), 32.0 (C-16), 20.0 (C-17), 14.2 (C-14, C-15)

HRMS (ESI) *m/z* calcd. for $C_{12}H_{20}IO_4$ $[M+H]^+$: 355.0401; found: 355.0399

2-phenyl-1H-indole-3-carbaldehyde, 133



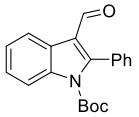
According to the procedure of Bonchio:[76] $POCl_3$ (1.7 mL, 18.6 mmol, 1.2 equiv.) was added dropwise to DMF (5.0 mL) at 0 °C. The reaction mixture was stirred 30 mins at this temperature. A solution of 2-phenyl-1H-indole (3.0 g, 15.5 mmol, 1.0 equiv.) in DMF (5.0 mL) was added slowly to the reaction mixture. The reaction was warmed up to 40 °C and stirred for 1 hr. 10 g of ice and NaOH solution (5.0 M, 30.0 mL) was added into the reaction mixture. The resulting mixture was heated up to 90 °C for 1 hr before cooled to room temperature. An addition of 10 g ice was added then a white precipitate was crashed out. The precipitate was filtered and washed with water and dried on the filter overnight. 2-phenyl-1H-indole-3-carbaldehyde **133** was yielded in 95% (3.27 g, 14.8 mmol) as a white solid.

^{1}H NMR (DMSO, 400 MHz) δ 12.38 (1H, s), 9.98 (1H, s), 8.26 - 8.19 (1H, m), 7.82 - 7.74 (2H, m), 7.64 - 7.56 (3H, m), 7.55 - 7.48 (1H, m), 7.27 (2H, dtd, J = 18.6, 7.2, 1.3 Hz)

^{13}C NMR (DMSO, 101 MHz) δ 186.0, 149.6, 136.4, 130.4, 130.3, 130.3, 129.4, 126.3, 124.2, 122.9, 121.5, 114.0, 112.5

All data are in accordance with those in literature.[94]

tert-butyl 3-formyl-2-phenyl-1H-indole-1-carboxylate, 134



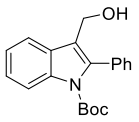
According to the procedure of Bonchio:[76] **133** (2.21 g, 10.0 mmol, 1.0 equiv.) and DMAP (122 mg, 1.0 mmol, 0.1 equiv.) were dissolved in CH_2Cl_2 (50 mL, 0.2 M). Then, di-*tert*-butyldicarbonate (3.28 g, 15 mmol, 1.5 equiv.) was added slowly at 0 °C. After the reaction completed, the mixture was quenched with HCl (10 mL, 4.0 M). The organic was washed with HCl (10 mL, 4.0 M), sat.$NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane : EtOAc = 95 : 5) to afford **134** as a white solid (3.06 g, 95%)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.72 (1H, s), 8.43 – 8.36 (1H, m), 8.26 – 8.19 (1H, m), 7.56 – 7.36 (7H, m), 1.27 (9H, s)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 188.3, 150.0, 149.3, 136.4, 131.1, 130.2, 129.4, 128.2, 126.1, 125.6, 124.9, 122.1, 119.9, 115.0, 85.1, 27.5

All data are in accordance with those in literature.[95]

tert-butyl 3-(hydroxymethyl)-2-phenyl-1H-indole-1-carboxylate, 132



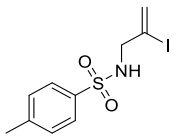
According to the procedure of Bonchio:[76] **134** (2.25 g, 7 mmol, 1.0 equiv.) was dissolved in MeOH (30 mL, 0.23 M). Subsequently, $NaBH_4$ (796 mg, 21 mmol, 3.0 equiv.) was added in portions (ca.,133 mg for each 30 mins). After the reaction completed, the mixture was quenched with water (20 mL) and was extracted with EtOAc three times. The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane : EtOAc = 4 : 1), affording the desired product **132** as a white solid (1.60g, 70%)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (1H, d, *J* = 8.3 Hz), 7.65 – 7.59 (1H, m), 7.37 – 7.28 (3H, m), 7.28 – 7.23 (3H, m), 7.22 – 7.16 (1H, m), 4.50 (2H, s), 1.13 (9H, s)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 150.2, 137.8, 136.7, 133.4, 129.8, 128.7, 128.0, 128.0, 124.9, 123.1, 119.7, 119.2, 115.4, 83.4, 55.9, 27.5

All data are in accordance with those in literature.[76]

_N_-(2-iodoallyl)-4-methylbenzenesulfonamide, 136

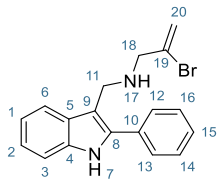


According to a modified procedure of Ihara:[96] To a solution of **70** (262 mg, 1.0 mmol, 1.0 equiv.) and *p*-toluenesulfonamide (206 mg, 1.2 mmol, 1.2 equiv.) in acetone (5 mL, 0.2 M), K_2CO_3 (415 mg, 3.0 mmol, 3.0 equiv.) was added. The reaction mixture was stirred under reflux for 16 hrs. The reaction was concentrated under reduced pressure. The residue was extracted with Et_2O and washed with brine. The organic was dried over $MgSO_4$. And concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, pentane : EtOAc = 9 : 1), affording the desired product **136** as a white solid (167 mg, 50%)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, 2H, *J* = 8.1 Hz), 7.30 (d, 2H, *J* = 8.1 Hz), 6.25 (d, 1H, *J* = 1.8 Hz), 5.89 (d, 1H, *J* = 1.8 Hz), 4.14 (d, 2H, *J* = 6.3 Hz), 2.42 (s, 3H)

All data are in accordance with those in literature.[96]

2-bromo-*N*-((2-phenyl-1H-indol-3-yl)methyl)prop-2-en-1-amine, 139



2-bromoprop-2-en-1-amine **138** (850 mg, 5.0 mmol, 2.0 equiv.) was syringed into a solution of 2-phenyl-1H-indole-3-carbaldehyde **133** (553 mg, 2.5 mmol, 1.0 equiv.) in MeOH (12.5 mL) under argon. The mixture was heated to 50 °C. The reaction was monitored with TLC. Once completed, the reaction was cooled to 0 °C and $NaBH_4$ (284 mg, 7.5 mmol, 3.0 equiv.) was added in portions. The reaction was warmed up to room temperature for another 3 hrs before quenched by H_2O (5.0 mL). The resulting mixture was extracted with EtOAc three times, and the combined organic was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexane) to afford the desired product in 96% (822 mg, 2.4 mmol) yield.

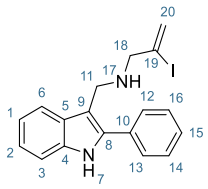
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.38 (1H, s, H-7), 7.84 (1H, d, *J* = 7.9 Hz, H-6), 7.78 – 7.69 (2H, m, H-13, H-17), 7.55 – 7.48 (2H, m, H-14, H-16), 7.47 – 7.36 (2H, m, H-3, H-15), 7.31 – 7.26 (1H, m, H-2), 7.26 – 7.21 (1H, m, H-1), 5.78 (1H, t, *J* = 1.3 Hz, 20''), 5.61 (1H, d, *J* = 1.7 Hz, 20'), 4.04 (2H, s, H-11), 3.59 (2H, s, H-18)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 136.2 (C-4), 135.9 (C-8), 133.8 (Ar/alkene), 132.7 (Ar/alkene), 129.2 (Ar/alkene), 128.9 (C-14, C-16), 128.2 (C-13, C-17), 128.0 (C-15), 122.5 (C-2), 120.0 (C-1), 119.1 (C-6), 118.0 (C-20), 111.0 (C-3), 57.4 (C-18), 41.9 (C-11)

HRMS (ESI) *m/z* calcd. for $C_{18}H_{17}BrN_2Na$ $[M+Na]^+$: 363.0467; found: 363.0466

FTIR (neat) ν/cm^{-1} = 3413, 3057, 1627, 1604, 1488, 1455, 1340, 1309, 1242, 1096, 953, 897, 766, 742

2-iodo-*N*-((2-phenyl-1H-indol-3-yl)methyl)prop-2-en-1-amine, S9



2-iodoprop-2-en-1-amine **S3** (823 mg, 4.5 mmol, 2.25 equiv.) was syringed into a solution of 2-phenyl-1H-indole-3-carbaldehyde **133** (443 mg, 2.0 mmol, 1.0 equiv.) in MeOH (10.0 mL) under argon. The mixture was heated to 50 °C. The reaction was monitored with TLC. Once completed, the reaction was cooled to 0 °C and $NaBH_4$ (378 mg, 10.0 mmol, 5.0 equiv.) was added in portions. The reaction was warmed up to room temperature for another 3 hrs before quenched by H_2O (5.0 mL). The resulting mixture was extracted with EtOAc three times, and the combined organic was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexane) to afford the desired product in 94% (728 mg, 1.9 mmol) yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (1H, s, H-7), 7.81 (1H, ddt, *J* = 7.6, 1.5, 0.8 Hz, H-6), 7.73 - 7.69 (2H, m, H-13, H-17), 7.52 - 7.46 (2H, m, H-14, H-16), 7.43 - 7.35 (2H, m, H-3, H-15), 7.23 (1H, ddd, *J* = 8.0, 7.1, 1.4 Hz, H-2), 7.18 (1H, ddd, *J* = 8.1, 7.0, 1.2 Hz, H-1), 6.19 (1H, q, *J* = 1.4 Hz, 20''), 5.84 (1H, dt, *J* = 1.5, 0.8 Hz, 20'), 3.96 (2H, s, H-11), 3.46 (2H, t, *J* = 1.1 Hz, H-18)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 136.3 (C-4), 135.9 (C-8), 132.8 (C-10), 129.3 (C-5), 129.1 (C-14, C-16), 128.3 (C-13, C-17), 128.1 (C-15), 126.5 (C-20), 122.6 (C-2), 120.1 (C-1), 119.3 (C-6), 113.6 (C-19), 111.1 (C-9), 111.0 (C-3), 61.1 (C-18), 41.9 (C-11)

HRMS (ESI) *m/z* calcd. for $C_{18}H_{18}IN_2$ $[M+H]^+$: 389.0509; found: 389.0500.

FTIR (neat) ν/cm^{-1} = 3414, 3056, 1615, 1488,1456, 1341, 1310, 1244, 1097, 1011, 908, 767, 742, 700

2-iodobenzenethiol, 214



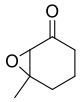
According to the procedure of Anselmi:[84] *O*-iodoaniline (2.19 g, 10.0 mmol, 1.0 equiv.) was added to a cold solution of HCl (37% w/w, 1.7 mL, 20.0 mmol, 2.0 equiv.) and ice (~2 g). A solution of $NaNO_2$ (0.69 g, 10.0 mmol, 1.0 equiv.) in water (2.0 mL) was cooled in an ice bath and added dropwise in to *O*-iodoaniline solution. During this process, the internal temperature of the solution should be controlled to 0 – 5 °C to form diazonium salt. After the addition, the solution of o-iodobenzenediazonium salt was added dropwise to a cold solution of potassium ethylxanthate (1.92 g, 12.0 mmol, 1.2 equiv.) in a mixture of water (2.5 mL) and ethanol (1.3 mL). The mixture was allowed to warm to room temperature carefully and stirring for 2 hrs. The reaction was extracted with Et_2O (20 mL) 3 times. The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The crude residue was refluxd with KOH (3.0 g, 53 mmol, 5.3 equiv.) in absolute ethanol (20 mL) for 16 hrs. The mixture was then neutralized with 10% HCl and was extracted with diethyl ether (20 mL) 3 times. The combined organics were dried over $MgSO_4$ and concentrated under reduce pressure. The crude residue was purified by flash column chromatography (silica gel, 1% Et_2O in pentane) to afford **214** (1.2 g, 5.1 mmol, 51%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (1H, dd, *J* = 7.9, 1.4), 7.40 (1H, dd, *J* = 7.9, 1.6), 7.21 (1H, td, *J* = 7.6, 1.4), 6.81 (1H, td, *J* = 7.7, 1.5 Hz), 4.14 (1H, s)

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8, 138.4, 128.9, 128.6, 126.7, 98.3

All data are in accordance with those in literature.[97]

3-methyl-2-morpholinocyclohex-2-en-1-one, 213

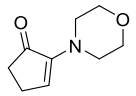


According to the procedure of Hodgson:[98] 3-methyl-2-cyclohexenone (2.20 g, 20.0 mmol, 1.0 equiv.) was added to a round-bottomed flask containing a stirrer bar, and dissolved in 20.0 mL methanol. The flask was cooled in an ice bath with stirring for 5 mins, before aqueous H_2O_2 (34.5 – 36.5 % w/w) (5.2 mL, 60.0 mmol, 3.0 equiv.) was added dropwise to the solution. After addition was complete, NaOH solution (3.0 M, 1.3 mL, 3.9 mmol, 0.2 equiv.) was added dropwise at a rate that ensured the temperature of the solution did not exceed 10 °C. The mixture was then allowed to warm to room temperature over a two-hour period, before it was quenched using a mixture of 50 mL brine, and 50 g ice. The product was extracted using 3 x 30 mL portions dichloromethane, dried over $MgSO_4$, filtered and finally concentrated *in vacuo*. This yielded a pale orange oil (2.1915 g, 17.4 mmol, 87 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.07 (s, 1H), 2.48 (dt, *J* = 17.3, 4.4 Hz, 2H), 2.12 (dt, *J* = 14.1, 3.6 Hz, 1H), 2.08 – 1.80 (m, 3H), 1.72 – 1.58 (m, 1H), 1.45 (s, 3H).

All data are in accordance with those in literature.[99]

2-morpholinocyclopent-2-en-1-one, 223



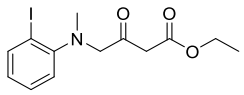
According to the procedure of Wrobleski:[100] A mixture of cyclohexane-1,2-dione (981 mg, 10.0 mmol, 1.0 equiv.) and morpholine (1.1 mL, 1.1 g, 12.5 mmol, 1.25 equiv.) in toluene (25.0 mL, 0.4 M) were heated to reflux under Dean–Stark conditions for 12 hrs. After cooling to room temperature, the orange liquid thus obtained was decanted from the viscous brown oil coating the bottom of the flask and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 50% EtOAc in pentane) to afford **223** (370 mg, 2.21 mmol, 21%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (1H, t, *J* = 3.1), 3.81 – 3.74 (4H, m), 3.10 – 3.03 (4H, m), 2.55 – 2.47 (2H, m), 2.45 – 2.39 (2H, m)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 205.3, 150.9, 133.9, 66.7, 48.6, 35.3.

All data are in accordance with those in literature.[100]

Ethyl 4-((2-iodophenyl)(methyl)amino)-3-oxobutanoate, 232

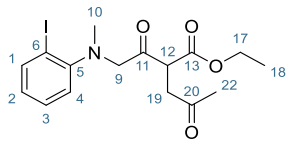


According to the procedure of Smith:[55] To a stirred mixture of 2-iodo-*N*-methylaniline (2.43 g, 10.4 mmol, 1.0 equiv.), sodium hydrogencarbonate (1.75 g, 20.8 mmol, 2.0 equiv.) and sodium iodide (3.13 g, 20.9 mmol, 2.0 equiv.) in MeCN (21 mL, 0.5 M), ethyl 4-chloroacetoacetate (3.0 mL, 21 mmol, 2.0 equiv.) was added in one portion at room temperature. The reaction mixture was heated to 75 °C for 18 hrs with stirring. After this time, the reaction mixture was allowed to cool to room temperature before adding triethylamine (4.4 mL, 32.0 mmol, 3.0 equiv.) in one portion and stirring for a further 30 min. The reaction mixture was concentrated *in vacuo*, and the crude residue thus obtained was dissolved in EtOAc (40 mL) and washed with sodium thiosulfate (sat. aq., 20 mL) and water (20 mL). The aqueous washings were extracted with EtOAc two times, and the combined organic extracts were washed with brine (60 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified twice by flash column chromatography (silica gel, 5% EtOAc in pentane) to afford **232** (1.44 g, 3.99 mmol, 38%) as a viscous pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 (1H, dd, *J* 7.9, 1.5), 7.31 (1H, ddd, *J* 8.0, 7.3, 1.5), 7.14 (1H, dd, *J* 8.0, 1.6), 6.81 (1H, ddd, *J* 7.8, 7.3, 1.6), 4.17 (2H, q, *J* 7.1), 3.90 (2H, s), 3.65 (2H, s), 2.79 (3H, s), 1.25 (3H, t, *J* 7.1)

All data are in accordance with those in literature.[55]

Ethyl 2-(*N*-(2-iodophenyl)-*N*-methylglycyl)-4-oxopentanoate, 231



To a stirred mixture of **232** (1.85 g, 5.0 mmol, 1.0 equiv.), sodium hydrogencarbonate (863.3 mg, 10.0 mmol, 1.0 equiv.) and sodium iodide (1.54 g, 10.0 mmol, 2.0 equiv.) in MeCN (25.0 mL, 0.2 M) at room temperature was added chloroacetone (0.82 mL, 10 mmol, 1.0 equiv.) in one portion. The reaction mixture was heated to 75 °C for 18 hrs with stirring. After cooling the reaction mixture to room temperature, 15 mL water was added into the reaction. The aqueous phase was extracted with 15 mL Et_2O three times. The combined organics were concentrated under reduce pressure. The crude residue was purified by flash column chromatography (silica gel, 100% DCM) to afford **231** (652 mg, 1.56 mmol, 31%) as a pale-yellow oil.

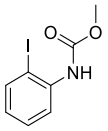
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1H, dd, *J* = 7.9, 1.5, H-1), 7.34 – 7.26 (2H, m, H-3), 7.18 (1H, dd, *J* = 8.0, 1.6, H-4), 6.82 – 6.74 (1H, m, H-2), 4.30 – 4.25 (1H, m, H-12), 4.24 – 4.14 (2H, m, H-9), 4.11 (2H, q, *J* = 1.5, H-17), 3.16 (1H, dd, *J* = 18.5, 8.8, H-19''), 3.00 (1H, dd, *J* = 18.5, 5.2, H-19'), 2.87 (3H, s, H-10), 2.18 (3H, s, H-22), 1.16 (3H, t, *J* = 7.1 Hz, H-18)

^{13}C NMR (101 MHz, $CDCl_3$) δ 205.7 (C-11), 203.0 (C-20), 168.7 (C-13), 153.2 (C-5), 140.3 (C-1), 129.2 (C-3), 125.7 (C-2), 122.9 (C-4), 96.9 (C-6), 65.7 (C-9), 61.9 (C-17), 50.1 (C-12), 42.6 (C-10), 41.8 (C-19), 29.8 (C-22), 14.1 (C-18)

HRMS (ESI) *m/z* calcd. for $C_{16}H_{21}INO_4$ $[M+H]^+$: 418.0510; found: 418.0509.

FTIR (neat) ν/cm^{-1} = 2988, 1746, 1719, 1472, 1445, 1428, 1399, 1366, 1350, 1268, 1234, 1187, 1161, 1132, 1016, 758, 743

methyl (2-iodophenyl)carbamate, 237



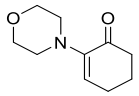
According to the procedure of Njardarson:[101] To a stirred solution of 2-iodoaniline (2.2 g, 10.0 mmol, 1.0 equiv.) and methyl chloroformate (0.93 mL, 12.0 mmol, 1.2 equiv.) in dry CH_2Cl_2 (50.0 mL, 0.2 M), pyridine (1.05 mL, 13.0 mmol, 1.3 equiv.) was added dropwise. After 30 mins, the reaction mixture was quenched with ice-cold water. The organic layer was separated and washed with ice-cold water three times and brine, then dried over $MgSO_4$. The residue was concentrated and isolated through flash column chromatography on silica gel to afford the product in 98% yield (2.71 g).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 – 8.02 (1H, m), 7.76 (1H, dd, *J* = 7.9, 1.6 Hz), 7.34 (1H, ddd, *J* = 8.7, 7.7, 1.6 Hz), 6.96 (1H, s), 6.80 (1H, td, *J* = 7.5, 1.6 Hz), 3.81 (3H, s)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 154.0, 139.0, 138.5, 129.5, 125.3, 120.4, 88.0, 52.7, 29.8.

All data are in accordance with those in literature.[102]

2-morpholinocyclohex-2-en-1-one, 238

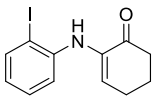


According to the procedure of Abboud:[103] A mixture of cyclohexane-1,2-dione (2.24 g, 20.0 mmol, 1.0 equiv.) and morpholine (2.2 mL, 2.2 g, 25.0 mmol, 1.3 equiv.) in toluene (50.0 mL, 0.4 M) were heated to reflux under Dean–Stark conditions for 12 h. After cooling to room temperature, the mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 50% EtOAc in pentane) to afford **S2** (3.04 g, 1.68 mmol, 84%) as a pale-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (1H, t, *J* = 4.6), 3.84–3.74 (4H, m), 2.85–2.77 (4H, m), 2.51–2.37 (4H, m), 2.00–1.88 (2H, m).

All data are in accordance with those in literature.[104]

2-((2-iodophenyl)amino)cyclohex-2-en-1-one, 240

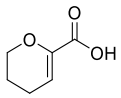


According to the procedure of Zhao:[105] 2-Iodoaniline (2.19 g, 10.0 mmol, 1.0 equiv.), morpholine enamine **238** (1.81 g, 10.0 mmol, 1.0 equiv.) and *para*-toluenesulfonic acid monohydrate (1.9 g, 10.0 mmol, 1.0 equiv.) were heated to 50 °C in toluene (50.0 mL, 0.2 M) for 3 h. The reaction was cooled to room temperature and diluted with EtOAc (100 mL). The solution was washed with sodium hydrogencarbonate (sat. aq., 3 x 50 mL) followed by brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, 5 to 10% Et_2O in pentane) to afford **240** (2.82 g, 9.0 mmol, 90%) as a white solid. The spectral data matched that previously reported in the literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, dd, *J* = 7.9, 1.4), 7.24 (1H, ddd, *J* = 8.2, 6.8, 1.3), 7.21 (1H, dd, *J* = 8.2, 2.0), 6.65 (1H, ddd, *J* = 7.9, 3.7, 2.0), 6.55 (1H, br s), 6.35 (1H, t, *J* = 4.8), 2.59 (2H, dd, *J* = 7.2, 6.1), 2.48–2.43 (2H, m), 2.08–2.00 (2H, m).

All data are in accordance with those in literature.[105]

3,4-dihydro-2H-pyran-6-carboxylic acid, 248



According to the procedure of Solon:[34] 3,4-Dihydropyran (4.6 mL, 25 mmol, 1.0 equiv.) was added to the solution of ^{n}BuLi (2.5 M in hexane, 10 mL, 25 mmol, 1.0 equiv.) at 0 ∘C. Then TMEDA (3.8 mL, 2.90 g, 25 mmol, 1.0 equiv.) was added before the reaction mixture was warmed to room temperature. The reaction was stirred for 2 hrs and THF (25 mL) was added. The reaction mixture was cooled to -78 °C and dry ice (ca. 5 g) was added. Reaction mixture was stirred for 3 hrs at room temperature. Et_2O (50 mL) was added to dilute the solution. The resulting solution was extracted three times with water. The combined aqueous layers were acidified with concentrated hydrochloric acid (37 % w/w). The aqueous layer was then extracted three times with EtOAc. The combined organic layers were washed with water. The solvent was then removed under reduced pressure to give 3,4-dihydro-2H-pyran-6-carboxylic acid **248** (1.51 g, 48%) as a waxy solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.23 (1H, t, *J* = 4.2 Hz), 4.17 – 4.08 (2H, m), 2.22 (2H, td, *J* = 6.4, 4.1 Hz), 1.93 – 1.83 (2H, m).

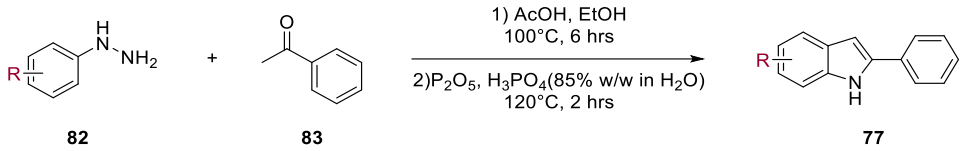
^{13}C NMR ($CDCl_3$, 101 MHz) δ 167.38, 143.5, 113.82, 66.89, 21.42, 20.82.

All data are in accordance with those in literature.[34]

Indole synthesis

General Procedures

General procedure A

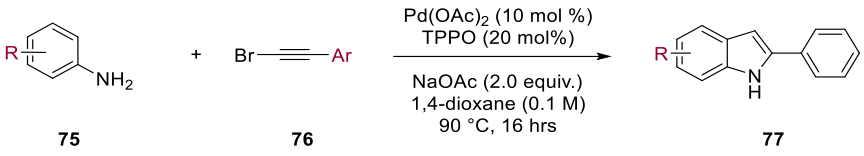


According to modified procedures[68-70]

Phenyl hydrazine **82** (1.0 equiv.) and acetophenone **83** (1.0 equiv.) were dissolved in EtOH (1.0 M) then followed by a quick addition of AcOH (2.0 equiv.). The reaction mixture was heated to reflux (ca., 100 °C) for 6 hrs before cooled to room temperature. The solvent was removed under vacuum, and the intermediate was used without further purification.

A suspension of P_2O_5 (5.7 equiv.) and H_3PO_4 (1.0 M, 85% w/w in H_2O) was heated to 120°C until it formed a clear solution. 1-phenyl-2-(1-phenylethylidene)hydrazine (1.0 equiv.) was added slowly and the reaction mixture was stirred under this temperature for 2 hrs. After the reaction cooled to room temperature, ice was added to quench the reaction. After putting ice, a suspension was obtained. The solid was filtered then recrystallised with EtOH/H_2O to obtain the desired indole.

General procedure B

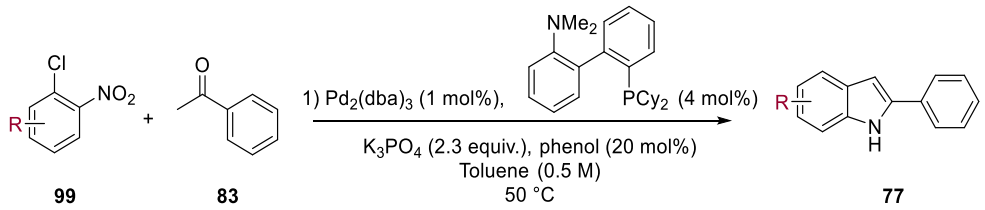


According to a modified procedure of Wu:[67]

Aniline **75** (1.0 equiv.), bromoalkyne **76** (2.5 equiv.), $Pd(OAc)_2$ (10 mol%), TPPO (20 mol%) and NaOAc (2.0 equiv.) were put in a sealed flask equipped with a stirring bar and the reaction was evacuated and back filled with argon three times. 1,4-dioxane (0.2 M)

was added and the mixture was sparged with argon for 15 mins before heated up to 90 °C for 16 hrs. Then the resulting mixture was cooled to room temperature and was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and then the solvent was removed under reduced pressure. The concentrated crude product was then purified by DCVC (0% EtOAc in pentane to 20% EtOAc in pentane) and recrystallized in Et_2O/Hexane.

General procedure C



According to the procedure of Buchwald:[72]

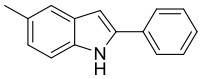
To a dried resealable tube equipped with a stir bar, $Pd_2(dba)_3$ (1 mol%), the ligand (4 mol%), K_3PO_4 (2.3 equiv.), the phenol (20 mol%) and *ortho*-nitro aryl halide **99**(1.0 equiv.) were added. The tube was evacuated and back filled with argon three times. Sparged toluene (0.5 M) and acetophenone **83** (1.0 equiv.) were syringed into the tube. The reaction was heated to 50 °C and monitored by TLC. After reaction completed, the mixture was quenched by H_2O and was extracted with EtOAc. The combined organics were concentrated under reduce pressure. The intermediate was used in next step without further purification.

Aqueous $TiCl_3$ (16.5 equiv.), aqueous ammonium acetate (6.6 M, 100.0 equiv.), and ethanol (0.2 M) were added in a flask equipped with stir bar under argon. The crude ketone was dissolved into ethanol (ca, 15.0 mL for 1.0 mmol scale reaction). The ketone solution was added into the reaction mixture dropwise and the resulting solution was stirred at room temperature for 15 mins. After reaction completed, the mixture was extracted with Et_2O three times. The organic was washed with saturated $NaHCO_3$ solution and followed by brine, dried

over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2 : hexane = 1: 1) to obtain desired indole.

Characterisation

5-methyl-2-phenyl-1H-indole, 85



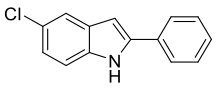
According to ***General procedure A*** by using *p*-tolylhydrazine (1.70 g, 14.0 mmol, 1.0 equiv.), acetophenone (1.6 mL,14.0 mmol, 1.0 equiv.), AcOH (1.6 mL, 28.0 mmol, 2.0 equiv.) in EtOH (14.0 mL). Followed by P_2O_5 (24.0 g, 5.7 equiv.) and H_3PO_4 (16.0 mL, 85% w/w in H_2O) to obtain 5-methyl-2-phenyl-1H-indole **85** in a yield of 38% in two steps (1.27 g, 5.4 mmol) as a brown solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.43 – 11.30 (1H, m), 7.91 – 7.76 (2H, m), 7.44 (2H, t, *J* = 7.8 Hz), 7.33 – 7.25 (3H, m), 6.92 (1H, dd, *J* = 8.3, 1.9 Hz), 6.80 (1H, dd, *J* = 2.3, 0.9 Hz), 2.36 (3H, s)

^{13}C NMR (DMSO, 101 MHz) δ 137.6, 135.5, 132.3, 128.9, 128.8, 127.8, 127.2, 124.9, 123.2, 119.6, 111.0, 98.2, 21.2.

All data are in accordance with those in literature.[106]

5-chloro-2-phenyl-1H-indole, 87



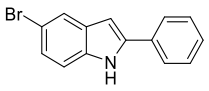
According to ***General procedure A*** by using (4-chlorophenyl)hydrazine (3.5 g, 24.0 mmol, 1.0 equiv.), acetophenone (2.8 mL,24.0 mmol, 1.0 equiv.), AcOH (2.8 mL, 48.0 mmol, 2.0 equiv.) in EtOH (24.0 mL). Followed by P_2O_5 (32.0 g, 5.7 equiv.) and H_3PO_4 (24.0 mL, 85% w/w in H_2O) to obtain 5-chloro-2-phenyl-1H-indole **87** in a yield of 72% in two steps (3.90 g, 17.2 mmol) as a green solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (1H, s), 7.68 - 7.62 (2H, m), 7.59 (1H, d, *J* = 2.0 Hz), 7.49 - 7.42 (2H, m), 7.39 - 7.28 (2H, m), 7.14 (1H, dd, *J* = 8.6, 2.0 Hz), 6.80 - 6.72 (1H, m)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 139.3, 135.1, 131.9, 130.3, 129.1, 128.1, 125.9, 125.3, 122.6, 120.0, 111.9, 99.6

All data are in accordance with those in literature.[107]

5-bromo-2-phenyl-1H-indole, 78



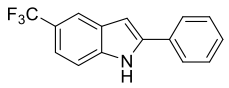
According to ***General procedure B*** by using 4-bromoaniline (688 mg, 4.0 mmol, 1.0 equiv.), (bromoethynyl)benzene (1.81 g, 10.0 mmol, 2.5 equiv.), $Pd(OAc)_2$ (90 mg, 0.4 mmol, 10 mol%), TPPO (223 mg, 0.8 mmol, 20 mol%) and NaOAc (656 mg, 8.0 mmol, 2.0 equiv.) in 1,4-dioxane (40.0 mL) to afford the desired product 5-bromo-2-phenyl-1H-indole **78** in a yield of 26% (283 mg, 1.04 mmol) as a white solid

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.36 (1H, s), 7.75 (1H, p, *J* = 1.0 Hz), 7.68 - 7.62 (2H, m), 7.49 - 7.43 (2H, m), 7.38 - 7.33 (1H, m), 7.28 - 7.26 (2H, m), 6.76 (1H, d, *J* = 2.2 Hz)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 139.1, 135.4, 131.8, 131.0, 129.1, 128.2, 125.3, 125.1, 123.1, 113.4, 112.3, 99.5

All data are in accordance with those in literature.[108]

2-phenyl-5-(trifluoromethyl)-1H-indole, 100



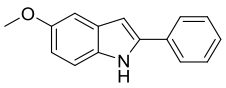
According to ***General procedure C*** by using $Pd_2(dba)_3$ (46 mg, 0.05 mmol, 1 mol%), the ligand (79 mg, 0.2 mmol, 4 mol%), K_3PO_4 (2.44 g, 11.5 mmol, 2.3 equiv.), 4-methyloxidephenol (124 mg, 1.0 mmol, 20 mol%) 2-chloro-1-nitro-4-(trifluoromethyl)benzene (0.75 mL, 5.0 mmol, 1.0 equiv.) and acetophenone (1.3 mL, 11 mmol, 2.2 equiv.) in toluene (10.0 mL) The followed by aqueous $TiCl_3$ (63.90 g, 82.5 mmol, 16.5 equiv., 20%w/v in 3% hydrochloric acid), aqueous ammonium acetate (75.0 mL, 6.6 M in H_2O), and ethanol (75.0 mL) to afford the desired product 2-phenyl-5-(trifluoromethyl)-1H-indole **100** in a yield of 44% (573 mg, 2.2 mmol) as a white solid.

^{1}H NMR (DMSO, 400 MHz) δ 12.03 (1H, s), 7.93 - 7.91 (1H, m), 7.90 - 7.86 (2H, m), 7.58 (1H, dq, *J* = 8.5, 0.8 Hz), 7.53 - 7.44 (2H, m), 7.42 - 7.33 (2H, m), 7.06 (1H, dd, *J* = 2.2, 0.9 Hz)

^{13}C NMR (DMSO, 101 MHz) δ 140.0, 138.7, 131.6, 129.2, 128.2, 128.1, 125.7 (q, *J* = 271.1 Hz), 125.4, 120.4 (q, *J* = 30.8 Hz), 118.0 (q, *J* = 3.4 Hz), 117.7 (q, *J* = 4.2 Hz), 112.1, 99.7 (q, *J* = 269.0 Hz)

All data are in accordance with those in literature.[109]

5-methoxy-2-phenyl-1H-indole, 79



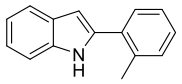
According to a modified ***General procedure B*** by using 4-methoxyaniline (1.20 g, 10.0 mmol, 1.0 equiv.), (bromoethynyl)benzene (4.50 g, 10.0 mmol, 2.5 equiv.), $Pd(OAc)_2$ (450 mg, 2.0 mmol, 20 mol%), TPPO (278 mg, 1.0 mmol, 10 mol%) and NaOAc (1.64 g, 20.0 mmol, 2.0 equiv.) in 1,4-dioxane (50.0 mL) to afford the desired product 5-methoxy-2-phenyl-1H-indole **79** in a yield of 11% (241 mg, 1.1 mmol) as a yellow solid

^{1}H NMR (DMSO, 400 MHz) δ 11.41 - 11.36 (1H, m), 7.87 - 7.78 (2H, m), 7.44 (2H, dd, *J* = 8.6, 7.1 Hz), 7.33 - 7.24 (2H, m), 7.02 (1H, d, *J* = 2.4 Hz), 6.80 (1H, dd, *J* = 2.3, 0.9 Hz), 6.74 (1H, dd, *J* = 8.7, 2.5 Hz), 3.75 (3H, s)

^{13}C NMR (DMSO, 101 MHz) δ 154.1, 138.5, 132.8, 132.7, 129.5, 129.4, 127.8, 125.3, 112.5, 112.3, 102.0, 99.0, 55.7

All data are in accordance with those in literature.[110]

2-(o-tolyl)-1H-indole, 80



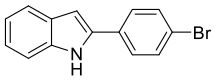
According to ***General procedure B*** by using aniline (0.9 mL, 10.0 mmol, 1.0 equiv.), 1-(bromoethynyl)-2-methylbenzene (4.88 g, 25.0 mmol, 2.5 equiv.), $Pd(OAc)_2$ (225 mg, 1.0 mmol, 10 mol%), TPPO (557 mg, 2.0 mmol, 20 mol%) and NaOAc (1.64 g, 20.0 mmol, 2.0 equiv.) in 1,4-dioxane (50 mL) to afford the desired product 2-(o-tolyl)-1H-indole **80** in a yield of 16% (330 mg, 1.6 mmol) as a yellow solid

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (1H, s), 7.66 (1H, ddt, *J* = 7.8, 1.4, 0.8 Hz), 7.48 (1H, dd, *J* = 5.3, 3.7 Hz), 7.41 (1H, dq, *J* = 8.1, 1.0 Hz), 7.31 (3H, dtd, *J* = 9.2, 5.5, 3.5 Hz), 7.21 (1H, ddd, *J* = 8.2, 7.1, 1.3 Hz), 7.14 (1H, ddd, *J* = 8.1, 7.0, 1.1 Hz), 6.62 (1H, dd, *J* = 2.2, 0.9 Hz), 2.51 (3H, s)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 137.6, 136.3, 136.2, 132.8, 131.2, 129.1, 129.0, 128.1, 126.2, 122.2, 120.7, 120.2, 110.9, 103.1, 21.3

All data are in accordance with those in literature.[111]

2-(4-bromophenyl)-1H-indole, 90



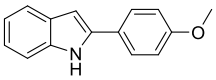
According to ***General procedure A*** by using phenylhydrazine (2.4 mL, 24.0 mmol, 1.0 equiv.), 1-(4-bromophenyl)ethan-1-one (4.80 g, 24.0 mmol, 1.0 equiv.), AcOH (2.8 mL, 48.0 mmol, 2.0 equiv.) in EtOH (24.0 mL). Followed by P_2O_5 (32.00 g, 5.7 equiv.) and H_3PO_4 (24.0 mL, 85% w/w in H_2O) to obtain 2-(4-bromophenyl)-1H-indole **90** in a yield of 56% in two steps (3.7 g, 13.5 mmol) as a white solid.

^{1}H NMR (DMSO, 400 MHz) δ 11.52 (1H, s), 7.83 - 7.78 (2H, m), 7.67 - 7.62 (2H, m), 7.54 (1H, ddt, *J* = 7.9, 1.3, 0.7 Hz), 7.40 (1H, dq, *J* = 8.1, 0.9 Hz), 7.11 (1H, ddd, *J* = 8.2, 7.0, 1.2 Hz), 7.00 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz), 6.92 (1H, dd, *J* = 2.2, 0.9 Hz)

^{13}C NMR (DMSO, 101 MHz) δ 137.2, 136.3, 131.7, 131.4, 128.5, 126.8, 121.8, 120.2, 120.1, 119.4, 111.3, 99.3

All data are in accordance with those in literature.[112]

2-(4-methoxyphenyl)-1H-indole, 91



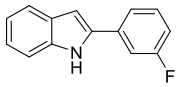
According to ***General procedure A*** by using phenylhydrazine (2.4 mL, 24.0 mmol, 1.0 equiv.), 1-(4-methoxyphenyl)ethan-1-one (3.60 g, 24.0 mmol, 1.0 equiv.), AcOH (2.8 mL, 48.0 mmol, 2.0 equiv.) in EtOH (24.0 mL). Followed by P_2O_5 (32.00 g, 5.7 equiv.) and H_3PO_4 (24.0 mL, 85% w/w in H_2O) to obtain 2-(4-methoxyphenyl)-1H-indole, **91** in a yield of 98% in two steps (5.25 g, 24.0 mmol) as a pale-yellow solid.

^{1}H NMR (DMSO, 400 MHz) δ 11.40 (1H, s), 7.85 - 7.76 (2H, m), 7.49 (1H, ddt, *J* = 7.8, 1.4, 0.7 Hz), 7.37 (1H, dq, *J* = 8.1, 0.9 Hz), 7.09 - 7.05 (1H, m), 7.04 - 7.01 (2H, m), 6.97 (1H, ddd, *J* = 8.0, 7.0, 1.1 Hz), 6.75 (1H, dd, *J* = 2.2, 0.9 Hz), 3.80 (3H, s)

^{13}C NMR (DMSO, 101 MHz) δ 159.3, 138.2, 137.4, 129.3, 126.8, 125.4, 121.5, 120.1, 119.7, 114.8, 111.5, 97.8, 55.7

All data are in accordance with those in literature.[113]

2-(3-fluorophenyl)-1H-indole, 93



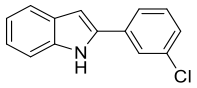
According to ***General procedure A*** by using phenylhydrazine (2.4 mL, 24.0 mmol, 1.0 equiv.), 1-(3-fluorophenyl)ethan-1-one (2.9 mL, 24.0 mmol, 1.0 equiv.), AcOH (2.8 mL, 48.0 mmol, 2.0 equiv.) in EtOH (24.0 mL). Followed by P_2O_5 (32.00 g, 5.7 equiv.) and H_3PO_4 (24.0 mL, 85% w/w in H_2O) to obtain 2-(3-fluorophenyl)-1H-indole **93** in a yield of 57% in two steps (3.03 g, 14.3 mmol) as a green solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (1H, s), 7.64 (1H, d, *J* = 7.8 Hz), 7.46 – 7.38 (3H, m), 7.38 – 7.33 (1H, m), 7.22 (1H, ddd, *J* = 8.2, 7.1, 1.2 Hz), 7.14 (1H, ddd, *J* = 8.1, 7.1, 1.1 Hz), 7.05 – 6.98 (1H, m), 6.85 (1H, dd, *J* = 2.1, 1.0 Hz)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 164.7, 137.1, 136.7, 134.7 (d, *J* = 8.2 Hz), 130.8 (d, *J* = 8.7 Hz), 129.2, 123.0, 121.0, 120.8 (d, *J* = 2.8 Hz), 120.6, 114.6 (d, *J* = 21.5 Hz), 112.2 (d, *J* = 23.0 Hz), 111.1, 101.1

All data are in accordance with those in literature.[114]

2-(3-chlorophenyl)-1H-indole, 94



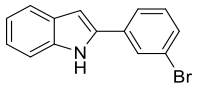
According to ***General procedure A*** by using phenylhydrazine (2.4 mL, 24.0 mmol, 1.0 equiv.), 1-(3-chlorophenyl)ethan-1-one (3.1 mL, 24.0 mmol, 1.0 equiv.), AcOH (2.8 mL, 48.0 mmol, 2.0 equiv.) in EtOH (24.0 mL). Followed by P_2O_5 (32.00 g, 5.7 equiv.) and H_3PO_4 (24.0 mL, 85% w/w in H_2O) to obtain 2-(3-chlorophenyl)-1H-indole **94** in a yield of 76% in two steps (4.16 g, 18.2 mmol) as a green solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (1H, s), 7.68 - 7.61 (2H, m), 7.54 (1H, ddd, *J* = 7.7, 1.7, 1.1 Hz), 7.41 (1H, dd, *J* = 8.1, 0.9 Hz), 7.39 - 7.34 (1H, m), 7.29 (1H, ddd, *J* = 8.0, 2.0, 1.1 Hz), 7.22 (1H, ddd, *J* = 8.2, 7.1, 1.3 Hz), 7.14 (1H, ddd, *J* = 8.0, 7.1, 1.1 Hz), 6.85 (1H, dd, *J* = 2.1, 1.0 Hz)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 137.0, 136.3, 135.0, 134.2, 130.3, 129.1, 127.6, 125.2, 123.2, 122.9, 120.9, 120.5, 111.0, 101.0

All data are in accordance with those in literature.[115]

2-(3-bromophenyl)-1H-indole, 95



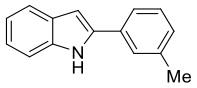
According to ***General procedure A*** by using phenylhydrazine (2.4 mL, 24.0 mmol, 1.0 equiv.), 1-(3-bromophenyl)ethan-1-one (3.2 mL, 24.0 mmol, 1.0 equiv.), AcOH (2.8 mL, 48.0 mmol, 2.0 equiv.) in EtOH (24.0 mL). Followed by P_2O_5 (32.00 g, 5.7 equiv.) and H_3PO_4 (24.00 mL, 85% w/w in H_2O) to obtain 2-(3-bromophenyl)-1H-indole **95** in a yield of 54% in two steps (3.50 g, 13.0 mmol) as an off-white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (1H, s), 7.80 (1H, t, *J* = 1.8 Hz), 7.68 - 7.61 (1H, m), 7.58 (1H, ddd, *J* = 7.8, 1.8, 1.0 Hz), 7.44 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz), 7.40 (1H, dq, *J* = 8.1, 0.9 Hz), 7.30 (1H, t, *J* = 7.9 Hz), 7.22 (1H, ddd, *J* = 8.2, 7.1, 1.2 Hz), 7.14 (1H, ddd, *J* = 8.0, 7.1, 1.1 Hz), 6.84 (1H, dd, *J* = 2.1, 1.0 Hz)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 137.1, 136.3, 134.6, 130.7, 130.6, 129.2, 128.2, 123.8, 123.3, 123.0, 121.0, 120.6, 111.2, 101.1

All data are in accordance with those in literature.[67]

2-(m-tolyl)-1H-indole, 96



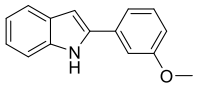
According to ***General procedure A*** by using phenylhydrazine (2.4 mL, 24.0 mmol, 1.0 equiv.), 1-(m-tolyl)ethan-1-one (3.3 mL, 24.0 mmol, 1.0 equiv.), AcOH (2.8 mL, 48.0 mmol, 2.0 equiv.) in EtOH (24.0 mL). Followed by P_2O_5 (32.00 g, 5.7 equiv.) and H_3PO_4 (24.0 mL, 85% w/w in H_2O) to obtain 2-(m-tolyl)-1H-indole **96** in a yield of 66% in two steps (3.4 g, 16.4 mmol) as a brown solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35 (1H, s), 7.64 (1H, d, *J* = 7.8 Hz), 7.52 - 7.45 (2H, m), 7.44 - 7.38 (1H, m), 7.34 (1H, t, *J* = 7.6 Hz), 7.20 (1H, ddd, *J* = 8.1, 7.0, 1.2 Hz), 7.17 - 7.09 (2H, m), 6.85 - 6.80 (1H, m), 2.44 (3H, s)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 138.8, 138.2, 136.9, 132.4, 129.4, 129.1, 128.7, 126.0, 122.4, 122.4, 120.8, 120.3, 111.0, 100.0, 21.7

All data are in accordance with those in literature.[115]

2-(3-methoxyphenyl)-1H-indole, 81



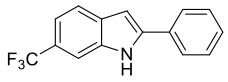
According to ***General procedure B*** by using aniline (1.4 mL, 15.0 mmol, 1.0 equiv.), 1-(bromoethynyl)-3-methoxybenzene (7.91 g, 37.5 mmol, 2.5 equiv.), $Pd(OAc)_2$ (337 mg, 1.5 mmol, 10 mol%), TPPO (835 mg, 3.0 mmol, 20 mol%) and NaOAc (2.46 g, 30.0 mmol, 2.0 equiv.) in 1,4-dioxane (75.0 mL) to afford the desired product 2-(3-methoxyphenyl)-1H-indole **81** in a yield of 20% (658 mg, 3.0 mmol) as a yellow solid

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (1H, s), 7.64 (1H, dt, *J* = 7.8, 1.0 Hz), 7.41 (1H, dd, *J* = 8.1, 1.0 Hz), 7.37 (1H, t, *J* = 7.9 Hz), 7.26 (1H, ddd, *J* = 7.6, 1.7, 1.0 Hz), 7.23 - 7.18 (2H, m), 7.13 (1H, ddd, *J* = 8.0, 7.1, 1.1 Hz), 6.88 (1H, ddd, *J* = 8.2, 2.6, 1.0 Hz), 6.83 (1H, dd, *J* = 2.2, 0.9 Hz), 3.89 (3H, s)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 160.3, 137.9, 136.9, 133.9, 130.2, 129.3, 120.8, 120.4, 117.8, 113.3, 111.1, 111.0, 100.4, 55.5

All data are in accordance with those in literature.[116]

2-phenyl-6-(trifluoromethyl)-1H-indole, 101



According to ***General procedure C*** by using $Pd_2(dba)_3$ (28 mg, 0.03 mmol, 1 mol%), the ligand (47 mg, 0.12 mmol, 4 mol%), K_3PO_4 (1.46 g, 6.9 mmol, 2.3 equiv.), phenol (17 µL, 0.6 mmol, 20 mol%) 1-chloro-2-nitro-4-(trifluoromethyl)benzene (0.5 mL, 3.0 mmol, 1.0 equiv.) and acetophenone (0.8 mL, 6.6mmol, 2.2 equiv.) in toluene (6.0 mL) The followed by aqueous $TiCl_3$ (38.14 g, 49.5 mmol, 16.5 equiv., 20%w/v in 3% hydrochloric acid), aqueous ammonium acetate (45.0 mL, 6.6M in H_2O), and ethanol (45.0 mL) to afford the desired product 2-phenyl-6-(trifluoromethyl)-1H-indole **101** in a yield of 47% (372 mg, 1.4 mmol) as a white solid.

^{1}H NMR (DMSO, 400 MHz) δ 12.02 (1H, s), 7.90 (2H, dd, *J* = 7.6, 1.3 Hz), 7.76 - 7.68 (2H, m), 7.53 - 7.47 (2H, m), 7.41 - 7.35 (1H, m), 7.29 (1H, dt, *J* = 8.3, 1.1 Hz), 7.05 - 7.02 (1H, m)

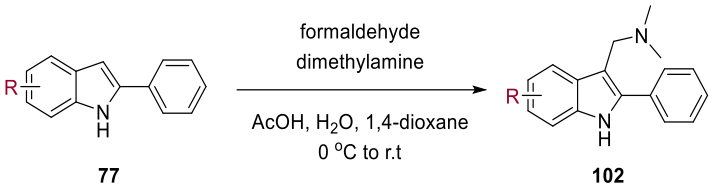
^{13}C NMR (DMSO, 101 MHz) δ 141.0, 135.9, 131.4, 131.3, 129.1, 128.3, 125.5, 125.5 (q, *J* = 271.2 Hz), 121.8 (q, *J* = 31.2 Hz), 120.9, 115.7 (q, *J* = 3.4 Hz), 108.5 (q, *J* = 4.1 Hz), 99.0

All data are in accordance with those in literature.[117]

Gramine Synthesis

General Procedure

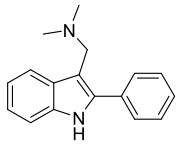
General procedure D



According to the procedures of Liu and You:[56, 59, 73] A mixture of formaldehyde (37% w/w in water, 1.1 equiv.), AcOH, H_2O in dioxane (0.5 M). The mixture was cooled to 0 °C and then dimethylamine (5.6 M in THF, 1.1 equiv.) was added in quickly, followed by phenylindole (1.0 equiv.) adding in portions. The reaction was stirred at 0 °C for 2 hrs then warm up to room temperature for 16 hrs. After reaction completed, the mixture was diluted with water and was stirred with celite for 10 mins. The suspension was filtered through a pad of celite. The filtrate was poured into a NaOH solution (2.0 M, 50 mL for a 2.5 mmol scale reaction) and resulting in precipitation of the desire product. The suspension was extracted with EtOAc three times. The organic was washed with water and brine, dried over $MgSO_4$. The solvent was removed under reduced pressure and the product was used in next step without further purification.

Characterisation

***N*,*N*-dimethyl-1-(2-phenyl-1H-indol-3-yl)methanamine, 66**



66 *was synthesis according to a modified* ***general procedure D***

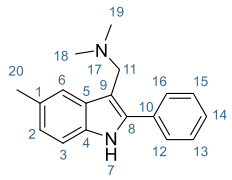
A 3-neck 250mL round-bottom flask equipped with a magnetic stirring bar was added with a mixture of formaldehyde (37% w/w in water, 2.1 mL, 28.0 mmol, 1.1 equiv.), AcOH (26.0 mL), and H_2O (2.0 mL) in dioxane (50.0 mL). The mixture was cooled to 0 °C and then dimethylamine (5.6 M in ethanol, 5.0 mL, 28.0 mmol, 1.1 equiv.) was added in quickly. After the addition of dimethylamine, phenylindole (5.00 g, 26.0 mmol, 1.0 equiv.) was added in portions. The reaction was stirred at 0 °C for 2 hrs and warmed up at room temperature for 12 hrs. After reaction completed, the mixture was diluted with water (32.0 mL) and was stirred with Celite (1.50 g) for 10 mins. The suspension was filtered through a pad of Celite and the filtrate was pour into NaOH solution (2.0 M, 400 mL) and resulting in precipitation of the product. The product was filtered, washed with water, and dried under the vacuum. The desired product was obtained as a pale white solid (5.31 g, 21.2 mmol, 82%)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (1H, s), 7.82 - 7.73 (3H, m), 7.48 (2H, t, J = 7.5 Hz,), 7.42 - 7.34 (2H, m), 7.22 (1H, t, J = 7.2 Hz), 7.17 (1H, t, J = 7.4 Hz), 3.65 (2H, s), 2.31 (6H, s).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 136.7, 135.6, 133.0, 130.1, 128.8, 128.4, 127.7, 122.2, 119.9, 119.6, 110.7, 110.7, 53.6, 45.5.

All data are in accordance with those in literature.[118]

***N*,*N*-dimethyl-1-(5-methyl-2-phenyl-1H-indol-3-yl)methanamine, S10**



S10 *was synthesis according to* ***general procedure D*** by using formaldehyde (37% w/w in water, 0.4 mL, 28.0 mmol, 1.1 equiv.), AcOH (5.2 mL), H_2O (0.4 mL) in dioxane (10.0 mL), dimethylamine (5.6 M in THF, 1.0 mL, 5.5 mmol, 1.1 equiv.) 5-methyl-2-phenyl-1H-indole **85** (1.04 g, 5.0 mmol, 1.0 equiv.), resulting a brown solid in 70% yield (923 mg, 3.50 mmol).

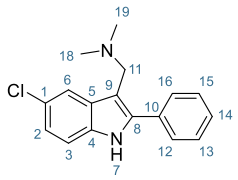
^{1}H NMR (DMSO, 400 MHz) δ 11.22 (1H, s, H-7), 7.91 – 7.85 (2H, m, H-12, H-16), 7.49 (2H, dd, *J* = 8.4, 7.1 Hz, H-13, H-15), 7.45 – 7.41 (1H, m, H-6), 7.39 – 7.32 (1H, m, H-14), 7.27 (1H, d, *J* = 8.1 Hz, H-3), 6.93 (1H, dd, *J* = 8.3, 1.8 Hz, H-2), 3.49 (2H, s, H-11), 2.39 (3H, s, H-20), 2.21 (6H, s, H-18, H-19).

^{13}C NMR (DMSO, 101 MHz) δ 136.4 (C-8), 134.1 (C-4), 132.8 (C-10), 129.8 (C-5), 128.5 (C-13, C-15), 128.0 (C-12, C-16), 127.3 (C-14), 127.2 (C-1), 123.1 (C-2), 118.4 (C-6), 110.9 (C-3), 108.8 (C-9), 53.3 (C-11), 45.0 (C-18, C-19), 21.4 (C-20).

HRMS (ESI) *m/z* calcd. for $C_{18}H_{21}N_2$ $[M+H]^+$: 265.1699; found: 265.1690.

FTIR (neat) ν/cm^{-1} = 3393, 2919, 2856, 2815, 2773, 1604, 1455, 1313, 1234, 1183, 1012, 843, 795, 768, 700.

1-(5-chloro-2-phenyl-1H-indol-3-yl)-*N*,*N*-dimethylmethanamine, S11



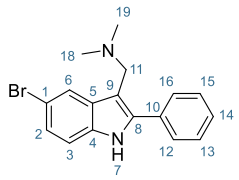
S11 *was synthesis according to* ***general procedure D*** by using formaldehyde (37% w/w in water, 0.4 mL, 5.5 mmol, 1.1 equiv.), AcOH (5.2 mL), H_2O (0.4 mL) in dioxane (10.0 mL), dimethylamine (5.6 M in THF, 1.0 mL, 5.5 mmol, 1.1 equiv.) 5-chloro-2-phenyl-1H-indole **87** (1.14 g, 5.0 mmol, 1.0 equiv.), resulting a brown solid in a yield of 73% (1.05 g, 3.7 mmol).

^{1}H NMR (DMSO, 400 MHz) δ 11.56 (1H, s), 7.89 - 7.81 (2H, m, H-12, H-16), 7.67 (1H, d, *J* = 2.1 Hz, H-6), 7.51 (2H, dd, *J* = 8.3, 7.1 Hz, H-13, H-15), 7.39 (2H, dd, *J* = 9.1, 8.0 Hz, H-3, H-14), 7.10 (1H, dd, *J* = 8.6, 2.1 Hz, H-2), 3.51 (2H, s, H-11), 2.19 (6H, s, H-18, H-19).

^{13}C NMR (DMSO, 101 MHz) δ 138.0 (Ar), 134.2 (Ar), 132.2 (Ar), 130.6 (Ar), 128.7 (C-13, C-15), 128.3 (C-12, C-16), 127.8 (C-14), 123.5 (Ar), 121.3 (C-2), 118.1 (C-6), 112.7 (C-3), 109.1 (C-9), 53.2 (C-11), 44.9 (C-18, C-19).

FTIR (neat) ν/cm^{-1} = 2941, 2857, 2820, 2776, 1460, 1308, 1032, 1000, 796, 764, 700.

1-(5-bromo-2-phenyl-1H-indol-3-yl)-*N*,*N*-dimethylmethanamine, S12



S12 *was synthesis according to* ***general procedure D*** by using formaldehyde (37% w/w in water, 192 µL, 2.6 mmol, 1.1 equiv.), AcOH (2.4 mL), H_2O (181 µL) in dioxane (4.5 mL), dimethylamine (5.6 M in THF, 461 µL, 5.5 mmol, 1.1 equiv.) 5-bromo-2-phenyl-1H-indole **78** (639 mg, 2.4 mmol, 1.0 equiv.), resulting a pale white solid in a yield of 66% (510 mg, 1.6 mmol).

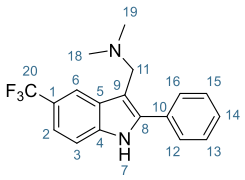
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 - 8.18 (1H, m, H-7), 7.90 (1H, dt, *J* = 1.9, 0.7 Hz, H-6), 7.77 - 7.71 (2H, m, H-12, H-16), 7.53 - 7.45 (2H, m, H-13, H-15), 7.42 - 7.36 (1H, m, H-14), 7.28 (1H, dd, *J* = 8.5, 1.8 Hz, H-2), 7.24 (1H, dd, *J* = 8.6, 0.6 Hz, H-3), 3.57 (2H, s, H-11), 2.27 (6H, s, H-18, H-19).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 137.9 (Ar), 134.3 (Ar), 132.5 (Ar), 131.9 (Ar), 129.0 (C-13, C-15), 128.5 (C-12, C-16), 128.2 (C-14), 125.2 (C-2), 122.4 (C-6), 113.3 (C-9), 112.2 (C-3), 110.7 (C-1), 53.7 (C-11), 45.6 (C-18, C-19).

HRMS (ESI) *m/z* calcd. for $C_{17}H_{18}BrN_2$ $[M+H]^+$: 329.0648; found: 329.0645.

FTIR (neat) ν/cm^{-1} = 2942, 2816, 2775, 1458, 1308, 1011, 909, 842, 794, 766, 735, 700.

***N*,*N*-dimethyl-1-(2-phenyl-5-(trifluoromethyl)-1H-indol-3-yl)methanamine, S13**



S13 *was synthesis according to* ***general procedure D*** by using formaldehyde (37% w/w in water, 110 µL, 1.1 mmol, 1.1 equiv.), AcOH (1.0 mL), H_2O (80 µL) in dioxane (2.0 mL), dimethylamine (5.6 M in THF, 200 µL, 1.1 mmol, 1.1 equiv.) 2-phenyl-5-(trifluoromethyl)-1H-indole **100** (261.3 mg, 1.0 mmol, 1.0 equiv.), resulting a pale white solid in a yield of 68% (215 mg, 0.7 mmol).

^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.53 (1H, s, H-7), 8.08 (1H, dt, *J* = 1.9, 0.9 Hz, H-6), 7.77 - 7.69 (2H, m, H-12, H-16), 7.52 - 7.46 (2H, m, H-13, H-15), 7.45 - 7.37 (3H, m, H-2, H-3, H-14), 3.65 (2H, s, H-11), 2.28 (6H, s, H-18, H-19).

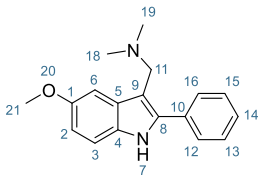
^{13}C NMR (CDCl$_3$, 101 MHz) δ 138.5 (Ar), 137.0 (Ar), 132.4 (Ar), 129.5 (Ar), 129.0 (C-13, C-15), 128.6 (C-12, C-16), 128.4 (C-14), 125.5 (q, *J* = 271.0 Hz, C-20), 122.4 (q, *J* = 31.4 Hz, C-1), 119.0 (q, *J* = 3.2 Hz, C-2), 117.5 (q, *J* = 4.0 Hz, C-6), 111.0 (C-3), 53.5 (C-11), 45.5 (C-18, C-19).

^{19}F NMR (CDCl$_3$, 377 MHz) δ -60.15.

HRMS (ESI) *m/z* calcd. for $C_{18}H_{18}F_3N_2$ $[M+H]^+$: 319.1417; found: 319.1439.

FTIR (neat) ν/cm^{-1} = 2944, 2861, 2822, 2778, 1454, 1333, 1301, 1263, 1160, 1112, 910, 888, 809, 768, 737, 700.

1-(5-methoxy-2-phenyl-1H-indol-3-yl)-*N*,*N*-dimethylmethanamine, S14



S14 *was synthesis according to* ***general procedure D*** by using formaldehyde (37% w/w in water, 110 µL, 1.1 mmol, 1.1 equiv.), AcOH (1.0 mL), H_2O (80 µL) in dioxane (2.0 mL), dimethylamine (5.6 M in THF, 200 µL, 1.1 mmol, 1.1 equiv.) 5-methoxy-2-phenyl-1H-indole **79** (223 mg, 1.0 mmol, 1.0 equiv.), resulting a yellow solid in a yield of 64% (180 mg, 0.7 mmol).

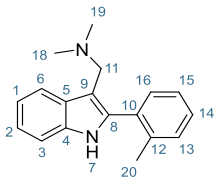
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (1H, s, H-7), 7.78 - 7.72 (2H, m, H-12, H-16), 7.49 - 7.43 (2H, m, H-13, H-15), 7.39 - 7.33 (1H, m, H-14), 7.26 (1H, dd, *J* = 8.7, 0.6 Hz, H-3), 7.22 (1H, d, *J* = 2.4 Hz, H-6), 6.87 (1H, dd, *J* = 8.7, 2.5 Hz, H-2), 3.89 (3H, s, H-21), 3.61 (2H, s, H-11), 2.30 (6H, s, H-18, H-19).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 154.4 (C-1), 137.7 (Ar), 133.1 (Ar), 130.9 (Ar), 130.7 (Ar), 128.9 (C-13, C-15), 128.4 (C-12, C-16), 127.8 (C-14), 112.3 (C-2), 111.5 (C-3), 110.5 (C-9), 101.8 (C-6), 56.1 (C-21), 53.7 (C-11), 45.5 (C-18, C-19).

HRMS (ESI) *m/z* calcd. for $C_{18}H_{20}N_2ONa$ $[M+Na]^+$: 303.1468; found: 303.1462.

FTIR (neat) ν/cm^{-1} = 2940, 2823, 2774, 1623, 1587, 1482, 1457, 1376, 1311, 1216, 1165, 769, 734, 700.

***N*,*N*-dimethyl-1-(2-(o-tolyl)-1H-indol-3-yl)methanamine, S15**



S15 *was synthesis according to* ***general procedure D*** by using formaldehyde (37% w/w in water, 116 µL, 1.6 mmol, 1.1 equiv.), AcOH (1.4 mL), H_2O (109 µL) in dioxane (2.7 mL), dimethylamine (5.6 M in THF, 279 µL, 1.6 mmol, 1.1 equiv.) 2-(o-tolyl)-1H-indole **80** (294 mg, 1.4 mmol, 1.0 equiv.), resulting a yellow solid in a yield of 98% (264 mg, 1.4 mmol).

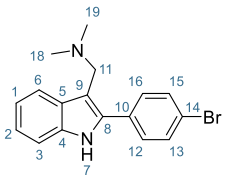
^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.29 - 8.22 (1H, m, H-7), 7.78 (1H, ddt, *J* = 8.3, 1.4, 0.6 Hz, H-6), 7.35 (4H, ddt, *J* = 8.3, 7.1, 1.2 Hz, Ar), 7.30 - 7.23 (1H, m, Ar), 7.18 (1H, ddd, *J* = 8.1, 7.0, 1.3 Hz, H-2), 7.11 (1H, ddt, *J* = 9.0, 7.1, 1.2 Hz, H-1), 3.49 (2H, d, *J* = 1.1 Hz, H-11), 2.23 (3H, d, *J* = 1.0 Hz, H-20), 2.11 (6H, d, *J* = 1.1 Hz, H-18, H-19).

^{13}C NMR (CD_2Cl_2, 101 MHz) δ 138.1 (Ar), 137.1 (Ar), 136.1 (Ar), 132.7 (Ar), 131.6 (Ar), 130.7 (Ar), 129.1 (Ar), 129.0 (Ar), 125.9 (Ar), 122.2 (C-2), 120.3 (C-6), 119.9 (C-1), 111.1 (C-9), 111.0 (C-3), 53.9 (C-11), 45.0 (C-18, C-19), 20.2 (C-20).

HRMS (ESI) *m/z* calcd. for $C_{18}H_{21}N_2$ $[M+H]^+$: 265.1699; found: 265.1697.

FTIR (neat) ν/cm^{-1} = 2960, 2677, 1460, 1346, 1227, 1133, 1099, 1043, 1014, 927, 750, 730.

1-(2-(4-bromophenyl)-1H-indol-3-yl)-*N*,*N*-dimethylmethanamine, S16



S16 *was synthesis according to* ***general procedure D*** by using formaldehyde (37% w/w in water, 0.4 mL, 5.5 mmol, 1.1 equiv.), AcOH (5.2 mL), H_2O (0.4 mL) in dioxane (10.0 mL), dimethylamine (5.6 M in THF, 1.0 mL, 5.5 mmol, 1.1 equiv.) 2-(4-bromophenyl)-1H-indole **90** (1.36 g, 5.0 mmol, 1.0 equiv.), resulting a yellow solid in a yield of 90% (1.49 g, 3.7 mmol).

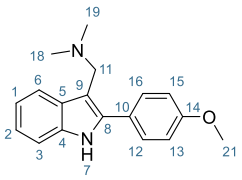
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (1H, s, H-7), 7.75 (1H, d, *J* = 7.9 Hz, H-6), 7.71 - 7.65 (2H, m, H-12, H-16), 7.61 - 7.56 (2H, m, H-13, H-15), 7.40 - 7.34 (1H, m, H-3), 7.22 (1H, ddd, *J* = 8.1, 7.0, 1.3 Hz, H-2), 7.16 (1H, ddd, *J* = 8.0, 7.0, 1.1 Hz, H-1), 3.58 (2H, s, H-11), 2.29 (6H, s, H-18, H-19).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 135.8 (Ar), 135.7 (Ar), 132.1 (C-13, C-15), 131.9 (Ar), 130.1 (Ar), 129.9 (C-12, C-16), 122.7 (C-2), 122.0 (C-14), 120.2 (C-1), 119.7 (C-6), 111.4 (C-9), 110.9 (C-3), 53.5 (C-11), 45.5 (C-18, C-19).

HRMS (ESI) m/z calcd. for $C_{17}H_{18}BrN_2$ $[M+H]^+$: 329.0648; found: 329.0633.

FTIR (neat) ν/cm^{-1} = 2940, 2857, 2816, 2775, 1486, 1456, 1344, 1313, 1233, 1170, 1073, 1011, 831, 743, 705.

1-(2-(4-methoxyphenyl)-1H-indol-3-yl)-*N*,*N*-dimethylmethanamine, S17



S17 *was synthesis according to* ***general procedure D*** by using formaldehyde (37% w/w in water, 116 µL, 1.4 mmol, 1.1 equiv.), AcOH (1.3 mL), H_2O (100 µL) in dioxane (2.5 mL), dimethylamine (5.6 M in THF, 250 µL, 1.4 mmol, 1.1 equiv.) 2-(4-methoxyphenyl)-1H-indole **91** (286 mg, 1.3 mmol, 1.0 equiv.), resulting a pale white solid in a yield of 86% (310 mg, 1.1 mmol).

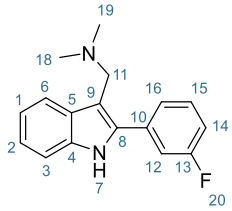
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (1H, s, H-7), 7.76 - 7.73 (1H, m, H-6), 7.73 - 7.68 (2H, m, H-12, H-16), 7.38 - 7.34 (1H, m, H-3), 7.19 (1H, ddd, *J* = 7.9, 7.1, 1.4 Hz, H-2), 7.14 (1H, ddd, *J* = 8.1, 7.1, 1.3 Hz, H-1), 7.04 - 6.98 (2H, m, H-13, H-15), 3.87 (3H, s, H-21), 3.60 (2H, s, H-11), 2.30 (6H, s, H-18, H-19).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 159.4 (C-14), 136.8 (Ar), 135.6 (Ar), 130.3 (Ar), 129.7 (C-12, C-16), 125.6 (Ar), 122.0 (C-2), 119.9 (C-1), 119.5 (C-6), 114.4 (C-13, C-15), 110.7 (C-3), 110.0 (C-9), 55.5 (C-21), 53.7 (C-11), 45.6 (C-18, C-19).

HRMS (ESI) m/z calcd. for $C_{18}H_{21}N_2O$ $[M+H]^+$: 281.1648; found: 281.1643.

FTIR (neat) ν/cm^{-1} = 2933, 2856, 2773, 1611, 1505, 1458, 1249, 1180, 1112, 1032, 1010, 835, 741.

1-(2-(3-fluorophenyl)-1H-indol-3-yl)-*N*,*N*-dimethylmethanamine, S18



S18 *was synthesis according to* ***general procedure D*** by using formaldehyde (37% w/w in water, 0.4 mL, 5.5 mmol, 1.1 equiv.), AcOH (5.2 mL), H_2O (0.4 mL) in dioxane (10.0 mL), dimethylamine (5.6 M in THF, 1.0 mL, 5.5 mmol, 1.1 equiv.) 2-(3-fluorophenyl)-1H-indole **93** (1.06 g, 5.0 mmol, 1.0 equiv.), resulting a brown solid in a yield of 70% (935 mg, 3.5 mmol).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31 (1H, s, H-7), 7.76 (1H, d, *J* = 7.9 Hz, H-6), 7.69 - 7.61 (1H, m, H-12), 7.54 (1H, dt, *J* = 7.7, 1.3 Hz, H-16), 7.43 (1H, dd, *J* = 8.1, 6.1 Hz, H-15), 7.38 (1H, dd, *J* = 8.9, 1.9 Hz, H-3), 7.25 - 7.20 (1H, m, H-2), 7.20 - 7.13 (1H, m, H-1), 7.09 - 7.02 (1H, m, H-14), 3.61 (2H, s, H-11), 2.31 (6H, s, H-18, H-19).

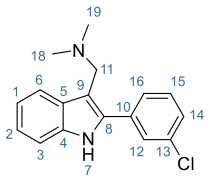
^{13}C NMR ($CDCl_3$, 101 MHz) δ 163.2 (d, *J* = 245.6 Hz, C-13), 135.8 (C-4), 135.5 (d, *J* = 2.3 Hz, C-8), 135.1 (d, *J* = 8.5 Hz, C-10), 130.4 (d, *J* = 8.5 Hz, C-15), 130.1 (C-5), 123.7 (d, *J* = 2.8 Hz, C-16), 122.8 (C-2), 120.2 (C-1), 119.7 (C-6), 115.5 (d, *J* = 23.1 Hz, C-12), 114.6 (d, *J* = 21.3 Hz, C-14), 111.6 (C-9), 111.0 (C-3), 53.4 (C-11), 45.4 (C-18, C-19).

^{19}F NMR ($CDCl_3$, 377 MHz) δ -112.19 (20).

HRMS (ESI) m/z calcd. for $C_{17}H_{17}FN_2Na$ $[M+Na]^+$: 291.1268; found: 291.1267.

FTIR (neat) ν/cm^{-1} = 2942, 2817, 2775, 1614, 1585, 1485, 1458, 1156, 1012, 884, 846, 788, 742.

1-(2-(3-chlorophenyl)-1H-indol-3-yl)-*N*,*N*-dimethylmethanamine, S19



S19 *was synthesis according to* ***general procedure D*** by using formaldehyde (37% w/w in water, 0.4 mL, 5.5 mmol, 1.1 equiv.), AcOH (5.2 mL), H_2O (0.4 mL) in dioxane (10.0 mL), dimethylamine (5.6 M in THF, 1.0 mL, 5.5 mmol, 1.1 equiv.) 2-(3-chlorophenyl)-1H-indole **94** (1.14 g, 5.0 mmol, 1.0 equiv.), resulting a brown solid in a yield of 65% (935 mg, 3.3 mmol).

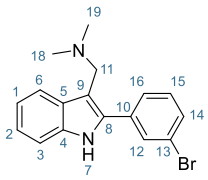
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.29 (1H, s, H-7), 7.89 (1H, t, *J* = 1.8 Hz, H-12), 7.76 (1H, d, *J* = 7.9 Hz, H-6), 7.66 (1H, dt, *J* = 7.5, 1.4 Hz, H-16), 7.42 - 7.30 (4H, m, H-3, H-14, H-15), 7.25 - 7.19 (1H, m, H-2), 7.19 - 7.13 (1H, m, H-1), 3.59 (2H, s, H-11), 2.31 (6H, s, H-18, H-19)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 135.8 (Ar), 135.3 (Ar), 134.9 (Ar), 134.8 (Ar), 130.1 (C-14), 130.1 (Ar), 128.5 (C-12), 127.7 (C-15), 126.3 (C-16), 122.8 (C-2), 120.2 (C-1), 119.8 (C-6), 111.9 (C-9), 111.0 (C-3), 53.5 (C-11), 45.5 (C-18, C-19)

HRMS (ESI) m/z calcd. for $C_{17}H_{18}ClN_2$ $[M+H]^+$: 285.1153; found: 285.1073. (Error = -8.0 mDa)

FTIR (neat) ν/cm^{-1} = 2943, 2816, 2771, 2248, 1599, 1567, 1011, 907, 839, 789, 731

1-(2-(3-bromophenyl)-1H-indol-3-yl)-*N*,*N*-dimethylmethanamine, S20



S20 *was synthesis according to* ***general procedure D*** by using formaldehyde (37% w/w in water, 0.4 mL, 5.5 mmol, 1.1 equiv.), AcOH (5.2 mL), H_2O (0.4 mL) in dioxane (10.0 mL), dimethylamine (5.6 M in THF, 1.0 mL, 5.5 mmol, 1.1 equiv.) 2-(3-bromophenyl)-1H-indole **95** (1.36 g, 5.0 mmol, 1.0 equiv.), resulting a pale white solid in a yield of 95% (1.56 g, 4.7 mmol).

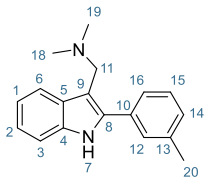
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (1H, s, H-7), 8.05 (1H, t, *J* = 1.8 Hz, H-12), 7.75 (1H, d, *J* = 7.9 Hz, H-6), 7.71 (1H, d, *J* = 7.8 Hz, H-14), 7.51 - 7.46 (1H, m, H-16), 7.40 - 7.28 (2H, m, H-3, H-15), 7.22 (1H, t, *J* = 7.5 Hz, H-2), 7.16 (1H, t, *J* = 7.4 Hz, H-1), 3.59 (2H, s, H-11), 2.31 (6H, s, H-18, H-19)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 135.8 (Ar), 135.1 (Ar), 135.0 (Ar), 131.4 (C-12), 130.6 (C-16), 130.4 (C-15), 130.1 (Ar), 126.7 (C-14), 123.1 (C-13), 122.8 (C-2), 120.2 (C-1), 119.7 (C-6), 112.0 (C-9), 111.0 (C-3), 53.5 (C-11), 45.5 (C-18, C-19)

HRMS (ESI) m/z calcd. for $C_{17}H_{18}BrN_2$ $[M+H]^+$: 329.0648; found: 329.0638.

FTIR (neat) ν/cm^{-1} = 2940, 2815, 2774, 1597, 1562, 1454, 1011, 883, 839, 821, 787, 753, 720

***N*,*N*-dimethyl-1-(2-(m-tolyl)-1H-indol-3-yl)methanamine, S21**



S21 *was synthesis according to* ***general procedure D*** by using formaldehyde (37% w/w in water, 0.4 mL, 5.5 mmol, 1.1 equiv.), AcOH (5.2 mL), H_2O (0.4 mL) in dioxane (10.0 mL), dimethylamine (5.6 M in THF, 1.0 mL, 5.5 mmol, 1.1 equiv.) 2-(m-tolyl)-1H-indole **96** (1.03 g, 5.0 mmol, 1.0 equiv.), resulting a yellow solid in a yield of 99% (1.31 g, 5.0 mmol).

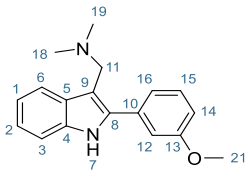
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (1H, s, H-7), 7.77 (1H, ddt, *J* = 7.8, 1.5, 0.7 Hz, H-6), 7.65 - 7.54 (2H, m, H-12, H-16), 7.40 - 7.34 (2H, m, H-3, H-15), 7.23 - 7.17 (2H, m, H-2, H-14), 7.17 - 7.12 (1H, m, H-1), 3.63 (2H, s, H-11), 2.44 (3H, s, H-20), 2.31 (6H, d, *J* = 0.6 Hz, H-18, H-19)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 138.5 (C-13), 136.9 (Ar), 135.7 (Ar), 133.0 (Ar), 130.2 (Ar), 129.1 (C-12), 128.8 (C-15), 128.6 (C-14), 122.3 (C-2), 120.0 (C-1), 119.7 (C-6), 110.8 (C-9), 110.8 (C-3), 53.8 (C-11), 45.6 (C-18, C-19), 21.7 (C-20)

HRMS (ESI) m/z calcd. for $C_{18}H_{21}N_2$ $[M+H]^+$: 265.1699; found: 265.1696.

FTIR (neat) ν/cm^{-1} = 2958, 2677, 1607, 1460, 1340, 1160, 1093, 1040, 909, 819, 791, 730, 706

1-(2-(3-methoxyphenyl)-1H-indol-3-yl)-*N*,*N*-dimethylmethanamine, S22



S22 *was synthesis according to* ***general procedure D*** by using formaldehyde (37% w/w in water, 160 µL, 2.2 mmol, 1.1 equiv.), AcOH (2.0 mL), H_2O (152 µL) in dioxane (4.0 mL), dimethylamine (5.6 M in THF, 390 µL, 2.2 mmol, 1.1 equiv.) 2-(3-methoxyphenyl)-1H-indole **81** (442 mg, 2.0 mmol, 1.0 equiv.), resulting a pale white solid in a yield of 67% (376 mg, 1.3 mmol).

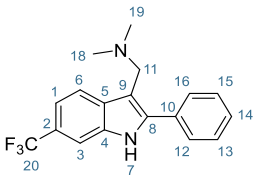
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (1H, s, H-7), 7.76 (1H, ddt, *J* = 7.8, 1.5, 0.7 Hz, H-6), 7.58 (1H, dd, *J* = 2.6, 1.5 Hz, H-12), 7.41 - 7.35 (2H, m, H-3, H-15), 7.31 (1H, ddd, *J* = 7.6, 1.6, 1.1 Hz, H-16), 7.21 (1H, ddd, *J* = 8.1, 7.0, 1.3 Hz, H-2), 7.15 (1H, ddd, *J* = 7.8, 7.1, 1.2 Hz, H-1), 6.93 (1H, ddd, *J* = 8.2, 2.6, 1.1 Hz, H-14), 3.89 (3H, s, H-21), 3.63 (2H, s, H-11), 2.31 (6H, s, H-18, H-19)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 160.1 (C-13), 136.7 (Ar), 135.6 (Ar), 134.4 (Ar), 130.3 (Ar), 129.9 (C-15), 122.4 (C-2), 120.3 (C-16), 120.0 (C-1), 119.7 (C-6), 114.0 (C-12), 113.9 (C-14), 111.0 (C-9), 110.8 (C-3), 55.5 (C-21), 53.7 (C-11), 45.6 (C-18, C-19)

HRMS (ESI) m/z calcd. for $C_{18}H_{21}N_2O$ $[M+H]^+$: 281.1648; found: 281.1646.

FTIR (neat) ν/cm^{-1} = 2929, 2854, 2773, 1605, 1462, 1343, 1286, 1234, 1165, 1041, 1011, 847, 788, 741

***N*,*N*-dimethyl-1-(2-phenyl-6-(trifluoromethyl)-1H-indol-3-yl)methanamine, S23**



S23 *was synthesis according to* ***general procedure D*** by using formaldehyde (37% w/w in water, 162 µL, 1.1 mmol, 1.1 equiv.), AcOH (1.0 mL), H_2O (80 µL) in dioxane (2.0 mL), dimethylamine (5.6 M in THF, 200 µL, 1.1 mmol, 1.1 equiv.) 2-phenyl-6-(trifluoromethyl)-1H-indole **101** (261 mg, 1.0 mmol, 1.0 equiv.), resulting a pale white solid in a yield of 66% (210 mg, 0.7 mmol).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.45 (1H, s, H-7), 7.85 (1H, dq, *J* = 8.4, 0.8 Hz, H-6), 7.78 - 7.74 (2H, m, H-12, H-16), 7.66 - 7.61 (1H, m, H-3), 7.53 - 7.47 (2H, m, H-13, H-15), 7.45 - 7.36 (2H, m, H-1, H-14), 3.63 (2H, s, H-11), 2.28 (6H, s, H-18, H-19)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 139.4 (Ar), 134.5 (Ar), 132.4 (Ar), 132.3 (Ar), 129.1 (C-13, C-15), 128.6 (C-12, C-16), 128.5 (C-14), 125.4 (q, *J* = 271.8 Hz, C-20), 124.3 (q, *J* = 31.8 Hz, C-2), 120.1 (C-6), 116.7 (q, *J* = 4.0 Hz, C-1), 111.2 (C-9), 108.4 (q, *J* = 4.4 Hz, C-3), 53.6 (C-11), 45.5 (C-18, C-19)

^{19}F NMR ($CDCl_3$, 377 MHz) δ -60.59 (20)

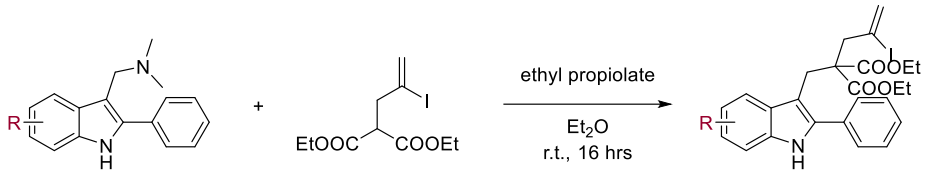
HRMS (ESI) m/z calcd. for $C_{18}H_{18}F_3N_2$ $[M+H]^+$: 319.1417; found: 319.1412.

FTIR (neat) ν/cm^{-1} = 2777, 1466, 1339, 1238, 1164, 1115, 1053, 1000, 927, 816, 769, 735, 700

Synthesis of Photochemical Substrates

General Procedure

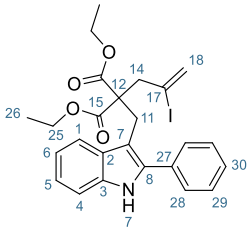
General procedure E



N,N-dimethyl-1-(2-phenyl-1H-indol-3-yl)methanamine (1.0 equiv.) was dissolved in Et_2O (0.2 M). Diethyl 2-(2-iodoallyl)malonate **72** (1.2 equiv.) was added to the solution followed by a quick addition of ethyl propiolate (1.1 equiv.). The reaction was stirred for 16 hrs at room temperature. The mixture was quenched by H_2O then was extracted with EtOAc three times. The combined organic phase was dried over $MgSO_4$ and solvent was removed under vacuum. The concentrated crude product was purified by flash column chromatography on aluminium oxide (EtOAc: pentane =1: 5, ca. 60 mL Al_2O_3 for a 1.5 mmol scale reaction). Then followed by a recrystallisation (Et_2O/Pentane) to give the desired product.

Characterisation

diethyl 2-(2-iodoallyl)-2-((2-phenyl-1H-indol-3-yl)methyl)malonate, 62



62 *was synthesised according to a modified* ***general procedure E*** by using N,N-dimethyl-1-(2-phenyl-1H-indol-3-yl)methanamine **66** (275 mg, 1.1 mmol, 1.1 equiv.), diethyl 2-(2-iodoallyl)malonate **72** (326 mg, 1.0 mmol, 1.0 equiv.) and ethyl propiolate (112 µL, 1.1 mmol, 1.1 equiv.) in Et_2O (5.0 mL) to afford **62** in a yield of 64% (340 mg, 0.64 mmol) as a white solid.

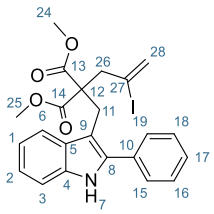
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.08 (1H, s, H-9), 7.64 (1H, ddd, *J* = 7.8, 1.5, 0.7 Hz, H-4), 7.58 - 7.51 (2H, m, H-29, H-31), 7.49 - 7.41 (2H, m, H-28, H-32), 7.41 - 7.35 (1H, m, H-30), 7.35 - 7.28 (1H, m, H-1), 7.18 (1H, ddd, *J* = 8.0, 7.0, 1.3 Hz, H-5), 7.13 (1H, ddd, *J* = 8.1, 7.1, 1.2 Hz, H-6), 5.95 (1H, dd, *J* = 2.8, 1.6 Hz, 18''), 5.70 (1H, dt, *J* = 2.6, 1.1 Hz, 18'), 3.94 (2H, dq, *J* = 10.8, 7.1 Hz, 22'', 25''), 3.84 (2H, s, H-11), 3.70 (2H, dq, *J* = 10.7, 7.1 Hz, 22', 25'), 2.97 (2H, t, *J* = 1.4 Hz, H-14), 1.06 (6H, t, *J* = 7.1 Hz, H-23, H-26)

^{13}C NMR (CDCl3, 101 MHz) δ 170.3 (C-15), 137.0 (C-3), 135.6 (C-8), 133.5 (C-27), 129.8 (C-7), 129.1 (C-29), 128.9 (C-28), 128.1 (C-30), 127.4 (C-18), 122.3 (C-5), 119.9 (C-6), 119.7 (C-1), 110.7 (C-4), 106.5 (C-17), 104.4 (C-2), 61.4 (C-25), 58.8 (C-12), 47.3 (C-14), 27.3 (C-11), 13.7 (C-26)

HRMS (+ESI): *m/z* calcd for $C_{25}H_{27}INO_4^+$ $[M^+H]^+$ 532.0979, found 532.0980

FT-IR (thin film): *ν*max (cm^{-1}) = 3402, 2989, 1725, 1623, 1449, 1367, 1297, 1215, 1189, 1094, 1070, 1013, 906, 859, 744, 697, 640

dimethyl 2-(2-iodoallyl)-2-((2-phenyl-1H-indol-3-yl)methyl)malonate, 178



178 *was synthesised according to a modified* ***general procedure E*** by using N,N-dimethyl-1-(2-phenyl-1H-indol-3-yl)methanamine **66** (625.9 mg, 3.6 mmol, 1.1 equiv.), dimethyl 2-(2-iodoallyl)malonate **S5** (681 mg, 3.0 mmol, 1.0 equiv.) and ethyl propiolate (280 µL, 1.1 mmol, 1.1 equiv.) in Et_2O (15.0 mL) to afford **178** in a yield of 17% (260 mg, 0.51 mmol) as a white solid.

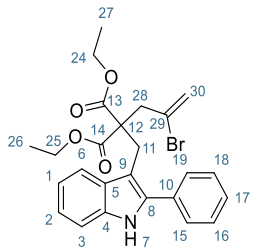
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (1H, s, H-7), 7.61 (1H, ddt, *J* = 7.6, 1.5, 0.8 Hz, H-6), 7.58 – 7.53 (2H, m, H-15, H-19), 7.48 – 7.43 (2H, m, H-16, H-18), 7.41 – 7.35 (1H, m, H-17), 7.35 – 7.30 (1H, m, H-3), 7.18 (1H, ddd, *J* = 8.0, 7.0, 1.4 Hz, H-2), 7.14 (1H, ddd, *J* = 8.3, 7.0, 1.3 Hz, H-1), 5.93 (1H, dt, *J* = 3.1, 1.6 Hz, 28'), 5.71 (1H, dt, *J* = 2.4, 1.1 Hz, 28''), 3.86 (2H, s, H-11), 3.38 (6H, s, H-24, H-25), 2.97 (2H, t, *J* = 1.4 Hz, H-26).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.8 (C-13, C-14), 137.1 (C-8), 135.7 (C-4), 133.6 (C-10), 129.2 (C-16, C-18), 129.0 (C-15, C-19), 128.3 (C-17), 127.9 (C-28), 122.4 (C-2), 120.1 (C-1), 119.7 (C-6), 110.9 (C-3), 106.3 (C-9), 104.1 (C-27), 58.9 (C-12), 52.5 (C-24, C-25), 47.6 (C-26), 28.0 (C-11).

HRMS (ESI) m/z calcd. for $C_{23}H_{22}INO_4K$ $[M+K]^+$: 542.0225,; found: 542.0222.

FTIR (neat) ν/cm^{-1} = 3383, 2950, 1727, 1606, 1435, 1295, 1218, 1126, 909, 738, 699

diethyl 2-(2-bromoallyl)-2-((2-phenyl-1H-indol-3-yl)methyl)malonate, S24



S24 *was synthesised according to a modified* ***general procedure E*** by using N,N-dimethyl-1-(2-phenyl-1H-indol-3-yl)methanamine **66** (1.37 g, 5.5 mmol, 1.1 equiv.), diethyl 2-(2-bromoallyl)malonate **S4** (1.40 g, 5.0 mmol, 1.0 equiv.) and ethyl propiolate (586 µL, 5.5 mmol, 1.1 equiv.) in Et_2O (25.0 mL) to afford **S24** in a yield of 42% (1.02 g, 2.10 mmol) as a white solid.

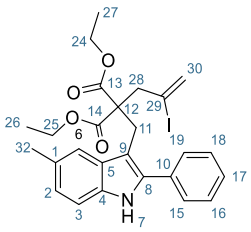
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (1H, s, H-7), 7.65 (1H, ddt, *J* = 7.9, 1.5, 0.7 Hz, H-6), 7.60 - 7.51 (2H, m, H-15, H-19), 7.48 - 7.41 (2H, m, H-16, H-18), 7.40 - 7.34 (1H, m, H-17), 7.34 - 7.29 (1H, m, H-3), 7.20 - 7.15 (1H, m, H-2), 7.12 (1H, ddd, *J* = 8.1, 7.0, 1.2 Hz, H-1), 5.49 (1H, dt, *J* = 2.7, 1.5 Hz, 30''), 5.39 (1H, dd, *J* = 2.5, 0.8 Hz, 30'), 3.94 (2H, dq, *J* = 10.7, 7.1 Hz, 24'', 25''), 3.83 (2H, s, H-11), 3.71 (2H, dq, *J* = 10.7, 7.1 Hz, 24', 25'), 2.91 (2H, dd, *J* = 1.5, 0.8 Hz, H-28), 1.06 (6H, t, *J* = 7.1 Hz, H-26, H-27)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.6 (C-13, C-14), 137.2 (C-4), 135.7 (C-8), 133.6 (C-10), 129.9 (C-5), 129.1 (C-15, C-19), 129.0 (C-16, C-18), 128.9 (C-29), 128.2 (C-17), 122.4 (C-2), 119.9 (C-1), 119.8 (C-6), 119.2 (C-30), 110.8 (C-3), 106.6 (C-9), 61.5 (C-24, C-25), 58.4 (C-12), 43.7 (C-28), 27.5 (C-11), 13.8 (C-26, C-27)

HRMS (ESI) *m/z* calcd. for $C_{25}H_{27}BrNO_4$ $[M+H]^+$: 484.1118; found: 484.1110.

FTIR (neat) ν/cm^{-1} = 3401, 2983, 1725, 1635, 1449, 1298, 1216, 1139, 900, 861, 743, 698

diethyl 2-(2-iodoallyl)-2-((5-methyl-2-phenyl-1H-indol-3-yl)methyl)malonate, S25



S25 *was synthesised according to* ***general procedure E*** by using N,N-dimethyl-1-(5-methyl-2-phenyl-1H-indol-3-yl)methanamine **S10** (397 mg, 1.5 mmol, 1.0 equiv.), diethyl 2-(2-iodoallyl)malonate **72** (733 mg, 2.25 mmol, 1.5 equiv.) and ethyl propiolate (168 µL, 1.65 mmol, 1.1 equiv.) in Et_2O (7.5 mL) to afford **S25** in a yield of 40% (311 mg, 0.60 mmol) as a white solid.

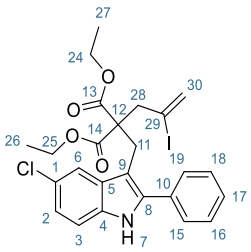
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (1H, s, H-7), 7.58 - 7.49 (2H, m, H-15, H-19), 7.47 - 7.32 (4H, m, H-6, H-16, H-17, H-18), 7.21 (1H, d, *J* = 8.2 Hz, H-3), 7.04 - 6.97 (1H, m, H-2), 5.98 (1H, dd, *J* = 2.8, 1.6 Hz, 30''), 5.72 (1H, dt, *J* = 2.7, 1.2 Hz, 30'), 3.95 (2H, dq, *J* = 10.7, 7.1 Hz, 24', 25'), 3.83 (2H, d, *J* = 1.8 Hz, H-11), 3.69 (2H, dq, *J* = 10.7, 7.1 Hz, 24'', 25''), 2.97 (2H, t, *J* = 1.5 Hz, H-28), 2.48 (3H, s, H-32), 1.16 - 1.03 (6H, m, H-26, H-27)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.4 (C-13, C-14), 137.2 (C-4), 134.0 (Ar), 133.8 (Ar), 130.2 (Ar), 129.1 (C-16, C-18), 129.1 (Ar), 129.0 (C-15, C-19), 128.1 (C-17), 127.1 (C-30), 124.0 (C-2), 119.4 (C-6), 110.5 (C-3), 106.0 (C-9), 104.9 (C-29), 61.5 (C-24, C-25), 58.9 (C-12), 47.2 (C-28), 27.2 (C-11), 21.8 (C-32), 13.9 (d, *J* = 4.1 Hz, C-26, C-27)

HRMS (ESI) m/z calcd. for $C_{26}H_{28}INO_4Na$ $[M+Na]^+$: 568.0955; found: 568.0952.

FTIR (neat) ν/cm^{-1} = 3380, 2980, 1723, 1449, 1367, 1293, 1216, 1154, 1074, 1026, 909, 860, 796, 768, 733

diethyl 2-((5-chloro-2-phenyl-1H-indol-3-yl)methyl)-2-(2-iodoallyl)malonate, S26



S26 *was synthesised according to* ***general procedure E*** by using 1-(5-chloro-2-phenyl-1H-indol-3-yl)-N,N-dimethylmethanamine **S11** (427 mg, 1.5 mmol, 1.0 equiv.), diethyl 2-(2-iodoallyl)malonate **72** (733 mg, 2.25 mmol, 1.5 equiv.) and ethyl propiolate (168 µL, 1.65 mmol, 1.1 equiv.) in Et_2O (7.5 mL) to afford **S26** in a yield of 54% (458 mg, 0.81 mmol) as a white solid.

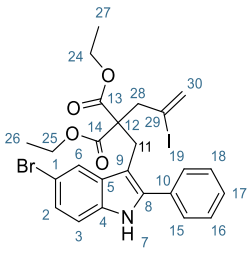
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (1H, s, H-7), 7.58 (1H, ddt, *J* = 1.9, 1.2, 0.6 Hz, H-6), 7.55 - 7.48 (2H, m, H-15, H-19), 7.48 - 7.42 (3H, m, H-16, H-18), 7.42 - 7.36 (1H, m, H-17), 7.23 (1H, dt, *J* = 8.6, 0.8 Hz, H-3), 7.12 (1H, dd, *J* = 8.6, 2.0 Hz, H-2), 5.89 (1H, dt, *J* = 2.8, 1.7 Hz, 30'), 5.67 (1H, dd, *J* = 2.6, 1.3 Hz, 30''), 4.07 - 3.92 (3H, m, 24'', 25'), 3.81 - 3.72 (4H, m, H-11, 24', 25''), 2.94 - 2.89 (2H, m, H-28), 1.13 (9H, dt, *J* = 15.3, 7.1 Hz, H-26, H-27)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.3 (C-13, C-14), 138.7 (C-4), 134.0 (Ar), 133.0 (Ar), 130.9 (Ar), 129.3 (C-16, C-18), 129.0 (C-15, C-19), 128.6 (C-17), 127.4 (C-30), 125.7 (Ar), 122.7 (C-2), 119.3 (C-6), 111.9 (C-3), 106.4 (C-9), 104.2 (C-29), 61.7 (C-24, C-25), 58.8 (C-12), 47.3 (C-28), 27.1 (C-11), 13.9 (C-26, C-27)

HRMS (ESI) m/z calcd. for $C_{25}H_{25}ClINO_4Na$ $[M+Na]^+$: 588.0409; found: 588.0428.

FTIR (neat) ν/cm^{-1} = 3367, 2981, 1721, 1466, 1367, 1306, 1216, 1066, 1025, 860, 798, 762, 700

diethyl 2-((5-bromo-2-phenyl-1H-indol-3-yl)methyl)-2-(2-iodoallyl)malonate, S27



S27 *was synthesised according to general procedure E* by using 1-(5-bromo-2-phenyl-1H-indol-3-yl)-N,N-dimethylmethanamine **S12** (480 mg, 1.45 mmol, 1.0 equiv.), diethyl 2-(2-iodoallyl)malonate **72** (618 mg, 1.9 mmol, 1.3 equiv.) and ethyl propiolate (163 µL, 1.60 mmol, 1.1 equiv.) in Et_2O (7.5 mL) to afford **S27** in a yield of 45% (398 mg, 0.65 mmol) as a yellow solid.

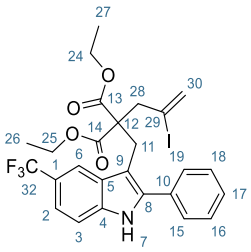
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (1H, s, H-7), 7.73 (1H, dd, *J* = 1.9, 0.7 Hz, H-6), 7.53 - 7.37 (5H, m, H-15, H-16, H-17, H-18, H-19), 7.29 - 7.22 (1H, m, H-2), 7.18 (1H, dd, *J* = 8.6, 0.6 Hz, H-3), 5.92 - 5.86 (1H, m, 30''), 5.66 (1H, dt, *J* = 2.6, 1.2 Hz, 30'), 4.00 (2H, dq, *J* = 10.8, 7.1 Hz, 24'', 25''), 3.86 - 3.73 (4H, m, H-11, 24', 25'), 2.91 (2H, t, *J* = 1.5 Hz, H-28), 1.12 (7H, t, *J* = 7.1 Hz, H-26, H-27)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.3 (C-13, C-14), 138.5 (C-4), 134.3 (C-8), 132.9 (C-10), 131.5 (C-5), 129.3 (C-16, C-18), 129.0 (C-15, C-19), 128.6 (C-17), 127.3 (C-30), 125.2 (C-2), 122.3 (C-6), 113.3 (C-1), 112.4 (C-3), 106.3 (C-9), 104.2 (C-29), 61.7 (C-24, C-25), 58.7 (C-12), 47.3 (C-28), 27.1 (C-11), 13.9 (C-26, C-27)

HRMS (ESI) m/z calcd. for C25H26BrINO4 [M+H]+: 610.0085; found: 610.0078.

FTIR (neat) ν/cm-1 = 3400, 2980, 1721, 1624, 1466, 1367, 1305, 1214, 1093, 1011, 912, 859, 796, 765, 734, 700

diethyl 2-(2-iodoallyl)-2-((2-phenyl-5-(trifluoromethyl)-1H-indol-3-yl)methyl)malonate, S28



S28 *was synthesised according to general procedure E* by using N,N-dimethyl-1-(2-phenyl-5-(trifluoromethyl)-1H-indol-3-yl)methanamine **S13** (160 mg, 0.5 mmol, 1.0 equiv.), diethyl 2-(2-iodoallyl)malonate **72** (245 mg, 0.75 mmol, 1.5 equiv.) and ethyl propiolate (56 µL, 0.55 mmol, 1.1 equiv.) in Et_2O (2.5 mL) to afford **S28** in a yield of 40% (120 mg, 0.20 mmol) as a white solid.

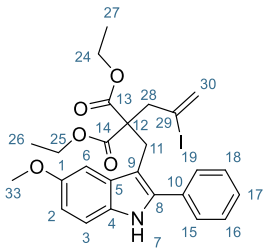
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (1H, s, H-7), 7.94 – 7.89 (1H, m, H-6), 7.60 – 7.36 (9H, m, H-2, H-3, H-15, H-16, H-17, H-18, H-19), 5.88 (1H, dd, *J* = 3.1, 1.4 Hz, 30'), 5.64 (1H, dt, *J* = 2.5, 1.1 Hz, 30''), 3.99 (2H, dq, *J* = 10.8, 7.2 Hz, 24'', 25'), 3.84 (2H, s, H-11), 3.79 (2H, dt, *J* = 10.7, 7.0 Hz, 24', 25''), 2.86 (2H, s, H-28), 1.09 (6H, t, *J* = 7.2 Hz, H-26, H-27).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.3 (C-13, C-14), 139.1 (C-4), 137.0 (C-8), 132.8 (C-10), 129.4 (C-16, C-18), 129.1 (C-15, C-19), 128.8 (C-17), 127.5 (d, *J* = 128.3 Hz), 127.4 (C-30, C-32), 122.4 (d, *J* = 31.8 Hz, C-1), 119.1 (d, *J* = 3.6 Hz, C-2), 117.5 (d, *J* = 4.2 Hz, C-6), 111.2 (C-3), 107.5 (C-9), 103.9 (C-29), 61.7 (C-24, C-25), 43.1 (C-28), 27.2 (C-11), 13.8 (C-26, C-27)

HRMS (ESI) *m/z* calcd. for $C_{25}H_{26}BrINO_4$ $[M+H]^+$: 610.0085; found: 610.0078.

FTIR (neat) ν/cm^{-1} = 3368, 2982, 1724, 1669, 1609, 1451, 1367, 1332, 1301, 1278, 1212, 1159, 1111, 1060, 1026, 907, 859, 810, 768, 736, 699

diethyl 2-(2-iodoallyl)-2-((5-methoxy-2-phenyl-1H-indol-3-yl)methyl)malonate, S29



S29 *was synthesised according to general procedure E* by using 1-(5-methoxy-2-phenyl-1H-indol-3-yl)-N,N-dimethylmethanamine **S14** (141 mg, 0.5 mmol, 1.0 equiv.), diethyl 2-(2-iodoallyl)malonate **72** (245 mg, 0.75 mmol, 1.5 equiv.) and ethyl propiolate (56 µL, 0.55 mmol, 1.1 equiv.) in Et_2O (2.5 mL) to afford **S29** in a yield of 40% (113 mg, 0.20 mmol) as a white solid.

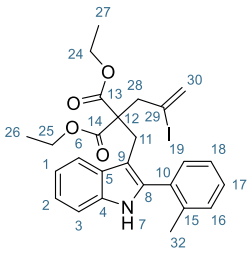
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (1H, s, H-7), 7.56 - 7.51 (2H, m, H-15, H-19), 7.44 (2H, tt, *J* = 6.8, 0.8 Hz, H-16, H-18), 7.39 - 7.33 (1H, m, H-17), 7.21 (1H, dd, *J* = 8.8, 0.5 Hz, H-3), 7.14 (1H, d, *J* = 2.4 Hz, H-6), 6.84 (1H, dd, *J* = 8.7, 2.4 Hz, H-2), 6.03 (1H, dt, *J* = 2.7, 1.7 Hz, 30''), 5.75 (1H, dt, *J* = 2.5, 1.2 Hz, 30'), 3.99 - 3.87 (5H, m, 24', 25', H-33), 3.82 (2H, s, H-11), 3.66 (2H, dq, *J* = 10.7, 7.1 Hz, 24'', 25''), 3.00 (2H, t, *J* = 1.5 Hz, H-28), 1.04 (6H, t, *J* = 7.1 Hz, H-26, H-27)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.5 (C-13, C-14), 154.4 (C-1), 137.8 (C-4), 133.7 (C-8), 130.8 (C-10), 130.5 (C-5), 129.1 (C-16, C-18), 128.9 (C-15, C-19), 128.1 (C-17), 127.2 (C-30), 112.8 (C-2), 111.6 (C-3), 106.4 (C-9), 105.0 (C-29), 101.5 (C-6), 61.5 (C-24, C-25), 58.9 (C-12), 56.1 (C-33), 47.5 (C-28), 27.5 (C-11), 13.8 (C-26, C-27)

HRMS (ESI) m/z calcd. for $C_{26}H_{28}INO_5Na$ $[M+Na]^+$: 584.0904; found: 584.0907.

FTIR (neat) ν/cm^{-1} = 3384, 2982, 1723, 1624, 1481, 1454, 1367, 1309, 1218, 1131, 1074, 1027, 909, 837, 801, 769, 734, 699

diethyl 2-(2-iodoallyl)-2-((2-(o-tolyl)-1H-indol-3-yl)methyl)malonate, S30



S30 *was synthesised according to general procedure E* by using 2-(o-tolyl)-1H-indole **80** (375 mg, 1.42 mmol, 1.0 equiv.), diethyl 2-(2-iodoallyl)malonate **72** (694 mg, 2.13 mmol, 1.5 equiv.) and ethyl propiolate (144 μL, 1.56 mmol, 1.1 equiv.) in Et_2O (7.0 mL) to afford **S30** in a yield of 58% (450 mg, 0.83 mmol) as a white solid.

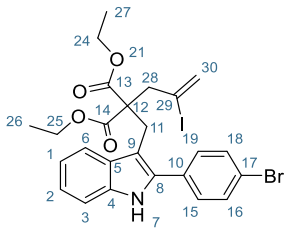
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (1H, s, H-7), 7.62 (1H, dd, *J* = 7.9, 1.2 Hz, H-6), 7.38 – 7.27 (5H, m, H-3, H-16, H-17, H-18, H-19), 7.18 (1H, ddd, *J* = 8.1, 7.0, 1.4 Hz, H-2), 7.12 (1H, ddd, *J* = 8.1, 7.0, 1.2 Hz, H-1), 5.74 (1H, t, *J* = 2.1 Hz, 30'), 5.64 (1H, dd, *J* = 2.4, 1.2 Hz, 30''), 3.86 (5H, ddq, *J* = 80.1, 10.8, 7.2 Hz, 24', 25'), 3.62 (2H, s, H-11), 2.92 (2H, d, *J* = 1.5 Hz, H-28), 2.31 (3H, s, H-32), 1.07 (6H, t, *J* = 7.2 Hz, H-26, H-27).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.4 (C-13, C-14), 137.7 (C-15), 136.8 (C-8), 135.6 (C-4), 132.6 (C-10), 131.4 (Ar), 131.0 (Ar), 129.3 (C-5), 128.9 (Ar), 128.0 (C-30), 126.2 (Ar), 122.1 (C-2), 119.7 (C-1), 119.7 (C-6), 110.6 (C-3), 107.5 (C-9), 103.8 (C-29), 61.5 (C-24, C-25), 58.8 (C-12), 47.2 (C-28), 27.8 (C-11), 13.8 (C-26, C-27).

HRMS (ESI) *m/z* calcd. for $C_{26}H_{29}INO_4$ $[M+H]^+$: 546.1136; found: 546.1131.

FTIR (neat) ν/cm^{-1} = 3379, 2917, 1725,1460, 1368, 1299, 1216, 1034, 909, 859, 735.

diethyl 2-((2-(4-bromophenyl)-1H-indol-3-yl)methyl)-2-(2-iodoallyl)malonate, S31



S31 *was synthesised according to general procedure E* by using 1-(2-(4-bromophenyl)-1H-indol-3-yl)-N,N-dimethylmethanamine **S16** (494 mg, 1.5 mmol, 1.0 equiv.), diethyl 2-(2-iodoallyl)malonate **72** (733 mg, 2.25 mmol, 1.5 equiv.) and ethyl propiolate (168 µL, 1.65 mmol, 1.1 equiv.) in Et_2O (7.5 mL) to afford **S31** in a yield of 70% (641 mg, 1.05 mmol) as a white solid.

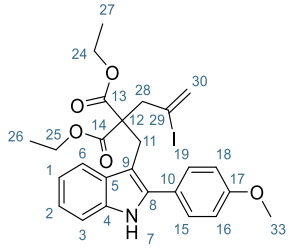
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (1H, s, H-7), 7.65 - 7.60 (1H, m, H-6), 7.58 - 7.52 (2H, m, H-15, H-19), 7.43 - 7.37 (2H, m, H-16, H-18), 7.31 (1H, dt, *J* = 8.0, 1.0 Hz, H-3), 7.19 (1H, ddd, *J* = 8.1, 7.0, 1.3 Hz, H-2), 7.13 (1H, ddd, *J* = 8.1, 7.0, 1.2 Hz, H-1), 5.98 (1H, q, *J* = 1.9 Hz, 30'), 5.73 (1H, dd, *J* = 2.7, 1.3 Hz, 30''), 3.96 (2H, dq, *J* = 10.7, 7.1 Hz, 24'', 25''), 3.81 (2H, s, H-11), 3.74 (2H, dq, *J* = 10.8, 7.1 Hz, 24', 25'), 2.97 (2H, t, *J* = 1.5 Hz, H-28), 1.07 (6H, t, *J* = 7.1 Hz, H-26, H-27)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.4 (C-13, C-14), 135.8 (Ar), 132.4 (Ar), 132.4 (C-15, C-19), 130.6 (Ar), 130.5 (C-16, C-18), 129.8 (Ar), 127.3 (C-30), 122.7 (Ar), 122.5 (C-2), 120.2 (C-1), 119.9 (C-6), 110.9 (C-3), 107.2 (C-9), 104.5 (C-29), 61.6 (C-24, C-25), 47.5 (C-28), 27.2 (C-11), 13.8 (C-26, C-27)

HRMS (ESI) m/z calcd. for $C_{25}H_{25}BrINO_4Na$ $[M+Na]^+$: 631.9904; found: 631.9892.

FTIR (neat) ν/cm^{-1} = 3373, 2981, 1720, 1623, 1484, 1457, 1438, 1367, 1296, 1216, 1071, 1011, 908, 859, 832, 740, 705

diethyl 2-(2-iodoallyl)-2-((2-(4-methoxyphenyl)-1H-indol-3-yl)methyl)malonate, S32



S32 *was synthesised according to general procedure E* by using 1-(2-(4-methoxyphenyl)-1H-indol-3-yl)-N,N-dimethylmethanamine **S17** (310 mg, 1.1 mmol, 1.0 equiv.), diethyl 2-(2-iodoallyl)malonate **72** (469 mg, 1.44 mmol, 1.3 equiv.) and ethyl propiolate (123 µL, 1.21 mmol, 1.1 equiv.) in Et_2O (5.5 mL) to afford **S32** in a yield of 62% (380 mg, 0.68 mmol) as a white solid.

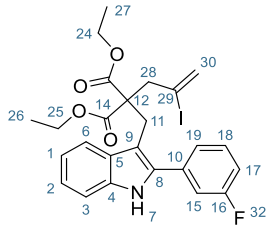
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (1H, s, H-7), 7.61 (1H, ddt, *J* = 7.7, 1.6, 0.7 Hz, H-6), 7.50 - 7.42 (2H, m, H-15, H-19), 7.30 (1H, ddd, *J* = 8.0, 1.3, 0.8 Hz, H-3), 7.19 - 7.08 (2H, m, H-1, H-2), 7.00 - 6.94 (2H, m, H-16, H-18), 5.98 - 5.92 (1H, m, 30''), 5.71 (1H, dt, *J* = 2.5, 1.1 Hz, 30'), 3.96 (2H, dq, *J* = 10.8, 7.1 Hz, 24', 25'), 3.86 (3H, s, H-33), 3.81 (2H, s, H-11), 3.74 (2H, dt, *J* = 10.7, 7.1 Hz, 24'', 25''), 2.96 (2H, d, *J* = 1.5 Hz, H-28), 1.07 (6H, t, *J* = 7.1 Hz, H-26, H-27)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.5 (C-13, C-14), 159.7 (C-17), 137.1 (C-4), 135.6 (C-8), 130.2 (C-15, C-19), 129.9 (C-5), 127.4 (C-30), 126.0 (C-10), 122.1 (C-2), 119.9 (C-6), 119.6 (C-1), 114.7 (C-16, C-18), 110.7 (C-3), 106.1 (C-9), 104.6 (C-29), 61.5 (C-24, C-25), 59.0 (C-12), 55.6 (C-33), 47.5 (C-28), 27.4 (C-11), 13.8 (C-26, C-27)

HRMS (ESI) *m/z* calcd. for $C_{26}H_{29}INO_5$ $[M+H]^+$: 562.1085; found: 562.1080.

FTIR (neat) ν/cm^{-1} = 3392, 3019, 1723, 1614, 1505, 1459, 1439, 1368, 1287, 1247, 1216, 1030, 902, 837, 755

diethyl 2-((2-(3-fluorophenyl)-1H-indol-3-yl)methyl)-2-(2-iodoallyl)malonate, S33



S33 *was synthesised according to general procedure E* by using 1-(2-(3-fluorophenyl)-1H-indol-3-yl)-N,N-dimethylmethanamine **S18** (403 mg, 1.5 mmol, 1.0 equiv.), diethyl 2-(2-iodoallyl)malonate **72** (733 mg, 2.25 mmol, 1.5 equiv.) and ethyl propiolate (168 µL, 1.65 mmol, 1.1 equiv.) in Et_2O (7.5 mL) to afford **S33** in a yield of 33% (275 mg, 0.50 mmol) as a white solid

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (1H, s, H-7), 7.63 (1H, d, *J* = 7.9 Hz, H-6), 7.43 (1H, td, *J* = 7.9, 5.8 Hz, H-19), 7.36 - 7.31 (2H, m, H-3, H-18), 7.30 - 7.23 (1H, m, H-17), 7.23 - 7.16 (1H, m, H-2), 7.16 - 7.11 (1H, m, H-1), 7.11 - 7.04 (1H, m, H-15), 5.97 (1H, q, *J* = 2.0 Hz, 30''), 5.71 (1H, d, *J* = 2.8 Hz, 30'), 3.97 (2H, dq, *J* = 10.8, 7.1 Hz, 24'', 25''), 3.84 (2H, s, H-11), 3.77 (2H, dq, *J* = 10.8, 7.1 Hz, 24', 25'), 2.98 (2H, d, *J* = 1.5 Hz, H-28), 1.07 (6H, t, *J* = 7.1 Hz, H-26, H-27)

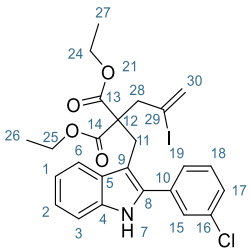
^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.4 (C-13, C-14), 163.1 (d, *J* = 247.0 Hz, C-16), 135.8 (C-5), 135.7 (d, *J* = 2.5 Hz, C-10), 135.6 (C-8), 130.9 (d, *J* = 8.4 Hz, C-19), 129.8 (C-4), 127.3 (C-30), 124.7 (d, *J* = 2.9 Hz, C-18), 122.8 (C-2), 120.2 (C-1), 120.0 (C-6), 116.0 (d, *J* = 22.1 Hz, C-17), 115.2 (d, *J* = 21.0 Hz, C-15), 110.9 (C-3), 107.4 (C-9), 104.3 (C-29), 61.6 (C-24, C-25), 58.9 (C-12), 47.5 (C-28), 27.2 (C-11), 13.8 (C-26, C-27)

^{19}F NMR ($CDCl_3$, 377 MHz) δ -111.86 (32)

HRMS (ESI) m/z calcd. for $C_{25}H_{25}FINO_4Na$ $[M+Na]^+$: 572.0705; found: 572.0707.

FTIR (neat) ν/cm^{-1} = 3401, 2983, 1722, 1615, 1587, 1457, 1368, 1299, 1263, 1216, 1190, 1156, 1093, 1069, 1014, 909, 875, 783, 736

diethyl 2-((2-(3-chlorophenyl)-1H-indol-3-yl)methyl)-2-(2-iodoallyl)malonate, S34



S34 *was synthesised according to general procedure E* by using 1-(2-(3-chlorophenyl)-1H-indol-3-yl)-N,N-dimethylmethanamine **S19** (427 mg, 1.5 mmol, 1.0 equiv.), diethyl 2-(2-iodoallyl)malonate **72** (733 mg, 2.25 mmol, 1.5 equiv.) and ethyl propiolate (168 µL, 1.65 mmol, 1.1 equiv.) in Et_2O (7.5 mL) to afford **S34** in a yield of 37% (314 mg, 0.56 mmol) as a white solid.

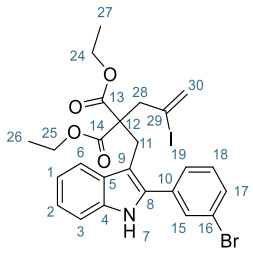
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (1H, s, H-7), 7.63 (1H, dq, *J* = 7.2, 0.7 Hz, H-6), 7.54 (1H, td, *J* = 1.7, 0.8 Hz, H-15), 7.46 - 7.42 (1H, m, H-19), 7.42 - 7.34 (2H, m, H-17, H-18), 7.32 (1H, dt, *J* = 8.0, 1.0 Hz, H-3), 7.19 (1H, ddd, *J* = 8.1, 7.0, 1.2 Hz, H-2), 7.13 (1H, ddd, *J* = 8.1, 7.0, 1.1 Hz, H-1), 5.97 (1H, dt, *J* = 2.8, 1.8 Hz, 30'), 5.71 (1H, dt, *J* = 2.6, 1.2 Hz, 30''), 3.97 (2H, dq, *J* = 10.7, 7.1 Hz, 24', 25'), 3.83 (2H, s, H-11), 3.78 (2H, dq, *J* = 10.7, 7.1 Hz, 24'', 25''), 2.98 (2H, t, *J* = 1.5 Hz, H-28), 1.07 (6H, t, *J* = 7.1 Hz, H-26, H-27)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.4 (C-13, C-14), 135.8 (C-4), 135.5 (C-8), 135.3 (C-16), 135.0 (C-10), 130.5 (Ar), 129.7 (C-5), 129.0 (C-15), 128.3 (Ar), 127.2 (C-19), 127.2 (C-30), 122.9 (C-2), 120.2 (C-1), 119.9 (C-6), 110.9 (C-3), 107.5 (C-9), 104.3 (C-29), 61.7 (C-24, C-25), 58.9 (C-12), 47.4 (C-28), 27.1 (C-11), 13.8 (C-26, C-27)

HRMS (ESI) m/z calcd. for $C_{25}H_{25}ClINO_4Na$ $[M+Na]^+$: 588.0409; found: 588.0406.

FTIR (neat) ν/cm^{-1} = 3376, 2982, 1721, 1600, 1455, 1367, 1298, 1216, 1132, 1095, 1014, 909, 860, 789, 735

diethyl 2-((2-(3-bromophenyl)-1H-indol-3-yl)methyl)-2-(2-iodoallyl)malonate, S35



S35 *was synthesised according to general procedure E* by using 1-(2-(3-bromophenyl)-1H-indol-3-yl)-N,N-dimethylmethanamine **S20** (330 mg, 1.0 mmol, 1.0 equiv.), diethyl 2-(2-iodoallyl)malonate 72 (490 mg, 1.5 mmol, 1.5 equiv.) and ethyl propiolate (112 µL, 1.1 mmol, 1.1 equiv.) in Et_2O (5.0 mL) to afford **S35** in a yield of 42% (262 mg, 0.42 mmol) as a white solid.

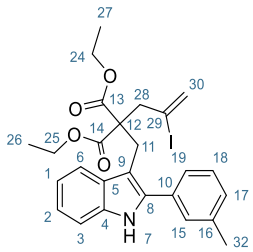
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (1H, s, H-7), 7.70 (1H, t, *J* = 1.8 Hz, H-15), 7.66 - 7.60 (1H, m, H-6), 7.55 - 7.46 (2H, m, H-17, H-19), 7.37 - 7.29 (2H, m, H-3, H-18), 7.19 (1H, ddd, *J* = 8.1, 7.0, 1.2 Hz, H-2), 7.13 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, H-1), 5.97 (1H, dd, *J* = 3.0, 1.6 Hz, 30'), 5.75 - 5.68 (1H, m, 30''), 3.97 (2H, dq, *J* = 10.7, 7.1 Hz, 24'', 25''), 3.83 (2H, s, H-11), 3.78 (2H, dq, *J* = 10.7, 7.5 Hz, 24', 25'), 2.98 (2H, t, *J* = 1.5 Hz, H-28), 1.08 (6H, t, *J* = 7.1 Hz, H-26, H-27)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.4 (C-13, C-14), 135.8 (C-4), 135.5 (Ar), 135.4 (Ar), 131.9 (C-15), 131.3 (C-17), 130.7 (C-18), 129.7 (C-5), 127.6 (C-19), 127.2 (C-30), 123.3 (C-16), 122.9 (C-2), 120.2 (C-1), 119.9 (C-6), 110.9 (C-3), 107.5 (C-9), 104.3 (C-29), 61.7 (C-24, C-25), 58.9 (C-12), 47.4 (C-28), 27.1 (C-11), 13.8 (C-26, C-27)

HRMS (ESI) m/z calcd. for $C_{25}H_{25}BrINO_4Na$ $[M+Na]^+$: 631.9904; found: 631.9900.

FTIR (neat) ν/cm^{-1} = 3374, 2980, 1721, 1598, 1561, 1455, 1367, 1341, 1298, 1215, 1131, 1092, 1072, 1013, 908, 859, 788, 742

diethyl 2-(2-iodoallyl)-2-((2-(m-tolyl)-1H-indol-3-yl)methyl)malonate, S36



S36 *was synthesised according to general procedure E* by using N,N-dimethyl-1-(2-(m-tolyl)-1H-indol-3-yl)methanamine **S21** (397 mg, 1.5 mmol, 1.0 equiv.), diethyl 2-(2-iodoallyl)malonate **72** (733 mg, 2.25 mmol, 1.5 equiv.) and ethyl propiolate (168 µL, 1.65 mmol, 1.1 equiv.) in Et_2O (7.5 mL) to afford **S36** in a yield of 72% (584 mg, 1.08 mmol) as a white solid.

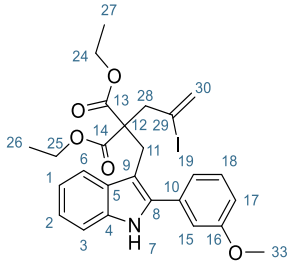
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (1H, s, H-7), 7.62 (1H, dd, *J* = 7.8, 1.3 Hz, H-6), 7.38 - 7.29 (5H, m, H-3, H-17, H-18, H-19), 7.21 - 7.08 (3H, m, H-1, H-2, H-15), 5.93 (1H, dd, *J* = 2.8, 1.6 Hz, 30'), 5.67 (1H, dd, *J* = 2.7, 1.3 Hz, 30''), 3.96 (2H, dq, *J* = 10.7, 7.1 Hz, 24'', 25''), 3.84 (2H, s, H-11), 3.75 (2H, dq, *J* = 10.7, 7.1 Hz, 24', 25'), 2.96 (2H, t, *J* = 1.4 Hz, H-28), 2.42 (3H, s, H-32), 1.06 (6H, t, *J* = 7.1 Hz, H-26, H-27)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.5 (C-13, C-14), 138.8 (C-16), 137.4 (C-8), 135.6 (C-4), 133.5 (C-10), 129.9 (Ar), 129.7 (C-5), 129.1 (Ar), 129.0 (Ar), 127.2 (C-30), 126.1 (Ar), 122.3 (C-2), 119.9 (C-1), 119.7 (C-6), 110.8 (C-3), 106.5 (C-9), 104.5 (C-29), 61.5 (C-24, C-25), 59.0 (C-12), 47.4 (C-28), 27.4 (C-11), 21.7 (C-32), 13.8 (C-26, C-27)

HRMS (ESI) *m/z* calcd. for $C_{26}H_{29}INO_4$ $[M+H]^+$: 546.1136; found: 546.1131.

FTIR (neat) ν/cm^{-1} = 3385, 2980, 1722, 1608, 1459, 1367, 1297, 1215, 1131, 1093, 1015, 908, 857, 790, 743

diethyl 2-(2-iodoallyl)-2-((2-(3-methoxyphenyl)-1H-indol-3-yl)methyl)malonate, S37



S37 *was synthesised according to general procedure E* by using 1-(2-(3-methoxyphenyl)-1H-indol-3-yl)-N,N-dimethylmethanamine **S22** (376 mg, 1.34 mmol, 1.0 equiv.), diethyl 2-(2-iodoallyl)malonate **72** (656 mg, 2.00 mmol, 1.5 equiv.) and ethyl propiolate (136 µL, 1.34 mmol, 1.0 equiv.) in Et_2O (6.7 mL) to afford **S37** in a yield of 49% (371 mg, 0.66 mmol) as a white solid.

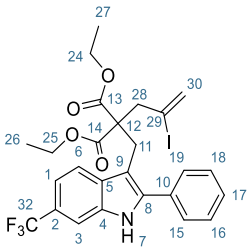
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (1H, s, H-7), 7.62 (1H, ddt, *J* = 7.8, 1.4, 0.7 Hz, H-6), 7.39 - 7.34 (1H, m, H-18), 7.34 - 7.30 (1H, m, H-3), 7.21 - 7.05 (4H, m, H-1, H-2, H-15, H-19), 6.93 (1H, ddd, *J* = 8.3, 2.6, 1.0 Hz, H-17), 5.95 (1H, dt, *J* = 2.8, 1.7 Hz, 30'), 5.69 (1H, dt, *J* = 2.6, 1.2 Hz, 30''), 3.96 (2H, dq, *J* = 10.8, 7.1 Hz, 24', 25'), 3.87 (3H, s, H-33), 3.85 (2H, s, H-11), 3.81 - 3.71 (2H, m, 24'', 25''), 2.99 - 2.96 (2H, m, H-28), 1.07 (6H, t, *J* = 7.1 Hz, H-26, H-27)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.5 (C-13, C-14), 160.1 (C-16), 137.0 (C-4), 135.6 (C-8), 134.8 (C-10), 130.3 (C-18), 129.9 (C-5), 127.4 (C-30), 122.5 (C-2), 121.4 (C-19), 120.0 (C-1), 119.8 (C-6), 114.4 (C-15), 114.1 (C-17), 110.8 (C-3), 106.8 (C-9), 104.4 (C-29), 61.6 (C-24, C-25), 59.0 (C-12), 55.5 (C-33), 47.5 (C-28), 27.4 (C-11), 13.8 (C-26, C-27)

HRMS (ESI) *m/z* calcd. for $C_{26}H_{29}INO_5$ $[M+H]^+$: 562.1085; found: 562.1080.

FTIR (neat) ν/cm^{-1} = 3381, 2981, 1726, 1609, 1461, 1439, 1367, 1342, 1298, 1216, 1096, 1042, 857, 746, 696

diethyl 2-(2-iodoallyl)-2-((2-phenyl-6-(trifluoromethyl)-1H-indol-3-yl)methyl)malonate, S38



S38 *was synthesised according to general procedure E* by using N,N-dimethyl-1-(2-phenyl-6-(trifluoromethyl)-1H-indol-3-yl)methanamine **S23** (160 mg, 0.5 mmol, 1.0 equiv.), diethyl 2-(2-iodoallyl)malonate **72** (245 mg, 0.75 mmol, 1.5 equiv.) and ethyl propiolate (56 µL, 0.55 mmol, 1.1 equiv.) in Et_2O (2.5 mL) to afford **S38** in a yield of 38% (113 mg, 0.19 mmol) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (1H, s, H-7), 7.79 - 7.70 (1H, m, H-6), 7.59 (1H, dt, *J* = 1.6, 0.8 Hz, H-3), 7.52 - 7.34 (7H, m, H-1, H-15, H-16, H-17, H-18, H-19), 5.96 (1H, dt, *J* = 2.7, 1.7 Hz, 30'), 5.73 (1H, dt, *J* = 2.5, 1.1 Hz, 30''), 3.95 (2H, dq, *J* = 10.7, 7.1 Hz, 24', 25'), 3.84 (2H, s, H-11), 3.70 (2H, dq, *J* = 10.7, 7.1 Hz, 24'', 25''), 2.95 (2H, t, *J* = 1.4 Hz, H-28), 1.06 (6H, t, *J* = 7.1 Hz, H-26, H-27)

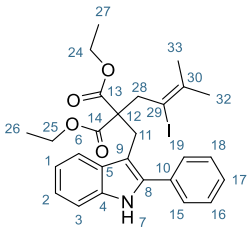
^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.3 (C-13, C-14), 139.8 (C-4), 134.5 (C-8), 132.7 (C-10), 132.2 (C-5), 129.3 (C-16, C-18), 129.0 (C-15, C-19), 128.8 (C-17), 127.7 (C-30), 125.4 (d, *J* = 246.9 Hz, C-32), 124.2 (d, *J* = 56.7 Hz, C-2), 120.2 (C-6), 116.7 (q, *J* = 3.4 Hz, C-1), 108.5 (q, *J* = 4.4 Hz, C-3), 107.0 (C-9), 104.1 (C-29), 61.7 (C-24, C-25), 58.8 (C-12), 47.5 (C-28), 27.2 (C-11), 13.8 (C-26, C-27)

^{19}F NMR ($CDCl_3$, 377 MHz) δ -60.65 (32)

HRMS (ESI) *m/z* calcd. for $C_{26}H_{26}F_3INO_4$ $[M+H]^+$: 600.0853; found: 600.0853.

FTIR (neat) ν/cm^{-1} = 3373, 2983, 1720, 1609, 1510, 1465, 1367, 1339, 1299, 1227, 1161, 1114, 1053, 909, 863, 819, 768, 735, 699

diethyl 2-(2-iodo-3-methylbut-2-en-1-yl)-2-((2-phenyl-1H-indol-3-yl)methyl)malonate, S39



S39 *was synthesised according to general procedure E* by using N,N-dimethyl-1-(2-phenyl-1H-indol-3-yl)methanamine **66** (300 mg, 1.2 mmol, 1.2 equiv.), diethyl 2-(2-iodo-3-methylbut-2-en-1-yl)malonate **S8** (354 mg, 1.0 mmol, 1.0 equiv.) and ethyl propiolate (122 µL, 1.2 mmol, 1.2 equiv.) in Et_2O (5.0 mL) to afford **S39** in a yield of 36% (200 mg, 0.36 mmol) as a white solid.

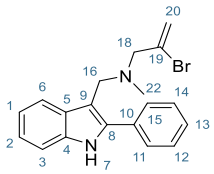
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (1H, s, H-7), 7.69 (1H, dd, *J* = 7.9, 1.3 Hz, H-6), 7.60 – 7.55 (2H, m, H-15, H-19), 7.49 – 7.43 (2H, m, H-16, H-18), 7.39 – 7.34 (1H, m, H-17), 7.31 (1H, dt, *J* = 8.0, 0.9 Hz, H-3), 7.16 (1H, ddd, *J* = 8.0, 7.0, 1.3 Hz, H-2), 7.10 (1H, ddd, *J* = 8.0, 7.1, 1.2 Hz, H-1), 3.90 (2H, dq, *J* = 10.6, 7.1 Hz, 24', 25'), 3.81 (2H, s, H-11), 3.79 – 3.68 (2H, m, 24", 25"), 3.14 (2H, s, H-28), 1.82 (3H, s, H-32), 1.49 (3H, s, H-33), 1.04 (6H, t, *J* = 7.1 Hz, H-26, H-27)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.1 (C-13, C-14), 140.6 (Ar or C-30), 137.0 (Ar or C-30), 135.7 (Ar or C-30), 133.9 (Ar or C-30), 130.0 (Ar or C-30), 129.1 (C-16, C-18), 129.1 (C-15, C-19), 128.1 (C-17), 122.3 (C-2), 120.3 (C-6), 119.7 (C-1), 110.7 (C-3), 107.3 (C-9), 94.3 (C-29), 61.3 (C-24, C-25), 59.3 (C-12), 43.7 (C-28), 32.4 (C-32), 30.2 (C-11), 20.3 (C-33), 13.8 (C-26, C-27)

HRMS (ESI) *m/z* calcd. for $C_{27}H_{31}INO_4$ $[M+H]^+$: 560.1292; found: 560.1316.

FTIR (neat) ν/cm^{-1} = 3384, 2951, 1725, 1488, 1457, 1296, 1217, 1126, 1074, 1024, 910, 857, 739, 700

2-iodo-*N*-methyl-*N*-((2-phenyl-1H-indol-3-yl)methyl)prop-2-en-1-amine, 140



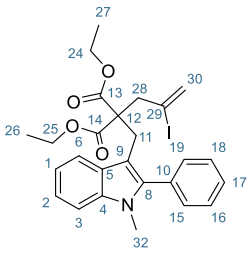
2-bromo-*N*-((2-phenyl-1H-indol-3-yl)methyl)prop-2-en-1-amine **139** (34.1 mg, 0.1 mmol, 1.0 equiv.) and formaldehyde (37% w/w in water, 23 μL, 0.3 mmol, 3.0 equiv.) was dissolved in MeCN (1 mL, 0.1 M). Then the mixture was cooled to 0 °C before the addition of $NaBH_3CN$ (19 mg, 0.3 mmol, 3.0 equiv.). The reaction was warmed to room temperature and stirred for 16 hrs. The mixture was washed with water then was extracted with EtOAc for three times. The organics were concentrated under reduced vacuum. The residue was purified by flash column chromatography (20% EtOAc in hexane) to afford the desired product in 100% yield (36 mg, 0.1 mmol).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (1H, s, H-7), 7.90 – 7.85 (2H, m, H-11, H-15), 7.83 (1H, ddt, *J* = 7.8, 1.6, 0.8 Hz, H-6), 7.55 – 7.46 (2H, m, H-12, H-14), 7.43 – 7.33 (2H, m, H-3, H-13), 7.23 (1H, ddd, *J* = 8.1, 7.0, 1.3 Hz, H-2), 7.17 (1H, ddd, *J* = 8.1, 7.0, 1.2 Hz, H-1), 5.85 (1H, q, *J* = 1.3 Hz, 20''), 5.56 (1H, d, *J* = 1.5 Hz, 20'), 3.79 (2H, s, H-16), 3.31 (2H, s, H-18), 2.26 (3H, s, H-22)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 137.1 (C-8), 135.7 (C-4), 132.9 (C-10), 132.4 (C-19), 130.2 (C-5), 129.0 (C-12, C-14), 128.7 (C-11, C-15), 127.9 (C-13), 122.4 (C-2), 120.1 (C-1), 119.8 (C-6), 118.7 (C-20), 110.8 (C-3), 110.1 (C-9), 65.9 (C-18), 51.8 (C-16), 41.3 (C-22)

FTIR (neat) ν/cm^{-1} = 2952, 2365, 1723, 1690, 1469, 1441, 1331, 1258, 1202, 1119, 1068, 1038, 1020, 914, 739

diethyl 2-(2-iodoallyl)-2-((1-methyl-2-phenyl-1H-indol-3-yl)methyl)malonate, 147



diethyl 2-(2-iodoallyl)-2-((2-phenyl-1H-indol-3-yl)methyl)malonate **62** (265 mg, 0.5 mmol, 1.0 equiv.) and KO^{t}Bu (84 mg, 0.75 mmol, 1.5 equiv.) was charged in DMF (2.5 mL, 0.4 M) and cooled to 0 °C. Then methyl iodide (94 µL, 1.5 mmol, 3.0 equiv.) was added dropwise. The mixture was warmed to room temperature and stirred for 16 hrs. The reaction was quenched with water then the aqueous was extracted with EtOAc for three times. The combined organics were concentrated under vacuum and the residue was purified by flash column chromatography (2.5% EtOAc in pentane) to afford the desired product in 82% yield (224 mg, 0.41mmol).

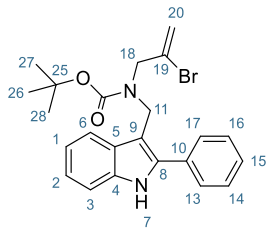
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 – 7.57 (1H, m, H-6), 7.54 – 7.46 (2H, m, H-15, H-19), 7.46 – 7.36 (3H, m, H-16, H-17, H-18), 7.30 (1H, dt, *J* = 8.2, 1.0 Hz, H-3), 7.22 (1H, ddd, *J* = 8.2, 7.0, 1.2 Hz, H-2), 7.12 (1H, ddd, *J* = 8.0, 6.9, 1.1 Hz, H-1), 5.72 (1H, dd, *J* = 3.0, 1.3 Hz, 30'), 5.56 (1H, dd, *J* = 2.5, 1.2 Hz, 30''), 3.99 (2H, dq, *J* = 10.7, 7.1 Hz, 24', 25'), 3.82 (2H, dq, *J* = 10.8, 7.1 Hz, 24'', 25''), 3.68 (2H, s, H-11), 3.52 (3H, s, H-32), 2.91 – 2.86 (2H, m, H-28), 1.08 (7H, t, *J* = 7.1 Hz, H-26, H-27).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.6 (C-13, C-14), 140.4 (C-4), 137.0 (C-8), 132.1 (C-10), 131.4 (C-16, C-18), 128.9 (C-15, C-19), 128.5 (C-5), 128.5 (C-17), 127.5 (C-30), 121.9 (C-2), 119.6 (C-6), 119.5 (C-1), 109.4 (C-3), 106.6 (C-29), 104.1 (C-9), 61.5 (C-24, C-25), 58.9 (C-12), 47.4 (C-28), 31.0 (C-32), 28.0 (C-11), 13.8 (C-26, C-27).

HRMS (ESI) *m/z* calcd. for $C_{26}H_{29}INO_4$ $[M+H]^+$: 546.1136; found: 546.1115.

FTIR (neat) ν/cm^{-1} = 2917, 1728, 1608, 1469, 1443, 1366, 1298, 1233, 1210, 1133, 1094, 1025, 908, 859, 731, 703

***tert*-butyl (2-bromoallyl)((2-phenyl-1H-indol-3-yl)methyl)carbamate, 142a**



To a solution of 2-bromo-*N*-((2-phenyl-1H-indol-3-yl)methyl)prop-2-en-1-amine **139** (819 mg, 2.4 mmol, 1.0 equiv.) in CH_2Cl_2 (0.2 M, 12.0 mL), di-tert-butyl decarbonate (1.4 mL, 6.0 mmol, 2.5 equiv.) and triethyl amine (400 µL, 2.9 mmol, 1.2 equiv.) were added. The resulting mixture was stirred at room temperature under argon for 16 hrs. The reaction was quenched by H_2O (10.0 mL) and the mixture was extracted with DCM for three times. The combined organic was washed with brine and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by flash column chromatography (20% EtOAc in Hexane) to give the desired product in 88% (936 mg, 2.12 mmol) yield.

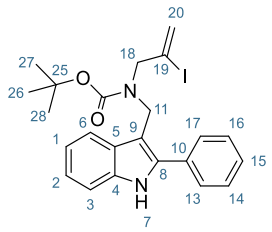
^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.2 (1H, s, H-7), 7.8 (1H, d, *J* = 7.8 Hz, H-6), 7.5 - 7.4 (4H, m, H-13, H-14, H-16, H-17), 7.4 (2H, t, *J* = 7.9 Hz, H-3, H-15), 7.2 (1H, ddd, *J* = 8.1, 7.1, 1.2 Hz, H-2), 7.2 (1H, ddd, *J* = 8.0, 7.1, 1.0 Hz, H-1), 5.3 - 5.1 (2H, m, H-20), 4.9 (2H, s, H-11), 3.8 (2H, d, *J* = 63.1 Hz, H-18), 1.6 - 1.4 (10H, m, H-26, H-27, H-28)

^{13}C NMR ($CDCl_3$, 126 MHz) δ 146.9 (C-22), 137.5 (C-8), 136.0 (C-4), 132.4 (C-10), 129.6 (C-19), 129.1 (C-13, C-17), 128.7 (C-14, C-16), 128.7 (C-5), 128.4 (C-15), 122.8 (C-2), 120.4 (C-1), 120.2 (C-6), 116.7 (C-20), 110.9 (C-3), 108.8 (C-9), 85.3 (C-25), 52.0 (C-18), 39.0 (C-11), 27.6 (C-26, C-27, C-28)

HRMS (ESI) m/z calcd. for $C_{23}H_{25}BrN_2O_2Na$ $[M+Na]^+$: 463.0992; found: 463.0994.

FTIR (neat) ν/cm^{-1} = 2980, 1808, 1671, 1455, 1370, 1249, 1213, 1157, 1120, 1072, 869, 767, 745, 700

***tert*-butyl (2-iodoallyl)((2-phenyl-1H-indol-3-yl)methyl)carbamate, 142b**



To a solution of 2-iodo-*N*-((2-phenyl-1H-indol-3-yl)methyl)prop-2-en-1-amine **S9** (388 mg, 1.0 mmol, 1.0 equiv.) in DCM (0.2 M, 5.0 mL), di-tert-butyl decarbonate (0.55 mL, 2.4 mmol, 2.4 equiv.) and triethyl amine (170 µL, 1.2 mmol, 1.2 equiv.) were added. The resulting mixture was stirred at room temperature under argon for 16 hrs. The reaction was quenched by H_2O (5.0 mL) and the mixture was extracted with DCM for three times. The combined organic was washed with brine and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by flash column chromatography (20% EtOAc in Hexane) to give the desired product in 98% (478 mg, 1.0 mmol) yield.

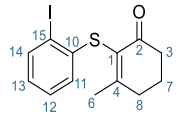
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (1H, s, H-7), 7.83 – 7.71 (1H, m, H-6), 7.54 – 7.42 (4H, m, H-3, H-13, H-15, H-17), 7.42 – 7.36 (2H, m, H-14, H-16), 7.23 (1H, ddd, *J* = 8.1, 7.0, 1.3 Hz, H-2), 7.14 (1H, ddd, *J* = 8.1, 7.0, 1.1 Hz, H-1), 5.74 – 5.47 (2H, m, H-20), 4.84 (2H, s, H-11), 3.91 – 3.63 (2H, m, H-18), 1.61 – 1.46 (9H, m, H-26, H-27, H-28)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 146.86 (C-22), 137.48 (C-8), 135.97 (C-4), 132.41 (C-10), 129.01 (C-13, C-17), 128.74 (C-14, C-16), 128.67 (C-5), 128.33 (C-15), 125.15 (C-20), 122.74 (C-2), 120.27 (C-1), 120.18 (C-6), 110.92 (C-3), 108.60 (C-9), 107.14 (C-19), 85.30 (C-25), 55.47 (C-18), 38.90 (C-11), 28.54 (C-26, C-27, C-28)

HRMS (ESI) m/z calcd. for $C_{23}H_{25}IN_2O_2Na$ $[M+Na]^+$: 511.0853; found: 511.0852.

FTIR (neat) ν/cm^{-1} = 2982, 1808, 1672, 1456, 1396, 1371, 1309, 1249, 1213, 1158, 1118, 1070, 869, 744, 699.

2-((2-iodophenyl)thio)-3-methylcyclohex-2-en-1-one, 212



This compound was prepared according to a literature procedure. The 2-iodobenzenethiol **214** (608 mg, 3.0 mmol, 1.5 equiv.), 3-methyl-2-morpholinocyclohex-2-en-1-one **213** (253 mg, 2.0 mmol, 1.0 equiv.) and potassium carbonate (276 mg, 2.0 mmol, 2.0 equiv.) was added to a 50 mL flask equipped with a condenser. The flask was evacuated and backfilled with argon three times. Degassed dry MeCN (8 mL) was then added to the reaction mixture. The reaction was heated to reflux for 18 hrs. The result mixture was poured into 1M NaOH solution (25 mL). The aqueous layer was extracted with diethyl ether 3 times (20 mL). The combined organics were washed with 20 mL brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography (EtOAc: pentane = 1 : 5) to afford target material **212** as an off-white solid (620 mg, 1.8 mmol, 60%).

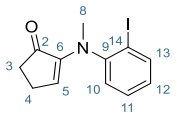
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (1H, dd, *J* = 7.8, 1.4, H14), 7.20 – 7.12 (1H, m, H13), 6.82 – 6.72 (2H, m, H11 & H12), 2.66 – 2.54 (4H, m, H3 & H8), 2.24 (3H, d, *J* = 0.8, H6), 2.08 (2H, dq, *J* = 7.8, 6.2, H7)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 194.0 (C2), 170.5 (C4), 141.4 (C10), 139.5 (C14), 130.2 (C1), 128.4 (C12), 126.3 (C11), 126.2 (C13), 96.8 (C15), 38.3 (C3), 34.4 (C8), 24.6 (C6), 21.8 (C7)

HRMS (ESI) *m/z* calcd. for $C_{13}H_{13}IOS$ $[M+H]^+$: 344.9805; found: 344.9805.

FTIR (neat) ν/cm^{-1} = 3047, 2950, 1669, 1583, 1438, 1421, 1360, 1320, 1271, 1191, 1037, 1010, 778.

2-((2-iodophenyl)(methyl)amino)cyclopent-2-en-1-one, 224



According to a modified procedure of Wrobleski:[119] Aniline **S4** (350 mg, 1.50 mmol, 1.0 equiv.), morpholine enamine **223** (250.5 mg, 1.50 mmol, 1.0 equiv.) and *para*-toluenesulfonic acid monohydrate (210 mg, 1.50 mmol, 1.0 equiv.) were heated to 50 °C in toluene (15 mL, 0.1 M) for 3 h. The reaction was cooled to room temperature and diluted with EtOAc (25 mL). The solution was washed with sodium hydrogencarbonate (sat. aq., 3 x 12.5 mL) followed by brine (25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (10% diethyl ether in pentane) to afford **224** (273 mg, 0.87 mmol, 58%) as a brown solid.

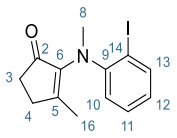
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, dd, *J* = 7.9, 1.5, H13), 7.29 (1H, ddd, *J* = 7.9, 7.3, 1.5, H11), 7.03 (1H, dd, *J* = 7.9, 1.6, H10), 6.90 (1H, ddd, *J* = 7.9, 7.3, 1.6, H12), 6.26 (1H, t, *J* = 3.2, H5), 3.09 (3H, s, H8), 2.54 (2H, ddd, *J* = 6.8, 4.4, 2.8, H4), 2.48 – 2.40 (2H, m, H3)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 203.2 (C2), 149.66 (C9), 148.3 (C6), 139.8 (C13), 132.2 (C5), 129.1 (C11), 126.2 (C10), 98.7 (C14), 40.5 (C8), 35.0 (C3), 23.3 (C4)

HRMS (ESI) *m/z* calcd. for $C_{12}H_{13}INO$ $[M+H]^+$: 314.0036; found: 314.0038.

FTIR (neat) ν/cm^{-1} = 1701, 1611, 1576, 1506, 1322, 1260,1043, 1029, 790, 766, 727

2-((2-iodophenyl)(methyl)amino)-3-methylcyclopent-2-en-1-one, 226



Sodium methoxide (30 wt% in methanol, 0.316 mL, 1.7 mmol, 1.1 equiv.) was added in one portion to a stirred, argon-sparged solution of diketone **231** (656 mg, 1.57 mmol, 1.0 equiv.) in methanol (15 mL, 0.1 M) at room temperature. The reaction mixture was stirred at this temperature for a further 2 h before adding a solution of lithium hydroxide monohydrate (65.6 mg, 1.57 mmol, 1.0 equiv.) in water (7.5 mL) and heating to 75 °C. After 10 min, the reaction mixture was cooled to room temperature and acidified to *ca.* pH 2 with HCl (1 M aq., *ca.* 7.5 mL). The reaction mixture was heated to 75 °C for a further 30 min before cooling to room temperature, adding water (40 mL) and extracting with DCM (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Due to target material degraded on silica gel, The crude residue was purified by flash column chromatography (neutral alumina gel, gradient elution from 20 to 40% EtOAc in pentane) to afford **226** (201 mg, 0.61 mmol, 40%) as a pale-yellow solid.

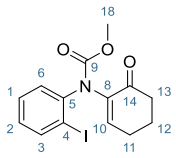
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (1H, dd, *J* = 7.9, 1.5, H13), 7.20 (1H, ddd, *J* = 8.0, 7.2, 1.5, H11), 7.03 (1H, dd, *J* = 8.1, 1.5, H10), 6.60 (1H, ddd, *J* = 7.8, 7.2, 1.5, H12), 3.13 (3H, s, H8), 2.40 (2H, ddq, *J* = 6.3, 2.2, 1.1, H3), 2.35 – 2.30 (2H, m, H4), 1.39 (3H, t, *J* = 1.0 Hz, H16)

^{13}C NMR (101 MHz, DCl_3) δ 206.2 (C2), 159.9 (C5), 150.8 (C9), 143.9 (C6), 140.7 (C13), 129.0 (C11), 124.0 (C12), 121.9 (C10), 92.5 (C14), 39.1 (C8), 33.7 (C4), 29.4 (C3), 17.3 (C16)

HRMS (ESI) *m/z* calcd. for $C_{13}H_{15}INO$ $[M+H]^+$: 328.0193; found: 328.0194.

FTIR (neat) ν/cm^{-1} = 2864, 2805, 1696, 1632, 1579, 1469, 1291, 1210, 1157, 1108, 1054, 1024, 1012, 746

methyl (2-iodophenyl)(6-oxocyclohex-1-en-1-yl)carbamate, 239



This compound was prepared according to a modified literature procedure.[119] ^{n}BuLi (2.48 M in hexanes, 0.88 mL, 2.2 mmol, 1.1 equiv.) was added dropwise to a solution of HMDS (0.46 mL, 2.2 mmol, 1.1 equiv.) in THF (5 ML, 0.44 M) at -78 °C in 10 mins. After warming up to r.t, the result solution was added in a solution of **240** (627 mg, 2 mmol, 1.0 equiv.) and methyl cyanoformate (0.63 mL, 8 mmol, 4.0 equiv.) over 1 hr *via* a syringe pump at -78 °C. After 15 min, saturated aqueous NH_4Cl (5mL) was added. The resultant mixture was warmed to room temperature and diluted with EtOAc (10 mL). The separated aqueous phase was washed with EtOAc (3 × 10 mL) and the combined organic phase was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude residue by column chromatography (20% to 40% EtOAc/pentane) gave **239** (210.6 mg, 0.57 mmol, 28%) as a white solid

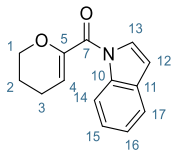
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.9 – 7.8 (1H, m, H3), 7.4 – 7.3 (2H, m, H1, H6), 7.2 (1H, t, *J* = 4.3, H10), 7.0 (1H, ddd, *J* = 7.9, 6.7, 2.3, H2), 3.7 (3H, s, H18), 2.5 (4H, m, H11, H-13), 2.0 (2H, m, H12)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 194.8 (C14), 154.6 (C9), 146.2 (C10), 145.2 (C5), 140.4 (C8), 139.7 (C3), 129.8 (C6), 129.2 (C2), 128.9 (C1), 100.3 (C4), 53.6 (C18), 38.5 (C13), 25.9 (C11), 22.6 (C12)

HRMS (ESI) *m/z* calcd. for $C_{14}H_{15}INO_3$ $[M+H]^+$: 372.0091; found: 372.0091.

FTIR (neat) ν/cm^{-1} = 1723, 1689, 1469, 1439, 1329, 1240, 1201, 1119, 1067, 1037, 745, 711

(3,4-dihydro-2H-pyran-6-yl)(1H-indol-1-yl)methanone, 243



Carboxylic acid **248** (1.153 g, 9.0 mmol, 1.0 equiv.), DCM (18.0 mL), and DMF (1 mol%) were added to 1-neck 100mL round-bottom flask equipped with a magnetic stirring bar. The mixture was cooled to 0 ∘C before oxalyl chloride (1.57 mmol, 18.0 mmol, 2.0 equiv.) was added dropwise. The reaction was warmed to room temperature and stirred for 2 hrs. The solvent and unreacted oxalyl chloride were removed under vacuum. The acid chloride was used without further purification. NaH (60% w/w dispersion in mineral oil, 396 mg, 9.9 mmol 1.1 equiv.) was weighted in 2-neck 50mL round-bottom flask equipped with a magnetic stirring bar under argon atmosphere, then wash with hexane. Back filled with argon for three times. THF (10 mL) was added in the flask. Indole (705 mg, 6 mmol, 1 equiv.) was dissolved in THF (10 mL), then add to the flask dropwise at 0 ∘C. And react at 0 ∘C for 0.5 hr. The solution of acid chloride (9 mmol, 1.5 equiv.) was dissolved in THF (10 mL), then add to the reaction mixture and it was stirred for overnight. Reaction mixture was quenched by 20 mL sat.NH_4Cl solution. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic solution was purified with a plug of silica before removed of the solvent under vacuum. The product was purified by flashing column chromatography (pentane : CH_2Cl_2 = 1:1) and **243** was obtained as yellow oil (913 mg, 67%).

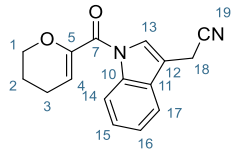
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.43 – 8.36 (1H, m, H-17), 7.76 (1H, d, *J* = 3.8 Hz, H-13), 7.56 (1H, ddd, *J* = 7.6, 1.4, 0.7 Hz, H-14), 7.38 – 7.22 (2H, m, H-15, H-16), 6.59 (1H, dd, *J* = 3.8, 0.8 Hz, H-12), 5.94 (1H, t, *J* = 4.1 Hz, H-4), 4.25 – 4.18 (2H, m, H-1), 2.30 (2H, td, *J* = 6.4, 4.1 Hz, H-3), 2.03 – 1.93 (2H, m, H-2).

^{13}C NMR (CDCl$_3$, 101 MHz) δ 163.0(C-7), 147.7(C-6), 136.0(C-10), 130.5(C-11), 127.2(C-13), 124.7(C-15), 123.8(C-16), 120.6(C-17), 116.5(C-5), 111.6(C-14), 108.3(C-12), 66.7(C-2), 21.6(C-3), 20.6(C-4).

HRMS (+ESI): *m/z* calcd for $C_{14}H_{15}N^+$ [M+H]+ 228.1019, found 228.1014

FTIR (neat) ν/cm^{-1} = 1767, 1687, 1638, 1536, 1451, 1390, 1357, 1342, 1325, 1288, 1246, 1222, 1204, 1150, 1125, 1068, 1043, 1017, 920, 891, 870, 750

2-(1-(3,4-dihydro-2H-pyran-6-carbonyl)-1H-indol-3-yl)acetonitrile, 249



Carboxylic acid **248** (308 mg, 2.4 mmol, 1.2 equiv.) was dissolved in anhydrous CH_2Cl_2 (10 mL), and 3-indoleacetonitrile (312.32 mg, 2.0 mmol, 1.0 equiv.), DCC (495 mg, 2.4 mmol, 1.2 equiv.), DMAP (29.32 mg, 0.24 mmol, 0.1 equiv.) was added to the solution. Reaction mixture was stirred overnight at room temperature. The resulting solution was filter through a plug of silica. The filtrate was concentrated under vacuum. **249** was purified by flash column chromatography (CH_2Cl_2: pentane = 7 : 3)(372 mg, 70%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 – 8.37 (1H, m, H-14), 7.84 (1H, t, *J* = 1.3 Hz, H-13), 7.50 (1H, ddd, *J* = 7.7, 1.4, 0.8 Hz, H-17), 7.45 – 7.37 (1H, m, H-15), 7.33 (1H, ddd, *J* = 7.6, 7.3, 1.1 Hz, H-16), 6.00 (1H, t, *J* = 4.1 Hz, H-4), 4.26 – 4.19 (2H, m, H-1), 3.77 (2H, d, *J* = 1.3 Hz, H-18), 2.30 (2H, td, *J* = 6.4, 4.1 Hz, H-3), 1.99 (2H, tt, *J* = 6.3, 4.7 Hz, H-2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 162.5 (C-7), 147.4 (C-5), 136.6 (C-10), 128.5 (C-11), 125.7 (C-15), 125.5 (C-13), 124.2 (C-16), 118.0 (C-17), 117.1 (C-19), 117.0 (C-14), 112.4 (C-4), 110.6 (C-12), 66.8 (C-1), 21.6 (C-2), 20.7 (C-3), 14.4 (C-18).

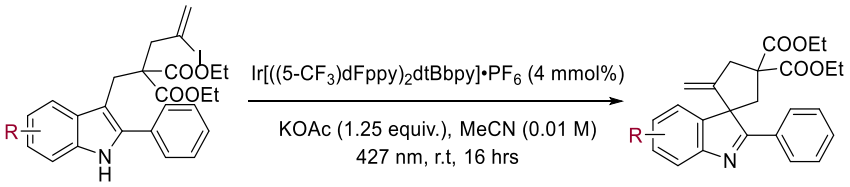
HRMS (+ESI): *m/z* calcd for $C_{16}H_{15}N_2O_2^+$ $[M+H]^+$ 267.1128, found 267.1123 (Δ*m/z* -2.32 ppm).

FTIR (neat) ν/cm^{-1} = 1694, 1648, 1457, 1414, 1373, 1349, 1332, 1289, 1259, 1215, 1177, 1154, 1106, 1073, 1052, 1035, 915, 878, 804, 758, 749.

Photochemical Products

General Procedure

General procedure F



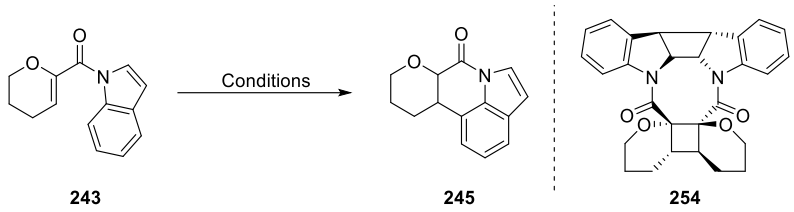
104 **105**

Indole substrate **104** (0.08 mmol, 1.0 equiv.), Ir[((5-CF_3)dFppy)$_2$dtBbpy]•PF_6 (4 mg, 0.0032 mmol, 4 mmol%) and KOAc (10 mg, 0.10 mmol, 1.25 equiv.) were charged into a 20 mL resealable microwave vial equipped with a stir bar. The vial was sealed, evacuated and back filled with argon for three times. Anhydrous MeCN (0.01 M, 8.0 mL) was syringed into the vial. The reaction mixture was sparged for 15 mins before putting into the photoreactor (described in **General information**). The reaction was stirred and constantly irradiated with two Kessil® PR160L 427 nm lamps for 16 hrs at room temperature. Once reaction completed, the solvent was removed under vacuum, and the residue was directly purified by flash column chromatography (10% EtOAc in pentane) to give the desired product.

General Procedure G

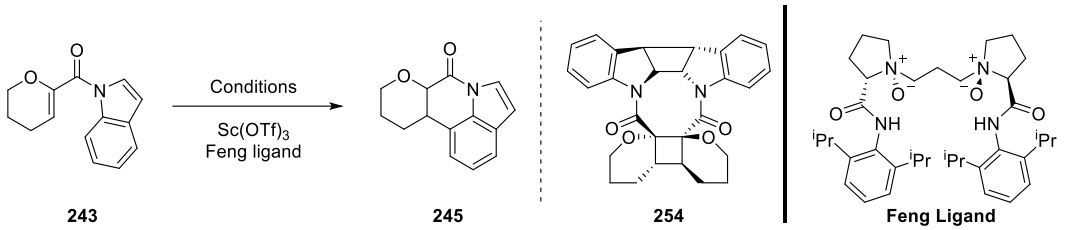
Enaminone (0.300 mmol, 1.0 equiv.) and (if non-volatile) the appropriate nucleophile (3.0 equiv., unless otherwise stated) and/or basic additive were charged to a Schlenk tube equipped with a magnetic stir bar. The vessel was sealed with a septum, and the flask was evacuated and back filled with argon three times. Solvent(s) and nucleophile (if volatile), both argon sparged, were added *via* syringe. The reaction mixture was stirred under constant irradiation with two Kessil PR160L 427 nm LED lamps (each positioned ca. 3 cm from the flask and directed toward it) for the specified time, with cooling to ambient temperature being achieved using a strong jet of nitrogen gas directed at the flask. Triethylamine (2.0 mL) was added to the reaction mixture at the end of the irradiation period, and the resulting mixture was concentrated in vacuo. The crude residue was purified by flash column chromatography to afford the corresponding indoline product.

General Procedure H: Racemic photocyclization



The appropriate iridium photocatalyst (1 mol%), starting material **243** (1 mmol, 1.0 equiv.) and $Sc(OTf)_3$ (0.25 mmol, 0.25 equiv.) was added to a 10 mL microwave vial equipped with a stirring bar. The vial was capped then evacuated and backfilled with argon three times. CH_2Cl_2 (0.02 M, 5.0 mL) was added into the vial. The reaction mixture was stirred for 30 mins under dark environment. The reaction was placed in a water jacketed beaker filled with water and irradiated with a kessil lamp centred at 427 nm for 16 h. After this, the solvent was removed under vacuum. The diastereoisomeric ratio and yields were obtained by quantitative ^{1}H-NMR. Partial of crude product was purified by preparative TLC to give the racemic reference material for chiral HPLC analysis.

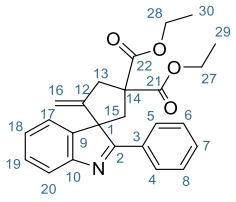
General procedure I: Enantioselective photocyclization



The appropriate iridium photocatalyst (1 mol%), starting material **243** (1 mmol, 1.0 equiv.), Feng ligand (0.25 mmol, 0.25 equiv.) and Sc(OTf)3 (0.25 mmol, 0.25 equiv.) was added in a 10 mL microwave vial equipped with a stirring bar. The vial was capped then evacuated and backfilled with argon three times. CH2Cl2 (0.02 M, 5.0 mL) was added into the vial. The reaction mixture was stirred for 30 mins under dark environment. The reaction was placed in a water jacketed beaker filled with water and irradiated with a kessil lamp centred at 427 nm for 16 h. After the reaction completing, the solvent was removed under vacuum. The diastereoisomeric ratio and yields were obtained by quantitative ^{1}H-NMR. Partial of crude product was purified by preparative TLC to give the racemic reference material for chiral HPLC analysis.

Characterisation

diethyl 2-methylene-2'-phenylspiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 73



73 *was prepared according to* ***general procedure F*** with **62** (43 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 89% yield (29 mg, 0.071mmol).

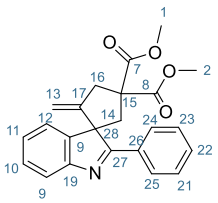
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 - 8.00 (2H, m, H-4, H-5), 7.71 - 7.65 (1H, m, H-20), 7.51 - 7.40 (3H, m, H-6, H-7, H-8), 7.34 (1H, td, *J* = 7.6, 1.3 Hz, H-19), 7.30 (1H, ddd, *J* = 7.6, 1.3, 0.6 Hz, H-17), 7.20 (1H, td, *J* = 7.5, 1.1 Hz, H-18), 4.93 (1H, t, *J* = 2.1 Hz, 16''), 4.50 (1H, t, *J* = 2.3 Hz, 16'), 4.36 - 4.18 (4H, m, H-27, H-28), 3.75 (1H, dt, *J* = 17.3, 2.4 Hz, 13''), 3.44 (1H, dt, *J* = 17.3, 2.0 Hz, 13'), 3.28 (1H, d, *J* = 15.1 Hz, 15'), 2.76 (1H, d, *J* = 15.1 Hz, 15''), 1.31 - 1.22 (6H, m, H-29, H-30)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 180.3 (C-2), 171.8 (C-21), 171.8 (C-22), 153.1 (C-12), 149.9 (C-10), 147.6 (C-9), 130.8 (C-7), 129.2 (C-4, C-5), 128.4 (C-6, C-8), 128.0 (C-19), 126.3 (C-18), 121.5 (C-17), 120.9 (C-20), 109.5 (C-16), 67.4 (C-1), 62.2 (C-27), 62.2 (C-28), 59.3 (C-14), 42.5 (C-15), 42.0 (C-13), 29.7 (C-29, C-30)

HRMS (ESI) m/z calcd. for $C_{25}H_{25}NO_4Na$ $[M+Na]^+$: 426.1686,; found: 426.1676.

FTIR (neat) ν/cm^{-1} = 2984, 1728, 1654, 1527, 1492, 1444, 1390, 1366, 1256, 1217, 1187, 1072, 1024, 903, 858, 758

dimethyl 2-methylene-2'-phenylspiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 106



106 *was prepared according to* ***general procedure F*** with **178** (40 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 84% yield (25 mg, 0.067mmol).

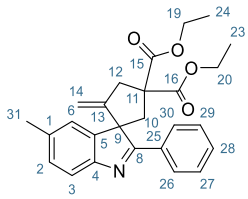
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 – 8.01 (2H, m, H-24, H-25), 7.69 (1H, d, *J* = 7.7 Hz, H-9), 7.51 – 7.43 (3H, m, H-21, H-22, H-23), 7.36 (1H, t, *J* = 7.5 Hz, H-10), 7.27 (1H, d, *J* = 6.1 Hz, H-12), 7.22 (1H, t, *J* = 7.4 Hz, H-11), 4.97 (1H, d, *J* = 2.6 Hz, 13''), 4.54 (1H, d, *J* = 2.7 Hz, 13'), 3.84 (3H, s, H-2), 3.79 (3H, s, H-1), 3.73 (1H, d, *J* = 5.0 Hz, 14'), 3.51 – 3.44 (1H, m, 14''), 3.28 (1H, d, *J* = 15.2 Hz, 16''), 2.78 (1H, d, *J* = 15.0 Hz, 16').

^{13}C NMR ($CDCl_3$, 101 MHz) δ 180.3 (C-27), 172.4 (C-7, C-8), 153.5 (C-19), 149.8 (C-20), 147.7 (C-17), 132.0 (C-26), 130.9 (C-22), 129.2 (C-24, C-25), 128.6 (C-21, C-23), 128.1 (C-10), 126.4 (C-11), 121.5 (C-12), 121.1 (C-9), 109.8 (C-13), 67.4 (C-28), 59.2 (C-15), 53.4 (C-1), 53.3 (C-2), 42.8 (C-16), 42.2 (C-14).

HRMS (ESI) m/z calcd. for $C_{23}H_{21}NO_4Na$ $[M+Na]^+$: 398.1363,; found: 398.1359.

FTIR (neat) ν/cm^{-1} = 2953, 1734, 1528, 1492, 1435, 1261, 1206, 1171, 1081, 1024, 911, 759, 735.

diethyl 5'-methyl-2-methylene-2'-phenylspiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 107



107 *was prepared according to* ***general procedure F*** with **S25** (44 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 90% yield (30 mg, 0.072mmol).

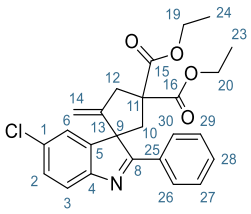
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 - 7.99 (2H, m, H-26, H-30), 7.58 - 7.51 (1H, m, H-3), 7.49 - 7.38 (3H, m, H-27, H-28, H-29), 7.14 (1H, ddd, *J* = 7.9, 1.7, 0.8 Hz, H-2), 7.08 (1H, dt, *J* = 1.8, 0.7 Hz, H-6), 4.93 (1H, t, *J* = 2.1 Hz, 14'), 4.51 (1H, t, *J* = 2.3 Hz, 14''), 4.39 - 4.18 (4H, m, H-19, H-20), 3.74 (1H, dt, *J* = 17.3, 2.4 Hz, 12'), 3.43 (1H, dt, *J* = 17.3, 2.0 Hz, 12''), 3.26 (1H, d, *J* = 15.0 Hz, 10'), 2.78 - 2.72 (1H, m, 10''), 2.42 - 2.36 (4H, m, H-31), 1.27 (6H, dt, *J* = 14.9, 7.1 Hz, H-23, H-24)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 179.4 (C-8), 172.0 (C-15), 171.9 (C-16), 151.3 (C-5), 150.2 (C-13), 148.0 (C-4), 136.3 (C-1), 132.2 (C-25), 130.6 (C-28), 129.1 (C-26, C-30), 128.7 (C-2), 128.5 (C-27, C-29), 122.4 (C-6), 120.6 (C-3), 109.5 (C-14), 67.3 (C-9), 62.3 (C-19), 62.2 (C-20), 59.5 (C-11), 42.7 (C-10), 42.1 (C-12), 21.8 (C-31), 14.2 (C-23), 14.1 (C-24)

HRMS (ESI) m/z calcd. for $C_{25}H_{25}NO_4Na$ $[M+Na]^+$: 426.1686,; found: 426.1676.

FTIR (neat) ν/cm^{-1} = 2981, 1730, 1444, 1255, 1186, 1081, 822, 693

diethyl 5'-chloro-2-methylene-2'-phenylspiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 109



109 *was prepared according to* ***general procedure F*** with **S26** (45 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 90% yield (32 mg, 0.072mmol).

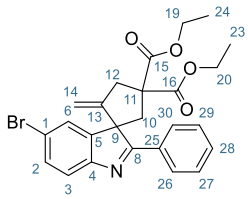
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.0 - 8.0 (2H, m, H-26, H-30), 7.6 (1H, dd, *J* = 8.2, 0.5 Hz, H-3), 7.5 - 7.4 (3H, m, H-27, H-28, H-29), 7.3 (1H, dd, *J* = 8.2, 2.0 Hz, H-2), 7.2 (1H, dd, *J* = 2.1, 0.5 Hz, H-6), 5.0 (1H, t, *J* = 2.1 Hz, 14'), 4.5 (1H, t, *J* = 2.3 Hz, 14''), 4.3 (2H, qd, *J* = 7.1, 1.2 Hz, 19', 20'), 4.2 (2H, q, *J* = 7.1 Hz, 19'', 20''), 3.8 - 3.7 (1H, m, 12'), 3.5 (1H, dt, *J* = 17.4, 2.1 Hz, 12''), 3.2 (1H, d, *J* = 15.1 Hz, 10'), 2.7 (1H, d, *J* = 15.1 Hz, 10''), 1.3 (8H, dt, *J* = 21.8, 7.1 Hz, H-23, H-24)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 180.8 (C-8), 171.8 (C-15), 171.7 (C-16), 152.2 (C-5), 149.4 (C-13), 149.3 (C-4), 131.9 (C-1), 131.7 (C-25), 131.1 (C-28), 129.2 (C-26, C-30), 128.6 (C-27, C-29), 128.2 (C-2), 122.5 (C-6), 121.9 (C-3), 110.4 (C-14), 67.7 (C-9), 62.5 (C-19), 62.4 (C-20), 59.5 (C-11), 42.8 (C-10), 42.1 (C-12), 14.2 (C-23), 14.1 (C-24)

HRMS (ESI) *m/z* calcd. for $C_{25}H_{25}ClNO_4$ $[M+H]^+$: 438.1467; found: 438.1461.

FTIR (neat) ν/cm^{-1} = 2981, 1729, 1527, 1444, 1256, 1186, 1074, 826, 775, 692

diethyl 5'-bromo-2-methylene-2'-phenylspiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 110



110 *was prepared according to* ***general procedure F*** with **S27** (49 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 82% yield (32 mg, 0.066mmol).

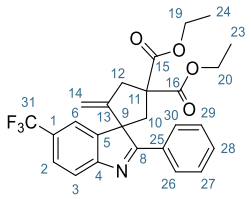
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 - 7.96 (2H, m, H-26, H-30), 7.52 (1H, d, *J* = 8.2 Hz, H-3), 7.50 - 7.41 (4H, m, H-2, H-27, H-28, H-29), 7.39 (1H, d, *J* = 1.9 Hz, H-6), 4.98 (1H, t, *J* = 2.2 Hz, 14''), 4.52 (1H, t, *J* = 2.3 Hz, 14'), 4.34 (2H, qd, *J* = 7.1, 1.5 Hz, 19', 20'), 4.23 (2H, q, *J* = 7.1 Hz, 19'', 20''), 3.71 (1H, dt, *J* = 17.3, 2.4 Hz, H-12), 3.45 (1H, dt, *J* = 17.4, 2.2 Hz, H-12), 3.24 (1H, d, *J* = 15.1 Hz, 10'), 2.74 (1H, d, *J* = 15.0 Hz, 10''), 1.28 (6H, dt, *J* = 24.2, 7.2 Hz, H-23, H-24)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 180.9 (C-8), 171.8 (C-15), 171.7 (C-16), 152.6 (C-5), 149.6 (C-13), 149.3 (C-4), 131.7 (Ar), 131.2 (Ar), 131.2 (Ar), 129.2 (C-26, C-30), 128.7 (C-27, C-29), 125.3 (C-6), 122.4 (C-3), 119.9 (Ar), 110.5 (C-14), 67.8 (C-9), 62.5 (C-20), 62.4 (C-19), 59.6 (C-11), 42.9 (C-10), 42.2 (C-12), 14.2 (C-23), 14.1 (C-24)

HRMS (ESI) m/z calcd. for $C_{25}H_{25}BrNO_4$ $[M+H]^+$: 426.1686,; found: 426.1676.

FTIR (neat) ν/cm^{-1} = 2917, 2849, 1730, 1528, 1444, 1257, 1187, 1081, 1022, 909, 824, 733, 692

diethyl 2-methylene-2'-phenyl-5'-(trifluoromethyl)spiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 111



111 *was prepared according to* ***general procedure F*** with **S28** (48 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 60% yield (23 mg, 0.048mmol).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 - 8.00 (2H, m, H-26, H-30), 7.74 (1H, dt, *J* = 8.1, 0.7 Hz, H-3), 7.63 (1H, ddt, *J* = 8.1, 1.8, 0.8 Hz, H-2), 7.53 - 7.43 (4H, m, H-6, H-27, H-28, H-29), 5.00 (1H, t, *J* = 2.2 Hz, 14'), 4.53 - 4.48 (1H, m, 14''), 4.41 - 4.18 (4H, m, H-19, H-20), 3.82 - 3.73 (1H, m, 12''), 3.47 (1H, dt, *J* = 17.5, 2.2 Hz, 12'), 3.28 (1H, d, *J* = 15.0 Hz, 10'), 2.74 (1H, dd, *J* = 15.1, 0.9 Hz, 10''), 1.27 (6H, dt, *J* = 8.4, 7.1 Hz, H-23, H-24)

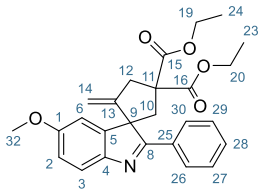
^{13}C NMR ($CDCl_3$, 101 MHz) δ 183.1 (C-8), 171.6 (C-16), 171.5 (C-15), 156.3 (d, *J* = 1.6 Hz, C-5), 149.0 (C-13), 148.0 (C-4), 131.4 (C-28), 131.4 (C-25), 129.3 (C-26, C-30), 128.6 (C-27, C-29), 128.0 (q, *J* = 32.2 Hz, C-1), 125.6 (q, *J* = 4.0 Hz, C-2), 124.4 (d, *J* = 272.0 Hz, C-31), 120.9 (C-3), 118.9 (q, *J* = 4.0 Hz, C-6), 110.6 (C-14), 67.6 (C-9), 62.3 (C-19), 62.3 (C-20), 59.5 (C-11), 42.9 (C-10), 42.0 (C-12), 14.0 (C-23), 13.9 (C-24)

^{19}F NMR ($CDCl_3$, 377 MHz) δ -61.43 (31)

HRMS (ESI) *m/z* calcd. for $C_{26}H_{25}F_3NO_4$ $[M+H]^+$: 482.0952; found: 482.0962.

FTIR (neat) ν/cm^{-1} = 2984, 2905, 1730, 1617, 1528, 1492, 1434, 1368, 1324, 1261, 1186, 1162, 1121, 1062, 1023, 859, 838, 778, 734

diethyl 5'-methoxy-2-methylene-2'-phenylspiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 112



112 *was prepared according to* ***general procedure F*** with **S29** (45 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 60% yield (21 mg, 0.048mmol).

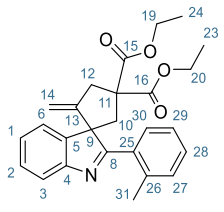
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 - 7.96 (2H, m, H-26, H-30), 7.60 - 7.53 (1H, m, H-3), 7.48 - 7.37 (3H, m, H-27, H-28, H-29), 6.94 - 6.89 (1H, m, H-6), 6.86 (1H, dd, *J* = 8.4, 2.5 Hz, H-2), 4.93 (1H, t, *J* = 2.1 Hz, 14''), 4.52 (1H, t, *J* = 2.3 Hz, 14'), 4.39 - 4.19 (4H, m, H-19, H-20), 3.82 (3H, s, H-32), 3.74 (1H, dt, *J* = 17.4, 2.4 Hz, 12''), 3.42 (1H, dt, *J* = 17.4, 2.0 Hz, 12'), 3.29 (1H, d, *J* = 15.1 Hz, 10''), 2.77 - 2.68 (1H, m, 10'), 1.27 (6H, dt, *J* = 8.9, 7.1 Hz, H-23, H-24)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 178.3 (C-8), 172.1 (C-15), 171.9 (C-16), 158.8 (C-1), 150.2 (C-13), 149.4 (C-5), 147.1 (C-4), 132.1 (C-25), 130.5 (C-28), 128.9 (C-26, C-30), 128.5 (C-27, C-29), 121.4 (C-3), 112.9 (C-2), 109.6 (C-14), 108.4 (C-6), 67.7 (C-9), 62.3 (C-19), 62.3 (C-20), 59.3 (C-11), 55.8 (C-32), 42.7 (C-10), 41.9 (C-12), 14.1 (C-23), 14.1 (C-24)

HRMS (ESI) *m/z* calcd. for $C_{26}H_{28}NO_5$ $[M+H]^+$: 434.1962; found: 434.1964.

FTIR (neat) ν/cm^{-1} = 2982, 1729, 1592, 1527, 1470, 1443, 1366, 1351, 1257, 1221, 1185, 1050, 1030, 894, 860, 822, 778, 736

diethyl 2-methylene-2'-(o-tolyl)spiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 113



113 *was prepared according to* ***general procedure F*** with **S30** (44 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 36% yield (12 mg, 0.029mmol).

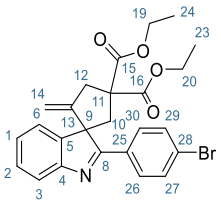
^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.59 (1H, dt, *J* = 7.7, 1.0 Hz, H-3), 7.51 – 7.46 (1H, m, H-30), 7.40 – 7.31 (3H, m, Ar), 7.28 – 7.17 (3H, m, Ar), 5.04 (1H, dd, *J* = 2.6, 1.3 Hz, 14'), 4.50 (1H, dd, *J* = 2.8, 1.3 Hz, 14''), 4.32 – 3.94 (4H, m, 19'', 20''), 3.22 (1H, d, *J* = 16.0 Hz, 12''), 2.90 (1H, dt, *J* = 16.0, 2.7 Hz, 12'), 2.82 (2H, s, 10'), 2.35 (3H, s, H-31), 1.26 (3H, t, *J* = 7.1 Hz, H-24), 1.12 (3H, t, *J* = 7.1 Hz, H-23).

^{13}C NMR (**CD_2Cl_2**, 101 MHz) δ 182.7 (C-8), 171.8 (C-15), 170.9 (C-16), 155.5 (Ar), 150.2 (Ar), 145.8 (Ar), 138.0 (Ar), 134.5 (Ar), 131.2 (Ar), 129.6 (Ar), 128.5 (Ar), 128.3 (C-30), 126.8 (Ar), 125.7 (Ar), 123.2 (Ar), 120.9 (C-3), 110.6 (C-14), 69.5 (C-9), 62.4 (C-19), 62.2 (C-20), 59.5 (C-11), 43.5 (C-12), 40.9 (C-10), 20.6 (C-31), 14.2 (C-24), 14.0 (C-23)

HRMS (ESI) *m/z* calcd. for $C_{26}H_{28}NO_4$ $[M+H]^+$: 418.2013; found: 418.2007.

FTIR (neat) ν/cm^{-1} = 2983, 1732, 1456, 1367, 1256, 1192, 1076, 1027, 908, 862, 768, 731

diethyl 2'-(4-bromophenyl)-2-methylenespiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 116



116 *was prepared according to* ***general procedure F*** with **S31** (49 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 86% yield (33 mg, 0.069mmol).

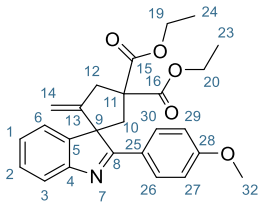
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 - 7.89 (2H, m, H-26, H-30), 7.66 (1H, ddd, *J* = 7.7, 1.1, 0.6 Hz, H-3), 7.62 - 7.55 (2H, m, H-27, H-29), 7.35 (1H, td, *J* = 7.6, 1.3 Hz, H-2), 7.30 (1H, ddd, *J* = 7.6, 1.3, 0.6 Hz, H-6), 7.20 (1H, td, *J* = 7.5, 1.1 Hz, H-1), 4.91 (1H, t, *J* = 2.1 Hz, 14''), 4.47 (1H, t, *J* = 2.3 Hz, 14'), 4.36 - 4.20 (4H, m, H-19, H-20), 3.78 (1H, dt, *J* = 17.4, 2.5 Hz, 12'), 3.38 (1H, dt, *J* = 17.5, 1.9 Hz, 12''), 3.25 (1H, d, *J* = 15.1 Hz, 10'), 2.71 (1H, d, *J* = 15.1 Hz, 10''), 1.27 (6H, t, *J* = 7.1 Hz, H-23, H-24)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 179.1 (C-8), 172.0 (C-15, C-16), 171.9, 153.2 (C-5), 149.9 (C-13), 147.7 (C-4), 137.8 (C-25), 131.8 (C-27, C-29), 130.8 (C-26, C-30), 128.2 (C-2), 126.6 (C-1), 125.6 (C-28), 121.6 (C-6), 121.2 (C-3), 109.6 (C-14), 67.4 (C-9), 62.4 (C-20), 62.3 (C-19), 59.2 (C-11), 42.5 (C-10), 42.0 (C-12), 14.2 (C-23, C-24)

HRMS (ESI) *m/z* calcd. for $C_{25}H_{25}BrNO_4$ $[M+H]^+$: 482.0961; found: 482.0963.

FTIR (neat) ν/cm^{-1} = 2981, 1729, 1587, 1489, 1464, 1395, 1256, 1184, 1071, 1009, 903, 835, 754

diethyl 2'-(4-methoxyphenyl)-2-methylenespiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 117



117 *was prepared according to* ***general procedure F*** with **S32** (49 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 63% yield (22 mg, 0.050mmol).

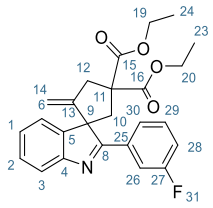
^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.0 – 8.0 (2H, m, H-26, H-30), 7.6 (1H, dt, *J* = 7.6, 0.9 Hz, H-3), 7.3 (1H, td, *J* = 7.5, 1.3 Hz, H-2), 7.3 (1H, ddd, *J* = 7.6, 1.3, 0.6 Hz, H-6), 7.2 (1H, td, *J* = 7.5, 1.1 Hz, H-1), 7.0 – 6.9 (2H, m, H-27, H-29), 4.9 (1H, t, *J* = 2.1 Hz, 14'), 4.4 (1H, t, *J* = 2.3 Hz, 14''), 4.4 – 4.2 (4H, m, H-19, H-20), 3.9 (3H, s, H-32), 3.8 (1H, dt, *J* = 17.4, 2.4 Hz, 12''), 3.4 (1H, dt, *J* = 17.5, 2.0 Hz, 12'), 3.3 (1H, d, *J* = 15.1 Hz, 10''), 2.7 (1H, d, *J* = 15.0 Hz, 10'), 1.3 (6H, t, *J* = 7.1 Hz, H-23, H-24)

^{13}C NMR (CD_2Cl_2, 101 MHz) δ 179.7 (C-8), 172.3 (C-16), 172.1 (C-15), 162.2 (C-28), 154.1 (C-5), 151.3 (C-13), 148.2 (C-4), 131.3 (C-26, C-30), 128.2 (C-2), 126.0 (C-1), 124.7 (C-25), 121.8 (C-6), 120.8 (C-3), 114.1 (C-27, C-29), 109.2 (C-14), 67.5 (C-9), 62.6 (C-20), 62.6 (C-19), 59.5 (C-11), 55.8 (C-32), 43.4 (C-10), 42.1 (C-12), 14.2 (C-23, C-24)

HRMS (ESI) *m/z* calcd. for $C_{26}H_{28}NO_5$ $[M+H]^+$: 434.1962; found: 434.1949.

FTIR (neat) ν/cm^{-1} = 2917, 1729, 1603, 1509, 1464, 1255, 1176, 1028, 900, 839, 754, 712.

diethyl 2'-(3-fluorophenyl)-2-methylenespiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 119



119 *was prepared according to* ***general procedure F*** with **S33** (44 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 63% yield (28 mg, 0.066mmol).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 - 7.75 (2H, m, H-26, H-30), 7.67 (1H, dt, *J* = 7.7, 0.8 Hz, H-3), 7.42 (1H, td, *J* = 8.1, 5.8 Hz, H-29), 7.35 (1H, td, *J* = 7.6, 1.3 Hz, H-2), 7.30 (1H, ddd, *J* = 7.6, 1.3, 0.6 Hz, H-6), 7.21 (1H, td, *J* = 7.5, 1.1 Hz, H-1), 7.16 (1H, tdd, *J* = 8.3, 2.6, 1.0 Hz, H-28), 4.94 (1H, t, *J* = 2.1 Hz, 14'), 4.49 (1H, t, *J* = 2.3 Hz, 14''), 4.37 - 4.20 (4H, m, H-19, H-20), 3.76 (1H, dt, *J* = 17.4, 2.4 Hz, 12'), 3.41 (1H, dt, *J* = 17.4, 2.0 Hz, 12''), 3.27 (1H, d, *J* = 15.1 Hz, 10'), 2.74 (1H, d, *J* = 15.1 Hz, 10''), 1.27 (6H, td, *J* = 7.1, 3.8 Hz, H-23, H-24)

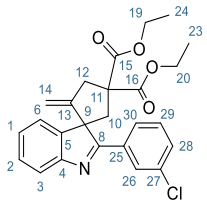
^{13}C NMR ($CDCl_3$, 101 MHz) δ 179.0 (d, *J* = 2.8 Hz, C-8), 171.9 (C-15), 171.9 (C-16), 162.8 (d, *J* = 245.9 Hz, C-27), 153.1 (C-5), 149.8 (C-13), 147.8 (C-4), 134.2 (d, *J* = 7.8 Hz, C-25), 130.0 (d, *J* = 8.0 Hz, C-29), 128.2 (C-2), 126.8 (C-1), 125.0 (d, *J* = 3.0 Hz, C-30), 121.6 (C-6), 121.4 (C-3), 117.8 (d, *J* = 21.3 Hz, C-28), 116.0 (d, *J* = 23.1 Hz, C-26), 109.7 (C-14), 67.5 (C-9), 62.4 (C-19), 62.3 (C-20), 59.3 (C-11), 42.4 (C-10), 42.1 (C-12), 14.1 (C-23), 14.1 (C-24)

^{19}F NMR ($CDCl_3$, 377 MHz) δ -112.25 (31)

HRMS (ESI) *m/z* calcd. for $C_{25}H_{25}FNO_4$ $[M+H]^+$: 422.1762; found: 422.1764.

FTIR (neat) ν/cm^{-1} = 2982, 1729, 1587, 1531, 1440, 1367, 1257, 1188, 1081, 1018, 891, 755

diethyl 2'-(3-chlorophenyl)-2-methylenespiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 120



120 *was prepared according to* ***general procedure F*** with **S34** (45 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 91% yield (32 mg, 0.073mmol).

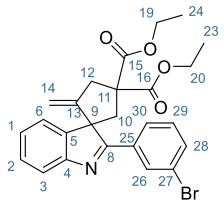
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.09 (1H, t, *J* = 1.9 Hz, H-26), 7.89 (1H, dt, *J* = 7.7, 1.4 Hz, H-30), 7.67 (1H, dt, *J* = 7.6, 0.9 Hz, H-3), 7.44 (1H, ddd, *J* = 8.0, 2.1, 1.2 Hz, H-28), 7.41 - 7.33 (2H, m, H-2, H-29), 7.32 - 7.29 (1H, m, H-6), 7.21 (1H, td, *J* = 7.5, 1.1 Hz, H-1), 4.94 (1H, t, *J* = 2.1 Hz, 14'), 4.48 (1H, t, *J* = 2.3 Hz, 14''), 4.36 - 4.18 (4H, m, H-19, H-20), 3.76 (1H, dt, *J* = 17.4, 2.4 Hz, 12''), 3.41 (1H, dt, *J* = 17.3, 2.0 Hz, 12'), 3.25 (1H, d, *J* = 15.1 Hz, 10'), 2.73 (1H, d, *J* = 15.1 Hz, 10''), 1.27 (7H, td, *J* = 7.1, 4.0 Hz, H-23, H-24)

^{13}C NMR (CDCl$_3$, 101 MHz) δ 178.8 (C-8), 171.9 (C-15), 171.8 (C-16), 153.1 (C-5), 149.7 (C-13), 147.8 (C-4), 134.7 (C-27), 133.8 (C-25), 130.8 (C-28), 129.7 (C-29), 129.1 (C-26), 128.2 (C-2), 127.3 (C-30), 126.8 (C-1), 121.6 (C-6), 121.4 (C-3), 109.7 (C-14), 67.5 (C-9), 62.4 (C-19), 62.3 (C-20), 59.3 (C-11), 42.3 (C-10), 42.0 (C-12), 14.1 (C-23, C-24)

HRMS (ESI) *m/z* calcd. for $C_{25}H_{25}ClNO_4$ $[M+H]^+$: 438.1467; found: 438.1465.

FTIR (neat) ν/cm^{-1} = 2981, 1729, 1527, 1464, 1257, 1186, 1079, 900, 754, 685

diethyl 2'-(3-bromophenyl)-2-methylenespiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 121



121 *was prepared according to* ***general procedure F*** with **S35** (49 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 69% yield (27 mg, 0.055mmol).

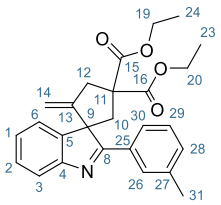
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (1H, t, *J* = 1.8 Hz, H-26), 7.96 - 7.89 (1H, m, H-30), 7.67 (1H, dt, *J* = 7.8, 0.9 Hz, H-3), 7.59 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz, H-28), 7.39 - 7.28 (3H, m, H-2, H-6, H-29), 7.21 (1H, td, *J* = 7.5, 1.1 Hz, H-1), 4.94 (1H, t, *J* = 2.1 Hz, H-14), 4.48 (1H, t, *J* = 2.3 Hz, H-14), 4.38 - 4.21 (4H, m, 19', 19'', 20', 20''), 3.76 (1H, dt, *J* = 17.4, 2.4 Hz, 12''), 3.41 (1H, dt, *J* = 17.4, 1.9 Hz, 12'), 3.25 (1H, d, *J* = 15.1 Hz, 10'), 2.73 (1H, d, *J* = 15.1 Hz, 10''), 1.27 (6H, td, *J* = 7.1, 3.4 Hz, H-23, H-24)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 178.6 (C-8), 171.8 (C-15), 171.7 (C-16), 153.0 (C-4), 149.6 (C-13), 147.6 (C-5), 133.9 (C-25), 133.6 (C-28), 131.9 (C-26), 129.9 (C-29), 128.1 (C-2), 127.6 (C-30), 126.7 (C-1), 122.7 (C-27), 121.5 (C-6), 121.2 (C-3), 109.6 (C-14), 67.3 (C-9), 62.3 (C-20), 62.2 (C-19), 59.2 (C-11), 42.2 (C-10), 41.9 (C-12), 14.0 (C-23), 14.0 (C-24)

HRMS (ESI) m/z calcd. for $C_{25}H_{24}BrNO_4Na$ $[M+Na]^+$: 504.0781,; found: 504.0782.

FTIR (neat) ν/cm^{-1} = 2980, 1729, 1464, 1256, 1185, 1071, 755

diethyl 2-methylene-2'-(m-tolyl)spiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 122



122 *was prepared according to* ***general procedure F*** with **S36**(44 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 85% yield (28 mg, 0.068mmol).

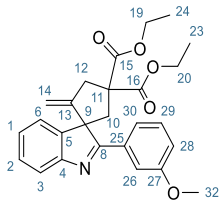
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (1H, tt, *J* = 1.8, 0.7 Hz, H-26), 7.78 (1H, dddd, *J* = 7.6, 2.0, 1.3, 0.6 Hz, H-30), 7.67 (1H, ddd, *J* = 7.7, 1.1, 0.6 Hz, H-3), 7.37 - 7.26 (4H, m, H-2, H-6, H-28, H-29), 7.19 (1H, td, *J* = 7.5, 1.1 Hz, H-1), 4.92 (1H, t, *J* = 2.1 Hz, 14''), 4.49 (1H, t, *J* = 2.3 Hz, 14'), 4.39 - 4.12 (4H, m, H-19, H-20), 3.73 (1H, dt, *J* = 17.3, 2.4 Hz, 12'), 3.46 (1H, dt, *J* = 17.3, 2.0 Hz, 12''), 3.28 (1H, d, *J* = 15.1 Hz, 10'), 2.76 (1H, d, *J* = 15.1 Hz, 10''), 2.45 - 2.40 (3H, m, H-31), 1.27 (6H, dt, *J* = 10.5, 7.1 Hz, H-23, H-24)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 180.5 (C-8), 172.0 (C-16), 171.9 (C-15), 153.5 (C-4), 150.2 (C-13), 147.8 (C-5), 138.4 (C-27), 131.8 (Ar), 131.7 (Ar), 129.8 (C-26), 128.3 (Ar), 128.0 (Ar), 126.4 (C-30), 126.3 (C-1), 121.6 (C-6), 121.0 (C-3), 109.5 (C-14), 67.5 (C-9), 62.2 (C-19), 62.2 (C-20), 59.3 (C-11), 42.7 (C-10), 42.1 (C-12), 21.5 (C-31), 14.1 (C-23), 14.1 (C-24)

HRMS (ESI) *m/z* calcd. for $C_{26}H_{28}NO_4$ $[M+H]^+$: 418.2013; found: 418.2014.

FTIR (neat) ν/cm^{-1} = 2982, 1730, 1530, 1458, 1256, 1186, 1053, 1019, 906, 754, 732, 693

diethyl 2'-(3-methoxyphenyl)-2-methylenespiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 123



123 *was prepared according to* ***general procedure F*** with **S37** (45 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 91% yield (32 mg, 0.073mmol).

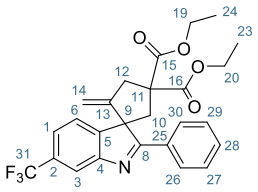
^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.66 – 7.54 (3H, m, H-2, H-3, H-30), 7.40 – 7.30 (2H, m, H-26, H-29), 7.28 (1H, dt, *J* = 7.6, 1.9 Hz, H-6), 7.21 (1H, ddd, *J* = 7.5, 4.6, 2.8 Hz, H-1), 7.08 – 7.00 (1H, m, H-28), 4.94 (1H, q, *J* = 2.2 Hz, 14'), 4.45 (1H, q, *J* = 2.2 Hz, 14''), 4.35 – 4.16 (4H, m), 3.87 (3H, s, H-32), 3.73 (1H, dq, *J* = 17.4, 2.4 Hz, 12'), 3.44 (1H, dq, *J* = 17.4, 2.1 Hz, 12''), 3.27 (1H, dd, *J* = 15.0, 2.1 Hz, 10''), 2.71 (1H, dd, *J* = 15.0, 2.4 Hz, 10'), 1.31 – 1.20 (6H, m, H-23, H-24).

^{13}C NMR (CD_2Cl_2, 101 MHz) δ 180.2 (C-8), 172.1 (C-15), 172.0 (C-16), 160.0 (C-27), 153.8 (C-4), 150.9 (C-13), 148.3 (C-5), 133.7 (Ar), 129.7 (Ar), 128.3 (Ar), 126.6 (C-1), 122.0, 122.0 (C-6), 117.3 (C-28), 114.2 (C-3, C-30), 109.4 (C-14), 67.8 (C-9), 62.6 (C-19), 62.6 (C-20), 59.6 (C-11), 55.8 (C-32), 42.9 (C-10), 42.2 (C-12), 14.2 (C-23), 14.2 (C-24).

HRMS (ESI) *m/z* calcd. for $C_{26}H_{28}NO_5$ $[M+H]^+$: 434.1962; found: 434.1956.

FTIR (neat) ν/cm^{-1} = 2982, 1729, 1597, 1530, 1465, 1427, 1366, 1273, 1256, 1186, 1051, 908, 755, 689.

diethyl 2-methylene-2'-phenyl-6'-(trifluoromethyl)spiro[cyclopentane-1,3'-indole]-4,4-dicarboxylate, 126



126 *was prepared according to* ***general procedure F*** with **S38** (44 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 85% yield (28 mg, 0.068mmol).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 - 8.00 (2H, m, H-26, H-30), 7.94 - 7.88 (1H, m, H-3), 7.53 - 7.44 (3H, m, H-1, H-27, H-28, H-29), 7.40 (1H, dt, *J* = 7.9, 0.7 Hz, H-6), 4.97 (1H, t, *J* = 2.1 Hz, 14''), 4.53 - 4.48 (1H, m, 14'), 4.40 - 4.20 (4H, m, H-19, H-20), 3.74 (1H, dt, *J* = 17.5, 2.4 Hz, 12''), 3.48 (1H, dt, *J* = 17.5, 2.0 Hz, 12'), 3.29 (1H, d, *J* = 15.2 Hz, 10'), 2.74 (1H, d, *J* = 15.2 Hz, 10''), 1.27 (6H, dt, *J* = 9.6, 7.1 Hz, H-23, H-24).

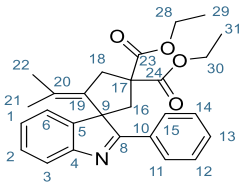
^{13}C NMR ($CDCl_3$, 101 MHz) δ 182.0 (C-8), 171.9 (C-16), 171.7 (C-15), 153.8 (C-4), 151.1 (d, *J* = 1.5 Hz, C-13), 149.3 (C-5), 131.4 (Ar), 130.7 (d, *J* = 32.4 Hz, C-2), 129.4 (C-26, C-30), 128.7 (C-27, C-29), 128.4 (Ar), 124.3 (d, *J* = 272.3 Hz, C-31), 123.3 (q, *J* = 3.8 Hz, C-1), 122.0 (C-6), 118.0 (t, *J* = 3.8 Hz, C-3), 110.4 (C-14), 67.7 (C-9), 62.4 (C-19), 62.4 (C-20), 59.4 (C-11), 42.6 (C-10), 42.1 (C-12), 14.2 (C-23), 14.1 (C-24).

^{19}F NMR ($CDCl_3$, 377 MHz) δ -62.08 (31).

HRMS (ESI) *m/z* calcd. for $C_{26}H_{25}F_3NO_4$ $[M+H]^+$: 472.1730; found: 472.1732.

FTIR (neat) ν/cm^{-1} = 2984, 1730, 1529, 1428, 1367, 1344, 1323, 1257, 1165, 1124, 1061, 1024, 944, 910, 860, 834, 776.

1,1'-(2'-phenyl-2-(propan-2-ylidene)spiro[cyclopentane-1,3'-indole]-4,4-diyl)bis(butan-1-one), 128



128 *was prepared according to* ***general procedure F*** with **S39** (45 mg, 0.08 mmol, 1.0 equiv.), KOAc (10 mg, 0.10 mmol, 1.25 equiv.) in anhydrous MeCN (0.01 M, 8.0 mL) in 86% yield (35 mg, 0.069mmol).

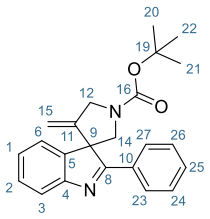
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 – 8.02 (2H, m, H-11, H-15), 7.65 (1H, d, *J* = 7.7 Hz, H-3), 7.51 – 7.40 (3H, m, H-12, H-13, H-14), 7.32 (1H, td, *J* = 7.4, 1.5 Hz, H-2), 7.18 – 7.08 (2H, m, H-1, H-6), 4.35 – 4.09 (4H, m, H-28, H-30), 3.85 (1H, d, *J* = 17.1 Hz, 16'), 3.27 – 3.11 (2H, m, 16'', 18''), 2.42 (1H, d, *J* = 14.3 Hz, 18'), 1.71 (3H, s, H-21), 1.25 – 1.15 (6H, m, H-29, H-31), 0.83 (3H, t, *J* = 1.9 Hz, H-22)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 181.8 (C-8), 172.0 (C-23), 171.7 (C-24), 153.7 (C-4), 146.6 (C-5), 132.8 (C-10), 132.2 (C-19), 130.9 (C-13), 130.0 (C-20), 128.8 (C-12, C-14), 128.4 (C-11, C-15), 127.8 (C-2), 125.9 (C-6), 122.2 (C-1), 121.0 (C-3), 66.5 (C-17), 62.1 (C-28), 62.0 (C-30), 59.5 (C-9), 45.2 (C-18), 40.9 (C-16), 23.0 (C-21), 19.5 (C-22), 14.1 (C-29), 14.0 (C-31)

HRMS (ESI) *m/z* calcd. for $C_{27}H_{30}NO_4$ $[M+H]^+$: 432.2169; found: 432.2164.

FTIR (neat) ν/cm^{-1} = 2985, 1730, 1526, 1444, 1367, 1265, 1244, 1195, 1097, 1070, 1025, 912, 865, 776, 757, 733, 692, 651

***tert*-butyl 4'-methylene-2-phenylspiro[indole-3,3'-pyrrolidine]-1'-carboxylate, 143**



143 *was prepared according to a modified* ***general procedure F*** with **142a** (35 mg, 0.08 mmol, 1.0 equiv.), Cs_2CO_3 (40 mg, 0.12 mmol, 1.5 equiv.) and *fac*-Ir(dFppy)$_3$ (2.4 mg, 4 mol%) in anhydrous $CHCl_3$ (0.01 M, 8.0 mL) at -20 °Cin 66% yield (19 mg, 0.053mmol).

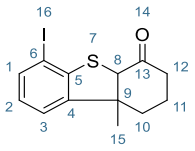
^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.02 (2H, t, *J* = 7.2 Hz, H-23, H-27), 7.71 (1H, d, *J* = 7.8 Hz, H-3), 7.47 (3H, tt, *J* = 7.8, 4.0 Hz, H-24, H-25, H-26), 7.39 (1H, t, *J* = 7.2 Hz, H-2), 7.31 (1H, d, *J* = 7.2 Hz, H-6), 7.26 - 7.22 (1H, m, H-1), 4.98 - 4.84 (1H, m, 15'), 4.68 - 4.41 (3H, m, 14', 14'', 15''), 4.09 - 3.98 (1H, m, 12'), 3.86 - 3.69 (1H, m, 12''), 1.55 (9H, d, *J* = 3.7 Hz, H-20, H-21, H-22)

^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.6 (C-8), 154.5 (C-16), 153.4 (C-4), 146.4 (C-11), 146.1 (C-5), 131.7 (C-10), 131.2 (C-25), 129.0 (C-23, C-27), 128.7 (C-24, C-26), 128.5 (C-2), 126.8 (C-1), 121.4 (C-3), 120.8 (C-6), 108.6 (C-15), 80.5 (C-19), 66.5 (C-9), 54.5 (C-12), 50.8 (C-14), 28.6 (C-20, C-21, C-22)

HRMS (ESI) *m/z* calcd. for $C_{23}H_{25}N_2O_2$ $[M+H]^+$: 361.1911; found: 361.1906.

FTIR (neat) ν/cm^{-1} = 2976, 2926, 1700, 1527, 1456, 1402, 1366, 1341, 1251, 1225, 1165, 1117, 909, 881, 770, 738

6-iodo-9b-methyl-2,3,4a,9b-tetrahydrodibenzo[b,d]thiophen-4(1H)-one, 216



This compound was prepared from **212** (34.4 mg, 0.100 mmol, 1.0 equiv.) according to ***General Procedure G***. Irradiation was performed in the presence of allyltrimethylsilane (0.08 mL, 0.6 g, 0.5 mmol, 5.0 equiv.), fac-Ir(dFppy)$_3$ (0.9 mg, 1 mol%) in a 9:1 (v/v) mixture of MeCN (1.8 mL) and hexafluoroisopropanol (0.2 mL) (0.05 M) over a period of 18 h. Flash column chromatography on silica gel (eluent: 20 % diethyl ether in pentane) yielded diastereoisomer mixture **216** (26.3 mg, 0.076 mmol, 76%) as an off-white solid.

NMR data for major isomer:

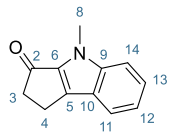
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53 (1H, dd, *J* = 7.8, 1.1, H1), 7.01 (1H, dd, *J* = 7.6, 1.1, H3), 6.83 (1H, t, *J* = 7.7, H2), 3.98 – 3.92 (1H, m, H8), 2.86 – 2.74 (1H, m, H12''), 2.36 (1H, dtt, *J* 15.4, 5.4, 1.2, H12'), 2.17 (1H, ddd, *J* = 13.8, 8.3, 5.3, H10'), 1.95 – 1.79 (2H, m, H11), 1.68 – 1.55 (1H, m, H10''), 1.44 (3H, s, H15)

^{13}C NMR (CDCl$_3$, 101 MHz) δ 207.5 (C13), 146.4 (C5), 137.2 (C1), 127.0 (C4), 126.7 (C2), 122.2 (C3), 88.8 (C6), 63.1 (C8), 56.5 (C9), 37.5 (C12), 34.7 (C10), 26.1 (C15), 21.1 (C11)

HRMS (ESI) *m/z* calcd. for $C_{13}H_{13}IOSNa$ $[M+Na]^+$: 366.9624; found: 366.9610.

FTIR (neat) ν/cm^{-1} = 2958, 2924, 2852, 1704, 1462, 1405, 1348, 1073, 1040, 807, 776, 721

4-methyl-1,4-dihydrocyclopenta[b]indol-3(2H)-one, 225



Enaminone **224** (31.31 mg, 0.1 mmol, 1.0 equiv.), *fac*-Ir(dFppy)$_3$ (0.9 mg, 1.0 μmol, 1 mol%) and potassium acetate (14 mg, 0.15 mmol, 1.5 equiv.) were charged to a 10 mL screw-capped glass vial equipped with a magnetic stir bar. The vial was sealed with a septum and then evacuated and back-filled with argon three times. Argon-sparged MeCN (3.7 mL, 0.05 M) was added *via* syringe to the vial, and the reaction mixture was sparging *via* argon for 15 mins. The vial was placed in water cooling photoreactor described above, and the reaction mixture was stirred under constant irradiation with blue light for 16 h. The reaction mixture was concentrated *in vacuo*, and the crude residue was loaded directly onto silica gel and purified by flash column chromatography (silica gel, 20% EtOAc in pentane) to afford indole **225** (16.9 mg, 0.091 mmol, 91%) as an off-white solid.

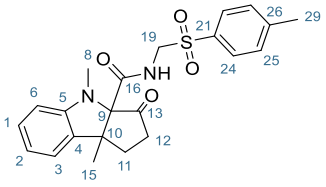
^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.69 (1H, dt, *J* 8.1, 1.0, H11), 7.42 (1H, ddd, *J* 8.1, 6.8, 1.2, H13), 7.36 (1H, dt, *J* 8.5, 1.0, H14), 7.18 (1H, ddd, *J* 8.0, 6.8, 1.1, H12), 3.91 (3H, s, H8), 3.09 – 3.02 (2H, m, H3), 3.01 – 2.94 (2H, m, H4)

^{13}C NMR (101 MHz, CDCl$_3$) δ = 194.94 (C2), 145.00 (C9), 138.95 (C6), 126.89 (C13), 123.19 (C10), 120.30 (C12), 111.06 (C14), 41.59 (C4), 19.70 (C3), 121.87 (C5), 121.86 (C11)

HRMS (ESI) *m/z* calcd. for $C_{12}H_{12}NO$ $[M+H]^+$: 186.0913; found: 186.0908.

FTIR (neat) ν/cm^{-1} = 2923, 2854, 1670, 1485, 1445, 1405, 1378, 1348, 1260, 1235, 1201, 1132, 1097, 1041, 1023, 884, 809, 743

4,8b-dimethyl-3-oxo-*N*-(tosylmethyl)-2,3,4,8b-tetrahydrocyclopenta[b]indole-3a(1H)-carboxamide, 233



This compound was prepared from **226** (102.4 mg, 0.300 mmol, 1.0 equiv.) according to General Procedure A, except that the reaction mixture was degassed by three freeze–pump–thaw cycles prior to irradiation. Irradiation was performed in the presence of *para*-toluenesulfonylmethyl isocyanide (TosMIC) (175.7 mg, 0.900 mmol, 3.0 equiv.) in a 9:1 (v/v) mixture of MeCN (5.4 mL) and water (0.6 mL) (0.05 M) over a period of 18 h. Flash column chromatography on silica gel (30% EtOAc in pentane) yielded **233** (70.1 mg, 0.17 mmol, 57%) as an pale-yellow solid.

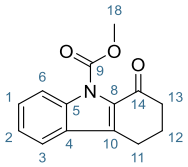
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.76 (2H, m, H24), 7.46 (1H, t, *J* = 6.9, H17), 7.41 – 7.34 (2H, m, H25), 7.19 (1H, td, *J* = 7.7, 1.3, H1), 7.04 (1H, dd, *J* = 7.4, 1.3, H3), 6.87 (1H, td, *J* = 7.4, 1.0, H2), 6.55 (1H, d, *J* = 7.9, H6), 4.88 (1H, dd, *J* = 14.2, 7.5, H19''), 4.61 (1H, dd, *J* = 14.2, 6.3, H19'), 2.91 (3H, s, H8), 2.46 (3H, s, H29), 2.40 (1H, ddd, *J* = 18.3, 7.5, 1.1, H12'), 2.29 – 2.19 (1H, m, H12''), 2.03 (1H, td, *J* = 13.0, 7.4, H11''), 1.75 (1H, ddd, *J* = 18.1, 13.0, 8.9, H11'), 1.17 (3H, s, H15)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 212.3 (C13), 169.1 (C16), 149.7 (C5), 145.7 (C4), 130.2 (C25, C27), 122.5 (C3), 120.9 (C2), 82.5 (C9), 59.7 (C19), 55.5 (C10), 39.1 (C11, C12), 33.1 (C8), 24.2 (C15), 21.9 (C29)

HRMS (ESI) *m/z* calcd. for $C_{22}H_{25}N_2O_4S$ $[M+H]^+$: 413.1530; found: 413.1532.

FTIR (neat) ν/cm^{-1} = 3356 (br), 2926, 2856, 1747, 1677, 1599, 1507, 1482, 1323, 1143, 1116, 1085, 1022, 992, 961, 910, 814, 734

methyl 1-oxo-1,2,3,4-tetrahydro-9H-carbazole-9-carboxylate, 241



Enaminone **239** (74.2 mg, 0.2 mmol, 1.0 equiv.), *fac*-Ir(dFppy)$_3$ (1.8 mg, 1.0 μmol, 1 mol%) and potassium acetate (25 mg, 0.25 mmol, 1.25 equiv.) were charged to a 10 mL microwave vial equipped with a magnetic stir bar. The vial was crimped with aluminium cap and then evacuated and back-filled with argon three times. Argon-sparged MeCN (4 mL, 0.05 M) was added *via* syringe to the vial, and the reaction mixture was sparging *via* argon for 15 mins. The vial was placed *ca.* 3 cm from the 427 nm Kessil lamb in the photoreactor, and the reaction mixture was stirred under constant irradiation for 18 h. The reaction mixture was concentrated *in vacuo*, and the crude residue was loaded directly onto silica gel and purified by flash column chromatography (silica gel, 20% EtOAc in pentane) to afford indole **241** (28.2 mg, 0.12 mmol, 58%) as a yellow solid.

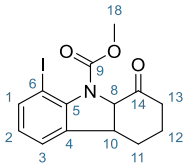
^{1}H NMR (None, 400 MHz) δ 8.01 (1H, dt, *J* = 8.5, 0.9 Hz, H-3), 7.65 (1H, ddd, *J* = 7.9, 1.3, 0.8 Hz, H-6), 7.50 (1H, ddd, *J* = 8.5, 7.2, 1.3 Hz, H-1), 7.31 (1H, ddd, *J* = 8.0, 7.2, 1.0 Hz, H-2), 3.99 (3H, s, H-18), 2.97 (2H, t, *J* = 6.1 Hz, H-13), 2.73 – 2.59 (2H, m, H-11), 2.25 (2H, tt, *J* = 7.3, 5.8 Hz, H-12)

^{13}C NMR (CD_2Cl_2, 101 MHz) δ 187.8 (C14), 151.7 (C9), 138.8 (C5), 137.7 (C8), 132.4 (C10), 128.8 (C1), 126.9 (C4), 123.2 (C2), 121.2 (C6), 114.6 (C3), 54.1 (C18), 39.2 (C11), 23.8 (C12), 21.7 (C13)

FTIR (neat) ν/cm^{-1} = 2953 (br), 1742, 1674, 1607, 1552, 1440, 1366, 1226, 1137

HRMS (ESI) *m/z* calcd. for $C_{14}H_{14}NO_3$ $[M+H]^+$: 244.0968; found: 244.0968.

methyl 8-iodo-1-oxo-1,2,3,4,4a,9a-hexahydro-9H-carbazole-9-carboxylate, 242



Enaminone **239** (74.2 mg, 0.2 mmol, 1.0 equiv.), *fac*-Ir(dFppy)$_3$ (1.8 mg, 1.0 μmol, 1 mol%) and potassium acetate (25 mg, 0.25 mmol, 1.25 equiv.) were charged to a 10 mL microwave vial equipped with a magnetic stir bar. The vial was crimped with aluminium and then evacuated and back-filled with argon three times. Argon-sparged MeCN (4 mL, 0.05 M) was added *via* syringe to the vial, and the reaction mixture was sparging *via* argon for 15 mins. The vial was placed *ca.* 3 cm from the 427 nm Kessil lamb in the photoreactor, and the reaction mixture was stirred under constant irradiation for 18 h. The reaction mixture was concentrated *in vacuo*, and the crude residue was loaded directly onto silica gel and purified by flash column chromatography (silica gel, 20% EtOAc in pentane) to afford **242** (9.5 mg, 0.026 mmol, 13%) as a yellow solid.

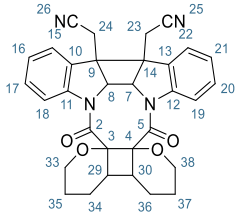
^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.66 (1H, dt, *J* = 8.0, 1.1 Hz, H-1), 7.04 (1H, dt, *J* = 7.4, 1.3 Hz, H-3), 6.79 (1H, t, *J* = 7.7 Hz, H-2), 5.05 (1H, d, *J* = 8.5 Hz, H-8), 4.25 – 4.12 (1H, m, H-10), 3.84 (3H, s, H-18), 2.45 – 2.34 (2H, m, H-13), 2.25 – 2.15 (2H, m, H-11), 2.03 – 1.91 (1H, m, 12'), 1.63 – 1.47 (1H, m, 12'')

^{13}C NMR (CDCl$_3$, 101 MHz) δ 205.9 (C14), 154.1 (C9), 146.2 (C5), 139.3 (C1), 136.7 (C4), 126.6 (C2), 122.2 (C3), 85.6 (C6), 71.6 (C8), 53.2 (C18), 45.7 (C10), 40.5 (C13), 25.0 (C11), 21.9 (C12)

HRMS (ESI) *m/z* calcd. for $C_{14}H_{15}INO_3$ $[M+H]^+$: 372.0091; found: 372.0089.

FTIR (neat) ν/cm^{-1} = 2951, 1722, 1444, 1375, 1332, 1284, 1246, 1197, 1098, 913, 735

Dimer of 2-(1-(3,4-dihydro-2H-pyran-6-carbonyl)-1H-indol-3-yl)acetonitrile,250



Dimer of 2-(1-(3,4-dihydro-2H-pyran-6-carbonyl)-1H-indol-3-yl)acetonitrile **250** was synthesised by **General procedure H** with *fac*-Ir(dFppy)$_3$ in a yield of 78%.

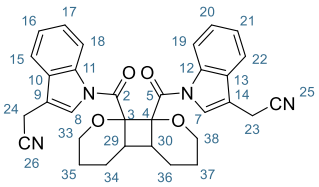
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.27 (2H, dd, *J* = 8.2, 0.6 Hz, H-18, H-19), 7.78 (2H, dd, *J* = 7.7, 0.6 Hz, H-15, H-22), 7.50 (2H, ddd, *J* = 8.2, 7.5, 1.3 Hz, H-17, H-20), 7.29 (3H, ddd, *J* = 7.6, 7.6, 1.1 Hz, H-16, H-21), 5.30 (2H, s, H-7, H-8), 3.88 – 3.77 (3H, m, 31", 36"), 3.33 – 3.24 (2H, m, 31', 36'), 3.22 – 3.10 (2H, m, H-27, H-28), 2.94 (3H, d, *J* = 16.7 Hz, 24"), 2.78 (3H, d, *J* = 16.7 Hz, 23'), 1.96 – 1.76 (4H, m, 32", 33", 34", 35"), 1.69 (3H, d, *J* = 9.8 Hz, 33', 35'), 1.50 – 1.40 (3H, m, 32', 34')

^{13}C NMR (CDCl$_3$, 101 MHz) δ 168.6 (C-2, C-5), 145.0 (C-10, C-13), 131.4 (C-17, C-20), 129.6 (C-11, C-12), 125.7 (C-15, C-22), 125.6 (C-16, C-21), 118.7 (C-18, C-19), 116.3 (C-37, C-39), 84.8 (C-3, C-4), 77.2, 65.0 (C-31, C-36), 64.7 (C-7, C-8), 53.4 (C-9, C-14), 29.5 (C-27, C-28), 24.8 (C-23, C-24), 19.9 (C-33, C-35), 19.8 (C-32, C-34)

LRMS (+ESI): *m/z*: calcd for $C_{32}H_{28}N_4O_4Na^+$ $[M+Na]^+$ 555.21, found 555.

FTIR (neat) ν/cm^{-1} = 2980, 1727, 1673, 1473, 1396, 1314, 1267, 1238, 1140, 1088, 956, 905, 834, 753, 642.

Dimer of 2-(1-(3,4-dihydro-2H-pyran-6-carbonyl)-1H-indol-3-yl)acetonitrile, 253



Dimer of 2-(1-(3,4-dihydro-2H-pyran-6-carbonyl)-1H-indol-3-yl)acetonitrile **253** was synthesised by **General procedure H** with Ir[(5-CF_3)ppy]$_3$ in a yield of 88%.

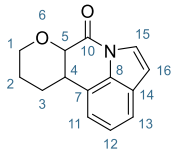
^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.65 (2H, dd, *J* = 8.3, 0.9 Hz, H-18, H-19), 7.56 (2H, ddd, *J* = 7.7, 1.3, 0.7 Hz, H-15, H-22), 7.53 (2H, t, *J* = 1.2 Hz, H-7, H-8), 7.47 (2H, ddd, *J* = 8.4, 7.2, 1.3 Hz, H-17, H-20), 7.40 (2H, ddd, *J* = 7.7, 7.3, 1.0 Hz, H-16, H-21), 3.94 (2H, ddd, *J* = 11.8, 3.6, 1.7 Hz, 33", 38"), 3.59 – 3.56 (2H, m, H-29, H-30), 3.20 (2H, ddd, *J* = 12.5, 11.7, 1.7 Hz, 33', 38'), 3.14 – 3.05 (4H, m, 23', 24'), 2.06 – 1.95 (2H, m, 35", 37"), 1.87 – 1.75 (4H, m, 34', 34", 36', 36"), 1.55 – 1.47 (2H, m, 35', 37')

^{13}C NMR ($CDCl_3$, 151 MHz) δ 166.9 (C-2, C-5), 136.6 (C-11, C-12), 127.7 (C-10, C-13), 126.2 (C-17, C-20), 124.7 (C-16, C-21), 124.5 (C-7, C-8), 118.4 (C-15, C-22), 117.4 (C-18, C-19), 116.7 (C-25, C-26), 111.2 (C-9, C-14), 84.4 (C-3, C-4), 65.0 (C-33, C-38), 30.5 (C-29, C-30), 20.0 (C-34, C-36), 19.5 (C-35, C-37), 13.8 (C-23, C-24)

HRMS (+ESI): *m/z* calcd for $C_{32}H_{28}N_4O_4^+$ $[M+H]^+$ 534.2244, found 534.2246.

FTIR (neat) ν/cm^{-1} = 2926, 2853, 2360, 2254, 1697, 1608, 1451, 1360, 1331, 1286, 1262, 1209, 1132, 1056, 1038, 1021, 973, 906, 826, 749, 678

9,10,11,11a-tetrahydropyrano[2,3-c]pyrrolo[3,2,1-ij]quinolin-7(7aH)-one, 245



9,10,11,11a-tetrahydropyrano[2,3-c]pyrrolo[3,2,1-ij]quinolin-7(7aH)-one **245** was synthesised by **General procedure H** and **I** as a white solid.

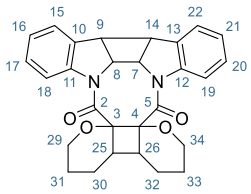
^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.69 (1H, d, *J* = 3.6 Hz, H-15), 7.49 (1H, ddd, *J* = 7.8, 1.0, 1.0 Hz, H-13), 7.26 (2H, dd, *J* = 7.6, 7.6 Hz, H-12), 7.16 (1H, dd, *J* = 7.3, 1.1 Hz, H-11), 6.72 (1H, dd, *J* = 9.2, 3.6 Hz, H-16), 4.40 – 4.34 (1H, m, 1''), 4.23 (1H, d, *J* = 12.1 Hz, H-18), 3.66 – 3.59 (1H, m, 1'), 3.39 – 3.31 (1H, m, H-19), 2.75 – 2.68 (1H, m, 3'), 1.97 – 1.78 (3H, m, H-2, 3'').

^{13}C NMR ($CDCl_3$, 151 MHz) δ 165.1 (C-10), 133.8 (C-8), 127.8 (C-14), 124.0 (C-12), 122.3 (C-7), 121.8 (C-15), 119.9 (C-13), 118.8 (C-11), 110.4 (C-16), 79.2 (C-5), 69.5 (C-1), 38.8 (C-4), 26.2 (C-3), 25.0 (C-2).

HRMS (+ESI): *m/z* calcd for $C_{14}H_{14}NO_2^+$ $[M+H]^+$ 228.1019, found 228.1013.

FTIR (neat) ν/cm^{-1} = 2920, 2851, 1734, 1466, 1439, 1395, 1300, 1256, 1222, 1133, 1113, 1068, 1043, 957, 946, 837, 796, 767, 741, 723, 633

Dimer of 3,4-dihydro-2H-pyran-6-yl)(1H-indol-1-yl)methanone, 254



9,10,11,11a-tetrahydropyrano[2,3-c]pyrrolo[3,2,1-ij]quinolin-7(7aH)-one **254** was synthesised by **General procedure H** and **I** as a white solid.

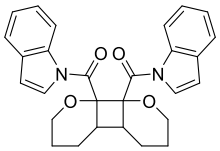
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.18 (2H, d, *J* = 8.1 Hz, H-18, H-19), 7.41 (2H, d, *J* = 7.5 Hz, H-15, H-22), 7.37 – 7.29 (2H, m, H-17, H-20), 7.16 (2H, ddd, *J* = 7.5, 7.4, 1.1 Hz, H-16, H-21), 5.62 (2H, d, *J* = 7.1 Hz, H-7, H-8), 4.03 (2H, d, *J* = 7.0 Hz, H-9, H-14), 3.84 – 3.76 (2H, m, 29'', 34''), 3.33 – 3.22 (2H, m, 29', 34'), 3.16 (2H, t, *J* = 1.7 Hz, H-25, H-26), 1.91 – 1.81 (4H, m, 30', 31'', 32', 33''), 1.72 – 1.63 (1H, m, 30'', 32''), 1.46 – 1.38 (3H, m, 31', 33').

^{13}C NMR (CDCl$_3$, 101 MHz) δ 168.9 (C-2, C-5), 128.9 (C-17, C-20), 126.3 (C-15, C-22), 64.7 (C-29, C-34), 62.8 (C-7, C-8), 47.2 (C-9, C-14), 29.8 (C-25, C-26), 20.0 – 19.8 (m), 20.0 (C-31, C-33), 20.0 – 19.8 (m), 145.1 (C-11, C-12), 133.0 (C-10, C-13), 124.6 (C-16, C-21), 117.7 (C-18, C-19), 85.2 (C-3, C-4), 19.9 (C-30, C-32).

HRMS (+ESI): m/z calcd for $C_{28}H_{27}N_2O_4^+$ $[M+H]^+$ 455.1965, found 455.1953

FTIR (neat) ν/cm^{-1} = 2981, 1734, 1678, 1596, 1472, 1459, 1391, 1336, 1253, 1218, 1170, 1127, 1052, 972, 907, 890, 829, 786, 756, 735, 635

Dimer of 3,4-dihydro-2H-pyran-6-yl)(1H-indol-1-yl)methanone, 255



Dimer of 3,4-dihydro-2H-pyran-6-yl)(1H-indol-1-yl)methanone was synthesised by **General procedure I** with Ir[(4-F)ppy]$_3$ as a white solid in a yield of 48%.

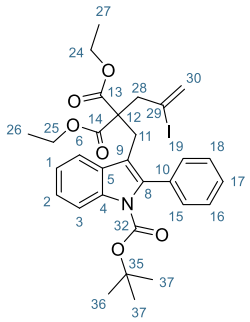
^{1}H NMR (CDCl$_3$, 600 MHz) δ 8.65 (2H, dq, *J* = 8.3, 0.8 Hz), 7.54 (2H, d, *J* = 3.9 Hz), 7.50 – 7.46 (2H, m), 7.37 (2H, ddd, *J* = 8.4, 7.2, 1.3 Hz), 7.29 (2H, td, *J* = 7.5, 1.1 Hz), 6.10 (2H, dd, *J* = 3.9, 0.7 Hz), 3.87 (2H, ddt, *J* = 11.7, 3.7, 1.7 Hz), 3.64 – 3.57 (2H, m), 3.15 (2H, td, *J* = 12.2, 1.7 Hz), 2.08 – 1.92 (2H, m), 1.85 – 1.71 (4H, m), 1.60 – 1.53 (4H, m), 1.46 (2H, ddq, *J* = 13.8, 4.3, 2.0 Hz)

^{13}C NMR (CDCl$_3$, 151 MHz) δ 167.6, 136.5, 130.3, 126.9, 125.0, 124.3, 120.7, 117.3, 108.9, 64.9, 30.7, 29.8, 20.3, 19.6.

All data are in accordance with those in literature.[120]

Mechanistic study

diethyl 2-((1-(tert-butoxycarbonyl)-2-phenyl-1H-indol-3-yl)methyl)-2-(2-iodoallyl)malonate, 151



To a solution of diethyl 2-(2-iodoallyl)-2-((2-phenyl-1H-indol-3-yl)methyl)malonate **66** (265 mg, 0.5 mmol, 1.0 equiv.) in CH_2Cl_2 (0.2 M, 2.5 mL), di-tert-butyl decarbonate (110 mg, 0.5 mmol, 1.0 equiv.) and DMAP (67.2 mg, 0.55 mmol, 1.1 equiv.) were added. The reaction was stirred overnight at room temperature. The reaction was quenched with H_2O (5 mL) and the aqueous phase was extracted with CH_2Cl_2 for three times. The combined organic was washed with brine and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (25% EtOAc in pentane) to give the desired product in 100% (314 mg, 0.50 mmol) yield as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (1H, dt, *J* = 8.4, 0.9 Hz, H-6), 7.62 (1H, ddd, *J* = 7.8, 1.4, 0.7 Hz, H-3), 7.48 - 7.42 (2H, m, H-16, H-18), 7.41 - 7.37 (1H, m, H-2), 7.37 - 7.33 (2H, m, H-15, H-19), 7.30 (1H, ddd, *J* = 8.4, 7.2, 1.4 Hz, H-17), 7.23 (1H, ddd, *J* = 8.1, 7.3, 1.2 Hz, H-1), 5.58 (2H, d, *J* = 1.2 Hz, 30', 30''), 3.89 (4H, ddq, *J* = 56.5, 10.8, 7.2 Hz, 24', 25'), 3.50 (2H, s, H-11), 2.84 (2H, d, *J* = 1.2 Hz, H-28), 1.20 (10H, s, H-36, H-37, H-38), 1.03 (7H, t, *J* = 7.1 Hz, H-26, H-27)

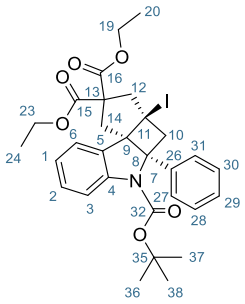
^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.4 (C-13, C-14), 150.2 (C-32), 138.4 (C-8), 136.3 (C-4), 134.1 (C-10), 130.7 (C-15, C-19), 130.0 (C-5), 128.8 (C-30), 128.4 (C-16, C-18), 128.1 (C-2), 124.6 (C-17), 122.6 (C-1), 120.0 (C-3), 115.3 (C-9), 115.0 (C-6), 103.1 (C-29), 83.3 (C-35),

61.7 (C-24, C-25), 58.4 (C-12), 48.4 (C-28), 27.6 (C-36, C-37, C-38), 27.0 (C-11), 13.7 (C-26, C-27)

HRMS (ESI) m/z calcd. for $C_{30}H_{34}INO_6Na$ $[M+Na]^+$: 654.1323,; found: 654.1347.

FTIR (neat) ν/cm^{-1} = 2981, 1730, 1457, 1360, 1327, 1232, 1155, 1074, 755, 701

5-(tert-butyl) 2,2-diethyl 3a-iodo-4a-phenyl-3,3a,4,4a-tetrahydro-1H-cyclopenta[2,3]cyclobuta[1,2-b]indole-2,2,5-tricarboxylate, 152



To a microwave vial equipped with a stir bar, diethyl 2-((1-(tert-butoxycarbonyl)-2-phenyl-1H-indol-3-yl)methyl)-2-(2-iodoallyl)malonate **151** (126 mg, 0.2 mmol, 1.0 equiv.), Ir[(5-CF_3)dFppy]$_2$dtBbpy•PF_6 (9 mg, 0.008 mmol, 4 mol%,) and MeCN (0.05 M, 4 mL) were charged in. The vial was sealed and sparged with argon for 15 mins. The reaction was put in photoreactor equipped two 427 nm Kessil lamps and under constant irradiation for 18 hrs. The reaction mixture was concentrated and purified by flash column chromatography (5% EtOAc in pentane) to give the desired product in 94% (119 mg, 0.19 mmol) yield as a yellow oil.

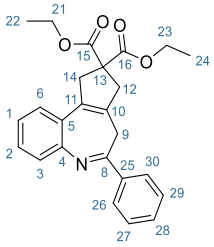
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (1H, d, *J* = 7.8 Hz, H-3), 7.40 – 7.36 (2H, m, H-6), 7.36 – 7.18 (5H, m), 7.12 (1H, tt, *J* = 7.5, 0.9 Hz, H-1), 4.28 – 4.07 (2H, m, H-23), 4.06 – 3.95 (2H, m, 12', 19''), 3.74 – 3.63 (1H, m, 19'), 3.42 (1H, d, *J* = 14.9 Hz, 14''), 3.27 (1H, d, *J* = 15.1 Hz, 12''), 3.07 (1H, d, *J* = 15.5 Hz, 10''), 2.96 (1H, d, *J* = 14.9 Hz, 14'), 2.23 (1H, d, *J* = 15.5 Hz, 10'), 1.24 (3H, td, *J* = 7.1, 0.7 Hz, H-24), 1.13 (9H, s, H-36, H-37, H-38), 0.97 (3H, td, *J* = 7.1, 0.7 Hz, H-20).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.7 (C-15), 170.6 (C-16), 151.2 (C-32), 146.0 (C-4), 139.5 (C-26), 134.9 (C-5), 129.6 (C-2), 128.5 (C-27, C-31), 127.7 (C-28, C-30), 127.1 (C-29), 124.4 (C-6), 122.9 (C-1), 114.9 (C-3), 81.1 (C-35), 72.8 (C-8), 71.2 (C-13), 62.4 (C-9), 62.3 (C-23), 61.9 (C-19), 54.4 (C-14), 49.5 (C-12), 47.5 (C-11), 37.6 (C-10), 28.1 (C-36, C-37, C-38), 14.1 (C-24), 13.7 (C-20).

HRMS (ESI) m/z calcd. for $C_{30}H_{34}INO_6Na$ $[M+Na]^+$: 654.1323,; found: 654.1325.

FTIR (neat) ν/cm^{-1} = 2926, 1731, 1709, 1482, 1461, 1370, 1317, 1248, 1166, 1095, 1064, 1016, 852, 754, 700

diethyl 6-phenyl-8,10-dihydrobenzo[b]cyclopenta[d]azepine-9,9(7H)-dicarboxylate, 180



5-(tert-butyl) 2,2-diethyl 3a-iodo-4a-phenyl-3,3a,4,4a-tetrahydro-1H-cyclopenta[2,3]-cyclobuta[1,2-b]indole-2,2,5-tricarboxylate **152** (102 mg, 0.16 mmol) was added in a 5 mL flask equipped with as stir bar. A solution of TFA in CH_2Cl_2 (1:1, 2 mL) was add into the flask at 0 °C. The reaction was stirred at this temperature for 1 hr. The mixture was dried under reduced pressure to give the desired product in 100% (64.6 mg, 0.16 mmol) yield as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 – 7.96 (2H, m, H-26, H-30), 7.52 (1H, ddd, *J* = 8.1, 1.3, 0.5 Hz, H-3), 7.50 – 7.43 (4H, m, H-6, H-27, H-28, H-29), 7.39 – 7.33 (1H, m, H-2), 7.21 (1H, ddd, *J* = 7.9, 7.2, 1.4 Hz, H-1), 4.17 (4H, q, *J* = 7.2 Hz, 21", 23"), 3.54 (2H, p, *J* = 1.7 Hz, H-12), 3.38 (2H, t, *J* = 1.8 Hz, H-14), 3.07 – 3.01 (2H, m, H-9), 1.20 (6H, t, *J* = 7.1 Hz, H-22, H-24).

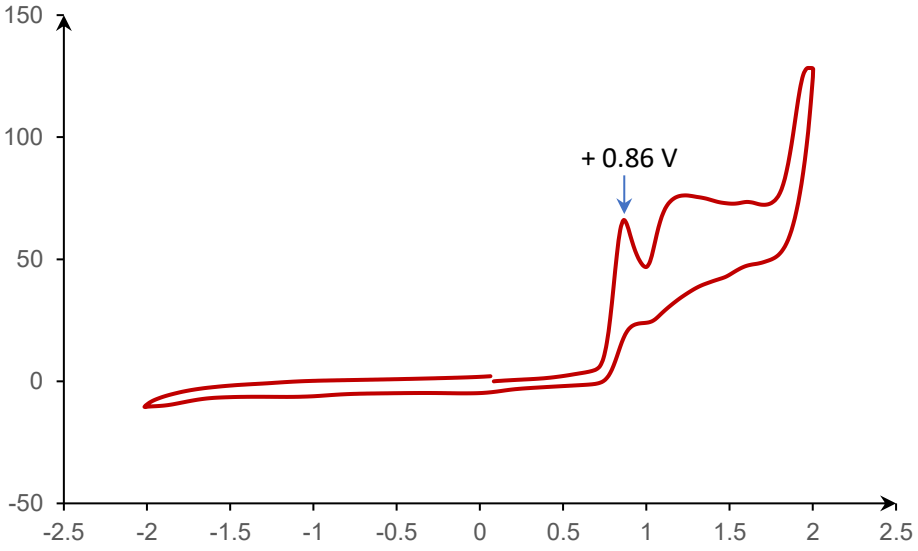
^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.70 (C-15, C-16), 157.17 (Ar), 146.40 (Ar), 138.61 (C-5), 133.26 (Ar), 131.13 (Ar), 130.32 (C-28), 128.68 (C-27, C-29), 128.19 (C-26, C-30), 128.02 (C-3), 126.82 (C-2), 126.80 (Ar), 126.55 (C-6), 124.13 (C-1), 61.85 (C-21, C-23), 59.16 (C-13), 44.19 (C-14), 41.28 (C-12), 31.34 (C-9), 14.07 (C-22, C-24).

HRMS (ESI) *m/z* calcd. for $C_{25}H_{26}NO_4$ $[M+H]^+$: 404.1856; found: 404.1856.

FTIR (neat) ν/cm^{-1} = 2923, 1732, 1447, 1257, 1256, 1186, 1073, 760

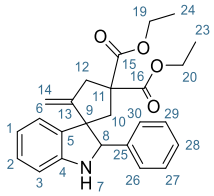
Cyclic Voltammetry (CV)

A PalmSens EmStat3 potentiostat, equipped with a carbon working electrode, Pt wire (diameter = 0.5 mm) counter electrode and leak-free $Ag/AgNO_3$ (0.1 M in MeCN) reference electrode, was used for redox measurement. The half-wave oxidation potential was found +0.86 V and no reduction potential was found under the redox applied redox window.



Product Transformations

diethyl 2-methylene-2'-phenylspiro[cyclopentane-1,3'-indoline]-4,4-dicarboxylate, 165



To a microwave vial equipped with a stir bar, **66** (53 mg, 0.10 mmol, 1.0 equiv.), Ir[(5-CF_3)dFppy]$_2$dtBbpy•PF_6 (4.5 mg, 0.004 mmol, 4 mol%,) and MeCN (0.01 M, 10 mL) were charged in. The vial was sealed and sparged with argon for 15 mins. The reaction was put in photoreactor equipped two 427 nm Kessil lamps and under constant irradiation for 18 hrs. The reaction mixture was concentrated and redissolved in MeOH (0.1 M, 1.0 mL). Then $NaBH_3CN$ (9.5 mg, 0.15 mmol, 1.5 equiv.) and AcOH (9 µL, 0.15 mmol, 1.5 equiv.) were added. The reaction was stirred at room temperature for 2 hrs and then quenched with H_2O (2 mL). The aqueous was extracted with EtOAc three times. The combined organic was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (10% EtOAc in hexane) to give the desired product 90% (36 mg, 0.09 mmol, yield was report for both isomers) in two steps as a yellow oil.

The ratio of diastereoisomers was determined by quantitative NMR (major: minor =3: 2)

Major diastereoisomer:

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.4 - 7.4 (1H, m, H-26, H-30), 7.3 - 7.3 (3H, m, H-27, H-29), 7.1 - 7.1 (2H, m, H-2, H-6), 6.8 (1H, td, *J* = 7.4, 1.0 Hz, H-1), 6.7 (1H, dd, *J* = 8.1, 1.2 Hz, H-3), 4.9 (1H, h, *J* = 1.0 Hz, 14'), 4.7 (1H, s, H-8), 4.3 (1H, dt, *J* = 2.8, 0.9 Hz, 14''), 4.2 (4H, dddd, *J* = 8.2, 7.1, 5.8, 3.1 Hz, 19', 19'', H-20), 3.1 (1H, dd, *J* = 14.8, 1.3 Hz, 10'), 2.8 (1H, d, *J* = 14.9 Hz, 10''), 2.6 (1H, dd, *J* = 15.5, 1.3 Hz, 12''), 2.0 - 1.9 (1H, m, 12'), 1.3 - 1.2 (6H, m, H-23, H-24)

^{13}C NMR (CDCl$_3$, 101 MHz) δ 171.8 (C-15, C-16), 150.9 (C-4), 150.4 (C-13), 139.1 (C-25), 134.1 (C-5), 128.2 (C-26, C-30), 128.1 (C-27, C-29), 128.0 (C-6), 128.0 (C-28), 124.9 (C-2), 119.8 (C-1), 112.0 (C-14), 109.1 (C-3), 75.5 (C-8), 61.7 (C-19, C-20), 60.9 (C-9), 57.6 (C-11), 46.5 (C-10), 42.3 (C-12), 14.2 (C-23)

HRMS (ESI) *m/z* calcd. for $C_{25}H_{28}NO_4$ $[M+H]^+$: 406.2013; found: 406.2021.

FTIR (neat) ν/cm^{-1} = 2918, 2850, 1729, 1604, 1483, 1465, 1366, 1254, 1192, 1079, 1023, 907, 861, 743, 702

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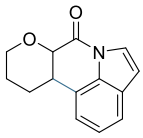
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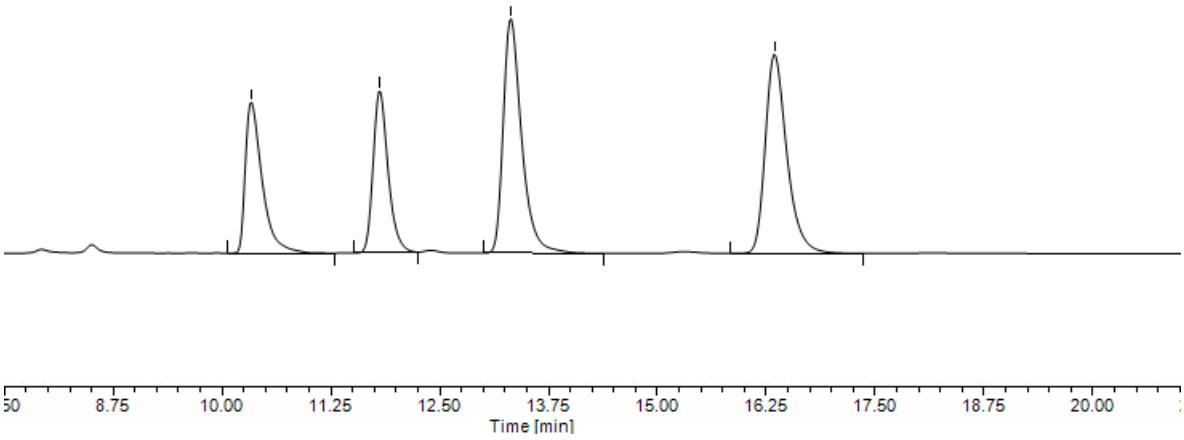
Appendix

HPLC Traces

9,10,11,11a-tetrahydropyrano[2,3-c]pyrrolo[3,2,1-ij]quinolin-7(7aH)-one, *rac*-245

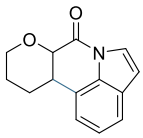
Chiral HPLC: (Chiralpak IG-3, 20% ethanol, 80% n-hexane, 1.0 mL min-1, λ = 210 nm

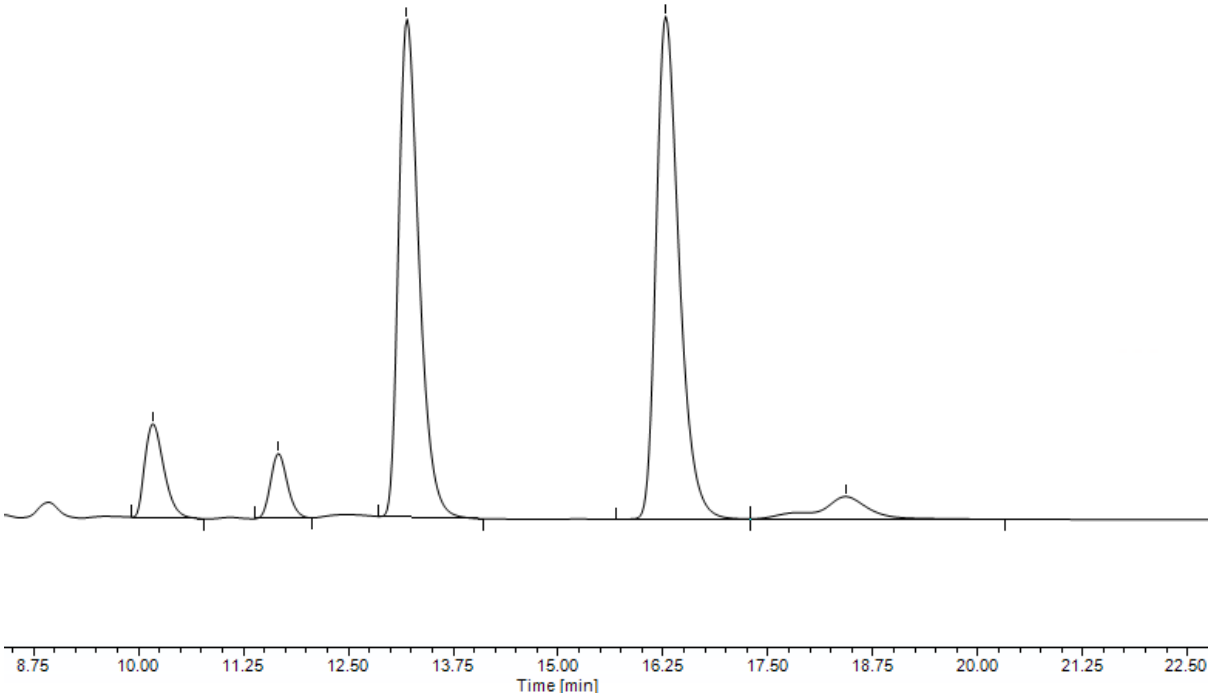




Peak	Retention time / min	Area / mAU*min	Height / mAU
1	10.333	13.2963	59.59
2	11.81	12.638	63.77
3	13.313	22.5284	92.28
4	16.343	22.5177	78.37

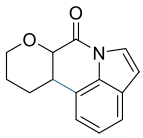
Chiral HPLC: (Chiralpak IG-3, 20% ethanol, 80% *n*-hexane, 1.0 mL min^{-1}, λ = 210 nm

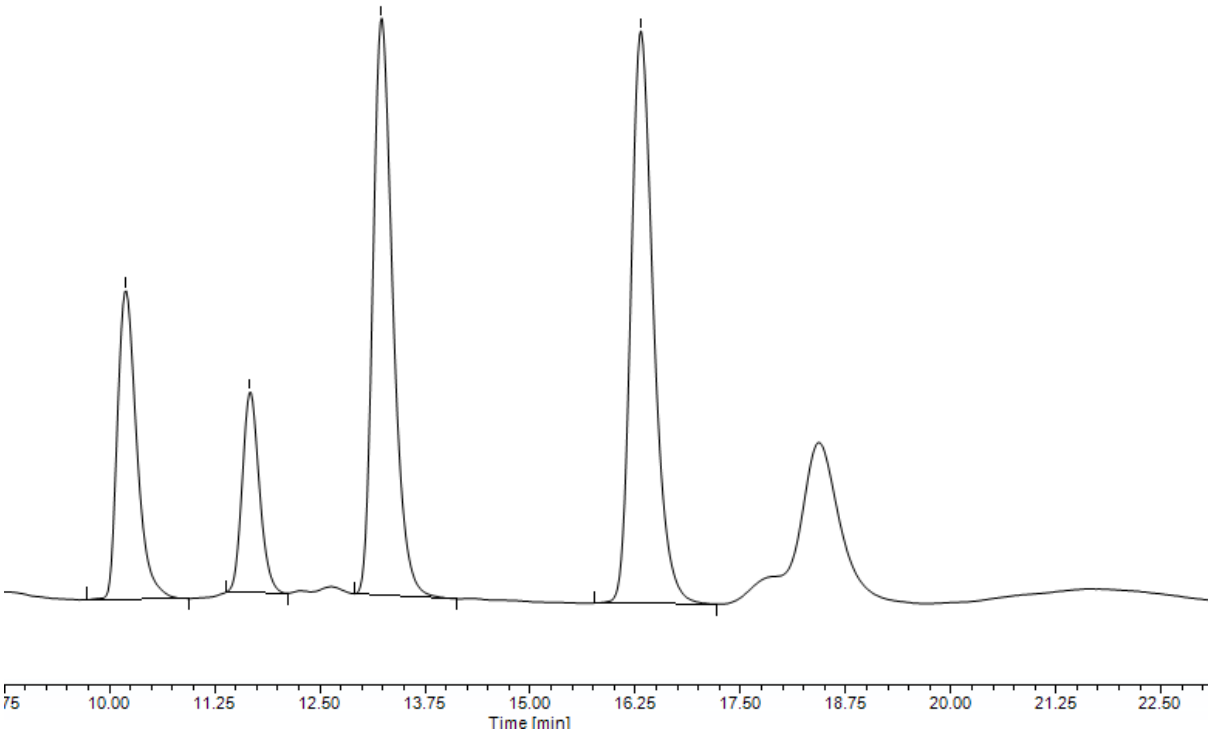




Peak	Retention time / min	Area / mAU*min	Height / mAU
1	10.17	10.1199	38.29
2	11.663	6.1753	26.4
3	13.197	57.4636	203.06
4	16.28	65.2725	205.18

Chiral HPLC: (Chiralpak IG-3, 20% ethanol, 80% *n*-hexane, 1.0 mL min^{-1}, λ = 210 nm

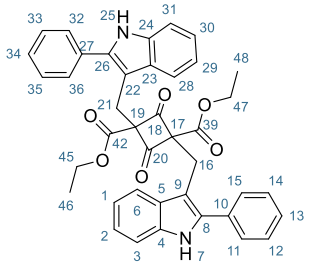




Peak	Retention time / min	Area / mAU*min	Height / mAU
1	10.19	17.66	20.97
2	11.69	10.19	13.65
3	13.233	34.02	39.12
4	16.313	38.14	38.81

Characterisation of Compounds 71 and 149

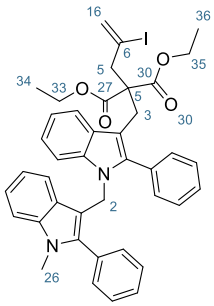
diethyl 2,4-dioxo-1,3-bis((2-phenyl-1H-indol-3-yl)methyl)cyclobutane-1,3-dicarboxylate, 71



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (2H, s, H-7, H-25), 7.61 – 7.54 (2H, m, H-6, H-28), 7.45 – 7.28 (10H, m, H-11, H-12, H-13, H-14, H-15, H-32, H-33, H-34, H-35, H-36), 7.24 (2H, dt, *J* = 8.1, 1.0 Hz, H-3, H-31), 7.11 (2H, ddd, *J* = 8.2, 7.1, 1.2 Hz, H-2, H-30), 7.02 (2H, ddd, *J* = 8.1, 7.0, 1.1 Hz, H-1, H-29), 3.60 (4H, s, H-16, H-21), 3.43 (4H, q, *J* = 7.2 Hz, H-45, H-47), 0.65 (6H, t, *J* = 7.2 Hz, H-46, H-48)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.8 (C-39, C-42), 136.7 (Ar), 135.7 (Ar), 133.9 (Ar), 130.0 (Ar), 129.0 (C-11, C-15, C-32, C-36), 128.8 (C-12, C-14, C-33, C-35), 127.9 (C-13, C-34), 122.0 (C-2, C-30), 120.6 (C-6, C-28), 119.5 (C-1, C-29), 110.5 (C-3, C-31), 108.2 (C-9, C-22), 60.8 (C-45, C-47), 60.2 (C-17, C-19), 30.5 (C-16, C-21), 13.3 (C-46, C-48)

diethyl 2-(2-iodoallyl)-2-((1-((1-methyl-2-phenyl-1H-indol-3-yl)methyl)-2-phenyl-1H-indol-3-yl)methyl)malonate, 149



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (1H, dt, *J* = 7.8, 1.1 Hz, Ar), 7.49 – 7.41 (3H, m, Ar), 7.39 – 7.33 (3H, m, Ar), 7.32 – 7.25 (3H, m, Ar), 7.22 – 7.13 (3H, m, Ar), 7.08 – 6.93 (4H, m, Ar), 6.79 (1H, dt, *J* = 8.0, 1.0 Hz, Ar), 5.67 (1H, dd, *J* = 2.8, 1.4 Hz, 16''), 5.57 – 5.52 (1H, m, 16'), 5.27 (2H, s, H-2), 4.06 – 3.92 (2H, m, 33'', 35''), 3.83 (2H, dq, *J* = 10.8, 7.1 Hz, 33', 35'), 3.66 (2H, s, H-3), 3.55 (3H, s, H-26), 2.92 (2H, t, *J* = 1.4 Hz, H-5), 1.07 (6H, t, *J* = 7.1 Hz, H-34, H-36)

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.6 (C-27, C-30), 140.4 (Ar), 137.9 (Ar), 137.2 (Ar), 136.5 (Ar), 132.2 (Ar), 131.6 (Ar), 131.4 (Ar), 130.7 (Ar), 128.8 (Ar), 128.6 (Ar), 128.6 (Ar), 128.3 (Ar), 127.7 (C-16), 126.6 (Ar), 121.9 (Ar), 121.7 (Ar), 120.1 (Ar), 119.5 (Ar), 119.3 (Ar), 110.6 (Ar), 109.3 (Ar), 109.1 (Ar), 107.1 (Ar), 104.0 (C-6), 61.5 (C-33, C-35), 59.0 (C-4), 47.5 (C-5), 41.2 (C-2), 30.9 (C-26), 28.1 (C-3), 13.8 (C-34, C-36)