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# **A concise and scalable total synthesis of dictyodendrin B by sequential C–H functionalisation**

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This dissertation is submitted to the degree of Doctor of Philosophy

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# **DECLARATION**

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This thesis is submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy. It describes work carried out in the Department of Chemistry from October 2011 to March 2015. Unless otherwise indicated, the research is my own and not the product of a collaboration. No parts of this dissertation have been submitted as part of any other qualification. The length of this dissertation does not exceed 60,000 words.

Andrew K. Pitts

Thursday, 15 October 2015

## **ACKNOWLEDGEMENTS**

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My thanks begin with Professor Matthew J. Gaunt who gave me the opportunity to pursue my Ph.D. studies in his lab. Through both the difficult and less difficult times, working with you and those in your group has undoubtedly helped me to become a better scientist and person. There are many lessons and skills, both professional and personal, that I will take away from my experience in Cambridge for which I am very grateful.

I am also indebted to Dr Fionn O'Hara and Dr Robert H. Snell, both of whom worked towards the total synthesis of dictyodendrin B before I joined the project. While many challenges remained for me in completing the synthesis, your vast contributions significantly lightened an otherwise impossible challenge for one person to undertake. Particular thanks are due to Dr Snell who assisted in handing this project over to me. My appreciation also goes to Dr Ruth E. Gilligan whose work on the total synthesis of staurosporinone provided a great platform on which I was able to supervise a Part III student. During my time here I have met many wonderful people in the lab and I would like to thank you all for your friendship and support. Particular thanks go to Dr Darren Willcox for proofreading this manuscript.

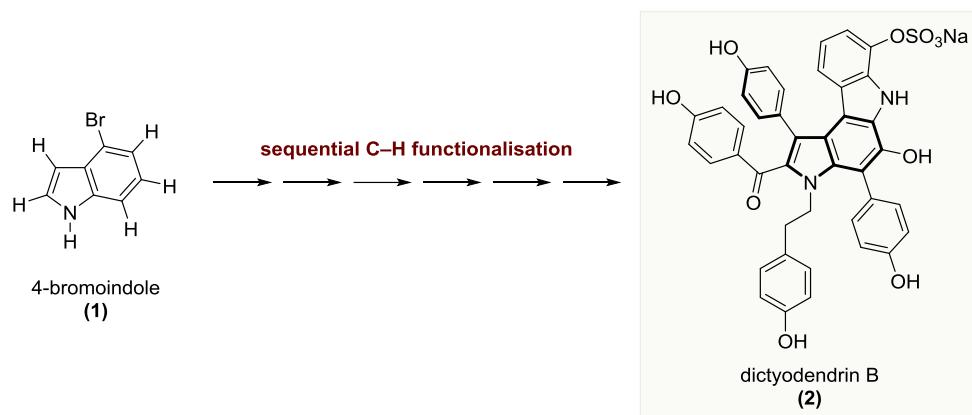
As my Ph.D. was co-sponsored by AstraZeneca I had the fantastic opportunity to revisit the research site in Mölndal, Sweden during the third year of my studies. I thank Dr Malin Lemurell and Dr Tord Inghardt for organising my placement and allowing me to return to such an excellent centre of research in an amazing country. Most of all, I would like to thank Dr Johan Kajanus who was incredibly helpful and welcoming during my time there.

The synthetic chemistry department would be lost without the continued support of the technicians who make our lives easier every single day. I relied on all of you, perhaps more than most, due to some of the unusual technical demands that transpired during my practical work. I am very grateful to Mr Melvyn Oriss, Mr Keith Parmenter, Mr Nic Davies and Mr Matt Pond for all the time you sacrificed to help me with my work.

Lastly, I would never have been able to achieve anywhere near as much or come this far without the unconditional support of my parents. Thank you for everything you do for me and I hope I've made you proud.

# ABSTRACT

This thesis describes the total synthesis of the marine alkaloid dictyodendrin B (**2**). Our investigations were primarily directed towards achieving this goal via a sequential C–H functionalisation strategy (Scheme 1).



**Scheme 1.** The synthesis of dictyodendrin B from 4-bromoindole.

The functionalisation of C–H bonds has attracted considerable interest due to its potential impact on the synthesis of complex molecules. Our aim was to demonstrate the advantages and feasibility of performing an extended sequence of C–H functionalisations to simplify and streamline the synthesis of a sufficiently challenging target.

The dictyodendrins, a family of telomerase-inhibiting marine alkaloids that have been investigated for their anti-cancer properties, became the focus of our attention due to their dense functionalisation. Each dictyodendrin can be viewed as having a central indole core that is peripherally decorated with a large number of substituents. We envisaged that performing sequential C–H functionalisations on a simple unfunctionalised indole would provide an excellent platform to demonstrate our strategy.

We were subsequently able to perform a sequence of reactions, including 5 C–H functionalisations, to afford dictyodendrin B (**2**) from the minimally functionalised and readily available 4-bromoindole (**1**). The complete functionalisation of the indole was performed on gram-scale and enabled rapid construction of this complex natural product in a highly concise manner.

# ABBREVIATIONS

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$\delta$	chemical shift	DIBAL	diisobutylaluminum
$^{\circ}\text{C}$	degrees Celsius		hydride
Ac	acetyl	DIPEA	<i>N,N</i> -diisopropylethylamine
AIBN	azobisisobutyronitrile	DMAP	4-(dimethylamino)pyridine
app	apparent	DMB	2,2-dimethylbutane
aq	aqueous	DME	dimethoxyethane
Ar	aryl	DMF	<i>N,N</i> -dimethylformamide
atm	atmosphere(s)	DMP	Dess-Martin periodinane
Bn	benzyl	DMSO	dimethylsulfoxide
Boc	<i>tert</i> -butyloxycarbonyl	DOSP	<i>N</i> -( <i>p</i> -dodecylphenylsulfonyl)prolinato
bp	boiling point	dppb	1,4-bis(diphenylphosphino)butane
BrettPhos	2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl	DPEPhos	bis[(2-diphenylphosphino)phenyl] ether
Bu	butyl	dppm	1,1-bis(diphenylphosphino)methane
$\sigma$ -CAM	$\sigma$ -complex assisted metathesis	dppp	1,3-bis(diphenylphosphino)propane
COD	1,5-cyclooctadiene	dr	diastereomeric ratio
conc.	concentrated	dtbp	2,6-di- <i>tert</i> -butylpyridine
$\text{cm}^{-1}$	wavenumber	dtbpy	4,4'-di- <i>tert</i> -butyl-2,2'-bipyridine
COSY	correlation spectroscopy	EDG	electron donating group
Cp	cyclopentadienyl	ee	enantiomeric excess
Cy	cyclohexyl	Et	ethyl
CyJohnPhos	(2-Biphenyl)dicyclohexyl phosphine	EWG	electron withdrawing group
d	doublet	equiv	equivalent(s)
DavePhos	2-dicyclohexylphosphino-2'-( <i>N,N</i> -dimethylamino)biphenyl	g	gram(s)
DCE	1,2-dichloroethane	GC	gas chromatography
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone	GCMS	gas chromatography-mass spectrometry

Abbreviations

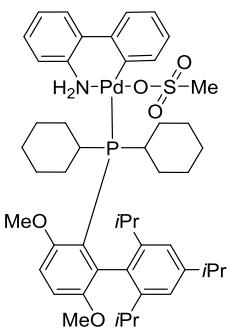
h	hour(s)		NOESY	nuclear Overhauser
IR	infrared			enhancement spectroscopy
J	coupling constant	<i>o</i>		ortho
JohnPhos	(2-biphenyl)di- <i>tert</i> -butylphosphine	Oxone®		potassium peroxyomonosulfate
HFIP	hexafluoroisopropanol	<i>p</i>		para
HIV	human immunodeficiency virus	pen		pentet
HRMS	high resolution mass spectrometry	PC		propylene carbonate
Hz	Hertz	Ph		phenyl
L	ligand	PIDA		phenyliodine(III) diacetate
LC	liquid chromatography	PIFA		phenyliodine(III)
LCMS	liquid chromatography-mass spectrometry	Piv		bis(trifluoroacetate)
LiHMDS	lithium bis(trimethylsilyl)amide	ppm		pivaloyl ( <i>tert</i> -butylcarbonyl)
<i>m</i>	meta	Pr		part(s) per million
M	molar	q		propyl
Me	methyl	R		quartet
mg	milligram(s)	<i>rac</i>		variable group
min	minute(s)	RBF		racemic
mL	millilitre(s)	rt		round bottomed flask
mmol	millimole(s)	s		retention factor
mol	mole(s)	sat.		room temperature
MOM	methoxymethyl	S <sub>E</sub> Ar		singlet
mp	melting point	SEM		saturated
MS	molecular sieves	SM		electrophilic aromatic substitution
MSA	methanesulfonic acid	<i>t</i>		2-(trimethylsilyl)ethyoxy methyl
MSAA	methanesulfonic acid anhydride	t		starting material
MTBE	<i>methyl tert</i> -butyl ether	TBAF		<i>tert</i>
NBS	<i>N</i> -bromosuccinimide		TBAI	triplet
NMR	nuclear magnetic resonance			tetra-butyl ammonium
nOe	nuclear Overhauser effect	Tf		fluoride
				tetra-butyl ammonium iodide
				trifluoromethanesulfonyl

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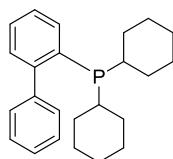
TFA	trifluoroacetate, trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMP	tetramethylpiperidyl
TMS	trimethylsilyl
Ts	<i>p</i> -toluenesulfonyl
TSE	2-(trimethylsilyl)ethoxy
TTMSS	tris(trimethylsilyl)silane
UV	ultraviolet
μW	microwave
W	Watt(s)
X	unspecified functional group
XPhos	2-dicyclohexylphosphino- 2',4',6'-tri-isopropylbiphenyl
XPhos-Pd-G2	(chloro(2-dicyclohexylphos- phino-2',4',6'-triisopropyl- 1,1'-biphenyl)[2-(2'-amino- 1,1'-biphenyl)] palladium(II))

# CATALYST AND LIGAND INDEX

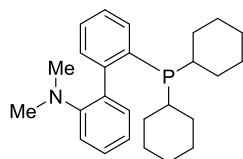
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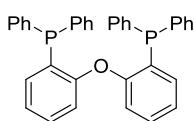
BrettPhos-Pd-G3  
**(299)**



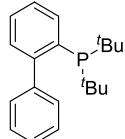
CyJohnPhos **(290)**



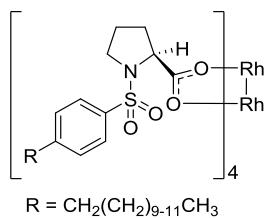
DavePhos **(74)**



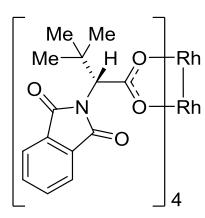
DPEPhos **(298)**



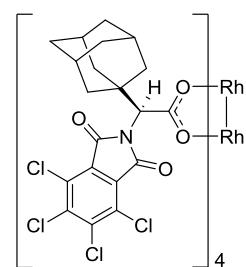
JohnPhos **(324)**



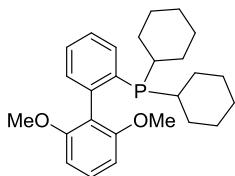
Rh<sub>2</sub>(S-DOSP)<sub>4</sub> **(79)**



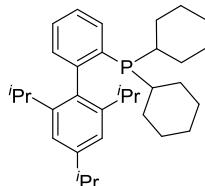
Rh<sub>2</sub>(R-PTTL)<sub>4</sub> **(107)**



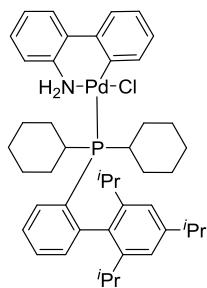
Rh<sub>2</sub>(S-TCPTAD)<sub>4</sub>  
**(178)**



SPhos **(196)**



XPhos **(297)**



XPhos-Pd-G2 **(197)**

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# 1 INTRODUCTION

## 1.1 The C–H bond

The ability to selectively transform any given C–H bond has the potential to revolutionise the landscape of chemical synthesis (Figure 1).<sup>1–5</sup> The C–H bond is the most ubiquitous bond found in organic molecules and its selective transformation allows for the streamlining of synthesis and the direct use of inexpensive and readily available hydrocarbon feedstocks.<sup>6</sup> The functionalisation of hydrocarbon feedstocks is known at high temperatures and pressures in large-scale industrial processes such as thermal dehydrogenation, but the nature of the forcing conditions leads to poor selectivity and great amounts (> 500 °C) of energy are required.<sup>7</sup>



**Figure 1.** C–H Bond functionalisation.

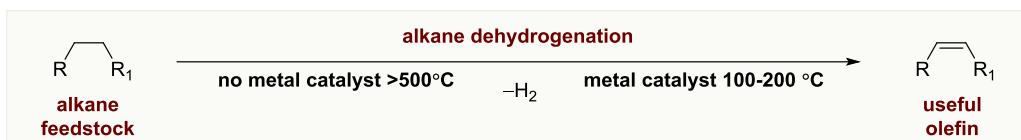
This dehydrogenation process typifies the challenges that chemists face in developing new methods for the selective functionalisation of C–H bonds (Figure 2). The reactivity of the C–H bond is comparatively low compared to that of other more commonly used functional groups due the low polarity of the bond arising from the smaller difference in electronegativity of hydrogen and carbon atoms. This results in a stronger and more highly localised bond with no low-lying orbitals available to participate in a chemical reaction. Furthermore, with nothing to differentiate C–H bonds from one another chemically, other factors such as directing groups, sterics and electronics must be used to regioselectively transform a single C–H bond in a molecule containing many.

REACTIVITY	STRENGTH	SELECTIVITY
<p>The C–H bond is less polar than many functional groups</p> <p>C–H bond (<math>\Delta_x = 0.35</math>)</p> <p>C–Cl bond (<math>\Delta_x = 0.61</math>)</p> <p>C–Br bond (<math>\Delta_x = 0.41</math>)</p>	<p>The C–H bond is stronger than many other bonds</p> <p>C–H bond (~100 kcal mol<sup>-1</sup>)</p> <p>C–Cl bond (~79 kcal mol<sup>-1</sup>)</p> <p>C–Br bond (~69 kcal mol<sup>-1</sup>)</p>	<p>The ubiquity of C–H bonds introduces selectivity issues</p> <p>FG</p>

**Figure 2.** Considering the challenges of C–H bond functionalisation.

The efficiency of enzymes in selectively catalysing C–H functionalisations at physiological temperatures and pressures has always demonstrated the possibility of performing such

powerful transformations under very mild conditions.<sup>8–10</sup> While the synthesis of ‘designer enzymes’ that can perform any desired reaction and the application of existing enzymes on large-scale remains elusive, the structure of the well-studied active sites continues to provide inspiration for synthetic enzyme-mimicking catalysts.



**Figure 3.** Metal-catalysts assist C–H bond functionalisation in alkane dehydrogenation.

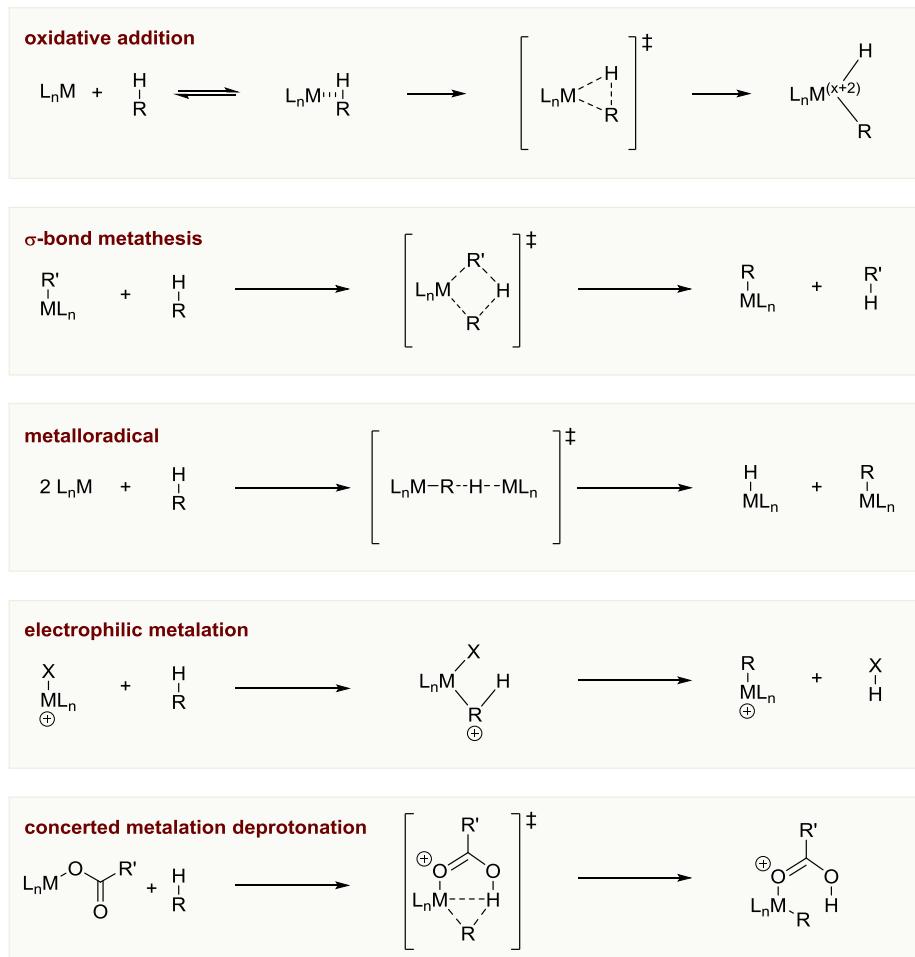
Returning to our example of the thermal dehydrogenation reaction used by the petrochemical industry and its excessive energy requirements, it has since been discovered some of the problems associated with this process can be overcome by the use of a metal catalyst.<sup>11</sup> Used in small quantities, a class of metal catalysts known as ‘pincer’ complexes has been shown to perform the same dehydrogenation reaction under much milder conditions with high turnovers (sometimes requiring a ‘hydrogen acceptor’) to generate the same useful olefinic products from feedstock alkanes with a much lower energy requirement.<sup>12–14</sup> This example clearly demonstrates one of the many benefits of using metal catalysts in C–H functionalisation and we shall continue to examine their pivotal role in this field in greater detail.

### 1.1.1 Metal-Catalysed C–H Functionalisation

The use of metal catalysts in the transformation of C–H bonds is well precedented and has become an increasingly active area of research due to the perceived benefits and academic fascination of studying such processes. This area of research is often more specifically referred to as C–H activation<sup>4,5,15–18</sup> and involves the cleavage of a C–H bond through the action of a metal to form a C–M intermediate. The increased reactivity of this new organometallic species is then exploited to form new carbon–carbon or carbon–heteroatom bonds. The metal catalyst is then regenerated to its active form, which may require the use of a stoichiometric reagent such as an oxidant, to re-enter the catalytic cycle.

Although no stable complex of a transition metal with a vacant d-orbital directly interacting with the electrons in a single C–H bond ( $\sigma$ -bonding) has been isolated to date, it is believed that this is the manner in which the initial interaction between the two species occurs. This is supported theoretically by the existence of the related agostic species, confirmed by x-ray diffraction studies, where a transition metal participates in a three-centre two-electron bond with the two C–H bond

electrons. After association of the metal with the C–H bond, the generation of the C–M intermediate is thought to occur via five distinct mechanistic pathways (Scheme 2); oxidative addition,  $\sigma$ -bond metathesis, metalloradical, electrophilic substitution and concerted metalation deprotonation (CMD).<sup>2,19</sup>

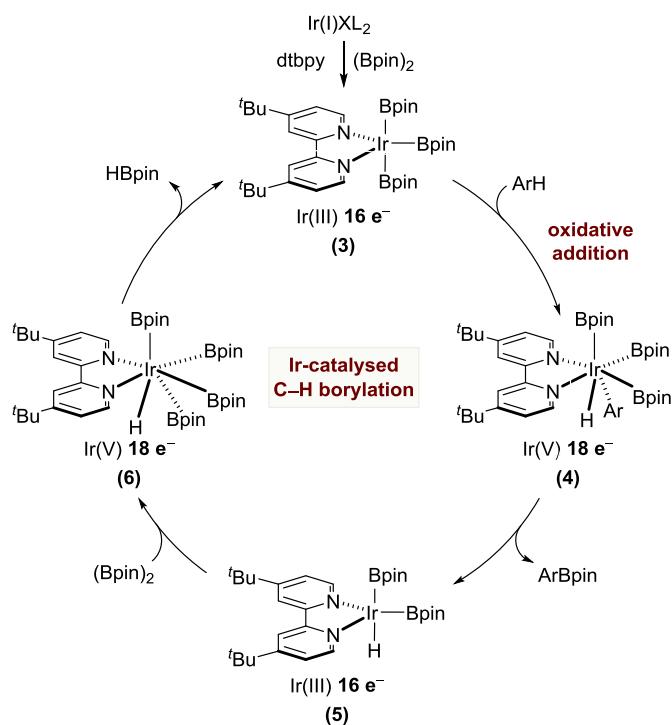


**Scheme 2.** Overview of the five main C–H activation mechanisms; oxidative addition,  $\sigma$ -bond metathesis, metalloradical, electrophilic substitution and concerted metalation deprotonation (CMD).

The first and most well understood of these is the oxidative addition mechanism where the metal inserts directly into the C–H  $\sigma$ -bond to give the metalated species. An excellent example is the iridium-catalysed C–H borylation that has been studied in detail by Hartwig and is thought to initiate by the dissociation of alkenyl ligands from the catalyst (Scheme 3).<sup>20,21</sup> This is followed by the association of a bidentate amino ligand before the oxidative addition of bis(pinacolboranes) to give the active 16-electron trigonal bi-pyramidal complex (**3**). The key oxidative addition to a C–H bond then takes place after initial association of the active catalyst with the substrate resulting in 18-electron complex (**4**). Reductive elimination of the substrate with a pinacolboryl ligand extrudes the desired borylated product and forms 16-electron iridium complex (**5**).

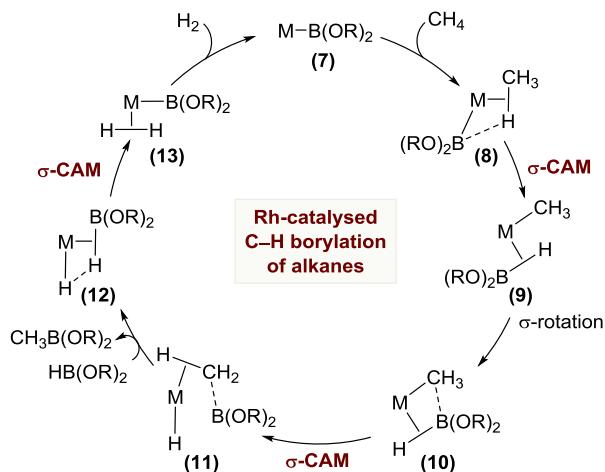
Oxidative addition of another bis(pinacolato)diboron molecule affords a second 18-electron complex intermediate (**6**) from which reductive elimination affords the regenerated active catalyst (**3**) along with pinacolborane.

This reactivity is most often observed in the late transition metals such as ruthenium, rhodium and iridium. Furthermore, the reactive species is a coordinatively unsaturated complex which necessitates that it must usually be generated *in situ* by thermal or photochemical decomposition of a precursor due to their inherent unstable nature.



**Scheme 3.** Oxidative addition of Ir(III) to an arene in the C–H borylation catalytic cycle.

In  $\sigma$ -bond metathesis, a metal ligand is exchanged for the desired substrate via a concerted transition state. This type of reactivity is commonly observed in alkyl and hydride complexes of group 3 transition metals such as scandium, the lanthanides and the actinides. Furthermore, it can be implicated as a likely reaction pathway in  $d^0$  metals as oxidative addition would be forbidden since the product would need to be  $d^2$ . In more recent years, evidence has been found to support a variation of the concerted 4-membered transition state. This is termed ‘ $\sigma$ -complex-assisted metathesis’ ( $\sigma$ -CAM) and operates via a sequence of  $\sigma$ -complex intermediates.<sup>22</sup> It is implicated in the C–H borylation of alkanes (Scheme 4) and can be seen operating between intermediates (**8**) to (**9**), (**10**) to (**11**) and (**12**) to (**13**).



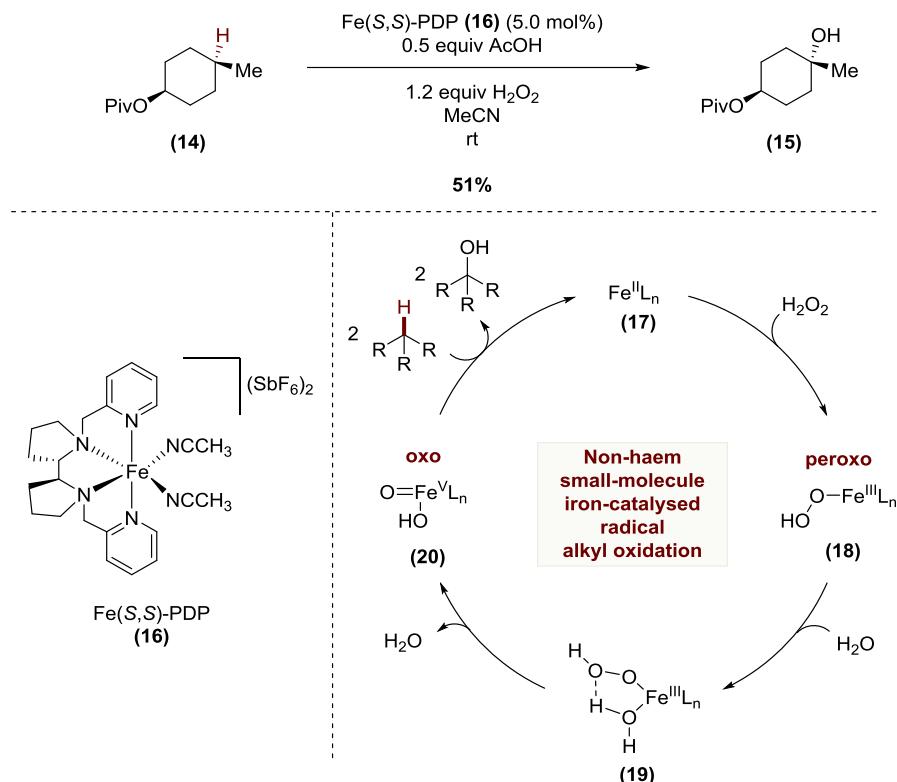
**Scheme 4.** The  $\sigma$ -CAM mechanism in the metal-catalysed borylation of alkanes.

Metalloradical reactivity is less commonly exploited in synthetic catalysts but is found in nature by virtue of metalloenzymes such as cytochrome P450 which catalyse a C–H oxidation, more commonly referred to as a monooxygenase reaction.<sup>23</sup>

The binuclear metalloradical mechanism<sup>24</sup> pictured in Scheme 2 is encountered less frequently than a hydrogen abstraction facilitated by a metalloradical species. Furthermore, existence of the radical solely on the metal centre is quite rare in synthetically useful transformations. Instead, the radical tends to be located on, or shared with, non-innocent ligands in what is termed open-shell metal catalysis.

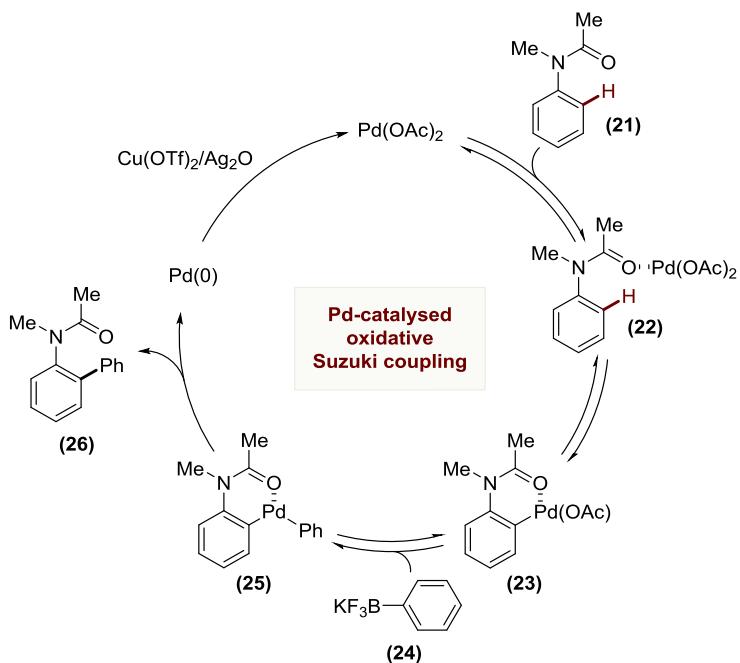
White and co-workers developed a non-haem small-molecule iron-catalyst that closely mimics the behaviour of iron in metalloenzymes to achieve radical hydrogen abstraction.<sup>25–28</sup> The main mechanistic pathway that the White-Chen catalyst (**16**) is thought to follow is shown below (Scheme 5).<sup>29,30</sup> First the iron catalyst (**17**) is oxidised by hydrogen peroxide to give a peroxy species (**18**) that is oxidised further in the presence of water to generate reactive iron-oxo species (**19**). It is thought an equivalent reactive carboxylate oxo species can also form in the presence of acetic acid. This high valent iron(V)-oxo species (**20**) can then perform a sequence of two alkyl hydrogen radical abstractions and ‘radical rebound’ oxidations as the catalyst is gradually reduced back to its original oxidation state (**17**).

The transition metals most often implicated in metalloradical chemistry are manganese, cobalt, ruthenium and rhodium. Moreover, as this type of reactivity is more often observed in the base-metals than the noble-metals there is great potential for developing new desirable transformations using cheap and abundant earth metals.<sup>31</sup>



**Scheme 5.** A radical intermediate is implicated during radical hydrogen abstraction in White's aliphatic oxidations.

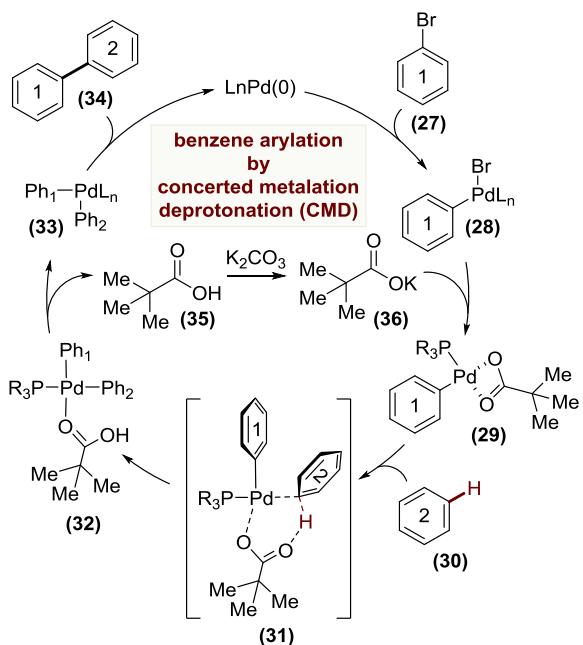
In instances where an electron rich substrate is used, the electrophilic metal catalyst may be directly attacked to form the metalated species. A simple illustrative example of such a process is a modified Suzuki coupling reaction by Wang et al. (Scheme 6).<sup>32</sup> Initial pre-complexation of the palladium with the carbonyl directing group of (21) allows for the metal to exist in close proximity to the *ortho* position, as in species (22), where it substitutes a C–H bond with the loss of acetic acid to give (23). The authors suggest this process occurs via an electrophilic substitution mechanism. Transmetalation with a potassium trifluoroborate species, followed by reductive elimination, generates the newly arylated product (26). As the substitution mechanism does not involve oxidation of the metal, an oxidant, in this case a combination of copper(II) triflate and silver(I) oxide, is required to regenerate the palladium(II) catalyst.



**Scheme 6.** Directed palladium-catalysed electrophilic aromatic C–H functionalisation.

In the final mechanistic pathway to consider, concerted metalation deprotonation, an anionic ligand (typically a carboxylate) simultaneously assists in the removal of the proton to allow metalation of the C–H carbon. A classic example of this from Fagnou, one of the pioneers investigating this mechanism, uses a pivalate ligand to facilitate the arylation of benzene (Scheme 7).<sup>33</sup>

Oxidative insertion of a palladium catalyst to bromoarene (27) gives intermediate (28) to which a carboxylate ligand associates to give (29). The palladium centre and an oxygen on the carboxylate ligand are then both thought to assist in the deprotonation of a C–H bond as pictured in transition state (31) to deliver complex (32). Dissociation of the neutral ligands is followed by reductive elimination of (33) to generate the coupled product (34) and reform the palladium(0) catalyst.



**Scheme 7.** Benzene arylation by a concerted metalation deprotonation mechanism.

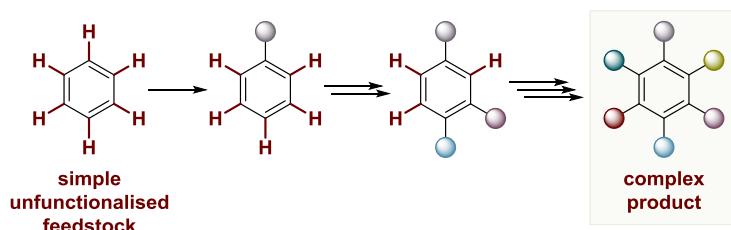
In all of the above instances, after reacting with a suitable coupling partner, the transition metal catalyst must return to its active form to repeat the process. The number of times that it is able to repeat the cycle without decomposing to an inactive state (turnover) determines the loading of the catalyst required to ensure maximum conversion. Regioselectivity of metal-catalysed C–H functionalisation reactions are known to be determined by a number of factors such as electronics, steric hindrance or directing groups that chelate the metal into the desired position (generally *ortho* and recently *meta*<sup>34–36</sup>).

We have so far discussed the variety of different ways that a transition metal catalyst can interact with a C–H bond to generate the key organometallic intermediate that is subsequently able to undergo highly desirable transformations. In line with our group's current research interest in this area we began to investigate the possibility of using transition metal catalysis to perform a sequence of C–H functionalisations to generate a product of high complexity from a simple starting material.

## 1.2 Sequential C–H functionalisation

There are a few examples of applying an extended sequence of C–H functionalisations in the synthesis of complex molecules.<sup>37,38</sup> However, uptake of this strategy to date is relatively rare despite the known advantages of C–H functionalisation processes.<sup>2</sup>

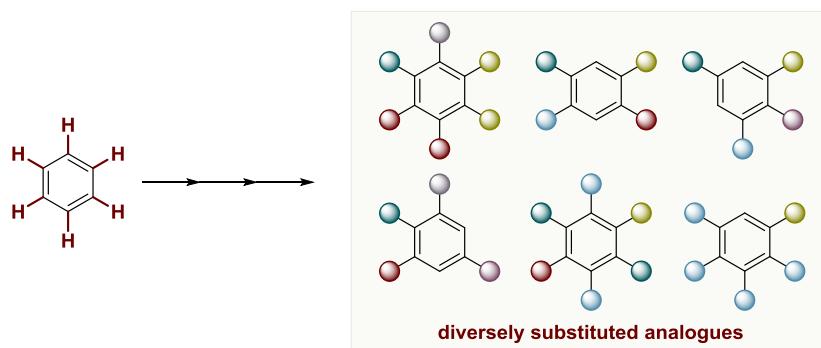
This may be due to two additional factors that must be considered when employing a sequential C–H functionalisation strategy. Firstly, maintaining C–H bond selectivity in each step as the molecule grows in complexity and secondly, choosing from many different synthetic routes when faced with a large number of potential C–H bonds that can be functionalised.



**Scheme 8.** Sequential C–H functionalisation concept.

Employing a sequential C–H functionalisation strategy (Scheme 8) with these considerations in mind can provide a number of benefits. As with any synthesis, a maximum theoretical number of possible routes can be calculated. However, in syntheses that rely on reactive functionality, many of these routes are likely to be impossible due to incompatibility with reagents or reaction conditions used in other steps. This would be especially true if all functionality were present at the start of a synthesis. By definition, a sequential C–H functionalisation cannot suffer from chemoselectivity in the same way, but regioselectivity should be taken into consideration. Fortunately, other factors such as different C–H bond strengths, electronics, sterics and directing groups are used to help distinguish between chemically identical C–H bonds to reduce the large number of theoretical routes to a more manageable amount.

The modular nature of this approach also allows for the construction of a diverse array of related analogues. This can be achieved by varying not only the nature of the substituents, but also the pattern and number of substitutions (Scheme 9). In an ideal scenario, this would enable the rapid synthesis and screening of analogues to find improvements in the desired properties of the original molecule.



**Scheme 9.** Synthesis of analogues by C–H functionalisation.

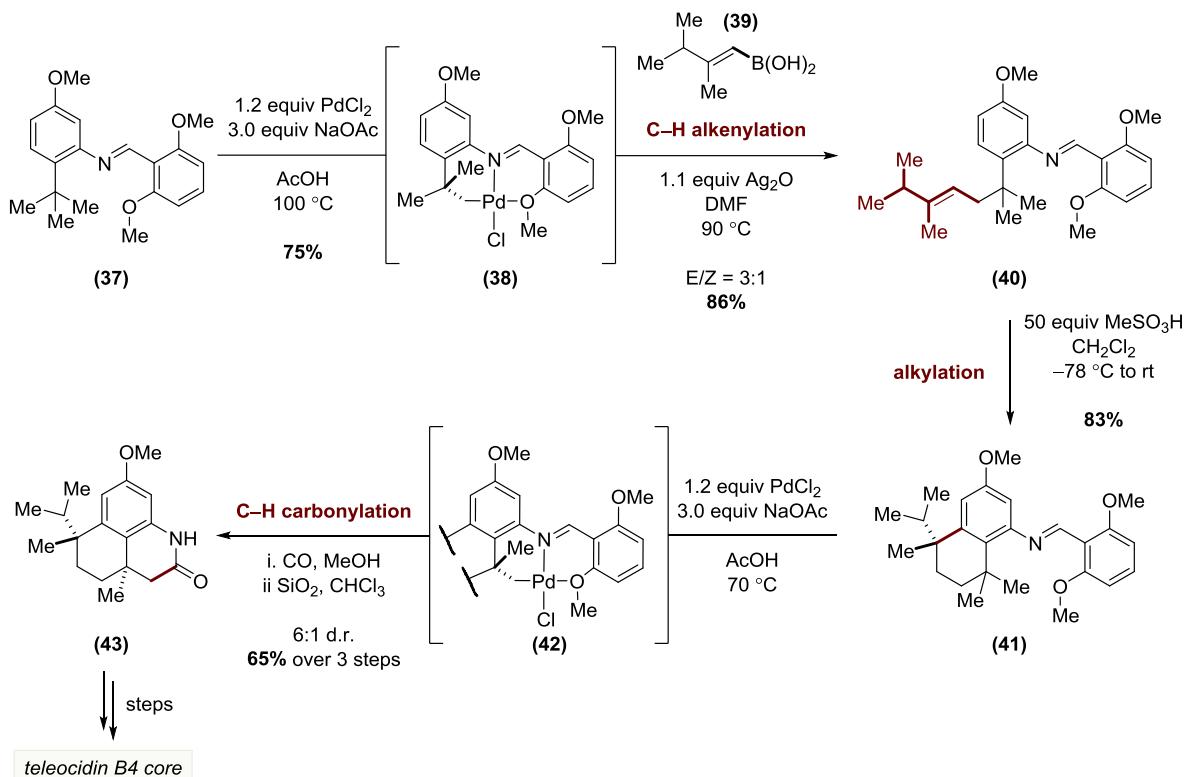
The overall result is a strategy that is highly complementary to existing methods and may decrease the number of steps required to make a complex molecule or simplify the synthesis by reducing the number of pre-installed functionalities or protecting groups required. In contemplating the blueprint for our own synthesis we began by closely examining previous significant examples of where C–H functionalisation has been applied more than once in the synthesis of a natural product.<sup>17,39</sup>

### 1.3 Multiple C–H functionalisations in natural product synthesis

#### 1.3.1 Teleocidin B4 core (Sames, 2002)

One of the first reports using multiple C–H functionalisations in the construction of a complex natural product came in 2002 when Sames published a synthesis of the core structure of teleocidin B4 (Scheme 10).<sup>40</sup> Impressively, two C–H functionalisations were performed in a row. This sequence began with exposure of (**37**) to 1.2 equivalents of palladium(II) chloride and 3 equivalents of sodium acetate in glacial acetic acid to afford palladacycle (**38**) in 75% yield.

Next, the first example of palladacycle ‘metalation’ with a boronic acid was performed using (**39**) in the presence of silver(I) oxide to complete an overall C–H alkenylation in 86% with 3:1 *E*-selectivity. The presence of the electron-donating methoxy group permitted a subsequent Friedel–Crafts alkylation of (**40**) using 50 equivalents of methanesulfonic acid in dichloromethane to deliver (**41**) in 83% yield.<sup>41</sup> Under prolonged exposure to the reaction conditions, the desired product undergoes a rearrangement of the alkyl chain to give the *ortho* regioisomer.



**Scheme 10.** Sames' synthesis of the teleocidin B4 core structure.

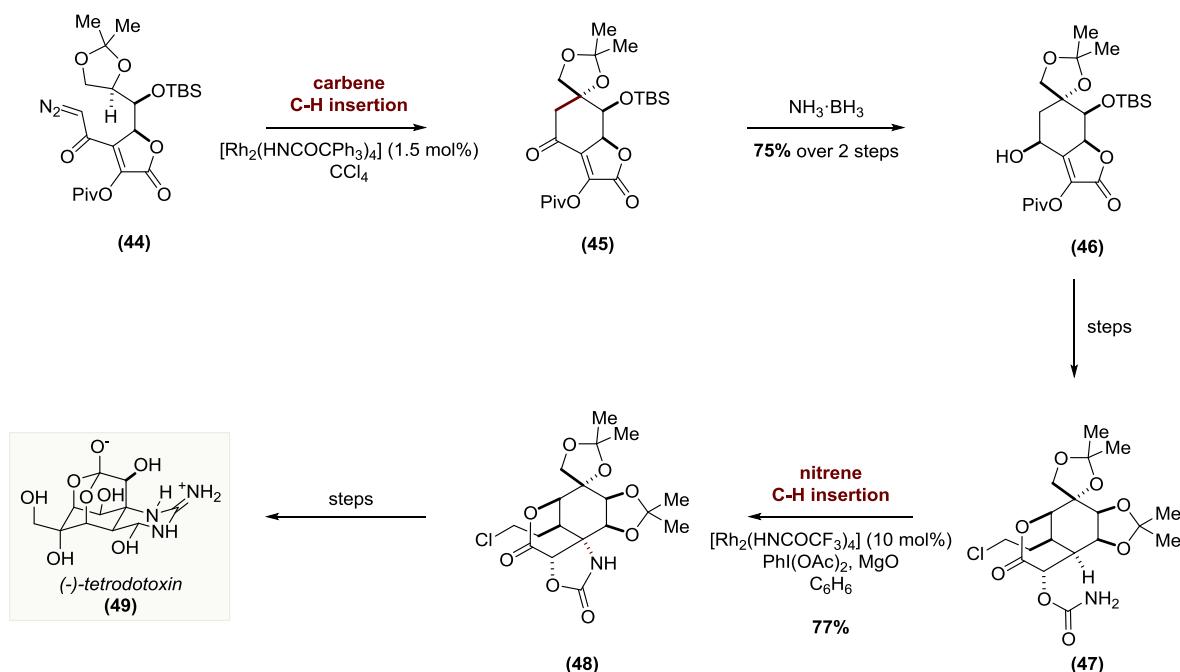
The second C–H functionalisation employed the same conditions as the first palladacycle formation to afford intermediate (**42**). This cyclopalladation was quite remarkable for its 6:1 diastereoselectivity that was determined to be inversely dependent on the reaction temperature. A 1,4-chiral transfer of the bulky isopropyl group was thought to help promote this selectivity.

The crude reaction mixture was then taken up in methanol and stirred under carbon monoxide at 35 atm for 12 hours. The resulting methyl ester was treated with silica gel to hydrolyse the imine and the free aniline underwent lactamisation to give intermediate (**43**). A few extra steps were then required to complete the synthesis of the teleocidin B4 core.<sup>42</sup>

### 1.3.2 Tetrodotoxin (Du Bois, 2003)

A small natural product of dense complexity, tetrodotoxin is a potent neurotoxin produced by the pufferfish and its close relatives. As only two syntheses of tetrodotoxin had been completed in the thirty years preceding this report, Du Bois' synthesis was a particularly impressive feat and an excellent showcase for the utility of incorporating C–H functionalisation chemistry. The synthesis began from D-isoascorbic acid from which diazoketone (**44**) was generated in 8 steps (Scheme 11).<sup>43,44</sup>

A metallocarbene C–H insertion was accomplished by employing 1.5 mol% of a rhodium(II) acetamide dimer catalyst to form cyclohexanone derivative (**45**). Attempts to use more conventional rhodium catalysts with acetate ligands for this transformation resulted in complex mixtures. The crude reaction mixture was then subjected to an ammonia borane reduction to deliver the alcohol (**46**) in 75% yield over two steps.



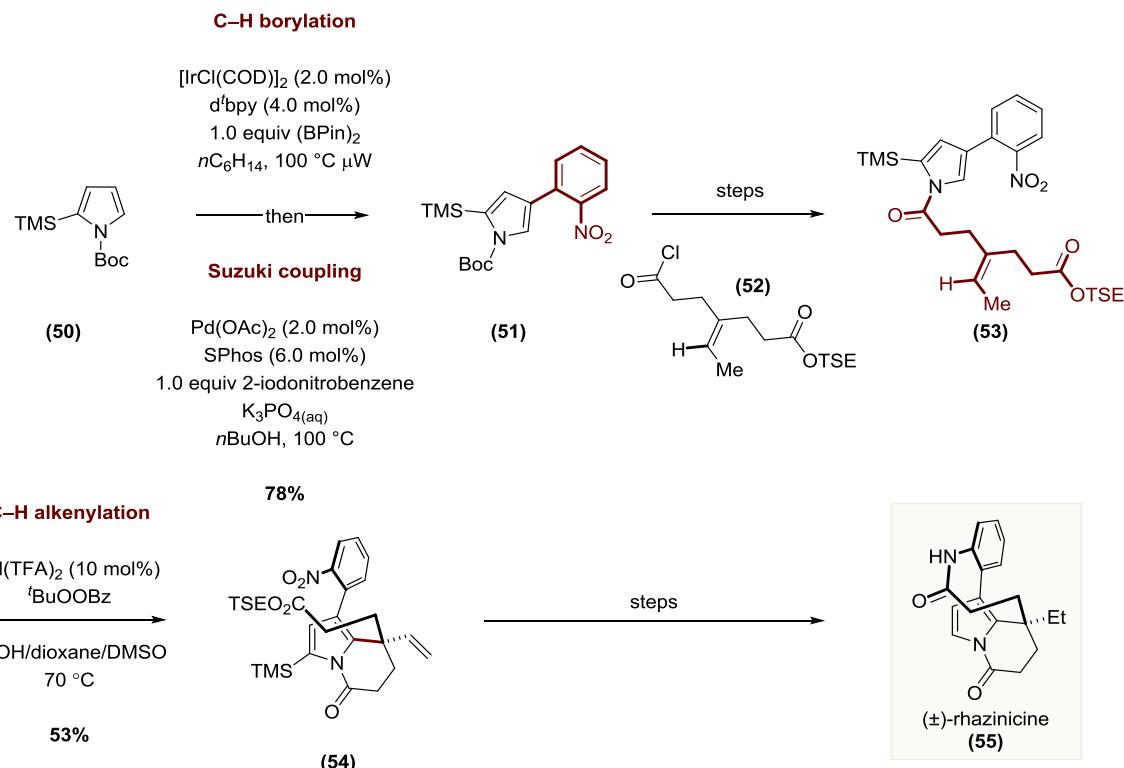
**Scheme 11:** Du Bois' total synthesis of *(-)*-tetrodotoxin.

After further manipulations to generate chloride (**47**), a stereospecific rhodium-catalysed nitrene insertion was performed using a higher 10 mol% loading of a different rhodium(II) acetamide dimer with (diacetoxyiodo)benzene (PIDA) as the oxidant. The role of magnesium oxide in the process is not entirely clear but it is thought to act as a base to facilitate the reaction.<sup>45</sup> The resultant oxazolidinone (**48**) was isolated in 77% yield and a number of additional steps completed the synthesis of *(-)*-tetrodotoxin (**49**).

### 1.3.3 ( $\pm$ )-Rhazinicine (Gaunt, 2008)

A cellular mimic of the anti-cancer drug paclitaxel, ( $\pm$ )-rhazinicine (**55**) is a natural product containing a substituted pyrrole core as part of a tetrahydroindolizine ring system. Gaunt and co-workers began their synthesis from *N*-Boc pyrrole (**50**) and started by installing a trimethylsilyl blocking group at the 5-position (Scheme 12).<sup>46</sup> In the absence of this blocking group, their initial results had shown that the palladium-catalysed alkenylation step was only selective for the undesired positions of the pyrrole.

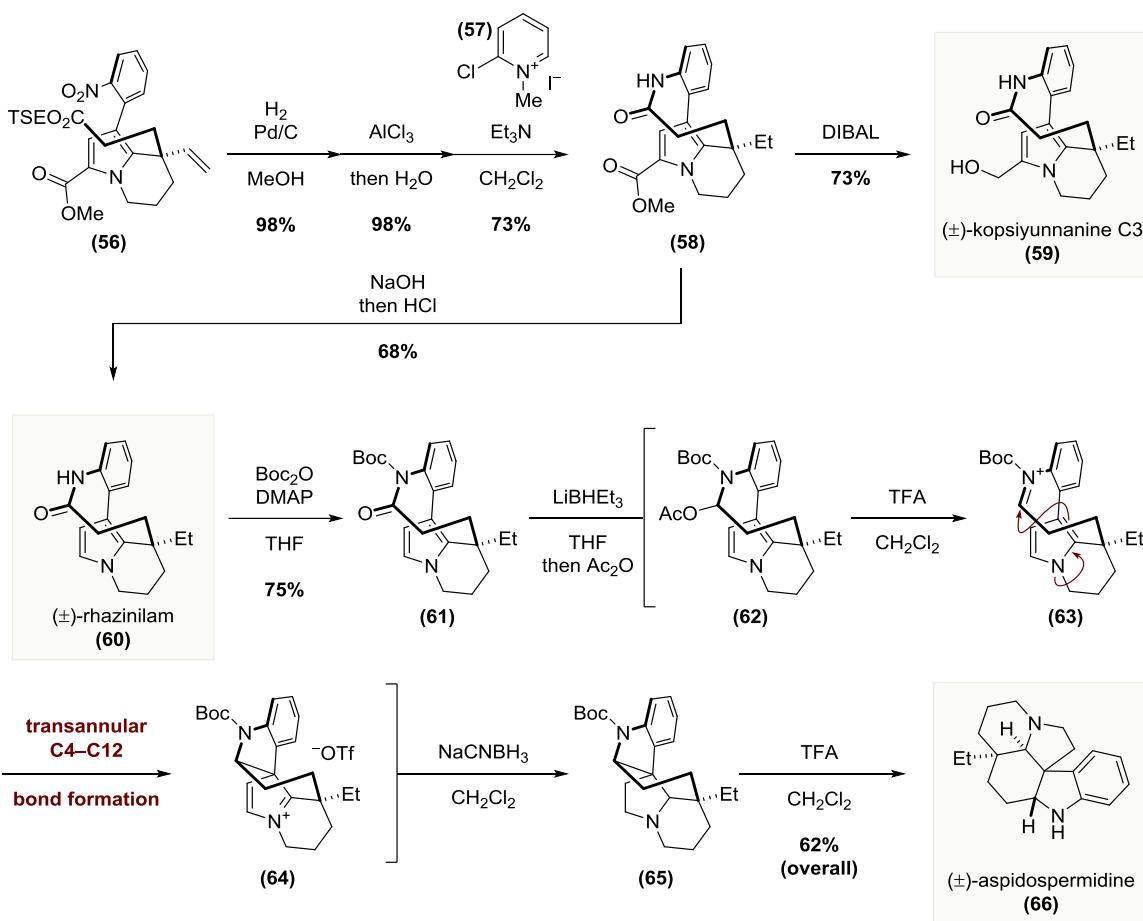
A one-pot iridium-catalysed C–H borylation and Suzuki coupling smoothly installed an *ortho*-nitro-phenyl group in the C3 position to deliver pyrrole (**51**) in 78% yield. Thermal removal of the Boc group at 120 °C in *N,N*-dimethylformamide was followed by *N*-acylation with acyl chloride (**52**) at –78 °C using lithium bis(trimethylsilyl)amide (LiHMDS) in tetrahydrofuran to give intermediate (**53**).



**Scheme 12.** Gaunt's total synthesis of (±)-rhazinicine.

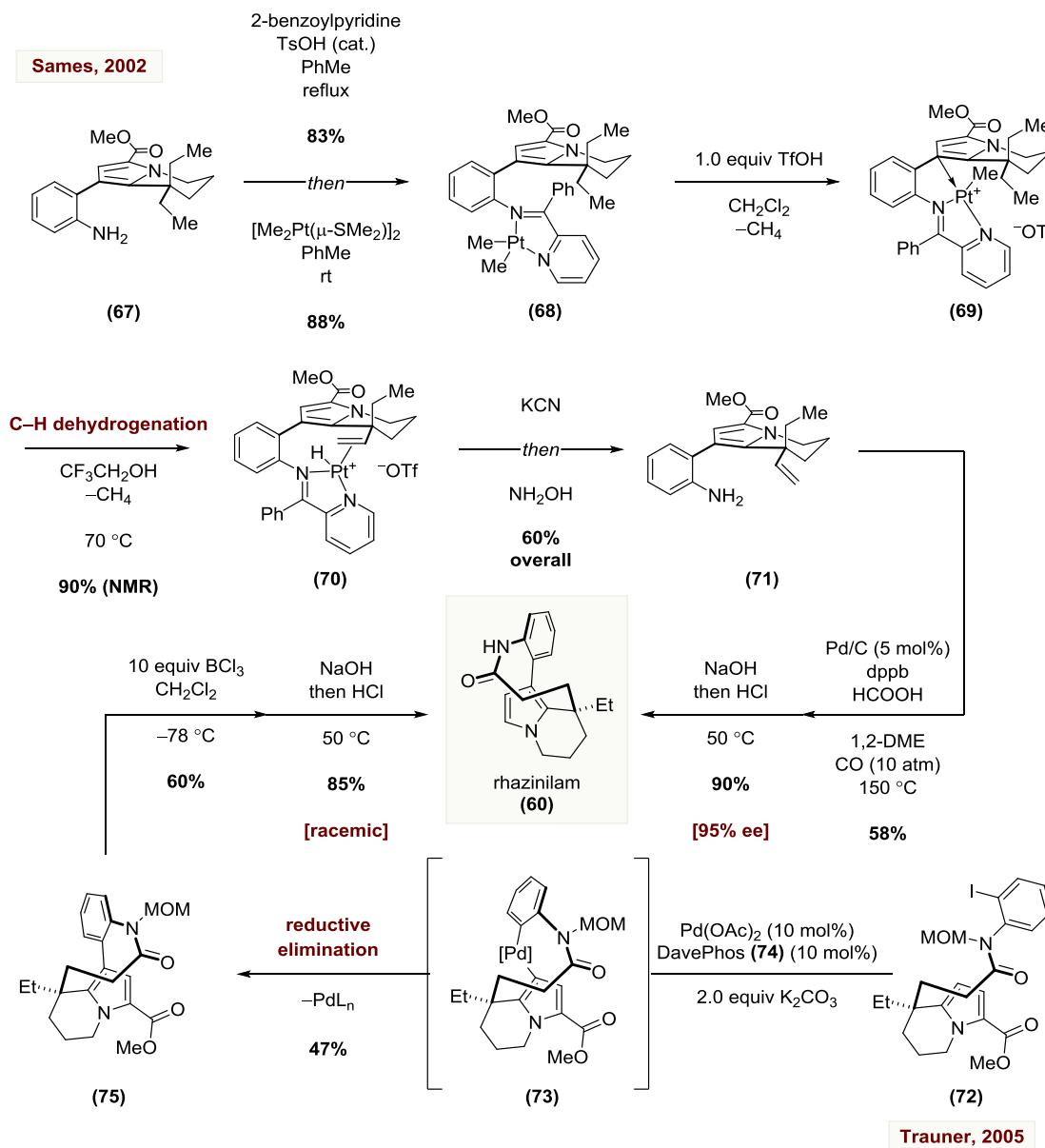
The next step finalised the tetrahydroindolizine ring via an intramolecular palladium-catalysed alkenylation reaction. Exposure to 10 mol% palladium(II) trifluoroacetate catalyst and *tert*-butylperoxybenzoate oxidant at 70 °C facilitated this transformation to deliver the cyclised product (**54**) in 53% yield.<sup>47</sup>

To complete the synthesis the final steps were employed as a telescoped protocol. The nitro group was hydrogenated over palladium on carbon, the silyl blocking group was removed with aluminium trichloride and Mukaiyama's reagent enabled macrolactamisation to afford (±)-rhazinicine (**55**) in a 74% yield over three steps.



**Scheme 13.** Gaunt's subsequent report of the total synthesis of **(±)-rhazinilam**, **(±)-kopsiyunnanine C3** and **(±)-aspidospermidine**.

A subsequent report in 2012 by Gaunt and co-workers detailed the synthesis of aspidosperma alkaloids inspired by a route that was inspired by synthetically reversing the biosynthesis of natural products closely related to rhazinicine (Scheme 13).<sup>48</sup> The C–H functionalisation strategy described above was applied again in the synthesis of **(±)-kopsiyunnanine C3** (**59**), **(±)-rhazinilam** (**60**) and **(±)-aspidospermidine** (**66**) through the synthesis of a new common intermediate (**58**). A DIBAL-mediated reduction of the methoxy ester furnished **(±)-kopsiyunnanine C3** (**59**) in 73 % yield and a base/acid-mediated decarboxylation delivered **(±)-rhazinilam** (**60**) in 68% yield. This was further transformed through a series of steps to deliver **(±)-aspidospermidine** (**66**) via a unique transannular cyclisation process that is made possible by exposing hemiaminal (**62**) to trifluoroacetic acid to access reactive iminium species (**63**) which undergoes nucleophilic attack by the pyrrole ring in a pivotal step that forms one of the embedded quaternary carbon centres. Addition of sodium cyanoborohydride stereoselectively reduced pyrrolium (**64**) to deliver (**65**) which, upon treatment with trifluoroacetic acid, afforded **(±)-aspidospermidine** (**66**) in a 62% yield from (**61**).



**Scheme 14.** Sames' and Trauner's total syntheses of rhazinilam.

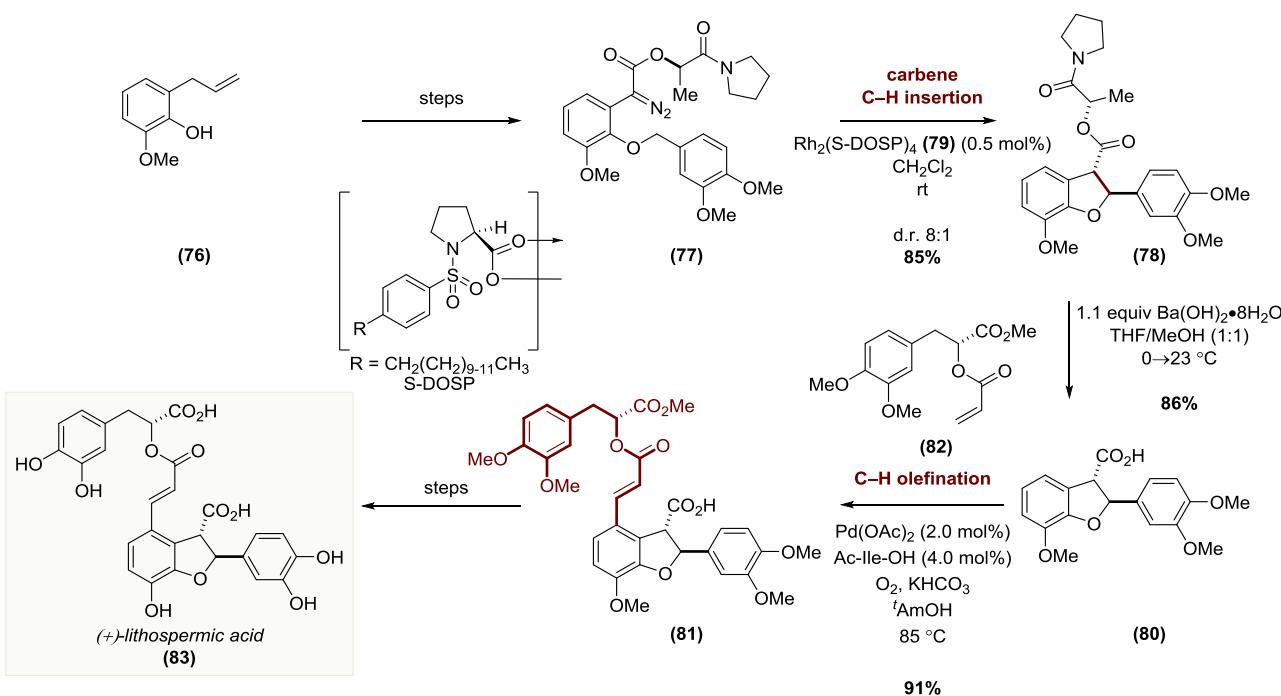
Two prior syntheses of rhazinilam (**60**) that each incorporate a single C–H functionalisation are also worth noting at this point (Scheme 14). The first of these was by Sames in 2002 and involved a key platinum-mediated dehydrogenation of alkane (**67**) to generate alkene (**71**) that proceeded to cyclise in a palladium-catalysed carbonylation reaction.<sup>49</sup> A number of imine auxiliaries were explored for this transformation and while 2-benzoylpyridine (shown above) provided the best yields (90% by NMR), a chiral pyridyl auxiliary displayed mild diastereoselectivity that allowed the products to be separated by preparative HPLC. A decarboxylation of the methyl ester furnished optically pure (–)-rhazinilam (**60**). The second synthesis was published in 2005 by Trauner and featured a palladium-catalysed direct C–H arylation using the Buchwald phosphine ligand DavePhos (**74**) to achieve the cyclisation of (**72**) to give (**75**) in 47% yield.<sup>50</sup> The use of boron

trichloride to deprotect the amide nitrogen and a base/acid-mediate decarboxylation delivered ( $\pm$ )-rhazinilam (**60**) as a racemate.

### 1.3.4 (+)-Lithospermic acid (Yu, 2011)

Due to studies showing potent and non-toxic anti-HIV activity, (+)-lithospermic acid (**83**) represented a target of great synthetic interest. While synthesised previously, Yu and co-workers unveiled a route comprising of two C–H functionalisations to enable rapid construction of the natural product (Scheme 15).<sup>51</sup> The synthesis commenced from *ortho*-eugenol (**76**) and, though a series of steps including an esterification and alkylation, diazo ester (**77**) was prepared to perform the first C–H functionalisation.

Application of Davies' chiral rhodium(II) *N*-sulfonyl proline (S-DOSP) dimer catalyst (**79**) in dichloromethane at room temperature furnished the *trans*-dihydrobenzofuran (**78**) in an excellent 85% yield and 8:1 diastereomeric ratio.<sup>52,53</sup> Saponification of the ester with barium hydroxide octahydrate in a 1:1 mixture of tetrahydrofuran/methanol occurred over 4 hours to give carboxylic acid (**80**) in 86% yield.



**Scheme 15:** Yu's total synthesis of (+)-lithospermic acid.

In its potassium carboxylate form, this acid was intended to act as a directing group for the key C–H olefination reaction that would unite two large fragments in a complex intermolecular C–C bond forming step. The authors anticipated complications with regioselectivity due to the

presence of multiple electron rich arenes and possible racemisation of the two potentially sensitive chiral centres.

However, using 2.0 mol% palladium(II) acetate, 4.0 mol% *N*-acetyl isoleucine ligand and potassium hydrogen carbonate in the presence of olefin (**82**) under an atmosphere of oxygen at 85 °C, the olefinated product (**81**) was afforded in an exceptional 91% yield.

The synthesis was then completed in two additional steps. Treatment of the methyl ester with trimethyltin hydroxide at 80 °C followed by heating to 130 °C with 1-trimethylsilylquinolinium iodide delivered (+)lithospermic acid (**83**) in a 28% yield over two steps.<sup>54,55</sup>

### 1.3.5 Piperarborenines (Baran, 2011)

An interesting family of cyclobutane containing natural products, the piperarborenines were selected by Baran and co-workers as an excellent target to illustrate the use of C–H functionalisation as an alternative synthetic strategy to the more commonly employed [2+2] cycloaddition (Scheme 16).<sup>56</sup>

Synthesis of amide (**84**) from methyl coumalate was realised by a photochemical 4π-electrocyclisation followed by hydrogenation of the resulting photopyrone to give the product as a single diastereoisomer. The resultant carboxylic acid was treated with 2-amino-methylthioanisole and a coupling reagent to afford amide (**84**) over the three-step telescoped sequence in 61% yield on gram-scale.

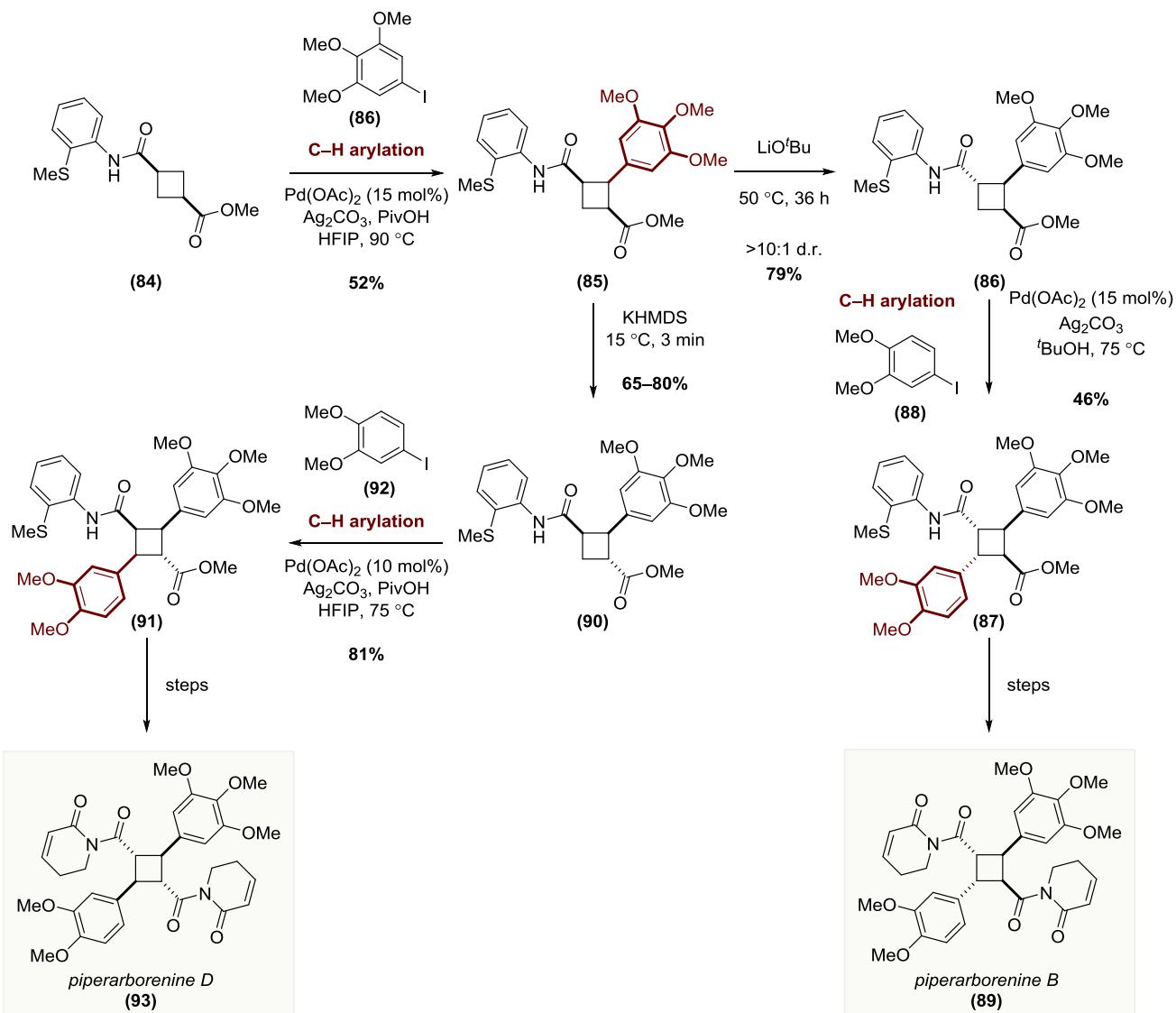
Selective C–H arylation was difficult to achieve, but after extensive experimentation the authors found that the addition of hexafluoroisopropanol (HFIP) and pivalic acid were vital for success.<sup>33,57</sup> With 15 mol% palladium(II) acetate, 3,4,5-trimethoxyiodobenzene (**86**) and silver(I) carbonate at 90 °C, the reaction proceeded to give 52% isolated yield of (**85**) along with 10% recovery of the starting material.

At this point, the synthesis diverged for the individual preparations of piperarborenines B (**89**) and D (**93**). The former required inversion of the amide directing group stereocentre and this was achieved by stirring with bulky lithium *tert*-butoxide base at 50 °C in toluene for 36 hours to deliver (**86**) in a yield of 79% and as a >10:1 mixture of diastereoisomers.

The second C–H arylation was then performed with 3,4-dimethoxyiodobenzene (**88**) in 46% yield to afford (**87**) on gram-scale. Unlike the first arylation event, this step was less efficient in the presence of HFIP and pivalic acid. Instead, the optimal reaction conditions were determined to

be palladium(II) acetate and silver(I) carbonate in *tert*-butanol at 75 °C with 20% recovery of starting material.

Using relatively mild conditions to avoid any epimerisation of the cyclobutane core, a three step carbamoylation, ester hydrolysis and amide formation procedure was used to complete the synthesis of piperarborenine B (89).<sup>58</sup>



**Scheme 16.** Baran's total synthesis of piperarborenines B and D.

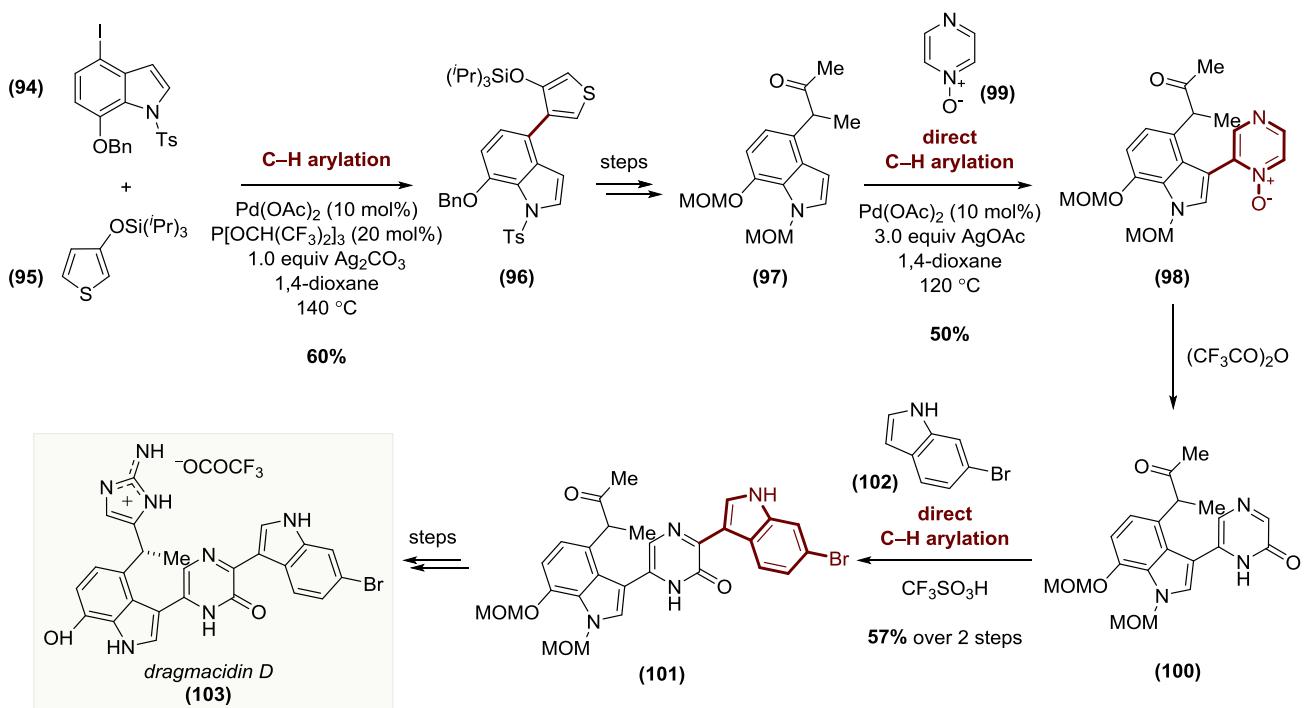
At the point of divergence, the use of potassium bis(trimethylsilyl)amide (KHMDS) with (85) instead of lithium *tert*-butoxide resulted in epimerisation of only the ester. This selectivity is due to initial deprotonation of the amide N–H that ensures only the ester enolate is generated to afford (90) in 65–80% yield as a single diastereoisomer.

Subjection to a second round of C–H arylation conditions, as used previously, delivered the tetra-substituted cyclobutane (**91**) in 81% yield. This C–H arylation was also found to perform better in the presence of HFIP and pivalic acid.

The second synthesis is completed after refluxing with sodium hydroxide in ethanol, which serves to epimerise the amide before a double hydrolysis delivers the bis-carboxylic acid in 86% yield. A double amide formation via conversion to the acid chloride using oxalyl chloride and subsequent reaction with dihydropyridone smoothly afforded the originally proposed structure of piperarborenine D (**93**). However, the total synthesis allowed the authors to revise the structure of this natural product as the spectral data of the synthetic products did not exactly match the isolated material.<sup>59</sup>

### 1.3.6 Dragmacidin D (Itami, 2011)

Until now, most syntheses relied on the use of C–H/C–X couplings, but Itami and co-workers synthesis of dragmacidin D (**103**) was particularly notable for its use of two ‘direct’ C–H/C–H couplings in the construction of the natural product.<sup>60</sup>



**Scheme 17.** Itami’s total synthesis of dragmacidin D.

Its interesting biological activities, namely as a lead compound for Parkinson’s, Alzheimer’s and Huntington’s diseases, meant it had already been the subject of total syntheses. However, the

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application of a C–H functionalisation strategy would prove advantageous as they were able to execute the most efficient synthesis to date (Scheme 17).

Indole (**94**) was afforded in 3 steps from commercially available 7-benzyloxyindole and thiophene (**95**) was prepared in 2 steps from commercially available 3-thienyl boronic acid. The first C–H arylation was realised in the presence of 10 mol% palladium(II) acetate, 20 mol% tris(hexafluoroisopropyl)phosphite ligand and 1 equivalent of silver(I) carbonate in 1,4-dioxane superheated to 140 °C.<sup>61</sup> The arylated product (**96**) was generated in 60% yield and over 6 grams of product was synthesised under these conditions.

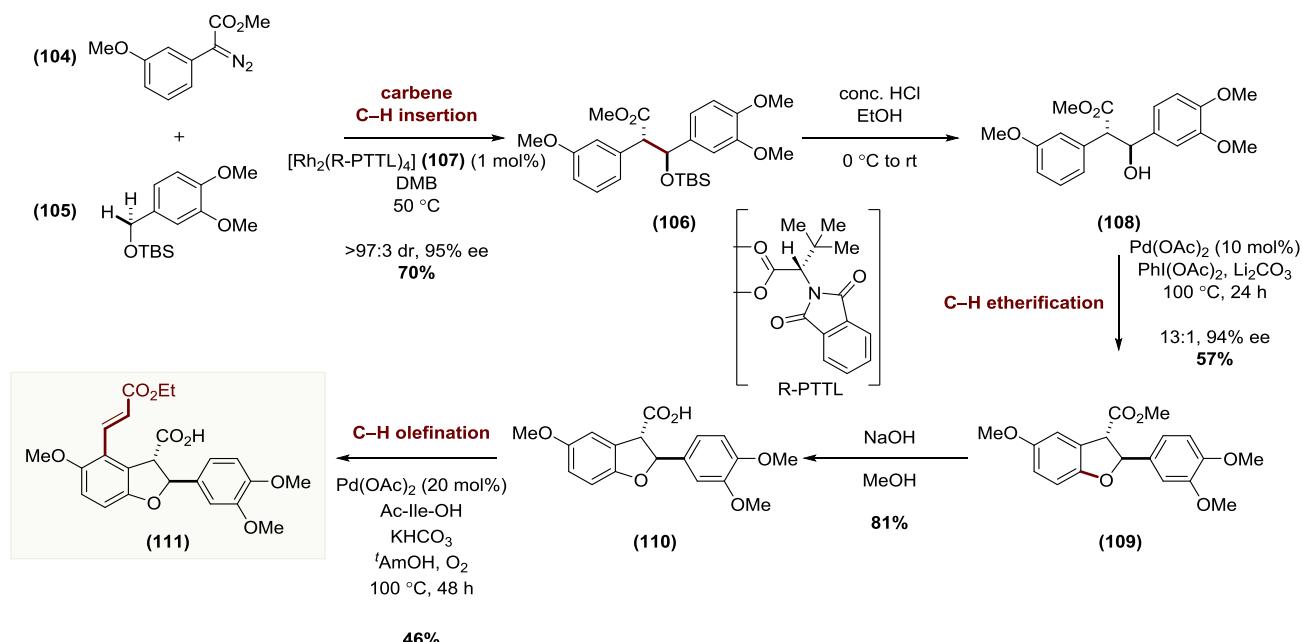
One-pot removal of the silyl group with tetrabutylammonium fluoride (TBAF) in acetic acid, followed by simultaneous reduction of the thiophene and debenzylation under Raney nickel conditions, produced the corresponding methyl ketone in 77% yield. Magnesium methoxide was then used to exchange the tosyl protecting group with a methoxymethyl (MOM) group and delivered (**97**) in 91% yield over 2 steps.

This prepared the substrate for the following key step, a direct C–H/C–H arylation of indole (**97**) with 4 equivalents of pyrazine *N*-oxide (**99**) in the presence of 10 mol% palladium(II) acetate and 3 equivalents silver(I) acetate in 1,4-dioxane superheated to 120 °C. Product (**98**) was furnished in a 50% yield and the pyrazine *N*-oxide moiety was transformed to the corresponding pyrazinone (**100**) (with a 5:1 selectivity for the desired regioisomer) in the presence of trifluoroacetic anhydride (TFAA).

This primed the substrate for the final direct C–H/C–H arylation. Exposure of (**100**) to 6-bromoindole (**102**) while stirring in *N,N*-dimethylformamide with trifluoroacetic acid at 80 °C supplied the bis(indolyl)-pyrazinone (**101**) in 57% yield over two steps. This intermediate was determined to be light sensitive in solution and so the final two steps were performed on a small amount of material in the dark. Treatment with diisopropylethylamine (DIPEA) and trimethylsilyl triflate (TMSOTf) followed by *N*-bromosuccinimide (NBS) afforded the α-bromo ketone product in a 73% yield. This was found to be exceptionally sensitive to nucleophilic substitution and was immediately treated with Boc-guanidine in tetrahydrofuran at 55 °C, concentrated and then stirred in the presence of triflic acid in dichloromethane at room temperature to furnish dragmacidin D (**103**) in a 51 % yield.<sup>62,63</sup>

### 1.3.7 Highly functionalised dihydrobenzofurans (Davies, 2013)

Following Yu's synthesis of (+)-lithospermic acid in 2011, both Yu and Davies saw an opportunity to improve the synthesis of the dihydrobenzofuran core<sup>64</sup> and began with an intermolecular enantioselective carbene C–H insertion of aryl diazoacetate (**104**) and *tert*-butyldimethylsilyl ether (**105**) developed in Davies's lab (Scheme 18).<sup>65</sup> Stirring at 50 °C with a chiral rhodium(II) *N*-phthaloyl-*tert*-leucinate dimer catalyst (**107**) in 2,2-dimethylbutane (DMB) delivered (**106**) in excellent diastereo- and enantioselectivity. Eleven different substrates were prepared in this fashion, demonstrating the robustness and wide applicability of the procedure.



**Scheme 18.** Davies's synthesis of highly functionalised 2,3-dihydrobenzofurans.

Before Yu's cyclisation methodology could be performed, the silyl protecting group was removed by reacting with hydrochloric acid in ethanol. The free alcohol (**108**) was then subjected to 10 mol% palladium(II) acetate and (diacetoxyiodo)benzene (PIDA) oxidant with lithium carbonate at 100 °C. This gave the 2,3-dihydrobenzofuran (**109**) in 57% yield with full retention of chirality.<sup>66</sup> The authors note common side products were the result of either a retro-aldol or aromatisation of the product to the corresponding benzofuran. Again, the method was applied to a number of substrates with moderate to good yields. It was noted that more vigorous conditions were required for less electron rich substrates.

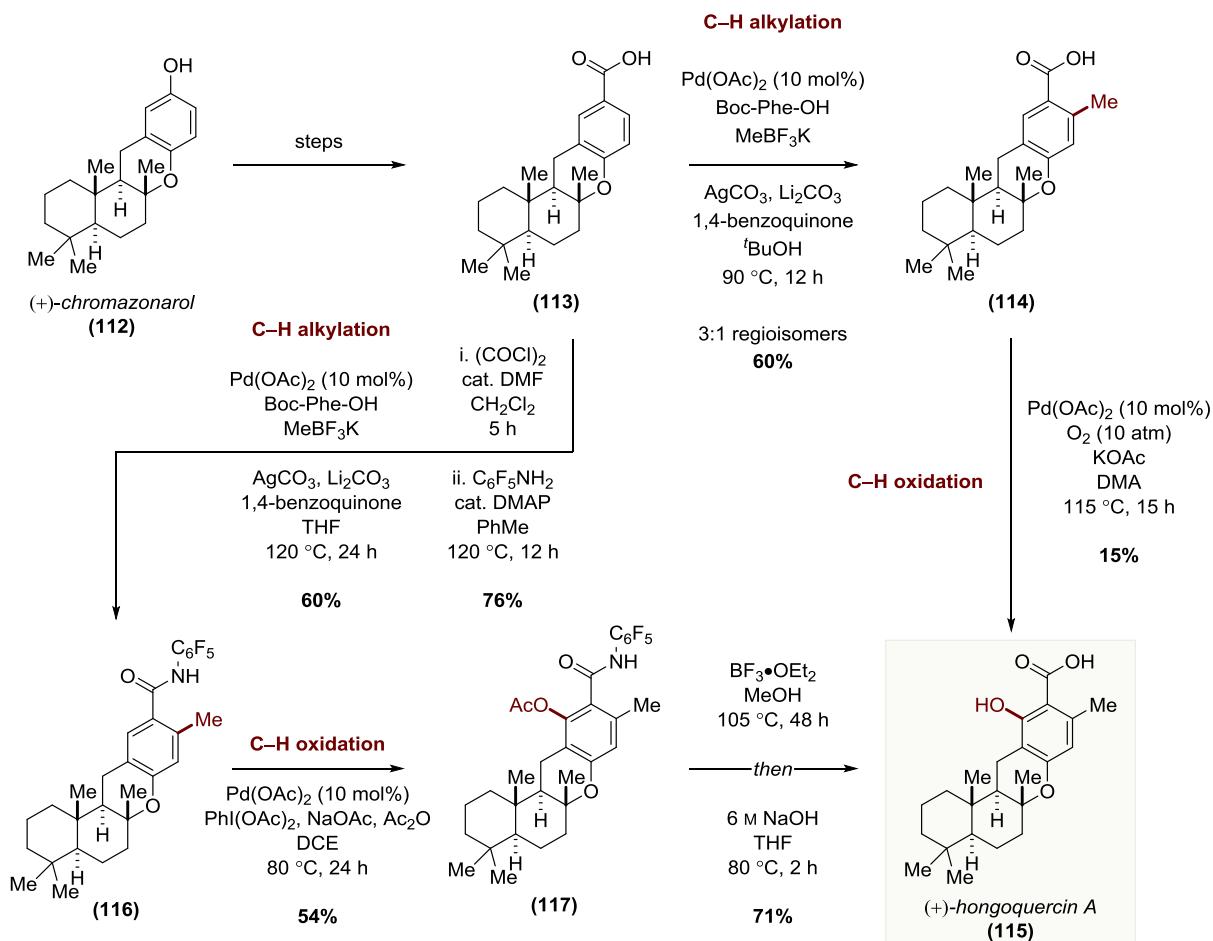
A third and final C–H functionalisation, an olefination, was applied only to substrate (**110**) to demonstrate the possibility of further reactivity. The conditions used were derived from the

related step in the previously outlined synthesis of (+)-lithospermic acid (**83**), but with a higher catalyst loading and temperature to afford the benzofuranylacrylate (**111**) in a 46% yield.

### 1.3.8 (+)-Hongoquercin A (Baran, 2013)

The late-stage C–H functionalisation of (+)-chromazonarol (**112**), prepared from the biologically available (+)-sclareolide in six steps,<sup>67</sup> provided Baran and co-workers expedient access to sesquiterpenoid fungal antibiotic (+)-hongoquercin A (Scheme 19).<sup>68</sup>

Firstly, triflation and hydroxycarbonylation provided the key intermediate (**113**) on gram-scale for further investigation.<sup>69</sup> At this point, the synthesis divided into two distinct pathways. The first pathway comprised of direct application of the desired C–H functionalisation steps. A palladium(II) acetate catalysed C–H alkenylation using a Boc-L-phenylalanine ligand with silver(II) carbonate, lithium carbonate and 1,4-benzoquinone in *tert*-butyl alcohol at 90 °C furnished the methylated product (**114**) in a 60% yield with 3:1 selectivity for the desired regioisomer.



Scheme 19. Baran's synthesis of (+)-hongoquercin.

It was noted that the ligand was particularly important for good reactivity as, in its absence, less than 10% product was recovered. The remaining mass balance was accounted for by isolation of the bismethylated product in 15% yield and 32% recovery of starting material (**113**).

The subsequent C–H hydroxylation turned out to be exceptionally difficult. A large screen of reaction conditions resulted in only recovery of starting material at atmospheric pressure and 15% yield of (+)-hongoquercin A (**115**) at 10 atmospheres of oxygen.<sup>70</sup> The remaining material was thought to be lost to oxidative decomposition processes and no improvement in yield was achieved. Although the synthesis was completed, it was clear that this route could be improved.

The second route diverging from intermediate (**113**) involved formation of the pentafluorobenzamide<sup>71</sup> from the corresponding acid chloride, which was obtained by treatment of (**113**) with oxalyl chloride and catalytic *N,N*-dimethylformamide in dichloromethane. This amide was exposed to almost identical C–H alkenylation conditions as in the direct route, albeit in superheated tetrahydrofuran at an increased temperature of 120 °C. The methylated product (**116**) was afforded in an identical 60% yield, but now with complete regioselectivity for the desired position.

A C–H acetoxylation was then performed in lieu of the direct C–H hydroxylation previously shown. Stirring with 10 mol% palladium(II) acetate catalyst, (diacetoxyiodo)benzene (PIDA) oxidant, sodium acetate and acetic anhydride in 1,2-dichloroethane at 80 °C delivered the acetoxylated product (**117**) in 54% yield. A two-step deprotection, boron trifluoride in refluxing methanol to cleave the amide and sodium hydroxide in superheated tetrahydrofuran to hydrolyse the acetate, synthesised (+)-hongoquercin A (**115**) in 71% yield. Although it required more transformations, the second and longer route provided an overall yield of 17% from common intermediate (**113**) when compared to the 7% yield of the shorter route.

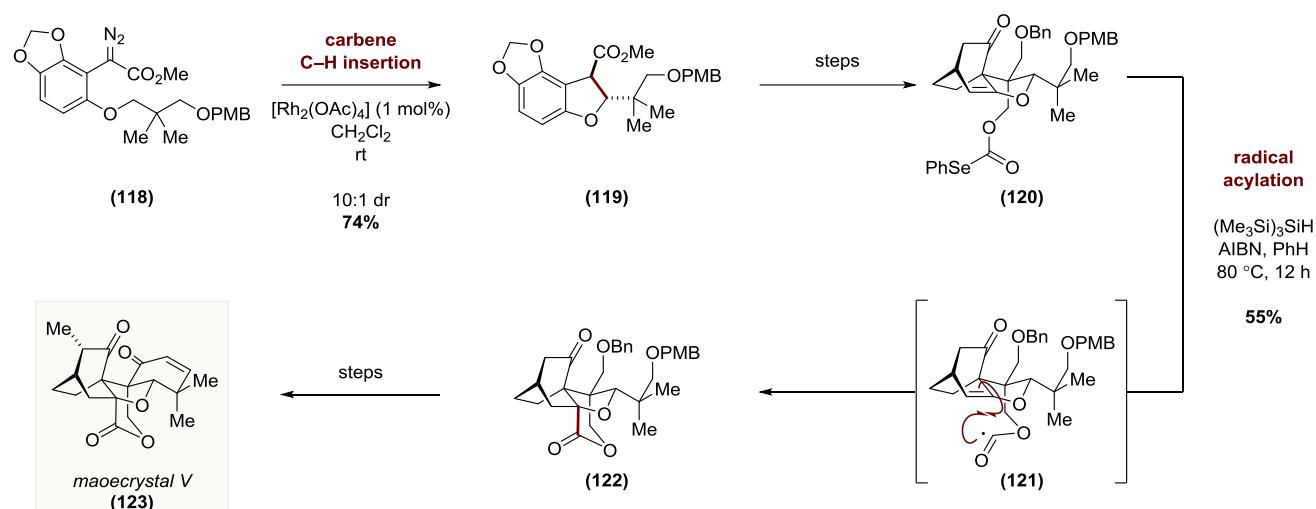
In conjunction with the semi-synthesis, the authors also disclose a number of versatile late-stage functionalisations of benzoic acid (**113**) and pentafluorobenzamide including vinylation, amination and carbonylation.

### 1.3.9 Maoecrystal V (Zakarian, 2013)

In one of the most recent contributions to the field of C–H functionalisations in natural product synthesis, Zakarian and co-workers total synthesis of maoecrystal V (**123**) (Scheme 20) stands out for its use of a carbene C–H insertion at an early stage. It also features a particularly impressive late-stage radical acylation to form one of the three quaternary centres.<sup>72</sup>

The synthesis commences from sesamol to afford diazoester (**118**) in three steps. This substrate is primed to undergo the desired carbene C–H insertion and in the presence of a rhodium(II) acetate dimer catalyst stirring in dichloromethane at room temperature, the transformation proceeds in a 74% yield with excellent 10:1 diastereoselectivity for the desired product (**119**). This is very similar to the strategy employed on a similar substrate by Yu in the synthesis of (+)-lithospermic acid (**83**) (Scheme 15) but much milder conditions are employed in the absence of a chiral ligand.

A number of transformations later, bicyclic intermediate (**120**) is primed to undergo a second key step in the synthesis. The authors initially attempted to use tri-*n*-butyl tin hydride with a variety of radical initiators. However, this only resulted in formation of the corresponding formate, indicating that donation of the hydrogen atom was faster than the desired cyclisation. By instead using the less reactive tris(trimethylsilyl)silane (TTMSS) with azobisisobutyronitrile (AIBN) in a solution that was added dropwise to substrate (**120**) stirring in benzene at 80 °C, the desired product (**122**) could be formed in 55% yield via postulated radical intermediate (**121**).



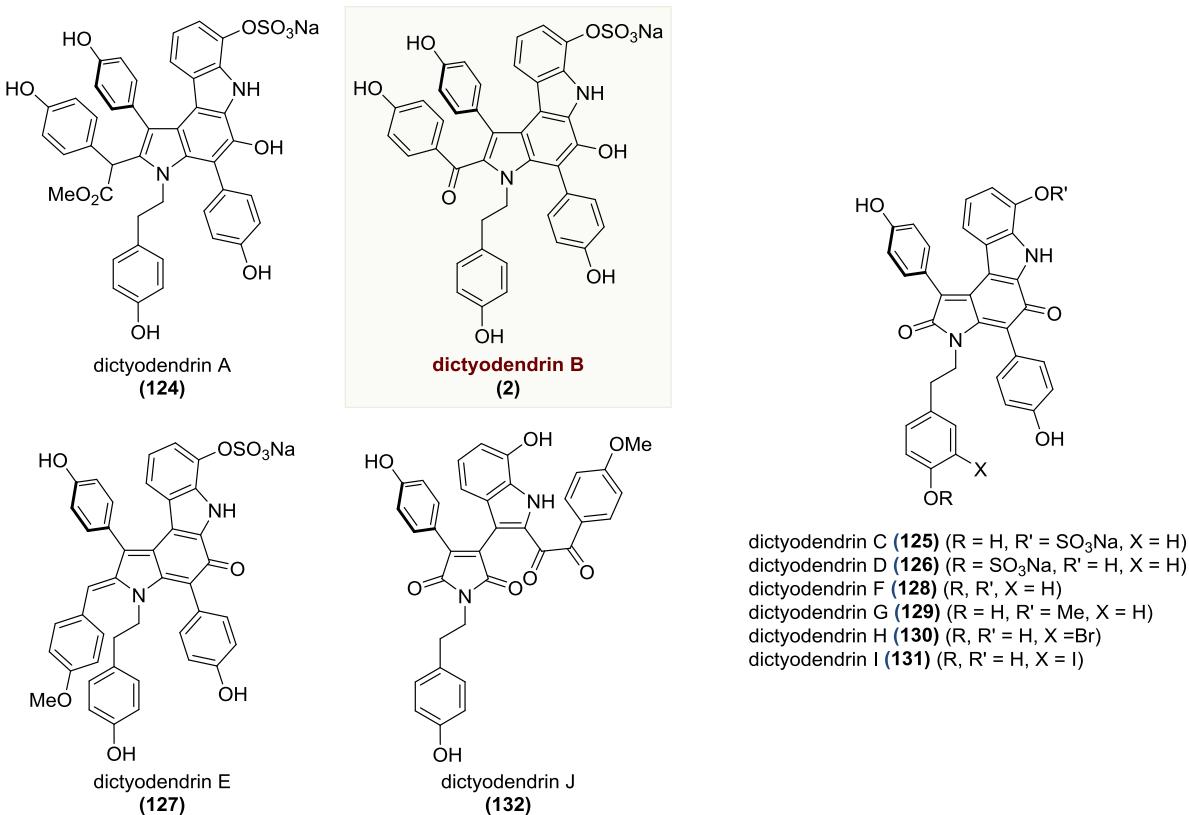
**Scheme 20.** Zakarian's total synthesis of maoecrystal V.

Formation of the remaining *gem*-dimethyl substituted cyclic enone ring was achieved by transformation of the paramethoxybenzyl cleaved alcohol substrate to the alkene via oxidation with Dess–Martin periodinane (DMP) and subsequent Wittig methylenation.  $\alpha$ -Methylation of the ketone after lithium hexamethyldisilazide (LiHMDS) enolate formation with methyl iodide followed. The benzyl ether was cleaved with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) before oxidation to the aldehyde with DMP and addition of vinylmagnesium bromide in the presence of anhydrous cerium(II) chloride afforded the allyl alcohol. Finally, ring-closing metathesis with Hoveyda–Grubbs 2nd generation catalyst and a third DMP-mediated oxidation to the enone completed the synthesis of maoecrystal V (**123**).

This concludes our review of previous examples of where C–H functionalisation has been applied more than once in the synthesis of a natural product.

## 1.4 The dictyodendrin marine alkaloids

Dictyodendrins A-E (Figure 4.) were isolated from the marine sponge *Dictyodendrilla verongiformis* found in the waters surrounding Nagashima Island on the South coast of Japan in 2002.<sup>73</sup> A decade later, the family was extended as dictyodendrins F-I were discovered from a *Ianthella* sp. marine sponge collected from the Bass Strait near Australia.<sup>74</sup>

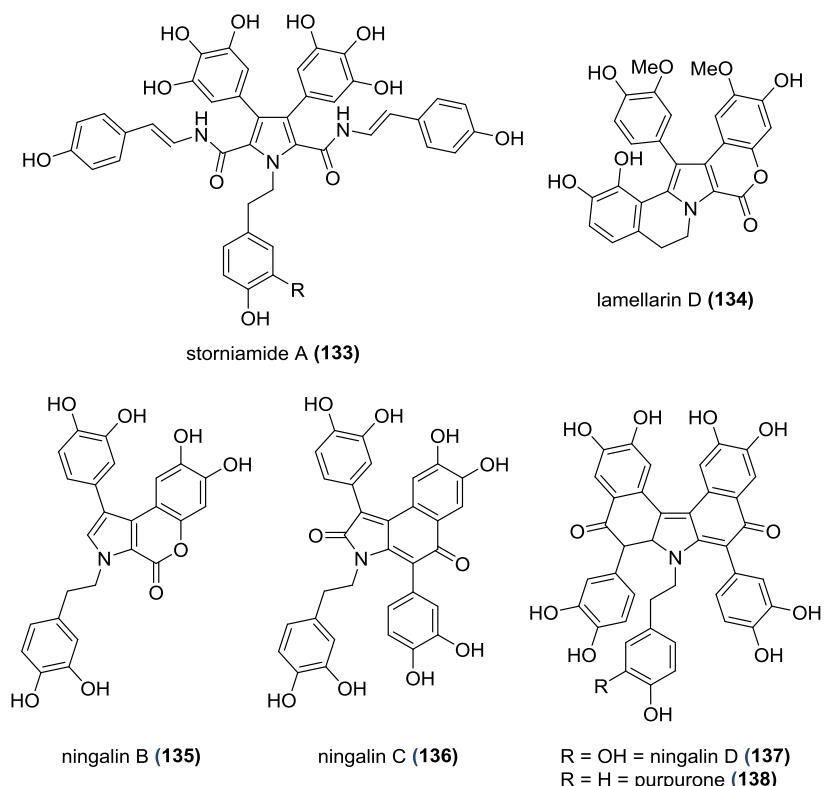


**Figure 4.** The dictyodendrin family of marine alkaloid natural products.

They were reported as the first marine alkaloids to show inhibitory telomerase activity with complete inhibition at a concentration of 50  $\mu\text{L}/\text{mL}$ . Telomerase enzymes are ribonuclearproteins that add sacrificial non-coding DNA repeats known as telomeres (typically TTAGGG) to the end of chromosomes. This ensures that during cell replication, when around 100-200 terminal chromosomal nucleotides are usually lost, the organism's vital genomic DNA remains intact. Cancerous cells exhibit heightened telomerase activity to support their excessive replication rates and represent an important drug target for anti-cancer medicines currently being trialled by pharmaceutical companies.

In general, the dictyodendrins differ mostly by their substitution at the C2 position and varying levels of oxidation of the more substituted indole moiety. The sulfate group was determined to be essential for the telomerase inhibiting activity of the dictyodendrins.

Dictyodendrin B (**2**) is thought to be the oxidative decarboxylation product of dictyodendrin A (**124**). Furthermore, dictyodendrin F (**128**) is thought to be the common degradation product of the dictyodendrin family via acid hydrolysis where the indol-2,6-dione core is thought to act as a thermodynamic sink.



**Figure 5.** Structurally similar alkaloid natural products.

While the pyrrolo[2,3-*c*]carbazole core is unique to the dictyodendrins, a number of structurally similar natural products with potential anti-cancer properties are also known (Figure 5). These include the ningalins<sup>75</sup>, lamellarins<sup>76</sup>, storniamides<sup>77</sup> and purpurone<sup>78</sup>.

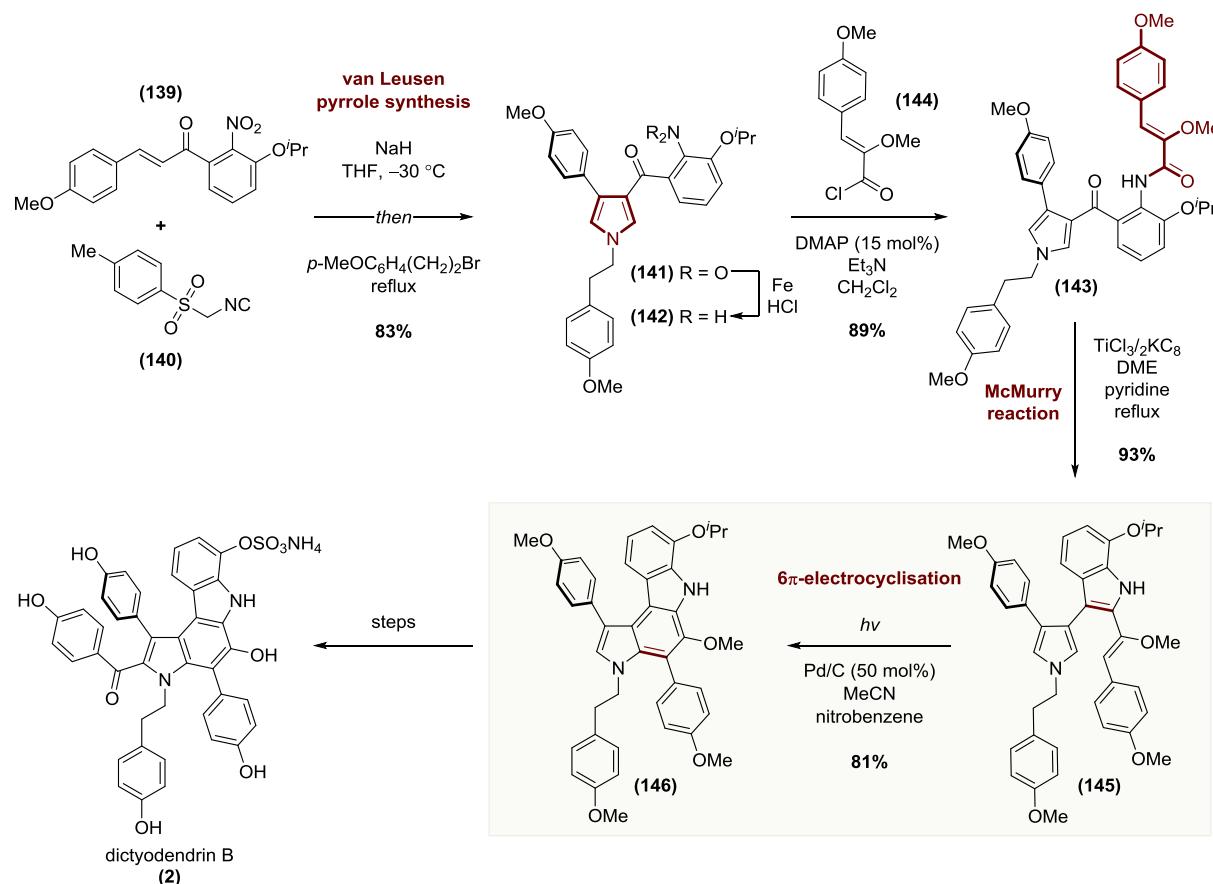
## 1.5 Previous synthetic approaches to the dictyodendrins

Over the years there have been a number of total, formal and core syntheses of dictyodendrin B (**2**) and closely related members of the dictyodendrin family. In the following section, these syntheses are briefly reviewed and the key steps are discussed. In particular, each example constructs the fully substituted indole part of the core en route to the final product and this key step is clearly highlighted in each scheme.

### 1.5.1 Fürstner (2005)

Fürstner and co-workers were the first to complete the total synthesis of dictyodendrin B (**2**) with a longest linear sequence of 13 steps and in an overall yield of 8% (Scheme 21).<sup>79</sup> The synthesis began from 3-hydroxy-2-nitrophenylethanone which, after protection of the phenol as an isopropyl ether, underwent an aldol condensation with 4-methoxybenzaldehyde to afford intermediate chalcone (**139**).

A van Leusen pyrrole synthesis was then used to initiate construction of the central core and involved the introduction of *p*-toluenesulfonylmethyl isocyanide (**140**) after deprotonation by sodium hydride. 4-Methoxyphenethyl bromide was then added directly to the reaction mixture which was refluxed for 2 hours to give the *N*-alkylated product (**141**) in 83% yield. A simple iron and hydrochloric acid mediated reduction of the nitro group in ethanol generated aniline intermediate (**142**) in 96% yield.



**Scheme 21:** Fürstner's total synthesis of dictyodendrin B.

Condensation of aniline (**142**) with acyl chloride (**144**) in the presence of trimethylamine and 4-dimethylaminopyridine (DMAP) in dichloromethane produced amide (**143**) in 89% yield.

Fürstner's lab had previously described the synthesis of indoles from ketoamides in a variant of the McMurry reaction and application of this methodology, involving exposure to freshly prepared titanium graphite, afforded indole (**145**) in an excellent 93% yield.<sup>80</sup> It was found advantageous to buffer the Lewis acid with pyridine to prevent simultaneous cleavage of the sensitive enol ether.

With this substrate in hand the central core was then completed by exposure to the UV light of a 250W mercury lamp which promoted a  $6\pi$ -electrocyclisation. The resulting tetracyclic core was re-aromatised upon treatment with palladium on charcoal and nitrobenzene to conclude construction of the pyrrolo[2,3-*c*]carbazole core architecture and deliver (**146**) in an 81% yield.<sup>81</sup>

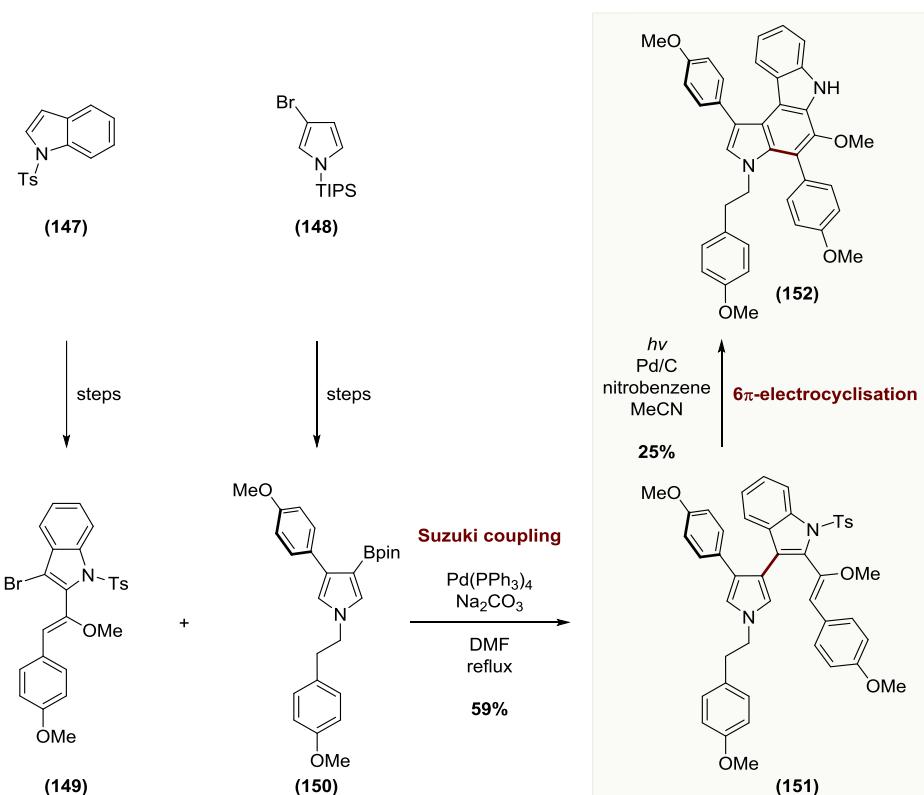
While a Friedel-Crafts approach was originally envisioned to functionalise the remaining C2 position, this resulted in unwanted skeletal rearrangements.<sup>82</sup> Instead, bromination followed by lithium-halogen exchange and quenching with 4-methoxybenzaldehyde produced the corresponding benzylic alcohol in an almost quantitative 97% yield. Oxidation of this alcohol under Ley-Griffith conditions (10 mol% tetra-*n*-propylammonium perruthenate and 2 equivalents of *N*-methylmorpholine *N*-oxide) generated the desired biphenone substrate in 66% yield, along with the product of an unwanted dimerization whose formation was partially suppressed by increased dilution of the reaction.

The final four step deprotection sequence would become the standard for all future syntheses of dictyodendrin B (**2**) and its relatives. Cleavage of the isopropyl protecting group by boron trichloride was followed by reaction of the phenol with trichloroethyl chlorosulfuric acid ester to generate the protected sulfate over two steps in 92% yield. Finally, a 'global deprotection' using tetra-butyl ammonium iodide (TBAI) treated *in situ* with boron trichloride (generating fresh boron triiodide) exhaustively demethylated the five methoxy groups. All that remained was deprotection of the trichloroethyl sulfate which was achieved by stirring with zinc dust in the presence of ammonium formate to give dictyodendrin B (**2**) in 58% over two steps.

The flexibility of late-stage functionalisation of the C2 position with their bromination/lithium-halogen exchange procedure enabled the subsequent synthesis of dictyodendrins C (**125**) and E (**127**).<sup>83</sup> Furthermore, Fürstner also pursued the synthesis of a series of compounds that were structurally similar to the dictyodendrin alkaloids to probe their DNA cleavage properties.<sup>84</sup>

## 1.5.2 Ayats and Álvarez's pyrrolo[2,3-*c*]carbazole core synthesis (2009)

The next report concerning the synthesis of the dictyodendrins was a number of years later by Ayats and Álvarez (Scheme 22).<sup>85</sup> They detailed the construction of a simplified pyrrolo[2,3-*c*]carbazole core via a convergent strategy.



**Scheme 22.** Ayats and Álvarez's synthesis of the pyrrolo[2,3-*c*]carbazole core.

The *N*-tosyl indole (**147**) starting material underwent lithiation with *n*-butyllithium at the C2 position, followed by transmetalation with trimethyltin chloride, which allowed for a Stille coupling with (4-methoxyphenyl)acetyl chloride to afford the desired acylated product. Smooth conversion to the enol ether was then achieved with sodium hydride and dimethyl sulfate in *N,N*-dimethylformamide in a 78% yield, but subsequent treatment with *N*-bromosuccinimide in tetrahydrofuran at -78 °C gave unwanted bromination of the enol ether moiety. However, through a tosyl deprotection/bromination/re-protection sequence, the reactivity of the indole was increased to allow for preparation of the brominated indole intermediate (**149**) in a 71% yield over three steps.

The second starting material, 3-bromo-*N*-(triisopropylsilyl)pyrrole (**148**), was converted to the boronic ester via lithium-halogen exchange before being quenched with methoxyboronic acid pinacol ester. A Suzuki coupling with tetrakis(triphenylphosphine)palladium(0) and 4-

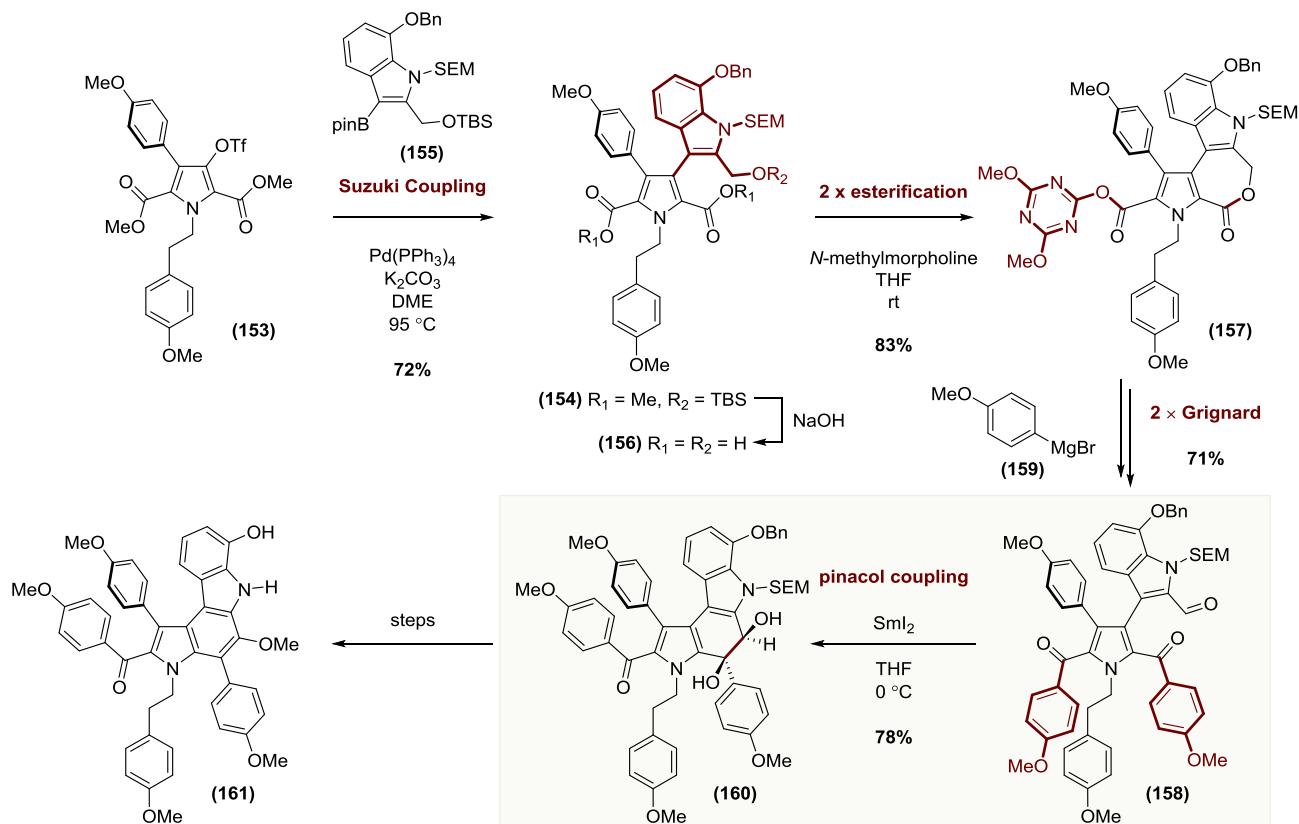
methoxyphenyl bromide afforded the arylated product in 81% yield over 2 steps. Iodination of the C3 position with iodine in the presence of mercuric acetate, followed by a tetra-*n*-butylammonium fluoride (TBAF) mediated deprotection of the indole nitrogen and subsequent N-alkylation with 4-methoxyphenethyl bromide using potassium carbonate in *N,N*-dimethylformamide at 80 °C gave the corresponding product in 49% yield over three steps. Finally, the boronic ester (**150**) was afforded by repeating the lithiation/borylation protocol applied at the beginning of this sequence.

A Suzuki coupling was then used to couple indole (**149**) and pyrrole (**150**) using tetrakis(triphenylphosphine)palladium(0) with sodium carbonate in *N,N*-dimethylformamide at reflux to bring the synthesis to a convergence to afford the coupled product (**151**) in a 59% yield. Finally, the pyrrolo[2,3-*c*]carbazole core was completed using the same 6π-electrocyclisation and rearomatisation conditions as Fürstner to give (**152**), albeit in a lower 25% yield. By also cross-coupling a number of side-products that were obtained at various points throughout the synthesis with pyrrole (**150**), an analogous pyrrolo[3,2-*c*]carbazole and a benzo[*c*]carbazole were also prepared.

### 1.5.3 Ishibashi (2010)

Within the next year, a formal synthesis of dictyodendrin B (**2**) was then unveiled by Ishibashi<sup>86</sup> who had already disclosed a synthetic approach to the core (Scheme 23).<sup>87</sup> The synthesis began with the dialkylation of 2-methoxyphenethyl amine with methyl bromoacetate in a 91% yield. A Hinsberg-type condensation with dimethyl oxalate in the presence of sodium methoxide then afforded a dihydroxy intermediate which immediately undergoes triflation with trifluoromethanesulfonic anhydride in pyridine at 0 °C.

One of the two triflate groups was reacted under Suzuki coupling conditions with tetrakis(triphenylphosphine)palladium(0), sodium carbonate and 4-methoxyphenylboronic acid to afford intermediate (**153**) in 78% yield over 4 hours. This intermediate had been prepared previously in a 2003 report by Ishibashi on a short and flexible route to 3,4-diarylpyrrole marine alkaloids.<sup>88</sup>



**Scheme 23.** Ishibashi's formal synthesis of dictyodendrin B.

Cross coupling of the second triflate group with separately prepared indole (**155**) afforded the desired product (**154**) in 72% yield over 26 hours at 95 °C in 1,2-dimethoxyethane. With 3 M sodium hydroxide in ethanol and dioxane at 90 °C, the two methyl esters were saponified and the *tert*-butyldimethylsilyl group removed to give intermediate (**156**).

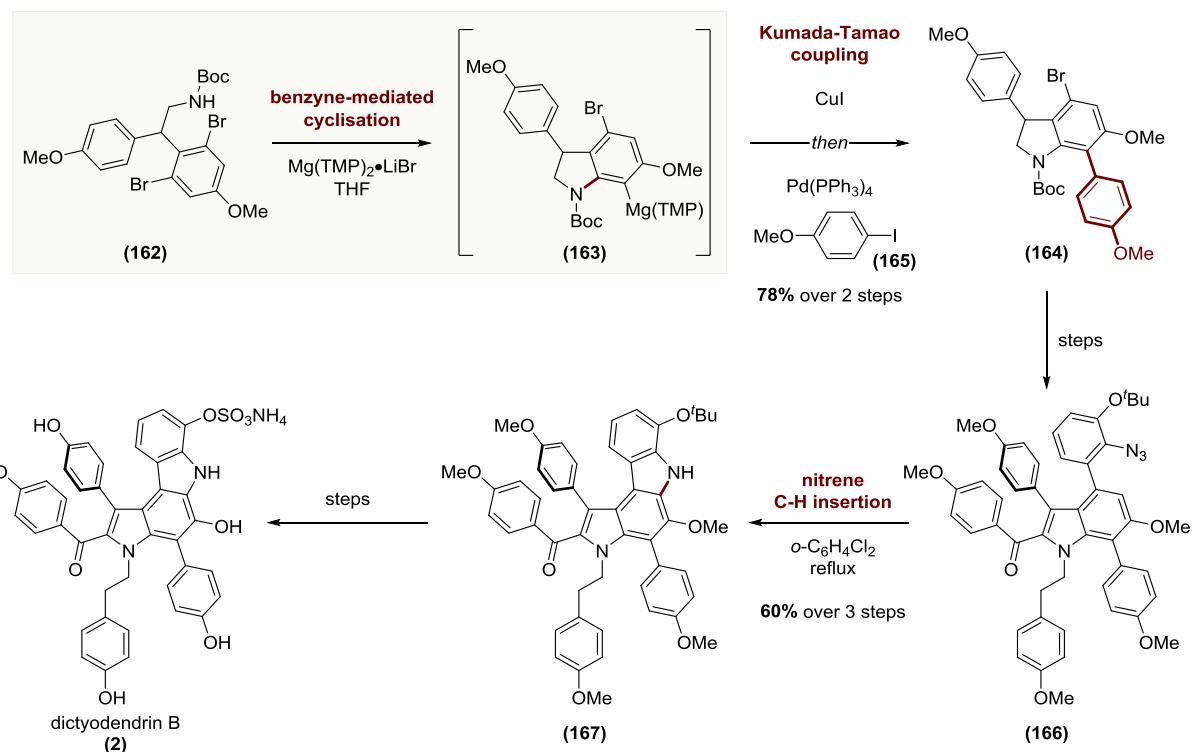
Treatment with peptide coupling reagent 2-chloro-4,6-dimethoxy-1,3,5-triazine and *N*-methylmorpholine in tetrahydrofuran at room temperature enabled preparation of the activated esters, one of which spontaneously underwent caprolactone formation with the free alcohol to afford (**157**) in 83% yield over two steps. Exposure of both esters to 4-methoxyphenylmagnesium bromide (**159**) resulted in phenone formation in 71% yield and subsequent treatment with Dess-Martin periodinane (DMP) in dichloromethane for 20 minutes at room temperature produced aldehyde (**158**) in 99% yield.

The pyrrolo[3,2-c]carbazole core was then completed via a samarium(II) iodide promoted pinacol coupling in tetrahydrofuran at 0 °C over 1 hour to give the cyclised product (**160**) in 78% yield.<sup>89</sup> Dehydration of the pinacol under acidic conditions was found to promote the migration of the 4-methoxyphenyl group. Instead, acetic anhydride and a catalytic amount of 4-dimethylaminopyridine in pyridine was used followed by deacetylation with sodium methoxide

and methylation with methyl iodide in an overall yield of 91%. Finally, deprotection of the nitrogen with camphorsulfonic acid in tetrahydrofuran and hydrogenation of the benzyl group with palladium hydroxide on carbon in ethyl acetate afforded late-stage intermediate (**161**) and completed their formal synthesis.

### 1.5.4 Tokuyama (2010)

Shortly after Ishibashi's formal synthesis, Tokuyama presented a total synthesis of dictyodendrin B (**2**) (Scheme 24).<sup>90,91</sup> The synthesis began with an extended sequence to convert 4-nitrophenol into intermediate (**162**). This involved methylation of the phenol, hydrogenation of the nitro group and double *ortho*-bromination of the resultant aniline. Transformation to the diazonium species with sodium nitrite in the presence of sulfuric acid enabled a Sandmeyer reaction with potassium iodide. Lithium-halogen exchange and addition of *trans*-4-methoxy- $\beta$ -nitrostyrene afforded a biaryl nitro intermediate that was reduced to the amine by iron in the presence of hydrochloric acid. Protection with di-*tert*-butyl dicarbonate and trimethylamine in a mixture of water and acetonitrile furnished intermediate (**162**) in an 85% yield over two steps.



**Scheme 24.** Tokuyama's total synthesis of dictyodendrin B.

This intermediate was primed to undergo the key benzyne-mediated cyclisation to begin construction of the central core. Exposure to 5 equivalents of bis(tetramethylpiperidyl)magnesium base at  $-78^{\circ}C$  to room temperature over 1 hour in

tetrahydrofuran promoted the formation of a phenyl anion that eliminated a bromide to form a benzyne species. This underwent cyclisation with the nearby nitranion to form the organomagnesium indoline species (**163**). Transmetalation to form the corresponding cuprate with 10 equivalents of copper(I) iodide facilitated a high yielding Kumada-Tamao coupling with 20 mol% tetrakis(triphenylphosphine)palladium(0) and 4-iodoanisole (**165**) at room temperature for 2 hours to deliver intermediate (**164**).<sup>92</sup>

The Boc group was removed with trimethylsilyl trifluoromethanesulfonate and 2,6-lutidine and a 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) facilitated oxidation gave the unprotected indole in 95 and 98% yields respectively. Stirring with 4-methoxyphenethyl bromide and potassium hydroxide in *N,N*-dimethylformamide delivered the *N*-alkylated product in 97% yield. A large excess of Lewis acid zinc(II) chloride and 4-methoxybenzoyl chloride expedited a Friedel-Crafts acylation before borylation of the bromide under relatively standard palladium-catalysed Miyaura conditions. The resultant boronic ester was then coupled with an *ortho*-azide iodoarene to deliver late-stage intermediate (**166**).

Lastly, the pyrrolo[3,2-*c*]carbazole core was finished via a thermal decomposition of the *ortho*-azide in 1,2-dichlorobenzene at 180 °C for 40 minutes to give a highly reactive nitrene species that performs a C–H insertion at the C5 position of the indole to give the cyclised product (**167**) in 60% yield over three steps.<sup>93</sup> Application of Fürstner's four step deprotection and sulfonylation sequence finalised this total synthesis of dictyodendrin B (**2**).

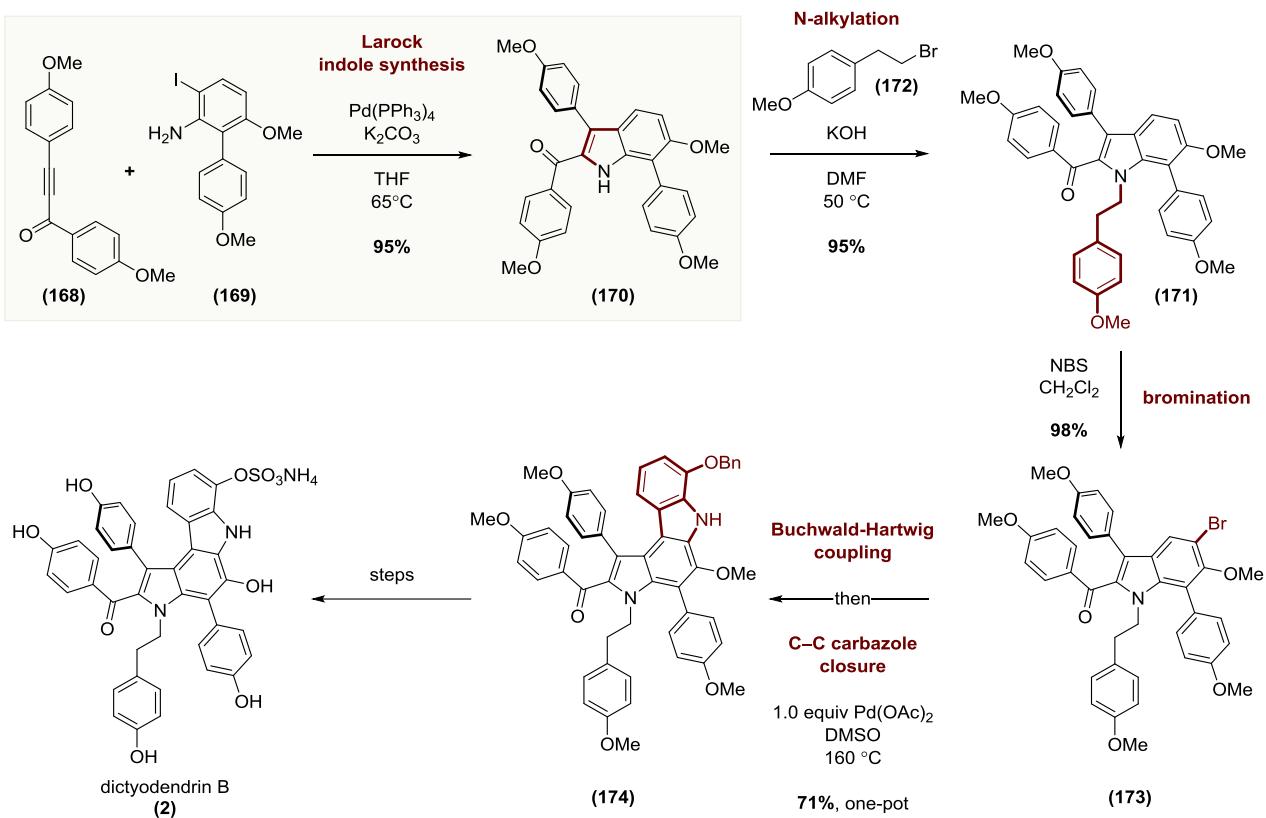
In the same report, the synthesis diverged at the Friedel-Crafts reaction which, when α-bromo-(4-methoxyphenyl)acetic acid methyl ester was used with 4 equivalents silver(I) triflate, resulted in alkylation in 81% yield. A sequence of identical steps to those above resulted in the first total synthesis of dictyodendrin A (**124**). The synthesis of dictyodendrins C (**125**), D (**126**) and E (**127**) by the same benzyne-mediated cyclisation strategy was also reported by Tokuyama around a year later.<sup>91</sup>

### 1.5.5 Jia (2013)

Two years later another synthesis of dictyodendrin B (**2**) was executed by Jia (Scheme 25).<sup>94,95</sup> The synthesis started from 1-(4-methoxy)phenyl-2-methoxyaniline (**169**) which was prepared in 5 steps from 2-amino-3-nitrophenol via the known intermediate 2-iodo-1-methoxy-3-nitrobenzene.<sup>96,97</sup> A Suzuki coupling was used to construct the biphenyl structure and iodination was performed in the final step with iodine monochloride and a saturated aqueous solution of sodium carbonate in diethyl ether to furnish iodide (**169**) in 83% yield. The second starting

material, known alkyne (**168**), was prepared through a palladium-catalysed Sonogashira acylation of 4-ethynylanisole with benzoyl chloride.<sup>98</sup>

The first step to construct the central core, a Larock indole synthesis with iodide (**169**) and alkyne (**168**), was then performed using tetrakis(triphenylphosphine)palladium(0) and potassium carbonate in tetrahydrofuran. After heating to 65 °C for 24 hours the indole product (**170**) was isolated in an excellent 95% yield.



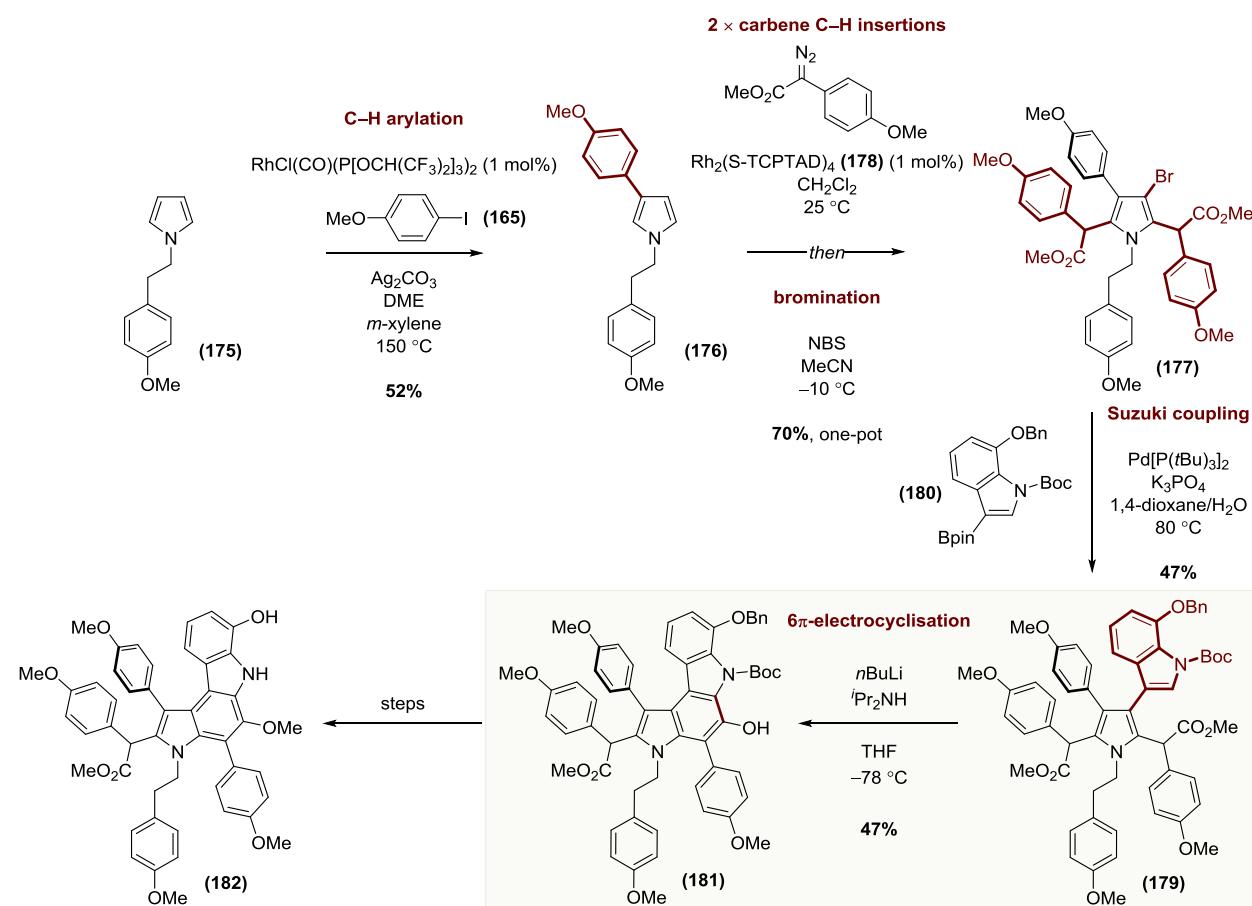
**Scheme 25.** Jia's total synthesis of dictyodendrin B.

This was followed by *N*-alkylation with 4-methoxyphenethyl bromide (**172**) and potassium hydroxide in *N,N*-dimethylformamide at 50 °C to afford (**171**) in 95% yield. A site-selective bromination with *N*-bromosuccinimide at room temperature in dichloromethane was also exceptionally efficient, delivering bromide (**173**) in 98% yield. The final key step in the synthesis, a one-pot Buchwald-Hartwig coupling with an *ortho*-chloro aniline and subsequent intramolecular C–H ring closure, required a stoichiometric amount of palladium(II) acetate in dimethylsulfoxide at 160 °C to furnish the fully constructed pyrrolo[3,2-*c*]carbazole intermediate (**167**) in 71% yield. High reaction temperatures prevented a deleterious protodebromination reaction from decreasing the yield of the desired product.

Hydrogenolysis of the benzyl protecting group with palladium on carbon in ethyl acetate at 50 °C delivered the free phenol which was processed through the remaining sulfonylation and deprotection steps, as performed by Fürstner, to give dictyodendrin B (**2**). Using similar conditions to Tokuyama, the synthesis of dictyodendrin E (**127**) was also accomplished by diisobutylaluminium hydride (DIBAL) reduction of common intermediate (**174**).

### 1.5.6 Davies and Itami (2015)

In concurrence with our synthesis of dictyodendrin B (**2**) using sequential C–H functionalisation strategy, the groups of Davies and Itami jointly reported the formal synthesis of dictyodendrin A (**124**) via a comparable strategy.<sup>99</sup> Starting from pyrrole (**175**) (synthesised from commercial starting materials by *N*-alkylation) they performed a rhodium-catalysed C–H arylation of the C3 position with 4-iodoanisole (**165**) to deliver pyrrole (**176**) in 52% yield.<sup>100,101</sup>



**Scheme 26.** Davies's and Itami's formal synthesis of dictyodendrin A by sequential C–H functionalisation.

The second step involves a one-pot double rhodium catalysed carbenoid C–H insertion at both the C2 and C5 positions followed by addition of *N*-bromosuccinimide directly to the reaction

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mixture to install a bromide at the remaining unfunctionalised position. This furnishes the completely functionalised pyrrole (**177**) in an overall yield of 70%.

A Suzuki coupling of bromide (**177**) with indole boronic ester (**180**) using bis(*tri-tert*-butylphosphine)palladium and potassium phosphate generated pyrrole (**179**) in 47% yield. The pyrrolo[3,2-*c*]carbazole core was then completed by treatment with lithium diisopropylamide which generates a lithium enolate species that undergoes a formal  $6\pi$ -electrocyclisation to furnish intermediate (**181**) in a 47% yield.

Methylation of the resulting free hydroxyl group was subsequently achieved in a 93% yield with methyl iodide and potassium carbonate in *N,N*-dimethylformamide. Finally, removal of the Boc group with triflic acid in dichloromethane and hydrogenation of the benzyl group with palladium hydroxide on carbon in ethyl acetate at 50 °C for 5 hours furnished final product (**182**) in an overall yield of 89% and completed the formal synthesis of dictyodendrin A (**124**).

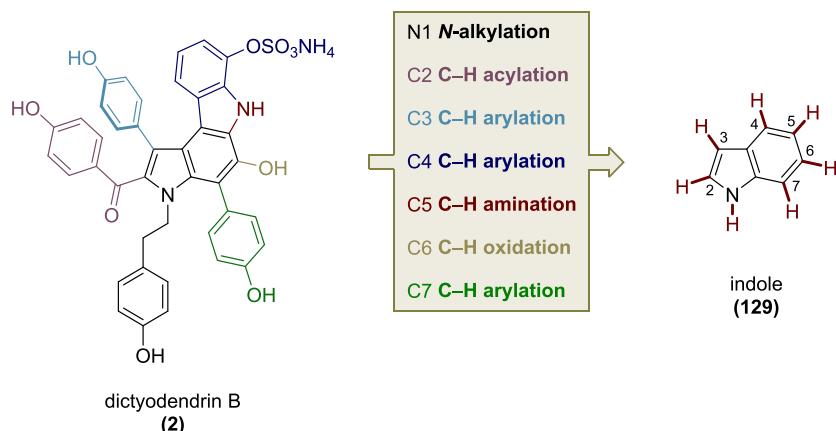
Interception of phenol (**181**), after a triflic acid mediated Boc deprotection, with (diacetoxyiodo)benzene in dichloromethane at room temperature, gave the oxidised indol-6-one product. Hydrolysis with hydrochloric acid in 26% yield and removal of multiple protecting groups in a single step with boron tribromide in 68% yield also gave dictyodendrin F (**128**).

## 2 AIMS AND BACKGROUND

### 2.1 Synthesis of dictyodendrin B by sequential C–H functionalisation

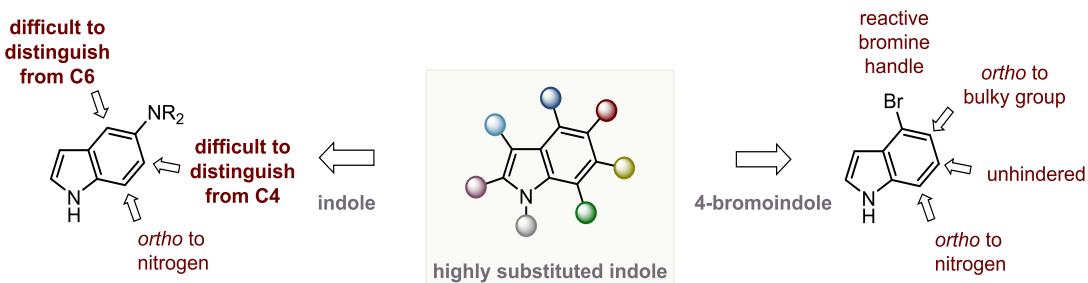
Our main goal was to demonstrate the utility of sequential C–H functionalisation as a viable strategy in the synthesis of complex molecules. At the outset, we were keen for the project to meet a set of very ambitious standards. It must be competitive with the overall yields and length of any previous total syntheses and efficient in its own right. Furthermore, it must be operationally simple, performed on gram-scale and require the use of inexpensive, non-toxic and readily available reagents.

When considering a platform on which to perform sequential C–H functionalisations, we were immediately drawn to the dictyodendrin marine alkaloids due to their densely functionalised heterocyclic cores. In the case of dictyodendrin B (**2**), we identified a hepta-substituted indole embedded in the centre of the natural product and retrosynthetically disconnected each of the seven bonds to identify suitable reactions for the functionalisation of each position (Scheme 27).



**Scheme 27.** Retrosynthetic analysis of an ideal sequential C–H functionalisation approach to dictyodendrin B.

After significant investigation by Dr Robert H. Snell, it became clear that a synthesis from unfunctionalised indole, as depicted above, was exceptionally challenging (Scheme 28). This was mainly due to the difficulty associated with distinguishing between the C4 and C6 positions once the C5 amine moiety had been installed. This in itself was particularly challenging and did not conform to the goals we set out above. This endeavour is documented in greater detail later in this section.



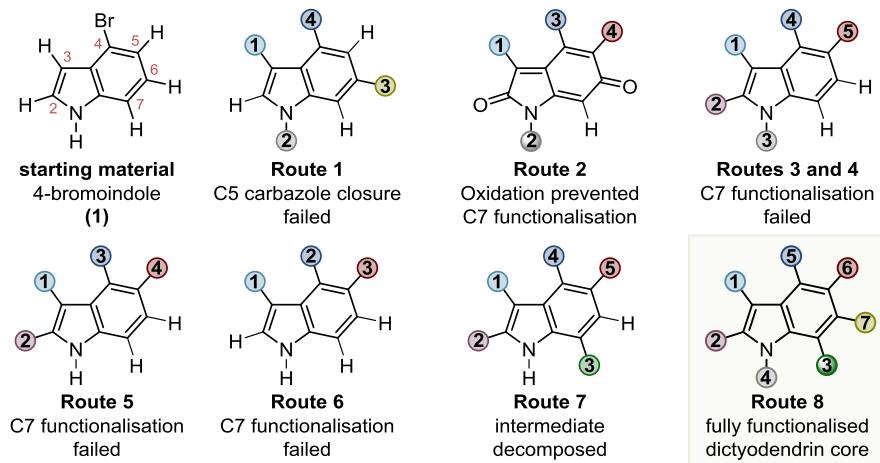
**Scheme 28.** Retrosynthetic analysis of regioselectivity issues associated with indole versus 4-bromoindole.

For these reasons, we opted to instead begin our total synthesis from the commercially available 4-bromoindole (**1**). At the time of writing, this starting material was readily available at the reasonable price of approximately £220/100 g from Combi-Blocks. The bromine handle at the C4 position would allow for initial functionalisation at the periphery of the benzenoid ring of indole to ensure that the final ring closing amination has only a single direction, the C5 position, in which to occur. Furthermore, by installing an arene at the C4 position with suitable amino functionality, a direct C–H amination at the C5 position is more likely to succeed when compared to the inefficient sequence that was required during our attempted synthesis from indole.

## 2.2 Previous Work (by Dr Fionn O'Hara)

Our total synthesis of dictyodendrin B began in 2007 by a former colleague, Dr Fionn O'Hara. The original aim, ‘to illustrate the utility of C–H functionalisation methodology as a general tool for the efficient synthesis of complex molecules’ has remained constant throughout the project since its inception.

The result of this earlier work was eight different attempted routes to the natural product where the order of functionalisation is indicated by numbers at each position (Scheme 29). Reasons for the failure of these routes were the inability to continue selective functionalisation of the indole (routes 1, 3, 4, 5 and 6), oxidation of the indole ring (route 2) and sensitivity of an intermediate to decomposition (route 7). Finally, Dr O'Hara's breakthrough was the synthesis of a fully functionalised dictyodendrin core in route 8. This was a landmark achievement in the project and helped to map a viable order of reactivity for the complete functionalisation of 4-bromoindole.



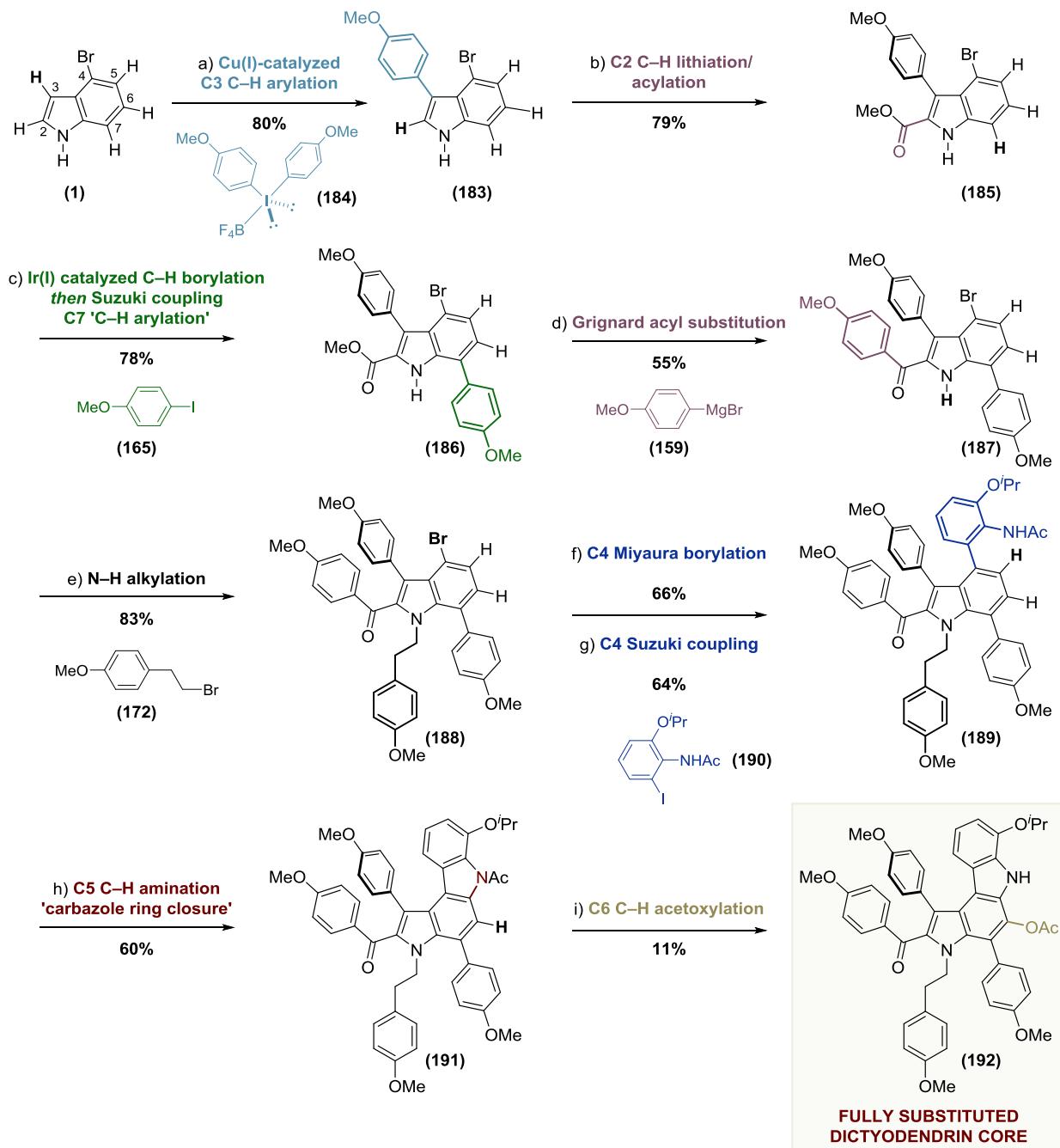
**Scheme 29.** An overview of Dr O'Hara's attempted routes that mapped a viable order of reactivity for the complete functionalisation of 4-bromoindole.

Further optimisation of route 8 culminated in a formal synthesis by intercepting the fully functionalised indole (**192**) of Fürstner et al. via four metal-catalysed C–H functionalisations and one lithiation in a 0.6% overall yield (Scheme 30). This was an excellent result that was the first major step in validating our sequential C–H functionalisation strategy.

The overall sequence of functionalisation in the successful route was C3, C2, C7, (C2), N1, C4, C5 and C6. However, as noted by Dr O'Hara, the C6 oxidation suffered from poor regioselectivity and yield. It was also not certain whether this was actually a palladium-mediated process or a variant of the Boyland-Sims oxidation. Unfortunately, detailed investigations on the latter steps of the synthesis were often precluded by the small quantities of material.

After the initial C2 functionalisation, a separate step was required to convert the methoxy ester (**186**) into the desired 4-methoxylanisoyl intermediate (**187**). The C4 Suzuki coupling also required two distinct steps: first the palladium-catalysed borylation of the 4-bromoindole fragment (**188**) which was isolated in a 66% yield, and the second; a Suzuki coupling of the aforementioned boronic ester with aryl iodide (**190**) in 64% yield which gave a low overall yield of 42%. The final two steps generated the C5 aminated product (**191**) and C6 acetoxylated product (**192**). However, both were performed on small quantities of material and suffered from reproducibility issues.

Clearly, although great progress was made towards the goals of this project, a large amount of work remained to be accomplished. Not only would the yields of some steps need to be optimised further, but the approach used to functionalise many of the positions would benefit from being revised.



**a)** (184) (3.5 equiv), 2,6-di-*tert*-butylpyridine (1.2 equiv), CuCl (10 mol%), CH<sub>2</sub>Cl<sub>2</sub> (0.24 M), 40 °C, 16 h, 80%; **b)** LDA, (1.02 equiv), methyl chloroformate (1.1 equiv), THF (0.17 M), –70 °C, 0.5 h; LDA (1.02 equiv) methyl chloroformate (1.1 equiv), 4 h; LDA (2.02 equiv), MeOH (dropwise quench), 75 °C, 12 h, 79%; **c)** (Bpin)<sub>2</sub> (1.1 equiv), [{IrOMe(cod)}<sub>2</sub>] (0.7 mol%), 4,4'-di-*tert*-butyl-2,2'-dipyridyl (1.2 mol%), THF (0.2 M), 80 °C, μW, 1 h; 4-iodoanisole (165) (9 equiv), [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] (13 mol%), 1 M Na<sub>2</sub>CO<sub>3</sub> (aq, 31 equiv), 60 °C, 11 h, 78%; **d)** (159) (10 equiv), AlMe<sub>2</sub>Cl (2.9 equiv), NHMe(OMe)•HCl (3.0 equiv), 0–40 °C, 22 h, 55%; **e)** 4-methoxyphenylthiomethyl bromide (3.2 equiv), K<sub>2</sub>CO<sub>3</sub> (2.4 equiv), DMF (0.2 M), 110 °C, 16 h, 82%; **f)** [PdCl<sub>2</sub>(dpdpf)]•CH<sub>2</sub>Cl<sub>2</sub> (20 mol%), (Bpin)<sub>2</sub> (2.5 equiv), KOAc (3.0 equiv), dioxane (0.11 M), 95 °C, 10 h, 66%; **g)** (190) (1.9 equiv), [PdCl<sub>2</sub>(dpdpf)]•CH<sub>2</sub>Cl<sub>2</sub> (18 mol%), K<sub>2</sub>CO<sub>3</sub> (4.5 equiv), DME/H<sub>2</sub>O (14:1, 0.03 M), 95 °C, 6 h, 64%; **h)** Pd(OAc)<sub>2</sub> (10 mol%), 3 Å MS, O<sub>2</sub>, DMSO (0.02 M), 120 °C, 12 h, 56%; **i)** Pd(OAc)<sub>2</sub> (70 mol%), AcOH (0.03 M), K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (1.3 equiv), 100 °C, 12 h, 11%.

**Scheme 30.** Dr O’Hara’s most successful route to a fully substituted dictyodendrin core.

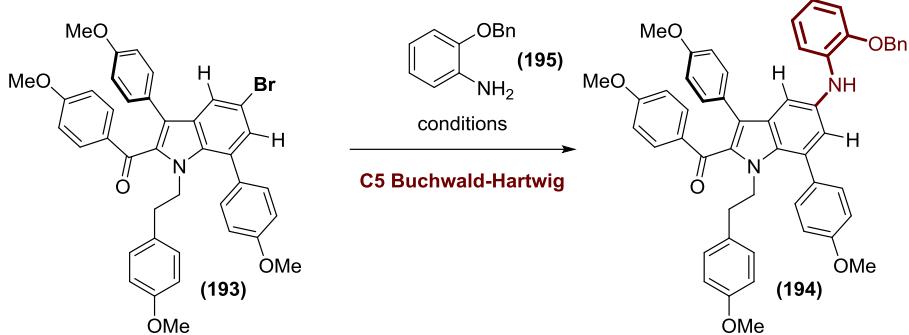
As discussed above, this work was primarily focused towards completing the synthesis by ‘sequential metal-catalysed C–H bond functionalisation’. While this provided some degree of success, most notably the development of a route to a fully functionalised dictyodendrin core and

defining a working order of installing the substituents, the total synthesis remained elusive. Furthermore, the synthesis did not conform to all of our aims outlined earlier in this section.

### 2.3 Attempted synthesis from indole (by Dr Robert H. Snell)

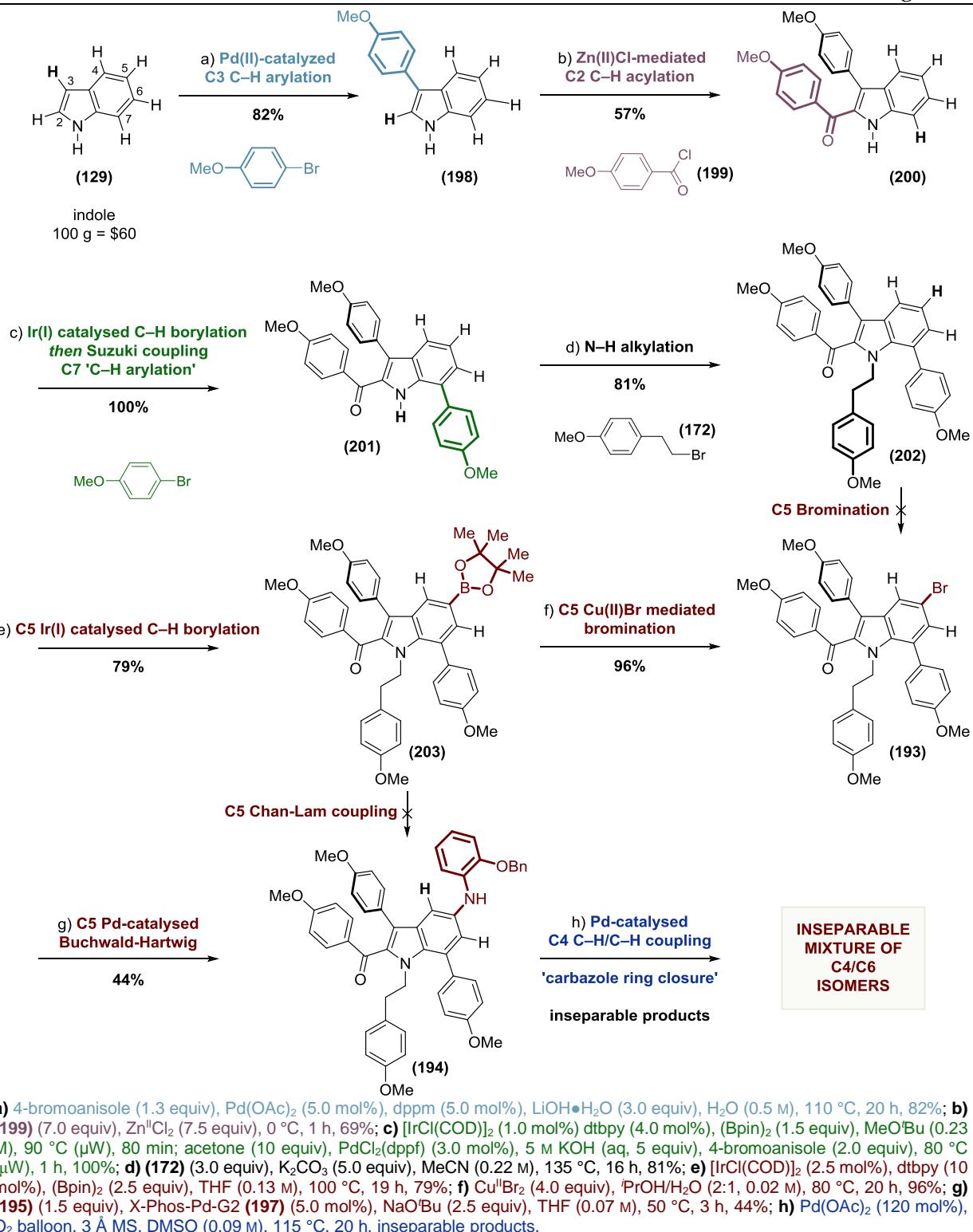
In our original plan, we asserted that it was very difficult to complete the synthesis from indole due to potential regiospecificity problems on the benzenoid ring and then used this as sound justification for starting our synthesis from the minimally functionalised 4-bromoindole. With a reliable set of conditions in place to bring sufficient material through the first few steps, Dr Robert H. Snell took the opportunity to apply them in an attempt to execute the synthesis from indole (Scheme 31).

**Table 1.** Investigation of Buchwald-Hartwig amination conditions.



entry	conditions	yield (%)
1	Pd(OAc) <sub>2</sub> (5.0 mol%), SPhos ( <b>196</b> ) (10 mol%), 1.1 equiv ( <b>195</b> ), 1.4 equiv Cs <sub>2</sub> CO <sub>3</sub> , PhMe (0.15 M), 100 °C, 20 h.	34
2	Pd(OAc) <sub>2</sub> (5.0 mol%), SPhos ( <b>196</b> ) (10 mol%), 1.1 equiv ( <b>195</b> ), 1.4 equiv NaO <i>t</i> Bu, PhMe (0.15 M), 100 °C, 20 h.	31
3	Pd(OAc) <sub>2</sub> (5.0 mol%), DavePhos ( <b>74</b> ) (10 mol%), 1.2 equiv ( <b>195</b> ), 1.4 equiv Cs <sub>2</sub> CO <sub>3</sub> , PhMe (0.11 M), 100 °C, 24 h.	11 (47% RSM)
4	X-Phos-Pd-G2 ( <b>197</b> ) (5.0 mol%), 1.2 equiv ( <b>195</b> ), 2.5 equiv NaO <i>t</i> Bu, THF (0.07 M), 50 °C, 2.5 h.	44

The first arylation at the C3 position was achieved using Djakovitch's conditions (Scheme 32) to generate (**198**) in 82% yield followed by a C2 arylation using a large excess of zinc, delivering indole (**200**) in 69% yield in only 1 hour. The latter procedure was adapted to our substrate from the total synthesis of Tokuyama. A subsequent one-pot nitrogen-directed borylation and Suzuki coupling at the C7 position of indole proceeded to give a quantitative yield of (**165**) over two steps. This highlights that the deleterious homocoupling in our final synthetic route from 4-bromoindole is likely the only cause for the lower yield of 63%. The following *N*-alkylation step proceeded in an almost identical yield of 81% in superheated acetonitrile at 135 °C for 16 hours.

**Scheme 31.** Unsuccessful sequential C–H functionalisation route from indole.

With the tetra-substituted indole (202) in hand, the defining point in this attempted synthetic route came when we tried to selectively functionalise one of the remaining three positions (C4, C5 and C6). Electrophilic aromatic bromination with *N*-bromosuccinimide proved unsuccessful as undesired regioisomers and multiple substitutions were detected. However, borylation using our early microwave conditions afforded the C5-borylated indole (203) in an excellent 79% yield

on a gram of material with complete selectivity for the desired position. The use of boronic esters in Chan-Lam couplings is known to not be as effective as the use of the free boronic acids. Furthermore, only a handful of examples of coupling boronic esters with anilines exist in the literature. It was then not surprising that the attempted coupling of aniline (**195**) with boronic ester (**203**) in the presence of copper(II) bromide was unsuccessful.

However, partial conversion of the boronic ester to the bromide was observed as the sole product. A freshly prepared reaction mixture comprising 4 equivalents of copper(II) bromide in a 2:1 mixture of isopropanol and water smoothly converted boronic ester (**203**) to bromide (**193**) over 20 hours at 80 °C in a near quantitative 96% yield.

From the conveniently obtained bromide (**193**), we were able to investigate the use of Buchwald-Hartwig conditions to couple aniline (**195**) (Table 1). First attempts with 5 mol% palladium(II) acetate catalyst along with the universal Buchwald phosphine ligand SPhos (**196**) (2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl) provided relatively low yields with caesium carbonate (entry 1) and sodium tert-butoxide (entry 2) as the bases. The use of another universal Buchwald phosphine ligand, DavePhos (**74**) (2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl) resulted in an even lower 11% isolated yield of the desired product. Finally, we found that use of a second generation Buchwald palladium-precatalyst XPhos-Pd-G2 (**197**) (chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)] palladium(II))<sup>102</sup> provided the best result in this small screen to provide the aminated product (**194**) in 44% yield and afford nearly one hundred milligrams of material.

It quickly became clear that the aminated indole (**194**) required a stoichiometric amount of palladium(II) acetate to undergo complete conversion and analysis of the complex mixture appeared to show both the desired C4 and undesired C6 regioisomers and possibly a third unwanted product. Due to the fact that this process was not catalytic with respect to the palladium (as observed in many of our oxidative ring closure attempts and also by Jia<sup>94</sup> in their synthesis of dictyodendrins B (**2**) and E (**127**)) we continued to focus our efforts on a synthetic route from 4-bromoindole (**1**) which resulted in the successful completion of the molecule and is described in the following results and discussion section.

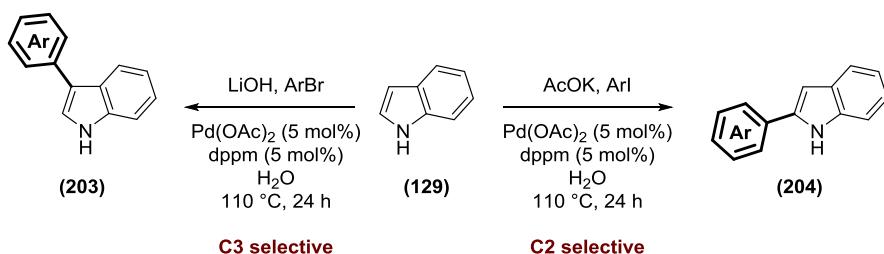
### 3 RESULTS AND DISCUSSION

### 3.1 Synthesis of dictyodendrin B from 4-bromoindole

### 3.1.1 Step 1. C3 Arylation

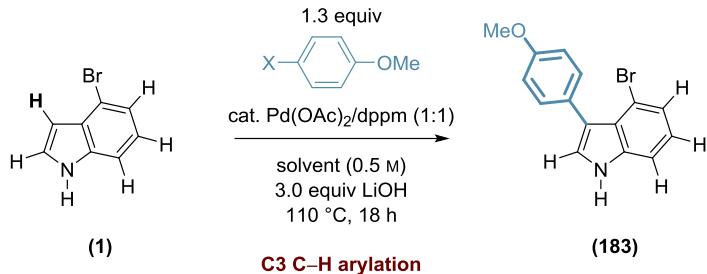
With the intent to functionalise the inherently more reactive pyrrole ring first, we began our synthesis by examining the prospect of a C–H arylation at the C3 position. Relatively few general protocols exist for the selective C3 arylation of indoles and two examples are highlighted in this chapter.

At the outset of the project, we began by using Djakovitch's palladium-catalysed C–H arylation protocol as a means to rapidly bring sufficient material forward to start work on the subsequent steps.<sup>103</sup> Performed 'on water', this method exhibits exception selectivity for the C2 or C3 positions dependant solely on the base used (Scheme 32). Using lithium hydroxide, almost exclusive C3 selectivity is observed whereas, with potassium acetate, the reaction is instead highly selective for the C2 position.



**Scheme 32.** Djakovitch's palladium-catalysed C2 and C3 selective arylation of indoles.

On first inspection, the advantages of using this method were the abundant commercial availability of 4-iodoanisole in large quantities and the relatively reasonable cost of the 1,1-bis(diphenylphosphino)methane (dppm) palladium ligand when working on gram-scale. During optimisation of the reaction (Table 2) we found that, while the reaction did not run to completion, a reasonable amount of unreacted starting material could be recovered during chromatographic purification and then resubjected.

**Table 2.** Optimisation of Djakovitch's C3 arylation coupling

entry	solvent	X	Pd(OAc) <sub>2</sub> (mol%)	SM (%) <sup>a</sup>	yield (%) <sup>a</sup>
1	H <sub>2</sub> O	Br	5	27	8
2	<b>H<sub>2</sub>O</b>	I	<b>5</b>	-	<b>57</b>
3	PhMe	I	5	99	0
4	neat	I	5	99	0
5	H <sub>2</sub> O	I	5 <sup>b</sup>	34	43
6	H <sub>2</sub> O	I	10	62	25
7	H <sub>2</sub> O	I	10 <sup>c</sup>	0	52
8	H <sub>2</sub> O	I	5	45	41 <sup>d</sup>

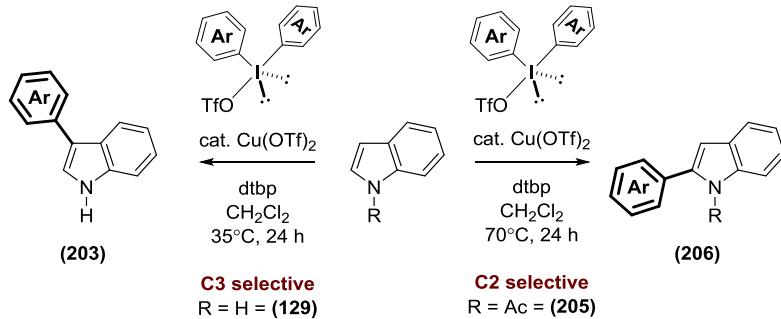
<sup>a</sup>Yield of isolated product. <sup>b</sup>Added in two portions of 2.5 mol% Pd over an 8 h interval. <sup>c</sup>Performed with 5 mol% Pd, then resubjected after an aqueous work-up with an additional 5 mol% Pd. <sup>d</sup>Performed on a 10 g scale.

The original conditions used by Djakovitch provided very little C3 arylated product (entry 1) but switching the aryl halide from a bromide to an iodide increased the yield to 57% (entry 2). Attempts to switch to a homogeneous reaction mixture with an organic solvent (entry 3) or remove solvents altogether (entry 4) showed no reactivity. Increased loading of the catalyst resulted in a drop in yield (entry 6). Finally the reaction was performed on a decagram-scale (entry 8) to give the desired C3 arylated product in a modest 41% yield with good recovery of unreacted starting material.

While this method served a valuable purpose to deliver material quickly at the beginning of the project, the yield was moderate at best and palladium is expensive when used on large scale. We were ultimately interested in employing the copper-catalysed C2 and C3 selective indole arylation methodology using diaryliodonium salts that had been developed in our group and had previously been used by Dr O'Hara to synthesise smaller quantities of (**183**) (Scheme 33).<sup>104</sup>

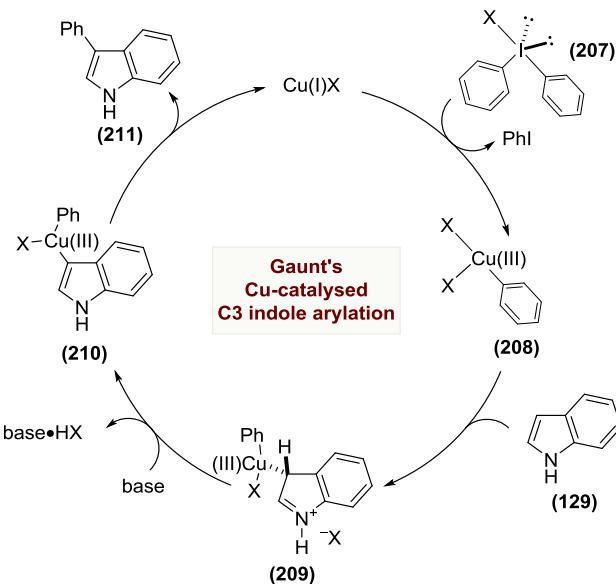
Performed with 5.0 mol% copper(II) triflate catalyst in dichloromethane under an ambient temperature of 35 °C for the C3 selective process (but a moderate 70 °C for the analogous C2

process), the reaction proceeds in good yields of 60–86% (but a more modest 39–57% for heteroarenes) and is thought to proceed via an electrophilic metalation process (Scheme 34).



**Scheme 33.** Gaunt's copper-catalysed C2 and C3 selective arylation of indoles.

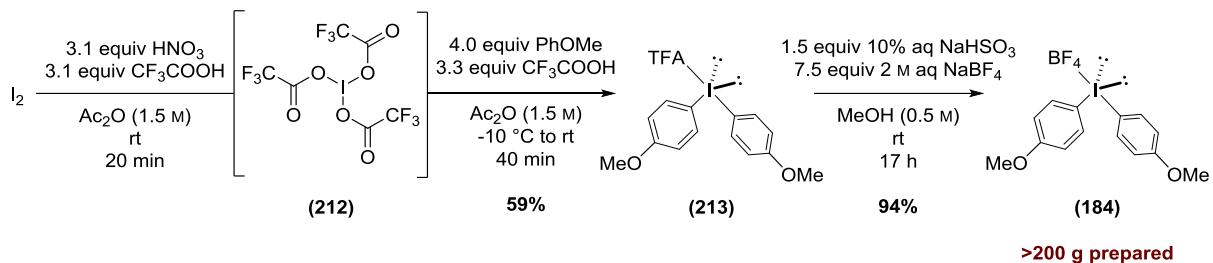
The biaryl iodine (III) reagent (**207**) undergoes oxidative addition with a copper(I) catalyst, which is proposed to form through the reduction of the copper(II) precatalyst by the indole. It is suggested that this forms a highly electrophilic copper(III) intermediate (**208**) which is readily attacked by the nucleophilic indole at the C3 position. Rearomatisation of (**209**) through abstraction of a proton by a base followed by reductive elimination of the final copper(III) intermediate (**210**) delivers the C3 arylated product (**211**) and reforms the copper(I) catalyst.



**Scheme 34.** Mechanism of Gaunt's copper-catalysed C2 and C3 selective arylation of indoles.

On large scale a substantial amount of bis(4-methoxyphenyl)iodonium tetrafluoroborate (**184**) was required to effect arylation at the C3 position of 4-bromoindole. This was readily synthesised via a one-pot preparation of tris(trifluoroacetoxy)iodonium (**212**) from iodine which was then treated in situ with anisole to undergo a double nucleophilic substitution at the iodine to afford

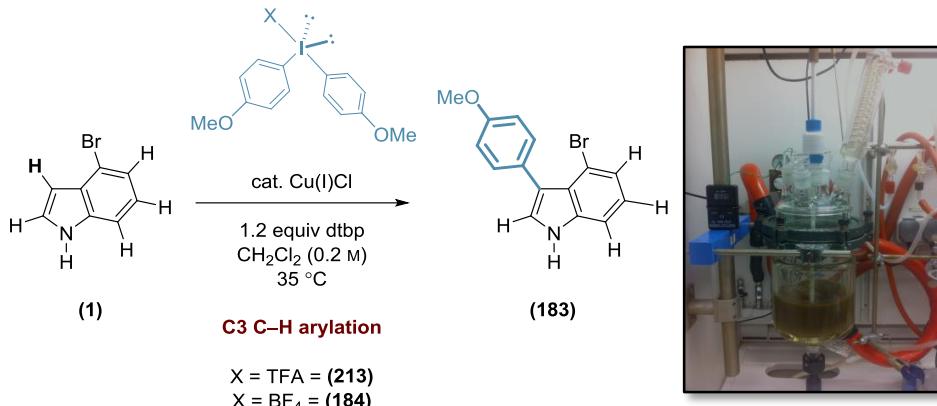
bis(4-methoxyphenyl)iodonium trifluoroacetate (**213**). This was then readily transformed to give the aforementioned iodonium tetrafluoroborate species through a simple anion metathesis.<sup>105</sup> The use of these and other related iodine(III) species is sometimes avoided due to concerns over their safety profile. However, experiments showed steady and controlled thermal decomposition of both species (**213**) and (**184**) with the latter producing an exotherm of only 821 J g<sup>-1</sup> between 225 to 229 °C, well above the temperatures used in our protocols. Furthermore, compound (**184**) was observed to be completely unreactive when subjected to a hammer test.



**Scheme 35.** Synthesis of the tetrafluoroborate iodonium salt.

Since the publication of Gaunt's C2/C3 indole arylation report, further work in our lab has demonstrated that copper(I) catalysts generally performed better with iodonium(III) species than the corresponding copper(II) catalyst.<sup>106-109</sup> With this in mind, we elected to start by using copper(I) chloride and we were delighted to observe that the reaction proceeded with only 5 mol% catalyst loading on a half-gram scale to give the C3 arylated product (**183**) in 67% yield using bis(4-methoxyphenyl)iodonium tetrafluoroborate (**184**) (Table 3, entry 1).

In an attempt to avoid the anion metathesis step we tried using bis(4-methoxyphenyl)iodonium trifluoroacetate (**213**) as the aryl source under identical conditions (entry 2). This resulted in a reduced yield and trace impurities that proved difficult to remove during purification of the product (**183**). Increasing the scale above one gram (entry 3) appeared to increase both the time required for complete consumption of the starting material and the isolated yield to 96 h and 90% respectively. With effective gram-scale conditions in hand we translated the reaction into a 5 L glass-lined reactor with an overhead stirrer at 300 rpm which, although not as high yielding as the initial gram-scale reaction, still provided good conversion (entry 5). Importantly, the expensive 2,6-di-*tert*-butylpyridine (dtbp) is easily recovered during chromatographic purification as it rapidly elutes ahead of the reaction mixture to be isolated and reused.

**Table 3.** Application of the copper catalysed C3 indole arylation.

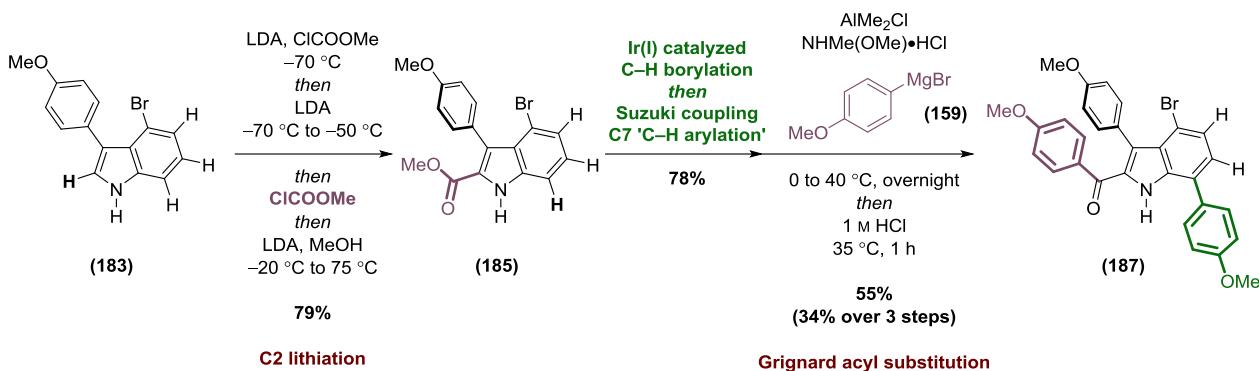
entry	scale <sup>a</sup>	$\text{Cu}(\text{I})\text{Cl}$ (mol%)	X	time (h)	yield (%) <sup>b</sup>
1	0.5 g	5	$\text{BF}_4^-$	18	67
2	0.3 g	5	TFA	18	38
3	1.4 g	5	$\text{BF}_4^-$	94	90
4	42 g	5	$\text{BF}_4^-$	48	68
5	42 g	10	$\text{BF}_4^-$	48	68

<sup>a</sup>Mass of product isolated. <sup>b</sup>Yield of isolated product.

A repeat of this reaction using 10 mol% of copper(I) catalyst showed no improvement in the yield or reaction time relative to an increase in catalyst loading (entry 5). The highly crystalline nature of the product also allowed for X-ray diffraction studies to definitively confirm substitution at the C3 position. The success of this step provided a great start to the synthesis and, combined with the material from the alternate method, brought hundreds of grams of material forward throughout the project.

### 3.1.2 Step 2. C2 Acylation

With the C3 position selectively arylated, our attention turned to find a catalytic method to acylate the C2 position of the indole (Table 4). Prior work by Dr Fionn O’Hara involved a multi-step one-pot sequence to install a traceless directing group to enable lithiation at the C2 position which was immediately quenched with methyl chloroformate. A subsequent transesterification with 4-methoxylphenyl magnesium bromide (**159**) provided the C2 acylated product (**187**) in a higher overall yield of 34% over 3 steps (including a C7 borylation/Suzuki) than the 19% afforded by a direct quench of the organolithium with 4-methoxybenzoyl chloride (**197**) on a similar substrate.



**Scheme 36.** Dr Fionn O'Hara's best method for functionalisation of the C2 position.

With the C3 position already substituted we reasoned that as regioselectivity would not be a problem. Furthermore, previously reported conditions that allow for C2 acylation in a single step required large excesses of both the corresponding acyl chloride and a Lewis acid (zinc(II) chloride).<sup>90,91</sup> We began our investigation by applying these conditions which turned out to be effective on our substrate giving a yield of 78% (Table 2, entry 1).

A green and operationally simple catalytic acylation protocol caught our attention and was applied using 4-methoxybenzoic acid and methanesulfonic anhydride (MSAA) in toluene under reflux for 48 h (entry 2).<sup>110</sup> Unfortunately only consumption of the starting material was observed without any formation of the desired product.

We then tried using stoichiometric amounts of a range of different Lewis acids with a small excess of 4-methoxybenzoyl chloride in nitromethane, a solvent well known to promote Friedel-Crafts reactions through high homogeneity and the formation of additional Lewis acid complexes to suppress isomerisation and disproportionation. The results ranged from no reactivity to a maximum of 56% which was achieved using titanium(IV) tetrachloride over 22 h (entry 5).

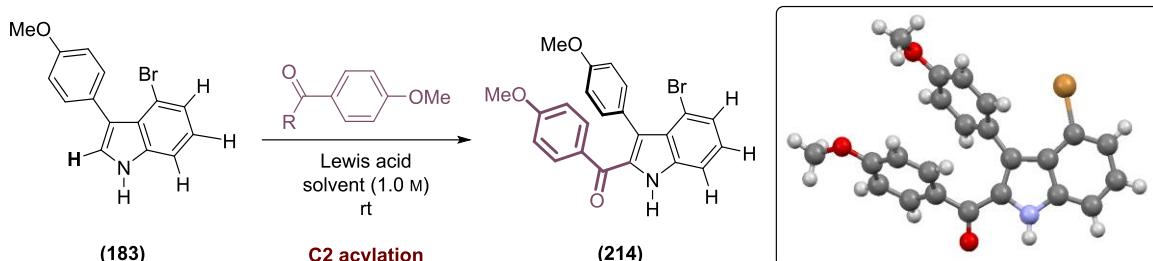
Another protocol we investigated was the use of 0.5 equivalents of zinc(II) oxide and an acyl chloride in solvent free conditions at room temperature.<sup>111</sup> After only 20 minutes the reaction yielded 49% of the desired product (entry 7). The heterogeneous nature of the reaction would prove difficult to translate to large scale and so the reaction was repeated using nitromethane as a solvent over 16 h to give a slightly improved yield of 67%.

Lastly, a report of the use of heavy-metal triflates to acylate furans, thiophenes and pyrroles prompted us to investigate whether this method would be applicable to indoles.<sup>112</sup> A quick screen of the scandium(III) (entry 9), ytterbium(III) (entry 10), gallium(III) (entry 11) and bismuth(III) (entry 12) triflates with 2 equivalents of 4-methoxylbenzoyl chloride proved the latter was

## Results and Discussion

marginally superior and gave an isolated yield of 73% with a 10 mol% loading in only 7 h. Reducing the amount of acyl chloride to 1.1 equivalents has almost no effect on the final yield (entry 13). Reduction of the catalyst loading to 5 mol% (entry 14) showed negligible decrease in yield but a further decrease to 1 mol% (entry 15) showed a small drop to 65%.

**Table 4:** Lewis acid optimisation of C2 indole Friedel-Crafts acylation.



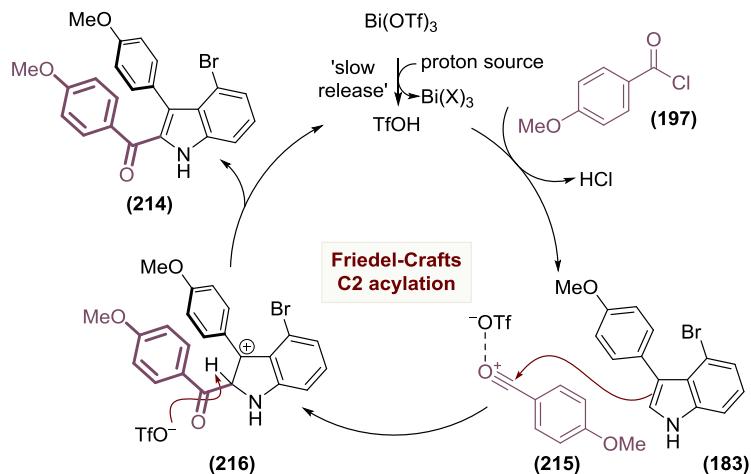
entry	Lewis acid (equiv)	R (equiv)	Solvent (M)	time (h)	SM (%) <sup>a,b</sup>	yield (%) <sup>a,b</sup>
1	ZnCl <sub>2</sub> (7)	Cl (7.5)	Et <sub>2</sub> O <sup>c</sup>	1	(0)	78 (77)
2 <sup>c</sup>	MSAA (0.8)	OH (1)	PhMe	42	(42)	0 (0)
3	AlCl <sub>3</sub> (1.2)	Cl (1.1)	MeNO <sub>2</sub>	22	(20)	28 (34)
4	FeCl <sub>3</sub> (1.2)	Cl (1.1)	MeNO <sub>2</sub>	22	(12)	26 (33)
5	TiCl <sub>4</sub> (1.2)	Cl (1.1)	MeNO <sub>2</sub>	22	(13)	56 (77)
6	Ti(O <i>i</i> Pr) <sub>4</sub> (1.2)	Cl (1.1)	MeNO <sub>2</sub>	22	(100)	0 (0)
7	ZnO (0.5)	Cl (2)	none	0.33	(50)	49 (50)
8	ZnO (0.5)	Cl (1.1)	MeNO <sub>2</sub>	16	(15)	67 (85)
9	Sc(OTf) <sub>3</sub> (0.1)	Cl (2)	MeNO <sub>2</sub>	18	(23)	52 (53)
10	Yt(OTf) <sub>3</sub> (0.1)	Cl (2)	MeNO <sub>2</sub>	18	(5)	47 (79)
11	Ga(OTf) <sub>3</sub> (0.1)	Cl (2)	MeNO <sub>2</sub>	20	(8)	67 (75)
12	Bi(OTf) <sub>3</sub> (0.1)	Cl (2)	MeNO <sub>2</sub>	18	(0)	73 (100)
13	Bi(OTf) <sub>3</sub> (0.1)	Cl (1.1)	MeNO <sub>2</sub>	7	(7)	72 (83)
14	Bi(OTf) <sub>3</sub> (0.05)	Cl (1.1)	MeNO <sub>2</sub>	24	(25)	69 (75)
15	Bi(OTf) <sub>3</sub> (0.01)	Cl (1.1)	MeNO <sub>2</sub>	24	(16)	65 (84)
16	TfOH (0.1)	Cl (2)	MeNO <sub>2</sub>	18	(11)	73 (87)
17	TfOH (0.1)	Cl (1.1)	MeNO <sub>2</sub>	23	(33)	47 (56)

<sup>a</sup>Methyl benzoate used as NMR standard. <sup>b</sup>Yield determined by NMR shown in parentheses. <sup>c</sup>Performed at 0.1 M and 110 °C.

Due to the increased yields afforded by the heavy-metal triflates when compared to the metal Lewis acids or triflic acid on their own, we postulated that this step is likely to work by activation

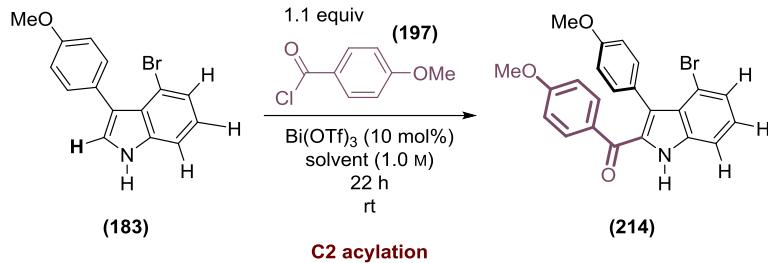
of the acyl chloride by both the bismuth triflate and triflic acid generated in situ. To substantiate these claims we performed the experiment by adding trifluoromethanesulfonic acid directly to the reaction mixture. When using 2 equivalents of acyl chloride (entry 16) the yield of 73% was comparable to the highest so far. However, on reducing the amount acyl chloride to 1.1 equivalents a significant drop in yield was observed (entry 17).

Following these observations we postulate a simple Friedel-Crafts acylation catalytic cycle (Scheme 37) whereby bismuth(III) trifluoromethanesulfonate acts as a Lewis acid and trifluoromethanesulfonic acid that is released by the hydrolysis of bismuth(III) triflate by trace water in the solvent and atmosphere also behaves as a Lewis acid. Either Lewis acid reacts with 4-methoxybenzoyl chloride (**197**) to generate a reactive acylium ion species (**215**) that is attacked by the nucleophilic indole (**183**) at the C2 position. Elimination of a proton affords the desired product (**214**) and regenerates the catalytic Lewis acid.



**Scheme 37.** Proposed mechanism for C2 acylation.

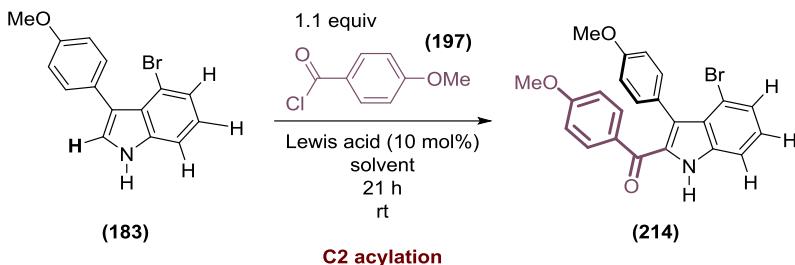
Using bismuth(III) triflate at a loading of 10 mol%, we opted to perform a solvent screen to see if further increases in yield were possible. Chlorinated solvents (Table 5, entries 1 and 2) showed moderate reactivity, but slightly lower yields than already achieved. Unusually, no reactivity was observed in tetrahydrofuran (entry 3), dimethylformamide (entry 4) or when using acetic acid as a solvent (entry 5). Hexane (entry 6) and acetonitrile (entry 7) gave competitive yields of 67% and 64% respectively, but the two best performing solvents were the highly polar nitromethane and propylene carbonate (entries 7 and 8) with yields of 72% and 81% respectively.

**Table 5:** Solvent optimisation of C2 indole Friedel-Crafts acylation.

entry	solvent	SM (%) <sup>a,b</sup>	yield (%) <sup>a,b</sup>
1	CH <sub>2</sub> Cl <sub>2</sub>	(23)	60 (59)
2	CCl <sub>4</sub>	(24)	58 (60)
3	THF	(100)	0 (0)
4	DMF	(100)	0 (0)
5	AcOH	(100)	0 (0)
6	hexane	(37)	67 (52)
7	MeCN	(9)	64 (85)
8	MeNO <sub>2</sub>	(7)	72 (83)
9	PC	(3)	81 (87)

<sup>a</sup>Methyl benzoate used as NMR standard. <sup>b</sup>Yield determined by NMR shown in parentheses.

For our final optimisation study, and in anticipation of the scale-up, the three best performing Lewis acids from Table 4 were screened them against our two best performing solvents from Table 5 on a 0.5 g scale. The isolated yields from the reactions using trifluoromethanesulfonic acid, gallium(III) trifluoromethanesulfonate and bismuth(III) trifluoromethanesulfonate were slightly higher in propylene carbonate (entries 1 to 3) than in nitromethane (entries 4 to 6). Bismuth(III) triflate was once again the highest performing Lewis acid and on initial scale up to 2 grams the yields in both solvents were identical (entries 7 and 8). As propylene carbonate proved more difficult to remove during purification as the scale was increased, nitromethane was selected as the optimal solvent.

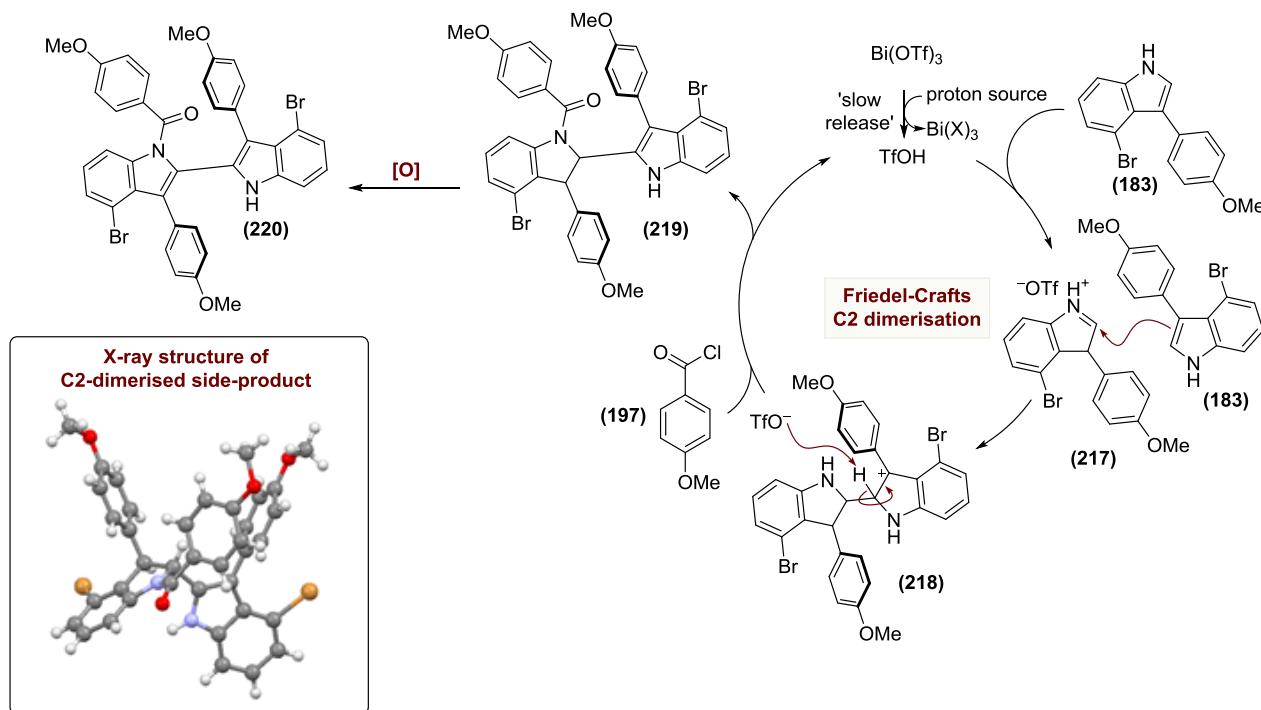
**Table 6:** Preliminary scale-up of C2 indole Friedel-Crafts acylation.

entry	Lewis acid	solvent	yield (%)
1	TfOH (10 mol%)	PC	31
2	Ga(OTf) <sub>3</sub> (10 mol%)	PC	65
3	Bi(OTf) <sub>3</sub> (10 mol%)	PC	77
4	TfOH (10 mol%)	MeNO <sub>2</sub>	32
5	Ga(OTf) <sub>3</sub> (10 mol%)	MeNO <sub>2</sub>	59
6	Bi(OTf) <sub>3</sub> (10 mol%)	MeNO <sub>2</sub>	71
7 <sup>a</sup>	Bi(OTf) <sub>3</sub> (10 mol%)	PC	64
8 <sup>a</sup>	Bi(OTf) <sub>3</sub> (10 mol%)	MeNO <sub>2</sub>	64

<sup>a</sup>Performed on 2 g scale.

At this point in our investigations we noticed that an as-yet unidentified side product was responsible for the mass balance of the reaction. We suspected that this side product could be the result of an indole dimerisation, an unwanted reaction that had been observed when working with indoles under acidic conditions in previous work from our lab.<sup>104</sup> During scale up of the reaction, crystals of sufficient quality were obtained that allowed us to use X-ray diffraction to determine the exact structure of species (**220**) (Scheme 38).

The mechanism of this dimerisation is thought to involve an acid-catalysed Friedel-Crafts dimerisation of the indole starting material (**183**). In the presence of acid, (**183**) forms an indolium species (**217**) that acts as an electrophile for the nucleophilic indole starting material (**183**). Loss of a proton from intermediate (**218**) still leaves a nucleophilic amine in the form of an indoline. The fact that X-ray studies show only one nitrogen undergoes *N*-acylation supports this mechanistic pathway and it is likely that the acylation of the indoline promotes the subsequent oxidation of (**219**) to give dimerised side-product (**220**). The loss of acyl chloride (**197**) to this side reaction not affect the conversion too greatly as the difference in yield is only negligible when larger quantities of the acyl chloride is used.

**Scheme 38.** X-ray crystal and proposed catalytic cycle of C2 dimerisation.

Just prior to scaling up the *N*-acylation reaction, we tried to address the dimerisation issue by dropwise addition of the indole to a mixture of 5 mol% bismuth(III) trifluoromethanesulfonate and 1.1 equivalents of acyl chloride in nitromethane. Unfortunately no improvement was observed as a result of this procedure.

**Table 7:** Large scale C2 indole Friedel-Crafts acylation.

**C2 acylation:**

entry	time (h)	scale (g)	Yield (%)
1	22	10	64
2	67	33	57 <sup>a</sup>

<sup>a</sup>Crystallised directly from crude material.

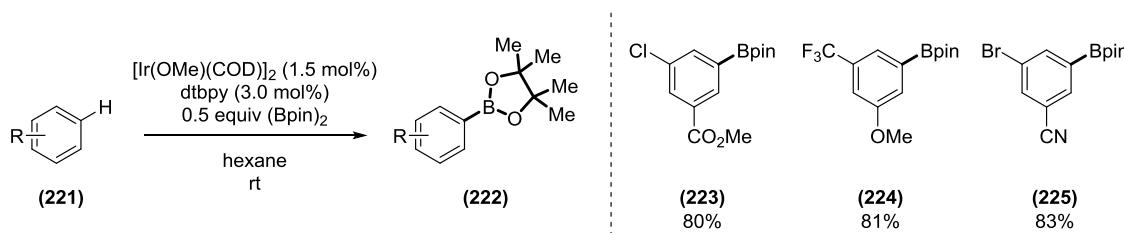
As the C2 acylation reaction was of a higher concentration than the C3 arylation and heating was not required, we were able to perform this step (Table 7) and all subsequent large scale reactions

in standard laboratory glassware. Increasing the scale of the reaction up to 10 g showed no deterioration in yield of (**214**) (entry 1). Although the product was highly crystalline, up until this point we were unable to use this property to avoid a difficult chromatographic purification. Fortunately, when the reaction was performed on 33 g scale, simple treatment of the crude mixture with excess 2 M KOH overnight to remove any remaining acyl chloride (**197**) through an aqueous work-up allowed for the direct crystallisation of the C2 acylated product from the crude mixture in a reasonable 57% yield (entry 2). The crystals obtained were analysed by X-ray crystallography thereby confirming the substitution pattern of the indole so far.

As with the previous step, the optimisation and scale-up of the C2 acylation reaction outlined in this section permitted approximately 150 grams of intermediate (**214**) to be synthesised. The synthesis so far was proving robust and material was in plentiful supply to optimise the next steps to gram scale.

### 3.1.3 Step 3. C7 Borylation and Suzuki Coupling

The first examples of the metal-catalysed C–H borylation of alkenes<sup>113,114</sup> and arenes<sup>115</sup> were reported in 1999 and 2000 by the groups of Hartwig and Smith. The resultant arylboronate esters formed in this process had already become a linchpin of modern synthetic chemistry due to their prevalent use in the Suzuki cross-coupling reaction and other related processes. Unusually, this reaction was predominantly controlled by sterics and afforded isomers that were hard to synthesise under electronic control.<sup>116</sup>

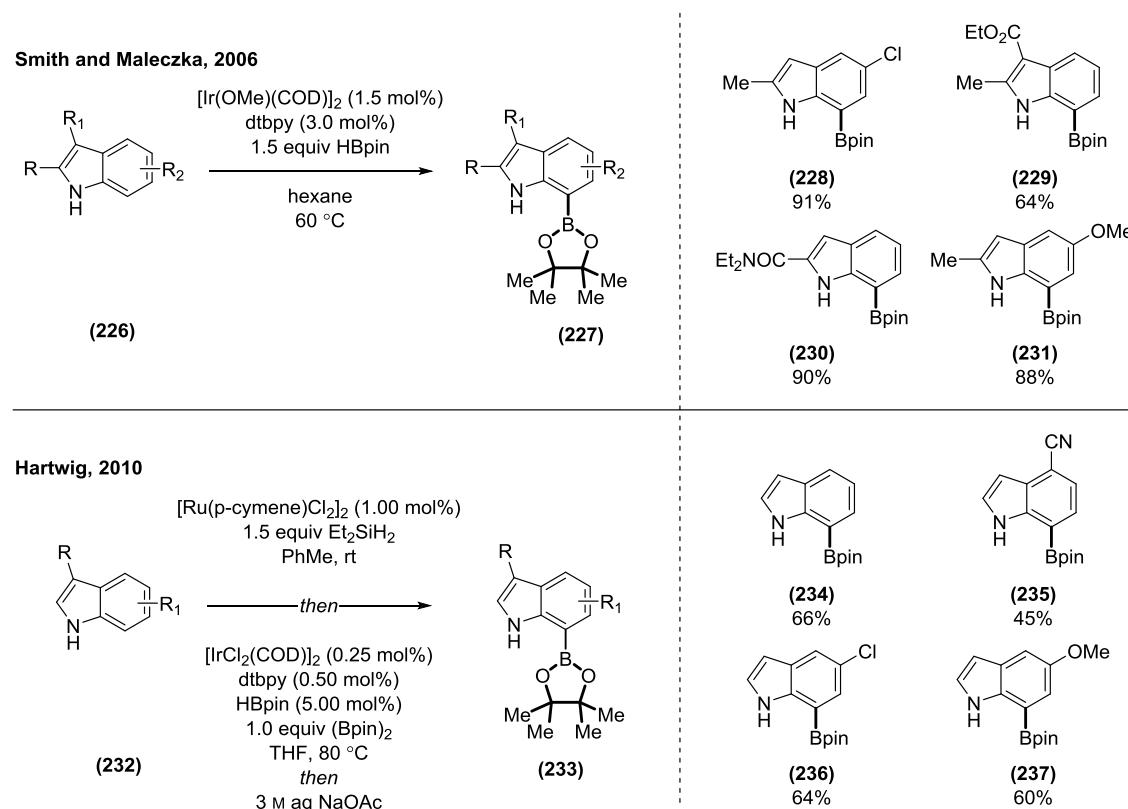


**Scheme 39.** Early C–H borylation of arenes by Hartwig with three examples to highlight steric specificity of the reaction.

One of the first examples of this using a viable catalytic system was reported by Hartwig in 2002 (Scheme 39).<sup>117</sup> The conditions transformed unfunctionalised arenes (**221**) into aryl boronic esters (**222**) and were exceptionally mild, high yielding and tolerant of a range of common functionality. However, we were keen to use the C–H borylation to functionalise the C7 position of indole, which is clearly not the least sterically hindered.

## Results and Discussion

Two important reports by Smith and Hartwig in 2006 and 2010 respectively detail the directed metal-catalysed C–H borylation of the C7 position of indole.<sup>118,119</sup> The first of these reports used a 1.5 mol% loading of an iridium dimer catalyst, 3.0 mol% of 4,4'-di-tert-butyl-2,2'-dipyridyl (dtbpy) ligand and pinacolborane as the boron source in hexane at 60 °C to transform 2,3-substituted indoles (**226**) into the corresponding 7-boronic ester indoles (**227**). Yields were typically very high (45–92%) and the conditions were tolerant of carbonyl, cyano and halogen functionality. As detailed in previous reports, the C2 position of indole is the most reactive towards C–H borylation and this must be blocked for the reaction to be C7 selective.



**Scheme 40.** Comparison of the two C7 indole borylation protocols.

The selectivity is thought to arise through co-ordination of the iridium catalyst to the indole nitrogen which guides it to the C7 position, overriding the usual steric selectivity that would likely result in a mixture of C5 and C6 borylated regioisomers.

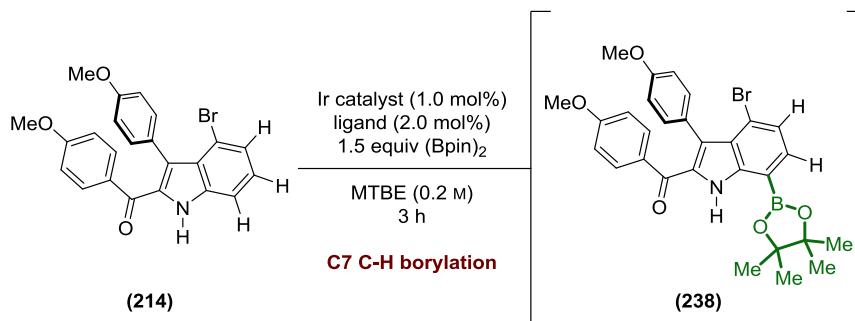
The latter of the two reports does not require initial substitution at the C2 position for C7 selectivity but instead requires the installation and removal of a traceless directing group on 3-substituted indoles (**232**) in a one-pot process to generate the corresponding 7-boronic ester indoles (**233**). Firstly, a ruthenium catalyst is used to install a diethylsilyl group on the indole nitrogen. After removal of the volatiles, the reaction is taken up in tetrahydrofuran with an

## Results and Discussion

iridium catalyst, 4,4'-di-*tert*-butyl-2,2'-dipyridyl (dtbpy) and 1 equivalent of bis(pinacolato)diboron. A catalytic amount of pinacolborane is added to assist with formation of the active catalyst and upon heating to 80 °C the borylation of the C7 position occurs, directed by the incumbent silyl protecting group. The volatiles are again removed and 3 M sodium acetate is added to facilitate removal of the silyl directing group. The length and complexity of this process, while useful, diminishes the yield significantly when compared to the previous example (44–66%).

As our substrate was already functionalised at the C2 position we opted to investigate the application of borylation conditions similar to those used by Smith (Table 8). As the complexity of the NMR spectrum increased greatly at this point, along with the generation of one or two side products, the reactions were readily followed by LCMS which allowed for easy identification of products through mass identification and qualitative comparison of reactions for optimisation. The mechanism of the iridium-catalysed C–H borylation has already been discussed as an example of an oxidative addition to a C–H bond in section 1.1.1.

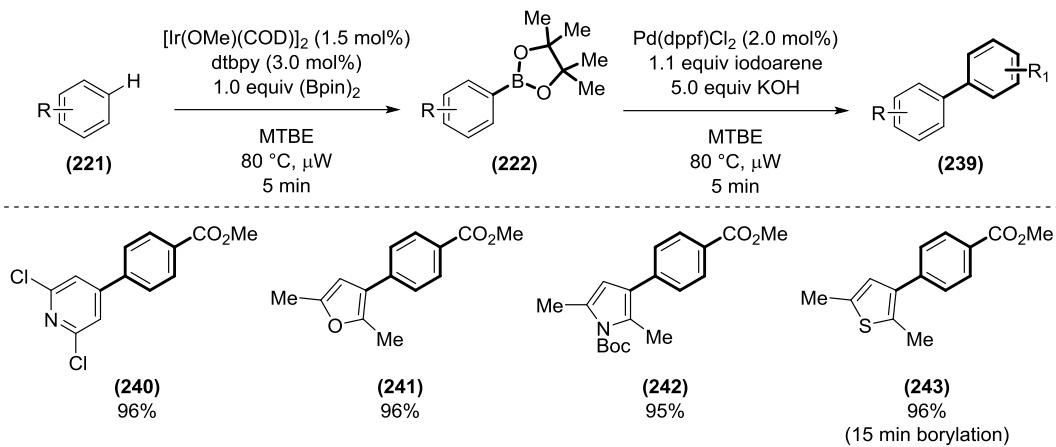
Initial results using 1.0 mol% commercially available (1,5-cyclooctadiene)(methoxy)iridium(I) and (1,5-cyclooctadiene)(chloro)iridium(I) dimer catalysts (entries 1 and 2) with 2.0 mol% of dtbpy ligand in methyl-*tert*-butyl ether at 125 °C showed significant formation of side-products with large amounts of unreacted starting material. As the iridium catalysts are known to be sensitive to gradual decomposition when stored on the bench, they were triturated under sonication with methanol in an attempt to remove soluble impurities. This proved successful as, after drying under high vacuum, both showed improved reactivity (entries 3 and 4). Although not many ligands are reported for the Ir-catalysed borylation, we tried using the other widely used ligand Me<sub>4</sub>phen (3,4,7,8-tetramethyl-1,10-phenanthroline).<sup>21,120</sup> However, no desired reactivity was observed and the methoxy iridium catalyst appeared to form single major side-product that was thought to be the hydrogenated phenone.

**Table 8:** Preliminary C7 iridium-catalysed borylation results.

entry	temp (°C)	catalyst	ligand	LCMS <sup>a</sup> 3 h		
				SM	SP	P
1 <sup>b</sup>	125	[IrCl(COD)] <sub>2</sub>	dtbpy	46	32	22
2 <sup>b</sup>	125	[IrOMe(COD)] <sub>2</sub>	dtbpy	75	21	4
3 <sup>c</sup>	125	[IrCl(COD)] <sub>2</sub>	dtbpy	32	44	24
4 <sup>c</sup>	125	[IrOMe(COD)] <sub>2</sub>	dtbpy	26	44	30
5	60–100	[IrCl(COD)] <sub>2</sub>	Me <sub>4</sub> phen	70	30 <sup>d</sup>	0
6	60–100	[IrOMe(COD)] <sub>2</sub>	Me <sub>4</sub> phen	96	4	0

<sup>a</sup>Used for qualitative analysis to compare spectrophotometer peak integrals of the starting material (SM), product (P) and side-products (SP). <sup>b</sup>Unpurified commercial catalyst was used. <sup>c</sup>Commercial catalyst washed with methanol and dried under high vacuum. <sup>d</sup>Identified as possible hydrogenation of the carbonyl group.

Given the limited success of these borylation reactions, we now sought to perform the subsequent Suzuki reaction in a single pot in order to conserve material. In addition to increased economy, we discovered that borylated indoles were difficult to purify as protodeboronation occurred readily during exposure to air or silica. Therefore a one-pot procedure would potentially maximise the yield over the two steps. We were further inspired by the increased reaction rate reported for a one-pot procedure under microwave conditions (Scheme 41), presumably due to the more efficient and uniform heating of the reaction mixture by microwave irradiation when compared to conventional heating.<sup>121</sup>



**Scheme 41.** Microwave-assisted one-pot C–H borylation/Suzuki coupling.

Early investigations into this microwave protocol were capricious (Table 9) and identification of the precise nature of the problem was challenging. We began by concentrating on the borylation step and using the (1,5-cyclooctadiene)(chloro)iridium(I) dimer catalyst and dtbpy ligand, the substrate was heated in methyl-*tert*-butyl ether in a microwave reactor. Intermittently, the yield, determined by LCMS, was quantitative but when repeated under exactly the same conditions the reaction would fail to convert any starting material or only show partial conversion in addition to side-product formation (entry 1).

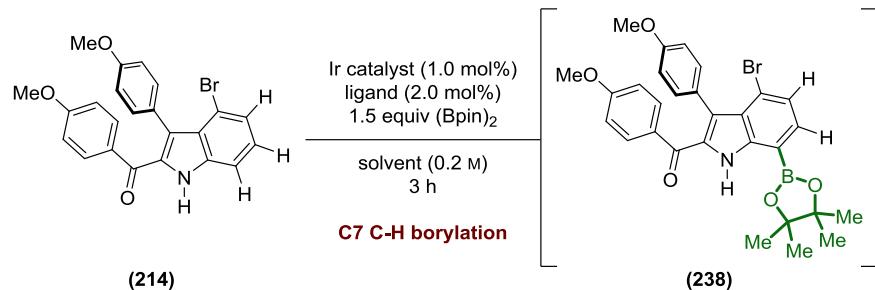
A number of avenues were explored to address the unreliability of this reaction. Firstly, attempts to use the Me4phen ligand failed again when using the microwave (entry 2), but this time no side-product formation was observed. Different catalyst or ligand loadings and pre-stirring for varying amounts of time to promote active catalyst formation before heating showed no discernible pattern and the addition of trace amounts of water also had no discernible effect on the outcome of the reaction. Likewise, meticulous purification of all the reagents provided no consistency in results.

Turning our attention to the microwave, a CEM Discover SP system, we found two distinct problems. Firstly, the microwave emitter was located slightly above the bottom of the vial meaning that small scale test reactions had likely received a lower dose of radiation from the emitter. Secondly, the design of the vials was such that an inert atmosphere was difficult to maintain. The microwave caps were composed of cardboard material and were only sealed to the vial when inserted into the microwave cavity where a screw mechanism held it firmly in place during the reaction.

We then began using a Biotage® Initiator microwave to overcome these problems. The caps for the vials used in this system are crimped on to give a fully sealed system and use

polytetrafluoroethylene (PTFE) that enables the easy insertion of a needle to evacuate and refill the vial with inert gas.

**Table 9:** Microwave C7 iridium-catalysed borylation.



entry	temp (°C)	catalyst (mol %)	ligand	solvent	LCMS <sup>a</sup>		
					SM	SP	P
1 <sup>b</sup>	90–125	1.0–5.0	dtbpy	MTBE	-	-	0–100
2 <sup>b</sup>	125	1.0	Me <sub>4</sub> phen	MTBE	100	0	0
3 <sup>c,d</sup>	90	1.0	dtbpy	MTBE	36	19	45
4 <sup>c,e</sup>	90	1.0	dtbpy	MTBE	0	0	100
5 <sup>f</sup>	90	1.5	dtbpy	THF	0	0	100

<sup>a</sup>Used for qualitative analysis to compare spectrophotometer peak integrals of the starting material (SM), product (P) and side-products (SP). <sup>b</sup>Performed in a CEM Discover SP microwave. <sup>c</sup>Performed in a Biotage Initiator microwave. <sup>d</sup>Performed in 1.1 mL in a 5 mL vial. <sup>e</sup>Performed in 2.2 mL in a 5 mL vial. <sup>f</sup>Performed on a 0.6 g scale.

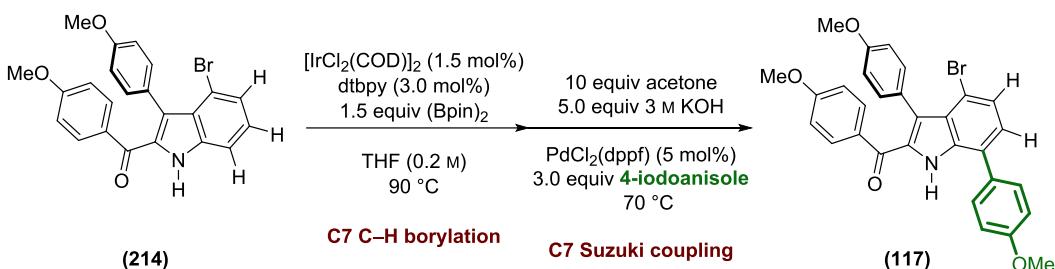
Greater success was achieved using the Biotage microwave, confirming our initial suspicions about the cause of the erratic results achieved in the CEM microwave. With the inert atmosphere assured we were able to see the effect of not having sufficient solvent for efficient absorption from the microwave emitter. Using 1.1 mL of solvent in a 5 mL vial gave incomplete conversion and side products (entry 3) but performing the reaction in 2.2 mL of solvent in the same sized vial (entry 4) gave quantitative conversion with a much higher reliability. We were also able to reduce the temperature to 90 °C at this point as the production of side-products seemed to be virtually eliminated without compromising the desired borylation reactivity. Unfortunately, although much improvement had been made so far, around one in four instances would still fail to react properly.

We identified the final problem as insolubility of the indole substrate in methyl *tert*-butyl ether at room temperature which, on the odd occasion, blocked the stir bar from moving while in the microwave which prevented the reaction from taking place. Switching the solvent to tetrahydrofuran, in which the substrate was highly soluble, led to a smooth reaction at 90 °C over

1 h to afford a maximum 600 mg of desired product with excellent reproducibility under microwave irradiation.

With the borylation now performing consistently, we turned our attention to the two remaining objectives; namely, performing the reaction on gram-scale and as a one-pot procedure with the subsequent Suzuki coupling (Table 10). Attempts to increase the reaction concentration with our optimal conditions to allow for more material to be processed in a single operation with the largest 20 mL vials were met with failure. The reaction would therefore have to be translated to conventional heating to circumvent the current limit on scale.

**Table 10:** One pot C7 iridium-catalysed borylation/Suzuki coupling.



entry	scale <sup>a</sup>	heating	time (borylation/Suzuki)	yield (%)
1 <sup>b</sup>	1.0 g	microwave	1.0 h / 0.5 h	54
2	3.0 g	thermal	24 h / N/A	0
3	6.0 g	thermal	1.5 h / 0.5 h	63

<sup>a</sup>Refers to amount of product submitted in a single operation. <sup>b</sup>Performed sixteen times consecutively with the same result.

The one-pot process proved versatile in the microwave (entry 1), consistently giving yields of around 54% with very little need to optimise the Suzuki conditions. The remaining mass balance is thought to be accounted for via protodeboronation and polymerisation side-reactions during the cross-coupling. The addition of 10 equivalents of acetone and slow addition of aqueous base avoid a potentially deleterious transfer hydrogenation reaction catalysed by the incumbent iridium catalyst. After hydrogen production ceased, the remaining aqueous base, catalyst and iodoarene could be added and heated to commence cross-coupling.

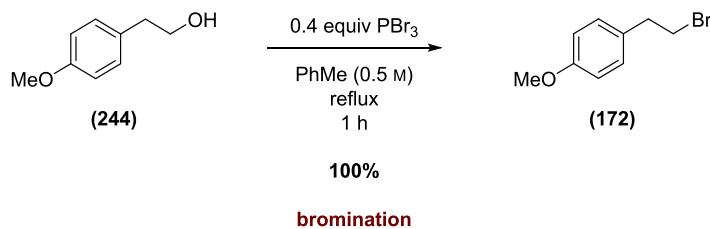
Although the Suzuki coupling with 4-iodoanisole is dominant to give good yields and up to 1 g could be processed every 1.5 h, it was time consuming to prepare and handle the material in separate batches as the microwave could only handle a single vial at once and this ultimately formed a large bottleneck for material throughput.

The first attempts to move our optimal conditions to conventional heating proved unsuccessful (entry 2). As the reaction solvent is super-heated under the microwave conditions (reactions performed at reflux temperature or below did not proceed) a large pressure vial was required. Fortunately, the pressure during the reaction never tended to exceed around 2 bar (as monitored by the microwave sensors) and so a basic pressure-resistant apparatus could be used. We began using nitrogen flushed thick borosilicate glass Ace pressure tubes with a PTFE ring seal immersed in a pre-heated oil bath. Disappointingly, our first attempt to achieve the one-pot procedure under these conditions suffered from lack of reactivity at the borylation stage.

From our previous experience in troubleshooting this step, we quickly determined that the large screw cap, like the large CEM vial cap before, made it difficult to perform the reaction under an inert atmosphere. By modifying the screw cap with an attachment that allowed secure connection to a Schlenk line and subsequent sealing for heating, reactivity was instantly restored and the reaction performance showed further improvement. Having increased the scale to 6 g using a 250 mL Ace round-bottomed flask, an isolated yield of 63% was obtained (entry 3). Unlike the initial scale-limited microwave assisted one-pot reaction, multiple instances could be performed at once to bring material forward with ease. Through many stages of practical problem solving, this step finally conformed to the aims set out at the start of the project.

### 3.1.4 Step 4. N-Alkylation

With the indole nitrogen having served its purpose as a directing group, we next performed the *N*-alkylation. The 2-(4-methoxy)phenethyl bromide (**172**) was commercially available, but too expensive for use in a gram-scale synthesis, particularly as it would be used in excess.



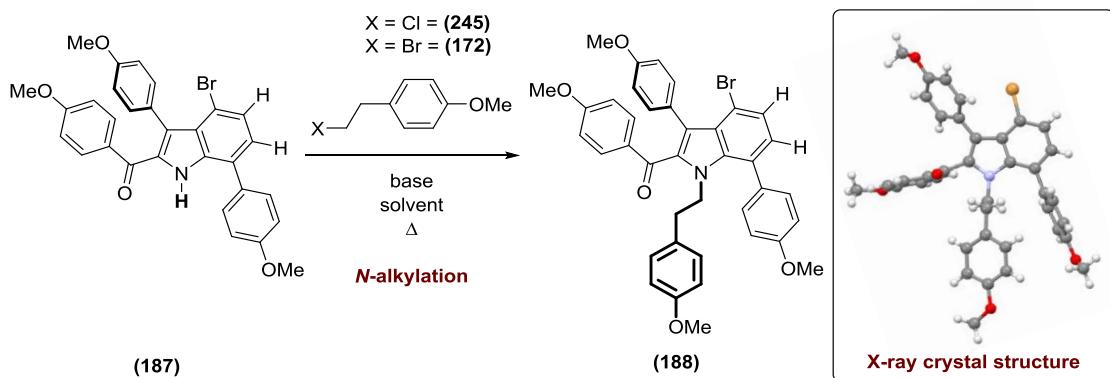
**Scheme 42.** Large-scale synthesis of 2-(4-methoxy)phenethyl bromide.

Fortunately, it could be readily synthesised in quantitative yield by reaction of 0.4 equivalents of phosphorus tribromide with the much cheaper 2-(4-methoxy)phenyl ethanol (**244**) (Scheme 42) without the need for chromatographic purification on a 50 g scale. A few batches of this reaction provided more than enough alkylating agent to optimise and bring material through this step of the synthesis (Table 11).

## Results and Discussion

Preliminary attempts to use the cheaper (4-methoxy)phenethyl chloride (**245**) alkylating reagent were unsuccessful when using potassium hydroxide in toluene at room temperature (entry 1) or when heated to 80 °C with a catalytic amount of potassium iodide to promote a Finkelstein reaction (entry 2). Although the iodide was likely formed, this was too unstable to the base and resulted in elimination to give the corresponding styrene without any trace of *N*-alkylation.

**Table 11:** *N*-alkylation optimisation and scale-up.



entry	temp (°C)	X (equiv)	base (equiv)	solvent	time (h)	yield (%)
1	rt	Cl (2.0)	KOH (5)	PhMe	1.0	0
2 <sup>a</sup>	80	Cl (2.0)	KOH (5)	PhMe	22	0
3 <sup>b</sup>	135	Br (3.5)	K <sub>2</sub> CO <sub>3</sub> (5)	MeCN	4.5	55
4	100	Br (5.0)	K <sub>2</sub> CO <sub>3</sub> (6)	DMF	30	91
5 <sup>c</sup>	100	Br (5.0)	K <sub>2</sub> CO <sub>3</sub> (7)	DMF	15	82

<sup>a</sup>Added a catalytic amount of KI. <sup>b</sup>Performed under microwave irradiation. <sup>c</sup>Performed on a 2 g scale.

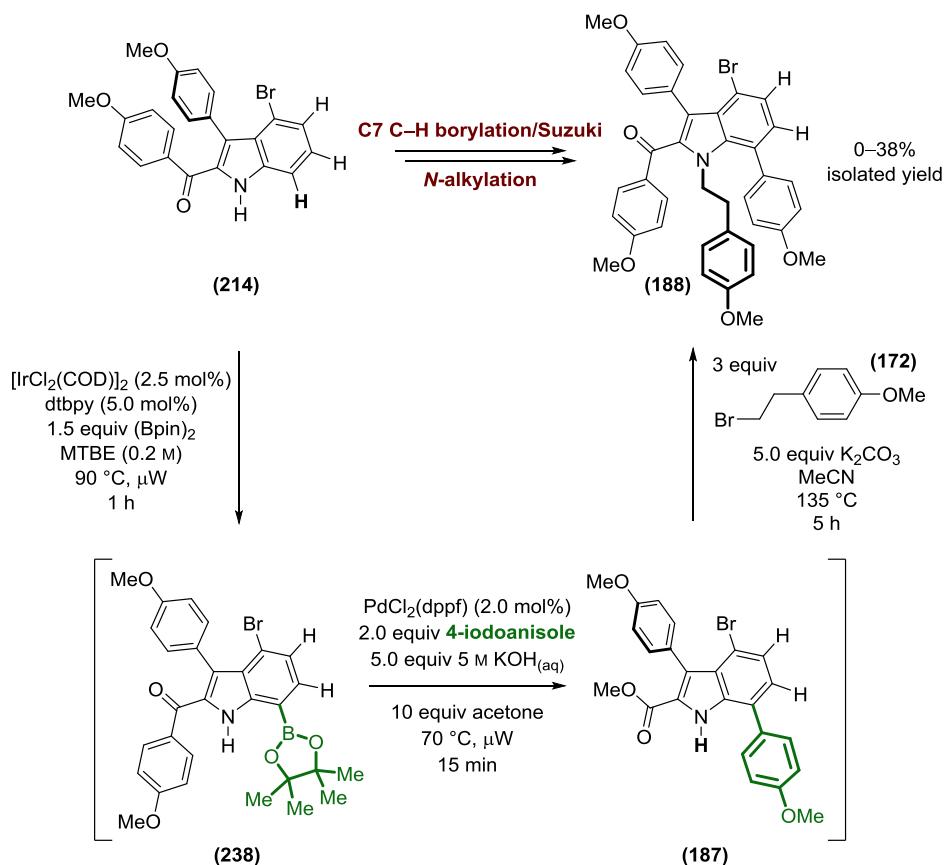
Using superheated acetonitrile in the microwave at 135 °C showed moderate reactivity with potassium carbonate as the base to give (**188**) in an isolated yield of 55% after reacting for 4.5 h. The bromide alkylating reagent (**172**) displayed higher reactivity than the chloride (**245**) and was less prone to elimination to the styrene. However, elimination was still an issue and 5 equivalents of (**172**) were required to bring the yield within an acceptable range.

Further experimentation determined that the heterogeneous nature of the reaction mixture was likely responsible for the erratic differences in the yields obtained. Performing the reaction in an oil bath with conventional heating allowed for monitoring of the stirring rate which needed to be sufficient to keep a uniform distribution of the heterogeneous base.

Further optimisation determined that *N,N*-dimethylformamide (entry 4) was a better solvent as it partially dissolved the base and did not require a pressure tube as it was performed at 100 °C,

well below the solvent's boiling point. A vastly improved yield of isolated (**188**) was obtained using 5 equivalents of (**172**) alkylating reagent on a sub-gram scale. Finally, performing the alkylation on a 2 gram scale delivered the *N*-alkylated product (**188**) in an 83% yield. Presumably, the yield is slightly lower due the difficulty in maintaining a uniform heterogeneous reaction mixture in a larger vessel.

During the course of investigating the previous two steps, we decided to try telescoping the crude material of the C7 functionalised indole directly into the *N*-alkylation reaction (Scheme 42). Unfortunately, even when reactivity was observed in each step, the maximum overall isolated yield obtained was 38% (62% per step over 2 steps) which was lower than performing the steps separately. Furthermore, the material was not completely pure as it was difficult to separate the increased number of side products as a result of the telescoped sequence.



**Scheme 43.** Telescoped C7 borylation/Suzuki and N-alkylation sequence.

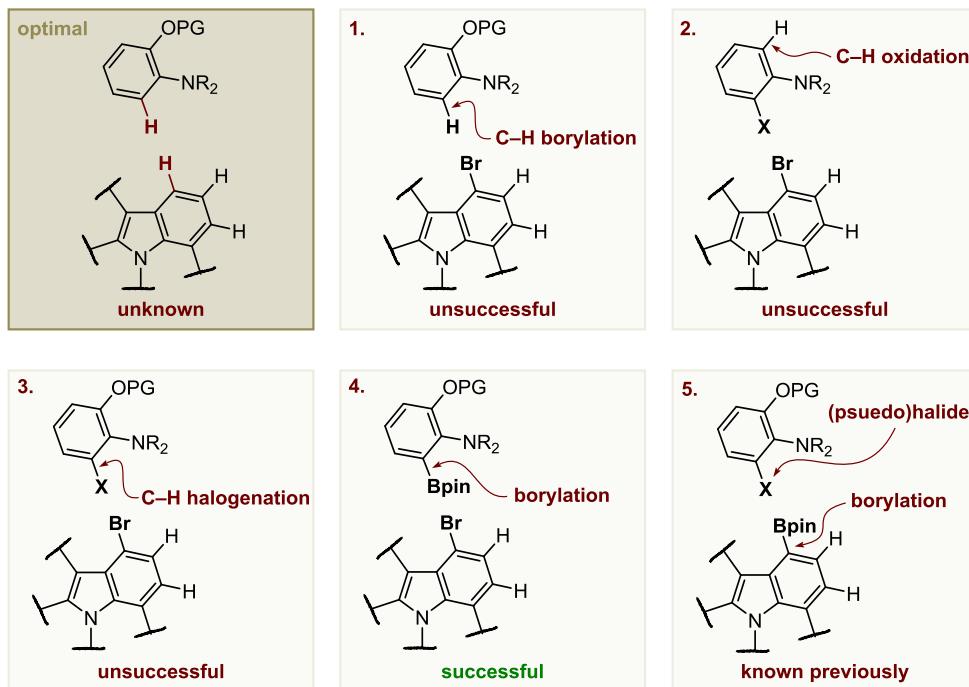
With the *N*-alkylated product (**188**) now in hand, we began to examine substitution at the C4 and C5 positions of the indole. There would be an inherent link between the aryl substrate used in the cross-coupling at the C4 position and the following C–H amination at the C5 position, as the *ortho*-amino moiety on the arene would be key to the reaction. This meant a number of arenes would

need to be synthesised to explore the possibility of performing these two steps one after the other. The following sections give detailed accounts of attempted syntheses, borylations and manipulations of 1,2,3-trisubstituted arenes to give an effective synthetic route to complete the pyrrolo[2,3-c]carbazole core of dictyodendrin B.

### 3.1.5 C4 Functionalisation

#### Overview

Under optimal conditions the C4 functionalisation of the indole core would be achieved by a direct C–H coupling with the desired arene (Scheme 44). As we began our synthesis with an indole that was pre-functionalised at the C4 position, our first priority was to perform a C–H functionalisation on the arene coupling partner. Although not performed directly on the indole fragment, it would increase the overall number of C–H functionalisation reactions in the total synthesis and afford 1,2,3-trisubstituted arenes from the less expensive and more readily available 1,2-disubstituted arenes. In particular, we envisaged that this C–H functionalisation would set up a subsequent one-pot Suzuki coupling to give the desired penta-substituted indole product.



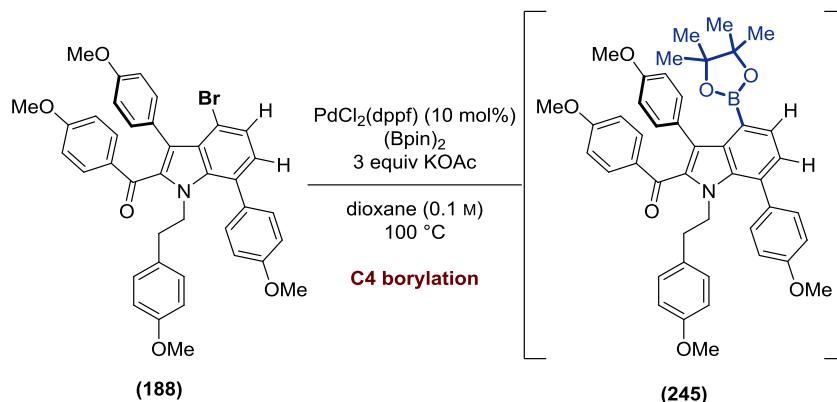
**Scheme 44.** Different approaches for the C4 arene coupling in order of priority.

The C–H functionalisation of this arene would involve either a C–H borylation, C–H oxidation or C–H halogenation of the corresponding 1,2-disubstituted arene. A C–H amination of a 1,3-disubstituted arene was excluded due to the impracticality of such a sterically demanding

transformation and lack of precedence in the literature. Our next priority was to borylate the arene, still removing a step from the longest linear sequence and preventing any loss of the main substrate in the borylation reaction. Our final priority was to continue borylating the 4-bromoindole fragment (as performed previously) and find a suitable 1,2,3-trisubstituted aryl (pseudo)halide coupling partner to continue the synthesis.

### Main fragment C4 borylation

To cross-couple aryl (pseudo)halides at the C4 position before we had developed a successful protocol for an alternative method, we used a similar set of conditions to that of Tokuyama *et al.* to borylate the main fragment (Table 12) allowing for the cross coupling of arenes that would permit us to further explore the desired C–H amination reaction at the C5 position. Using  $\text{PdCl}_2(\text{dppf})$  at a loading of 10 mol% with 3 equivalents of potassium acetate in dioxane at 100 °C we observed good progress of the reaction at 6 h (entry 1). The reaction proceeded smoothly to give complete conversion of the starting material to the boronic ester after 17 h (entry 2). While attempting to lower the quantity of the dimer reagent bis(pinacolato)diboron used, we still achieved complete conversion at 1.1 equivalents (entry 3) but starting material still remained when this was further reduced to 0.6 equivalents (entry 4)

**Table 12.** Miyaura borylation.

entry	time (h)	(Bpin) <sub>2</sub> (equiv)	LCMS <sup>a</sup>	
			SM	P
1	6	2.5	62	38
2	17	2.5	0	100
3	21	1.1	0	100
4	21	0.6	39	61

<sup>a</sup>Used for qualitative analysis to compare spectrophotometer peak integrals of the starting material (SM) and product (P).

The resulting boronic ester was then used *in situ* to develop one-pot Suzuki processes with various 1,2,3 trisubstituted aryl halides as in our hands, and as reported by Dr Fionn O'Hara, the boronic ester product (**245**) is either unstable to chromatography or decomposes on the bench. It could never be isolated in a high yield or purity relative to the amount detected by NMR assay in the crude reaction mixture immediately after the reaction was complete. As this was the least desired route of those discussed, we then investigated the other possibilities in ascending order of preference, starting with attempts to perform C–H functionalisation to synthesise the 1,2,3-trisubstituted aryl halides.

#### Attempted synthesis of 1,2,3-trisubstituted aryl halides by C–H functionalisation.

As discussed previously, it was deemed preferable for the aryl fragment to undergo borylation, rather than the main substrate, prior to the Suzuki coupling. This was simply because, while protodehalogenation of the C4 position did not appear to occur, protodeboronation was a major problem and it would be more efficient and less costly to sacrifice excess arene over the course of the coupling.

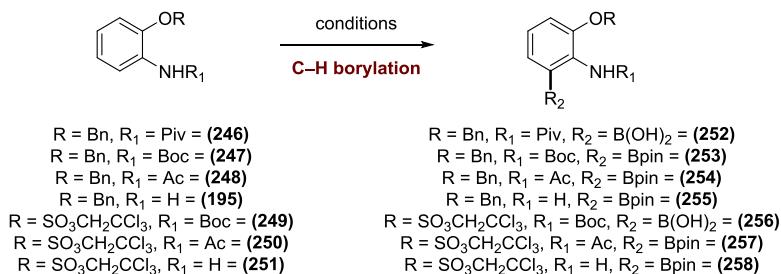
The preliminary work towards this focused on accomplishing an *ortho* C–H borylation. This was performed by Dr Robert H. Snell and is presented below (Table 13). This began by probing *ortho*-

## Results and Discussion

lithiation followed by a quench with trimethyl borate as a quick, albeit stoichiometric, route to access a boronic acid. Employing over 2 equivalents of *s*BuLi with *N*-pivaloyl (**246**) (entry 1) and *N*-Boc (**249**) (entry 2) arenes provided no evidence of borylation after quenching. A repeat of the latter conditions with 4 equivalents of tetramethylethylenediamine (TMEDA), known to form more reactive clusters of organolithium reagents, also met with failure (entry 3). Finally, the use of *t*BuLi under similar conditions (entry 4) appeared to give only elimination of hydrochloric acid from the trichloroethyl protecting group to afford the related dichlorovinyl sulfate group.

Dr Snell then explored the possibility of an *ortho*-acetanilide directed palladium-catalysed C–H borylation.<sup>122</sup> Treatment of the corresponding trichloroethylsulfate (**250**) (entry 5) and benzyl (**248**) (entry 6) protected acetanilide substrates with 5 mol% palladium(II) acetate, 2 equivalents of bis(pinacolato)diboron and benzoquinone in the presence of *p*-toluenesulfonic acid stirred in trifluorotoluene, at 30 and 60 °C respectively, afforded no trace of the borylated product. Exposure of the same two acetanilide substrates to a similar set of conditions used by Yu<sup>123</sup> on *N*-arylbenzamide also gave no desired product (entries 7 and 8).

**Table 13.** Dr Snell's attempted C–H borylation of 1,2-disubstituted arenes.



entry <sup>a</sup>	R	R <sub>1</sub>	R <sub>2</sub>	conditions	yield (%) <sup>b</sup>
1	Bn	Piv	B(OH) <sub>2</sub>	2.1 equiv <i>s</i> BuLi, 3.8 equiv B(OMe) <sub>3</sub> , THF (0.24 M), –35 °C to –78 °C to rt, 3 h.	0
2	SO <sub>3</sub> CH <sub>2</sub> CCl <sub>3</sub>	Boc	B(OH) <sub>2</sub>	2.5 equiv <i>s</i> BuLi, 4 equiv B(OMe) <sub>3</sub> , THF (0.12 M), –78 °C to rt.	0
3	SO <sub>3</sub> CH <sub>2</sub> CCl <sub>3</sub>	Boc	B(OH) <sub>2</sub>	2.5 equiv <i>s</i> BuLi, 4 equiv TMEDA, 4 equiv B(OMe) <sub>3</sub> , THF (0.12 M), –78 °C to rt.	0
4	SO <sub>3</sub> CH <sub>2</sub> CCl <sub>3</sub>	Boc	B(OH) <sub>2</sub>	3.5 equiv <i>t</i> BuLi, 4 equiv B(OMe) <sub>3</sub> , THF (0.12 M), –78 °C to rt.	0
5	SO <sub>3</sub> CH <sub>2</sub> CCl <sub>3</sub>	Ac	Bpin	Pd(OAc) <sub>2</sub> (5.0 mol%), 2 equiv (Bpin) <sub>2</sub> , 2 equiv benzoquinone, 0.33 equiv <i>p</i> TsOH (12% in AcOH), PhCF <sub>3</sub> (0.77 M), 30 °C, 16 h.	0
6	Bn	Ac	Bpin	Pd(OAc) <sub>2</sub> (5.0 mol%), 2 equiv (Bpin) <sub>2</sub> , 2 equiv benzoquinone, 0.33 equiv <i>p</i> TsOH (12% in AcOH), PhCF <sub>3</sub> (0.77 M), 60 °C, 8 h.	0

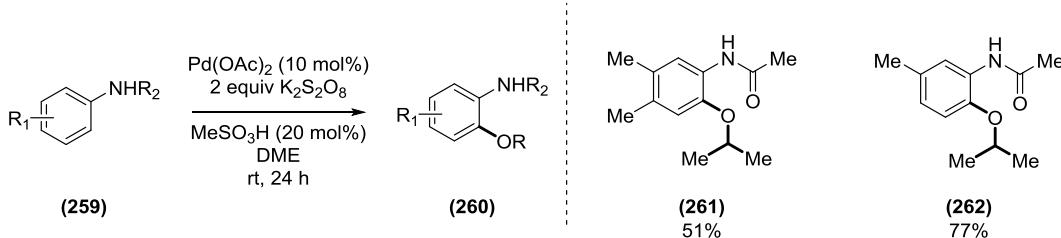
**Table 13.** Dr Snell's attempted C–H borylation of 1,2-disubstituted arenes.

7	SO <sub>3</sub> CH <sub>2</sub> CCl <sub>3</sub>	Ac	Bpin	Pd(OAc) <sub>2</sub> (1.0 mol%), 2 equiv (Bpin) <sub>2</sub> , 2 equiv K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> , 1.5 equiv TsONa, MeCN (0.1 M), 80 °C, 10 days.	0	
8	Bn	Ac	Bpin	Pd(OAc) <sub>2</sub> (10 mol%), 2 equiv (Bpin) <sub>2</sub> , 2 equiv K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> , 1.5 equiv TsONa, MeCN (0.14 M), 80 °C, 16 h.	0	
9	SO <sub>3</sub> CH <sub>2</sub> CCl <sub>3</sub>	Ac	Bpin	[IrCl(COD)] <sub>2</sub> (1.0 mol%), dtbpy (2.0 mol%), 1.5 equiv (Bpin) <sub>2</sub> , MTBE (0.23 M), 80 °C, 30 min, μW.	0	
10	SO <sub>3</sub> CH <sub>2</sub> CCl <sub>3</sub>	Ac	Bpin	[IrOMe(COD)] <sub>2</sub> (2.0 mol%), dtbpy (4.0 mol%), 2.0 equiv (Bpin) <sub>2</sub> , 0.2 equiv 0.2 HBpin, MTBE (0.5 M), 50 °C, 16 h.	0	
11	Bn	Boc	Bpin	[IrOMe(COD)] <sub>2</sub> (2.0 mol%), dtbpy (4.0 mol%), 2.0 equiv (Bpin) <sub>2</sub> , 0.2 equiv 0.2 HBpin, MTBE (0.5 M), 50 °C, 16 h.	0	
12	SO <sub>3</sub> CH <sub>2</sub> CCl <sub>3</sub>	H	Bpin	[IrOMe(COD)] <sub>2</sub> (2.0 mol%), Me <sub>4</sub> phen (4.0 mol%), 2.0 equiv (Bpin) <sub>2</sub> , THF (0.2 M), 80 °C, 4 h.	0	
13	Bn	H	Bpin	[IrOMe(COD)] <sub>2</sub> (2.0 mol%), Me <sub>4</sub> phen (4.0 mol%), 2.0 equiv (Bpin) <sub>2</sub> , THF (0.17 M), 80 °C, 1.5 h.	0	

<sup>a</sup>Work in this table was performed by Dr Robert H. Snell <sup>b</sup>Yield of isolated product.

Finally, in the hope of observing directing group control as opposed steric control, the iridium-catalysed borylation was employed. Using relatively standard conditions, as seen earlier in this report, no borylation of the *ortho*-trichloroethylsulfate acetanilide substrate (**250**) was observed with (entry 9) and without (entry 10) the addition of 0.2 equivalents of pinacolborane to promote active catalyst formation and turnover. Exposure of *O*-benzyl protected *N*-Boc arene (**247**) to conditions with pinacolborane was also unsuccessful. Switching the ligand from dtbpy to Me<sub>4</sub>phen to attempt borylation with *ortho*-trichloroethylsulfate (**251**) (entry 12) and -benzyloxy (**195**) (entry 13) anilines was also met with disappointment as no traces of product were found.

As the nitrogen moiety was required to be in the 2-position in all instances to allow for the C5 amination reaction in the main sequence, this left us with the possibility of instead performing a C–H oxidation to give the desired 1,2,3-trisubstituted aryl halides. Taking three 1,2-*N*-acetyl aryl halides (Table 14) the possibility of an *ortho* C–H isopropoxylation<sup>124</sup> was explored using Wang's *ortho*-alkoxylation of acetanilides (Scheme 45).

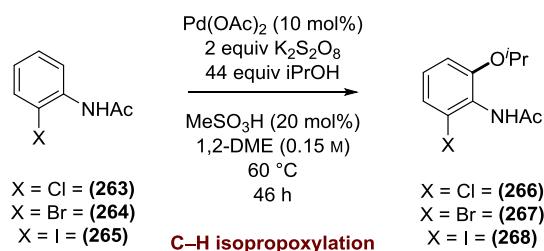


**Scheme 45.** Wang's *ortho*-alkoxylation of anilides illustrated with two of the most sterically demanding substrates.

This was chosen in particular as *N*-acetyl groups are known to undergo C–H amination reactions and, if that were also successful, we thought it may be possible to use the *N*-acetyl group for a third time to direct the final substitution at the C6 position of the indole by co-ordinating a metal catalyst towards the position to facilitate a direct C–H functionalisation.

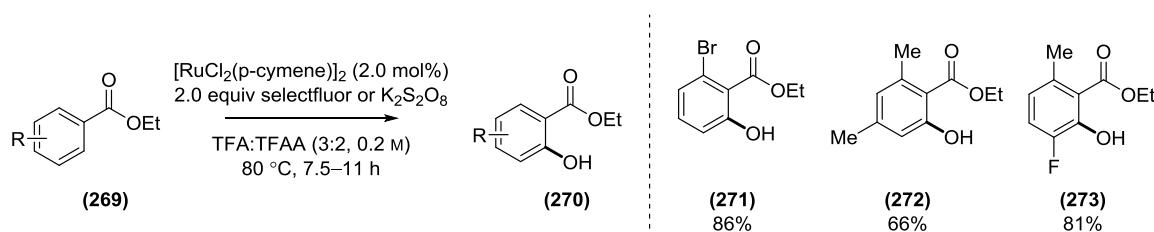
Use of both 2-chloroacetanilide (**263**) (entry 1) and 2-iodoacetanilide (**265**) (entry 3) showed no reactivity with palladium(II) acetate (10 mol%), two equivalents of potassium persulfate and a large excess of isopropanol heated to 60 °C in 1,2-dimethoxyethane for nearly two days. However, 2-bromoacetanilide (**264**) (entry 2) showed an initial hit for the mass of desired product, but attempts to isolate this yielded nothing but starting material.

**Table 14.** C–H isopropoxylation.



entry	X	yield (%)
1	Cl	0
2	Br	trace
3	I	0

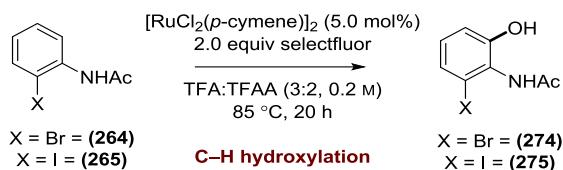
These results were unsurprising as the report did not include any examples of successful *ortho*-alkoxylation on substrates already containing an *ortho*-substituent. With an isopropyl group providing a large steric demand, we wondered whether a direct C–H hydroxylation would provide greater chances of success. The resulting phenol could then be protected with any suitable protecting group of our choice giving increased flexibility in the arene synthesis.



**Scheme 46.** Rao's *ortho*-hydroxylation of esters illustrated with some selected sterically challenging examples.

Our attention was drawn to a procedure developed by Rao *et al.* that, although using esters as the directing group, was one of very few reports at the time where *ortho*-substituted arenes gave excellent yields to afford tri- and tetra-substituted products (Scheme 46).<sup>125</sup> While we did not expect an acetanilide directing group to provide identical results from the outset, we hoped to at least detect some reactivity that we could further optimise to generate larger quantities of material.

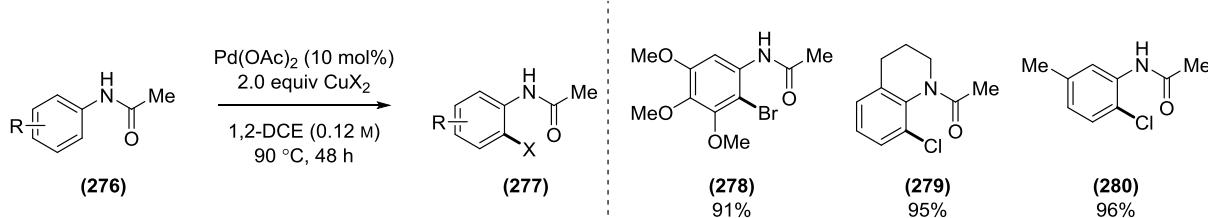
**Table 15.** Attempted C-H hydroxylation.



entry	X	yield (%)
1	Br	0
2	I	0

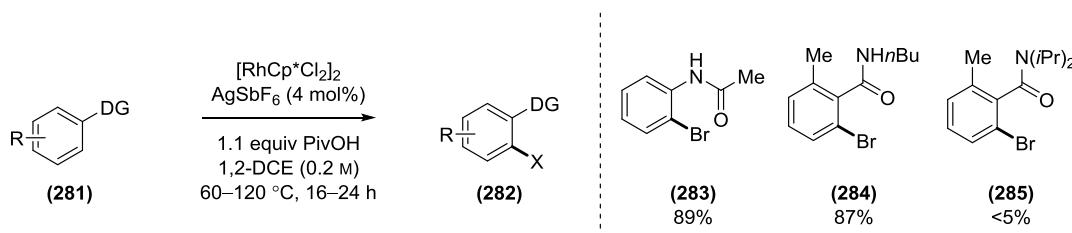
Applying the literature conditions (Table 15) with a ruthenium catalyst (using a slightly higher loading of 5.0 mol%) and two equivalents of Selectfluor® stirring in a mixture of trifluoroacetic acid and trifluoroacetic anhydride at 85 °C for 20 hours gave only undesired deacylation of the starting materials (**264**) and (**265**) and unidentified side product formation (entries 1 and 2).

With little success in our efforts to synthesise a 1,2,3-trisubstituted aryl halide by oxidation of a 1,2-*N*-acetyl aryl halide, we instead turned our attention towards the final possibility of using a C-H functionalisation which was a C-H halogenation of selected substrates previously used in our attempts towards a C-H borylation. We continued to use an acetanilide substrate for the reasons already outlined above and opted to use a benzyl protecting group on the phenol as it would likely prove straightforward to remove by hydrogenation in the final deprotection sequence.



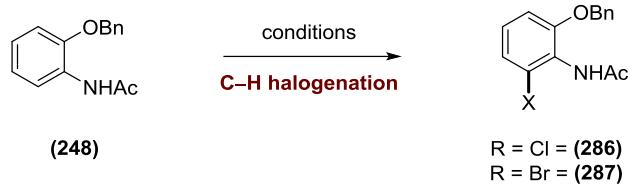
**Scheme 47.** Shi's *ortho*-halogenation of acetanilides illustrated with some selected sterically challenging examples.

The first protocol we considered was an *ortho*-halogenation by Shi *et al.* that provided two examples using sterically congested substrates that gave excellent yields of (278) and (279).<sup>126</sup> Using palladium(II) acetate (5 mol%), 2 equivalents of the respective copper(II) halide and copper(II) acetate stirring in 1,2-dichloroethane at 90 °C for nearly two days gave only trace detection of the desired chloride product (Table 16, entry 1) and no trace of the bromide product (entry 2).



**Scheme 48.** Glorius' versatile *ortho*-halogenation using a variety of directing groups illustrated with some selected sterically challenging examples.

We then set about using a more recent catalytic *ortho*-halogenation method (Scheme 48) by Glorius *et al.* that proved very versatile with respect to directing group compatibility. Although the acetanilide directing group showed no reactivity for iodination in their report, a yield of 89% was achieved for bromination. Furthermore, it showed some promise in the synthesis of 1,2,3-trisubstituted arenes as with an *ortho*-substituted *N*-butyl anilide a yield of 87% of (**284**) was achieved. However, with an *ortho*-substituted *N*-diisopropyl anilide the yield dropped to below 5%.

**Table 16.** Attempted C–H *ortho*-halogenation of *N*-(2-(benzyloxy)phenyl)acetamide.

entry	X	conditions	yield (%)
1	Cl	Pd(OAc) <sub>2</sub> (5.0 mol%), 2 equiv Cu(OAc) <sub>2</sub> , 2 equiv CuCl <sub>2</sub> , 1,2-DCE (0.12 M), 90 °C, 42.5 h.	traces
2	Br	Pd(OAc) <sub>2</sub> (5.0 mol%), 2 equiv Cu(OAc) <sub>2</sub> , 2 equiv CuBr <sub>2</sub> , 1,2-DCE (0.12 M), 90 °C, 42.5 h	0
3	Br	[RhCp*Cl <sub>2</sub> ] <sub>2</sub> (2.5 mol%), AgSbF <sub>6</sub> (10 mol%), 1.1 equiv PivOH, 1.5 equiv NBS, 1,2-DCE (0.2 M), 60 °C, 16.5 h.	74 (mixture of products)

Using the same rhodium catalyst (2.5 mol%), catalytic quantities of silver(I) hexafluoroantimonate with 1.1 equivalents of pivalic acid and 1.5 equivalents of *N*-bromosuccinimide stirring in 1,2-dichloroethane at 60 °C for 16.5 h complete conversion of the starting material (248) was observed (entry 3). Upon analysis, a mixture of what appeared to be two major products had formed in approximately equal amounts. This was likely a mixture of mono- and di-brominated products which were promptly subjected to chromatographic purification. However, due to almost identical retention times they could not be separated for further analysis of regioselectivity to confirm whether catalyst-controlled *ortho* substitution had indeed occurred to afford (287).

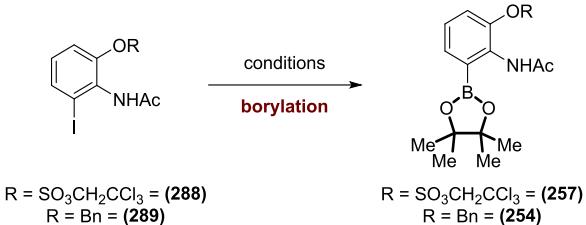
In most examples of directed *ortho*-functionalisation, both positions next to the directing group are almost always unfunctionalised. In each report, exposure to the reaction conditions typically results in only one of the positions being substituted. The observed lack of any major di-substitution is a possible indicator that the newly introduced steric bulk from the mono-functionalisation prevents the directing group from re-aligning in the plane of the ring to allow for another substitution. The consistent lack of reactivity witnessed during our attempts at *ortho* C–H functionalisation of a range of 1,2-disubstituted arenes is likely to be for the same reason. We therefore turned our attention towards trying to borylate the 1,2,3-trisubstituted aryl (pseudo)halides already in hand.

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**Attempted borylation of 1,2,3-trisubstituted aryl (pseudo)halides**

Submission of 2-acetamido-3-iodophenyl (2,2,2-trichloroethyl) sulfate (**288**) to standard Miyaura borylation conditions using 10 mol% [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), bis(pinacolato)diboron and potassium acetate in toluene under microwave conditions for 30 min (entry 1) and in dimethylsulfoxide with conventional heating for 20 h (entry 2) yielded none of the desired corresponding boronic ester (**257**). Further experimentation using pinacolborane as the boron source (entry 3) or with Buchwald's CyJohnPhos (**290**) (2-biphenyl)dicyclohexylphosphine) ligand<sup>127</sup> (entry 4) gave no trace of desired product either.

With no progress so far using the sulfate substrate (**288**), *N*-(2-(benzyloxy)-6-iodophenyl)acetamide (**289**) was subjected to a couple of borylation conditions. Despite being sterically and functional group tolerant, an unusual borylation reaction employing 1.5 equivalents of (dimethylphenylsilyl)boronic acid pinacol ester and potassium methoxide in 1,2-dimethoxyethane at ambient temperature, as reported by Ito<sup>128</sup>, failed to yield the corresponding boronic ester (**254**). Lastly, a copper(I) iodide catalysed borylation<sup>129</sup> using a tri-*n*-butylphosphine ligand, 1.5 equivalents of bis(pinacolato)diboron and potassium *tert*-butoxide at room temperature did not yield any trace of the desired borylated product after 19 h.

**Table 17:** Attempted borylation of *N*-acetyl iodoarenes.

entry	R	conditions	yield (%) <sup>c</sup>
1 <sup>a</sup>	$\text{SO}_3\text{CH}_2\text{CCl}_3$	PdCl <sub>2</sub> (dppf) (10 mol%), 1.2 equiv (Bpin) <sub>2</sub> , 3 equiv KOAc, PhMe (0.1 M), 100 °C, μW, 30 min.	0
2 <sup>a</sup>	$\text{SO}_3\text{CH}_2\text{CCl}_3$	PdCl <sub>2</sub> (dppf) (10 mol%), 1.1 equiv (Bpin) <sub>2</sub> , 3 equiv KOAc, DMSO (0.1 M), 95 °C, 20 h.	0
3 <sup>a</sup>	$\text{SO}_3\text{CH}_2\text{CCl}_3$	PdCl <sub>2</sub> (dppf) (10 mol%), 1.1 equiv HBpin, 3 equiv Et <sub>3</sub> N, dioxane (0.1 M), 100 °C, 3.0 h.	0
4 <sup>a</sup>	$\text{SO}_3\text{CH}_2\text{CCl}_3$	Pd(OAc) <sub>2</sub> (5.0 mol%), CyJohnPhos ( <b>290</b> ) (20 mol%) 3.0 equiv HBpin, 4 equiv Et <sub>3</sub> N, dioxane (0.4 M), 105 °C, 16 h.	0
5 <sup>b</sup>	Bn	1.5 equiv PhMe <sub>2</sub> SiBpin, 1.2 equiv KOMe, 1,2-DME (0.2 M), 30–60 °C, 16 h.	0
6 <sup>b</sup>	Bn	CuI (10 mol%), <i>n</i> Bu <sub>3</sub> P (13 mol%), 1.5 equiv (Bpin) <sub>2</sub> , 1.5 equiv K <sup>t</sup> OBu, THF (0.1 M), rt, 19 h.	0

<sup>a</sup>Performed by Dr Robert H. Snell. <sup>b</sup>Performed by Andrew K. Pitts. <sup>c</sup>Yield of isolated product.

We speculated that, if the adjacent *N*-acetyl group is preventing reactivity, perhaps we would have more success using an aryl substrate with a different nitrogen-derived moiety. As the nitro was readily accessible, and we hoped that a Cadogan-type C5 ring-closure may be possible after the C4 Suzuki coupling, we opted to investigate the borylation of a range of (pseudo)halide nitroarenes (Table 18).

We began our study with the substrate 1-(benzyloxy)-3-chloro-2-nitrobenzene (**291**). Palladium-catalysed borylation conditions with SPhos (**196**) (entry 1) and XPhos (**297**) (entry 2) as ligands gave traces of the product mass by LCMS but we were unable to isolate any product after chromatography.<sup>130</sup> The same substrate (entry 3) along with its bromide analogue (**292**) (entry 4) were subjected to 5 mol% dichlorobis(trimethylphosphine)nickel(II), 1.1 equivalents bis(pinacolato)boron, 2 equivalents caesium fluoride and trimethyl(2,2,2-trifluoroethoxy)silane as an additive in dioxane at 100 °C for 24 hours to yield nothing but unreacted starting material.

Continuing the investigation of the aryl bromide (**292**), attempted lithiation with *n*BuLi followed by a quench with boric acid (entry 5) or triisopropyl borate (entry 6) showed no trace of (**296**) with only decomposition of the starting material into unidentified side-products. Wondering whether

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organolithium reagents were simply too harsh and may in fact be undergoing counterproductive reactions with the nitro group, we turned to the slightly softer organometallic isopropylmagnesium chloride to see if metal-halogen exchange could still be achieved (entry 7). Unfortunately, this was still not the case, although significantly less decomposition of the starting material was observed.

Submission of the aryl bromide (**292**) to standard Miyaura borylation conditions using 10 mol% [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), 3 equivalents bis(pinacolato)-diboron and 3 equivalents potassium acetate in dioxane at 90 °C for 16 hours (entry 8) failed to yield any boronic ester (**295**). However, the first indication of a successful borylation was realised when using virtually identical Miyaura borylation conditions with 3-(benzyloxy)-2-nitrophenyl trifluoromethanesulfonate (**293**) (entry 9), which was successfully converted into the corresponding boronic ester (**295**), albeit in only 7% isolated yield. However, further attempts at borylating the trifluoromethanesulfonate substrate (**293**) with palladium-catalysed<sup>131</sup> and copper-catalysed<sup>129</sup> methods failed (entries 10 and 11).

Subjection of the complimentary 3-(benzyloxy)-2-nitrophenyl 4-methylbenzenesulfonate (**294**) substrate to the same Miyaura borylation conditions as the trifluoromethanesulfonate did not present any of the desired boronic ester (**295**) (entry 12). Repeating the reaction with the purportedly more active BrettPhos-Pd-G3 (**299**) pre-catalyst (entry 13), no discernible traces of borylation were found.

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**Table 18.** Attempted borylation of selected benzyloxy (pseudo)halide nitroarenes.

entry	X	R	conditions	yield (%) <sup>a</sup>
1	Cl	Bpin	Pd(OAc) <sub>2</sub> (3.0 mol), SPhos ( <b>196</b> ) (7.5 mol%), 3 equiv (BPin) <sub>2</sub> , 3 equiv K <sub>3</sub> PO <sub>4</sub> , dioxane (0.5 M), rt to 50 °C., 24 h.	0
2	Cl	Bpin	Pd <sub>2</sub> dba <sub>3</sub> (2.0 mol%), XPhos ( <b>297</b> ) (4.0 mol %), 3.0 equiv (BPin) <sub>2</sub> , 3.0 equiv KOAc, dioxane (0.5 M), 110 °C, 94 h.	0
3	Cl	Bpin	NiCl <sub>2</sub> (PMe <sub>3</sub> ) <sub>2</sub> (5.0 mol%), 1.1 equiv (Bpin) <sub>2</sub> , 2.0 equiv CsF, 2.1 equiv, TMSOCH <sub>2</sub> CF <sub>3</sub> , dioxane (1.0 M), 100 °C,	0
4	Br	Bpin	24 h.	0
5	Br	B(OH) <sub>2</sub>	1.2 equiv <i>n</i> BuLi, 1.25 equiv B(OH) <sub>3</sub> , THF (0.3 M), -78 °C, 1 h.	0
6	Br	B(OH) <sub>2</sub>	1.2 equiv <i>n</i> BuLi, 1.5 equiv B(O <i>i</i> Pr) <sub>3</sub> , THF (0.3 M), -78 °C, 2.5 h.	0
7	Br	B(OH) <sub>2</sub>	1.2 equiv <i>i</i> PrMgCl , 1.1 equiv B(OMe) <sub>3</sub> , THF (0.3 M) , 0 °C, 2 h.	0
8	Br	Bpin	PdCl <sub>2</sub> (dppf) (10 mol%), 3 equiv (Bpin) <sub>2</sub> , 3 equiv KOAc, dioxane (0.1 M), 90 °C, 16 h	0
9	OTf	Bpin	PdCl <sub>2</sub> (dppf) (10 mol%), 2 equiv (Bpin) <sub>2</sub> , 2 equiv KOAc, dioxane (0.1 M), 95 °C, 16 h	7
10	OTf	Bpin	Pd(OAc) <sub>2</sub> (5 mol%), DPEPhos ( <b>298</b> ) (10 mol%), 1.5 equiv HBpin, 2.0 equiv Et <sub>3</sub> N, dioxane (0.25 M), 60 °C, 20 h	0
11	OTf	Bpin	CuI (10 mol%), <i>n</i> Bu <sub>3</sub> P (13 mol%), 1.5 equiv (Bpin) <sub>2</sub> , 1.5 equiv KO <i>t</i> Bu, THF (0.1 M), rt, 19 h.	0
12	OTs	Bpin	PdCl <sub>2</sub> (dppf) (10 mol%), 3 equiv (Bpin) <sub>2</sub> , 4 equiv KOAc, dioxane (0.1 M), 95 °C, 16 h.	0
13	OTs	Bpin	BrettPhos-Pd-G3 ( <b>299</b> ), 3 equiv (Bpin) <sub>2</sub> , 3 equiv KOAc, dioxane (0.1 M), 90 °C, 15 h.	0

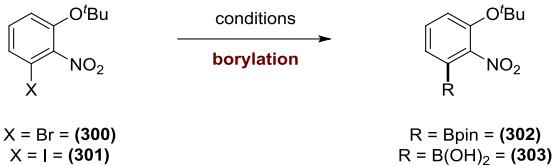
<sup>a</sup>Yield of isolated product.

For reasons that will become apparent later in this report, we also worked on the borylation of of *tert*-butyl protected substrates (**300**) and (**301**) (Table 19). Further success was attained through the application of Miyaura borylation conditions to 1-bromo-3-(*tert*-butoxy)-2-nitrobenzene (**300**), giving the corresponding boronic ester in an isolated yield of 20% (entry 1). This was the most

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significant amount of 1,2,3-trisubstituted aryl boronic ester synthesised so far and indicated that the *tert*-butoxy and nitro groups were perhaps more tolerant of the required reaction conditions.

**Table 19.** Attempted borylation of selected *tert*-butoxy (pseudo)halide nitroarenes.

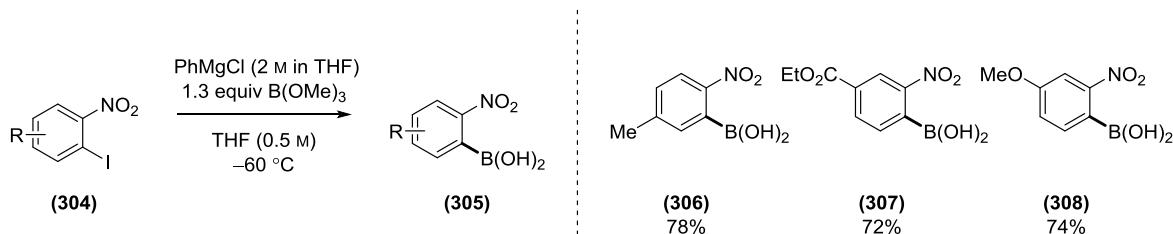


entry	X	R	conditions	yield (%) <sup>c</sup>
1	Br	Bpin	PdCl <sub>2</sub> (dpff) (5.0 mol%), 1.5 equiv (Bpin) <sub>2</sub> , 2.5 equiv KOAc, DMSO (0.2 M), 80 °C, 24 h.	20
2	Br	B(OH) <sub>2</sub>	XPhos-Pd-G2 ( <b>192</b> ) (2.0 mol%), XPhos ( <b>297</b> ) (4.0 mol%), 3 equiv (B(OH) <sub>2</sub> ) <sub>2</sub> , 3 equiv KOAc, EtOH (0.1 M), 80 °C, 23 h.	0
3	Br	B(OH) <sub>2</sub>	3.0 equiv <i>n</i> BuLi, 2 equiv B(O <i>i</i> Pr) <sub>3</sub> , THF, (0.1 M), -78 °C., 45 min.	47
4	Br	Bpin	2.0 equiv <i>n</i> BuLi, 2 equiv BpinO <i>i</i> Pr, THF (0.2 M), -78 °C, 3.5 h.	0
5	Br	B(OH) <sub>2</sub>	1.2 equiv <i>i</i> PrMgCl•LiCl, 1.3 equiv B(OMe) <sub>3</sub> , THF (0.3 M), -78 °C, 3 h.	0
6 <sup>a</sup>	I	B(OH) <sub>2</sub>	1.1 equiv PhMgCl, 1.3 equiv B(OMe) <sub>3</sub> , THF (0.5 M), -60 °C, 1 h.	82
7 <sup>b</sup>	I	Bpin	1.1 equiv PhMgCl, 1.3 equiv BpinO <i>i</i> Pr, THF (0.5 M), -60 °C, 1 h.	91

<sup>a</sup>Performed on a 0.5 gram scale <sup>b</sup>Performed three times on 3.5 gram scale. <sup>c</sup>Yield of isolated product.

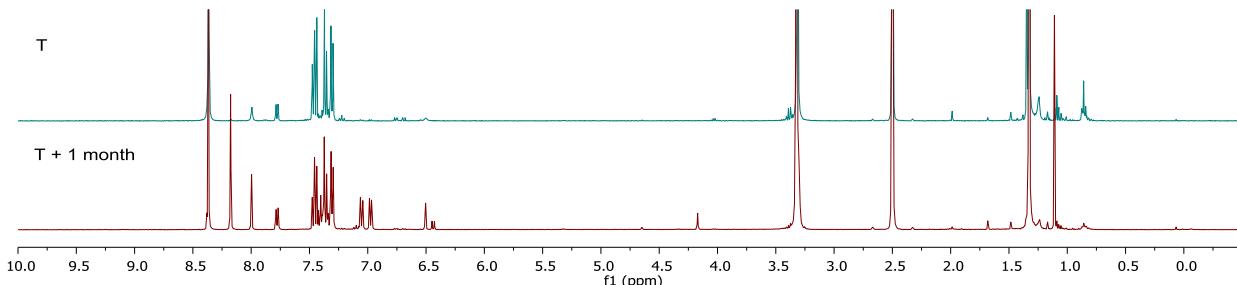
We were interested in synthesising the related boronic acid as, when compared to the ester, they are more reactive when used in Suzuki couplings. Using methodology developed by Molander<sup>132</sup>, aryl bromide (**300**) was subjected to a 2 mol% XPhos-Pd-G2 (**192**) pre-catalyst, 4 mol% XPhos (**297**), 3 equivalents of bis-boronic acid and 3 equivalents of potassium acetate in ethanol at 80 °C for 23 hours (entry 2). However, only protodebromination of the arene was observed.

Lithium-halogen exchange with 3.0 equiv *n*-butyl lithium, quenched by *in situ* triisopropyl borate, granted some improvement to give aryl boronic acid (**303**) in an isolated yield of 47% (entry 3). Attempts to quench with isopropoxyboronic acid pinacol ester (entry 4) or use the softer organometallic isopropylmagnesium chloride lithium chloride (“Turbo Grignard”) did not yield any borylated product.



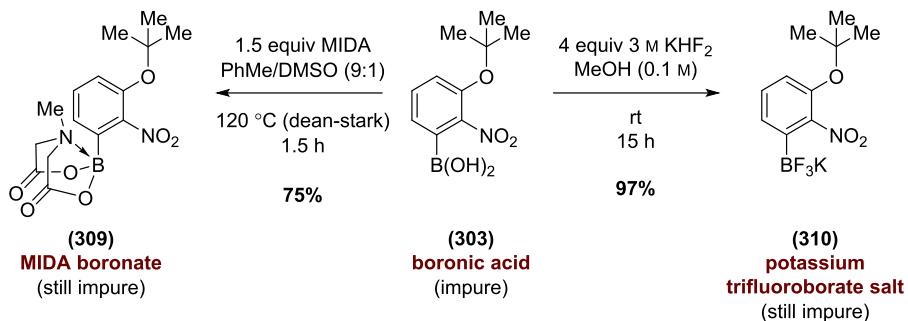
**Scheme 49.** Yu's synthesis of *ortho*-nitrophenylboronic acids.

A report by Knochel demonstrated magnesium-iodine exchange *ortho* to a nitro group was to facilitate the high-yielding functionalisation of nitroarenes.<sup>133</sup> A subsequent report by Yu (Scheme 49) then utilised this to generate a simple method for the synthesis of *ortho*-nitrophenylboronic acids.<sup>134</sup> While the starting material to synthesise the related 1-(*tert*-butoxy)-3-iodo-2-nitrobenzene (**301**) was more expensive, it was still available in gram quantities that would be sufficient to perform the remainder of the synthesis on a suitably large scale.



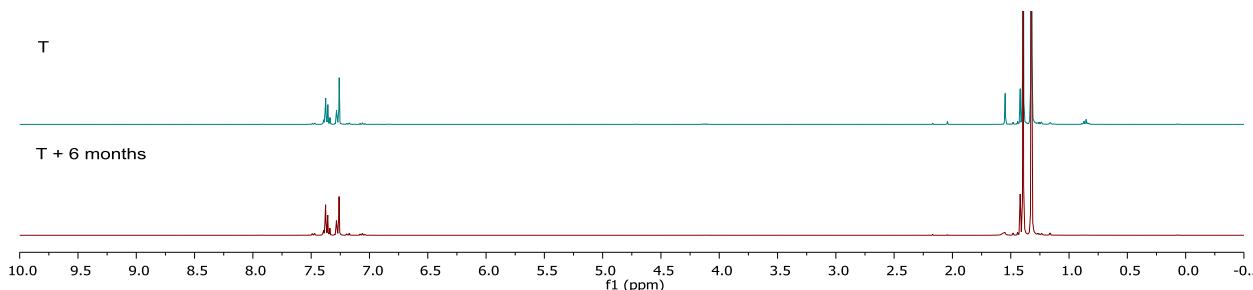
**Figure 6.** Decomposition of boronic acid (**303**) on the bench at room temperature over 1 month.

Using much softer phenylmagnesium chloride reagent, the transformation of the aryl iodide (**301**) to the boronic acid (**303**) was achieved in an excellent 82% yield on 0.5 gram scale (entry 6). Unfortunately, purifying this compound to a high standard for use in a subsequent Suzuki reaction was quite problematic. A <sup>1</sup>H NMR of the same sample taken immediately after silica gel chromatography and again 1 month later (Figure 6), stored as a solid in a vial on the bench, clearly shows steady decomposition of (**303**) to an unidentified species at room temperature. While this could be the formation of the corresponding boroxine species, the spoiled physical appearance and decreased reactivity of this compound encouraged the discovery of a better solution.



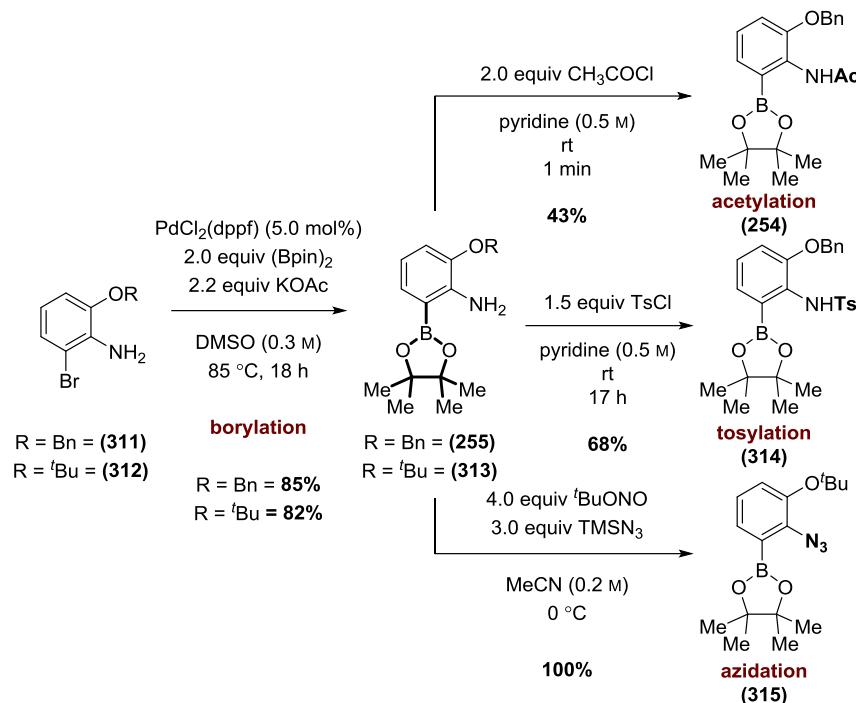
**Scheme 50.** Attempted transformation of boronic acid (303) to a more stable species.

In the hope of stabilising the boronic acid (303) for storage and use in a Suzuki coupling (as it would likely be even more unstable at elevated temperatures) we sought to transform it into either *N*-methyliminodiacetic boronate (309) or potassium trifluoroborate salt (310). While good mass retention was achieved, the products of both reactions still contained significant impurities that could not be removed that were brought through from the contaminated starting material.



**Figure 7.** Stability of boronic ester (302) on the bench at room temperature over 6 months.

Before continuing any further with any of these boronic species, we instead tried quenching the organomagnesium with isopropoxyboronic acid pinacol ester to form the analogous, and hopefully more stable, boronic ester. We were delighted to find the desired product (302) could be reliably obtained in 91% isolate yield on a multi-gram scale (entry 7). Furthermore, the boronic ester was readily purified and stable on the bench at room temperature. A  $^1\text{H}$  NMR of the same sample taken just after isolation and again 6 months later (Figure 7), stored as a solid in a vial on the bench, shows no decomposition.



**Scheme 51.** Synthesis and derivation of *ortho*-aniline boronic esters.

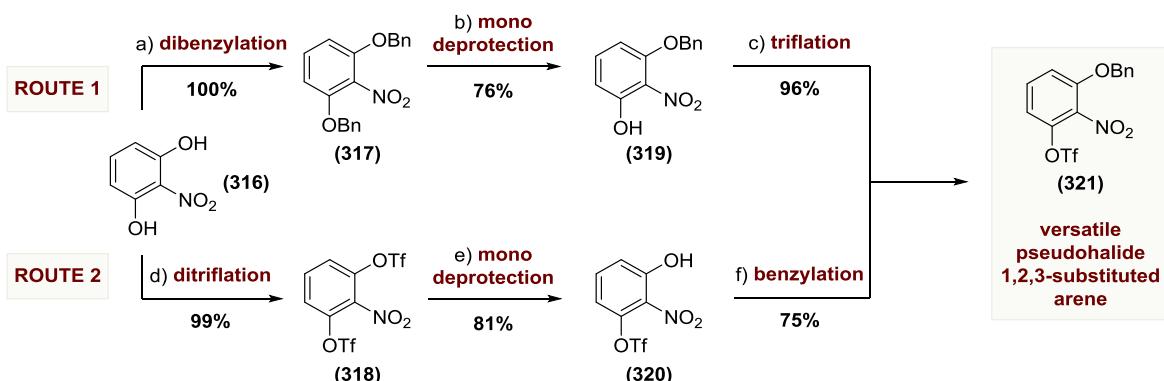
At a later stage in the project another discovery was made that enabled the synthesis of a larger variety of aryl boronic esters. Specifically, the Miyaura borylation of the *O*-benzyl aniline (**311**) was found to occur in excellent yield on gram-scale. Full conversion was only observed by LCMS when using dimethylsulfoxide as the solvent and chromatography delivered the boronic ester (**255**) in 84% yield. This was further reacted to afford the corresponding *N*-acetyl (**254**) and *N*-tosyl (**314**) boronic esters.

Furthermore, after eventually switching to using a *tert*-butyl protecting group (for reasons outlined in Scheme 77) the same conditions were employed to generate the *O*-*tert*-butyl aniline boronic ester (**313**) in a similar 82% yield on gram-scale. This was further reacted to afford the *ortho*-azide boronic ester (**315**).

This concludes the majority our work on the synthesis of a variety of 1,2,3-trisubstituted arenes for coupling at the C4 position. A number of 1,2,3-trisubstituted aryl boronic acids and esters were now easily accessed from commercially available starting materials on gram-scale to facilitate the remainder of our synthesis and to examine a variety of possible routes. From section 3.1.6 onwards, these will be used to synthesise a number of different C4-substituted intermediates to probe conditions for a successful C5 amination. However, the section that immediately follows details work carried out alongside the work already described towards the use of 1,2,3-trisubstituted pseudohalides in the C4 functionalisation step.

**Attempted use of 1,2,3-trisubstituted pseudohalide arenes.**

With little success so far in the synthesis of 1,2,3-trisubstituted aryl halides by C–H functionalisation we opted to try the use of pseudohalides. The advantage of using a pseudohalide, while notably less reactive in coupling reactions than true halides, is that they can be prepared from the much cheaper and more abundantly available 2-nitroresorcinol (**316**). We opted to synthesise the trifluoromethanesulfonate as this is generally more reactive than its *para*-toluenesulfonate counterpart.



**a)** 2.2 equiv  $\text{K}_2\text{CO}_3$ , 2.2 equiv  $\text{BnCl}$ , cat.  $\text{KI}$ , acetone (1 M),  $60^\circ\text{C}$ , 51 h, 100%; **b)** 1.5 equiv  $\text{BCl}_3$ ,  $\text{CH}_2\text{Cl}_2$  (0.12 M),  $-78^\circ\text{C}$ , 1 h, 76%; **c)** 1.2 equiv  $\text{Tf}_2\text{O}$ , 1.2 equiv  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$  (0.5 M),  $-78^\circ\text{C}$ , 1 h, 96%; **d)** 2.4 equiv  $\text{Tf}_2\text{O}$ , 2.4 equiv  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$  (0.5 M),  $-78^\circ\text{C}$  to rt, 20 h, 99%; **e)** 1.5 equiv  $\text{Cs}_2\text{CO}_3$ , DME (0.5 M),  $80^\circ\text{C}$ , 4 h, 81%; **f)** 1.2 equiv  $\text{BnBr}$ , 1.2 equiv  $\text{K}_2\text{CO}_3$ , DMF (0.9 M),  $0^\circ\text{C}$  to rt, 19 h, 75%.

**Scheme 52.** Plan for the synthesis of aryl trifluoromethanesulfonate from 2-nitroresorcinol.

We began the first of two planned synthetic routes to quickly access this arene (Scheme 52) by assessing a simple dibenzylation of 2-nitroresorcinol. A good yield of 82% was achieved on the first attempt using 2 equivalents of potassium carbonate and benzyl chloride with a catalytic amount of potassium iodide at  $60^\circ\text{C}$  in acetone. The reaction was conducted at high concentration which assisted in the gradual scale-up process. On a 23 gram scale the desired product (**317**) was isolated in quantitative yield.

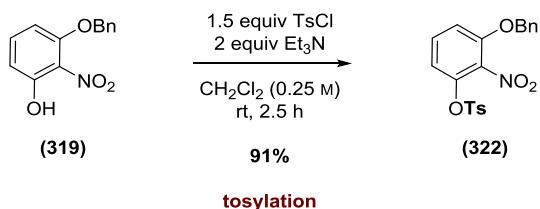
With plenty of the dibenzylated substrate (**317**) in hand, we found that one benzyl group could be selectively removed by treatment with 1.5 equivalents of  $\text{BCl}_3$  at  $-78^\circ\text{C}$  in dichloromethane over 1 hour.<sup>135</sup> On a sub-gram scale (**319**) was obtained in a yield of 65 %, but on a larger scale reaction of 2 grams this was increased to 76%.

Finally, the monobenzylated arene (**319**) was subjected to a set of standard triflation conditions. Using 1.2 equivalents of trifluoromethanesulfonate anhydride and trimethylamine in dichloromethane at  $-78^\circ\text{C}$ , an initial small scale test reaction yielded only 50% isolated product, but upon gram-scale execution a near quantitative 96% isolated yield of (**321**) was recovered.

## Results and Discussion

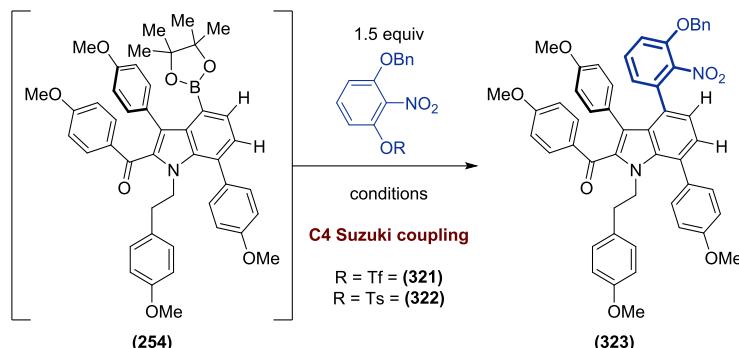
At the same, we had been working on the second route discussed above that involving manipulation of the trifluoromethanesulfonate group before installation of the benzyl moiety. This route required no optimisation whatsoever and afforded nearly a gram of (**321**) in a similar three step sequence.

2-Nitroresorcinol (**316**) underwent ditriflation to afford (**318**) in a 99% isolated yield using 2.4 equivalents of trifluoromethanesulfonic anhydride and trimethylamine in dichloromethane at -78 °C. One trifluoromethanesulfonate group was then removed selectively in an 81% yield by heating with 1.5 equivalents of caesium carbonate in 1,2-diemthoxyethane at 80 °C for 3 hours before benzylating the resultant free phenol (**320**) to give (**321**) in 75% yield using 1.2 equivalents of benzyl bromide and potassium carbonate in *N,N*-dimethylformamide. The first route to (**321**) discussed above gave a higher overall yield of 73% compared to 60% using the second and proved easier to scale up.



**Scheme 53.** Tosylation of the mono benzyl-protected arene.

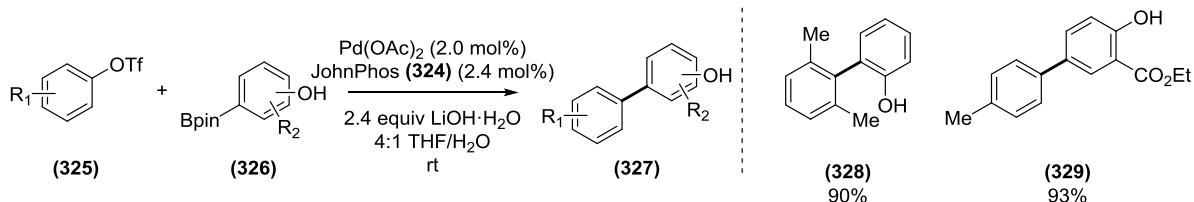
Furthermore, we were able to quickly synthesise the corresponding tosyl arene (**322**) to increase the possibilities to try in the C4 Suzuki coupling. Tosylation was easily achieved in 91% yield with 1.5 equivalents of tosyl chloride and 2 equivalents of trimethylamine in dichloromethane at room temperature.

**Table 20.** C4 Suzuki Coupling with pseudohalides.

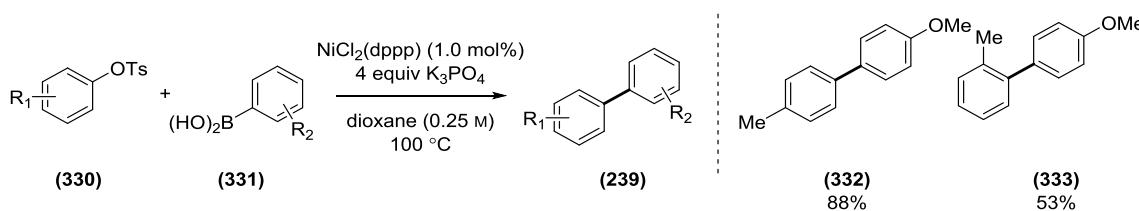
entry	R	conditions	yield
1	Tf	Pd(OAc) <sub>2</sub> (2.0 mol%), JohnPhos (324) (2.4 mol%), 2.4 equiv LiOH·H <sub>2</sub> O, 4:1 THF/H <sub>2</sub> O (0.5 M), rt, 2.5 h.	0 <sup>a</sup>
2	Tf	Pd(OAc) <sub>2</sub> (2.0 mol%), JohnPhos (324) (2.4 mol%), 2.4 equiv LiOH·H <sub>2</sub> O, 4:1 THF/H <sub>2</sub> O (0.5 M), 60 °C, 15 h.	0 <sup>b</sup>
3	Ts	NiCl <sub>2</sub> (dppp) (5.0 mol%), 4 equiv K <sub>3</sub> PO <sub>4</sub> , dioxane (0.25 M), 110 °C, 19 h.	0 <sup>b</sup>

<sup>a</sup>No reaction. <sup>b</sup>Protodeboronation observed.

With the trifluoromethanesulfonate (321) and *para*-toluenesulfonate (322) arenes in hand, we next attempted to perform the C4 Suzuki coupling as part of a one-pot process via boronic ester (254) that was prepared *in situ* as described at the beginning of this section (Table 20). We became aware of mild conditions for the coupling of aryl triflates with boronic esters reported by Manabe<sup>136</sup> (Scheme 54).

**Scheme 54.** Manabe's report of the Suzuki cross coupling of triflates with boronic esters.

Application of these conditions with 1.5 equivalents of the aryl triflate (321), 2.0 mol % palladium(II) acetate, 2.5 mol % JohnPhos (324) ((2-biphenyl)di-*tert*-butylphosphine) ligand and 2.4 equivalents lithium hydroxide monohydrate in a 4:1 solvent mixture of tetrahydrofuran and water showed no conversion of starting material when stirring at room temperature for nearly 3 hours (entry 1). Using the same conditions at 80 °C caused protodeboronation of the substrate and decomposition of (321) (entry 2).



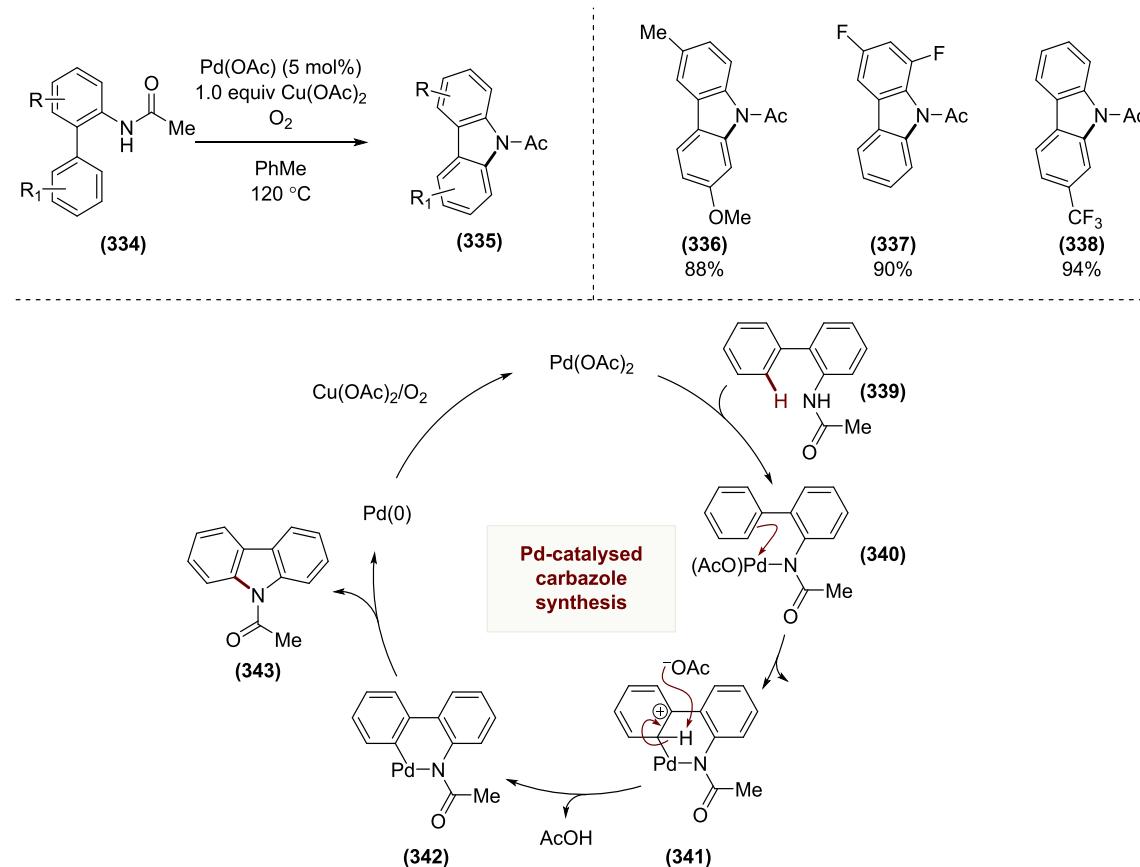
**Scheme 55.** Lin's report of conditions for the Suzuki cross coupling of tosylates with boronic acids.

To examine the Suzuki coupling with the aryl tosylate (**322**) we studied a report by Lin that disclosed the coupling of methanesulfonic and *para*-toluenesulfonic arenes (**330**) with boronic acids (**331**) in moderate to high yields.<sup>137</sup> Treatment of our substrate (**254**) and the arene (**322**) with 1.0 mol% dichloro(1,3-bis(diphenylphosphino)propane)nickel(II) catalyst and 4 equivalents of potassium phosphate in dioxane at 100 °C (entry 3) lead only to partial protodeboronation of the starting material, although (**322**) was unaffected.

Our modest study of pseudohalides had so far not revealed even trace activity when applied in the Suzuki coupling. This avenue of exploration was therefore discontinued for the time being while efforts were concentrated in other areas where more success was being realised. The next sections explore the efforts towards the C5 amination through the coupling of the arenes synthesised in this section at the C4 position of intermediate (**188**).

### 3.1.6 Attempted N-Acyl C5 amination

The first attempts at a ring closing amination were performed with an *ortho* N-acetyl group. We envisaged the application of Buchwald's palladium-catalysed C-H functionalisation protocol for the formation of carbazoles (Scheme 56).<sup>138</sup> Importantly, this methodology had been shown to work in *ortho*-substituted examples such as (**337**) and had high yields with electron donating or withdrawing substituents on both rings of the biphenyl starting material.

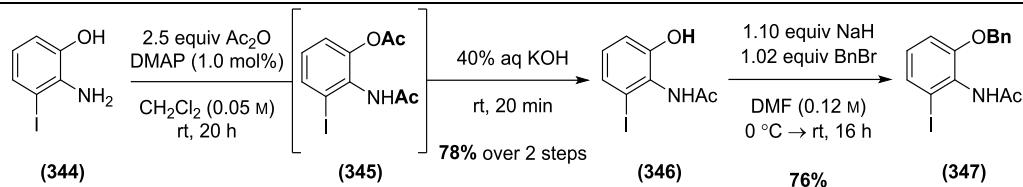


**Scheme 56.** Buchwald's palladium-catalysed synthesis of carbazoles.

The reaction is thought to proceed via pre-association of the palladium(II) acetate with the amide (**339**) resulting in *ortho*-palladation to generate six-membered palladacycle (**342**). Reductive elimination forms the desired C–N bond in product (**343**) and extrudes palladium(0) which is reoxidised to its active form by copper(II) acetate, which in turn is reoxidised by oxygen.

To translate this into our synthesis, we required a suitable arene to couple at the C4 position of the indole. Our first success in this regard began from the expensive 3-iodo-2-amino-phenol (**344**) (approx. \$148/g). The acylation of both the phenol and aniline with acetic anhydride in the presence of catalytic DMAP then allowed for selective hydrolysis with aqueous potassium hydroxide at room temperature to afford acetanilide (**346**) in a 78% crude yield over two steps on gram-scale.

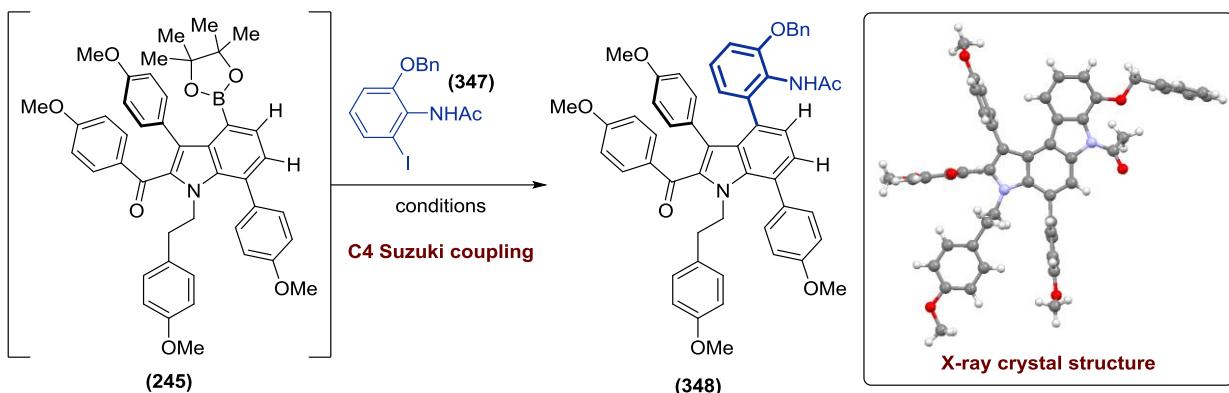
Deprotonation with sodium hydride followed by addition of benzyl bromide delivered the desired iodoarene (**347**) in a 76% yield after chromatography and crystallisation. Aside from being quite expensive, another problem with this aryl preparation was the near insolubility of the starting material and all intermediates. Fortunately, the final product was much easier to handle and could be purified relatively easily.



**Scheme 57:** Preparation of aryl fragment by protection of commercially available 2-amino-3-iodophenol.

With the aryl iodide (347) in hand we turned our attention to performing the C4 Suzuki coupling. By directly subjecting the reaction mixture of the freshly prepared C4 boronic ester (245) (see Table 12) to a couple of standard Suzuki conditions (Table 21) we attempted to synthesise the corresponding penta-substituted indole product (348).

**Table 21.** C-4 Suzuki Coupling



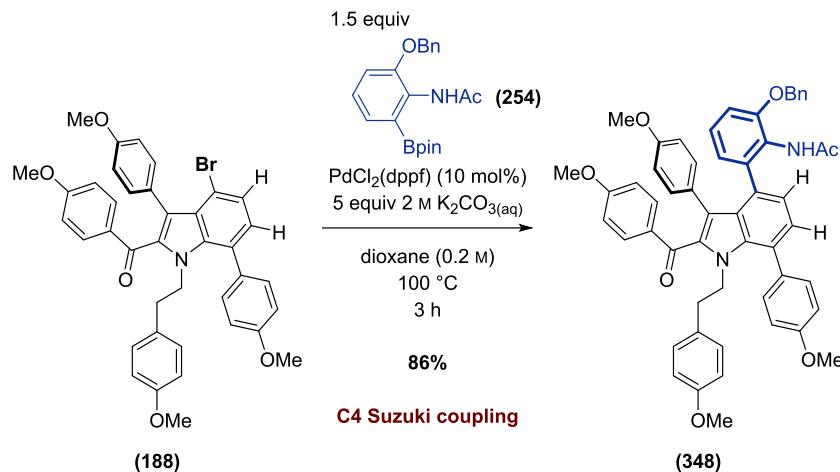
entry	temp (°C)	conditions	LCMS <sup>a</sup>
			SM   PD <sup>a</sup>   P
1	95	Pd(PPh <sub>3</sub> ) <sub>4</sub> (3.0 mol%), 2.0 equiv Na <sub>2</sub> CO <sub>3</sub> , 1.1 equiv iodoarene, EtOH/PhMe, H <sub>2</sub> O (2:2:1, 0.1 M), 95 °C, 22 h.	41      49      10
2	100	PdCl <sub>2</sub> (dppf) (10 mol%), 4.0 equiv 1.75 M KOH <sub>(aq)</sub> , 1.5 equiv iodoarene, dioxane, 100 °, 17 h.	65      0      35
3	100	PdCl <sub>2</sub> (dppf) (10 mol%), 4.0 equiv 1.75 M KOH <sub>(aq)</sub> , 1.5 equiv iodoarene, dioxane, 100 °, 19 h. (N <sub>2</sub> sparged)	65      0      35

<sup>a</sup>Used for qualitative analysis to compare spectrophotometer peak integrals of the starting material (SM), protodeboronated material (PD) and product (P).

Use of tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in a solvent mixture of ethanol, toluene and water resulted in major protodeboronation of the boronic ester (entry 1). Transition to a [1,1'-bis(diphenylphosphino) ferrocene]dichloropalladium(II) catalyst with potassium hydroxide in a mixture of water and dioxane showed an improvement in conversion to the desired product and no trace of protodeboronation (entry 2). In the hands of Dr Snell and

Dr O'Hara, sparging of the reaction mixture appeared to help during the Suzuki couplings of this boronic ester, however in this instance no improvement was observed (entry 3)

With only limited success in the one-pot borylation/Suzuki coupling of the main fragment, we were fortunately able to instead synthesise the boronic ester of the desired aryl fragment for use in the Suzuki coupling, therefore avoiding borylation, and subsequent loss by protodeboronation of, intermediate (**188**).



**Scheme 58.** Suzuki coupling to afford *O*-benzyl protected acetamide intermediate.

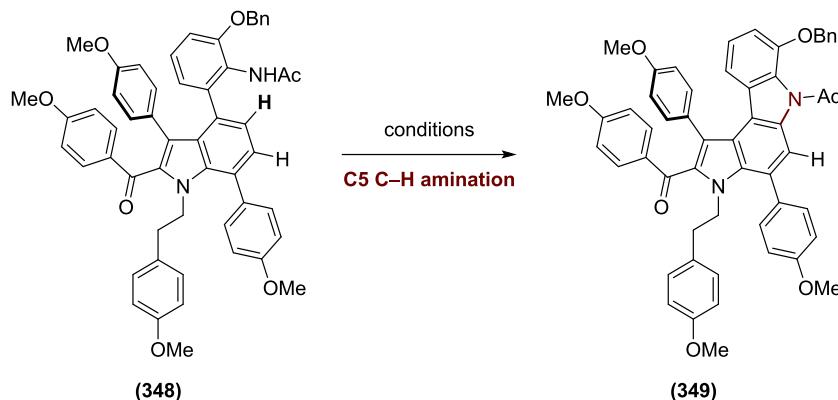
Using 1.5 equivalents of boronic ester (**254**) (see Scheme 51 for preparation) the cross-coupled product (**348**) could be produced in an 86% isolated yield with no optimisation in just three hours. This marked a significant improvement over the maximum 34% achieved on average using the previous two-step protocol by Dr Snell.

We began our examination of *N*-acetyl amination conditions (Table 22) with conditions reported by Buchwald.<sup>138,139</sup> Treatment of indole (**348**) with 20 mol% palladium acetate in dimethylsulfoxide at 120 °C resulted in no observable conversion to (**349**) by LCMS (entry 1). However, under the same conditions with a small excess of stoichiometric palladium(II) acetate, mixed with either Celite® (entry 2) or molecular sieves (entry 3) for accurate weighing on a small reaction scale, good conversion was observed indicating that either the metal catalyst is 'inactivated' after reductive elimination or reoxidation of the metal catalyst posed a challenge.

Next, we surveyed an interesting report by Chang<sup>140</sup> that simultaneously disclosed a copper-catalysed and copper-free method for the synthesis of carbazoles (Scheme 59). It was discovered that use of copper(II) triflate in the presence of (diacetoxyiodo)benzene (PIDA) catalysed the

intramolecular amination of *ortho*-N-sulfonylamide biphenyl substrates in good yields over a short reaction time of only 10 minutes.

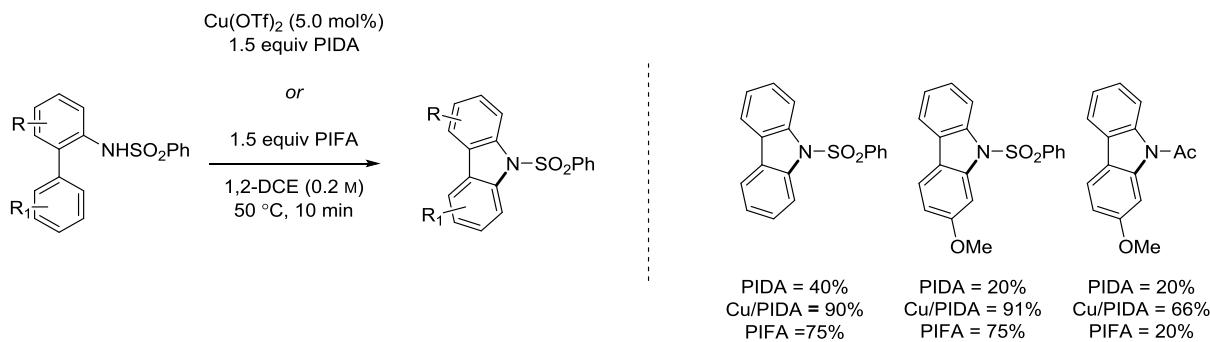
**Table 22:** Initial carbazole closure investigations.



entry <sup>a</sup>	conditions	LCMS	
		SM	P
1 <sup>b</sup>	Pd(OAc) <sub>2</sub> (20 mol%) <sup>c</sup> , 3 equiv Ac <sub>2</sub> O, O <sub>2</sub> balloon, 3Å MS, DMSO (0.03 M), 120 °C, 4h.	100	0
2 <sup>c</sup>	Pd(OAc) <sub>2</sub> (120 mol%) <sup>b</sup> , O <sub>2</sub> balloon, 3Å MS, DMSO (0.03 M), 120 °C, 4h.	23	77
3 <sup>b</sup>	Pd(OAc) <sub>2</sub> (120 mol%) <sup>c</sup> , O <sub>2</sub> balloon, 3Å MS, DMSO (0.03 M), 120 °C, 4h.	25	75
4 <sup>c</sup>	Cu(OTf) <sub>2</sub> (10 mol%) <sup>b</sup> , 1.5 equiv PIDA, 1,2-DCE (0.2 M), rt, 30 min.	78	22
5	1.5 equiv PIFA, 3 equiv TFA, 1,2-DCE (0.2 M), 50 °C, 15 min.	0	0
6	Pd(OAc) <sub>2</sub> (20 mol%) <sup>c</sup> , 0.5 equiv <i>p</i> -TsOH•H <sub>2</sub> O, 1.0 equiv Oxone®, PivOH/DMF (1:3, 0.1 M), 80 °C, 16 h.	85	15
7	Pd(OAc) <sub>2</sub> (20 mol%) <sup>c</sup> , 1.2 equiv PIDA, 1.0 equiv AcOH, PhMe (0.055 M), 50 °C, 16 h.	40	20

<sup>a</sup>Performed on a 0.024 mmol (20 mg) scale. <sup>b</sup>Catalyst (10%) cut with Celite®. <sup>c</sup>Catalyst (10%) cut with 3Å MS.

The use of PIDA in promoting the cyclisation in the absence of copper catalyst proved less effective than (bis(trifluoroacetoxy)iodo)benzene (PIFA) which achieved lower yields than the copper-catalysed version. The reaction failed to produce more than trace amounts of product in the presence of radical inhibitors leading the authors to postulate a radical based mechanism for the amination. Furthermore, the fact that the reaction proceeds in the absence of copper also led the authors to hypothesise that the copper acts as a Lewis acid rather than proceeding through a Cu(III) mediated mechanism.



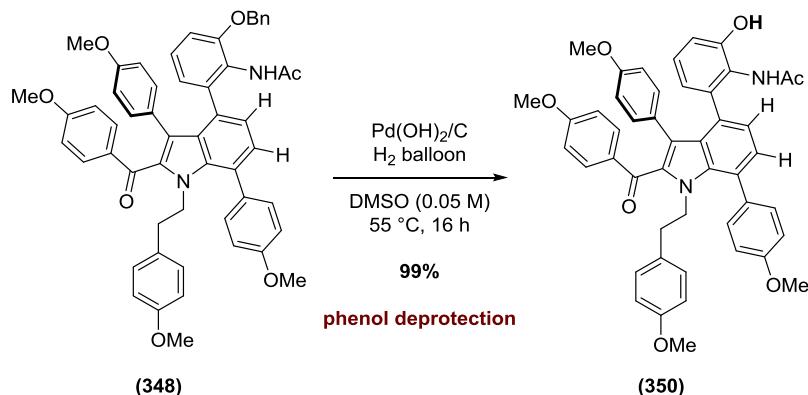
**Scheme 59.** Chang's copper and copper-free carbazole syntheses.

As the protocol had also been demonstrated to work on *N*-acyl substrates, we decided to apply the conditions to intermediate (**348**). Exposure to 10 mol% copper(II) triflate and 1.5 equivalents PIDA in 1,2-dichloroethane at 50 °C for half an hour delivered a minimal 22% conversion to (**349**) by LCMS (entry 4). Under similar conditions with PIFA in the absence of metal-catalyst, no conversion was observed. Although this protocol did not work as well with *N*-acetyl substrates when compared to *N*-sulfonyl, this was still an unsatisfactory result.

We subsequently attempted to use a set of conditions developed by Kim<sup>141</sup> designed for *N*-tosyl substrates (Scheme 62). Unlike the previous protocol this had no foundation for suitability to promote the amination of *N*-acyl groups. Nonetheless, we stirred substrate (**348**) with 20 mol% palladium(II) acetate, 0.5 equivalents *p*-toluenesulfonic acid and 1 equivalent of Oxone® in a solvent mixture of pivalic acid and *N,N*-dimethylformamide at 80 °C. After 16 hours, conversion to the (**349**) was determined to be only 15% by LCMS with mostly unreacted starting material remaining.

Finally, we applied amination conditions developed in our lab (entry 7). Usually applied to *N*-benzyl substrates (see Scheme 61) we hoped it might at least show catalytic activity that could be improved upon with further optimisation. However, heating at 50 °C with PIDA as the oxidant and with 1 equivalent of acetic acid we observed only low conversion to (**349**), as determined by LCMS, along with a similar amount of unwanted acetylated side product (entry 7). When this reaction was performed without acetic acid no conversion to the product was observed.

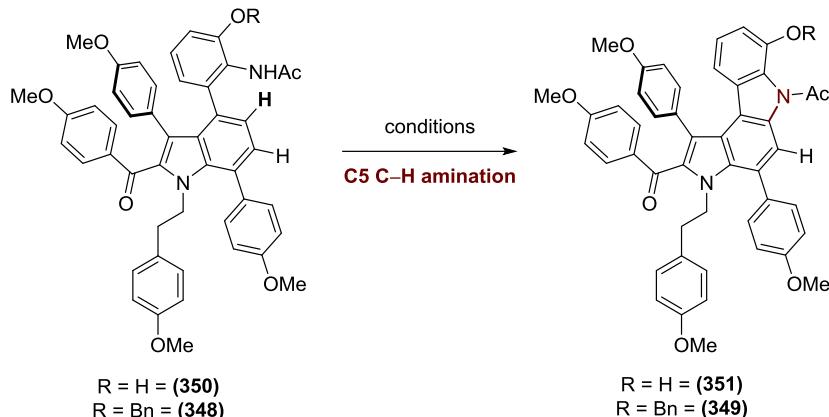
We speculated that relieving the steric hindrance *ortho* to the acetanilide may help to improve our chances of success. The benzyl group was easily removed with palladium(II) hydroxide in dimethylsulfoxide at 55 °C under an atmosphere of hydrogen to deliver the free phenol (**350**) in 99% yield.



**Scheme 60.** Removal of the benzyl group to attempt further carbazole closures.

We first applied Buchwald's conditions again in a side-by-side comparison of the benzyl protected substrate (**348**) and the free phenol substrate (**350**) (Table 23). Intriguingly, an unidentified product appeared to form in the reaction of the latter (entry 1) which was isolated in 23% yield and appeared to be the result of an acetylation, although the exact location of the acetylation could not be confirmed. However, the benzyl protected substrate (**348**) seemed to decompose as no traces of starting material, product or identifiable side products could be found.

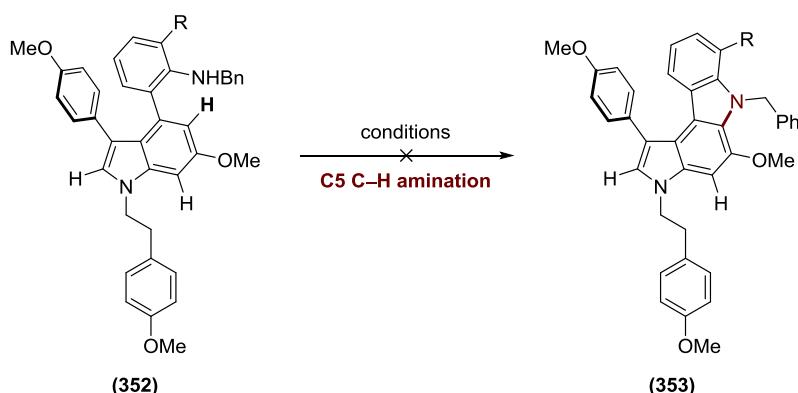
Lastly, we investigated the use of an amidation reaction developed by Glorius that, although designed to form indolines, had also demonstrated the capability of forming carbazoles.<sup>142</sup> Exposure of our two substrates to palladium(II) acetate with 3 equivalents of silver(I) acetate oxidant and 3 equivalents sodium carbonate in mesitylene at 160 °C for 24 hours showed almost identical 30% conversion to the product in both cases by LCMS. Notably, the benzyl protected intermediate (**348**) also showed almost equal conversion to side-products whereas the free phenol (**350**) exhibited clean conversion.

**Table 23.** Attempted carbazole closure on the free phenol intermediate.

entry	R	conditions	LCMS <sup>b</sup>		
			SM	SP	P
1	H	Pd(OAc) <sub>2</sub> (10 mol%) <sup>a</sup> , 1.0 equiv Cu(OTf) <sub>2</sub> , 3 Å MS, O <sub>2</sub> balloon, PhMe (0.1 M), 120 °C, 24h	23%	acetylated product	
2	Bn		0	0	0
3	H	Pd(OAc) <sub>2</sub> (10 mol%) <sup>a</sup> , 3.0 equiv AgOAc, 3 Å MS, 3.0 equiv Na <sub>2</sub> CO <sub>3</sub> , mesitylene (0.1 M), 160 °C, 24h	70	0	30
4	Bn		44	27	29

<sup>a</sup>Catalyst (10%) cut with 3 Å MS. <sup>b</sup>Used for qualitative analysis to compare spectrophotometer peak integrals of the starting material (SM), product (P) and side-products (SP)

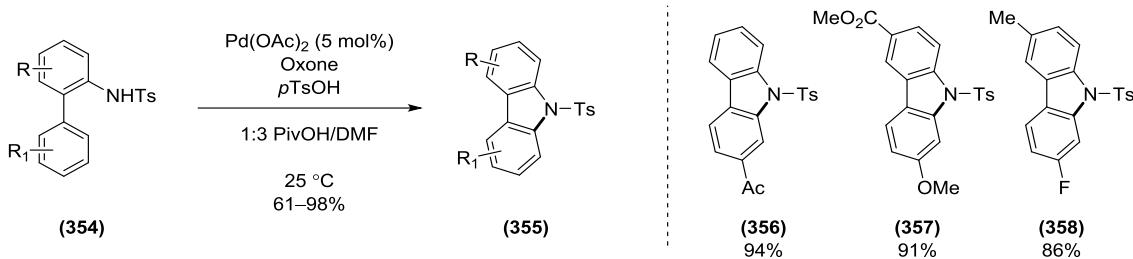
Paucity of material at this point prevented intensive optimisation studies towards the development of a catalytic process. It is worth mentioning that a similar palladium-catalysed *N*-benzyl carbazole synthesis was attempted by Dr O'Hara using conditions developed in our lab (Scheme 61).<sup>143</sup> However, these attempts were also unsuccessful as no carbazole product was ever detected.

**Scheme 61.** Dr O'Hara's attempts to use Gaunt's C–H amination conditions.

Before the opportunity arose to bring enough material to this point to conduct further studies on the *N*-acyl system, a solution to the amination was found by an alternative means described later in this report. But before this solution was realised, similar studies were performed on *N*-tosyl intermediates.

### 3.1.7 Attempted *N*-Tosyl C5 amination

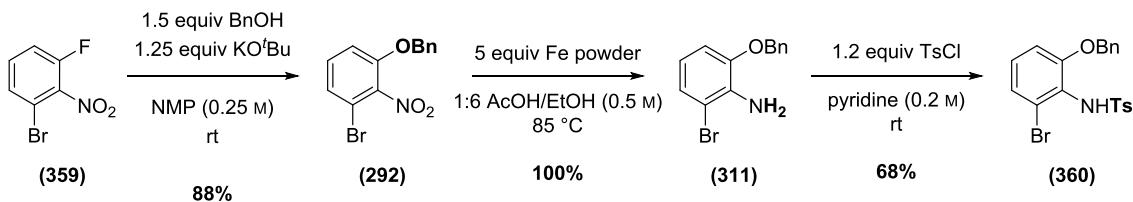
Along with the related *N*-acyl and *N*-benzyl procedures already described, the *N*-tosyl-2-phenyl anilines (**354**) are also known to undergo an oxidative amination processes to afford carbazoles (**355**) (Scheme 62).<sup>141</sup> This protocol proceeds under similarly mild conditions to Gaunt's *N*-benzyl methodology and is also thought to operate through a Pd(II)/Pd(IV) catalytic cycle.



**Scheme 62.** Kim's palladium-catalysed oxidative C–H amination of *N*-tosyl-2-phenyl anilines.

In addition to being easier to synthesise than their *N*-benzyl counterparts, the corresponding carbazoles can be formed using the much cheaper oxidant potassium peroxymonosulfate (Oxone) in excellent yields ranging from 61 to 98%.

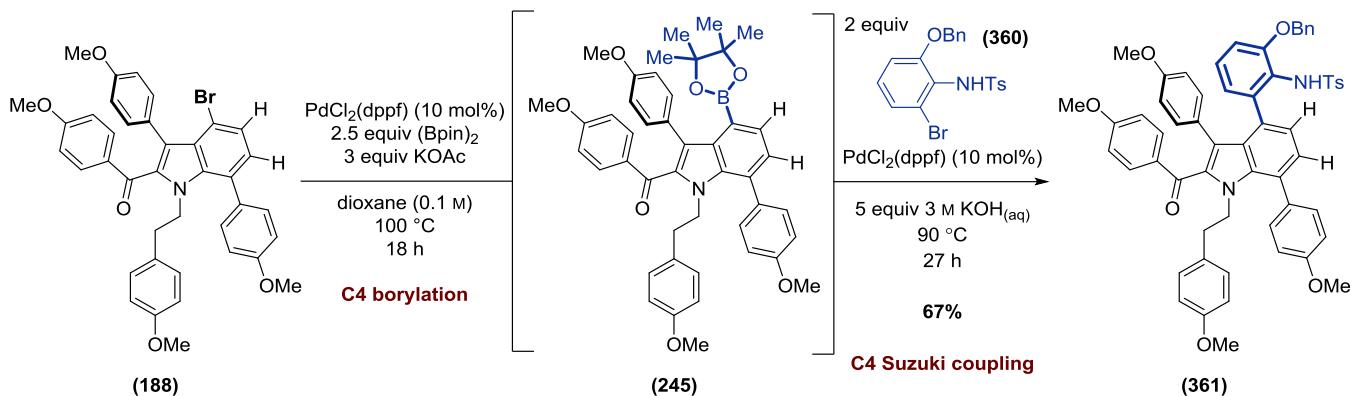
We sought to apply this methodology to our own system and we were able to synthesise *N*-(2-(benzyloxy)-6-bromophenyl)-4-methylbenzenesulfonamide (**360**) from commercially available 1-bromo-3-fluoro-2-nitrobenzene (**359**) (Scheme 63). A simple nucleophilic aromatic substitution afforded 1-(benzyloxy)-3-bromo-2-nitrobenzene (**292**) which was reduced in quantitative yield using iron powder in a mixture of acetic acid and ethanol at 85 °C. The free aniline (**311**) was then tosylated to afford aryl bromide (**360**) for the C4 Suzuki coupling



**Scheme 63.** Synthesis of *N*-(2-(benzyloxy)-6-bromophenyl)-4-methylbenzenesulfonamide (**360**).

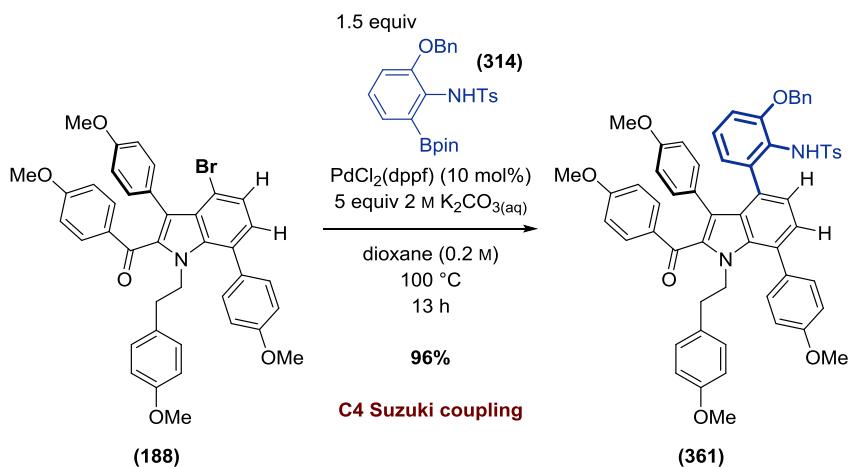
## Results and Discussion

We were delighted to find that this aryl bromide underwent Suzuki coupling at the C4 position of indole over 27 hours to afford the desired product (**361**) in 67% yield.



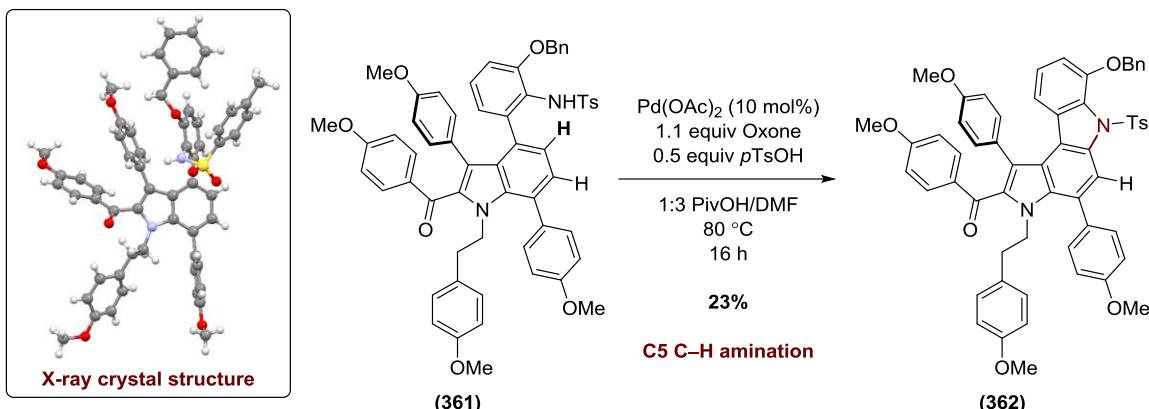
**Scheme 64.** One-pot Suzuki coupling of N-tosyl arene (**360**) with in situ prepared boronic ester (**245**).

However, much like the Suzuki coupling performed in the previously described work towards an *N*-acyl amination, we were confident that a significant improvement could be made if the boronic ester functionality was installed on the arene rather than intermediate (**188**). Gratifyingly, we were able to achieve this (see Scheme 51 for preparation of (**314**)) and were pleased to observe successful coupling with virtually no optimisation to deliver the penta-substituted indole (**361**) in an exceptional 96% yield.



**Scheme 65.** Suzuki coupling to afford an *O*-benzyl protected tosylamide intermediate.

With the *N*-tosyl substrate (**361**) in hand, we attempted to perform the aforementioned C5 C–H amination under the conditions described in Kim's report (Scheme 64). Unfortunately, the result was a low 23% isolated yield after 16 hours at 80 °C. With larger error margins on such a small scale, it is likely that this reaction was operating stoichiometrically with respect to the palladium catalyst.

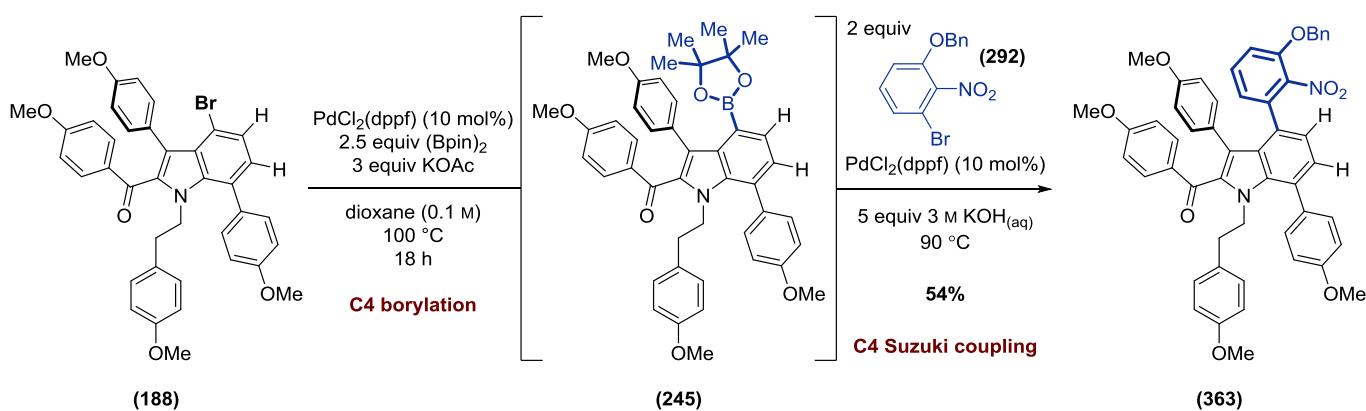


**Scheme 66.** Palladium-catalysed oxidative C–H amination of *N*-tosyl substrate (361).

As the inability to achieve catalytic turnover appeared to be a recurring theme in all attempts to achieve an oxidative metal-catalysed C–H amination ring-closure at the C5 position, we next turned the focus of our efforts towards developing a reductive process from either the related nitro or azide substrates.

### 3.1.8 Attempted nitro C5 amination

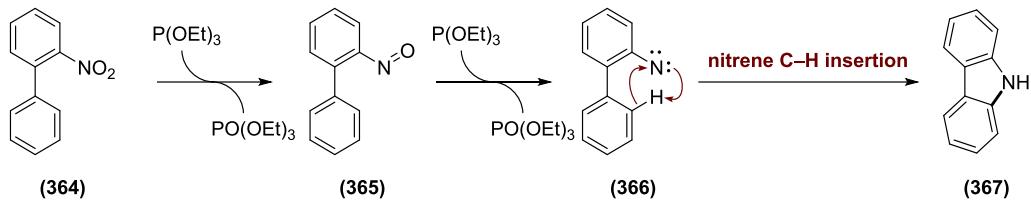
With oxidative processes not yielding the desired results, we instead began probing reductive procedures for the solution. The nitro group appeared to be a good place to start as a successful one-pot borylation/Suzuki coupling could be performed to deliver the corresponding nitro intermediate (363) in 54% yield.



**Scheme 67.** One-pot Suzuki coupling to afford *O*-benzyl protected nitro substrate.

With the nitro intermediate (362) in hand, we began investigating the simplest of nitro carbazole protocols, the Cadogan cyclisation (Scheme 68) and variants thereof (Table 24). A microwave-accelerated protocol using an excess of triethyl phosphite as the reagent and solvent proved

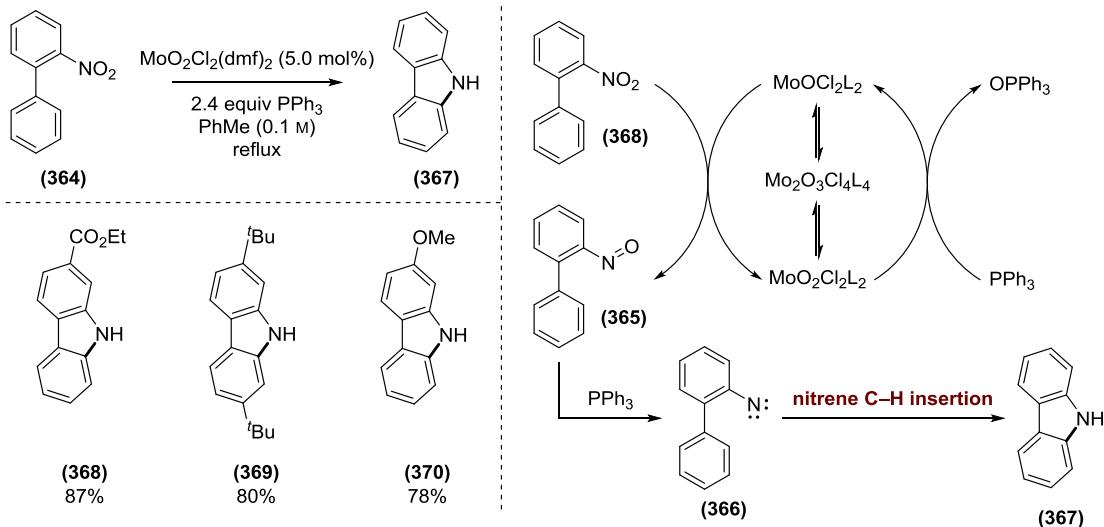
ineffective at a power of 300 W for 9 minutes and after a further 3 hours at 400 W the starting material had fully decomposed (entry 1).



**Scheme 68.** Cadogan cyclisation overview.

We then sought to utilise a different phosphine source and opted for 2.5 equivalents of triphenylphosphine in 1,2-dichlorobenzene, a solvent that would allow us to reach a high temperature in the microwave (entry 2). However, the low microwave absorbance of the solvent meant the reaction was heated slowly from 180 to 300 °C over 30 minutes, after which time the starting material (363) completely decomposed with no trace of product being formed.

We then attempted to use an excess of the more reactive tributylphosphine in 1,2-dichlorobenzene and a slightly lower temperature range. Heating up to 250 °C over 30 minutes again resulted in full decomposition of the starting material. As our substrate appeared to be sensitive to the temperature ranges under which Cadogan cyclisations are performed, we became interested in a procedure that used relatively mild conditions by employing a molybdenum-catalyst as an ‘oxygen-shuttle’.<sup>144</sup>

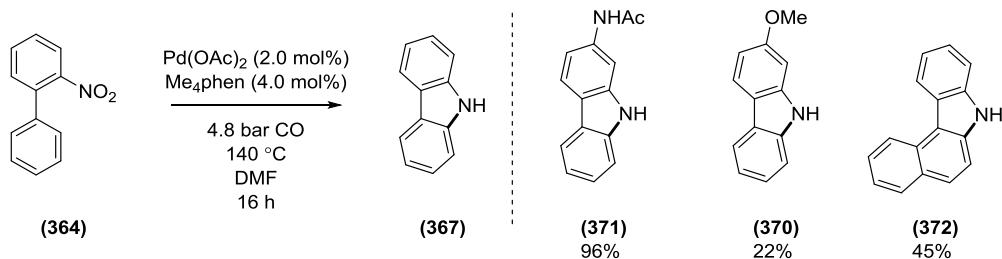


**Scheme 69.** Arnaiz’s molybdenum-catalysed Cadogan cyclisation overview.

The first deoxygenation step is known to be the most difficult and it is thought that the molybdenum catalyst assists in this step to form the corresponding nitroso compound (Scheme

69) which is known to undergo deoxygenation at much lower temperatures in the presence of phosphines and phosphites.

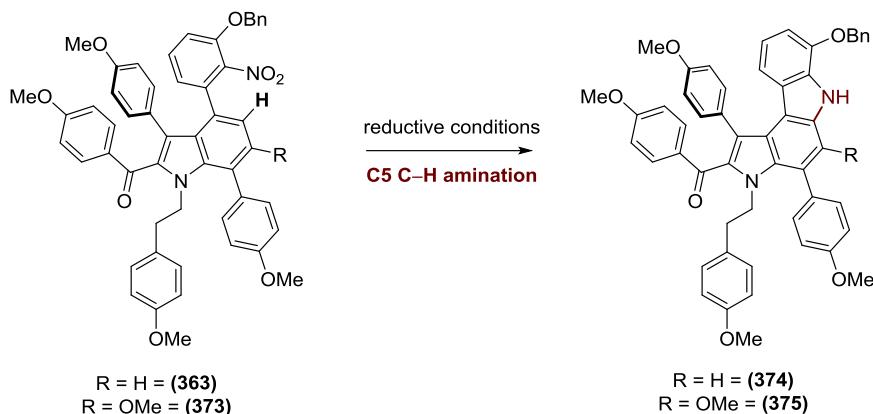
We executed this protocol with 2.4 equivalents of triphenylphosphine in the presence of 50 mol% freshly prepared bis(*N,N*-dimethylformamide)dichlorodioxymolybdenum(VI) catalyst stirred in toluene at 120 °C for 24 hours which yielded only a trace amount of product by LCMS. With such a high catalyst loading this was clearly an unsatisfactory result.



**Scheme 70.** Smitrovich's palladium-catalysed synthesis of carbazole.

In contrast to the Cadogan-type processes explored above, we next chose to apply a set of conditions developed by Smitrovich that employed carbon monoxide as a traceless reductant in a palladium-catalysed amination to synthesise carbazoles from *ortho*-nitro biphenyl substrates.<sup>145</sup> After stirring with 5.0 mol% palladium(II) acetate and 10 mol% 1,10-phenanthroline ligand in *N,N*-dimethylformamide at 140 °C for 20 hours under a 5 bar pressure of carbon monoxide only trace product was detected by LCMS.

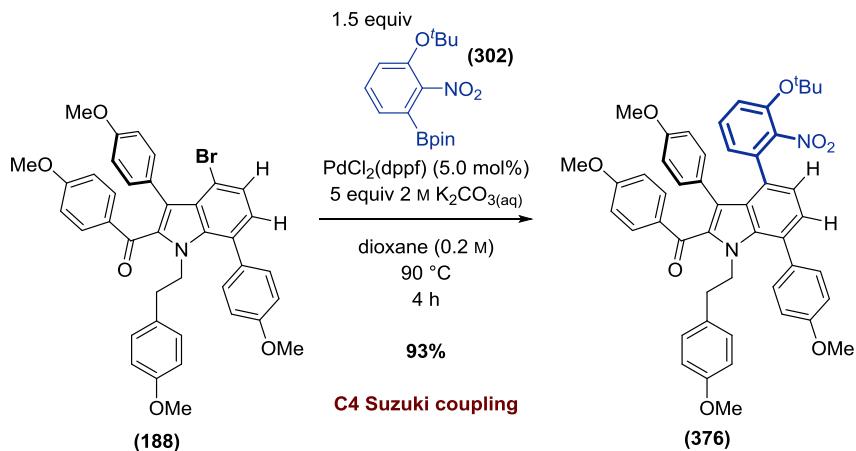
So far we had focused on using penta-substituted indole (**363**) as our starting material (entries 1–5), but next we turned our attention to using the C6-methoxy substituted indole (**373**) to see whether the presence of an *ortho*-electron donating group would help to promote the cyclisation process. Unfortunately, use of Cadogan conditions resulted in either no reaction (entries 6 and 7) or incomplete reduction to the aniline (entry 8). An attempt to use Merck's palladium-catalysed protocol also gave no reaction (entry 9).

**Table 24.** Efforts towards a reductive nitro carbazole closure.

entry	R	conditions	result
1	H	417 equiv P(OEt) <sub>3</sub> , 300 W, 9 min ( $\mu\text{W}$ ) <i>then</i> 400W 3 h.	decomposed
2	H	2.5 equiv PPh <sub>3</sub> , 1,2-DCB (0.25 M), 180–300 °C ( $\mu\text{W}$ ), 30 min.	decomposed
3	H	33 equiv P(Bu) <sub>3</sub> , 1,2-DCB (0.04 M), 150–250 °C ( $\mu\text{W}$ ), 30 min.	decomposed
4	H	2.4 equiv PPh <sub>3</sub> , MoO <sub>2</sub> Cl <sub>2</sub> (DMF) <sub>2</sub> (50 mol%), PhMe (0.06 M), 120 °C, 24 h.	aniline and trace product
5	H	Pd(OAc) <sub>2</sub> (5 mol%), 1,10-phen (10 mol%), 5 bar CO, DMF (0.05 M), 140 °C, 20 h.	trace product
6	OMe	2.5 equiv PPh <sub>3</sub> , 1,2-DCB (0.1 M), 200 °C ( $\mu\text{W}$ ), 23 h.	no reaction
7	OMe	2.4 equiv PPh <sub>3</sub> , MoO <sub>2</sub> Cl <sub>2</sub> (DMF) <sub>2</sub> (50 mol%), DMF (0.05 M), 130 °C, 24 h.	no reaction
8	OMe	2.4 equiv PPh <sub>3</sub> , MoO <sub>2</sub> Cl <sub>2</sub> (DMF) <sub>2</sub> (50 mol%), PhMe (0.06 M), 120 °C, 24 h.	incomplete reduction to aniline
9	OMe	Pd(OAc) <sub>2</sub> (5 mol%), 1,10-phen (10 mol%), 5 bar CO, DMF (0.05 M), 140 °C, 20 h.	no reaction
10	OMe	Ru <sub>3</sub> (CO) <sub>12</sub> (10 mol%), 1.5 equiv NaCl, 7.5 bar CO, NMP (0.05 M), 200 °C, 2h.	complete reduction to aniline

Finally, we examined a ruthenium-catalysed reductive amination using carbon monoxide promoted by the presence of alkali halide salts.<sup>146</sup> The authors hypothesise that the alkali halide salts are responsible for breaking one bridge of the Ru–N cluster intermediate which is then thought to more easily undergo C–H insertion. With this in mind, stirring with 10 mol% triruthenium(0) dodecacarbonyl and 1.5 equivalents of sodium chloride additive in *N*-methyl-2-pyrrolidone at 200 °C under a 7.5 bar pressure of carbon monoxide yielded only complete reduction to the aniline by LCMS (entry 10).

With no success using the *O*-benzyl protected intermediates (**363**) and (**373**) under reductive nitro amination conditions, we instead began using *O*-*tert* butyl intermediate (**376**) for reasons that are outlined later in this report (see Scheme 77). The synthesis of (**376**) was more straightforward as, by this point, we had developed a successful borylation protocol from the corresponding aryl halide. This meant we no longer needed to borylate the indole fragment (**188**) and lose precious mass to the protodehalogenation reaction.

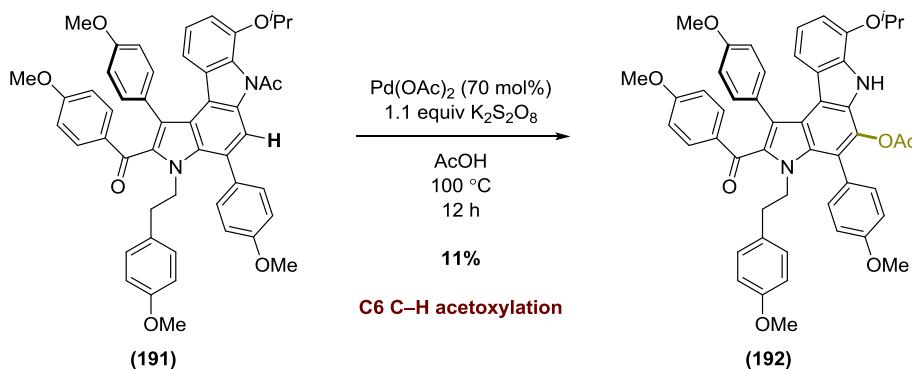


**Scheme 71.** One-pot Suzuki coupling to afford *O*-*tert*-butyl protected nitro substrate.

With no optimisation we were able to generate (**376**) in 93% yield on gram-scale using only 1.5 equivalents of the aryl boronic ester (**302**) in 4 hours at 90 °C (Scheme 71). This marked an exceptional improvement in the project overall as boronic ester (**302**) was formed from a relatively cheap starting material in simple and scalable processes. This allowed for a greater amount of material to be pushed forward with increased ease and this substrate allowed for the elucidation of the successful route that is described in the final sections of this report.

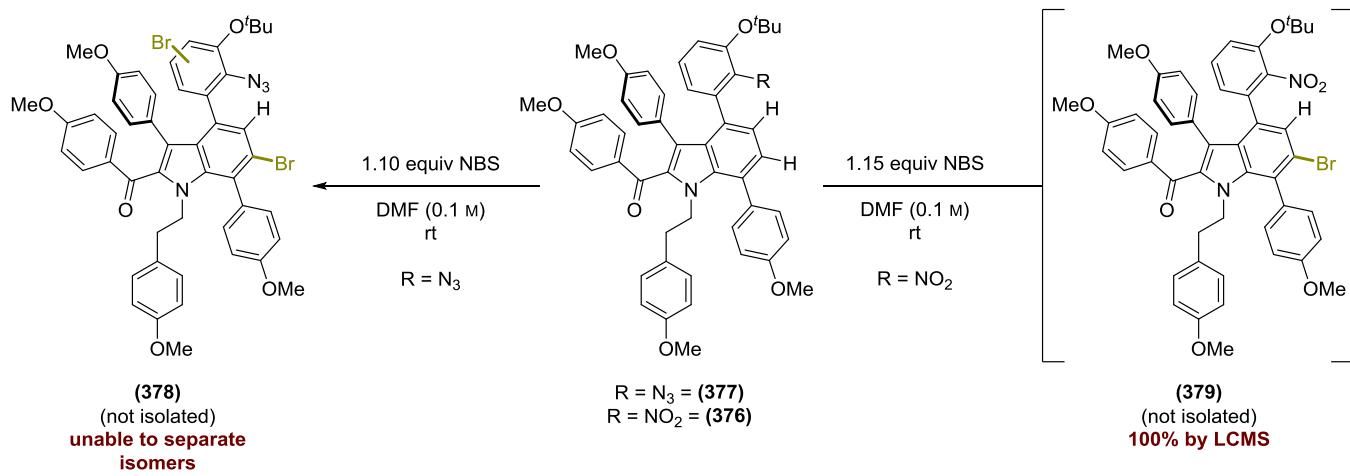
### 3.1.9 Step 7. C6 Etherification

With two functionalisations remaining, much effort had already been expended on a possible directed metal-catalysed C–H functionalisation on model systems and earlier stage intermediates by Dr Fionn O’Hara. Unfortunately, these were met with very limited success with the best result shown below (Scheme 72). Subjection of hexa-substituted indole (**191**) to a 70 mol% loading of palladium (II) acetate with potassium persulfate oxidant in acetic acid afforded 11% isolated yield of the desired product (**192**). Significant material was lost via a highly competitive acetoxylation on the C4 arene and attempts to screen different reaction conditions gave no discernable improvement.



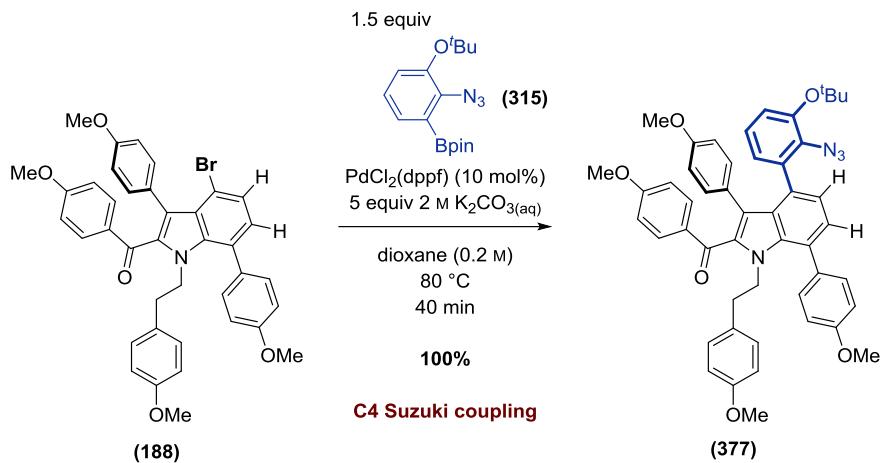
**Scheme 72.** Dr Fionn O’Hara’s most significant C6 functionalisation result.

Previously, Dr O’Hara had also attempted an electrophilic aromatic substitution with *N*-bromosuccinimide, but mono-bromination proved difficult to control and efforts on this approach were stopped when only the dibrominated product was isolated in 28% yield. With the knowledge that unwanted bromination was likely to occur on the C4 arene, we wondered whether the regioselectivity could be moderated if this arene was sufficiently electron deficient to deliver only the desired C6 mono-bromination product. By selecting two electron withdrawing ortho-nitrogen substituents, an azide (**377**) and a nitro (**376**), the selectivity of bromination was examined (Scheme 73).



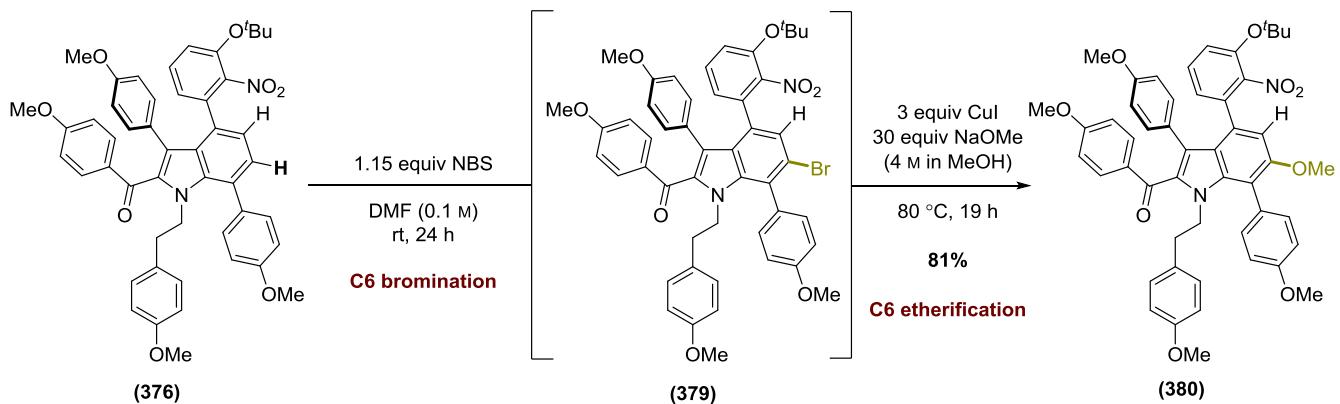
**Scheme 73.** Subjection of the azide and nitro substrates to bromination conditions.

Unfortunately, this was not the case with azide substrate (**377**) as two significant brominated isomers were observed in line with the unselective reactivity observed previously on these systems, indicating that an azide was not sufficiently electron withdrawing. But introduction of a small excess of *N*-bromosuccinimide to nitro substrate (**376**) in *N,N*-dimethylformamide at room temperature gave full conversion to the desired C6 mono-brominated product (**379**).



**Scheme 74.** One-pot Suzuki coupling to afford *O*-*tert*-butyl protected nitro substrate.

While this was a great result, it meant that we would be unable to use our quantitative and more direct coupling of *ortho*-azide boronic ester (**315**) to tetra-substituted intermediate (**188**) (Scheme 74). Instead, we would have to transform the nitro group into an azide as part of the main synthesis, adding a step to our longest linear sequence.



**Scheme 75.** One-pot C6 bromination/etherification.

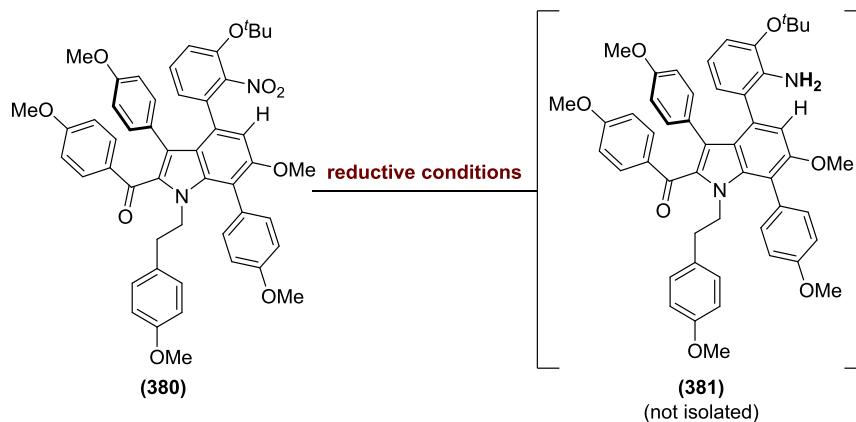
Before this, we would have to complete etherification of the brominated intermediate via a one-pot Ullman condensation. We were delighted to find that subjection to copper(I) iodide in the presence of freshly prepared sodium methoxide at 80 °C smoothly converted bromide intermediate (**379**) to deliver the methoxylated hexa-substituted indole product (**380**) with virtually no optimisation in an excellent 81% yield (Scheme 75).

### 3.1.10 Steps 8 and 9. Transformation of Nitro to Azide and Azide C5

#### Amination

As all previous methods to perform the C5 amination had failed to give desirable results, including the various nitro intermediates, we began to investigate accessing the nitrene via an azide. Thermal decomposition of an azide has already been used for an amination in the synthesis of the dictyodendrins.

**Table 25:** Optimising reduction of the nitro intermediate.



entry	conditions	result
1	10 equiv iron powder, AcOH/EtOH (1:4, 0.25 M), 100 °C, 2 weeks	100% conversion by LCMS
2	10 equiv iron powder, AcOH/DMF (1:4, 0.25 M), 100 °C, 18 h	incomplete conversion
3	palladium on carbon (10 mol%), THF (0.1 M), H <sub>2</sub> (1 bar), 25 h, rt	trace conversion
4	palladium on carbon (20 mol%), MeCN (0.05 M), H <sub>2</sub> (10 bar), 3 h, rt	incomplete conversion
5	palladium on carbon (10 mol%), MeCN (0.05 M), H <sub>2</sub> (50 bar), 3 h, rt	multiple side products
6	palladium(II) hydroxide on carbon (20 mol%), MeCN (0.05 M), H <sub>2</sub> (10 bar), 3 h, rt	100% conversion by LCMS
7	platinum on carbon (20 mol%), MeCN (0.05 M), H <sub>2</sub> (10 bar), 3 h, rt	multiple side products

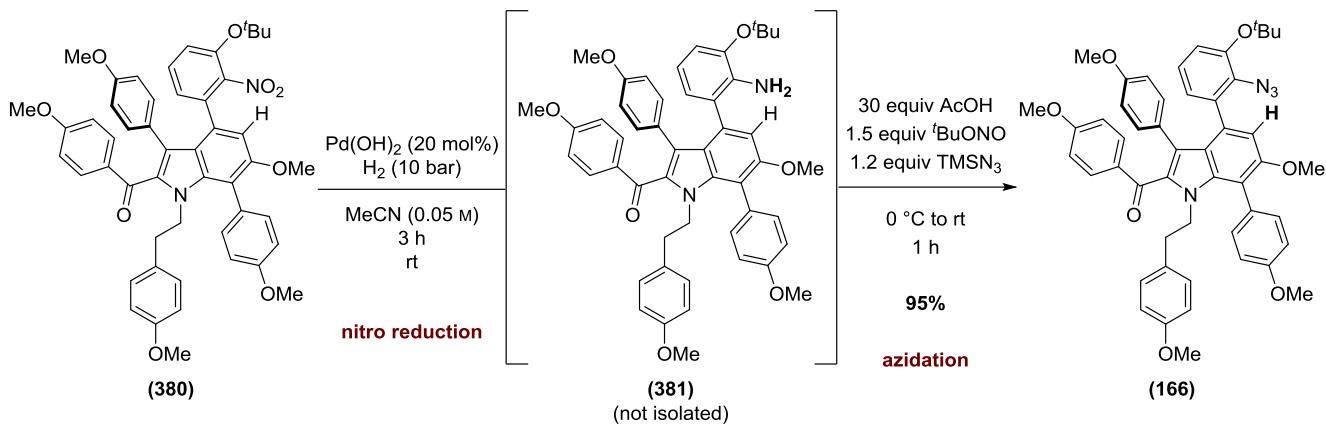
Generally, at temperatures above 150 °C the loss of nitrogen becomes favourable to form a free nitrene species that undergoes C–H insertion with the neighbouring aryl ring in *ortho*-azide biaryl systems.

As the nitro group proved pivotal to the C6 etherification process, a method to access the azide from this intermediate would be required (Table 25). To begin with, we examined the possibility of an iron mediated reduction. However, we found that with 10 equivalents of iron powder in ethanol and acetic acid superheated to 100 °C, conversion to the desired product was undesirably slow, taking two weeks to achieve completion (entry 1). A second attempt to utilise iron in *N,N*-dimethylformamide was met with similar results as little conversion was observed after 18 h (entry 2).

In a reassessment of this transformation, we considered how we might telescope this nitro reduction with the subsequent azidation process. This would have been rather impractical with the iron mediated reduction as various iron deposits may have interfered with subsequent procedures. As the azidation was conducted in acetonitrile, we examined the possibility of conducting a hydrogenation of the nitro group in the same solvent. This would allow for the metal catalyst to simply be filtered off, leaving the desired aniline dissolved in acetonitrile ready for immediate treatment in the next reaction. We reasoned that, although nitriles are susceptible to hydrogenation, acetonitrile would be unlikely to reduce at room temperature under relatively mild conditions.

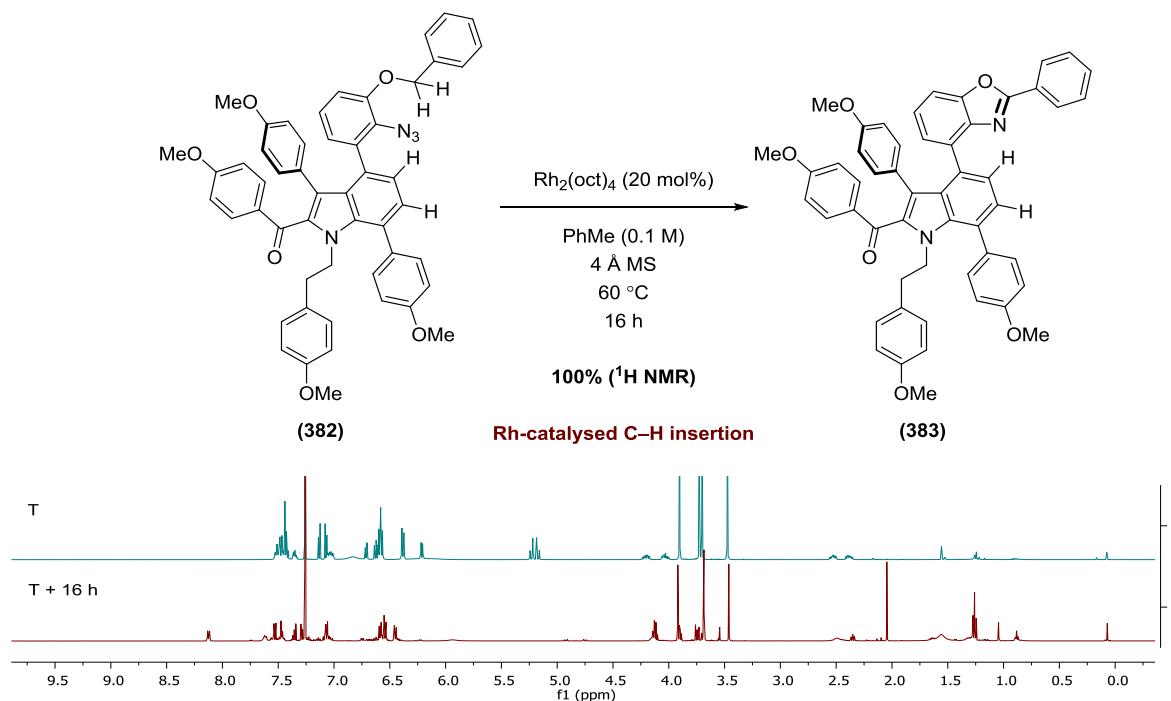
To this end, we had already subjected (**380**) to palladium on carbon (10 mol%) in tetrahydrofuran under an atmospheric pressure of hydrogen (entry 3). Only trace conversion to the aniline was observed and so we began to increase the pressure of hydrogen with acetonitrile as the solvent. At 10 bar pressure of hydrogen we began to see conversion to the desired product (entry 4), however it proved slow in approaching completion. Increasing the pressure to 50 bar in a Carl Roth autoclave gave complete conversion of the starting material, however an undesirable amount of side products began to form (entry 5).

Conducting the reaction at 50 bar would really have been a last resort and fortunately we were able to complete the reduction cleanly by using the slightly more active palladium(II) hydroxide catalyst at 10 bar pressure of hydrogen (entry 6). Simultaneously, a reaction with platinum on carbon under the same conditions resulted in complete conversion of the starting material to give a large number of unidentified side products (entry 7).



**Scheme 76.** One-pot conversion of nitro (**380**) to azide (**166**).

With acceptable conditions for the nitro reduction in hand, the metal catalyst was filtered off and the mixture treated in quick succession with *tert*-butyl nitrite and azidotrimethylsilane to synthesise the azide (**166**) (Scheme 76). In the first instance, no reactivity was observed. While puzzling at first, it became evident that trace reduction of acetonitrile in the previous step had resulted in a basic reaction mixture that hindered diazotization of the amine. This was fixed simply by the addition of 30 equivalents of acetic acid to the mixture which fully restored reactivity with complete conversion to (**166**) usually observed in less than 30 minutes.

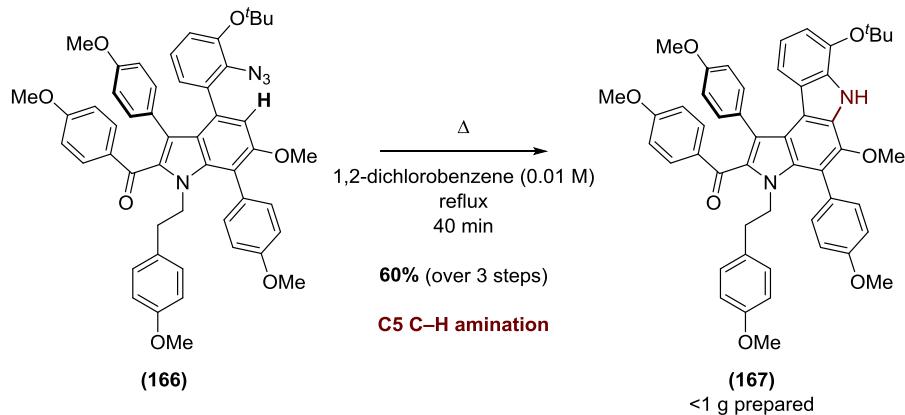


**Scheme 77.** Unwanted formation of benzoxazole (**383**) under rhodium-nitrenoid catalysis.

Our preliminary investigations into azide-mediated carbazole closures found that rhodium-nitrene formation was indeed occurring, but unwanted C–H insertion to the nearby benzyl

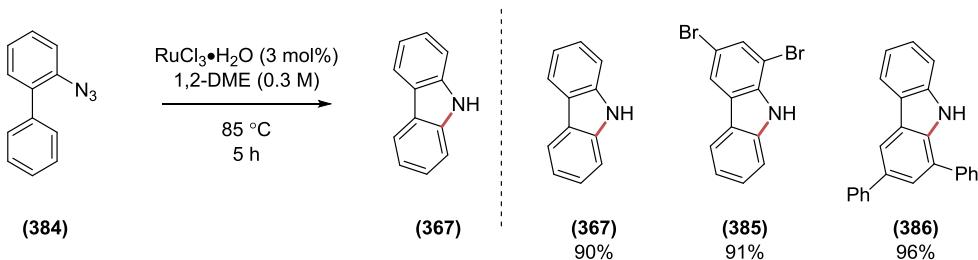
position dominated all reactivity (Scheme 77). Complete conversion to benzoxazoline (**383**) was observed by LCMS and a crude <sup>1</sup>H NMR confirmed disappearance of the benzyl peaks.

With the knowledge that C–H insertion of a nitrene species into the benzyl position may be a problem in achieving the desired C–H amination, we set about switching the phenol protecting group to a *tert*-butyl (the synthesis of intermediate (**166**) discussed earlier). This gave a formal synthesis with respect to Tokuyama and Fukuyama's total synthesis.



**Scheme 78.** Thermal azide decomposition as performed by Tokuyama and Fukuyama *et al.*

In their approach, azide **(166)** was decomposed thermally at temperatures above 180 °C in the high-boiling solvent 1,2-dichlorobenzene (Scheme 78). High reaction dilution of 0.01 M was required to prevent a large concentrated discharge of nitrogen or, worse, an explosion. Fortunately, the molecule has a very large molecular weight relative to the number of oxygen and nitrogen atoms which makes this outcome highly unlikely. After heating for 40 minutes, the product **(167)** was isolated in 60% yield (over three steps including a previous borylation and Suzuki coupling) on a sub-gram scale.



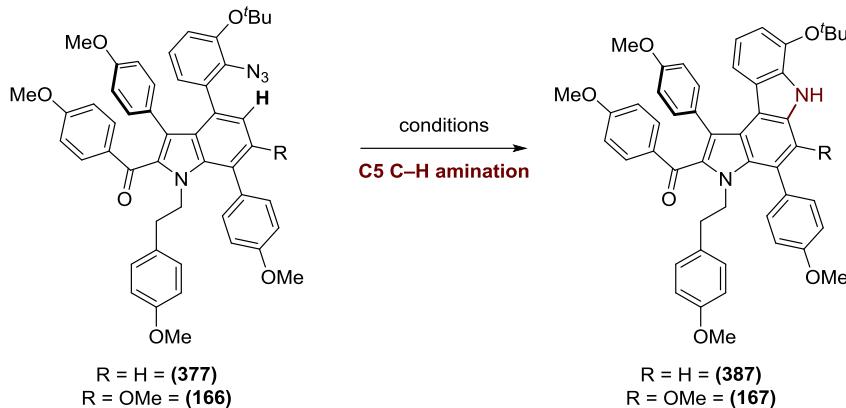
**Scheme 79.** Jia's ruthenium-catalysed intramolecular amination of biaryl azides.

As before, we were still interested in attempting this C–H amination as a metal-catalysed nitrenoid facilitated process. This was due to the drastically less harsh reaction conditions required relative to those above and the use of a low boiling solvent would greatly simplify

## Results and Discussion

purification. We also hoped this would improve the yield as material may be lost under the extreme thermal conditions. This type of reactivity generally also exhibits a better safety profile as the emission of nitrogen is better controlled over a more prolonged and steadier reaction time.

**Table 26.** Efforts towards a reductive azide carbazole closure.



entry	R	conditions	result
1	OMe	RuCl <sub>3</sub> •H <sub>2</sub> O (30 mol%), 1,2-DME (0.05 M), 85 °C, 5 h.	decomposed
2	H	Rh <sub>2</sub> (esp) <sub>2</sub> (20 mol%), toluene (0.05 M), 105 °C, 19 h.	~30% conversion (LCMS)
3	H	Rh <sub>2</sub> (oct) <sub>4</sub> (20 mol%), toluene (0.05 M), 105 °C, 19 h.	100% ( <sup>1</sup> H NMR)
4	OMe	Rh <sub>2</sub> (oct) <sub>4</sub> (10 mol%), PhMe (0.2 M), 115 °C, 22 h.	inseparable mixture of aniline and product (~1:2)
5	OMe	2.2 equiv BCl <sub>3</sub> , PhH (0.2 M), rt, 1 h.	decomposed
6	OMe	1,2-DCB (0.05 M), 175 °C, 30 min.	53% <sup>b</sup> (lit. 60% over 3 steps)
7 <sup>a</sup>	OMe	dioxane (0.1 M), 180 °C, flow reactor (10 mL, 0.333 mL min <sup>-1</sup> )	62% <sup>b</sup>

<sup>a</sup>Performed on gram-scale. <sup>b</sup>Yield of isolated product.

We began our investigation with a ruthenium-catalysed intramolecular amination procedure developed by Jia (Scheme 79).<sup>147</sup> After screening a range of catalysts, they discovered the process was best catalysed by a simple ruthenium(III) chloride catalyst. Exposure of biaryl azides to this metal complex in 1,2-dimethoxyethane at 85 °C for 5 hours gave the corresponding amination products in excellent yields. Interestingly, exceptionally high yields are still achieved when the *ortho* positions of the cyclised product are substituted. Most methods suffer drops in yield when substituted at this position or the results of such substrates are not disclosed in some reports.

Application of this method to our azide substrate (**166**) (Table 26, entry 1) resulted in decomposition of the starting material. This was disappointing and we reasoned that perhaps presence of two *ortho*-substituents was too much for the metal-catalysed transformation to be successful. Therefore, we instead exposed the non-methoxylated intermediate (**377**) to a bis[rhodium(II)( $\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid)] catalyst in toluene at 105 °C.<sup>148</sup> After 19 h, a reasonable amount of the material appeared to have converted to the desired product (entry 2). However, application of a rhodium(II) octanoate dimer catalyst under the same conditions (entry 3) gave complete conversion over the same period of time. A crude <sup>1</sup>H NMR spectrum quickly confirmed 100% clean conversion to the desired product (**387**). Unfortunately, our previous work had determined it was very difficult to functionalise the C6 position after the C5 amination and so attempts were made to translate this reaction success to the methoxylated azide intermediate (**166**).

Unfortunately, all attempts in an intramolecular C5 amination with the methoxy group in place resulted in concurrent aniline formation in significant quantities which was determined to be inseparable from the desired product. The two products appeared to be in an approximate 1:2 ratio of (**167**) to (**381**).

This result meant the use of a metal-catalysed C–H amination process was becoming increasingly unlikely and we decided to attempt an ambitious Lewis acid mediated process. Exposure of biaryl azides to boron trichloride has been shown to instigate the formation of carbazoles. We envisaged that, if successful, this could simultaneously remove the *tert*-butyl group ready for sulfonylation. Unfortunately, on prolonged exposure to over 2 equivalents of boron trichloride at room temperature resulted in decomposition to unidentified side-products (entry 5).

Finally, we attempted to reproduce Tokuyama and Fukuyama's reaction and were delighted to find that, on heating to 180 °C in 1,2-dichlorobenzene for 30 minutes at a fivefold higher concentration than in their original report, the desired amination product (**167**) was afforded in 53% yield.

While it was clear that the thermal decomposition of azide (**166**) was the best option of all the aminations discussed so far, we were still keen to increase the scalability, economics and safety profile of the reaction. We realised that flow chemistry was an ideal platform to meet these demands.



**Figure 8.** The basic flow-reactor setup used for the thermal nitrene amination.

The continuous flow of the substrate solution through the reactor would allow for constant production of multi-gram amounts of thermal azide decomposition product (**167**). As the reaction takes place in a dispersed stream of the reaction mixture, raising the concentration of the reaction to increase the reaction economy should not be a problem as the nitrogen gas would be produced steadily and remain comfortably within the reactor tubing. This in turn would increase the safety profile of performing thermal azide decompositions as the risk of an explosion is non-existent (excluding the azide reagent solution source).

We eventually opted to perform the reaction at 0.1 M concentration in the comparatively low boiling solvent dioxane with a 30 minute residence time in a stainless steel flow reactor (Figure 8). We were delighted to observe complete conversion by LCMS and precipitation of the product from dichloromethane with hexanes gave cyclised product (**167**) in a 62% yield in gram-scale quantities. Analysis of the concentrated filtrate by <sup>1</sup>H NMR spectrometry appeared to show only baseline noise, indicating that the remaining mass balance was likely lost to decomposition.

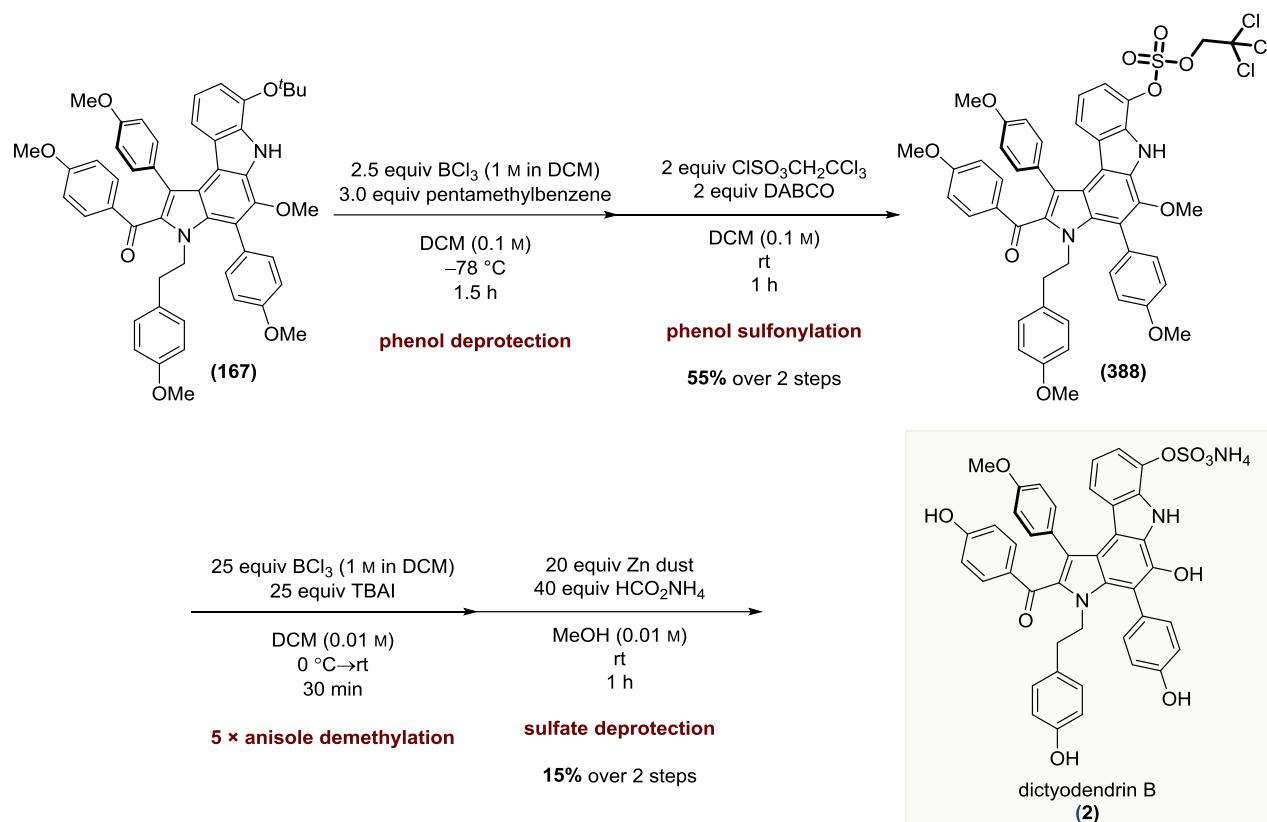
### 3.1.11 Steps 10–13: Final Deprotection Sequence

As discussed previously, the general protecting group strategy first used by Fürstner has been applied in all subsequent syntheses of the dictyodendrins and comprises of four distinct operations. The sensitive nature of the molecule's functional groups makes any improvement on this protecting group strategy unlikely at present.

Firstly, the *tert*-butyl phenol protecting group is removed in the presence of boron trichloride at -78 °C in just under 2 hours. After aqueous work-up, the crude reaction mixture is stirred in dichloromethane at room temperature with 1,4-diazabicyclo[2.2.2]octane (DABCO) and freshly prepared 2,2,2-trichloroethyl sulfurochloridate (**392**) to deliver the 'protected natural product' (**388**) in a 55% yield over 2 steps. The crystalline nature of this intermediate allowed for adequate

## Results and Discussion

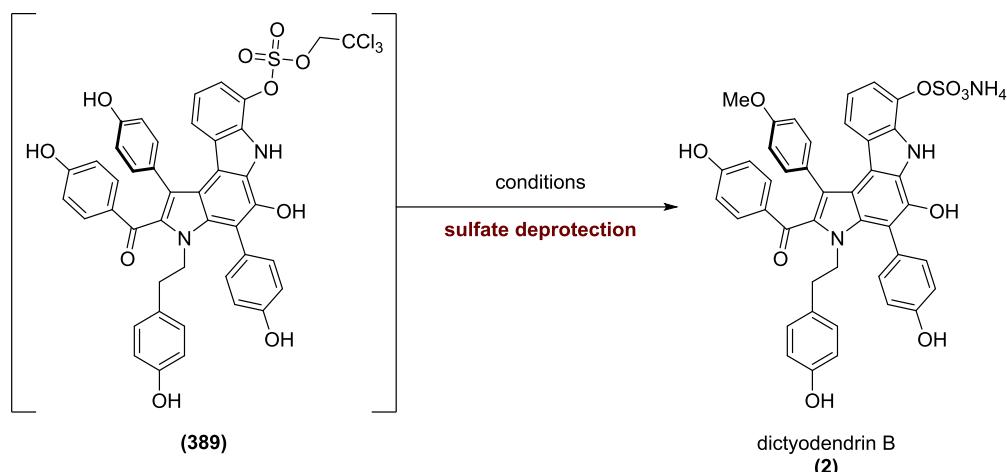
X-ray crystallographic data to be obtained to confirm the substitution pattern around the indole core (Figure 9).



**Scheme 80.** Final four-step deprotection sequence to afford dictyodendrin B.

The trichloroethyl group acts to protect the sulfate during the next step which involves exposure to a large excess of boron triiodide (generated *in situ* by the combination of 25 equivalents of boron trichloride and tetra-*n*-butylammonium iodide at  $0^\circ\text{C}$ ). The reaction appeared to stall at around 30 minutes by LCMS with conversion to the desired product observed as the major process along with a smaller, but still significant, presence of a partially deprotected monomethoxy intermediate.

Separate deprotection studies on a similar system indicated that the C6 methoxy group was more challenging to completely demethylate than the four anisole groups and it is thought that the same incompletely deprotected intermediate is also persistent in this instance. Addition of excess Lewis acid to try and force completion of the reaction was difficult due to the highly heterogeneous and viscous nature of the reaction, particularly when cooled.

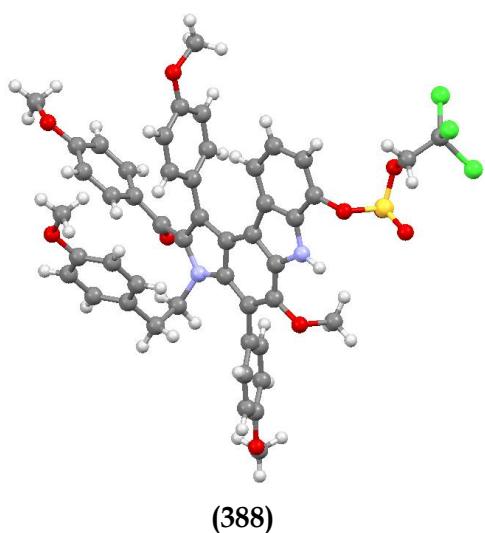
**Table 27.** Sulfate deprotection studies to deliver dictyodendrin B.

entry	conditions	yield (%) <sup>a</sup>
1	20 equiv Zn (acid activated), 40 equiv HCO <sub>2</sub> NH <sub>4</sub> , MeOH (0.01 M), rt	0
2	20 equiv Zn (1,2-dibromoethane and TMSCl activated), 40 equiv HCO <sub>2</sub> NH <sub>4</sub> , MeOH (0.01 M), rt	0
3	20 equiv Zn (ground overnight to activate), 40 equiv HCO <sub>2</sub> NH <sub>4</sub> , MeOH (0.01 M), rt	0
4	20 equiv Zn (sonicated), 40 equiv HCO <sub>2</sub> NH <sub>4</sub> , MeOH (0.01 M), rt	0
5	0.5 equiv Pd(OH) <sub>2</sub> , 40 equiv HCO <sub>2</sub> NH <sub>4</sub> , MeOH (0.01 M), rt	0
6	0.5 equiv Pd(OH) <sub>2</sub> , 40 equiv HCO <sub>2</sub> NH <sub>4</sub> , MeOH (0.01 M), 50 °C	0
7	10 equiv NaN <sub>3</sub> , MeOH (0.01 M), rt	0
8	10 equiv NaN <sub>3</sub> , MeOH (0.01 M), 50 °C	0
9	30 equiv 1 M NaOMe in MeOH, rt	0
10	30 equiv 1 M NaOMe in MeOH, 50 °C	0
11	silica plug <i>then</i> 20 equiv Zn (1,2-dibromoethane and TMSCl activated), 40 equiv HCO <sub>2</sub> NH <sub>4</sub> , MeOH (0.01 M), rt	15

<sup>a</sup>Yield given over two steps.

After aqueous work-up the crude mixture was subjected to conditions for the final step; removal of the trichloroethyl group to afford the free sulfate (Table 27). Unlike the previous three steps, this proved more challenging as the trichloroethyl group appeared remarkably stable. The use of

zinc activated by a number of methods such as exposure to hydrochloric acid (entry 1), sequential exposure to 1,2-dibromoethane and trimethylsilyl chloride (entry 2), grinding (entry 3) and sonication (entry 4), showed no conversion of the starting material after stirring at room temperature in methanol with ammonium formate. Attempts to use another metal known to remove sulfate trichloroethyl protecting groups, palladium(II) hydroxide, under similar conditions (entry 5) provided no improvement and heating to 50 °C (entry 6) also proved ineffective.<sup>149</sup> A similar survey with sodium azide (entries 7 and 8) was met with the same result.<sup>150</sup>

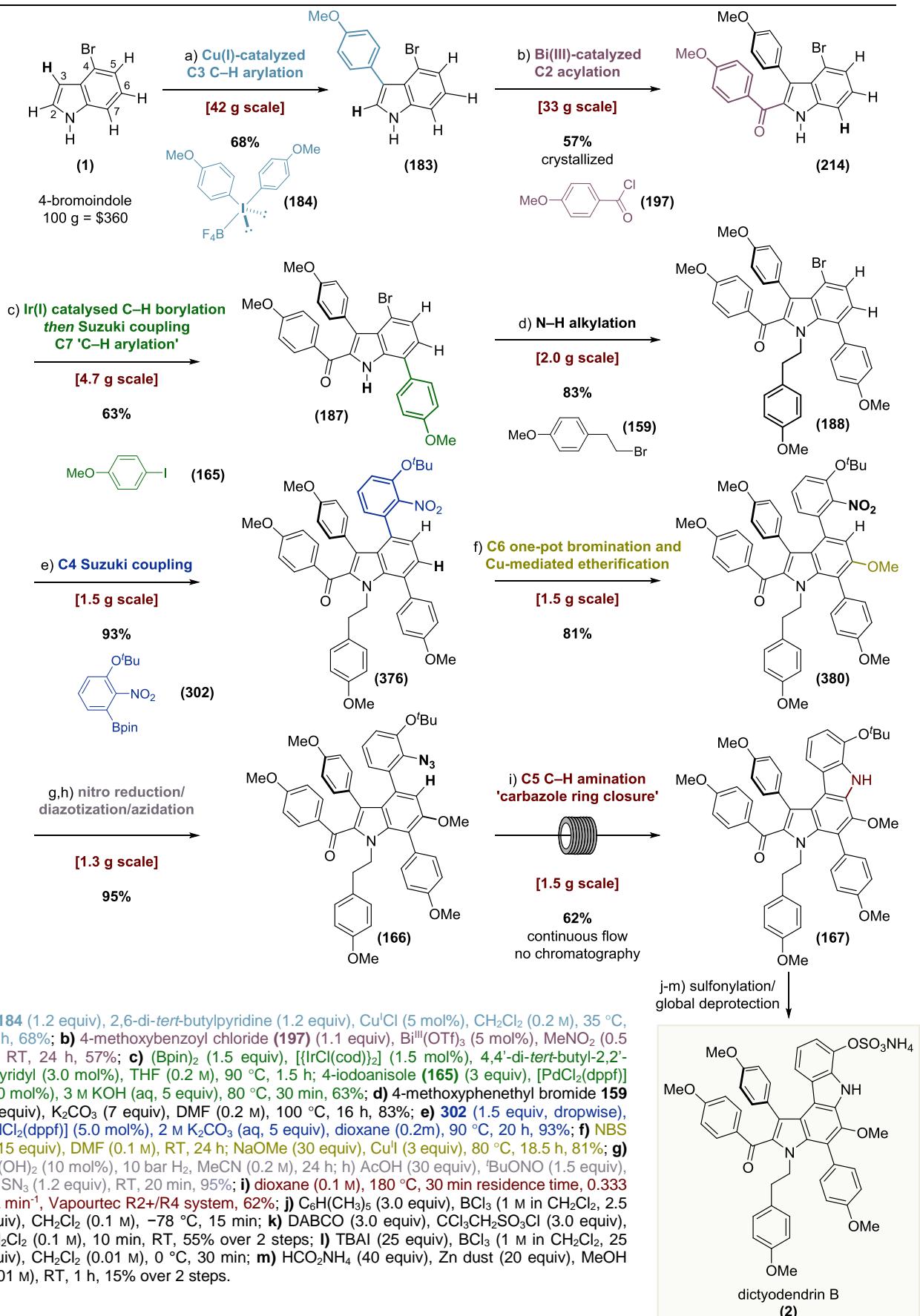


**Figure 9.** X-ray crystal of protected natural product (388)  
(solvent molecules removed for clarity).

The use of sodium methoxide to deprotect aryl sulfates usually results in basic cleavage of the ArO–S bond, but as this substrate was proving particularly challenging we decided to expose it to these conditions.<sup>151</sup> This proved futile as at both room temperature (entry 9) and 50 °C (entry 10) the sulfate remained intact and the starting material could be recovered.

Finally, we found that a small reverse-phase silica plug with 3:1 methanol/water eluent prior to stirring with activated zinc (1,2-dibromoethane and trimethylsilyl chloride) at room temperature under an inert atmosphere gave complete cleavage of the protecting group over an hour (entry 11). Separation of the incompletely deprotected C6-methoxy analogue and dictyodendrin B (**2**) proved exceptionally difficult during both chromatographic steps and this is thought to account for the low final yield of 15% as only pure fractions were combined to give the natural product in sufficient purity for determining yield and spectral data.

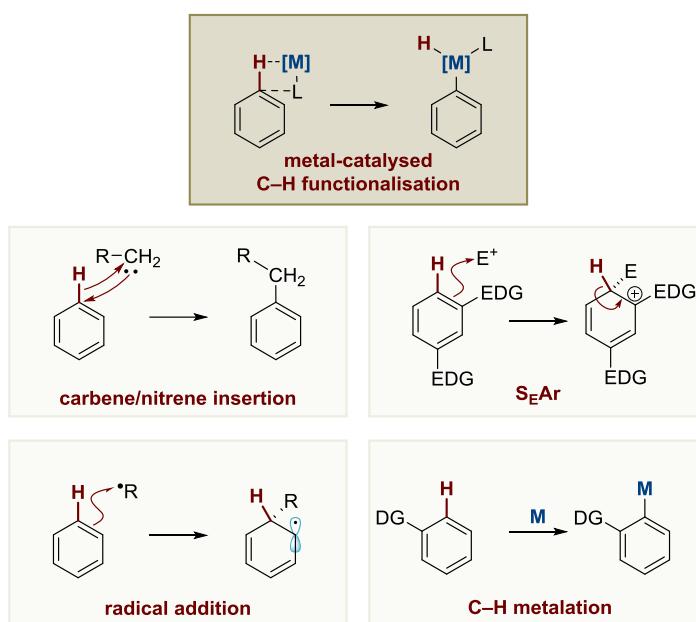
## 4 TOTAL SYNTHESIS OF DICTYODENDRIN B



Scheme 81. Total synthesis of dictyodendrin B by sequential C-H functionalisation.

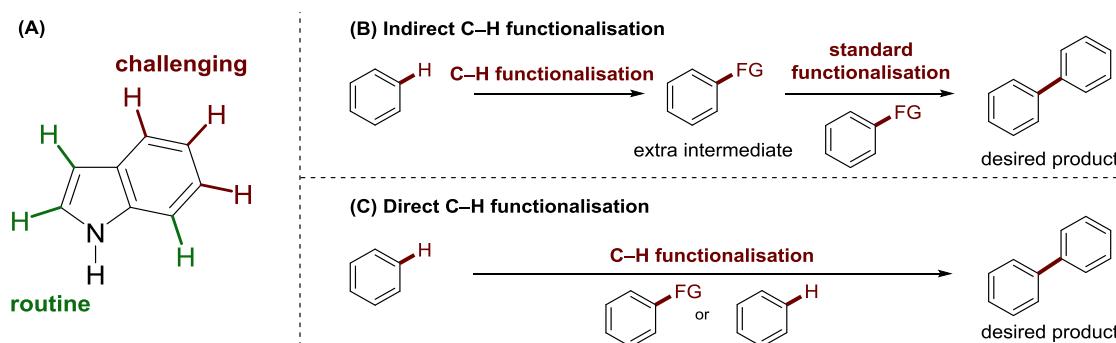
## 5 SUMMARY AND CONCLUSIONS

On reflection, the most challenging aspect of our synthesis arose during the functionalisation of the C4, C5 and C6 positions of the indole. Our original aim at the outset of the project was to use metal-catalysed C–H functionalisation (see section 2.2) for the majority of synthetic steps. However, as the synthesis progressed we became increasingly reliant on a broader spectrum of C–H functionalisations, such as the Friedel-Crafts acylation and electrophilic bromination. It had proven exceptionally challenging to be restricted to only one reactivity mode to transform C–H bonds in the synthesis of such a complex molecule.



**Scheme 82.** The well-established reactivity modes of  $C_{sp^2}$ -H bond transformation.

This highlights two important points: Firstly, the power of traditional C–H functionalisation methods should not be underestimated in conjunction with more modern metal-catalysed methods (Scheme 82) and, secondly, the C2, C3 and C7 positions of indole are much more readily and routinely functionalised than the C4, C5 and C6 positions (Scheme 83A). This is because the indole nitrogen (or protected variants thereof) can be used as a directing group to functionalise the neighbouring positions and the pyrrolo- ring of indole is inherently more reactive. Without any intrinsic reactivity or directing groups, the remaining three benzenoid positions are very difficult to react or target.



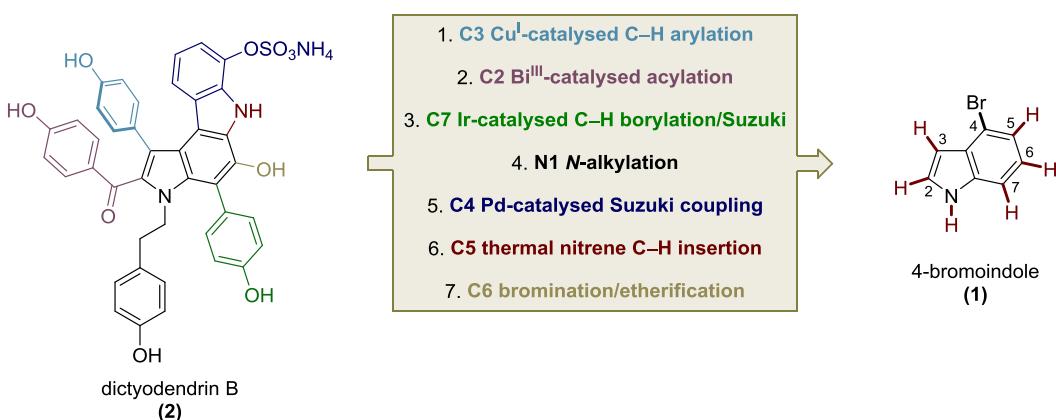
**Scheme 83.** The varying difficulty in the regioselective C–H functionalisation of indole and comparison of indirect and direct C–H functionalisation.

Furthermore, a truly concise sequential C–H functionalisation synthesis would theoretically involve direct installation of the required groups in single-step operations (Scheme 83C, without the introduction of any intermediate reactive functionality (Scheme 83B). Unfortunately, the use of solely direct C–H functionalisations proved beyond our reach in this total synthesis. However, indirect C–H functionalisation does still avoid carrying sensitive and reactive functionality through other steps of a synthetic route which helps to reduce the chance of complications or multi-step protecting group manipulations.

Returning more specifically to our total synthesis, the final deprotection steps offer limited scope for scalability compared to the previous steps that functionalise the indole core. To generate dictyodendrin B (**2**) in significant quantities, these final steps could be improved by finding other more easily removed orthogonal phenol protecting groups that still allow for the selective deprotection of the first phenol prior to sulfation. Also, a sulfate protecting group that is robust enough to no longer require the *tert*-butyl protecting group and that can be removed by a more reliable method would remove two steps and improve the efficiency of this sequence.

Overall, this highlights both the advantages and limitations currently facing C–H functionalisation (both direct and indirect). Further work is on-going in the synthetic chemical community to bring C–H functionalisation methodology in line with traditional methods to enable its definitive and widespread use by the synthetic chemist.

In summary, we have successfully executed a total synthesis of dictyodendrin B (**2**) by sequential C–H functionalisation (Scheme 84). Our work has resulted in a publication that is appended at the end of this thesis.<sup>152</sup> In a number of direct and one-pot procedures, we were able to sequentially functionalise all seven positions around 4-bromoindole on gram-scale.



**Scheme 84.** Overview of our final retrosynthetic disconnections in our sequential C–H functionalisation total synthesis of dictyodendrin B (2).

In accordance with our original aims, the synthesis is highly competitive in length and yields with those outlined in section 1.5. Furthermore, each step is very simple to perform (including the thermal decomposition of an azide which requires only the most basic setup of a flow reactor) and all major steps that functionalise the indole core were executed on gram-scale due to the wide availability and inexpensive nature of the reagents used. Most importantly the synthesis successfully implements our original plan of using multiple C–H functionalisations in an extended sequence for the construction of a complex molecule.

## 6 EXPERIMENTAL

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### 6.1 General Information

**Solvents:** All anhydrous solvents were dried by standard techniques and freshly distilled before use. Diethyl ether and tetrahydrofuran were distilled from lithium aluminium hydride; acetonitrile, dichloromethane and toluene from calcium hydride; and triethylamine from potassium hydroxide.

**Reagents:** All reagents were purified by standard procedures<sup>153</sup> or used as obtained from commercial sources. Copper(II) triflate was purchased from Alfa Aesar, dried under vacuum at 80 °C and stored under nitrogen before use. 4-Bromoindole was purchased from Apollo Scientific and used as supplied. Di-*tert*-butyl pyridine was purchased from Molecular and used as supplied.

**Chromatography:** All flash chromatography was carried out using dry packed Merck 9385 Kieselgel 60 silica gel and thin layer chromatography was carried out on Merck Kieselgel 60 PF254 0.2 mm plates. Visualisation was accomplished using ultra violet light (254 nm) and chemical staining with ceric ammonium molybdate or acidic potassium permanganate solutions as appropriate.

**Equipment:** Liquid Chromatography-Mass Spectrometry (LCMS) was performed on a Shimadzu UFLC-XR/LCMS 2020 system using a Shim-pack XR-ODS column (C18, 2.2µm, 3.0 mm x 50 mm). The LCMS acetonitrile (Rathburn) was pre-treated with water (5% vol) and formic acid (12.5 mM) and the LCMS water (Rathburn) was pre-treated with formic acid (25 mM) and ammonium acetate (10 mM). Gas Chromatography-Mass Spectrometry (GCMS) was performed on a Shimadzu MDGC/GCMS-2010 system. Microwave experiments were performed in a Biotage® Initiator+ System. Flow chemistry was performed using a Vapourtec-HT Reactor with a resolution of 1 °C, stainless steel, volume 10mL, 250 psi back pressure regulator. The reactor was heated using a Vapourtec R4 convection heating system and the pumps were controlled using a Vapourtec R2+ unit.

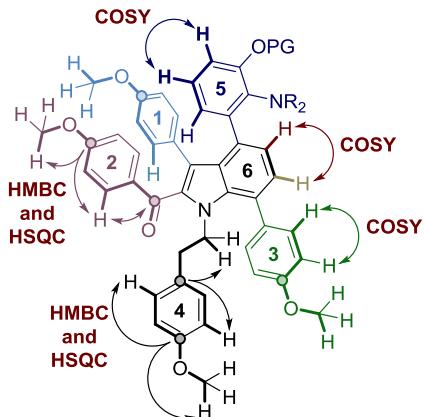
**Reactions:** All reactions were carried out using oven dried glassware and under an atmosphere of nitrogen unless otherwise stated.

**Data Collection:**  $^1\text{H}$  NMR spectra were recorded on a Bruker DPX 400 or 500 spectrometer in deuteriochloroform ( $\text{CDCl}_3$ ), unless stated otherwise.  $^{13}\text{C}$  NMR spectra were recorded at 100 or 125 MHz on the same machines. Chemical shifts ( $\delta$ ) are quoted in parts per million (ppm) relative to residual solvent ( $\text{CHCl}_3$ :  $\delta = 7.26$  ppm for  $^1\text{H}$  and  $\delta = 77.0$  for  $^{13}\text{C}$ ; Coupling constants ( $J$ ) are corrected and quoted in Hz to the nearest 0.1 Hz. The following abbreviations are used to indicate the multiplicity of the signals: s = singlet; d = doublet; t = triplet; q = quartet; qn = quintet; st = sextet, sp = septet; m = multiple; br = broad; app = apparent; and associated combinations, e.g. dd = doublet of doublets. The temperature of the acquisition of the NMR spectra was  $298 \pm 3\text{K}$ . DEPT135, nOe experiments and 2-dimensional experiments (COSY, HMBC and HMQC) were used to support assignments where appropriate but are not included. High resolution mass spectra (HRMS) were measured on a Micromass Q-TOF spectrometer using EI (electron impact) or ES (electrospray ionisation) techniques at the Department of Chemistry, University of Cambridge or at the EPSRC Mass Spectrometry Service at the University of Swansea. Measured values are reported to 4 decimal places and are within  $\pm 5$  ppm of the calculated value. The calculated values are based on the most abundant isotope (e.g.  $^{79}\text{Br}$ ). Infrared (IR) spectra were recorded on a Perkin Elmer 1FT-IR Spectrometer fitted with an ATR sampling accessory as either solids or neat films, either through direct application or deposited in  $\text{CHCl}_3$ , with absorptions reported in wavenumbers ( $\text{cm}^{-1}$ ). Melting points (mp) were recorded using a Reichert hot stage or Stanford Research Systems MPA100 apparatus. X-ray crystallography was performed on a Nonius Kappa CCD at the Cambridge University Chemistry X-Ray by Dr John E. Davies and Mr Peter D. Matthews and the data was deposited with the Cambridge Crystallographic Database.

**Assignments:**  $^1\text{H}$  NMR data of all molecules were assigned to the greatest extent possible using accompanying COSY, HSQC and HMBC spectra and by cross-referencing the spectra of structurally similar intermediates. The indoles were numbered using the standard convention of working clockwise, starting at the nitrogen, around the periphery of the ring.

The  $^1\text{H}$  NMR spectra of the main synthetic intermediates all required the use of correlation spectroscopy to accurately assign the peaks. The assignment of  $^{13}\text{C}$  NMR spectra is beyond the scope of this report and would not be possible without large amounts of each synthetic intermediate to perform a  $^{13}\text{C}/^{13}\text{C}$  incredible natural-abundance double-quantum transfer experiment (INADEQUATE). In aromatic systems  $^3J_{\text{HC}}$  coupling is much stronger than  $^2J_{\text{HC}}$  and  $^4J_{\text{HC}}$  couplings in  $^1\text{H}/^{13}\text{C}$  HMBC spectra.

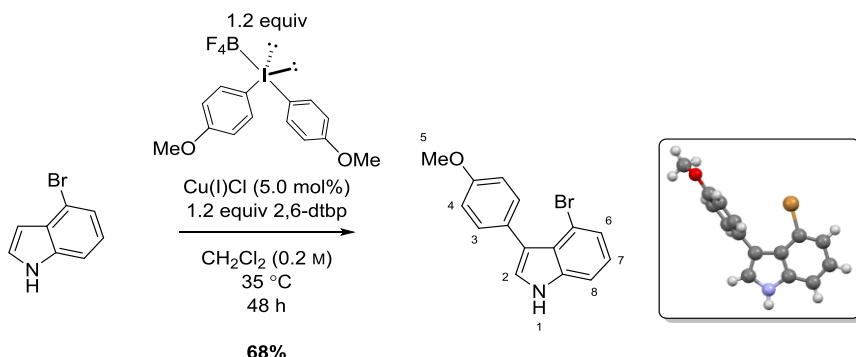
The general method of assigning the  $^1\text{H}$  NMR is outlined below:



The first ring was assigned by using the anisole methoxy group as a handle and using HMBC to correlate the protons with a quaternary carbon that was confirmed by absence in DEPT-135 spectra and no correlation in the HSQC. Intermediates containing the second ring were assigned in a similar fashion using the second anisole methoxy group. The aromatic protons could be differentiated from one another using COSY. The assignment of the second ring could be further confirmed by HMBC correlation of one of the aromatic protons with the carbonyl carbon. Assignment of the third ring was identical to the first. The fourth ring was also identified by the new anisole methoxy signal and could be further confirmed by HMBC coupling with the neighbouring two benzyl protons. The middle proton on ring five could be assigned by coupling with the two neighbouring protons. However, these two protons could not be distinguished from one another due to the lack of a desymmetrisation handle on the ring. Similarly, the two protons on ring six could be observed coupling to one another but it was difficult to discriminate between them.

## 6.2 Synthesis from 4-bromoindole

### 4-Bromo-3-(4-methoxyphenyl)-1*H*-indole (183)



2,6-Di-*tert*-butylpyridine (55.0 mL, 244 mmol, 1.2 equiv) was added to a suspension of bis(4-methoxyphenyl)iodonium tetrafluoroborate (**184**) (105 g, 244 mmol, 1.2 equiv) and copper(I) chloride (1.01 g, 10.2 mmol, 5.0 mol%) in anhydrous dichloromethane (1.02 L, 0.2 M) stirred at 300 rpm using an overhead stirrer in a 5 L glass-walled reactor vessel. 4-Bromoindole (**1**) (25.6 mL, 204 mmol, 1.0 equiv) was added and the mixture stirred at 35 °C for 48 h. The reaction mixture was cooled to rt and 8% aq sodium bicarbonate solution (500 mL) was added and the biphasic mixture stirred vigorously for 1 h. The reaction mixture was extracted with dichloromethane (2 x 500 mL) and concentrated on silica *in vacuo*. Purification by silica gel column chromatography (1:19 to 1:9 ethyl acetate/heptane) to give the title compound as a colourless solid (42.1 g, 68%).

**mp** 115–121 °C (dichloromethane/40–60 petroleum ethers).

**R<sub>f</sub>** 0.26 (1:1 diethyl ether/40–60 petroleum ethers).

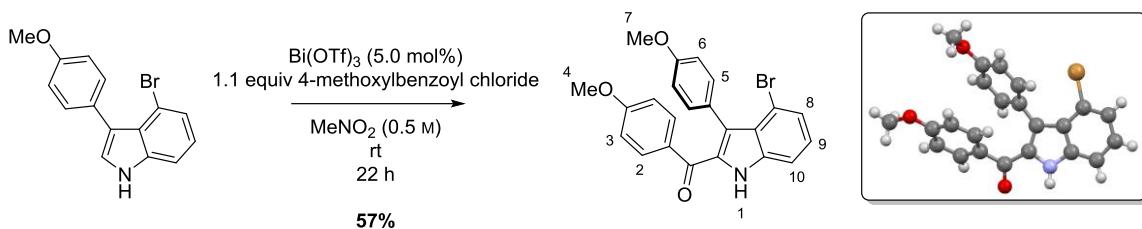
**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3412, 3000, 2936, 2834, 1611, 1574, 1550, 1500, 1476, 1464, 1440, 1425, 1337, 1281, 1302, 1235, 1193, 1175, 1144, 1121, 1105, 1069, 1050, 1028, 964, 907, 891, 833, 808.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.26 (s, 1H, H<sub>1</sub>), 7.42 (d, J = 8.8 Hz, 2H, H<sub>3</sub>), 7.38 (dd, J = 7.9, 0.8 Hz, 1H, H<sub>6/8</sub>), 7.32 (dd, J = 7.9, 0.8 Hz, 1H, H<sub>6/8</sub>), 7.17 (d, J = 2.5 Hz, 1H, H<sub>2</sub>), 7.06 (t, J = 7.9 Hz, 1H, H<sub>7</sub>), 6.94 (d, J = 8.8 Hz, 2H, H<sub>4</sub>), 3.87 (s, 3H, H<sub>5</sub>).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 158.8, 137.1, 132.6, 127.2, 125.0, 124.8, 124.5, 123.1, 119.4, 114.6, 112.8, 110.7, 55.4.

**HRMS** (APCI) found [M+H]<sup>+</sup> 302.0183 ([C<sub>15</sub>H<sub>12</sub><sup>79</sup>BrNO+H]<sup>+</sup> requires 302.0175; error 2.6 ppm).

**X-RAY** CCDC 888148.

**(4-Bromo-3-(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (214)**

Bismuth(III) triflate (4.34 g, 6.62 mmol, 5.0 mol%) was added in a single portion to a stirred solution of 4-bromo-3-(4-methoxyphenyl)-1*H*-indole (**183**) (40.0 g, 132 mmol, 1.0 equiv) and 4-methoxybenzoyl chloride (**197**) (19.7 ml, 146 mmol, 1.1 equiv) in nitromethane (510 mL, 0.5 M). The reaction was stirred at room temperature for 22 h before being concentrated. The dry residue was taken up in dichloromethane, filtered and stirred vigorously with 2 M aq potassium hydroxide (350 mL, approx. 5 equiv) overnight. The organic layer was separated, concentrated and the residue recrystallized from dichloromethane/heptane (32.9 g, 57%).

*NOTE: A C2/C2 dimerisation accounts for the remaining mass balance of this reaction.*

**mp** 145–146 °C (dichloromethane/hexane).

**R<sub>f</sub>** 0.55 (1:19 ethyl acetate/dichloromethane).

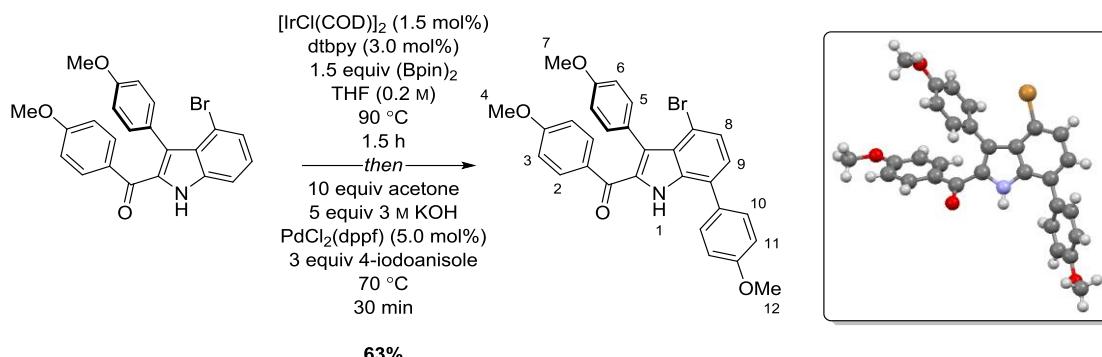
**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3306, 3059, 3036, 3000, 2959, 2936, 2910, 2836, 1609, 1597, 1572, 1555, 1533, 1510, 1490, 1463, 1442, 1418, 1403, 1373, 1333, 1313, 1285, 1249, 1167, 1138, 1110, 1054, 1036, 1021, 1004, 949, 935, 925, 871, 841, 827.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.55 (s, 1H, **H<sub>1</sub>**), 7.49 – 7.43 (m, 3H, **H<sub>2</sub>** and **H<sub>8/10</sub>**), 7.34 (d, J = 7.4 Hz, 1H, **H<sub>8/10</sub>**), 7.18 (t, J = 7.7 Hz, 1H, **H<sub>9</sub>**), 7.13 (d, J = 8.7 Hz, 2H, **H<sub>5</sub>**), 6.65 (d, J = 8.7 Hz, 2H, **H<sub>6</sub>**), 6.58 (d, J = 8.8 Hz, 2H, **H<sub>3</sub>**), 3.75 (s, 3H, **H<sub>4</sub>**), 3.74 (s, 3H, **H<sub>7</sub>**).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 188.8, 162.5, 159.1, 137.3, 134.1, 133.4, 131.7, 130.0, 126.5, 126.0, 125.5, 125.4, 124.2, 116.8, 113.0, 112.5, 111.5, 55.5, 55.3.

**HRMS** (ESI) found [M+H]<sup>+</sup> 436.0545 ([C<sub>23</sub>H<sub>18</sub><sup>79</sup>BrNO<sub>3</sub>+H]<sup>+</sup> requires 436.0543; error 0.5 ppm).

**X-RAY** CCDC 888149.

**(4-Bromo-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (187)**

To a mixture of bis(pinacolato)diboron (5.23 g, 20.6 mmol, 1.5 equiv), dichlorobis(cycloocta-1,5-diene)diiridium (I) (138 mg, 0.206 mmol, 1.5 mol%) and 4,4'-di-*tert*-butyl-2,2'-dipyridyl (107 mg, 0.412 mmol, 3.0 mol%) in an oven-dried pressure flask flushed with N<sub>2</sub> was added tetrahydrofuran (34.3 mL). The mixture was stirred at room for 5 min to give a homogeneous dark blue solution. A previously prepared homogeneous solution of (4-bromo-3-(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (**214**) (6.00 g, 13.7 mmol, 1.0 equiv) in tetrahydrofuran (34.3 mL, 0.2 M overall) was added and the reaction mixture was stirred at 90 °C in a pre-heated drybath. After 1.5 h LCMS showed full conversion of the starting material. Directly to the cooled reaction mixture was added acetone (10.1 mL, 137 mmol, 10 equiv) and 3 M aq potassium hydroxide (22.9 mL, 68.7 mmol, 5 equiv) (CAUTION - VENTILATE GAS) followed by a mixture of 4-iodoanisole (**165**) (10.0 g, 41.22 mmol, 3 equiv) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (502 mg, 0.687 mmol, 5.0 mol%). The reaction was stirred at 70 °C for 1 h in a pre-heated drybath. After 30 min LCMS showed full conversion of the starting material. The cooled reaction was concentrated to  $\frac{1}{4}$  volume *in vacuo*, diluted with ethyl acetate and washed with sat. aq ammonium chloride, water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrate on silica *in vacuo*. Purification by silica gel column chromatography (1:9 to 1:4 ethyl acetate/40–60 petroleum ethers) afforded the title compound as a bright yellow solid (4.72 g, 63%).

**mp** 121–123 °C (ethyl acetate/40–60 petroleum ethers).

**R<sub>f</sub>** 0.28 (3:7 ethyl acetate/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3431, 3258, 3054, 3001, 2958, 2936, 2910, 2836, 1610, 1599, 1572, 1535, 1510, 1492, 1463, 1440, 1418, 1383, 1360, 1315, 1304, 1281, 1242, 1174, 1138, 1110, 1092, 1031, 1022, 1004, 963, 928, 895, 836, 810.

Experimental

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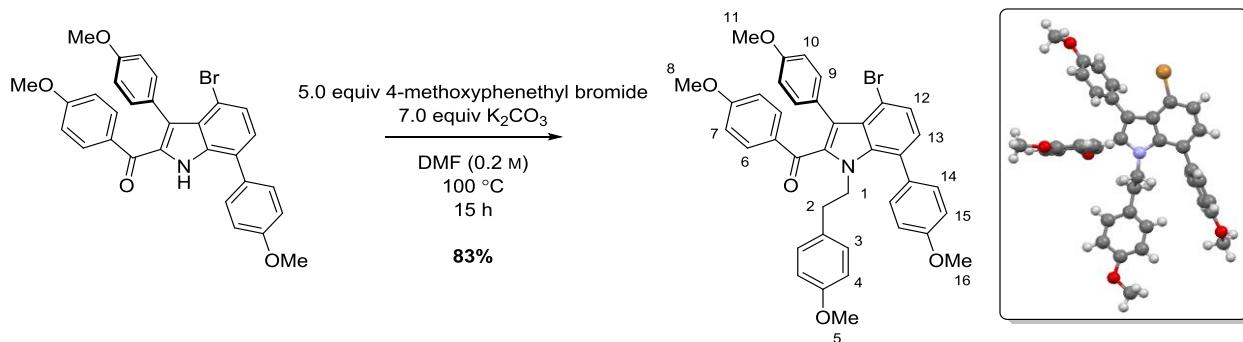
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.30 (s, 1H, H<sub>1</sub>), 7.57 (d, J = 8.8 Hz, 2H, H<sub>10</sub>), 7.44 (d, J = 8.9 Hz, 2H, H<sub>2</sub>), 7.41 (d, J = 7.7 Hz, 1H, H<sub>8</sub>), 7.19 – 7.11 (m, 3H, **H<sub>5</sub> and H<sub>9</sub>**), 7.08 (d, J = 8.8 Hz, 2H, H<sub>11</sub>), 6.66 (d, J = 8.8 Hz, 2H, H<sub>6</sub>), 6.57 (d, J = 8.9 Hz, 2H, H<sub>3</sub>), 3.90 (s, 3H, H<sub>12</sub>), 3.75 (s, 3H, H<sub>4</sub>) 3.749 (s, 3H, H<sub>7</sub>).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 188.5, 162.5, 159.7, 159.1, 135.3, 134.1, 133.5, 131.6, 130.0, 129.8, 129.5, 126.5, 125.9, 125.8, 125.5, 125.4, 124.4, 115.3, 115.0, 113.0, 112.5, 55.6, 55.5, 55.3.

**HRMS** (ESI) found [M+H]<sup>+</sup> 542.0957 ([C<sub>30</sub>H<sub>24</sub><sup>79</sup>BrNO<sub>4</sub>+H]<sup>+</sup> requires 542.0961; error -0.7 ppm).

**X-RAY** CCDC 896897.

**(4-Bromo-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (188)**



4-Methoxyphenethyl bromide (**159**) (2.88 mL, 18.4 mmol, 5.0 equiv) was added to a slurry of dry, ground potassium carbonate (3.57 g, 25.8 mmol, 7.0 equiv) and (4-Bromo-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (**187**) (2.00 g, 3.69 mmol, 1.0 equiv) in dry *N,N*-dimethylformamide (18.4 mL, 0.2 M). The mixture was stirred vigorously in a pre-heated oil bath at 100 °C for 15 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed with sat. aq ammonium chloride, water (×3) and brine (×2). The organics were dried over magnesium sulfate, filtered and concentrated on silica *in vacuo*. Purification by silica gel column chromatography (1:9 to 3:7 ethyl acetate/40–60 petroleum ethers) and subsequent recrystallisation from dichloromethane/hexane gave the title compound (2.07 g, 83%) as bright yellow crystals.

*NOTE: Elimination of the bromine to give 4-(methoxy)styrene is a competing side reaction. On occasions where stirring is not vigorous enough, small amounts of additional bromide can be added to drive the reaction to completion.*

**mp** 139.6–142.0 °C (dichloromethane/hexane).

**R<sub>f</sub>** 0.28 (1:4:5 toluene/diethyl ether/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 2988, 2968, 2958, 2935, 2902, 2837, 1638, 1601, 1597, 1572, 1538, 1511, 1463, 1441, 1422, 1405, 1384, 1356, 1316, 1303, 1285, 1242, 1174, 1165, 1150, 1107, 1086, 1066, 1030, 970, 908, 891, 837, 811.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.60 (d, J = 8.9 Hz, 2H, **H<sub>6</sub>**), 7.47 (d, J = 8.6 Hz, 2H, **H<sub>15</sub>**), 7.38 (d, J = 7.7 Hz, 1H, **H<sub>13</sub>**), 7.20 (d, J = 8.7 Hz, 2H, **H<sub>9</sub>**), 7.02 (d, J = 8.7 Hz, 2H, **H<sub>14</sub>**), 6.97 (d, J = 7.8 Hz, 1H, **H<sub>12</sub>**), 6.70 (d, J = 8.9 Hz, 2H, **H<sub>7</sub>**), 6.68 (d, J = 8.7 Hz, 2H, **H<sub>10</sub>**), 6.59 (d, J = 8.6 Hz, 2H, **H<sub>3</sub>**),

Experimental

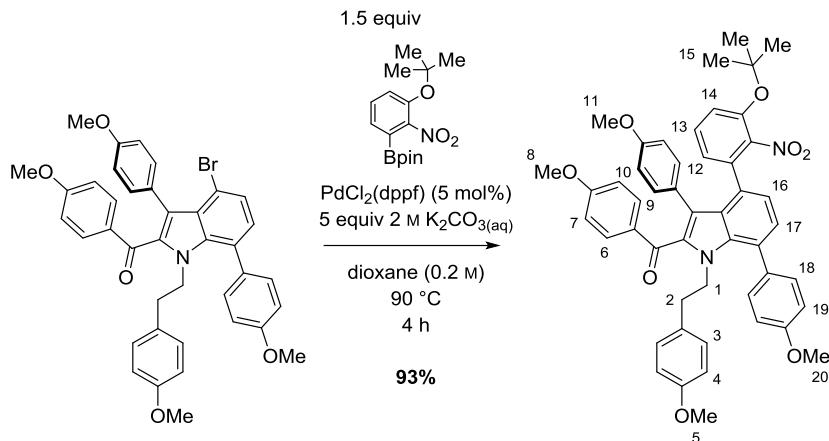
6.42 (d,  $J = 8.6$  Hz, 2H, H<sub>4</sub>), 4.00 (t,  $J = 8.2$  Hz, 2H, H<sub>1</sub>), 3.89 (s, 3H, H<sub>16</sub>), 3.79 (s, 3H, H<sub>8</sub>), 3.74 (s, 3H, H<sub>11</sub>), 3.69 (s, 3H, H<sub>5</sub>), 2.46 (t,  $J = 8.2$  Hz, 2H, H<sub>2</sub>).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 190.1, 163.7, 159.5, 158.8, 158.2, 137.8, 135.4, 133.6, 132.5, 132.1, 131.0, 130.9, 129.9, 129.6, 128.0, 126.7, 125.7, 125.5, 125.4, 121.0, 114.8, 113.9, 113.7, 113.5, 112.4, 55.6, 55.6, 55.3, 55.2, 47.7, 36.5.

**HRMS** (ESI) found [M+H]<sup>+</sup> 676.1695 ([C<sub>39</sub>H<sub>34</sub><sup>79</sup>BrNO<sub>5</sub>+H]<sup>+</sup> requires 676.1693; error 0.3 ppm).

**X-RAY** CCDC 888150.

**(4-(3-(*tert*-butoxy)-2-nitrophenyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (376)**



To (4-bromo-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (**188**) (1.50 g, 2.22 mmol, 1.0 equiv) and bis(triphenylphosphine)palladium(II) dichloride (81.1 mg, 0.111 mmol, 5.0 mol%) under nitrogen in an oven-dried glass round bottomed flask was added dioxane (11.1 mL, 0.2 M) and 2 M aq potassium carbonate (5.54 mL, 11.1 mmol, 5.0 equiv) and the mixture stirred at 90 °C in a pre-heated oil bath. A solution of 2-(3-(*tert*-butoxy)-2-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**302**) (1.07 g, 3.33 mmol, 1.5 equiv) in dioxane (11.1 mL) was added dropwise to this mixture by syringe pump over approximately 12 h. Complete conversion of the starting material was observed at 20 h by LCMS. The reaction was cooled to room temperature, diluted with ethyl acetate and washed with sat. aq ammonium chloride, water and brine. The organic layer was dried over magnesium sulphate, filtered and concentrated on silica *in vacuo*. Purification by silica gel column chromatography (1:4 to 1:2 ethyl acetate/40–60 petroleum ethers) gave the title compound as a pale yellow solid (1.64 g, 93%).

**mp** 117.5–120.5 °C (ethyl acetate/40–60 petroleum ethers).

**R<sub>f</sub>** 0.31 (3:7 ethyl acetate/40–60 petroleum ethers).

**IR**  $\nu_{\max}$  (film)/cm<sup>-1</sup> 2979, 2937, 2904, 2837, 1734, 1635, 1597, 1573, 1532, 1511, 1500, 1464, 1442, 1422, 1368, 1302, 1241, 1163, 1108, 1030, 1003, 951, 886, 849, 837, 804.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.53 – 7.46 (m, 4H, **H<sub>6</sub>** and **H<sub>18</sub>**), 7.12 (d, *J* = 7.4 Hz, 1H, **H<sub>16</sub>**), 7.04 (d, *J* = 7.4 Hz, 1H, **H<sub>17</sub>**), 7.05 – 7.01 (m, 2H, **H<sub>19</sub>**) 6.87 (dd, *J* = 8.3, 1.1 Hz, 1H, **H<sub>12</sub>**), 6.86 (br. s, 2H, **H<sub>9</sub>**) 6.63 (dd, *J* = 8.4, 7.8 Hz, 1H, **H<sub>13</sub>**), 6.59 (d, *J* = 8.6 Hz, 2H, **H<sub>3</sub>**), 6.57 (d, *J* = 9.1 Hz, 2H, **H<sub>7</sub>**), 6.38 (d, *J* = 8.6 Hz, 2H, **H<sub>4</sub>**), 6.31 (dd, *J* = 7.8, 1.1 Hz, 1H, **H<sub>14</sub>**), 6.29 (br. s, 2H, **H<sub>10</sub>**), 4.24 – 3.98 (m,

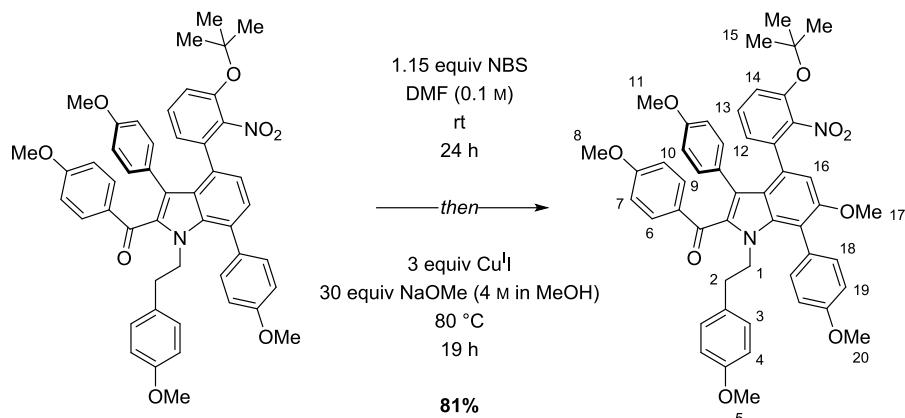
Experimental

2H, H<sub>1</sub>), 3.90 (s, 3H, H<sub>20</sub>), 3.73 (s, 3H, H<sub>8</sub>), 3.70 (s, 3H, H<sub>5</sub>), 3.59 (s, 3H, H<sub>11</sub>), 2.57 – 2.34 (m, 2H, H<sub>2</sub>), 1.47 (s, 9H, H<sub>15</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 190.2, 163.4, 159.4, 158.2, 157.8, 147.3, 145.6, 137.0, 135.7, 133.5, 132.7, 132.6, 131.5, 131.4, 130.8, 130.8, 130.1, 129.7, 129.0, 127.8, 127.7, 127.3, 127.1, 126.1, 125.4, 122.2, 121.6, 120.3, 113.9, 113.7, 113.6, 113.2, 112.6, 81.9, 55.6, 55.5, 55.3, 55.2, 47.6, 36.6, 29.3.

**HRMS** (ESI) found 791.3323 [M+H]<sup>+</sup> ([C<sub>49</sub>H<sub>46</sub>N<sub>2</sub>O<sub>8</sub>+H]<sup>+</sup> requires 791.3327 ; error –0.5 ppm).

**(4-(3-(*tert*-butoxy)-2-nitrophenyl)-6-methoxy-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (380)**



To a stirred solution of (4-(3-(*tert*-butoxy)-2-nitrophenyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (**376**) (1.876 g, 2.37 mmol, 1 equiv) in *N,N*-dimethylformamide (23.7 mL, 0.1 M) in a loosely capped glass vial at rt was added *N*-bromosuccinimide (443 mg, 0.50 mmol, 1.05 equiv) in a single portion. Additional *N*-bromosuccinimide (42 mg, 0.1 equiv) was added at 22 h to push the reaction to completion as determined by LCMS at 24 h. A fresh solution of sodium methoxide (3.84 g, 30 equiv, 4.0 M in MeOH) was prepared separately in a loosely capped vial by the portionwise addition of sodium metal (1.636 g, 71.2 mmol, 30 equiv) to vigorously stirred methanol (17.8 mL, 4.0 M). The freshly prepared sodium methoxide solution and copper(I) iodide (1.36 g, 7.12 mmol, 3 equiv) were added sequentially to the reaction mixture. The vial was sealed and stirred in a pre-heated oil bath at 80 °C until complete conversion was observed by LCMS at 19 h. After cooling to rt, the reaction was filtered through a thin pad of Celite® with excess ethyl acetate and the organic was washed with sat. aq ammonium chloride and water. The organic layer was dried over magnesium sulphate, filtered and concentrated on silica *in vacuo*. Purification by silica gel column chromatography (1:4 to 3:7 ethyl acetate/40–60 petroleum ethers) gave the title compound as a dark yellow solid (1.57 mg, 81%).

**mp** 110.2–112.8 °C (dichloromethane/hexane).

**R**<sub>f</sub> 0.44 (1:2 ethyl acetate/40–60 petroleum ethers).

**IR**  $\nu_{\max}$  (film)/cm<sup>-1</sup> 2980, 2956, 2937, 2905, 2838, 1633, 1597, 1572, 1533, 1511, 1463, 1443, 1422, 1393, 1368, 1302, 1285, 1242, 1205, 1174, 1153, 1108, 1090, 1031, 1005, 976, 960, 918, 902, 883, 838, 808.

Experimental

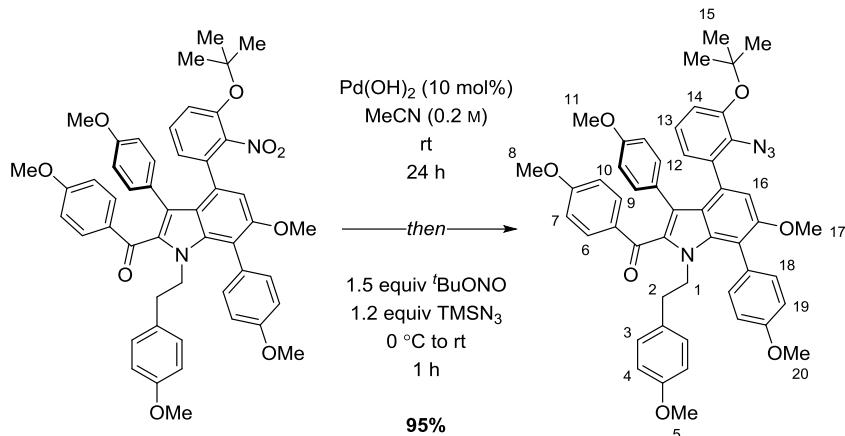
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**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.49 – 7.39 (m, 2H, H<sub>18</sub>), 7.45 (d, J = 8.2 Hz, 2H, H<sub>6</sub>), 7.08 – 6.99 (m, 2H, H<sub>19</sub>), 6.88 (dd, J = 8.4, 1.2 Hz, 1H, H<sub>12</sub>), 6.83 (br. s, 2H, H<sub>9</sub>), 6.82 (s, 1H, H<sub>16</sub>), 6.63 (d, J = 8.0 Hz, 1H, H<sub>13</sub>), 6.60 (d, J = 8.7 Hz, 2H, H<sub>3</sub>), 6.55 (d, J = 9.0 Hz, 2H, H<sub>7</sub>), 6.47 (d, J = 8.7 Hz, 2H, H<sub>4</sub>), 6.30 (dd, J = 7.8, 1.2 Hz, 1H, H<sub>14</sub>), 6.28 (br. s, 2H, H<sub>10</sub>) 4.13 – 3.75 (m, 2H, H<sub>1</sub>), 3.88 (s, 3H, H<sub>20</sub>), 3.74 (s, 3H, H<sub>17</sub>), 3.71 (s, 3H, H<sub>8</sub>), 3.69 (s, 3H, H<sub>5</sub>), 3.59 (s, 3H, H<sub>11</sub>), 2.58 – 2.36 (s, 1H, H<sub>2</sub>), 1.47 (s, 9H, H<sub>15</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 189.8, 163.2, 159.3, 158.2, 157.8, 154.6, 147.3, 145.5, 137.5, 136.5, 133.5, 132.6, 132.3, 132.3, 131.5, 131.0, 130.4, 129.8, 129.5, 127.9, 127.3, 127.1, 125.8, 122.0, 120.3, 120.3, 114.9, 113.9, 113.7, 113.1, 112.6, 109.5, 81.9, 57.1, 55.4, 55.3, 55.3, 47.0, 36.6, 29.3.

**HRMS** (APCI) found 821.3432 [M+H]<sup>+</sup> ([C<sub>50</sub>H<sub>48</sub>N<sub>2</sub>O<sub>9</sub>+H]<sup>+</sup> requires 821.3433; error –0.1 ppm).

**(4-(2-azido-3-(*tert*-butoxy)phenyl)-6-methoxy-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (166)**



A solution of (4-(3-(*tert*-butoxy)-2-nitrophenyl)-6-methoxy-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (**380**) (1.38 g, 1.68 mmol, 1.0 equiv) in acetonitrile (8.4 mL, 0.2 M) was transferred to a glass lined Carl-Roth autoclave primed with palladium hydroxide on carbon (236 mg, 10 mol%, 10 wt. %). The autoclave was sealed and the reaction mixture stirred vigorously at rt under an atmosphere of H<sub>2</sub> (10 bar). After 24 h LCMS showed complete conversion and the mixture was filtered through a thin pad of Celite® with acetonitrile (8.6 mL, 0.1 M overall). The solution was cooled to 0 °C and acetic acid (2.89 mL, 50.4 mmol, 30 equiv) was added and the mixture stirred for 1 min. *tert*-Butyl nitrite (0.300 mL, 2.52 mmol, 1.5 equiv) and trimethylsilyl azide (0.268 mL, 2.02 mmol, 1.2 equiv) were then added dropwise in immediate succession before the ice bath was removed and the mixture stirred at rt until complete conversion was observed by LCMS at 1 h. The reaction mixture was concentrated directly on silica *in vacuo*. Purification by silica gel column chromatography (3:7 ethyl acetate/40–60 petroleum ethers) gave the title compound as a brown solid (1.30 g, 95%).

The data were in accordance with the literature.<sup>90</sup>

**mp** 140–160 °C (decomposed).

**R<sub>f</sub>** 0.17 (1:4 ethyl acetate/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3067, 2976, 2935, 2909, 2837, 2117, 1632, 1609, 1597, 1574, 1540, 1512, 1463, 1442, 1421, 1393, 1355, 1340, 1303, 1286, 1244, 1206, 1174, 1154, 1132, 1110, 1092, 1033, 1004, 977, 960, 905, 884, 838, 803.

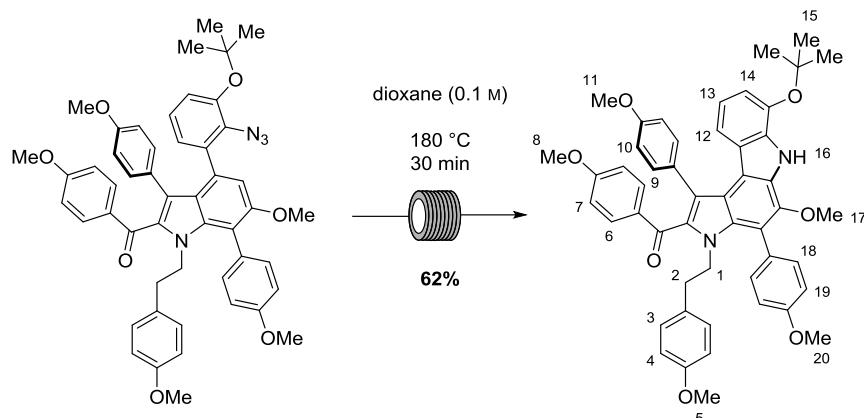
Experimental

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.54 – 7.48 (m, 4H, H<sub>6</sub> and H<sub>18</sub>), 7.05 (d, J = 8.8 Hz, 2H, H<sub>19</sub>), 6.83 – 6.79 (m, 4H, H<sub>9</sub> and H<sub>10</sub>), 6.70 (s (br), 2H, H<sub>12/13/14/16</sub>), 6.59 (d, J = 8.7 Hz, 2H, H<sub>3</sub>), 6.56 (d, J = 9.0 Hz, 2H, H<sub>7</sub>), 6.52 (d, J = 8.7 Hz, 2H, H<sub>4</sub>), 6.29 (s (br), 2H, H<sub>12/13/14/16</sub>), 4.04 – 3.98 (m, 1H, H<sub>1a</sub>), 3.92 – 3.86 (m, 1H, H<sub>2b</sub>), 3.89 (s, 3H, H<sub>20</sub>), 3.79 (s, 3H, H<sub>11</sub>), 3.72 (s, 3H, H<sub>8</sub>), 3.69 (s, 3H, H<sub>5</sub>), 3.60 (s, 3H, H<sub>16</sub>), 2.57 – 2.52 (m, 1H, H<sub>2b</sub>), 2.48 – 2.42 (m, 1H, H<sub>2a</sub>), 1.36 (s, 9H, H<sub>15</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 189.9, 163.0, 159.1, 157.9, 157.5, 154.6, 149.3, 136.7, 135.9, 134.1, 133.3, 132.3, 132.3, 132.1, 131.3, 131.1, 130.6, 130.3, 129.6, 127.6, 126.3, 125.2, 123.4, 122.6, 120.7, 120.5, 113.8, 113.8, 113.7, 113.5, 113.0, 112.1, 109.6, 80.3, 57.1, 55.3, 55.3, 55.1, 55.1, 46.8, 36.5, 28.4.

**HRMS** (ESI) found 817.3594 [M+H]<sup>+</sup> ([C<sub>50</sub>H<sub>48</sub>N<sub>4</sub>O<sub>7</sub>+H]<sup>+</sup> requires 817.3596; error –0.2 ppm).

**(7-(*tert*-butoxy)-5-methoxy-3-(4-methoxyphenethyl)-1,4-bis(4-methoxyphenyl)-3,6-dihydropyrrolo[2,3-c]carbazol-2-yl)(4-methoxyphenyl)methanone (167)**



(4-(2-Azido-3-(*tert*-butoxy)phenyl)-6-methoxy-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (**166**) (2.50 g, 3.06 mmol) was dissolved in dioxane (30.6 mL, 0.1 M). The solution was passed through a steel flow reactor (10 mL, 30 min residence time, flow rate 0.333 mL min<sup>-1</sup>) at 180 °C. The product was collected in an open flask and concentrated *in vacuo*. The residue was then triturated using dichloromethane/hexane to give the title compound as a light brown solid (1.50 g, 62%).

The data were in accordance with the literature.<sup>90</sup>

**mp** 210.2–212.6 °C (dichloromethane/hexane).

**R<sub>f</sub>** 0.32 (1:2 ethyl acetate/40–60 petroleum ethers).

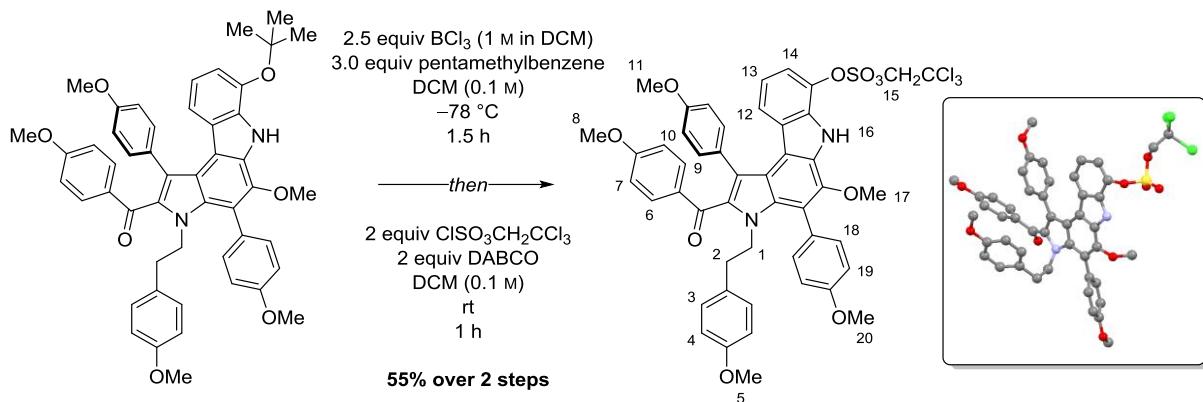
**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3356, 2975, 2933, 2837, 1599, 1573, 1533, 1512, 1462, 1440, 1420, 1391, 1366, 1352, 1302, 1284, 1244, 1173, 1160, 1108, 1068, 1033, 1007, 971, 928, 904.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.42 (s, 1H, **H<sub>16</sub>**), 7.60 (d, J = 8.6 Hz, 2H, **H<sub>18</sub>**), 7.54 (d, J = 8.8 Hz, 2H, **H<sub>6</sub>**), 7.28 (d, J = 8.6 Hz, 2H, **H<sub>9</sub>**), 7.08 (d, J = 8.6 Hz, 2H, **H<sub>19</sub>**), 6.93 (d, J = 7.8, 1H, **H<sub>12/14</sub>**), 6.78 (d, J = 8.6 Hz, 2H, **H<sub>10</sub>**), 6.67 – 6.63 (m, 3H, **H<sub>7</sub>** and **H<sub>13</sub>**), 6.60 (d, J = 8.7 Hz, 2H, **H<sub>3</sub>**), 6.52 (d, J = 8.6 Hz, 2H, **H<sub>4</sub>**), 5.95 (d, J = 8.2 Hz, 1H, **H<sub>12/14</sub>**), 4.02 – 3.99 (m, 2H, **H<sub>1</sub>**), 3.91 (s, 3H, **H<sub>20</sub>**), 3.81 (s, 3H, **H<sub>11</sub>**), 3.78 (s, 3H, **H<sub>8</sub>**), 3.69 (s, 3H, **H<sub>5</sub>**), 3.64 (s, 3H, **H<sub>17</sub>**), 2.55 – 2.52 (m, 2H, **H<sub>2</sub>**), 1.48 (s, 9H, **H<sub>15</sub>**).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 190.0, 163.1, 159.5, 159.0, 158.2, 142.8, 140.6, 136.4, 134.6, 133.3, 132.4, 131.9, 131.3, 130.5, 129.7, 129.6, 128.7, 127.4, 125.2, 122.3, 119.71, 119.67, 118.8, 118.2, 117.4, 116.0, 114.0, 113.7, 113.4, 113.3, 113.2, 80.1, 61.3, 55.6, 55.5, 55.3, 47.7, 36.8, 29.3.

**HRMS** (ESI) found 789.3531 [M+H]<sup>+</sup> ([C<sub>50</sub>H<sub>48</sub>N<sub>2</sub>O<sub>7</sub>+H]<sup>+</sup> requires 789.3534; error –0.4 ppm).

**5-methoxy-2-(4-methoxybenzoyl)-3-(4-methoxyphenethyl)-1,4-bis(4-methoxyphenyl)-3,6-dihydropyrrolo[2,3-c]carbazol-7-yl (2,2,2-trichloroethyl) sulfate (388)**



(7-(*tert*-Butoxy)-5-methoxy-3-(4-methoxyphenethyl)-1,4-bis(4-methoxyphenyl)-3,6-dihydropyrrolo[2,3-c]carbazol-2-yl)(4-methoxyphenyl)methanone (**167**) (263 mg, 0.333 mmol, 1.0 equiv) and pentamethylbenzene (148 mg, 1.00 mmol, 3.0 equiv) were stirred in dichloromethane (3.33 mL, 0.1 M) at -78 °C. Boron trichloride (1 M in dichloromethane, 0.833 mL, 0.833 mmol, 2.5 equiv) was added dropwise by syringe pump over 10 min (approx. 0.08 mL/min). After 15 min complete conversion was observed by LCMS and the reaction quenched with 10% methanol in chloroform (5 mL) and warmed to rt. The reaction mixture was concentrated *in vacuo* and partitioned between dichloromethane/sat. aq ammonium chloride. The aqueous layer was separated and further extracted with dichloromethane ( $\times 2$ ) before the organics were combined, dried over sodium sulfate, filtered and concentrated *in vacuo*.

The crude mixture and 1,4-diazabicyclo[2.2.2]octane (122 mg, 1.00 mmol, 3.0 equiv) were taken up in dichloromethane (3.33 mL, 0.1 M). 2,2,2-Trichloroethyl sulfurochloridate (248 mg, 1.00 mmol, 3.0 equiv) was added and the mixture stirred at rt. After 10 min complete conversion to the desired product was observed by LCMS and the reaction was diluted with sat. aq ammonium chloride (5 mL). The aqueous layer was separated and further extracted with dichloromethane ( $\times 2$ ) before the organics were combined, dried over sodium sulfate, filtered and concentrated on silica *in vacuo*. Purification by silica gel column chromatography (1:3 ethyl acetate/hexane) gave the title compound as a yellow amorphous solid (174 mg, 55% over 2 steps, 74% per step).

Data are in accordance with the literature.<sup>79</sup>

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**mp** 115.1–118.0 °C (decomposed).

**R<sub>f</sub>** 0.35 (1:2 ethyl acetate/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3005, 2956, 2934, 2837, 1609, 1598, 1572, 1535, 1512, 1464, 1443, 1419, 1366, 1351, 1313, 1302, 1286, 1245, 1195, 1174, 1160, 1108, 1069, 1032, 1008, 998, 967, 927, 887, 869, 850, 838, 815.

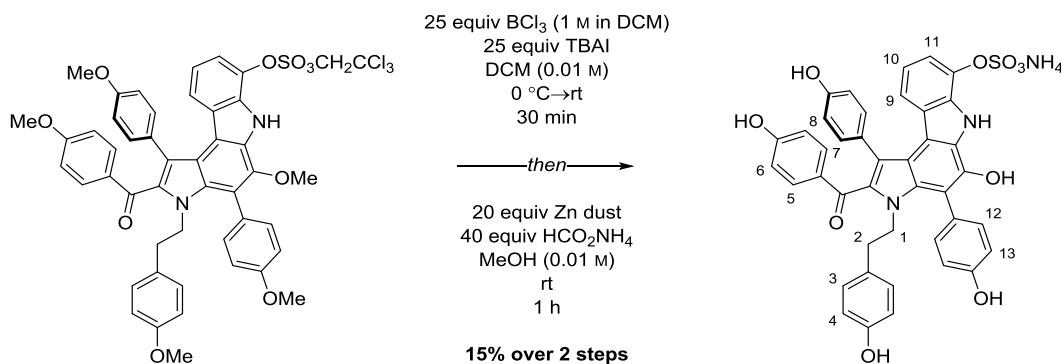
**<sup>1</sup>H NMR** (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 8.89 (s, 1H, H<sub>16</sub>), 7.59 (t, J = 8.7 Hz, 4H, H<sub>18</sub>), 7.32 (d, J = 8.0 Hz, 1H, H<sub>12/14</sub>), 7.27 (d, J = 8.7 Hz, 2H, H<sub>9</sub>), 7.12 (d, J = 8.7 Hz, 2H, H<sub>19</sub>), 6.82 (d, J = 8.7 Hz, 2H, H<sub>10</sub>), 6.78 (t, J = 8.1 Hz, 1H, H<sub>13</sub>), 6.73 (d, J = 8.9 Hz, 2H, H<sub>7</sub>), 6.62 (d, J = 8.7 Hz, 2H, H<sub>3</sub>), 6.53 (d, J = 8.7 Hz, 2H, H<sub>4</sub>), 6.19 (d, J = 8.2 Hz, 1H, H<sub>12/14</sub>), 4.87 (s, 2H, H<sub>15</sub>), 3.99 – 3.94 (m, 2H, H<sub>1</sub>), 3.93 (s, 3H, H<sub>20</sub>), 3.83 (s, 3H, H<sub>11</sub>), 3.80 (s, 3H, H<sub>8</sub>), 3.70 (s, 3H, H<sub>5</sub>), 3.66 (s, 3H, H<sub>17</sub>), 2.58 – 2.51 (m, 2H, H<sub>2</sub>).

**<sup>13</sup>C NMR** (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 189.9, 163.7, 160.1, 159.6, 158.6, 142.9, 136.9, 135.1, 133.5, 132.6, 132.6, 131.8, 131.7, 131.0, 131.0, 130.6, 129.9, 128.6, 127.6, 127.1, 124.6, 121.6, 120.0, 119.6, 119.0, 116.3, 115.3, 114.3, 113.9, 113.7, 113.6, 92.8, 81.3, 61.7, 55.8, 55.8, 55.8, 55.5, 48.0, 37.0.

**HRMS** (ESI) found [M+H]<sup>+</sup> 943.1610 ([C<sub>48</sub>H<sub>41</sub>Cl<sub>3</sub>N<sub>2</sub>O<sub>10</sub>S+H]<sup>+</sup> requires 943.1620; error –1.1 ppm).

**X-RAY** CCDC 1033480.

## Dictyodendrin B (2)



To a stirred solution of 5-methoxy-2-(4-methoxybenzoyl)-3-(4-methoxyphenethyl)-1,4-bis(4-methoxyphenyl)-3,6-dihydropyrrolo[2,3-c]carbazol-7-yl (2,2,2-trichloroethyl) sulfate (**388**) (73.7 mg, 0.078 mmol, 1.0 equiv) and tetrabutylammonium iodide (720 mg, 1.95 mmol, 25 equiv) in dichloromethane (7.8 mL, 0.01 M) at 0 °C was added boron trichloride (1 M in dichloromethane, 1.95 mL, 1.95 mmol, 25 equiv) over 10 min by syringe pump (approx. 0.17 mL/min). The mixture was stirred at rt until LCMS determined full conversion at 30 min. The mixture was quenched with distilled water (10 mL) and stirred at rt for 10 min before it was diluted with ethyl acetate. The organic layer was washed with sat. aq sodium sulfite, water and brine before it was dried over sodium sulfate and concentrated *in vacuo*. The crude residue was taken up in 3:1 methanol/water and passed through a small pad of reverse-phase silica gel (C18). The methanol was removed *in vacuo* and the remaining water was lyophilised to give the crude product.

The crude material and ammonium formate (197 mg, 3.12 mmol, 40 equiv) were stirred in dry methanol (7.8 mL, 0.01 M) at rt and an activated suspension of Zn dust\* (102 mg, 1.56 mmol, 20 equiv) was added and the mixture stirred at rt. After 1 h LCMS showed complete conversion and the suspension was filtered through a thin pad of Celite® with excess methanol. The filtrate was concentrated on diol-functionalized silica gel (CAS: 126850-04-2) and purified by diol-functionalized silica gel column chromatography (1:9 to 1:4 methanol/dichloromethane). The residue obtained was taken up in a small amount of distilled water and lyophilised to give the natural product as a yellow amorphous solid (8.0 mg, 15% over 2 steps, 39% per step).

\*Activated zinc dust was prepared as follows: commercial zinc dust (102 mg) was stirred with 2 drops of 1,2-dibromoethane in THF (0.5 mL) in a sealed glass vial. The suspension was heated to reflux with a heatgun for 1 min and allowed to cool to rt before adding 2 drops trimethylsilyl chloride. The suspension was again heated to reflux for 1 min and then stirred at rt for 5 min before use.

*NOTE: The sulfate group is very labile under acidic conditions.*

*Data are in accordance with the literature.*

**R<sub>f</sub>** 0.27 (1:3 methanol/dichloromethane).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3372, 2504, 1609, 1594, 1572, 1532, 1514, 1487, 1461, 1443, 1409, 1374, 1356, 1324, 1306, 1223, 1166, 1130, 1105, 1051, 1006, 949, 923, 882, 870, 836, 817, 801.

**<sup>1</sup>H NMR** (400 MHz, CD<sub>3</sub>OD) δ 7.45 (d, J = 8.4 Hz, 2H, H<sub>12</sub>), 7.34 (d, J = 8.7 Hz, 2H, H<sub>5</sub>), 7.18 (d, J = 7.7 Hz, 1H, H<sub>9/11</sub>), 7.06 (d, J = 8.5 Hz, 2H, H<sub>7</sub>), 7.03 (d, J = 8.5 Hz, 2H, H<sub>13</sub>), 6.65 (d, J = 8.5 Hz, 2H, H<sub>8</sub>), 6.59–6.54 (m, 3H, H<sub>6</sub> and H<sub>10</sub>), 6.47 (d, J = 8.5 Hz, 2H, H<sub>3</sub>), 6.41 (d, J = 8.6 Hz, 2H, H<sub>4</sub>), 6.01 (d, J = 7.7 Hz, 1H, H<sub>9/11</sub>), 3.96 (t, J = 7.5 Hz, 2H, H<sub>1</sub>), 2.47 (t, J = 7.7 Hz, 2H, H<sub>2</sub>).

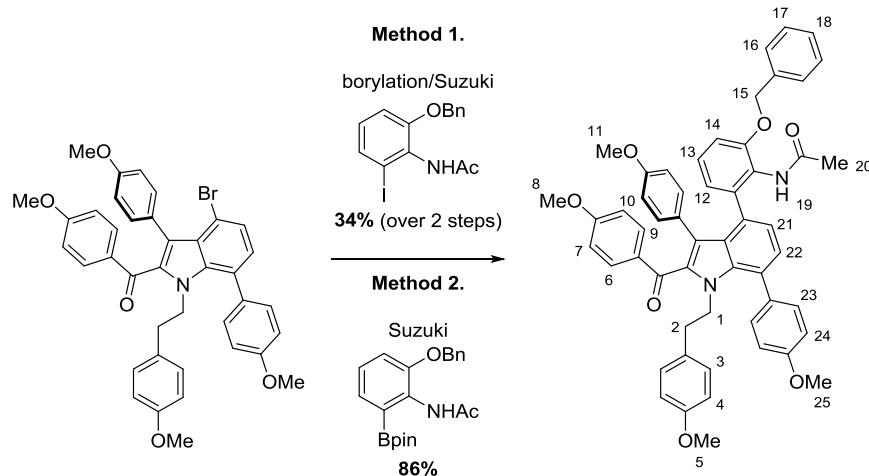
**<sup>13</sup>C NMR** (125 MHz, CD<sub>3</sub>OD) δ 191.9, 163.1, 158.6, 157.7, 156.8, 141.7, 138.8, 136.2, 134.3, 134.3, 134.0, 133.8, 131.9, 130.6, 129.3, 129.2, 127.1, 126.7, 125.8, 122.6, 118.8, 118.2, 117.2, 116.7, 116.1, 116.0, 115.5, 112.6, 48.4 (visible in DEPT-135), 37.7.

**HRMS** (ESI) found [M-H]<sup>-</sup> 741.1530 ([C<sub>41</sub>H<sub>29</sub>N<sub>2</sub>O<sub>10</sub>S-H]<sup>-</sup> requires 741.1548; error -2.4 ppm).

Isolated <sup>1</sup> H NMR <sup>73</sup> (600 MHz, CD <sub>3</sub> OD)	Fürstner <sup>1</sup> H NMR <sup>79</sup> (600 MHz, CD <sub>3</sub> OD)	Tokuyama <sup>1</sup> H NMR <sup>90</sup> (600 MHz, CD <sub>3</sub> OD)	Gaunt <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD)
10.21 (s, 1H)	8.48 (s, 1H)	not observed	not observed
7.43 (d, J = 8.6 Hz, 2H)	7.44 (d, J = 8.4 Hz, 2H)	7.44 (d, J = 7.2 Hz, 2H)	7.45 (d, J = 8.4 Hz, 2H)
7.32 (d, J = 8.8 Hz, 2H)	7.34 (d, J = 9.0 Hz, 2H)	7.34 (d, J = 8.4 Hz, 2H)	7.34 (d, J = 8.7 Hz, 2H)
7.16 (d, J = 7.9 Hz, 1H)	7.18 (dd, J = 7.8, 1.2 Hz, 1H)	7.18 (d, J = 6.6 Hz, 1H)	7.18 (d, J = 7.7 Hz, 1H)
7.04 (d, J = 8.6 Hz, 2H)	7.05 (d, J = 8.4 Hz, 2H)	7.05 (d, J = 8.4 Hz, 2H)	7.06 (d, J = 8.5 Hz, 2H)
7.00 (d, J = 8.8 Hz, 2H)	7.03 (d, J = 8.4 Hz, 2H)	7.02 (d, J = 8.4 Hz, 2H)	7.03 (d, J = 8.5 Hz, 2H)
6.63 (d, J = 8.6 Hz, 2H)	6.65 (d, J = 9.0 Hz, 2H)	6.64 (d, J = 7.8 Hz, 2H)	6.65 (d, J = 8.5 Hz, 2H)
6.55 (dd, J = 8.3, 7.9 Hz, 1H)	6.57 (dd, J = 7.8, 7.8 Hz, 1H)	6.60 – 6.55 (m, 3H)	6.59 – 6.54 (m, 3H)
6.53 (d, J = 8.8 Hz, 2H)	6.56 (d, J = 9.0 Hz, 2H)		
6.45 (d, J = 8.8 Hz, 2H)	6.47 (d, J = 9.0 Hz, 2H)	6.47 (d, J = 8.4 Hz, 2H)	6.47 (d, J = 8.5 Hz, 2H)
6.39 (d, J = 8.8 Hz, 2H)	6.41 (d, J = 8.4 Hz, 2H)	6.41 (d, J = 8.4 Hz, 2H)	6.41 (d, J = 8.6 Hz, 2H)
5.99 (d, J = 8.3 Hz, 1H)	6.02 (dd, J = 8.4, 0.6 Hz, 1H)	6.02 (d, J = 7.2 Hz, 1H)	6.01 (d, J = 7.7 Hz, 1H)
3.94 (t, J = 7.4 Hz, 2H)	3.96 (t, J = 7.2 Hz, 2H)	3.99–3.91 (m, 2H)	3.96 (t, J = 7.5 Hz, 2H)
2.46 (t, J = 7.4 Hz, 2H)	2.47 (t, J = 7.2 Hz, 2H)	2.50–2.43 (m, 2H)	2.47 (t, J = 7.7 Hz, 2H)

### 6.3 N-Acetyl Amination

**N-(2-(benzyloxy)-6-(2-(4-methoxybenzoyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-4-yl)phenyl)acetamide (348)**



#### Method 1

A mixture of (4-bromo-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (**188**) (1.26 g, 1.86 mmol, 1.0 equiv), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (136 mg, 0.186 mmol, 10 mol%), bis(pinacolato)diboron (946 mg, 3.72 mmol, 2.0 equiv) and potassium acetate (547 mg, 5.58 mmol, 3.0 equiv) in 1,4-dioxane (17 mL, 0.1 M) was stirred under an atmosphere of nitrogen at 95 °C in a pre-heated oil bath until LCMS showed full conversion at 20 h. The reaction mixture was partitioned between ethyl acetate/water, washed with brine, dried over magnesium sulfate and concentrated on silica *in vacuo*. The crude material was purified by silica gel column chromatography (1:4 ethyl acetate/40–60 petroleum ethers) to give a mixture of the desired pinacol ester and protodeboronated material (1.31 g, 98%).

This was added directly to a mixture of *N*-(2-(benzyloxy)-6-iodophenyl)acetamide (1.50 g, 4.09 mmol, 2.2 equiv), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (136 mg, 0.186 mmol, 10 mol%) and 1.9 M aq potassium hydroxide (4.0 mL, 7.44 mmol, 4.0 equiv) which was then stirred in 1,4-dioxane (14 mL, 0.13 M) at 100 °C in a pre-heated oil bath under nitrogen for 3.5 h. The reaction was allowed to cool to room temperature and partitioned between dichloromethane/sat. aq ammonium chloride. The aqueous layer was separated and further extracted with dichloromethane (×2) before the organics were combined, dried over sodium sulfate, filtered and concentrated on silica *in vacuo*. Purification by silica gel column

chromatography (1:4 to 1:1 ethyl acetate/hexane) gave the title compound as a yellow amorphous solid (530 mg, 35%, 34% over 2 steps).

## Method 2

A mixture of (4-bromo-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (100 mg, 0.148 mmol, 1.0 equiv), *N*-(2-(benzyloxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (81.4 mg, 0.222 mmol, 1.5 equiv) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (16.2 mg, 0.022 mmol, 10 mol%) in 2.0 M aq potassium carbonate (0.55 mL, 1.108 mmol, 5.0 equiv) and dioxane (0.74 mL, 0.2 M) was stirred at 90 °C under an atmosphere of N<sub>2</sub> in a pre-heated oil bath. Complete conversion of the starting material was observed by LCMS at 3 h and the reaction was allowed to cool to room temperature after 19 h. The reaction mixture was diluted with ethyl acetate and washed with sat. aq ammonium chloride, water and brine. The organic layer was dried over magnesium sulphate, filtered and concentrated on silica *in vacuo*. Purification by silica gel column chromatography (1:2 to 3:2 ethyl acetate/40–60 petroleum ethers) afforded the title compound as a bright yellow powder (107 mg, 86%).

**mp** 126–127 °C (ethyl acetate/40–60 petroleum ethers).

**R<sub>f</sub>** 0.29 (1:8:1 toluene/diethyl ether/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 2931, 2838, 1637, 1596, 1538, 1511, 1501, 1457, 1422, 1361, 1302, 1241, 1164, 1026.

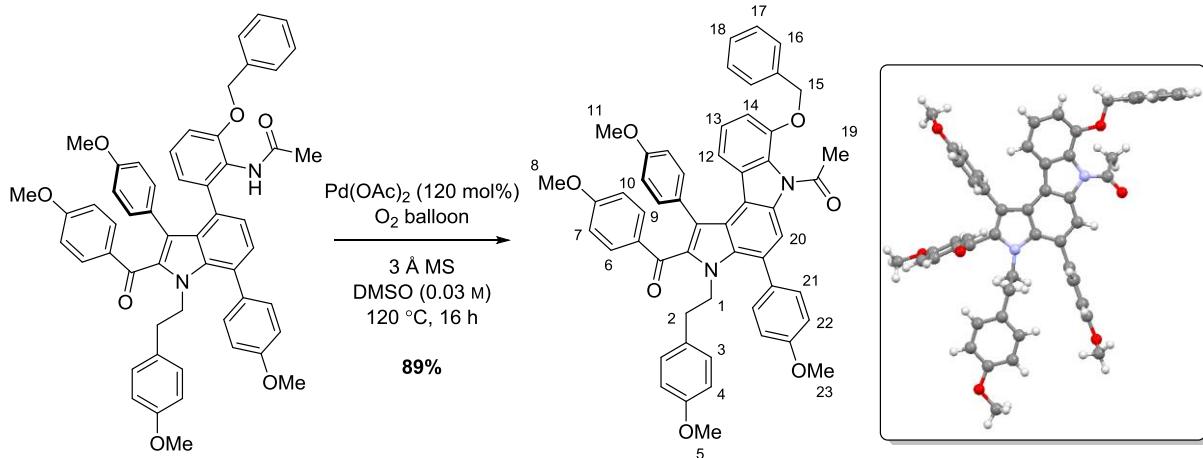
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.02 (s, 1H, H<sub>19</sub>), 7.61 – 7.52 (m, 4H H<sub>7</sub> and H<sub>23</sub>), 7.50 (d, J = 7.5 Hz, 2H, H<sub>16</sub>), 7.41 (t, J = 7.6 Hz, 2H, H<sub>17</sub>), 7.32 (t, J = 7.3 Hz, 1H, H<sub>18</sub>), 7.14 – 7.05 (m, 4H, H<sub>21</sub>, H<sub>22</sub> and H<sub>24</sub>), 6.79 (d, J = 9.0 Hz, 4H, H<sub>6</sub> and H<sub>9</sub>), 6.72 (d, J = 8.2 Hz, 1H, H<sub>12/14</sub>), 6.64 (d, J = 8.7 Hz, 2H, H<sub>3</sub>), 6.43 (t, J = 8.0 Hz, 1H, H<sub>13</sub>), 6.35 (d, J = 8.7 Hz, 2H, H<sub>4</sub>), 6.22 (s (br), 2H, H<sub>10</sub>), 6.05 (d, J = 7.6 Hz, 1H, H<sub>12/14</sub>), 5.10 (s, 2H, H<sub>15</sub>), 4.01 – 3.91 (m, 1H, H<sub>1b</sub>), 3.86 (s, 4H, H<sub>1a</sub> and H<sub>25</sub>), 3.73 (s, 3H, H<sub>8</sub>), 3.64 (s, 3H, H<sub>5</sub>), 3.46 (s, 3H, H<sub>11</sub>), 2.55 – 2.45 (m, 1H, H<sub>2b</sub>), 2.29 – 2.19 (m, 1H, H<sub>2a</sub>), 1.94 (s, 3H, H<sub>20</sub>).

**<sup>13</sup>C NMR** (126 MHz, DMSO-d<sub>6</sub>) δ 189.8, 169.2, 163.4, 159.0, 157.9, 157.1, 154.4, 138.5, 137.7, 135.7, 134.5, 132.4, 132.2, 132.1, 131.2, 131.0, 130.7, 130.1, 129.3, 129.1, 128.4, 127.6, 126.9, 126.4, 126.2, 125.7, 125.3, 124.7, 123.9, 122.0, 120.3, 113.8, 113.7, 112.2, 111.4, 69.6, 55.6, 55.4, 55.0, 54.9, 47.1, 36.1, 22.9.

**HRMS** (ESI) found [M+H]<sup>+</sup> 837.3533 ([C<sub>54</sub>H<sub>48</sub>N<sub>2</sub>O+H]<sup>+</sup> requires 837.3521; error 1.4 ppm).

\*Method 1 performed by Dr Robert H. Snell.

**1-(7-(benzyloxy)-2-(4-methoxybenzoyl)-3-(4-methoxyphenethyl)-1,4-bis(4-methoxyphenyl)pyrrolo[2,3-c]carbazol-6(3H-yl)ethan-1-one (349)**



Dimethylsulfoxide (38 mL, 0.03 M) was added to a pressure tube containing palladium(II) acetate (308 mg, 120 mol%), *N*-(2-(benzyloxy)-6-(2-(4-methoxybenzoyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-4-yl)phenyl)acetamide (**348**) (950 mg, 1.14 mmol, 1.0 equiv) and activated 3 Å molecular sieves (100 mg). The vessel was evacuated and charged with an atmosphere of oxygen before being slowly heated to 120 °C and stirred for 16 h. The solvent was removed by distillation under reduced pressure and the residue was allowed to cool to room temperature before being partitioned between ethyl acetate and water. The organic layer was isolated and the aqueous layer extracted with further ethyl acetate. The combined organic extracts were washed sequentially with water and brine then dried over magnesium sulfate and concentrated *in vacuo*. The crude product was precipitated from dichloromethane/methanol to give the title compound (840 mg, 89%). For analytically pure material the product was further purified by silica gel column chromatography (1:1 to 1:0 diethyl ether/40–60 petroleum ethers).

**mp** 191–193°C (diethyl ether/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (solid)/cm<sup>-1</sup> 2930, 2837, 1703, 1636, 1598, 1577, 1536, 1512, 1463, 1432, 1347, 1363, 1297, 1245, 1166.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.20 (s, 1H, H<sub>20</sub>), 7.59 (dd, J = 8.6, 1.7 Hz, 4H, H<sub>6</sub> and H<sub>21</sub>), 7.45 – 7.33 (m, 5H, H<sub>16</sub>, H<sub>17</sub> and H<sub>18</sub>), 7.28 (d, J = 8.6 Hz, 2H, H<sub>9</sub>), 7.04 (d, J = 8.6 Hz, 2H, H<sub>22</sub>), 6.91 (d, J = 8.0 Hz, 1H, H<sub>12/14</sub>), 6.83 (d, J = 8.0 Hz, 1H, H<sub>13</sub>), 6.79 (d, J = 8.5 Hz, 2H, H<sub>10</sub>), 6.70 (d, J = 8.8 Hz, 2H, H<sub>7</sub>), 6.58 (d, J = 8.6 Hz, 2H, H<sub>3</sub>), 6.43 (d, J = 8.5 Hz, 2H, H<sub>4</sub>), 5.96 (d, J = 8.0 Hz, 1H, H<sub>12/14</sub>), 5.18 (s, 2H, H<sub>15</sub>), 4.10 – 4.03 (m, 2H, H<sub>1</sub>), 3.91 (s, 3H, H<sub>23</sub>), 3.81 (s, 3H, H<sub>11</sub>), 3.79 (s, 3H, H<sub>8</sub>), 3.69 (s, 3H, H<sub>5</sub>), 2.51 (s, 5H, H<sub>19</sub> and H<sub>2</sub>).

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Experimental

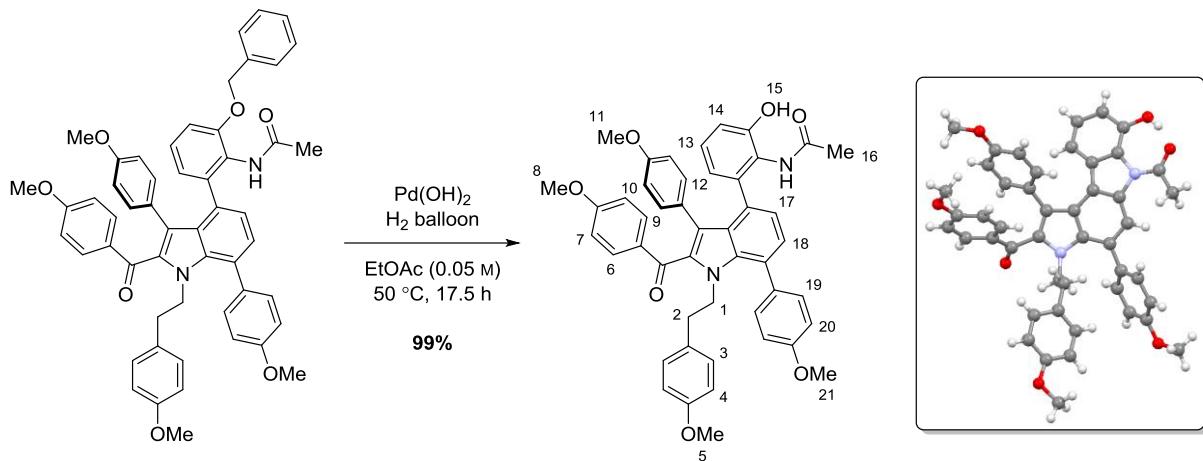
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 190.4, 173.8, 163.6, 159.5, 159.1, 158.2, 146.9, 137.7, 136.4, 136.2, 133.0, 133.0, 132.5, 132.3, 131.3, 131.2, 130.2, 129.7, 128.9, 128.8, 128.6, 128.4, 128.4, 127.8, 127.2, 123.4, 122.2, 121.1, 118.2, 116.9, 115.2, 113.8, 113.7, 113.5, 113.5, 109.2, 71.5, 55.6, 55.6, 55.5, 55.3, 48.1, 36.5, 28.1.

**HRMS** (ESI) found [M+H]<sup>+</sup> 835.3377 ([C<sub>54</sub>H<sub>46</sub>N<sub>2</sub>O<sub>7</sub>+H]<sup>+</sup> requires 835.3378; error -0.1 ppm).

**X-RAY** CCDC 896910.

\*Best isolated yield achieved by Dr Robert H. Snell.

**N-(2-hydroxy-6-(2-(4-methoxybenzoyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-4-yl)phenyl)acetamide (350)**



*N*-(2-(benzyloxy)-6-(2-(4-methoxybenzoyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-4-yl)phenyl)acetamide (**348**) (50 mg, 0.060 mmol, 1.0 equiv) and 20% wt. palladium(II) hydroxide on carbon (8.39 mg, 0.012 mmol, 20 mol%) were stirred in ethyl acetate (1.20 mL, 0.05 M) at 50 °C for 1 h under a balloon of H<sub>2</sub>. After 1.5 h an additional spatula of catalyst was added and the mixture stirred overnight. After 17.5 h the reaction showed complete conversion by LCMS and was filtered through a plug of Celite® on cotton with excess ethyl acetate and concentrated *in vacuo* to give the title compound as a bright green solid (44.3 mg, 99 % yield).

**mp** 83.6–85.7 °C (ethyl acetate).

**IR**  $\nu_{\max}$  (film)/cm<sup>-1</sup> 2928, 2837, 1640, 1597, 1536, 1512, 1464, 1422, 1359, 1303, 1244, 1175, 1164, 1110, 1032, 1001, 963, 910, 837, 804.

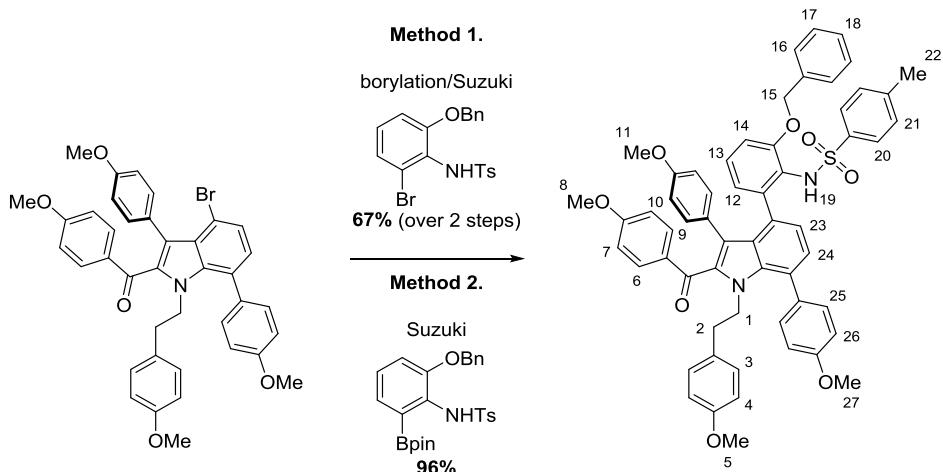
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.19 (s, 1H, H<sub>17</sub>), 7.58 – 7.52 (m, 4H, H<sub>6</sub> and H<sub>19</sub>), 7.24 (d, J = 7.3 Hz, 1H, H<sub>17/18</sub>), 7.06 (app d, J = 7.3 Hz, 3H, H<sub>17/18</sub> and H<sub>20</sub>), 7.00 (s, 1H, H<sub>15</sub>), 6.95 – 6.90 (m, 1H, H<sub>13</sub>), 6.77 (dd, J = 8.2, 1.4 Hz, 1H, H<sub>12/14</sub>), 6.71 (dd, J = 7.4, 1.4 Hz, 1H, H<sub>12/14</sub>), 6.64 – 6.56 (m, 6H, H<sub>3</sub>, H<sub>7</sub> and H<sub>9</sub>), 6.44 (d, J = 8.6 Hz, 2H, H<sub>4</sub>), 6.28 (d, J = 7.0 Hz, 2H, H<sub>10</sub>), 4.21 – 4.05 (m, 2H, H<sub>1</sub>), 3.92 (s, 3H, H<sub>21</sub>), 3.73 (s, 3H, H<sub>8</sub>), 3.69 (s, 3H, H<sub>5</sub>), 3.62 (s, 3H, H<sub>11</sub>), 2.56 – 2.38 (m, 2H, H<sub>2</sub>), 1.90 (s, 3H, H<sub>16</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 190.4, 169.9, 163.7, 159.6, 158.3, 158.1, 148.9, 136.9, 135.1, 133.6, 132.6, 132.4, 131.1, 131.0, 130.7, 130.5, 129.9, 129.6, 127.8, 127.6, 126.4, 125.2, 124.7, 123.9, 123.3, 122.4, 121.2, 119.3, 114.0, 113.9, 113.7, 113.4, 112.8, 55.6, 55.5, 55.3, 47.6, 36.7, 24.0.

**HRMS** (NSI) found [M+H]<sup>+</sup> 747.3061([C<sub>47</sub>H<sub>42</sub>N<sub>2</sub>O<sub>7</sub>+H]<sup>+</sup> requires 747.3065; error −0.5 ppm).

## 6.4 N-Tosyl Amination

**N-(2-(benzyloxy)-6-(2-(4-methoxybenzoyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1H-indol-4-yl)phenyl)-4-methylbenzenesulfonamide (361)**



### Method 1

A mixture of (4-bromo-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1H-indol-2-yl)(4-methoxyphenyl)methanone (**188**) (100 mg, 0.148 mmol, 1.0 equiv), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (11 mg, 0.015 mmol, 10 mol%), bis(pinacolato)diboron (94 mg, 0.37 mmol, 2.5 equiv) and potassium acetate (44 mg, 0.443 mmol, 3.0 equiv) in 1,4-dioxane (1.5 mL, 0.1 M) was stirred under an atmosphere of nitrogen at 95 °C in a pre-heated oil bath until LCMS showed full conversion at 18 h.

To the cooled crude reaction mixture was directly added *N*-(2-(benzyloxy)-6-bromophenyl)-4-methylbenzenesulfonamide (128 mg, 0.296 mmol, 2.0 equiv), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (11 mg, 14.8 µmol, 10 mol%) and 1.5 M aqueous potassium hydroxide (500 µL, 0.740 mmol, 5.0 equiv). The vessel was resealed, flushed with argon and stirred at 90 °C until LCMS showed no further change at 27 h. The reaction was allowed to cool to rt and additional *N*-(2-(benzyloxy)-6-bromophenyl)-4-methylbenzenesulfonamide (0.5 equiv), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (5.0 mol%) and 1.5 M aqueous potassium hydroxide (2.5 equiv) were added. The reaction was stirred at 90 °C until complete consumption of starting material was observed by LCMS at 47 h. The reaction mixture was allowed to cool and was then partitioned between ethyl acetate/sat. aq ammonium chloride. The organic layer was further washed with water and brine, dried over magnesium sulphate, filtered and concentrated on silica *in vacuo*. The crude material was purified by silica gel column chromatography (1:2 ethyl acetate/40–60

petroleum ethers) to give the title compound as a beige solid (94 mg, 67% over two steps, 82% per step).

## Method 2

A mixture of (4-bromo-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (100 mg, 0.148 mmol, 1.0 equiv), *N*-(2-(benzyloxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-methylbenzenesulfonamide (106 mg, 0.222 mmol, 1.5 equiv), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (16.2 mg, 0.022 mmol, 10 mol%) in 2.0 M potassium carbonate (0.55 mL, 1.11 mmol, 5.0 equiv) and dioxane (0.74 mL, 0.2 M) was stirred at 90 °C under an atmosphere of N<sub>2</sub> in a pre-heated oil bath until complete conversion was observed by LCMS at 13 h. The reaction mixture was cooled, diluted with ethyl acetate and washed with sat aq ammonium chloride, water and brine. The organic layer was then dried over magnesium sulfate, filtered and concentrated on silica *in vacuo*. The crude material was purified by silica gel column chromatography (1:4 to 1:2 ethyl acetate/40–60 petroleum ethers) to give the title compound as a bright yellow solid (134 mg, 96%).

**mp** 149–150 °C (ethyl acetate/40–60 petroleum ethers).

**R<sub>f</sub>** 0.23 (1:2 ethyl acetate/40–60 petroleum ethers).

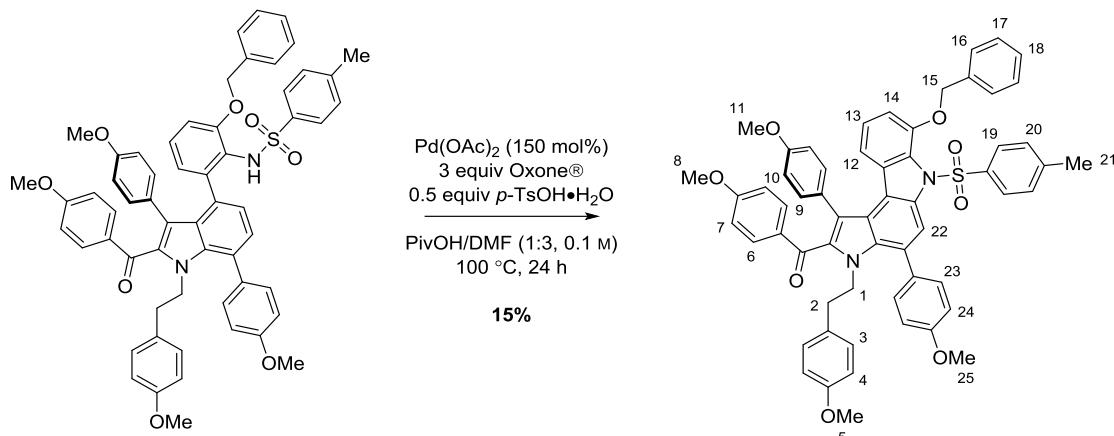
**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3340, 2935, 2838, 1634, 1611, 1597, 1575, 1538, 1511, 1501, 1455, 1422, 1383, 1358, 1326, 1302, 1285, 1241, 1173, 1163, 1110, 1092, 1057, 1028, 909, 837, 813.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.62 – 7.46 (m, 5H, Ar<sub>H</sub>), 7.37 – 7.28 (m, 4H, Ar<sub>H</sub>), 7.22 (d, J = 7.8 Hz, 4H, Ar<sub>H</sub>), 7.09 – 7.02 (m, 4H, Ar<sub>H</sub>), 6.99 – 6.91 (m, 4H, Ar<sub>H</sub>), 6.59 (d, J = 8.7 Hz, 5H, Ar<sub>H</sub>), 6.42 (d, J = 8.5 Hz, 2H, Ar<sub>H</sub>), 6.21 (s (br), 3H, Ar<sub>H</sub>), 5.54 (s, 1H, H<sub>19</sub>), 4.62 (s, 2H, H<sub>15</sub>), 4.19 – 3.98 (m, 2H, H<sub>1</sub>), 3.92 (s, 3H, H<sub>27</sub>), 3.72 (s, 3H, H<sub>8</sub>), 3.69 (s, 3H, H<sub>5</sub>), 3.47 (s, 3H, H<sub>11</sub>), 2.56 – 2.28 (m, 2H, H<sub>2</sub>), 2.25 (s, 3H, H<sub>22</sub>).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 190.3, 163.3, 159.3, 158.1, 157.4, 154.3, 142.3, 140.5, 138.1, 136.8, 136.6, 134.8, 132.9, 132.5, 131.5, 131.1, 131.0, 130.8, 130.2, 129.7, 128.8, 128.5, 127.8, 127.6, 127.5, 126.8, 126.8, 126.5, 126.5, 124.8, 123.9, 123.3, 123.2, 121.6, 113.9, 113.7, 113.5, 113.3, 111.5, 70.3, 55.6, 55.5, 55.3, 55.0, 47.5, 36.6, 21.6.

**HRMS** (NSI) found 949.3503 [M+H]<sup>+</sup> ([C<sub>59</sub>H<sub>52</sub>N<sub>2</sub>O<sub>8</sub>S+H]<sup>+</sup> requires 949.3517; error -1.5 ppm).

**(7-(benzyloxy)-3-(4-methoxyphenethyl)-1,4-bis(4-methoxyphenyl)-6-tosyl-3,6-dihydropyrrolo[2,3-c]carbazol-2-yl)(4-methoxyphenyl)methanone (362)**



*N*-(2-(benzyloxy)-6-(2-(4-methoxybenzoyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-4-yl)phenyl)-4-methylbenzenesulfonamide (**361**) (50.0 mg, 0.053 mmol, 1.0 equiv), palladium(II) acetate (17.7 mg, 0.079 mmol, 150 mol%), Oxone® (potassium peroxyomonosulfate, 48.6 mg, 0.158 mmol, 3.0 equiv) and *p*-toluenesulfonic acid (5.0 mg, 0.027 mmol, 0.5 equiv) were stirred under N<sub>2</sub> in a mixture of pivalic acid/*N,N*-dimethylformamide (1:3, 0.53 mL, 0.1 M) at 100 °C for 24 h. Partial conversion was observed by LCMS and the mixture allowed to cool to room temperature. The reaction mixture was filtered through a pad of cotton and purified directly by reverse-phase preparative-HPLC (C18, 80% acetonitrile/water) to give the title compound as a dark yellow solid (7.4 mg, 15%).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 2952, 2930, 2861, 1675, 1639, 1598, 1541, 1513, 1497, 1463, 1445, 1423, 1378, 1346, 1286, 1244, 1202, 1165, 1109, 1092, 1060, 1028, 987, 955, 909, 837, 812.

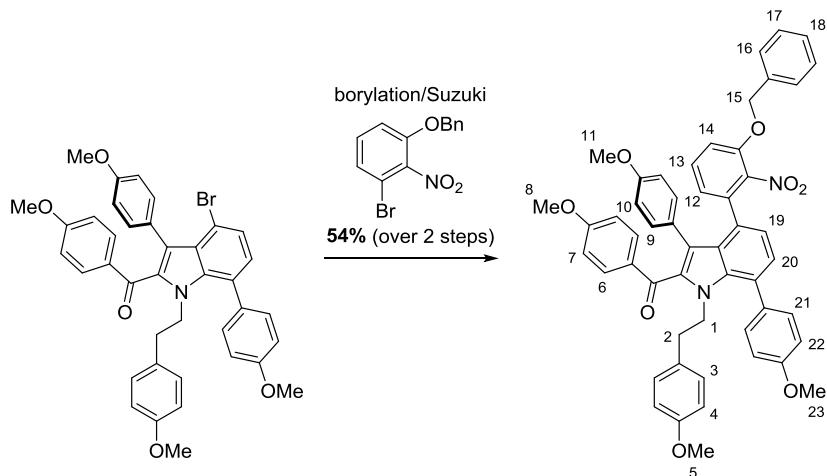
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.14 (s, 1H, H<sub>22</sub>), 7.66 – 7.59 (m, 4H, H<sub>19</sub> and H<sub>23</sub>), 7.52 (d, J = 8.9 Hz, 2H, H<sub>6</sub>), 7.28 (s, 5H, H<sub>16</sub>, H<sub>17</sub> and H<sub>18</sub>), 7.16 (d, J = 8.7 Hz, 2H, H<sub>9</sub>), 7.05 (app d, J = 8.6 Hz, 4H, H<sub>20</sub> and H<sub>24</sub>), 6.72 (d, J = 8.7 Hz, 2H, H<sub>10</sub>), 6.69 – 6.66 (m, 4H, H<sub>7</sub>, H<sub>12/14</sub> and H<sub>13</sub>), 6.57 (d, J = 8.7 Hz, 2H, H<sub>3</sub>), 6.40 (d, J = 8.6 Hz, 2H, H<sub>4</sub>), 5.82 (dd, J = 6.6, 2.4 Hz, 1H, H<sub>12/14</sub>), 5.01 (s, 2H, H<sub>15</sub>), 4.11 – 4.05 (m, 2H, H<sub>1</sub>), 3.90 (s, 3H, H<sub>25</sub>), 3.79 (s, 3H, H<sub>8</sub>), 3.76 (s, 3H, H<sub>11</sub>), 3.69 (s, 3H, H<sub>5</sub>), 2.49 – 2.44 (m, 2H, H<sub>2</sub>), 2.32 (s, 3H, H<sub>21</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 190.4, 163.6, 159.6, 159.1, 158.2, 147.9, 143.3, 138.2, 137.8, 137.1, 132.9, 132.8, 132.5, 131.3, 131.1, 130.2, 130.1, 129.7, 129.5, 129.1, 128.5, 128.2, 127.8, 127.5, 126.6, 126.5, 124.4, 122.2, 121.4, 119.9, 118.0, 117.8, 113.9, 113.7, 113.5, 113.4, 111.0, 70.8, 55.6, 55.6, 55.5, 55.3, 48.1, 36.5, 21.7.

**HRMS** (ESI) found [M+H]<sup>+</sup> 947.3358 ([C<sub>59</sub>H<sub>50</sub>N<sub>2</sub>O<sub>8</sub>S+H]<sup>+</sup> requires 947.3361; error -0.3 ppm).

## 6.5 Other indole fragments

**(4-(3-(benzyloxy)-2-nitrophenyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (363)**



A mixture of (4-bromo-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (**188**) (500 mg, 0.74 mmol, 1.0 equiv), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (54 mg, 0.074 mmol, 10 mol%), bis(pinacolato)diboron (470 mg, 1.85 mmol, 2.5 equiv) and potassium acetate (218 mg, 2.22 mmol, 3.0 equiv) in 1,4-dioxane (7.4 mL, 0.1 M) was stirred under an atmosphere of nitrogen at 95 °C in a pre-heated oil bath until LCMS showed full conversion at 15 h.

To the cooled crude reaction mixture was directly added 1-(benzyloxy)-3-bromo-2-nitrobenzene (570 mg, 1.85 mmol, 2.5 equiv), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (54 mg, 74 µmol, 10 mol%) and 3 M aqueous potassium hydroxide (1.30 mL, 3.7 mmol, 5.0 equiv). The vessel was resealed, flushed with argon and stirred at 90 °C until complete consumption over the starting material was observed by LCMS at 21.5 h. The reaction mixture was allowed to cool to rt and was then filtered through a thin pad of Celite with excess ethyl acetate. The collected organics were partitioned with sat. aq ammonium chloride. The organic layer was further washed with water and brine, dried over magnesium sulphate, filtered and concentrated on silica in vacuo. The crude material was purified by silica gel column chromatography (2:7:1 to 3:6:1 ethyl acetate/40–60 petroleum ethers/toluene) to give the title compound as a beige solid (329 mg, 54% over two steps).

**mp** 122–125 °C (ethyl acetate/40–60 petroleum ethers).

**R<sub>f</sub>** 0.30 (1:2 ethyl acetate/40–60 petroleum ethers).

Experimental

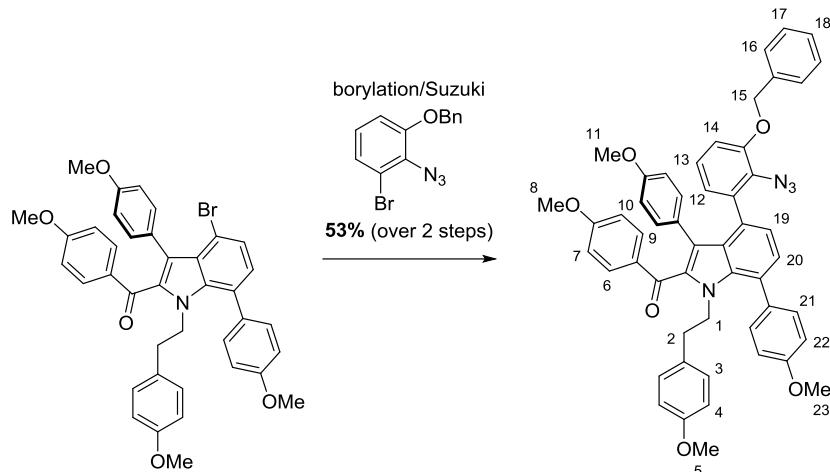
**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 2988, 2970, 2902, 2841, 1635, 1610, 1598, 1575, 1532, 1511, 1500, 1464, 1443, 1421, 1405, 1393, 1373, 1302, 1244, 1175, 1166, 1150, 1110, 1057, 1028, 983, 927, 852, 839, 804.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.59 – 7.39 (m, 8H, H<sub>6</sub>, H<sub>16</sub>, H<sub>17</sub> and H<sub>21</sub>), 7.37 – 7.31 (m, 1H, H<sub>18</sub>), 7.13 (d, J = 7.4 Hz, 1H, H<sub>9</sub>), 7.07 (d, J = 7.4 Hz, 1H, H<sub>10</sub>), 7.05 (d, J = 8.4 Hz, 1H, H<sub>19/20</sub>), 7.02 (d, J = 8.3 Hz, 1H, H<sub>19/20</sub>), 6.83 (s, 2H), 6.71 (dd, J = 8.4, 1.1 Hz, 1H, H<sub>12/14</sub>), 6.62 (dd, J = 8.4, 7.7 Hz, 1H, H<sub>13</sub>), 6.58 (appt t, J = 8.4 Hz, 4H, H<sub>3</sub> and H<sub>7</sub>), 6.38 (d, J = 8.6 Hz, 2H, H<sub>4</sub>), 6.21 (dd, J = 7.8, 1.1 Hz, 1H, H<sub>12/14</sub>), 5.28 – 5.14 (m, 2H, H<sub>15</sub>), 4.25 – 3.99 (m, 2H, H<sub>1</sub>), 3.90 (s, 3H, H<sub>23</sub>), 3.73 (s, 3H, H<sub>8</sub>), 3.70 (s, 3H, H<sub>5</sub>), 3.47 (s, 3H, H<sub>11</sub>), 2.57 – 2.33 (m, 2H, H<sub>2</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 190.1, 163.4, 159.4, 158.2, 157.8, 149.2, 141.4, 137.0, 136.1, 135.7, 133.9, 132.7, 132.5, 131.4, 130.8, 130.8, 130.1, 129.7, 128.9, 128.7, 128.6, 128.4, 127.8, 127.3, 127.1, 126.8, 125.5, 124.6, 122.0, 121.7, 113.9, 113.7, 113.6, 113.2, 112.6, 111.9, 71.1, 55.6, 55.5, 55.3, 47.5, 36.6.

**HRMS** (NSI) found 825.3187 [M+H]<sup>+</sup> ([C<sub>52</sub>H<sub>44</sub>N<sub>2</sub>O<sub>8</sub>+H]<sup>+</sup> requires 825.3170; error 2.0 ppm).

**(4-(2-azido-3-(benzyloxy)phenyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (382)**



A mixture of (4-bromo-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (**188**) (250 mg, 0.37 mmol, 1.0 equiv), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (27 mg, 0.037 mmol, 10 mol%), bis(pinacolato)diboron (236 mg, 0.93 mmol, 2.5 equiv) and potassium acetate (109 mg, 1.11 mmol, 3.0 equiv) in 1,4-dioxane (3.7 mL, 0.1 M) was stirred under an atmosphere of nitrogen at 95 °C in a pre-heated oil bath until LCMS showed full conversion at 16 h.

To the cooled crude reaction mixture was directly added 2-azido-1-(benzyloxy)-3-bromobenzene (225.1 mg, 0.740 mmol, 2.0 equiv), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (27 mg, 37 µmol, 10 mol%), potassium hydroxide (83 mg, 1.48 mmol, 4 equiv), 1,4-dioxane (2.78 mL, 1:3) and water (0.925 mL, 1:3, 0.1 M overall). The vessel was sealed, flushed with argon and stirred at 90 °C until LCMS showed no further change at 1.5 h. The reaction mixture was allowed to cool and was then filtered through a thin pad of Celite with excess ethyl acetate. The collected organic layer was then partitioned between ethyl acetate/sat. aq ammonium chloride. The organic layer was further washed with sat. aq ammonium chloride, water (×2) and brine (×2) before being dried over magnesium sulphate, filtered and concentrated on silica in vacuo. The crude material was purified by silica gel column chromatography (1:8:1 to 2:7:1 ethyl acetate/40–60 petroleum ethers/toluene) to give the title compound as a brown solid (161 mg, 53% over two steps).

**mp** 94–95 °C (ethyl acetate/40–60 petroleum ethers).

**R<sub>f</sub>** 0.45 (1:2 ethyl acetate/40–60 petroleum ethers).

Experimental

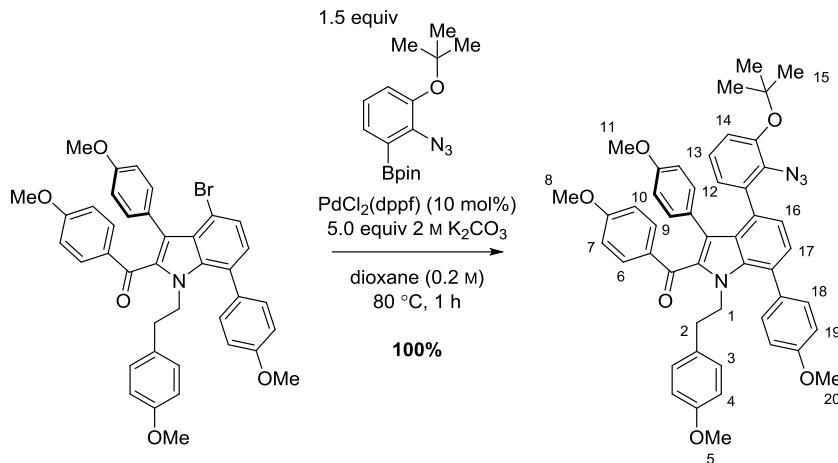
**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 2988, 2970, 2905, 2838, 2097, 1635, 1610, 1597, 1574, 1538, 1511, 1500, 1455, 1443, 1421, 1382, 1358, 1302, 1285, 1241, 1174, 1164, 1108, 1076, 1054, 1028, 981, 963, 927, 896, 836, 824, 802.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.64 – 7.52 (m, 4H, Ar<sub>H</sub>), 7.41 – 7.29 (m, 5H, Ar<sub>H</sub>), 7.21 (d, J = 7.3 Hz, 1H, Ar<sub>H</sub>), 7.04 (dd, J = 8.0, 4.4 Hz, 3H, Ar<sub>H</sub>), 6.95 – 6.87 (m, 1H, Ar<sub>H</sub>), 6.86 (dd, J = 7.6, 1.8 Hz, 1H, Ar<sub>H</sub>), 6.76 – 6.66 (m, 2H, Ar<sub>H</sub>), 6.64 – 6.53 (m, 5H, Ar<sub>H</sub>), 6.46 (s, 2H, Ar<sub>H</sub>), 6.42 – 6.16 (m, 2H, Ar<sub>H</sub>), 4.90 (dd, J = 47.2, 11.8 Hz, 2H, H<sub>15</sub>), 4.23 – 4.01 (m, 2H, H<sub>1</sub>), 3.91 (s, 3H, H<sub>23</sub>), 3.74 (s, 3H, H<sub>8</sub>), 3.69 (s, 3H, H<sub>5</sub>), 3.56 (s, 3H, H<sub>11</sub>), 2.61 – 2.37 (m, 2H, H<sub>2</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 190.3, 163.3, 159.3, 158.0, 157.4, 152.4, 136.3, 134.8, 134.1, 132.8, 132.5, 132.4, 131.3, 131.0, 130.8, 130.1, 129.5, 129.0, 128.5, 128.5, 128.2, 128.0, 127.3, 126.8, 126.7, 126.3, 125.6, 125.3, 124.2, 124.0, 122.1, 113.7, 113.5, 113.2, 112.0, 71.5, 55.5, 55.3, 55.1, 55.0, 47.4, 36.6.

**HRMS** (ESI) found 821.3328 [M+H]<sup>+</sup> ([C<sub>52</sub>H<sub>44</sub>N<sub>4</sub>O<sub>6</sub>+H]<sup>+</sup> requires 821.3334; error -0.7 ppm).

**(4-(2-azido-3-(*tert*-butoxy)phenyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (377)**



To an oven dried vial was added (4-bromo-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (**188**) (67.7 mg, 0.10 mmol, 1.0 equiv), 2-(2-azido-3-(*tert*-butoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**315**) (47.6 mg, 0.15 mmol, 1.5 equiv), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (7.3 mg, 10 µmol, 10 mol%), 2 M aq potassium carbonate (0.25 mL, 0.50 mmol, 5.0 equiv), 1,4-dioxane (0.5 mL, 0.2 M). The vessel was sealed, flushed with nitrogen and stirred at 80 °C in a pre-heated oil bath until LCMS showed complete conversion at 1 h. The reaction mixture was allowed to cool and was then partitioned between ethyl acetate/sat. aq ammonium chloride. The organic layer was further washed with water and brine before being dried over magnesium sulphate, filtered and concentrated on silica *in vacuo*. The crude material was purified by silica gel column chromatography (1:4 ethyl acetate/40–60 petroleum ethers) to give the title compound as a dark yellow solid (78.7 mg, 100%).

**mp** 95–97 °C (dichloromethane/hexane).

**R<sub>f</sub>** 0.12 (1:4 ethyl acetate/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 2977, 2956, 2933, 2905, 2836, 2127, 2095, 1636, 1610, 1610, 1596, 1573, 1537, 1511, 1501, 1462, 1441, 1422, 1392, 1367, 1302, 1286, 1240, 1173, 1163, 1130, 1109, 1031, 1001, 948, 887, 833, 804.

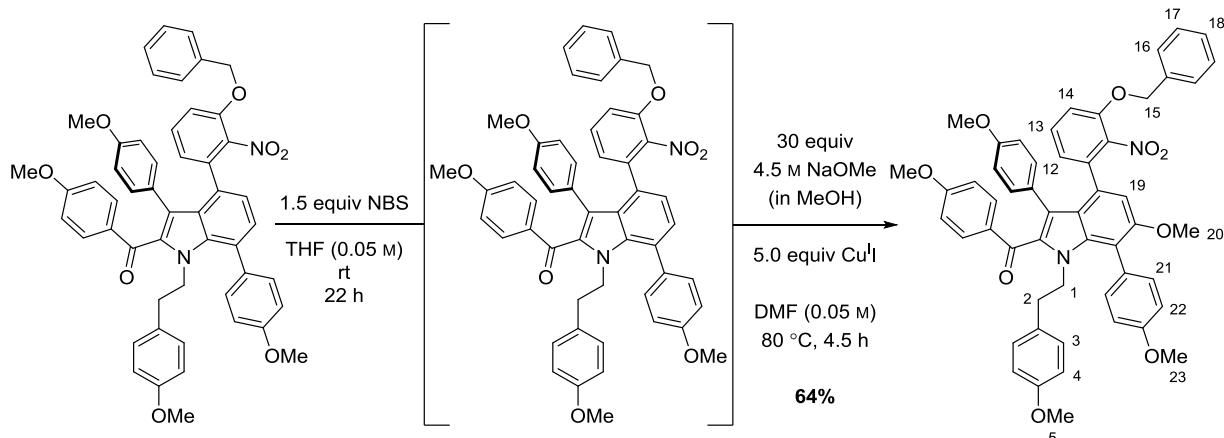
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.61 (d, J = 8.4 Hz, 1H, **H<sub>18a</sub>**), 7.56 (d, J = 8.8 Hz, 3H, **H<sub>6</sub>** and **H<sub>18b</sub>**), 7.20 (d, J = 7.4 Hz, 1H, **H<sub>16/17</sub>**), 7.03 (app t, J = 7.5 Hz, 3H, **H<sub>16/17</sub>** and **H<sub>19</sub>**), 6.80 – 6.65 (m, 5H, **H<sub>9</sub>**, **H<sub>12</sub>**, **H<sub>13</sub>** and **H<sub>14</sub>**), 6.60 (d, J = 8.8 Hz, 2H, **H<sub>7</sub>**), 6.58 (d, J = 8.5 Hz, 2H, **H<sub>3</sub>**), 6.44 (d, J = 8.6 Hz, 2H, **H<sub>4</sub>**), 6.30 (d, J = 5.7 Hz, 2H, **H<sub>10</sub>**), 4.19 – 4.04 (m, 2H, **H<sub>1</sub>**), 3.90 (s, 3H, **H<sub>20</sub>**), 3.73 (s, 3H, **H<sub>8</sub>**), 3.69 (s, 3H, **H<sub>5</sub>**), 3.61 (s, 3H, **H<sub>11</sub>**), 2.56 – 2.41 (m, 2H, **H<sub>2</sub>**), 1.35 (s, 9H, **H<sub>15</sub>**).

Experimental

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 190.5, 163.4, 159.4, 158.1, 157.7, 149.4, 136.5, 135.1, 134.2, 133.0, 132.8, 132.5, 131.4, 131.4, 131.0, 131.0, 130.8, 130.2, 129.7, 127.3, 126.6, 126.4, 125.6, 123.5, 122.7, 122.1, 120.9, 113.8, 113.7, 113.6, 113.3, 112.3, 80.4, 55.6, 55.5, 55.3, 55.2, 47.5, 36.7, 28.5.

**HRMS** (ESI) found 787.3484 [M+H]<sup>+</sup> ([C<sub>49</sub>H<sub>46</sub>N<sub>4</sub>O<sub>6</sub>+H]<sup>+</sup> requires 787.3490; error -0.8 ppm).

**(4-(3-(benzyloxy)-2-nitrophenyl)-6-methoxy-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (390)**



*N*-bromosuccinimide (94 mg, 0.53 mmol, 1.5 equiv) was added portion wise at intervals over a 22 h period to a gently stirred solution of (4-(3-(benzyloxy)-2-nitrophenyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (**363**) (300 mg, 0.36 mmol, 1.0 equiv) in tetrahydrofuran (7.2 mL, 0.05 M) until the starting material was determined to be completely consumed by LCMS. The reaction was concentrated and partitioned between ethyl acetate/sat. aq sodium hydrogen carbonate. The organic layer was dried over magnesium sulphate, filtered and concentrated *in vacuo* to give the crude brominated intermediate as a beige powder (325 mg, 100%).

Solid sodium (98 mg, 4.26 mmol, 30 equiv) was added portion wise to a well-ventilated oven-dried vial of stirred methanol (0.95 mL, 33% vol) (WARNING: HYDROGEN GAS RELEASED). The vial was then loosely covered and stirred vigorously to give a completely homogeneous solution. Copper(I) iodide (135 mg, 0.709 mmol, 5.0 equiv) and a portion of the brominated intermediate (128 mg, 0.142 mmol, 1.0 equiv) prepared above in *N,N*-dimethylformamide (2.84 mL, 0.05 M) were added in quick succession and the vial was sealed and stirred at 80 °C in a preheated oil bath until the complete consumption of starting material was observed by LCMS at 4.5 h. The reaction mixture was allowed to cool to rt and was filtered through a thin pad of Celite with excess ethyl acetate before being partitioned with water. The organic layer was further washed with water ( $\times 2$ ) and brine, dried over magnesium sulphate and concentrated on silica *in vacuo*. The crude material was purified by silica gel column chromatography (1:4 to 1:2 ethyl acetate/40–60 petroleum ethers) to give the title compound as a bright yellow solid (77 mg, 64%).

**mp** 187–189 °C (ethyl acetate/40–60 petroleum ethers).

**R<sub>f</sub>** 0.43 (33% ethyl acetate/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3004, 2960, 2937, 2917, 2838, 1631, 1610, 1597, 1574, 1531, 1511, 1463, 1443, 1421, 1372, 1358, 1302, 1284, 1241, 1206, 1175, 1153, 1108, 1091, 1056, 1029, 1011, 987, 968, 940, 908, 854, 838, 808.

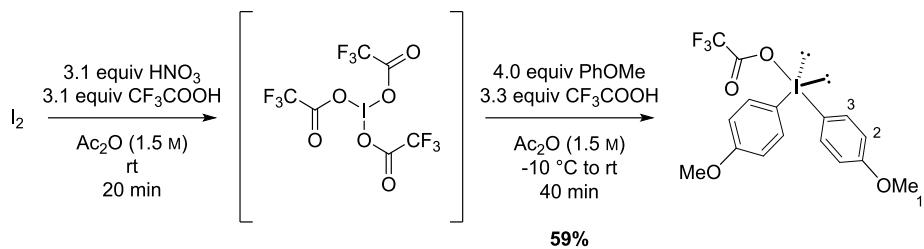
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.49 – 7.39 (m, 8H, H<sub>6</sub>, H<sub>16</sub>, H<sub>17</sub> and H<sub>21</sub>), 7.38 – 7.33 (m, 1H, H<sub>19</sub>), 7.06 – 7.01 (m, 2H, H<sub>22</sub>), 6.85 (s, 1H, H<sub>19</sub>), 6.79 (s (br), 4H, H<sub>9</sub> and H<sub>10</sub>), 6.72 (dd, J = 8.4, 1.0 Hz, 1H, H<sub>12/14</sub>), 6.63 (d, J = 7.9 Hz, 1H, H<sub>13</sub>), 6.60 (d, J = 8.7 Hz, 2H, H<sub>3</sub>), 6.54 (d, J = 9.0 Hz, 2H, H<sub>7</sub>), 6.47 (d, J = 8.7 Hz, 2H, H<sub>4</sub>), 6.21 (dd, J = 7.8, 1.0 Hz, 1H, H<sub>12/14</sub>), 5.21 (app q, J = 12.4 Hz, 3H, H<sub>15</sub>), 4.15 – 4.07 (m, 1H, H<sub>1a</sub>), 3.89 (s, 3H, H<sub>23</sub>), 3.81 – 3.76 (m, 1H, H<sub>1b</sub>), 3.75 (s, 3H, H<sub>20</sub>), 3.71 (s, 3H, H<sub>8</sub>), 3.70 (s, 3H, H<sub>5</sub>), 3.47 (s, 3H, H<sub>11</sub>), 2.58 – 2.50 (m, 1H H<sub>2b</sub>), 2.43 – 2.35 (m, 1H, H<sub>2a</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 189.8, 163.2, 159.3, 158.2, 157.7, 154.6, 149.2, 141.4, 137.5, 136.4, 136.1, 133.8, 132.6, 132.3, 132.2, 131.4, 131.0, 130.4, 129.8, 129.3, 128.9, 128.6, 128.4, 127.3, 127.1, 126.9, 124.4, 122.2, 120.5, 115.0, 113.9, 113.7, 113.1, 112.5, 112.0, 109.3, 71.1, 57.1, 55.5, 55.3, 47.0, 36.5, 29.9.

**HRMS** (NSI) found 855.3273 [M+H]<sup>+</sup> ([C<sub>53</sub>H<sub>46</sub>N<sub>2</sub>O<sub>7</sub>+H]<sup>+</sup> requires 855.3276; error –0.4 ppm).

## 6.6 Iodonium salts

### bis(4-Methoxyphenyl)iodonium 2,2,2-trifluoroacetate (213)



Fuming nitric acid (10.9 mL, 244 mmol, 3.1 equiv) was added dropwise to acetic anhydride (50 mL) at  $-10^\circ C$ . The reaction mixture was removed from the cooling bath and iodine (10.00 g, 78.8 mmol, 1.0 equiv) was added in a single portion. Trifluoroacetic acid (18.7 mL, 244 mmol, 3.1 equiv) was then added slowly over 20 min under a steady stream of nitrogen (CAUTION - NITROUS OXIDES RELEASED). Once gas release ceased the reaction mixture was concentrated *in vacuo* at 40 °C. The residue was dissolved in acetic anhydride (50 mL) and cooled to  $-10^\circ C$  before a cooled solution of anisole (31.5 mL, 315 mmol, 4.0 equiv) and trifluoroacetic acid (19.9 mL, 260 mmol, 3.3 equiv) in acetic anhydride (70 mL) was added gradually over 20 min. The mixture was stirred at  $rt$  for 20 min before being concentrated *in vacuo*. The oily residue was precipitated with excess diethyl ether, cooled in a freezer and promptly filtered with excess diethyl ether. The title compound was obtained as a light brown solid (21.2 g, 59%).

The data were in accordance with the literature.<sup>154</sup>

**mp** 120–123 °C (dichloromethane/diethyl ether).

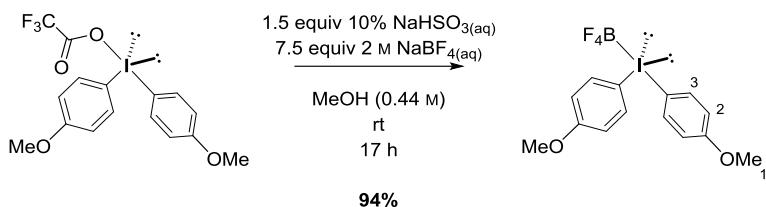
**IR**  $\nu_{max}$  (film)/cm<sup>-1</sup> 3346, 3056, 3032, 3002, 2937, 2912, 2837, 1613, 1574, 1551, 1507, 1464, 1453, 1440, 1355, 1338, 1315, 1300, 1282, 1227, 1195, 1176, 1122, 1101, 1029, 964, 908, 824, 794.

**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  8.05 (d,  $J$  = 9.2 Hz, 4H, H<sub>3</sub>), 7.07 (d,  $J$  = 9.1 Hz, 4H, H<sub>2</sub>), 3.86 (s, 6H, H<sub>1</sub>).

**<sup>13</sup>C NMR** (100 MHz, MeOD)  $\delta$  163.4, 137.0, 117.7, 104.1, 55.3.

**<sup>19</sup>F NMR** (376 MHz, MeOD)  $\delta$  -77.29.

**HRMS** (ESI) found [M-C<sub>2</sub>F<sub>3</sub>O<sub>2</sub>]<sup>+</sup> 341.0034 (C<sub>14</sub>H<sub>14</sub>IO<sub>2</sub> requires 341.0033; error 0.3 ppm).

**bis(4-Methoxyphenyl)iodonium tetrafluoroborate (184)**

Crude bis(4-methoxyphenyl)iodonium-2,2,2-trifluoroacetate (**213**) (100 g, 220 mmol, 1 equiv) was dissolved in methanol (400 mL, 0.44 M) and treated with 10% aqueous sodium bisulfite (344 mL, 330 mmol, 1.5 equiv) and 2 M aqueous sodium tetrafluoroborate solution (826 mL, 1.65 mol, 7.5 equiv). The mixture was stirred at room temperature for 17 h, the precipitate collected by filtration, washed with minimal water, heptane and dried *in vacuo* over phosphorus pentoxide to give the title compound as a free-flowing colourless powder (88.2 g, 94%).

*The data were in accordance with the literature.*

**mp** 157–165 °C (dichloromethane/diethyl ether).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3415, 3318, 3046, 3004, 2956, 2835, 1612, 1574, 1551, 1501, 1477, 1465, 1441, 1425, 1338, 1314, 1282, 1239, 1139, 1177, 1146, 1122, 1106, 1052, 1032, 964, 907, 836, 807.

**<sup>1</sup>H NMR** (400 MHz, MeOD) δ 8.05 (d,  $J$  = 9.2 Hz, 4H, H<sub>3</sub>), 7.06 (d,  $J$  = 9.2 Hz, 4H, H<sub>2</sub>), 3.86 (6H, s, H<sub>1</sub>).

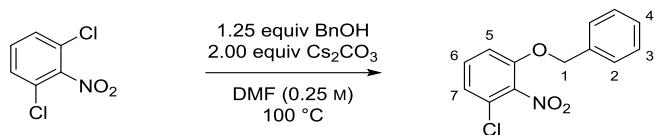
**<sup>13</sup>C NMR** (100 MHz, MeOD) δ 163.4, 137.2, 117.8, 104.0, 55.3.

**<sup>19</sup>F NMR** (376 MHz, MeOD) δ -156.97.

**HRMS** (ESI) found [M-BF<sub>4</sub>]<sup>+</sup> 341.0032 (C<sub>14</sub>H<sub>14</sub>IO<sub>2</sub> requires 341.0033); error -0.3 ppm.

## 6.7 Chloroarenes

### 1-(benzyloxy)-3-chloro-2-nitrobenzene (291)



An oven dried vial was charged with 1,3-dichloro-2-nitrobenzene (500 mg, 2.60 mmol, 1 equiv) and caesium carbonate (1.69 g, 5.20 mmol, 2 equiv) and flushed with argon. *N,N*-Dimethylformamide (10.4 mL, 0.25 M) and benzyl alcohol (338  $\mu$ L, 3.25 mmol, 1.25 equiv) were added sequentially and the reaction mixture stirred at 100 °C in a preheated oil bath until complete consumption of the starting material was determined by LCMS at 53 h. The mixture was allowed to cool to room temperature before being partitioned between ethyl acetate/sat. aq. ammonium chloride. The aqueous layer was further extracted with ethyl acetate ( $\times 3$ ) and the combined organics were washed with water ( $\times 2$ ) and brine before being dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (1:9 to 1:4 ethyl acetate/40–60 petroleum ethers) to give the title compound as yellow crystals (317 mg, 46%).

**mp** 76–77 °C (ethyl acetate/40–60 petroleum ethers).

**R<sub>f</sub>** 0.39 (20% ethyl acetate/40–60 petroleum ether).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3092, 3038, 2954, 2881, 1598, 1576, 1537, 1496, 1474, 1459, 1452, 1407, 1372, 1321, 1287, 1275, 1222, 1200, 1179, 1128, 1079, 1066, 1012, 991, 920, 888, 878, 853, 841.

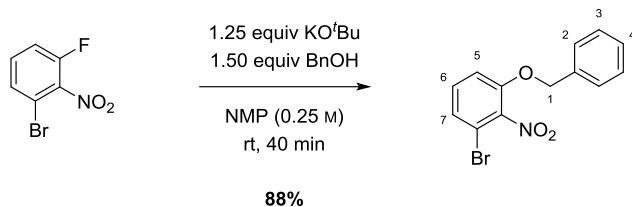
**<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44 – 7.32 (m, 5H, H<sub>2</sub>, H<sub>3</sub> and H<sub>4</sub>), 7.30 (t,  $J$  = 8.4 Hz, 1H, H<sub>6</sub>), 7.06 (dd,  $J$  = 8.2, 1.0 Hz, 1H, H<sub>5</sub>), 6.97 (dd,  $J$  = 8.5, 0.9 Hz, 1H, H<sub>7</sub>), 5.19 (s, 2H, H<sub>1</sub>).

**<sup>13</sup>C NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  151.0, 141.0, 135.1, 131.1, 128.9, 128.6, 127.2, 126.1, 122.1, 112.7, 71.5.

**HRMS** (ESI) found 281.0686 [M+NH<sub>4</sub>]<sup>+</sup> ([C<sub>13</sub>H<sub>10</sub>ClNO<sub>3</sub>+H]<sup>+</sup> requires 281.0687; error −0.5 ppm).

## 6.8 Bromoarenes

### 1-(benzyloxy)-3-bromo-2-nitrobenzene (292)



An oven dried flask was charged with potassium *tert*-butoxide (637 mg, 5.68 mmol, 1.25 equiv) and flushed with nitrogen. *N*-Methyl-2-pyrrolidone (9.1 mL) and benzyl alcohol (709  $\mu$ L, 6.82 mmol, 1.50 equiv) were sequentially added and stirred at room temperature for 5 min. 2-Bromo-6-fluoronitrobenzene (1.00 g, 4.55 mmol, 1.00 equiv) in *N*-methyl-2-pyrrolidone (9.1 mL, 0.25 M overall) was added in a single portion (WARNING: EXOTHERM). The reaction mixture stirred at room temperature until complete conversion of the starting material was observed by LCMS at 40 min. The reaction mixture was partitioned between diethyl ether/sat. ammonium chloride and the organic layer washed further with water and brine, dried over magnesium sulphate and concentrated on silica gel. The crude residue was purified by silica gel column chromatography (1:9 ethyl acetate/40–60 petroleum ether) to give the title compound as a pale yellow solid (1.23 g, 88%).

**mp** 103–104 °C (ethyl acetate/40–60 petroleum ethers)

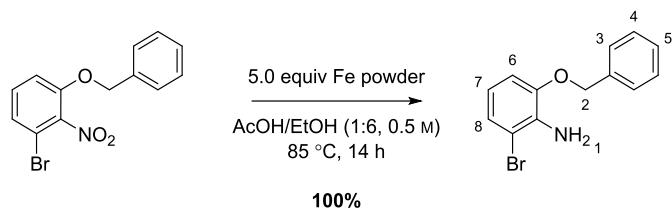
**R<sub>f</sub>** 0.35 (1:4 ethyl acetate/40–60 petroleum ethers)

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>−1</sup> 1592, 1576, 1537, 1496, 1473, 1452, 1371, 1332, 1321, 1282, 1265, 1221, 1197, 1178, 1165, 1124, 1079, 1065, 1004, 918, 873, 853, 835.

**<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43 – 7.28 (m, 5H, H<sub>2</sub>, H<sub>3</sub> and H<sub>4</sub>), 7.26 – 7.18 (m, 2H, H<sub>6</sub> and H<sub>5/7</sub>), 7.01 (dd,  $J$  = 7.4, 2.1 Hz, 1H, H<sub>5/7</sub>), 5.18 (s, 2H, H<sub>1</sub>).

**<sup>13</sup>C NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  151.0, 142.9, 135.1, 131.4, 128.9, 128.6, 127.2, 125.1, 113.8, 113.3, 71.5.

**HRMS** (APCI) found 325.0182 [M+NH<sub>4</sub>]<sup>+</sup> ( $[\text{C}_{13}\text{H}_{10}\text{BrNO}_3+\text{NH}_4]^+$  requires 325.0182; error 0.0 ppm).

**2-(benzyloxy)-6-bromoaniline (311)**

An oven dried vial was charged with 1-(benzyloxy)-3-bromo-2-nitrobenzene (**292**) (1.00 g, 3.25 mmol, 1.0 equiv) and iron powder (906 mg, 16.23 mmol, 5.0 equiv). The vial was sealed and flushed with argon. Acetic acid (930  $\mu$ L, **1:6**) and absolute ethanol (5.57 mL, **1:6**, 0.5 M overall) were added sequentially and the mixture stirred in a preheated oil bath at 85 °C until complete conversion of the starting material was observed by LCMS at 14 h. The reaction was allowed to cool to room temperature, filtered through a thin pad of Celite® and concentrated to a syrup. The residue was partitioned between diethyl ether/10% sodium hydroxide. The organic layer was further washed with brine, dried over magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound, without need for further purification, as an amber oil (903 mg, 100%).

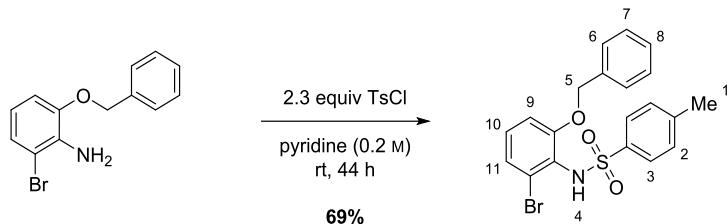
**R<sub>f</sub>** 0.63 (1:4 ethyl acetate/40-60 petroleum ether).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3477, 3380, 2989, 2968, 2902, 2334, 1606, 1573, 1499, 1484, 1453, 1407, 1393, 1381, 1338, 1285, 1251, 1203, 1154, 1074, 1066, 1039, 1025, 1017, 865, 811.

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  7.52 – 7.45 (m, 2H, **H<sub>3</sub>**), 7.42 – 7.36 (m, 2H, **H<sub>4</sub>**), 7.32 (t, J = 7.3 Hz, 1H, **H<sub>5</sub>**), 6.99 (dd, J = 8.2, 1.2 Hz, 1H, **H<sub>6/8</sub>**), 6.92 (dd, J = 8.2, 1.2 Hz, 1H, **H<sub>6/8</sub>**), 6.50 (t, J = 8.1 Hz, 1H, **H<sub>7</sub>**), 5.14 (s, 2H, **H<sub>2</sub>**), 4.79 (s (br), 2H, **H<sub>1</sub>**).

**<sup>13</sup>C NMR** (101 MHz, DMSO-d<sub>6</sub>)  $\delta$  145.9, 137.0, 135.7, 128.4, 127.8, 127.5, 124.2, 117.0, 111.2, 107.1, 69.8.

**HRMS** (NSI) found 278.0178 [M+H]<sup>+</sup> ([C<sub>13</sub>H<sub>12</sub>BrNO+H]<sup>+</sup> requires 278.0175; error 1.1 ppm).

**N-(2-(benzyloxy)-6-bromophenyl)-4-methylbenzenesulfonamide (360)**

Tosyl chloride (335 mg, 3.44 mmol, 2.3 equiv) was added at intervals over a 44 h period to a stirred solution of 2-(benzyloxy)-6-bromoaniline (430 mg, 1.50 mmol, 1.0 equiv) in pyridine at rt in an open flask. The reaction mixture was concentrated and partitioned between diethyl ether/1 M aq hydrogen chloride. The organic layer was further washed with 1 M aq hydrogen chloride and brine, dried over magnesium sulphate, filtered and concentrated on silica *in vacuo*. The crude material was purified by silica gel column chromatography (1:9 to 1:2 ethyl acetate/40–60 petroleum ethers) to give the title compound as light yellow crystals (459 mg, 69%).

**mp** 146–147 °C (ethyl acetate/40-60 petrol ether).

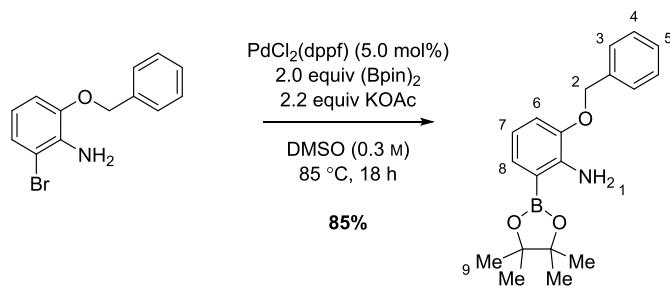
**R<sub>f</sub>** 0.33 (1:4 ethyl acetate/40-60 petroleum ether).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3252, 1577, 1497, 1452, 1399, 1334, 1289, 1264, 1164, 1091, 1023, 909, 869, 813, 769, 739, 697, 673, 664, 656.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.63 (d, J = 8.3 Hz, 2H, H<sub>3</sub>), 7.37 – 7.28 (m, 3H, H<sub>6/7</sub> and H<sub>8</sub>), 7.24 – 7.16 (m, 3H, H<sub>9/11</sub> and H<sub>6/7</sub>), 7.10 (d, J = 8.2 Hz, 2H, H<sub>2</sub>), 7.04 (t, J = 8.2 Hz, 1H, H<sub>10</sub>), 6.79 (d, J = 8.3 Hz, 1H, H<sub>9/11</sub>), 6.35 (s, 1H), 4.77 (s, 2H, H<sub>5</sub>), 2.35 (s, 3H, H<sub>1</sub>).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 155.3, 143.4, 138.0, 135.9, 129.2, 129.1, 128.7, 128.2, 127.5, 127.2, 125.7, 124.8, 124.1, 112.0, 70.8, 21.7.

**HRMS** (NSI) found 432.0262 [M+H]<sup>+</sup> ([C<sub>20</sub>H<sub>18</sub>BrNO<sub>3</sub>S+H]<sup>+</sup> requires 432.0264; error –0.4 ppm).

**2-(benzyloxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (255)**

A mixture of 2-(benzyloxy)-6-bromoaniline (**311**) (5.00 g, 17.9 mmol, 1.0 equiv), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (657 mg, 0.898 mmol, 5.0 mol%), bis(pinacolato)diboron (9.13 g, 36.0 mmol, 2.0 equiv) and potassium acetate (3.88 g, 39.6 mmol, 2.2 equiv) in dimethylsulfoxide (59.7 mL, 0.3 M) was stirred at 85 °C under N<sub>2</sub> in a pre-heated dry bath. Complete conversion was observed by LCMS at 18 h and the reaction allowed to cool to room temperature. The reaction mixture was diluted with ethyl acetate and washed with sat. aq ammonium chloride, water (x3) and brine before being dried over magnesium sulfate, filtered and concentrated on silica. The crude material was purified by silica gel column chromatography (1:99 to 1:19 ethyl acetate/40–60 petroleum ethers) to give the title compound as a pale blue solid (8.09 g, 138%).

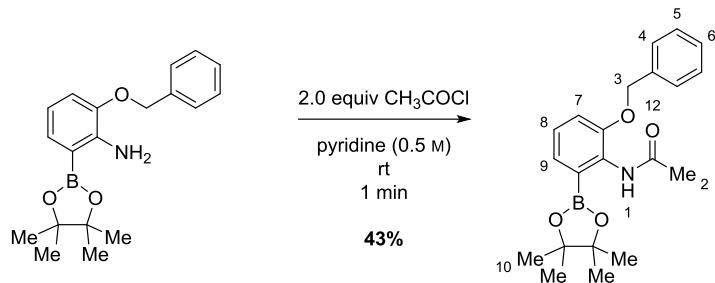
<sup>1</sup>H NMR showed the title compound co-eluted with unreacted (Bpin)<sub>2</sub> and the actual yield (4.98 g, 85%) could be calculated by the integrations of the methyl peaks relative to their respective molar masses.

**IR**  $\nu_{\max}$  (film)/cm<sup>-1</sup> 3502, 3365, 2979, 2929, 1614, 1563, 1499, 1464, 1390, 1371, 1332, 1305, 1279, 1203, 1185, 1173, 1143, 1123, 1092, 1045, 1027, 962, 892, 878, 849.

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>) δ 7.46 (d, J = 7.3 Hz, 2H, H<sub>3</sub>), 7.38 (t, J = 7.4 Hz, 2H, H<sub>4</sub>), 7.31 (t, J = 7.2 Hz, 1H, H<sub>5</sub>), 7.00 (d, J = 7.5 Hz, 1H, H<sub>6/8</sub>), 6.95 (d, J = 7.8 Hz, 1H, H<sub>6/8</sub>), 6.45 (t, J = 7.7 Hz, 1H, H<sub>7</sub>), 5.18 (s (br), 2H, H<sub>1</sub>), 5.10 (s, 2H, H<sub>2</sub>), 1.29 (s, 12H, H<sub>9</sub>).

**<sup>13</sup>C NMR** (100 MHz, DMSO-d<sub>6</sub>) δ 144.7, 144.3, 137.4, 128.4, 127.9, 127.7, 127.4, 115.2, 114.9, 83.3, 82.9, 69.3, 24.8.

**HRMS** (NSI) found 325.1959 [M+H]<sup>+</sup> ([C<sub>19</sub>H<sub>24</sub>BNO<sub>3</sub>+H]<sup>+</sup> requires 325.1958; error 0.3 ppm).

***N*-(2-(benzyloxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (254)**

2-(Benzyl oxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**255**) (200 mg, 0.615 mmol, 1.0 equiv) was stirred in pyridine (1.2 mL, 0.5 M) at room temperature. Acetyl chloride (88  $\mu$ L, 1.23 mmol, 2.0 equiv) was added gradually by hand and a small exotherm was observed. The desired product precipitated within 1 min of the addition and the reaction mixture was concentrated directly on silica *in vacuo*. Purification by silica gel column chromatography (1:9 to 1:99 methanol/dichloromethane) and trituration with diethyl ether afforded the title compound as a colourless solid (97 mg, 43%).

**mp** 176.9–177.7 °C (ethyl acetate/40–60 petroleum ethers).

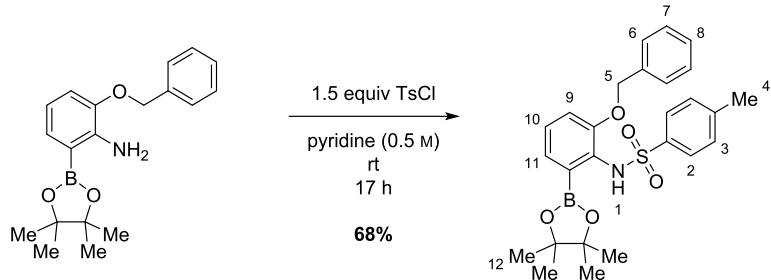
**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3415 (br), 2988, 2963, 2925, 1629, 1598, 1471, 1451, 1384, 1371, 1364, 1336, 1300, 1271, 1246, 1219, 1159, 1123, 1106, 1080, 1035, 1018, 950, 916, 892, 860, 848, 836.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.79 (s, 1H, H<sub>1</sub>), 7.42 – 7.33 (m, 5H, H<sub>4</sub>, H<sub>5</sub> and H<sub>6</sub>), 7.25 (d, *J* = 7.1 Hz, 1H, H<sub>7/9</sub>), 7.13 (t, *J* = 7.8 Hz, 1H, H<sub>8</sub>), 6.83 (d, *J* = 8.1 Hz, 1H, H<sub>7/9</sub>), 5.08 (s, 2H, H<sub>3</sub>), 2.31 (s, 3H, H<sub>2</sub>), 1.33 (s, 12H, H<sub>10</sub>).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  169.3, 145.2, 136.4, 128.9, 128.6, 128.0, 126.8, 126.6, 125.6, 110.8, 81.0, 71.0, 26.1, 23.2.

**HRMS** (NSI) found 367.2062 [M+H]<sup>+</sup> ([C<sub>21</sub>H<sub>26</sub><sup>10</sup>BNO<sub>4</sub>+H]<sup>+</sup> requires 367.2064; error -0.5 ppm).

**N-(2-(benzyloxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-methylbenzenesulfonamide (314)**



2-(BenzylOxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**255**) (1.00 g, 3.07 mmol, 1.0 equiv) and tosyl chloride (878 mg, 4.61 mmol, 1.5 equiv) were stirred in pyridine (6.14 mL, 0.5 M) at room temperature until complete conversion was observed by LCMS at 17 h. The reaction mixture was poured onto ice, diluted with ethyl acetate and washed with sat. aq ammonium chloride, water and brine. The organic layer was dried over magnesium sulphate, filtered and concentrated on silica *in vacuo*. Purification by silica gel column chromatography (1:9 to 1:4 to 1:2 ethyl acetate/40–60 petroleum ethers) afforded the title compound as a colourless solid (994 mg, 68%).

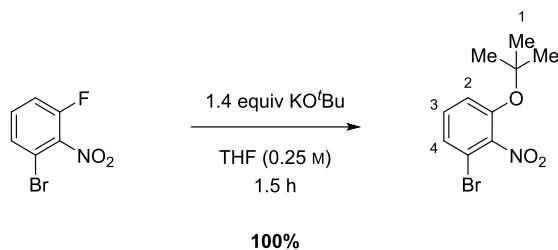
**mp** 130.7–131.5 °C (ethyl acetate/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3279, 3067, 1724, 1599, 1575, 1497, 1481, 1450, 1389, 1373, 1350, 1286, 1265, 1212, 1183, 1163, 1150, 1137, 1092, 1026, 967, 916, 892, 854, 814.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.42 (d, J = 8.2 Hz, 2H, **H<sub>2</sub>**), 7.31 (d, J = 15.7 Hz, 4H, **H<sub>6/7</sub>**, **H<sub>8</sub>** and **H<sub>10</sub>**), 7.13 (s, 1H, **H<sub>1</sub>**), 7.11 (d, J = 7.8 Hz, 1H, **H<sub>9/11</sub>**), 7.05 (d, J = 8.2 Hz, 2H, **H<sub>3</sub>**), 7.02 (d, J = 9.3 Hz, 2H, **H<sub>6/7</sub>**), 6.81 (d, J = 8.1 Hz, 1H, **H<sub>9/11</sub>**), 4.62 (s, 2H, **H<sub>5</sub>**), 2.34 (s, 3H, **H<sub>4</sub>**), 1.40 (s, 12H, **H<sub>12</sub>**).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 151.6, 143.0, 137.5, 136.4, 129.8, 129.1, 128.6, 128.1, 127.5, 127.3, 127.0, 126.9, 114.7, 84.3, 70.2, 25.1, 21.6.

**HRMS** (NSI) found 479.2040 [M+H]<sup>+</sup> ([C<sub>26</sub>H<sub>30</sub><sup>10</sup>BNO<sub>5</sub>S+H]<sup>+</sup> requires 479.2047; error –1.5 ppm).

**1-bromo-3-(*tert*-butoxy)-2-nitrobenzene (300)**

To a stirred solution of 2-bromo-6-fluorobenzene (1.00 g, 4.54 mmol, 1 equiv) in THF (13.2 mL) under argon at 0 °C was added a suspension of potassium *tert*-butoxide (714 mg, 6.36 mmol, 1.4 equiv) in THF (5 mL, 0.25 M total). The ice bath was removed and the reaction stirred at rt. A colour change from colourless to orange was observed. An additional portion of potassium *tert*-butoxide (204 mg, 1.82 mmol) was added at 1.25 h. The reaction was stirred further at room temperature until complete conversion of the starting material was observed by LCMS at 1.5 h. The reaction mixture was concentrated *in vacuo* to an orange syrup, partitioned between diethyl ether/sat. ammonium chloride. The organic layer was further washed with water and brine before being dried over magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound in excellent purity as a dark green oil (1.244 g, 100%).

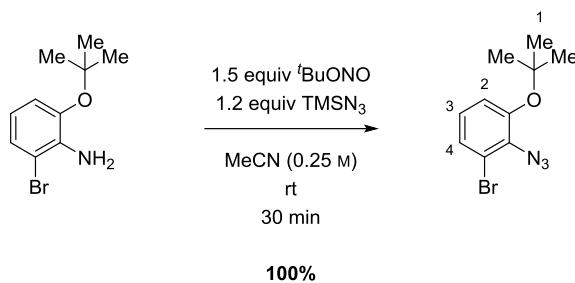
**R<sub>f</sub>** 0.50 (1:4 ethyl acetate/40-60 petroleum ether).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 2983, 1586, 1538, 1456, 1395, 1368, 1274, 1158, 1120, 1062, 937, 916, 850, 828, 791, 750, 696, 669.

**<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ ) δ 7.27 (dd,  $J = 7.9, 1.5$  Hz, 1H, H<sub>2/4</sub>), 7.22 (t,  $J = 8.1$  Hz, 1H, H<sub>3</sub>), 7.17 (dd,  $J = 8.2, 1.5$  Hz, 1H, H<sub>2/4</sub>), 1.43 (s, 9H, H<sub>1</sub>).

**<sup>13</sup>C NMR** (100 MHz,  $\text{CDCl}_3$ ) δ 149.4, 147.1, 130.7, 126.6, 121.1, 113.2, 83.2, 29.1.

**HRMS** (ESI) found 274.0075 [M+H]<sup>+</sup> ( $[\text{C}_{10}\text{H}_{12}\text{BrNO}_3+\text{H}]^+$  requires 274.0073; error 0.6 ppm).

**2-azido-1-bromo-3-(*tert*-butoxy)benzene (391)**

To a stirred solution of 2-bromo-6-(*tert*-butoxy)aniline (**312**) (388 mg, 1.59 mmol, 1.0 equiv) in acetonitrile (6.36 mL, 0.25 M) at rt under air was added dropwise *tert*-butyl nitrite (283  $\mu$ L, 2.38 mmol, 1.5 equiv) immediately followed by trimethylsilyl azide (0.253  $\mu$ L, 1.91 mmol, 1.2 equiv) (WARNING: GAS RELEASED). The reaction mixture was stirred until complete consumption of the starting material was determined by LCMS at 30 min. The reaction mixture was concentrated on silica and purified by silica gel column chromatography (1:9 ethyl acetate/40–60 petroleum ethers) to give the title compound as an amber oil (428 mg, 100%).

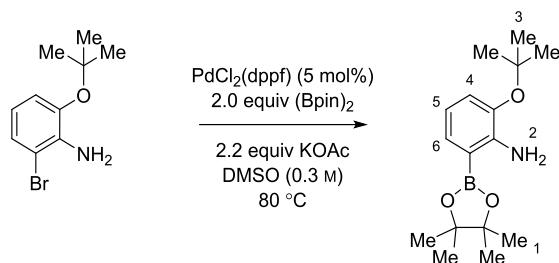
**R**<sub>f</sub> 0.65 (1:4 ethyl acetate/40-60 petrol ether).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 2981, 2937, 2133, 2097, 1711, 1580, 1562, 1544, 1441, 1393, 1369, 1320, 1259, 1160, 931, 913, 830.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.23 (dd, J = 8.0, 1.3 Hz, 1H, H<sub>2/4</sub>), 7.02 (dd, J = 8.2, 1.4 Hz, 1H, H<sub>2/4</sub>), 6.90 (t, J = 8.2 Hz, 1H, H<sub>3</sub>), 1.44 (s, 9H, H<sub>1</sub>).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  150.7, 132.6, 127.7, 125.3, 122.1, 115.4, 82.2, 28.5.

**HRMS** (APCI) found 287.0500 [M+NH<sub>4</sub>]<sup>+</sup> ([C<sub>10</sub>H<sub>12</sub>BrN<sub>3</sub>O+NH<sub>4</sub>]<sup>+</sup> requires 287.0502; error -0.7 ppm).

**2-(*tert*-butoxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (313)**

A solution of 2-bromo-6-(*tert*-butoxy)aniline (**312**) (1.71 g, 6.99 mmol, 1.0 equiv), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (256 mg, 0.35 mmol, 5.0 mol%) bis(pinacolato)diboron (3.55 g, 14.0 mmol, 2.0 equiv) and potassium acetate (1.51 g, 15.37 mmol, 2.2 equiv) in dimethylsulfoxide (23.3 mL, 0.3 M) was stirred at 80 °C for 18 h. The reaction was cooled to room temperature, diluted with ethyl acetate and washed with sat. ammonium chloride, water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated on silica *in vacuo*. Purification by silica gel column chromatography (1:99 to 1:19 ethyl acetate/40–60 petroleum ethers) afforded the title compound as a lime green solid (1.66 g, 82%).

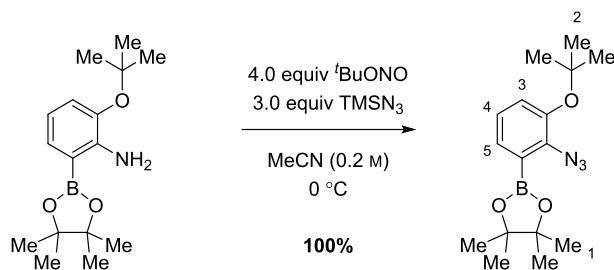
**mp** 78.0–79.5 °C (dichloromethane).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3503, 3395, 2978, 2933, 1605, 1562, 1473, 1451, 1390, 1360, 1300, 1270, 1240, 1210, 1161, 1141, 1110, 1088, 1068, 1005, 966, 936, 913, 865, 845.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.32 (dd, J = 7.5, 1.5 Hz, 1H, **H<sub>4</sub>**), 7.01 (dd, J = 7.8, 1.5 Hz, 1H, **H<sub>6</sub>**), 6.55 (t, J = 7.6 Hz, 1H, **H<sub>5</sub>**), 1.40 (s, 9H, **H<sub>3</sub>**), 1.34 (s, 12H, **H<sub>1</sub>**).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 148.6, 142.3, 131.0, 125.5, 116.0, 111.8 (*visible in HMBC*), 83.6, 79.5, 29.2, 25.1.

**HRMS** (NSI) found 291.2113 [M+H]<sup>+</sup> ([C<sub>16</sub>H<sub>26</sub><sup>10</sup>BNO<sub>3</sub>+H]<sup>+</sup> requires 291.2115; error –0.7 ppm).

**2-(*tert*-butoxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**315**)**

To a solution of 2-(*tert*-butoxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**313**) (250 mg, 0.859 mmol, 1.0 equiv) in acetonitrile (4.3 mL, 0.2 M) at 0 °C was added *tert*-butyl nitrite (0.407 mL, 3.43 mmol, 4.0 equiv) dropwise followed immediately by trimethylsilyl azide (0.342 mL, 2.58 mmol, 3.0 equiv) dropwise. After 10 min the reaction mixture was concentrated *in vacuo* to afford the title compound without further purification as a brown oil (272 mg, 100%).

**IR**  $\nu_{\max}$  (film)/cm<sup>-1</sup> 2980, 2934, 2110, 1588, 1571, 1473, 1430, 1389, 1352, 1304, 1268, 1239, 1213, 1193, 1161, 1139, 1071, 1058, 1035, 1005, 972, 946, 921, 858, 843, 817, 809.

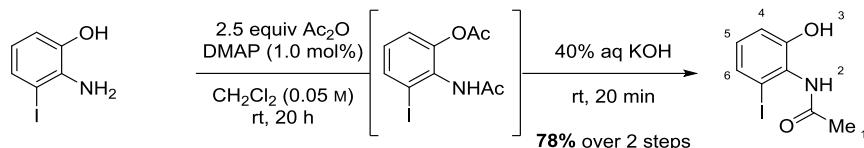
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.39 – 7.34 (dd, J = 8.1, 0.9 Hz, 1H, H<sub>3</sub>), 7.12 (dd, J = 8.1, 0.9 Hz, 1H, H<sub>5</sub>), 7.02 (t, J = 7.7 Hz, 1H, H<sub>4</sub>), 1.41 (s, 9H, H<sub>2</sub>), 1.36 (s, 12H, H<sub>1</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 149.5, 138.1, 130.7, 126.5, 124.7, 124.1 (*visible in HMBC*), 84.1, 81.1, 28.6, 24.9.

**HRMS** (APCI) found 334.2280 [M+NH<sub>4</sub>]<sup>+</sup> ([C<sub>16</sub>H<sub>24</sub><sup>10</sup>BN<sub>3</sub>O<sub>3</sub>+NH<sub>4</sub>]<sup>+</sup> requires 334.2285; error -1.5 ppm).

## 6.9 Iodoarenes

### *N*-(2-Hydroxy-6-iodophenyl)acetamide (346)



Acetic anhydride (1.00 mL, 10.6 mmol, 2.5 equiv) and *N,N*-dimethylaminopyridine (5 mg, 0.04 mmol) were added sequentially to a stirred solution of 2-amino-3-iodophenol (**344**) (1.00 g, 4.25 mmol, 1.0 mol%) in dichloromethane (90 mL, 0.05 M). The reaction mixture was stirred at room temperature for 20 h before being treated with aq 40% potassium hydroxide solution (50 mL). The biphasic mixture was stirred vigorously for 20 min before being diluted with additional dichloromethane and water. The aqueous layer was isolated and acidified with aqueous hydrochloric acid before being extracted with dichloromethane ( $\times 3$ ). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo* to give the title compound as a white solid (942 mg, 78%).

**mp** 160–161 °C (dichloromethane).

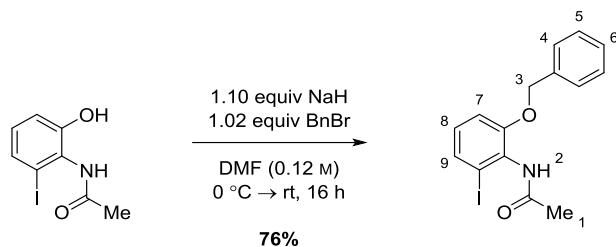
**R**<sup>f</sup> 0.14 (2:3 ethyl acetate/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3250 (br), 1625, 1580, 1521, 1442, 1349, 1288, 867, 768.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.83 (s, 1H, H<sub>3</sub>), 7.50 (s, 1H, (br), H<sub>2</sub>), 7.40 (dd, J = 7.9, 1.4 Hz, 1H, H<sub>4/6</sub>), 7.04 (dd, J = 8.1, 1.4 Hz, 1H, H<sub>4/6</sub>), 6.88 (t, J = 8.0 Hz, 1H, H<sub>5</sub>), 2.36 (s, 3H, H<sub>1</sub>).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 171.2, 150.2, 131.0, 129.1, 127.1, 121.4, 93.1, 24.0.

**HRMS** (ESI) found [M+H]<sup>+</sup> 277.9673 ([C<sub>8</sub>H<sub>9</sub>NO<sub>2</sub>I+H]<sup>+</sup> requires 277.9672; error –2.3 ppm).

***N*-(2-(BenzylOxy)-6-iodophenyl)acetamide (347)**

Sodium hydride (60 % dispersion in mineral oil, 316 mg, 7.85 mmol, 1.10 equiv) was added to a solution of *N*-(2-hydroxy-6-iodophenyl)acetamide (**346**) (1.99 g, 7.13 mmol, 1.00 equiv) in dry *N,N*-dimethylformamide (60 mL, 0.12 M) at 0 °C. Benzyl bromide (0.86 mL, 7.27 mmol, 1.02 equiv) was added immediately and the reaction mixture allowed to warm to room temperature and stirred for 16 h. The reaction mixture was diluted with ethyl acetate and poured into water. The organic phase was separated, washed with water and brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by crystallisation from a mixture of diethylether and petrol to afford the aryl halide as a pale pink solid (1.99 g, 76%).

**mp** 140–142 °C (diethyl ether/40–60 petroleum ethers).

**IR**  $\nu_{\max}$  (film)/cm<sup>-1</sup> 3186, 1667, 1572, 1525, 1471, 1460, 1439, 1369, 1288, 1256, 1232, 1011.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.45 (s (br), 1H, H<sub>8</sub>), 7.41 – 7.27 (m, 5H, H<sub>4</sub>, H<sub>5</sub> and H<sub>6</sub>), 6.94 (s (br), 2H, H<sub>7</sub> and H<sub>9</sub>), 6.78 (s (br), 1H, H<sub>2</sub>), 5.06 (s, 2H, H<sub>3</sub>), 2.16 (s (br), 3H, H<sub>1</sub>).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 168.6, 154.6, 136.3, 131.2, 129.7, 128.7, 128.1, 127.2, 113.3, 100.1, 77.2, 70.8, 23.6.

**HRMS** (ESI) found [M+H]<sup>+</sup> 368.0146 ([C<sub>15</sub>H<sub>14</sub>NO<sub>2</sub>I+H]<sup>+</sup> requires 368.0142; error −0.3 ppm).

**2-Acetamido-3-iodophenyl (2,2,2-trichloroethyl) sulphate (288)**

1,4-Diazabicyclo[2.2.2]octane (1.10 g, 9.78 mmol, 3.0 equiv) and a solution of 1,1,1-trichloroethyl sulfonyl chloride (1.13 g, 4.89 mmol, 2.0 equiv) in dichloromethane (5 mL) were added sequentially to a stirred solution of *N*-(2-hydroxy-6-iodophenyl)acetamide (**346**) (910 mg, 3.26 mmol, 1.0 equiv) in dichloromethane (20 mL, 0.13 M overall). The reaction was stirred at room temperature for 1 h before being quenched with saturated aqueous ammonium chloride solution. The organic layer was isolated and the aqueous layer extracted with additional dichloromethane, the combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by crystallisation from dichloromethane/hexane to afford the title compound as a pale pink solid (1.29 g, 84%).

**mp** 101–103 °C (dichloromethane/hexanes).

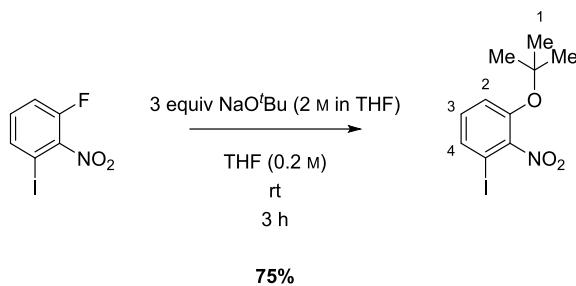
**IR**  $\nu_{\max}$  (film)/cm<sup>-1</sup> 3232, 3008, 2962, 1668, 1588, 1568, 1512, 1459, 1437, 1409, 1370, 1278, 1245, 1220, 1197, 1164, 1119, 1086, 1047, 1000, 965, 904, 849.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.86 (d, J = 8.0 Hz, 1H, H<sub>46</sub>), 7.49 (d, J = 8.3 Hz, 1H, H<sub>46</sub>), 7.11 (t, J = 8.2 Hz, 1H, H<sub>5</sub>), 7.05 (s, 1H, H<sub>2</sub>), 4.88 (s, 2H, H<sub>3</sub>), 2.26 (s, 3H, H<sub>1</sub>).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 168.4, 145.5, 138.4, 132.0, 130.0, 122.0, 100.3, 92.2, 23.5.

**HRMS** (ESI) found 487.8380 [M+H]<sup>+</sup> ([C<sub>10</sub>H<sub>9</sub>Cl<sub>3</sub>INO<sub>5</sub>+H]<sup>+</sup> requires 487.8384; error −0.9 ppm).

\*Performed by Dr Robert H. Snell

**1-(*tert*-butoxy)-3-iodo-2-nitrobenzene (301)**

To a stirred solution of sodium *tert*-butoxide (2 M in THF, 28.1 mL, 18.73 mmol, 3 equiv) in an open 250 mL RBF was added dropwise a solution of 1-(*tert*-butoxy)-3-iodo-2-nitrobenzene (5.00 g, 56.19 mmol, 1 equiv) in THF (93.7 mL, 0.2 M) over approximately 1 h. Complete conversion was observed by LCMS at 3 h. The reaction mixture was diluted with diethyl ether and washed with 1 M aq hydrochloric acid, water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The crude residue was taken up in minimum hot heptane and upon cooling the title compound recrystallised as light yellow needles (4.30 g, 75%).

*NOTE: An unidentified transition metal free cross-coupling by-product appears to account for the remaining mass balance.*

**mp** 63.4–64.4 °C (heptane).

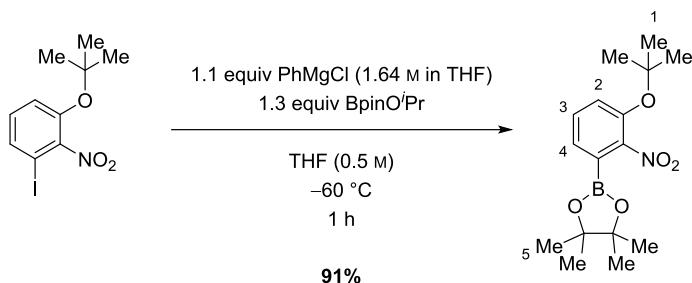
**R<sub>f</sub>** 0.25 (1:19 ethyl acetate/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 2986, 2937, 2905, 1919, 1582, 1562, 1527, 1454, 1427, 1395, 1369, 1284, 1245, 1162, 1116, 1061, 936, 914, 850, 823.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.47 (d, *J* = 7.9 Hz, 1H, H<sub>2/4</sub>), 7.18 (d, *J* = 8.4 Hz, 1H, H<sub>2/4</sub>), 7.06 (*t*, *J* = 8.2 Hz, 1H, H<sub>3</sub>), 1.41 (*s*, 9H, H<sub>1</sub>).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 151.0, 148.8, 132.9, 131.2, 122.1, 85.2, 83.1, 29.1.

**HRMS** (APCI) found 321.9936 [M+H]<sup>+</sup> ([C<sub>10</sub>H<sub>12</sub>INO<sub>3</sub>+H]<sup>+</sup> requires 321.9935; error 0.3 ppm).

**2-(3-(*tert*-butoxy)-2-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (302)**

To a stirred solution of 1-(*tert*-butoxy)-3-iodo-2-nitrobenzene (**301**) (4.00 g, 12.5 mmol, 1.0 equiv) in THF (24.9 mL, 0.5 M) at -60 °C was added phenylmagnesium chloride (titrated as 1.64 M in THF, 8.35 mL, 1.1 equiv) by syringe pump over 20 min. The reaction mixture was stirred for 20 min before 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.30 mL, 16.2 mmol, 1.3 equiv) was added dropwise by syringe pump over 20 min. The cooling bath was removed and the reaction mixture gradually warmed to rt. The reaction mixture was diluted with ethyl acetate and washed with sat. aq ammonium chloride, water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated on silica *in vacuo*. Purification by silica gel column chromatography (1:19 ethyl acetate/40–60 petroleum ethers) afforded the title compound as a light orange solid (3.62 g, 91%).

*NOTE: Using an Alizarin (Mordant Red 11) TLC stain allows for good visualisation of the desired product.*

**mp** 82.4–84.3 °C (ethyl acetate/40–60 petroleum ethers).

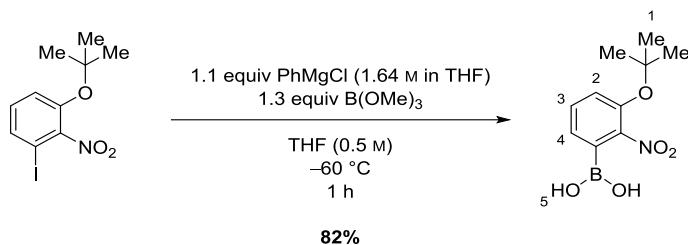
**R<sub>f</sub>** 0.50 (1:4 ethyl acetate/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 2980, 2937, 1603, 1569, 1538, 1474, 1428, 1393, 1369, 1352, 1329, 1273, 1214, 1196, 1162, 1139, 1060, 1006, 975, 951, 860, 841, 806.

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>) δ 7.54 – 7.48 (m, 2H), H<sub>2/4</sub> and H<sub>3</sub>, 7.38–7.32 (m, 1H, H<sub>2/4</sub>), 1.33 (s, 9H, H<sub>1</sub>), 1.25 (s, 12H, H<sub>5</sub>).

**<sup>13</sup>C NMR** (100 MHz, DMSO-d<sub>6</sub>) δ 149.5, 146.7, 131.1, 128.4, 125.9, 123.0 (br), 84.5, 81.8, 40.1, 28.5, 24.3.

**HRMS** (APCI) found 338.2123 [M+NH<sub>4</sub>]<sup>+</sup> ([C<sub>16</sub>H<sub>24</sub><sup>10</sup>BNO<sub>5</sub>+NH<sub>4</sub>]<sup>+</sup> requires 338.2122; error 0.3 ppm).

(3-(*tert*-butoxy)-2-nitrophenyl)boronic acid (303)

To a stirred solution of 1-(*tert*-butoxy)-3-iodo-2-nitrobenzene (**301**) (940 mg, 2.93 mmol, 1.0 equiv) in THF (5.85 mL, 0.5 M) in an oven-dried flask at -60 °C was added phenylmagnesium chloride solution (2 M in THF, 1.61 mL, 3.22 mmol, 1.1 equiv) by syringe pump over approximately 10 min. A colour change from yellow to red was observed. The solution was stirred for 5 min before the dropwise addition of trimethylborate (0.425 mL, 3.81 mmol, 1.3 equiv) by syringe pump over approximately 2 min. A colour change from red to orange was observed. The reaction mixture was stirred for a further 20 min at -60 °C. After slowly warming to -20 °C, 1.0 M aq hydrochloric acid (20 mL) was added and the cooling bath removed to allow the mixture to warm to rt. The reaction was diluted with diethyl ether and washed with water and brine. The organic layer was dried over magnesium sulphate, filtered and concentrated on silica gel *in vacuo*. Purification by silica gel column chromatography (1:2 ethyl acetate/40–60 petroleum ethers) gave the title compound and an orange solid (572 mg, 82%).

*NOTE: Using an Alizarin (Mordant Red 11) TLC stain allows for good visualisation of the desired product.*

**mp** 82.5–83.8 °C (dichloromethane/hexanes).

**R<sub>f</sub>** 0.08 (1:2 ethyl acetate/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 2982, 2941, 2902, 1614, 1538, 1473, 1392, 1369, 1312, 1273, 1193, 1144, 1066, 1057, 960, 934, 913, 853, 839.

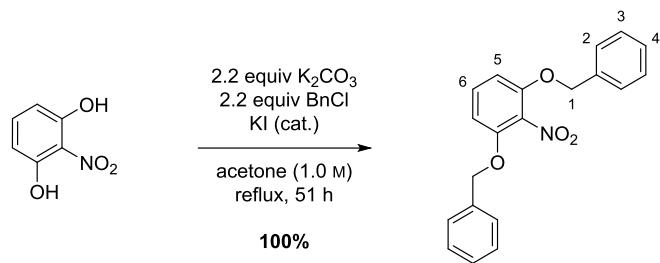
**<sup>1</sup>H NMR** (400 MHz, DMSO-d6) δ 8.39 (s, 2H, **H<sub>5</sub>**), 7.46 (t, J = 7.8 Hz, 1H, **H<sub>3</sub>**), 7.36 (dd, J = 8.3, 1.3 Hz, 1H, **H<sub>2/4</sub>**), 7.30 (dd, J = 7.2, 1.3 Hz, 1H, **H<sub>2/4</sub>**), 1.33 (s, 9H, **H<sub>1</sub>**).

**<sup>13</sup>C NMR** (101 MHz, DMSO-d6) δ 149.1, 146.7, 130.7, 127.6, 124.0, 81.3, 28.6. (Nitro or boronic acid carbon not visible in <sup>13</sup>C NMR).

**HRMS** (ESI) found [M-H]<sup>-</sup> 237.0931 ([C<sub>10</sub>H<sub>14</sub><sup>10</sup>BNO<sub>5</sub>-H]<sup>-</sup> requires 237.0929; error 0.8 ppm).

## 6.10 Aryl Triflates

### ((2-nitro-1,3-phenylene)bis(oxy))bis(methylene)dibenzene (317)



2-Nitroresorcinol (**316**) (10.0 g, 64.4 mmol, 1.0 equiv) and potassium carbonate (19.6 g, 141.8 mmol, 2.2 equiv) were stirred in acetone (65 mL, 1.0 M) at reflux. A catalytic amount of potassium iodide was added and benzyl chloride (16.3 mL, 141.8 mmol, 2.2 equiv) added dropwise over 10 min. The reaction was allowed to cool to rt when complete consumption of the starting material was observed by LCMS at 51 h. The mixture was filtered through a thin pad of Celite with excess acetone and concentrated *in vacuo*. The crude residue was partitioned between ethyl acetate/10% aqueous sodium hydroxide and the organic layer was washed further with 10% aqueous sodium hydroxide ( $\times 2$ ), water and then brine before being dried over sodium sulphate, filtered and concentrated *in vacuo* to give the title compound, without the need for further purification, as a colourless solid (21.6 g, quant.).

*Data were in accordance with the literature.*<sup>135</sup>

**mp** 101–102 °C (ethyl acetate).

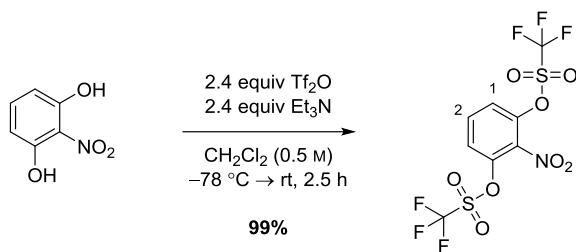
**R<sub>f</sub>** 0.35 (1:4 ethyl acetate/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3666, 2989, 2902, 1610, 1585, 1535, 1498, 1481, 1454, 1375, 1262, 1241, 1099, 1077, 1057, 1029, 904, 853, 777, 738, 696.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.39 – 7.34 (m, 10H, H<sub>2</sub>, H<sub>3</sub> and H<sub>4</sub>), 7.23 (t, J = 8.6 Hz, 1H, H<sub>6</sub>), 6.64 (d, J = 8.5 Hz, 2H, H<sub>5</sub>), 5.16 (s, 4H, H<sub>1</sub>).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 150.9, 135.6, 133.0, 130.9, 128.7, 128.2, 127.0, 106.3, 71.0.

**HRMS** (ESI) found 336.1224 [M+H]<sup>+</sup> ([C<sub>20</sub>H<sub>17</sub>NO<sub>4</sub>+H]<sup>+</sup> requires 336.1230; error -1.9 ppm).

**2-nitro-1,3-phenylene bis(trifluoromethanesulfonate) (318)**

2-Nitroresorcinol (**316**) (8.45 g, 54.5 mmol, 1.0 equiv) was stirred in dichloromethane (109 mL, 0.5 M) under argon at -78 °C. Triethylamine (18.4 mL, 131 mmol, 2.4 equiv) and triflic anhydride (22 mL, 131 mmol, 2.4 equiv) were added sequentially and the mixture was stirred for 10 min before being allowed to warm to rt. The mixture was stirred until complete consumption of the starting material was observed by LCMS at 2.5 h. Water (350 mL) was cautiously added and the organic layer diluted with dichloromethane (250 mL). The aqueous layer was further extracted ( $\times 3$ ) and the combined organics extensively washed with sat. aq ammonium chloride to remove residual triethylamine. They were then dried over magnesium sulphate, filtered through a thin pad of silica with ethyl acetate and concentrated *in vacuo* to give the title compound, without the need for further purification, as a light brown solid (22.7 g, 99%).

**mp** 37–38 °C (ethyl acetate/40–60 petroleum ethers).

**R<sub>f</sub>** 0.13 (1:9 ethyl acetate/40–60 petroleum ethers).

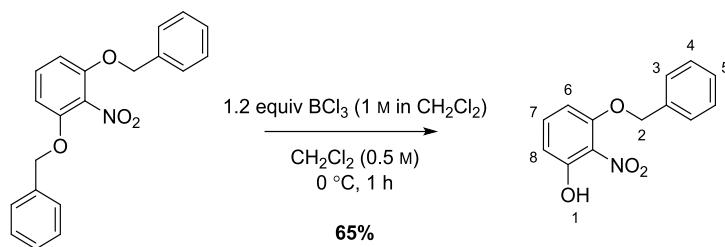
**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3677, 3106, 2989, 2902, 1602, 1547, 1471, 1423, 1394, 1363, 1210, 1174, 1132, 1066, 999, 878, 834, 810.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.77 (dd, J = 9.1, 8.1 Hz, 1H, H<sub>2</sub>), 7.59 (d, J = 8.6 Hz, 2H, H<sub>1</sub>).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 141.4, 137.2, 133.0, 122.8, 118.51 (q, <sup>1</sup>J (C–F) = 321.0 Hz).

**<sup>19</sup>F NMR** (377 MHz, CDCl<sub>3</sub>) δ -72.88.

**HRMS** (ESI) found 417.9126 [M–H]<sup>-</sup> ([C<sub>8</sub>H<sub>3</sub>F<sub>6</sub>NO<sub>8</sub>S<sub>2</sub>–H]<sup>-</sup> requires 417.9131; error -1.3 ppm).

**3-(benzyloxy)-2-nitrophenol (319)**

Boron trichloride (6.36 mL, 6.36 mmol, 1.2 equiv, 1 M in dichloromethane) was added drop wise over 10 min to a stirred solution of (((2-nitro-1,3-phenylene)bis(oxy))bis(methylene))dibenzene (**317**) in dichloromethane (10.5 mL, 0.5 M) under argon at 0 °C. The reaction mixture was stirred for 1 h before being allowed to warm to rt. Methanol (3 mL) was added dropwise and the resultant mixture partitioned between diethyl ether/water. The aqueous layer was further extracted with dichloromethane ( $\times$  3), dried over sodium sulphate and concentrated on silica *in vacuo*. The crude material was purified by silica gel column chromatography (1:4 ethyl acetate/40–60 petroleum ethers) to give the title compound as a light orange solid (850 mg, 65 %).

**mp** 64–65 °C (ethyl acetate/40–60 petroleum ethers).

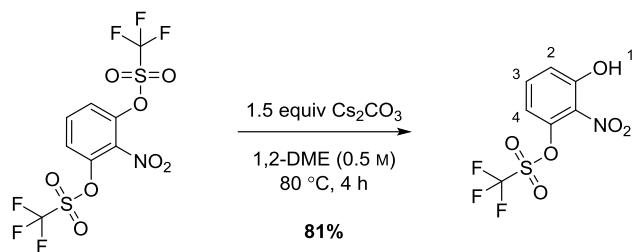
**R<sub>f</sub>** 0.17 (1:4 ethyl acetate/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 1609, 1590, 1537, 1498, 1456, 1356, 1296, 1205, 1175, 1089, 1075, 1030, 854.

**<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.18 (s, 1H, H<sub>1</sub>), 7.48 (d,  $J$  = 7.1 Hz, 2H, H<sub>3/4</sub>), 7.43 – 7.32 (m, 4H, H<sub>3/4</sub>, H<sub>5</sub> and H<sub>7</sub>), 6.72 (d,  $J$  = 8.5 Hz, 1H, H<sub>6/8</sub>), 6.60 (d,  $J$  = 8.4 Hz, 1H, H<sub>6/8</sub>), 5.21 (s, 2H, H<sub>2</sub>).

**<sup>13</sup>C NMR** (1001 MHz,  $\text{CDCl}_3$ )  $\delta$  155.9, 154.9, 135.8, 135.6, 128.8, 128.4, 127.6, 127.0, 111.1, 105.2, 71.5.

**HRMS** (NSI) found 244.0609 [M-H]<sup>-</sup> ([C<sub>13</sub>H<sub>11</sub>NO<sub>4</sub>–H]<sup>-</sup> requires 244.0615; error –2.6 ppm).

**3-hydroxy-2-nitrophenyl trifluoromethanesulfonate (320)**

A stirred solution of 2-nitro-1,3-phenylene bis(trifluoromethanesulfonate) (**318**) (22.69 g, 54.12 mmol, 1.0 equiv) and caesium carbonate (26.5 g, 81.2 mmol, 1.5 equiv) in 1,2-dimethoxyethane (108 mL, 0.5 M) under argon was heated to 80 °C until complete consumption of starting material was observed by LCMS at 4 h. The reaction mixture was partitioned between dichloromethane/1 M aq hydrogen chloride and the aqueous layer further extracted with dichloromethane (×2). The combined organics were dried over sodium sulphate, filtered and concentrated on silica *in vacuo*. The crude residue was purified by silica gel column chromatography (1:2 to 1:1 ethyl acetate/40–60 petroleum ethers) to give the title compound as a dark yellow solid (12.63 g, 81%).

**mp** 41–42 °C (ethyl acetate/40–60 petroleum ethers).

**R<sub>f</sub>** 0.1 (1:2 ethyl acetate/40–60 petroleum ethers).

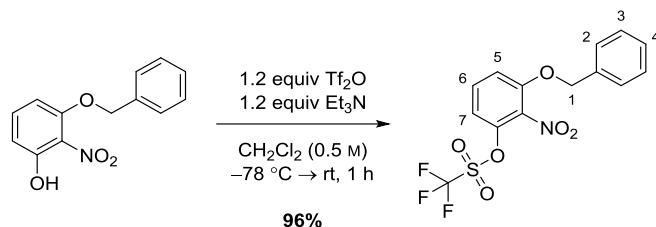
**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 2988, 2902, 1624, 1580, 1547, 1464, 1430, 1394, 1351, 1259, 1212, 1135, 1059, 1010, 867, 827, 805.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 10.35 (s, 1H, H<sub>1</sub>), 7.60 (t, J = 8.5 Hz, 1H, H<sub>3</sub>), 7.26 (dd, J = 8.7, 1.3 Hz, 1H, H<sub>2/4</sub>), 6.97 (dd, J = 8.2, 1.0 Hz, 1H, H<sub>2/4</sub>).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 156.4, 142.7, 135.9, 128.8, 120.7, 118.70 (q, <sup>1</sup>J (C–F) = 321.0 Hz), 113.9.

**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>) δ -72.80.

**HRMS** (ESI) found 285.9642 [M–H]<sup>-</sup> ([C<sub>7</sub>H<sub>4</sub>F<sub>3</sub>NO<sub>6</sub>S–H]<sup>-</sup> requires 285.9639; error 1.2 ppm).

**3-(benzyloxy)-2-nitrophenyl trifluoromethanesulfonate (321)**

Triethylamine (611 µL, 4.39 mmol, 1.2 equiv) was added dropwise to a stirred solution of 3-(benzyloxy)-2-nitrophenol (**319**) (897 mg, 3.66, 1.0 equiv) in dichloromethane (7.3 mL, 0.5 M) under argon at -78 °C. After 10 min, triflic anhydride (739 µL, 4.39 mmol, 1.2 equiv) was added drop wise and the mixture stirred for another 10 min before being allowed to warm to rt. Complete consumption of starting material was determined by LCMS at 1 h. The reaction was quenched with sat. aq sodium hydrogen carbonate and partitioned with ethyl acetate. The organic layer was further washed with water and brine, dried over magnesium sulphate, filtered and concentrated *in vacuo* to give the title compound, without the need for further purification, as a pale yellow solid (1.32 g, 96%).

**mp** 61–62 °C (ethyl acetate/40–60 petroleum ethers).

**R<sub>f</sub>** 0.53 (1:2 ethyl acetate/40–60 petroleum ethers).

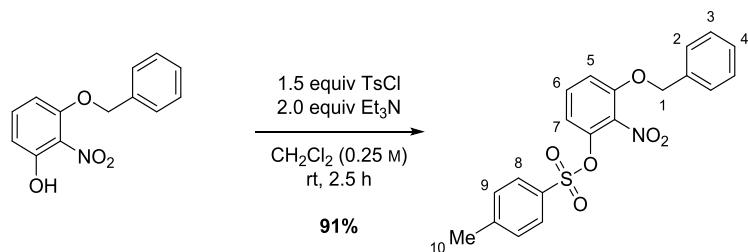
**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 2919, 1611, 1586, 1541, 1498, 1479, 1466, 1455, 1429, 1364, 1291, 1134, 1082, 1072, 1043, 957, 912, 857, 816.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.47 (t, J = 8.6 Hz, 1H, **H<sub>6</sub>**), 7.43 – 7.32 (m, 5H, **H<sub>2</sub>**, **H<sub>3</sub>** and **H<sub>4</sub>**), 7.11 (dd, J = 8.7, 0.8 Hz, 1H, **H<sub>5/7</sub>**), 7.07 (dd, J = 8.5, 0.9 Hz, 1H, **H<sub>5/7</sub>**), 5.23 (s, 2H, **H<sub>1</sub>**).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 151.8, 140.9, 134.6, 131.8, 128.9, 128.7, 127.1, 113.95, 113.91, 71.8, 118.39 (q, <sup>1</sup>J (C-F) = 320.8 Hz).

**<sup>19</sup>F NMR** (377 MHz, CDCl<sub>3</sub>) δ -73.27.

**HRMS** (ESI) found 395.0518 [M+NH<sub>4</sub>]<sup>+</sup> ([C<sub>14</sub>H<sub>10</sub>F<sub>3</sub>NO<sub>6</sub>S+NH<sub>4</sub>]<sup>+</sup> requires 395.0519; error -0.3 ppm).

**3-(benzyloxy)-2-nitrophenyl 4-methylbenzenesulfonate (322)**

To an oven dried vial was added 3-(benzyloxy)-2-nitrophenol (850 mg, 3.46 mmol, 1.0 equiv) and tosyl chloride (989 mg, 5.19 mmol, 1.5 equiv). The vial was sealed and flushed with argon before adding CH<sub>2</sub>Cl<sub>2</sub> (13.8 mL, 0.25 M) and triethylamine (966 µL, 6.93 mmol, 2.0 equiv). The mixture was stirred at rt until complete conversion of starting material was determined by LCMS at 2.5 h. The reaction mixture was partitioned between dichloromethane/1 M aq. hydrochloric acid and the organic layer separated, dried over magnesium sulfate, filtered and concentrated onto silica. The crude residue was purified by silica gel column chromatography (1:4 to 1:2 ethyl acetate/40–60 petroleum ethers) to give the title compound as a colourless solid (1.249 g, 91%).

**mp** 123–125 °C (ethyl acetate/40–60 petroleum ethers).

**R**<sub>f</sub> 0.18 (1:4 ethyl acetate/40–60 petroleum ethers).

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3038, 1606, 1587, 1538, 1498, 1475, 1454, 1366, 1290, 1236, 1192, 1178, 1121, 1083, 1052, 1029, 958, 911, 854, 815.

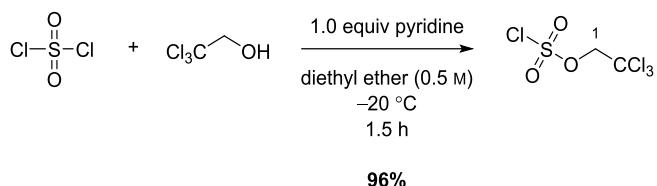
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.77 (d, J = 8.4 Hz, 2H, H<sub>8</sub>), 7.45 – 7.28 (m, 8H, H<sub>2</sub>, H<sub>3</sub>, H<sub>4</sub>, H<sub>6</sub> and H<sub>9</sub>), 7.14 (dd, J = 8.5, 0.9 Hz, 1H, H<sub>5*m*), 6.95 (dd, J = 8.6, 0.8 Hz, 1H, H<sub>5*p*), 5.15 (s, 2H, H<sub>1</sub>), 2.47 (s, 3H, H<sub>10</sub>).</sub></sub>

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 151.1, 146.3, 141.5, 135.2, 135.0, 131.6, 131.2, 130.0, 128.8, 128.6, 128.5, 127.0, 115.1, 112.3, 71.4, 21.8.

**HRMS** (ESI) found 400.0843 [M+H]<sup>+</sup> ([C<sub>20</sub>H<sub>17</sub>NO<sub>6</sub>S+H]<sup>+</sup> requires 400.0849; error −1.6 ppm).

## 6.11 Miscellaneous

### 2,2,2-Trichloroethyl sulfurochloride (392)



Sulfuryl chloride (5.00 mL, 8.37 g, 62.0 mmol) was added dropwise over 30 min to a stirred solution of 2,2,2-trichloroethanol (6.00 mL, 9.26 g, 62.0 mmol) and pyridine (5.00 mL, 4.90 g, 62.0 mmol) in diethyl ether (120 mL, 0.5 M) at  $-20\text{ }^{\circ}\text{C}$ . The reaction mixture was then stirred at room temperature for 1 h after which water (20 mL) was slowly added to quench the reaction. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated *in vacuo* ( $30\text{ }^{\circ}\text{C}/50\text{ mbar}$ ). The crude material was purified by vacuum distillation to give the title compound as a colourless oil (14.7 g, 96%).

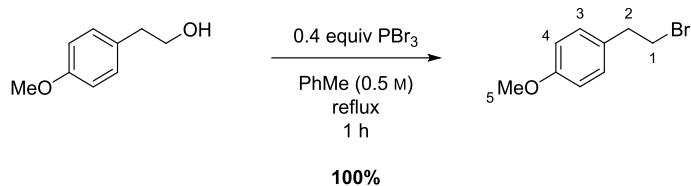
*The data were in accordance with the literature.<sup>79</sup>*

**bp** 82–83  $^{\circ}\text{C}/3.0\text{ mbar}$ .

**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 1415, 1376, 1262, 1189, 1087, 1045, 985, 869.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.82 (2H, s, H<sub>1</sub>).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  91.5, 81.3.

**1-(2-bromoethyl)-4-methoxybenzene (159)**

2-(4-Methoxyphenyl)ethan-1-ol (**244**) (47.0 g, 309 mmol, 1 equiv) was stirred in toluene (297 mL, 0.5 M) at rt. Tribromophosphine (11.6 mL, 124 mmol, 0.4 equiv) was added in portions (CAUTION – MILD EXOTHERM) and heated to reflux for 1 h. Complete conversion of the starting material was observed by LCMS and the reaction mixture allowed to cool to rt and concentrated to ¼ volume. The reduced mixture was diluted with diethyl ether and carefully washed with 1:1 8% aq sodium hydrogen carbonate/sat. aq sodium thiosulfate, water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the title compound in high purity as a colourless oil (66.3 g, 100%).

The data were in accordance with the literature.<sup>79</sup>

**IR**  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 2999, 2957, 2937, 2909, 2834, 1611, 1584, 1511, 1464, 1441, 1302, 1264, 1243, 1215, 1177, 1127, 1100, 1033, 921, 882, 819.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.13 (d, *J* = 8.3 Hz, 2H, H<sub>3</sub>), 6.86 (d, *J* = 8.5 Hz, 2H, H<sub>4</sub>), 3.80 (s, 3H, H<sub>5</sub>), 3.53 (t, *J* = 7.6 Hz, 2H, H<sub>2</sub>), 3.11 (t, *J* = 7.6 Hz, 2H, H<sub>1</sub>).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 158.7, 131.2, 129.8, 114.1, 55.4, 38.7, 33.5.

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## 8 TALKS ATTENDED

Date	Speaker	Institution	Title	Location
17/10/2011	Erik Carreira	ETH	Studies in Natural Product Synthesis	Chemistry Dept.
22/11/2011	Thomas Carell	LMU Munich	The Chemistry of Genome Maintenance	Chemistry Dept.
20/12/2011	Ben Davis	Oxford	Sugars and Proteins	MRC LMB
21/02/2012	Ben Feringa	Groningen	Exploring New Chiral Space in Asymmetric Catalysis	Chemistry Dept.
05/03/2012	Scott Miller	Yale	Natural Products, Synthetic Catalyst and Unnatural Products	Chemistry Dept.
12/03/2012	Chris Schofield	Oxford	Chemistry of Oxygen Sensing in Animals	Chemistry Dept.
13/03/2012	Daniel Nocera	MIT	Personalized Energy for 1 ( $\times 6$ Billion): A Solution to the Global Energy Challenge	Chemistry Dept.
14/03/2012	Daniel Nocera	MIT	The Artificial Leaf	Chemistry Dept.
30/04/2012	Chris Lowe and Andrew Sandham	Cambridge and Industry	Bench to Board: A Path to Biotech Leadership	Judge Business School
08/05/2012	Carl Djerassi	Stanford University	Insufficiency	Chemistry Dept.
03/07/2012	Sydney Brenner	Cambridge	Reading 'The Human Genome	Chemistry Dept
09/07/2012	Various	Cambridge	Graduate Chemistry Symposium	Chemistry Dept
17/01/2013	Kendall Houk	UCLA	Theory, Dynamics, and Mechanisms of Cycloadditions	Chemistry Dept
07/03/2013	Amos B. Smith III	Pennsylvania	Evolution of Anion Relay Chemistry (ARC) Leading to Siloxane-Based Transfer Agents for Palladium Cross-Coupling Reactions	Chemistry Dept

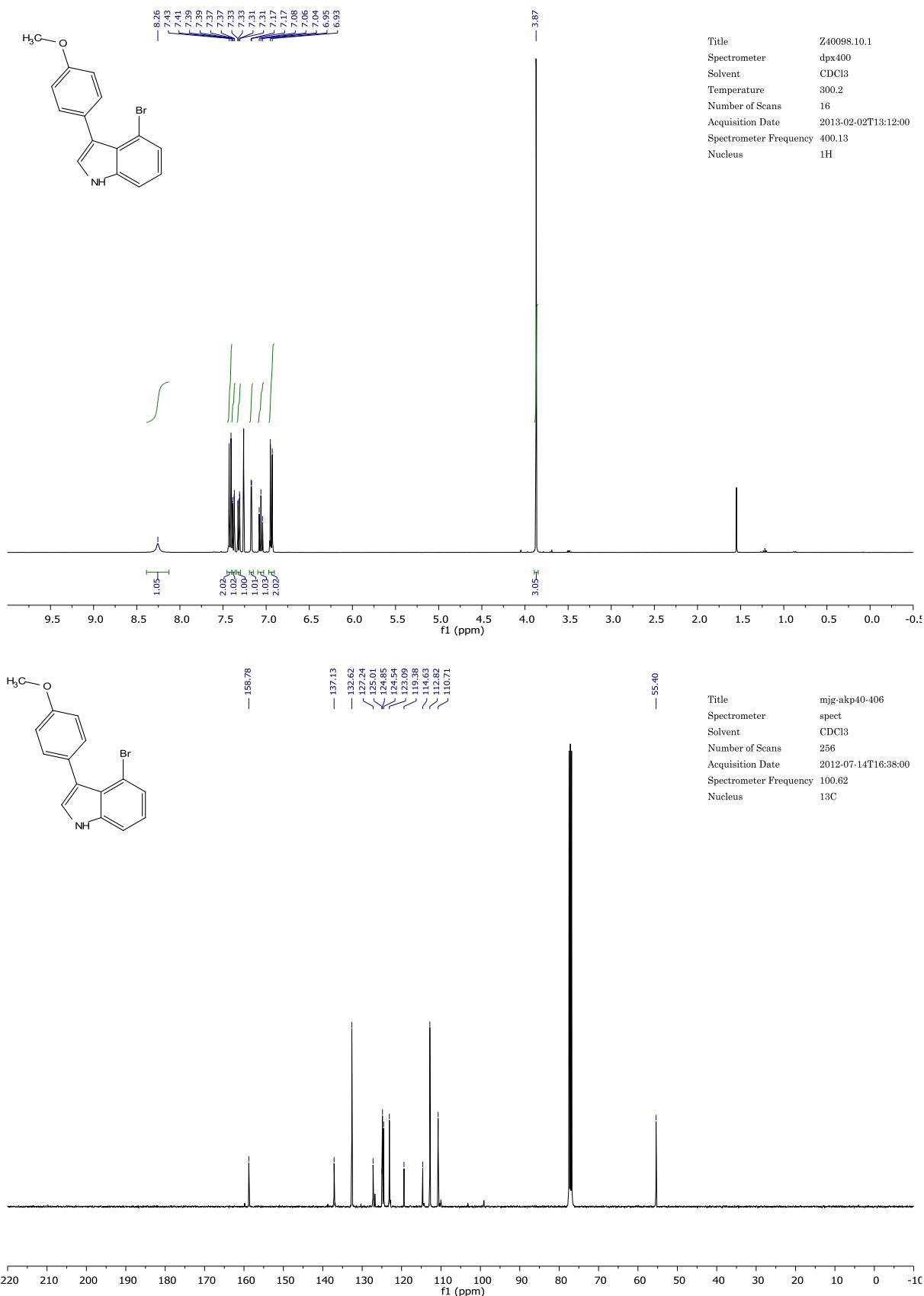
Date	Speaker	Institution	Title	Location
09/05/2013	Chad A. Mirkin	Northwestern University	Spherical Nucleic Acid (SNA) Nanostructures: Establishing a New Paradigm in Molecular Diagnostics and Intracellular Gene Recognition	Chemistry Dept
10/05/2013	Chad A. Mirkin	Northwestern University	Nucleic Acid-Modified Nanostructures as Programmable Atom Equivalents: Forging a New Periodic Table	Chemistry Dept
16/05/2013	Jeffrey S. Moore	University of Illinois (UC)	Mechanoresponsive Materials and Self-Healing Systems	Chemistry Dept
22/05/2013	Christopher J Chang	University of California, Berkeley	Molecular Imaging Approaches to Mapping and Studying Chemistry in the Brain	Chemistry Dept
17/06/2013	Ada E. Yonath	Weizmann Institute of Science	What was first: the genetic code or its products?	Chemistry Dept
21/10/2013	Tom Rovis	Colorado State University	From Conventional Ligands to Engineered Enzymes: Rh Catalysis for C–H Activation	Chemistry Dept
29/10/2013	John Gurdon	University of Cambridge	Stem Cells, Clones and Prospects for Cell Replacement	Peterhouse
	Beatrice Collins (Gaunt) Marco di Antonio (Balasubramanian) Rhiannon Holvey (Abell) Fezile Lakadamyali (Reisner) Yu Heng Lau (Spring) Kenneth Ng (Paterson)	University of Cambridge	Chemical & Biological Synthesis & Catalysis Symposium	Chemistry Dept
21/11/2013	Tim Jamison	MIT	Continuous Flow Multistep Synthesis	Chemistry Dept

Date	Speaker	Institution	Title	Location
21/11/2013	Kenichiro Itami	Nagoya University	Catalyst-Enabling Chemistry toward Transformative Molecules	Chemistry Dept
11/12/2013	Charles Marson	UCL	Unusual Ring Systems and the Changing Landscape of Medicinal Chemistry	Chemistry Dept
11/12/2013	Adam Nelson	University of Leeds	Towards the Systematic Exploration of Chemical Space	Chemistry Dept
11/12/2013	Erick Carreira	ETH Zurich	Surprises and Discoveries with Small Molecules	Chemistry Dept
03/04/2014	Kevin D. Moeller	University of Washington, St. Louis	From Molecules to Microelectrode Arrays: Using Electrochemistry to Solve Problems of Structure and Location	Chemistry Dept
04/04/2014	Paolo Melchiorre	ICIQ	Organocatalytic photochemical processes	Chemistry Dept
04/04/2014	Alan Armstrong	Imperial College London	Mechanistic insights into organocatalytic reactions	Chemistry Dept
04/04/2014	Karl Anker Jørgensen	Aarhus University	Organocatalysis - From simple to complex molecules	Chemistry Dept
18/04/2014	Alexander Radosevich	Pennsylvania State University	Catalytic Atom Transfer and Bond Activation Methods Based on P(III)↔P(V) Cycling	Chemistry Dept
23/04/2014	Robert Phipps	University of Cambridge	Using Chiral Anions as Phase-Transfer Catalysts - A New Approach to Asymmetric Fluorination	Chemistry Dept
24/04/2014	Christina White	University of Illinois (UC)	Site Selective C-H Oxidations	Chemistry Dept
10/09/2014	Various	Various	ACS San Francisco	Moscone Centre

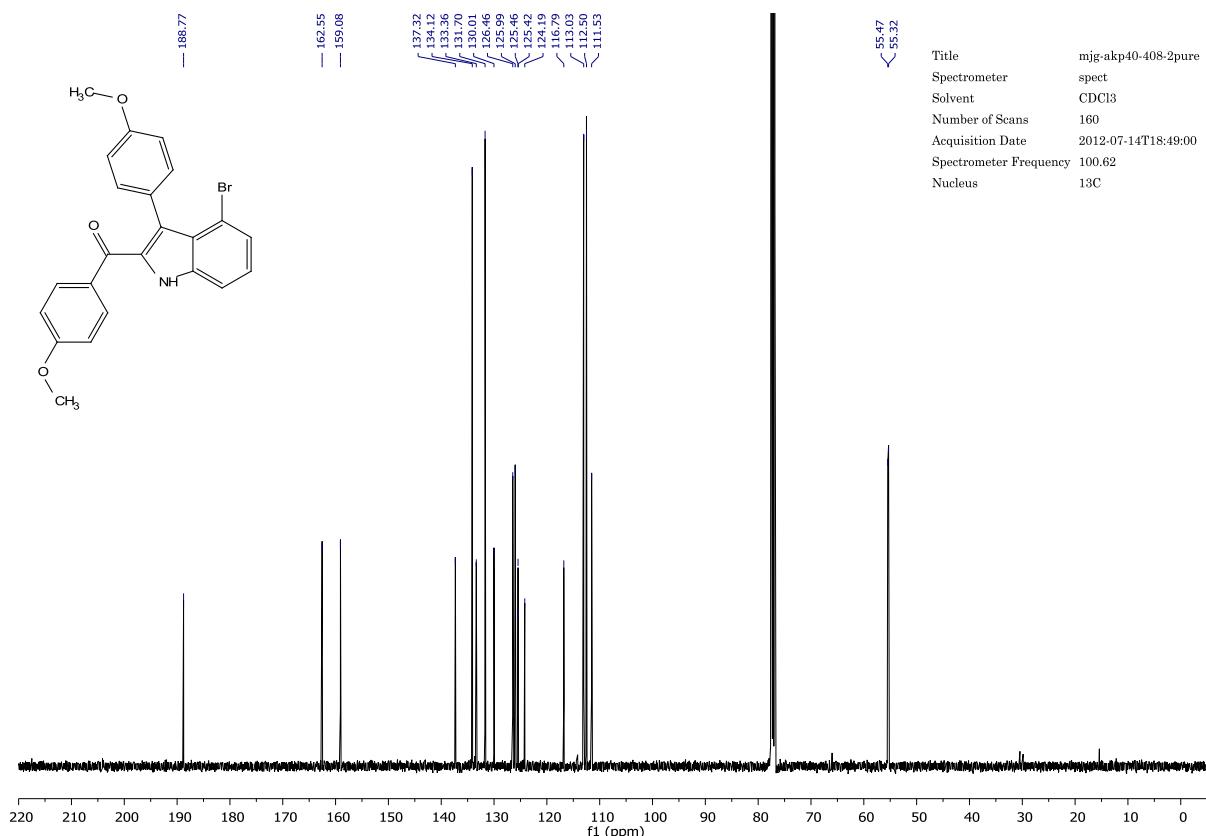
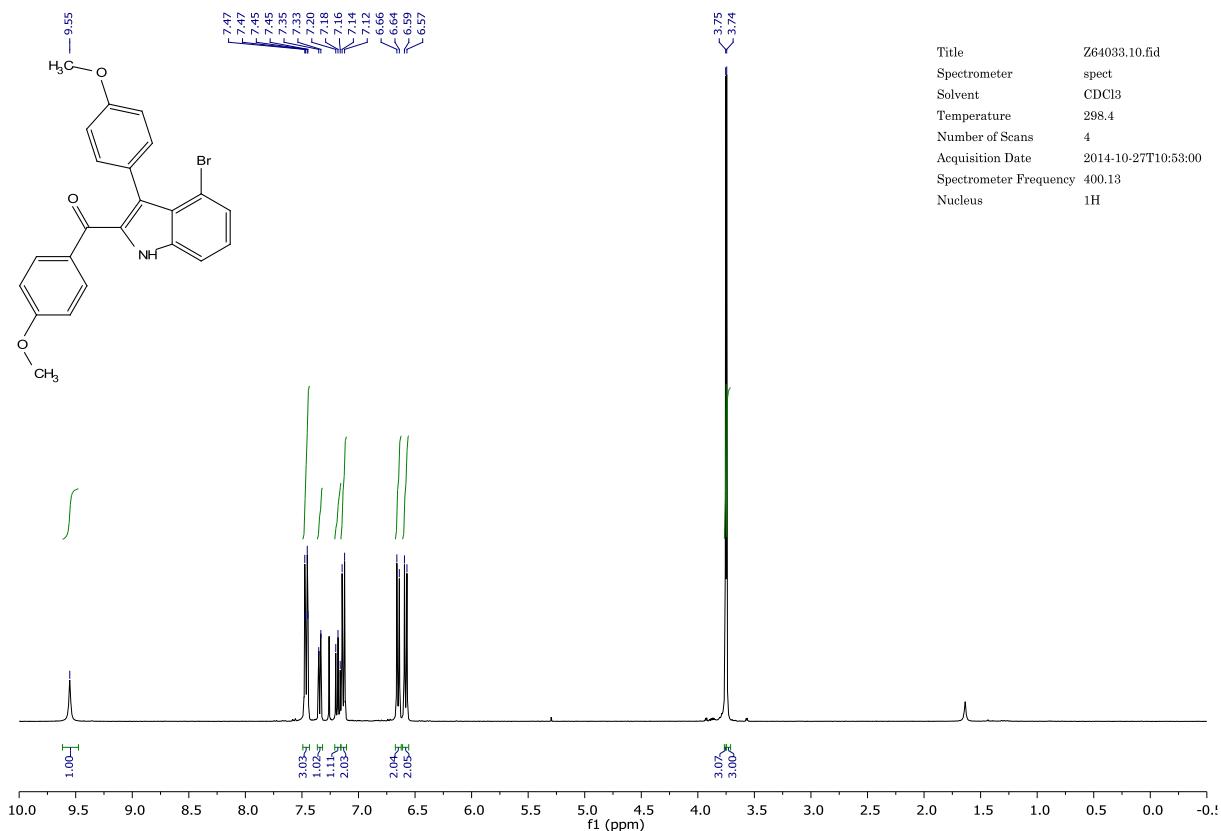
## **9 SPECTRAL DATA**

## 9.1 Synthesis from 4-bromoindole

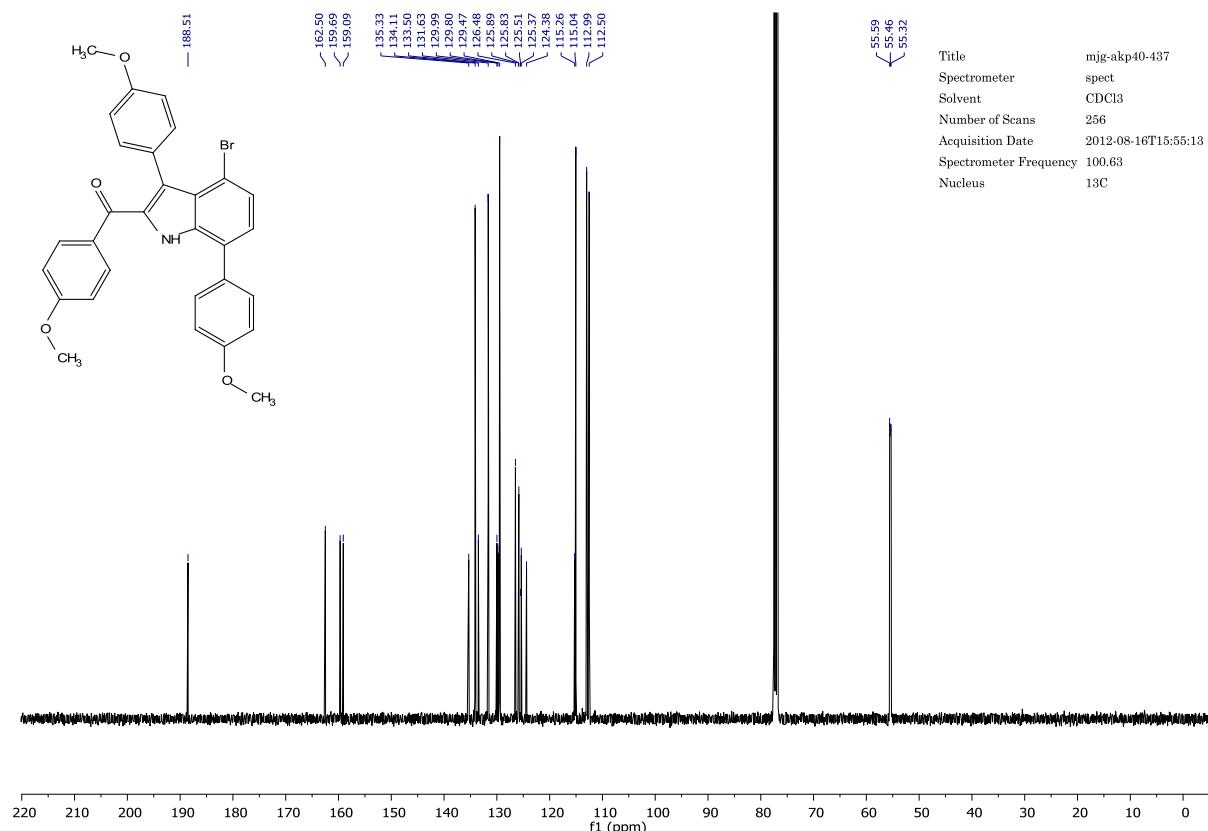
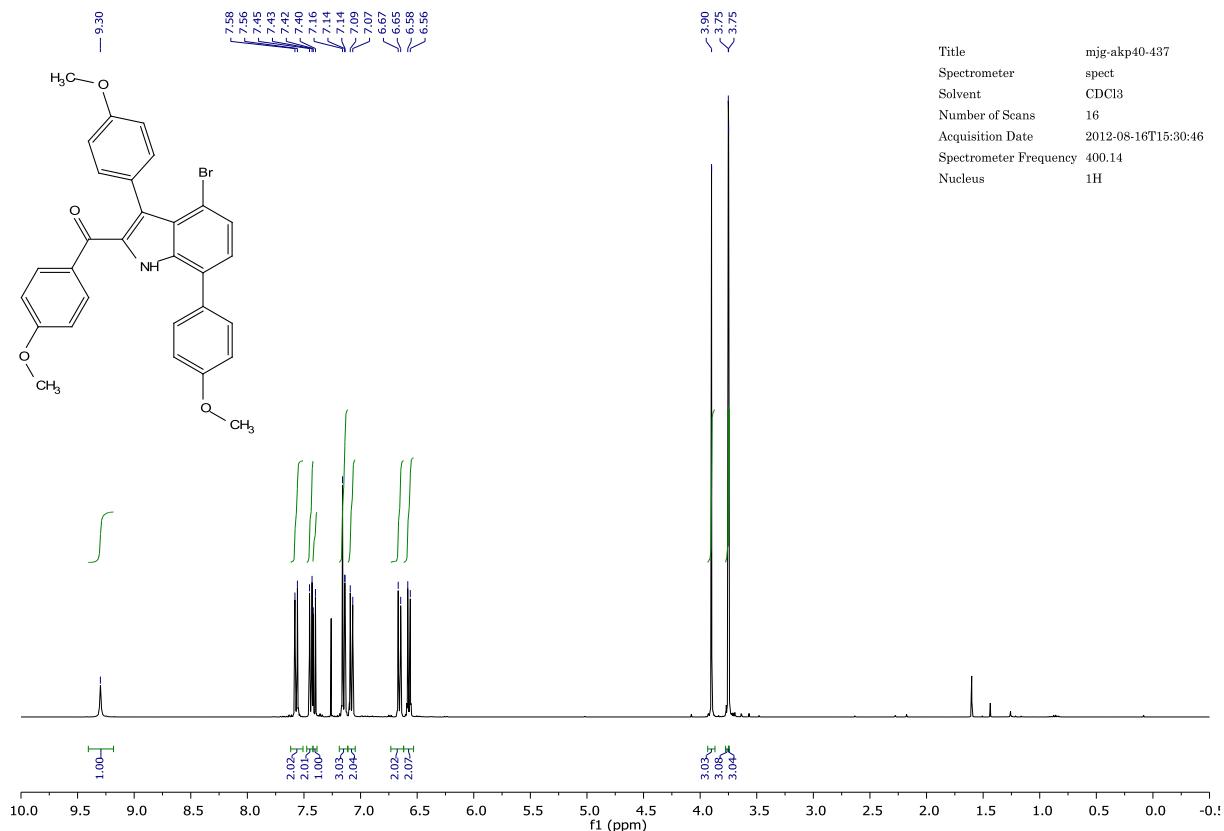
### 4-Bromo-3-(4-methoxyphenyl)-1H-indole (183)



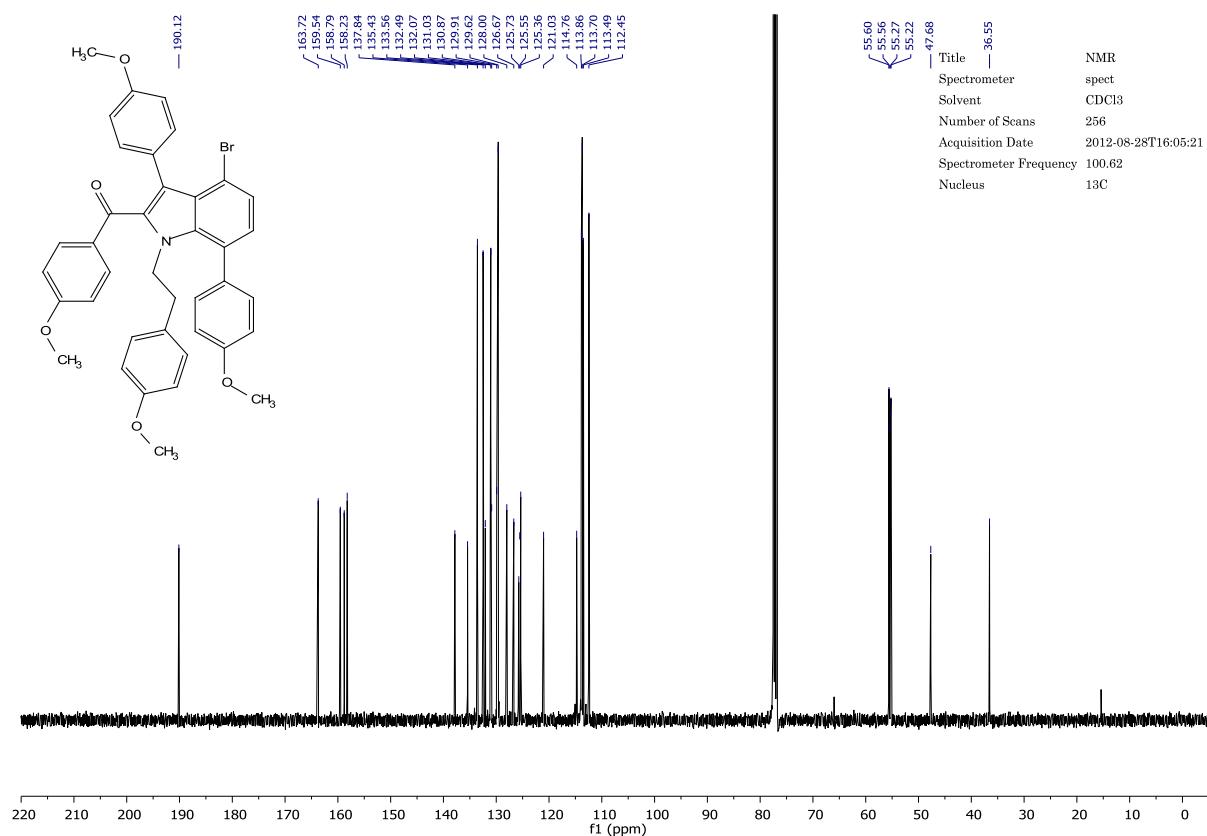
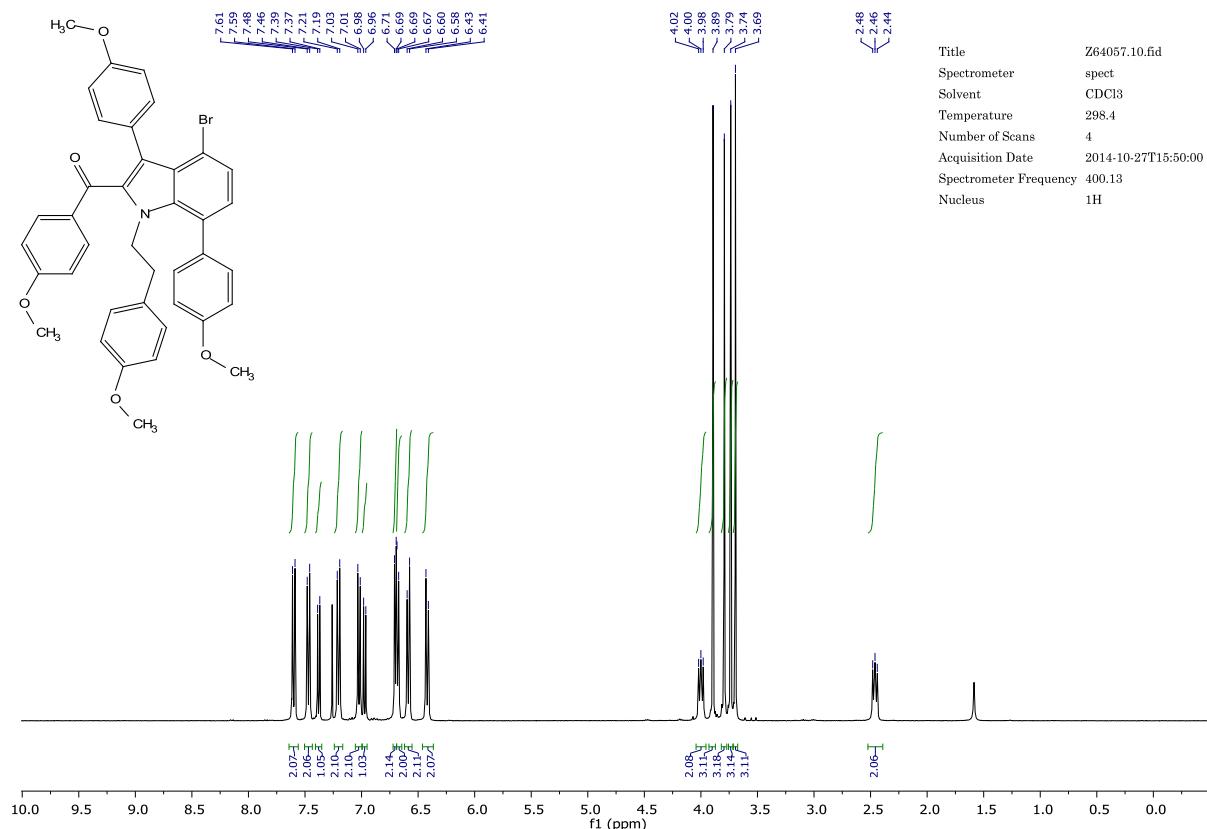
**(4-Bromo-3-(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (214)**



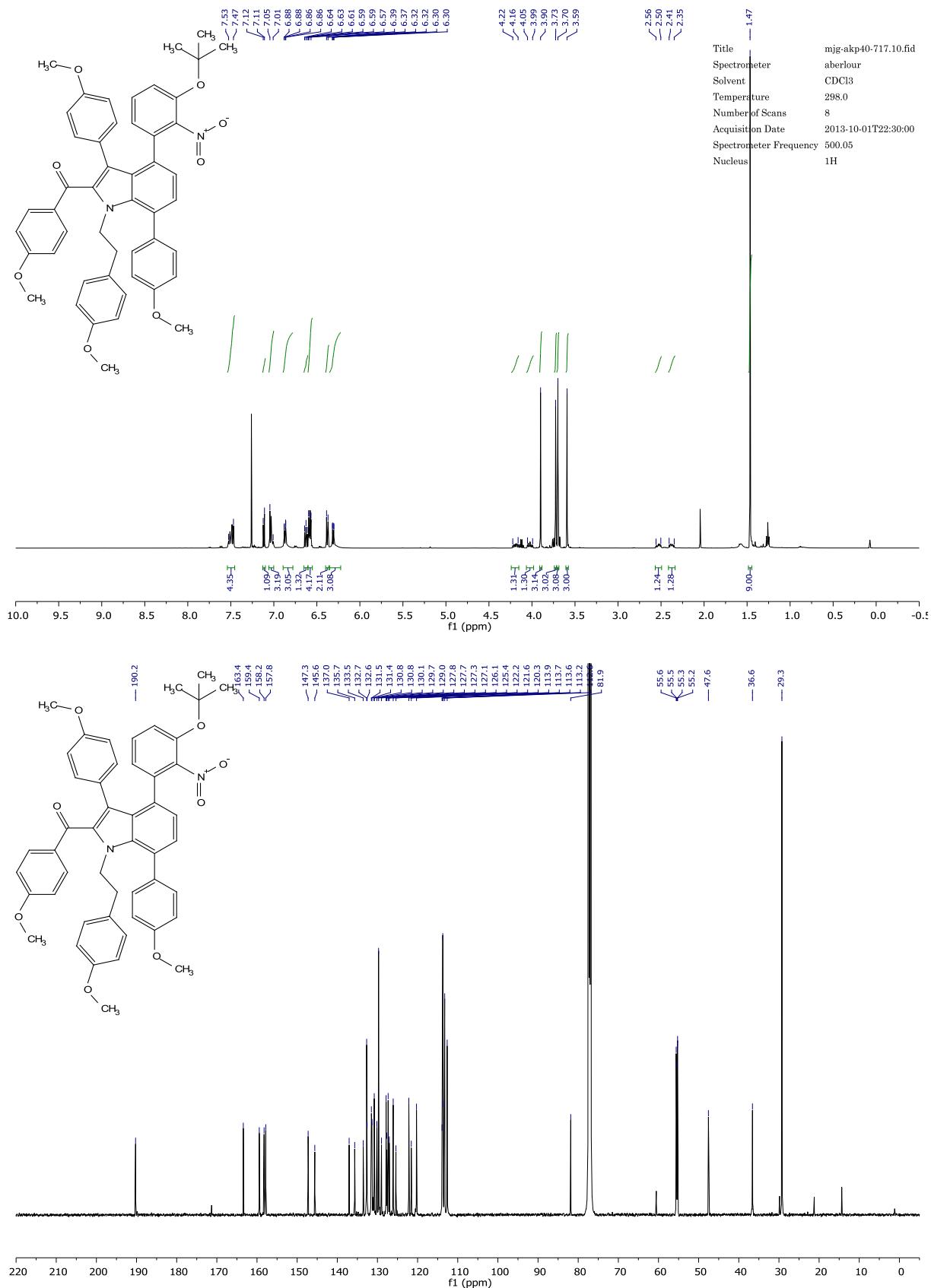
**(4-Bromo-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (187)**



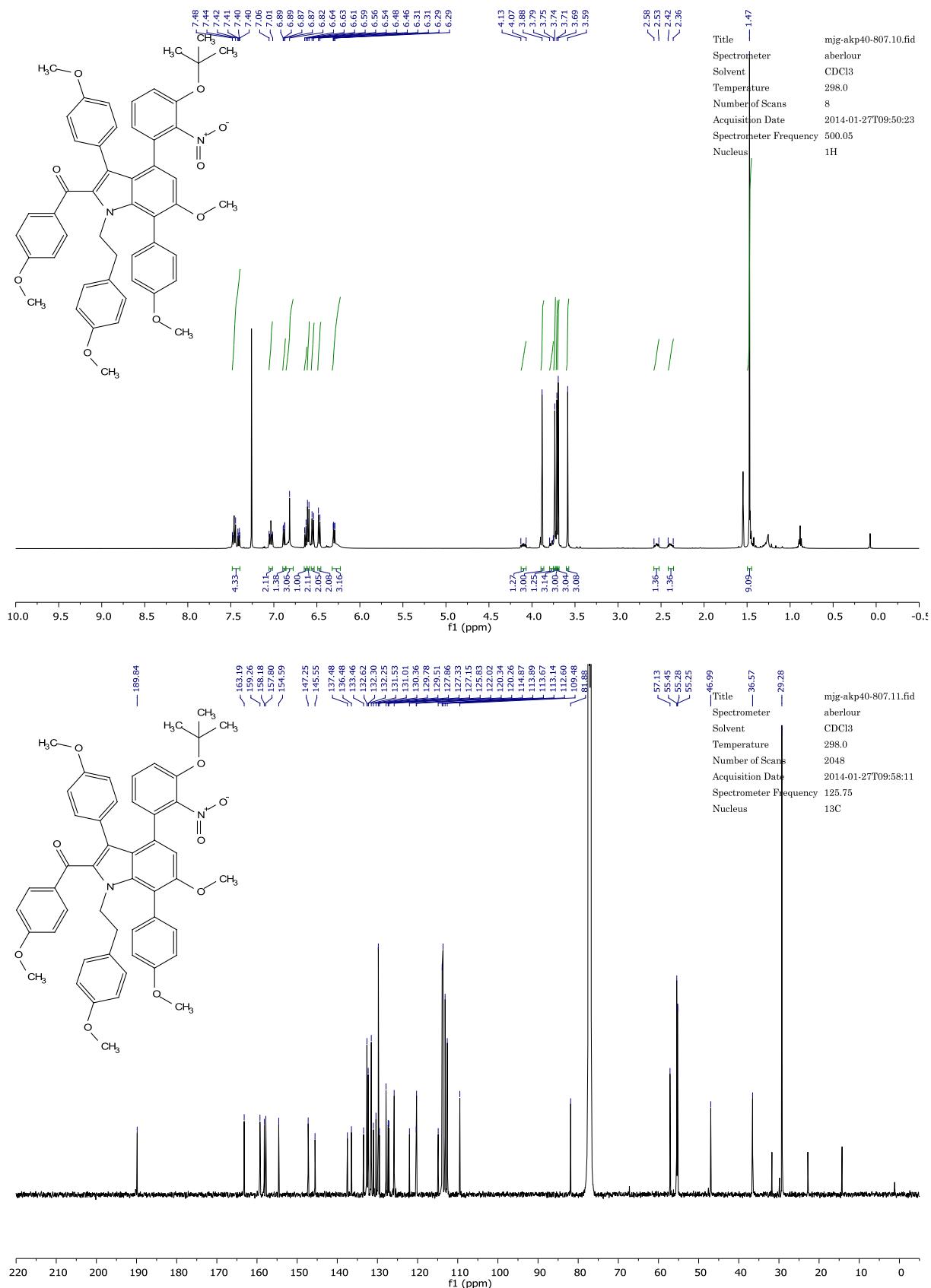
**(4-Bromo-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (188)**



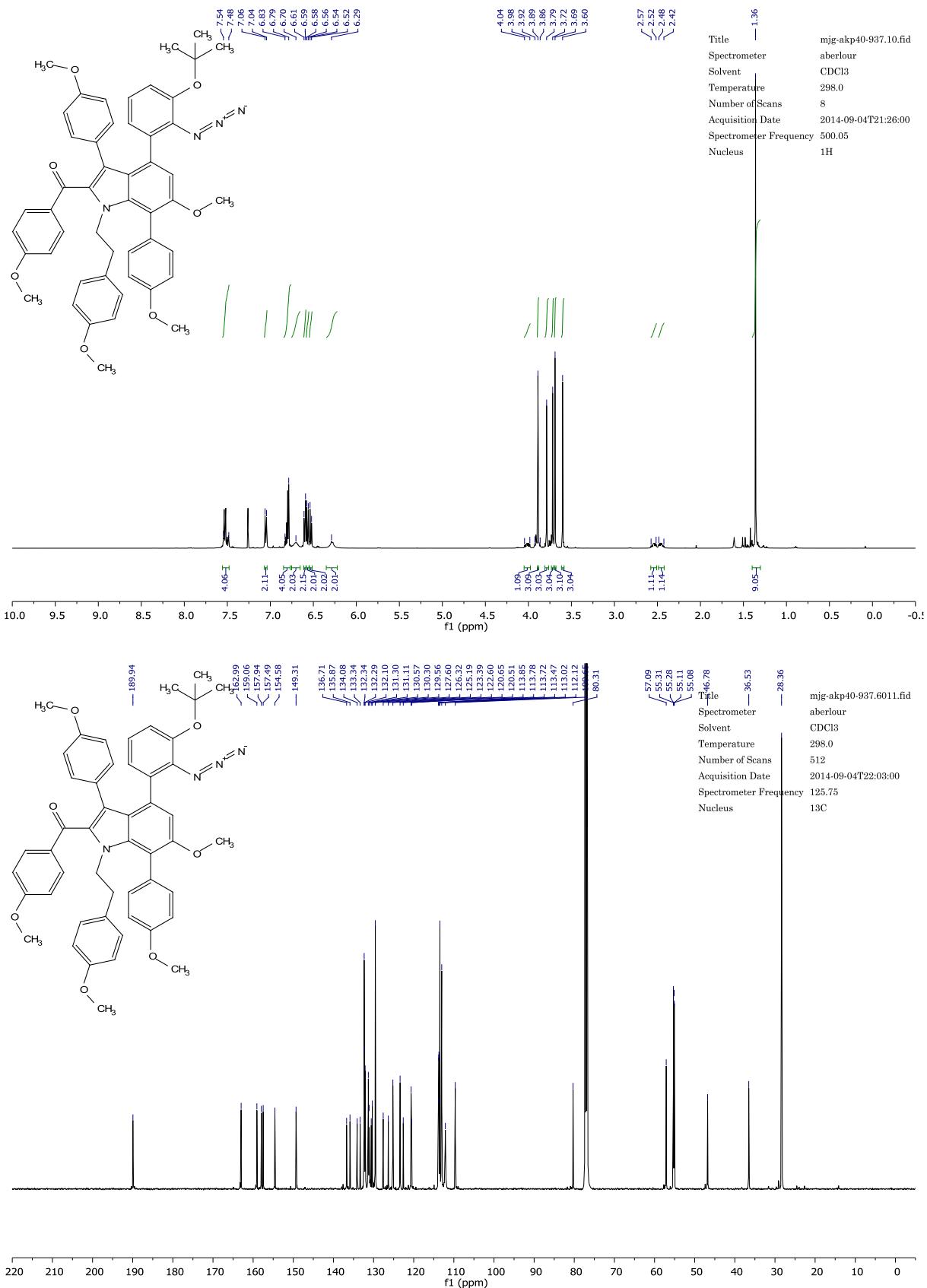
**(4-(3-(tert-butoxy)-2-nitrophenyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (376)**



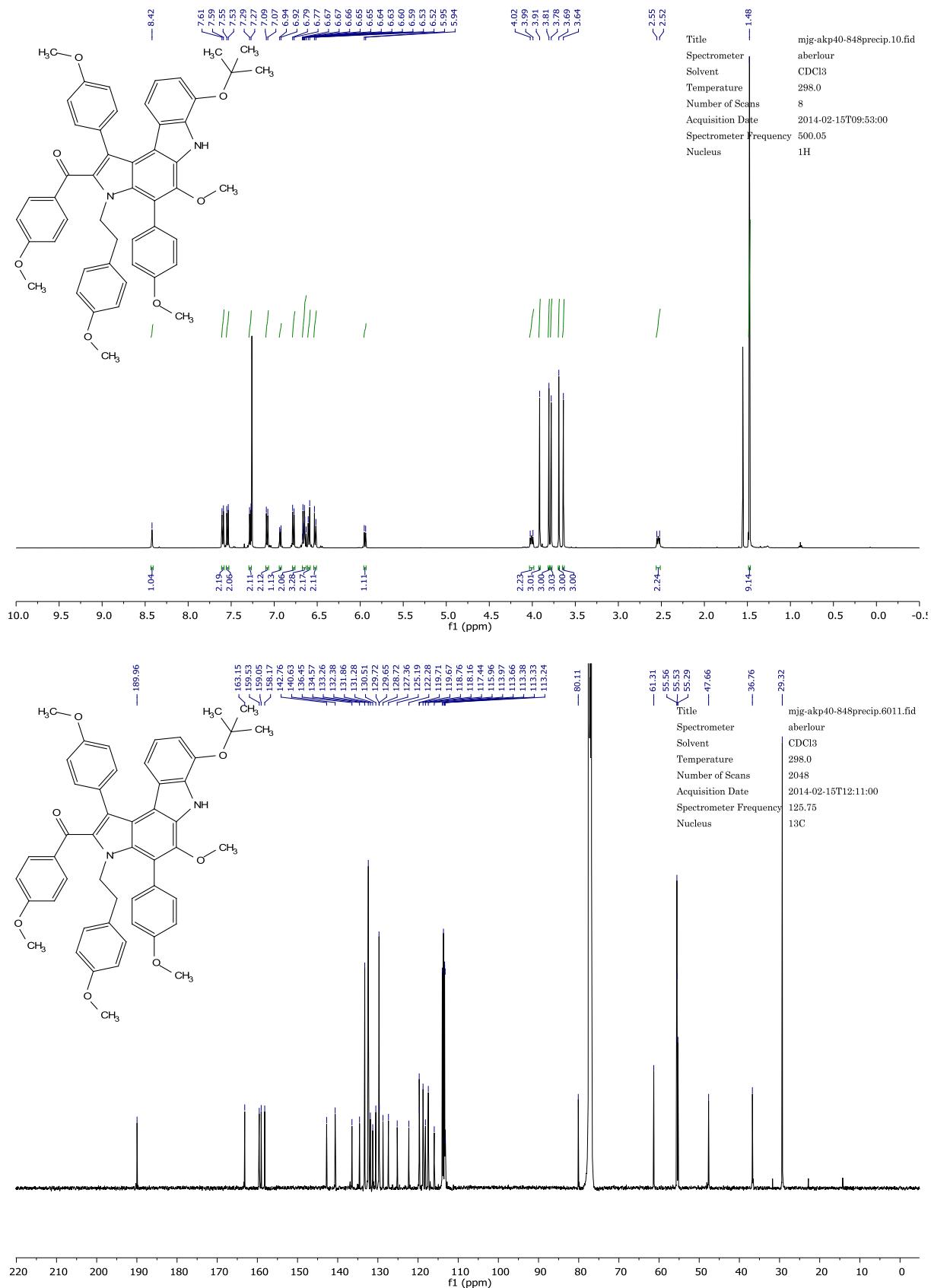
**(4-(3-(tert-butoxy)-2-nitrophenyl)-6-methoxy-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (380)**



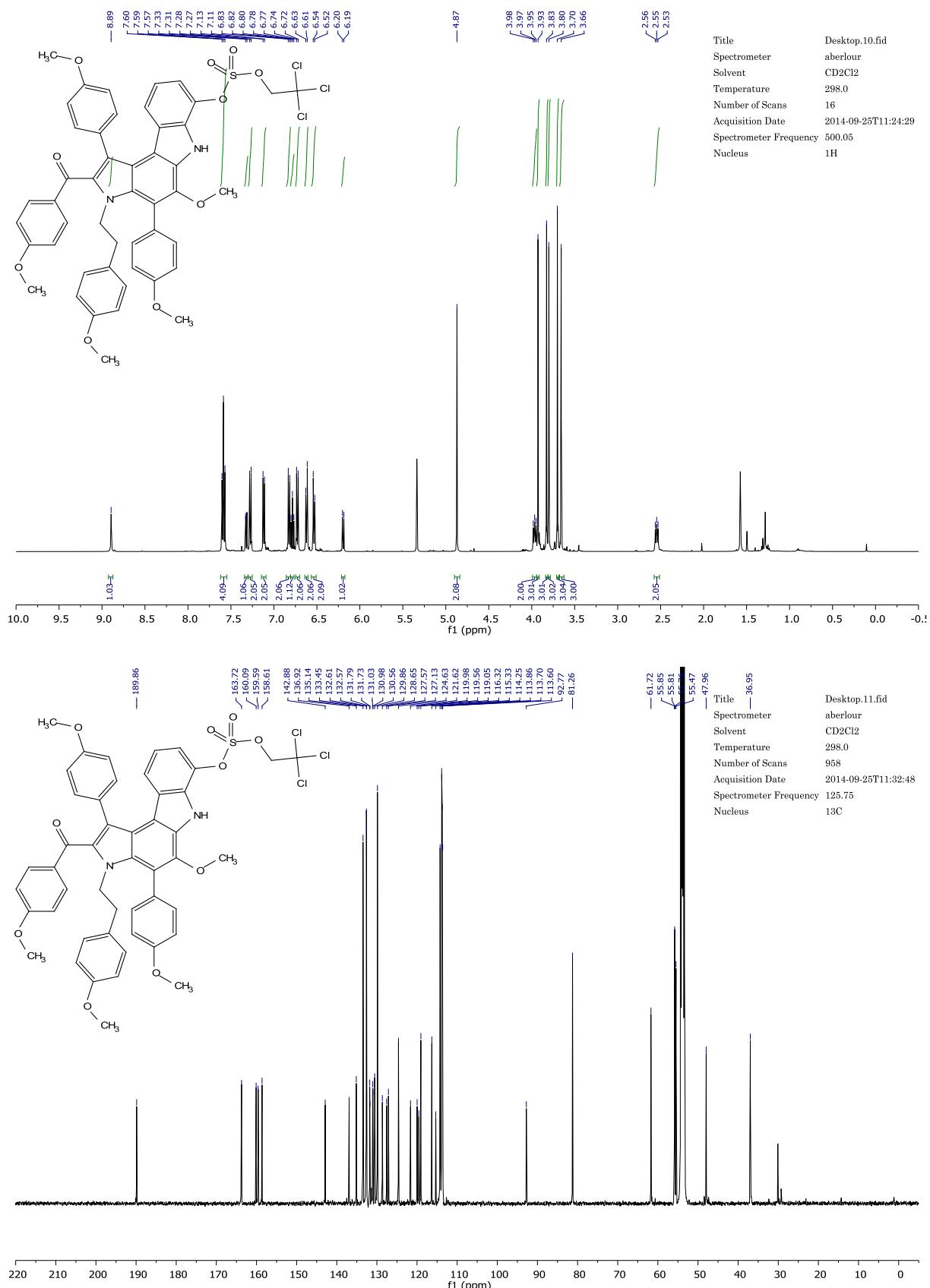
**(4-(2-azido-3-(tert-butoxy)phenyl)-6-methoxy-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (166)**



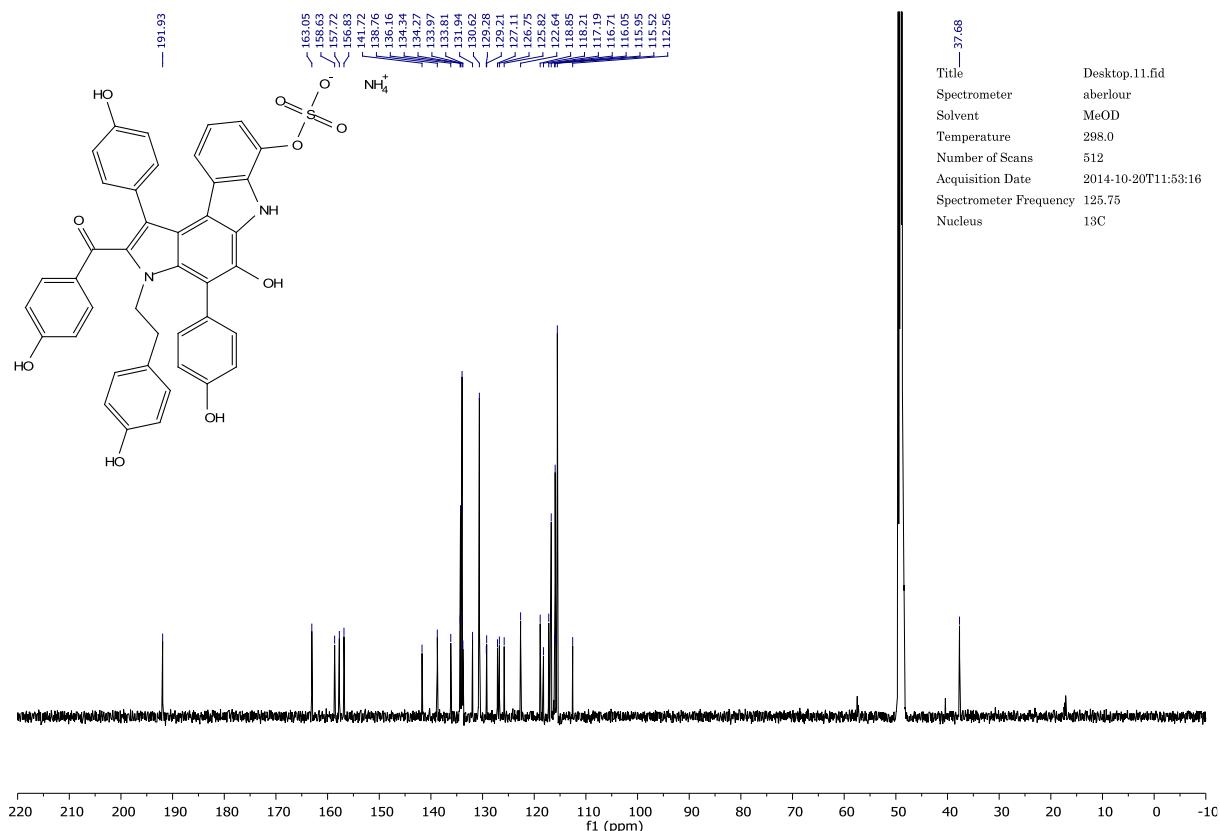
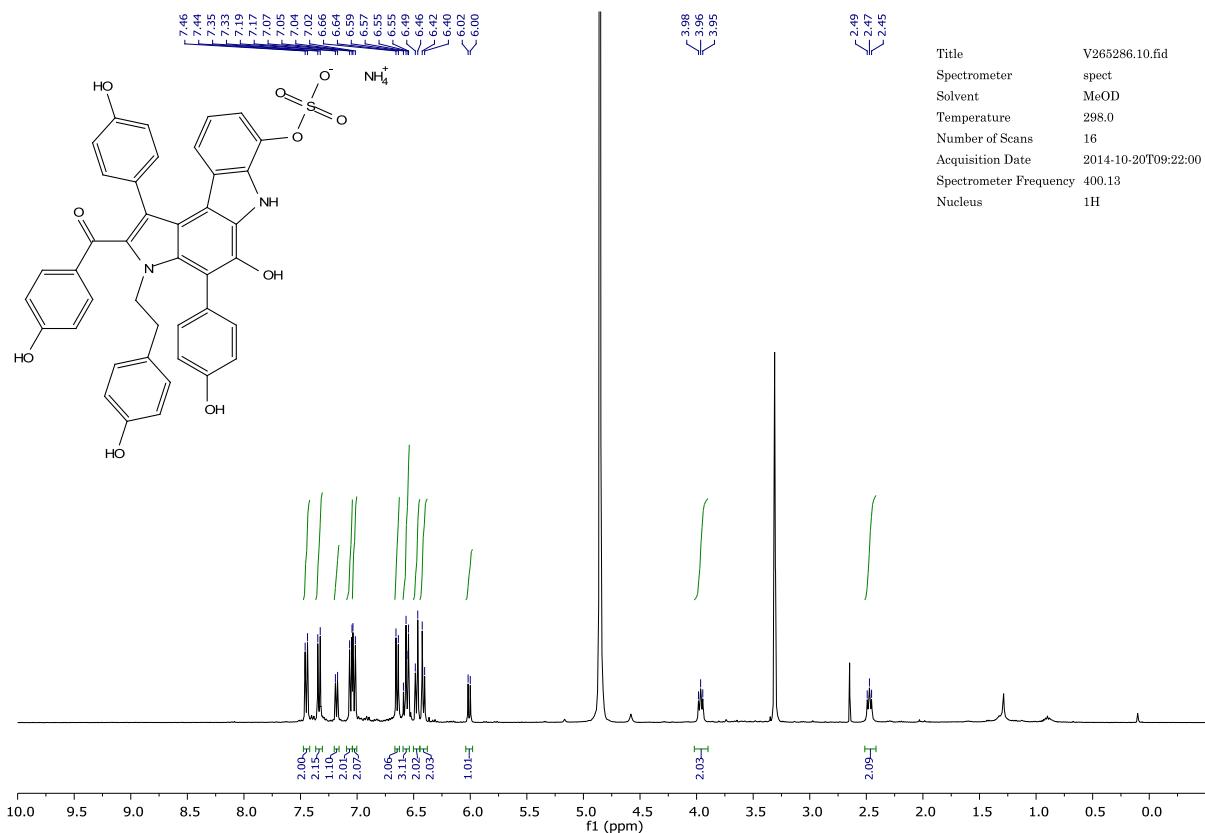
**(7-(*tert*-butoxy)-5-methoxy-3-(4-methoxyphenethyl)-1,4-bis(4-methoxyphenyl)-3,6-dihydropyrrolo[2,3-c]carbazol-2-yl)(4-methoxyphenyl)methanone (167)**



**5-methoxy-2-(4-methoxybenzoyl)-3-(4-methoxyphenethyl)-1,4-bis(4-methoxyphenyl)-3,6-dihydropyrrolo[2,3-c]carbazol-7-yl (2,2,2-trichloroethyl) sulfate (388)**

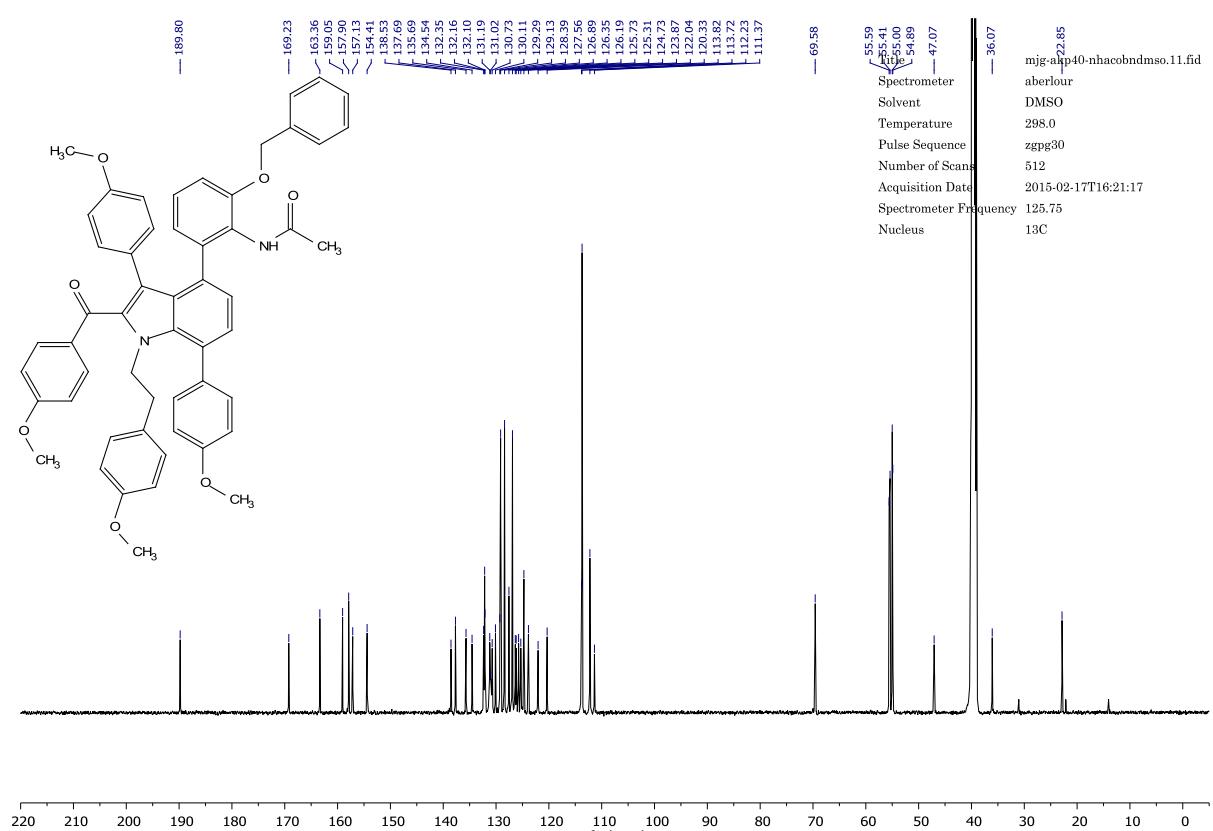
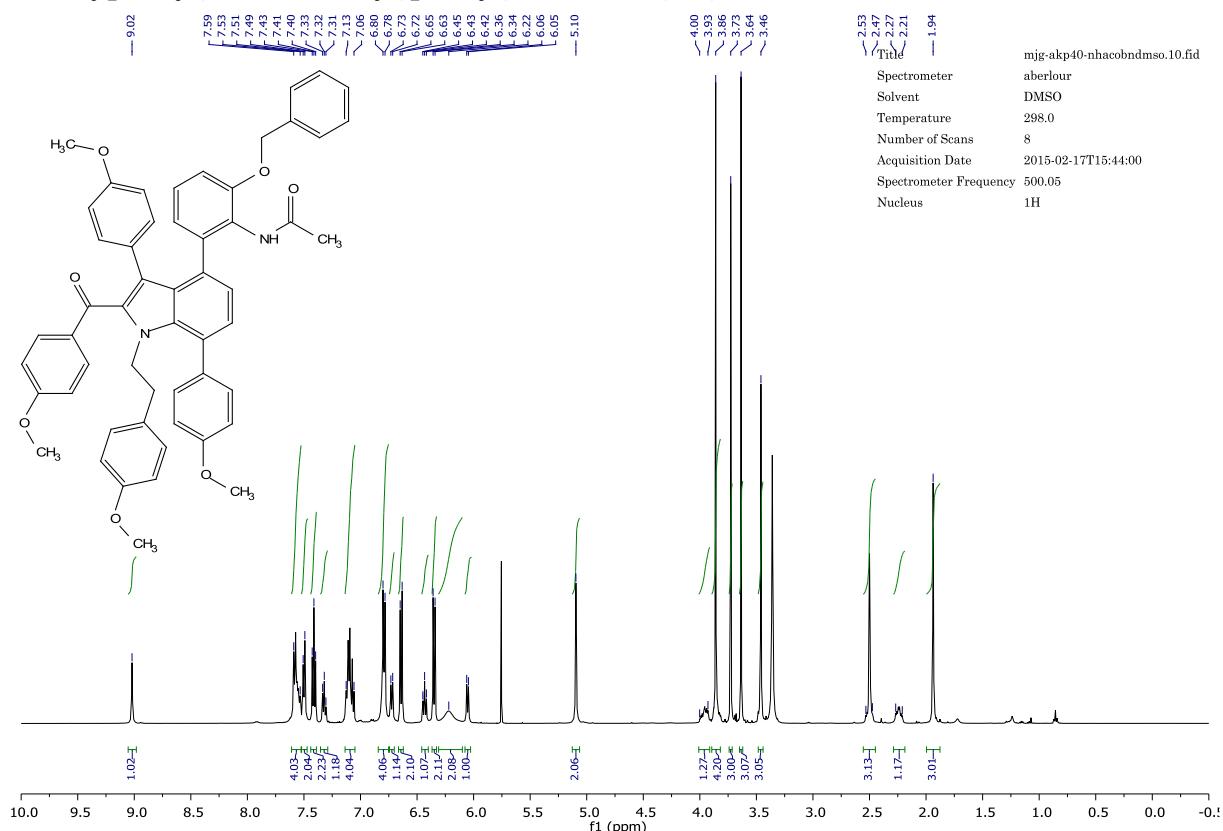


## Dictyodendrin B (2)

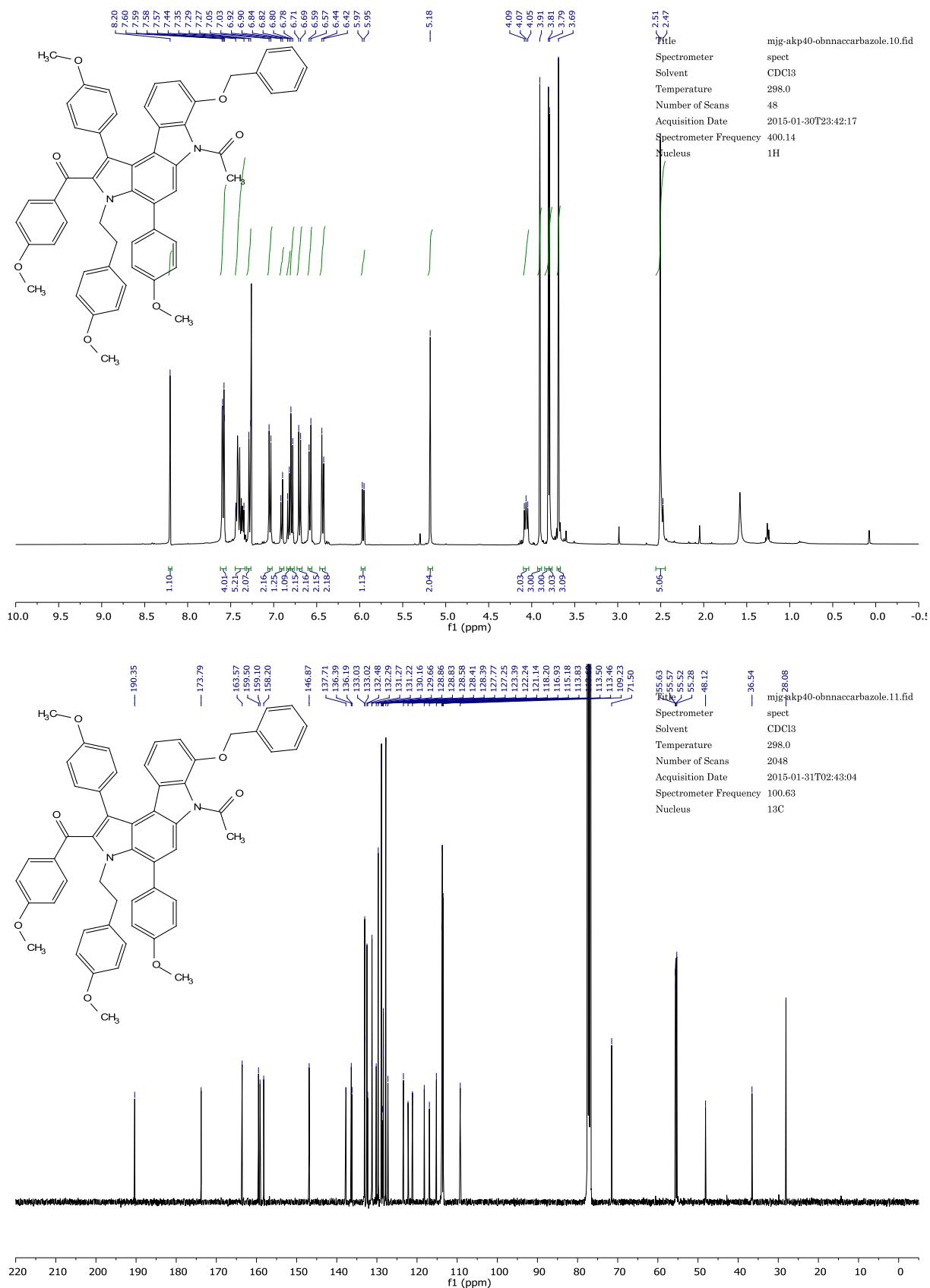


## 9.2 N-Acetyl Amination

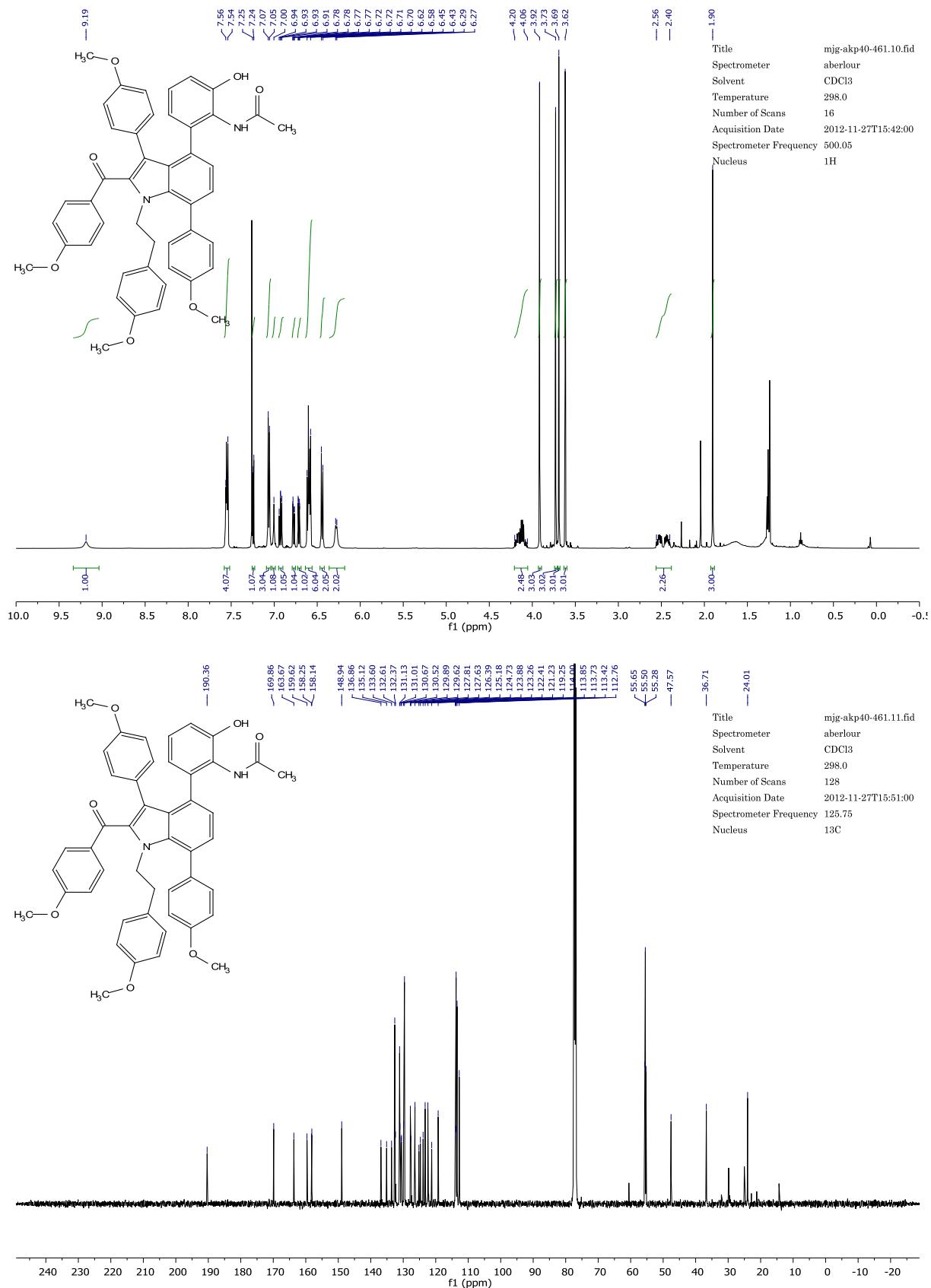
**N-(2-(benzyloxy)-6-(2-(4-methoxybenzoyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1H-indol-4-yl)phenyl)acetamide (348)**



**1-(7-(benzyloxy)-2-(4-methoxybenzoyl)-3-(4-methoxyphenethyl)-1,4-bis(4-methoxyphenyl)pyrrolo[2,3-c]carbazol-6(3H)-yl)ethan-1-one (349)**

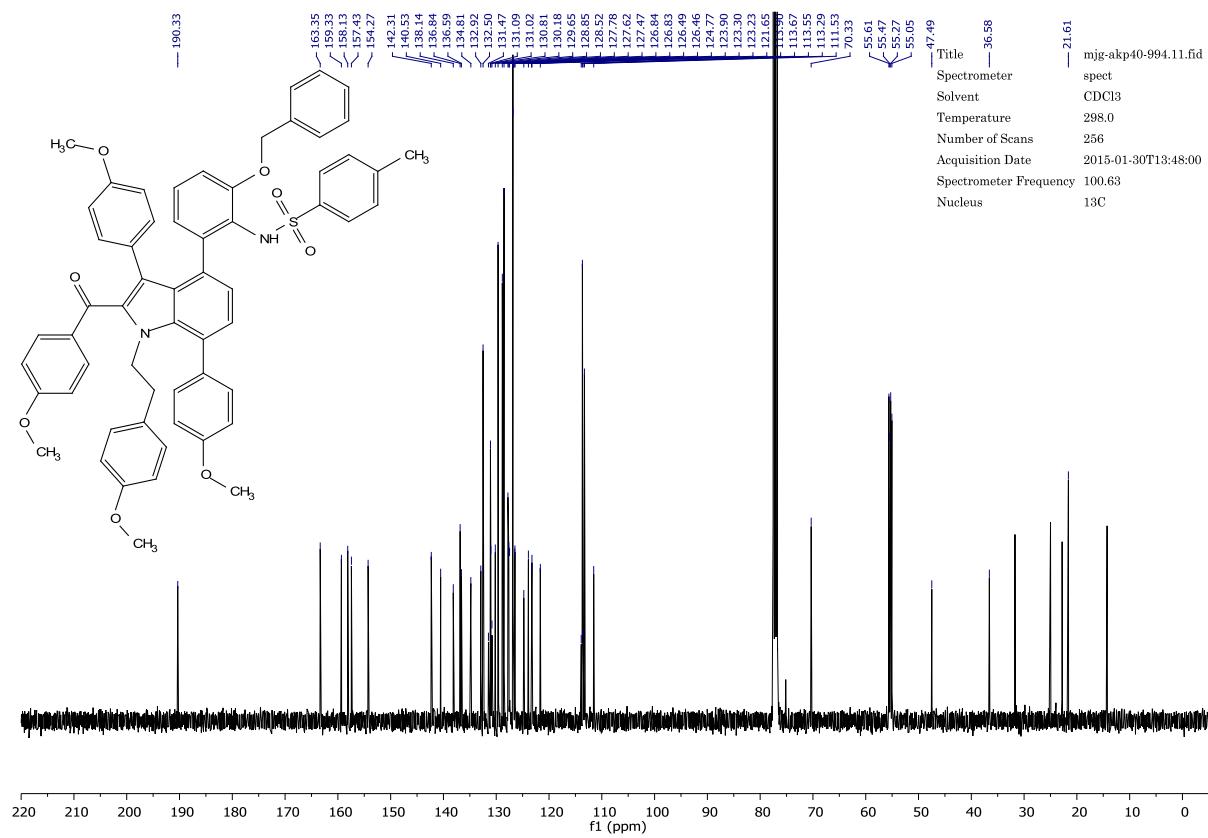
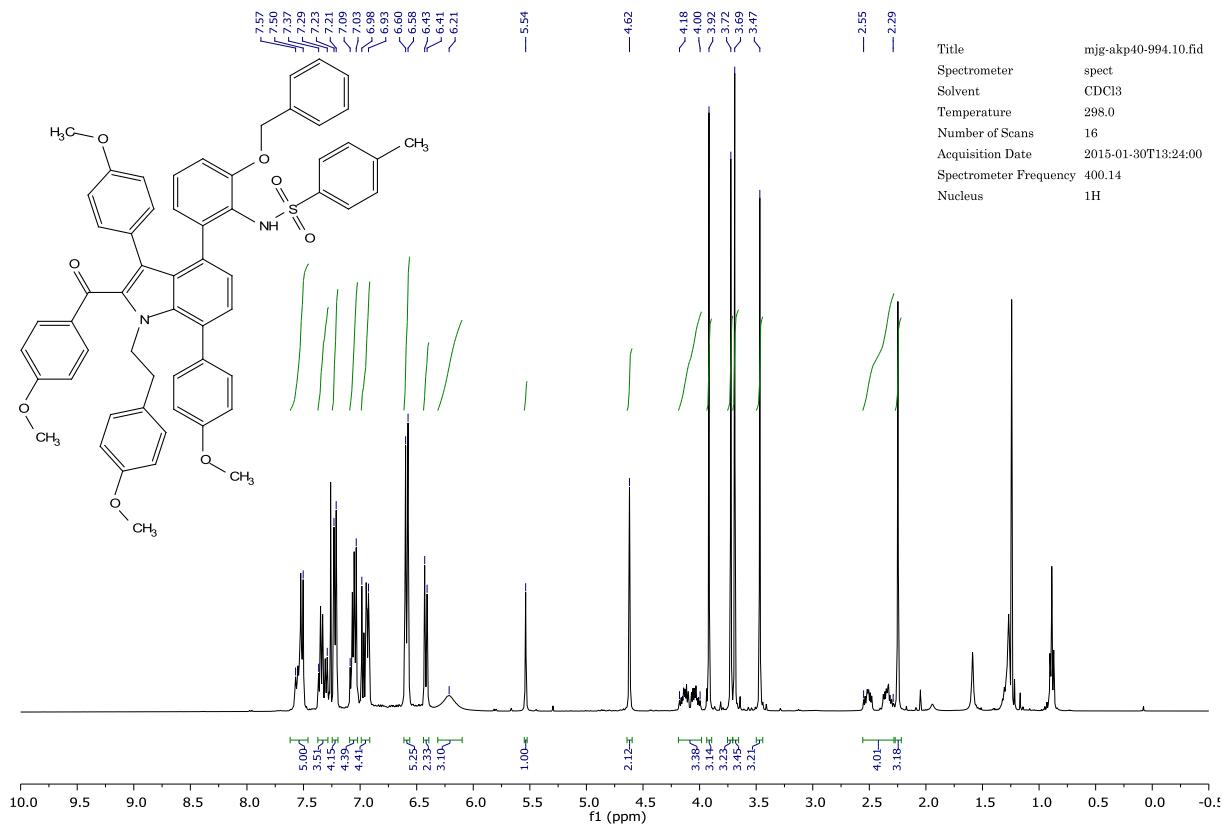


**N-(2-hydroxy-6-(2-(4-methoxybenzoyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-4-yl)phenyl)acetamide (350)**

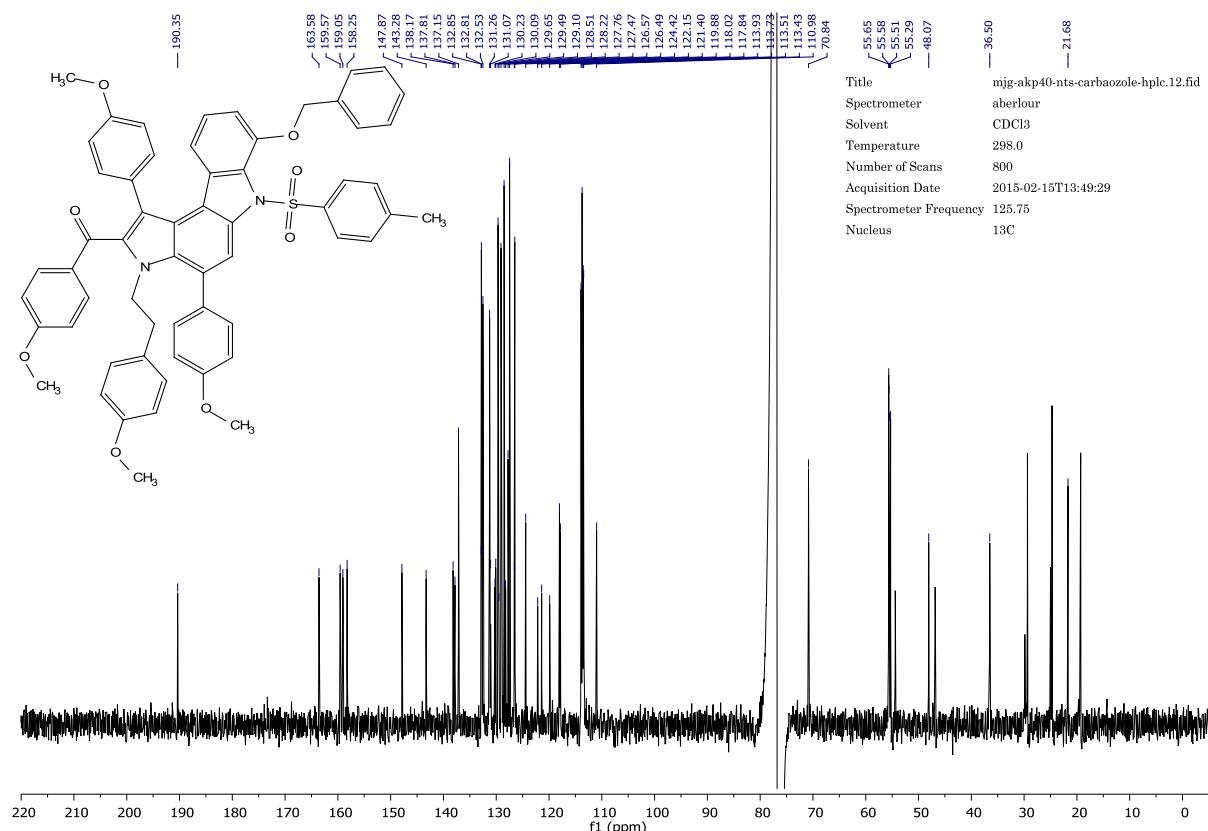
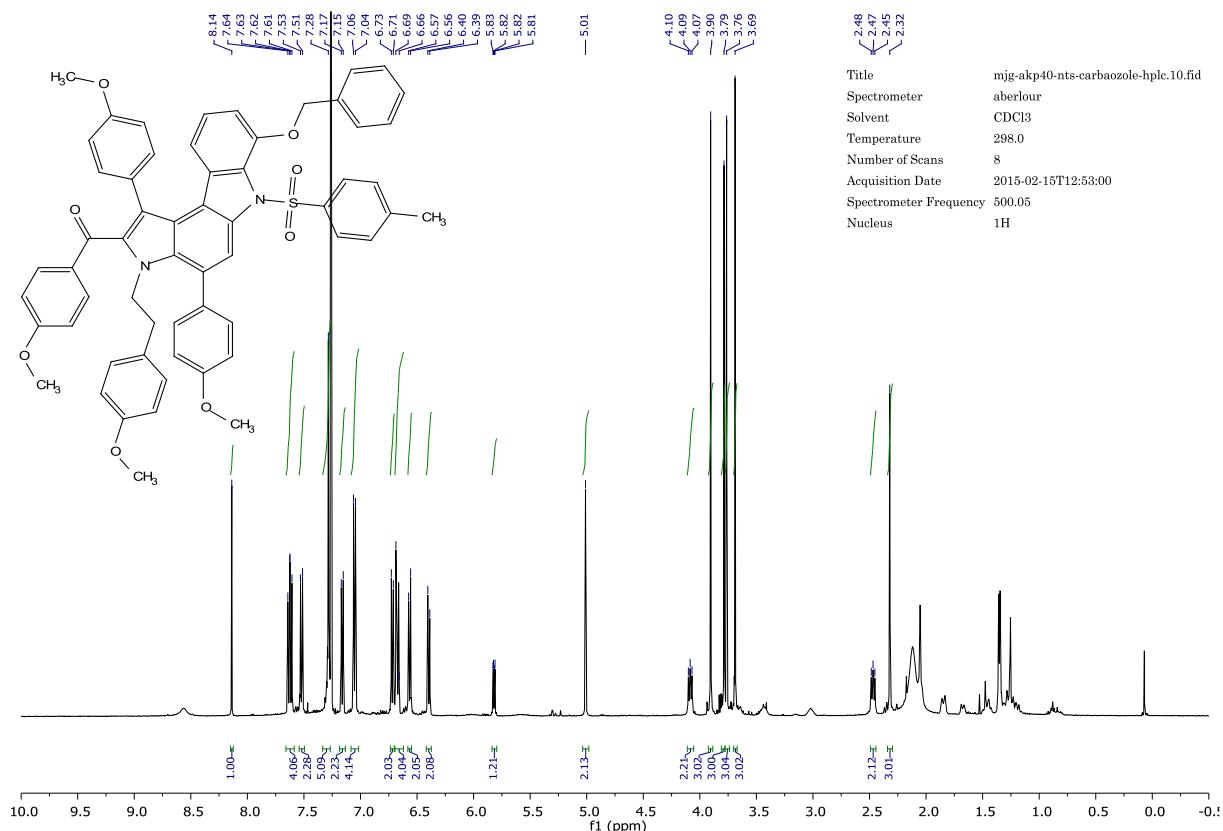


### 9.3 N-Tosyl Amination

#### *N*-(2-(benzyloxy)-6-(2-(4-methoxybenzoyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1H-indol-4-yl)phenyl)-4-methylbenzenesulfonamide (361)

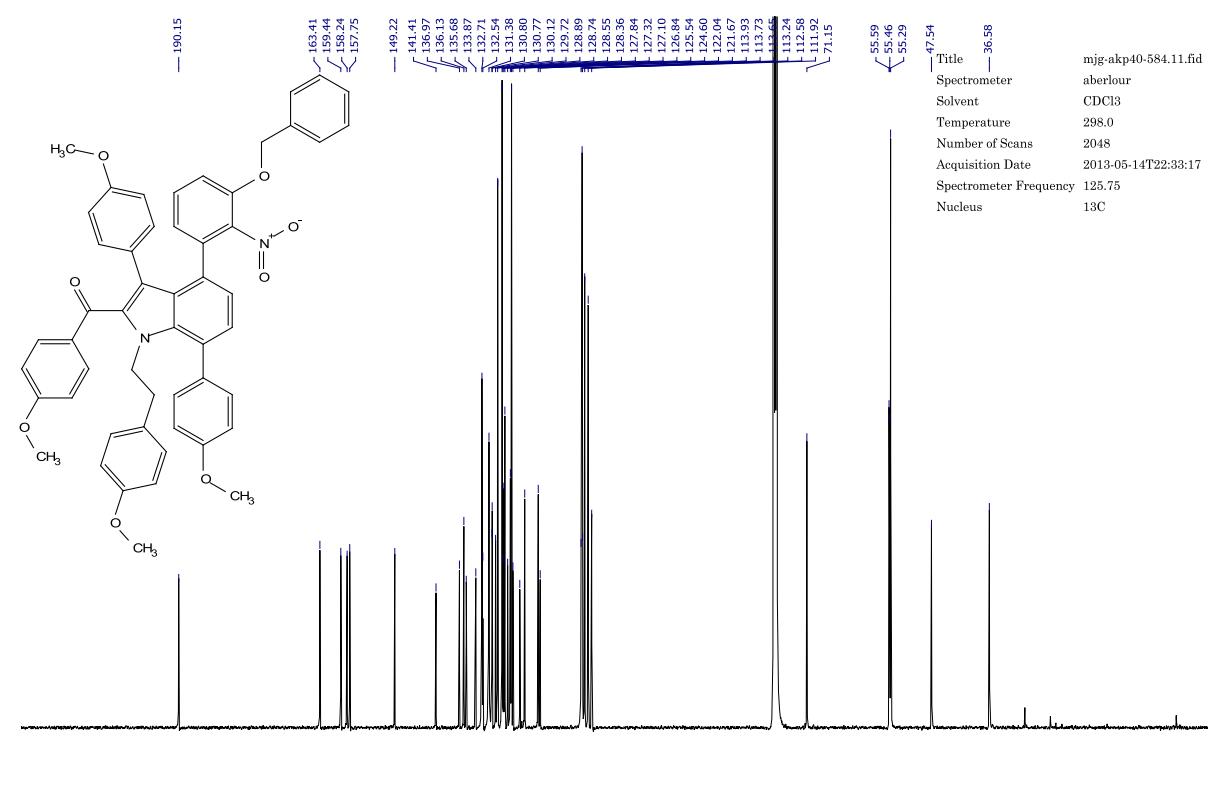
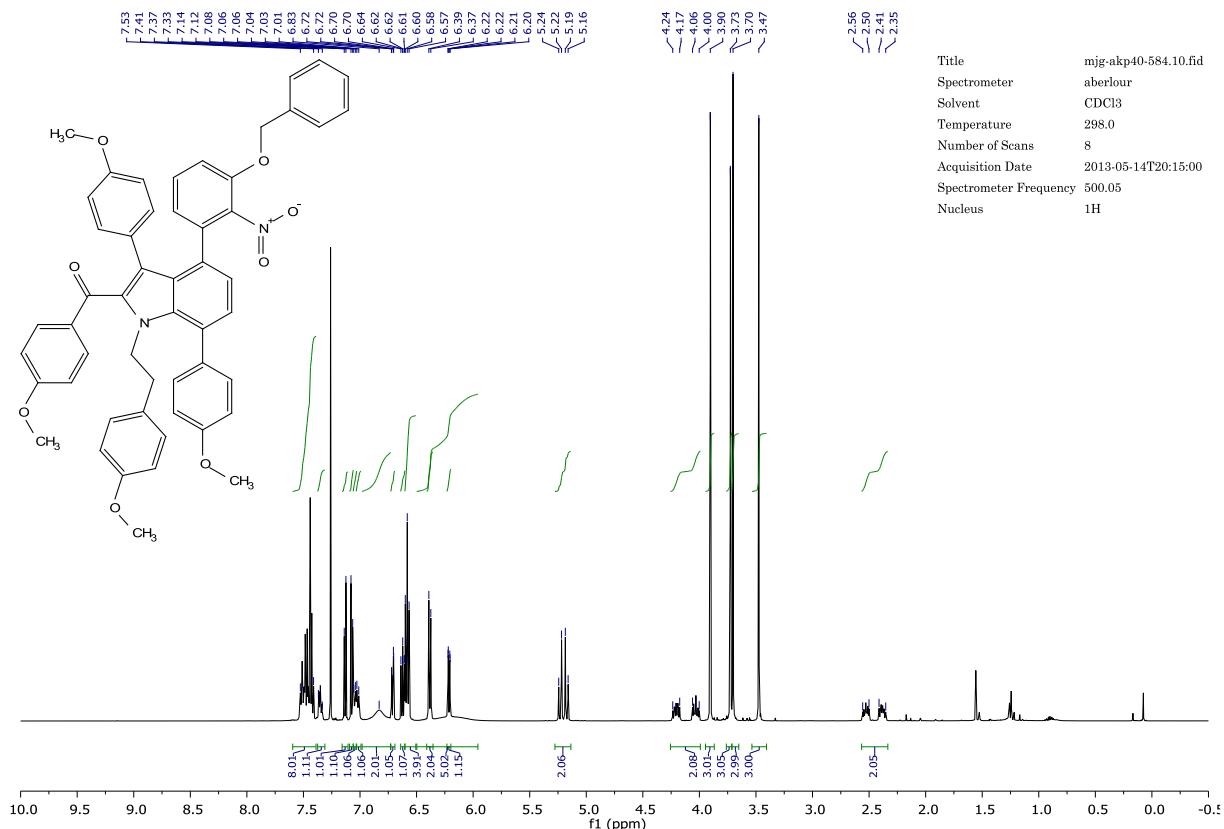


**(7-(benzyloxy)-3-(4-methoxyphenethyl)-1,4-bis(4-methoxyphenyl)-6-tosyl-3,6-dihdropyrrolo[2,3-c]carbazol-2-yl)(4-methoxyphenyl)methanone (362)**

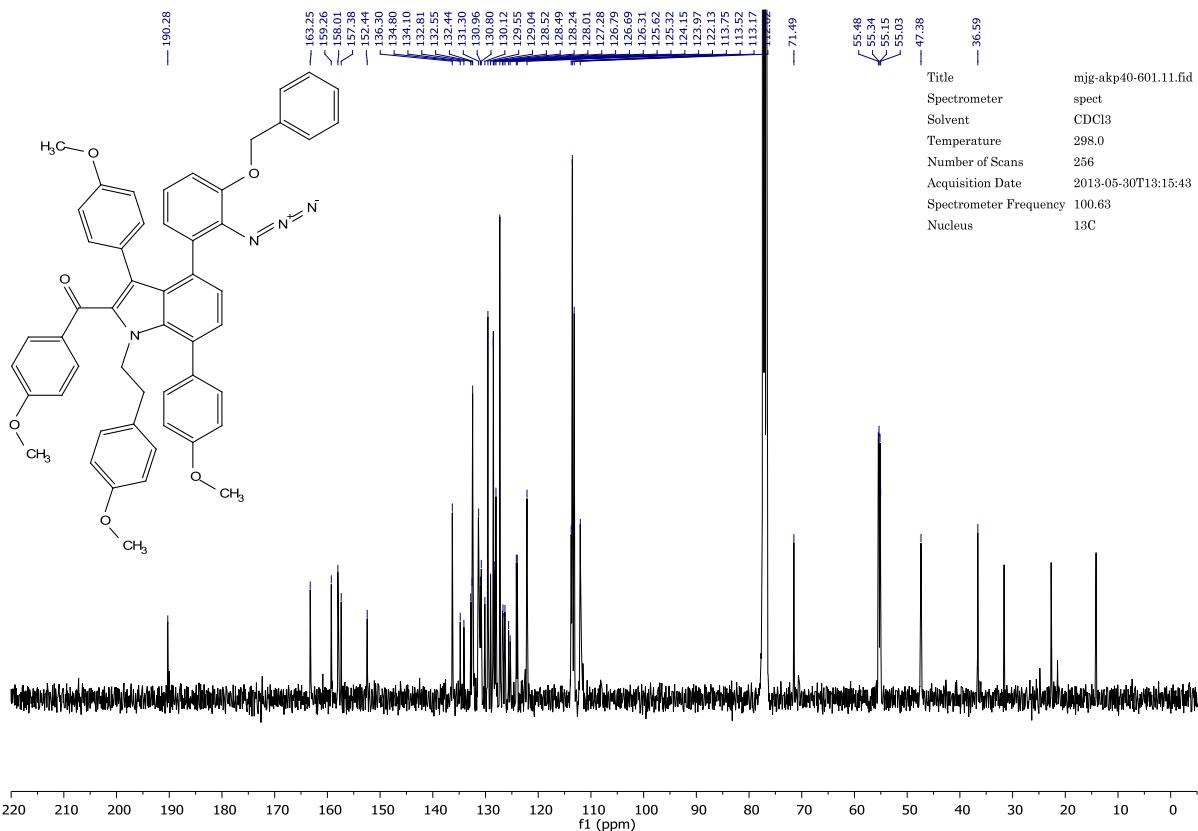
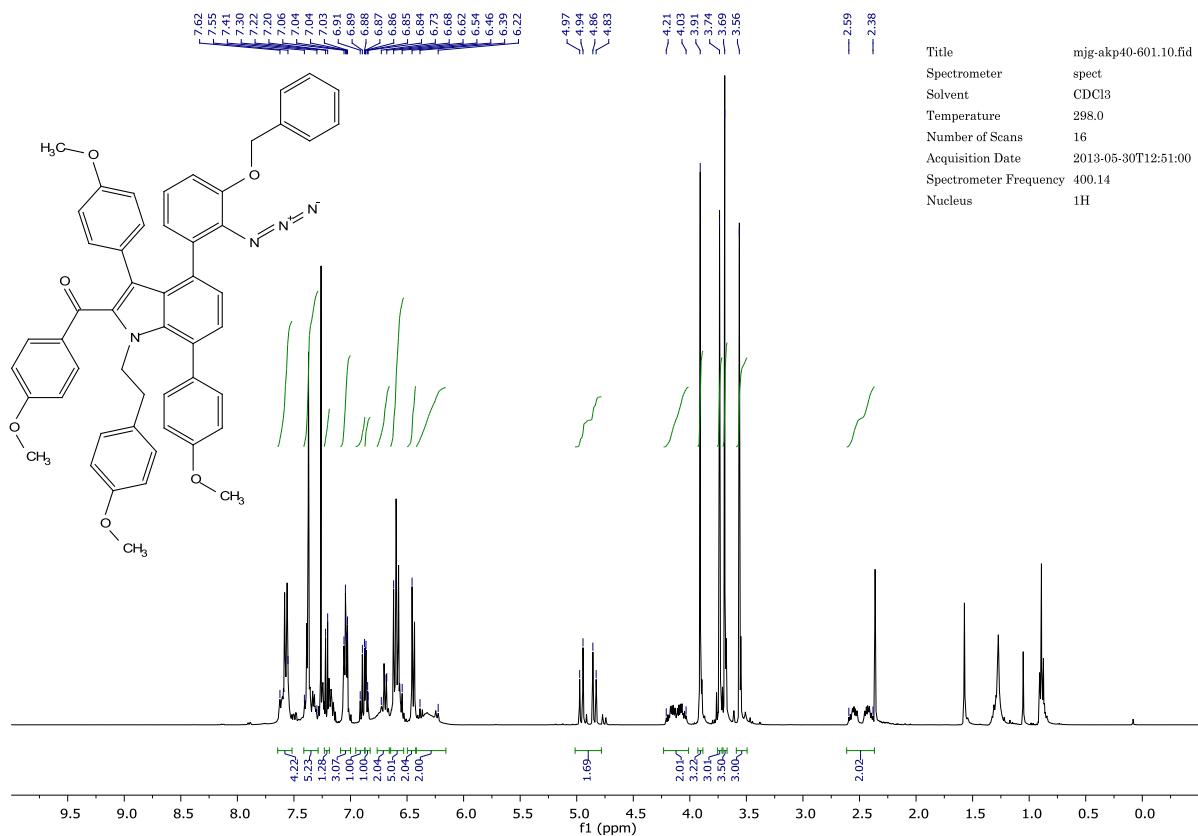


## 9.4 Other indole fragments

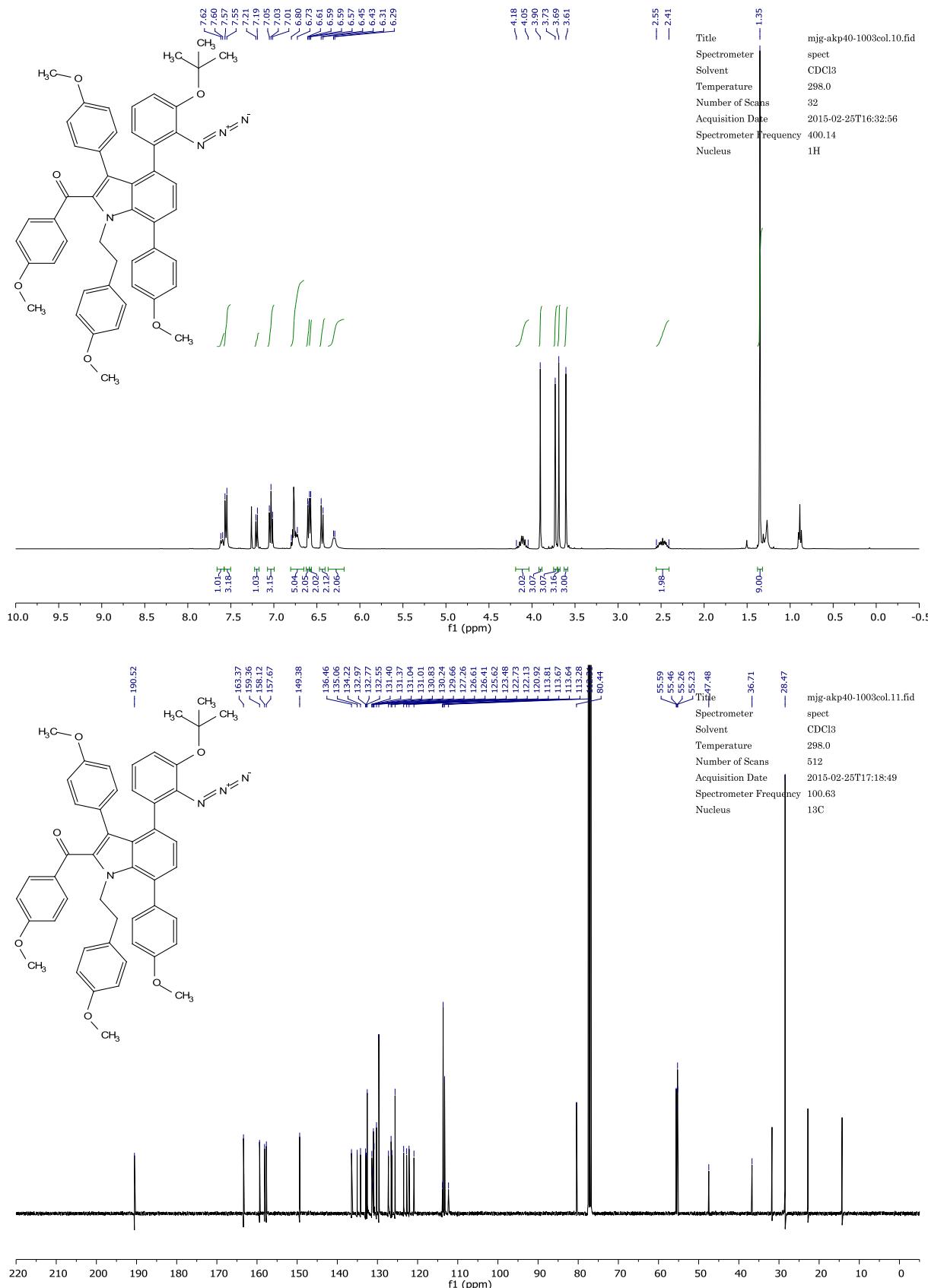
### (4-(3-(benzyloxy)-2-nitrophenyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (363)



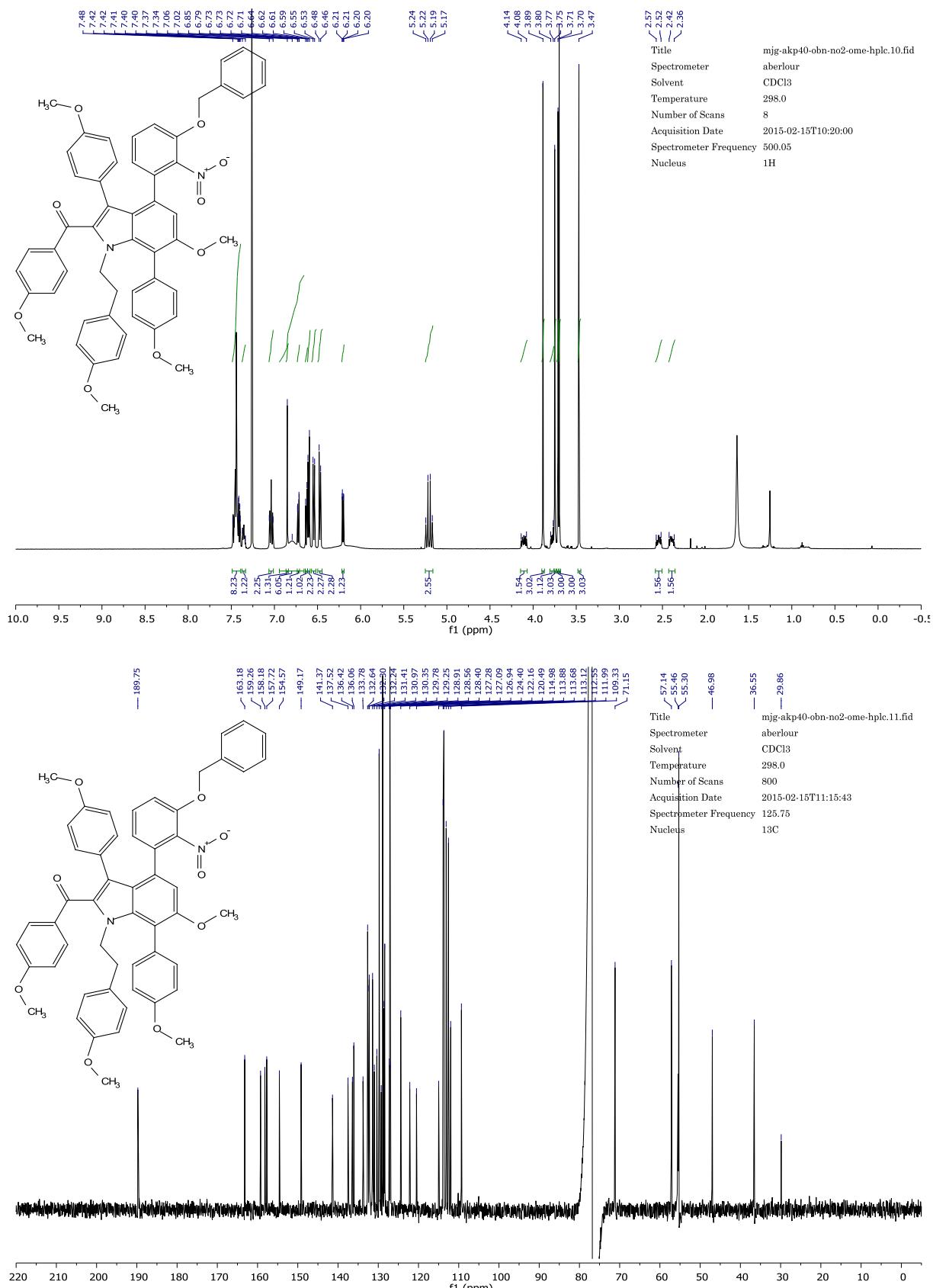
**(4-(2-azido-3-(benzyloxy)phenyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (382)**



**(4-(2-azido-3-(*tert*-butoxy)phenyl)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (377)**

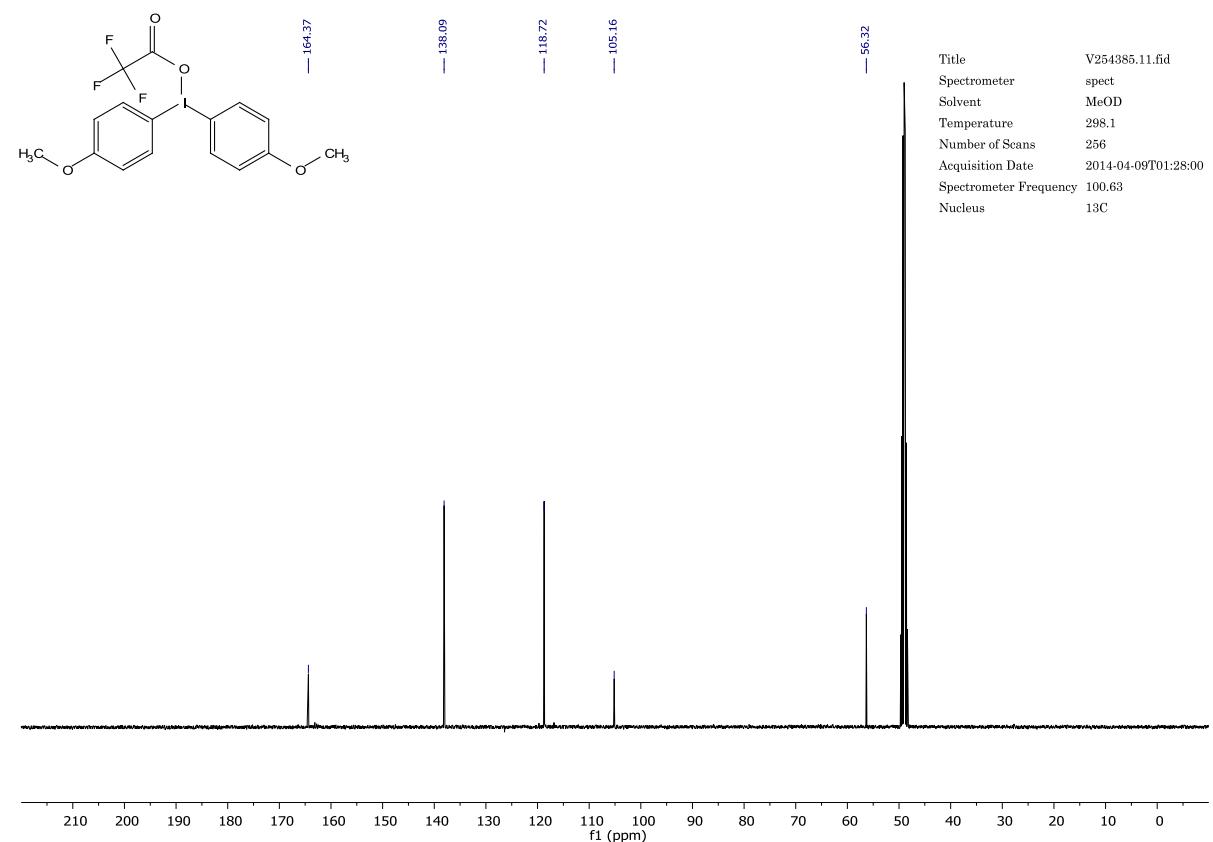
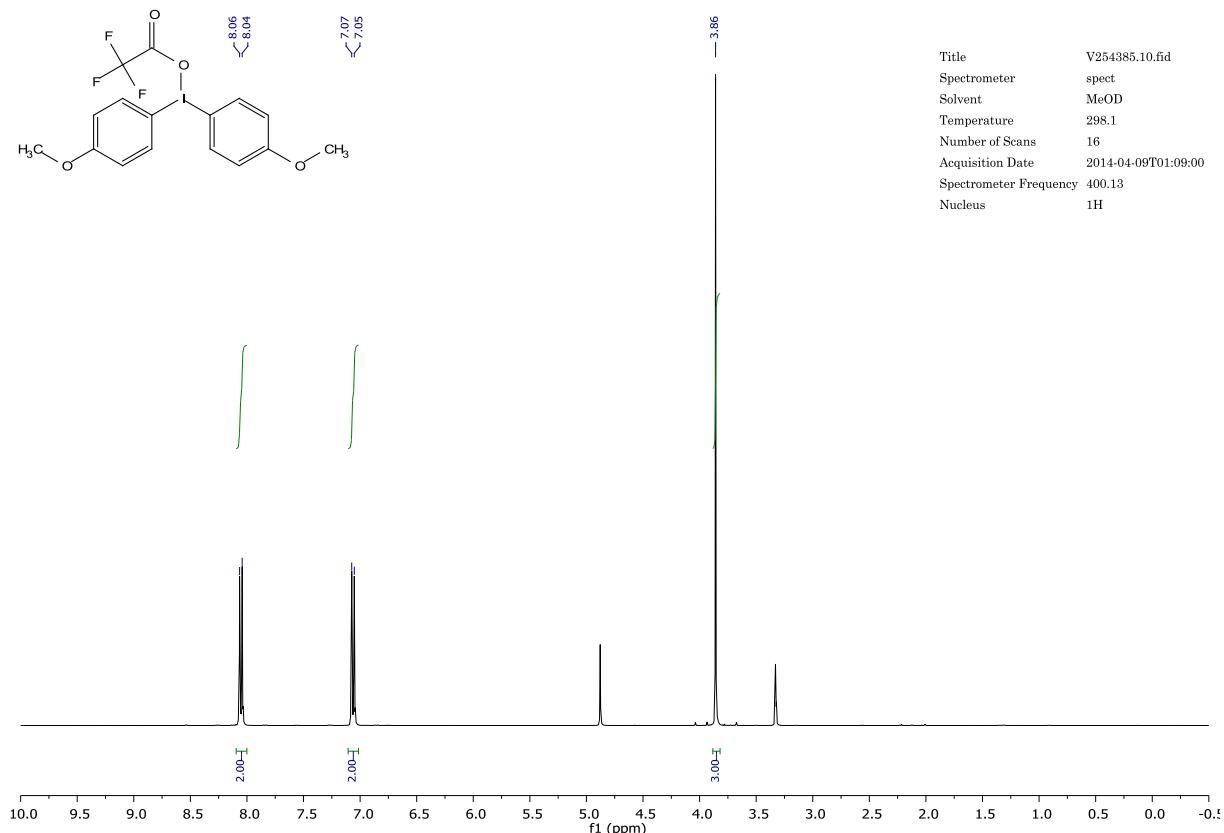


**(4-(3-(benzyloxy)-2-nitrophenyl)-6-methoxy-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (390)**



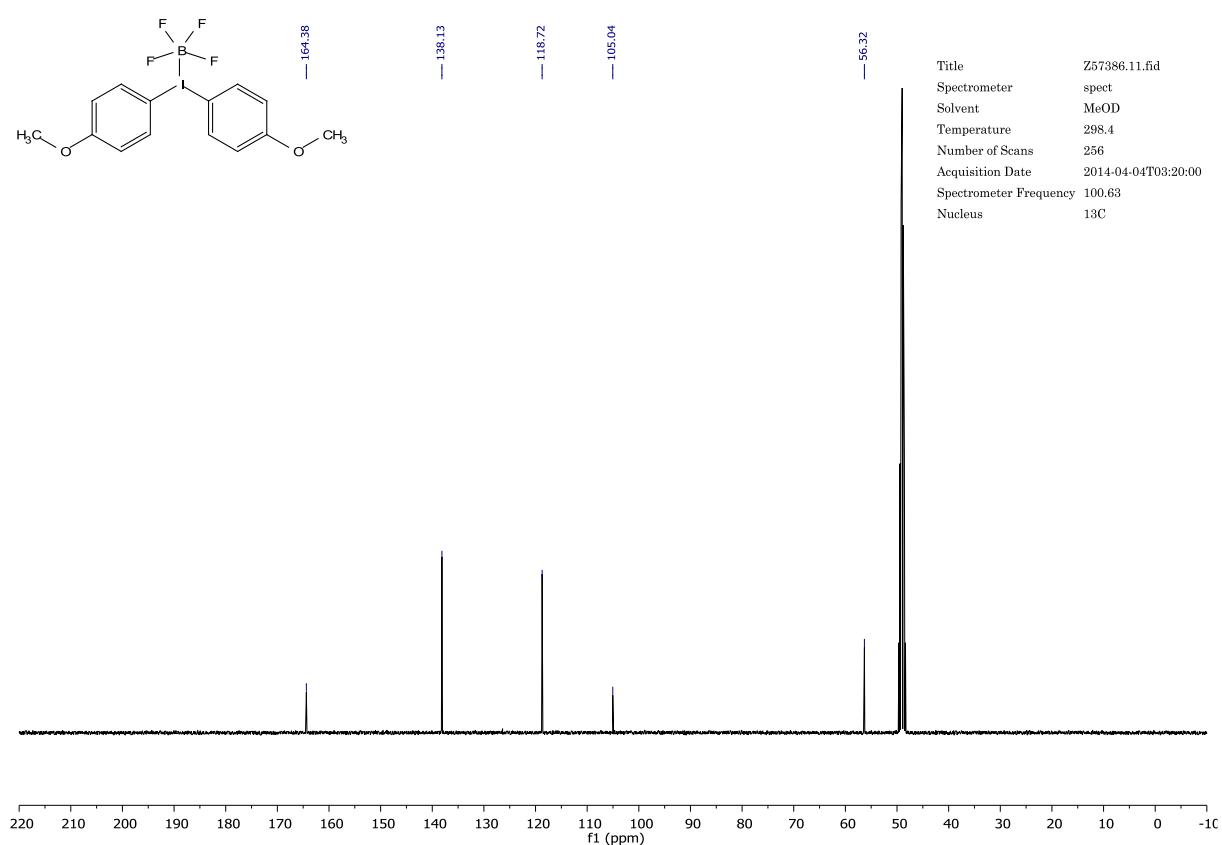
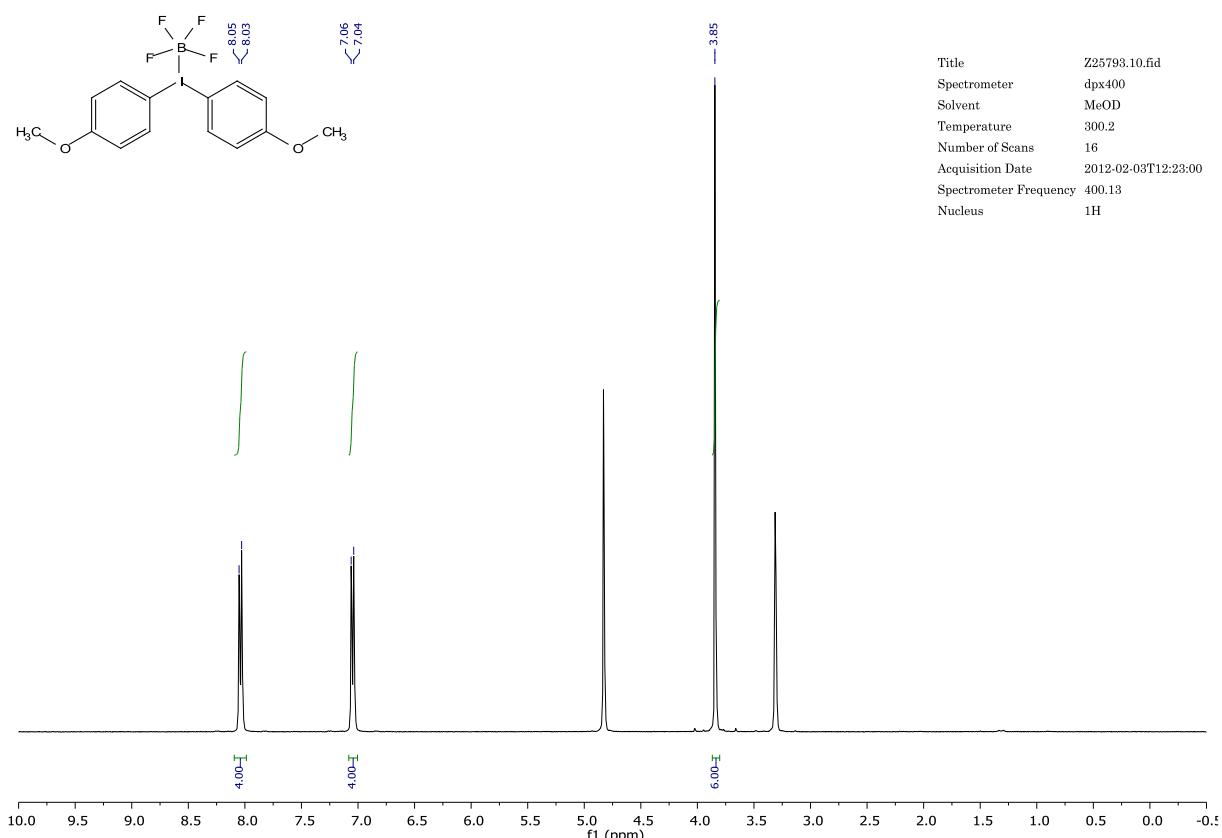
## 9.5 Iodonium Salts

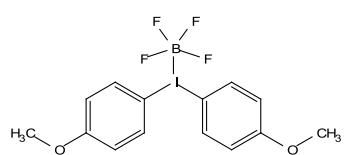
### bis(4-Methoxyphenyl)iodonium 2,2,2-trifluoroacetate (213)





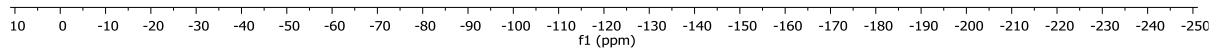
**bis(4-Methoxyphenyl)iodonium tetrafluoroborate (184)**





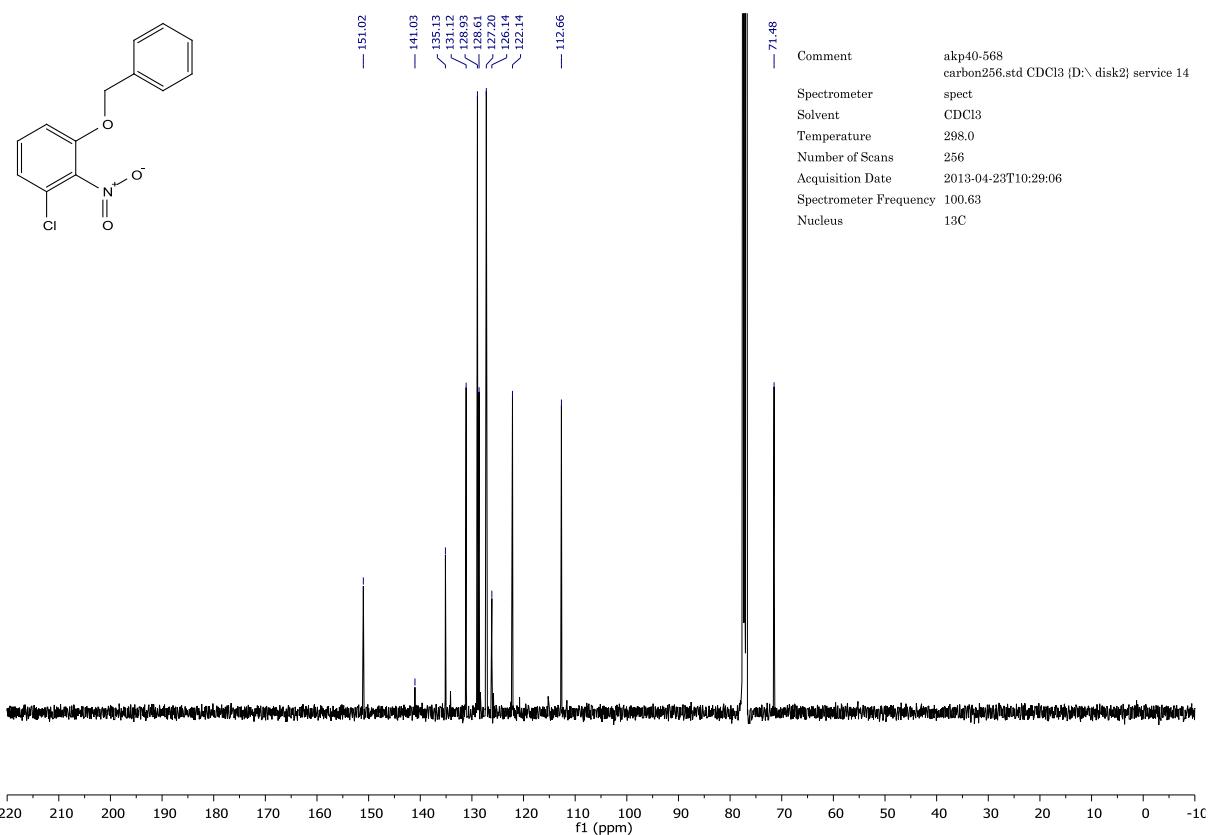
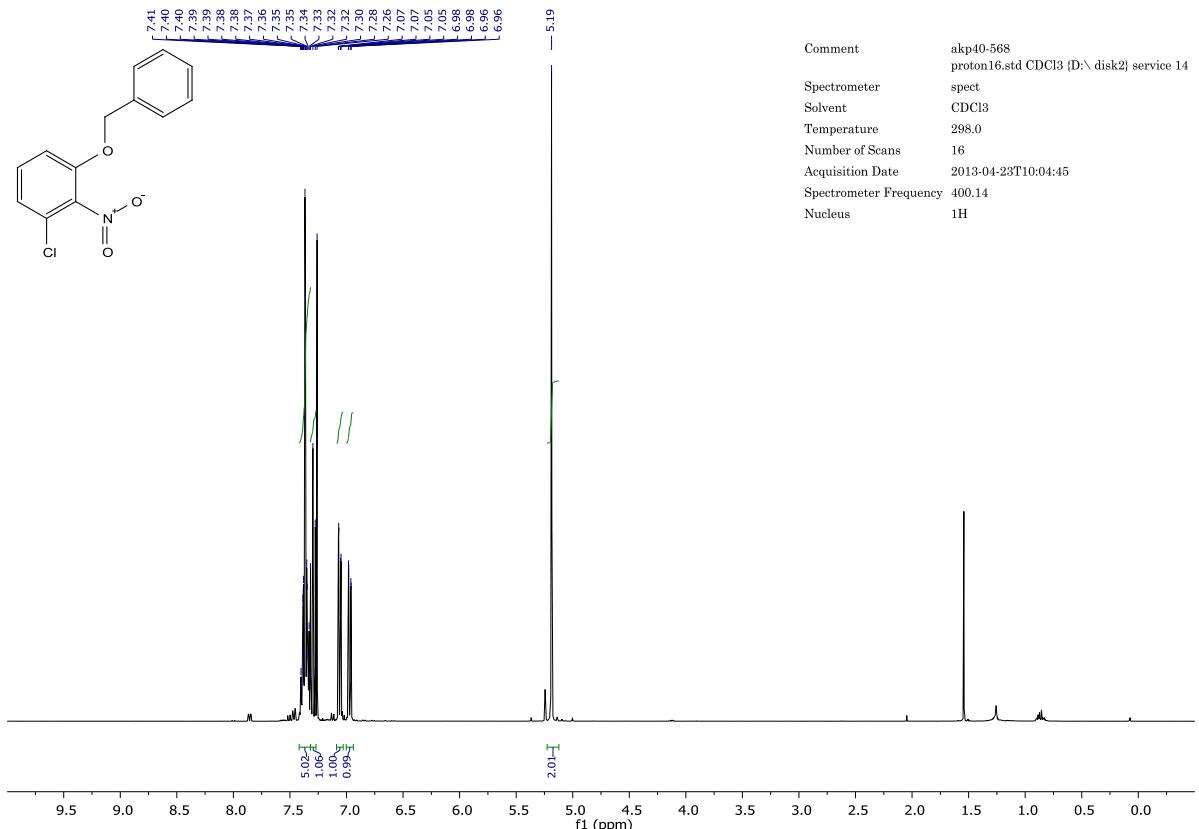
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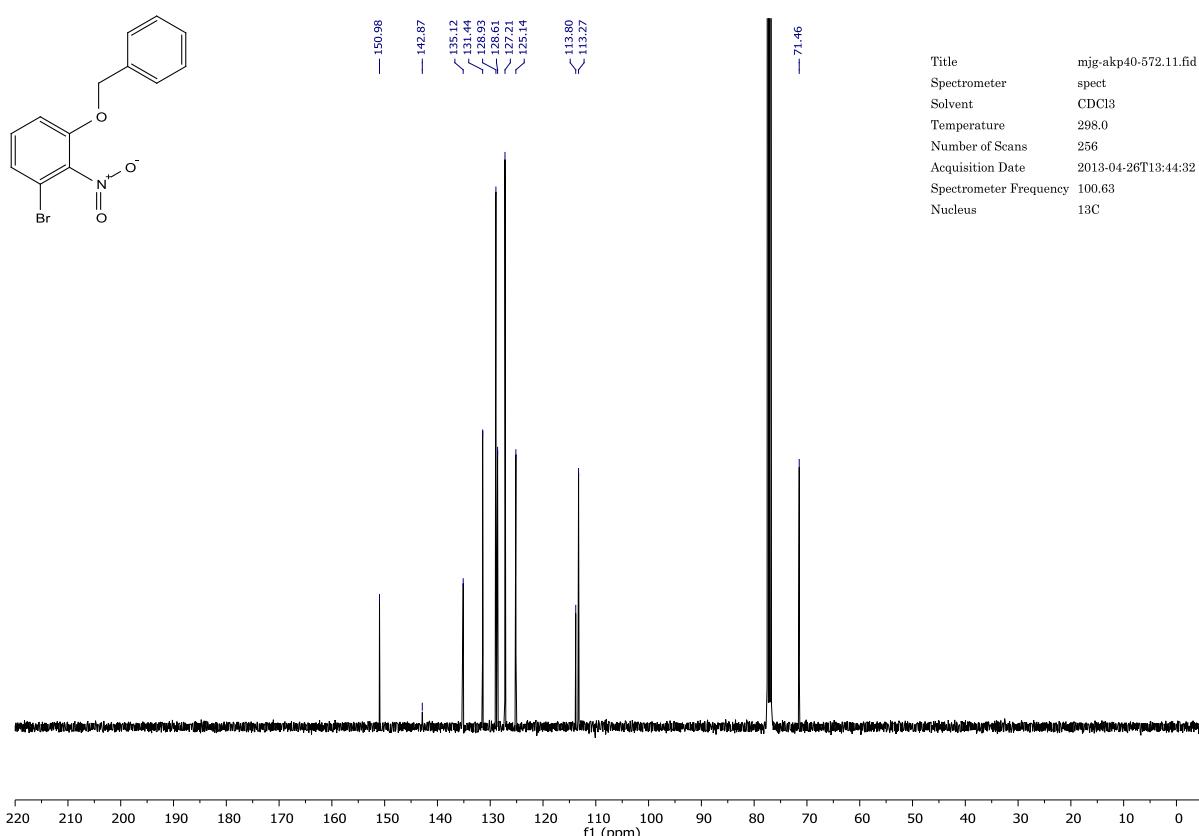
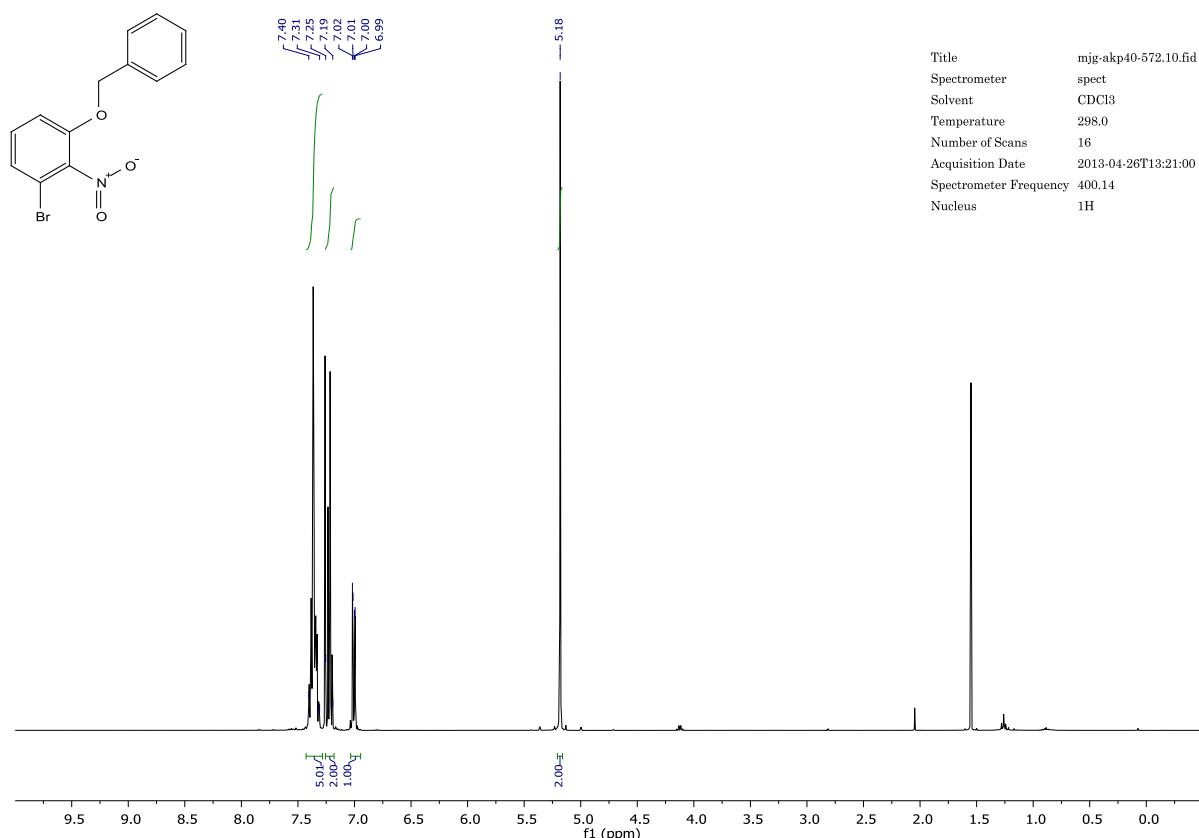
## 9.6 Chloroarenes

### 1-(benzyloxy)-3-chloro-2-nitrobenzene (291)

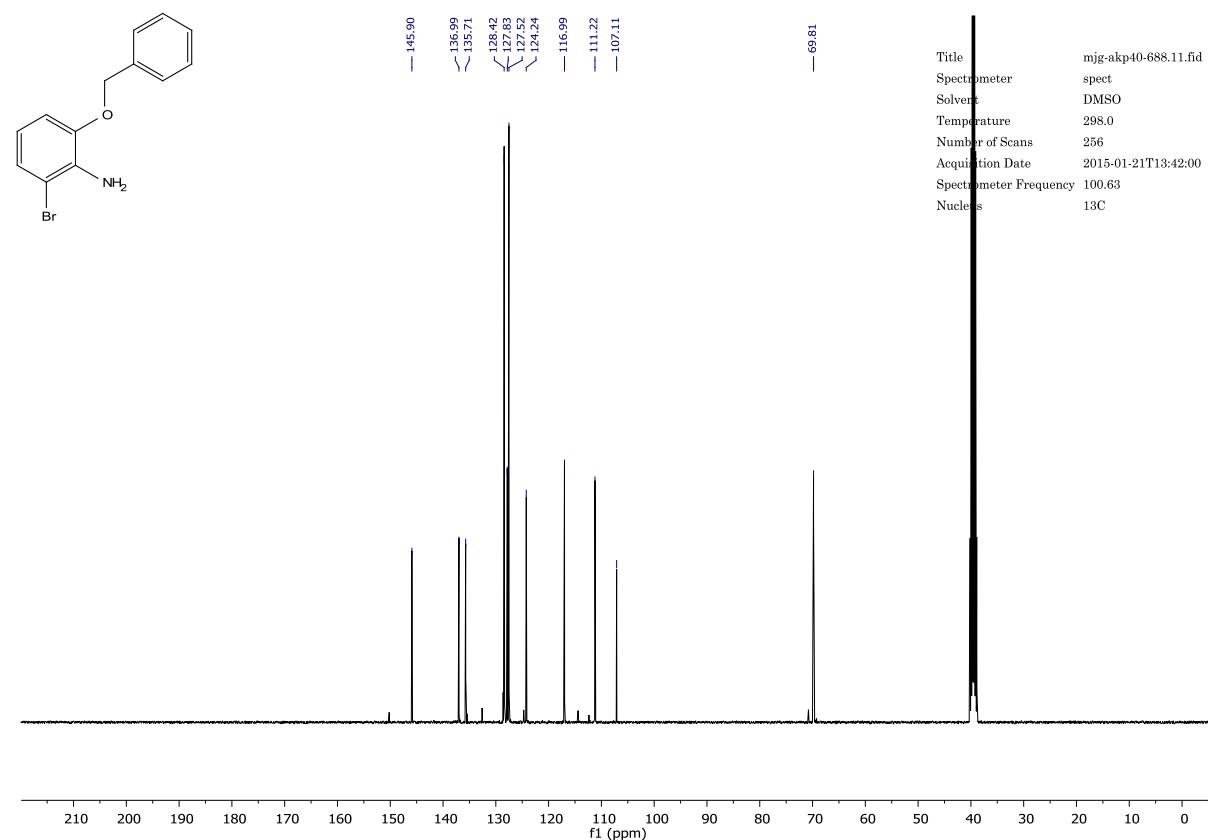
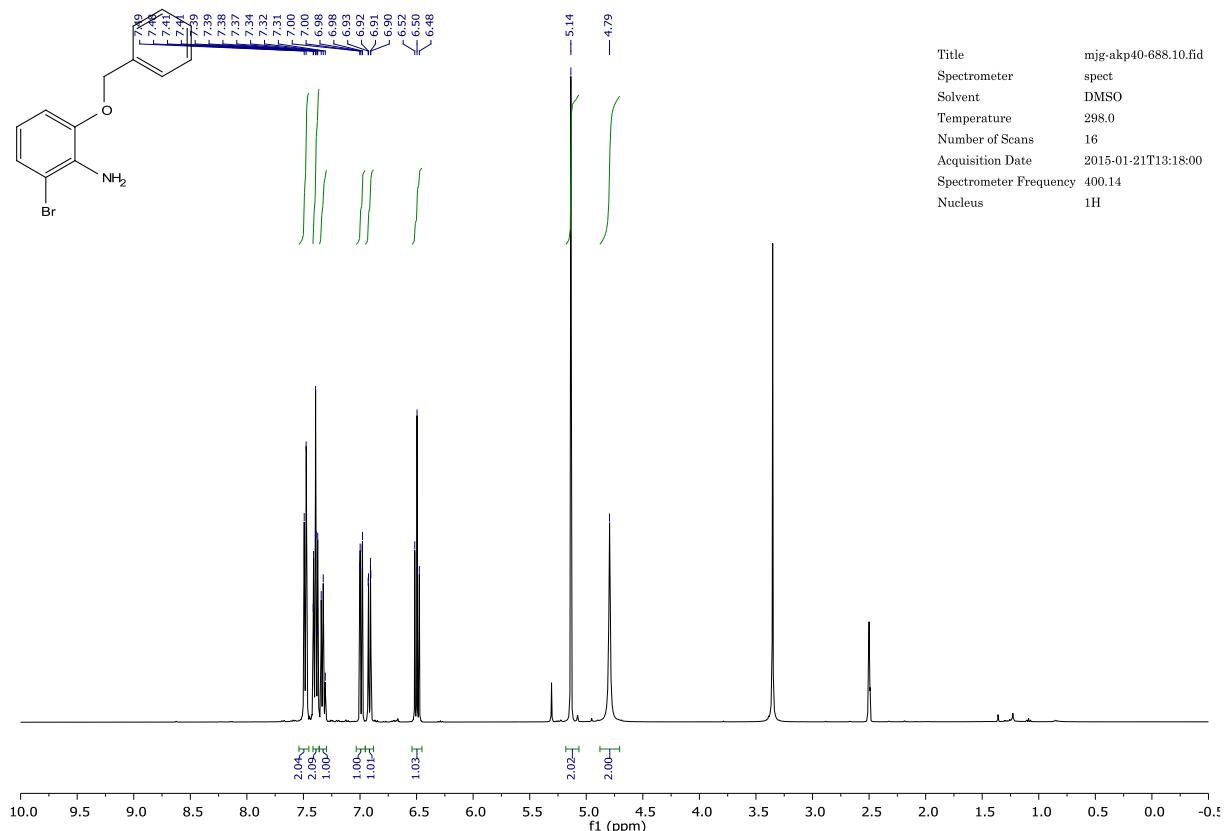


## 9.7 Bromoarenes

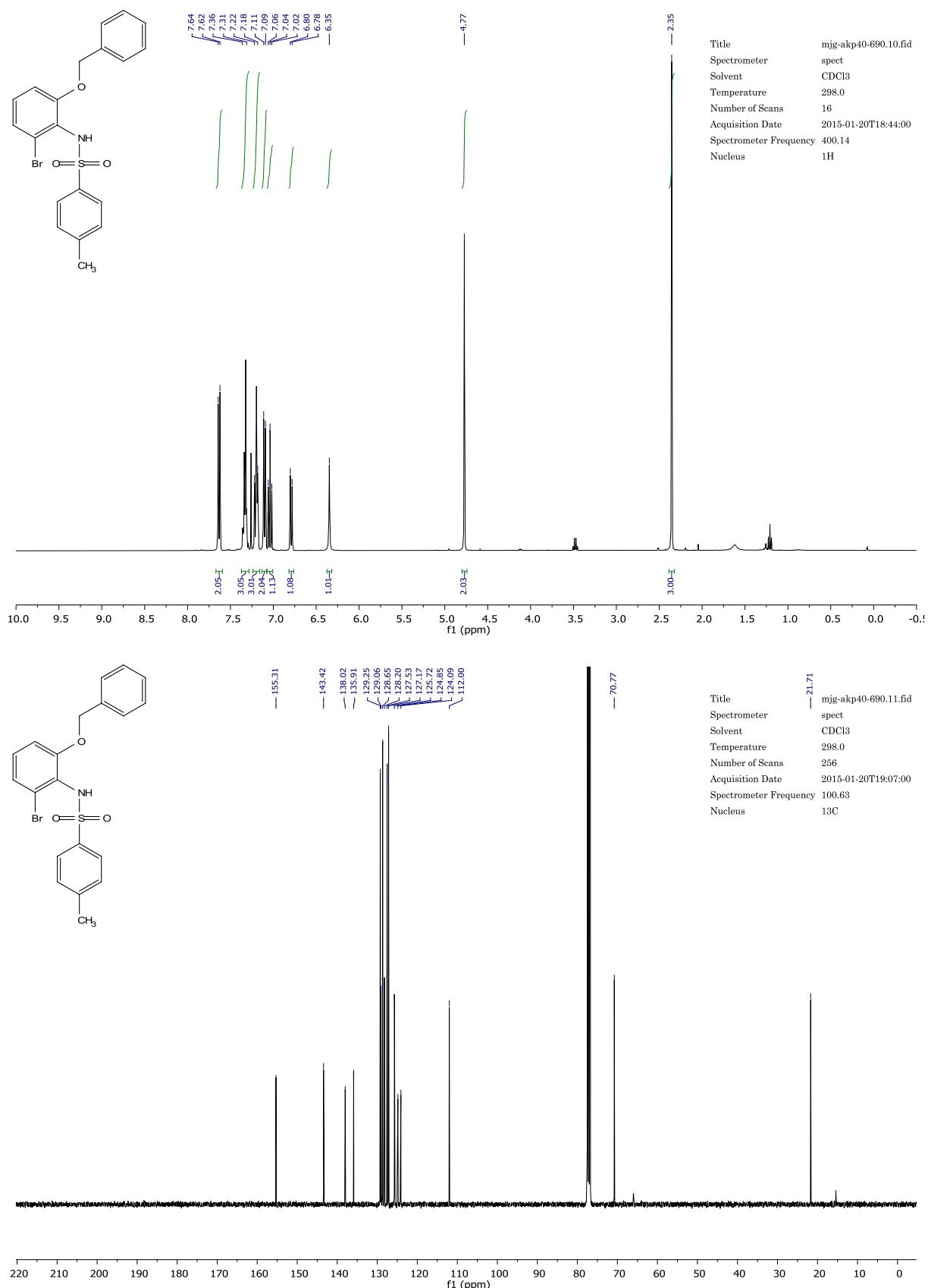
### 1-(benzyloxy)-3-bromo-2-nitrobenzene (292)



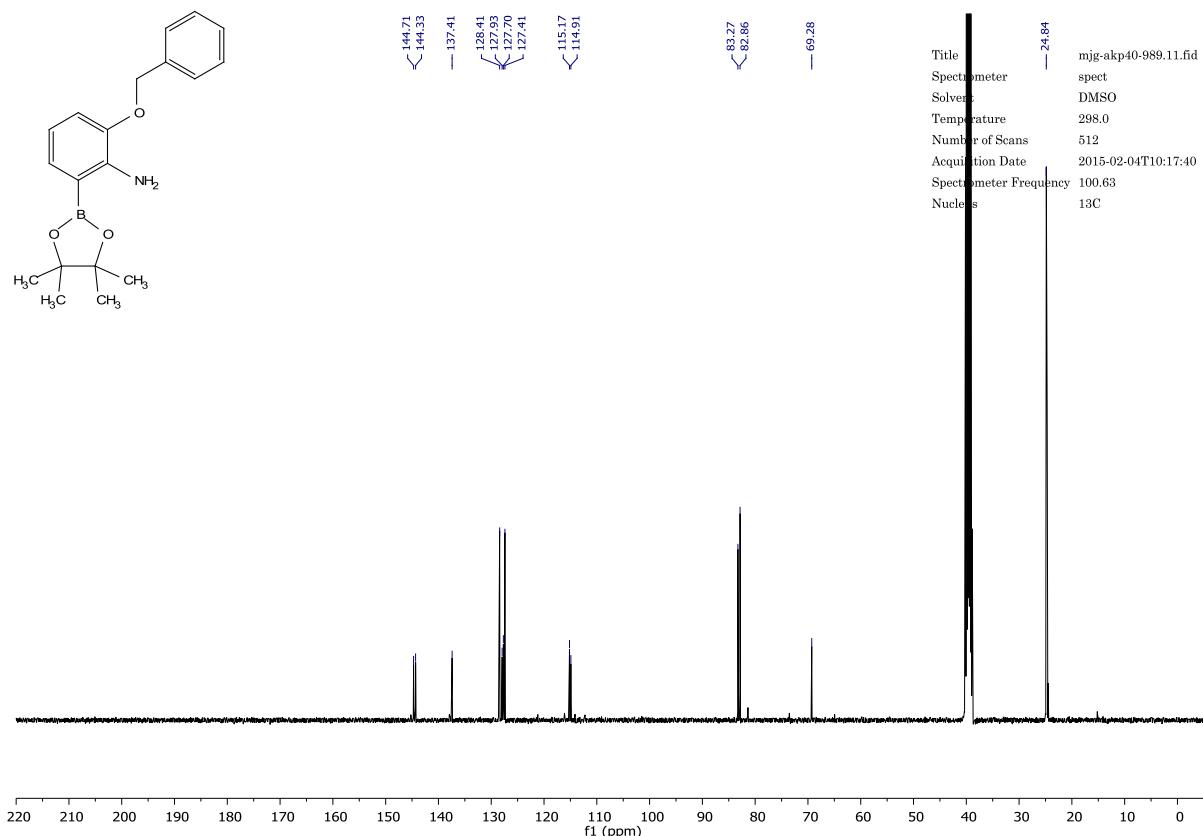
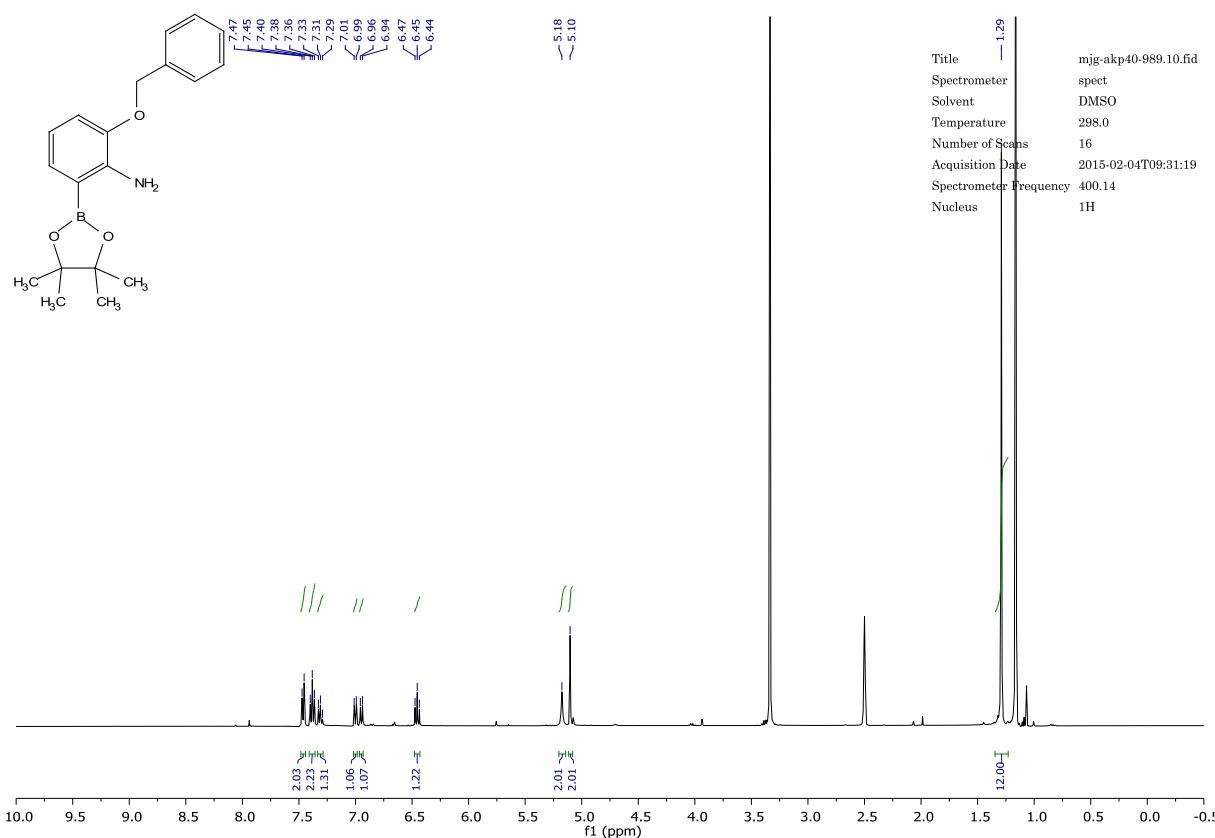
**2-(benzyloxy)-6-bromoaniline (311)**



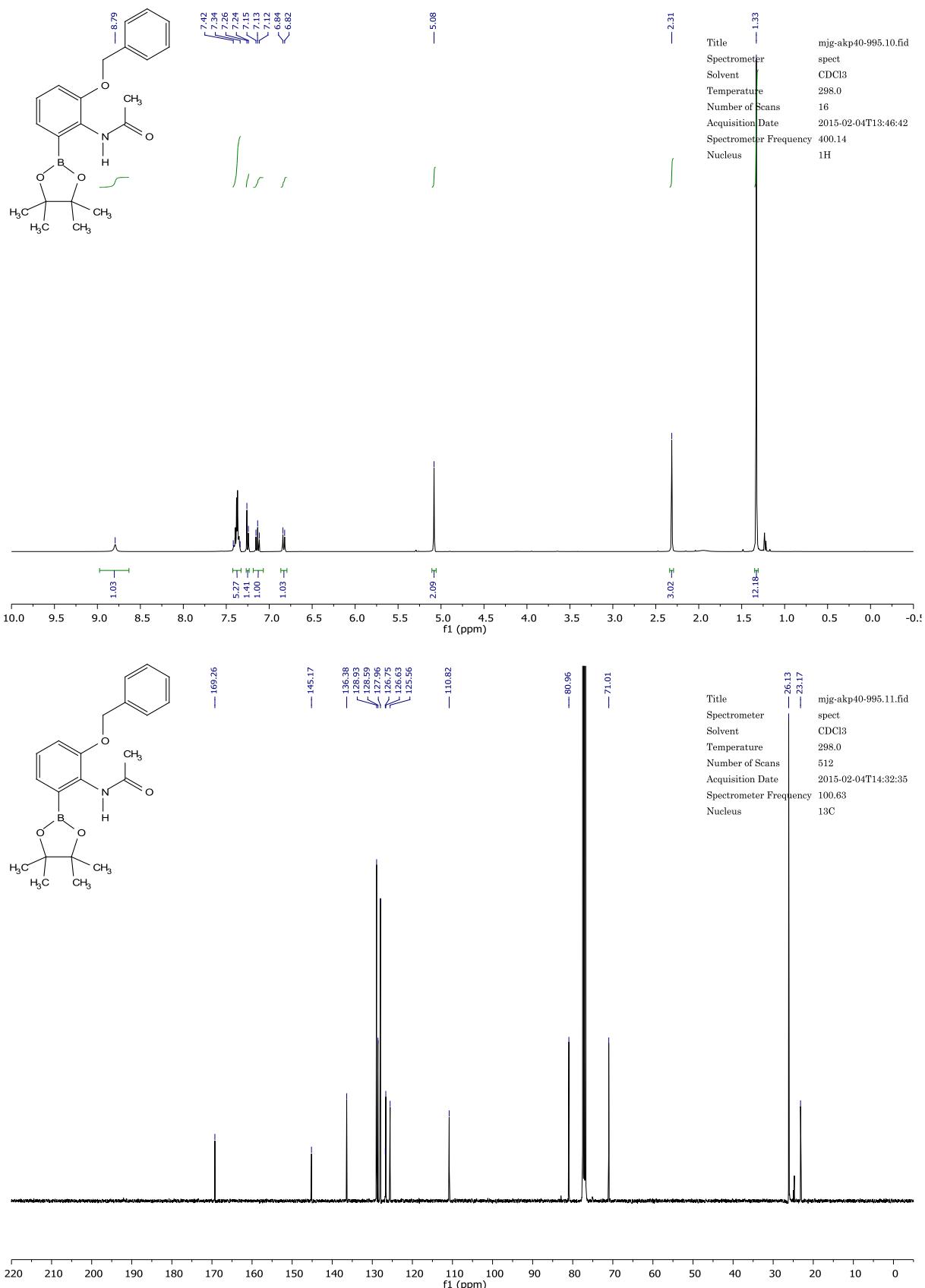
**N-(2-(benzyloxy)-6-bromophenyl)-4-methylbenzenesulfonamide (360)**



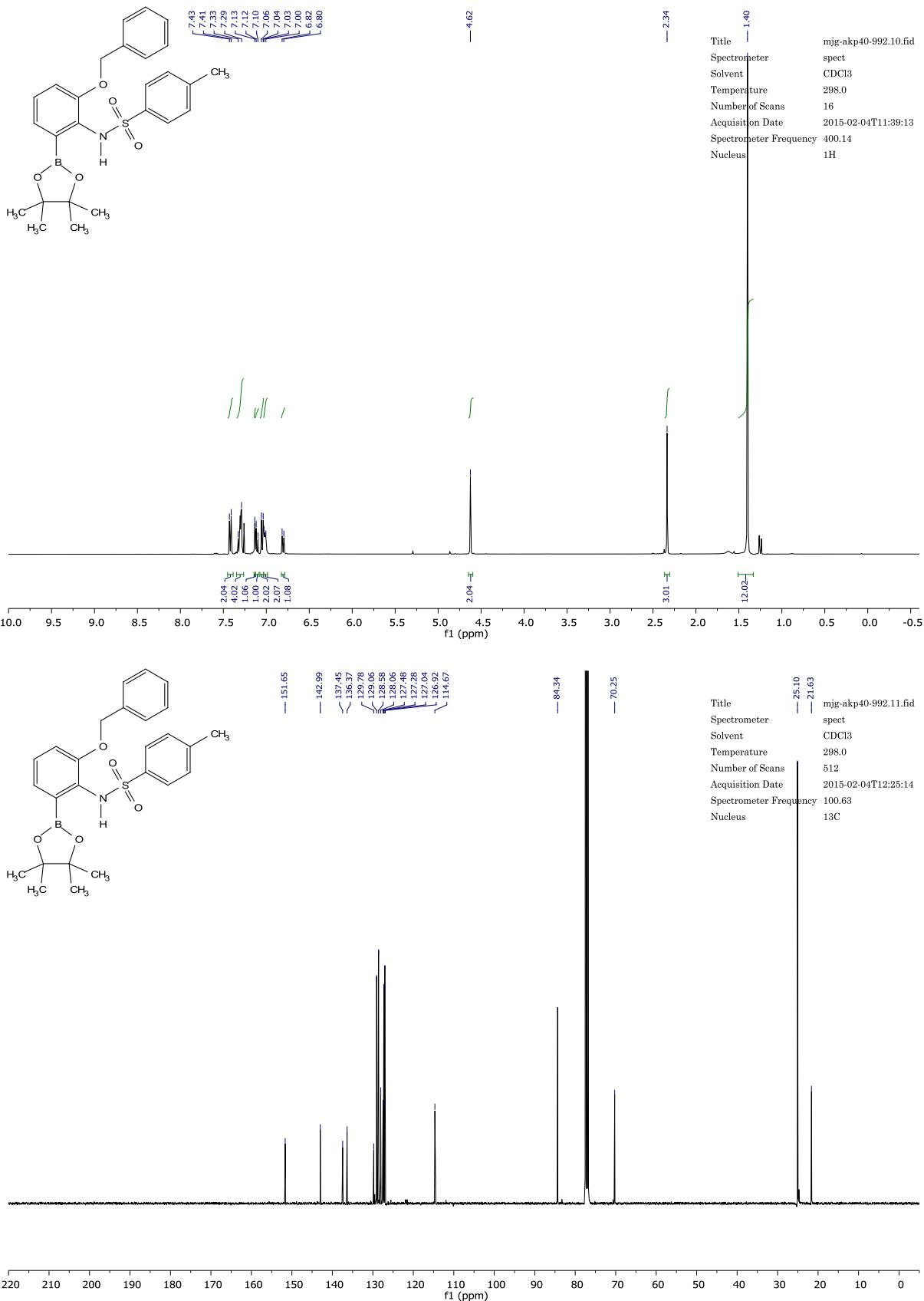
**2-(benzyloxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (255)**



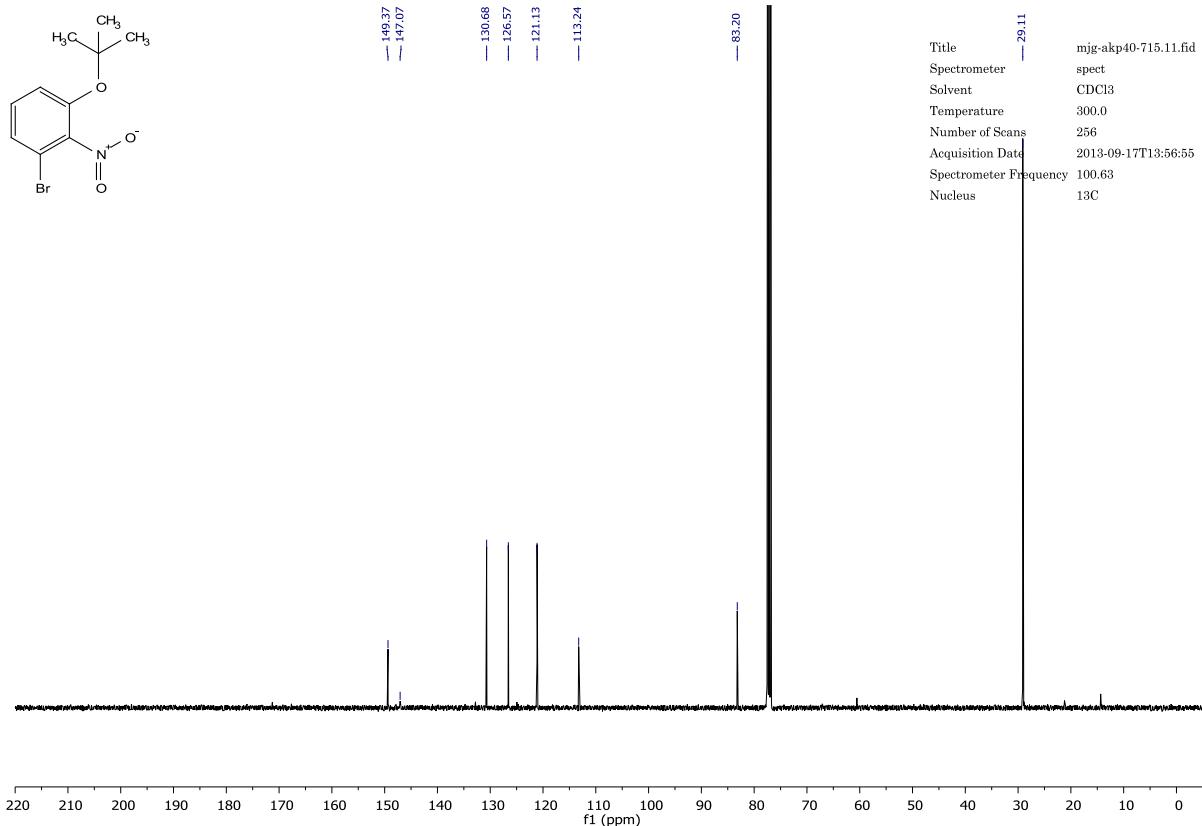
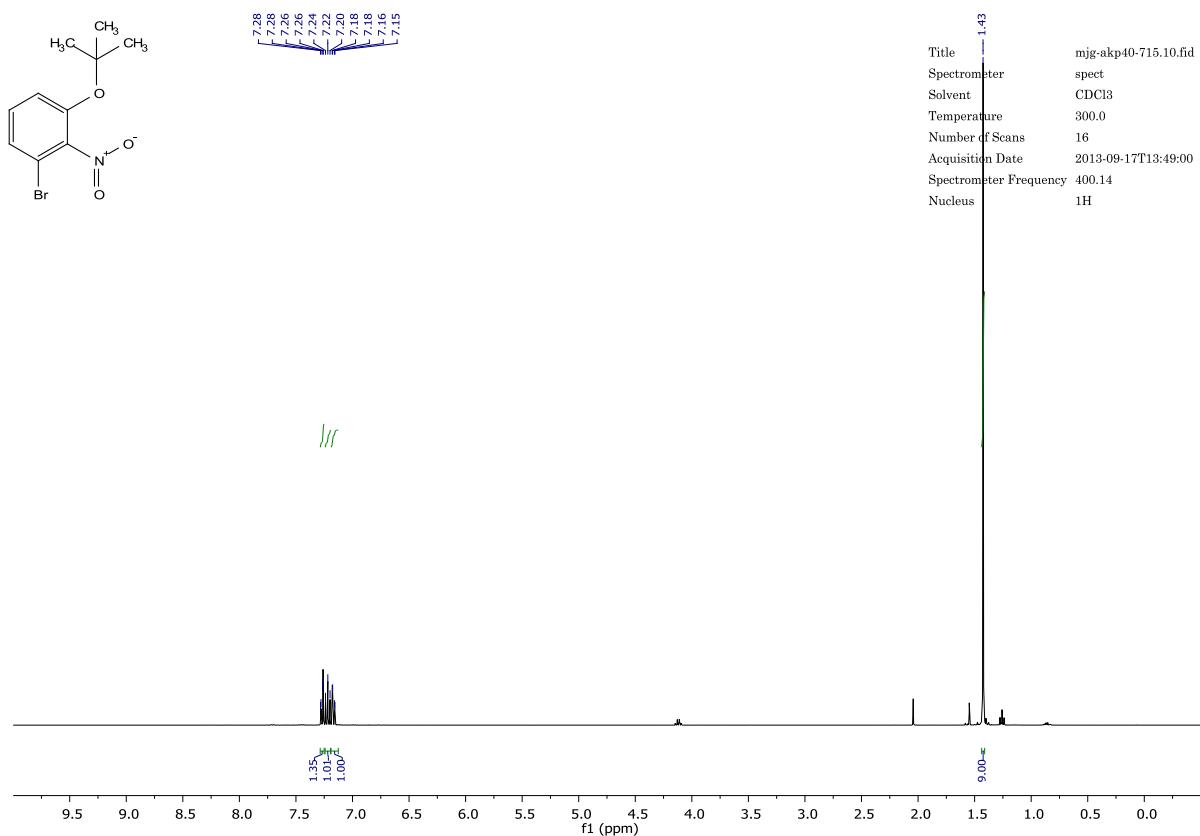
**N-(2-(benzyloxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (254)**



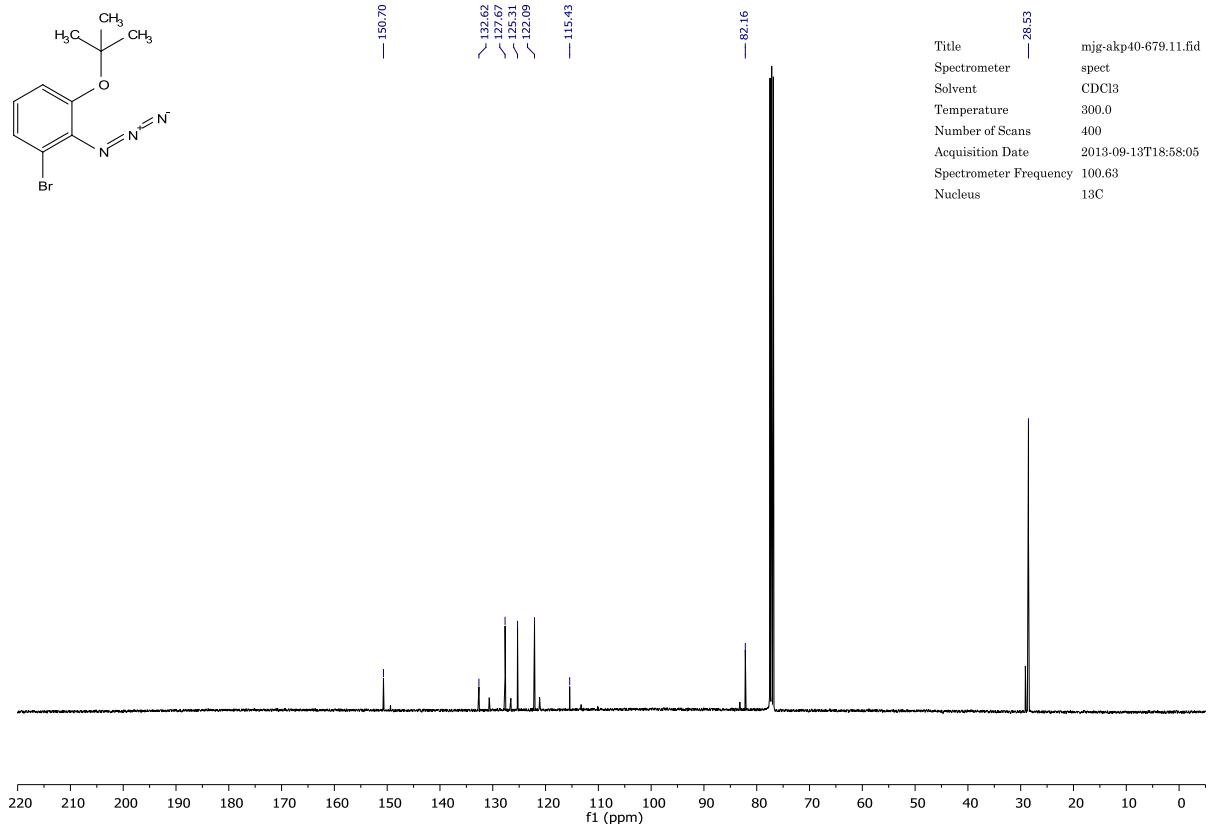
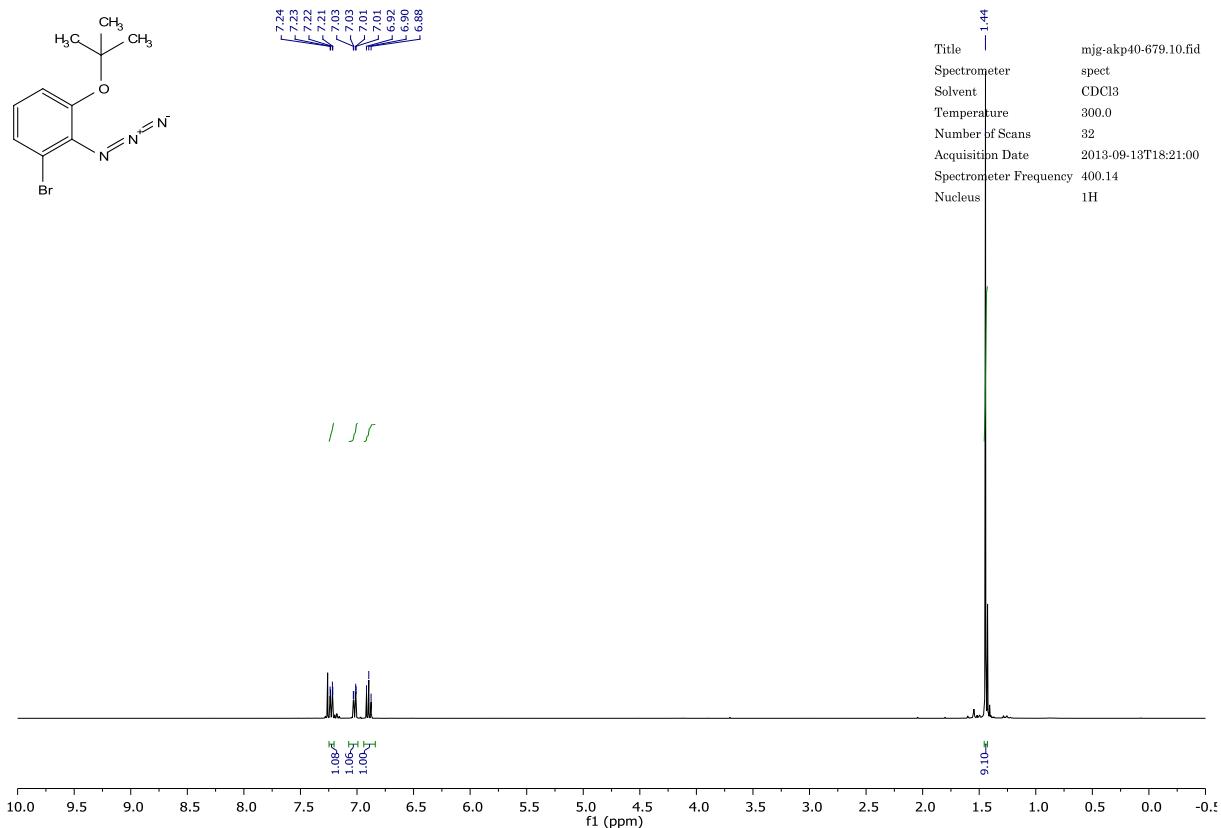
**N-(2-(benzyloxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-methylbenzenesulfonamide (314)**



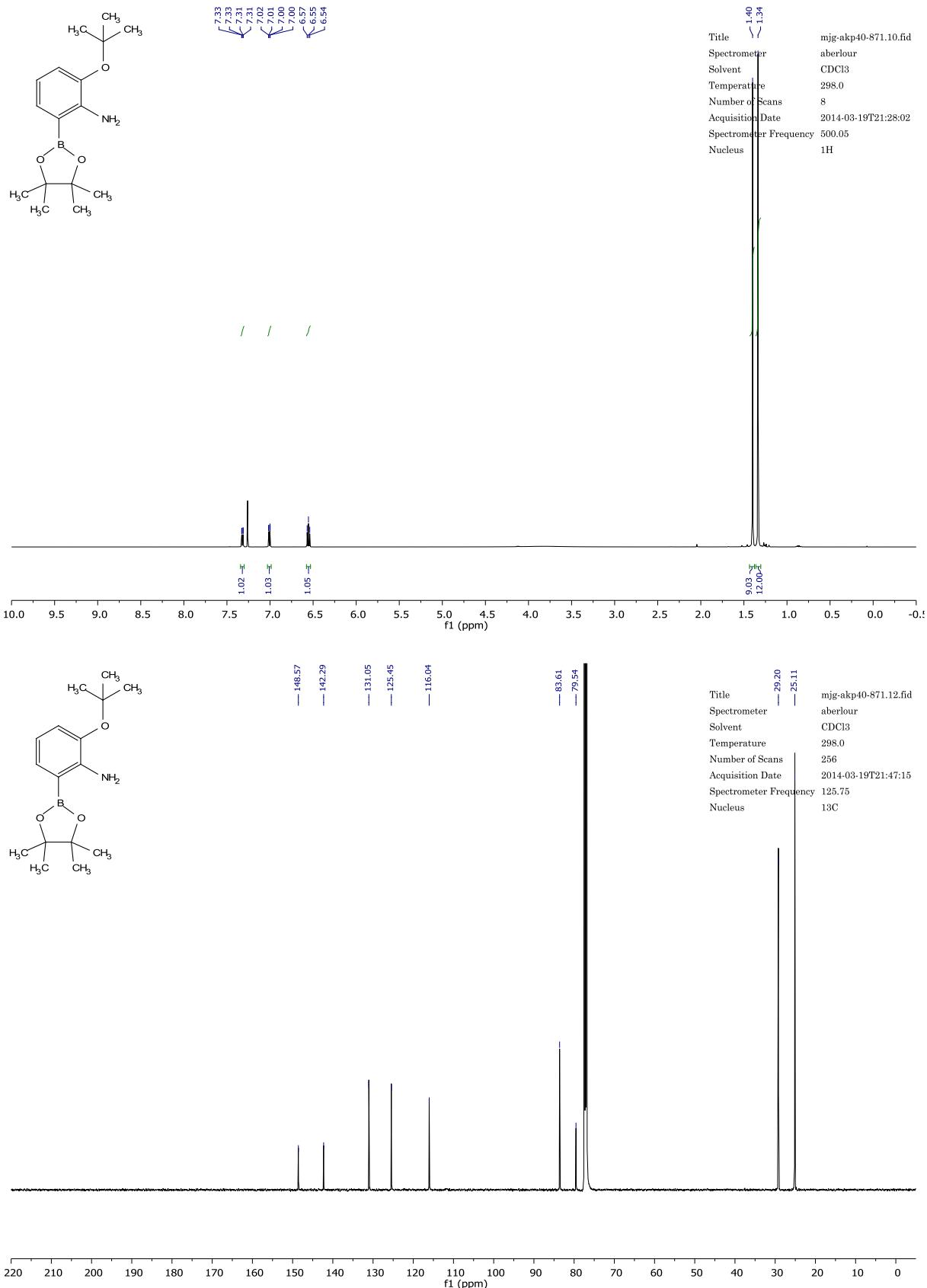
**1-bromo-3-(*tert*-butoxy)-2-nitrobenzene (300)**



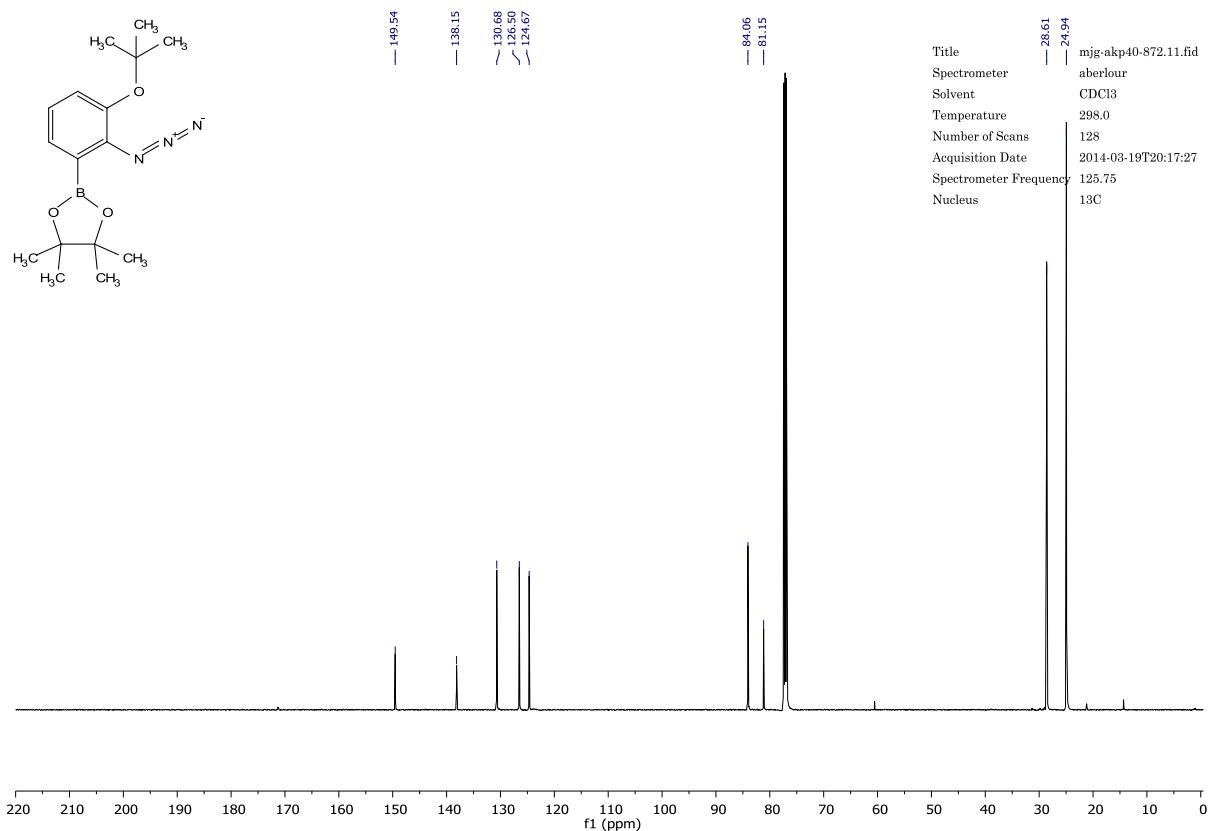
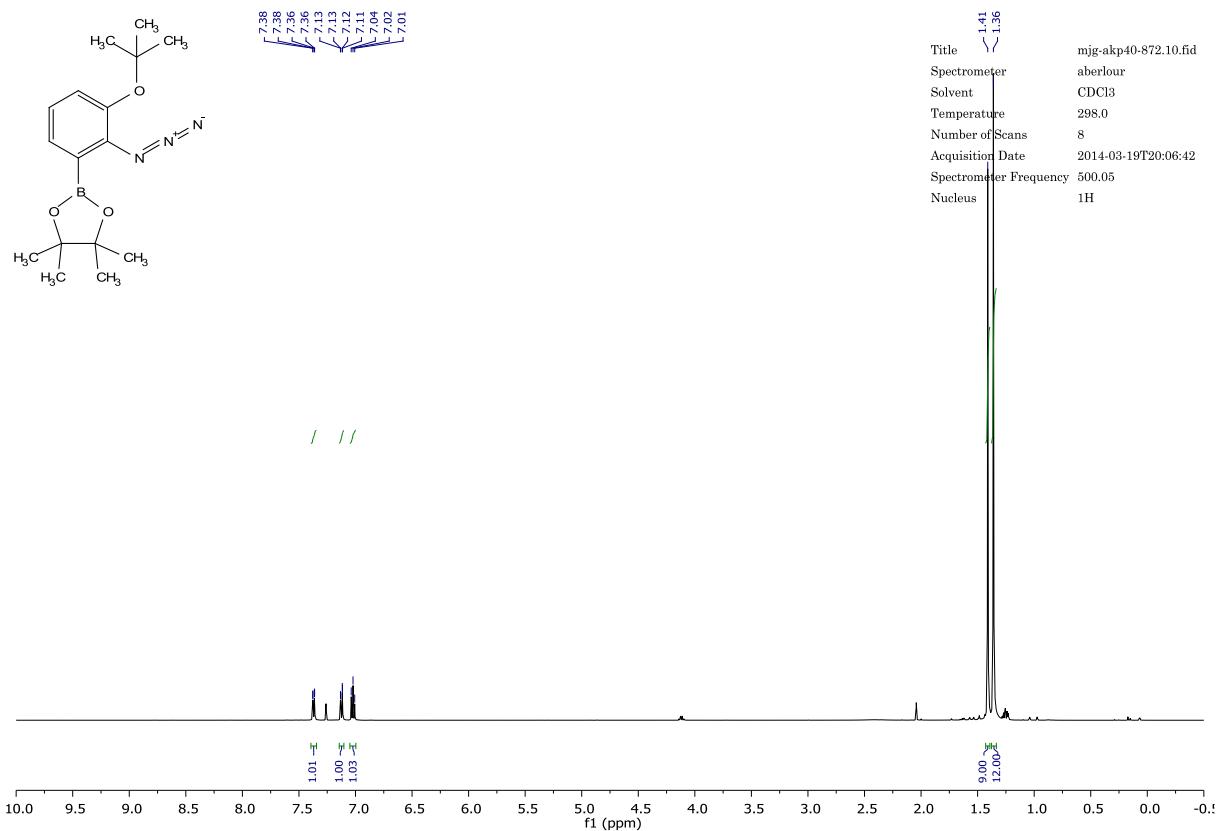
**2-azido-1-bromo-3-(*tert*-butoxy)benzene (391)**



**2-(*tert*-butoxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (313)**

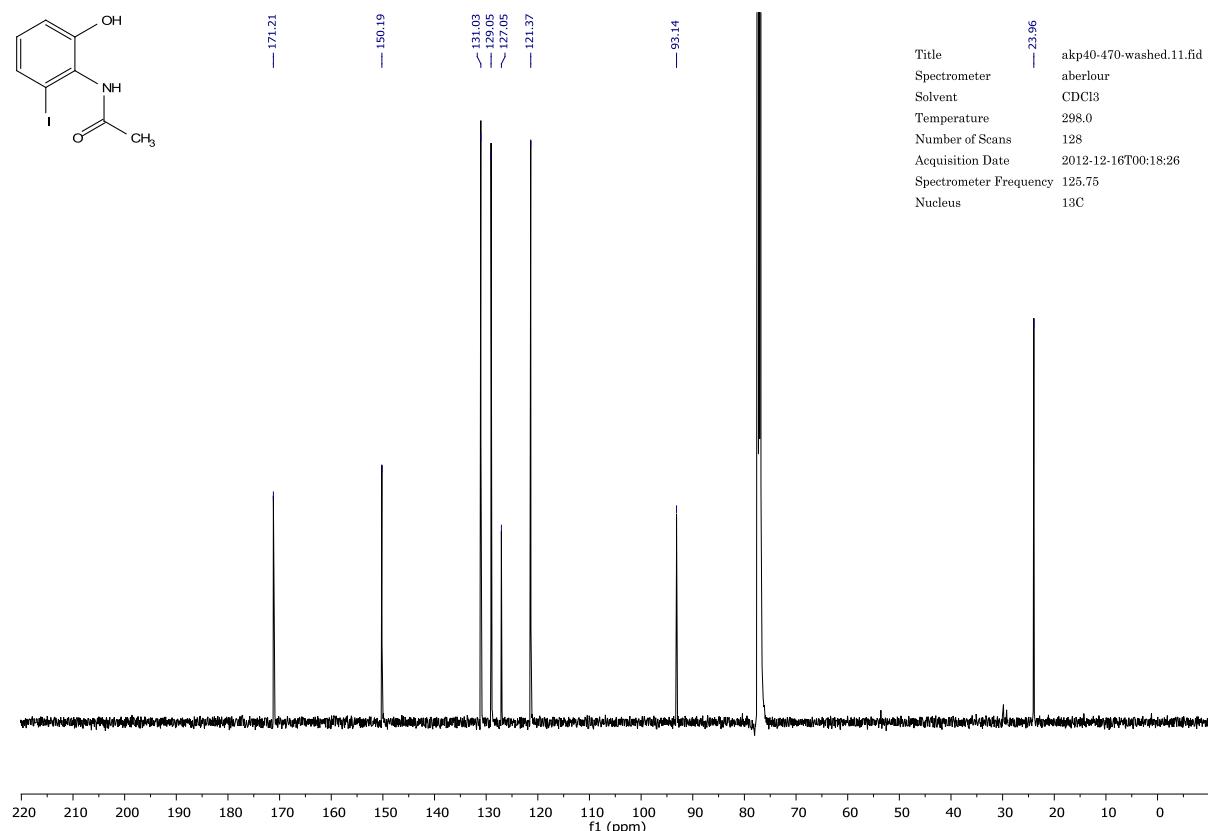
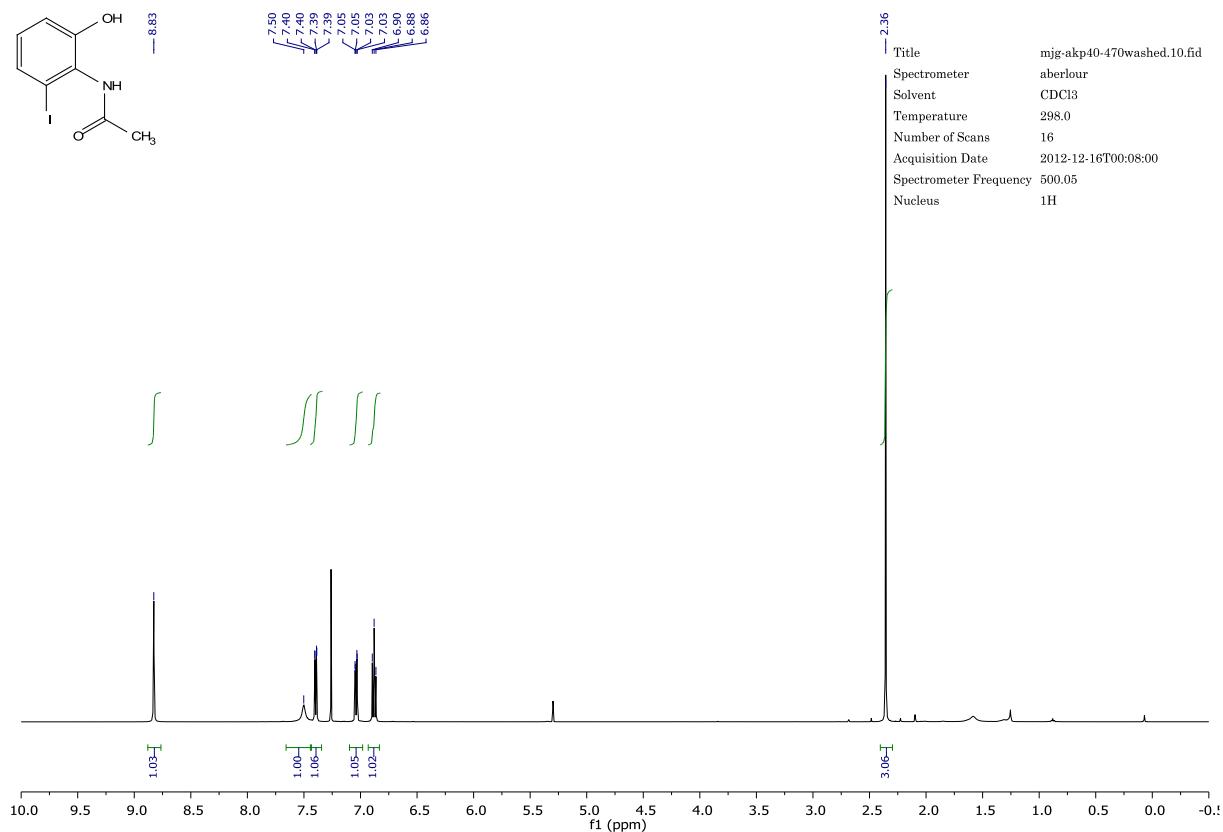


**2-(*tert*-butoxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (315)**

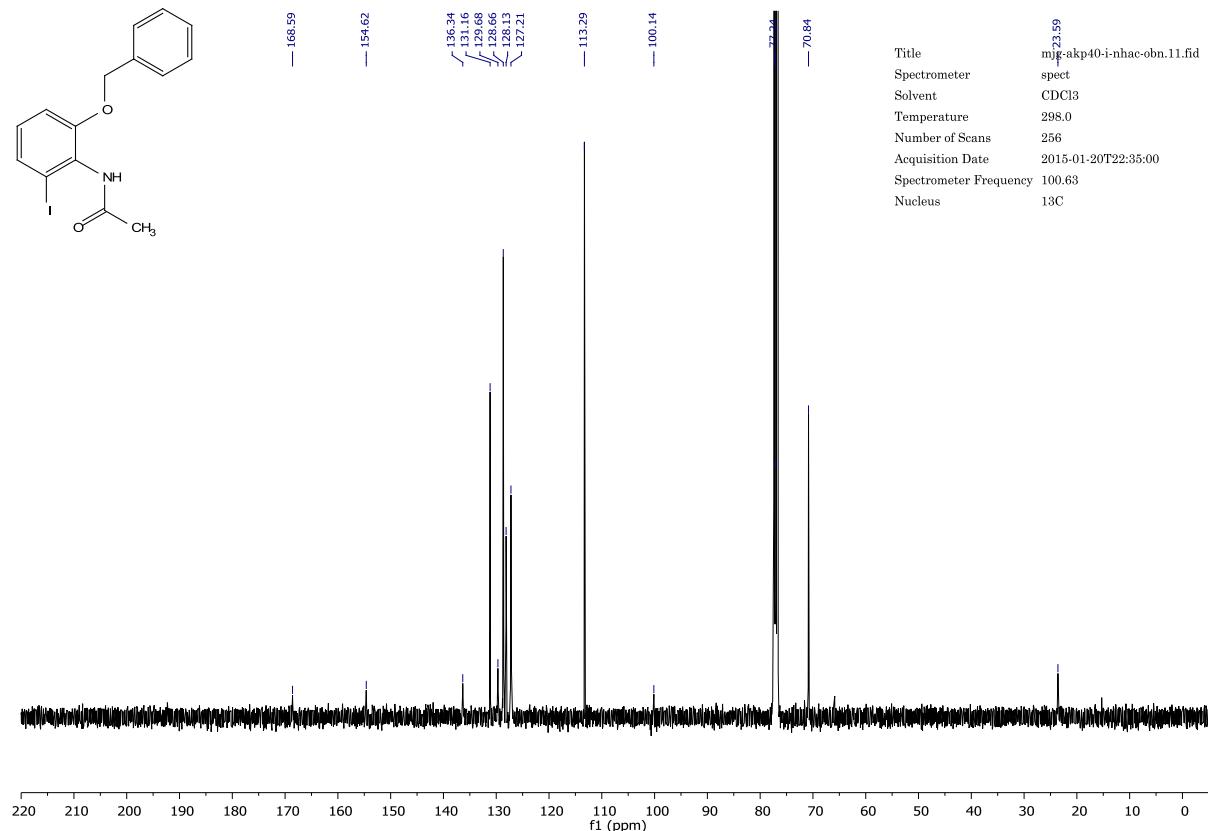
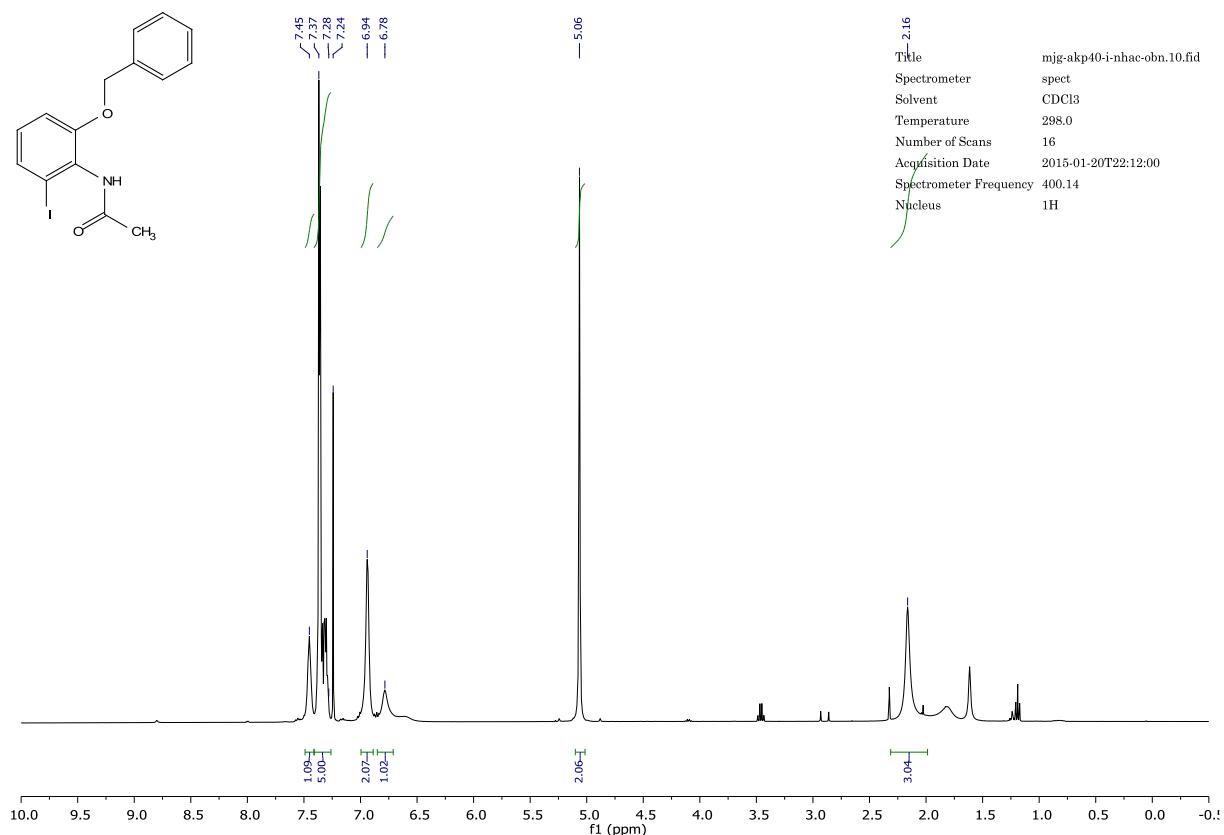


## 9.8 Iodoarenes

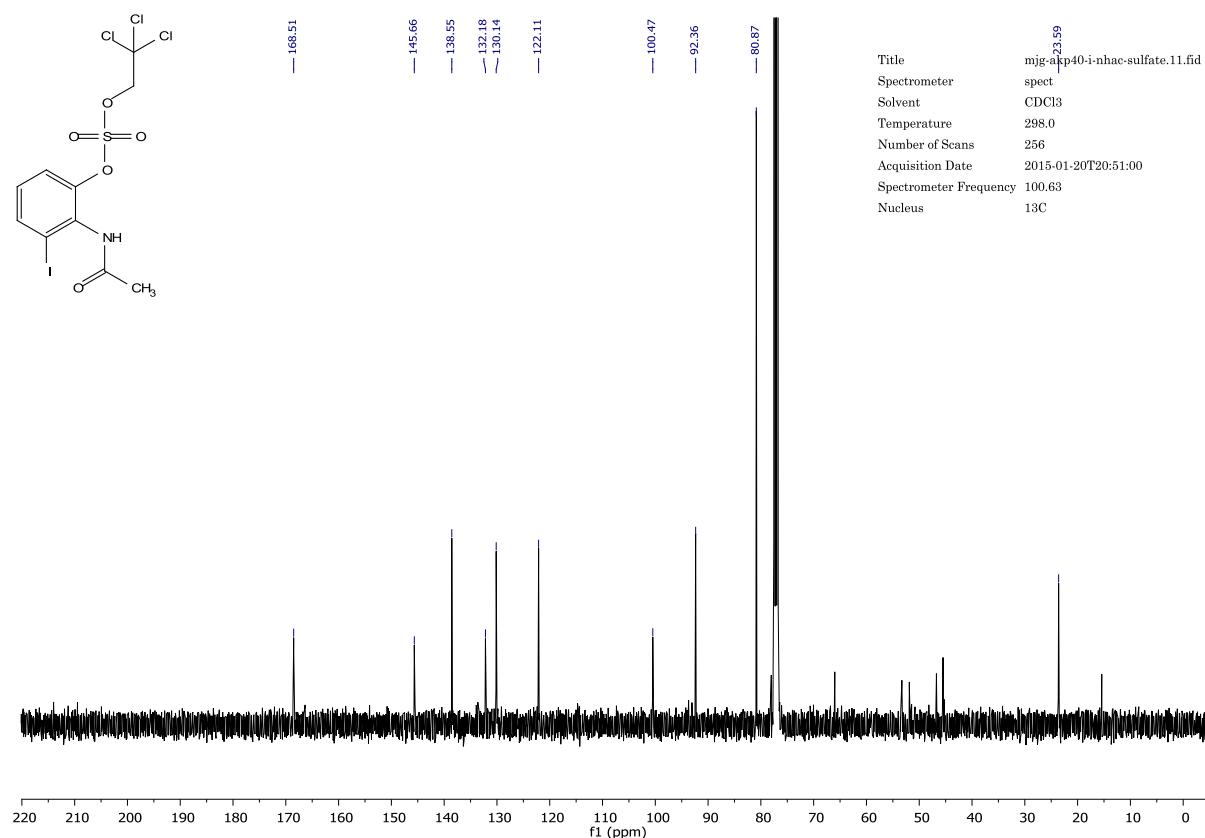
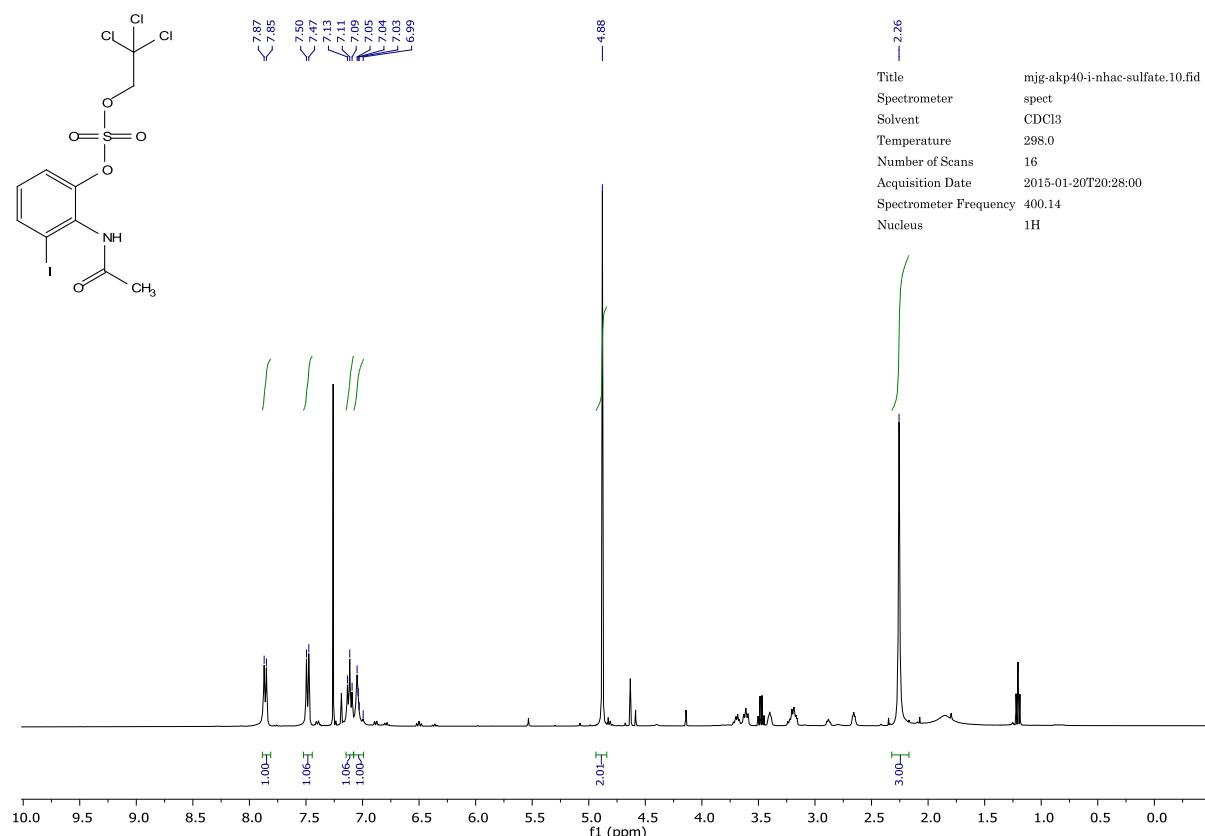
### *N*-(2-Hydroxy-6-iodophenyl)acetamide (346)



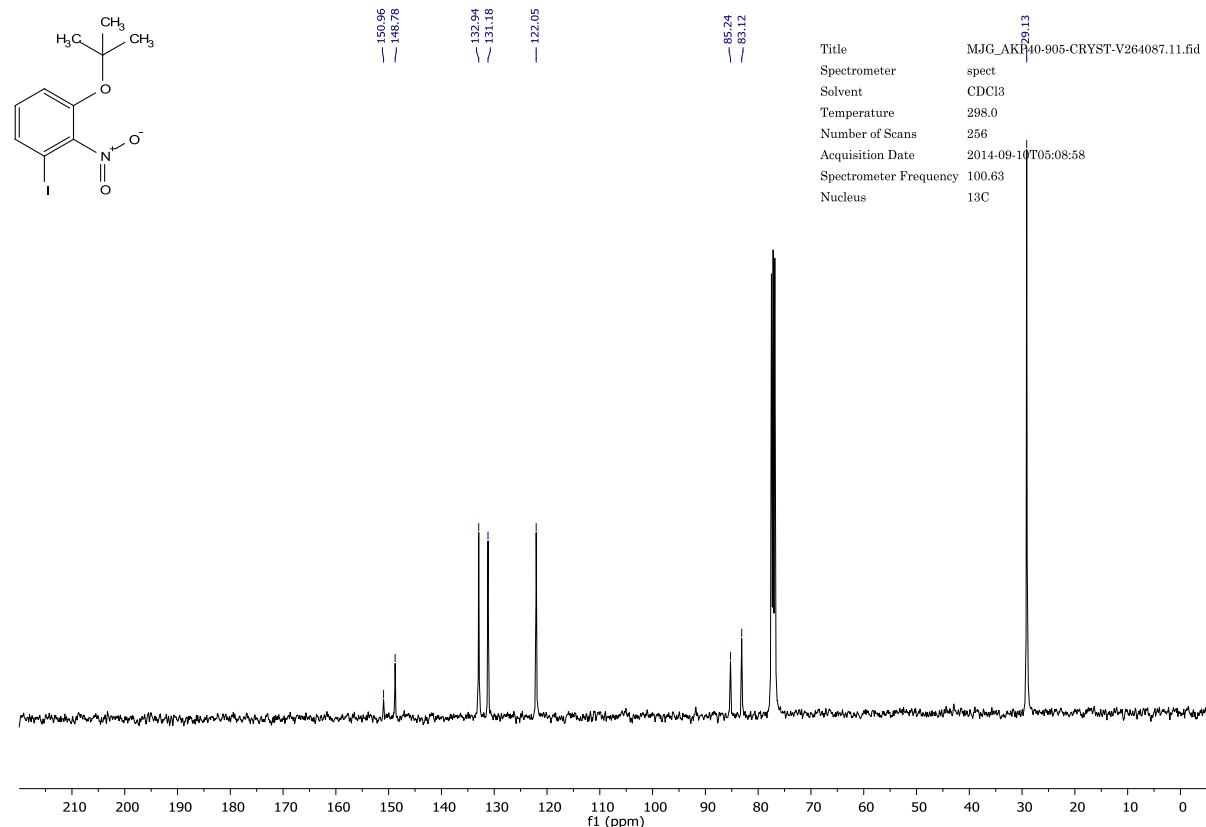
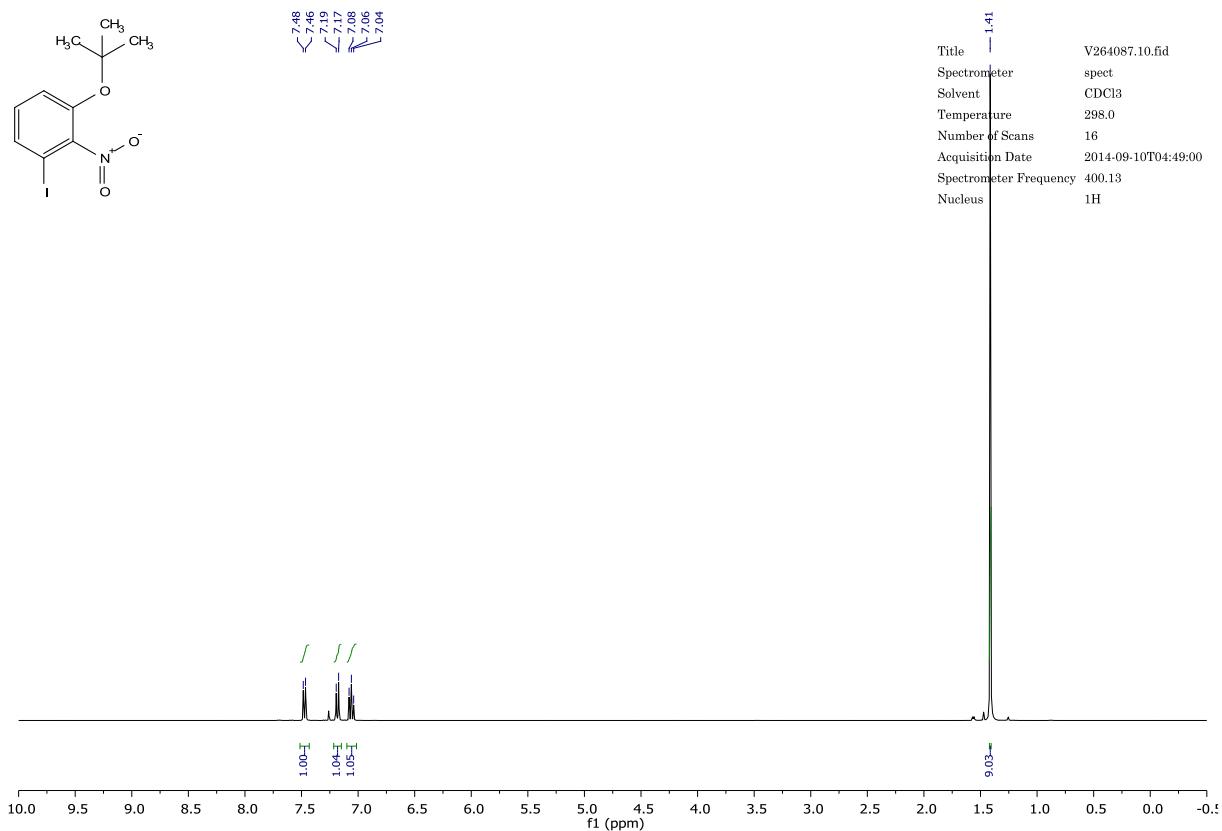
**N-(2-(BenzylOxy)-6-iodophenyl)acetamide (347)**



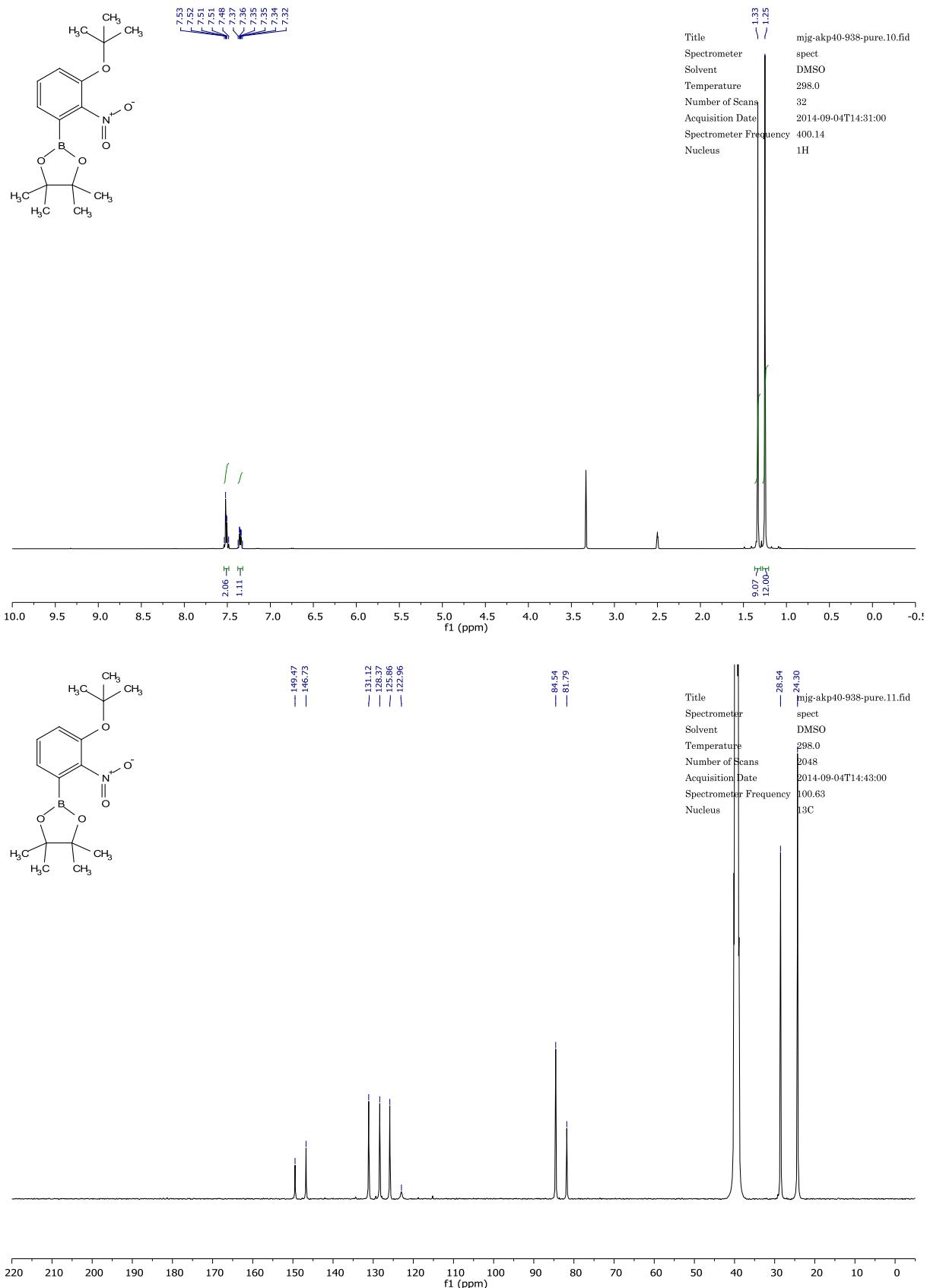
**2-Acetamido-3-iodophenyl (2,2,2-trichloroethyl) sulphate (288)**



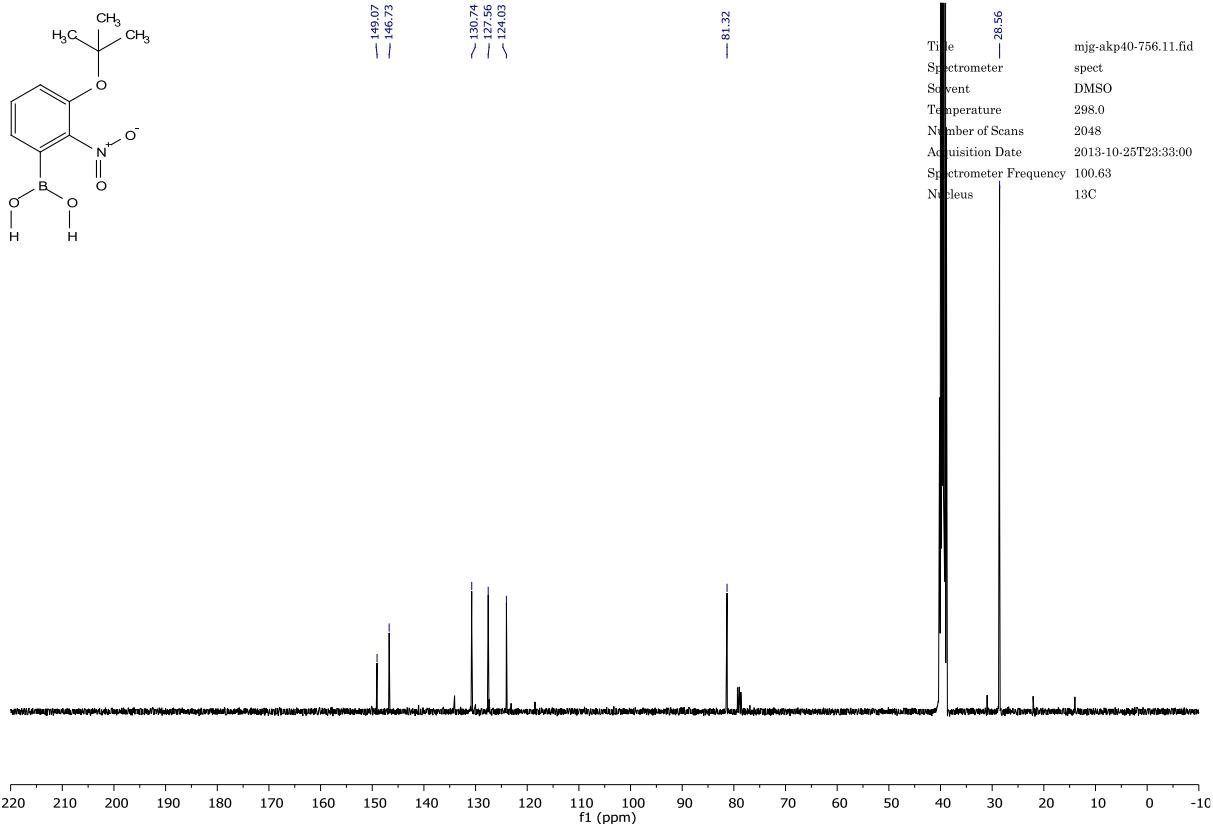
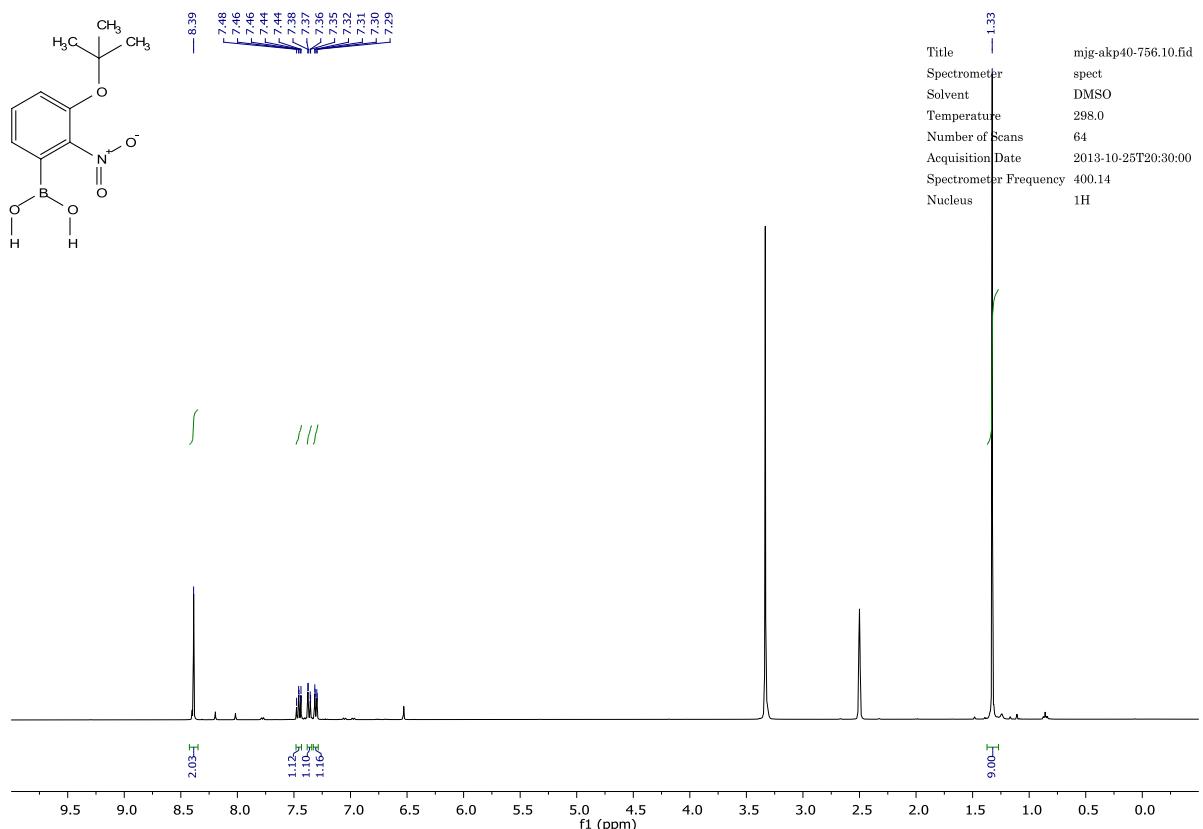
**1-(*tert*-butoxy)-3-iodo-2-nitrobenzene (301)**



**2-(3-(*tert*-butoxy)-2-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (302)**

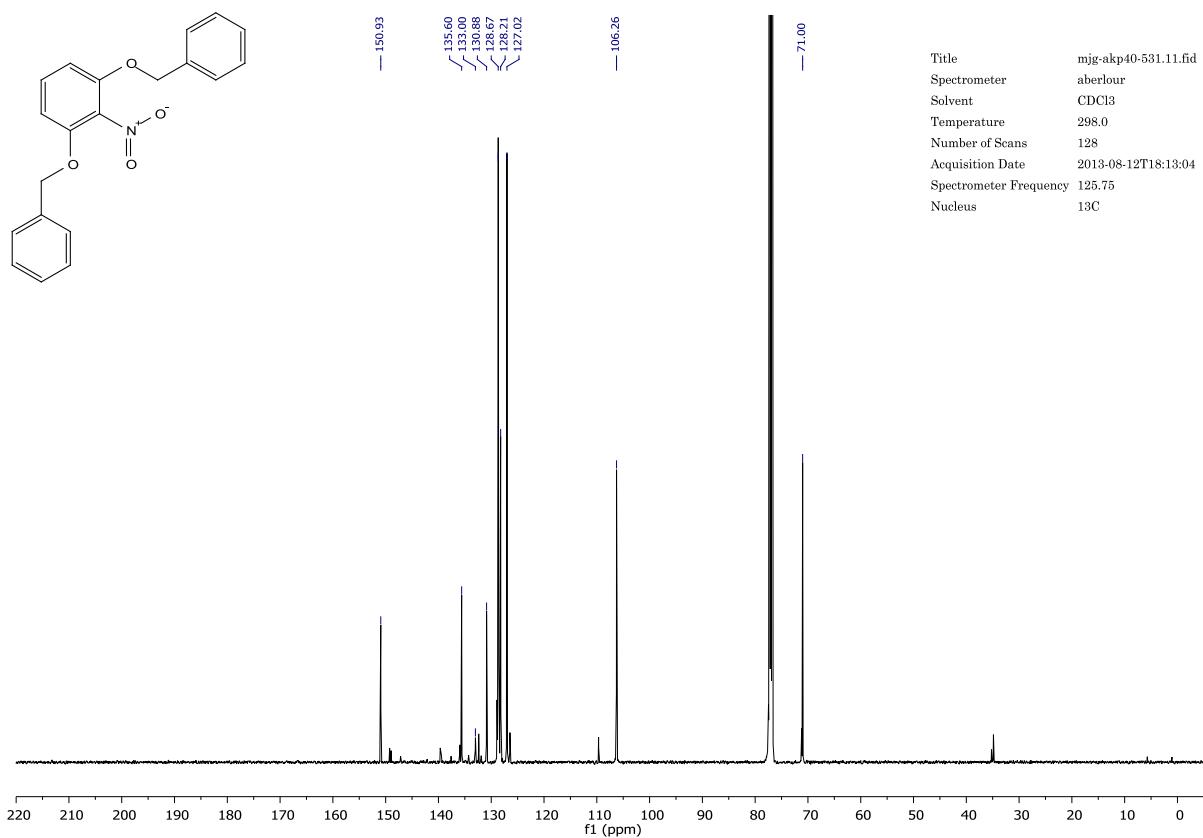
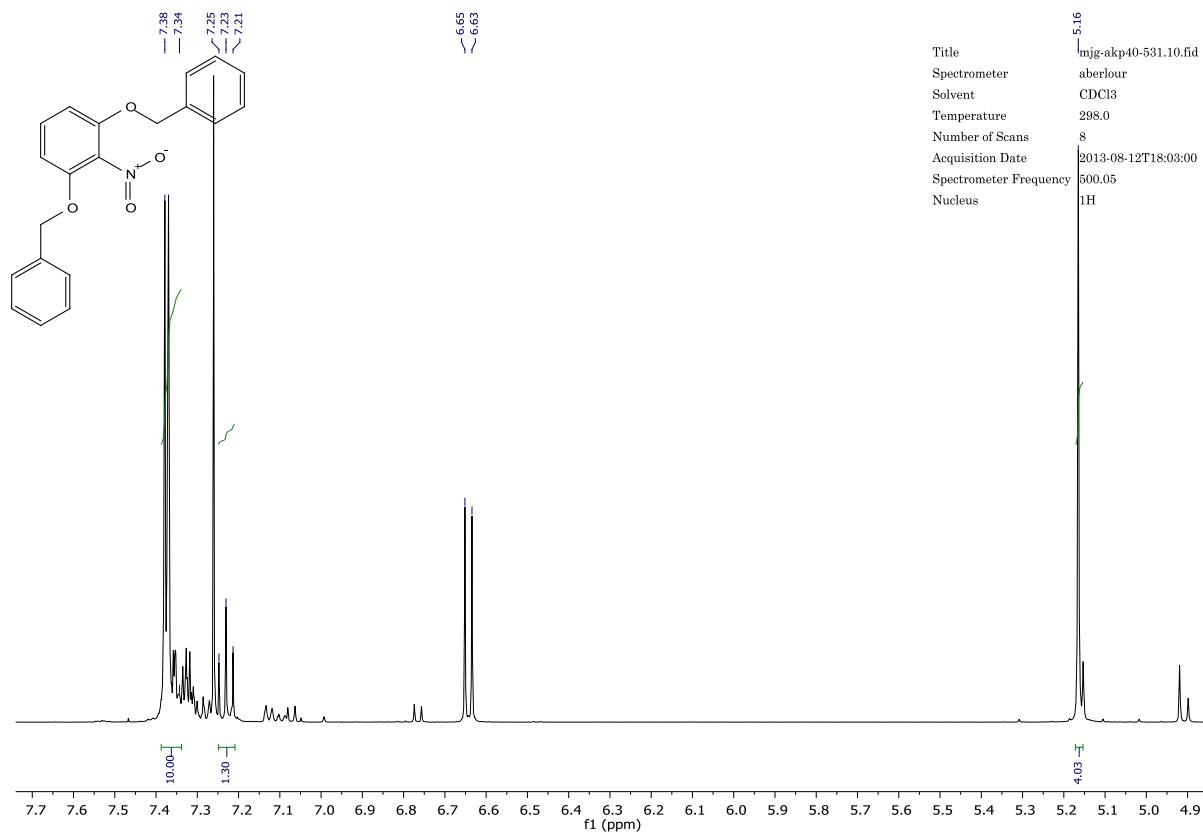


**(3-(*tert*-butoxy)-2-nitrophenyl)boronic acid (303)**

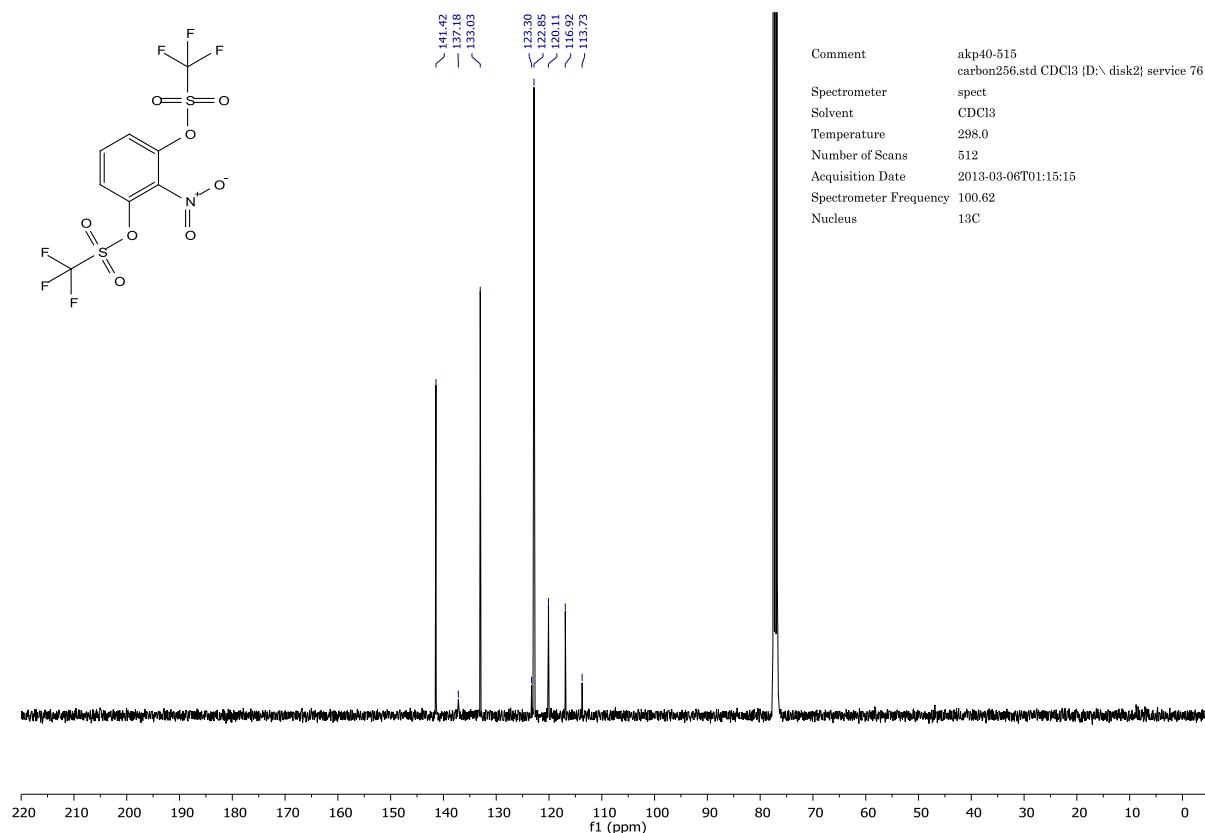
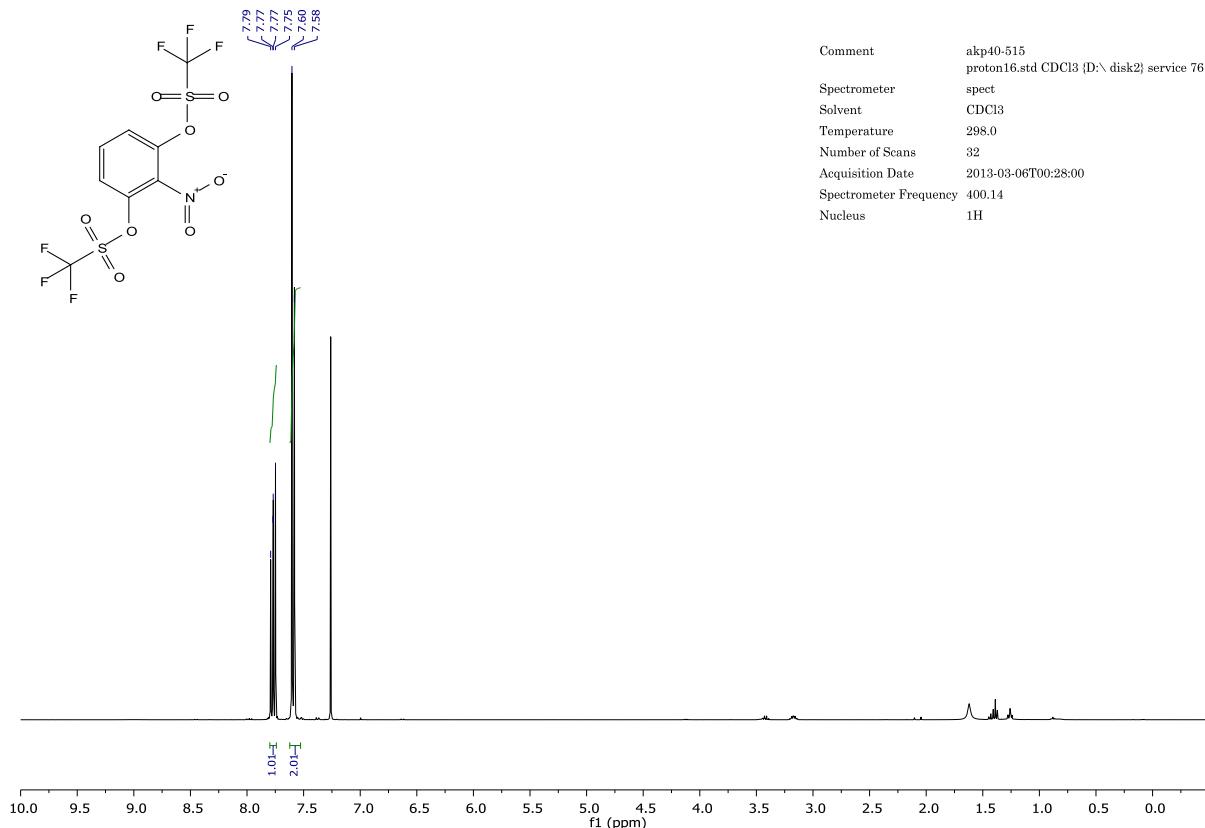


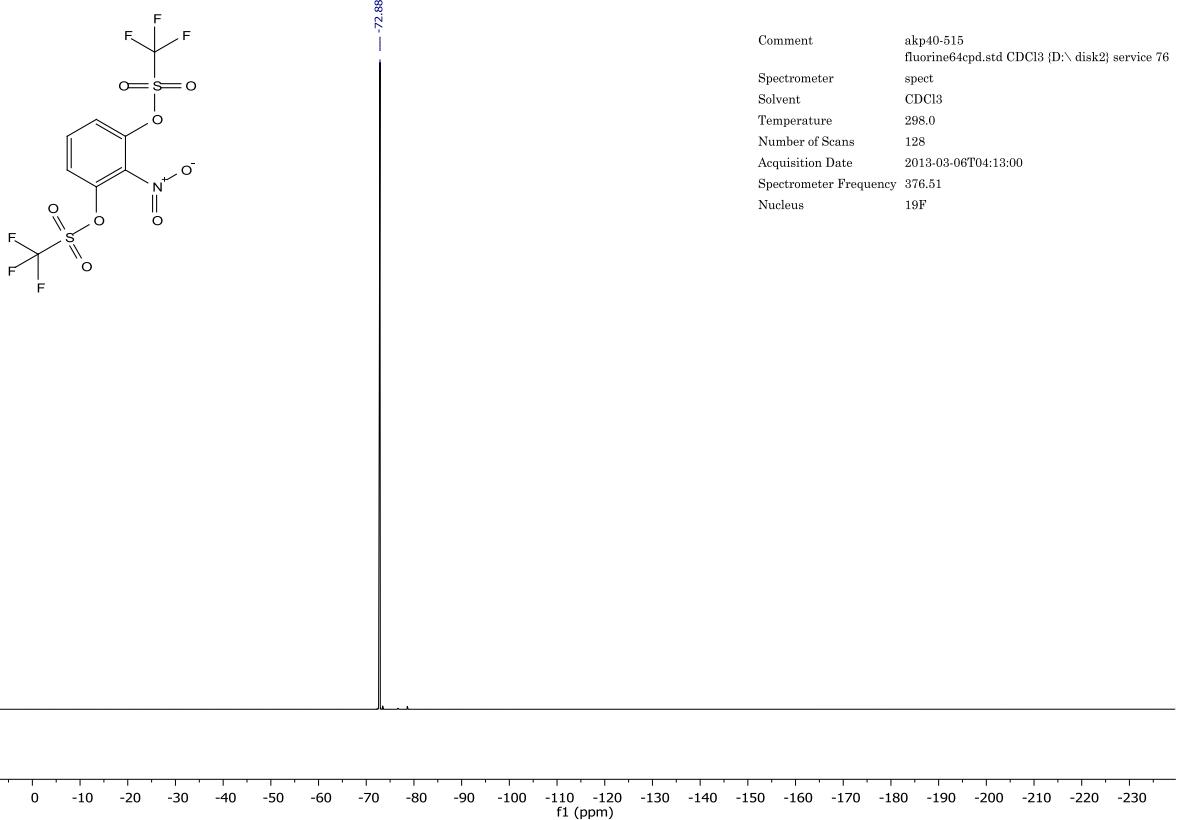
## 9.9 Aryl Triflates

### ((2-nitro-1,3-phenylene)bis(oxy))bis(methylene)dibenzene (317)

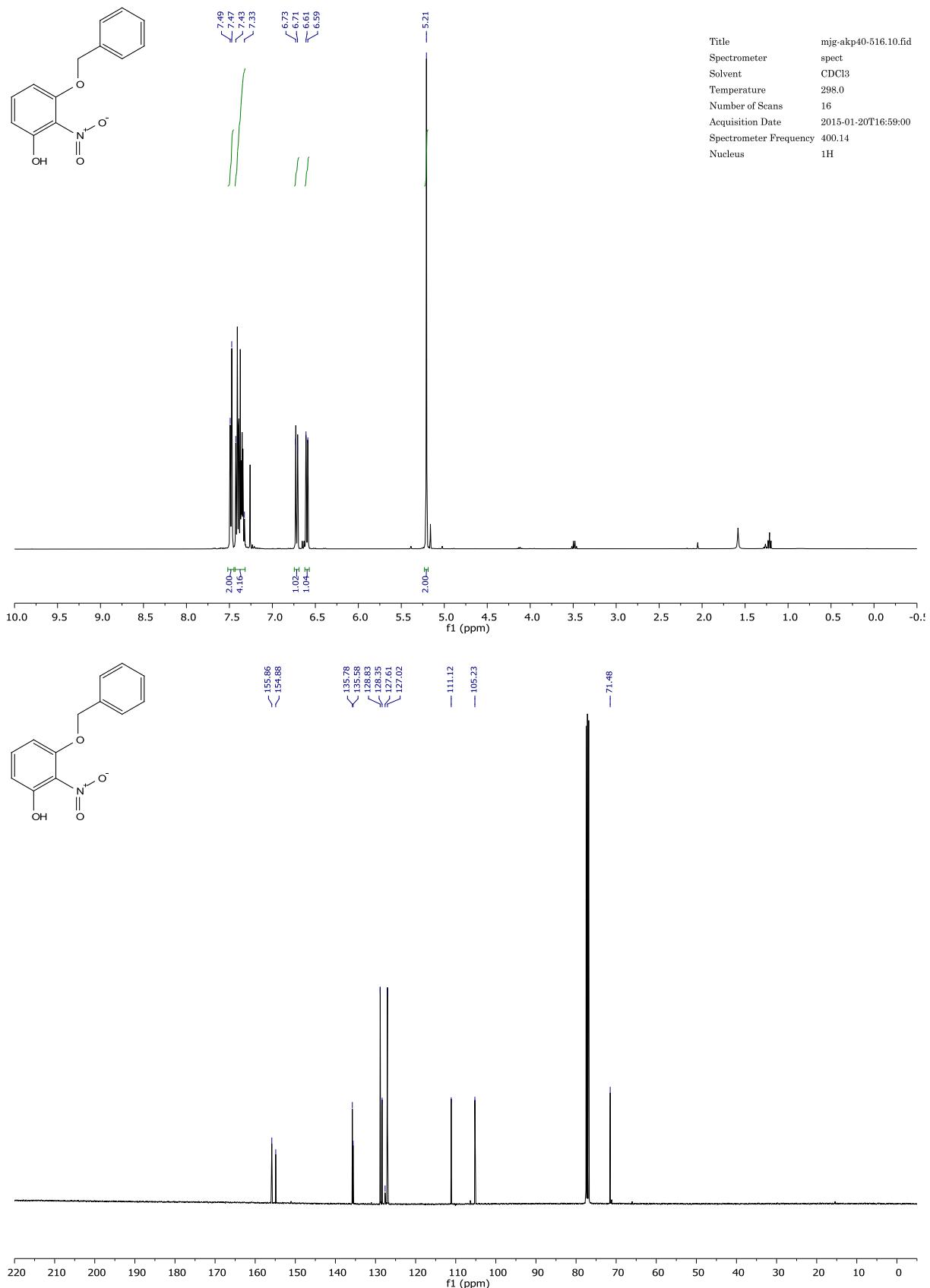


**2-nitro-1,3-phenylene bis(trifluoromethanesulfonate) (318)**

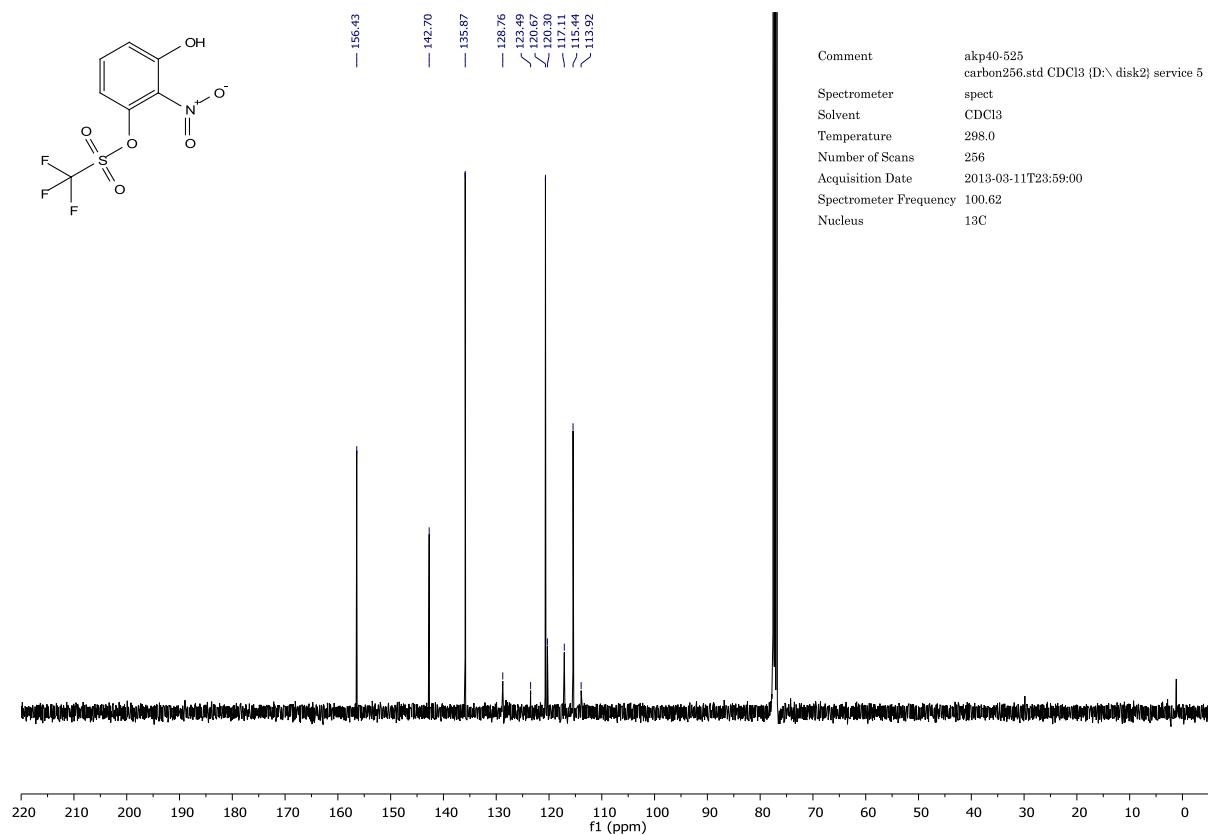
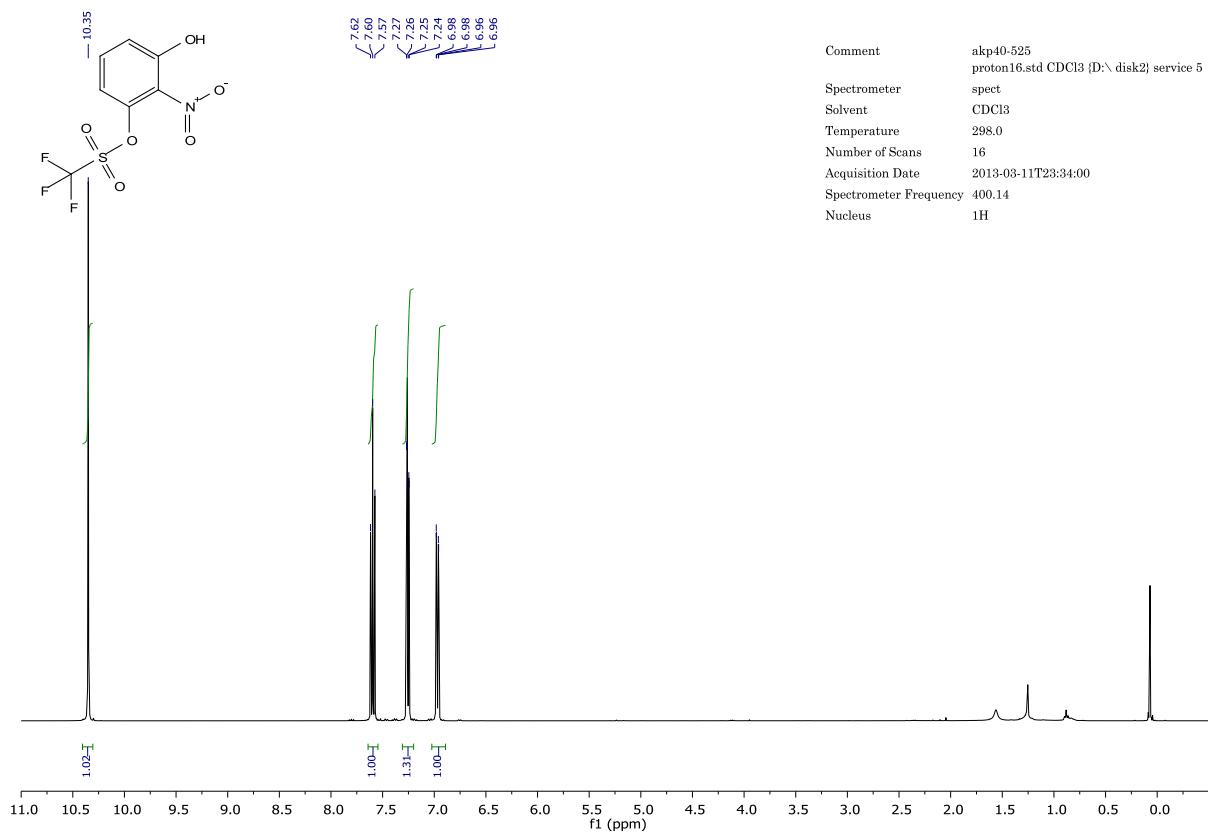


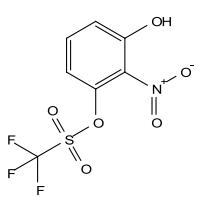


**3-(benzyloxy)-2-nitrophenol (319)**



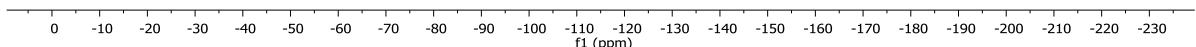
**3-hydroxy-2-nitrophenyl trifluoromethanesulfonate (320)**



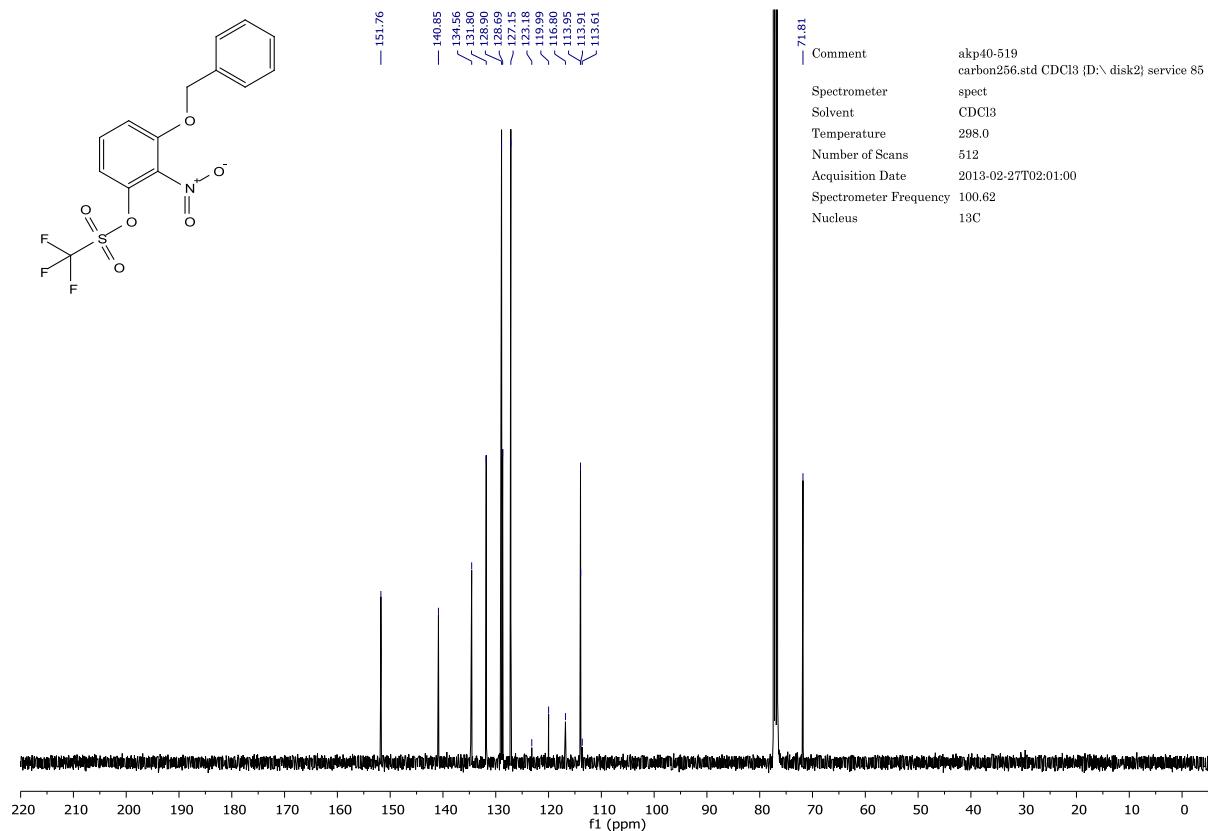
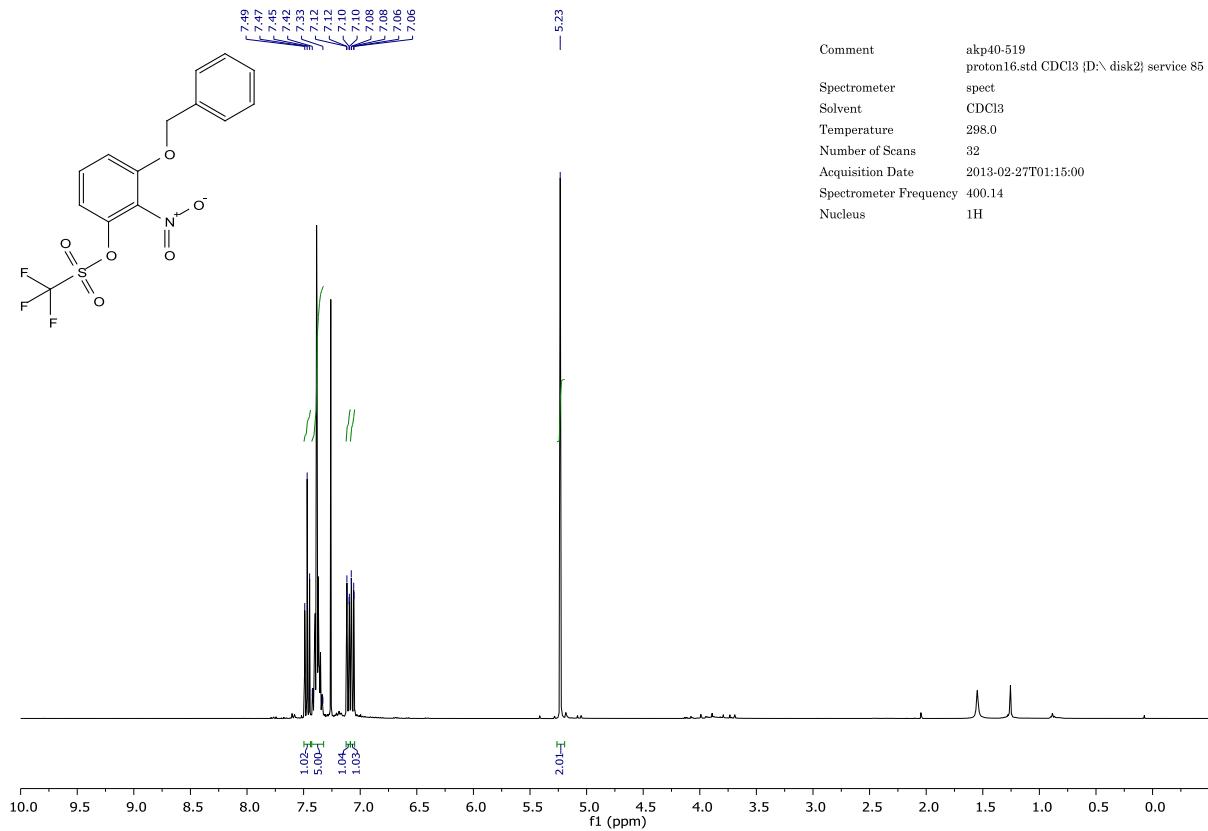


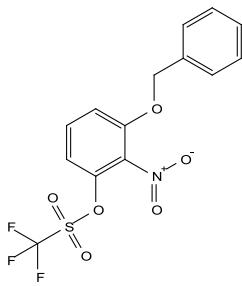
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Nucleus 19F



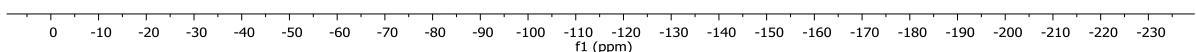
**3-(benzyloxy)-2-nitrophenyl trifluoromethanesulfonate (321)**



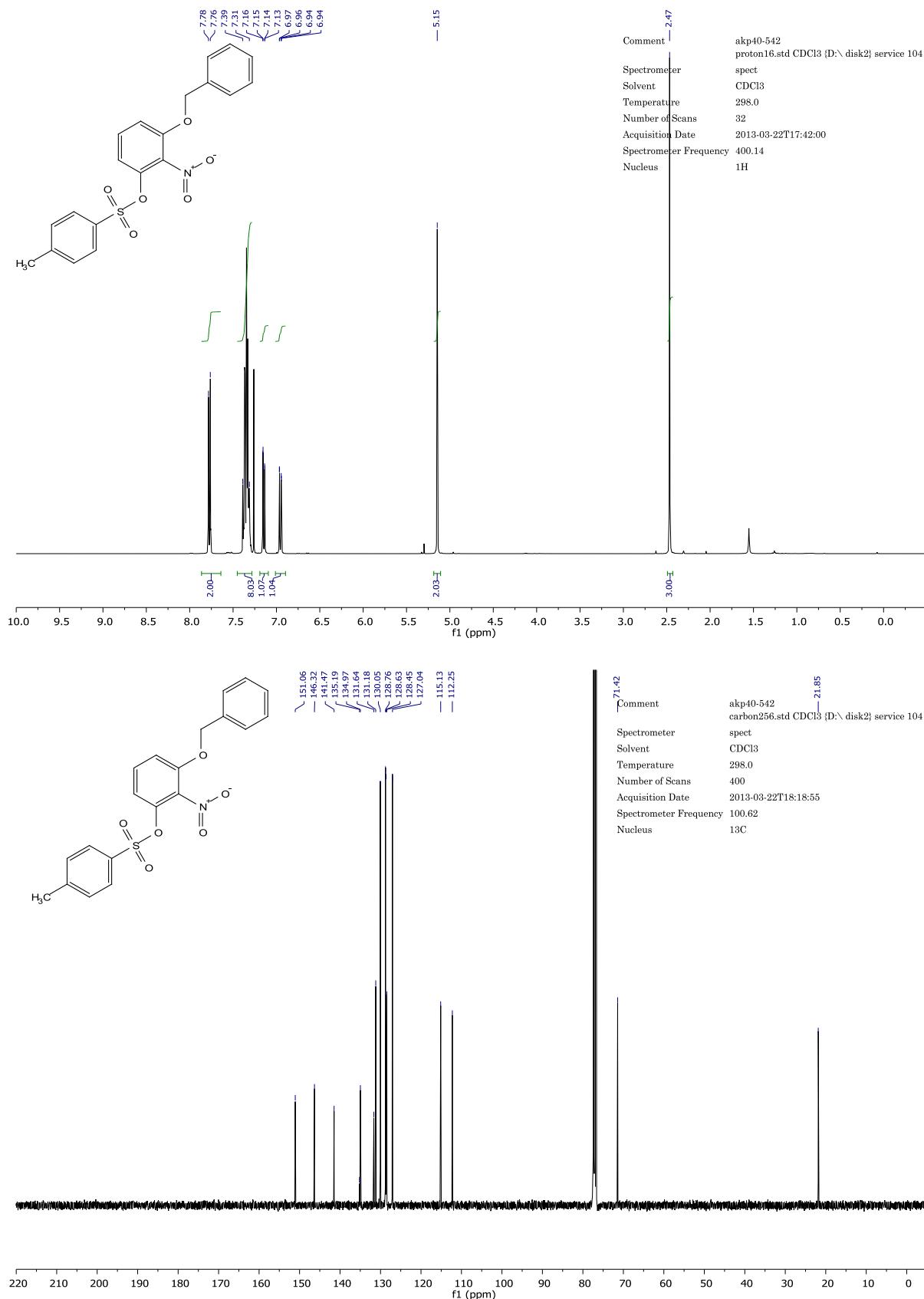


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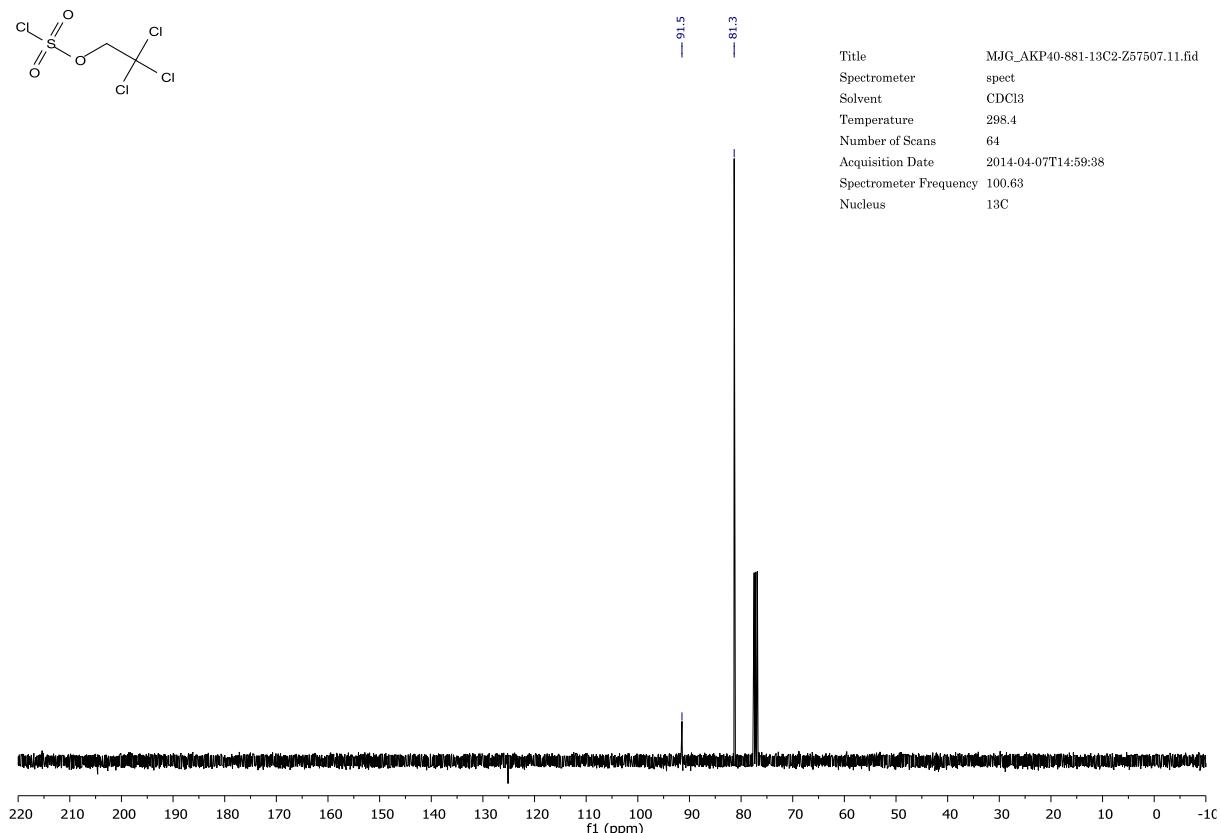
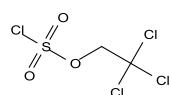
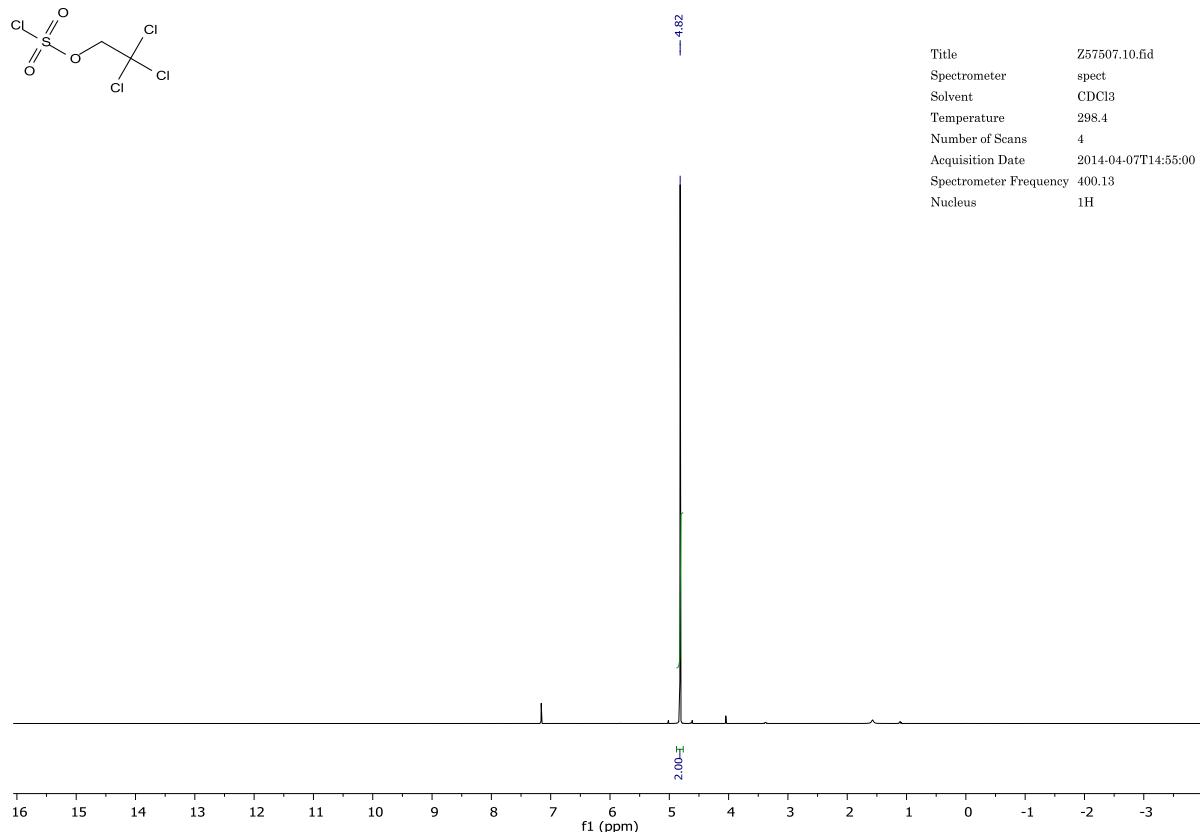
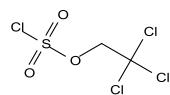


**3-(benzyloxy)-2-nitrophenyl 4-methylbenzenesulfonate (322)**

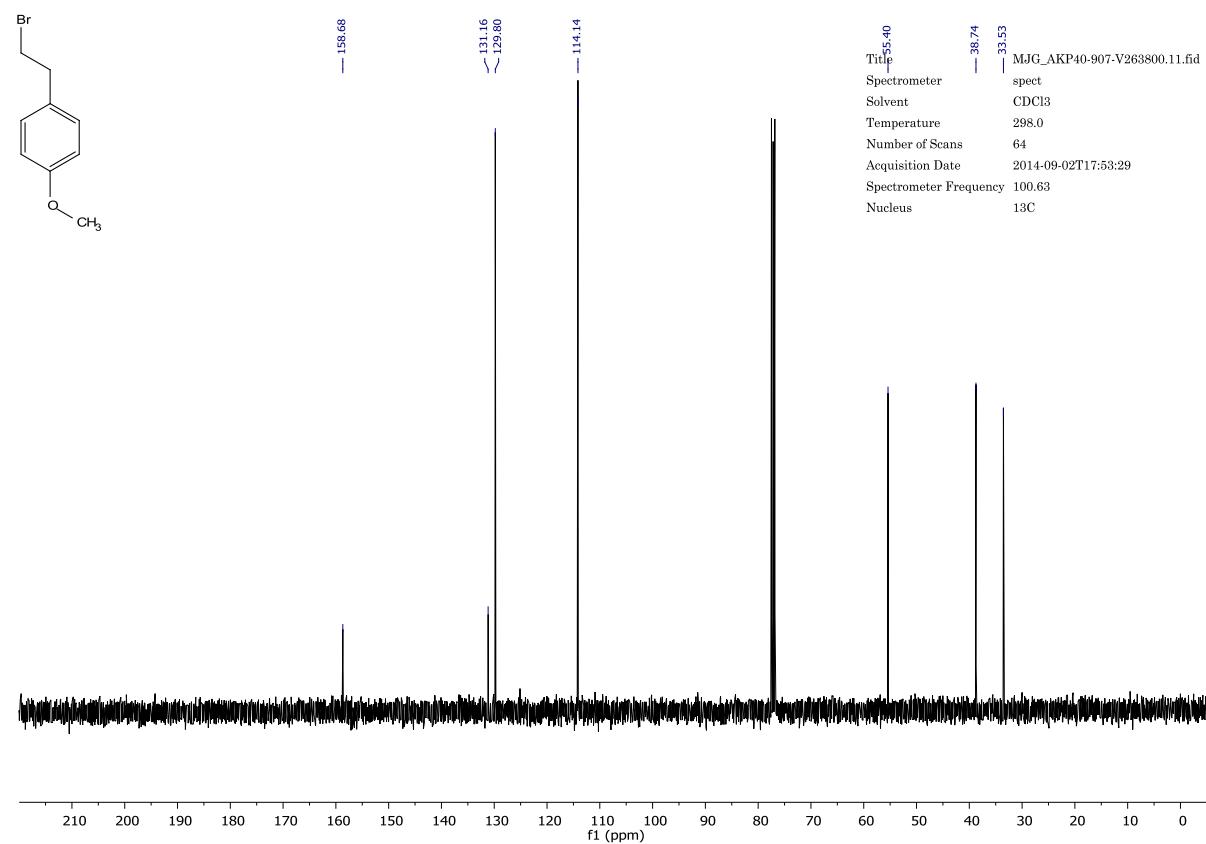
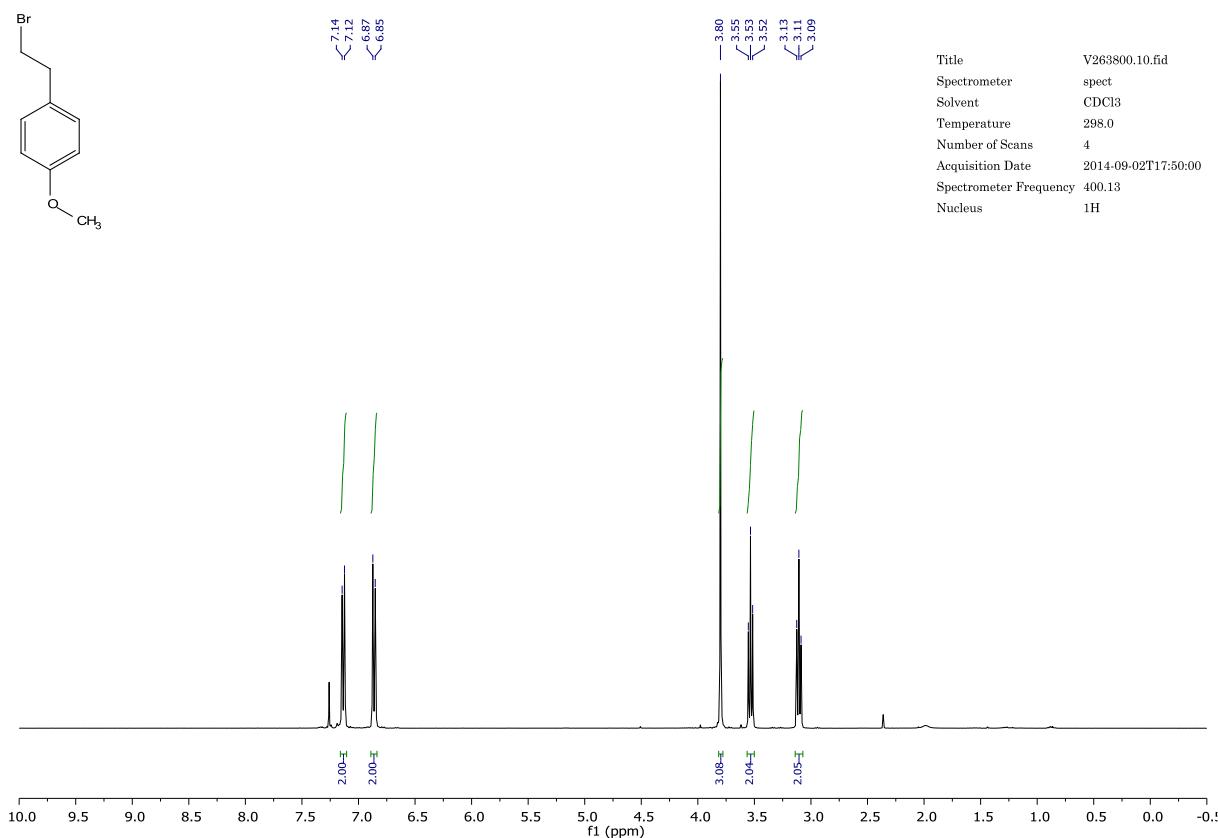


## 9.10 Miscellaneous

### 2,2,2-Trichloroethyl sulfurochloridate (392)



**1-(2-bromoethyl)-4-methoxybenzene (159)**



## **APPENDIX A: PUBLICATIONS**



## A Concise and Scalable Strategy for the Total Synthesis of Dictyodendrin B Based on Sequential C–H Functionalization\*\*

Andrew K. Pitts, Fionn O'Hara, Robert H. Snell, and Matthew J. Gaunt\*

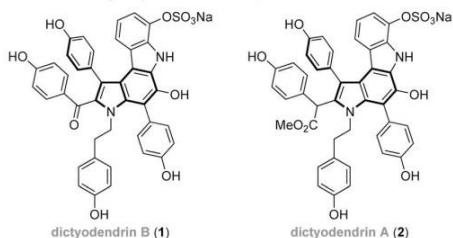
**Abstract:** A sequential C–H functionalization strategy for the synthesis of the marine alkaloid dictyodendrin B is reported. Our synthesis begins from commercially available 4-bromoindole and involves six direct functionalizations around the heteroarene core as part of a gram-scale strategy towards the natural product.

The dictyodendrins are a collection of pyrrolo[2,3-*c*]-carbazole-derived natural products, first isolated in 2003,<sup>[1]</sup> that display interesting inhibitory activities towards telomerasers<sup>[2]</sup> and β-site APP cleaving enzyme 1 (BACE1; APP = amyloid precursor protein) and have received significant interest within the scientific community owing their potential as chemotherapy agents and neurodegenerative probes.<sup>[3]</sup> Furthermore, their complex poly(hetero)aromatic architecture has inspired number of elegant total syntheses from the groups of Fürstner,<sup>[4a–c]</sup> Iwao and Ishibashi,<sup>[4d–e]</sup> Tokuyama,<sup>[4f–g]</sup> and Jia.<sup>[4h–i]</sup> We envisaged a possible strategy to the dictyodendrins that involves sequential direct functionalizations of a simple, readily available heteroaromatic building block that would constitute the core of the natural product framework. Herein, we report a concise total synthesis of dictyodendrin B starting from a commercially available mono-substituted indole. Our strategy exploits selective reactions at each of the positions on the unfunctionalized heteroaromatic scaffold to consecutively add the architecture required for the natural product and enables the gram-scale synthesis of this biologically interesting natural product.

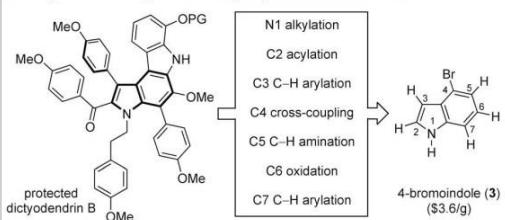
The development of new methods that enable the direct transformation of C–H bonds into useful functional groups remains an important goal for the continued advance of complex-molecule synthesis.<sup>[5,6]</sup> Our group has a long-standing interest in the metal-catalyzed C–H functionalization of

aromatic heterocycles<sup>[7]</sup> and the deployment of these methods in the total synthesis of complex molecules.<sup>[8]</sup> A central theme in these strategies has been the exploitation of latent reactivity within simple, readily available, and relatively unfunctionalized heteroaromatic starting materials to streamline the assembly of the framework of the target natural products.

The indole-containing dictyodendrin natural products



Total synthesis of dictyodendrin B by sequential direct functionalization



In considering a strategy for the synthesis of dictyodendrin B, we were attracted by a heptasubstituted indole embedded within the core of these complex aromatic molecules. We speculated that a simple indole building block could form the starting point for a strategy that would involve sequential direct functionalizations to append each of the seven substituents around the heteroaromatic framework. This strategy is distinct from all other approaches to this molecule as these elegant syntheses involved the construction of the central indole motif from elaborated fragments.<sup>[4]</sup> Such a sequential functionalization of a central heteroaromatic scaffold could have a number of advantages: A wide range of readily available and functionally simple hydrocarbon building blocks would be effective starting materials, syntheses would be streamlined, and the preparation of analogues for biological assessment would be greatly facilitated. We were, however, mindful of at least two major challenges that could arise from such a design plan: First, direct functionalization of

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\*\* We are grateful to AstraZeneca, Pfizer, and the EPSRC (A.K.P., F.O., R.H.S., and M.J.G.) and the ERC (M.J.G.) for fellowships. Mass spectrometry data were acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University. X-ray crystallography data was collected and solved by Peter D. Matthews. We are grateful to Phillip Murray and Prof. Steven V. Ley for assistance with and advice on flow chemistry. We also acknowledge Dr. Johan Kajanus (AstraZeneca) and Dr. Abid Massood (Pfizer) for useful discussions.

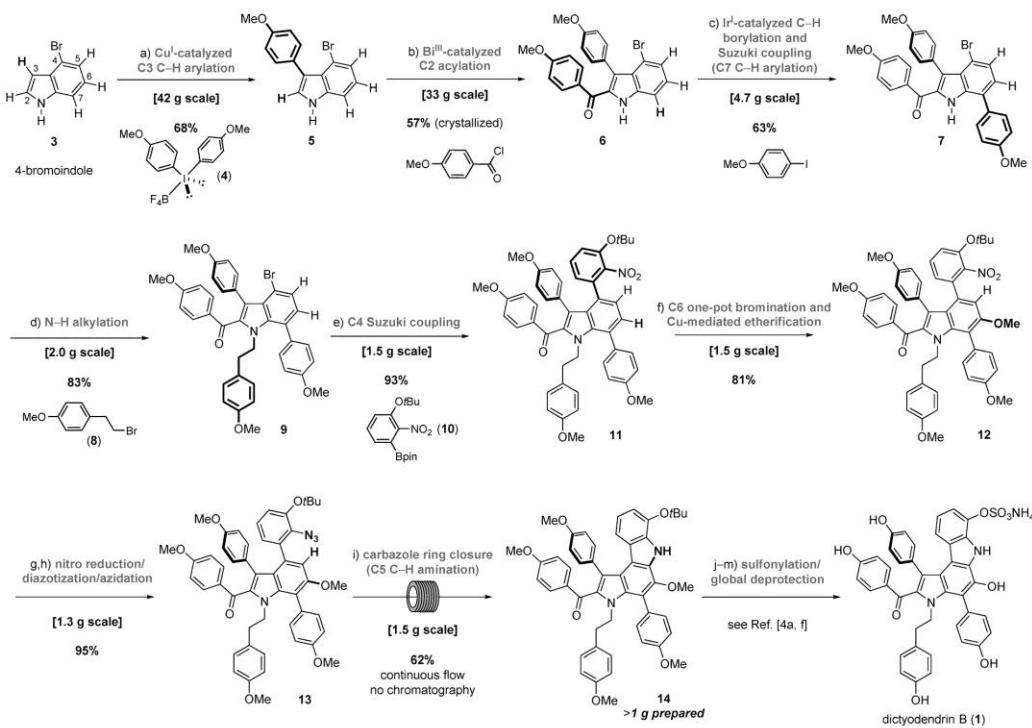
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201500067>.

the heteroaromatic core is likely to become increasingly difficult with every step owing to the growing complexity of the molecule,<sup>[9]</sup> and second, how does one choose the correct route from the many hypothetical sequences of iterative direct functionalizations on the indole core? By taking advantage of the broad range of distinct C–H functionalization processes that are available to us (metal-catalyzed C–H activation, electrophilic aromatic substitution, radical addition, and directed metalation), we reasoned that we would be well equipped to meet the ever-changing demands of the evolving molecule as the synthesis progressed. We elected to begin the synthesis of dictyodendrin B from commercially available 4-bromoindole and follow a strategy that would ultimately elaborate each position on the framework of this heteroaromatic starting material.

The inherent nucleophilicity of indole makes reactions through the C3 position an ideal starting point from which to execute our conceptually distinct approach to the synthesis of dictyodendrin B. Accordingly, our synthesis began with a copper-catalyzed C–H arylation using diaryliodonium

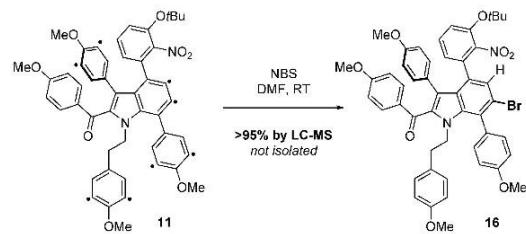
salt, which was established in our laboratory (Scheme 1).<sup>[10]</sup> Using conditions modified from our original work, we found that inexpensive Cu<sup>1</sup>Cl (5 mol %) functioned effectively as the catalyst to combine 4-bromoindole with bis(4-methoxyphenyl)iodonium tetrafluoroborate **4** (1.2 equiv) in 68% yield on 42 gram scale. Importantly, the 2,6-di-*tert*-butylpyridine base can be easily recovered from these large-scale reactions for reuse.

We were able to further exploit the intrinsic reactivity of indole for the C2 acylation. After significant experimentation, we found that a bismuth(III) triflate catalyzed Friedel–Crafts-type acylation of **5** with 4-methoxybenzoyl chloride (1.1 equiv) gave the 2,3-disubstituted indole product as a single isomer in 57% yield.<sup>[11]</sup> The reaction could be performed at high concentration and at room temperature, allowing for large amounts of material to be processed with ease (40 gram batches). After aqueous workup, the product could be directly crystallized from the resulting crude mixture without the need for further chromatographic purification.

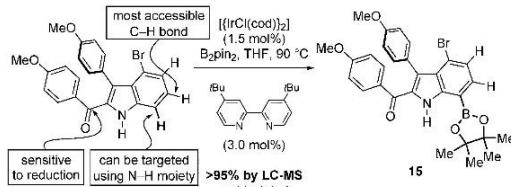


**Scheme 1.** Synthesis of dictyodendrin B by sequential C–H functionalization. Reagents and conditions: a) **4** (1.2 equiv), 2,6-di-*tert*-butylpyridine (1.2 equiv),  $\text{Cu}^1\text{Cl}$  (5 mol %),  $\text{CH}_2\text{Cl}_2$  (0.2 M), 35 °C, 48 h, 68%; b) 4-methoxybenzoyl chloride (1.1 equiv),  $\text{Bi}(\text{OTf})_3$  (5 mol %),  $\text{MeNO}_2$  (0.5 M), RT, 24 h, 57%; c)  $[\text{PdCl}_2(\text{dpdf})]$  (5.0 mol %), 3 M KOH (aq, 5 equiv), 80 °C, 30 min, 63%; d) 4-methoxyphenethyl bromide (5 equiv),  $\text{K}_2\text{CO}_3$  (7 equiv), DMF (0.2 M), 100 °C, 16 h, 83%; e) **10** (1.5 equiv, dropwise),  $[\text{PdCl}_2(\text{dpdf})]$  (5.0 mol %), 2 M  $\text{K}_2\text{CO}_3$  (aq, 5 equiv), dioxane (0.2 M), 90 °C, 20 h, 93%; f) NBS (1.15 equiv), DMF (0.1 M), RT, 24 h;  $\text{NaOMe}$  (30 equiv),  $\text{Cu}^1$  (3 equiv), 80 °C, 18.5 h, 81%; g, h)  $\text{Pd}(\text{OH})_2$  (10 mol %), 10 bar  $\text{H}_2$ , MeCN (0.2 M), 24 h; AcOH (30 equiv), *t*BuONO (1.5 equiv), TMSN<sub>3</sub> (1.2 equiv), RT, 20 min, 95%; i) dioxane (0.1 M), 180 °C, 30 min residence time, 0.333 mL min<sup>-1</sup>, Vapourtec R2 + /R4 system, 62%; j–m) see Ref. [4a, f]. cod = 1,5-cyclooctadiene, dpdf = 1,1'-bis(diphenylphosphoryl)ferrocene, NBS = N-bromosuccinimide, pin = pinacolato, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

We next turned our attention to the installation of the C7 substituent with the intention of utilizing the indole N–H motif to direct an iridium-catalyzed C–H borylation, as previously described by Maleczka, Smith and co-workers,<sup>[12]</sup> that could be directly combined with a Suzuki–Miyaura coupling to complete the C–H arylation in a one-pot process. The C–H borylation at the C7 position of indole **6** was successfully implemented using  $[\text{IrCl}(\text{cod})_2]$  (1.5 mol %) as the catalyst with  $\text{B}_2\text{pin}_2$  (1.5 equiv) in THF at 90 °C in a sealed tube and afforded boronic ester **15** on a gram scale (see also Scheme 2). Adding  $[\text{PdCl}_2(\text{dpdpf})]$  (5 mol %), 4-iodoanisole



**Scheme 3.** Selective electrophilic bromination at the C6 position. Viable sites for electrophilic bromination are indicated (●).



**Scheme 2.** Iridium-catalyzed C–H borylation at the C7 position.

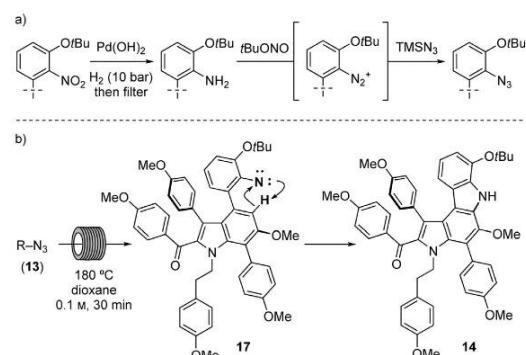
(3 equiv), and an aqueous solution of KOH (3 M) directly to the reaction mixture and stirring at 80 °C for 30 minutes afforded **7** in 63% yield. We were able to scale up this reaction to 4.7 gram batches, enabling effective material throughput. With the indole N–H moiety having served its purpose for directing the C–H arylation, we next performed the N-alkylation, which also served to prevent this nucleophilic motif from interfering with any subsequent metal-catalyzed processes. Treatment of compound **7** with commercial 4-methoxyphenethyl bromide (**8**) and  $\text{K}_3\text{CO}_3$  afforded the desired product **9** in 83% yield; this process could be conducted in batches of two grams.

Suzuki–Miyaura coupling of the C4 bromide was next investigated to incorporate the final aryl component into the structure of dictyodendrin B (Scheme 1). The nitrophenol-derived boronic ester **10** could be assembled in two steps from a commercial building block, and subsequent cross-coupling was performed using relatively standard conditions. These involved the dropwise addition of the aryl boronic ester<sup>[13]</sup> to a mixture of  $[\text{PdCl}_2(\text{dpdpf})]$  (5 mol %) and an aqueous solution of  $\text{K}_2\text{CO}_3$  (2 M) in dioxane at 90 °C to furnish the C4-arylated product **11** in 93% yield on a 1.5 gram scale. The dropwise addition was important to avoid the competing deleterious protodeboronation process that we observed when the aryl boronic ester was present in the reaction mixture from the outset.

The nitro group of the arena at the C4 position was critical to successful oxygenation at the C6 position (Scheme 1). Unfortunately, all attempts to secure a direct C–H oxygenation at this position failed. However, with the nitro group deactivating the C4 aryl moiety, we found that electrophilic bromination at the C6 position of the indole occurred with exclusive selectivity at room temperature using a slight excess of *N*-bromosuccinimide (see Scheme 3). All other nitrogen-based substituents (azide, amide, and amine moieties) resulted in bromination on the C4 aryl substituent. After

24 hours, direct addition of a sodium methoxide solution in methanol (4 M) and copper(I) iodide to the bromination reaction mixture led to the formation of the methyl ether,<sup>[14]</sup> completing a two-step one-pot etherification process from **11** and affording **12** in 81% yield on a 1.5 gram scale.

The choice of the nitro group was also important to provide maximum flexibility in the carbazole ring-closure process that we hoped to achieve by a C–H amination process. Despite considerable efforts, we were unable to effect a phosphite-mediated Cadogan cyclization<sup>[15a]</sup> or Merck's reductive palladium-catalyzed process directly from the nitro group.<sup>[15b]</sup> Attempts to use Buchwald's catalytic C–H carbazole synthesis (from a corresponding acetamide)<sup>[15c]</sup> as well as our own palladium-catalyzed method (from a corresponding benzylamine) also failed.<sup>[15d]</sup> Finally, we found that the transformation of the nitro group into the azide by a two-step reduction/diazotization/azidation process provided **13** in 95% yield on 1.5 gram scale (Scheme 1 and Scheme 4a).<sup>[16]</sup> Although we investigated metal-catalyzed C–H insertion processes using the azide, none of these reactions resulted in the desired heterocycle.<sup>[17]</sup> Carbazole **14** could be isolated using Tokuyama's batch conditions for the thermal decomposition of the azide;<sup>[4f–g]</sup> however, this approach is not without issues, and we sought to address some of the problems associated with this procedure that may preclude a larger scale reaction. For instance, the sudden and exothermic production of nitrogen gas on scale can be very dangerous, and solvents with high boiling points are often required to



**Scheme 4.** C–H amination for carbazole formation.

reach the azide decomposition temperature, which can make isolation difficult.

We speculated that a flow process could provide the ideal platform with which to perform this reaction without any of these disadvantages.<sup>[18]</sup> Pleasingly, we were able to execute the C–H amination, presumably via the formation of nitrene intermediate **17** (Scheme 4b), in super-heated dioxane at 180 °C in a continuous-flow process, processing over one gram of azide **13** in 30 minutes. To this point, the synthesis has produced one gram of protected dictyodendrin B. From here, the known four-step deprotection and sulfonylation sequence was applied on a small scale to obtain the natural product. Selective removal of the *tert*-butyl ether and subsequent sulfonylation afforded crystalline material suitable for X-ray diffraction, confirming the regioslectivity of all direct functionalization reactions.<sup>[19]</sup> Global demethylation and zinc-mediated cleavage of the sulfonyl protecting group afforded dictyodendrin B, which matched authentic material in every respect.<sup>[1,4]</sup>

In summary, we have successfully executed a synthesis of dictyodendrin B by functionalizing all positions of a commercially available monosubstituted indole building block. Novel aspects of our synthesis include the deployment of a number of catalytic C–H functionalization processes, highly selective electrophilic aromatic substitutions performed in complex environments, and a late-stage application of a carbazole ring closure using flow chemistry. Moreover, the synthesis was performed on multigram scale to produce over one gram of the protected natural product. Our work clearly demonstrates the utility of sequential C–H functionalizations in the rapid and modular construction of complex molecules from minimally functionalized and widely available aromatic precursors. This overall approach is streamlined and will allow for the diversification and testing of complex analogues towards the identification of more potent variants of this interesting natural product. We see this as a highly complementary and competitive strategy to existing synthetic approaches, and current studies are focused on the synthesis of other natural products by disconnection strategies based on the logic of such C–H functionalization processes.

Received: January 5, 2015

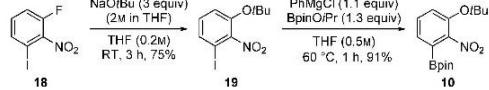
Published online: ■■■■■

**Keywords:** C–H functionalization · flow chemistry · metal catalysis · natural products · total synthesis

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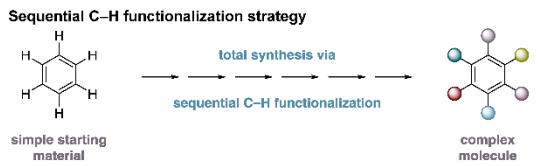
## **APPENDIX B: POSTER PRESENTED AT ACS BOSTON 2015**



# A concise and scalable strategy for the total synthesis of dictyodendrin B based on sequential C–H functionalization

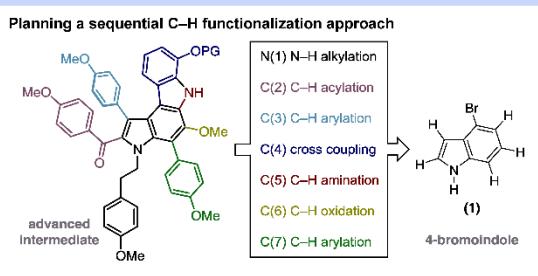
Catalysis  
at Cambridge

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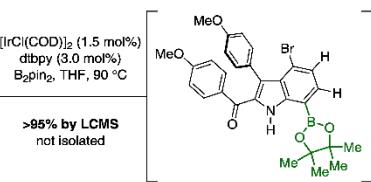


**The dictyodendrin marine alkaloids**

- A collection of pyrrolo[2,3-c]carbazole-derived natural products first isolated in 2003 off the south coast of Japan.
- Interesting inhibitory activities towards telomerases and  $\beta$ -site APP cleaving enzyme 1 (BACE1; APP=amyloid precursor protein) and investigated therapeutically.
- A number of elegant total syntheses have previously come from the groups of Fürstner, Iwao and Ishibashi, Tokuyama and Jia.

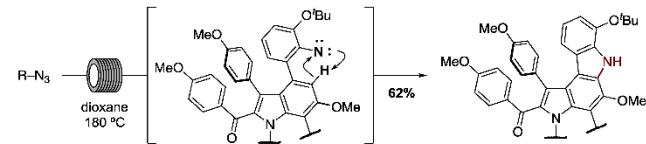


## Highlighted Step: C7 Ir-Catalyzed C–H borylation



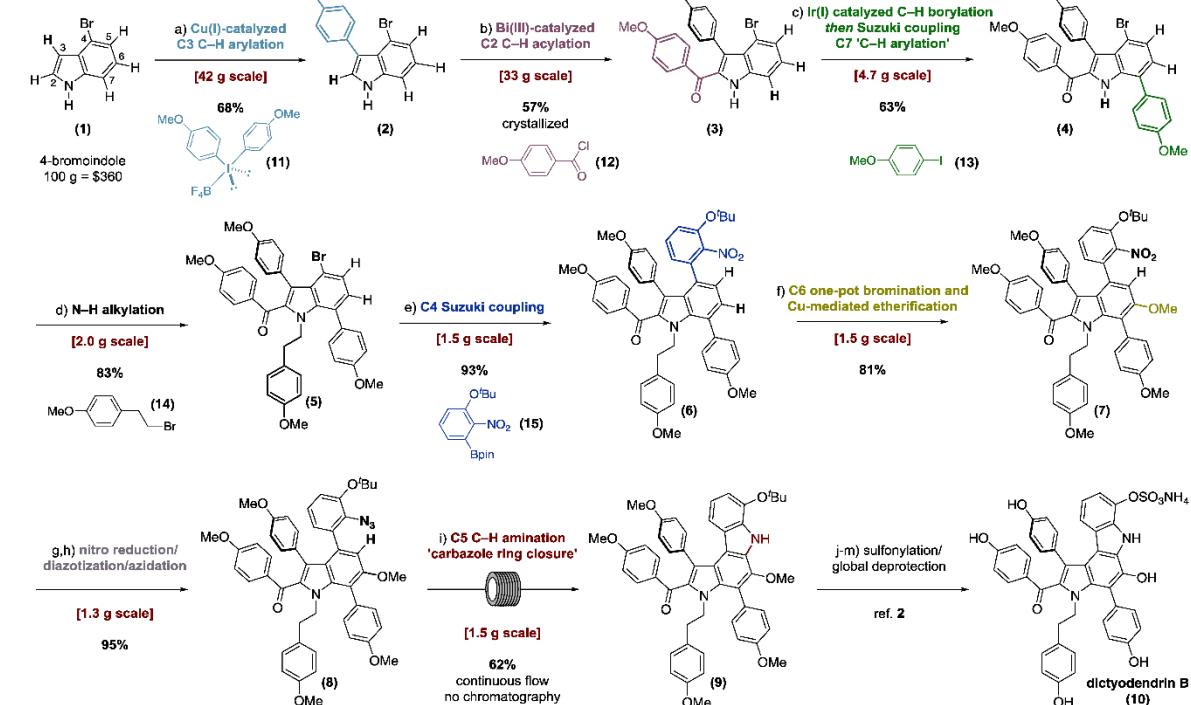
- The C7 borylation of indoles can be achieved when the C2 position is substituted using methodology by Maleczka, Smith and co-workers that uses the innate directing ability of the indole nitrogen (see ref. 3).
- The reaction can be performed on gram-scale in super-heated tetrahydrofuran using a simple pressure tube.
- Full conversion was observed by LCMS allowing the reaction to be telescoped in a one-pot Suzuki process.

## Highlighted Step: C5 C–H nitrene insertion



- Previously performed by Tokuyama and co-workers in batch as part of their total synthesis (see ref. 4).
- Although we investigated alternative metal-catalyzed C–H functionalizations using the related *N*-acyl, *N*-benzyl, *N*-tosyl, nitro and azide substrates, we observed no significant formation of the desired heterocycle.
- We then sought to address some of the problems associated with the thermal azide decomposition procedure that may have precluded a large scale reaction, such as the dangerous exothermic production of nitrogen gas and use of high-boiling solvents which can make isolation difficult. We subsequently developed a simple flow process without these disadvantages that enabled easy production of the product on gram-scale.

## Total synthesis of dictyodendrin B:



**Reagents and conditions:** a) 11 (1.2 equiv), 2,6-di-*tert*-butylpyridine (1.2 equiv), CuCl (5.0 mol%), CH<sub>2</sub>Cl<sub>2</sub> (0.2 M), 35 °C, 48 h, 68%; b) 4-methoxybenzoyl chloride (1.1 equiv), Bi<sup>III</sup>(OTf)<sub>5</sub> (5.0 mol%), MeNO<sub>2</sub> (0.5 M), RT, 24 h, 57%; c) (Bpin)<sub>2</sub> (1.5 equiv), [(IrCl(COD))<sub>2</sub>] (1.5 mol%), 4,4'-di-*tert*-butyl-2,2'-dipyridyl (3.0 mol%), THF (0.2 M), 90 °C, 1.5 h; 4-iodoanisole (3 equiv), [PdCl<sub>2</sub>(dppt)] (5.0 mol%), 3 M KOH (aq, 5 equiv), 80 °C, 30 min, 63%; d) 4-methoxyphenyl bromide (5 equiv), K<sub>2</sub>CO<sub>3</sub> (7 equiv), DMF (0.2 M), 100 °C, 16 h, 83%; e) 15 (1.5 equiv, dropwise), [PdCl<sub>2</sub>(dppt)] (5.0 mol%), 2 M K<sub>2</sub>CO<sub>3</sub> (aq, 5 equiv), dioxane (0.2 M), 90 °C, 20 h, 93%; f) NBS (1.15 equiv), DMF (0.1 M), RT, 24 h; NaOEt (30 equiv), CuI (3 equiv), 80 °C, 18.5 h, 81%; g) Pd(OH)<sub>2</sub> (10 mol%), 10 bar H<sub>2</sub>, MeCN (0.2 M), 24 h; h) AcOH (30 equiv), tBuONa (1.5 equiv), TMSN<sub>3</sub> (1.2 equiv), RT, 20 min, 95%; i) dioxane (0.1 M), 180 °C, 30 min residence time, 0.333 mL min<sup>-1</sup>, Vapourtec R2+R4 system, 62%; j-m) see ref. 2; cod=1,5-cyclooctadiene, dppt=1,1'-bis(diphenylphosphanyl)ferrocene, NBS=N-bromosuccinimide, pin=pinacolato, Tf=trifluoromethanesulfonyl, TMS=trimethylsilyl.

**Acknowledgements:** We are grateful to AstraZeneca, Pfizer, and the EPSRC (A.K.P., F.O., R.H.S., and M.J.G.) and the ERC (M.J.G.) for fellowships. Mass spectrometry data were acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

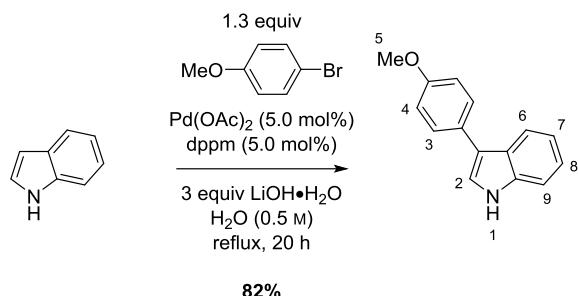
**References:** (1) Gaunt et al. *Angew. Chem. Int. Ed.* 2015, 54(18), 5451. (2) Fürstner et al. *JACS* 2005, 127(33), 11620. (3) Maleczka and Smith et al. *JACS* 2006, 128(49), 15552. (4) Tokuyama et al. *Angew. Chem. Int. Ed.* 2010, 49(34), 5925. For a similar strategy applied in the synthesis of dictyodendrin A, Davies et al. *JACS*, 2015, 137(2), 644.

## **APPENDIX C: DATA FOR ATTEMPTED SYNTHESIS FROM INDOLE**

Experiments in this appendix were performed by Dr Robert H. Snell and spectral data was collected and interpreted by Andrew K. Pitts.

## Appendix C1: Attempted Synthesis from Indole (Experimental)

### 3-(4-methoxyphenyl)-1*H*-indole (198)



Indole (5.00 g, 42.7 mmol, 1.0 equiv), palladium(II) acetate (480 mg, 2.13 mmol, 5.0 mol%), 1,1-bis(diphenylphosphino)methane (820 mg, 2.13 mmol, 5.0 mol%) and lithium hydroxide (5.38 g, 128 mmol, 3.0 equiv) were combined in a flask and purged with nitrogen. Degassed water (86 mL, 0.5 M) and 4-bromoanisole (6.96 mL, 55.5 mmol, 1.3 equiv) were added sequentially and the mixture heated at reflux for 16 h. The reaction was allowed to cool to room temperature before being partitioned between dichloromethane and saturated aqueous ammonium chloride solution. The organic layer was isolated and the aqueous layer extracted with additional dichloromethane, the combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by silica gel column chromatography (40–60 petroleum ether to 1:2 ethyl acetate/40–60 petroleum ethers). The resultant product was further purified by crystallisation (dichloromethane/40–60 petroleum ethers) to give the title compound as a colourless solid (7.84 g, 82%).

**mp** 126–128 °C (dichloromethane/40–60 petroleum ethers).

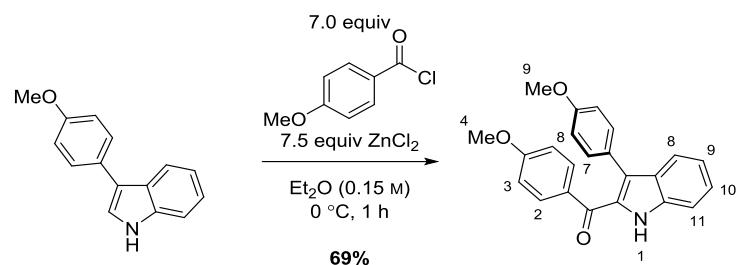
**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3409, 3052, 3001, 2956, 2909, 2835, 1612, 1580, 1549, 1501, 1456, 1442, 1427, 1408, 1346, 1332, 1318, 1303, 1281, 1243, 1179, 1154, 1142, 1108, 1098, 1031, 1015, 962, 932, 836, 810.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.17 (s, 1H, H<sub>1</sub>), 7.91 (d, *J* = 7.9 Hz, 1H, H<sub>6</sub>), 7.60 (d, *J* = 8.8 Hz, 2H, H<sub>3</sub>), 7.43 (d, *J* = 8.1 Hz, 1H, H<sub>9</sub>), 7.30 (d, *J* = 2.5 Hz, 1H, H<sub>2</sub>), 7.28–7.23 (m, 1H, H<sub>8</sub>), 7.22–7.18 (m, 1H, H<sub>7</sub>), 7.02 (d, *J* = 8.7 Hz, 2H, H<sub>4</sub>), 3.87 (s, 3H, H<sub>5</sub>).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 158.2, 136.7, 128.8, 128.2, 126.0, 122.4, 121.3, 120.3, 119.9, 118.2, 114.4, 111.5, 55.5.

**HRMS** (ESI) found [M+H]<sup>+</sup> 224.1070 ([C<sub>15</sub>H<sub>13</sub>NO+H]<sup>+</sup> requires 224.1070; error 0 ppm).

**(4-methoxyphenyl)(3-(4-methoxyphenyl)-1*H*-indol-2-yl)methanone (200)**



4-Methoxybenzoyl chloride (**199**) (5.08 mL, 37.7 mmol, 7.0 equiv) was added via syringe pump over 20 min to a stirred solution of 3-(4-methoxyphenyl)-1*H*-indole (**198**) (1.20 g, 5.38 mmol, 1.0 equiv) and zinc chloride (5.49 g, 40.4 mmol, 7.5 equiv) in diethylether (36 mL, 0.15 M) at 0 °C. After complete addition of the acid chloride, the reaction was stirred at 0 °C for 1 h before being allowed to warm to room temperature. Aqueous sodium hydroxide solution (20 mL, 10% w/v) was added and the reaction stirred vigorously for 15 min. The biphasic mixture was extracted with dichloromethane and the combined organic extracts washed with additional aqueous sodium hydroxide solution, dried over magnesium sulfate and filtered through a plug of silica. The crude mixture was concentrated *in vacuo* and the product precipitated (ethyl acetate/40–60 petroleum ethers). The crude product was recrystallised (ethyl acetate/40–60 petroleum ethers) to afford the title compound as a bright yellow powder (1.32 g, 69%).

**mp** 165–168 °C (ethyl acetate/40–60 petroleum ethers).

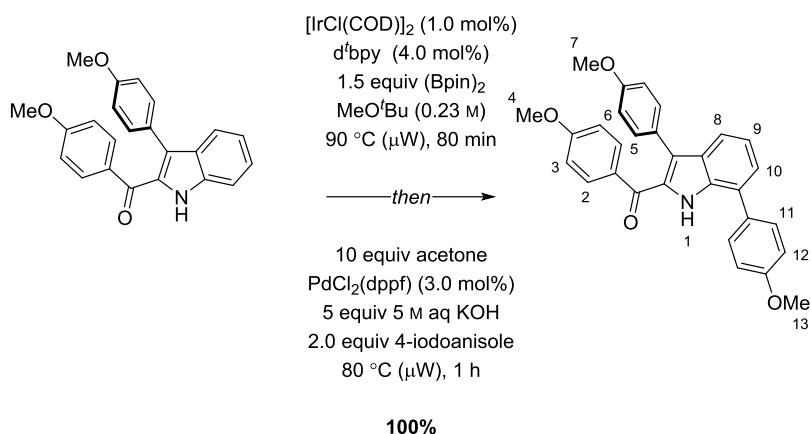
**IR**  $\nu_{\max}$  (film)/cm<sup>−1</sup> 3311, 3057, 3004, 2960, 2934, 2837, 1596, 1568, 1537, 1510, 1497, 1463, 1432, 1381, 1331, 1305, 1287, 1246, 1174, 1165, 1147, 1110, 1039, 1023, 1001, 945, 936, 907, 839, 818.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.29 (s, 1H, H<sub>1</sub>), 7.74 (d, J = 8.2 Hz, 1H, H<sub>8</sub>), 7.57 (d, J = 8.8 Hz, 2H, H<sub>2</sub>), 7.49 (d, J = 8.3 Hz, 1H, H<sub>11</sub>), 7.39 (d, J = 16.1 Hz, 1H, H<sub>10</sub>), 7.22 – 7.12 (m, 3H, H<sub>5</sub> and H<sub>9</sub>), 6.73 (d, J = 8.7 Hz, 2H, H<sub>6</sub>), 6.60 (d, J = 8.8 Hz, 2H, H<sub>3</sub>), 3.77 (s, 3H, H<sub>7</sub>), 3.75 (s, 3H, H<sub>4</sub>).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 188.4, 162.7, 158.7, 136.4, 132.1, 132.1, 131.1, 130.2, 127.9, 126.5, 126.3, 124.2, 122.1, 121.0, 113.8, 113.1, 112.0, 55.5, 55.4.

**HRMS** (ESI) found [M+H]<sup>+</sup> 358.1439 ([C<sub>23</sub>H<sub>19</sub>NO<sub>3</sub>+H]<sup>+</sup> requires 358.1438; error 0.3 ppm).

**(3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (201)**



Methyl-*tert*-butylether (12 mL, 0.23 M) was added to a mixture of bis(pinacolato)diboron (1.07 g, 4.2 mmol, 1.5 equiv), dichlorobis(cycloocta-1,5-diene)diiridium (I) (37 mg, 0.028 mmol, 1.0 mol%) and 4,4'-di-*tert*-butyl-2,2'-dipyridyl (30 mg, 4 mol%). The mixture was purged with nitrogen before being stirred at room for 5 min; the now blue/black solution was treated with (4-methoxyphenyl)(3-(4-methoxyphenyl)-1*H*-indol-2-yl)methanone (**200**) (1.00 g, 2.80 mmol, 1.0 equiv) and purged a second time with nitrogen before being heated by microwave irradiation at 90 °C for 75 min. The reaction was allowed to cool to room temperature before analysis by LCMS confirmed complete conversion to the 7-boronate ester. The crude mixture was treated sequentially with acetone (2 mL, 28.00 mmol, 10 equiv), water (2.8 mL), ground potassium hydroxide (252 mg, 14.00 mmol, 5.0 equiv) and a mixture of 4-bromoanisole (0.7 mL, 5.60 mmol, 2.0 equiv) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (62 mg, 0.084 mmol, 3.0 mol%). The reaction was re-sealed and flushed with nitrogen before being heated by microwave irradiation at 80 °C for 1 h. The reaction was allowed to cool to room temperature before being partitioned between water and dichloromethane. The organic layer was isolated and the aqueous layer extracted thoroughly with additional dichloromethane. The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography eluting with (1:9 ethyl acetate/40–60 petroleum ethers) to give the title compound as a yellow foam (1.29 g, 100% over two steps)

**mp** 76.9–79.6 °C (dichloromethane/hexane).

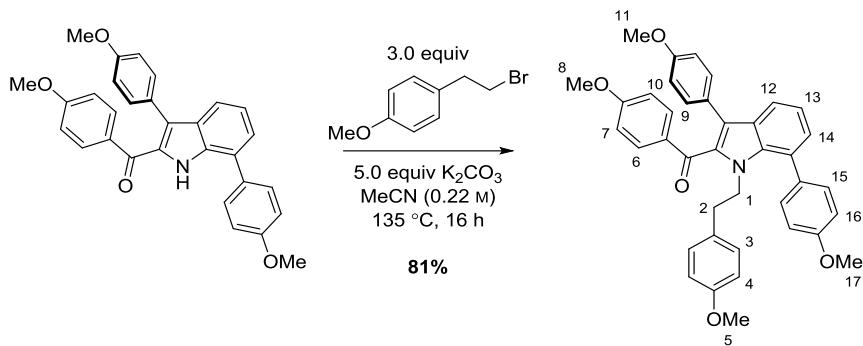
**IR**  $\nu_{\max}$  (film)/cm<sup>-1</sup> 3254, 3056, 3002, 2933, 2905, 2836, 1610, 1597, 1571, 1539, 1509, 1497, 1463, 1440, 1402, 1375, 1315, 1302, 1287, 1242, 1169, 1110, 1058, 1030, 1020, 963, 913, 898, 834.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.24 (s, 1H, H<sub>1</sub>), 7.70 (d, *J* = 8.1 Hz, 1H, H<sub>10</sub>), 7.62 (d, *J* = 8.6 Hz, 2H, H<sub>11</sub>), 7.55 (d, *J* = 8.8 Hz, 2H, H<sub>2</sub>), 7.37 (d, *J* = 7.1 Hz, 1H, H<sub>8</sub>), 7.27 – 7.24 (m, 1H, H<sub>9</sub>), 7.17 (d, *J* = 8.6 Hz, 2H, H<sub>5</sub>), 7.09 (d, *J* = 8.6 Hz, 2H, H<sub>12</sub>), 6.74 (d, *J* = 8.6 Hz, 2H, H<sub>6</sub>), 6.59 (d, *J* = 8.8 Hz, 2H, H<sub>3</sub>), 3.91 (s, 3H, H<sub>13</sub>), 3.77 (s, 3H, H<sub>7</sub>), 3.75 (s, 3H, H<sub>4</sub>).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 188.2, 162.7, 159.5, 158.7, 134.5, 132.1, 132.1, 131.3, 130.7, 130.1, 129.5, 128.3, 126.5, 126.3, 125.6, 124.4, 121.6, 120.8, 114.9, 113.8, 55.6, 55.5, 55.4.

**HRMS** (ESI) found [M+H]<sup>+</sup> 464.1851 ([C<sub>30</sub>H<sub>25</sub>NO<sub>4</sub>+H]<sup>+</sup> requires 464.1856; error -1.1 ppm).

**(1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (202)**



4-Methoxyphenethyl bromide (**172**) (0.61 mL, 3.88 mmol, 3.0 equiv) was added to a pressure tube containing a stirred suspension of (3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (**201**) (600 mg, 1.29 mmol, 1.0 equiv) and ground potassium carbonate (890 mg, 6.45 mmol, 5.0 equiv) in anhydrous acetonitrile (6 mL, 0.22 M) and the reaction was heated at 135 °C for 16 h. The reaction was allowed to cool to room temperature before being partitioned between sat. aq ammonium chloride solution and dichloromethane. The organic layer was isolated and the aqueous layer extracted thoroughly with additional dichloromethane. The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (1:25 to 9:1 ethyl acetate/40–60 petroleum ethers) to give the title compound as a yellow foam (624 mg, 81%).

**mp** 156.8–158.5 °C (ethyl acetate/40–60 petroleum ethers).

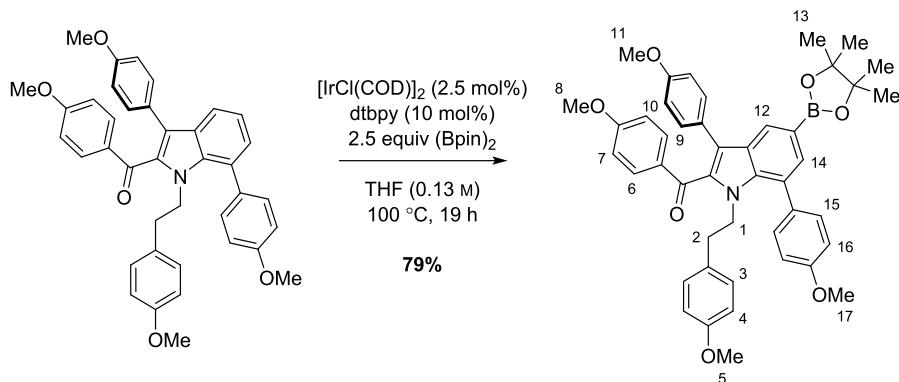
**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3001, 2934, 2913, 2836, 1631, 1610, 1596, 1572, 1541, 1510, 1463, 1442, 1421, 1399, 1338, 1318, 1302, 1286, 1241, 1175, 1160, 1110, 1085, 1066, 1031, 958, 930, 837, 823.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.74 (dd, *J* = 7.8, 1.4 Hz, 1H, **H<sub>12</sub>**), 7.61 (d, *J* = 8.9 Hz, 2H, **H<sub>6</sub>**), 7.50 (d, *J* = 8.7 Hz, 2H, **H<sub>15</sub>**), 7.25 – 7.19 (m, 3H, **H<sub>10</sub>** and **H<sub>13</sub>**), 7.17 (dd, *J* = 7.1, 1.4 Hz, 1H, **H<sub>14</sub>**), 7.02 (d, *J* = 8.7 Hz, 2H, **H<sub>16</sub>**), 6.75 (d, *J* = 8.8 Hz, 2H, **H<sub>9</sub>**), 6.63 (d, *J* = 8.9 Hz, 2H, **H<sub>7</sub>**), 6.57 (d, *J* = 8.7 Hz, 2H, **H<sub>3</sub>**), 6.46 (d, *J* = 8.7 Hz, 2H, **H<sub>4</sub>**), 4.17 – 4.11 (m, 2H, **H<sub>1</sub>**), 3.90 (s, 3H, **H<sub>17</sub>**), 3.76 (s, 3H, **H<sub>8</sub>**), 3.75 (s, 3H, **H<sub>11</sub>**), 3.68 (s, 3H), **H<sub>5</sub>**, 2.49 – 2.42 (m, 2H, **H<sub>2</sub>**).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 189.8, 163.4, 159.4, 158.4, 158.1, 135.2, 134.8, 132.9, 132.6, 131.3, 131.1, 131.0, 130.3, 129.7, 128.1, 127.4, 126.5, 122.3, 120.5, 120.4, 113.8, 113.7, 113.6, 113.3, 55.6, 55.5, 55.3, 55.2, 47.3, 36.7.

**HRMS** (ESI) found [M+H]<sup>+</sup> 598.2585 ([C<sub>39</sub>H<sub>35</sub>NO<sub>5</sub>+H]<sup>+</sup> requires 598.2588; error −0.5 ppm).

**(1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (203)**



A stirred solution of bis(pinacolato)diboron (1.06 g, 4.18 mmol, 2.5 equiv), dimethoxybis(cycloocta-1,5-diene)diiridium (I) (55 mg, 0.042 mmol, 2.5 mol%) and 4,4'-di-*tert*-butyl-2,2'-dipyridyl (45 mg, 0.17 mmol, 10 mol%) in tetrahydrofuran (7 mL) was added in 10 equal portions at 20 min intervals to a stirred solution of (1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (**202**) (1.00 g, 1.67 mmol, 1.0 equiv) in tetrahydrofuran (6 mL, 0.14 M overall). The reaction was carried out in a pressure tube at 100 °C and each addition of the catalyst solution necessitated cooling of the reaction vessel. Upon addition of all the catalyst solution, the reaction was stirred at 100 °C for 16 h. The reaction was allowed to cool to room temperature before being concentrated *in vacuo* and purified directly by silica gel column chromatography (1:25 to 9:1 ethyl acetate/40–60 petroleum ethers) to give the title compound as a yellow foam (952 mg, 79%).

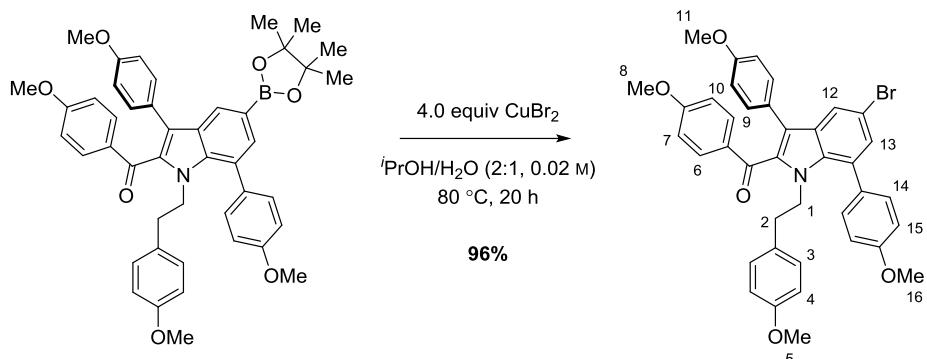
**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 2976, 2933, 2836, 1632, 1610, 1597, 1573, 1542, 1511, 1458, 1443, 1421, 1371, 1350, 1317, 1302, 1286, 1243, 1167, 1143, 1109, 1088, 1031, 992, 959, 928, 890, 874, 837.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.20 (d, *J* = 1.1 Hz, 1H, H<sub>14</sub>), 7.62 (d, *J* = 1.2 Hz, 1H, H<sub>12</sub>), 7.58 (d, *J* = 8.9 Hz, 2H, H<sub>6</sub>), 7.50 (d, *J* = 8.7 Hz, 2H, H<sub>10</sub>), 7.23 (d, *J* = 8.7 Hz, 2H, H<sub>16</sub>), 7.00 (d, *J* = 8.7 Hz, 2H, H<sub>9</sub>), 6.75 (d, *J* = 8.8 Hz, 2H, H<sub>15</sub>), 6.62 (d, *J* = 9.0 Hz, 2H, H<sub>7</sub>), 6.55 (d, *J* = 8.7 Hz, 2H, H<sub>3</sub>), 6.45 (d, *J* = 8.7 Hz, 2H, H<sub>4</sub>), 4.18 – 4.13 (m, 2H, H<sub>1</sub>), 3.89 (s, 3H, H<sub>11</sub>), 3.76 (s, 3H, H<sub>8</sub>), 3.75 (s, 3H, H<sub>17</sub>), 3.67 (s, 3H, H<sub>5</sub>), 2.47 – 2.43 (m, 2H, H<sub>2</sub>), 1.34 (s, 12H, H<sub>13</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 189.6, 163.3, 159.2, 158.3, 158.0, 137.0, 134.7, 133.9, 132.7, 132.5, 131.4, 131.2, 131.1, 131.0, 130.8, 130.2, 130.1, 129.6, 128.0, 128.0, 127.8, 126.5, 126.3, 122.9, 120.4, 120.3, 83.6, 55.5, 55.4, 55.2, 55.1, 47.2, 36.5.

**HRMS** (ESI) found [M+H]<sup>+</sup> 724.3439 ([C<sub>45</sub>H<sub>46</sub>BNO<sub>7</sub>+H]<sup>+</sup> requires 724.3448; error −1.2 ppm).

**(5-bromo-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (193)**



Water (6 mL) and copper(II) bromide (339 mg, 1.52 mmol, 4.0 equiv) were added sequentially to a stirred solution of (1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (**203**) (275 mg, 0.38 mmol, 1.0 equiv) in warm isopropanol (12 mL, 0.02 M overall). The mixture was stirred at 80 °C for 16 h before being concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was isolated and the aqueous layer extracted with additional ethyl acetate. The combined organic extracts were washed with water, dried over magnesium sulfate and concentrated under reduced pressure to give the title compound, without further purification, as a yellow solid (247 mg, 96%).

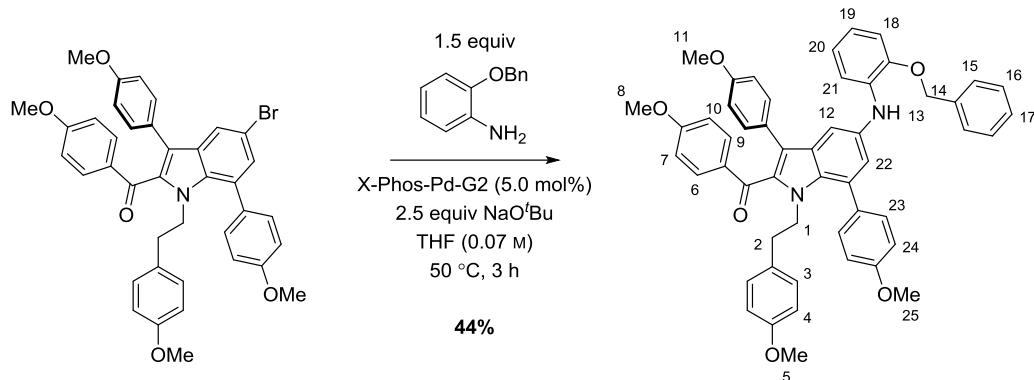
**IR**  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3004, 2956, 2932, 2836, 1724, 1635, 1610, 1596, 1572, 1541, 1510, 1463, 1442, 1422, 1393, 1358, 1314, 1303, 1287, 1242, 1173, 1168, 1149, 1109, 1031, 977, 958, 837.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.83 (d, *J* = 2.0 Hz, 1H, H<sub>12</sub>), 7.58 (d, *J* = 9.0 Hz, 2H, H<sub>6</sub>), 7.46 (d, *J* = 8.7 Hz, 2H, H<sub>14</sub>), 7.27 (d, *J* = 2.0 Hz, 1H, H<sub>13</sub>), 7.19 (d, *J* = 8.7 Hz, 2H, H<sub>9</sub>), 7.02 (d, *J* = 8.7 Hz, 2H, H<sub>15</sub>), 6.76 (d, *J* = 8.8 Hz, 2H, H<sub>10</sub>), 6.63 (d, *J* = 9.0 Hz, 2H, H<sub>7</sub>), 6.55 (d, *J* = 8.7 Hz, 2H, H<sub>3</sub>), 6.43 (d, *J* = 8.7 Hz, 2H, H<sub>4</sub>), 4.13 – 4.08 (m, 2H, H<sub>1</sub>), 3.90 (s, 3H, H<sub>16</sub>), 3.76 (s, 3H, H<sub>8</sub>), 3.75 (s, 3H, H<sub>11</sub>), 3.67 (s, 3H, H<sub>5</sub>), 2.45 – 2.40 (m, 2H, H<sub>2</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 189.3, 163.5, 159.6, 158.4, 158.1, 135.4, 133.8, 132.5, 131.2, 131.1, 130.9, 130.5, 130.2, 130.0, 129.8, 128.9, 125.7, 122.4, 121.2, 114.0, 113.9, 113.7, 113.6, 113.3, 63.9, 55.5, 55.4, 55.2, 55.1, 47.2, 38.3.

**HRMS** (ESI) found [M+H]<sup>+</sup> 676.1692 ([C<sub>39</sub>H<sub>34</sub>Br<sup>79</sup>NO<sub>5</sub>+H]<sup>+</sup> requires 676.1693; error -0.2 ppm).

**(5-((2-(benzyloxy)phenyl)amino)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (194)**



Tetrahydrofuran (2.8 mL, 0.07 M) was added to a flask containing (5-bromo-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (**193**) (140 mg, 0.21 mmol, 1.0 equiv), 2-benzyloxyaniline (**195**) (62 mg, 0.31 mmol, 1.5 equiv), X-Phos-Pd-G2 (**197**) (7.6 mg, 0.01 mmol, 5.0 mol%) and sodium *tert*-butoxide (50 mg, 0.52 mmol, 2.5 equiv). The reaction was heated at 50 °C for 3 h before being allowed to cool to room temperature. The reaction was partitioned between ethyl acetate and sat. aq ammonium chloride solution. The organic layer was isolated and the aqueous layer extracted with additional ethyl acetate. The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (1:9 ethyl acetate/40–60 petroleum ethers) to afford the title compound as a yellow foam (73 mg, 44%).

**IR**  $\nu_{\max}$  (film)/cm<sup>-1</sup> 3036, 2956, 2931, 2837, 1740, 1631, 1596, 1573, 1540, 1510, 1499, 1461, 1442, 1421, 1398, 1368, 1314, 1302, 1287, 1242, 1206, 1150, 1111, 1089, 1030, 958, 928, 836.

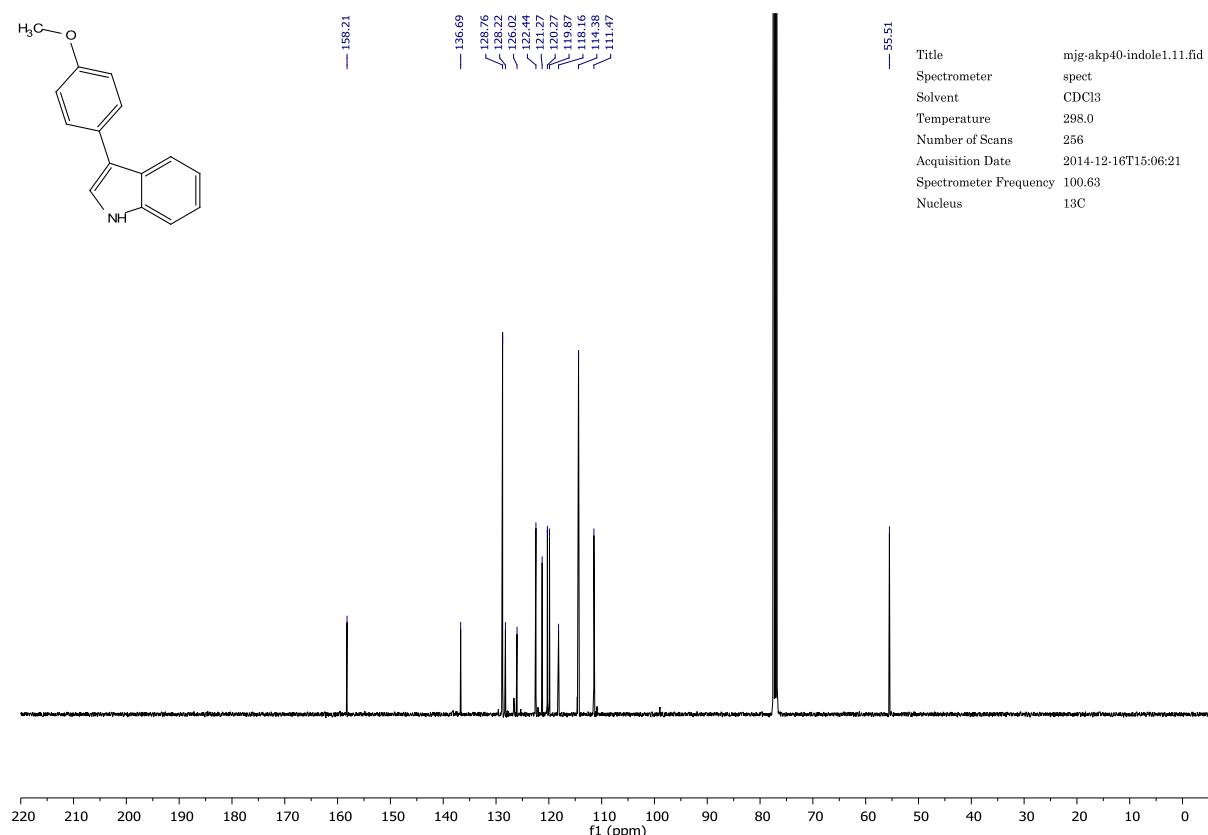
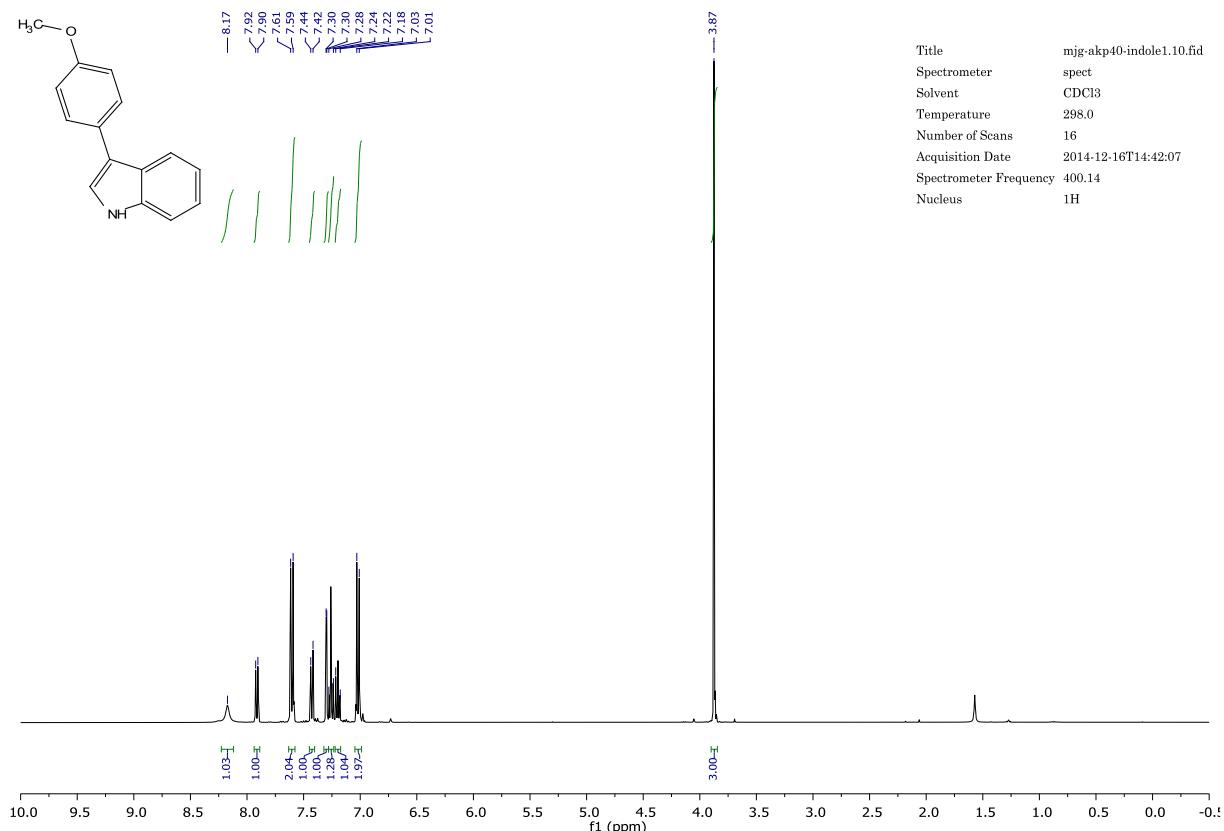
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.81 (d, J = 2.1 Hz, 1H, H<sub>13</sub>), 7.61 (d, J = 9.0 Hz, 2H, H<sub>6</sub>), 7.51 (d, J = 2.2 Hz, 1H, H<sub>12</sub>), 7.50 (d, J = 8.7 Hz, 2H, H<sub>23</sub>), 7.47 – 7.43 (m, 2H, H<sub>15</sub>), 7.40 – 7.36 (m, 2H, H<sub>16</sub>), 7.35 – 7.32 (m, 1H, H<sub>17</sub>), 7.20 (d, J = 8.9 Hz, 2H, H<sub>9</sub>), 7.07 (d, J = 2.2 Hz, 1H, H<sub>22</sub>), 7.01 (d, J = 8.6 Hz, 2H, H<sub>24</sub>), 6.93 (dd, J = 8.0, 1.4 Hz, 1H, H<sub>21</sub>), 6.85 (td, J = 7.7, 1.4 Hz, 2H, H<sub>19</sub> and H<sub>20</sub>), 6.75 (dd, J = 7.7, 1.6 Hz, 1H, H<sub>18</sub>), 6.72 (d, J = 8.8 Hz, 2H, H<sub>10</sub>), 6.63 (d, J = 9.0 Hz, 2H, H<sub>7</sub>), 6.57 (d, J = 8.7 Hz, 2H, H<sub>3</sub>), 6.46 (d, J = 8.7 Hz, 2H, H<sub>4</sub>), 5.12 (s, 2H, H<sub>14</sub>), 4.14 – 4.10 (m, 2H, H<sub>1</sub>), 3.89 (s, 3H, H<sub>25</sub>), 3.76 (s, 3H, H<sub>8</sub>), 3.72 (s, 3H, H<sub>11</sub>), 3.68 (s, 3H, H<sub>5</sub>), 2.49 – 2.44 (m, 2H, H<sub>2</sub>).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) 189.5, 163.2, 159.3, 158.2, 146.5, 137.0, 135.6, 135.3, 132.5, 132.2, 132.0, 131.1, 131.0, 130.9, 130.2, 129.6, 129.5, 128.7, 128.6, 128.1, 128.0, 127.7, 127.0, 126.4, 124.0, 121.9, 121.4, 118.3, 113.7, 113.6, 113.5, 113.2, 112.6, 111.9, 111.7, 70.7, 55.5, 55.4, 55.2, 55.1, 47.2, 36.6.

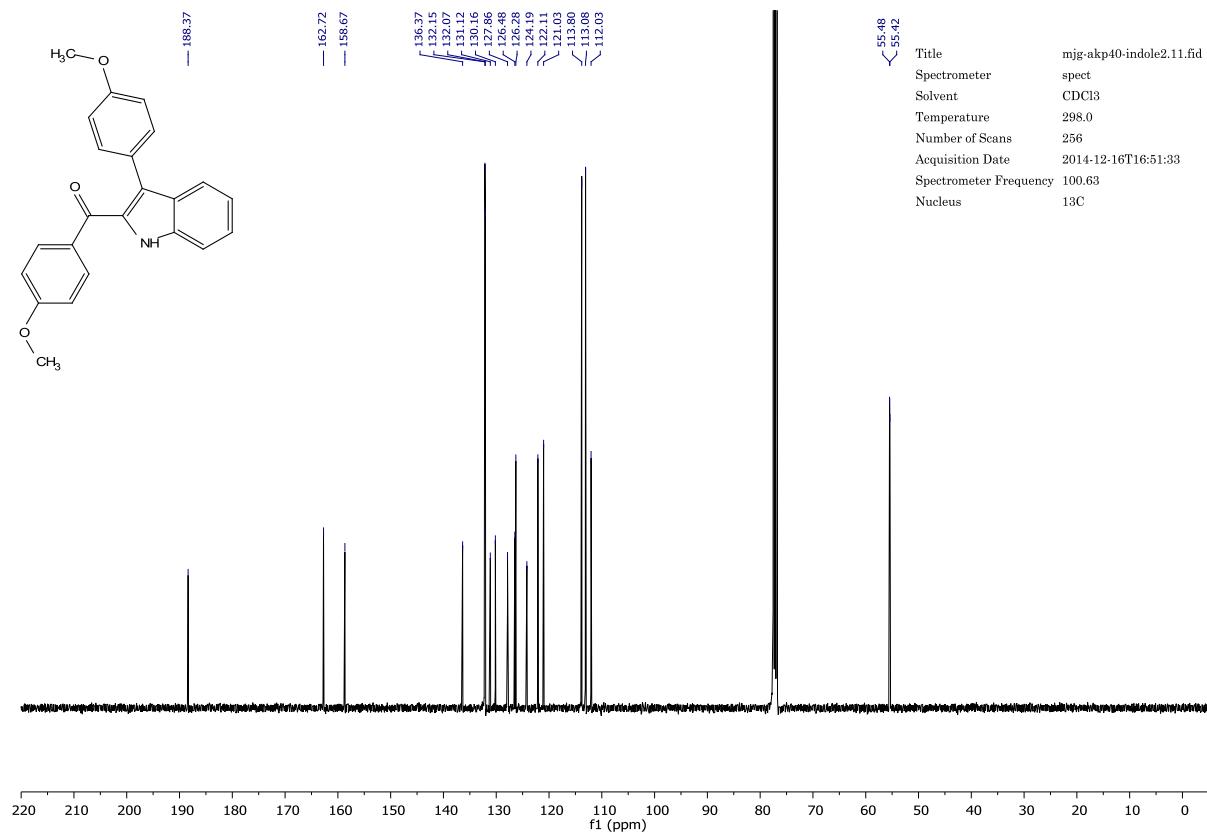
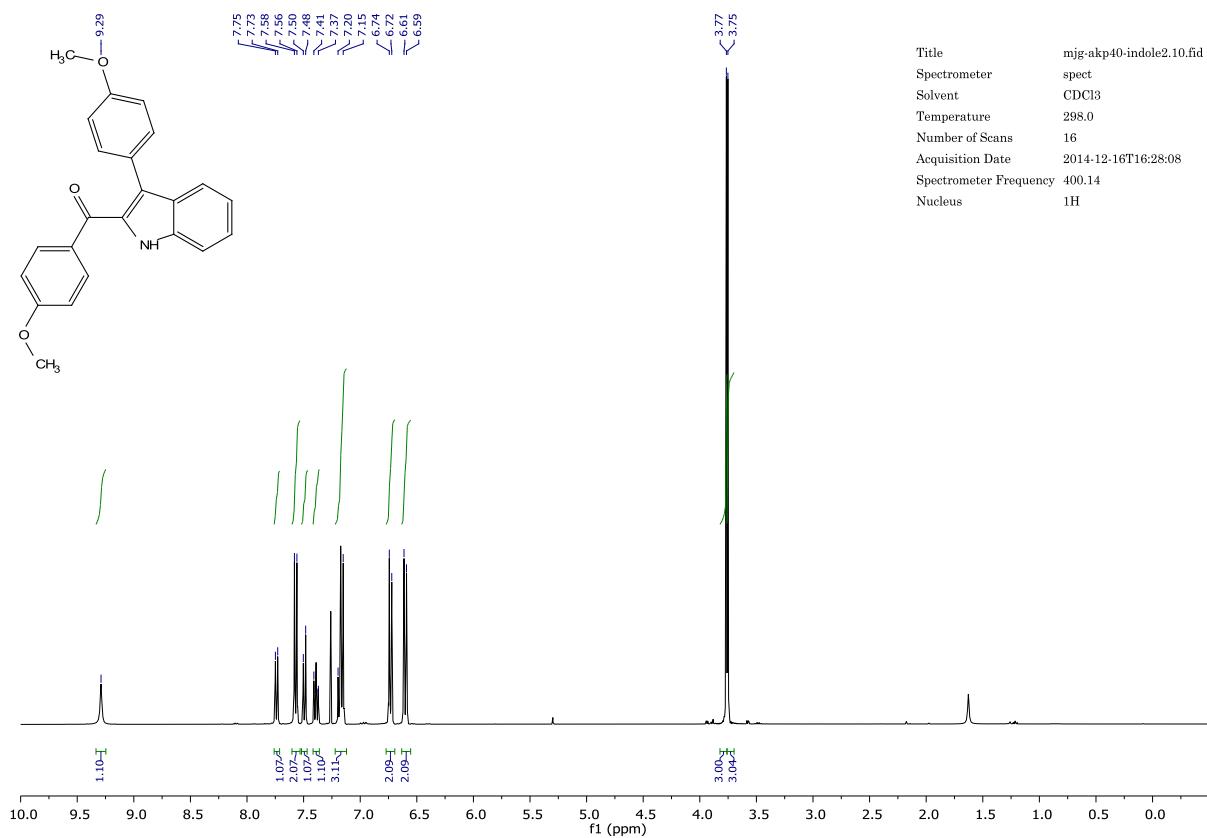
**HRMS** (ESI) found [M+H]<sup>+</sup> 795.3428 ([C<sub>52</sub>H<sub>46</sub>N<sub>2</sub>O<sub>6</sub>+H]<sup>+</sup> requires 795.3429; error -0.1 ppm).

## Appendix C2: Attempted Synthesis from Indole (Spectral Data)

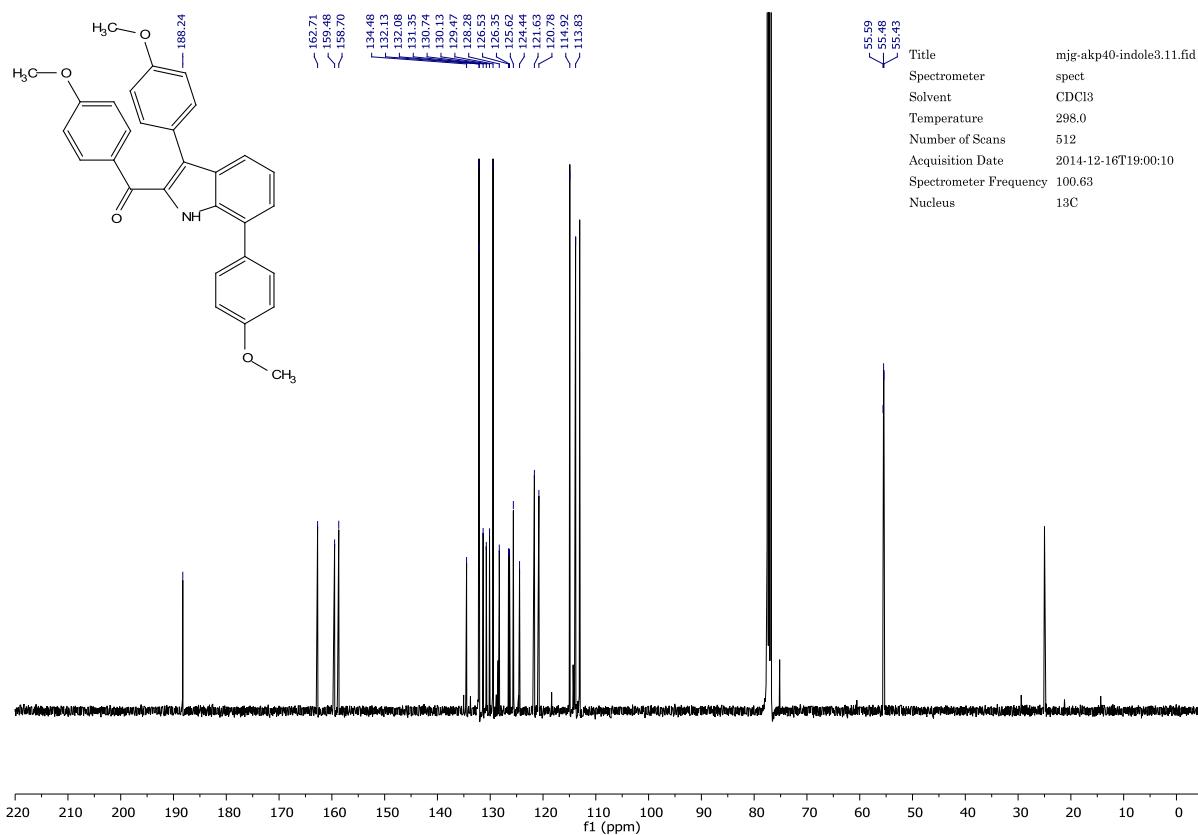
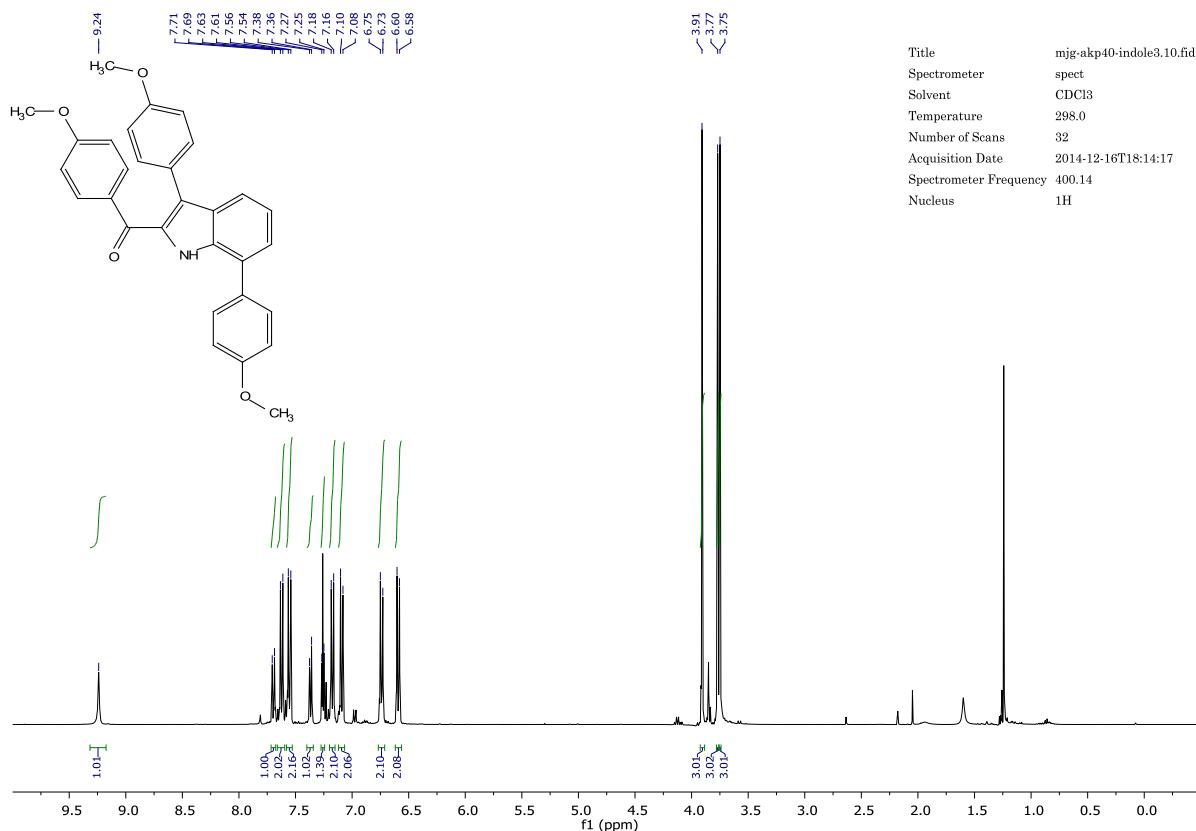
### 3-(4-methoxyphenyl)-1H-indole (195)



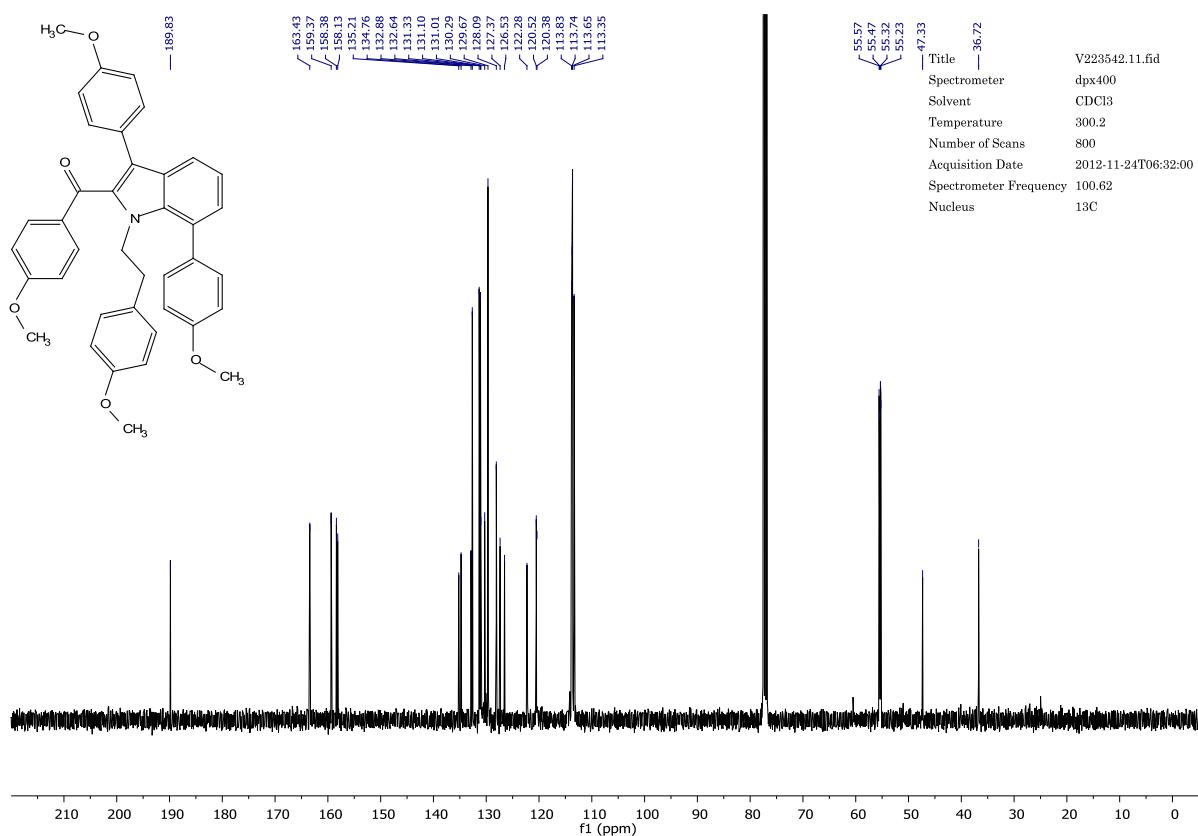
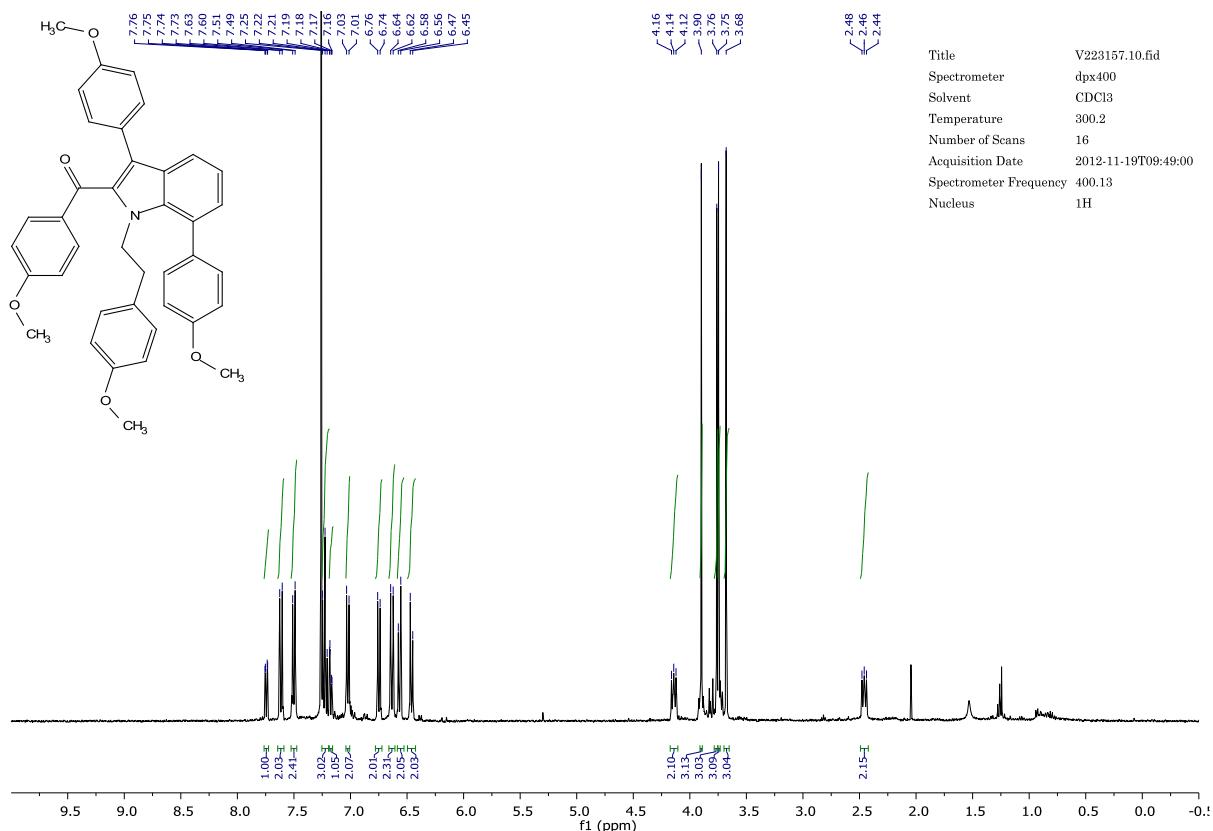
**4-methoxyphenyl)(3-(4-methoxyphenyl)-1*H*-indol-2-yl)methanone (196)**



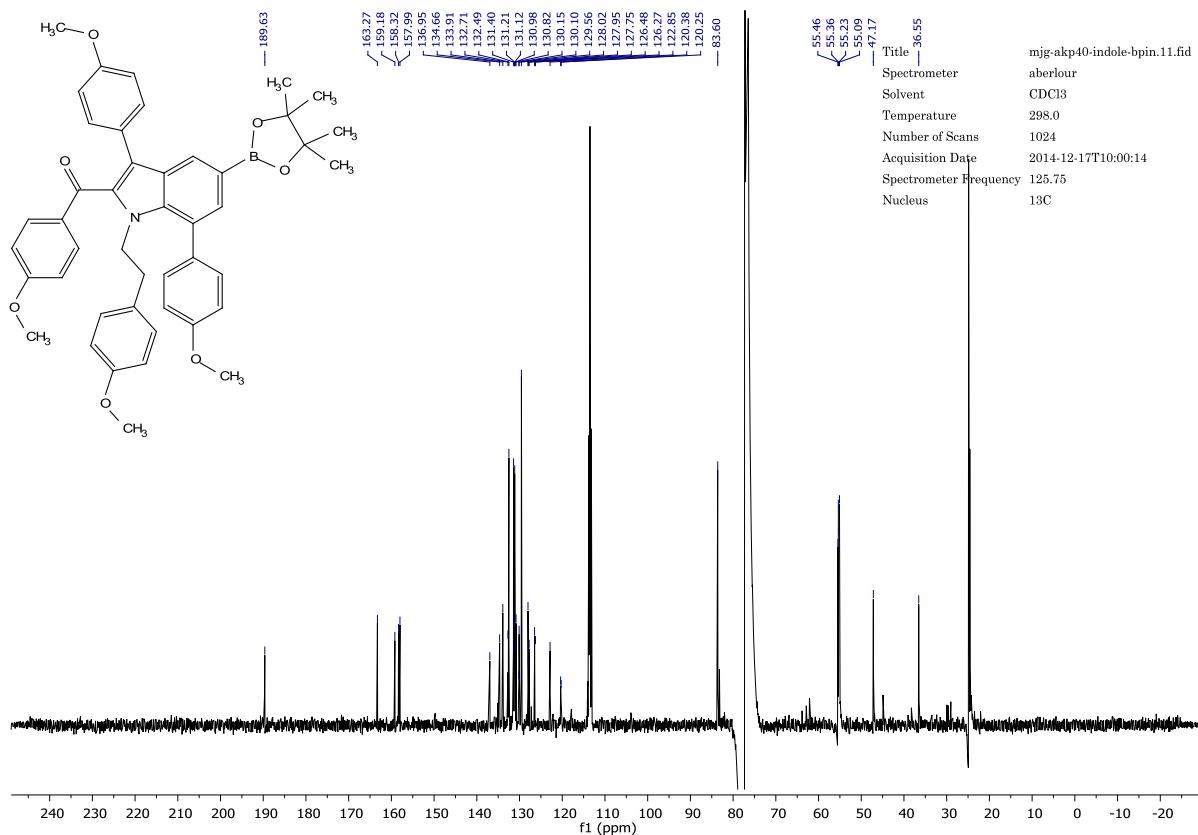
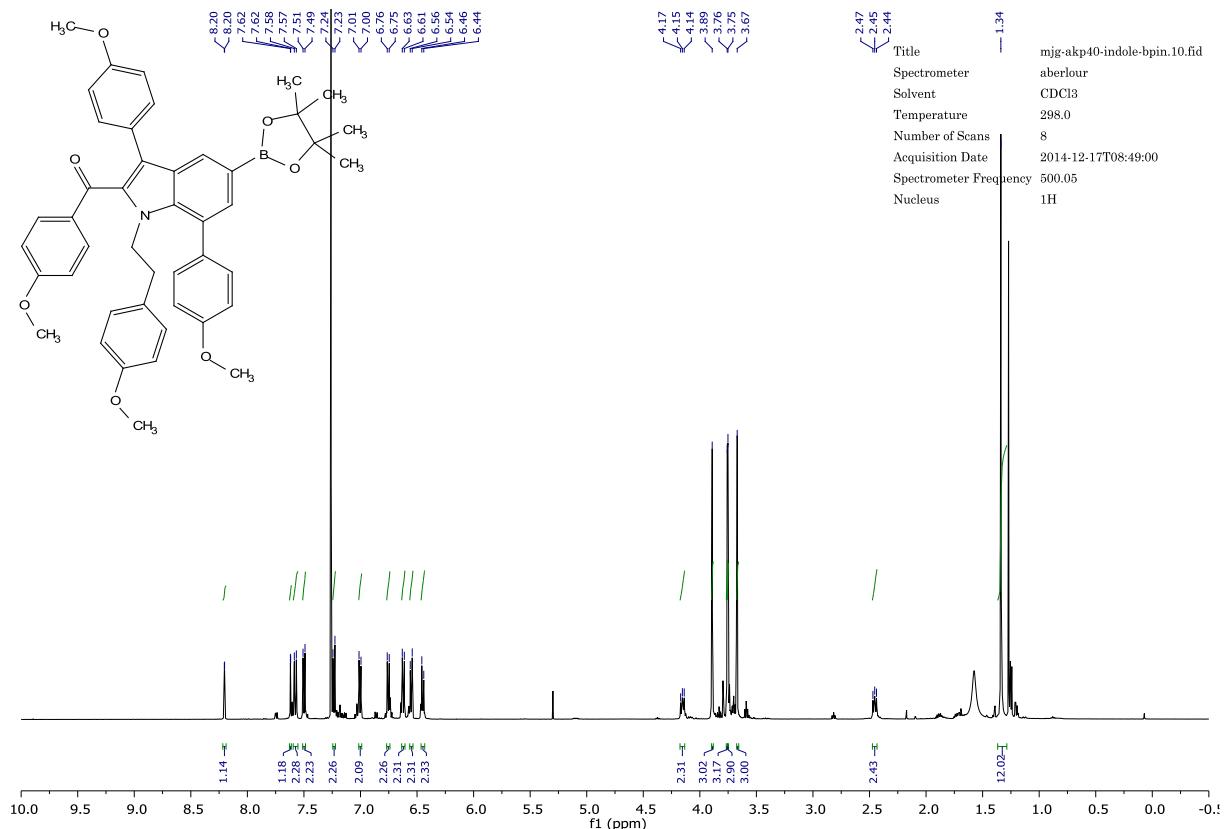
**(3,7-bis(4-methoxyphenyl)-1H-indol-2-yl)(4-methoxyphenyl)methanone (198)**



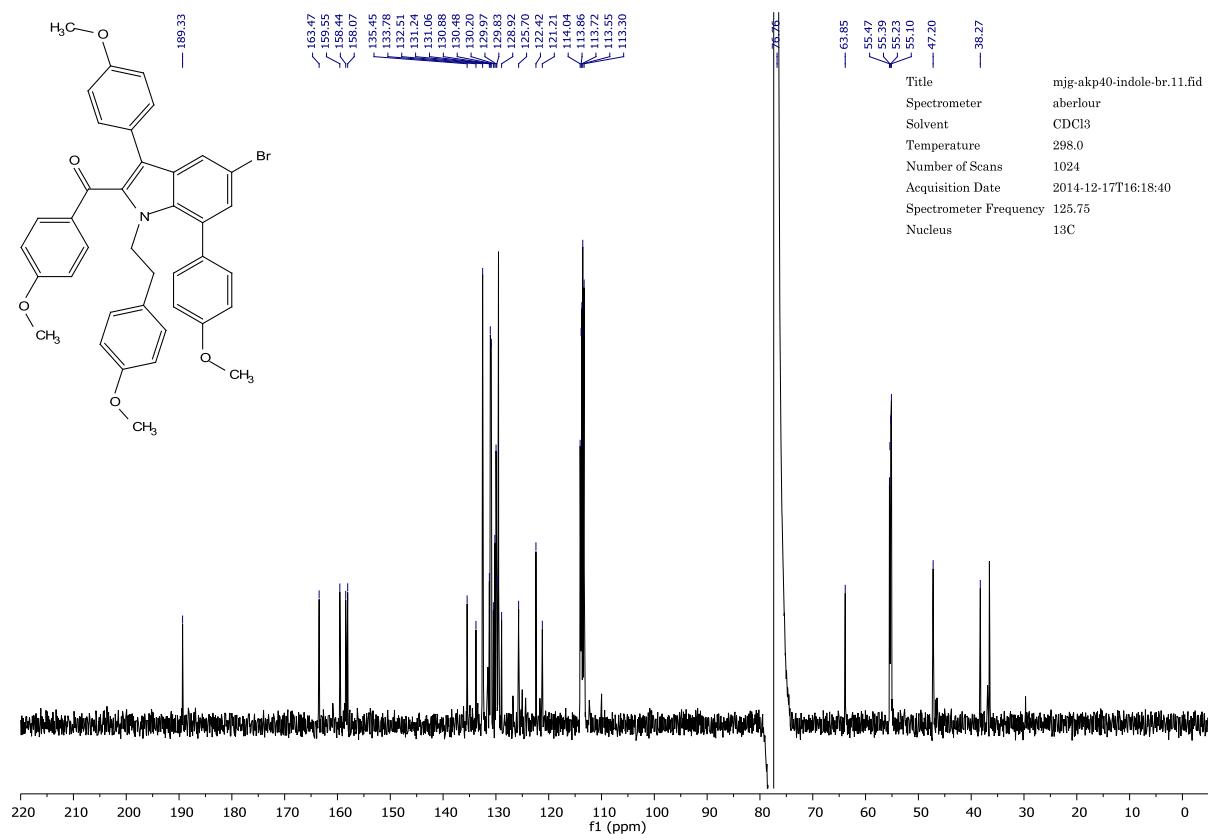
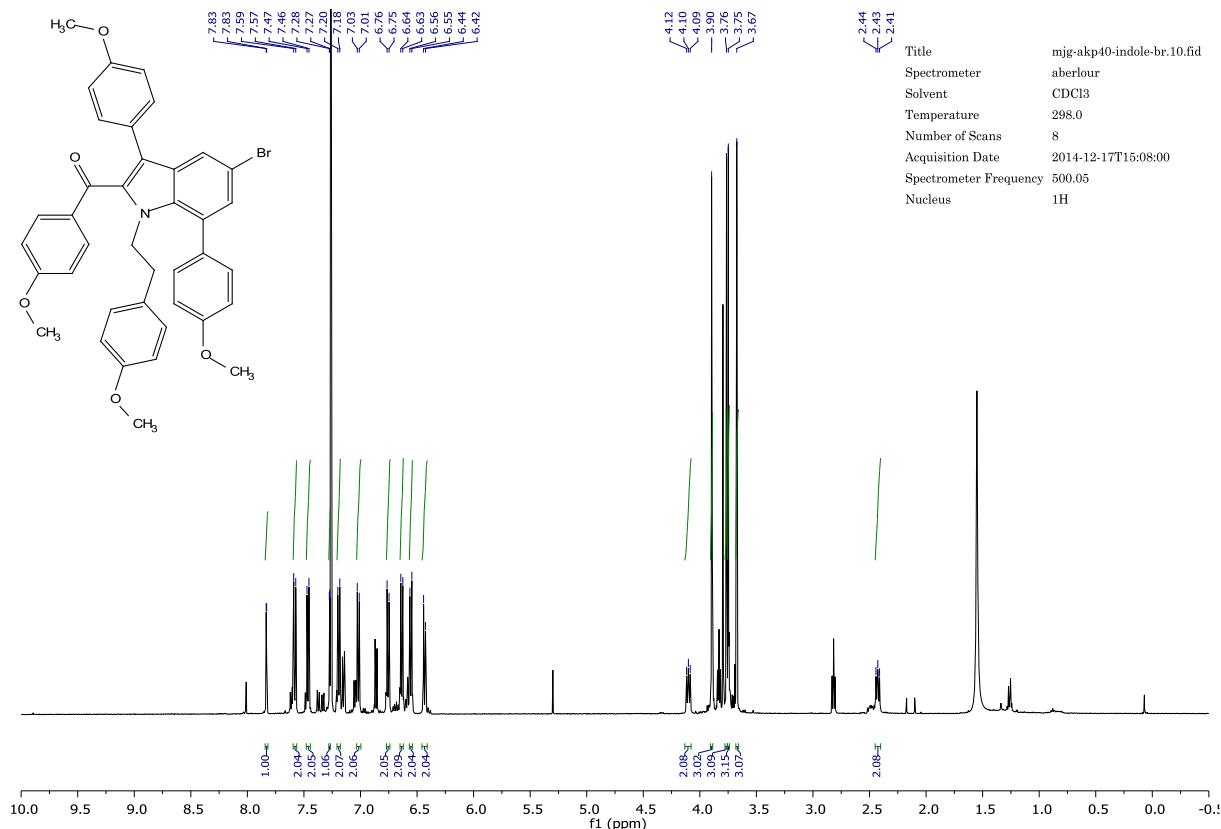
**(1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (199)**



**(1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-2-yl)(4-methoxyphenyl)methanone (200)**



**(5-bromo-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (201)**



**(5-((2-(benzyloxy)phenyl)amino)-1-(4-methoxyphenethyl)-3,7-bis(4-methoxyphenyl)-1*H*-indol-2-yl)(4-methoxyphenyl)methanone (202)**

