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**Synthesis and Photochromism of Fused Pyran
Systems**

Nicola Soltowska

A thesis presented to the University of Huddersfield, School of
Applied Sciences, as partial fulfilment for the Degree of MSc by
Research.

Submitted 24/05/2021

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Abstract

Two complementary approaches have been employed to synthesise an extensive series of photochromic 4,6-diaryl-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-2*H*-naphtho[1,2-*b*]pyrans. In the former approach 1,1,3-triarylprop-2-yn-1-ols, derived either from the addition of an arylacetylides to substituted benzophenones or from the Sonogashira cross-coupling between an aryl halide and 1-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)prop-2-yn-1-ol, were subjected to an acid-catalysed condensation with 4-bromo-1-naphthol to afford a series of 6-bromo-4-aryl-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-2*H*-naphtho[1,2-*b*]pyrans. Subsequent replacement of the 6-bromo substituent with an aryl group was achieved using a Suzuki-Miyaura cross-coupling reaction with a range of arylboronic acids to efficiently afford the 4,6-diaryl-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-2*H*-naphtho[1,2-*b*]pyrans.

The alternative approach relied upon the preparation of 4-aryl-1-naphthols from 4-bromo-1-naphthol via a Suzuki-Miyaura cross-coupling reaction. Condensation of the foregoing 4-aryl-1-naphthols with 1,1,3-triarylprop-2-yn-1-ols afforded the 4,6-diaryl-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-2*H*-naphtho[1,2-*b*]pyrans directly in good yield.

A limited number of 6-methoxy-4-aryl-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-2*H*-naphtho[1,2-*b*]pyrans were also obtained by the acid-catalysed reaction between 4-methoxy-1-naphthol and 1,1,3-triarylprop-2-yn-1-ols.

Whilst the majority of the novel 4,6-diaryl-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-2*H*-naphtho[1,2-*b*]pyrans displayed a photochromic response generating red hues upon irradiation, the best photochromic response was noted from the combination of a strongly electron-withdrawing 4-aryl moiety with an electron-donating 6-aryl unit; such a combination in the secondary chromophore results in opposition of the traditional donor-acceptor system in the photomerocyanine i.e. a cross-conjugated system is established upon irradiation. Remarkably inverting the donor-acceptor properties of the 4- and 6-aryl groups, establishing a secondary chromophore which supported that of the photomerocyanine, resulted in complete loss of photochromism and instead lead to fluorescence.

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List of abbreviations	Full form
APTS	(3-Aminopropyl)triethoxysilane
BCD	β -cyclodextrin
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
1,2-DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAB	4-Dimethylaminobenzaldehyde
DMAc	<i>N,N</i> -Dimethylacetamide
DME	Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulfoxide
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
PPA	Polyphosphoric acid
PPTS	Pyridinium 4-Toluenesulfonate
PTSA	4-Toluenesulfonic acid
TBAB	Tetra- <i>n</i> -butylammonium bromide
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TMEDA	Tetramethylethylenediamine
Tol	Toluene

A note on the reference system

The referencing system employed throughout this thesis is that devised by A. R. Katritzky and which is widely utilized in the discipline of heterocyclic chemistry including in the encyclopaedic reference works *Comprehensive Heterocyclic Chemistry* Pergamon Press (Oxford), 1984, *Comprehensive Heterocyclic Chemistry II* Elsevier (Oxford) 1996, *Comprehensive Heterocyclic Chemistry III*, Elsevier (Oxford), 2008, *Advances in Heterocyclic Chemistry*, and the annual reviews *Progress in Heterocyclic Chemistry*.

This system is used in place of traditional numerical references and allows the reader to extract the reference directly from the text. The references are given in the format <NNNNLLLNNNN> where the initial four numbers (N) denote the year in which the citation was published, the letters (L) indicate the journal, book or patent from which the citation has originated, and the final numbers refer to the page number. For journals which publish more than one volume per year, the volume number is given in parentheses after the journal code. Books are assigned the code B and personal communications are designated as PC. A full citation of the reference is provided in the references chapter.

Chapter 1.0 Introduction

1.1 Nomenclature and structure of naphthopyrans

Naphthopyrans, often termed benzochromenes, result from the fusion of a pyran ring to a naphthalene unit. This ring fusion generates three possible isomeric naphthopyrans where the pyran ring *b*-face is fused to one face of the naphthalene moiety (Figure 1.1).

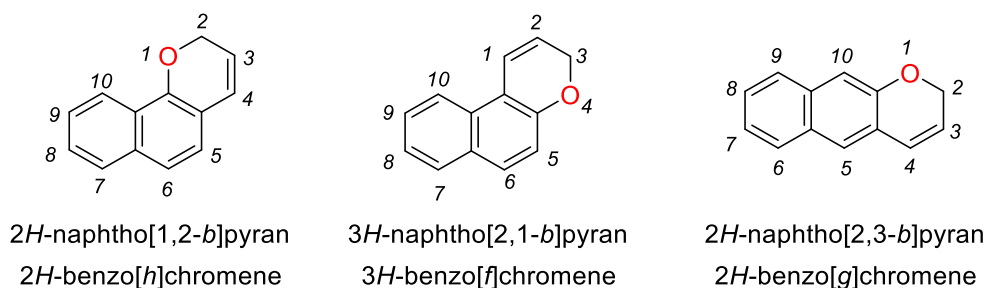


Figure 1.1: Isomeric *b*-fused naphthopyrans

1.2 A note on photochromism

The widely accepted definition of the phenomenon known as photochromism was provided by Glenn H. Brown in his book entitled 'Photochromism' which forms Volume III of the Techniques of Chemistry series <1971B-1>. Brown defined photochromism as "a reversible change of a single chemical species between two states having distinguishably different absorption spectra, such change being induced in at least one direction by the action of electromagnetic radiation". The phenomenon can be illustrated by equation 1 (Figure 1.2).

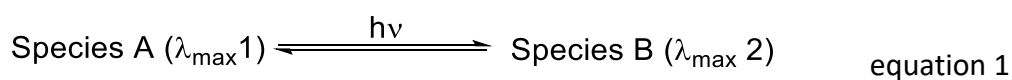


Figure 1.2: Equation to represent the phenomenon of photochromism

In other words, when the substance is subjected to UV-irradiation it is converted from stable chemical structure A (invariably colourless or pale-yellow) into the less stable isomer B (usually intensely coloured) showing different properties and absorption characteristics. The return to the original form A usually occurs either spontaneously in the dark at room temperature (termed T-type photochromism) or under illumination with visible light (termed P-type photochromism). <2011CSR672>

The phenomenon of photochromism has featured in several major books <1971B-1; 1990B-1; 1999B-1; 1998B-2; 2003B-1; 2006FD85; 2008B-1; 2011B-1; 2011B-2; 2016B-1; 2016B-2> and in numerous review articles <2000CR1683; 2001JCE645; 2002CC2804; 2003ARPC277; 2004CSR85; 2004CSR579; 2008EC84; 2010PJA472; 2010PPS1535; 2015CSR3719 2016NC11118; 2018JMCC191>. This present thesis concerns the photochromism of naphthopyrans, more specifically the 2*H*-naphtho[1,2-*b*]pyran isomer and as such the following section focusses on the naphthopyran systems with an emphasis on the target isomer.

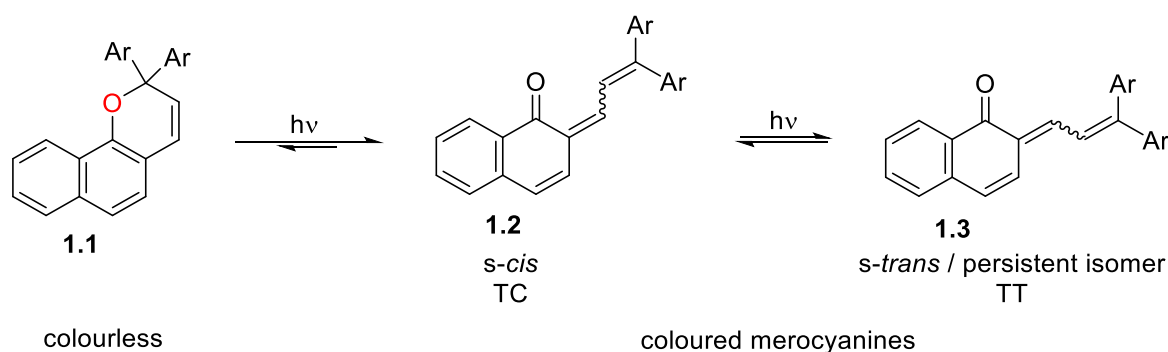
1.3 Photochromic naphthopyrans

In 1966 Becker and Michl first investigated photochromism of 2*H*-1-benzopyrans after they noticed colour switching at room temperature. <1966JACS5931> A few years later, the photochromism was again observed when the compound was subjected to UV-irradiation at -40 °C and then returned back to the colourless form at room temperature. <1971PP3567605> In 1986 Lenoble and Becker conducted in-depth research on absorption characteristics that enabled them to record the colour of the open form (photoisomer or photomerocyanine) as being yellow with λ_{max} 430 nm, however with limited evidence of the lifetime it was simply stated that the photoisomer was stable over a few hundred microseconds. <1986JP187>

From these initial studies naphthopyrans have attracted significant interest and manipulation of their chromophore unit, through the judicious placement of substituents on their molecular core, has allowed significant tailoring of their photochromic properties, leading to a wide variety of academic investigations and importantly commercial applications. The foregoing research effort led to opportunities in the fields of data storage for signal recording <1971DEP1947715>, sunglass material (including photochromic ophthalmic glasses <1980USP4211569; 2004JPP2004339184> and lenses <1985USP4498919; 1996WOP9627488; 2002WOP2002022594>, plastic lenses <1971USP3627690; 1996FRP2728576; 2008USP7465415, 2008EPP1978022>, photoreactive lenses <1987EPP250193>), thin films <1973ZN786>, optical instruments <1987JPP62195076>, light-controlling glass, masking and temp-indicating materials <1989JPP02237987>, textile printing paste and print articles <1994GBP2270321>. Further research on these reversible photo-

switchable compounds enabled extension into a wider range of materials such as molecular switches, wires or sensors. <2013AM378>

These thermally reversible (T-type) naphthopyrans have been embedded into the ophthalmic spectacle lens industry because of their cheap and easy manufacturing process and fantastic properties in view of fast and reversible reaction to sunlight contrasting with a wide spectrum of colours. <2007JMC1885> UV-irradiation of the stable and essentially colourless naphthopyran **1.1** results in ring opening to produce the coloured photomerocyanine isomers. <1998JCS(P2)1153> These isomers are thermally unstable and usually revert back to the original and colourless state at different rates. For the *s-cis* (TC) isomer **1.2** the fade rate is fairly quick ranging from a few seconds to several minutes. However, the *s-trans* (TT) isomer **1.3** was found to be more stable with a fade rate that could range from minutes to hours and thus affording a very persistent colour. <2015JOC12177>



Scheme 1.1: Photochemical ring-opening of the 2H-naphtho[1,2-*b*]pyran to form isomeric photomerocyanine species

Due to the potential photochemical decomposition (fatigue) of all organic photochromic systems, including naphthopyrans, related to their continued coloration upon exposure of electromagnetic radiation there is an obstruction in functional applications. <2019AM1805661> Smart windows, which required long term stability have become an interesting inspiration for further research in which photochromic naphthopyrans could be enhanced to provide upgraded colourability, faster response and longer lifetime along with lower costs and large-scale manufacturing. <2016ARCBE283>

For naphthopyrans to exhibit good photochromism at room temperature there are two important caveats: (i) the saturated C-atom adjacent to the pyran ring O-atom must be

geminally substituted with (hetero)aryl groups, and (ii) the angular arrangement (**1.4** and **1.5**) must be employed. The latter point arises as a consequence of the photochromic reaction of the naphthopyran system which relies upon the electrocyclic ring-opening of the pyran ring to afford a dieneone (photomerocyanine) system (Figure 1.3). For the linear isomer **1.6** the aromaticity of each of the rings of the naphthalene unit is disrupted and this is energetically unfavourable, whereas for the two angular isomers, **1.4** and **1.5**, only the aromaticity of one of the naphthalene rings is lost, which is countered by the gain in stabilization through the generation of an extended conjugated system.

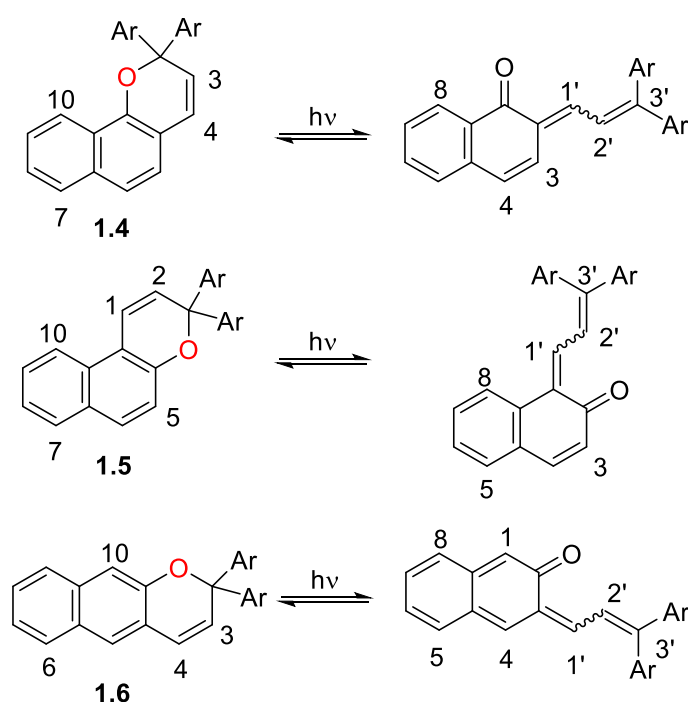


Figure 1.3: Photochemically induced ring-opening of the naphthopyran isomers

Extensive research has been conducted mainly on the 3*H*-naphtho[2,1-*b*]pyran isomer <1960JCS3094; 1972AC458; 1999B-1; 2001DP(49)65; 2006T737; 2007JM1885; 2015DP(113)239> while studies on the 2*H*-naphtho[1,2-*b*]pyran isomer <2004H567; 2014CC7900> are comparatively rare. However, it has been noted that in contrast to 3*H*-naphtho[2,1-*b*]pyran system, the 2*H*-naphtho[1,2-*b*]pyran isomers are described to generate photomerocyanines which are much more intense colouring, have bathochromically shifted absorption maxima (λ_{max}) and are significantly much slower to fade thus having a longer half-life ($t_{1/2}$). Exposure of 2,2-diaryl-2*H*-naphtho[1,2-*b*]pyrans to UV-radiation produces an

equilibrium which favours the photomerocyanine isomers and thus presents a much more intense colour. <1999B-1>

There are relatively few reports of single-crystal X-ray structures of 2*H*-naphtho[1,2-*b*]pyrans reported in the literature. Four structures have been reported and are collected in Figure 1.4. Key features of these structures are the bond distances around the pyran ring and the planarity of the O-(1)C-Ar₂ unit according to the ring conformations. It was reported that the pyran ring of **1.8** <2011AC980> and of **1.9** <2011AC1067> in their crystal structures have an envelope conformation with the O-(1)C-Ar₂ unit out of ring plane whereas the pyran ring of **1.10** <1999AC1123> adopted the half-chair conformation. The bond lengths O-(1)C and (1)C-(2)C vary only slightly with each naphthopyran ring system. Interestingly, a large variation has been noted for the bond angle Ar¹-(1)C-Ar² when the naphthopyran has various substituents. For the molecules **1.7** and **1.8** with aryl rings possessing substituents at the *para* positions <2003JPPA7> the bond angles are 111.7 ° and 112.3 ° respectively. However, for the molecule **1.9** with a phenyl and the strongly electron donating 4-Et₂NC₆H₄-substituent showed much smaller bond angle of 93.0 °. The smallest bond angle (72.8 °) has been noted when the molecule has an *o*-MeO substituent on each of the aryl rings **1.10**.

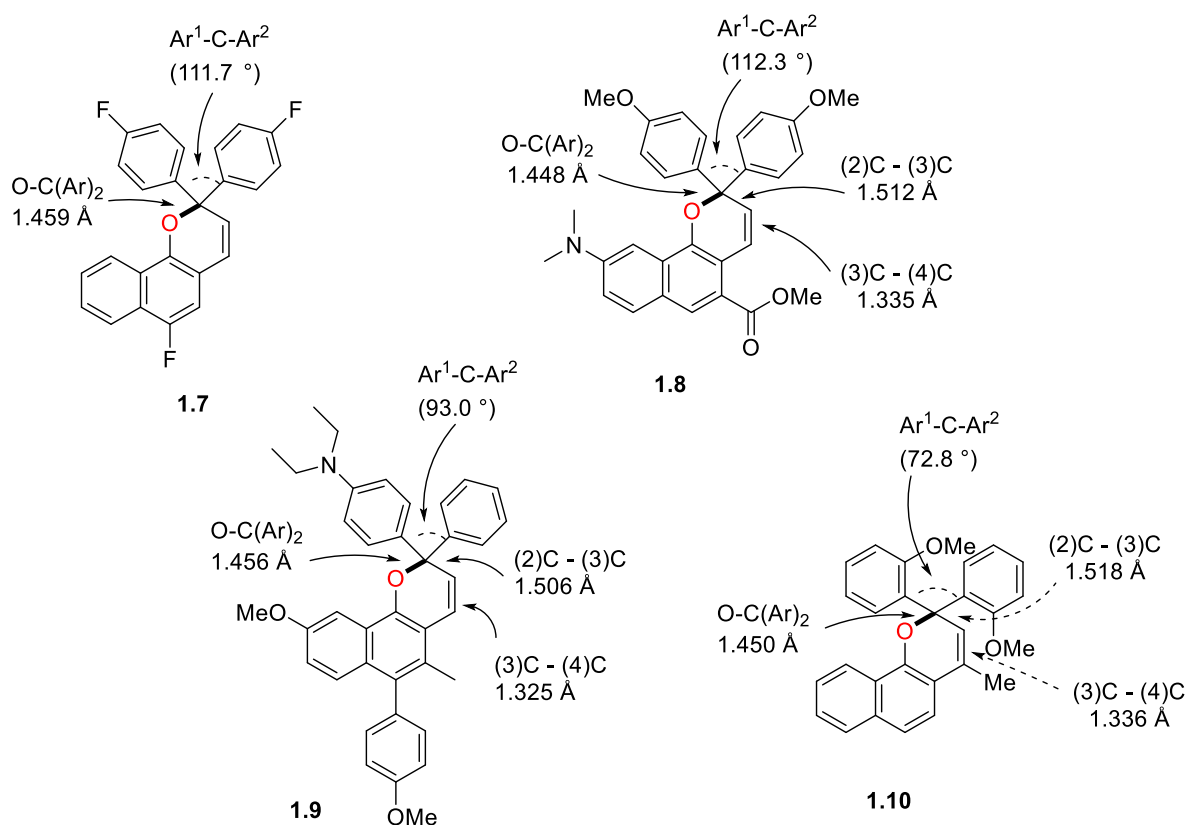


Figure 1.4: Structures and crystallographic properties of some 2*H*-naphtho[1,2-*b*]pyrans

Bond lengths of the photomerocyanine **1.11** have been reported and are contrasted in Figure 1.5. For the TT isomer **1.11** the single bonds between (1)C-(2)C and (1')C-(2')C are shorter than in the case of single bond length (2)C-(3)C between closed form naphthopyrans. In addition, double bond characters of the open pyran ring are longer in the photomerocyanine isomer than in the closed pyran ring. <2014CC7900>

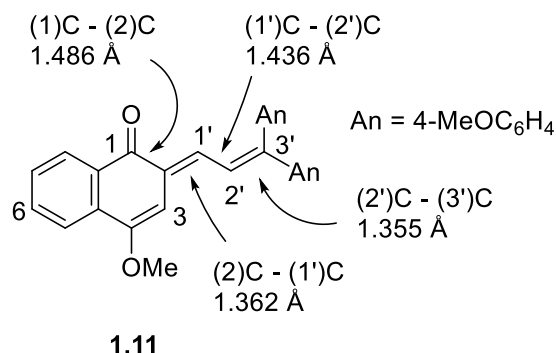


Figure 1.5: Structure and crystallographic properties of merocyanine dye **1.11**

1.3.1 NMR spectroscopy

The majority of NMR data appears in journal articles which are predominantly devoted to the synthesis and routine characterization of naphthopyrans. For the simple substituted naphthopyrans it can be stated that in their ¹H NMR spectra 3-H in the pyran resonates at approximately 6.4 ppm as a doublet with $J = 9.6 - 10.1$ Hz and its partner 4-H resonates further downfield as a consequence of its benzylic nature at ca. 6.9 ppm and may sometimes be obscured by aromatic ring protons. The 7-H and 10-H protons, being in α -positions on the naphthalene moiety, resonate furthest downfield at ca. 8.2 ppm and ca. 8.4 ppm, respectively. The key signal in the ¹³C NMR spectra, which can be used to confirm the presence of the pyran unit is the carbon attached to two aryl units that is identified as sp³ hybridized ring carbon, which resonates at ca. 82 ppm (Figure 1.6). <1999MRC159>

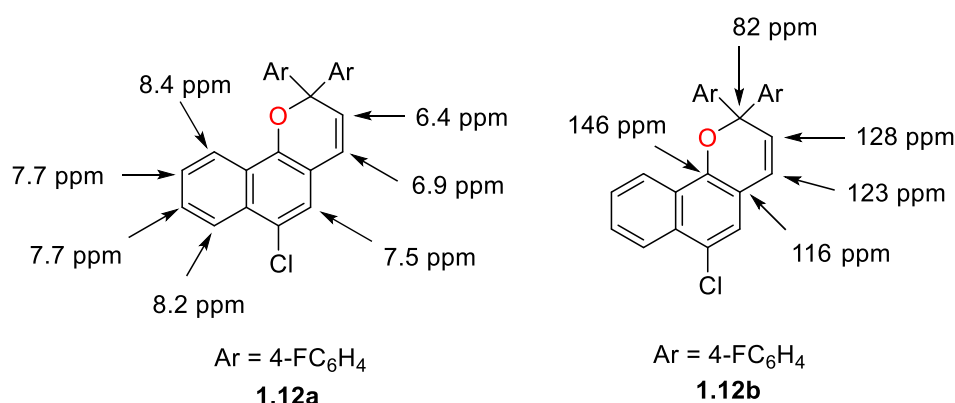
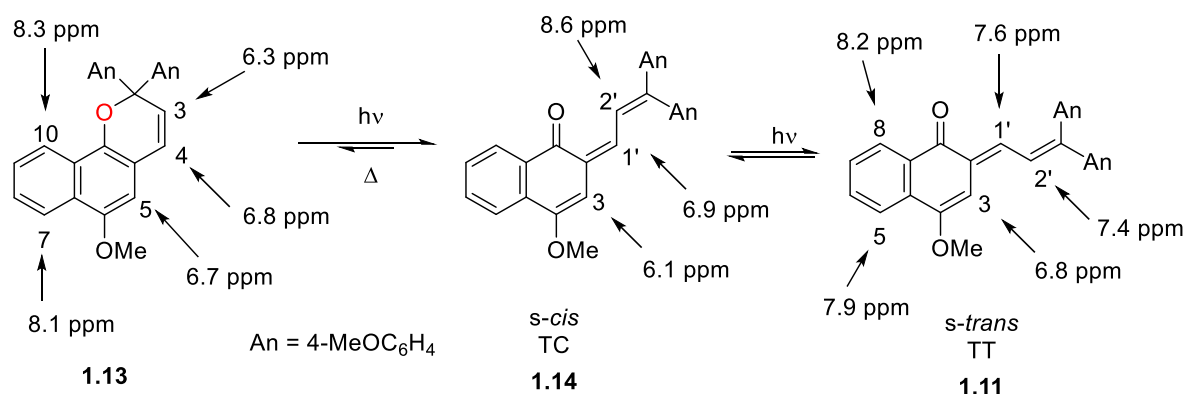


Figure 1.6: Key ¹H and ¹³C NMR signals for the 2*H*-naphtho[1,2-*b*]pyran system

Replacement of the 6-chloro substituent of **1.12a** with a 6-methoxy group **1.13** leads to predictable differences in the chemical shifts of the nearby protons but the remaining signals are relatively unaffected (Scheme 1.2). Thus for **1.13** 5-H, where the hydrogen is adjacent to the methoxy group, is shifted upfield and resonates at 6.7 ppm relative to that next to the halogen in **1.12a** which resonates further downfield at 7.5 ppm. Just a small change in the chemical shift was observed between 3-H and 4-H that resonates at 6.3 ppm and 6.8 ppm, respectively with a coupling constant of 9.6 Hz. To contrast the chemical shifts between naphthopyran and their photomerocyanine isomers, the ¹H NMR spectrum of **1.13** was recorded in d₆-acetone and subjected to UV-irradiation for a short period of time. This allowed the observation some of new, transient signals in the ¹H NMR spectrum such as a singlet for 3-H that resonates at 6.1 ppm for the TC isomer as well as the signals with the great interest resonating at 8.6 ppm and 6.9 ppm with a coupling constant of 12.2 Hz confirming the open form of TC isomer. Prolonged UV-irradiation resulted in the photoisomerization of the TC to the TT isomer leading to an equilibrium mixture which contained **1.13**, **1.14** and **1.11** from which key NMR signals could be extracted (Scheme 1.2). <2014CC7900>



Scheme 1.2: ¹H NMR signals for the 2*H*-naphtho[1,2-*b*]pyran and their ring-opened isomers

1.3.2 Infrared spectroscopy

The major absorptions for substituted diaryl naphthopyrans are typically due to the stretching vibrations for the C-O and C=C bonds which appears at around 1250 cm^{-1} and $1630 - 1650\text{ cm}^{-1}$, respectively. <2003EJOC1220; 2006GXH75; 2016OBC6703>

1.3.3 Mass spectrometry

There is scant information concerning the mass spectral fragmentation of naphthopyrans. It was previously reported that the diaryl naphthopyran fragments by initial loss of one of the C-2 aryl substituents forming a relatively stable naphthopyrylium cation (Figure 1.7) which then undergoes a more complex, multiple fragmentation. <1996CHC325; 2009DP(81)85>

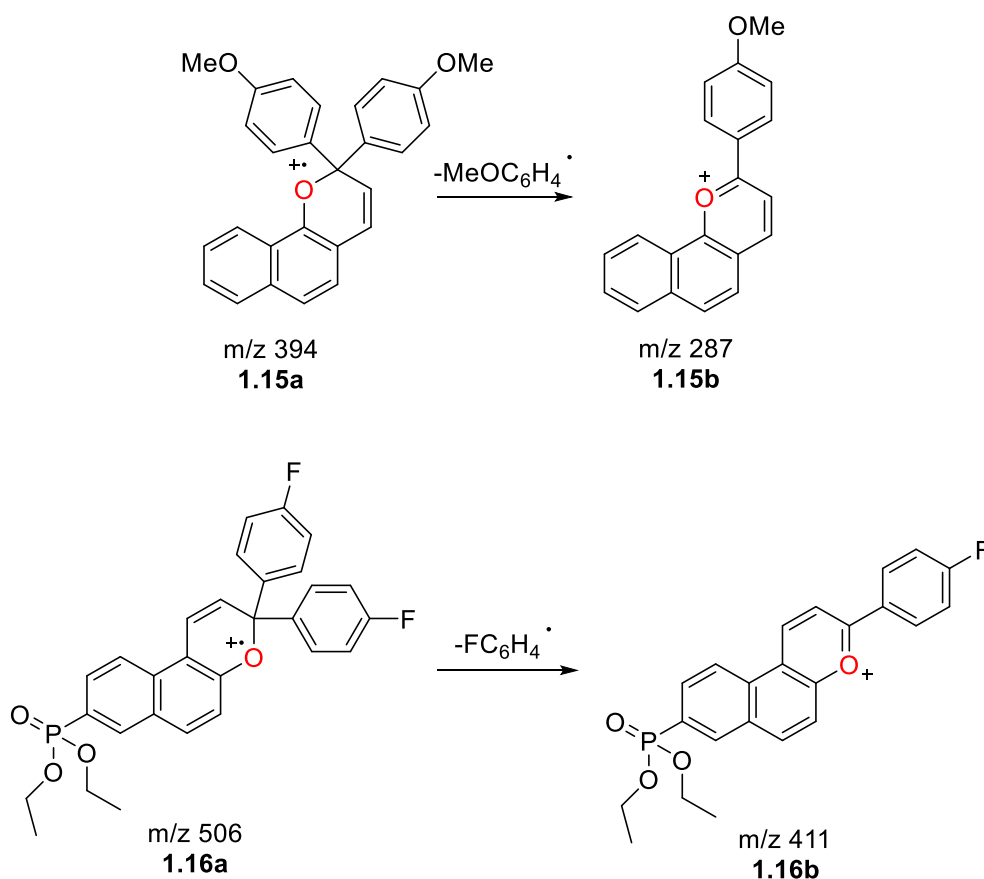
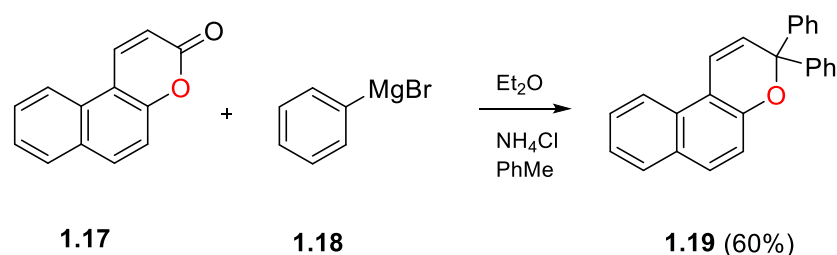


Figure 1.7: Mass spectral fragmentation of a 2H-naphtho[1,2-b]pyran **1.15a** and 3H-naphtho[2,1-b]pyran **1.16a** to afford a pyrylium cations **1.15b** and **1.16b**

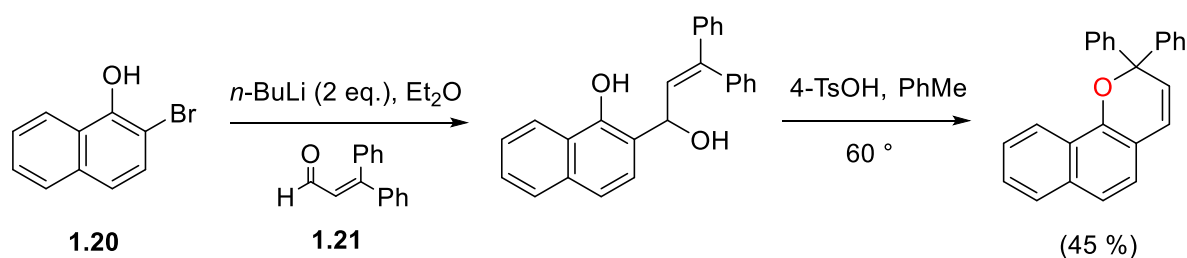
1.4 Synthetic Methods

There are limited number of efficient synthetic approaches to form *gem* diaryl substituted naphthopyrans. Many of the methods have been used to obtain the more commonly encountered 3*H*-naphtho[2,1-*b*]pyran isomer, however such methods can be extrapolated to prepare the isomer of interest in this work, the 2*H*-naphtho[1,2-*b*]pyran, provided that the requisite starting material is available. Among a range of reported procedures for the preparation of simple benzopyrans (chromenes) <1975AHC159; 1977CHC11; 1992BSCQ305; 1996CHC351; 1998T6457> there are a few suitable methods that can be adapted to synthesize a *gem* diaryl substituted photochromic naphthopyrans in good yield. The most traditional method concerns the reaction of excess aryl Grignard reagents with (benzo)coumarins **1.17** giving a moderate yield of naphthopyran **1.19** which results from addition of the phenylmagnesium bromide **1.18** to the lactone unit (Scheme 1.3). <2013CNP102993156>



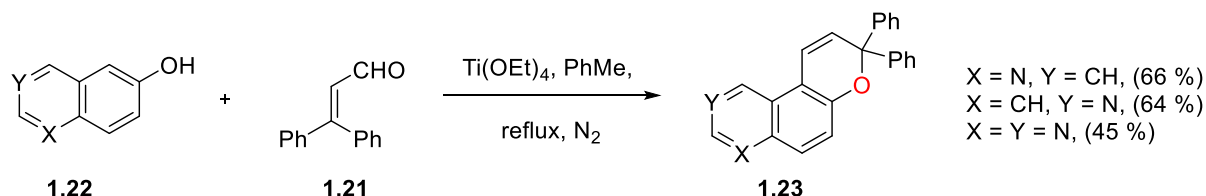
Scheme 1.3: Reaction of aryl Grignard reagent with coumarin

The application of α,β -unsaturated aldehydes to provide the 3-carbon C-2 – C-4 pyran ring unit has proved useful. Generation of the di-anion from bromophenol **1.20** and quenching with β -phenylcinnamaldehyde **1.21** resulted in a diol which could be cyclized to the pyran in 45% yield under acid catalysis (Scheme 1.4). <1997MCLC123>



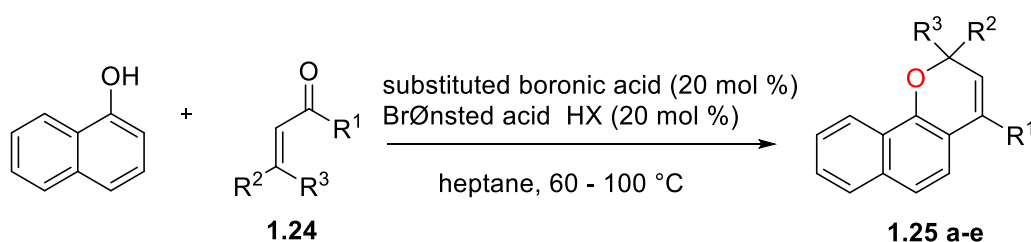
Scheme 1.4: Reaction of an α,β -unsaturated aldehyde with 2-bromo-1-naphthol

β -Phenylcinnamaldehyde **1.21** condenses with hetero substituted 2-naphthol **1.22** in the presence of titanium (IV) ethoxide and toluene. It was reported that the fusion of an electron-withdrawing heterocyclic ring onto the phenol unit resulted in greater yields than the use of the naphthol itself. However, this observed effect proved true when just one hetero atom containing system was fused onto the naphthol ring (Scheme 1.5). <1997HCA725>



Scheme 1.5: Reaction of an α,β -unsaturated aldehyde with hetero substituted 2-naphthols

The condensation of a range of α,β -unsaturated carbonyl compounds **1.24** with 1-naphthol has recently been explored by Dimakos and co-workers who employed a variety of aryl boronic acids and Brønsted acid catalysts to afford new naphthopyrans in very good yield (Table 1.1). It was found that pentafluorophenylboronic acid and diphenylphosphinic acid were the most efficient catalysts for the reaction of α,β -unsaturated ketones whereas (3,5-bis(trifluoromethyl)phenyl)boronic acid and benzoic acid are highly effective for the condensation of α,β -unsaturated aldehydes. <2016OBC6703>



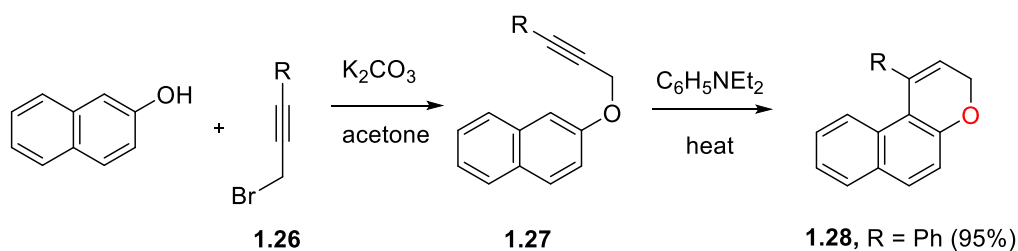
Compound	R ¹	R ²	R ³	Yield (%)
1.25a^a	Ph	Ph	H	75
1.25b^a	Me	Ph	Ph	72
1.25c^a	Me	Ph	H	88
1.25d^a	Me	Me	Me	48
1.25e^b	H	Me	Me	93

^a C₆F₅B(OH)₂/Ph₂PO₂H (20/20 mol %) in heptane at 100 °C for 3 h under argon.

^b 3,5-(CF₃)₂C₆H₃B(OH)₂/PhCO₂H (20/20 mol %) in heptane at 60 – 100 °C for 17 h.

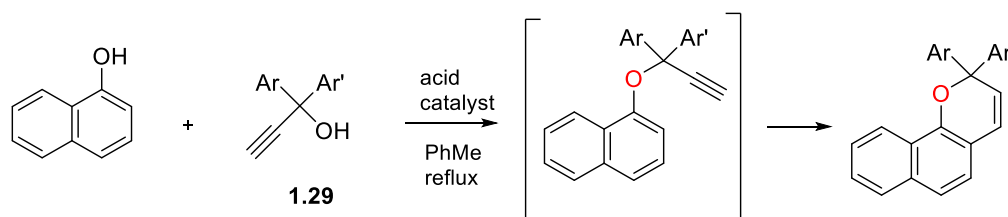
Table 1.1: Reactions of α,β -unsaturated carbonyl compounds with 1-naphthol in the presence of catalyst

Perhaps the most effortless and flexible method was first described by Iwai and Ide in 1963 wherein the reaction involved thermal rearrangement of naphthyl propargyl ether **1.27** (Scheme 1.6) produced from the alkylation of 2-naphthol with a propargylbromide **1.26** to afford the naphthopyran **1.28**. <1963CPB926> Reinvestigation of this seminal work using a phenyl substituted haloalkyne enabled the 1-phenylnaphthopyran to be obtained in an excellent yield of 95 %. <1997JOC7024>



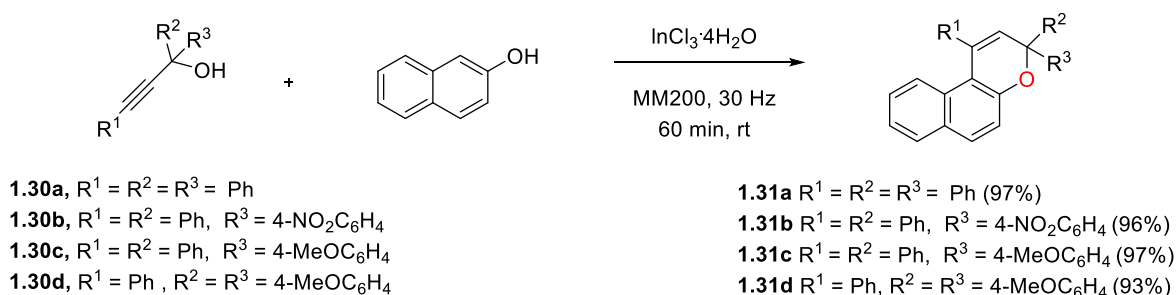
Scheme 1.6: Reaction of propargylbromides with 2-naphthol and subsequent thermal cyclisation

The foregoing 'Claisen rearrangement' has been extensively modified for hydroxy-substituted alkyne containing precursors which has allowed the synthesis of the ether intermediate and hence the naphthopyran in a one-step, acid-catalysed process. In this case, the reactants, a naphthol and a 1,1-diarylprop-2-yn-1-ol **1.29** were heated in toluene containing the acid catalyst which promotes the formation of the naphthyl propargyl ether and subsequently the requisite naphthopyran (Scheme 1.7). <1991USP5066818> A variety of acid catalysts have been used for the reaction of 1,1-diarylprop-2-yn-1-ols including sulfonic acids <2004ACST55; 2009M1500; 2010JPP2010248159>, acidic alumina <2003EJOC1220; 2008OBC3096>, Montmorillonite K-10 and Amberlyst 15. <2014JCS1081> The mechanism of the acid-catalysed reaction of 1,1-diarylprop-2-yn-1-ols with 1- and 2- naphthols and an exploration of by-product formation has been documented by Gabbutt *et al.* <2003EJOC1220> Interestingly, the related condensation of 3-methylbut-2-enal with 1-naphthol to afford a 2,2-dimethyl substituted 2*H*-naphtho[1,2-*b*]pyran was catalysed by ethylenediamine diacetate. <2007HCA2401>



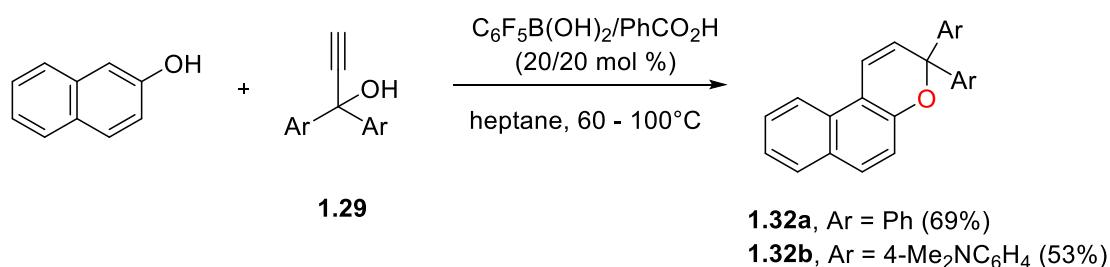
Scheme 1.7: Reaction of 1,1-diarylprop-2-yn-1-ol with 1- naphthol in the presence of catalyst

Further improvements to the Claisen protocol were described by Zhao and Carreira and photochromic pyrans were synthesized in excellent yields with addition of 5 mol % PPTS as the weak acid catalyst and $\text{CH}(\text{OCH}_3)_3$ as a dehydrating agent that readily improved this one-pot procedure. <2003OL4153> A few years later Dong and co-workers investigated an attractive methodology that enabled the synthesis of naphthopyrans **1.31a-d** under solvent free conditions. In this work the cyclization of propargylic alcohols **1.30a-d** with 2-naphthols in the presence of indium trichloride tetrahydrate catalyst under ball-milling conditions was examined (Scheme 1.8). <2008T10148>



Scheme 1.8: Synthesis of naphthopyrans under ball-milling conditions

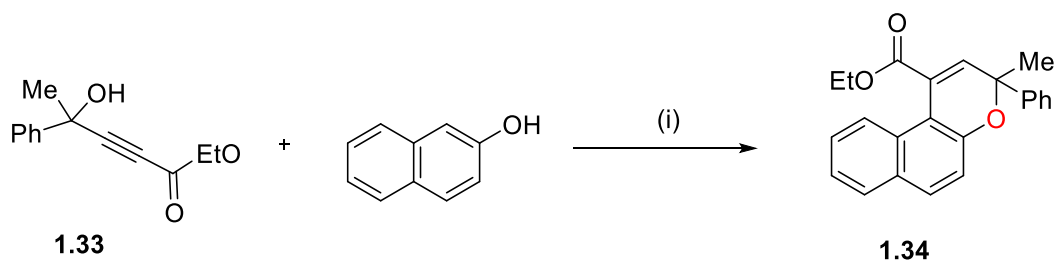
Furthermore, Dimakos and co-workers also investigated the synthesis of naphthopyrans from 2-naphthol with 1,1-diarylpropyn-1-ols **1.29** using a mixture of benzoic acid and a pentafluoroboronic acid, however the yields under these conditions were moderate (Scheme 1.9). <2016OBC6703>



Scheme 1.9: Reaction of 1,1-diarylpropyn-1-ol with 2-naphthol in the presence of benzoic acid and a pentafluoroboronic acid

In 2017, Yaragorla and co-workers studied the highly regioselective and solvent free method for making naphthopyrans using calcium triflate as the Lewis acid catalyst. This highly facile approach was achieved via annulation of naphthols with propargyl alcohols **1.33**. A range of combinations of catalysts were tested (Table 1.2), however not all provided good yields of 1-

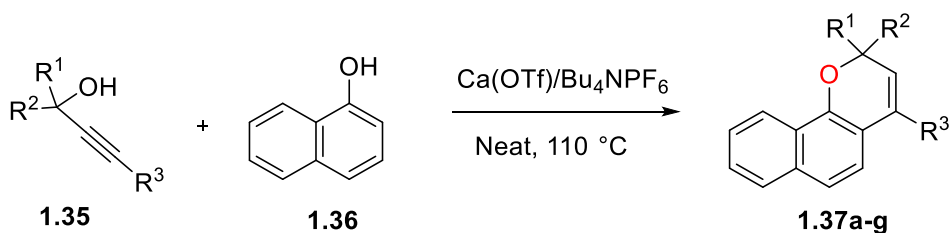
substituted naphthopyrans. Poor or moderate yields were observed when there was either an absence of additive or their action was performed in ethanol or a metal catalyst was used. In addition, a combination of calcium triflate with KPF₆, NH₄BF₄, and Bu₄NF failed to afford an improved yield. <2017TL4642>



Entry	Catalyst (mol %)	(i)	% Yield
1	Ca(OTf) ₂ /Bu ₄ NPF ₆ (05/05)	Neat, 110 °C, 5 h	75
2	Ca(OTf) ₂ /Bu ₄ NPF ₆ (05/10)	Neat, 110 °C, 1.5 h	81
3	Ca(OTf) ₂ (10)	Neat, 110 °C, 10 h	20
4	Ca(OTf) ₂ /KPF ₆ (10/10)	Neat, 110 °C, 3 h	65
5	Ca(OTf) ₂ /NH ₄ BF ₄ (10/10)	Neat, 110 °C, 6 h	55
6	Ca(OTf) ₂ / Bu ₄ NF (10/10)	Neat, 110 °C, 3 h	62
7	FeCl ₃ (10)	Neat, 110 °C, 10 h	53
8	Ca(OTf) ₂ /Bu ₄ NPF ₆ (10/10)	Ethanol, 90 °C, 10 h	20
9	Ca(OTf) ₂ /Bu ₄ NPF ₆ (10/10)	Toluene, 110 °C, 6 h	45
10	Ca(OTf) ₂ /Bu ₄ NPF ₆ (10/10)	1,2-DCE, 90 °C, 5 h	74

Table 1.2: Reaction of propargyl alcohols with naphthols under different conditions

With the optimal conditions of Ca(OTf)₂ / Bu₄NPF₆ in the absence of solvent the selection of naphthopyrans were synthesized (Table 1.3).



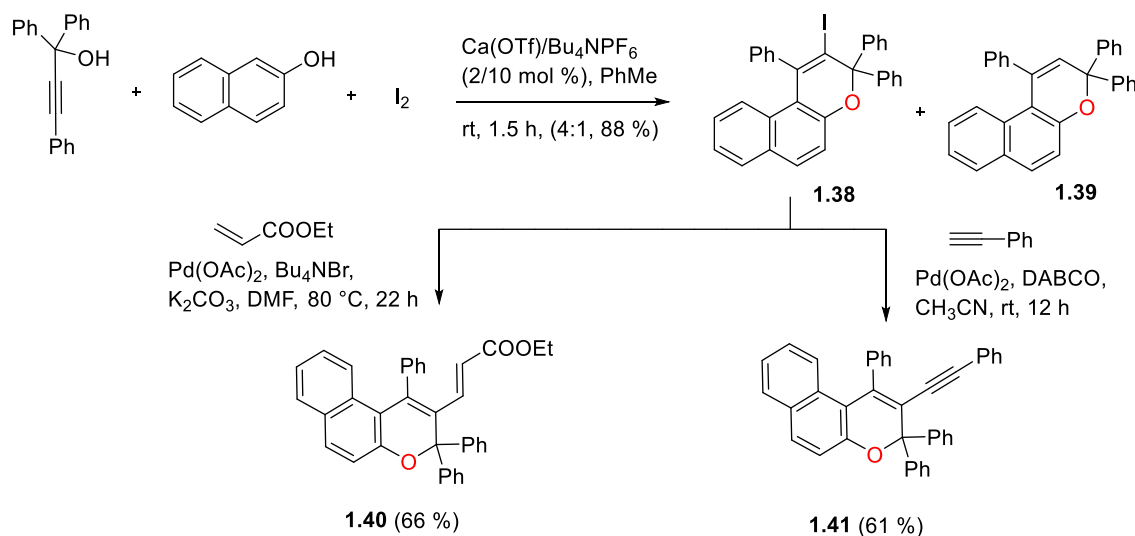
Compound	R ¹	R ²	R ³	Time / % Yield
1.37a^a	Me	Ph	CO ₂ Et	2 h / 86
1.37b^a	Ph	Ph	CO ₂ Et	2 h / 86
1.37c^a	Ph	Ph	CO ₂ Me	3 h / 72
1.37d^b	Ph	Ph	Ph	1 h / 81
1.37e^b	Ph	Me	Ph	1 h / 77
1.37f^b	Me	PhMe	Ph	2 h / 70
1.37g^b	Me	Me	Ph	40 min / 89

^a 1 eq. of **1.35**, 1.2 eq. of **1.36**, (5/10 mol%) of Ca(OTf)/Bu₄NPF₆

^b 1 eq. of **1.35**, 1.2 eq. of **1.36**, (2/10 mol%) of Ca(OTf)/Bu₄NPF₆

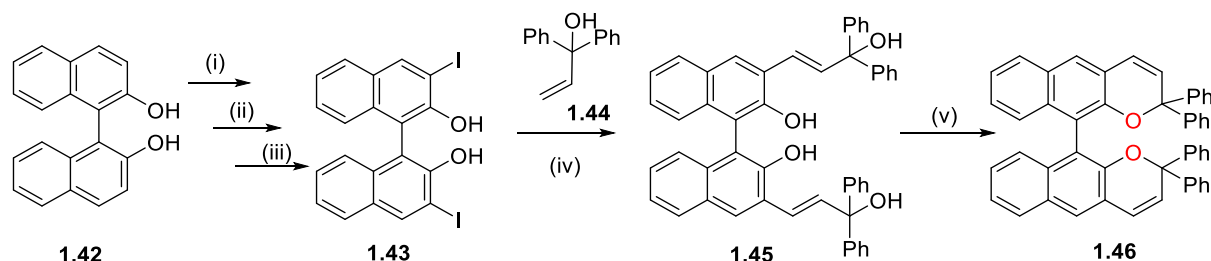
Table 1.3: Optimal conditions for synthesis of substituted naphthopyrans

Extension of the foregoing methodology, by the addition of I₂, led to the formation of the iodo substituted naphthopyran **1.38** together with the iodine free derivative **1.39**. The iodo substituent proved useful for further derivatization using cross-coupling reactions (Scheme 1.10). The inseparable mixture of iodo-pyran derivative **1.38** and **1.39** was reacted under both Heck conditions to give **1.40** in 66 % and also under Sonogashira coupling conditions to give **1.41** in 61 %. <2017TL4642>



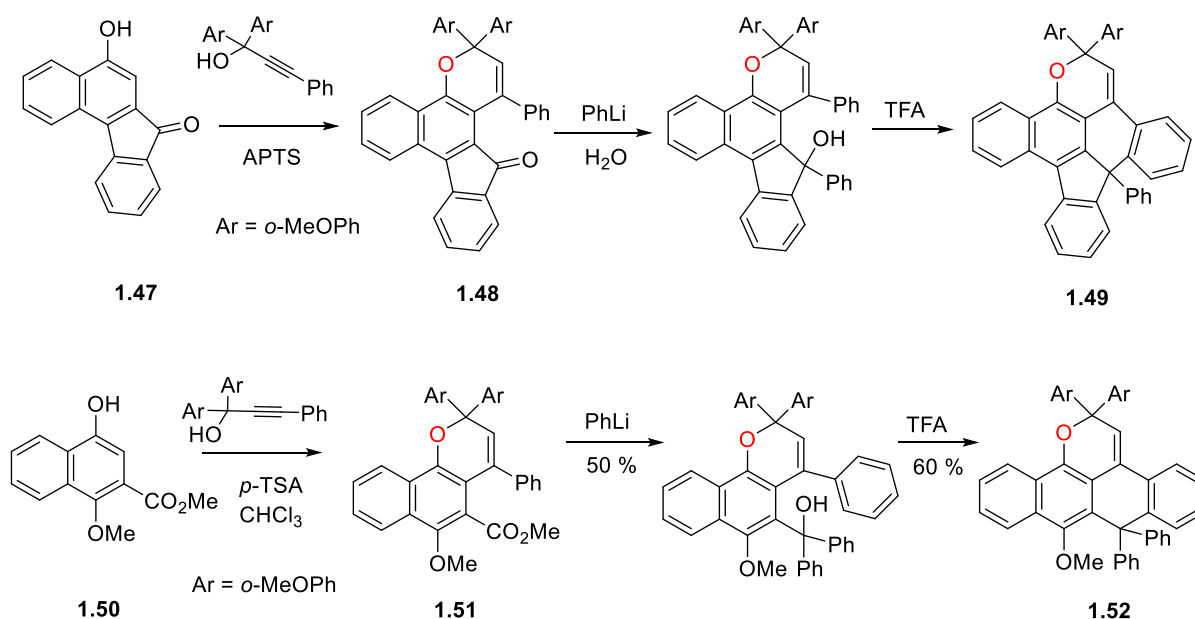
Scheme 1.10: Synthesis of iodo-naphthopyran required for further cross-coupling reactions

A Heck-coupling strategy with an iodo-substituted binaphthol has been employed in the simultaneous construction of the pyran rings of a chiroptical binaphthopyran switch (Scheme 1.11). <2010NJC1109>



Scheme 1.11: Reaction conditions (i) CH_3I , K_2CO_3 , acetone, reflux, 36 h, 98% yield; (ii) $n\text{-BuLi}$, TMEDA, diethyl ether, r.t., 4 h, I_2 , $-78\text{ }^\circ\text{C}$ to r.t., 5 h, 63% yield; (iii) BBr_3 , CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 4 h, 97% yield; (iv) **1.44**, $\text{Pd}(\text{OAc})_2$, K_2CO_3 , CH_3CN , $100\text{ }^\circ\text{C}$, 4 h, 82% yield; (v) silica, toluene, reflux, 24 h, 63% yield.

A variety of complex polycyclic naphthols have been subjected to the acid-catalysed Claisen protocol with substituted prop-2-yn-1-ols to afford a range of fused pyran containing systems. <2000USP6022497; 2004USP20040185255; 2005JPP300; 2006USP20060226401; 2009JPP180; 2012USP20120214992; 2013JMCC5387; 2015JOC12177; 2019DP(169)118; 2019CNP110343084; 2020EJOC985> One example of a complex polycyclic naphthopyran synthesis has been reported in a three-step process. However, the initial naphthopyran was produced in the first step through the established Claisen protocol. The first sequence depicted in Scheme 1.12 describes the condensation of a 3-phenyl-1,1-bis(4-methoxyphenyl) substituted propargylic alcohol with 5-hydroxy-7*H*-benzo[*c*]fluoren-7-one **1.47** furnishing the fused pyran, 5-oxo-2,2-bis(2-methoxyphenyl)-2*H*-4-phenylindeno[2,3-*f*]naphtho[1,2-*b*]pyran, **1.48**. However, in the second sequence 4-toluenesulfonate acid in chloroform was used to affect the pyran ring formation. Subsequent steps of these sequences involved treatment with PhLi /THF at $0\text{ }^\circ\text{C}$ providing a tertiary alcohol that required further reaction with trifluoroacetic acid in order to obtain the fused naphthopyrans **1.49** and **1.52**. <2015JOC12177; 2019DP(169)118>



Scheme 1.12: Synthesis of fused naphthopyrans

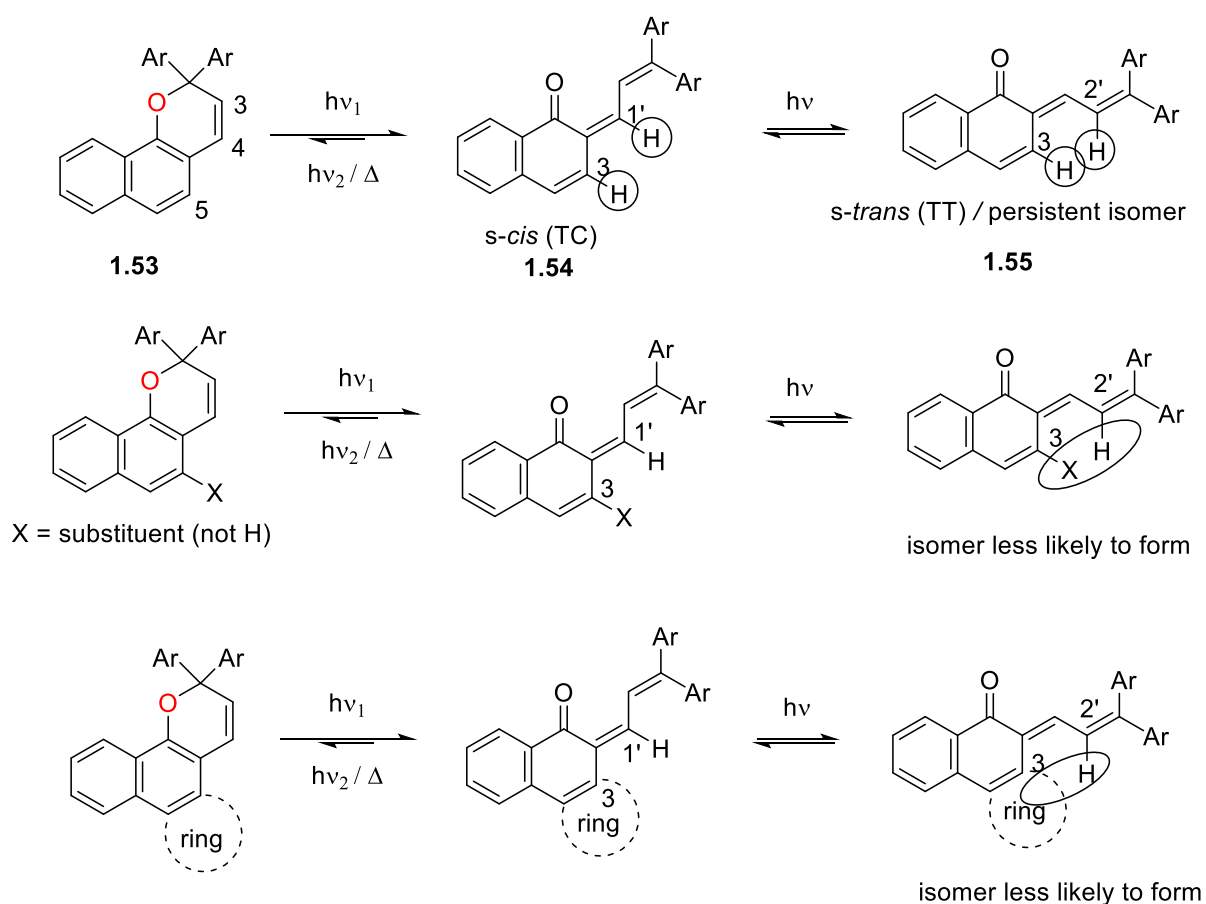
1.5 Effect of substituents on photochromism

As previously mentioned (Section 1.3), the *2H*-naphtho[1,2-*b*]pyrans have a higher equilibrium concentration of their photomerocyanines under steady state conditions than their *3H*-naphtho[2,1-*b*]pyran isomers, which provide the [1,2-*b*] isomers with intense colour for a significant period of time. Of the two photomerocyanines **1.54** recyclizes relatively quickly and thermally whereas the isomeric photomerocyanine **1.55** isomer has to photochemically isomerize back to the **1.54** isomer before it can thermally recyclize hence the process takes significantly longer. This slow recyclizations due to the lack of steric interaction between hydrogens in the *s-cis* and *s-trans* quinoidal open form of the *2H*-naphtho[1,2-*b*]pyran isomers (Scheme 1.13) that strongly destabilize the photomerocyanine isomers resulting in faster ring closure for the alternate *3H*-naphtho[2,1-*b*]pyran isomer. The ability of these photomerocyanines **1.54** and **1.55** to revert to the original naphthopyran structure can be controlled by careful placement of substituents (Scheme 1.13). <2002JPCA9236>

The best approach for ophthalmic lenses is to have intensely coloured photomerocyanines that undergo rapid switching in both colour -forming and -fading reactions. Therefore, for photochromic *2H*-naphtho[1,2-*b*]pyrans to exhibit useful photochromic properties at room temperature the 5-position of the molecule **1.53** required either a substituent (e.g. alkyl, aryl,

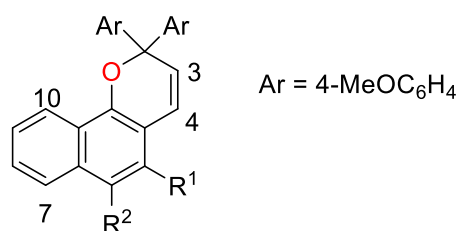
CO₂R) or a fused ring (Scheme 1.13) which was sufficiently bulky to induce congestion in the ring-opened photomerocyanine isomers such that either their lifetime was significantly shorter than the photomerocyanine of the unsubstituted parent molecule or the photomerocyanine interconversion was minimized (Table 1.4). <2015AHC160>

In order to mimic the steric interactions between 3-H and 1'-H in the *s-cis* isomer **1.54** or 3-H and 2'-H in the *s-trans* open form of isomer **1.55** the molecule was substituted with larger atoms which enabled in much faster fade rate as shown in Table 1.4.



Scheme 1.13: Steric interactions in the photomerocyanines derived from 2*H*-naphtho[1,2-*b*]pyrans

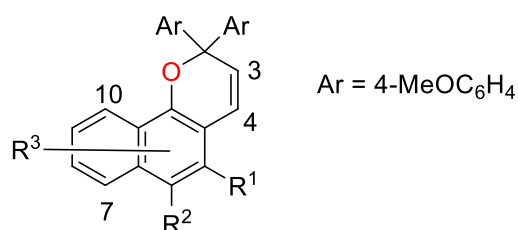
The effect of the ester substituent attached to the C-5 position showed an increase in absorption as well as decrease of the half-life. Incorporation of substituents at the C-6 position with an adjacent ester group at C-5 allowed the observation of either similar or even higher absorption along with relatively longer half-lives. <1999DPC161>



R ¹	R ²	λ_{max} (nm) in PhMe	$t_{1/2}$ (s)
H	H	412, 508	>1800
Me	H	416, 496	178
CO ₂ Me	H	492	2
CO ₂ Me	Me	416, 492	4
CO ₂ Me	Ph	416, 506	7
CO ₂ Me	OMe	502	73

Table 1.4: Effect of substituents at C-5 and C-6 position on 2*H*-naphtho[1,2-*b*]pyran

In addition, the methoxy-substituents attached to various positions on the naphthopyran ring could result in either a bathochromic or a hypsochromic shift in the absorption maxima. Placing a methoxy unit at either the 7- or 9- position on the ring resulted in a red shift in absorption maxima and half-lives of ca. 3 s. However, the open forms possessing a 6- or 8- or a 10- methoxy substituent were blue shifted in absorption maxima with a relatively long half-life; therefore, a slower fade rate (Table 1.5). <2004H567>



R ¹	R ²	R ³	λ_{max} (nm) in PhMe	$t_{1/2}$ (s)
CO ₂ Et	H	H	493	3
CO ₂ Me	OMe	H	502	73
CO ₂ Et	H	7-MeO	508	3
CO ₂ Me	H	8-MeO	480	11
CO ₂ Et	H	9-MeO	505	3
CO ₂ Me	H	10-MeO	485	21

Table 1.5: Effect of substituents at different positions on 2*H*-naphtho[1,2-*b*]pyran

Extensive colour and rate of fade control has accompanied the placement of dialkylamine functions. Thus, when dialkylamine units have been incorporated into one of the *gem* diaryl substituents a more intense coloured compound with relatively slow fade rates resulted (Figure 1.8). <1998WOP42693>

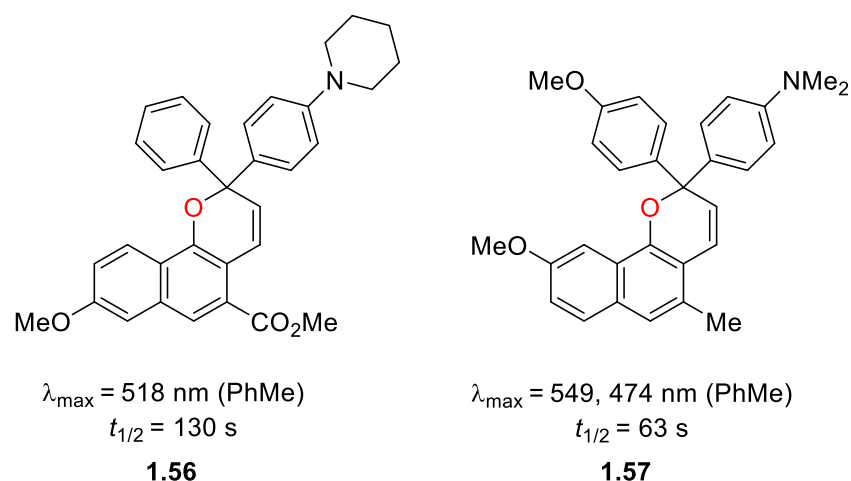


Figure 1.8: Photochromic properties of amino-substituted 2*H*-naphtho[1,2-*b*]pyrans

Based on **1.57** when the molecule possesses a tertiary amine group attached to the ring two absorption bands are observed. Structures that contain an electron-donating dialkylamino group at the 9-position are presented in Figure 1.9. Each of the naphthopyrans **1.58** – **1.60** exhibit two absorption bands with a weaker shorter wavelength band and a more intense longer wavelength band above 500 nm resulting in a range of different shades such as brown, grey, purple or blue. <1998WOP42693>

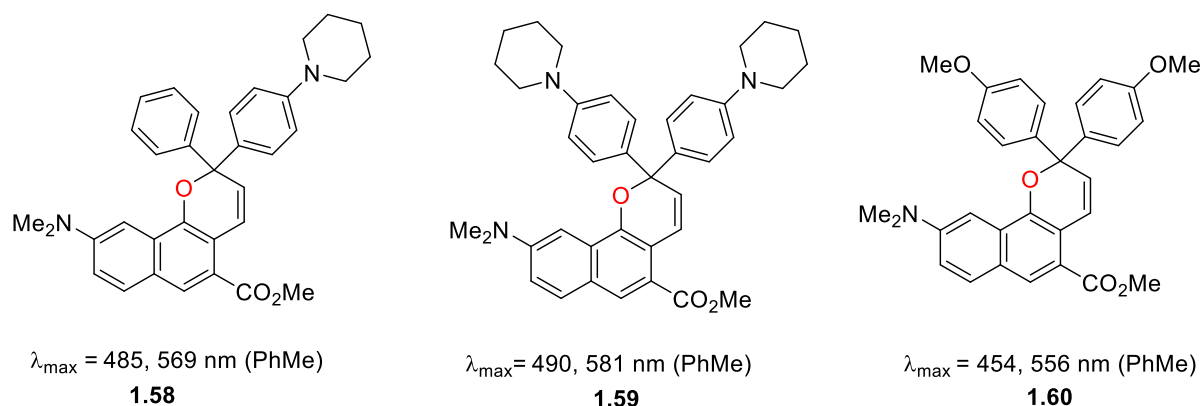


Figure 1.9: Photochromic properties of 9-dialkylamino substituted 2*H*-naphtho[1,2-*b*]pyrans

Aiken and co-workers compared the structure of 6-MeO substituted 2*H*-naphtho[1,2-*b*]pyran **1.13** with substituted furan ring fused into the naphthalene unit in 2*H*-naphtho[1,2-*b*]pyran **1.61** which showed a significant difference in a fade rate of the absorption maximum of the photomerocyanine derived from **1.13** is slightly hypsochromically shifted however the fade rate is much quicker with a half-life of 2.3 min compared to the **1.13** structure that has a half-life of 42.3 min (Figure 1.10). <2014T9351>

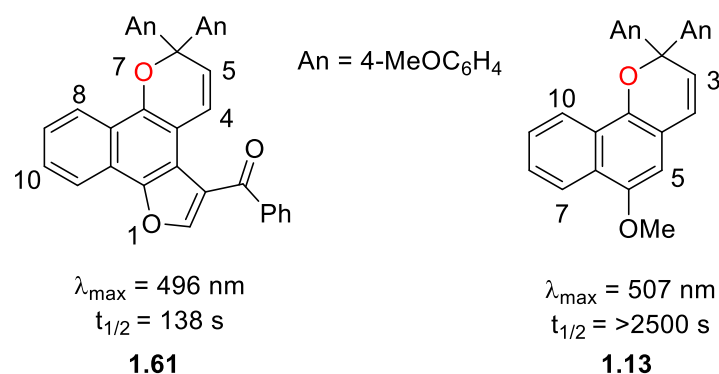


Figure 1.10: Photochromic properties of 5,6-furan fused and 6-methoxy substituted 2*H*-naphtho[1,2-*b*]pyrans

Gabbutt and co-workers have shown that the insertion of a vinyl moiety has an interesting impact on the photochromism of naphthopyrans. It was found that the 1,1-diaryl-substituted vinyl unit in **1.63** delivered a bathochromic shift in absorption maximum and also increases the half-life of the photomerocyanine relative to that derived from **1.62** (Figure 1.11). <2010OBC4874>

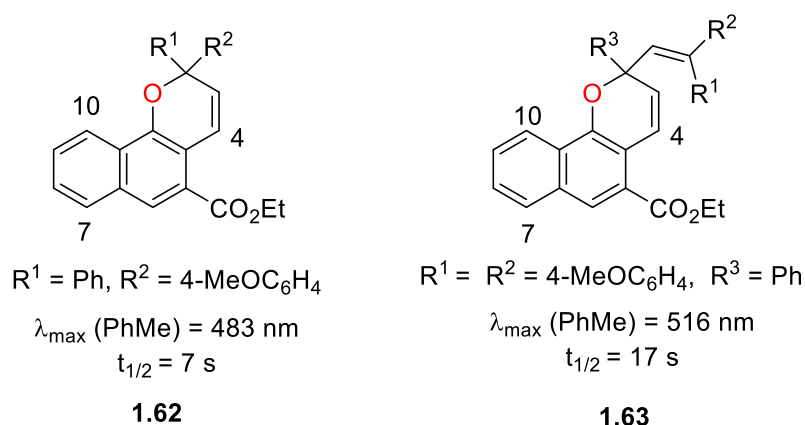


Figure 1.11: Photochromic properties of 2*H*-naphtho[1,2-*b*]pyrans

Varying the location of a MeO- substituent in the fused naphthopyran showed different absorption behaviour and fade rates. Pyran **1.64**, where MeO is attached at position 9- gave a short half-life and longer wavelength absorption band whereas substitution of MeO at position 6- **1.65** gave a fade rate four times longer and has shorter wavelength absorption band. In addition, compound **1.66**, when dissolved in chloroform and under continuous irradiation, showed approximately twice as long a half-life than in in toluene solution (Figure 1.12). <2019DP(169)118>

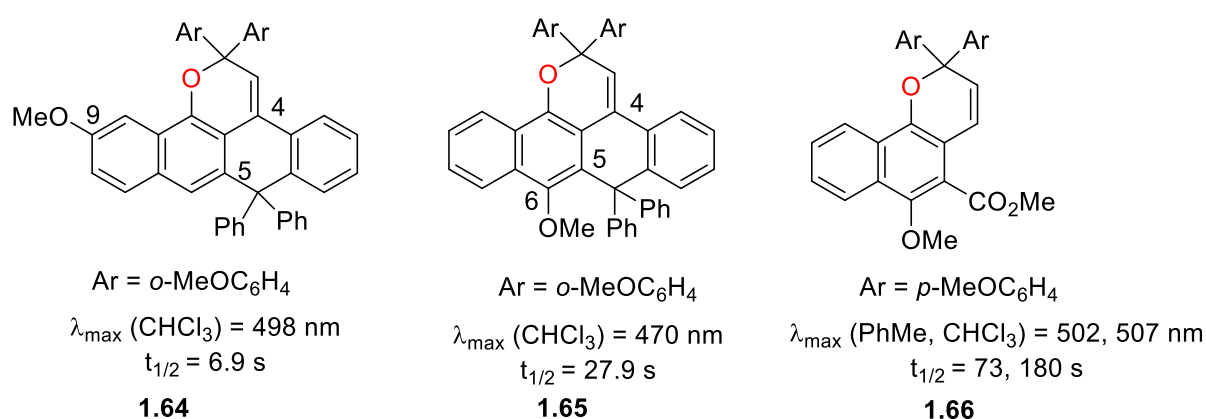
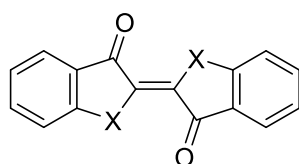


Figure 1.12: Photochromic properties of variously substituted naphthopyrans

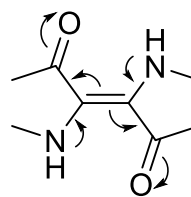
It should be emphasized that to date the photomerocyanines derived from the ring-opening of the naphthopyran unit generate a simple donor – acceptor chromophore system which may or may not possess extended or lateral conjugation which gives rise to multiple absorption maxima in some instances. There are apparently no examples of the photogeneration of a cross-conjugated chromophore system.

1.6 Cross-conjugation

A cross-conjugated chromophore may be considered to be a chromophore unit in which there is an opposing ‘flow’ of electron density from two pairs of conjugated donor-acceptor systems. Historically, the most significant crossed-chromophore, often termed the ‘H-chromophore’, is that of the relatively low molecular weight colorant known as indigo and its sulfur derivative, thioindigo (Figure 1.13). <1991B-1> Indigoids, as a consequence of their crossed-chromophore, exhibit a very bathochromic λ_{max} for their size (molecular weight), for example in the vapor phase λ_{max} = 540 nm, in a non-polar solvent λ_{max} = 588 nm (CCl₄) and in polar solvents λ_{max} = 606 nm (EtOH) and 620 nm (DMSO).



1.67a X = NH indigo
1.67b X = S thioindigo



crossed-chromophore unit

Figure 1.13: The cross-conjugated chromophore of indigoids

An interesting comparison of the wavelength of absorption maxima of chromophoric units is presented in Figure 1.14. Here it can be seen that the non-crossed chromophoric systems absorb at significantly shorter wavelength and have a decreased molar extinction coefficient ($\log \epsilon$). Of particular note is the inclusion of the traditional linear merocyanine **1.68** and cyanine **1.69** systems where an extensive number of C=C units are required to afford an absorption maximum of a similar wavelength to that of indigo, serving to further illustrate the unique long wavelength absorption of the cross-chromophore systems. <2001B-1, 1991B-1>

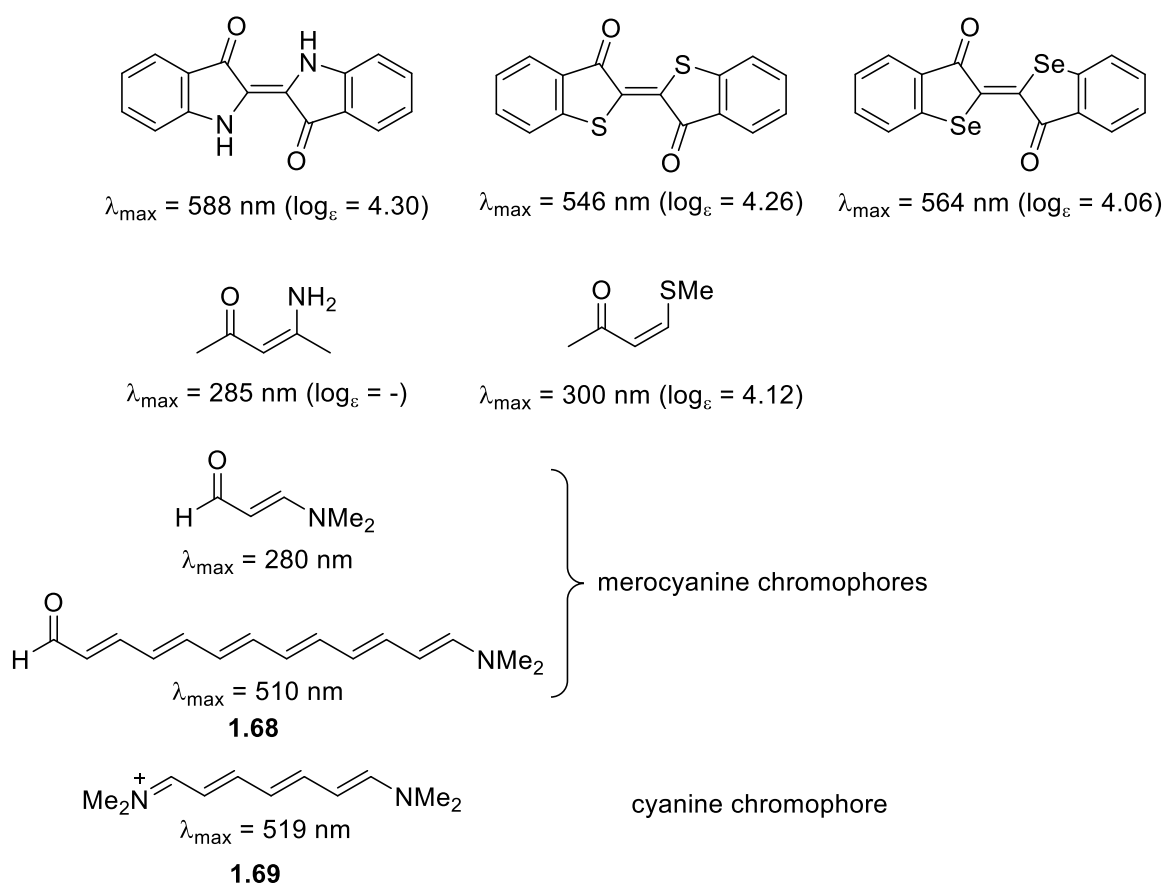


Figure 1.14: Comparison of crossed and non-crossed chromophores (from <1991B-1>)

Interestingly, separating the two indolone units of thioindigo by incorporation of additional C=C units resulted in a ca. 40 nm hypsochromic shift in the absorption maxima, rather than the expected 100 nm bathochromic shift (vinylene shift) common to cyanine dyes (Figure 1.15). <1980B-1>

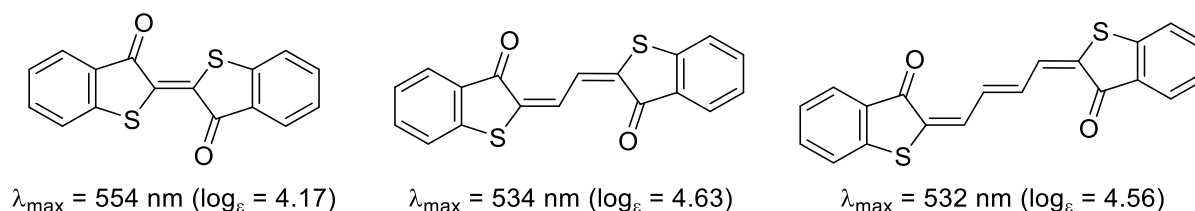


Figure 1.15: Vinylene separated indigoids

Further examples of colorants which possess a H-type chromophore include the diketopyrrolopyrroles **1.70** <1993B-1, 2009B-1> and the benzodifuranones **1.71** <2003B-1> (Figure 1.16).

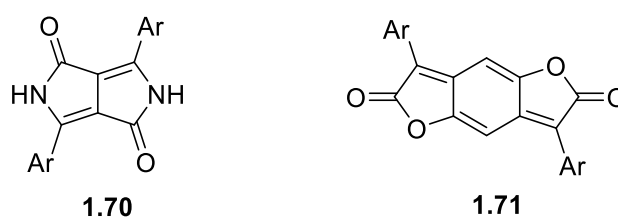


Figure 1.16: Diketopyrrolopyrrole and benzodifuranone systems

More recently Diederich *et al.*, have studied an extensive series of push-pull chromophores <2010CC1994, 2009ACR235> and have shown that the absorption maxima of the arylacetylene system **1.72** can be shifted bathochromically by reconfiguration about the central double bond to facilitate a cross-conjugation arrangement **1.73** (Figure 1.17). The incorporation of donor-acceptor systems which present cross-conjugation in emissive cruciform systems has been reviewed. <2010CC1994; 2010ACR397>

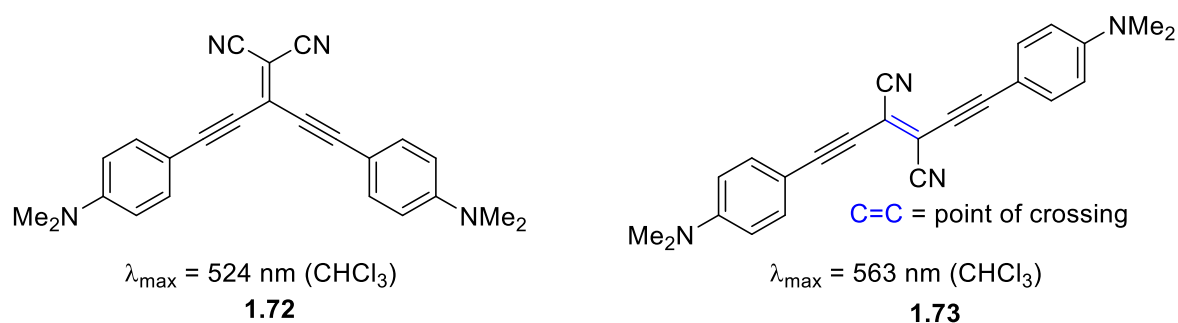


Figure 1.17: Arylacetylene conjugated systems

In addition, the compound **1.74** with neutral substituents attached to the π -conjugated linear arms gave much smaller absorption spectra than in the case when the molecule possesses some of donor or acceptor substituents. However, upon both donor-acceptor substitutions **1.76**, it was observed that the absorption spectra dramatically go up giving really intense bathochromic shift (Figure 1.18). <2010ACR397>

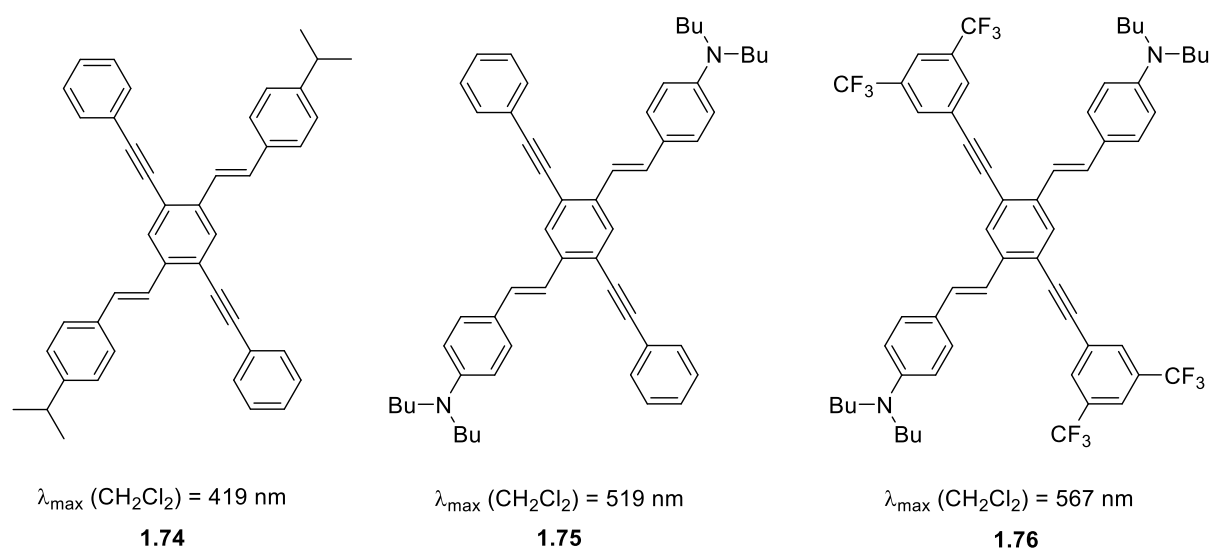
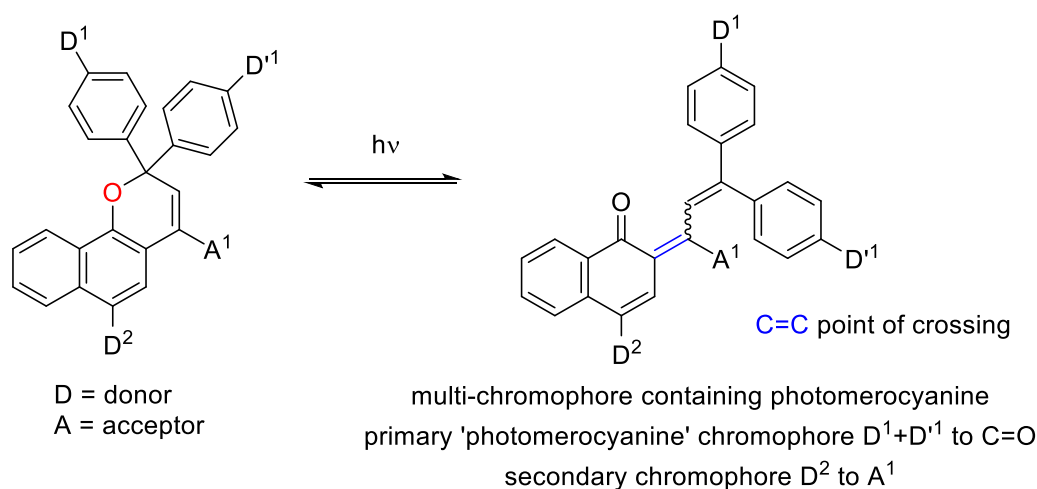


Figure 1.18: Spectroscopic properties for 'X-shaped' conjugated compounds

1.7 Aim of the present study

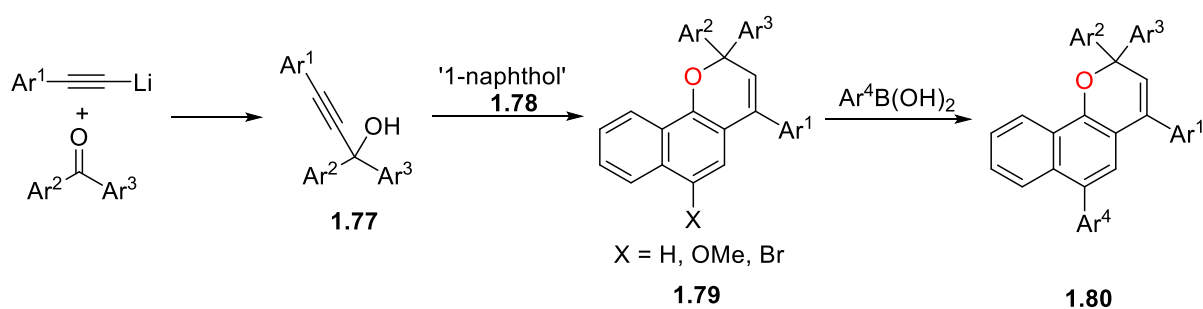
The aim of the present project is to explore the synthesis and photochromic response of some novel 2*H*-naphtho[1,2-*b*]pyrans which possess a previously unexplored substitution pattern such that upon UV-irradiation the pyran unit will undergo ring-opening to generate a multi-chromophore containing a traditional photomerocyanine which additionally incorporates an

integral crossed-chromophore unit which may provide for a more intense and longer wavelength absorption than a typical photomerocyanine (Scheme 1.14).



Scheme 1.14: Proposed UV-irradiation of a naphthopyran leading to a photogenerated crossed-chromophore

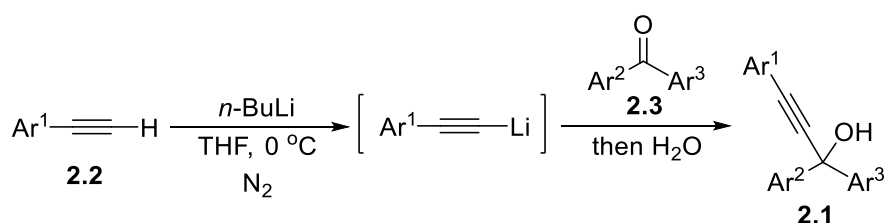
The strategy employed to synthesise the new naphthopyrans is depicted in Scheme 1.15 and requires the preparation of a series of 1,1,3-triarylprop-2-yn-1-ols **1.77** which will be used in the acid-catalysed reaction with a range of 1-naphthols **1.78** to obtain naphthopyran intermediates **1.79**. The 6-bromo substituent of **1.79** X = Br will be replaced by a substituted aryl group using Suzuki cross-coupling methodology to afford the target tetra-aryl substituted naphthopyrans **1.80**, wherein Ar¹ – Ar⁴ are appropriately substituted with Donor (D) and acceptor (A) functions. An alternative strategy involving the initial preparation of a 4-aryl-1-naphthol via Suzuki cross-coupling between 4-bromo-1-naphthol and a benzeneboronic acid and thence conversion to the naphthopyran will additionally be examined.



Scheme 1.15: Outline synthetic strategy to obtain substituted naphthopyrans

Chapter 2.0 Synthesis of key intermediates

As identified in the aims of the present study (Chapter 1.7) the key precursors for the construction of the naphthopyrans are substituted 1-naphthols and 1,1,3-triarylprop-2-yn-1-ols **2.1**. Whilst the former 1-naphthols are commercially available e.g. 1-naphthol, 4-methoxy- and 4-bromo- 1-naphthol, the triarylpropynols require synthesis. The most obvious route to **2.1** involves the addition of an arylacetylide, generated by the deprotonation of an arylacetylene **2.2** using *n*-butyllithium, to the requisite benzophenone **2.3** (Scheme 2.1). <2000EP1038870; 2001JOC6662; 2003EJOC1220; 2003RJGC1406; 2007JOC7229 2010OBC4874; 2014T9351; 2014JOC7616; 2015JOC12177; 2016AJC755; 2018JOC15043>



Scheme 2.1: Preparation of triarylpropynols

It was important that the benzophenones **2.3** required for the present investigation were electron rich; a feature which facilitates cation formation upon treatment with acid that constitutes the first step in the formation of the naphthopyrans. An additional requirement was for the presence of a substituent *ortho* to the C=O group on one of the aryl rings. The placement of such an *ortho*-substituent has been shown to be useful for controlling the rate of fade of the photomerocyanines derived upon UV-irradiation of the naphthopyrans in solution. <1993WOP9310112; 2003H(60)843> The preliminary target benzophenones were identified as **2.3a** and **2.3b** (Figure 2.1). Benzophenone **2.3a** possesses an *ortho*-methoxy function whereas benzophenone **2.3b**, as a consequence of the naphthalene moiety, possesses a *peri*-H atom.

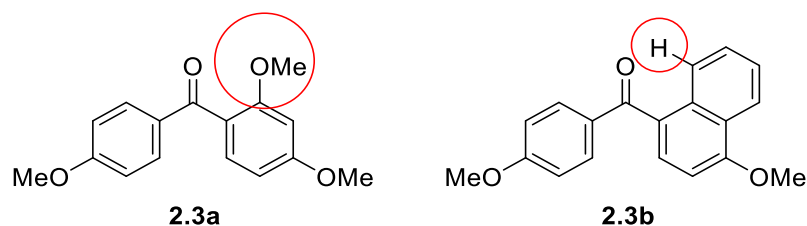
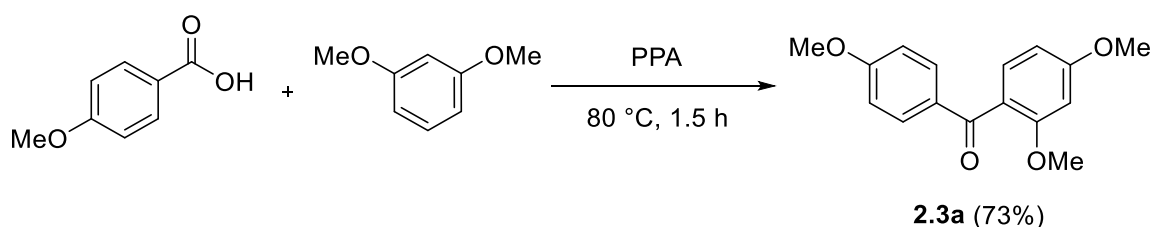


Figure 2.1: Target benzophenones **2.3a** and **2.3b**

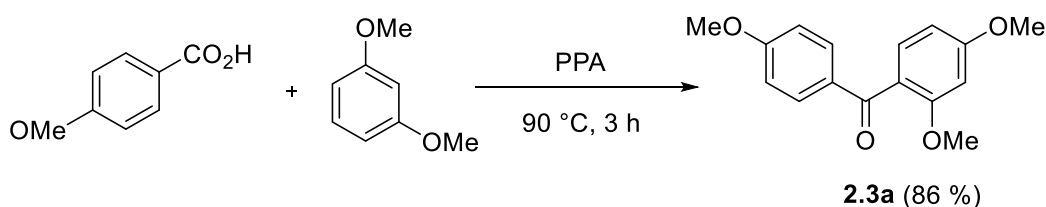
2.1 Friedel-Crafts synthesis of benzophenones

The first reported synthesis of 2,4,4'-trimethoxybenzophenone **2.3a** appeared in 1910 in a study concerning methylation reactions with dimethylsulfate using NaOH as the base. <1910B1882> A variant of this reaction was reported in 1986 in which the alkylation of 2,4,4'-trihydroxybenzophenone was accomplished with methyl iodide in the presence of a hydroxide base e.g. NaOH, in DMSO. <1986RP89575> A related synthesis employed dimethylsulfate as the methylating agent using K₂CO₃ as the base in refluxing acetone. <2015WOP2015022779> An alternative direct synthesis involving formation of the ketone moiety employed the regioselective Friedel-Crafts acylation reaction of 1,3-dimethoxybenzene with 4-methoxybenzoic acid in polyphosphoric acid (PPA) at 80 °C for 1.5 h which furnished **2.3a** in 73% yield (Scheme 2.2). <2015BC49>



Scheme 2.2: Preparation of trimethoxybenzophenone **2.3a**

The efficiency, versatility and less hazardous nature of the Friedel-Crafts methodology was attractive and this protocol was employed for the preparation of **2.3a** and **2.3b**. Thus heating 1,3-dimethoxybenzene and *p*-anisic acid in polyphosphoric acid (PPA) for 3 h at 90 °C gave, after cooling, aqueous work-up and recrystallization from hot EtOH colourless needles of **2.3a** in a slightly improved 86% yield (Scheme 2.3). The melting point of the colourless crystalline product was 71 - 73 °C which compared favourably with that of the literature compound of 73 - 74 °C. <1910B1882>



Scheme 2.3: Friedel-Crafts preparation of ketone **2.3a**

The structure of **2.3a** was confirmed by ^1H NMR spectroscopy (Figure 2.2). The protons on the monomethoxy substituted aryl ring afforded a multiplet at 7.78 ppm and at 6.90 ppm each accounting for 2H. Proton **c** adjacent to the C=O group appears as an *ortho*-split doublet with $J = 8.3$ Hz and the signals for protons **d** and **d'** almost overlap at ca. 6.53 ppm. The **4**- and **4'**- methoxy groups are accidentally equivalent and resonate at 3.87 ppm and the remaining *ortho* methoxy group gives rise to a singlet at 3.72 ppm. The structure of **2.3a** was further confirmed by ^{13}C NMR spectroscopy which exhibited a deshielded signal at 194.3 ppm that is indicative of the carbonyl group. The other significant peaks in the ^{13}C NMR spectrum are those from the methoxy groups which appeared at 55.5 ppm and 55.6 ppm. The remaining peaks appear between 99 – 163 ppm and are assigned to the carbons from the aromatic rings. Infrared spectroscopy confirmed the presence of a diaryl substituted C=O group with a stretching band at 1645 cm^{-1} .

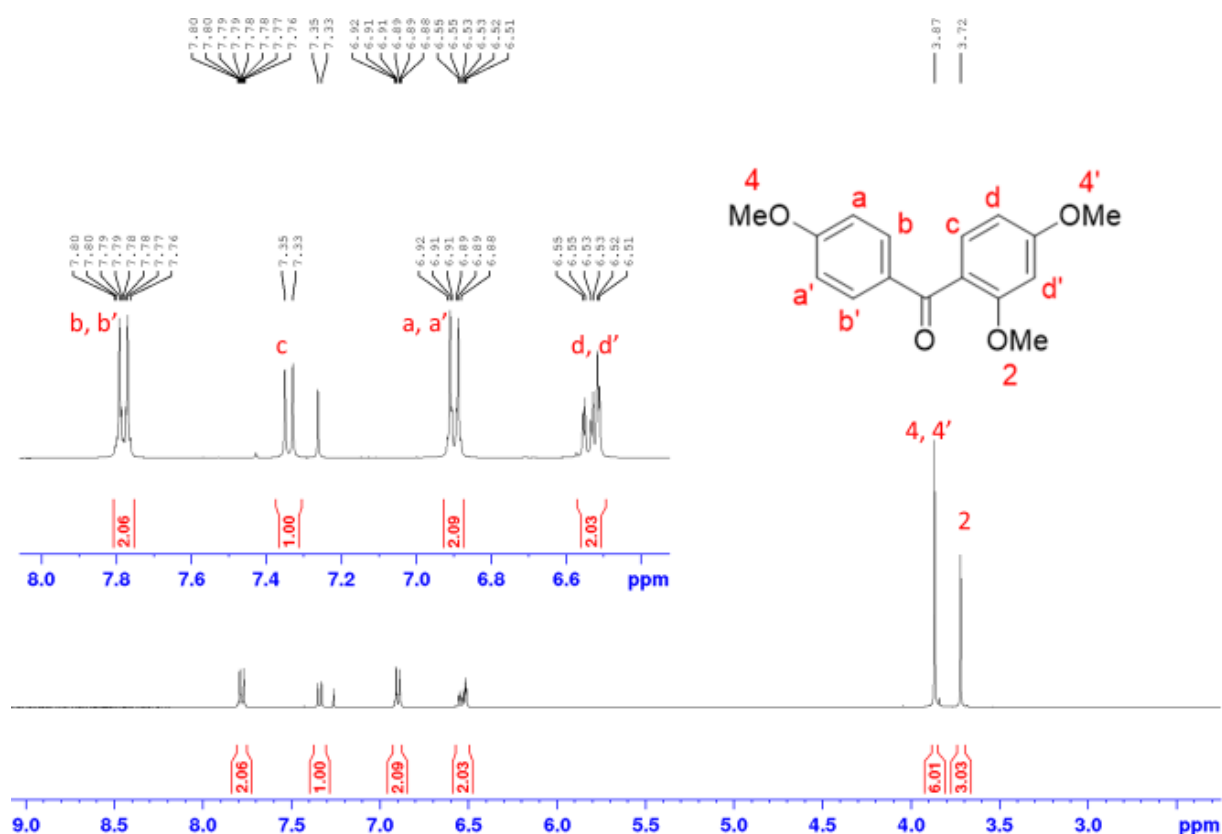
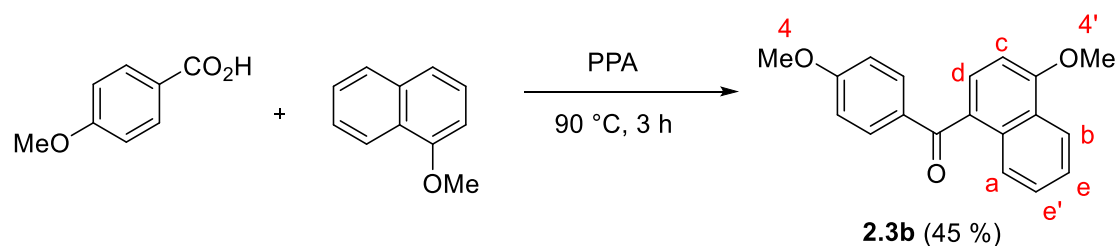


Figure 2.2: ^1H NMR spectrum of benzophenone **2.3a**

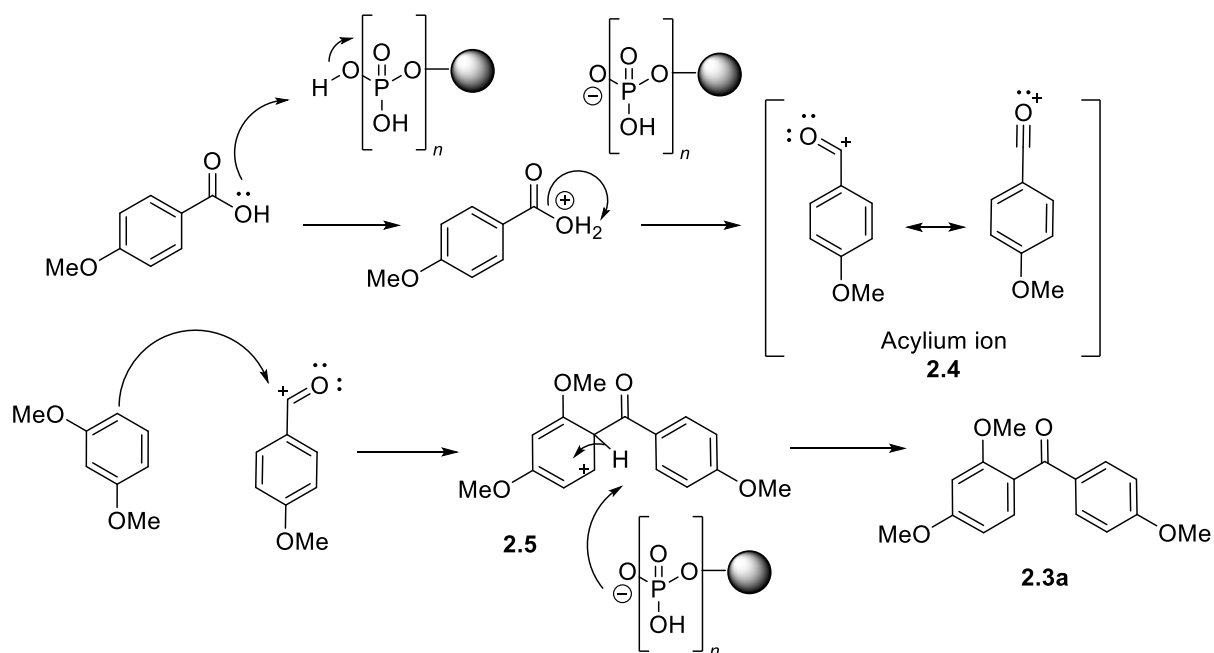
Employing the same reaction conditions as those used for the formation of **2.3a** but replacing 1,3-dimethoxybenzene with 1-methoxynaphthalene gave ketone **2.3b** in a disappointingly lower yield of 45% (Scheme 2.4).



Scheme 2.4: Friedel-Crafts preparation of ketone **2.3b**

The structure of **2.3b** was clearly established from its ^1H NMR spectrum which showed multiplets for the naphthalene ring protons **b** and **a** at 8.35 and 8.21 ppm, and slightly upfield overlapping multiplets corresponding to the **e**, **e'**, **d** protons at ca. 7.52 ppm. A distinct doublet was assigned to proton **c** at 6.80 ppm with $J = 8.0$ Hz. The signals for the anisyl ring protons resonated at 7.84 and 6.93 ppm, comparable with those in **2.3a**, and the OMe protons **4'** and **4** appeared at 4.1 and 3.9 ppm. The presence of the carbonyl unit was supported by ^{13}C NMR spectroscopy as the signal appeared downfield at 196.2 ppm together with adjacent aromatic carbon signals that resonated at 163.4 and 157.8 ppm. The melting point of the pale brown crystalline compound **2.3b** showed a broadened melting range of 103 – 109 °C rather than a melting point similar to that reported in the literature (107 °C). <1960JCS2272>

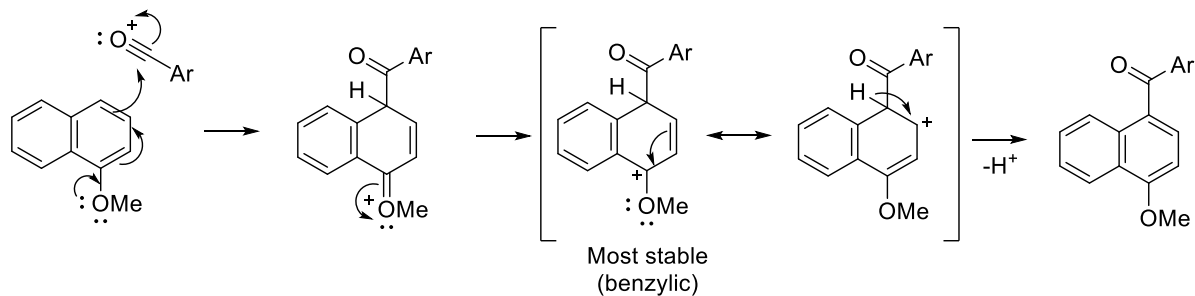
Mechanistically the Friedel-Crafts acylation reaction is an electrophilic aromatic substitution ($\text{S}_{\text{E}}\text{Ar}$) process. The reaction typically involves formation of a complex between an acyl halide and a Lewis acid-catalyst such as AlCl_3 which leads to an acylium ion that undergoes reaction with the electron rich aromatic ring. <1991B-1> In this case, PPA is acting as a solvent and also as an acid-catalyst for the reaction <1969CJC1529; 1999NJOS324>. Generally, protonation and elimination of water from the *p*-anisic acid affords the resonance stabilised acylium ion **2.4**. The electron rich 1,3-dimethoxybenzene undergoes attack at a reactive but unhindered site (C-4) by the acylium ion leading to a σ -complex **2.5** which is efficiently resonance stabilised. Elimination of a proton regenerates the acidic catalyst and simultaneously forms a new π - bond which restores the aromaticity to afford the Friedel-Crafts product **2.3a/b** (Scheme 2.4).



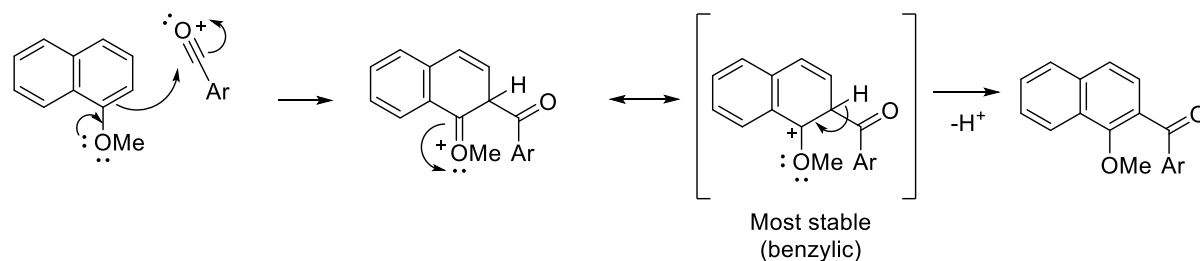
Scheme 2.4: Mechanism for the Friedel-Crafts acylation reaction.

The same mechanism operates for the acylation of 1-methoxynaphthalene however attack occurs at C-4 since the generated carbocationic intermediate is more efficiently resonance stabilised by one oxonium and two carbocationic intermediates rather than one oxonium and one carbocationic form resulting from attack at C-2 (Scheme 2.5).

Attack at C-4:



Attack at C-2:

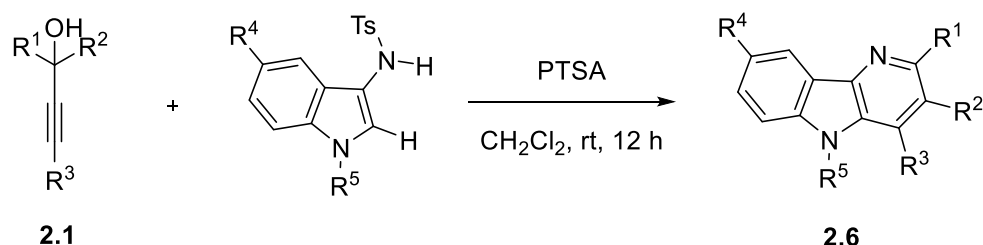


Scheme 2.5: Rationale of the regioselectivity of 1-methoxynaphthalene benzoylation

With the two aromatic ketones to hand their conversion into a series of 1,1,3-triarylprop-2-yn-1-ols **2.1** was next investigated.

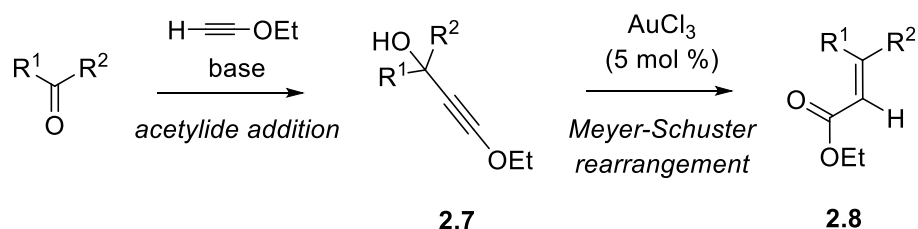
2.2 Formation of prop-2-yn-1-ols (alkynols)

The addition of aryl acetylides, derived from the deprotonation of an arylacetylene with a suitable base, to substituted benzophenones is well documented in the scientific literature. <2000EP1038870; 2003EJOC1220; 2010OBC4874; 2014T9351; 2016AJC755> Recently, Kumara Swamy *et al.*, synthesised an extended series of 1,1,3-triarylprop-2-yn-1-ols **2.1** in typically excellent yields via the arylacetylide addition route and explored their use, under acidic conditions, to synthesise a series of highly substituted carbolines **2.6** (Scheme 2.6). <2018JOC15043>



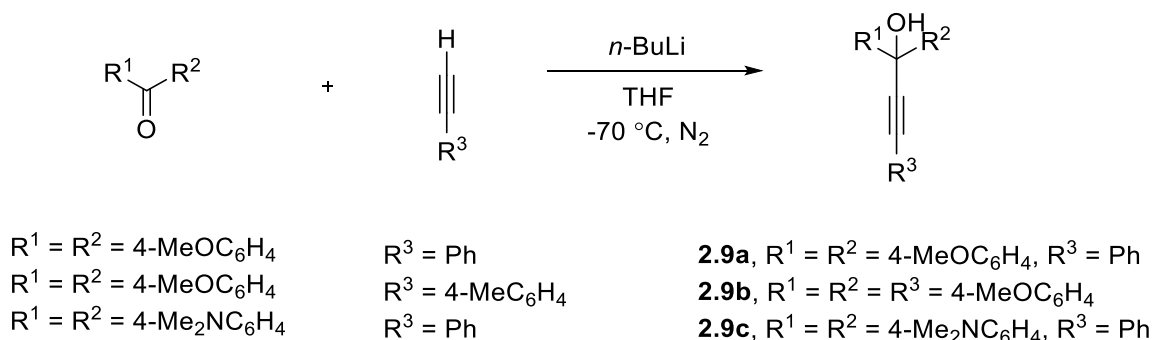
Scheme 2.6: Synthesis of substituted carbolines under acidic conditions

Dudley *et al.*, have extended the versatility of the acetylide addition to benzophenones through the use of ethoxyacetylide, from ethoxyacetylene and a base, to afford a series of 3-ethoxy-1,1-di(aryl)prop-2-yn-1-ols **2.7** in good yield. The Meyer-Schuster rearrangement of **2.7** was affected by treatment with acid to afford α,β -unsaturated esters **2.8** in good overall yield (Scheme 2.7) <2006OL4027>



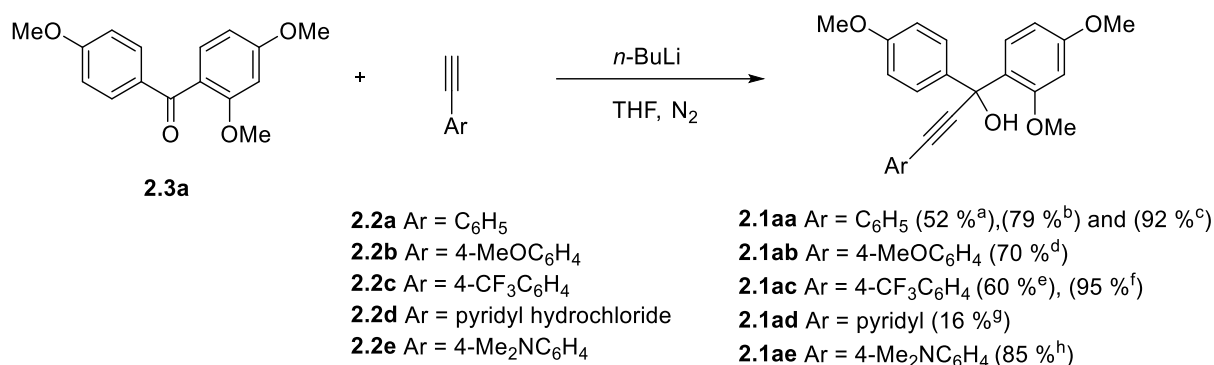
Scheme 2.7: Synthesis of 3-ethoxy-1,1-di(aryl)prop-2-yn-1-ols **2.7** and their rearrangement to α,β -unsaturated esters **2.8**

Gabbutt and co-workers have synthesised propynols **2.9a-c** using the same arylacetylide addition methodology, however a slight excess of the acetylides were employed to achieve excellent yields (Scheme 2.8). For **2.9a-c** ^1H NMR spectroscopy enabled the hydroxyl protons to be identified as a broadened singlet at 2.88 ppm for **2.9a**, 2.89 ppm for **2.9b** and 2.68 ppm for **2.9c** as well as the protons belonging to the OMe and NMe₂ substituents which resonated at 3.78 ppm (**2.9a**), 3.79-3.81 ppm (**2.9b**) and 2.93 ppm (**2.9c**). <2010OBC4874>



Scheme 2.8: Synthesis of 1,1,3-triarylprop-2-yn-1-ols

Guided by the literature preparations of 1,1,3-triarylprop-2-yn-1-ols <2003EJOC1220; 2010OBC4874; 2014T9351; 2016AJC755; 2018JOC15043; 2000EP1038870>, *n*-BuLi (1.11 eq.) was added portionwise via syringe to a cold stirred solution of phenylacetylene (1.11 eq.) in anhydrous THF under a nitrogen. After stirring at -70 °C for 30 minutes the benzophenone **2.3a** (1.0 eq.) was added in a single portion and the mixture left to stir and warm to room temperature. When no further change in the composition of the reaction mixture was apparent by TLC examination, the mixture was subjected to an aqueous work-up to afford the target compound (Scheme 2.9). Examination of the crude product indicated a mixture of unreacted benzophenone **2.3a** and product **2.1aa** which was subjected to flash chromatographic purification using 5% EtOAc in PhMe. The target propynol **2.1aa** was isolated in 52% yield as viscous yellow oil.



^a Reagents and conditions: **2.3a** (1.0 eq.), **2.2a** (1.11 eq.), *n*-BuLi (1.11 eq.), THF dry, - 70 °C to r.t., 20 h

^b Reaction conditions: **2.3a** (1.0 eq.), **2.2a** (1.20 eq.), *n*-BuLi (1.21 eq.), THF dry, - 10 °C to r.t., 20 h

^c Reaction conditions: **2.3a** (1.0 eq.), **2.2a** (2.20 eq.), *n*-BuLi (2.20 eq.), THF dry, - 10 °C to r.t., 20 h

^d Reaction conditions: **2.3a** (1.0 eq.), **2.2b** (1.45 eq.), *n*-BuLi (1.45 eq.), THF dry, - 10 °C to r.t., 20 h

^e Reaction conditions: **2.3a** (1.0 eq.), **2.2c** (1.20 eq.), *n*-BuLi (1.21 eq.), THF dry, - 10 °C to r.t., 20 h

^f Reaction conditions: **2.3a** (1.0 eq.), **2.2c** (2.0 eq.), *n*-BuLi (2.01 eq.), THF dry, - 10 °C to r.t., 20 h

^g Reaction conditions: **2.3a** (1.0 eq.), **2.2d** (1.5 eq.), *n*-BuLi (2.5 eq.), THF dry, - 70 °C to r.t., 20 h

^h Reaction conditions: **2.3a** (1.0 eq.), **2.2e** (2.0 eq.), *n*-BuLi (2.0 eq.), THF dry, - 70 °C to r.t., 20 h

Scheme 2.9: The reaction of benzophenone **2.3a** with some commercial arylacetylenes

The formation of **2.1aa** was clearly evident by ¹³C NMR spectroscopy; the carbonyl C=O signal was no longer present at 194.3 ppm (for **2.3a**) and a new upfield signal at 74.1 ppm was apparent due to the tertiary C-atom <1974JACS5855>. In the ¹H NMR spectrum the OH group **q** appeared as a singlet at 4.8 ppm (Figure 2.3), shifted further downfield than those for **2.9a-c** as a consequence of H-bonding of the OH to the proximal MeO group. The extra phenyl ring provided additional signals at ca. 7.5 ppm and 7.3 ppm which appeared as multiplets and are assigned to the phenyl protons (**a**, **a'**, **b**, **b'**, **c**). Proton **z** appears as a doublet (*J* = 8.4 Hz) at 7.24 ppm and proton **y** as a doublet (*J* = 3.2 Hz) at 6.52 ppm; both **y** and **z** are mutually coupled to proton **x** which appears as a dd at 6.44 ppm. The presence of the OH group was corroborated by the presence of an OH stretching band at ca. 3500 cm⁻¹ in the infrared spectrum. The moderate yield of this transformation necessitated repeating the reaction to obtain sufficient propynol **2.1aa** for transformation into the target naphthopyrans. In an attempt to optimise the process a higher reaction temperature was employed (-10 °C) together with a greater excess (2.20 eq.) of phenylacetylide (Scheme 2.7). Pleasingly these new conditions gave **2.1aa**, which was spectroscopically identical to the material isolated from the initial attempt, in a superior 92% yield.

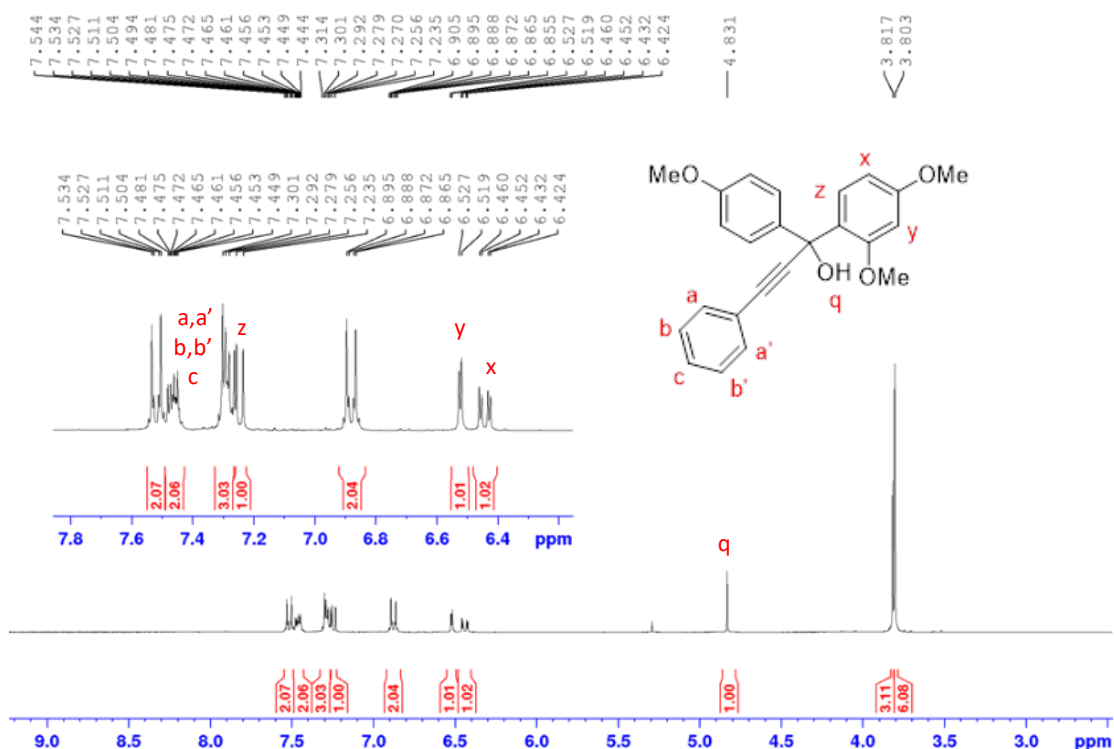


Figure 2.3: ^1H NMR spectrum of 1,1,3-triarylprop-2-yn-1-ol **2.1aa**

The methodology used to obtain propynol **2.1aa** was then employed to prepare propynol **2.1ab** from 4-methoxyphenylacetylene; pleasingly these conditions afforded **2.1ab** in 70% yield. In a similar manner propynol **2.1ac** was obtained from 1-ethynyl-4-(trifluoromethyl)benzene in a diminished yield of 60%. However, when a greater excess (2.0 eq.) of 1-ethynyl-4-(trifluoromethyl)benzene was used and the reaction mixture cooled to $-70\text{ }^\circ\text{C}$ an improved yield of **2.1ac** of 95% was recorded. In addition, a greater excess (2.0 eq.) of 4-ethynyl-*N,N*-dimethylaniline and very low temperature ($-70\text{ }^\circ\text{C}$) enabled propynol **2.1ae** also to be isolated in high yield (85%). Only a low yield was obtained for the pyridyl substituted propynol **2.1ad** where the reaction proceeded with a much larger excess of *n*-BuLi (2.5 eq.) which was necessary in order to neutralise the HCl salt of the starting 4-ethynylpyridine hydrochloride.

Formation of the desired 1,1,3-triarylprop-2-yn-1-ols was proven by the appearance of a singlet (*q*) at 4.79 ppm for **2.1ab**, 4.83 ppm for **2.1ac**, 4.93 ppm for **2.1ad** and 4.76 ppm for **2.1ae** corresponding to the hydroxyl protons. The introduced aryl substituent derived from the arylacetylene brings about extra signals in the ^1H NMR spectra that resonate at the aromatic region (Figure 2.4); of particular note are the low field signals associated with the C-

2/6 pyridine H atoms that resonate as broadened doublet at 8.54 ppm. ^{13}C NMR spectroscopy confirmed the presence of a tertiary C-atom for all propynols **2.1ab-ae** with signals at 74.2 ppm, 74.0 ppm, 73.9 ppm and 74.3 ppm, respectively. ^{19}F NMR spectroscopy presented a signal at -62.8 ppm proving the incorporation of the CF_3 unit in **2.1ac**.

Infrared spectroscopy proved the presence of an alcohol group with a broad band at ca. 3500 cm^{-1} (except compound **2.1ae** with a broad band at ca. 3100 cm^{-1}); a carbon-carbon triple bond stretch was apparent as a sharp and weak band at ca. 2223 cm^{-1} for **2.1ab**, ca. 2180 cm^{-1} for **2.1ac**, ca. 2360 cm^{-1} for **2.1ad** and ca. 2217 cm^{-1} for **2.1ae**.

Propynols **2.1aa** and **2.1ab** were in the form of viscous yellow oils and **2.1ad** and **2.1ae** were isolated as an orange powders with low and narrow melting point range of $42 - 43\text{ }^{\circ}\text{C}$ and $49 - 50\text{ }^{\circ}\text{C}$, respectively. Interestingly only the CF_3 substituted propynol **2.1ac** (pale yellow microcrystals) exhibited with much higher melting point range of $106 - 108\text{ }^{\circ}\text{C}$.

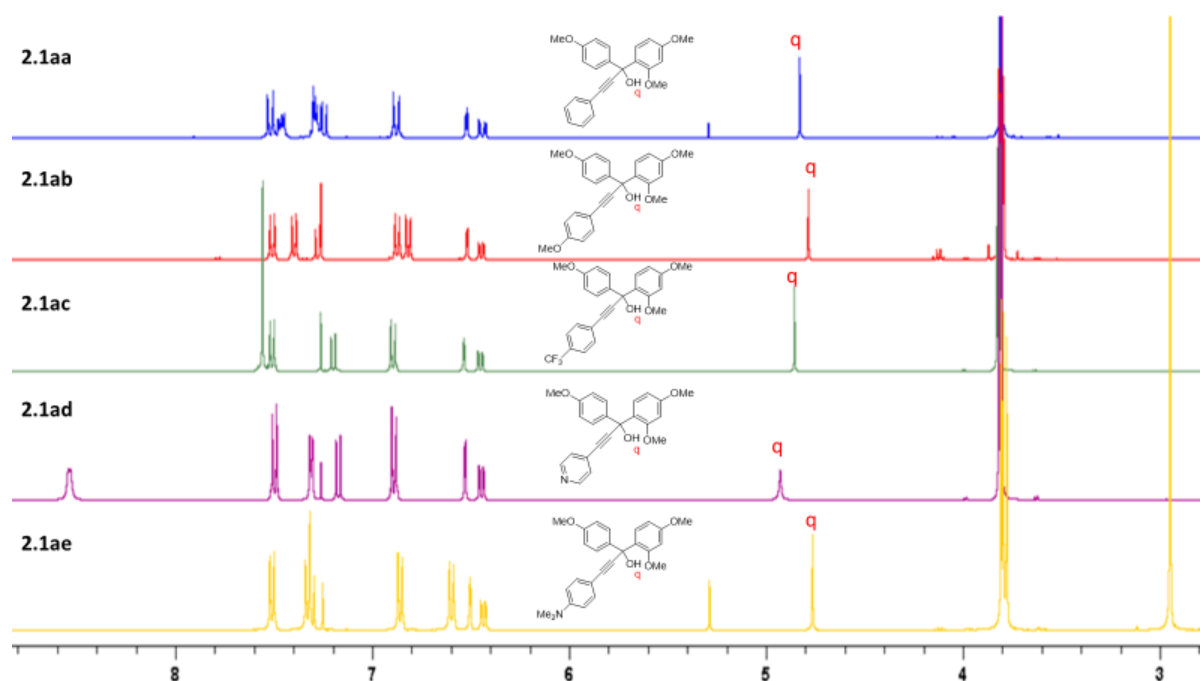
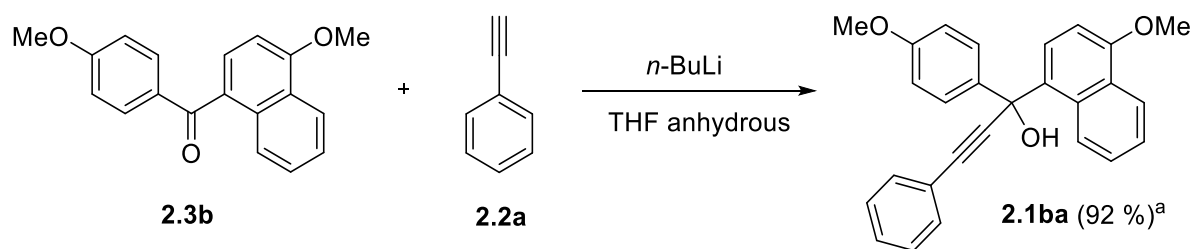


Figure 2.4: ^1H NMR spectra of 1,1,3-triarylprop-2-yn-1-ols **2.1aa-2.1ae**.

Employing the improved reaction conditions for the preparation of propynol **2.1aa-ac** but replacing benzophenone **2.3a** with **2.3b** gave the crude propynol **2.1ba** which was subjected to flash chromatographic purification using 5% EtOAc in PhMe. The target propynol was isolated in 92% yield as yellow flakes with a melting point range of $69 - 72\text{ }^{\circ}\text{C}$ (Scheme 2.10).



^a Reaction conditions: **2.3b** (1 eq.), **2.2a** (2 eq.), *n*-BuLi (2 eq.), THF dry, - 10 °C to r.t., 20 h

Scheme 2.10: The reaction of benzophenone **2.3b** with phenylacetylene **2.2a**

In common with the spectroscopic data for the other propynols **2.1aa-ac**, the formation of **2.1ba** was evident by the disappearance of carbonyl signal at 196.2 ppm (for **2.3b**) and appearance of a new signal corresponding to the tertiary C-atom at 74.3 ppm. In the ¹H NMR spectrum (Figure 2.5), the OH group appeared as a singlet however in this case the signal was slightly more shielded and resonated at ca. 2.9 ppm, as a consequence of the absence of the *ortho*-methoxy group. The signals for the methoxy groups were well resolved with that from the anisyl ring affording a singlet at 3.8 ppm with the signal at 4.0 ppm assigned to the methoxy group from naphthalene unit. Protons from the monomethoxy substituted aryl ring (**e,e',f',f'**) appear as a multiplet at ca. 7.6 ppm and overlapping multiplet at ca. 6.8 ppm. The naphthalene ring protons **a**, **b** and **c** gave a rise to the furthest downfield signals at ca. 8.3, 8.2 and 8.0 ppm respectively, and additionally proton **d** was found to be overlapped with the multiplet for the anisyl ring protons which resonate at ca. 6.8 ppm. The infrared spectrum revealed a weak stretching band at 3670 and 2223 cm⁻¹ that proved the presence of an alcohol group and carbon-carbon triple bond, respectively.

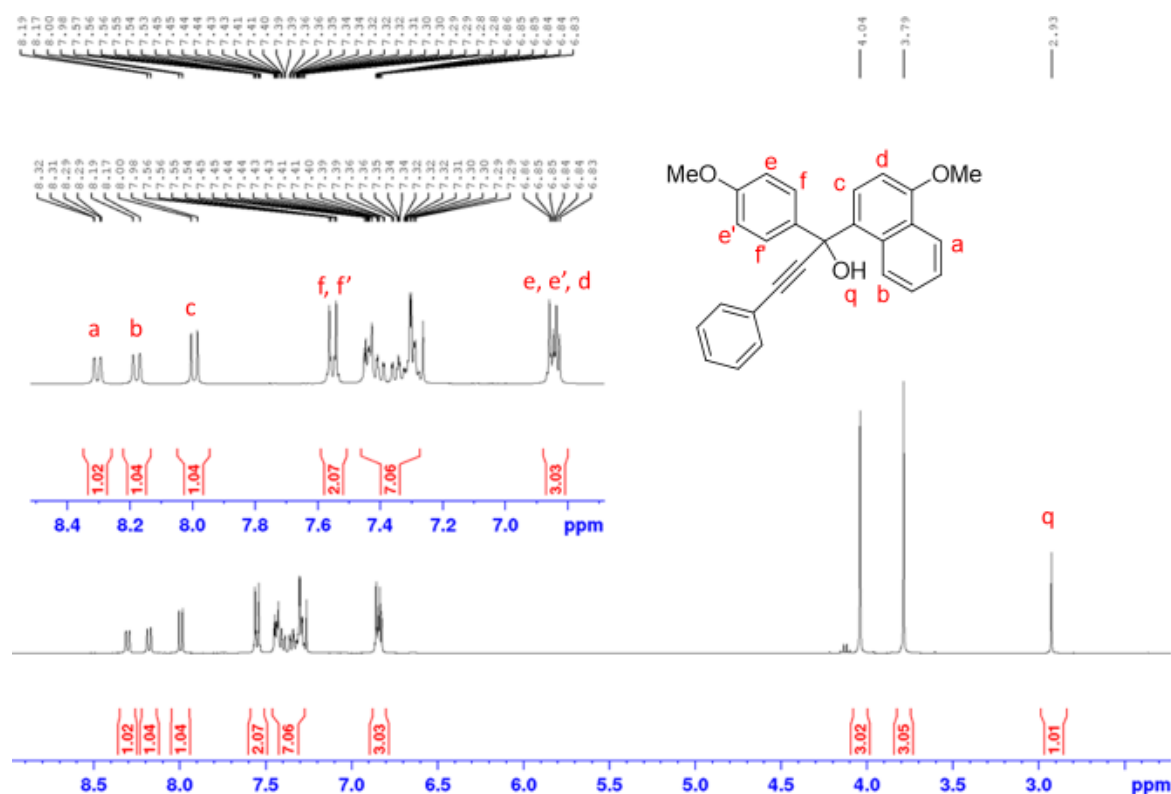
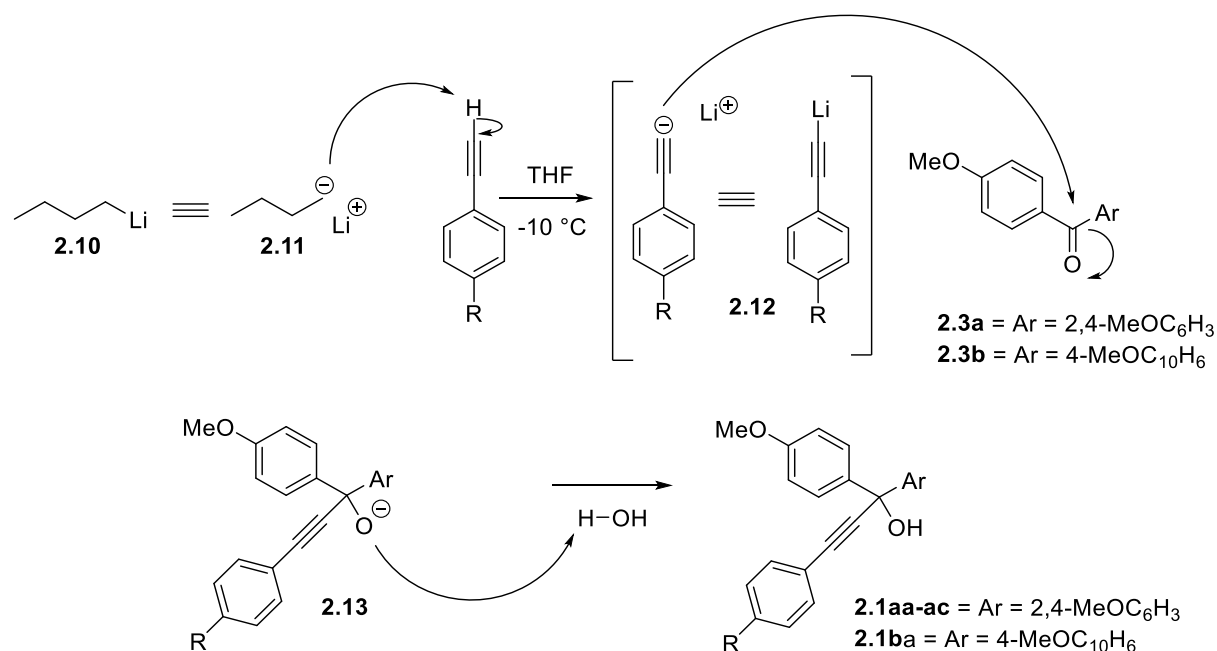


Figure 2.5: ^1H NMR spectrum of 1,1,3-triarylprop-2-yn-1-ol **2.1ba**

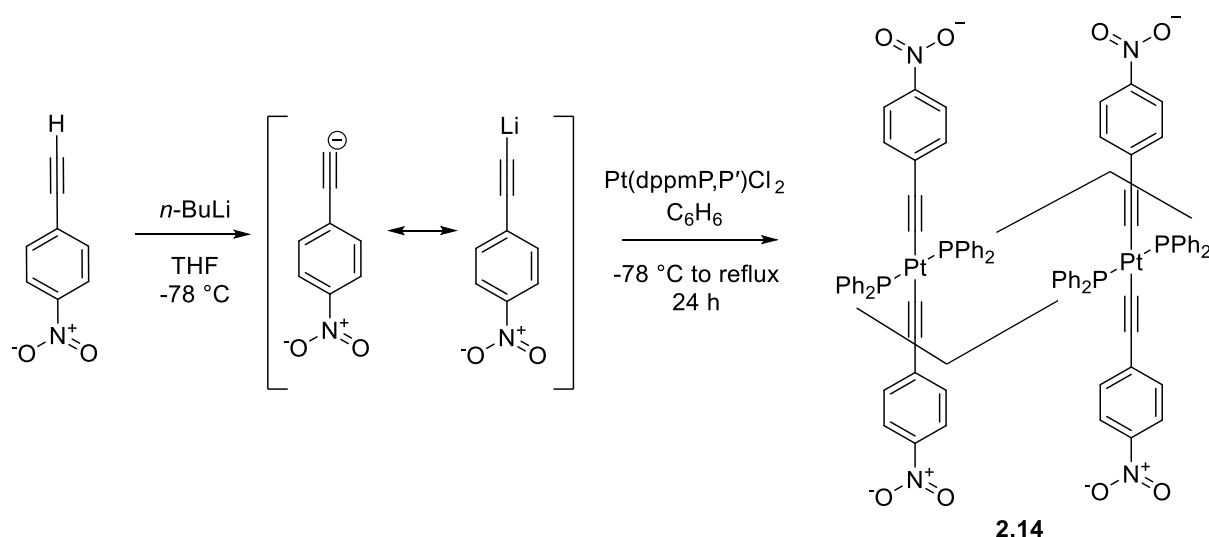
The mechanism to account for the formation of the 1,1,3-triarylprop-2-yn-1-ols **2.1** is presented in Scheme 2.11. The reaction uses a commercial organolithium reagent, *n*-butyllithium **2.10**, that serves as extremely strong base with a pK_a about ~50 ^{<2016JVE54705>} and is therefore able to deprotonate less acidic compounds. Acetylene is an example of weak acid which has acidic terminal hydrogen (pK_a ~25) and therefore it is easy for the strong base *n*-BuLi to remove the proton. ^{<1969B-1>} Arylacetylenes such as phenylacetylene (pK_a = 28.6) tend to have a higher pK_a so the base must be strong enough to generate a sufficient amount of the anion for the reaction to proceed. ^{<2014DC126>} Initially, the *n*-BuLi **2.11** attacks the acetylene proton forming lithium acetylide **2.12** and butane. Deprotonation of the acetylene function allowed for formation of a highly nucleophilic centre that is able to undergo nucleophilic addition to the carbonyl group of the benzophenone **2.3a/b** affording an alkoxide **2.13**. The last step of the reaction involves protonation of the alkoxide intermediate upon work-up that finally generates the alcohol group thus furnishing the final product **2.1** in good yield. ^{<1997B-1>}



Scheme 2.11: Outline mechanism for the preparation of the triarylpropynols

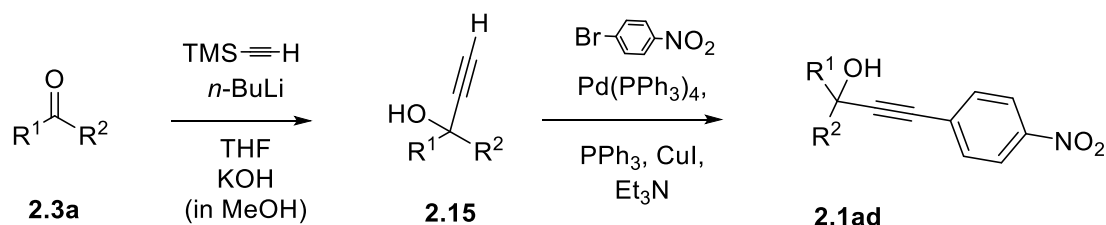
One of the limitations of strong bases/nucleophiles such as *n*-BuLi and acetylides is that their properties are not compatible with various functional groups such as alcohols, amines, amides and carboxylic acids. This is because each of these functional groups contain labile hydrogen atoms that can be deprotonated by the organolithium reagent leading to undesirable side-reactions. <1974B-1> In addition, there are a few reactive functional groups such as esters, nitriles and nitro that are also essentially incompatible with organolithium reagents because of their electrophilic nature. <1957AK325; 1971IANSK877; 1997JHM183>

In order to generate an effective cross-conjugated system in the photomerocyanine derived from UV irradiation of a naphthopyran it was essential to synthesise an alkynol with a strong electron withdrawing -NO₂ group. Examination of the literature revealed that there were very few convenient examples of deprotonation of 4-nitrophenylecetylene with *n*-butyllithium. Yam *et al.*, report such a reaction performed in scrupulously dry THF on a small scale (1.44 mmol) at -78 °C and employed the acetylide for the formation of dinuclear platinum(II) alkynyl complexes e.g. [Pt₂(μ-dppm)₂(CtCC₆H₄NO₂-p)₄] **2.14** (Scheme 2.12). <2002O4326>



Scheme 2.12: Deprotonation of 4-nitrophenylacetylene with *n*-butyllithium leading to dinuclear platinum(II) alkynyl complex

It was decided that instead of the direct synthesis of 1,1,3-triarylprop-2-yn-1-ol via the previously employed organolithium method to obtain **2.1aa-ac** and **2.1ba**, an alternative strategy would be explored to synthesise **2.1ad** with a 4-nitrophenyl moiety. This new strategy relied upon the formation of the 1,1-diarylprop-2-yn-1-ol **2.15** followed by a Sonogashira cross-coupling reaction <1975JOC253; 1998JOC8551; 2008S1657; 2011JCS937; 2015RSCA18960; 2018EJOC6134> between the terminal alkyne **2.15** and 1-bromo-4-nitrobenzene. The functionality of this complementary approach warrants an efficient coupling of a 4-nitrophenyl unit within the propynol **2.15** via a single-step process of Pd-Cu catalysed alkynylation where a new C-C bond is formed between the terminal acetylene C atom and aryl halide. <1975TL4467> The overall two-step sequence is depicted in Scheme 2.13.

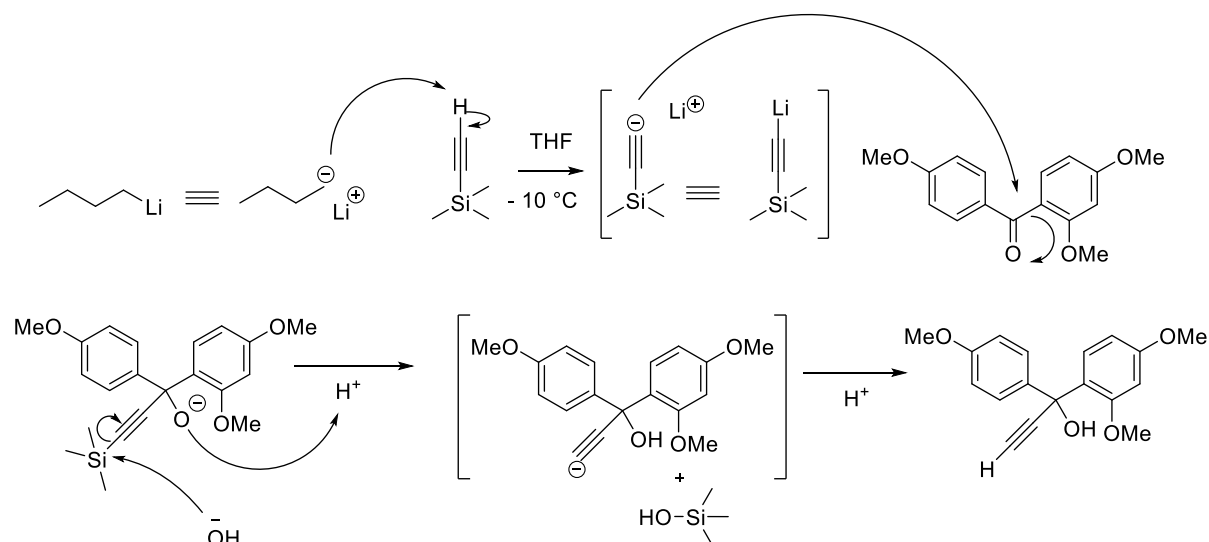


Scheme 2.13: Alternative route for the synthesis of the nitroaryl substituted alkynol **2.1ad**

Propynol **2.15** was a crucial intermediate that was required for the next step reaction and can be synthesised via a similar methodology as for the 1,1,3-triarylprop-2-yn-1-ols **2.1aa-ac**. The

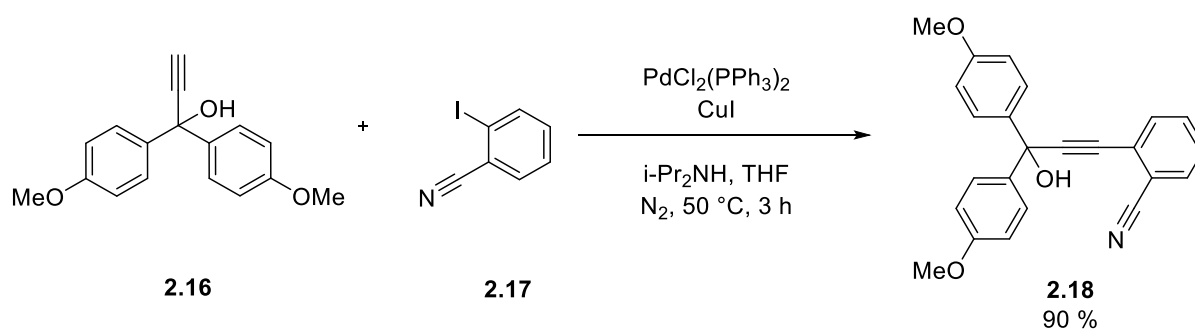
deviations between the methods used were (i) the use of TMS-acetylene in place of an arylacetylene, and (ii) the *in-situ* potassium hydroxide-mediated unmasking of the TMS-protected terminal acetylene function. <2003EJOC1220; 2009JMC5612; 2016AMI7221> Thus, lithiumtrimethylsilylacetylide was generated by addition of *n*-butyllithium to a cold (-10 °C) stirred solution of TMS-acetylene in THF. After 30 minutes benzophenone **2.3a** was added and the reaction was allowed to stir whilst warming to room temperature over 4 h. The solution was then re-cooled (-10 °C) and methanolic KOH was added in a single portion to remove the TMS group. Aqueous work-up gave the target intermediate **2.15** as a pale-yellow powder in an excellent yield of 92 % with a melting point of 82 - 83°C (Scheme 2.16). The formation of **2.15** was confirmed by ¹H NMR spectroscopy which exhibited a singlet at 2.8 ppm assigned to the acetylene proton and the expected singlet at 4.8 ppm due to the H-bonded hydroxyl proton. In the ¹³C NMR spectrum, the carbonyl C=O signal was no longer present at 194.3 ppm (for **2.3a**) and the spectrum exhibited three new signals assigned to the tertiary C-atom at 73.6 ppm and acetylene C-atoms at 74.5 and 86.1 ppm. Additionally, infrared spectroscopy gave a weak band at ca. 3548 cm⁻¹ that correlates to the alcohol group and a sharp band at 2359 cm⁻¹ that indicates the presence of the acetylene.

The mechanism for the formation of the intermediate propargylic alcohol **2.15** is presented in Scheme 2.14. The start of the process is essentially identical to that for the previous examples **2.1aa-ac**, however this reaction mechanism has an additional step as a consequence of the hydroxide ion mediated de-silylation step. *n*-Butyllithium behaves as a base and abstracts the TMS-acetylene proton forming a lithiumtrimethylsilylacetylide whereupon this nucleophile attacks the carbonyl unit of the benzophenone affording an alkoxide intermediate. Elimination of TMS group is accomplished by hydroxyl ion attack at the Si atom then loss of the acetylenic moiety with re-protonation. <1997B-1>



Scheme 2.14: Mechanism for the formation of intermediate alkynol **2.15**

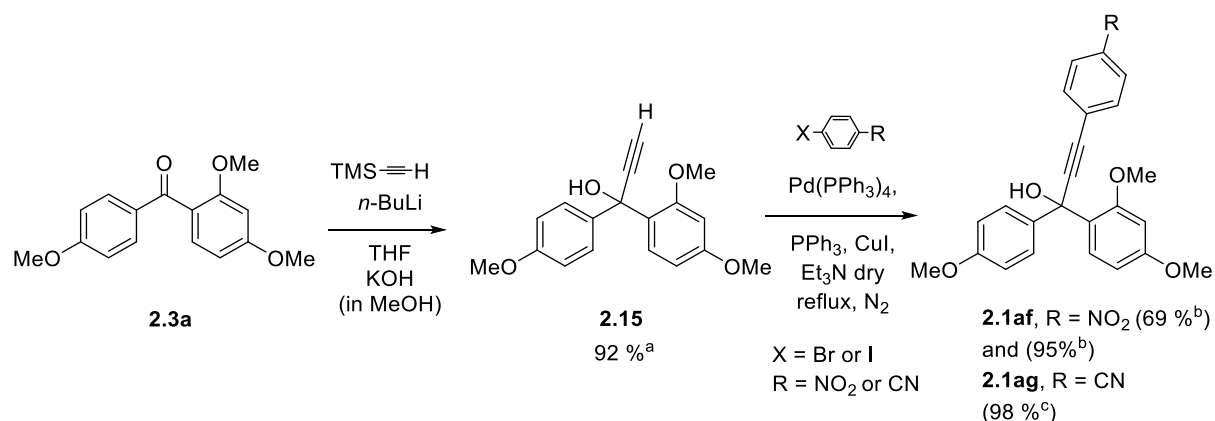
Lang and co-workers have synthesised a 1,1,3-triarylprop-2-yn-1-ol **2.18** that contains an electron-withdrawing nitrile substituent in the *ortho*-position of the terminal aryl ring (Scheme 2.15). The *o*-benzonitrile prop-1-yn-1-yl derivative **2.18** was prepared by Sonogashira cross-coupling reaction of 2-iodobenzonitrile **2.17** with 1,1-bis(4-methoxyphenyl)prop-2-yn-1-ol **2.16** in the presence of diisopropylamine under combined palladium- and copper-catalysed conditions. The reaction proceeded within 3 h at 50 °C under a N₂ atmosphere giving a high yield of **2.18**. <2017JOC8407>



Scheme 2.15: Sonogashira cross-coupling reaction to afford **2.18**

Encouraged by the foregoing successful Sonogashira reaction on a propynol reported by Lang *et al.*, closely related reaction conditions were employed in this present study. Thus, alkynol **2.15** was dissolved in freshly distilled anhydrous Et₃N and stirred with 1-bromo-4-nitrobenzene in the presence of Pd(PPh₃)₄ CuI and PPh₃ under reflux for 3 h furnishing a crude

product that was purified by column chromatography to give **2.1af** as a pale brown waxy solid (melting point 54 – 56 °C) in a yield of 69% (Scheme 2.16). The yield was significantly improved when the reaction was repeated giving the product in 95% yield. The nitrile substituted analogue, **2.1ag**, was obtained using 4-iodobenzonitrile as the coupling partner by the same methodology but with longer refluxing time of 20 h, as a brown powder in 98% yield and with a melting point range 76 – 77 °C.



^a Reagents and conditions: **2.3a** (1 eq.), TMS acetylene (2 eq.), $n\text{-BuLi}$ (2 eq.), KOH (2.2 eq.) in MeOH (20 mL) THF dry, - 10 °C to r.t., 20 h

^b Reaction conditions: **2.15** (1 eq.), 1-bromo-4-nitrobenzene (1 eq.), PPh_3 (15 mol %), $\text{Pd(PPh}_3)_4$ (3 mol %), CuI (7.5 mol %), Et_3N dry (7 mL/mmol), reflux under N_2 , 3 h

^c Reaction conditions: **2.15** (1 eq.), 1-iodobenzonitrile (1 eq.), PPh_3 (15 mol %), $\text{Pd(PPh}_3)_4$ (3 mol %), CuI (7.5 mol %), Et_3N dry (7 mL/mmol), reflux under N_2 , 20 h

Scheme 2.16: Two-step process of synthesis NO_2 and CN substituted propynol **2.1af** and **2.1ag**

The structures **2.1af**, **ag** were confirmed from their ^1H NMR spectra (Figure 2.6) that showed a singlet (**q**) at ca. 4.9 ppm for the hydroxyl proton which was slightly shifted downfield relatively to the propynol **2.1ab**. Compound **2.1af** give a rise to an extra two multiplets at ca. 8.2 ppm and ca. 7.6 ppm which are assigned to the aromatic protons of the nitrophenyl moiety. Compound **2.1ag** has shown an additional multiplet signals corresponding to the cyanophenyl substituent attached which resonates at ca. 7.6 ppm and are assigned with 4H. The presence of the tertiary C-atom was confirmed by ^{13}C NMR spectroscopy by the appearance of a signal at 74.0 ppm for compound **2.1af** and signal at 74.1 ppm for compound **2.1ag**. Infrared spectroscopy revealed a broad band at ca. 3500 cm^{-1} for compound **2.1af** and sharp stretch signal at 3655 cm^{-1} for compound **2.1ag** that indicates the presence of the

alcohol group. In addition, a weak stretch was noticed at ca. 2250 cm⁻¹ that corresponds to the CN triple bond for compound **2.1ag**.

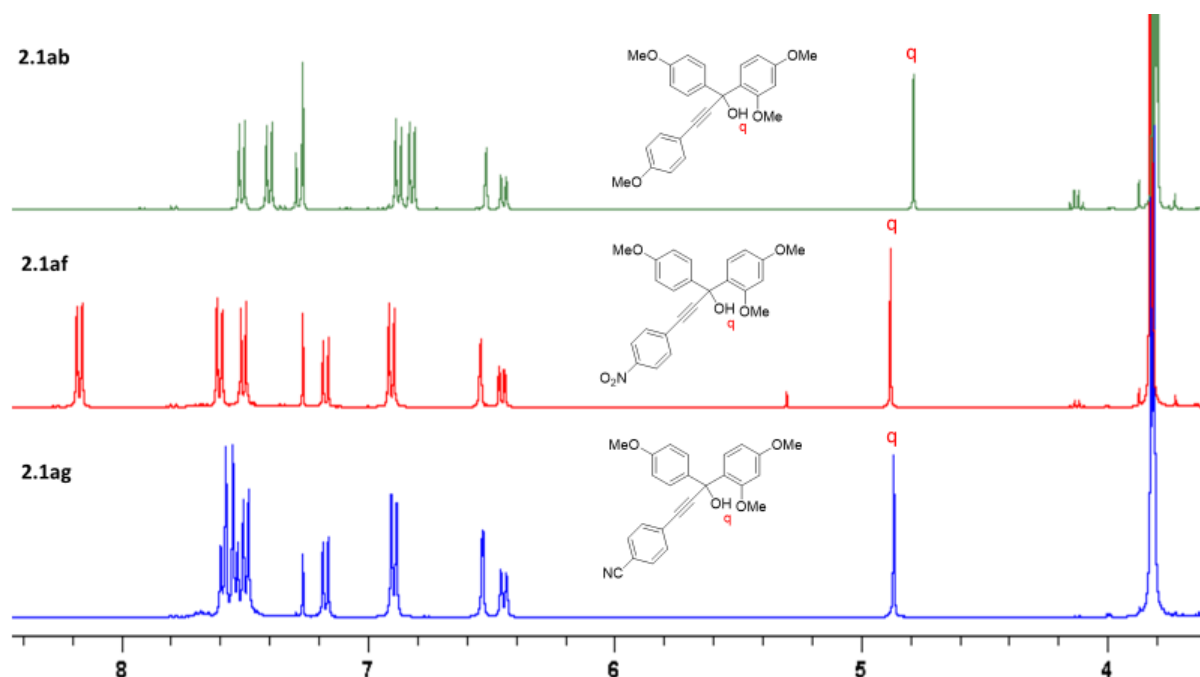
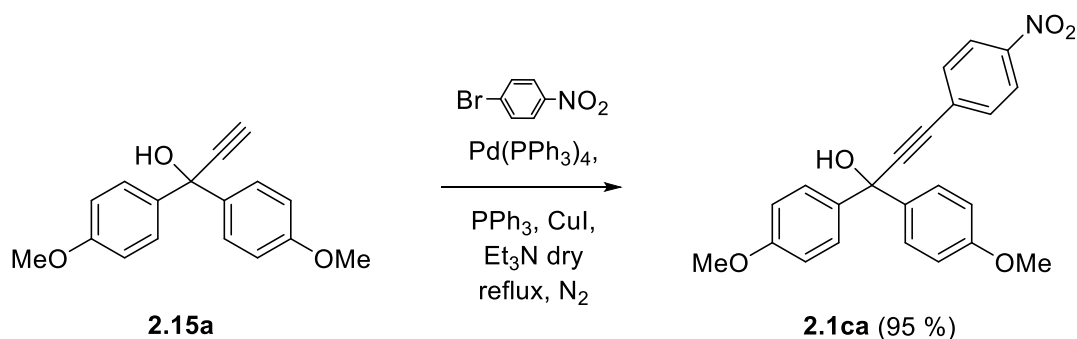


Figure 2.6: ¹H NMR spectra of 1,1,3-triarylprop-2-yn-1-ols **2.1ab**, **af**, **ag**

To contrast with the synthesised 1,1,3-triarylprop-2-yn-1-ols **2.1a-g** which bear an *ortho*-methoxy substituent, the formation of **2.1ca** derived from 1,1-bis(4-methoxyphenyl)prop-2-yn-1-ol **2.15a** was next examined. Therefore by employing the standard Sonogashira cross-coupling conditions, 1,1-bis(4-methoxyphenyl)prop-2-yn-1-ol **2.15a** was refluxed with 4-bromo-1-nitrobenzene for 20 h affording a crude product that was purified by flash column chromatography to give dark brown gum in 95% yield (Scheme 2.17).



Scheme 2.17: The reaction of 1,1-bisarylprop-2-yn-1-ol **2.15a** with 4-bromonitrobenzene

^1H NMR spectra (Figure 2.7) showed an upfield singlet at 2.9 ppm which corresponds to the hydroxyl proton. Interestingly, the peak was found to be shifted upfield which is due to the absence of an *ortho* methoxy unit. <2010OBC4874> The structure of **2.1ca** was further confirmed by the presence of two multiplets at ca. 8.2 ppm and ca. 7.6 ppm which are assigned to the aromatic protons of the nitrophenyl unit. ^{13}C NMR spectroscopy showed the signal of the tertiary C-atom at 74.2 ppm and infrared spectroscopy revealed a sharp stretch signal at 3500 cm^{-1} that proved the presence of the alcohol group.

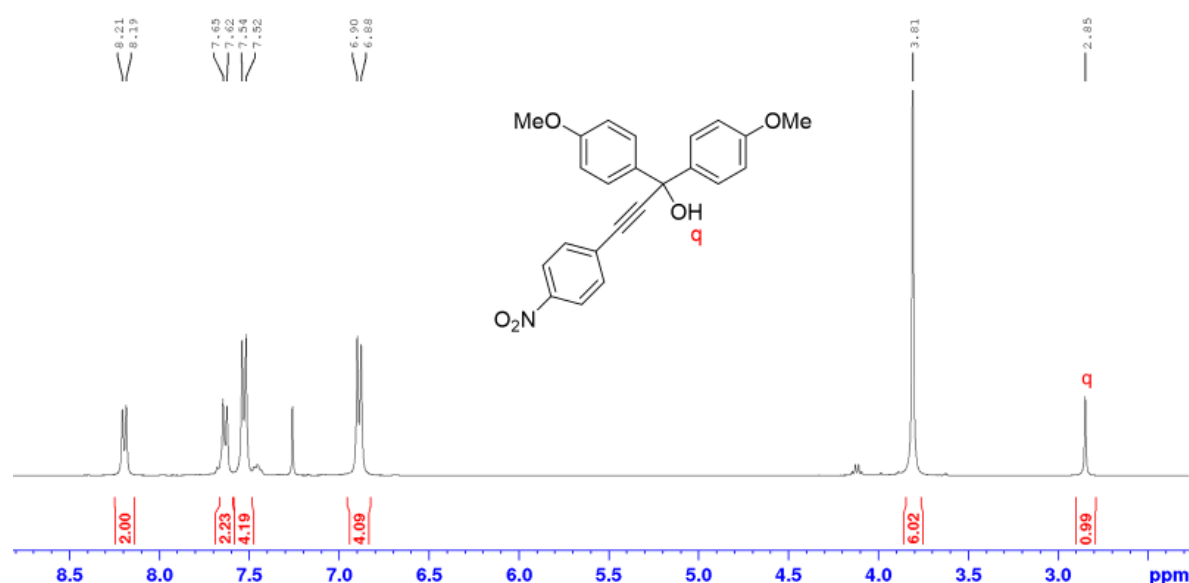
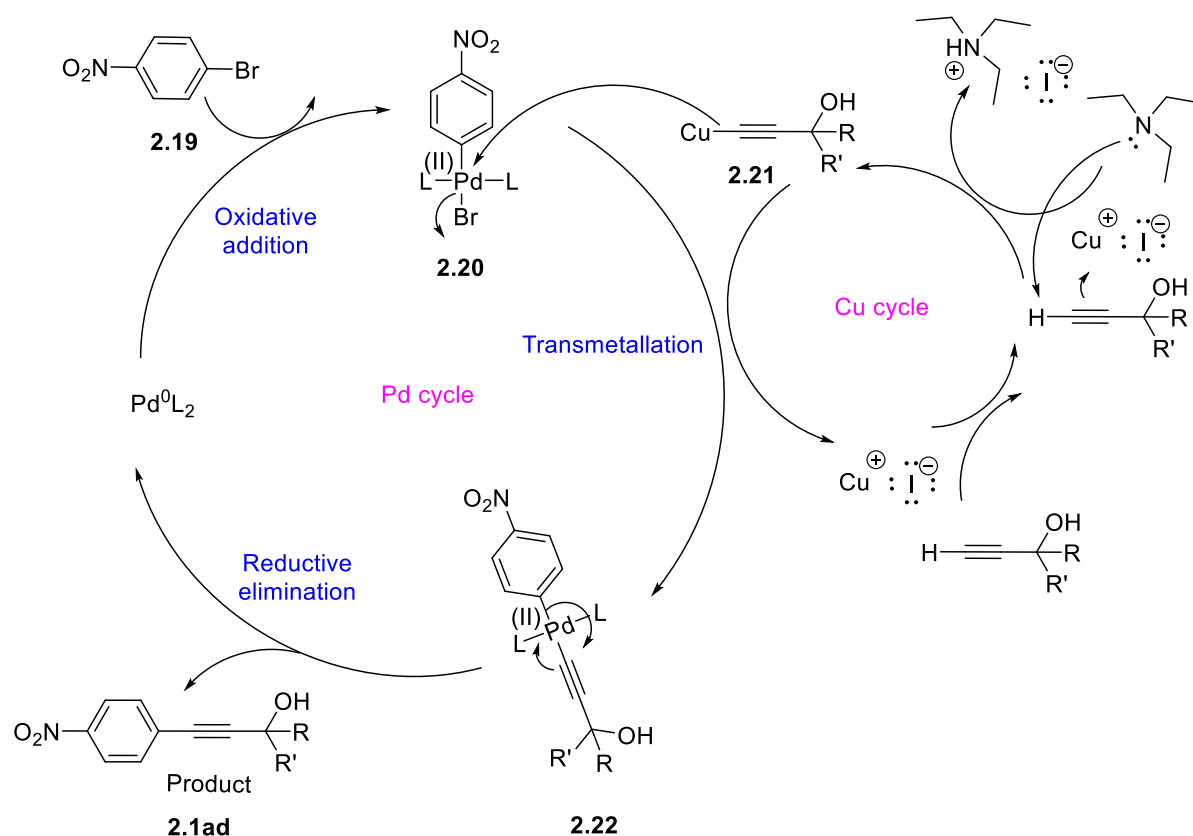


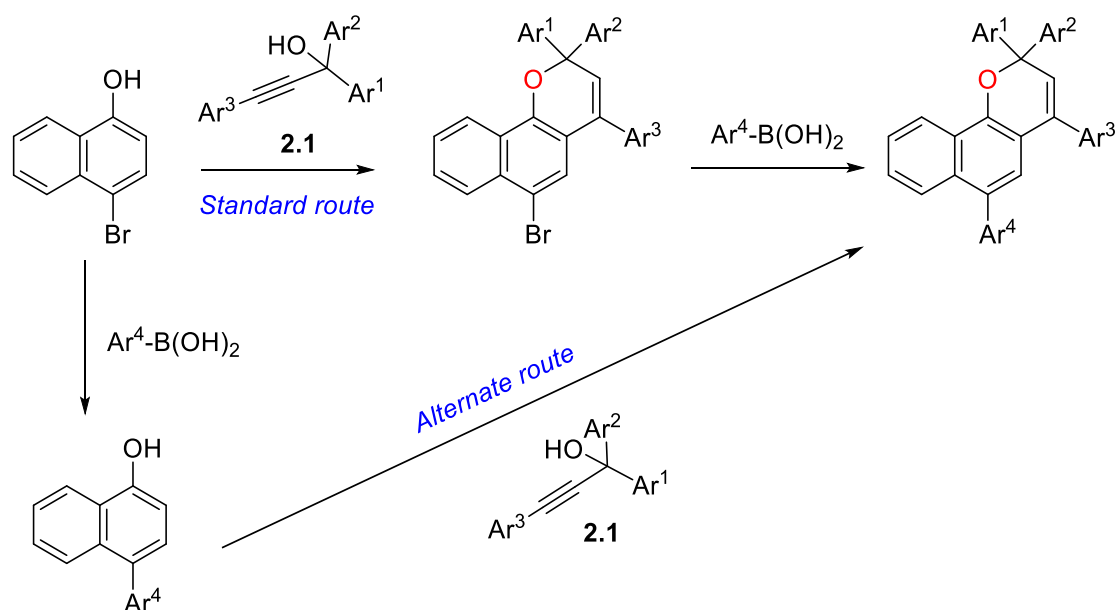
Figure 2.7: ^1H NMR spectrum of 1,1,3-triarylprop-2-yn-1-ol **2.1ca**

The mechanism for the Sonogashira cross-coupling reaction is well-established <1995OPPI127; 2002JOC46; 2009B-1> and is outlined in Scheme 2.18. The reaction proceeds via a 'palladium cycle' and an additional co-promoter 'copper cycle' that facilitates the movement of an acetylenic group to the palladium metal centre. In order for the reaction to commence the active $\text{Pd}(0)$ catalyst firstly undergoes an oxidative addition step to the aryl halide **2.19** to afford a $\text{Pd}(\text{II})$ complex **2.20**. In the subsequent step of the catalytic cycle, termed transmetalation, the co-catalytic copper cycle exchanges the terminal alkyne into copper acetylide **2.21** that contains an electron deficient metal which attacks the ligand unit affording a complex intermediate **2.22**. In the last step, the reductive elimination process detaches the alkyne compound creating a new C-C bond thus forming the final product and re-generates the palladium catalyst that is suitable for the next reaction cycle. <2009B-1>



Scheme 2.18: The mechanism for Sonogashira cross-coupling reaction

With the key propynols prepared in generally good yield their reaction with a series of 1-naphthols to form the naphthopyrans could be investigated (Scheme 2.19). Whilst the vast majority of the 1-naphthols were commercially available it was envisaged that it would be of interest to explore the construction of a 2,2,4,6-tetraaryl substituted naphthopyran from a 1-naphthol in which a 4-aryl substituent had already been installed (alternate route) rather than introducing the aryl substituent by post-modification of a suitably substituted naphthopyran (standard route).

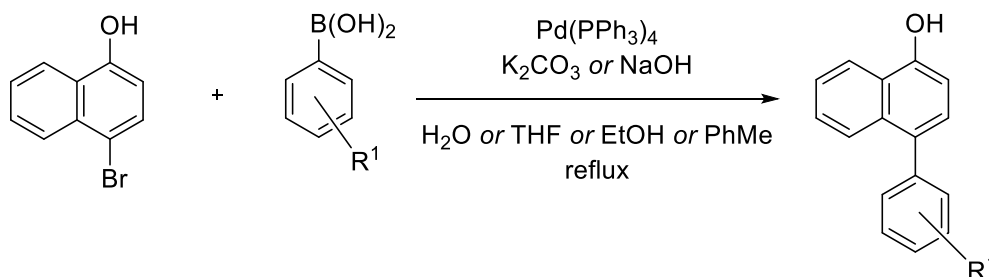


Scheme 2.19: Proposed routes to tetra-aryl substituted naphthopyrans

2.3 Preparation of 4-aryl-1-naphthols

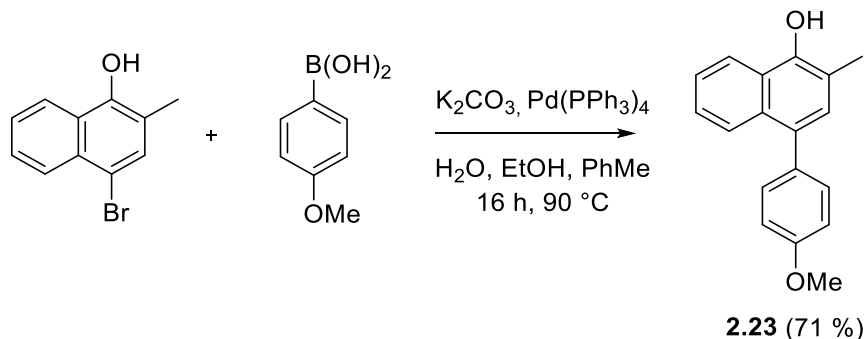
Perhaps the most convenient route to prepare 4-aryl-1-naphthols relies upon the Suzuki cross-coupling reaction <1981SC513; 2013CEJ15565; 2017CEJ4542; 2018ASC852; 2019ASC4468> between readily available 4-bromo-1-naphthol and an arylboronic acid. This strategy has been employed for the construction of pharmaceutical intermediates <1997JAC10073; 2018WOP2018193476; 2019WOP201908964> and intermediates employed in the synthesis of emissive compounds. <2015WOP2015002038; 2018CNP108623554>

The conditions that have been reported for the formation of biaryls by Suzuki cross-coupling reactions can be readily applied to the synthesis of 4-aryl-1-naphthols (Scheme 2.20). <2013CEJ15565; 2017CEJ4542; 2018ASC852; 2019ASC4468>



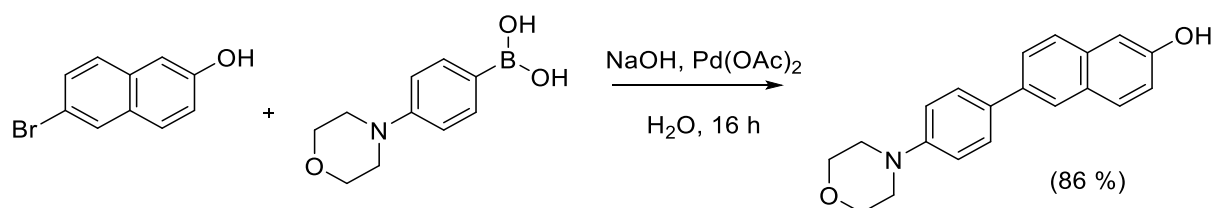
Scheme 2.20: Reaction conditions for the synthesis of 4-aryl-1-naphthols

For example, 4-bromo-2-methyl-1-naphthol has been coupled to 4-methoxybenzeneboronic acid to afford **2.23** in 71% yield using a toluene ethanol mixed solvent system, K_2CO_3 as a base and tetrakis(triphenylphosphine)Pd(0) as the Pd-catalyst (Scheme 2.21). <2019ASC4468>



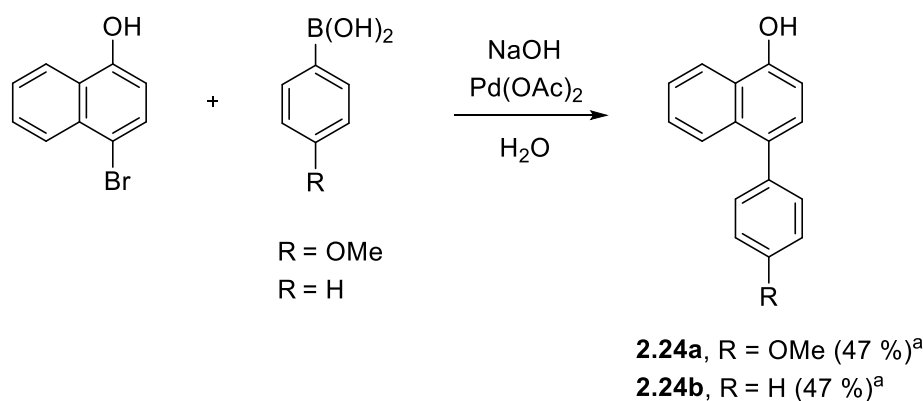
Scheme 2.21: Suzuki cross-coupling reaction to afford a 4-aryl-1-naphthol **2.23**

However, perhaps one of the simplest and most efficient methods for the synthesis of aryl substituted naphthols is outlined in Scheme 2.22 where the coupling reaction proceeded using $Pd(OAc)_2$ and NaOH in tap water at room temperature overnight. <2020PC1>



Scheme 2.22: Suzuki cross-coupling reaction under mild reaction conditions

Thus adopting the foregoing mild reaction conditions a mixture of 4-bromo-1-naphthol, 4-methoxyphenylboronic acid, NaOH and $Pd(OAc)_2$ were dissolved in tap water and stirred under air in a closed flask at room temperature until TLC examination of the reaction mixture indicated no further change in composition. The reaction suspension was then neutralised with HCl, extracted with EtOAc, washed with water and isolated from silica with 10 % EtOAc-petroleum ether $40\text{--}60\text{ }^\circ\text{C}$ affording the compound **2.24a** as a beige powder in 47% yield and with melting point of $130\text{--}131\text{ }^\circ\text{C}$ (Scheme 2.23). The methodology used to obtain compound **2.24a** was also employed to prepare compound **2.24b** from phenylboronic acid in 47% yield.



^aReaction conditions: 4-bromo-1-naphthol (1 eq.), arylboronic acid (1.5 eq.), NaOH (4 eq.), Pd(OAc)₂ (2.7 mol %), water (4.5 mL/mmol)

Scheme 2.23: Suzuki cross-coupling of 4-bromo-1-naphthol

The structures of **2.24a** and **2.24b** were readily established by ¹H NMR spectroscopy (Figure 2.8) due to the low complexity of the molecules. The upfield region of the spectrum showed singlet (**4**) at ca. 3.9 ppm accounting for three protons which is assigned to the methoxy unit of compound **2.24a**. The hydroxyl proton was observed as a singlet (**q**) at 5.30 ppm and 5.34 ppm for **2.24a** and **2.24b**, respectively. The naphthalene ring protons are found to be similar for compound **2.24a** and **2.24b** which give a rise to the signals corresponding to 2-H (**c**) at ca. 6.9 ppm with *J* = 7.6 Hz, 3-H (**d**) at ca. 7.2 ppm with *J* = 7.6 Hz, 5-H (**b**) at ca. 7.9 ppm and 8-H (**a**) at ca. 8.3 ppm. The remainder of the aromatic protons appeared as multiplets at region 7.40 - 7.55 ppm. Additionally, the signals for the anisyl ring protons of compound **2.24a** resonated at 7.03 and 7.40 ppm. The structures of **2.24a** and **2.24b** were further confirmed by ¹³C NMR spectroscopy which exhibited a low field signal at ca. 151.0 ppm that is indicative of C-1 with the alcohol substituent. Compound **2.24a**, that possesses a methoxy substituent, has an additional signal at 158.7 ppm for the C atom attached to the methoxy unit and also has the signal for the methoxy group which appeared at 55.4 ppm. Infrared spectroscopy confirmed the presence of a OH group with a broad band at ca. 3320 cm⁻¹ for both compounds.

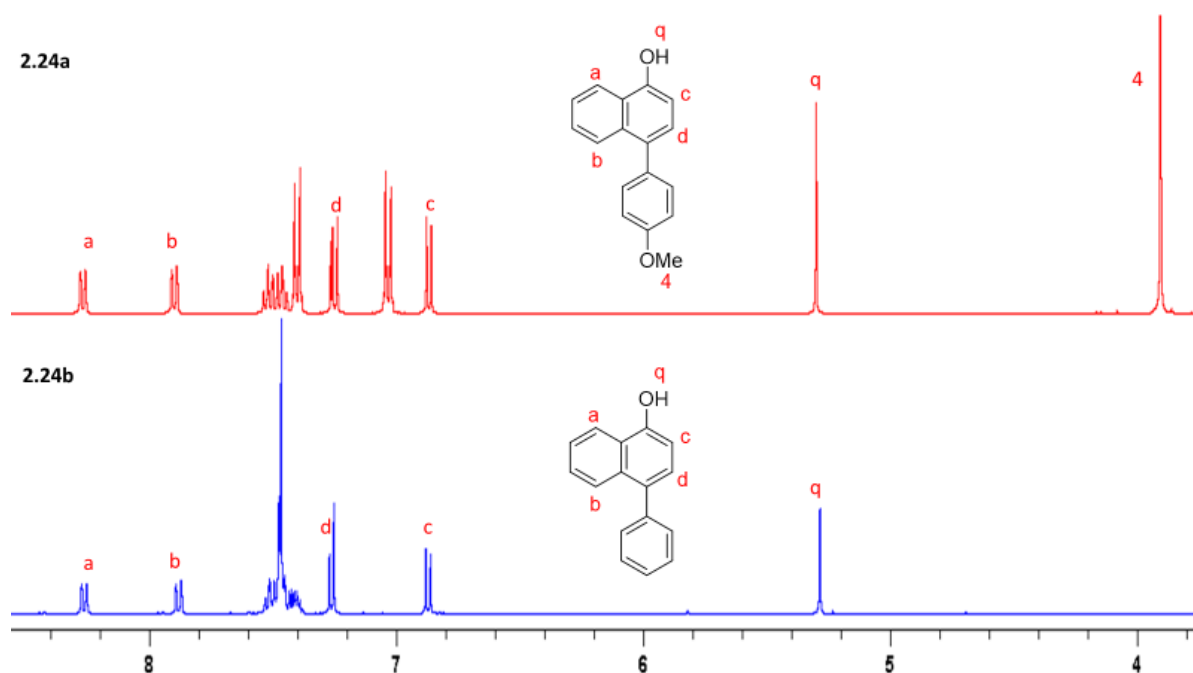
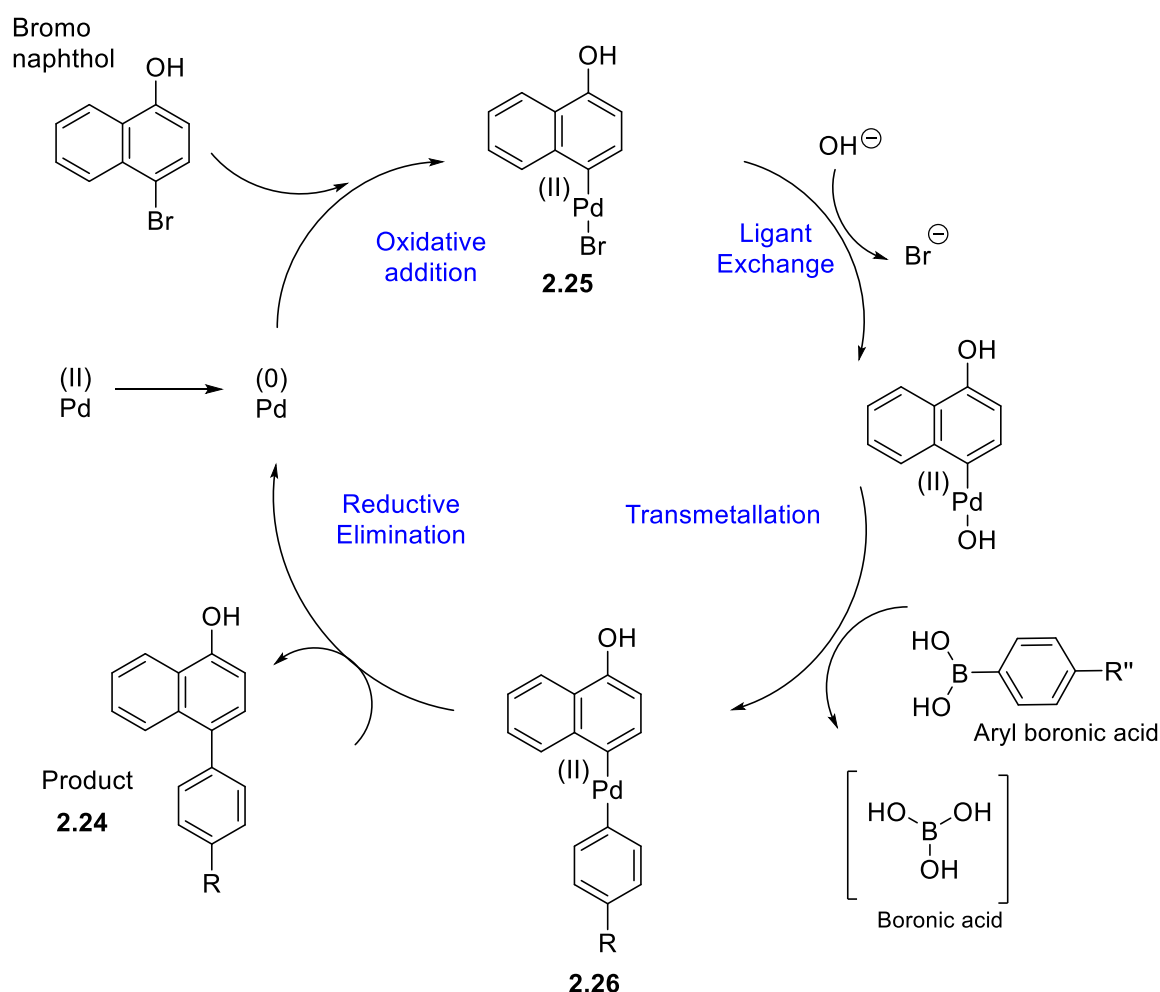


Figure 2.8: ^1H NMR spectra of 4-aryl-1-naphthols **2.23a** and **2.23b**

The mechanism of the Suzuki reaction is shown in Scheme 2.24. Initially, the $\text{Pd}(\text{OAc})_2$ pre-catalyst is activated into a $\text{LnPd}(0)$ palladium-ligand species under the reaction conditions where it follows the oxidative addition step. During this process the $\text{Pd}(0)$ species inserts into the C-Br bond of the 4-bromo-1-naphthol which generates the $\text{Pd}(\text{II})$ intermediate **2.25** that then follows a ligand exchange with hydroxyl displacing the bromine atom. In a subsequent transmetallation step, the base attacks the boron unit of the arylboronic acid and as a consequence boric acid is lost with the aryl unit available for the formation of $\text{Pd}(\text{Ar})(\text{Ar}')$ complex **2.26**. The last step of the reaction mechanism is reductive elimination in which cross-coupling reaction occurs where the C-C bond is formed between substituted aryl derivative and naphthol forming the final product **2.24** together with regeneration of the $\text{Pd}(0)$ catalyst.

<1995CR2457; 2005JACS4685; 2009B-1>

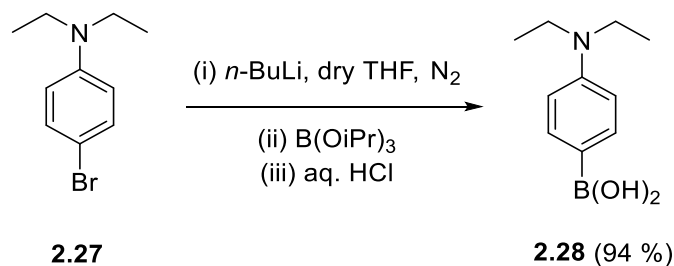


Scheme 2.24: The mechanism for the Suzuki cross-coupling reaction

2.4 Preparation of 4-diethylaminophenylboronic acid

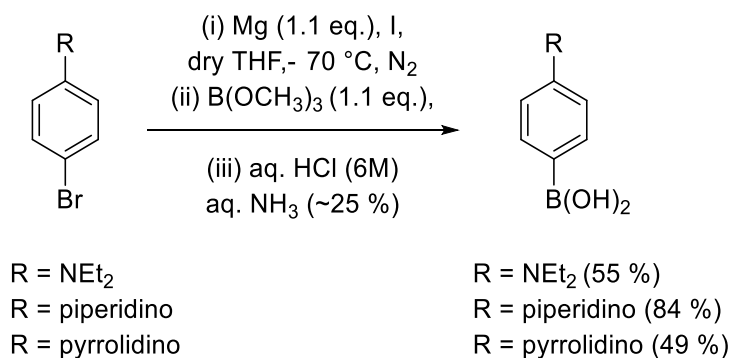
Formation of 4-diethylaminophenylboronic acid was very important in order to introduce a very strong electron donating aryl group at C-6 in the target naphthopyrans. Potentially the most favourable method used to synthesise 4-dialkylaminobenzeneboronic acids was through the standard procedure using an organolithium reagent *n*-BuLi that initiates the bromine-lithium exchange followed by the formation of arylboronic acid upon quenching the aryllithium intermediate with a trialkylborate and acidic hydrolysis. This strategy was widely used in biological study of glutamate <2000WOP2000006537> and retinoic acid receptors <2006WOP2006066978> as well as in chemistry related research for semiconductor materials <2016CNP105367451> and fluorescent dyes <2011CEJ14273>.

Biadatti *et al.*, have synthesised a 4-diethylaminophenylboronic acid **2.28** in an excellent yield using the typical procedure where *n*-BuLi was slowly added to the solution of 4-bromo-*N,N*-diethylaniline **2.27** in THF at -78°C whereupon triisopropyl borate and aq. HCl finalised the reaction leading to the crude product as a white solid in high yield (Scheme 2.25). <2006WOP2006066978>



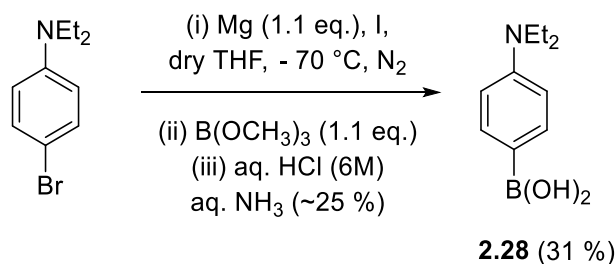
Scheme 2.25: Preparation of 4-diethylaminophenylboronic acid **2.28** using a standard Li-Br exchange method

One of the intriguing methods for the synthesis of a wide range of 4-dialkylaminobenzeneboronic acids is outlined in Scheme 2.26 where the reaction proceeded using a Grignard reagent in dry THF which was subsequently quenched with trimethylborate and the resulting boronic ester hydrolysed with aq. HCl. <2020PC2>



Scheme 2.26: Preparation of 4-dialkylaminobenzeneboronic acids using a Grignard reagent

Thus, adopting the Grignard reagent conditions as depicted in Scheme 2.26, the formation of 4-diethylaminophenylboronic acid **2.28** was accomplished in 31% yield as a dark blue powder with narrow melting point range of 229 – 230 °C (Scheme 2.27).



Scheme 2.27: Synthesis of 4-(diethylamino)phenylboronic acid **2.28** using Grignard reagent

The formation of compound **2.28** was proved by ^1H NMR spectroscopy giving the characteristic signals for diethyl protons that resonates as a triplet ($J = 6.5$ Hz) at 1.23 ppm accounting for 6H and quartet ($J = 6.8$ Hz) at 3.45 ppm accounting for 4H. The aromatic protons give a rise to a signal at 6.75 ppm and 8.08 ppm with coupling constant $J = 7.8$ Hz. ^{13}C NMR spectroscopy confirmed the presence of 4-diethylamino substituent as the ethyl group C-atoms resonated upfield at 12.64 ppm and 44.33 ppm. In addition, there are only three peaks that resonate in the aromatic region which corresponds to the carbons from the aryl ring however the carbon-boron directly attached is unrevealed possibly due to the relaxation of coupling that drastically reduced the intensity of the peak. <1979PNMRS227>

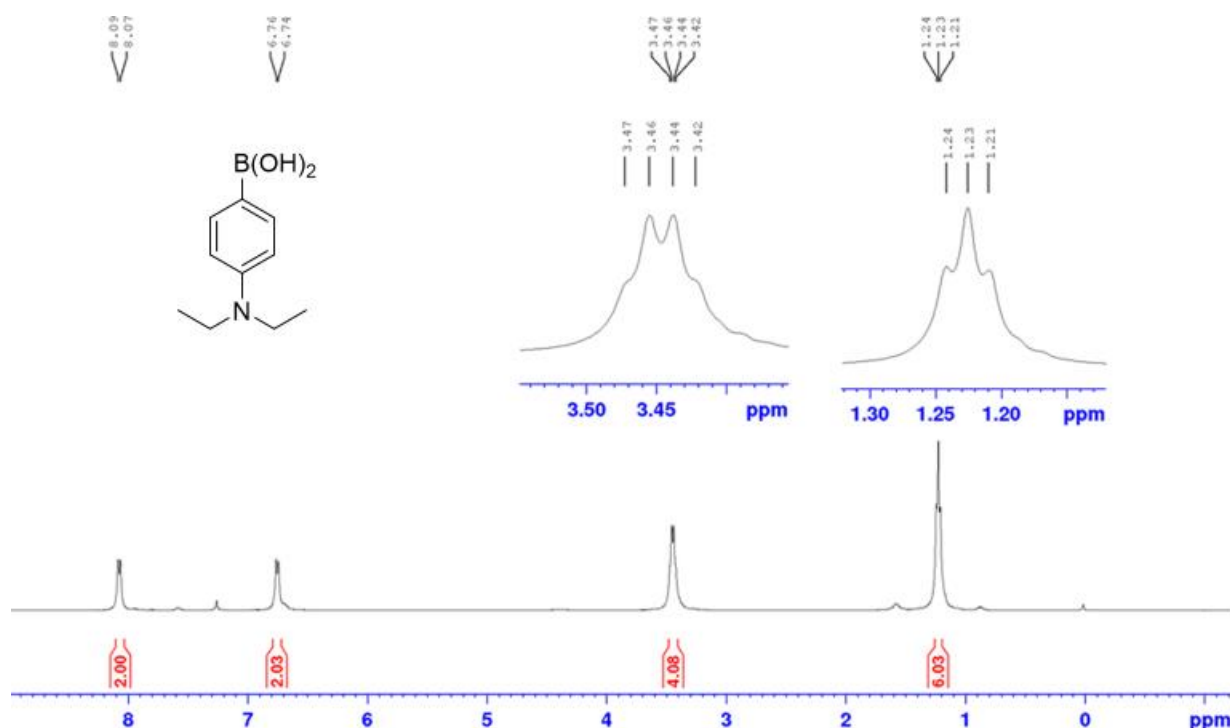
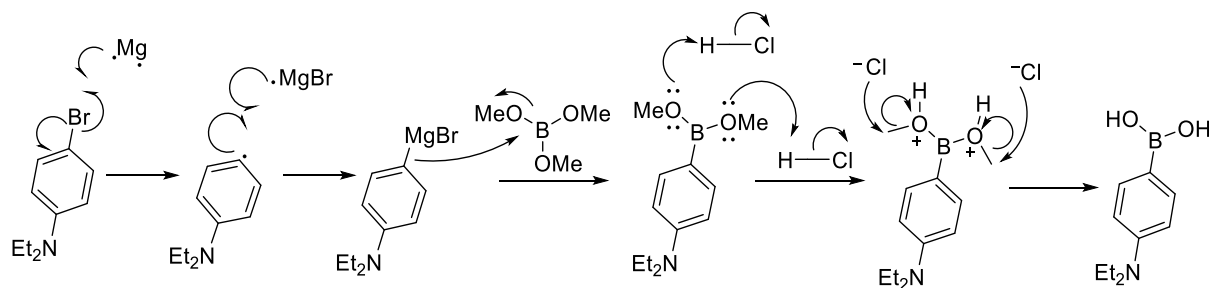


Figure 2.9: ^1H NMR spectrum of 4-diethylaminophenylboronic acid **2.28**

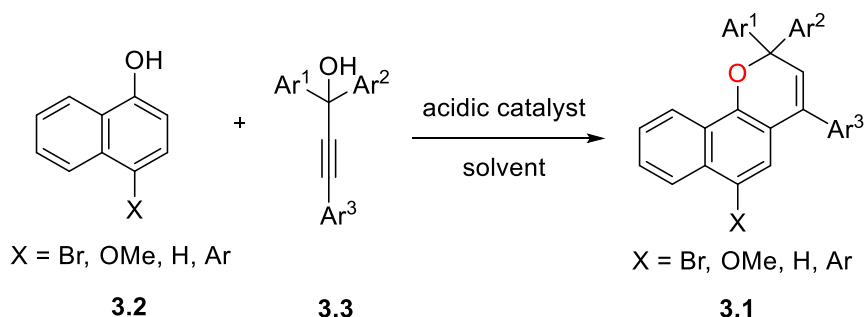
The straightforward mechanism of the reaction to prepare **2.28** is shown in Scheme 2.28. The very first steps rely upon formation of the Grignard reagent with a free radical insertion of the Mg atom between the aryl ring and the bromine atom. This process creates strongly nucleophilic arylcarbon atom which readily attacks the trimethyl borate via a nucleophilic addition step. Next, the ester groups are hydrolysed to form the boronic acid. <2014OC287>



Scheme 2.28: The mechanism for the formation of (4-(diethylamino)phenyl)boronic acid

Chapter 3.0 Synthesis of naphthopyrans

With the range of substituted 1,1,3-triarylprop-2-yn-1-ols prepared (Chapter 2.2) and a series of commercial and synthesised 4-aryl-1-naphthols available (Chapter 2.3) their union to form a series of substituted 2*H*-naphtho[1,2-*b*]pyrans was next examined (Scheme 3.1).



Scheme 3.1: Preparation of substituted 2*H*-naphtho[1,2-*b*]pyrans

The diversely substituted propynols **3.3a-i** shown in Figure 3.1 are the main building blocks for the formation of the first series of naphthopyrans **3.1** (Scheme 3.1).

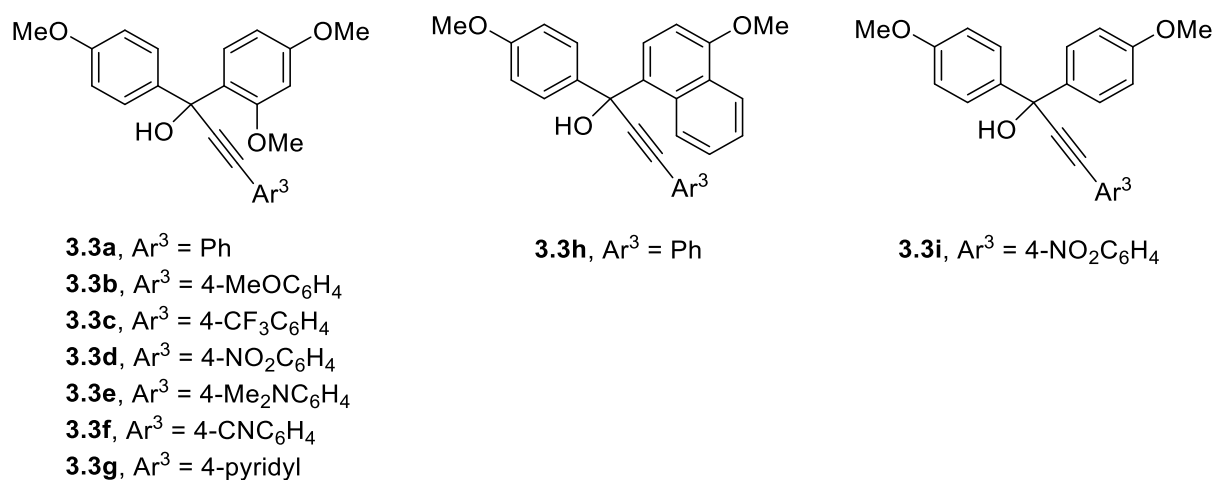
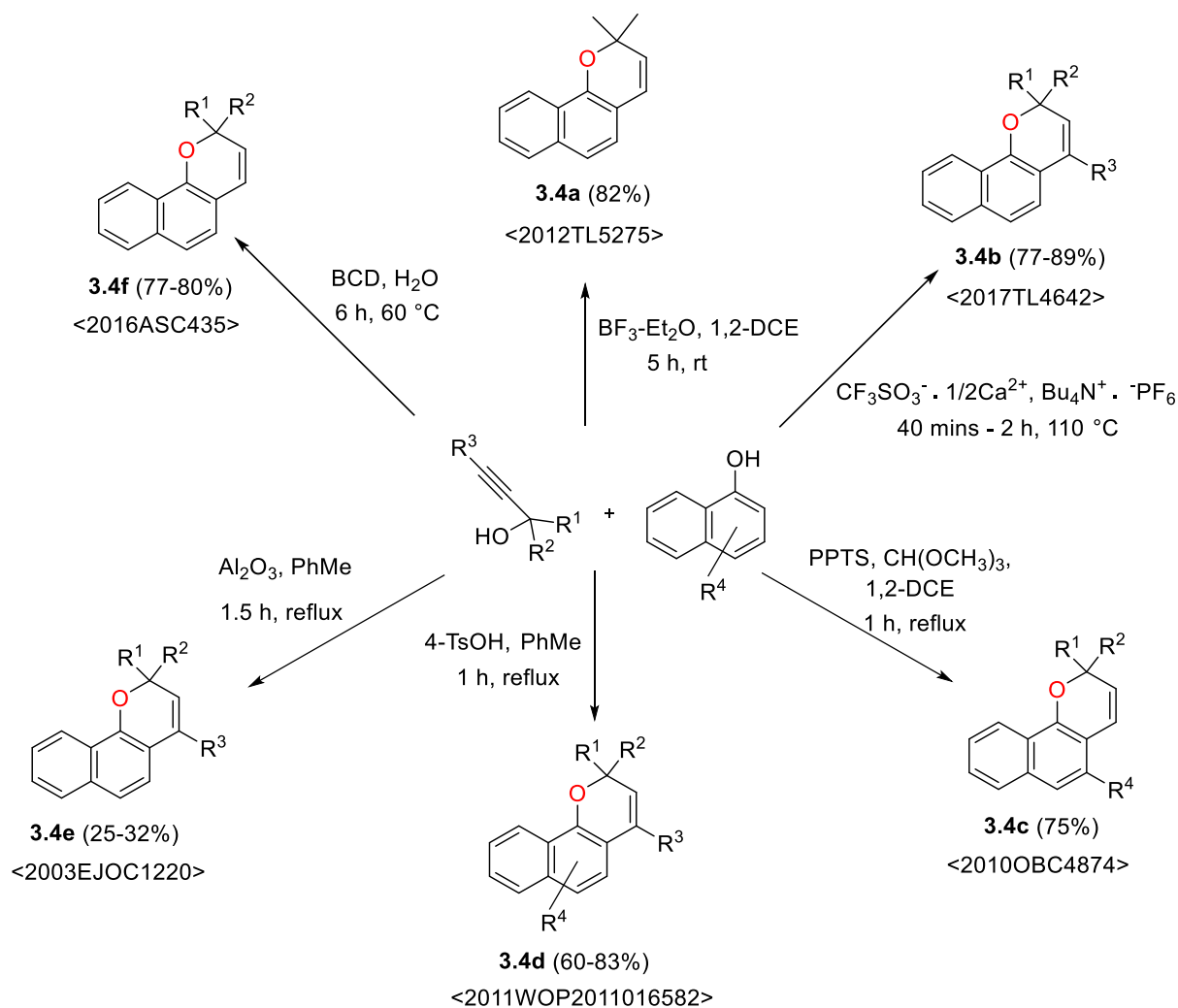


Figure 3.1: Target prop-2-yn-1-ols **3.3a-i**

The presence of the 6-bromine substituent in the naphthopyran system **3.1** $\text{X} = \text{Br}$ was particularly attractive since a promising approach to the 2,2,4,6-tetraaryl substituted 2*H*-naphtho[1,2-*b*]pyrans required in the present study was to synthesise a range of 6-Br substituted 2*H*-naphtho[1,2-*b*]pyrans and then examine their transformation into the requisite 2,2,4,6-tetraaryl compounds via a Suzuki-Miyaura cross-coupling reaction with a series of aryl boronic acids (Chapter 4.1).

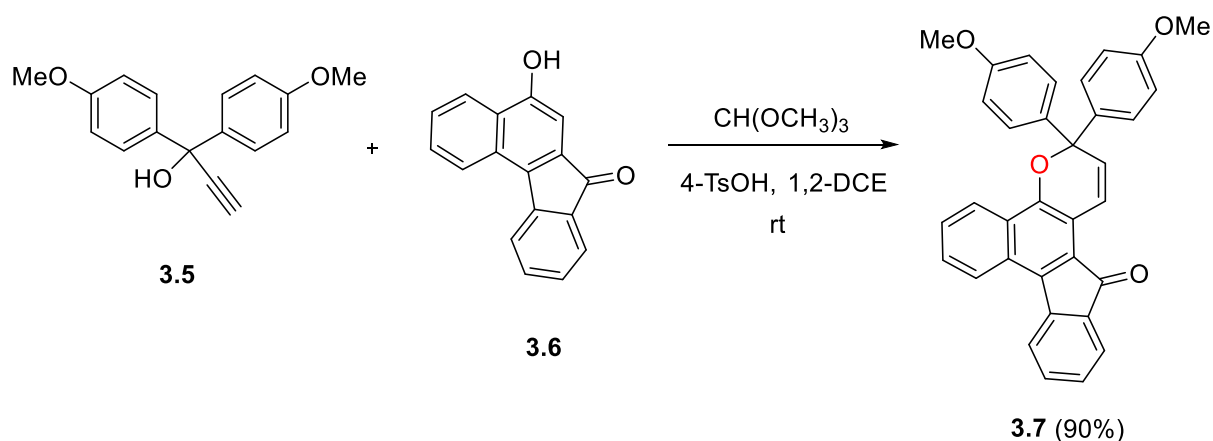
3.1 Synthesis of 2,2,4-aryl-6-bromo and 2,2,4-aryl-6-methoxy substituted 2H-naphtho[1,2-*b*]pyrans

A wide variety of acidic catalysts have been employed for the synthesis of 2,2-disubstituted 2H-naphtho[1,2-*b*]pyrans from 1-naphthols and propynols (Scheme 3.2); Madabhushi *et al.*, used the Lewis acid borontrifluoride etherate in 1,2-DCE at room temperature furnishing the dimethyl substituted naphthopyran **3.4a** in 82% yield <2012TL5275>, Ghatak *et al.*, employed β -cyclodextrin (BCD) and H₂O at 60 °C which offered the pyran product **3.4f** in 80% yield <2016ASC435> and Yaragorla *et al.*, employed a combination of a calcium trifluoromethanesulfonate and tetra(*n*-butyl)ammonium hexafluorophosphate catalysts in a solvent free environment and under relatively high temperature to give the pyran **3.4b** in 89% yield. <2017TL4642> More commonly the synthesis of substituted naphthopyrans employs established acid-catalysed reaction conditions including the application of either acidic alumina in toluene <1997JOC7024; 2000DP(47)73; 2002T925; 2003EJOC1220; 2008DP(76)24; 2010OBC4874>, 4-toluenesulfonic acid (4-TsOH) in toluene <2004ACST55; 2011WOP2011016582; 2012DP(54)79> 4-TsOH in chloroform at room temperature <2019DP(169)118; 2020EJOC985> or pyridinium 4-toluenesulfonate (PPTS) with trimethyl orthoformate in 1,2-dichloroethane (Scheme 3.2). <2003OL4153; 2014T9351>



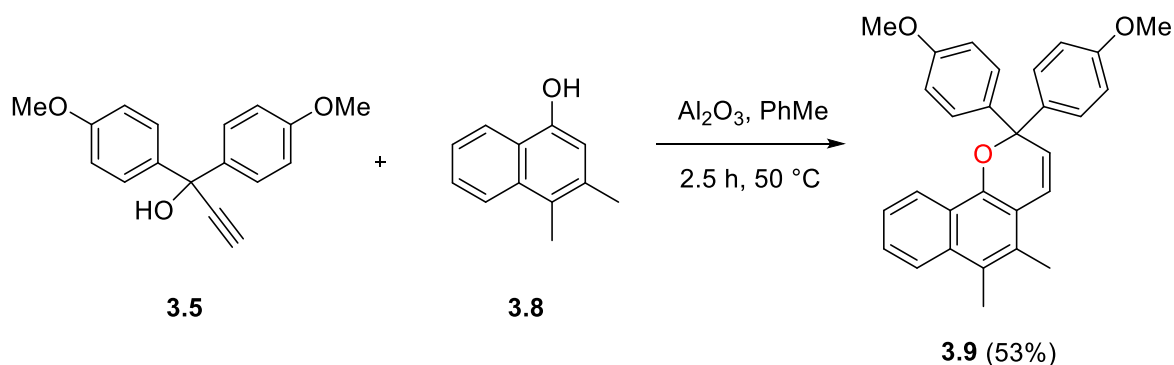
Scheme 3.2: Synthesis of 2*H*-naphtho[1,2-*b*]pyrans under different conditions

Of particular note was the reaction of 1,1-bis(4-methoxyphenyl)prop-2-yn-1-ol **3.5** with the indeno-fused naphthol **3.6** in the presence of 4-toluenesulfonic acid and trimethyl orthoformate in 1,2-dichloroethane giving the fused naphthopyran **3.7** in an impressive 90% yield (Scheme 3.3).<2003OL4153>



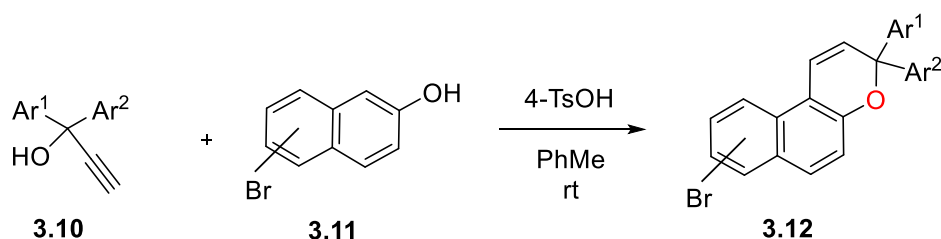
Scheme 3.3: Synthesis of indeno-fused 2H-naphtho[1,2-b]pyran **3.7**

The reaction of the same alkynol, 1,1-bis(4-methoxyphenyl)prop-2-yn-1-ol **3.5**, with 3,4-dimethyl-1-naphthol **3.8** using acidic alumina in toluene delivered the expected naphthopyran **3.9** however, in only 53% yield (Scheme 3.4); this feature indicates the variability of the reaction with catalyst and naphthol structure. <2016CC1474>



Scheme 3.4: Synthesis of naphthopyran **3.9** using acidic alumina and toluene

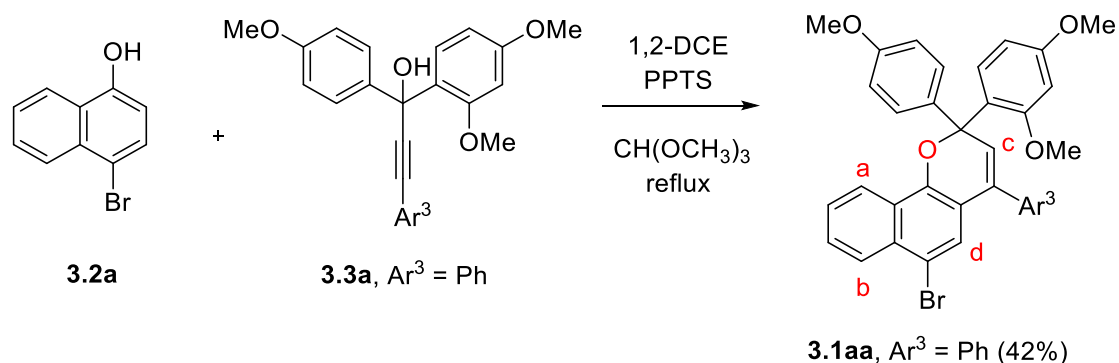
Of interest to the current work was the report, in a Japanese patent, of the synthesis of a range of bromo substituted 3H-naphtho[2,1-b]pyrans **3.12** from a variety of 1,1-diarylprop-2-yn-1-ols **3.10** and bromo-2-naphthols **3.11** which used 4-toluenesulfonic acid in toluene under mild conditions furnishing the products **3.12** with yields in excess of 65% (Scheme 3.5). <2015JPP2015127371>



Scheme 3.5: Formation of bromo substituted 3*H*-naphtho[2,1-*b*]pyrans **3.12**

Generally, the use of weakly acidic pyridinium 4-toluenesulfonate (PPTS) catalysis in the presence of trimethyl orthoformate, which serves as a dehydrating agent, in 1,2-dichloroethane has been more widely employed as it routinely provides moderate to high yields of the naphthopyrans <2003OL4153; 2010OBC4874; 2011JMC4961; 2015TL4840; 2018WOP2018215371; 2020JOC952>. Consequently, the PPTS-catalysis / $\text{CH}(\text{OCH}_3)_3$ approach was employed with the substituted 1,1,3-triarylprop-2-yn-1-ols **3.3a-i** to synthesise a series of novel 6-Br, 6-OMe and 6-aryl substituted 2*H*-naphtho[1,2-*b*]pyrans **3.1** X = Br, OMe and Ar.

Thus, heating 4-bromo-1-naphthol **3.2a** and triarylprop-2-yn-1-ol **3.3a** in the presence of PPTS and $\text{CH}(\text{OCH}_3)_3$ in 1,2-DCE gave a deep red multicomponent gum. Elution from silica enabled the isolation of the desired bromonaphthopyran **3.1aa** as fluffy pale pink micro-needles in 42% yield (melting point 86 - 88 °C), (Scheme 3.6).



Scheme 3.6: The reaction of prop-2-yn-1-ol **3.3a** with 4-bromo-1-naphthol **3.2a** to obtain a 6-bromo naphthopyran **3.1aa**

The ^1H NMR spectrum (Figure 3.2a) of **3.1aa** showed distinct highly deshielded signals for α -naphthalene ring protons 7-H (**b**) and 10-H (**a**) which resonate as multiplets at ca. 8.1 ppm

and ca. 8.4 ppm, respectively. The signal for 3-H (**c**) appeared as a singlet at 6.43 ppm confirming presence of the pyran ring. Unfortunately, the signal for 5-H (**d**) was obscured by the other aromatic signals but is likely to be present in the multiplet centred at ca. 7.45 ppm. The structure of **3.1aa** was further confirmed by the presence of a signal for the sp^3 hybridised C atom (C-2) which resonated at 82.3 ppm in the ^{13}C NMR spectrum (Figure 3.2b) and which compared favourably with literature data. <2006FD85; 2014T9351; 2019DP(169)118>

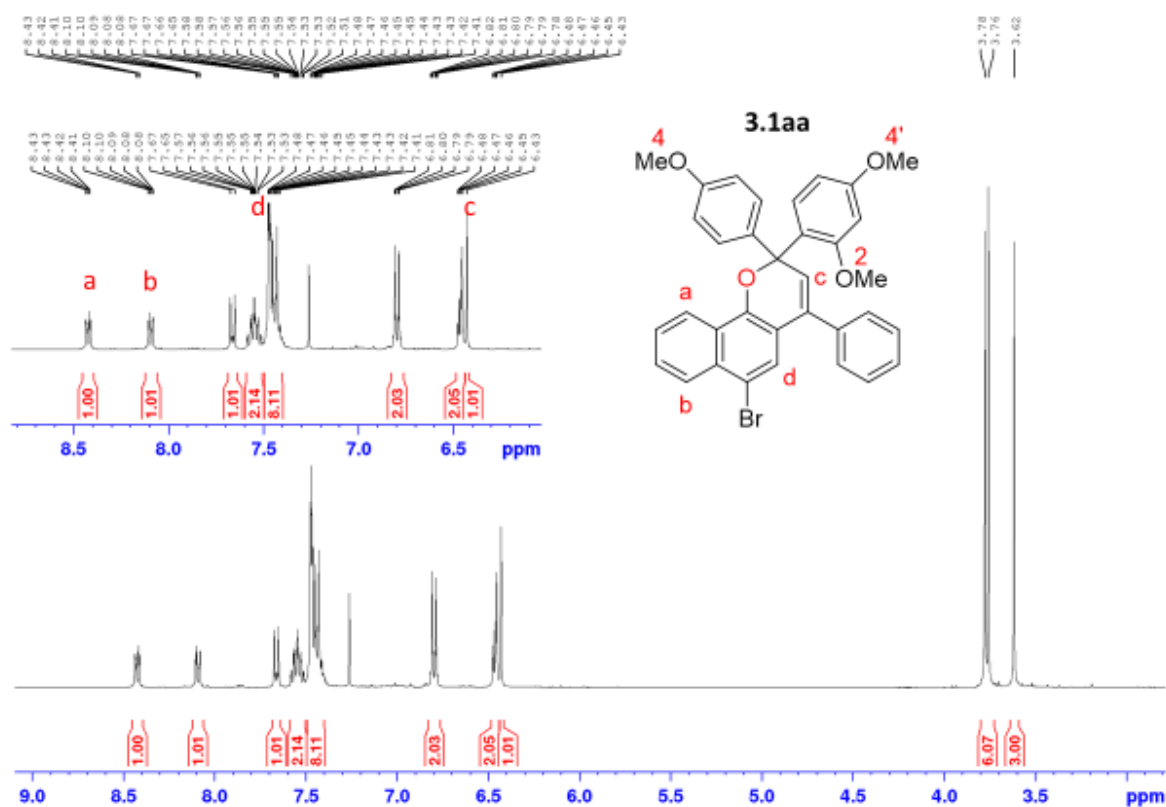


Figure 3.2a: 1H NMR spectrum of 6-bromo substituted 2H-naphtho[1,2-b]pyran **3.1aa**

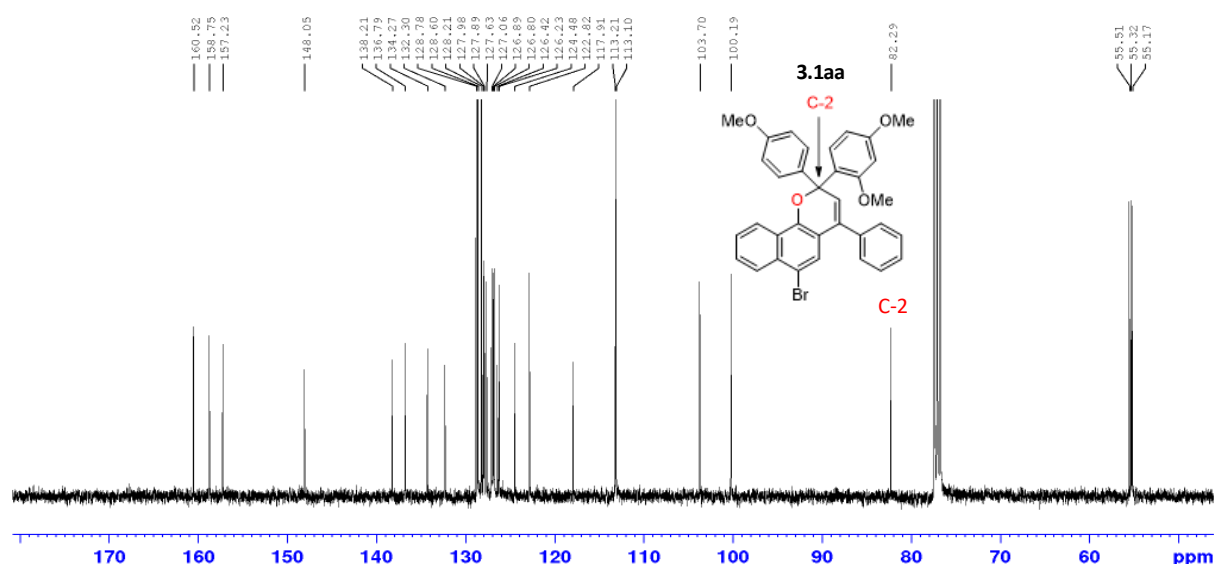


Figure 3.2b: ^{13}C NMR spectrum of 6-bromo substituted 2*H*-naphtho[1,2-*b*]pyran **3.1aa**

The mass spectrum of **3.1aa** indicated two molecular ions m/z 578.1086 $[\text{M}]^+$ and m/z 580.1100 $[\text{M}]^+$, in approximately 1:1 ratio as a consequence of the ^{79}Br and ^{81}Br isotopes, and thus accounts for $\text{C}_{34}\text{H}_{27}^{79}\text{BrO}_4$ and $\text{C}_{34}\text{H}_{27}^{81}\text{BrO}_4$, respectively. Furthermore, two corresponding peaks were present in an approximate 1:1 ratio for the $[\text{M}+\text{H}]^+$ molecular ions with m/z 579.1160 and m/z 581.1145 (Figure 3.3). Good agreement was observed between the measured mass m/z 578.1086 $[\text{M}]^+$ and the calculated theoretical mass m/z 578.1093 $[\text{M}]^+$ for the formula $\text{C}_{34}\text{H}_{27}^{79}\text{BrO}_4$.

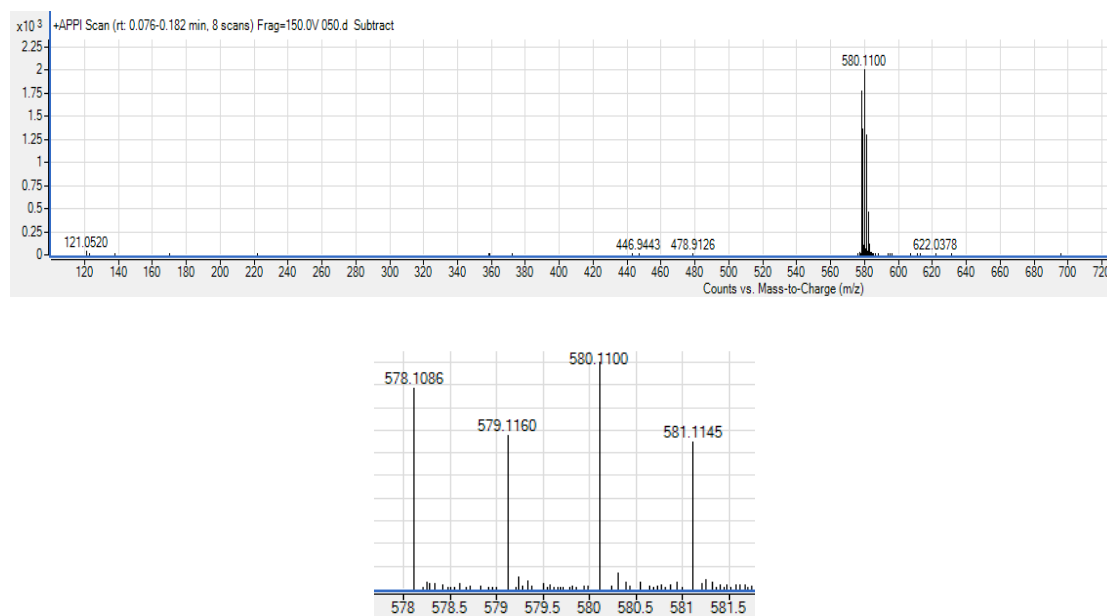
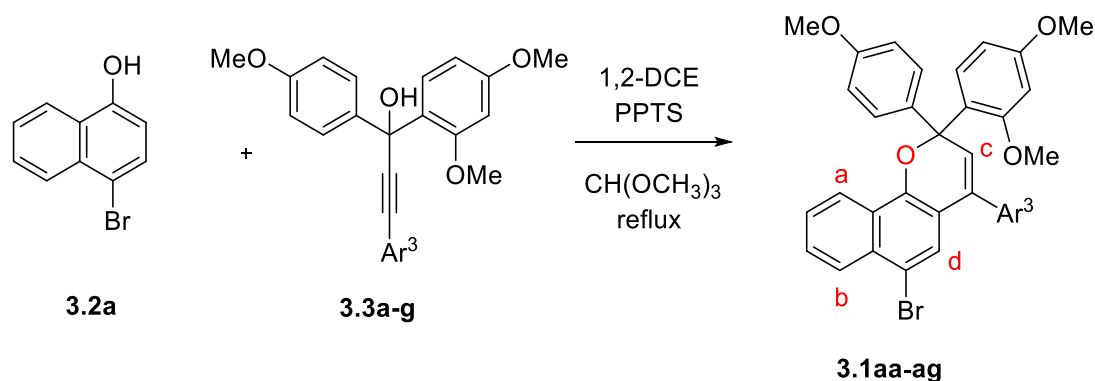


Figure 3.3: Mass spectrum and expansion of molecular ion region for bromopyran **3.1aa**

The following bromo-naphthopyrans **3.1ab-ag** were obtained by the foregoing PPTS / $\text{CH}(\text{OCH}_3)_3$ protocol; their isolated yields and key NMR characterization data are presented in Table 3.1.



N°	Ar ³	Yield (%)	δ 3-H (ppm)	δ 5-H (ppm)	δ 7-H (ppm)	δ 10-H (ppm)	δ C-2 (ppm)
3.1aa	Ph	42	6.43	7.45**	8.08-8.10	8.41-8.44	82.29
3.1ab	4-MeOC ₆ H ₄	48	6.36	7.48	8.07-8.10	8.40-8.43	82.27
3.1ac	4-CF ₃ C ₆ H ₄	48	6.47	7.37	8.09-8.11	8.41-8.43	82.32
3.1ad	4-NO ₂ C ₆ H ₄	26, 33*	6.52	7.32	8.09-8.11	8.41-8.43	82.34
3.1ae	4-Me ₂ NC ₆ H ₄	55	6.33	7.56	8.06-8.08	8.39-8.41	82.08
3.1af	4-CNC ₆ H ₄	36	6.47	7.32	8.08-8.10	8.39-8.42	82.32
3.1ag	4-pyridyl	0	-	-	-	-	-

* In addition to the isolation of naphthopyran **3.1ad** an unequal mixture of two isomeric α,β -unsaturated ketones [Scheme 3.9, structures **3.21a,b**] was also isolated and characterised.

** Signal obscured by those of other aromatic protons.

Table 3.1: Synthesis of 6-bromo naphthopyrans **3.1aa-ag** with key characteristic data

Overall poor to moderate yields were recorded for the series of 6-bromonaphthopyrans. Of note was the reaction between the 4-pyridyl substituted propynol **3.3g** and 4-bromo-1-naphthol which failed to afford any target naphthopyran **3.1ag** under the applied reaction conditions. Here it is thought that the basicity of the pyridine ring N-atom subverts the acid-catalyst which prevents protonation of the propynol hydroxy group which is essential for the chromenization (pyran ring forming) reaction to proceed.

From the ^1H NMR data for **3.1aa-f** it was noted that the naphthopyrans possessing an electron-withdrawing aryl ring at C-4 especially the stronger deactivating group ($-\text{NO}_2$) **3.1ad** shifted the signal for 3-H further downfield than that of their electron rich counterparts (**3.1aa**, **3.1ab** and **3.1ae**). Conversely, the signal for 5-H shifts further upfield when an electron-withdrawing aryl ring is present at C-4. The naphthalene ring protons 7-H (**b**) and 10-H (**a**) gave similar signals for all the compounds which are found at ca. 8.1 ppm and ca. 8.4 ppm, respectively. Interestingly the signal for the protons *ortho* to the NO_2 group in **3.1ad** bisected the naphthalene ring proton signals and afforded an apparent doublet at 8.35 ppm (Figure 3.4a). The ^{13}C NMR spectra confirmed the signal for C-2 for **3.1ab-f** which appeared in the predictable region at ca. 82.3 ppm (Figure 3.4b). Mass spectral analysis of each of the new bromopyrans **3.1ab-f** gave the expected molecular ion patterns which were in close agreement with that theoretically predicted for their formulae.

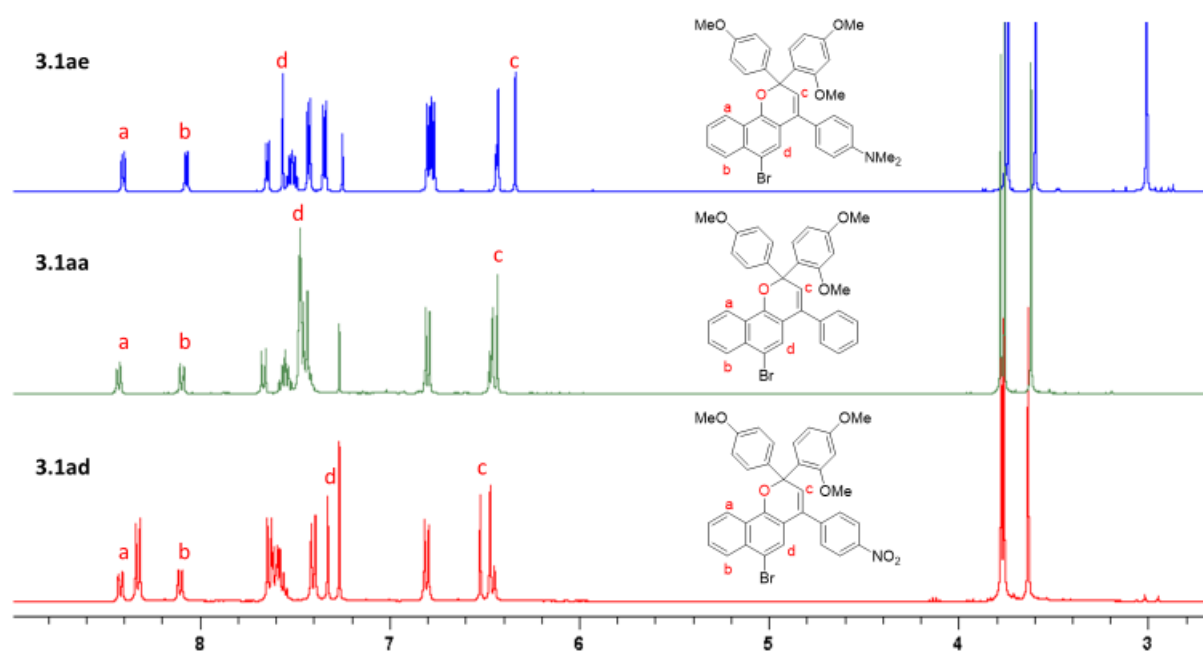


Figure 3.4a: ^1H NMR spectra of 6-bromo substituted 2H-naphtho[1,2-*b*]pyrans **3.1ae**, **3.1aa** and **3.1ad**

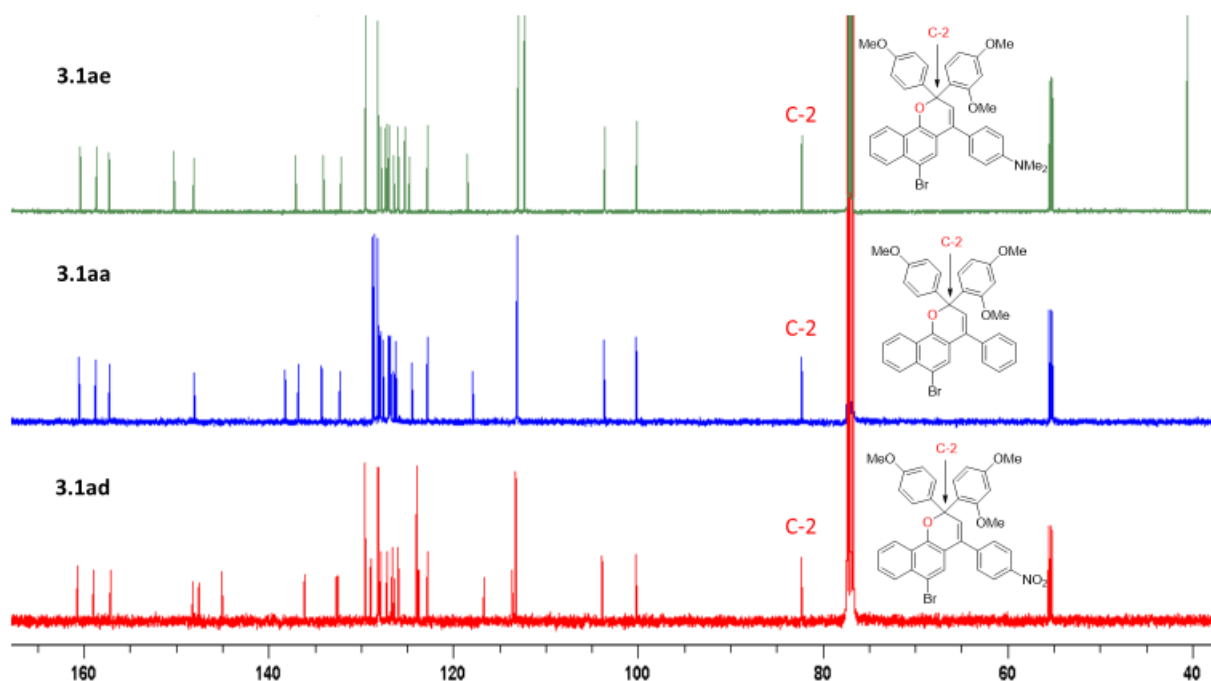
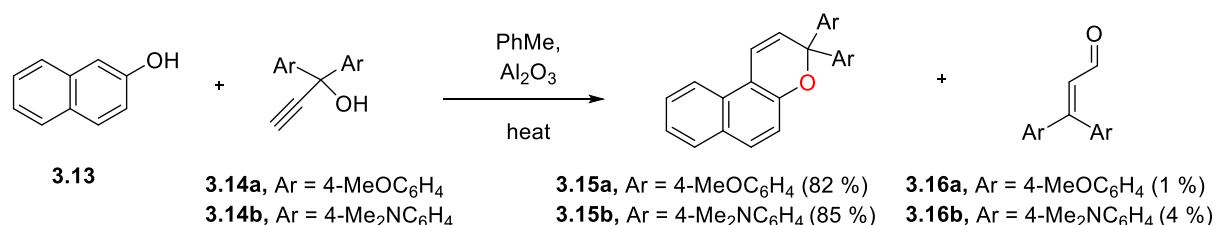


Figure 3.4b: ^{13}C NMR spectra of 6-bromo substituted 2H-naphtho[1,2-b]pyrans **3.1ae**, **3.1aa** and **3.1ad**

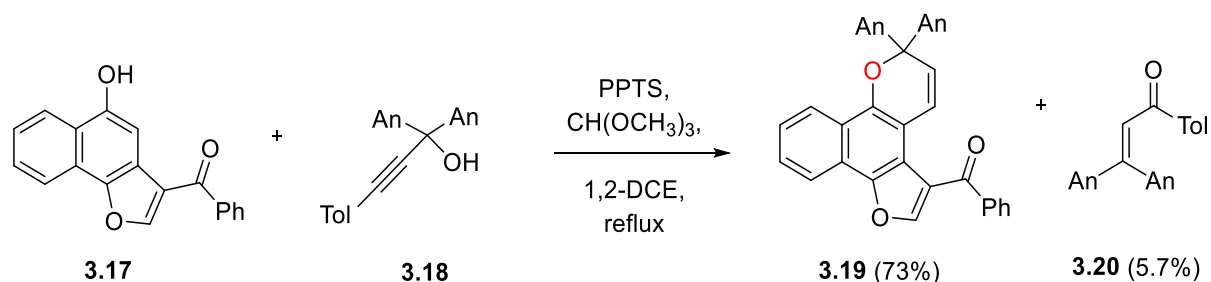
It has been previously noted that the formation of photochromic naphthopyrans by the acid-catalysed condensation of naphthols with propynols is often accompanied by varying amounts of α,β -unsaturated carbonyl by-products. <2003EJOC1220; 2014T9351> Small amounts of the rearranged electron rich alkynols were isolated from the synthesis of the simple photochromic 3H-naphtho[2,1-b]pyrans **3.15a,b** reported by Gabbutt and co-workers. The α,β -unsaturated aldehydes **3.16a,b** were formed during the reflux reaction with 2-naphthol **3.13** and propynols **3.14a,b** in the presence of acidic aluminium oxide in toluene (Scheme 3.7). <2003EJOC1220>



Scheme 3.7: Formation of naphthopyrans **3.15a,b** and α,β -unsaturated aldehydes **3.16a,b**

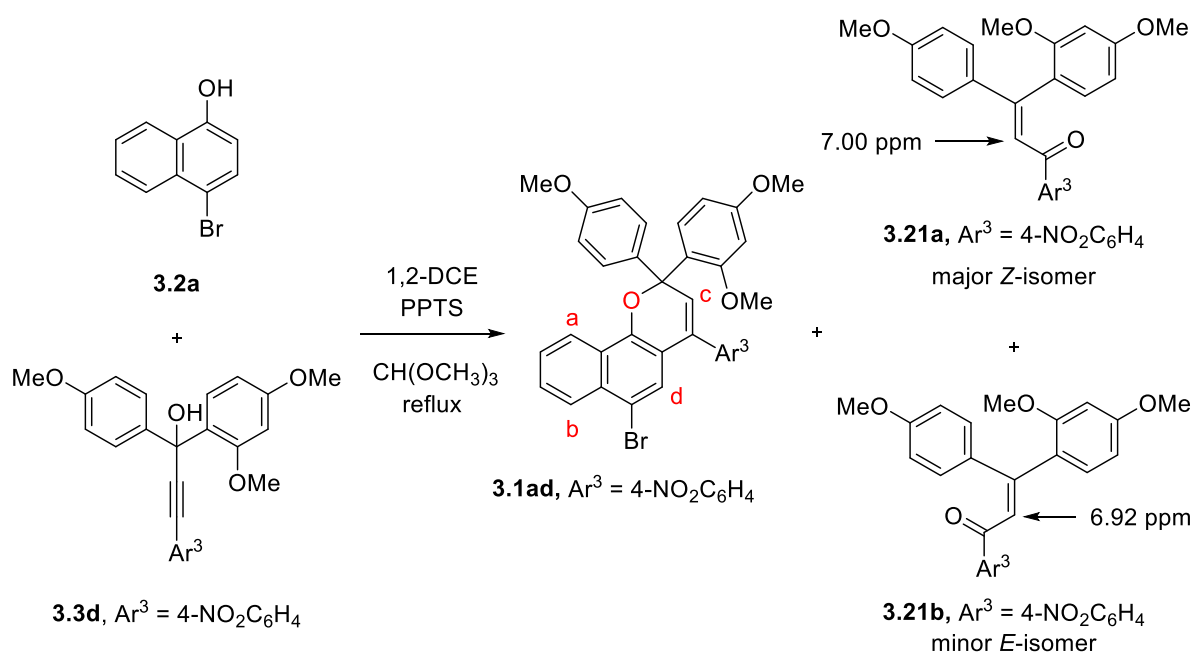
Aiken and co-workers have reported the formation of the furan fused naphthopyran **3.19** and α,β -unsaturated ketone **3.20** when refluxing the triarylpropynol **3.18** with the fused naphthol

3.17 using pyridinium 4-toluenesulfonate and trimethyl orthoformate in 1,2-dichloroethane (Scheme 3.8). <2014T9351>



Scheme 3.8: Formation of naphthopyran **3.19** and α,β -unsaturated ketone **3.20**

In this thesis, during the repeat preparation of naphthopyran **3.1ad** which resulted in a marginally improved yield of 33% (Table 3.1), a mixture of the unsaturated ketone by-products **3.21a,b** was isolated in 14% yield (Scheme 3.9).



Scheme 3.9: Formation of naphthopyran **3.1ad** and α,β -unsaturated ketones **3.21a** and **3.21b**

The ¹H NMR spectrum of the mixture confirmed the presence of two isomeric ketones **3.21a** and **3.21b** (in a ratio of 10:1). The ¹³C NMR spectrum showed the absence of a signal at 74.0 ppm (tertiary carbon atom of propynol **3.3d**) and additional downfield signals at ca. 191 ppm confirmed the presence of the α,β -unsaturated ketones. Infrared spectroscopy also confirmed the presence of the α,β -unsaturated ketones.

confirmed the presence of the α,β -unsaturated carbonyl unit which showed a C=O stretching band at ca. 1658 cm^{-1} , typical for such a C=O moiety. <2018IJB662> Notable in the ^1H NMR spectrum of **3.21a** and **3.21b** was the absence of an OH signal which normally resonates at 4.88 ppm in the propynols however, the ^1H NMR spectrum exhibited a singlet at 7.0 ppm (**x**) for **3.21a** (Z-isomer, major) and a singlet at 6.92 ppm (**x'**) for **3.21b** (E-isomer, minor) assigned to the α -hydrogen atom of each ketone (Figure 3.5). The assignment of resonance of the lower field signal (7.0 ppm) to the alkene proton of the major Z-isomer (**3.21a**) was in accord with data from a battery NMR experiments conducted on a mixture of related ketones **3.25a,b** for which there was more sample available for detailed spectroscopic analysis. The signals for the methoxy substituents of the major isomer **3.21a** resonated at 3.53 ppm, 3.76 ppm and 3.84 ppm. However, the methoxy substituents for minor isomer **3.21b** were coincidental with some of the methoxy unit signals from the major isomer but could be discerned at 3.71 ppm, 3.76 ppm and 3.84 ppm.

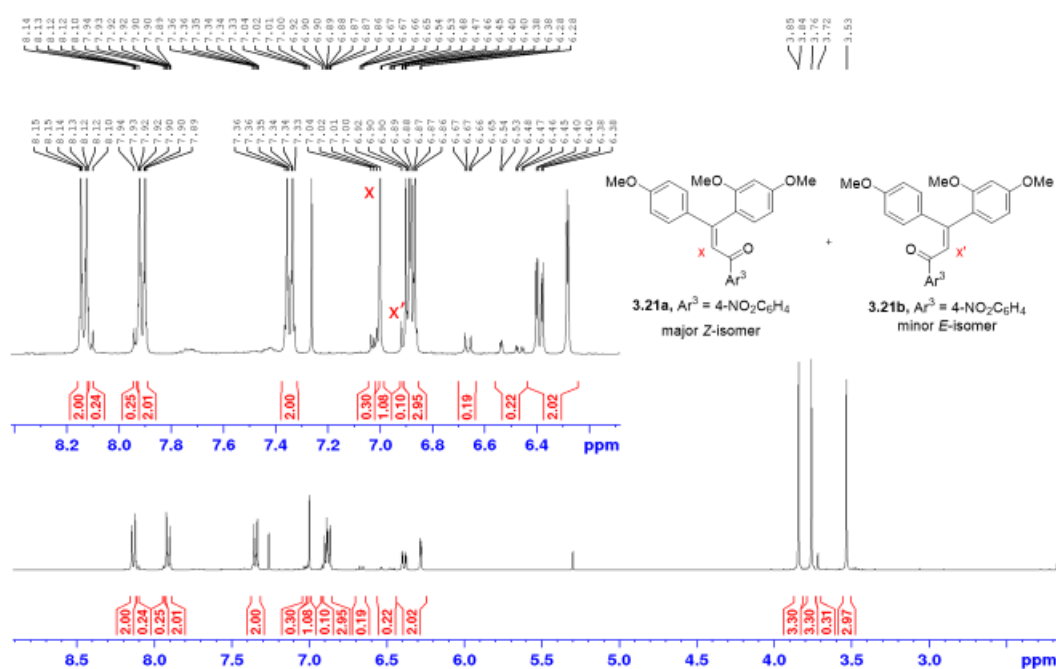
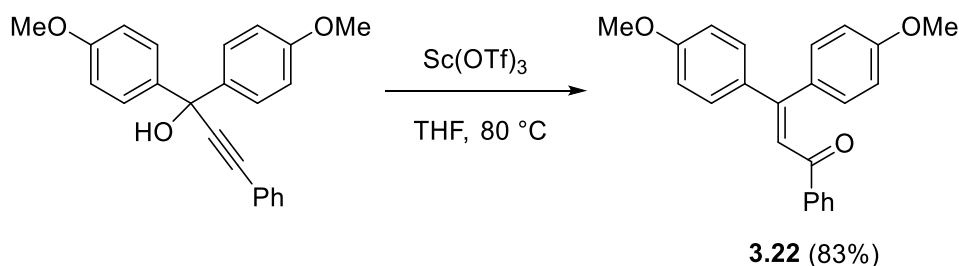


Figure 3.5: ^1H spectrum of α,β -unsaturated ketones **3.21a,b**

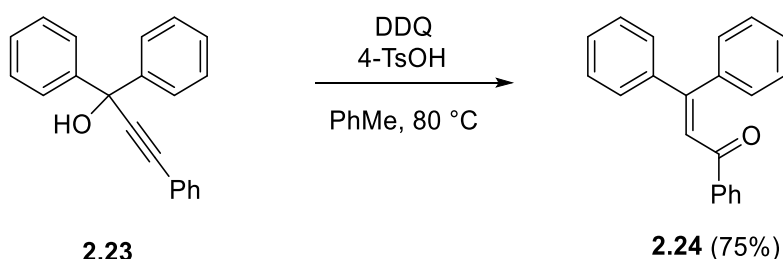
The formation of such α,β -unsaturated ketones by the rearrangement of propynols during the preparation of photochromic naphthopyrans has been capitalised upon as an efficient route to these difficultly accessible ketones. The Meyer-Schuster rearrangement of propynols

has been carefully studied by Liu *et al.*, who employed a lanthanum catalyst and microwave heating to prepare ketone **3.22** in excellent yield (Scheme 3.10). <2015CNP104909970>



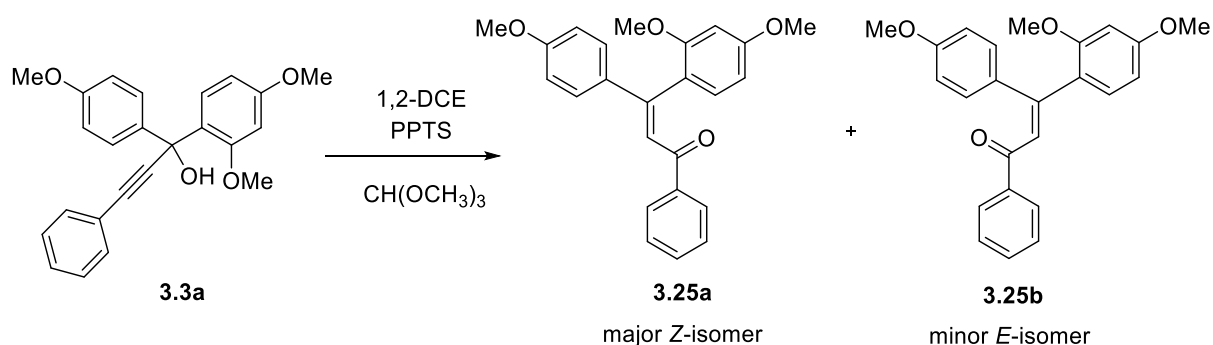
Scheme 3.10: Alkynol rearrangement based on lanthanum catalyst to generate an α,β-unsaturated carbonyl compound **3.22**

A similar rearrangement was observed for the alkynol **2.23** upon heating with 4-toluenesulfonic acid and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in toluene to afford ketone **2.24** in 75% yield (Scheme 3.11). <2019JOC4246>



Scheme 3.11: Rearrangement of alkynol **2.23** into α,β-unsaturated ketone **2.24**

In the present work, for the purposes of obtaining reference material, the alkynol **3.3a** was deliberately rearranged to form the isomeric unsaturated ketones. Thus, heating of triarylpropynol **3.3a** with PPTS and trimethyl orthoformate in 1,2-dichloroethane afforded an inseparable mixture of *Z*- **3.25a** (major) and *E*- **3.25b** (minor) 1,3,3-triarylprop-2-en-1-ones (10:1) as a dark orange viscous gum isolated in a combined yield of 67% (Scheme 3.12).



Scheme 3.12: Formation of α,β -unsaturated ketones **3.25a** and **3.25b**

The formation of the isomeric ketones **3.25a,b** was established by NMR spectroscopy (Figure 3.6a-c). The ^{13}C NMR spectrum exhibited two significantly deshielded signals at 192.26 ppm and 193.85 ppm (Figure 3.6b) confirming the presence of the α,β -unsaturated carbonyl unit which was additionally proven by infrared spectroscopy which showed a C=O stretching band at ca. 1657 cm^{-1} . Moreover, in the ^1H NMR spectrum singlets were present at 7.14 ppm for **3.25a** and 7.06 ppm for **3.25b** that relate to the α -hydrogen atom in each of the isomeric conjugated ketones. The methoxy substituents of the major isomer **3.25a** resonated at 3.52 ppm, 3.79 ppm and 3.84 ppm and for the minor isomer **3.25b** at 3.71 ppm, 3.75 ppm and 3.84 ppm (Figure 3.6a).

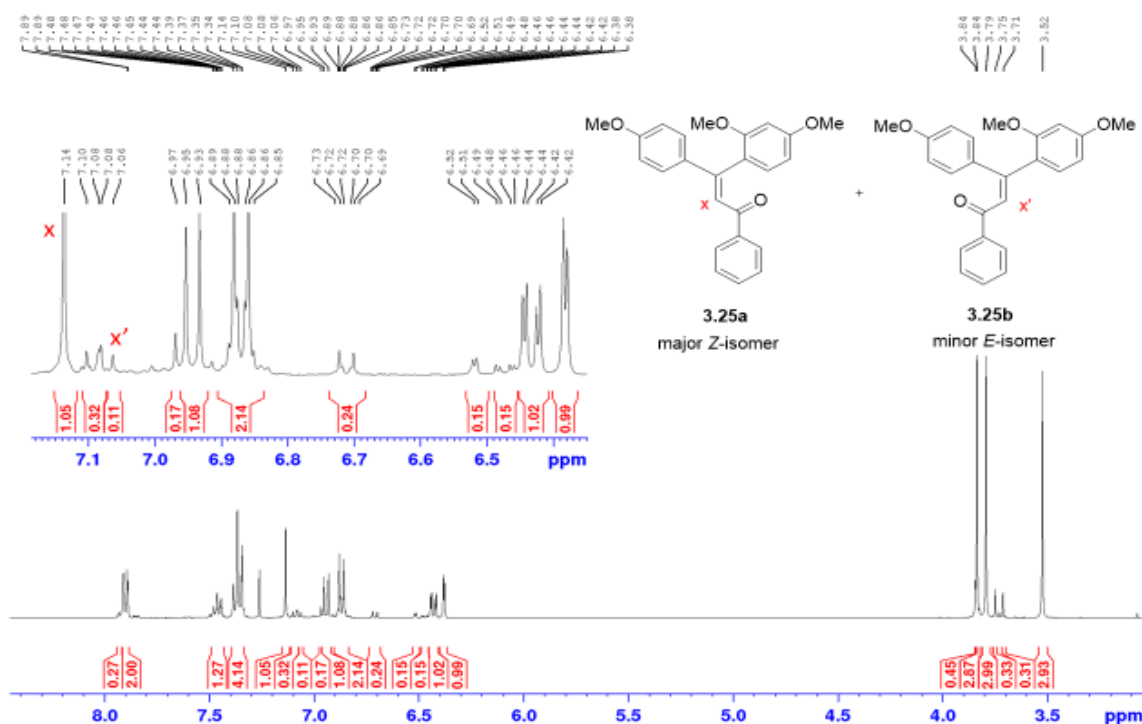


Figure 3.6a: ^1H NMR spectrum of α,β -unsaturated ketones **3.25a,b**

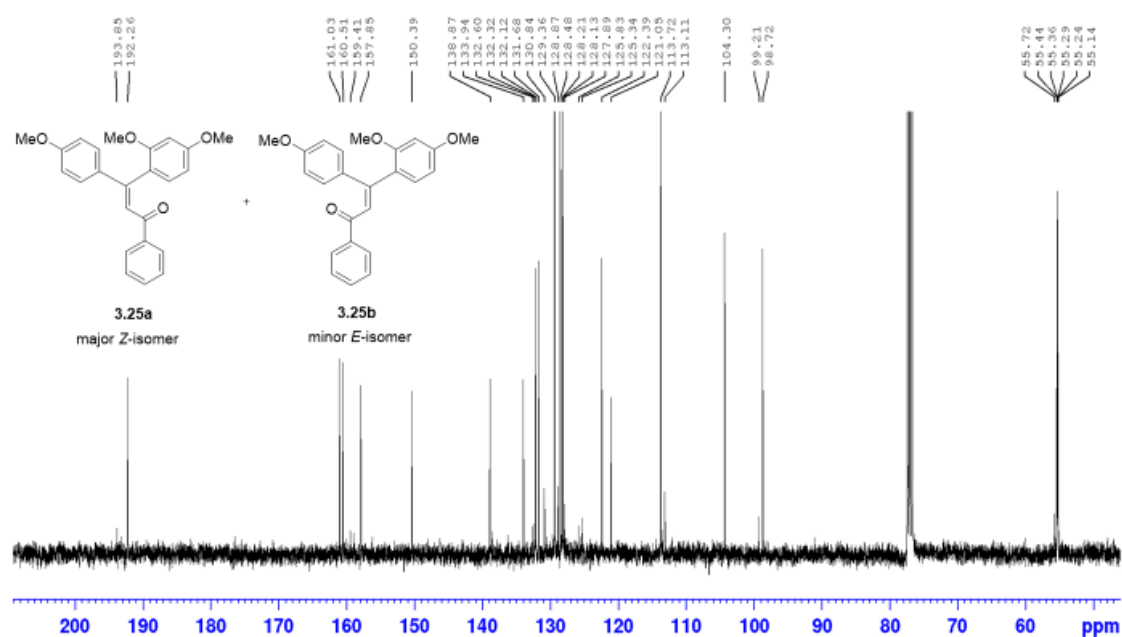


Figure 3.6b: ^{13}C NMR spectrum of α,β -unsaturated ketones **3.25a,b**

Identification of the major isomer **3.25a** was verified by a ^1H - ^1H NOESY experiment which showed a key interaction (red box on Figure 3.6c) between the aromatic protons (H_d) of the 4-methoxyphenyl ring at ca. 7.36 ppm and the alkene proton (H_x) at 7.14 ppm. An additional interaction was noted between H_x and the protons of the phenyl ring (H_e) at 7.90 ppm.

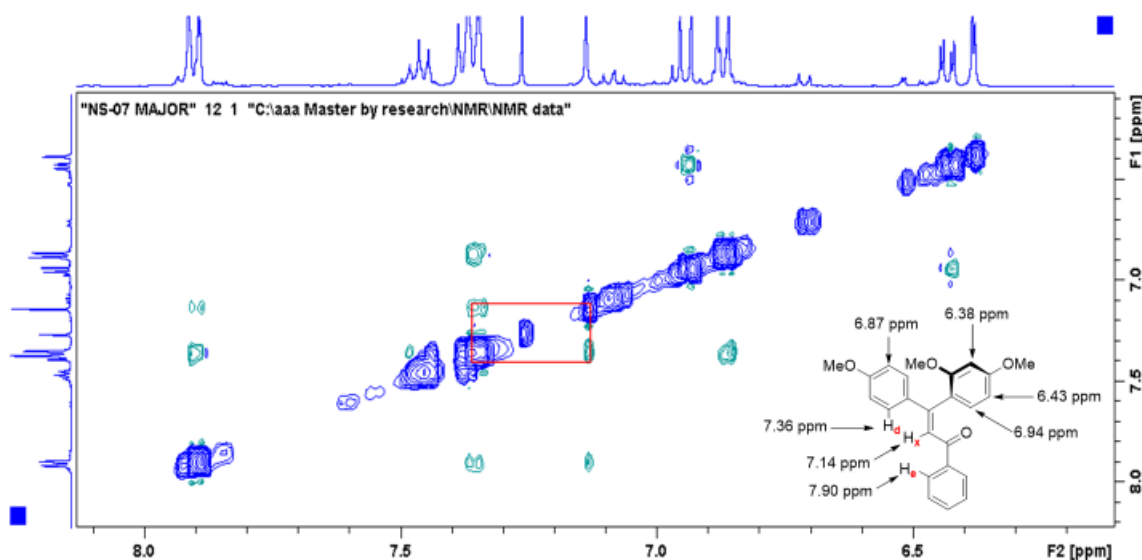
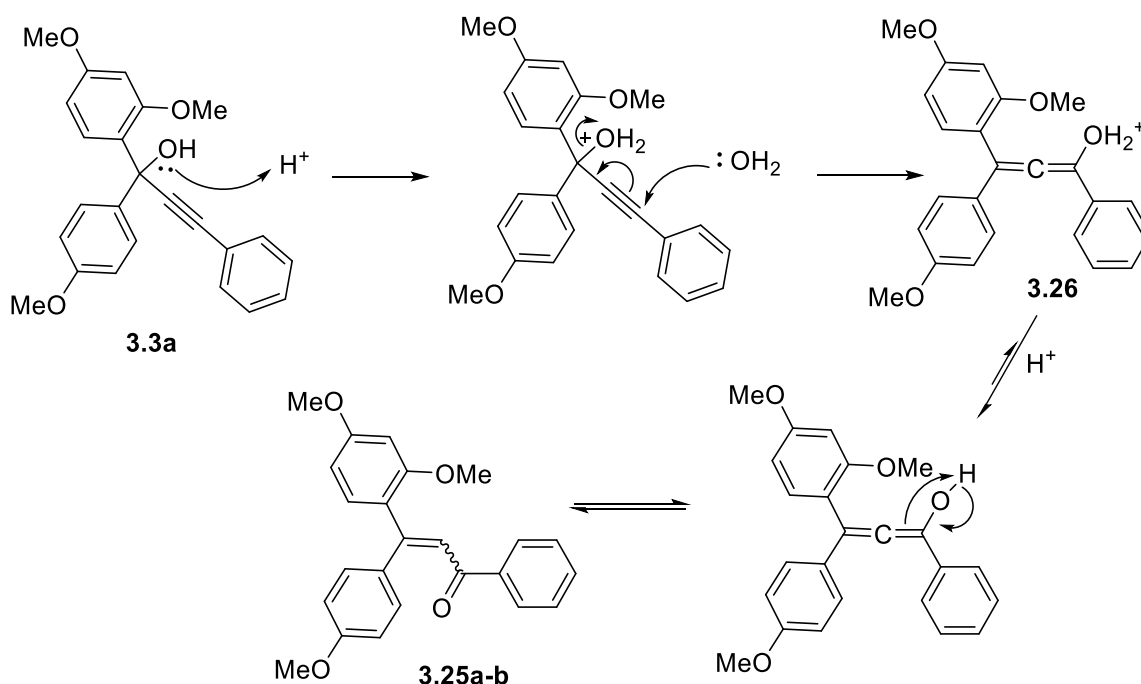


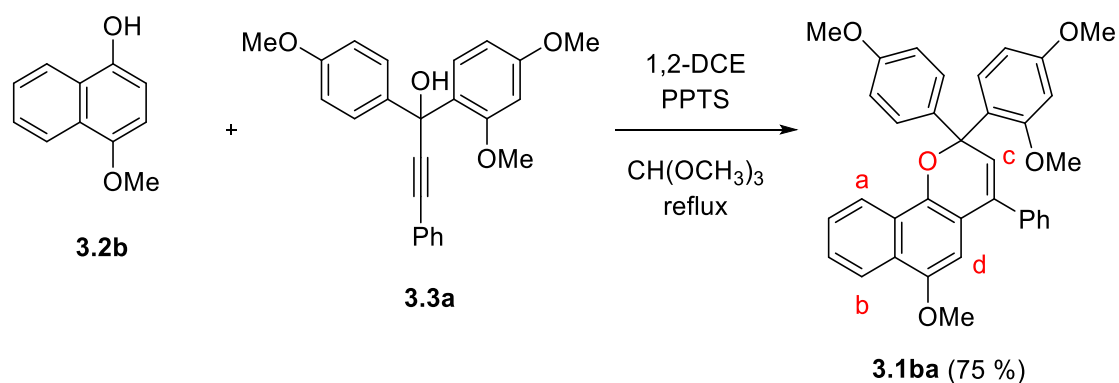
Figure 3.6c: NOESY spectrum of α,β -unsaturated ketones **3.25a,b**

The mechanism for the formation of α,β -unsaturated ketones **3.25a,b** is illustrated in Scheme 3.13. Firstly, the propargylic alcohol **3.3a** is protonated and eliminates water to form a resonance stabilised carbocation. In the subsequent step, water attacks C-3 of alkyne to form an allene intermediate **3.26**. In the last step, loss of a proton, thus regenerating the acidic catalyst, affords an enol, which through tautomerization provides the carbonyl products **3.25a,b**. <1977JOC3403>



Scheme 3.13: The mechanism for the formation of α,β -unsaturated ketones **3.25a,b**

With the series of 6-bromonaphthopyrans prepared the reaction of the propynol **3.3a** was investigated with 4-methoxy-1-naphthol (Scheme 3.14). Thus, employing the same acidic reaction conditions as those used for the formation of **3.1aa-af**, 4-methoxy-1-naphthol **3.2b** was reacted with propynol **3.3a** to afford **3.1ba**, after flash chromatography, as two different coloured fractions. The initial fraction appeared as an off-white microcrystalline powder, isolated in 56% yield whereas the second fraction was isolated as a pale blue crystalline powder in 19% yield, however both samples were identical by 1H NMR spectroscopy. It is noteworthy that a significantly higher yield was noted for **3.1ba** (75%) than for **3.1aa** (42%) which was derived from the same propynol but with 4-bromo-1-naphthol.



Scheme 3.14: The reaction of prop-2-yn-1-ol **3.3a** with 4-methoxy-1-naphthol **3.2b**

The ^1H NMR spectrum of **3.1ba** displayed two singlets corresponding to 3-H (**c**) and 5-H (**d**) at 6.4 ppm and 6.5 ppm respectively, which are significantly closer to each other than in the case of the corresponding protons from bromopyrans **3.1aa-af**. The presence of the 6-methoxy substituent shifts 5-H upfield resonating closer to 3-H which is essentially unaffected by the 6-MeO group (Figure 3.7a). The ^{13}C NMR spectrum (Figure 3.7b) of **3.1ba** revealed the expected signal at 81.4 ppm which confirmed the presence of C-2 and the mass spectrum exhibited a molecular ion m/z 531.2160 $[\text{M}+\text{H}]^+$ for $\text{C}_{35}\text{H}_{30}\text{O}_5$ which was in good agreement with the calculated mass of 531.2171.

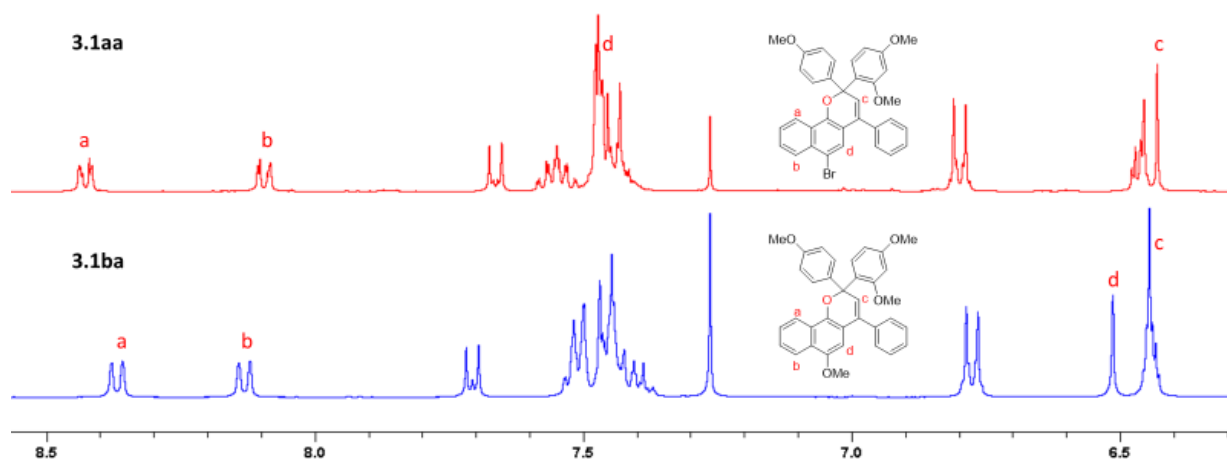


Figure 3.7a: ^1H NMR spectra of 6-bromo **3.1aa** and 6-methoxy substituted 2H-naphtho[1,2-b]pyran **3.1ba**

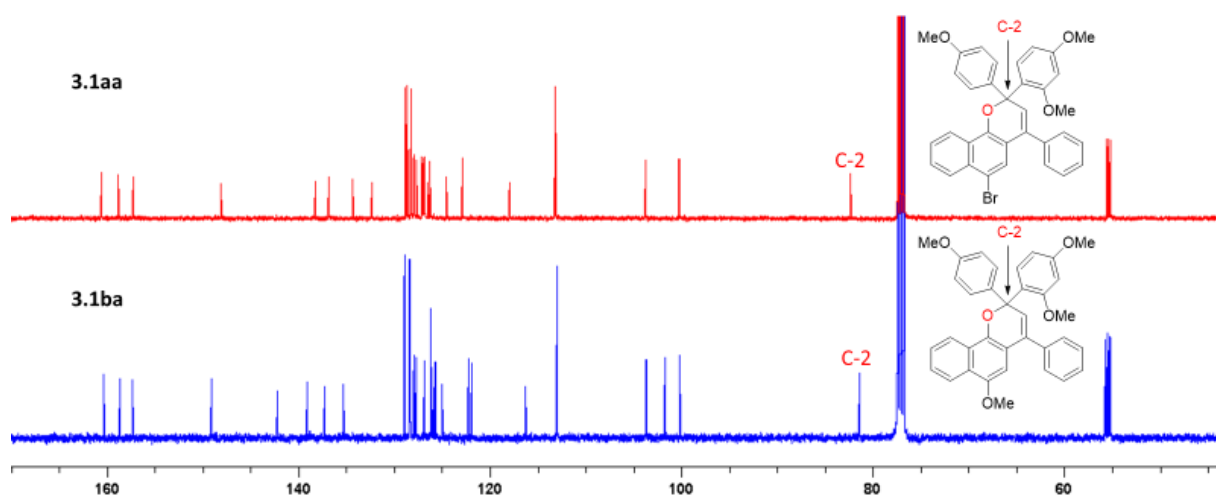
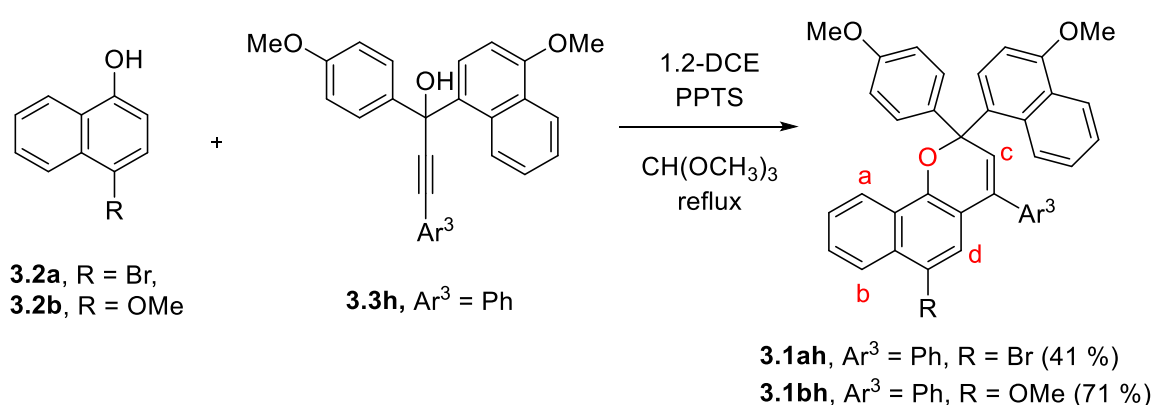


Figure 3.7b: ^{13}C NMR spectra of 6-bromo **3.1aa** and 6-methoxy substituted 2H-naphtho[1,2-*b*]pyran **3.1ba**

By employing the same methodology as for the previously synthesised compounds **3.1aa-af** and **3.1ba**, the reaction between the 4-methoxynaphthalene substituted propynol **3.3h** and 4-bromo-1-naphthol **3.2a** gave the 6-bromo substituted naphthopyran **3.1ah** as an off-white microcrystalline powder in 41% yield, however the related reaction between propynol **3.3h** and 4-methoxy-1-naphthol **3.2b** furnished the 6-methoxy substituted naphthopyran **3.1bh** as a beige powder with a significantly higher yield of 71% suggesting that the presence of the methoxy group in the starting naphthol is important for the enhanced success of the chromenization reaction (Scheme 3.15).



Scheme 3.15: The reaction of prop-2-yn-1-ol **3.3h** with 4-bromo-1-naphthol **3.2a** and 4-methoxy-1-naphthol **3.2b**

Both structures **3.1ah** and **3.1bh** were confirmed by ^1H NMR spectroscopy and their spectra are displayed in Figure 3.8a. Each compound exhibited the expected signal for 3-H at ca. 6.1 ppm however the signal for 5-H was only discernible for **3.1bh** as the singlet appeared upfield at 6.6 ppm whereas the signal for 5-H of compound **3.1ah** was obscured by the other aromatic signals at ca. 7.25 ppm. The furthest downfield signals in each example are attributed to the four α -naphthalene protons and resonate as multiplets in the range ca. 8.0 – 8.4 ppm. The structure of each compound was further supported by ^{13}C NMR spectroscopy (Figure 3.8b); the signal for C-2 appeared at 84.2 ppm for **3.1ah** and 83.3 ppm for **3.1bh**. Distinctively, these peaks resonated slightly downfield relative to the comparable signals from other naphthopyran examples **3.1aa-3.1af**. Once again mass spectral analysis of each of the **3.1ah** and **3.1bh** gave the expected molecular ions which were in close agreement with that theoretically predicted for their formulae.

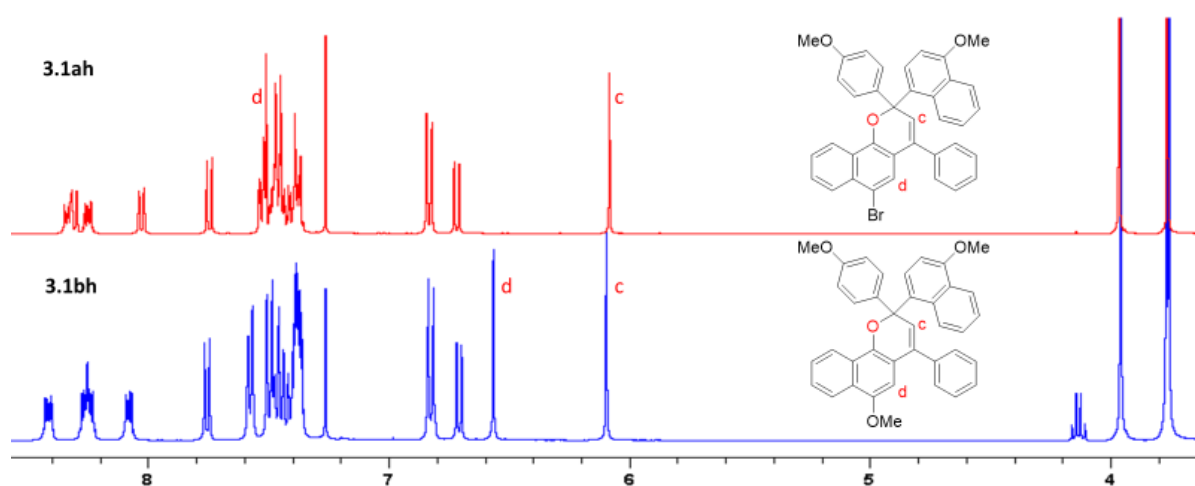


Figure 3.8a: ^1H NMR spectra of 6-bromo substituted 2*H*-naphtho[1,2-*b*]pyran **3.1ah** and 6-methoxy substituted 2*H*-naphtho[1,2-*b*]pyran **3.1bh**

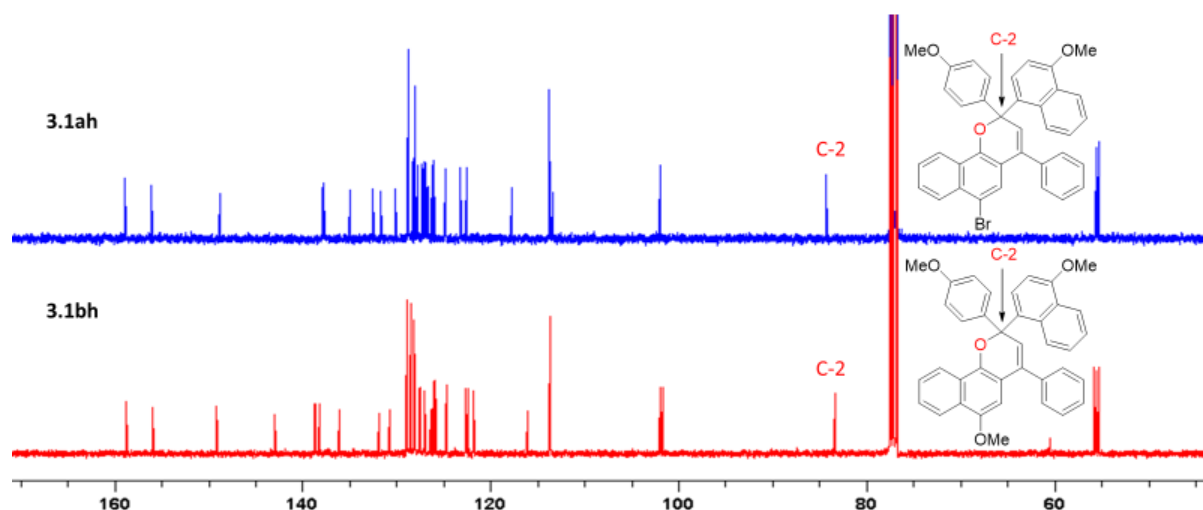
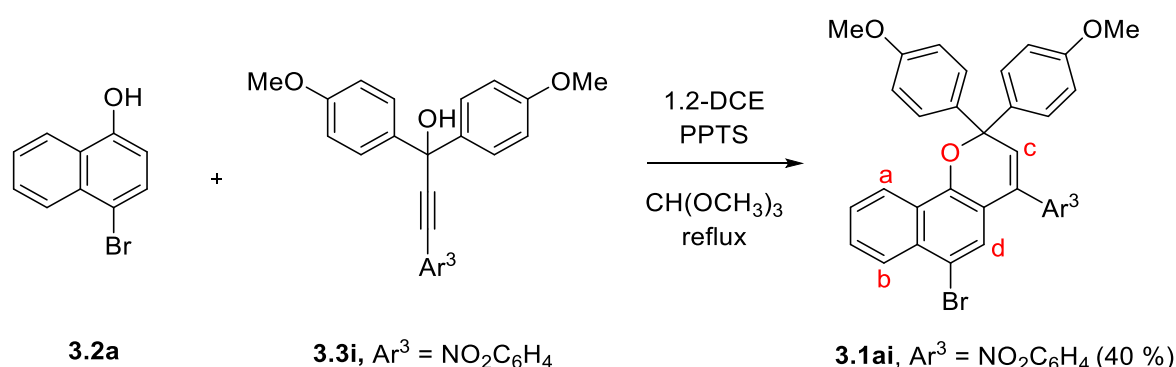


Figure 3.8b: ^{13}C NMR spectra of 6-bromo substituted 2*H*-naphtho[1,2-*b*]pyran **3.1ah** and 6-methoxy substituted 2*H*-naphtho[1,2-*b*]pyran **3.1bh**

Based on the same methods as for the previously synthesised naphthopyrans **3.1aa-af** and **3.1ah-bh**, the reaction between the symmetrically substituted 1,1-bis(4-methoxyphenyl) propynol **3.3i** and 4-bromo-1-naphthol **3.2a** gave 6-bromo-2,2-bis(4-methoxyphenyl)-4-aryl-2*H*-naphtho[1,2-*b*]pyran **3.1ai** as a pale yellow powder in 40% yield (melting point 245 – 246 °C), (Scheme 3.16). The rationale for the preparation of naphthopyran **3.1ai** possessing a 4-nitrophenyl ring at 4-C was to enable the comparison of the 4-methoxyphenyl and 2,4-dimethoxyphenyl substituted C-2 rings on the photochromism of the derived 2,2,4,6-tetraaryl naphthopyrans (Chapter 4.1).



Scheme 3.16: The reaction of prop-2-yn-1-ol **3.3i** with 4-bromo-1-naphthol **3.2a**

^{13}C NMR spectroscopy confirmed the formation of 6-bromo substituted naphthopyran **3.1ai** by the appearance of the signal at 83.0 ppm assigned to the C-2 carbon atom (Figure 3.9b).

^1H NMR spectroscopy (Figure 3.9a) revealed the signals for 3-H (**c**) at 6.21 ppm which is significantly more shielded compared to the same signal from compound **3.1ad**; this shielding may be a consequence of the absence of the *ortho*-methoxy group which now enables an alternative conformation of the pyran ring in which 3-H experiences shielding from one of the 4-methoxyphenyl rings located at C-2. Predictably, the signals for 5-H (**d**), 7-H (**b**) and 10-H (**a**) resonate at approximately the same environment at ca. 7.32 ppm, ca. 8.1 ppm and ca. 8.4 ppm in **3.1ai** and **3.1ad**, respectively. Mass spectral analysis of **3.1ai** gave the expected molecular ion patterns which were in close agreement with that theoretically predicted for their formulae.

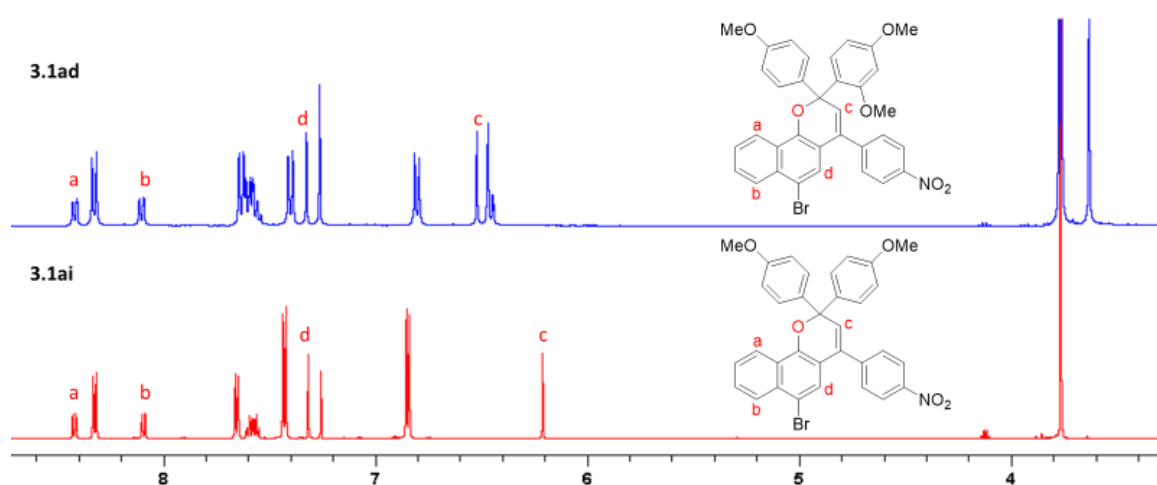


Figure 3.9a: ^1H NMR spectra of 6-bromo substituted 2*H*-naphtho[1,2-*b*]pyrans **3.1ad** and **3.1ai**

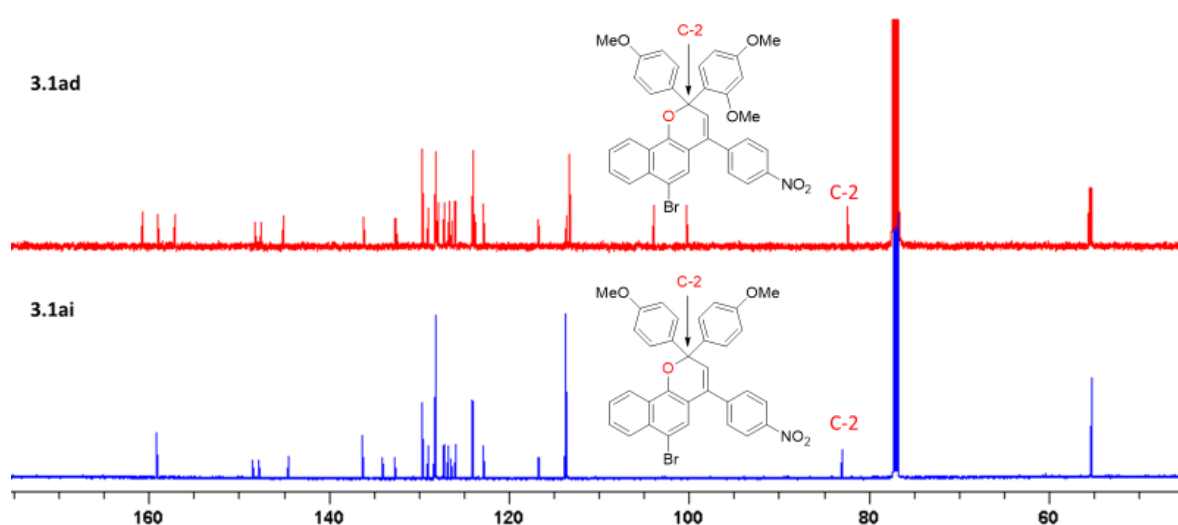
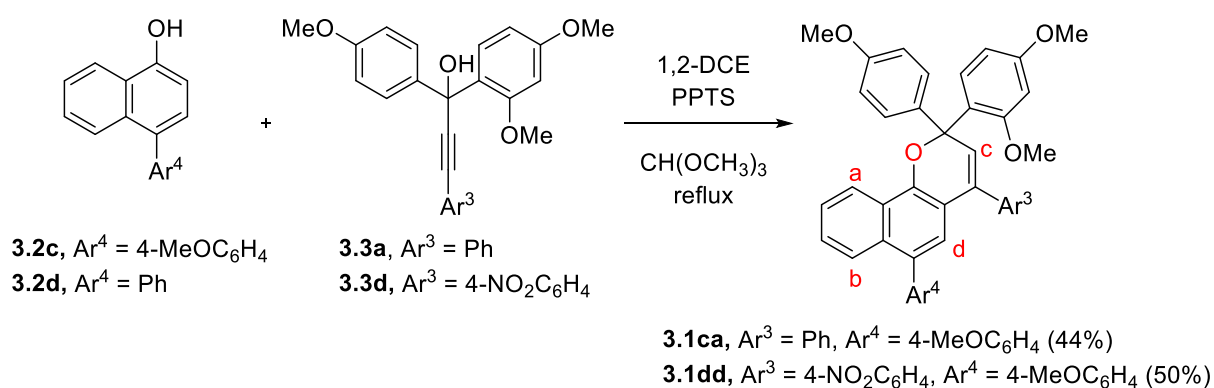


Figure 3.9b: ^{13}C NMR spectra of 6-bromo substituted 2*H*-naphtho[1,2-*b*]pyrans **3.1ad** and **3.1ai**

3.2 Direct synthesis of 2,2,4,6-tetraryl substituted 2*H*-naphtho[1,2-*b*]pyrans

Whilst the 4-bromo-1-naphthol and 4-methoxy-1-naphthol were commercially available it was decided to prepare 4-(4-methoxyphenyl)-1-naphthol **3.2c** and 4-phenyl-1-naphthol **3.2d** (Chapter 2.3) which could then be employed to prepare a 2,2,4,6-tetra-aryl substituted naphthopyrans directly rather than introducing the aryl substituent by post-modification of a 6-bromo substituted naphthopyran via the proposed Suzuki-Miyaura protocol. Thus, using the foregoing acid-catalysed chromenization methodology as applied for the previously synthesised naphthopyrans **3.1aa-bh**, the naphthopyran **3.1ca** was isolated after flash column chromatography as an off-white crystalline powder in 44% yield and naphthopyran **3.1dd** which was isolated as bright yellow powder in 50% yield (Scheme 3.17).



Scheme 3.17: The reaction of prop-2-yn-1-ols **3.3a/3.3d** with 4-aryl-1-naphthols **3.2c/3.2d**

The ^1H NMR spectra of **3.1ca** and **3.1dd** showed well resolved signals for 3-H (**c**) at 6.4 ppm and 6.5 ppm; and 5-H (**d**) at 7.1 ppm and 7.0 ppm, respectively. For both compounds **3.1ca** and **3.1dd**, the most deshielded aromatic signal corresponded to 10-H (**a**) which resonated as a doublet ($J = 8.3$ Hz) at ca. 8.5 ppm do to its proximity to the *peri*-O atom and the signal for 7-H (**b**) appeared upfield as a doublet at ca. 7.8 ppm ($J = 8.3$ Hz) as a consequence of shielding by the ring current of the proximal 6-aryl ring (Figure 3.10a). The ^{13}C NMR spectra displayed the expected signals for C-2 at ca. 82 ppm (Figure 3.10b). For each synthesised naphthopyrans **3.1ca** and **3.1dd**, the mass spectral analysis gave the expected molecular ions that were in good agreement with their calculated mass.

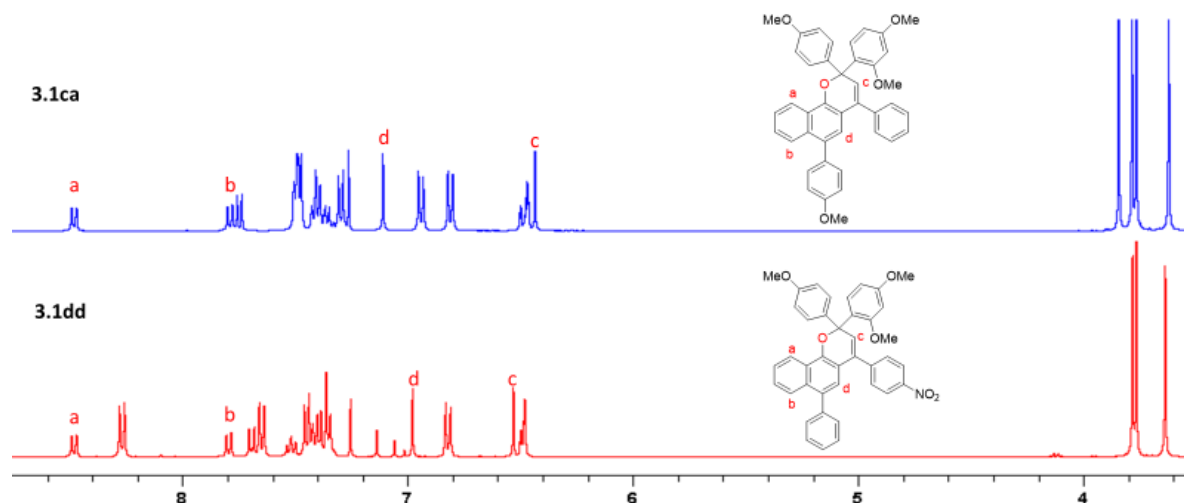


Figure 3.10a: ^1H NMR spectra of 6-aryl substituted 2H-naphtho[1,2-b]pyrans **3.1ca** and **3.1dd**

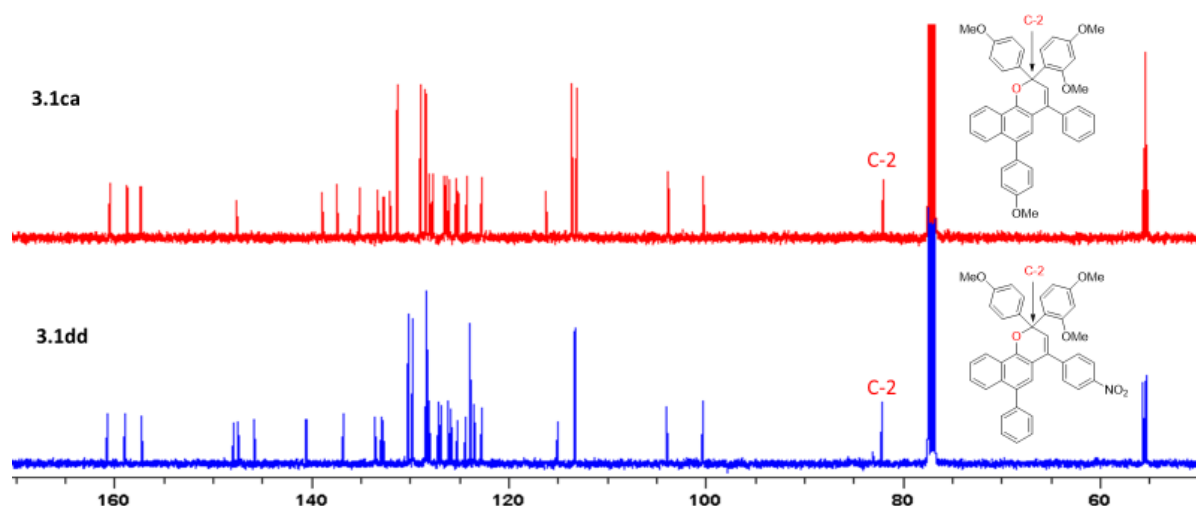
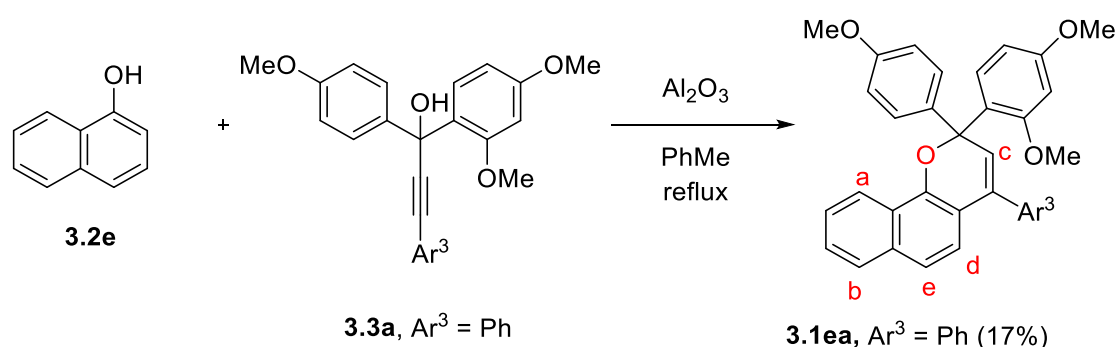


Figure 3.10b: ^{13}C NMR spectra of 6-aryl substituted 2H-naphtho[1,2-b]pyrans **3.1ca** and **3.1dd**

3.3 Synthesis of 2,2,4-triaryl substituted 2H-naphtho[1,2-b]pyran

To contrast with the synthesised 6-Br, 6-OMe and 6-aryl substituted naphthopyrans, formation of **3.1da** derived from 1-naphthol itself was next examined. Thus, by employing the standard reaction conditions 1-naphthol **2.3e** was condensed with propargyl alcohol **3.3a** to afford an intense red multicomponent mixture which clearly contained a photochromic compound that was indicated by TLC examination of the mixture. Unfortunately, even through the use of extensive column chromatography, the expected pure naphthopyran

3.1ea could not be isolated. As a consequence of the fact that the foregoing mixture could not be resolved by chromatography, alternative heterogeneous reaction conditions were chosen and the condensation was repeated. The other most frequently used method for the synthesis of photochromic naphthopyrans involves the condensation reaction of a propynol with a naphthol in a presence of an acidic alumina catalyst in toluene <1990USP4931221; 1994MCLC67; 1997JOC7024; 2000DP(47)73; 2002T925; 2003EJOC1220; 2010OBC4874; 2013VS65>. Thus, heating 1-naphthol **2.3e** with propynol **3.3a** in the presence of suspended acidic alumina in toluene produced a deep red gum which was subjected to column chromatography which finally gave the expected pure naphthopyran **3.1ea** as a microcrystalline powder in a disappointingly low yield (17%), (Scheme 3.18).



Scheme 3.18: The reaction of prop-2-yn-1-ol **3.3a** with 1-naphthol **3.2e**

The ^1H NMR spectrum of the synthesised compound **3.1ea** is displayed in Figure 3.11a. The signal for the pyran ring proton 3-H (**c**) appeared at 6.43 ppm as a singlet however the signal for 5-H was obscured by the signals for the aromatic protons. Interestingly, there was an apparent doublet at ca. 7.7 ppm accounting for 2H which corresponds to proton **b** and **e** which are coincidental. The ^{13}C NMR spectrum (Figure 3.11b) confirmed the signal for C-2 that showed at the expected region at 81.9 ppm. Mass spectral analysis of **3.1ea** exhibited a molecular ion m/z 501.2067 $[\text{M}+\text{H}]^+$ for $\text{C}_{34}\text{H}_{28}\text{O}_4$ which was in good agreement with the calculated mass of 501.2066.

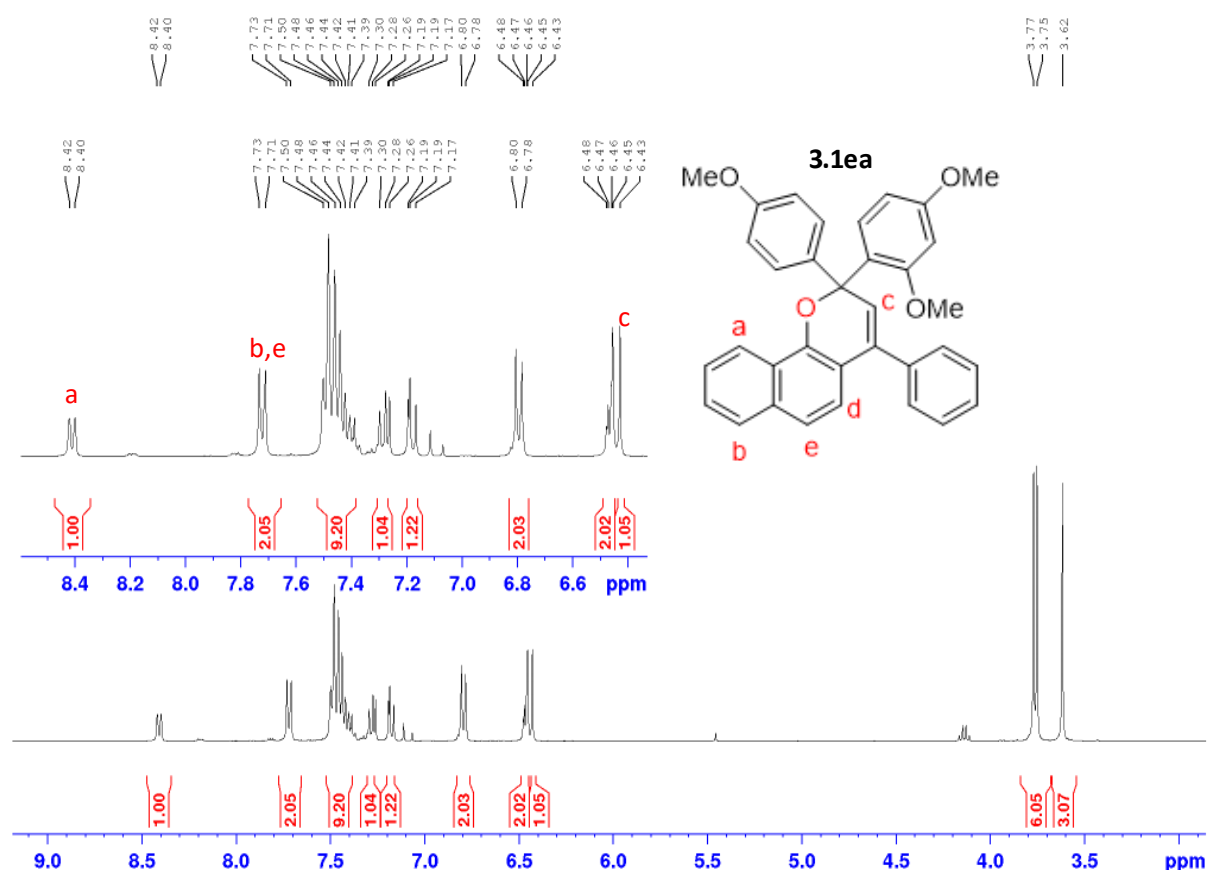


Figure 3.11a: ^1H NMR spectrum of 2H-naphtho[1,2-b]pyran **3.1ea**

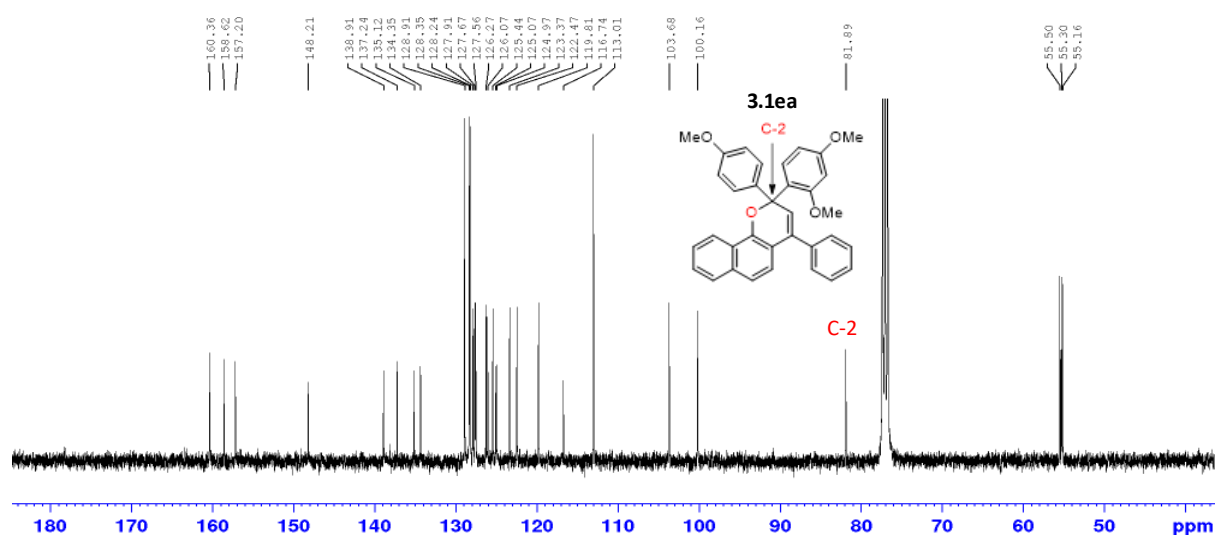


Figure 3.11b: ^{13}C NMR spectrum of 2H-naphtho[1,2-b]pyran **3.1ea**

Given access to the series of naphthopyrans it was of interest to contrast their ^1H NMR spectra to assess the influence of the 6-substitute upon the chemical shift of 5-H (**d**) and of the *peri* naphthalene ring proton 7-H (**b**) (Figure 3.12). In all of the spectra the chemical shift of 3-H

(c) is essentially constant at ca. 6.44 ppm and the position of 10-H (a) shows some slight variation and resonates in the range 8.4 – 8.5 ppm. Significant upfield shifts of ca. 0.4 ppm are noted for 7-H (b) for **3.1ca** and **3.1ea** when the 6-Br and 6-OMe substituents are absent. However, the most striking shift is noted for 5-H (d) which resonates in the midst of the aromatic signals at ca. 7.45 ppm for **3.1aa** and **3.1ea** but is shifted upfield by ca. 0.9 ppm to ca. 6.5 ppm in **3.1ba** as a consequence of the 6-MeO substituent and shifted upfield by ca. 0.3 ppm to ca. 7.1 ppm as a consequence of the 4-methoxyphenyl substituent in **3.1ca**.

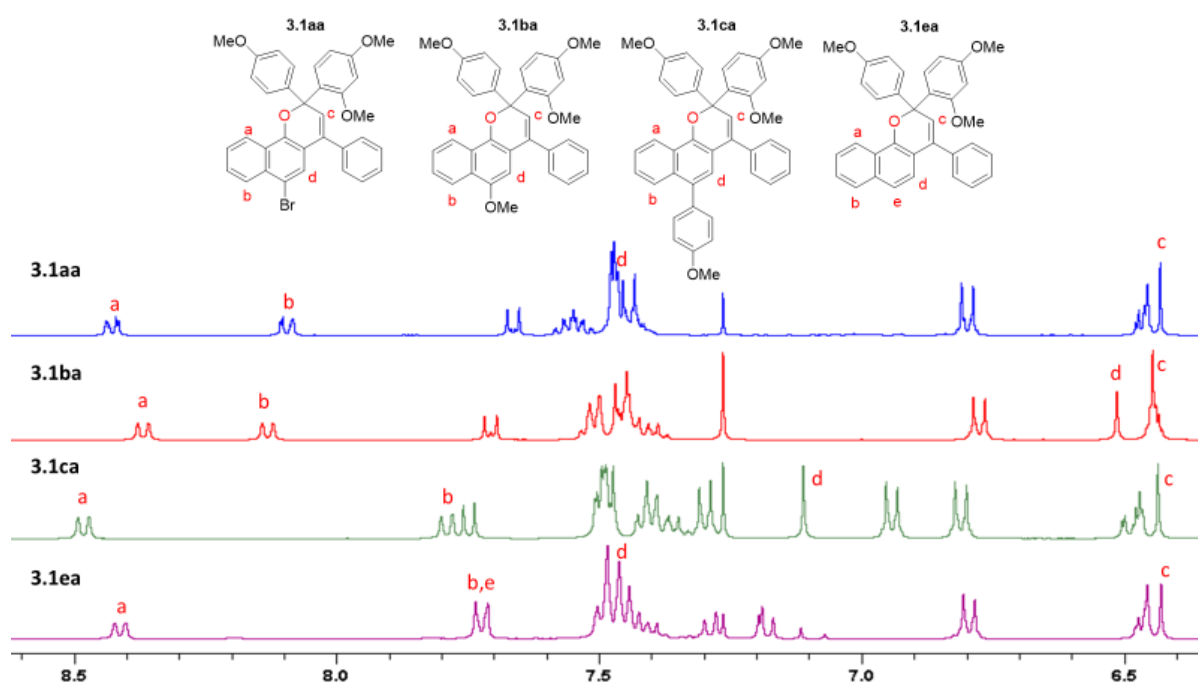
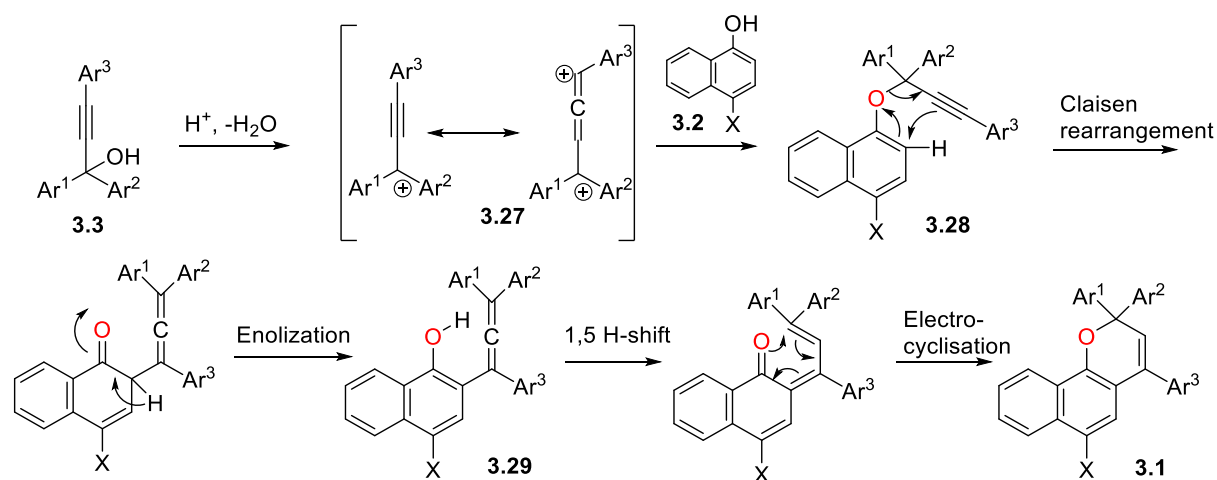


Figure 3.12: ^1H NMR spectra of **3.1aa**, **3.1ba**, **3.1ca** and **3.1ea** recorded in CDCl_3

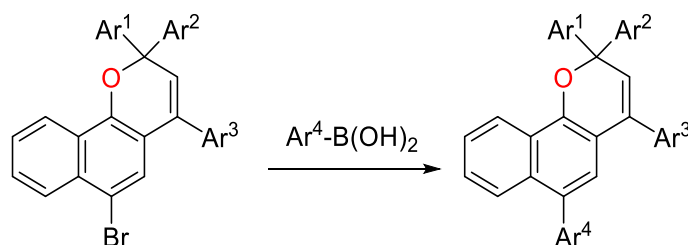
Finally, to conclude this section on the formation of naphthopyrans the mechanism of the pyran ring forming reaction, which has on occasion been referred to as chromenization ^{<2003EJOC2799; 2020JOC10772>}, is outlined in Scheme 3.19. The first step of the reaction involves the protonation of propynol **3.3** followed by loss of water which forms the carbocation intermediate **3.27**. The interception of the carbocation **3.27** with naphthol **3.2** produces the propargyl naphthyl ether **3.28** which then undergoes a Claisen rearrangement followed by enolization forming an allenynaphthol **3.29**. A subsequent 1,5-sigmatropic-H shift and finally electrocyclization affords the 2*H*-naphtho[1,2-*b*]pyran **3.1**. This mechanism has been previously documented alongside an alternative in which a purported allenyl

carbocation **3.27** undergoes an S_EAr reaction on the 2-position of the naphthalene ring to afford **3.29**. <2003EJOC1220>



Scheme 3.19: The mechanism for the formation of 2*H*-naphtho[1,2-*b*]pyran **3.1**

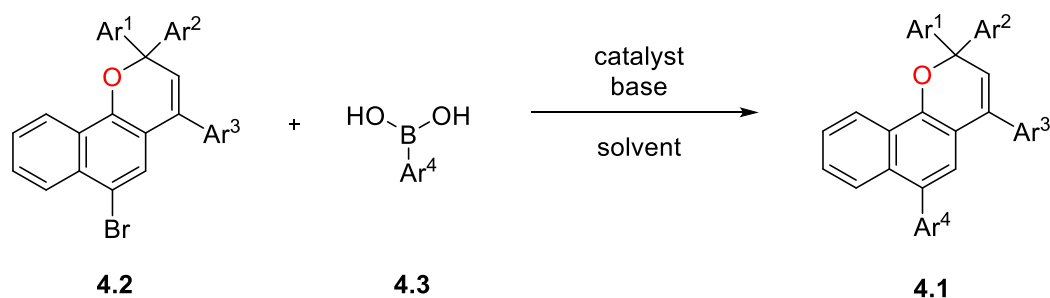
With the range of 6-bromo substituted naphthopyrans isolated in moderate yield their modification using the Suzuki-Miyaura cross-coupling with a series of arylboronic acids to form the target 2,2,4,6-tetra-aryl substituted naphthopyrans was next investigated (Scheme 3.20) (Chapter 4.1).



Scheme 3.20: Proposed route to 2,2,4,6-tetra-aryl substituted naphthopyran

Chapter 4.0 Functionalisation of naphthopyrans

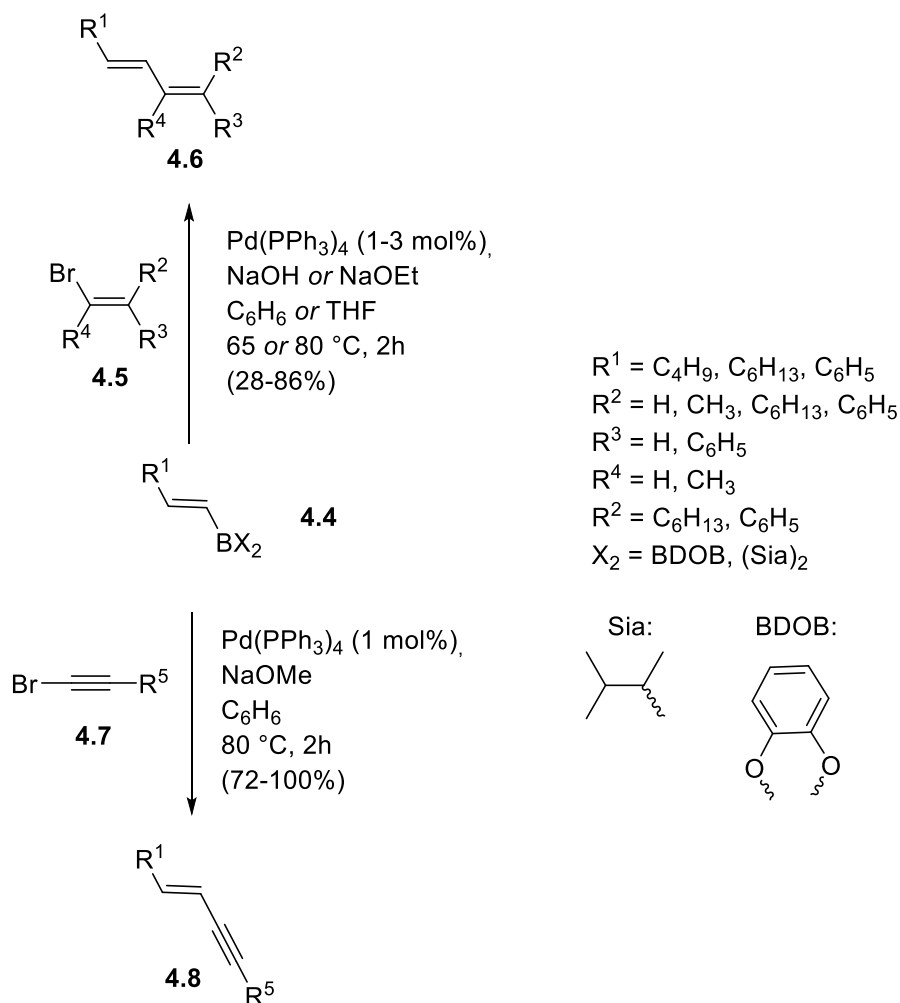
As discussed in the aims of this thesis (Chapter 1.7) the Suzuki-Miyaura cross-coupling reaction will be employed to further functionalise the series of 6-bromo-2,2,4-triaryl-2*H*-naphtho[1,2-*b*]pyrans prepared in the preceding chapter (Chapter 3.1) in order to obtain the target 2,2,4,6-tetraaryl-2*H*-naphtho[1,2-*b*]pyrans for spectroscopic characterization (Scheme 4.1).



Scheme 4.1: Preparation of substituted 2,2,4,6-tetraaryl-2*H*-naphtho[1,2-*b*]pyrans

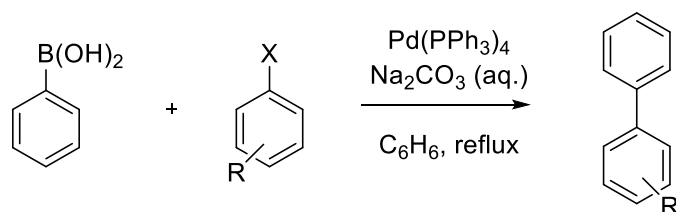
4.1 Suzuki-Miyaura cross-coupling reaction of 6-bromo substituted 2*H*-naphtho[1,2-*b*]pyran

The Suzuki, nowadays frequently termed the Suzuki-Miyaura, cross-coupling reaction was first explored by N. Miyaura, K. Yamada and A. Suzuki in 1979. <1979TL3437> The original transformation described the coupling of alkenyl boronic esters **4.4** to either bromoalkenes **4.5** or alkynyl bromides **4.7** to construct either conjugated dienes **4.6** or enynes **4.8** and relied upon the use of a palladium(0) catalyst, tetrakis(triphenylphosphonium)palladium(0) [Pd(PPh₃)₄], and either an alkoxide or hydroxide base (Scheme 4.2).



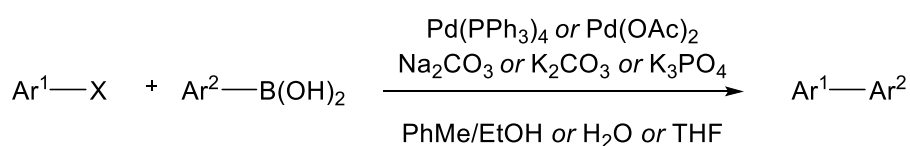
Scheme 4.2: The original Suzuki-Miyaura Palladium-catalysed cross-coupling reaction of (*E*)-1-alkenylboranes

A couple years later, Suzuki reported the extension of this methodology with the first cross-coupling reaction of aryl boronic acids and aryl halides to form biaryl compounds in typically excellent yields (Scheme 4.3). <1981SC513>



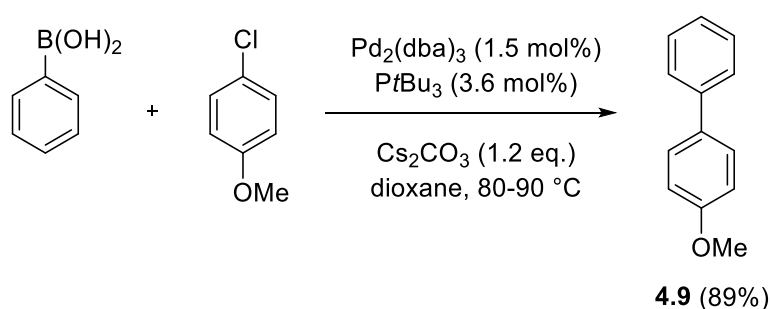
Scheme 4.3: Formation of a simple biaryl compounds

Since its inception, the scope of the Suzuki-Miyaura reaction has been significantly expanded and is perhaps now synonymous with the formation of bi(hetero)aryls from the cross-coupling between various (hetero)aryl bromides or iodides and (hetero)aryl- boronic acids and -boronic esters using Pd(0) catalysts in the presence of a base (Scheme 4.4). Given the breadth of the Suzuki-Miyaura reaction there have been numerous review articles covering the scope of the transformation. <1981SC513; 1985PAC1749; 1995CR2457; 1998T263; 2005CC4759; 2013CEJ15565; 2017CEJ4542; 2018ASC852; 2019ASC4468; 2019GC2164; 2019OR547; 2020JOC121538>



Scheme 4.4: Generalised Suzuki-Miyaura reaction for the preparation of biaryls

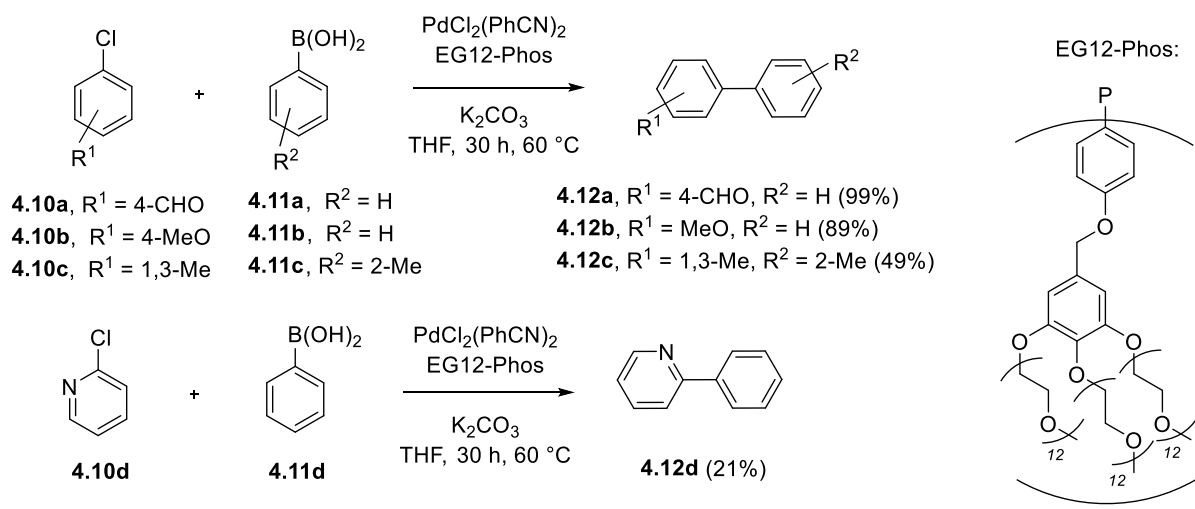
The following reactions illustrate some of the more common catalyst and base systems which have been employed for the Suzuki-Miyaura cross-coupling reaction to form biaryls. Fu and co-workers reported the reaction of 4-methoxychlorobenzene and phenylboronic acid using tri-*tert*-butylphosphine, tris(dibenzylideneacetone)dipalladium(0) and caesium carbonate giving 4-methoxybiphenyl **4.9** in excellent yield (Scheme 4.5). <1998ACIE3387> In later studies it was established that both potassium phosphate and potassium fluoride can act as successful bases in this cross-coupling strategy. <1999ACIE2413>



Scheme 4.5: Formation of 4-methoxybiphenyl using tris(dibenzylideneacetone)dipalladium(0) and caesium carbonate

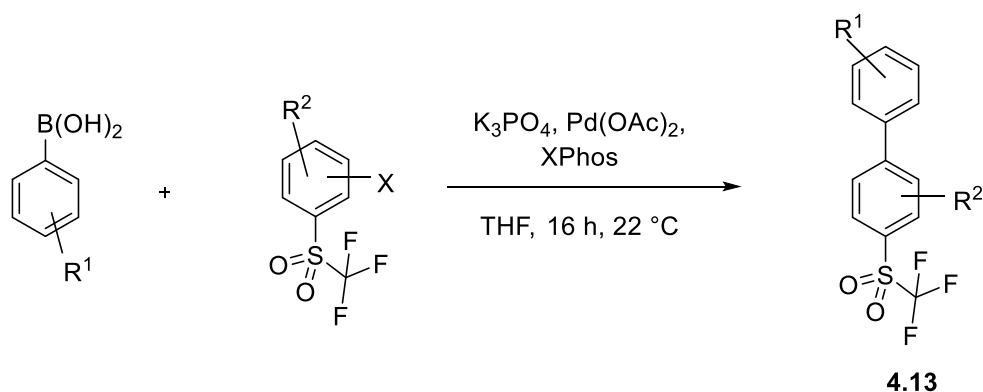
Fujihara *et al.*, have synthesised a range of biaryls during the reaction of aryl chlorides **4.10a-d** and arylboronic acids **4.11a-d** in the presence of bis(benzonitrile)palladium(II) chloride

catalyst with potassium carbonate as a base. It was found that these conditions were not favourable for 2-chloropyridine **4.10d** and 1,3-dimethyl-2-chlorobenzene **4.10c** which resulted in the lowest yields of 21% and 49%, respectively. The other biaryls formed were isolated in excellent yields of 89 – 99% (Scheme 4.6). <2009OL2121>



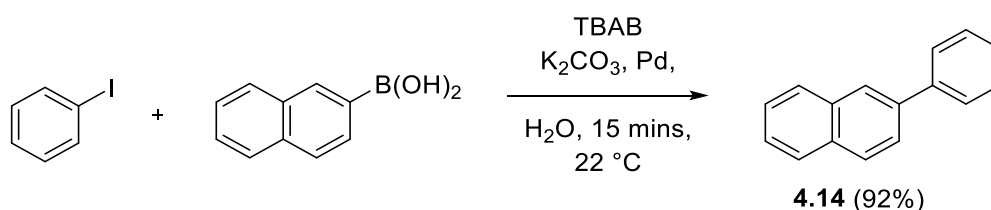
Scheme 4.6: Formation of biaryls using bis(benzonitrile)palladium(II) chloride with potassium carbonate

Chatelain *et al.*, reported a range of Suzuki-Miyaura coupling reactions on aryl sulfones using the phosphine ligand 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos), palladium(II) acetate and potassium phosphate in THF with overall good yields (Scheme 4.7). <2019ACIE(58)14959>



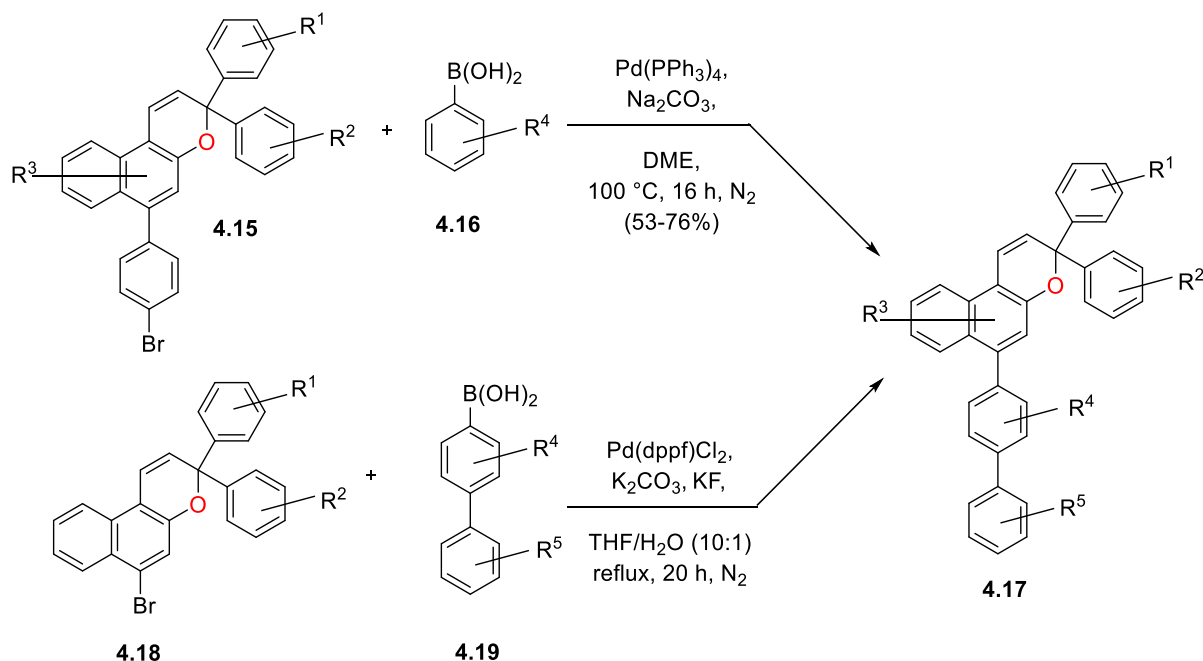
Scheme 4.7: Synthesis of biaryl sulfones **4.13** using palladium(II) acetate and potassium phosphate

An excellent yield of the Suzuki coupled product was noted by Manjare and co-workers when using tetrabutylammonium bromide, potassium carbonate and palladium in water. The reaction was rapid and proceeded at room temperature giving 92% yield of 2-phenylnaphthalene **4.14**. <2020JECE104213>



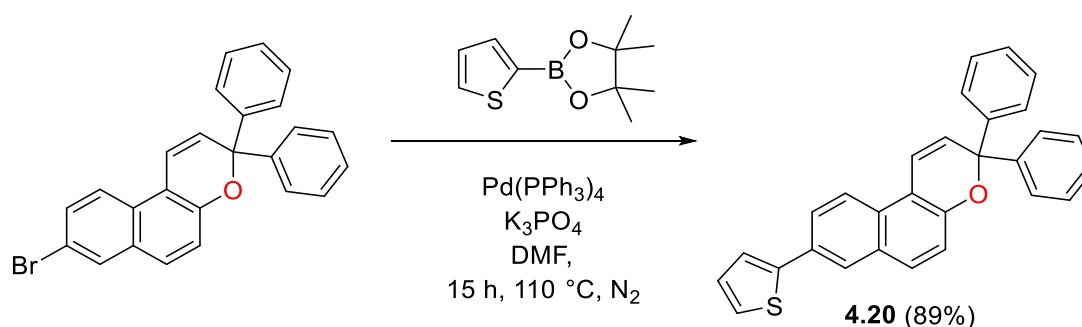
Scheme 4.8: Suzuki-Miyaura coupling reaction using palladium and potassium carbonate

Given the widespread utility of the Suzuki-Miyaura reaction it is not surprising to note that this Pd-mediated cross-coupling methodology has been employed to functionalise photochromic naphthopyran systems. The 6-(4-bromophenyl)- and 6-bromo- substituted naphthopyrans **4.15** and **4.18**, respectively were used as a substrates for further modification by Suzuki-Miyaura coupling to give extended 3*H*-naphtho[2,1-*b*]pyrans which exhibited mesogenic and photochromic properties. <2008WOP2008029194> The reaction of bromonaphthopyran derivatives **4.15** with arylboronic acids **4.16** in the presence of $\text{Pd(PPh}_3)_4$ and sodium carbonate in 1,2-dimethoxyethane furnished the coupled 3*H*-naphtho[2,1-*b*]pyrans **4.17** (53 – 76%). With different reaction conditions, the reaction of 6-bromonaphthopyrans **4.18** with substituted 4-biphenylboronic acids **4.19** also gave the expected 6-biphenyl substituted naphtho[2,1-*b*]pyrans **4.17** (Scheme 4.9). <2008WOP2008030226>



Scheme 4.9: Preparation of mesogenic photochromic naphthopyrans by the Suzuki-Miyaura reaction

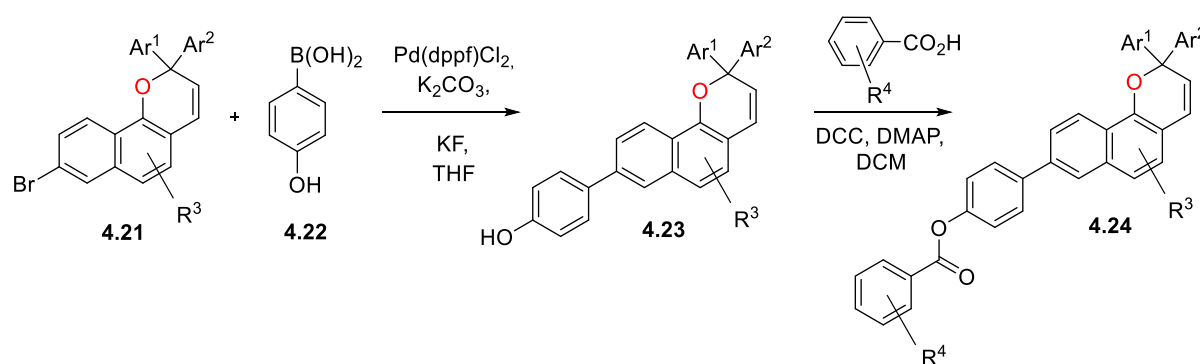
Frigoli *et al.*, reported the synthesis of a range of thiophene-substituted 3,3-diaryl-3H-naphtho[2,1-*b*]pyrans via Suzuki cross-coupling reaction using $\text{Pd}(\text{PPh}_3)_4$, tripotassium phosphate (K_3PO_4) as a base and dimethylformamide as the solvent. The foregoing reaction conditions allowed a series of cross-coupled naphthopyrans to be obtained in excellent yields as exemplified by the example shown in Scheme 4.10. <2003EJOC2799>



Scheme 4.10: Formation of a thiophene-substituted 3,3-diaryl-3H-naphtho[2,1-*b*]pyran **4.20**

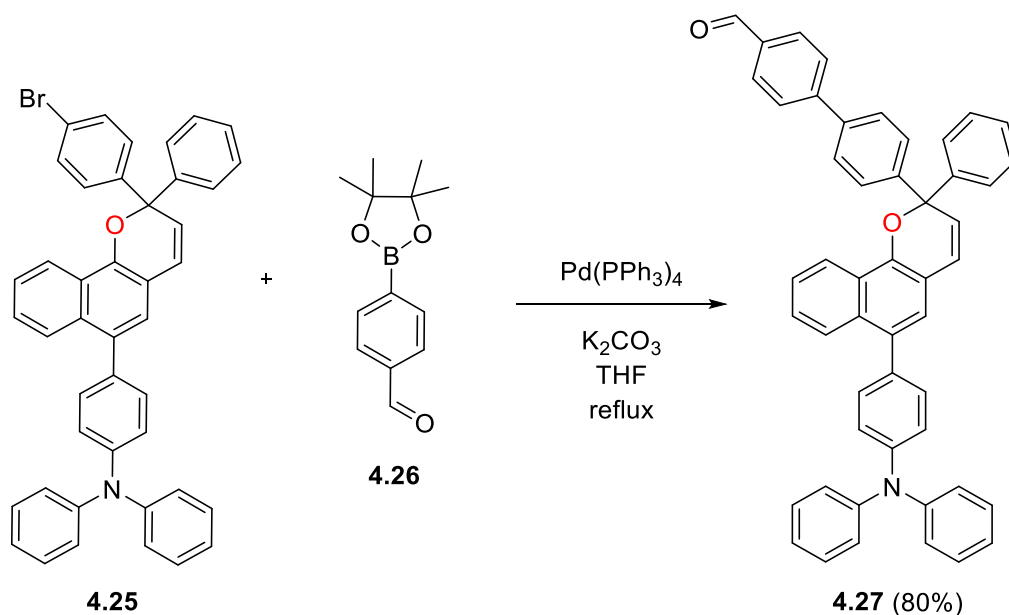
A range of highly substituted naphthopyrans **4.24** were obtained by a Suzuki-Miyaura coupling reaction which provided the key phenolic intermediate **4.23** required for subsequent transformation to obtain expanded naphthopyrans **4.24** (Scheme 4.11). The reaction of 8-

bromo-2*H*-naphtho[1,2-*b*]pyrans **4.21** with 4-(hydroxyphenyl)boronic acid **4.22** in the presence of Pd(dppf)Cl₂, potassium carbonate and potassium fluoride in THF gave the 8-(4-hydroxyphenyl) substituted naphthopyrans **4.23** that were esterified with a series of substituted benzoic acids to form the final branched naphthopyrans **4.24**. <2014USP2014197361> These substituted naphthopyrans **4.24** exhibit mesogenic properties and therefore they could be classified as a photoresponsive liquid-crystal materials. <2012N347>



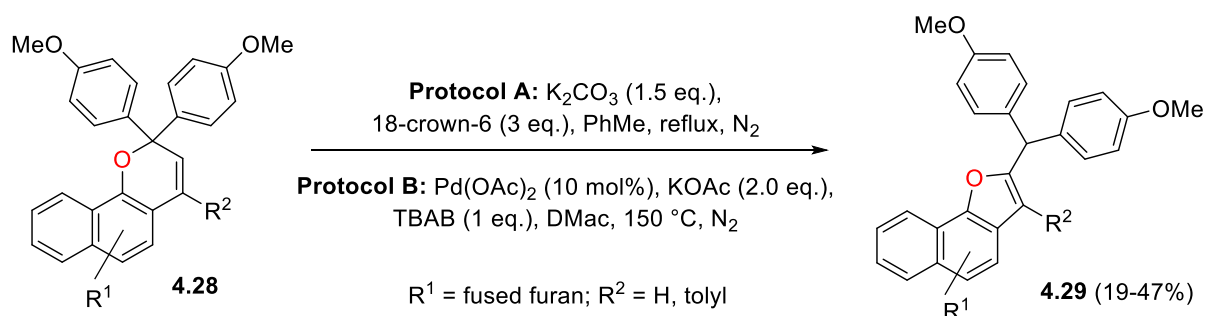
Scheme 4.11: Synthesis of a range of polyalkyl linear branched naphthopyrans **4.24**

Another example of the elaboration of a bromo-containing unit in a 2*H*-naphtho[1,2-*b*]pyran is illustrated in Scheme 4.12. Thus, the cross-coupling reaction between 2,2,6-triaryl-2*H*-naphtho[1,2-*b*]pyran **4.25** and 4-formylphenylboronic acid pinacol ester **4.26** in the presence of Pd(PPh₃)₄ and potassium carbonate gave the extended naphthopyran product **4.27** in 80% yield. These compounds were used as a photochromic dyes with the capability of being transparent to different weather conditions within solar cell devices. <2018WOP2018215371>



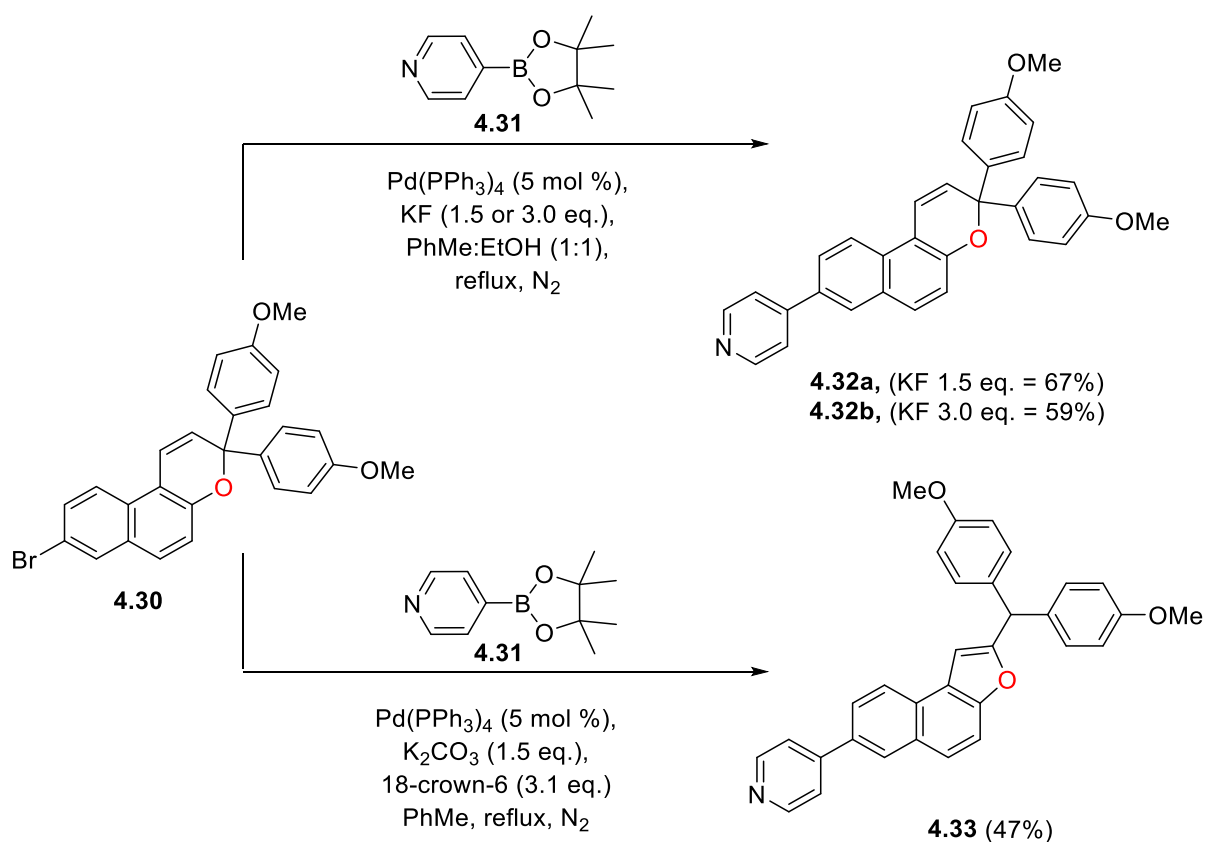
Scheme 4.12: Suzuki cross-coupling reaction on bromo substituted 2*H*-naphtho[1,2-*b*]pyran **4.25**

Interestingly, ring contraction has been noted as a common problem in Suzuki cross-coupling with substituted naphthopyrans in the presence of certain bases and Pd-catalysts. Aiken *et al.*, reported a study concerning the ring-contraction of naphthopyrans **4.28** and described their optimal reaction conditions which could be mediated by Pd-catalysis and/or carbonate base. It was noted by Aiken *et al.*, the ring-contraction of 3*H*-naphtho[2,1-*b*]pyrans generally gave a higher yield of furan products than the isomeric 2*H*-naphtho[1,2-*b*]pyrans which afforded only diminished yields (19-47%) of the furan (Scheme 4.13). <2020JOC952>



Scheme 4.13: Optimal conditions for the 2*H*-naphtho[1,2-*b*]pyrans **4.28** ring contraction to form 2*H*-naphtho[1,2-*b*]furans **4.29**

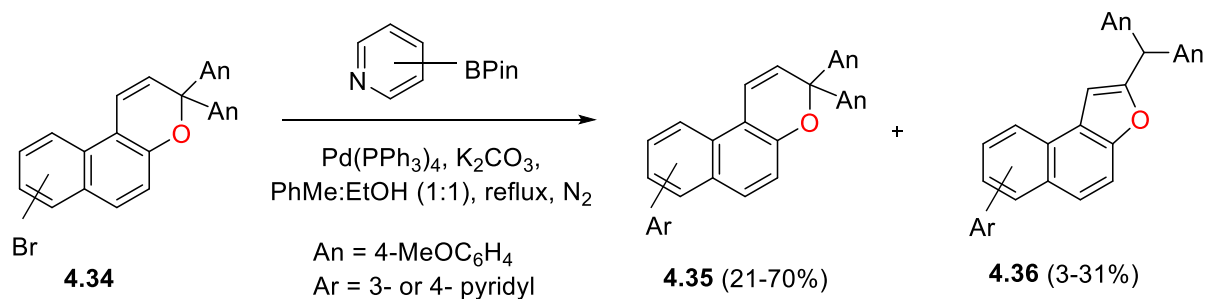
In the latter work Aiken and co-workers also described reaction conditions to enable the selective Suzuki-coupling reaction on, for example, the 8-bromo substituted naphthopyran **4.30** with 4-pyridineboronic acid pinacol ester **4.31** with the use of varying amounts of potassium fluoride base in a mixture of toluene and ethanol which gave a good yield of the naphthopyran coupled products **4.32a,b**. Moreover, repeating the Suzuki-coupling reaction on the same 8-bromo substituted naphthopyran **4.30** with 4-pyridineboronic acid pinacol ester **4.31** in the presence of potassium carbonate and 18-crown-6 in toluene furnished coupled naphthofuran product **4.33** exclusively in 47 % (Scheme 4.14). <2020JOC952>



Scheme 4.14: Selective Suzuki-coupling reaction conditions for synthesis of pyridyl substituted naphthopyrans **4.32a,b** or naphthofuran **4.33**

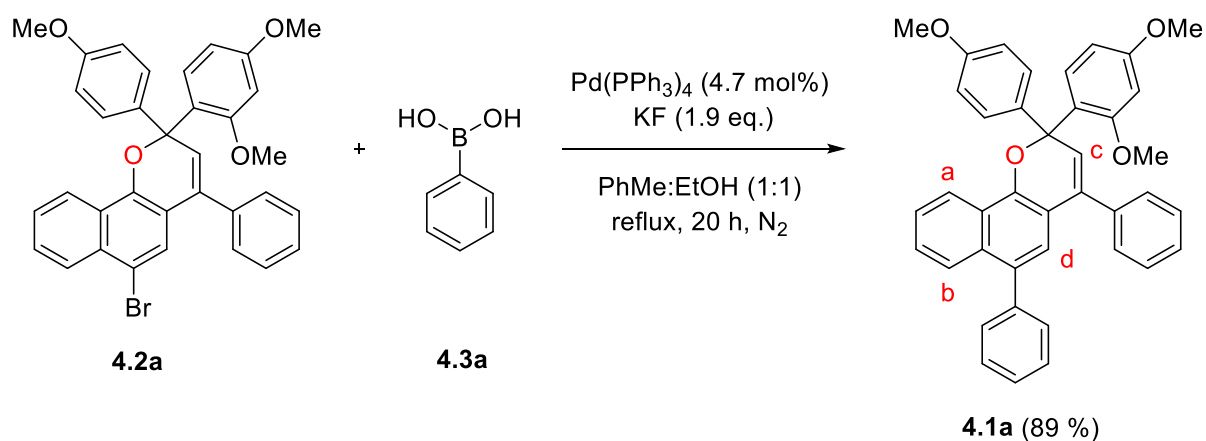
Building upon the reported conditions described for the optimal Suzuki-Miyaura coupling to afford naphthopyrans regioselectively, a series of pyridyl substituted naphthopyrans were constructed from the coupling reactions between bromo, iodo or trifloxy substituted naphthopyrans. According to Azevedo *et al.*, the Suzuki cross-coupling reactions performed on various bromo-substituted naphthopyrans **4.34** with pyridylboronic acid pinacol ester with

the use of potassium fluoride base in toluene and ethanol gave the expected naphthopyrans **4.35** however, in some instances the formation of varying amounts of naphthofurans **4.36** was also reported (Scheme 4.15). <2020JOC10772>



Scheme 4.15: Formation of a range of pyridyl substituted naphthopyrans **4.35** with additional formation of naphthopyrans **4.36** using the optimal Suzuki-Miyaura coupling conditions

From the variety of conditions described above for the Suzuki-Miyaura coupling reactions on naphthopyrans; the optimal coupling conditions of KF (1.9 eq.) with Pd(PPh₃)₄ (4.7 mol%) in toluene:ethanol (1:1) <2020JOC952> were employed in the present study to couple the 6-bromo substituted naphthopyran **4.2a** with phenylboronic acid **4.3a** (Scheme 4.16). Purification of the crude product by flash column chromatography gave a target 2,2,4,6-tetraaryl substituted naphthopyran **4.1a** as an off-white microcrystalline powder in 89 % yield with a melting point range of 84 – 87 °C.



Scheme 4.16: The coupling of 6-bromo naphthopyran **4.2a** with phenylboronic acid **4.3a** to obtain a 2,2,4,6-tetraaryl substituted naphthopyran **4.1a**

The ^1H NMR spectrum of compound **4.1a** clearly displayed the crucial singlet for the pyran ring proton (3-H) at 6.42 ppm and the unique singlet for 5-H at 7.12 ppm. Moreover, the *peri* naphthalene ring proton (7-H) was found as doublet at 7.76 ppm (**b**) with $J = 8.4$ Hz and signal for naphthalene proton (10-H) appeared as multiplet and resonated at ca. 8.48 ppm (**a**). Therefore, the attachment of 6-aryl ring showed a significant upfield shift for the signals for 5-H and 7-H; a slightly downfield shifted signal for 10-H and almost no change in the chemical shift for 3-H relative to the 6-bromo naphthopyran precursor **4.2a**. In addition, the chemical shifts of naphthopyran **4.1a** were closely related to the synthesised example of the 2,2,4,6-tetraaryl substituted naphthopyran **3.1ca** from Chapter 3.2. The ^{13}C NMR spectrum revealed a signal at 82.03 ppm which confirmed the presence of C-2 in naphthopyran structure (Figure 4.1b).

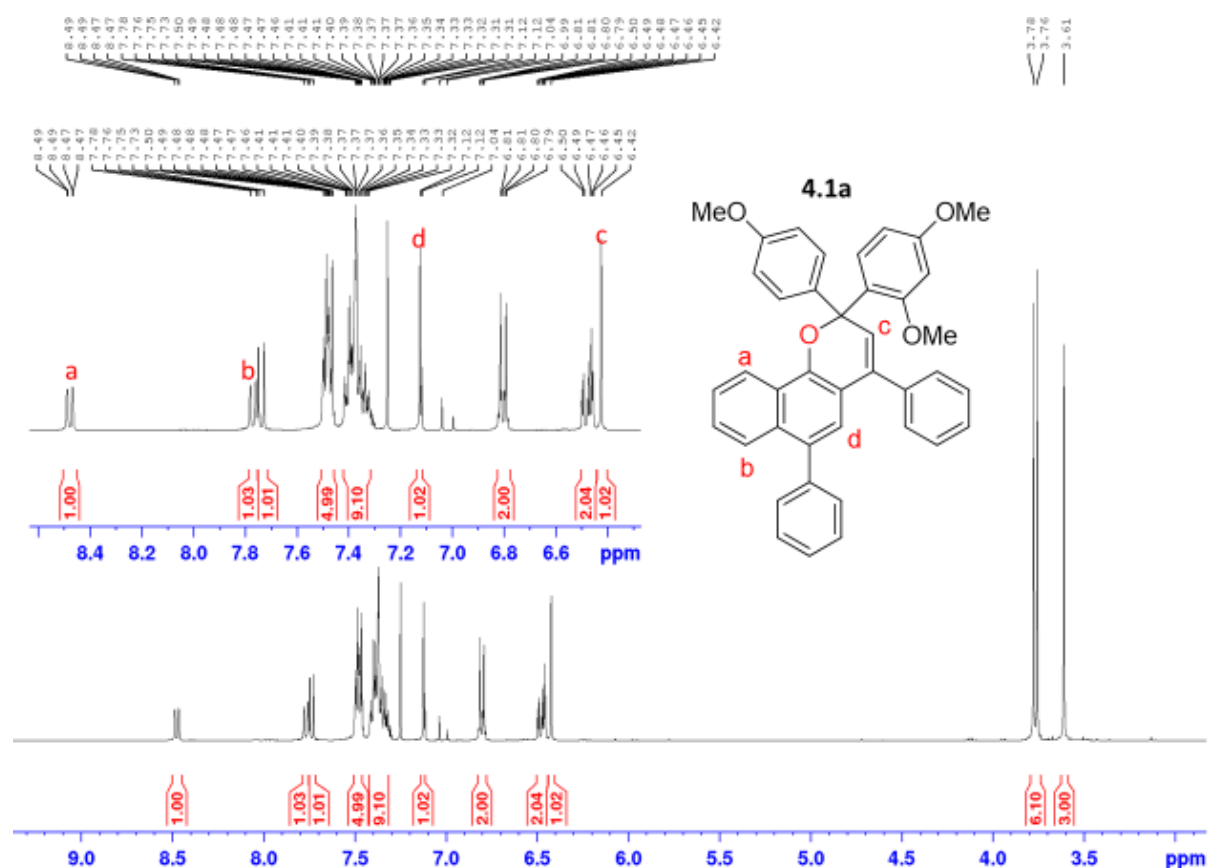


Figure 4.1a: ^1H NMR spectrum of 2,2,4,6-tetraaryl substituted 2H-naphtho[1,2-b]pyran **4.1a**

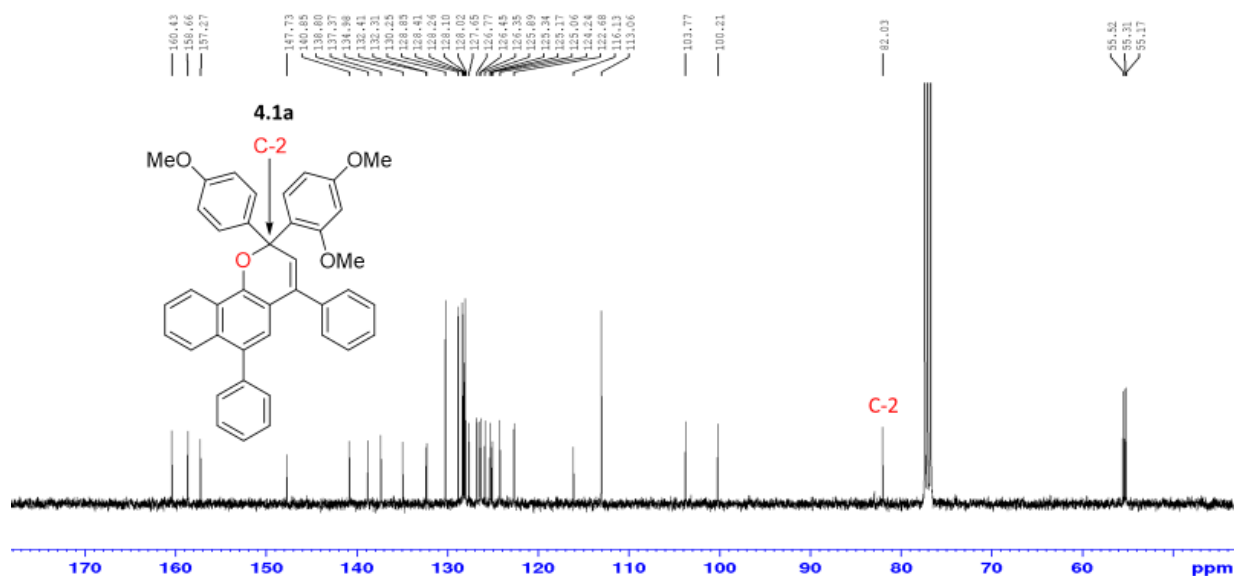


Figure 4.1b: ^{13}C NMR spectrum of 2,2,4,6-tetraryl substituted 2H-naphtho[1,2-b]pyran **4.1a**

Good agreement was observed between the measured mass m/z 577.2365 $[\text{M}+\text{H}]^+$ and the calculated theoretical mass m/z 577.2379 $[\text{M}+\text{H}]^+$ with the molecular formula $\text{C}_{40}\text{H}_{32}\text{O}_4$ in the mass spectrum of **4.1a** (Figure 4.2).

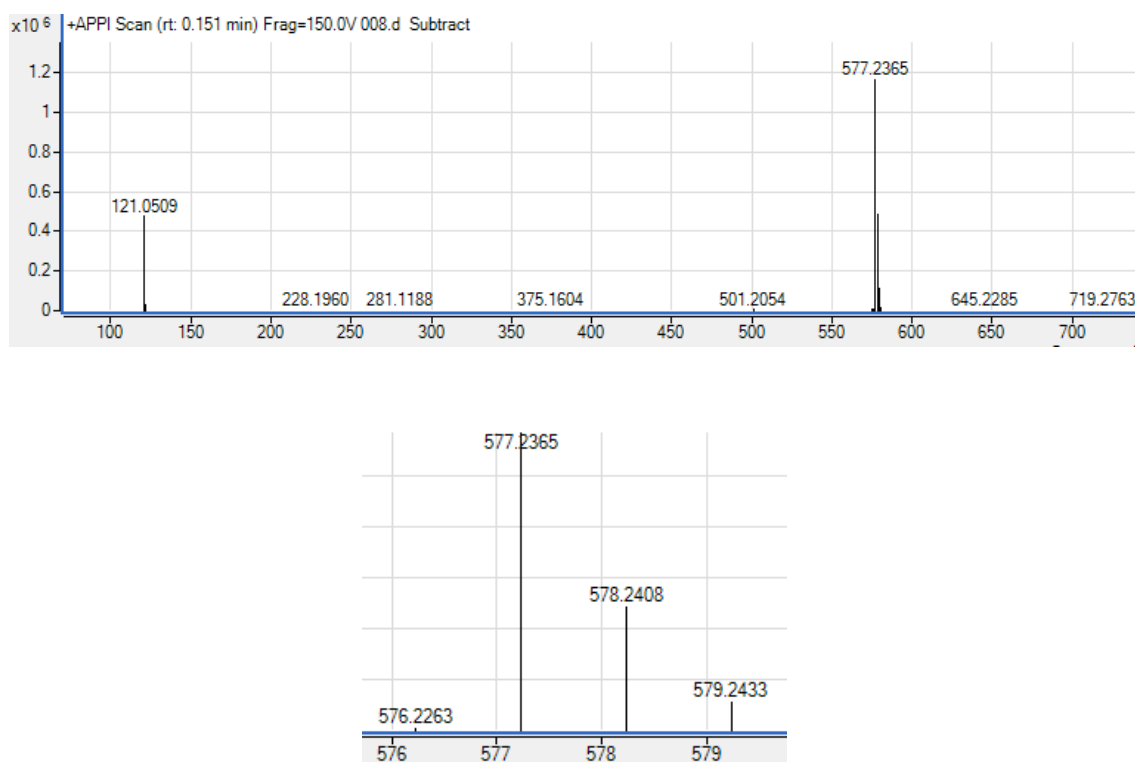
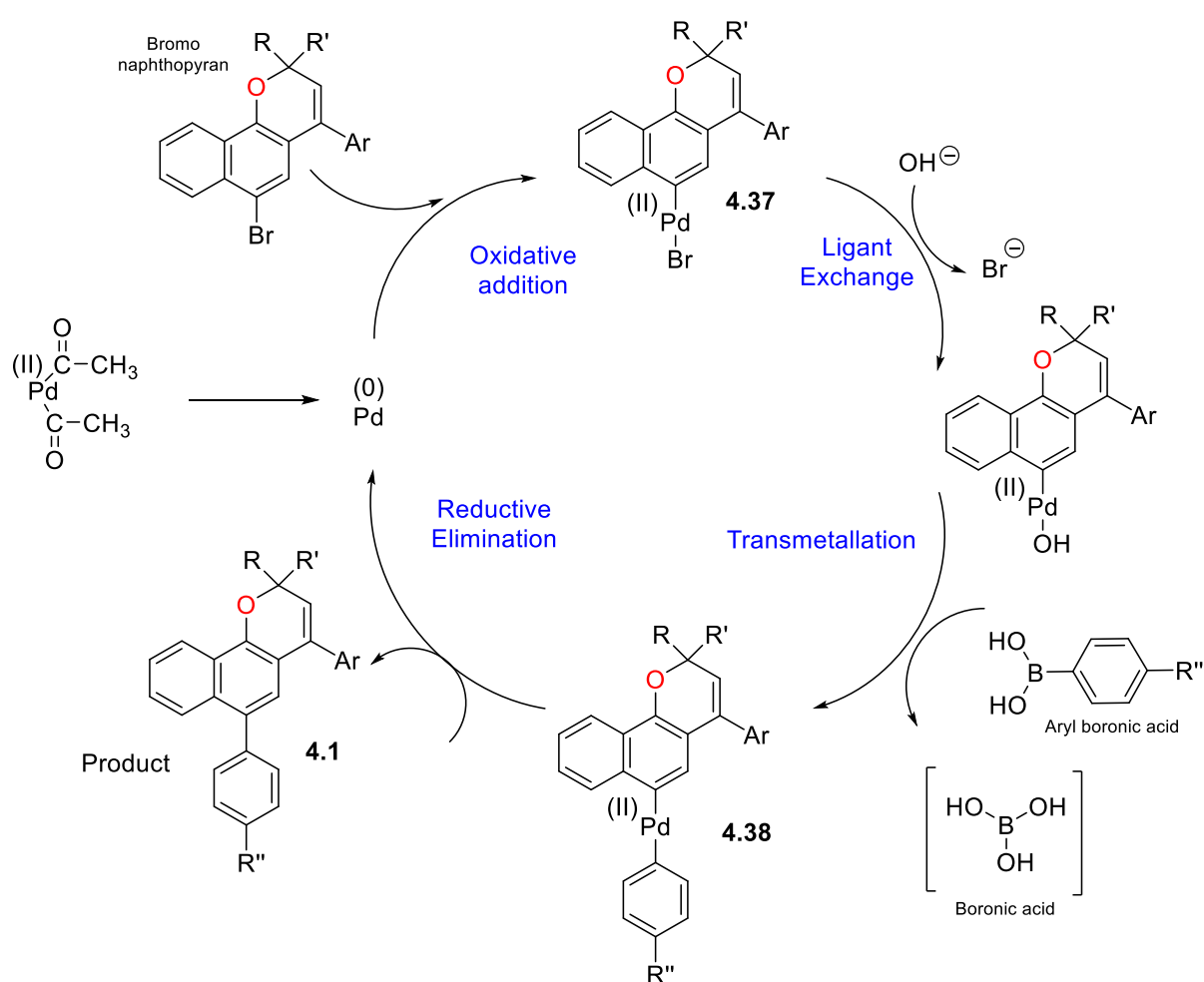


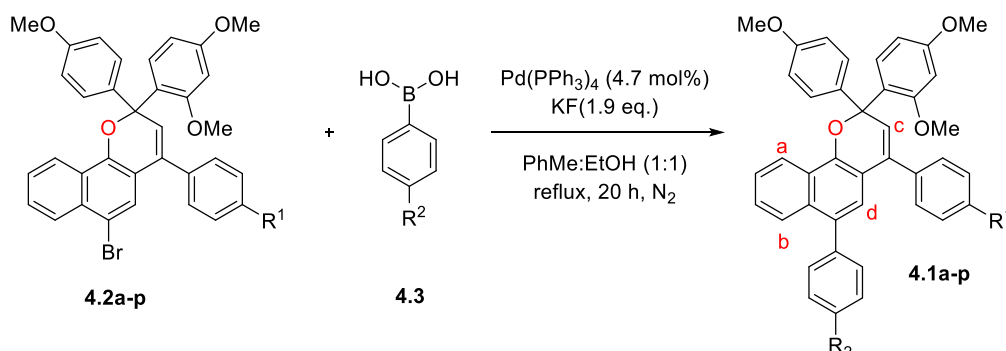
Figure 4.2: Mass spectrum and expansion of molecular ion region for 2,2,4,6-tetraryl substituted 2H-naphtho[1,2-b]pyran **4.1a**

The mechanism of the Suzuki reaction was previously explained in Chapter 2.3 when forming 4-aryl-1-naphthol intermediates. The current modification reaction is subjected to the same process which falls into four steps; oxidative addition, ligand exchange, transmetallation and reductive elimination that finally deliver the coupled product. Thus, the activated palladium-ligand species Pd(0) insert into the C-Br bond of the 6-bromo substituted naphthopyran promoting the Pd(II) intermediate **4.37** which then replacing the bromine atom with hydroxyl unit. In the following steps, the Pd(Ar)(Ar') complex **4.38** is made which then undergoes reductive elimination process where the C-C bond is formed giving the final product **4.1** together with regeneration of the Pd(0) catalyst (Scheme 4.17). <1995CR2457; 2005JACS4685; 2009B-1>



Scheme 4.17: The mechanism for the Suzuki cross-coupling reaction on 6-bromo naphthopyrans

The following 2,2,4,6-tetraaryl substituted 2*H*-naphtho[1,2-*b*]pyrans **4.1b-p** were obtained by the foregoing Pd(PPh₃)₄ / KF protocol using 1.9 eq. of the base. Their aryl substituents at C-4 and C-6, isolated yield, key NMR characterization data and mass spectral data are presented in Table 4.1.



Nº	R ¹	R ²	Yield (%)	δ 3-H (ppm)	δ 5-H (ppm)	δ 7-H (ppm)	δ 10-H (ppm)	δ C-2 (ppm)	HRMS found	HRMS required
4.1a	H	H	89	6.42	7.12	7.76	8.48	82.03	577.2365	577.2379
4.1b	H	MeO	72	6.43	7.11	7.79	8.48	81.97	606.2396	606.2406
4.1c	H	CF ₃	85	6.46	7.12	7.72**	8.51	82.20	645.2236	645.2252
4.1d	MeO	H	92	6.40	7.16	7.79	8.49	82.02	607.2475	607.2484
4.1e	MeO	MeO	86	6.39	7.13	7.79	8.48	81.97	637.2581	637.2590
4.1f	MeO	CF ₃	73	6.40	7.13	7.71**	8.49	82.21	675.2347	675.2358
4.1g	CF ₃	H	81	6.48	7.03	7.78	8.48	82.06	645.2244	645.2252
4.1h	CF ₃	MeO	81	6.48	7.00	7.79	8.48	82.00	675.2352	675.2358
4.1i	CF ₃	Me ₂ N	80	6.46	7.00	7.87	8.46	81.94	688.2666	688.2674
4.1j	CF ₃	CF ₃	79	6.49	7.02	7.72**	8.50	82.26	713.2125	713.2126
4.1k	CN	Me ₂ N	94	6.46	6.95	7.87	8.45	81.92	645.2745	645.2753
4.1l[†]	NO ₂	H	-*	6.53	6.98	7.80	8.48	82.08	622.2222	622.2229
4.1m	NO ₂	MeO	63	6.53	6.96	7.80	8.47	82.02	652.2323	652.2335
4.1n	NO ₂	Me ₂ N	85	6.53	6.97	7.89	8.47	81.94	655.2640	655.2651
4.1o	NO ₂	Et ₂ N	94	6.51	6.96	7.93	8.46	81.93	693.2951	693.2964
4.1p	Me ₂ N	NO ₂	79	6.41	7.27	7.73**	8.53	82.42	665.2644	665.2651

* Inseparable mixture isolated which contained ca. 70% of the target product **4.1l** based on comparison of the relative integrals of key naphthalene ring ¹H NMR signals; 10-H (8.48 ppm) in **4.1l** and precursor naphthopyran 10-H (8.40 ppm)].

[†] ¹H, ¹³C NMR and mass spectral data for **4.1l** provided from the pure material obtained by the alternative synthetic strategy (Chapter 3.2) and included in the above table for comparative purposes.

** Signal obscured by those of other aromatic protons.

Table 4.1: Synthesis of 2,2,4,6-tetraaryl substituted 2*H*-naphtho[1,2-*b*]pyrans **4.1a-p** with key characterization data

Overall very good to excellent yields were recorded for the range of synthesised 2,2,4,6-tetraaryl substituted 2*H*-naphtho[1,2-*b*]pyrans obtained by the Suzuki-Miyaura protocol. Unfortunately, even through the use of extensive column chromatography, the naphthopyran **4.1l** could only be isolated as an inseparable mixture. Fortunately, naphthopyran **4.1l** had been prepared by an alternative strategy in 50% yield that involved the initial preparation of 4-phenyl-1-naphthol (**3.2d**) which was then reacted with propynol (**3.3d**) under acid-catalysed conditions to afford the target naphthopyran (Chapter 3.2).

The ¹H NMR spectra of a small selection of naphthopyrans **4.1a-c** in which the 4-substituent remained constant as a phenyl ring and the 6-aryl group is varied was selected for comment and their ¹H NMR spectra are illustrated in Figure 4.3a. The signal for 3-H (**c**) is found to resonate at ca. 6.43 ppm for compound **4.1a** and **4.1b** however, the presence of the electron-withdrawing unit shifted the peak slightly downfield for compound **4.1c**. It was worth noting that there is no significant variation in the chemical shift of the 5-H signal when the 6-aryl group was varied; in each case **4.1a-c** 5-H resonated at ca. 7.12 ppm. The signal for 7-H was found to vary its chemical shift slightly with the nature of the substituent present at C-6; electron-donating aryl groups shifted the peak downfield whereas electron-withdrawing units shifted the peak upfield relatively to 7-H in the neutral bis(4,6-diphenyl) analogue **4.1a**. The signal for 10-H was noted to shift marginally downfield in the presence of the electron-withdrawing substituted aryl groups at C-6 (**4.1c**).

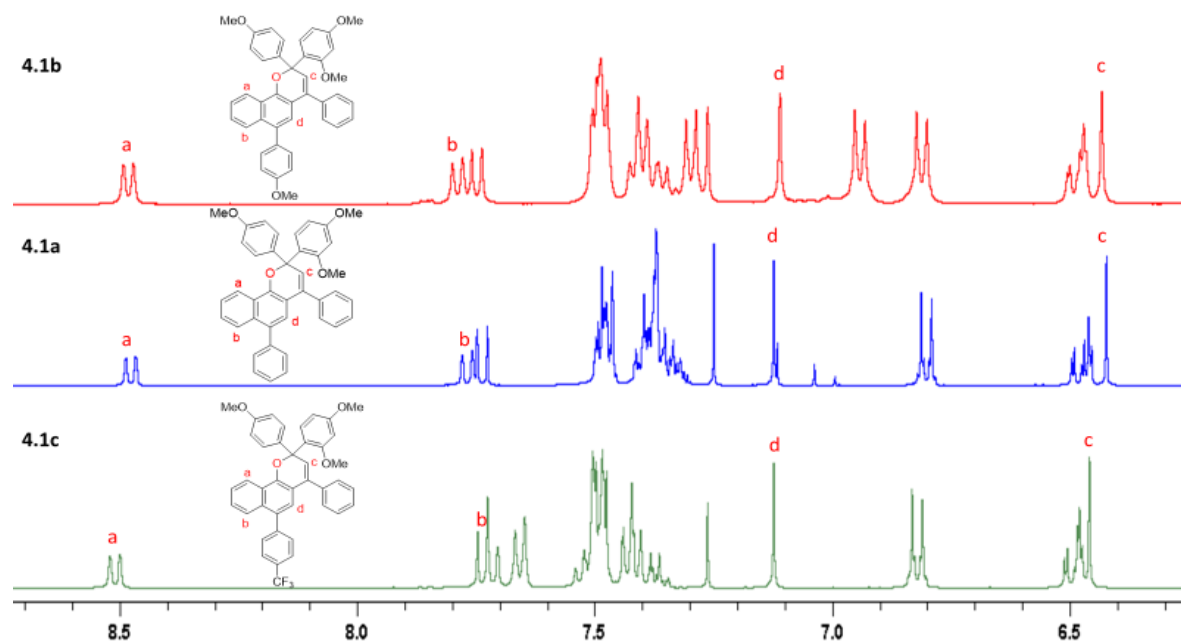


Figure 4.3a: ^1H NMR spectra of 2,2,4,6-tetraryl substituted 2*H*-naphtho[1,2-*b*]pyrans **4.1b**, **4.1a** and **4.1c**

The ^{13}C NMR spectra (Figure 4.3b) of the naphthopyrans **4.1a-c** shows a minor variation for C-2 signal; compound **4.1b** possessing an electron-donating 6-aryl ring is found to shift the signal upfield whereas for compound **4.1c** having an electron-withdrawing unit shifts the signal slightly downfield relatively to that of C-2 in the neutral bis(4,6-diphenyl) analogue **4.1a**.

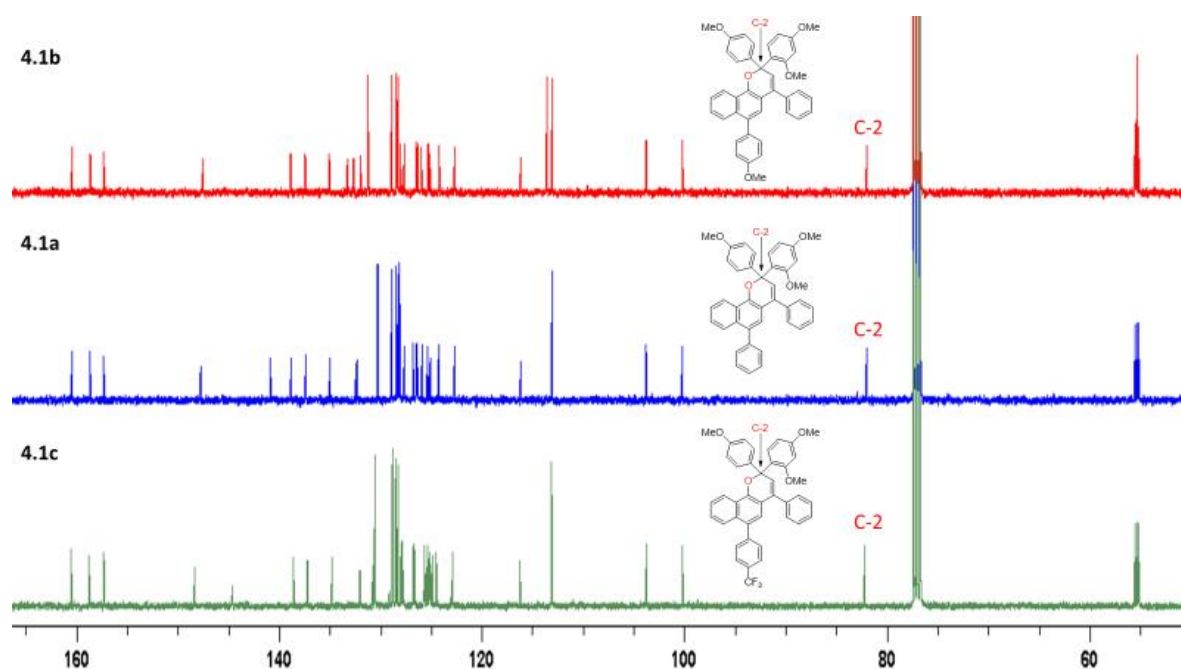


Figure 4.3b: ^{13}C NMR spectra of 2,2,4,6-tetraryl substituted 2*H*-naphtho[1,2-*b*]pyrans **4.1b**, **4.1a** and **4.1c**

With access to the regioisomeric naphthopyrans **4.1n** and **4.1p** it was thought to be useful to contrast their NMR spectra (Figure 4.4a,b). The presence of the 4-(4-nitrophenyl) ring in **4.1n** induces a downfield shift in 3-H which resonates at ca. 6.5 ppm whereas the corresponding proton in **4.1p**, which contains an electron donating 4-(4-dimethylaminophenyl) ring resonates upfield of this value at 6.4 ppm. 5-H is similarly influence by the electronic nature of the proximal aryl group at C-6. Thus 5-H resonates at ca. 6.95 ppm in **4.1n** as a consequence of the electron releasing group at C-6; whereas 5-H appears downfield at ca. 7.27 ppm when adjacent to the electron-withdrawing nitroaryl group. The ^{13}C NMR spectra (Figure 4.4b) revealed the signals for C-2 at 81.95 ppm for **4.1n** and 82.42 ppm for **4.1p** which show relatively little differentiation.

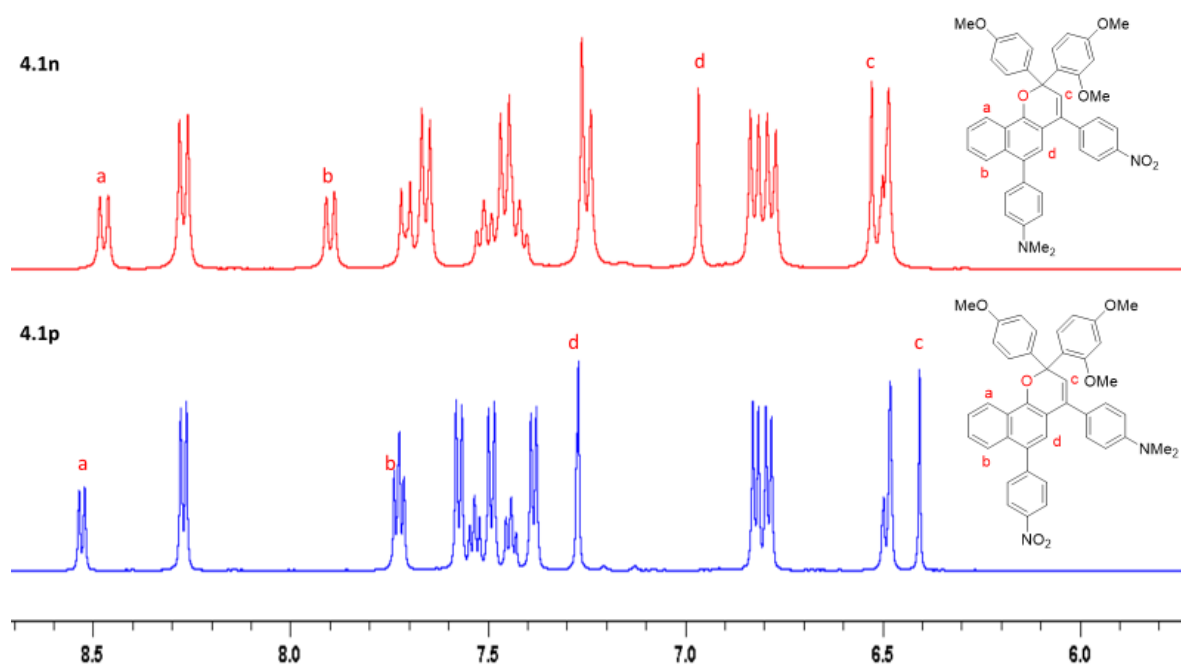


Figure 4.4a: ^1H NMR spectra of 2,2,4,6-tetraryl substituted 2*H*-naphtho[1,2-*b*]pyrans **4.1n** and **4.1p**

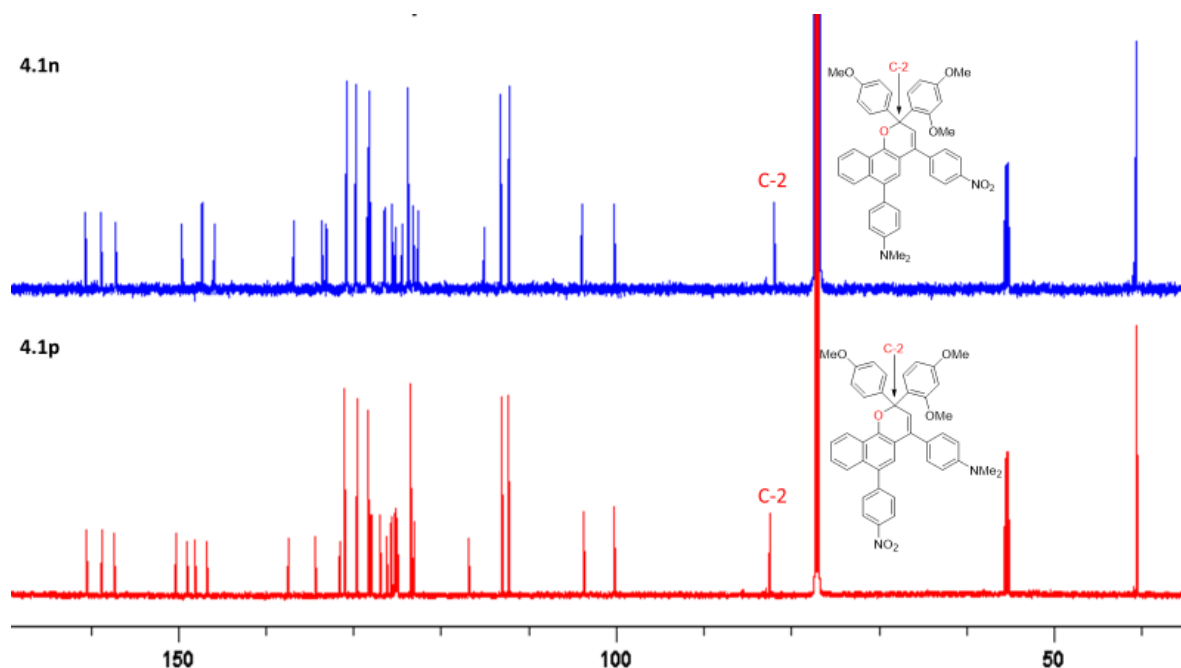
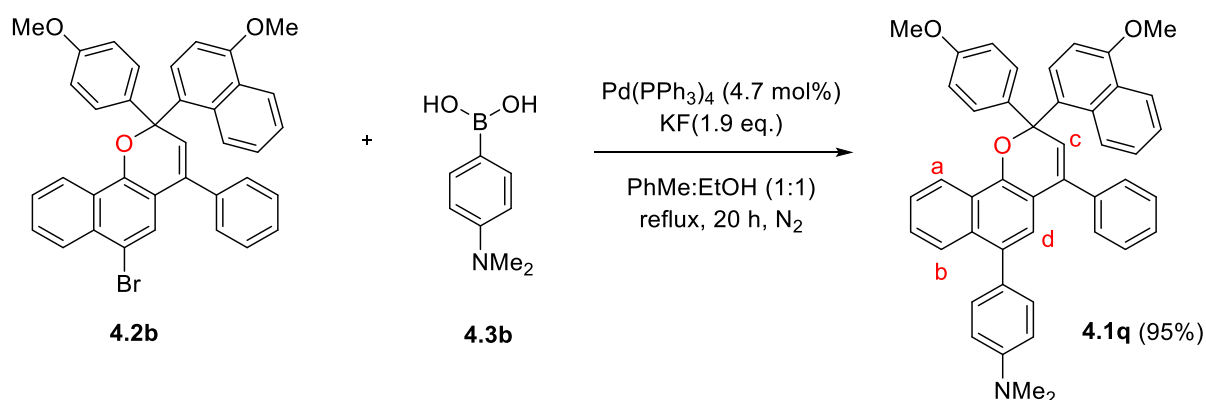


Figure 4.4b: ^{13}C NMR spectra of 2,2,4,6-tetraryl substituted 2*H*-naphtho[1,2-*b*]pyrans **4.1n** and **4.1p**

In summary the introduction of the 6-aryl substituent resulted in variable shifts of the signals for 5-H and 7-H in particular and less significant shifts noted for 3-H and 10-H which are more

remote from the newly introduced 6-aryl ring. In addition to the shifts for the naphthalene and pyran ring protons, signals were also noted for the substituents on the newly introduced ring at C-6. For example, the ^1H NMR spectrum revealed signals for the NMe_2 and NEt_2 substituents; these signals were found at ca. 2.98 ppm as a singlet accounted for 6H for compounds **4.1i**, **4.1k** and **4.1n** and also peaks at ca. 1.18 ppm appearing as a triplet which accounted for 6H and a quartet at ca. 3.37 ppm which accounted for 4H of compound **4.1o**. ^{19}F NMR spectroscopy showed a signal at -62.3 ppm for the CF_3 group of the 6-aryl ring in compounds **4.1c** and **4.1f**. The CF_3 group in the 4-aryl ring gave rise to a signal at ca -62.45 ppm for the naphthopyrans **4.1g-i**. As an example, **4.1j**, which contained two CF_3 groups, showed a signal at -62.4 ppm and at -62.5 ppm. For all of the coupled naphthopyran products **4.1a-o**, the ^{13}C NMR spectra showed a signal for the sp^3 hybridised carbon atom, C-2, at approximately 82 ppm; the chemical shift of this signal whilst indicative of the presence of the pyran ring, was relatively insensitive to the type of aryl substituent at C-4 and C-6. For all compounds **4.1a-o** illustrated in the Table 4.1 the mass spectral analysis (HRMS) indicated a molecular ion peak $[\text{M}+\text{H}]^+$ which was in a good agreement between the measured and the calculated theoretical mass $[\text{M}+\text{H}]^+$ for their formulae.

The methodology used to obtain naphthopyrans **4.1a-p** was employed to prepare naphthopyran **4.1q**, which possessed a 1-(4-methoxynaphthalene) moiety at C-2, in 95 % yield.



Scheme 4.18: The coupling of 6-bromo naphthopyran **4.2b** with 4-dimethylaminophenylboronic acid **4.3b** to obtain a 2,2,4,6-tetraaryl substituted naphthopyran **4.1q**

The ^1H NMR spectrum of **4.1q** exhibited a singlet at 6.08 ppm and at 7.17 ppm for 3-H (**c**) and 5-H (**d**), respectively. The furthest downfield signals are attributed to the 7-H (**b**) at ca. 7.8 ppm and 10-H (**a**) at ca. 8.4 ppm (Figure 4.5a). The ^{13}C NMR spectrum confirmed the signal for C-2 which appeared at 83.8 ppm (Figure 4.5b) and mass spectral analysis exhibited a molecular ion m/z 640.2844 $[\text{M}+\text{H}]^+$ for $\text{C}_{45}\text{H}_{37}\text{NO}_3$ which was in good agreement with the calculated mass of for $[\text{M}+\text{H}]^+$ of 640.2852.

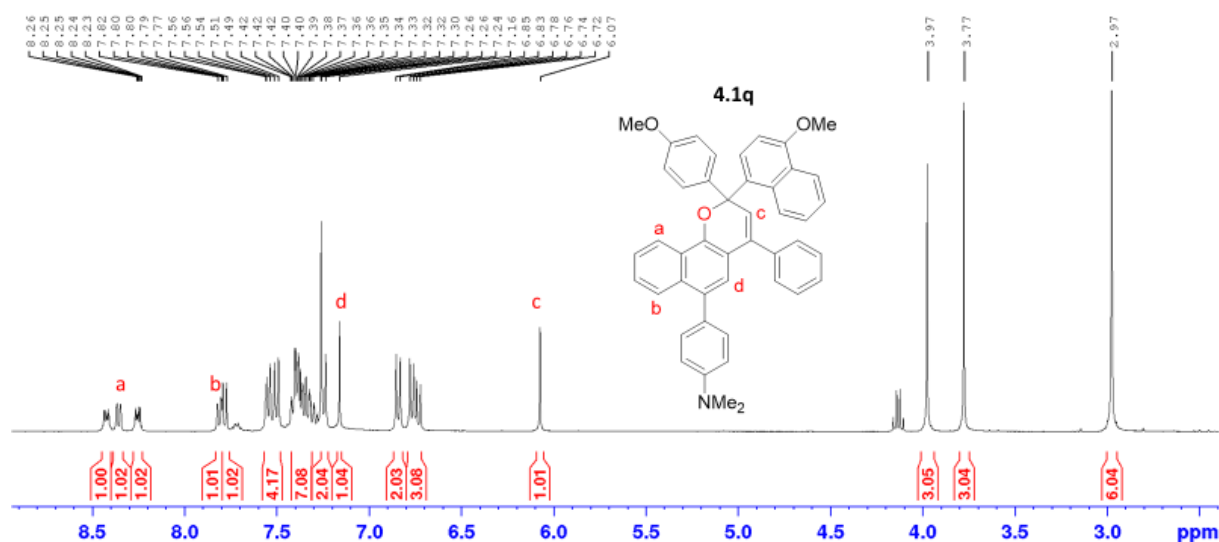


Figure 4.5a: ^1H NMR spectrum of 2,2,4,6-tetraryl substituted 2*H*-naphtho[1,2-*b*]pyran **4.1q**

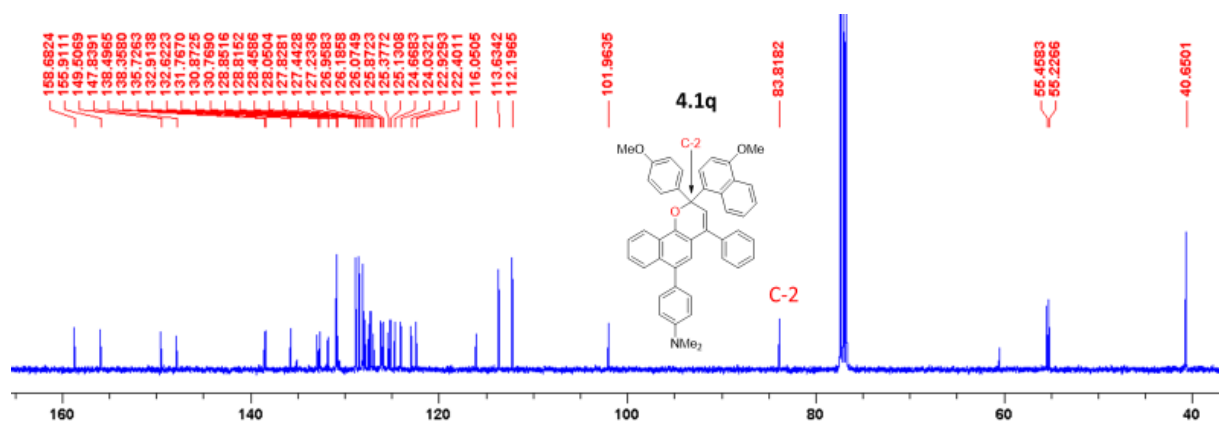
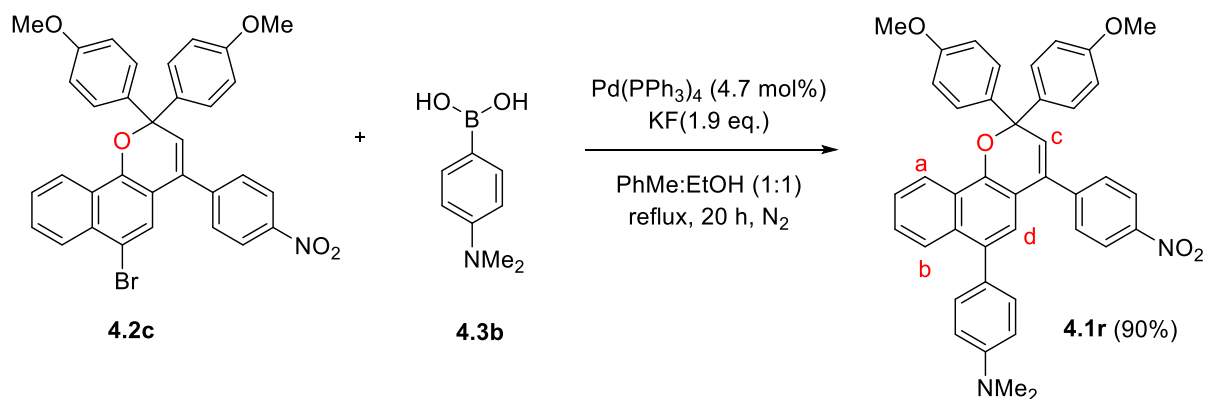


Figure 4.5b: ^{13}C NMR spectrum of 2,2,4,6-tetraryl substituted 2*H*-naphtho[1,2-*b*]pyran **4.1q**

Based on the same methods employed for the previously obtained naphthopyrans **4.1a-p**, the cross-coupling reaction between 6-bromo naphthopyran **4.2c**, which was symmetrically substituted at C-2, and 4-dimethylaminophenylboronic acid **4.3b** gave **4.1r** in an excellent 90 % yield.



Scheme 4.19: The coupling of 6-bromo naphthopyran **4.2c** with 4-dimethylaminophenylboronic acid **4.3b** to obtain a 2,2,4,6-tetraaryl substituted naphthopyrans **4.1r**

The ^1H NMR spectrum of **4.1r** revealed the singlet at 6.20 ppm for 3-H (**c**) and 6.95 ppm for 5-H (**d**). The most deshielded aromatic signal corresponded to 10-H (**a**) which resonated at ca. 8.5 ppm and the signal for 7-H (**b**) appeared upfield at ca. 7.9 ppm (Figure 4.6a). The symmetrical substitution at C-2 resulted in a singlet at 3.77 ppm accounting for the equivalent OMe protons whilst the NMe_2 protons resonated at 2.97 ppm. The ^{13}C NMR spectrum confirmed the C-2 carbon atom by the appearance of the signal at 83.0 ppm (Figure 4.6b). The mass spectral analysis exhibited a molecular ion m/z 635.2542 $[\text{M}+\text{H}]^+$ for $\text{C}_{41}\text{H}_{34}\text{N}_2\text{O}_5$ which was in good agreement with the corresponding calculated mass $[\text{M}+\text{H}]^+$ of 635.2546.

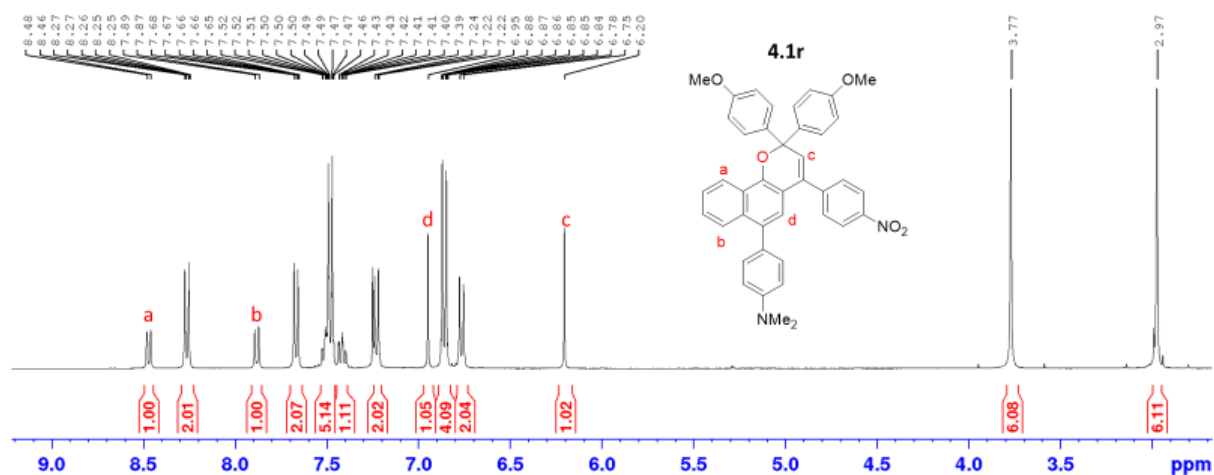


Figure 4.6a: ¹H NMR spectrum of 2,2,4,6-tetraryl substituted 2*H*-naphtho[1,2-*b*]pyran **4.1r**

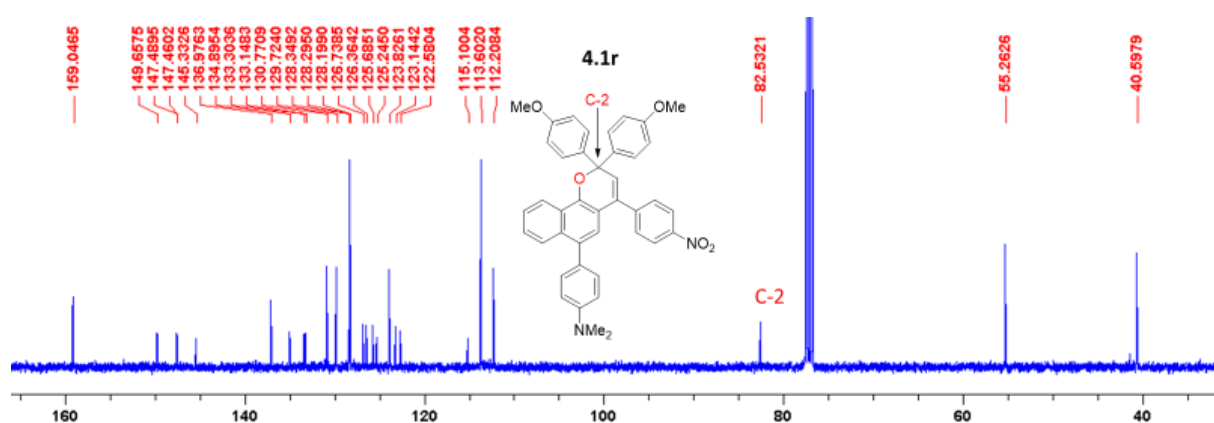
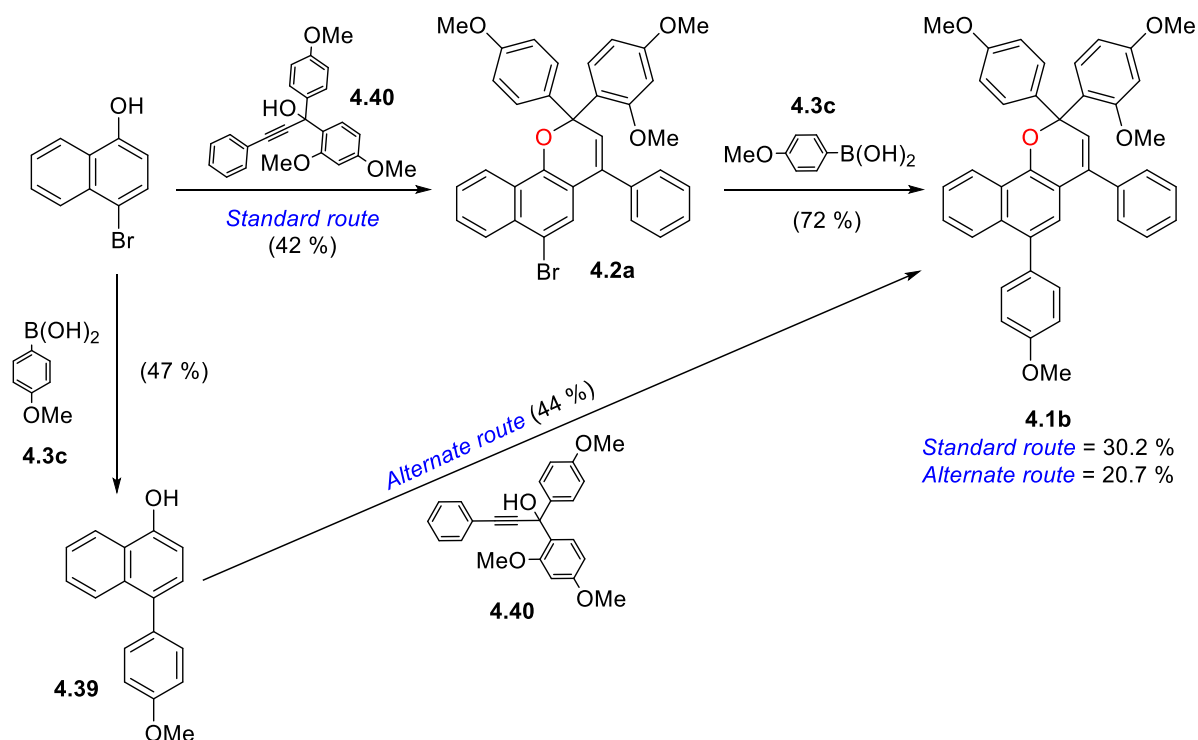


Figure 4.6b: ¹³C NMR spectrum of 2,2,4,6-tetraryl substituted 2*H*-naphtho[1,2-*b*]pyran **4.1r**

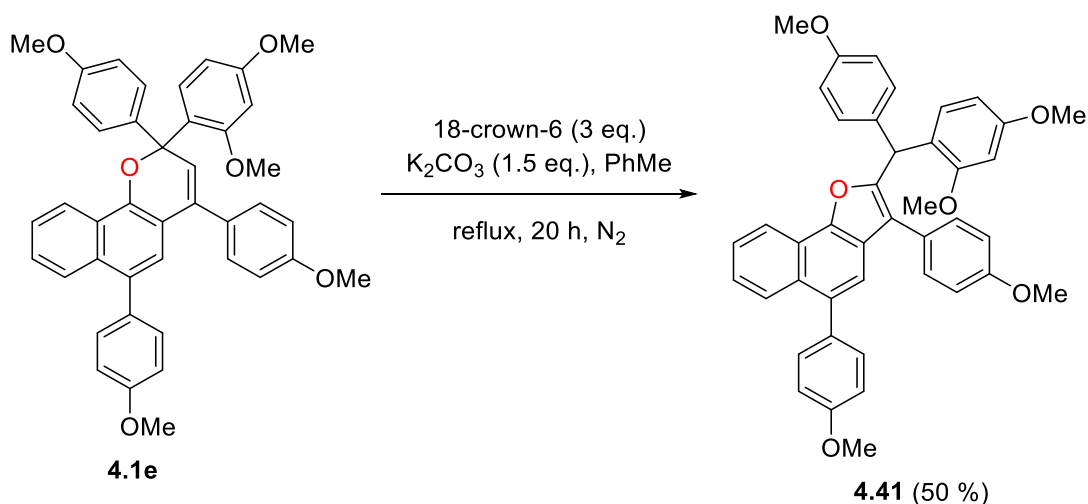
With the series of 2,2,4,6-tetraaryl naphthopyrans **4.1a-p** obtained by the Suzuki-Miyaura strategy it was possible to compare the efficiency of this late-stage cross-coupling route for **4.1b** (replacement of the 6-Br group in the naphthopyran) with the example of the early-stage introduction of the aryl group at C-4 in the 1-naphthol precursor (Chapter 3.2) (Scheme 4.20). From this scheme it is evident that the late-stage introduction of the 6-aryl ring by Suzuki-Miyaura cross-coupling (Standard route) was more efficient than modifying the 1-naphthol and then performing the chromenization reaction (Alternate route).



Scheme 4.20: Proposed routes to 2,2,4,6-tetraryl substituted 2*H*-naphtho[1,2-*b*]pyran **4.1b**

4.2 Naphthopyran ring-contraction

It was of interest to examine whether the previously described <2020JOC952> (Scheme 4.14) conditions of base-catalysis, K_2CO_3 in the presence of 18-crown-6, would affect the ring contraction of the tetraarylnaphthopyran **4.1e**. Thus, employing the aforementioned reagents in refluxing PhMe resulted in the smooth formation of naphthofuran **4.41** in a moderate 50 % yield after trituration of the crude product with *n*-pentane.



Scheme 4.21: Naphthopyran ring contraction

^{13}C NMR spectroscopy (Figure 4.7b) proved the formation of **4.41** by the absence of the C-2 signal which typically resonated at ca. 82 ppm for each of the naphthopyrans **4.1a-r** and the appearance of a new signal at ca. 40 ppm that related to the α -C atom (c). The ^1H NMR spectrum supported the ring contracted structure by the presence of a singlet at 6.13 ppm which is assigned to the methine proton and compares favourably with the signals for the methine protons in a series of naphthofurans. <2020JOC952> The absence of the signal for 3-H (of **4.1e** at ca. 7.15 ppm) was also noteworthy as was the slight, ca. 0.1 ppm, upfield shift of 9-H (Figure 4.7a).

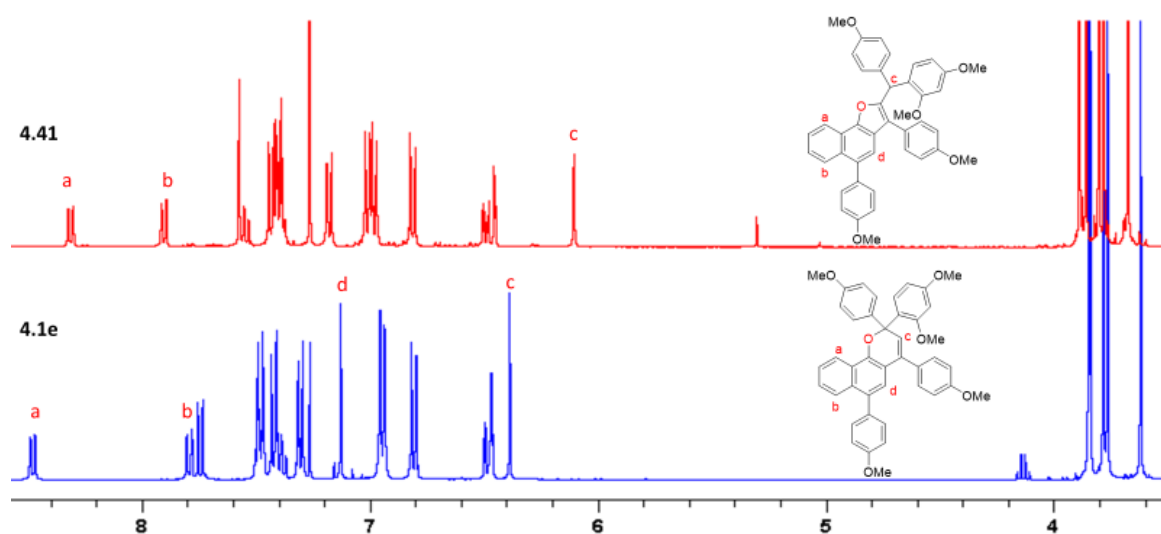


Figure 4.7a: ^1H NMR spectra of 2H-naphtho[1,2-b]furan **4.41** and 2H-naphtho[1,2-b]pyran **4.1e**

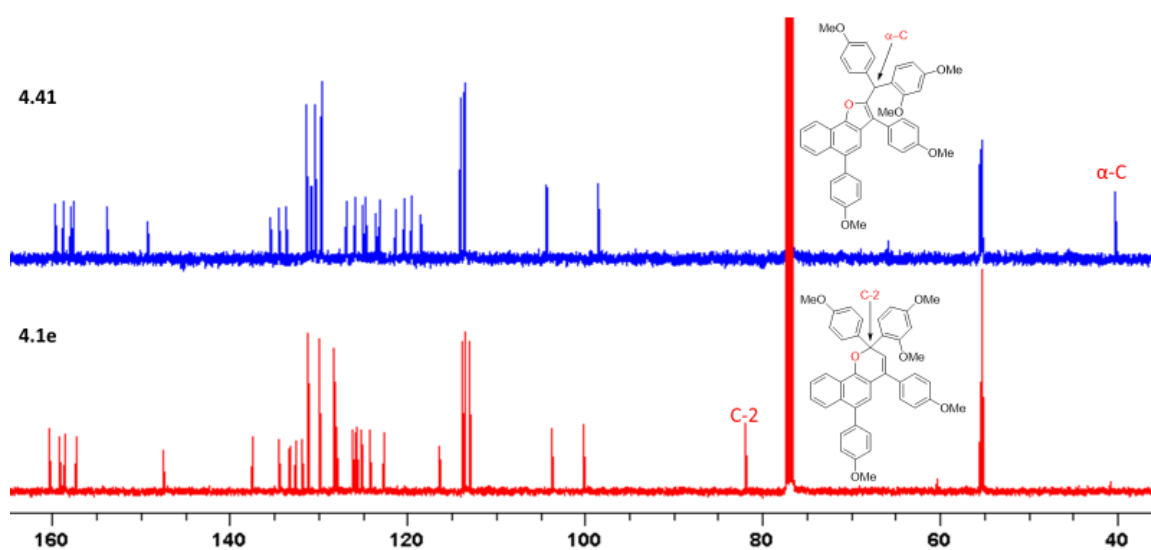
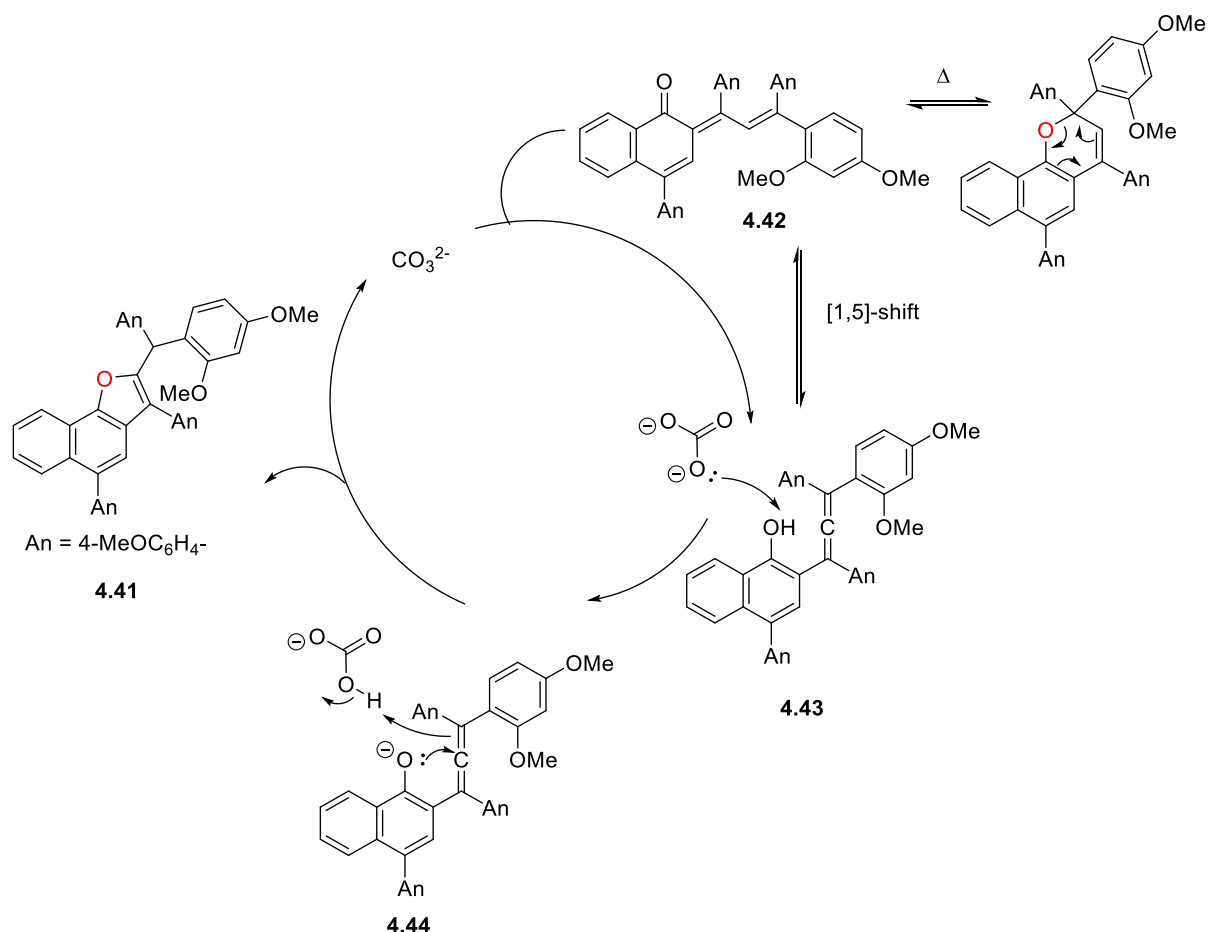


Figure 4.7b: ^{13}C NMR spectra of 2H-naphtho[1,2-b]furan **4.41** and 2H-naphtho[1,2-b]pyran **4.1e**

The proposed mechanism for the ring-contraction is outlined in Scheme 4.22. Thermal ring opening of the pyran induces the formation of dienone **4.42** that then proceeds via the subsequent 1,5-sigmatropic-H shift affording allenynaphthol **4.43**. In the next step, carbonate anion abstracts the proton from the hydroxyl unit and generates negative charge on oxygen atom. In the final step, the cyclisation of **4.44** leads to the formation of naphthofuran **4.41**. <2020JOC952>



Scheme 4.22: The proposed mechanism for the ring-contraction

With the series of 2,2,4,6-tetraaryl substituted naphthopyrans to hand their photochromic response was evaluated (Chapter 5.0).

Chapter 5.0 Photochromic properties of substituted 2*H*-naphtho[1,2-*b*]pyrans

5.1 Introductory remarks

This chapter concerns the examination of the photochromic properties of 2,2,4,6-tetraaryl- and 2,2,4-triaryl-6-methoxy- 2*H*-naphtho[1,2-*b*]pyrans that were synthesised in chapters 3 and 4. For ease of comparison, the structures of the synthesised naphthopyrans have been renumbered in this chapter and each structure number is of the style **5.1x** e.g. **5.1a**, **5.1b** etc...

The optimal combination of photochromic properties for variable optical transmission devices, such as sun lenses, is the rapid (sub-second) intense colour generation [i.e. low transmittance (%) in the visible region] from a colourless inactivated state with a reasonably rapid rate of fade, often termed bleaching, (of the order of tens of seconds) of the coloured form at ambient temperature with temperature independence. It is also important that the compound exhibits good fatigue resistance; the ring-opening – ring-closing cycle must be repeatable many, many times ($> 10^6$) without loss of performance.

Background discussion on the photochemical ring-opening and thermal ring-closing (photochromism) of the 2*H*-naphtho[1,2-*b*]pyran isomer is provided in the introduction to this thesis (Chapter 1.5) and information of the irradiation system – spectrophotometer which was used to acquire the bleached and coloured spectra of the naphthopyrans prepared in this work is presented in the experimental instrumentation section (Chapter 6.1).

5.2 Photochromism of 2,2,4,6-tetraaryl substituted 2*H*-naphtho[1,2-*b*]pyrans

Ultraviolet (UV)-irradiation of the 2,2,4,6-tetraaryl naphthopyrans can lead to a variety of ring-opened structures, termed photomerocyanines. However, as a consequence of the highly substituted naphthopyran structure there are predictably, significant steric interactions in the photomerocyanines such that the generation of some of the potential structures is highly unlikely; the most probable, least sterically hindered photomerocyanines are depicted in Figure 5.1. The *primary* chromophore of the photomerocyanines is highlighted in blue and possess electron rich mono- and di- methoxy substituted aryl units (located on C-2 in the pyran system) and a carbonyl acceptor (formerly the ether O-atom of the pyran ring). A *secondary* 1,4-diarylbutadiene chromophore is highlighted in red and the

donor-acceptor nature is dependent upon the terminal aryl ring substituents X and Y. The C=C bond common to both primary and secondary chromophores is indicated in purple.

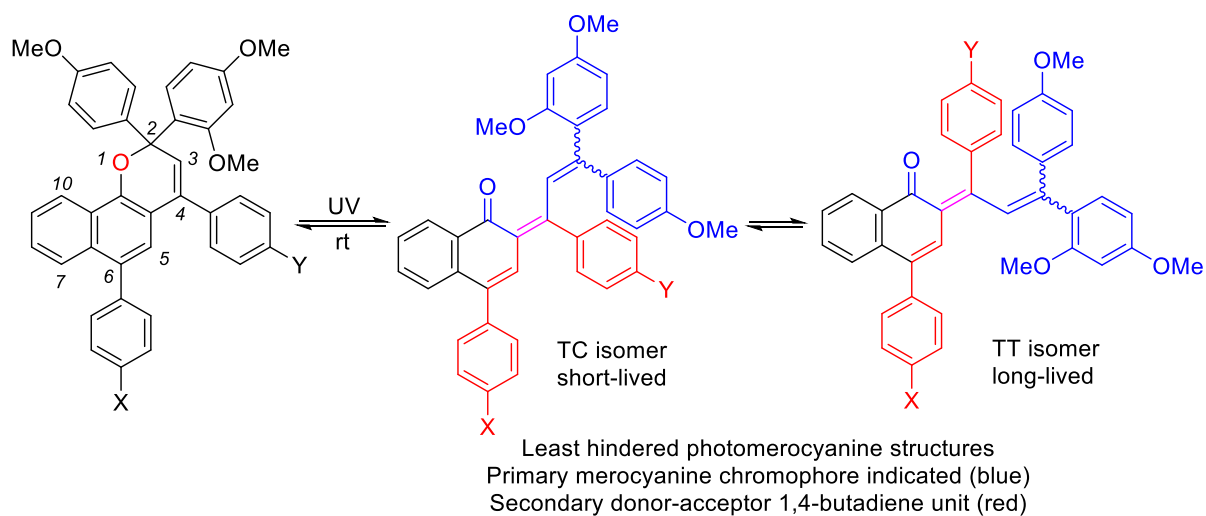


Figure 5.1: Proposed UV-irradiation of a naphthopyran leading to a photogenerated crossed-chromophore system.

The series of naphthopyrans **5.1a-c** in which the 6-aryl group is varied with the 4-aryl substituent remaining constant as an unsubstituted phenyl ring was first examined (Figure 5.2).

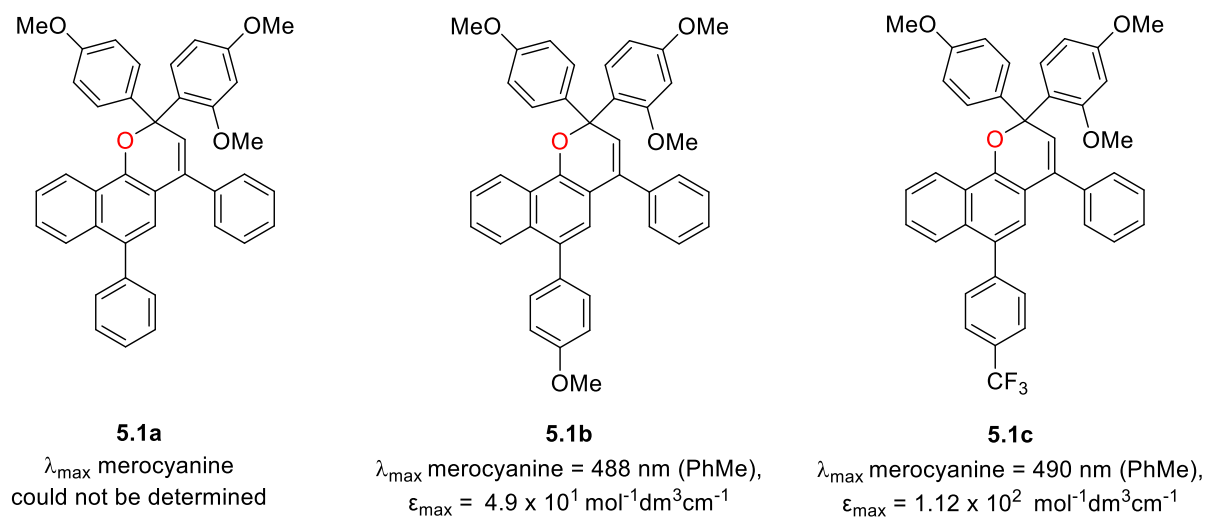


Figure 5.2: Naphthopyrans **5.1a-c** possessing a constant 4-phenyl moiety

Preliminary visual evaluation of the initial colourless solutions of **5.1a-c** in toluene revealed the momentary generation of a weak pink hue for solution **5.1b** and **c** when irradiated with a

LED portable UV flashlight detection light (Weltool M2-BF, λ_{max} 365 nm), however the solution of **5.1a** remained essentially colourless. The photomerocyanines thus generated faded almost instantaneously upon cessation of the UV irradiation (Figure 5.3).

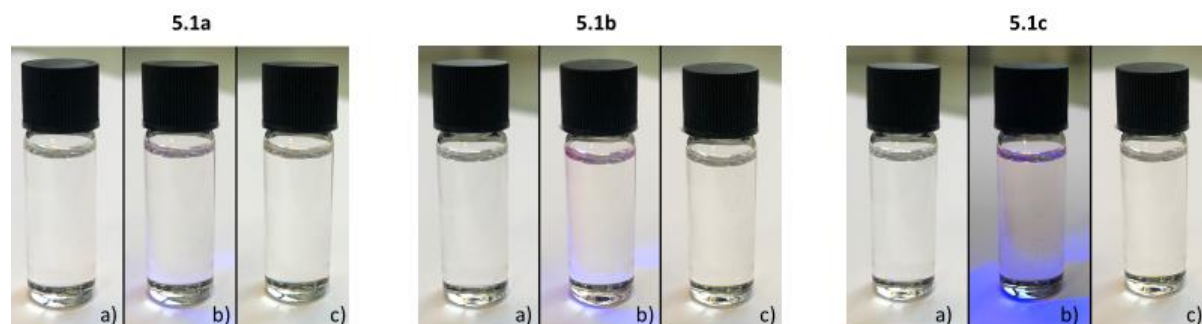


Figure 5.3: Solutions of **5.1a-c** in toluene (ca. 1.5 mM); a) before UV-irradiation, b) under continuous UV-irradiation (λ_{max} 365 nm) and c) immediately after the UV-irradiation ceased

Irradiation of a toluene solution (ca. 0.87 mM) of **5.1a** to a photostationary / steady state (5 mins irradiation) using a bespoke irradiation spectrophotometer system (Oriel 300 W xenon arc lamp source set at 150 W with irradiation delivery via a liquid light guide) (See Chapter 6.1 for more details) resulted in no discernible absorption maximum when the spectrum was acquired immediately upon cessation of the UV-irradiation (Figure 5.4). Introduction of an electron-donating methoxy group at the *para*-position of the 6-aryl ring (**5.1b**) afforded a weak pink hue with $\lambda_{\text{max}} = 488$ nm (PhMe solution ca. 1.22 mM, 55 mins irradiation;) whereas the presence of an electron-withdrawing CF_3 group (**5.1c**) gave $\lambda_{\text{max}} = 490$ nm (PhMe solution ca. 1.16 mM, 88 mins irradiation). As a consequence of the transient nature of the photomerocyanines it was not possible to determine the half-lives using our spectrophotometer system.

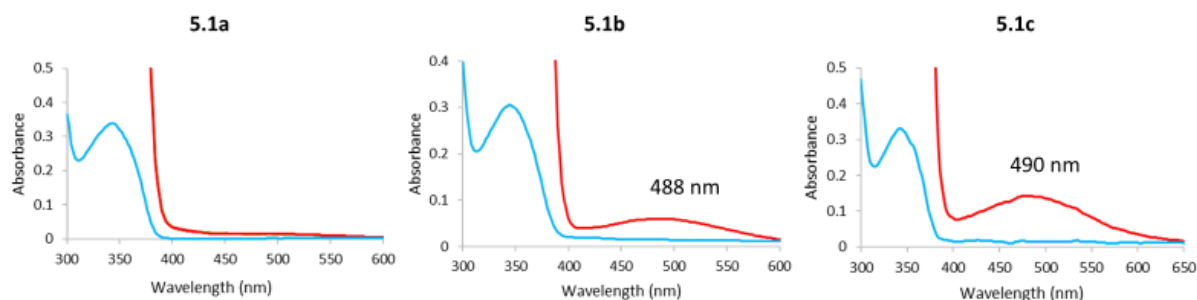


Figure 5.4: UV-Vis absorption spectra of the 2,2,4,6-tetraaryl-2*H*-naphtho[1,2-*b*]pyrans in aerated toluene in the closed form (blue) before UV-irradiation and in the photostationary / steady state (PSS; red) immediately after cessation of UV-irradiation: **5.1a** (blue [43.4 μ M]; red [0.87 mM]), **5.1b** (blue [61.0 μ M]; red [1.22 mM]) and **5.1c** (blue [58.2 μ M]; red [1.16 mM])

Comparison of the spectroscopic data for **5.1a**, **5.1b** and **5.1c** would suggest that generating a donor - acceptor butadiene unit within the photomerocyanine upon irradiation of the naphthopyran confers some marginal stability to the photomerocyanine such that absorbance maxima can be detected under steady state irradiation. For the purposes of a preliminary analysis and comparison of the photochromic properties it was thought useful to calculate the colourability for each sample that has a distinct λ_{max} (maximum wavelength of absorption at PSS) in its visible spectrum. In this work the term colourability relates to the pseudo molar extinction coefficient (ϵ_{max} , $\text{mol}^{-1}\text{dm}^3\text{cm}^{-1}$) of the photogenerated isomer measured at its wavelength of maximum absorption (λ_{max} , nm) under the very specific applied irradiation conditions. It should be pointed out that this simplified preliminary analysis does not account for such factors as the varying quantum yield of the photocoloration process and the fading kinetics but of course remains instructive for comparative purposes within a series of structurally similar compounds. Thus, the data obtained from the UV-Vis absorption spectra of the irradiated naphthopyrans were employed in the Beer Lambert Law as shown below:

$$A = \epsilon_{\text{max}} \times c \times l$$

The pathlength of the cuvette (l) was 1 cm and the values for absorption (A) and concentration (c) of the solution were reported then rearrangement of the equation to calculate the molar extinction coefficient was necessary:

$$\epsilon_{max} = \frac{A}{c \times l}$$

This allowed the easy comparison of the intensity of colour generation for each photomerocyanine immediately after cessation of irradiation to its PSS. Thus, using the absorbance data obtained for **5.1b** and **5.1c**, the colourability of the photomerocyanines were calculated as $4.9 \times 10^1 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$ and $1.12 \times 10^2 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$, respectively that suggested an overall exceptionally weak persistence of shade formed. Curiously, a hyperchromic shift (an increase in intensity of an absorption band) was noted for the photomerocyanines derived from naphthopyran **5.1c** which possesses an electron-withdrawing 6-(*para*-CF₃C₆H₄-) unit over the photomerocyanines from naphthopyran **5.1b** with electron-donating 6-(*para*-MeOC₆H₄-) moiety.

Another set of naphthopyrans **5.1d-f** wherein the 4-aryl substituent is fixed as a 4-methoxyphenyl moiety and the 6-aryl substituent is varied were next examined (Figure 5.5)

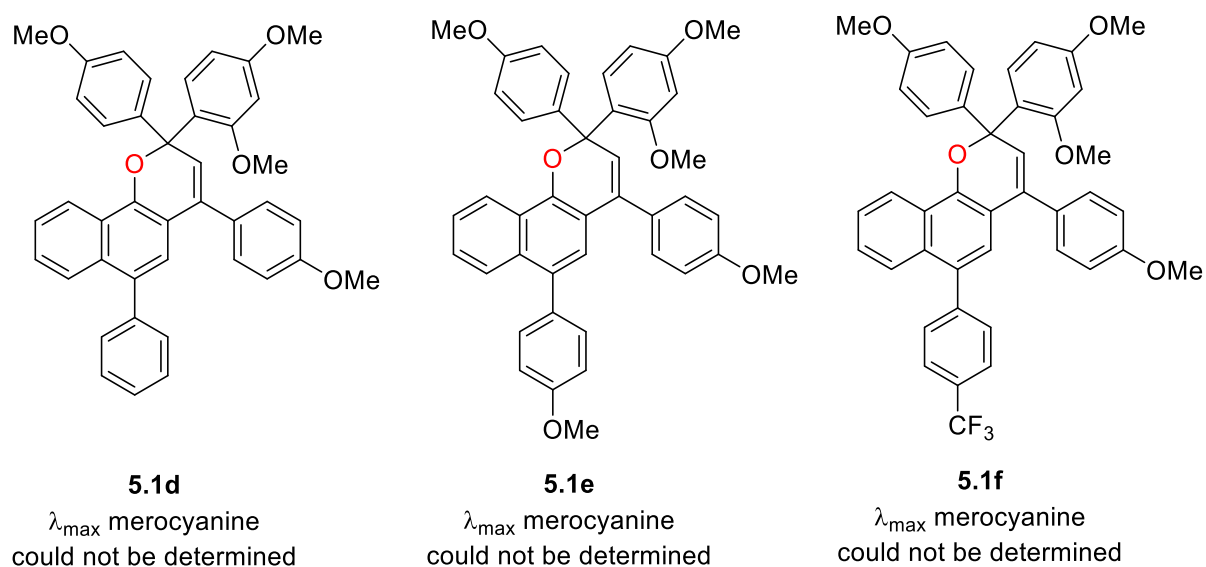


Figure 5.5: Naphthopyrans **5.1d-f** with a fixed 4-(*para*-MeOC₆H₄-) moiety

Visual evaluation of initially colourless PhMe solutions of the series **5.1d-f** revealed no discernible hue when irradiated with a UV-light (Weltool M2-BF, λ_{max} 365 nm), (Figure 5.6).

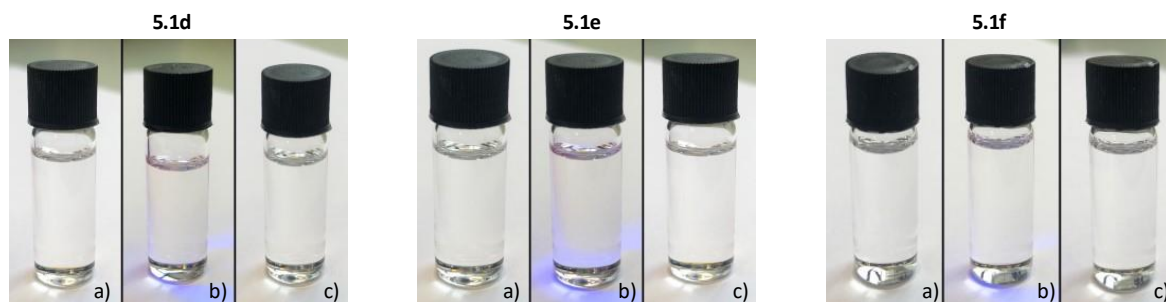


Figure 5.6: Solutions of **5.1d-f** in toluene (ca. 1.0 mM) a) before UV-irradiation, b) under continuous UV-irradiation (λ_{max} 365 nm) and c) immediately after the UV-irradiation ceased

Attempts to measure λ_{max} for PhMe solutions of **5.1d-f** using our irradiation / spectrophotometer system were unsuccessful as a consequence of the lack of persistence of the photomerocyanines (Figure 5.7). The absence of discernible colour development is suggestive that an electron-donating 4-methoxyphenyl ring at the 4-position is detrimental to the stability of the photomerocyanine irrespective of the establishment of any donor-acceptor arrangement of the secondary chromophore.

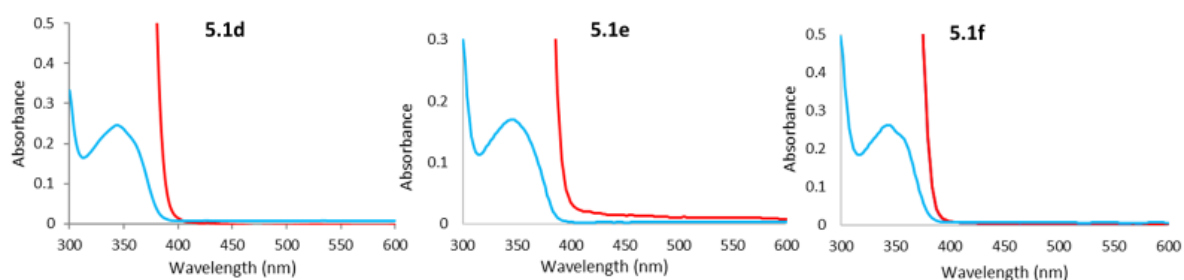
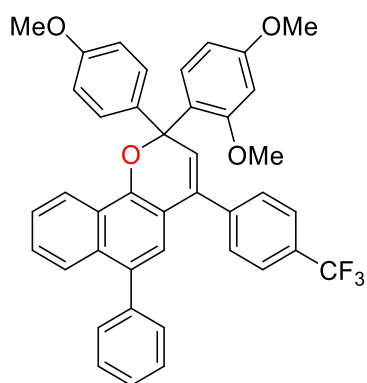


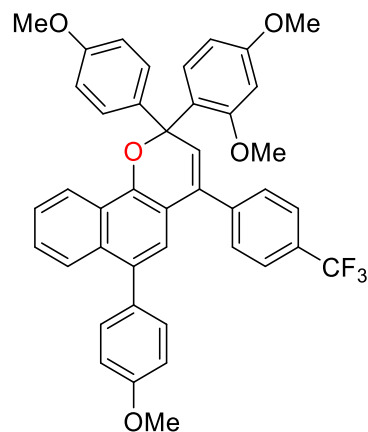
Figure 5.7: UV-Vis absorption spectra of the 2,2,4,6-tetraaryl-2*H*-naphtho[1,2-*b*]pyrans in aerated toluene in the closed form (blue) before UV-irradiation and immediately after cessation of UV-irradiation (red): **5.1d** (blue [55.0 μM]; red [1.10 mM]), **5.1e** (blue [39.3 μM]; red [0.79 mM]) and **5.1f** (blue [51.9 μM]; red [0.52 mM])

The next series of naphthopyrans to be investigated concerned molecules in which the 4- (*para*-MeOC₆H₄-) of unit **5.1d-f** had been replaced with an electron-withdrawing 4- (*para*-CF₃C₆H₄-) moiety leading to the series **5.1g-j** (Figure 5.8).



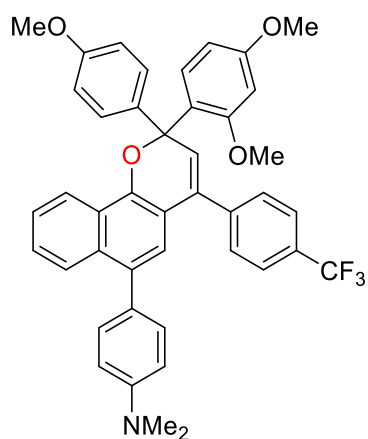
5.1g

λ_{max} merocyanine = 486 nm (PhMe),
 $\epsilon_{\text{max}} = 1.76 \times 10^2 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$,



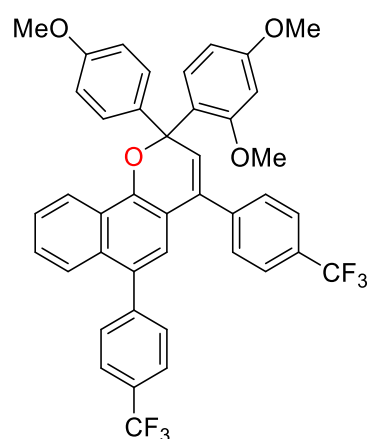
5.1h

λ_{max} merocyanine = 502 nm (PhMe),
 $\epsilon_{\text{max}} = 1.87 \times 10^2 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$,



5.1i

λ_{max} merocyanine = 510 nm (PhMe),
 $\epsilon_{\text{max}} = 8.8 \times 10^1 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$,



5.1j

λ_{max} merocyanine = 492 nm (PhMe),
 $\epsilon_{\text{max}} = 1.06 \times 10^2 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$,

Figure 5.8: A series of naphthopyrans **5.1g-j** with 4-(*para*-CF₃C₆H₄-) moiety

Visual examination of PhMe solutions of each of the foregoing compounds **5.1g-j** revealed a weak pink hue for **5.1g,h** and **5.1j**, and a scarcely discernible weak pink hue for **5.1i** when irradiated with a UV-light (Weltool M2-BF, λ_{max} 365 nm) which then faded rapidly when UV-irradiation was terminated (Figure 5.9). Once again, the initial solutions were completely colourless.

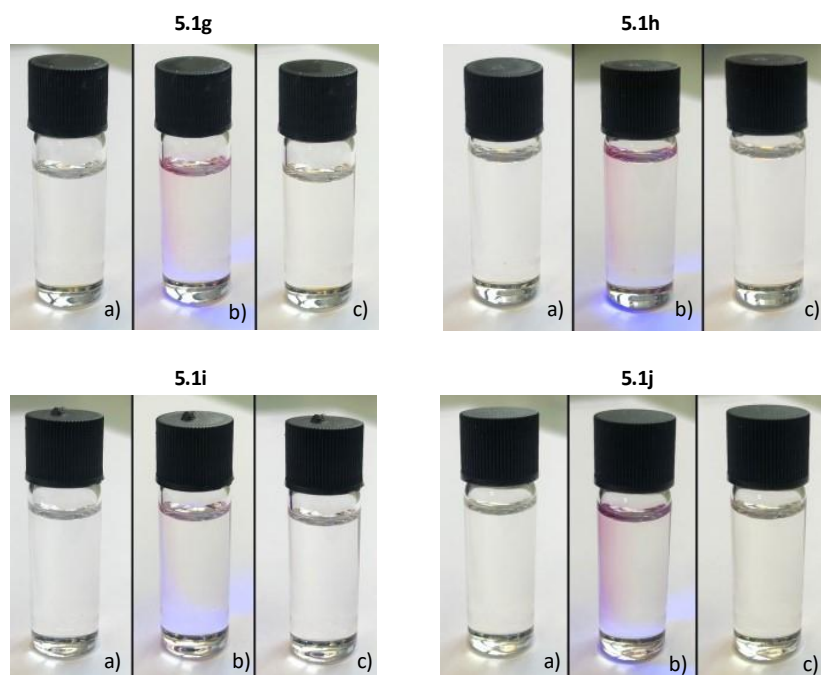


Figure 5.9: Solutions of **5.1g-j** in toluene (ca. 1.0 mM) a) before UV-irradiation, b) under continuous UV-irradiation (λ_{max} 365 nm) and c) immediately after the UV-irradiation ceased

When the UV-visible absorption spectra of PhMe solutions of **5.1g-j** were recorded (Figure 5.10) the following λ_{max} values were determined: **5.1g** 486 nm (ca. 0.98 mM, 65 mins irradiation), **5.1h** 502 nm (ca. 0.64 mM, 40 mins irradiation), **5.1i** 510 nm (ca. 0.86 mM, 28 mins irradiation) and **5.1j** 492 nm (ca. 0.81 mM, 14 mins irradiation), though once again the rapid fading of the photomerocyanine was such that a half-life could not be reliably determined for each example using our irradiation system. It is noteworthy that the combination of an electron-withdrawing (*para*-CF₃C₆H₄-) unit at C-4 with a strong electron-donating (*para*-Me₂NC₆H₄-) unit at C-6 in **5.1i** induced a bathochromic shift in λ_{max} of 24 nm over **5.1g**. The most hypsochromically shifted λ_{max} value is noted for the photomerocyanines from 6-phenyl substituted naphthopyran **5.1g**.

It is clear from the foregoing absorption data for this series that an electron-withdrawing (*para*-CF₃C₆H₄-) unit at C-4 of the pyran ring is beneficial to the stability of the photomerocyanine. Thus, according to the generally fairly weak colourability for the toluene samples **5.1g-j**; the best colourability was recorded for **5.1h** with value of $1.87 \times 10^2 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$ however, the weakest colour and most hypochromic shift was reported for naphthopyran **5.1i** with value of $8.8 \times 10^1 \text{ mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$. The colourability of **5.1j** and **5.1g** fell

between the values calculated for **5.1i** and **5.1h** and were $1.06 \times 10^2 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$ and $1.76 \times 10^2 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$, respectively. Moreover, the largest hyperchromic shift was observed for compound **5.1h** despite the smallest concentration used.

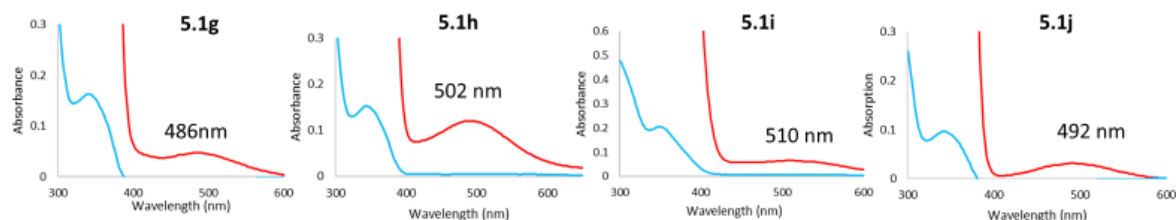
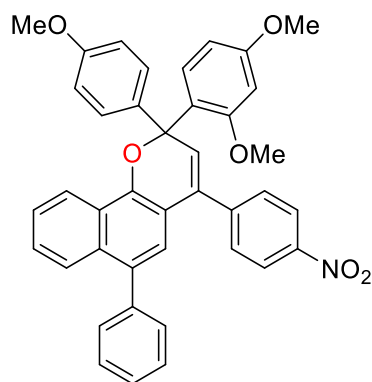


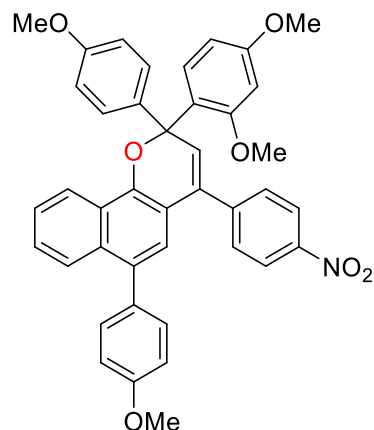
Figure 5.10: UV-Vis absorption spectra of the 2,2,4,6-tetraaryl-2*H*-naphtho[1,2-*b*]pyrans in aerated toluene in the closed form (blue) before UV-irradiation and in the photostationary / steady state (PSS; red) immediately after cessation of UV-irradiation: **5.1g** (blue [48.9 μM]; red [0.98 mM]), **5.1h** (blue [31.9 μM]; red [0.64 mM]), **5.1i** (blue [40.7 μM]; red [0.86 mM]) and **5.1j** (blue [42.9 μM]; red [0.81 mM])

Considering the best colourability for compound **5.1h** and most bathochromically shifted maximum for **5.1i**, a series of naphthopyrans with a fixed, strongly electron withdrawing, 4- (*para*-nitrophenyl) moiety **5.1k-n** was next investigated (Figure 5.11).



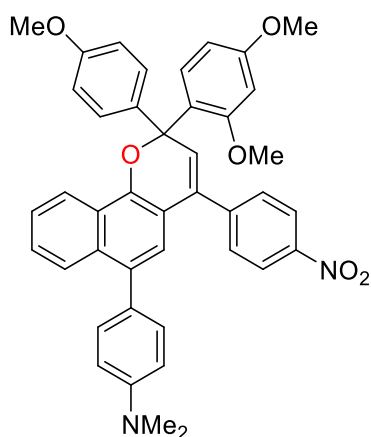
5.1k

$\lambda_{\max}$ merocyanine = 496 nm (PhMe),
 $\epsilon_{\max} = 1.06 \times 10^4 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$,
 $t_{1/2} = 1868 \text{ s}$



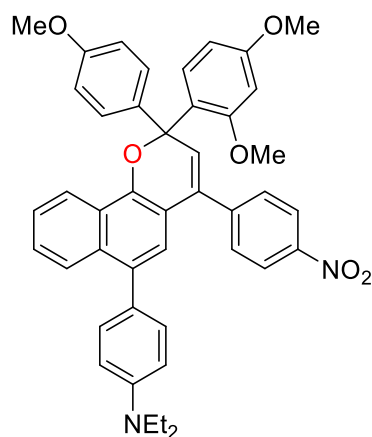
5.1l

$\lambda_{\max}$ merocyanine = 502 nm (PhMe),
 $\epsilon_{\max} = 1.04 \times 10^4 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$,
 $t_{1/2} = 1025 \text{ s}$



5.1m

$\lambda_{\max}$ merocyanine = 450 and 522 nm (PhMe),
 $\epsilon_{\max} = 7.77 \times 10^3 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$,
 $t_{1/2} = 546 \text{ s}$



5.1n

$\lambda_{\max}$ merocyanine = 448 and 538 nm (PhMe),
 $\epsilon_{\max} = 4.74 \times 10^3 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$,
 $t_{1/2} = 415 \text{ s}$

Figure 5.11: A series of naphthopyrans **5.1k-n** with 4-(*para*-NO₂C₆H₄-) moiety

Visual examination of the irradiated PhMe solutions of each of the compounds **5.1k-n** showed a distinct intense red / cherry-red / red-purple hue which persist for a relatively long time when UV-irradiation (Weltool M2-BF, $\lambda_{\max}$ 365 nm) was stopped (Figure 5.12). The initial solutions of **5.1k-n** all possessed a very pale-yellow hue.

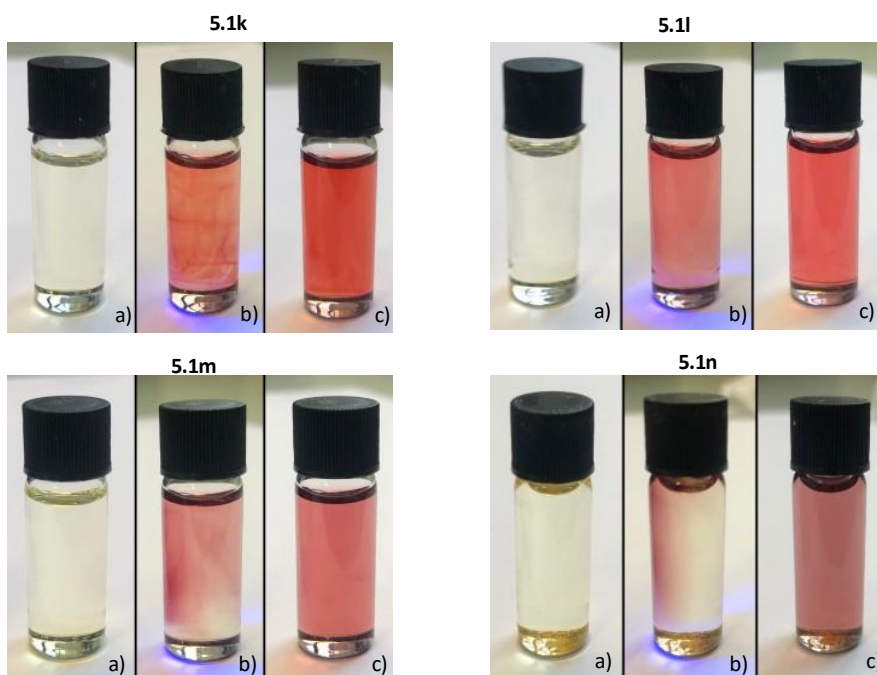


Figure 5.12: Solutions of **5.1k-n** in toluene (ca. 0.5 mM); a) before UV-irradiation, b) under continuous UV-irradiation (λ_{max} 365 nm) and c) immediately after the UV-irradiation ceased

The UV-visible absorption spectra of foregoing PhMe solutions of **5.1k-n** enabled the determination of the following λ_{max} values; **5.1k** 496 nm (ca. 0.32 mM, 4 mins irradiation), **5.1l** 502 nm (ca. 0.07 mM, 10 mins irradiation), **5.1m** 450 and 522 nm (ca. 0.09 mM, 20 mins irradiation) and **5.1n** 448 and 538 nm (ca. 0.13 mM, 8 mins irradiation), (Figure 5.13). Of particular interest was the appearance of absorption bands for **5.1m** and for **5.1n**, which is possibly due to the interaction of the strong electron-donating dialkylamino unit. Indeed, the shorter wavelength band / shoulder may arise from the conjugation between the $\text{R}_2\text{NC}_6\text{H}_4$ - unit at C-6 and the nitrophenyl moiety i.e. the secondary chromophore. Computational chemistry studies may reveal the true origins of these absorption spectra, but such studies are outside the scope of this current 1-year investigation. The attachment of the weaker electron-donor (4-MeOC₆H₄-) unit at C-6 in **5.1l** induced a small bathochromic shift in λ_{max} of 6 nm relative to the absorption maxima of **5.1k** whereas the presence of a stronger (4-Me₂NC₆H₄-) unit gave a significantly greater bathochromic shift in λ_{max} of 26 nm. The enhanced electron donating Et₂NC₆H₄- moiety in **5.1n** resulted in the greatest bathochromic shift in λ_{max} of 42 nm relatively to **5.1k**.

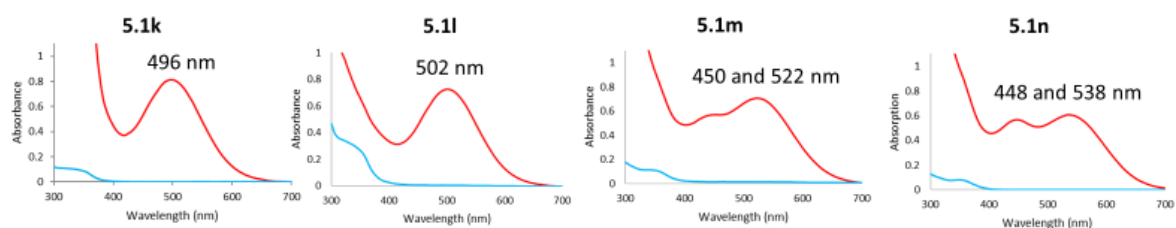


Figure 5.13: UV-Vis absorption spectra of the 2,2,4,6-tetraaryl-2*H*-naphtho[1,2-*b*]pyrans in aerated toluene in the closed form (blue) before UV-irradiation and in the photostationary / steady state (PSS; red) immediately after cessation of UV-irradiation: **5.1k** (blue [1.58 μ M]; red [0.32 mM]), **5.1l** (blue [17.6 μ M]; red [0.07 mM]), **5.1m** (blue [9.03 μ M]; red [0.09 mM]) and **5.1n** (blue [12.7 μ M]; red [0.13 mM])

It is clear from the foregoing absorption data for the series **5.1k-n** that a strong electron-withdrawing (4-NO₂C₆H₄-) unit at C-4 of the pyran ring is key to the stability and hence persistence of the photomerocyanine and their colourability increased hugely compared to the previously described naphthopyrans **5.1g-j**. The greatest colourability and most intense red hue was obtained for naphthopyran **5.1k** with a phenyl ring at C-6 giving a value of $1.06 \times 10^4 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$ whereas the naphthopyran **5.1l** with 4-methoxyphenyl ring at C-6 showed cherry-red hue with slightly reduced colourability of $1.04 \times 10^4 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$. Furthermore, it was found that the colourability decreased when a strong electron-donor group (R₂NC₆H₄-) was placed at C-6 leading to **5.1m** and **5.1n**. The largest hypochromic shift was reported for naphthopyran **5.1n** possessing 6-(*para*-Et₂NC₆H₄-) moiety with colourability of $4.74 \times 10^3 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$. A very similar hue was observed for naphthopyran **5.1m** with the 6-(*para*-Me₂NC₆H₄-) moiety however, the colourability was slightly hyperchromically shifted relatively to the **5.1n** giving the value of $7.77 \times 10^3 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$. It should be noted that whilst the colourability is diminished slightly for **5.1m,n** relative to **5.1k,l** the colourability remains significantly larger than that for **5.1a-j**.

The persistence of the photomerocyanines for **5.1k-n** enabled the determination of the thermal bleaching rate constants (k_{Δ}) and half-life ($t_{1/2} = s$) for each example. Thus, the decay of the photomerocyanines followed a mono-exponential fit with rate constants of the order of $3.71 \times 10^{-4} \text{ s}^{-1}$ for **5.1k**, $6.76 \times 10^{-4} \text{ s}^{-1}$ for **5.1l**, $1.27 \times 10^{-3} \text{ s}^{-1}$ for **5.1m** and $1.67 \times 10^{-3} \text{ s}^{-1}$ for **5.1n** confirmed that the photomerocyanines **5.1m** and **5.1n** were faster to fade (Figure 5.14).

Moreover, the half-life for each photomerocyanines was calculated: **5.1k** ca. 1868 s, **5.1l** ca. 1025 s, **5.1m** of ca. 546 s and **5.1n** of ca. 415 s, which further confirmed that the photomerocyanines **5.1m** and **5.1n** faded much faster. It should be noted that whilst the correlation coefficients are very good ($R^2 = 0.9817 - 0.9989$) for the mono-exponential fit for the series **5.1k – n** there is some slight deviation which is perhaps suggestive of the formation of a second photoisomer which possesses slightly different fading properties (see discussion in Section 1.5). A more detailed and extensive analysis of the present spectrokinetic data, perhaps recorded over a range of solution temperatures would be useful to establish such a feature.

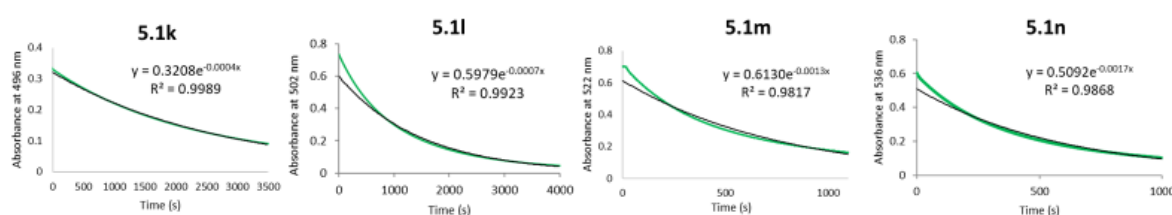


Figure 5.14: Bleaching of the PSS of **5.1k-n** in aerated PhMe after UV irradiation presented as mono-exponential fit of absorbance versus time (s); **5.1k** (ca. 0.03 mM), **5.1l** (ca. 0.07 mM), **5.1m** (ca. 0.09 mM) and **5.1n** (ca. 0.13 mM mM)

Given the good photochromic response of the naphthopyrans **5.1k-n** it was prudent to make a very preliminary evaluation of their reversibility without loss of performance (a measure of their fatigue resistance). Thus, toluene solutions of **5.1k-n** were subjected to repeated cycles of continuous irradiation for ca. 50 min with Oriel 300 W xenon arc lamp source (set at 150 W). The plots illustrated in Figure 5.15 represent each sample being irradiated with UV-light (λ_{max} 325 nm, filter UG11) to the point where PSS (photostationary / steady state) was reached and then subsequently thermal bleaching occurred which was affected by continued irradiation with visible light (λ_{max} 455 nm, filter GG455) to obtain the initial form of photochrome that required to be re-irradiated with UV-light then followed by thermal bleaching and so on. From the plots illustrated below, it can be seen that each photochrome **5.1k-n** cycled three times without any apparent deterioration (Figure 5.15) which was sufficient to illustrate their reversibility.

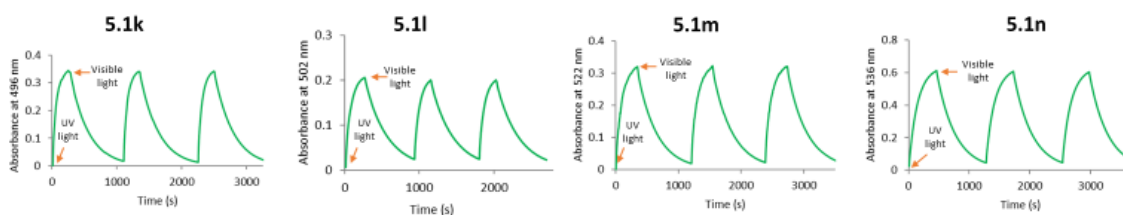


Figure 5.15: Fatigue resistance plots of **5.1k** (0.03 mM), **5.1l** (0.05 mM), **5.1m** (0.03 mM) and **5.1n** (0.13 mM) for reaching PSS and bleaching out using suitable UV irradiation filters

As a consequence of the performance of the 4-(*para*-nitrophenyl) substituted analogues **5.1k-n** some further examples of naphthopyrans with variation of an electron-withdrawing (NO_2 , CN) and electron-donating (NMe_2) groups on either 4- or 6- aryl rings have been investigated and are illustrated in Figure 5.16.

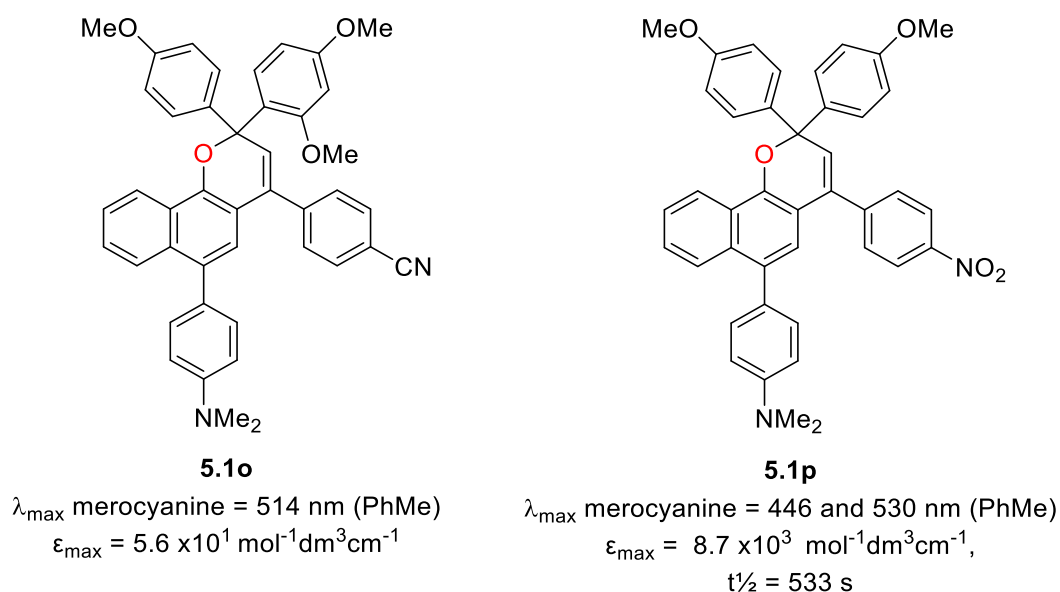


Figure 5.16: Naphthopyrans **5.1o,p** with electron-withdrawing aryl ring at C-4 and electron-donating aryl ring at C-6

Replacement of the NO_2 group of **5.1m** with a nitrile group to afford **5.1o** resulted in a weak purple hue upon irradiation with a UV-light (Weltool M2-BF, λ_{max} 365 nm) that faded rapidly after the irradiation was ceased. Removal of the sterically demanding *ortho*-methoxy group from **5.1m** gave **5.1p**. When the initial colourless solution of **5.1p** was irradiated with the UV-light (λ_{max} 365 nm), a significant pink hue was observed which persisted upon cessation of irradiation (Figure 5.17).



Figure 5.17: Solutions of **5.1o,p** in toluene (ca. 1.5 mM); a) before UV-irradiation, b) under continuous UV-irradiation (λ_{max} 365 nm) and c) immediately after the UV-irradiation ceased

The UV- visible absorption spectra of PhMe solutions of **5.1o** and **5.1p** afforded the following λ_{max} values: **5.1o** 514 nm (0.90 mM, 10 mins irradiation) and **5.1p** 446 and 530 nm (0.07 mM, 8 mins irradiation), (Figure 5.18). Whilst the half-life of **5.1o** could not be reliably determined, for the photomerocyanine of **5.1p** the half-life was ca. 533 s. The colourability of these two compounds was significantly different; a PhMe solution of **5.1o** exhibited poor colourability of $5.6 \times 10^1 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$, whereas a PhMe solution of **5.1p** displayed significant colourability of $8.7 \times 10^3 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$ which was comparable with the values determined for the related 4-(*para*-nitrophenyl) analogues. For the latter example **5.1p** the comparable colourability with that of **5.1m**, which possesses the additional *ortho*-methoxy group in the one of the C-2 aryl rings, ($8.7 \times 10^3 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$ versus $7.77 \times 10^3 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$) suggests that the presence of the donor-acceptor unit in the secondary chromophore has an important role in determining the stability and hence persistence (rate of fade) and colourability of the photomerocyanine. This new effect of the donor-acceptor system is of similar importance to the well-known influence of the location of an *ortho*-substituent on one of the C-2 *geminal* aryl rings which slows the rate of fade and enhances colourability. <1993WOP9310112; 2006FD85; 2003H(60)843>

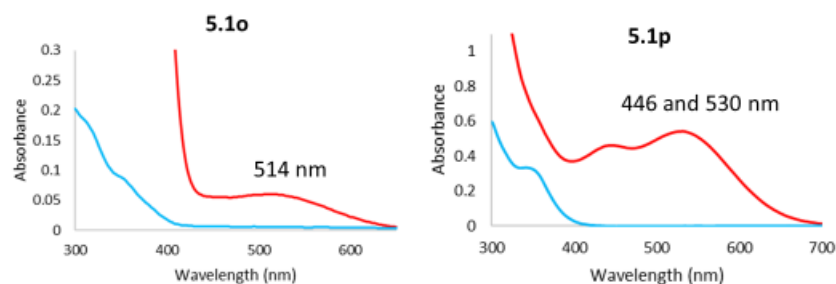


Figure 5.18: UV-Vis absorption spectra of the 2,2,4,6-tetraaryl-2*H*-naphtho[1,2-*b*]pyrans in aerated toluene in the closed form (blue) before UV-irradiation and in the photostationary / steady state (PSS; red) immediately after cessation of UV-irradiation: **5.1o** (blue [18.0 μ M]; red [0.90 mM]) and **5.1p** (blue [33.4 μ M]; red [0.07 mM])

Replacement of 2,4-dimethoxy unit at C-2 with a sterically demanding 4-methoxy-1-naphthyl moiety led to the formation of naphthopyran **5.1q** (Figure 5.19).

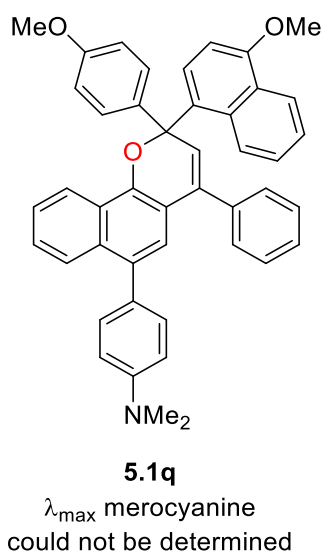


Figure 5.19: Naphthopyran **5.1q** with an extra steric bulk 4-methoxy-1-naphthyl moiety

Visual examination of the initial colourless solution of **5.1q** in toluene revealed faint creation of a pink hue upon irradiation with a UV light (Weltool M2-BF, λ_{max} 365 nm) that faded immediately when the light was ceased. Efforts to measure λ_{max} for PhMe solution of **5.1q** using our spectrophotometer system was unsuccessful (Figure 5.20).

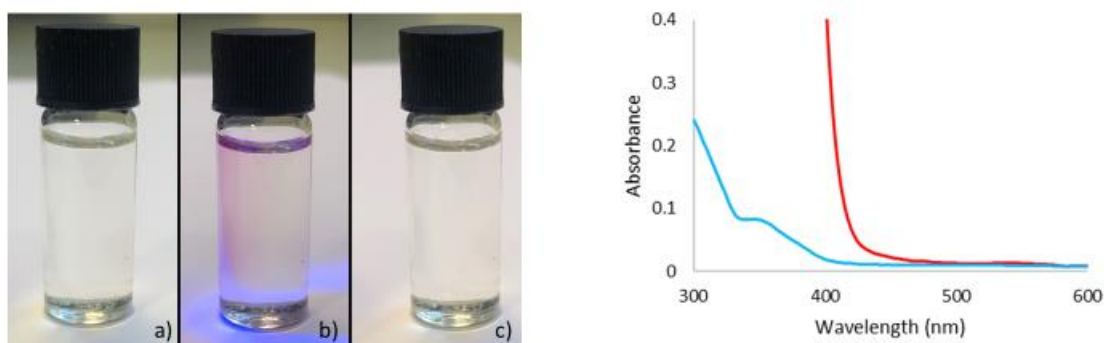


Figure 5.20: Solution of **5.1q** in toluene (ca. 0.80 mM); a) before UV-irradiation, b) under continuous UV-irradiation (λ_{max} 365 nm) and c) immediately after the UV-irradiation ceased; and UV-Vis absorption spectra of **5.1q** in aerated toluene in the closed form (blue) before UV-irradiation and in the photostationary / steady state (PSS; red) immediately after cessation of UV-irradiation (blue [11.3 μM]; red [0.56 mM])

The potentially useful photochromic response of **5.1m**, which showed two absorption maxima and good colourability; properties which were thought to arise as a consequence of the donor aryl group at C-6 and the acceptor aryl group at C-4 prompted an investigation of the regioisomer **5.1r** in which the donor and acceptor aryl groups were inverted. The photomerocyanines (TC and TT) of **5.1m** showed the ‘opposing flow of electrons’ from the primary and secondary chromophores however, the isomeric photomerocyanines (TC and TT) derived from **5.1r** showed the ‘flow of electrons’ of the primary and secondary chromophores to be reinforced i.e. in the same direction (Figure 5.21).

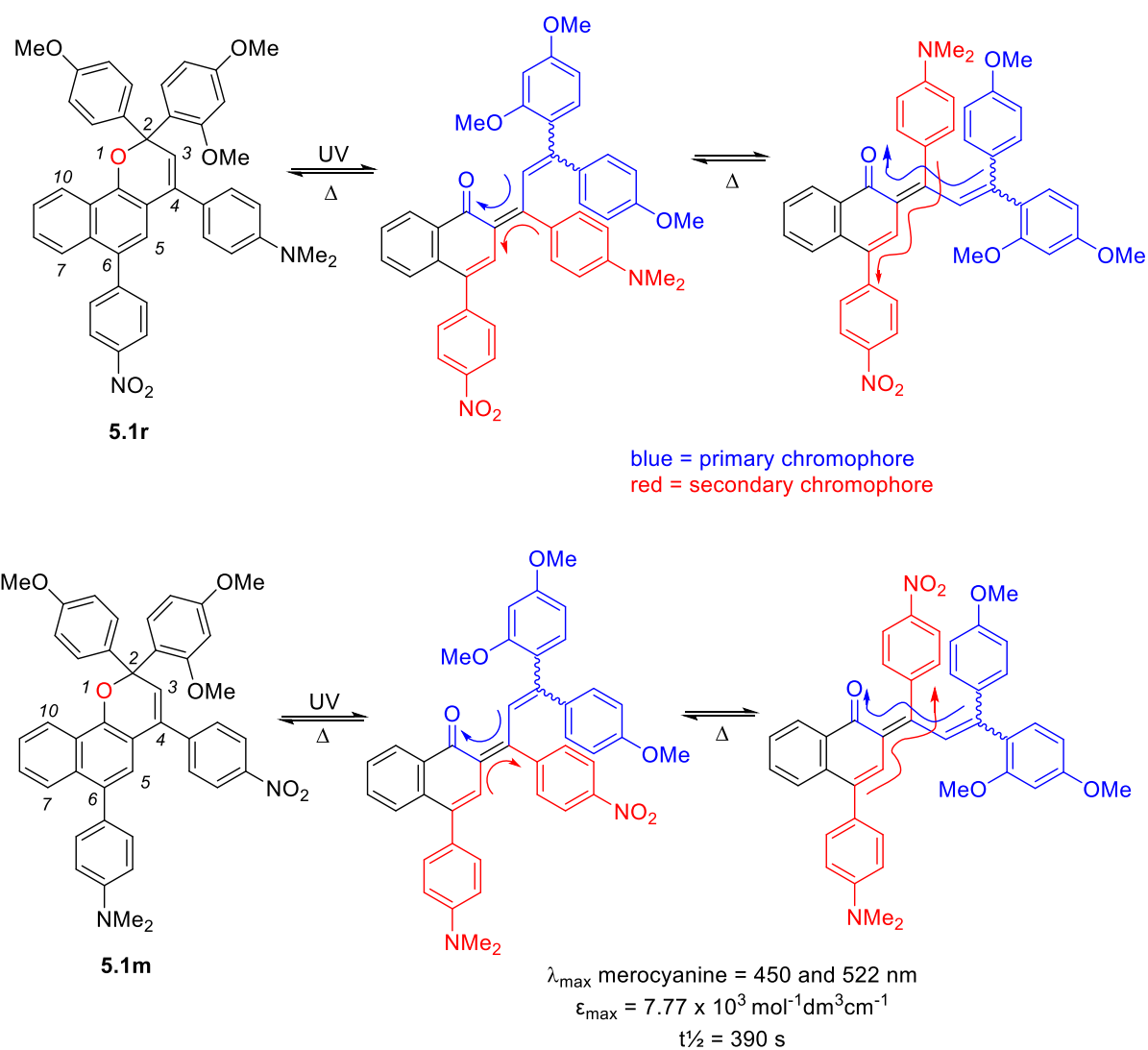


Figure 5.21: Regioisomeric naphthopyrans **5.1r** and **5.1m**

The initial toluene solution of **5.1r** was pale yellow. However, upon excitation with UV-irradiation from a LED Portable UV Flashlight (Weltool M2-BF 2W, λ_{max} 365 nm) the solution exhibited a moderate yellow fluorescence. In contrast, the toluene solution of **5.1m** exhibited a strong photochromic response with the development of an intense persistent cherry-red hue (Figure 5.22).

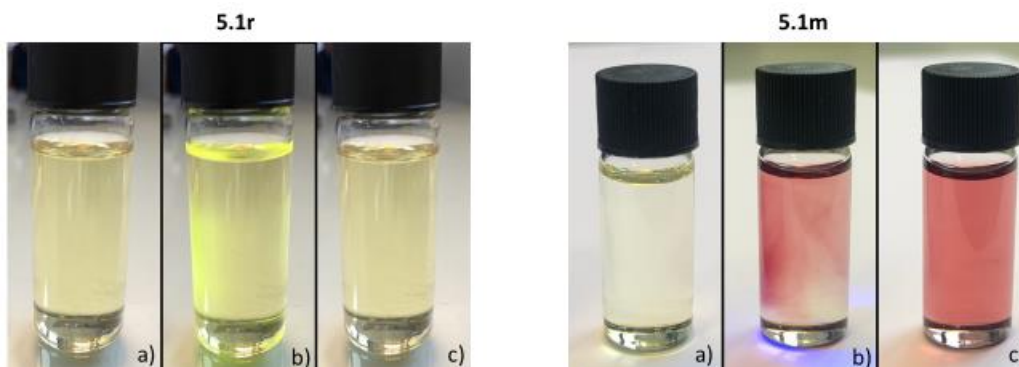


Figure 5.22: Solutions of **5.1r,m** in toluene (ca. 1.0 mM) a) before UV-irradiation, b) under continuous UV-irradiation (10 s, λ_{max} 365 nm) and c) immediately after the UV-irradiation ceased

Recording the UV - visible absorption spectra of a PhMe solution (ca. 0.33 mM) of **5.1r** revealed no appreciable photochromism as there was no distinct absorption band in the visible region comparable to those bands which resulted from the irradiation of the related tetraarylnaphthopyrans, though discernible changes in the range 300 – 420 nm were apparent and the tailing of an intensified UV absorption band into the visible region may result in a pale-yellow appearance of the solution however, this is complicated by the emission (Figure 5.23).

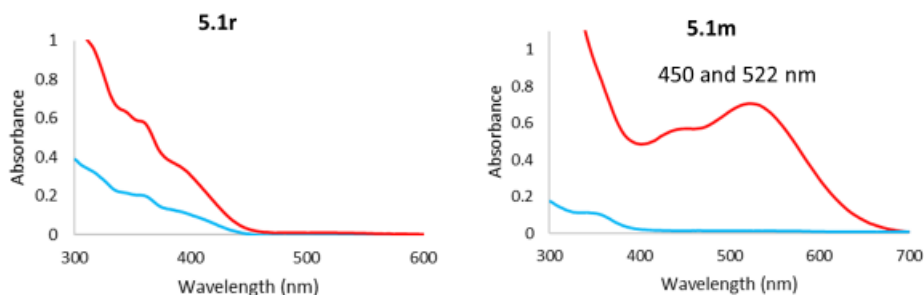


Figure 5.23: UV-Vis absorption spectra of the 2,2,4,6-tetraaryl-2*H*-naphtho[1,2-*b*]pyrans **5.1r** (0.33 mM) and **5.1m** (0.09 mM) before (blue) and immediately after (red) cessation of irradiation

The fluorescence of a toluene solution of **5.1r** was next examined. The emission maximum (λ_{em}) was determined to be 549 nm with an excitation wavelength of 358 nm (Figure 5.24). The magnitude of the fluorescence of a compound is expressed as the quantum yield (Φ) ^{<1988JPPB523; 2011B-3>} and this is determined by comparing the fluorescence of a standard

material, in this case anthracene, against that of the naphthopyran **5.1r** and applying the equation below:

$$\Phi = \Phi(R) \times \frac{\text{Integral}}{\text{Integral (R)}} \times \frac{1 - 10^{-Abs(R)}}{1 - 10^{-Abs}} \times \frac{\eta^2}{\eta^2(R)}$$

The standard (R) used was anthracene ($\Phi(R) = 0.28\%$ in EtOH under air; excitation window: 300–500 nm),¹ η is the refractive index of the various solvents (PhMe = 1.496; EtOH = 1.360). Through application of the foregoing equation the quantum yield for **5.1r** was determined to be 3.2%. In addition to the quantum yield, fluorescence is also characterised by the Stokes shift, which is often referred to as the difference in energy between the positions of the band maxima of the absorption and emission (fluorescence) spectra of the same electronic transition for a molecule (Figure 5.24). It is common to see values of Stokes shift reported in either units of wavelength (nm) or wavenumbers (cm^{-1}). <2011B-3> The Stokes shift for naphthopyran **5.1r** was calculated to be 191 nm ($\lambda_{\text{em}} = 549 \text{ nm} - \lambda_{\text{ex}} = 358 \text{ nm}$). A large Stokes shift for a fluorescent molecule has classically been inferred to arise as the consequence of a large change in dipole moment (i.e. a difference between ground state and the excited state dipole moment) upon excitation, which in this instance could be due to a structural reorganisation, such as ring-opening of the naphthopyran unit from which the emission may be derived. For the spectra of **5.1r** in Figure 5.23 there is a change in the absorption spectrum evident in the UV region upon irradiation which may give rise to a small amount of a photomerocyanine which absorbs in the UV region that could fluoresce (hence a relatively low quantum yield of 3.2 %). However, there are other reasons which may account for the low quantum yield of fluorescence such as extensive vibrational relaxation of the excited state to the ground state.

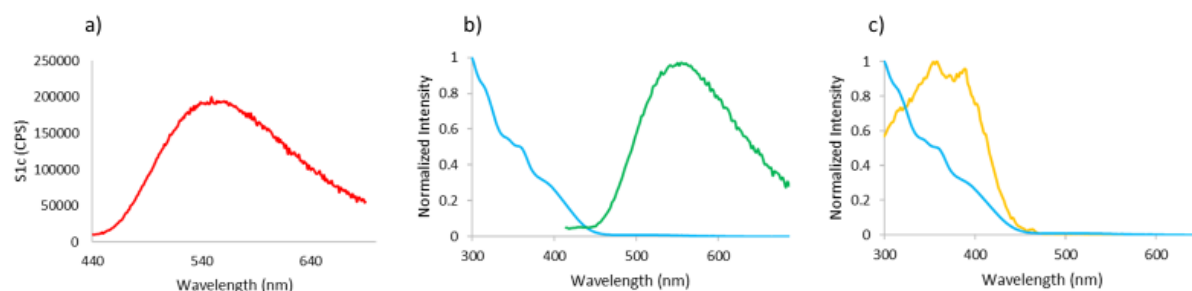


Figure 5.24: The properties of a toluene solution of **5.1r** (ca. 0.03 mM); a) Emission spectra, b) Normalized UV-Vis absorption and emission spectra, and c) Normalized UV-Vis absorption and excitation (emission at 549 nm) spectra

It is remarkable that the simple inversion of two substituents on the aryl rings at C-4 and C-6 of a naphthopyran effectively inhibits the photochromism and ‘turns on’ fluorescence. To further probe this effect detailed molecular modelling is required to establish the relative energy levels of the molecular orbitals involved in the photochromism and fluorescence processes of both the naphthopyran and the proposed photomerocyanines and such a study is beyond the scope of this initial synthetic chemistry investigation.

5.3 Photochromism of 2,2,4-triaryl-6-MeO substituted 2*H*-naphtho[1,2-*b*]pyrans

With access to the 4- and 6- aryl rings naphthopyrans **5.1a-r** it was thought to be useful to compare photochromic properties of 4-aryl and 6-methoxy substituted naphthopyrans **5.1s,t** which are illustrated in Figure 5.25.

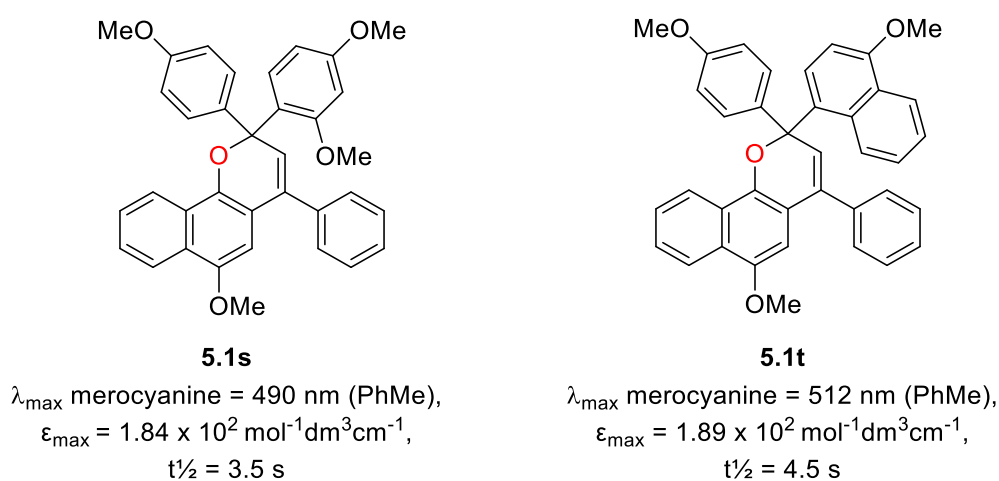


Figure 5.25: Naphthopyrans **5.1s,t** with 4-phenyl and 6-methoxy moiety

Upon UV-irradiation (λ_{max} 365 nm) the initial colourless PhMe solutions of **5.1s,t** generated an intense red hue which persisted for a short period of time (Figure 2.26).

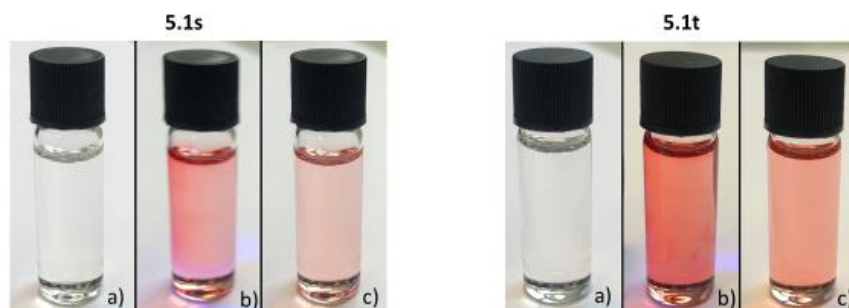
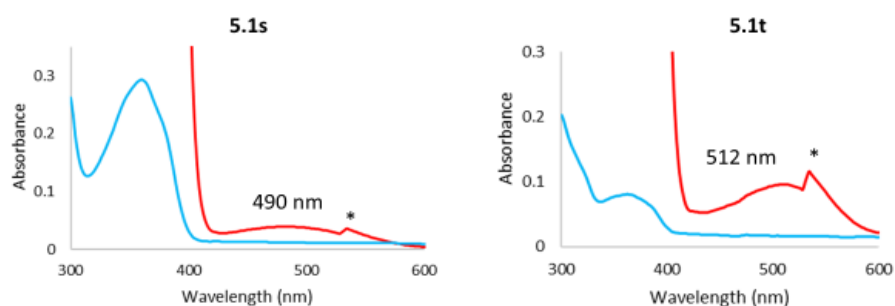


Figure 5.26: Solutions of **5.1s,t** in toluene (ca. 1.0 mM) a) before UV-irradiation, b) under continuous UV-irradiation (10 s, λ_{max} 365 nm) and c) immediately after the UV-irradiation ceased

UV-visible absorption spectra of PhMe solutions of **5.1s,t** provided the following λ_{max} values under steady state conditions: **5.1s** 490 nm (ca. 0.57 mM, 3 mins irradiation) and **5.1t** 512 nm (ca. 0.98 mM, 40 sec irradiation), (Figure 2.27). The attachment of the sterically demanding 4-methoxy-1-naphthyl moiety at C-2 in **5.1t** induced a bathochromic shift in λ_{max} of 22 nm relative to that of the 2,4-dimethoxy containing naphthopyran **5.1s**. The colourability of these two compounds was similar with a PhMe solution of **5.1t** exhibiting slightly better colourability of $1.89 \times 10^2 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$ compared to PhMe solution of **5.1s** $1.84 \times 10^2 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$.



*inflection in the spectra at ca. 540 nm is an artifact due to the spectrophotometer

Figure 2.27: UV-Vis absorption spectra of the 2,2,4-triaryl-6-MeO substituted 2*H*-naphtho[1,2-*b*]pyrans in aerated toluene in the closed form (blue) before UV-irradiation and in the photostationary / steady state (PSS; red) immediately after cessation of UV-irradiation: **5.1s** (blue [56.5 μM]; red [0.57 mM]) and **5.1t** (blue [19.2 μM]; red [0.98 mM])

The photomerocyanines of the naphthopyrans with 6-methoxy substituents showed significant decrease in half-life and remarkable increase in thermal bleaching rate constants ($k\Delta$) relative to the 6-aryl substituted naphthopyrans (**5.1k-n** and **5.1p**). Thus, the rates constant were recorded as 0.189 s^{-1} for **5.1s** and 0.149 s^{-1} for **5.1t** whereas their half-lives were calculated to be 3.5 s for **5.1s** and 4.5 s for **5.1t** (Figure 5.28).

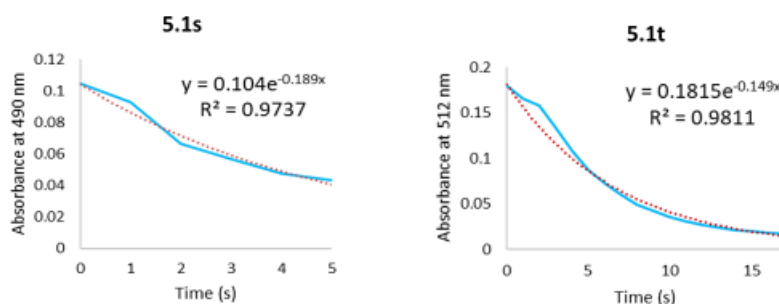


Figure 5.28: Bleaching of the PSS of **5.1s,t** in aerated PhMe after UV-irradiation presented as mono-exponential fit of absorbance versus time (s); **5.1s** (ca. 2.26 mM) and **5.1t** (ca. 0.07 mM)

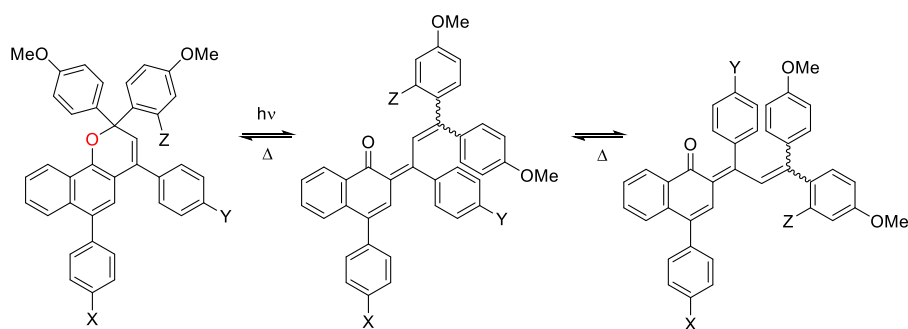
5.4 Summary of the photochromic response of the 2*H*-naphtho[1,2-*b*]pyrans

The photochromic properties of the 2,2,4,6-tetraaryl substituted 2*H*-naphtho[1,2-*b*]pyrans are outlined in Table 5.1. From the data it is apparent that the best photochromic response results when the 4-aryl group is substituted with an electron withdrawing group such as CF_3 , NO_2 or CN . Indeed, the stronger the electron withdrawing group the more persistent is the photogenerated colour; thus, the NO_2 group is most beneficial to the persistence of the photomerocyanine. Within the series of 4-(*para*-nitrophenyl) substituted compounds **5.1k-5.1n** the nature of the 6-aryl substituent has a significant role to play. When the 6-aryl ring is weakly electron donating e.g. when $\text{X} = \text{H}$ or MeO , then slow fading is recorded with half-lives in excess of 1000 s. However, introduction of strongly electron donating $\text{R}_2\text{N-}$ groups significantly decreases half-life with the interesting evolution of a short wavelength shoulder at ca. 450 nm. The presence of a strong electron donating group ($\text{R}_2\text{N-}$) in the *para*-position of the 6-aryl ring also promotes the most bathochromic absorption bands at wavelengths of up to ca. 540 nm.

From the data it is clear that generating a crossed (opposing) donor - acceptor arrangement of the secondary chromophore within the photomerocyanine upon UV-irradiation of the naphthopyran confers stability to the photomerocyanine such that a good photochromic response is obtained e.g. **5.1k-n** and **5.1p**. Conversely, the generation of a donor - acceptor secondary chromophore which reinforces the primary chromophore (Y = NMe₂ and X = NO₂; **5.1r**) is detrimental to photochromism and instead induces fluorescence.

Removal of the important sterically demanding *ortho*-methoxy group of **5.1m** to afford **5.1p** which retains good photochromism is noteworthy. It is suggested that removal of this *ortho*-methoxy group enables the resulting 4-(*para*-methoxyphenyl) groups to become more co-planar and hence better donor groups which is manifest in the longer wavelength absorption of the main absorption band (530 nm *versus* 522 nm). However, there is only a small change in the position of the short wavelength band (secondary chromophore) as this is relatively unaffected by the change in structure. The half-life of **5.1p**, without the *ortho*-methoxy group, remains comparable to that of **5.1m**.

It may be speculated that the prolonged irradiation of some of the weakly photochromic compounds e.g. **5.1b,c** revealed a very weak pink hue which may be due to an initially ring-opened TC species which has been isomerised to the TT isomer. The recalcitrance of the minor amounts of the TT isomer of the ring-opened naphthopyrans to cyclise to the colourless pyran form has been noted and much interesting work concerning the structural modification of the pyran ring system has been undertaken to obviate this isomerisation effect <2011OL4040; 2012JOC3956; 2019DP(169)118; 2020EJOC985>.



N°	X	Y	Z	Visible hue	$\lambda_{\max}$ (nm)	$t_{1/2}$ (s) k (s ⁻¹)	Colourability (mol ⁻¹ dm ³ cm ⁻¹)
5.1a	H	H	MeO	-	-	-	-
5.1b	MeO	H	MeO	weak pink	488	< 1 s	4.9×10^1
5.1c	CF ₃	H	MeO	weak pink	490	< 1 s	1.12×10^2
5.1d	H	MeO	MeO	-	-	-	-
5.1e	MeO	MeO	MeO	-	-	-	-
5.1f	CF ₃	MeO	MeO	-	-	-	-
5.1g	H	CF ₃	MeO	moderately intense pink	486	< 1 s	1.79×10^2
5.1h	MeO	CF ₃	MeO	moderately intense pink	502	< 1 s	1.87×10^2
5.1i	Me ₂ N	CF ₃	MeO	weak pink	510	< 1 s	8.8×10^1
5.1j	CF ₃	CF ₃	MeO	moderately intense pink	492	< 1 s	1.06×10^2
5.1k	H	NO ₂	MeO	intense red	496	1868 s $3.71 \times 10^{-4} \text{ s}^{-1}$	1.06×10^4
5.1l	MeO	NO ₂	MeO	intense cherry-red	502	1025 s $6.76 \times 10^{-4} \text{ s}^{-1}$	1.04×10^4
5.1m	Me ₂ N	NO ₂	MeO	Intense red-violet	522, 450 [†]	546 s $1.27 \times 10^{-3} \text{ s}^{-1}$	7.77×10^3
5.1n	Et ₂ N	NO ₂	MeO	Intense mulberry-purple	538, 448 [†]	415 s $1.67 \times 10^{-3} \text{ s}^{-1}$	4.74×10^3
5.1o	Me ₂ N	CN	MeO	moderately intense pink	514	< 1 s	5.6×10^1
5.1p	Me ₂ N	NO ₂	H	Intense red-violet	530, 446 [†]	533 s $1.3 \times 10^{-3} \text{ s}^{-1}$	8.7×10^3
5.1r	NO ₂	Me ₂ N	MeO	weak yellow	fluorescent	-	-

[†] Short wavelength band presents as a distinct shoulder

Table 5.1: Photochromic properties of 2,2,4,6-tetraaryl substituted 2*H*-naphtho[1,2-*b*]pyrans

6.0 Experimental

6.1 Instrumentation

Melting points were determined in glass capillary tubes using Stuart Digital Melting Point Apparatus and are uncorrected.

FT-IR spectra were recorded on neat samples using a Nicolet 380 Spectrum Spotlight system equipped with a diamond probe ATR attachment.

NMR spectra were routinely recorded using a Bruker Avance 400 instrument (^1H 400 MHz, $^{13}\text{C}\{^1\text{H}\}$ NMR 100 MHz, ^{19}F 376 MHz) for either CDCl_3 or $\text{d}_6\text{-DMSO}$ or $\text{d}_4\text{-MeOH}$ or $\text{d}_6\text{-acetone}$ and were either calibrated to an internal tetramethylsilane signal at 0.00 ppm or calibrated to the residual, non-deuterated solvent signal. Coupling constants J were measured and are reported in Hz. Occasional ^1H and ^{13}C NMR spectra were recorded using a Bruker Avance 300 MHz and 600 MHz instrument in CDCl_3 .

High resolution accurate mass (HRMS) measurements were obtained from the Innovative Physical Organic Solutions (IPOS) centre at the University of Huddersfield using either an Agilent 6210 TOF or Agilent 6530 Q-TOF mass spectrometer with dual-ESI or jet-stream ESI ionisation sources, respectively.

Visual examination of photomerocyanines were recorded in PhMe solutions under irradiation with a LED portable UV flashlight detection light (Weltool M2-BF, λ_{max} 365 nm).

UV-visible spectra were recorded for PhMe (spectroscopic grade) solutions of the samples (10 mm path length quartz cuvette, PTFE capped, concentration in the range 10^{-2} – 10^{-5} mol dm $^{-3}$). A bespoke Shimadzu UV-3600 Plus UV-Vis-NIR spectrophotometer (Figure 6.1) was used and equipped with a single cell Peltier temperature controlled (23 °C) stirred fluorescence cell holder attachment. The spectrophotometer sample chamber door was modified to accept activating irradiation delivered from the light source by liquid light guides (Newport 77557, Newport 77569). Irradiation was provided by a xenon ozone free arc lamp (Newport 6255) powered by an Oriel 300-Watt xenon arc lamp source (Newport 66906) with power manually limited to 150 Watts (Figure 6.1). An in-line distilled water liquid filter (Newport 6177), multiple filter holder (Newport 62020), UG11 filter (Newport FSO-UG11), fibre optic coupler

(Newport 77799) completed the irradiation equipment. Spectra (350 – 750 nm) were recorded prior to (ground state) and immediately after cessation of activating irradiation to a steady state (20 sec – 80 min irradiation time). Activation of the colourless closed forms of the naphthopyran samples to a photostationary state was achieved by UV-irradiation using Newport filter (UG11). Bleaching of the coloured (opened forms), when required, was induced by irradiation with visible light (GG420, GG455).

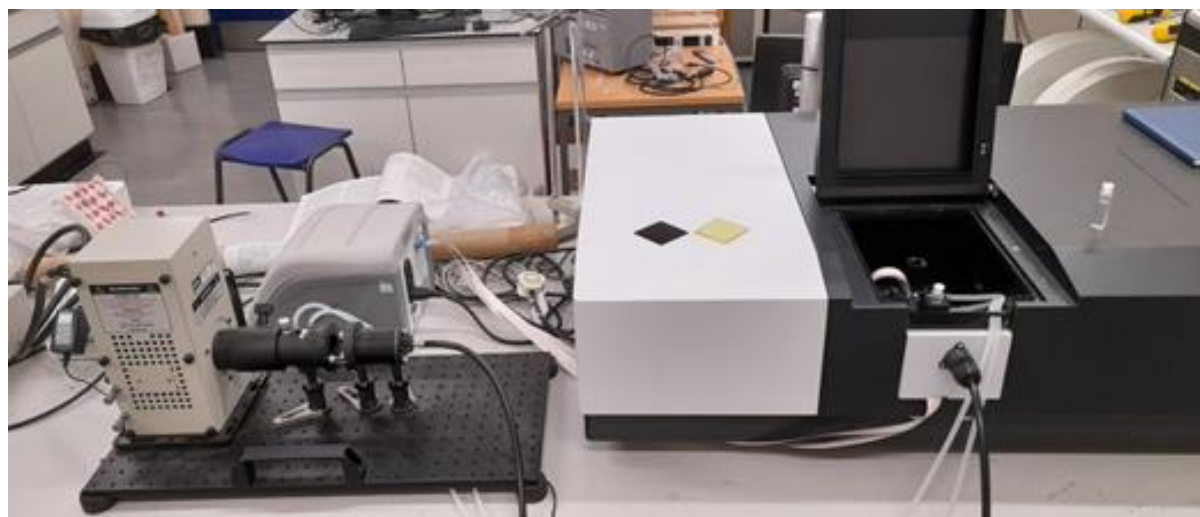


Figure 6.1: Oriel 300-Watt xenon arc lamp source and modified Shimadzu UV-3600 Plus UV-Vis-NIR spectrophotometer

Emission and excitation spectra were acquired on a Horiba Scientific Fluoromax-4 fluorimeter. Quantum yields (Φ_f) were calculated using the standard equation:

$$(1) \quad \Phi_f = \Phi(R) \times \frac{\text{Integral}}{\text{Integral (R)}} \times \frac{1 - 10^{-Abs(R)}}{1 - 10^{-Abs}} \times \frac{\eta^2}{\eta^2(R)}$$

The standard (R) used was anthracene ($\Phi(R) = 0.28$ % in EtOH under air; excitation window: 300–500 nm),¹ η is the refractive index of the solvent (EtOH = 1.360, PhMe = 1.496).

6.2 Chromatography

TLC was performed on either Merck TLC Aluminium sheets (silica gel 60 Å F254), or on Alugram pre-coated TLC sheets (silica gel 60 Å F254) or on Fluorochem aluminium backed TLC sheets (silica gel 60 Å F254), using a range of eluent systems of differing polarity. TLC plates were visualised using a hand-held Spectroline UV Lamp (ENF-280C/FE, 8 Watt, Sigma-Aldrich).

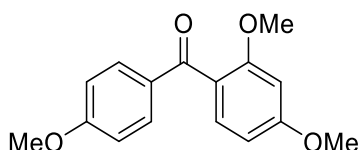
Flash chromatography separations were routinely performed on either Aldrich silica gel (60 Å, 230-400 mesh, 40-63 µm), or on Aldrich silica gel (60 Å, 70-230 mesh, 63-200 µm), or on Fluorochem silica gel (60 Å, 40-63 µm) using Aldrich flash column assemblies according to the published procedure <1978JOC2923>.

6.3 Chemicals

Reagents and solvents were purchased from routine major chemical suppliers (Alfa Aesar, Acros, Apollo Chemicals, Fisher Scientific, Fluorochem, Manchester Organics, TCI (UK) and Sigma-Aldrich) and were used without further purification unless otherwise stated. 1,1-Bis(4-methoxyphenyl)prop-2-yn-1-ol was obtained from routine stock, prepared in-house, held within the research laboratory.

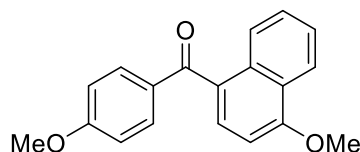
6.4 Preparation of ketones

6.4.1 Synthesis of (2,4-dimethoxyphenyl)(4-methoxyphenyl)methanone **2.3a**



A solution of *p*-anisic acid (32.0 g, 0.210 mol) and 1,3-dimethoxybenzene (26.2 mL, 0.200 mol) in polyphosphoric acid (380 g) was stirred and heated at 80 °C for 3 hours. The mixture was cooled to *ca.* 35 °C and then carefully poured onto a large excess of ice water (1.5 L) and stirred overnight. The mixture was neutralised with NaOH (5M aq.) and then extracted into DCM (3 × 300 mL). The combined organic extracts were washed with NaOH (2M aq. 2 × 750 mL), water (2 × 500 mL), dried with anhydrous sodium sulfate and evaporated to afford viscous red oil that crystallized on standing. Recrystallization of the crude solid from hot ethanol gave the title compound **2.3a** as colourless needles (46.7 g, 86 %); mp = 71 – 73 °C [lit.mp. 73 – 74 °C <1910B1882>; $\nu_{\max}$ (neat) 2992, 1643, 1596, 1502, 1251, 1185, 1156, 1027, 820, 797, 576, 524 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 3.72 (3H, s, OMe), 3.87 (6H, s, 2 × OMe), 6.51 – 6.55 (2H, m, Ar-H), 6.88 – 6.92 (2H, m, Ar-H), 7.34 (1H, d, *J* = 8.3 Hz, Ar-H), 7.76 – 7.80 (2H, m, Ar-H); δ_{C} (100 MHz, CDCl₃) 55.51, 55.63, 98.86, 104.44, 113.30, 122.04, 131.58, 132.18, 159.15, 162.88, 163.20, 194.33; HRMS (ESI) found [M+H]⁺ = 273.1126 C₁₆H₁₆O₄ requires [M+H]⁺ = 273.1127.

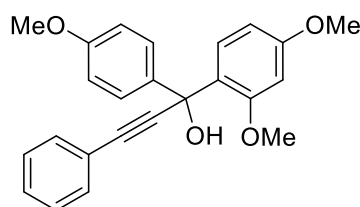
6.4.2 Synthesis of (4-methoxynaphthalen-1-yl)(4-methoxyphenyl)methanone **2.3b**



A solution of *p*-anisic acid (5.05 g, 33.2 mmol) and 1-methoxynaphthalene (4.59 mL, 31.6 mmol) in polyphosphoric acid (80 g) was stirred and heated to 80 °C for 3 h. The mixture was cooled to room temp and then ice water (600 mL) was added and the reaction mixture stirred overnight. The mixture was neutralised with NaOH (5M aq.) and then extracted into EtOAc (3 × 50 mL). The combined organic extracts were washed with NaOH (2M aq. 3 × 80 mL), water (150 mL), dried with anhydrous sodium sulfate and evaporated to afford a red crystalline solid. Recrystallization of the crude solid from hot ethanol gave the title compound **2.3b** as pale brown crystals (4.14 g, 45 %); mp = 103 – 109 °C [lit.mp. 107 °C <1960JCS2272>]; ν_{max} (neat) 2970, 2360, 1604, 1506, 1243, 1157, 1026, 828, 586 cm^{-1} ; δ_{H} (300 MHz, CDCl_3) 3.88 (3H, s, OMe), 4.06 (3H, s, OMe), 6.80 (1H, d, J = 8.0 Hz, Ar-H), 6.91 – 6.96 (2H, m, Ar-H), 7.49 – 7.58 (3H, m, Ar-H), 7.82 – 7.87 (2H, m, Ar-H), 8.18 – 8.24 (1H, m, Ar-H), 8.31 – 8.38 (1H, m, Ar-H); δ_{C} (75 MHz, CDCl_3) 55.52, 55.76, 102.05, 113.53, 122.21, 125.72, 125.74, 127.74, 128.89, 129.92, 131.92, 132.49, 132.70, 157.79, 163.36, 196.23; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 293.1178$ $\text{C}_{19}\text{H}_{16}\text{O}_3$ requires $[\text{M}+\text{H}]^+ = 293.1177$.

6.5 Preparation of 1,1,3-triarylprop-2-yn-1-ols

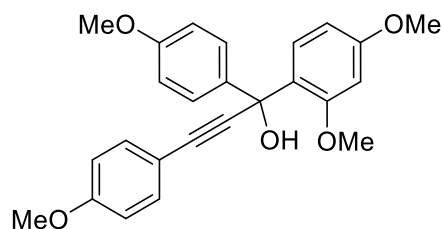
6.5.1 Synthesis of 1-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol **2.1aa**



n-Butyllithium (2.5 M in hexanes) (9.76 mL, 24.4 mmol) was added portionwise *via* syringe to a cold (-70 °C) stirred solution of phenylacetylene (2.68 mL, 2.49 g, 24.4 mmol) in anhydrous THF (50 mL) under N_2 . The cold solution was stirred for 30 minutes and then (2,4-dimethoxyphenyl)(4-methoxyphenyl)methanone (6.00 g, 22.0 mmol) was added in a single

portion. The cooling bath was removed and the mixture stirred for 20 h at room temperature under N₂. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with water (100 mL), dried with anhydrous sodium sulfate and evaporated to afford a yellow oil. Elution from silica with 5 % EtOAc/PhMe afforded the title compound **2.1aa** as a yellow gum (4.25 g, 52 %); ν_{max} (neat) 3500, 2380, 2150, 1155, 1012, 751, 689, 634, 510 cm⁻¹; δ_{H} (300 MHz, CDCl₃) 3.80 (6H, s, 2 × OMe), 3.82 (3H, s, OMe), 4.83 (1H, s, OH), 6.44 (1H, dd, J = 8.6, 2.4 Hz, Ar-H), 6.52 (1H, d, J = 2.4 Hz, Ar-H), 6.86 – 6.90 (2H, m, Ar-H), 7.24 (1H, d, J = 6.4 Hz, Ar-H), 7.27 – 7.31 (3H, m, Ar-H), 7.44 – 7.48 (2H, m, Ar-H), 7.49 – 7.54 (2H, m, Ar-H); δ_{C} (75 MHz, CDCl₃) 55.29, 55.43, 55.93, 74.08, 86.26, 91.65, 100.11, 103.96, 113.27, 123.02, 125.70, 127.73, 128.17, 128.26, 129.15, 131.75, 136.78, 157.91, 158.93, 160.70; HRMS (ESI) found $[M+H]^+ = 375.1590$ C₂₄H₂₂O₄ requires $[M+H]^+ = 375.1596$.

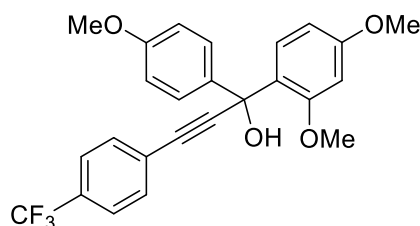
6.5.2 Synthesis of 1-(2,4-dimethoxyphenyl)-1,3-bis(4-methoxyphenyl)prop-2-yn-1-ol **2.1ab**



n-Butyllithium (2.5 M in hexanes) (9.76 mL, 24.4 mmol) was added portionwise via a syringe to a cold (-70 °C) stirred solution of 4-methoxyphenylacetylene (3.16 mL, 3.22g, 24.4 mmol) in anhydrous THF (50 mL) under N₂. The cold solution was stirred for 30 minutes and then (2,4-dimethoxyphenyl)(4-methoxyphenyl)methanone (6.00 g, 22.0 mmol) was added in a single portion. The cooling bath was removed and the mixture stirred for 20 h at room temperature under N₂. TLC examination of the reaction mixture after this time indicated that some of the (2,4-dimethoxyphenyl)(4-methoxyphenyl)methanone remained. Thus further ((4-methoxyphenyl)ethynyl)lithium solution was prepared [from 4-methoxyphenylacetylene (0.98 mL, 7.6 mmol) and *n*-BuLi (3.04 mL, 7.8 mmol)] at -10 °C and added via syringe to the foregoing alkynol reaction mixture. The resulting mixture was stirred for an additional 17 h at room temperature and then diluted with water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with water (100 mL), dried with anhydrous

sodium sulfate and evaporated to afford a yellow oil. Gradient elution from silica with 10 % EtOAc/hexane → 30 % EtOAc/hexane → 50 % EtOAc/hexane afforded the title compound **2.1ab** as a viscous yellow oil (6.26 g, 70 %); $\nu_{\max}$ (neat) 3509, 2935, 2835, 2223, 1604, 1506, 1243, 1125, 1026, 828, 586 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.79 (3H, s, OMe), 3.80 (3H, s, OMe), 3.81 (3H, s, OMe), 3.82 (3H, s, OMe), 4.79 (1H, s, OH), 6.44 (1H, dd, $J = 8.6, 2.4$ Hz Ar-H), 6.52 (1H, d, $J = 2.4$ Hz, Ar-H), 6.80 – 6.84 (2H, m, Ar-H), 6.86 – 6.89 (2H, m, Ar-H), 7.27 (1H, d, $J = 8.6$ Hz, Ar-H), 7.38 – 7.42 (2H, m, Ar-H), 7.49 – 7.52 (2H, m, Ar-H); δ_{C} (100 MHz, CDCl_3) 55.28, 55.42, 55.91, 74.15, 86.25, 90.25, 100.14, 103.99, 113.23, 113.78, 115.17, 125.90, 127.68, 129.17, 133.18, 137.09, 157.91, 158.87, 159.57, 160.67; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 405.1702$ $\text{C}_{25}\text{H}_{24}\text{O}_5$ requires $[\text{M}+\text{H}]^+ = 405.1702$.

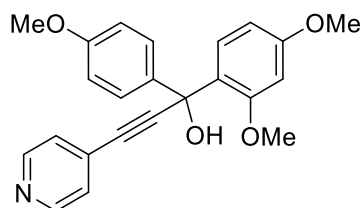
6.5.3 Synthesis of 1-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-ol **2.1ac**



n-Butyllithium (2.5 M in hexanes) (8.92 mL, 22.3 mmol) was added portionwise via a syringe to a cold ($-10\text{ }^{\circ}\text{C}$) stirred solution of 4-(trifluoromethyl)phenylacetylene (3.60 mL, 3.76 g, 22.1 mmol) in anhydrous THF (50 mL) under N_2 . The cold solution was stirred for 30 minutes and then (2,4-dimethoxyphenyl)(4-methoxyphenyl)methanone (5.00 g, 18.4 mmol) was added in a single portion. The cooling bath was removed and the mixture stirred for 20 h at room temperature under N_2 and then diluted with water (100 mL) and extracted with EtOAc (3 $\times$ 100 mL). The combined organic extracts were washed with water (100 mL), dried with anhydrous sodium sulfate and evaporated to afford yellow oil. Elution from silica with 10 % EtOAc/PhMe afforded the title compound **2.1ac** as a pale yellow microcrystals (4.92 g, 60 %); mp = $106 - 108\text{ }^{\circ}\text{C}$; $\nu_{\max}$ (neat) 3545, 3010, 2180, 1606, 1320, 1251, 1207, 1156, 1123, 1029, 843, 523 cm^{-1} ; δ_{H} (600 MHz, CDCl_3) 3.80 (6H, s, 2 $\times$ OMe), 3.81 (3H, s, OMe), 4.83 (1H, s, OH), 6.44 (1H, dd, $J = 8.6, 2.4$ Hz Ar-H), 6.52 (1H, d, $J = 2.3$ Hz, Ar-H), 6.88 (2H, d, $J = 8.8$ Hz, Ar-H), 7.19 (1H, d, $J = 8.6$ Hz, Ar-H), 7.48 – 7.51 (2H, m, Ar-H), 7.53 – 7.56 (4H, m, Ar-H); δ_{F} (376 MHz, CDCl_3) -62.8; δ_{C} (150 MHz, CDCl_3) 55.30, 55.44, 55.91, 74.02, 84.77, 94.25, 100.14, 104.07,

113.38, 123.94 (q, $J = 272.5$ Hz, $\underline{\text{C}}\text{F}_3$), 125.14 (q, $J = 3.8$ Hz, $=\underline{\text{C}}\text{H}-\text{C}-\text{CF}_3$), 125.27, 126.86 (q, $J = 1.3$ Hz, $\underline{\text{C}}-\text{CH}=\text{CH}-\text{C}-\text{CF}_3$), 127.72, 129.07, 129.99 (q, $J = 32.5$ Hz, $\underline{\text{C}}-\text{CF}_3$), 131.97, 136.30, 157.91, 159.10, 160.86; HRMS (ESI) found $[\text{M}-\text{H}_2\text{O}+\text{H}]^+ = 425.1358$ $\text{C}_{25}\text{H}_{19}\text{F}_3\text{O}_3$ requires $[\text{M}-\text{H}_2\text{O}+\text{H}]^+ = 425.1364$.

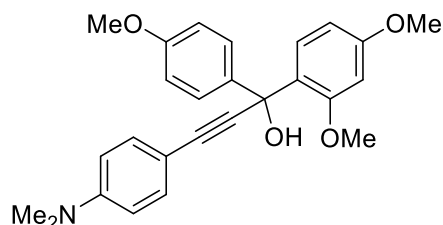
6.5.4 Synthesis of 1-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-3-(pyridin-4-yl)prop-2-yn-1-ol **2.1ad**



n-Butyllithium (2.5 M in hexanes) (14.70 mL, 36.7 mmol) was added portionwise via a syringe to a cold (-70 °C) stirred suspension of 4-ethynylpyridine hydrochloride (3.08 g, 22.0 mmol) in anhydrous THF (30 mL) under N_2 . The cold solution was stirred for 30 minutes and then (2,4-dimethoxyphenyl)(4-methoxyphenyl)methanone (4.00 g, 14.7 mmol) was added in a single portion. The cooling bath was removed and the mixture stirred for 20 h at room temperature under N_2 . TLC examination of the reaction mixture after this time indicated that some of the (2,4-dimethoxyphenyl)(4-methoxyphenyl)methanone remained. Thus further (pyridin-4-ylethynyl)lithium solution was prepared [from 4-ethynylpyridine hydrochloride (1.03 g, 7.33 mmol) and *n*-BuLi (4.90 mL, 12.2 mmol)] at -70 °C and added to the foregoing alkynol reaction mixture. The resulting mixture was stirred for an additional 20 h at room temperature and then diluted with water (300 mL) and extracted with EtOAc (3 $\times$ 100 mL). The combined organic extracts were washed with water (200 mL), dried with anhydrous sodium sulfate and evaporated to afford a brown gum. Elution from silica with 50 % EtOAc/petroleum ether (bp. $40 - 60$ °C) afforded the title compound **2.1ad** as a brown powder (0.89 g, 16 %); mp = $42 - 43$ °C; ν_{max} (neat) 3108, 2955, 2834, 2360, 1584, 1500, 1246, 1207, 1029, 820 and 588 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.80 (6H, s, 2x OMe), 3.82 (3H, s, OMe), 4.93 (1H, s, OH), 6.45 (1H, dd, $J = 8.6$ Hz, 2.4 Hz, Ar-H), 6.53 (1H, d, $J = 2.4$ Hz, Ar-H), 6.87 – 6.91 (2H, m, Ar-H), 7.17 (1H, d, $J = 8.6$ Hz, Ar-H), 7.30 – 7.32 (2H, m, Ar-H), 7.48 – 7.52 (2H, m, Ar-H), 8.54 (2H, d, $J = 4.2$ Hz, Py-H); δ_{C} (100 MHz, CDCl_3) 55.29, 55.44, 55.89, 73.87, 83.35, 96.70, 100.13, 104.08, 113.41,

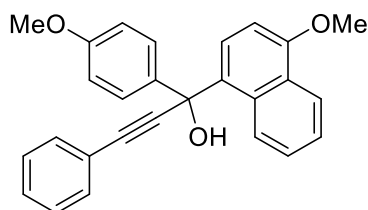
125.02, 125.76, 127.72, 128.97, 131.31, 135.96, 149.58, 157.88, 159.15, 160.92; HRMS (ESI) found $[M+H]^+ = 376.1539$ $C_{23}H_{21}NO_4$ requires $[M+H]^+ = 376.1549$.

6.5.5 Synthesis of 1-(2,4-dimethoxyphenyl)-3-(4-(dimethylamino)phenyl)-1-(4-methoxyphenyl)prop-2-yn-1-ol **2.1ae**



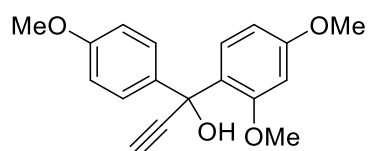
n-Butyllithium (2.5 M in hexanes) (11.80 mL, 29.4 mmol) was added portionwise *via* syringe to a cold (-70 °C) stirred solution of 4-ethynyl-*N,N*-dimethylaniline (4.27 g, 29.4 mmol) in anhydrous THF (30 mL) under N_2 . The cold solution was stirred for 30 minutes and then (2,4-dimethoxyphenyl)(4-methoxyphenyl)methanone (4.00 g, 14.7 mmol) was added in a single portion. The cooling bath was removed and the mixture stirred for 20 h at room temperature under N_2 . The reaction mixture was diluted with water (150 mL) and extracted with EtOAc (3 $\times$ 75 mL). The combined organic extracts were washed with water (150 mL), dried with anhydrous sodium sulfate and evaporated to afford a brown oil. Elution from silica with 20 % EtOAc/petroleum ether (bp. 40 – 60 °C) afforded the title compound **2.1ae** as an orange powder (0.87 g, 85 %); mp = 49 – 50 °C ν_{max} (neat) 3506, 2932, 2834, 2217, 1605, 1503, 1245, 1206, 1156, 1028, 816, 586 and 523 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 2.95 (6H, s, NMe_2), 3.78 (3H, s, OMe), 3.80 (3H, s, OMe), 3.81 (3H, s, OMe), 4.77 (1H, s, OH), 6.44 (1H, dd, $J = 8.6, 2.4$ Hz, Ar-H), 6.51 (1H, d, $J = 2.4$ Hz, Ar-H), 6.58 – 6.62 (2H, m, Ar-H), 6.84 – 6.88 (2H, m, Ar-H), 7.30 – 7.35 (3H, m, Ar-H), 7.49 – 7.53 (2H, m, Ar-H); δ_C (10 MHz, $CDCl_3$) 40.24, 55.27, 55.41, 55.93, 74.27, 87.39, 89.35, 100.16, 103.97, 109.97, 111.69, 113.17, 126.25, 127.71, 129.22, 132.82, 137.45, 150.12, 157.94, 158.78, 160.58; HRMS (ESI) found $[M+H]^+ = 418.2002$ $C_{26}H_{27}NO_4$ requires $[M+H]^+ = 418.2018$.

6.5.6 Synthesis of 1-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol **2.1ba**



n-Butyllithium (2.5 M in hexanes) (9.58 mL, 23.9 mmol) was added portionwise via a syringe to a cold (-10 °C) stirred solution of phenylacetylene (2.63 mL, 2.45 g, 23.9 mmol) in anhydrous THF (50 mL) under N₂. The ice-bath was removed and the mixture was stirred for 30 minutes at 15 °C. The reaction mixture was cooled to 0 °C and (4-methoxynaphthalen-1-yl)(4-methoxyphenyl)methanone (3.50 g, 12.0 mmol) was added in a single portion whereupon the ice-bath removed and mixture stirred at room temperature for 20 h under N₂. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (3 × 70 mL). The combined organic extracts were washed with water (100 mL), dried with anhydrous sodium sulfate and evaporated to afford a yellow oil. Elution from silica with 5 % EtOAc/PhMe gave the title compound **2.1ba** as a yellow flakes (4.34 g, 92 %); mp = 69 – 72 °C; ν_{max} (neat) 3670, 2981, 2029, 1580, 1508, 1246, 1167, 1028, 830, 754, 557 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 2.94 (1H, s, OH), 3.79 (3H, s, OMe), 4.04 (3H, s, OMe), 6.82 – 6.87 (3H, m, Ar-H), 7.28 – 7.45 (7H, m, Ar-H), 7.53 – 7.57 (2H, m, Ar-H), 7.99 (1H, d, *J* = 8.2 Hz, Ar-H), 8.18 (1H, d, *J* = 8.2 Hz, Ar-H), 8.30 – 8.32 (1H, m, Ar-H); δ_{C} (100 MHz, CDCl₃) 55.27, 55.57, 74.28, 87.59, 92.27, 102.24, 113.71, 122.32, 122.67, 124.74, 124.89, 125.91, 126.62, 126.74, 127.88, 128.25, 128.48, 131.04, 131.06, 131.69, 137.24, 155.90, 159.19; HRMS (ESI) found [M-H₂O+H]⁺ = 377.1534 C₂₇H₂₂O₃ requires [M-H₂O+H]⁺ = 377.1536.

6.5.7 Synthesis of 1-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)prop-2-yn-1-ol **2.15**



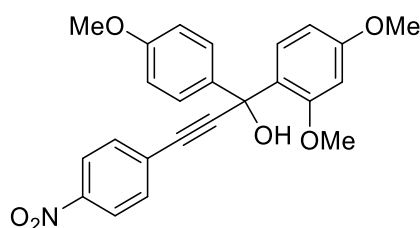
n-Butyllithium (2.5 M in hexanes) (20.57 mL, 51.4 mmol) was added portionwise via a syringe to a chilled (-10 °C) stirred solution of trimethylsilylacetylene (7.12 mL, 5.05 g, 51.4 mmol) in

anhydrous THF (50 mL) under N₂. The ice-bath was removed and mixture stirred for 30 minutes at 15 °C. Reaction mixture was cooled down to 0 °C and the (2,4-dimethoxyphenyl)(4-methoxyphenyl)methanone (7.00 g, 25.7 mmol) was added in a single portion whereby ice-bath removed and mixture stirred for additional 30 minutes. The reaction mixture was cooled down once again to 0 °C and then a cold solution of KOH (3.73 g, 56.6 mmol) in MeOH (20.2 mL) was added portionwise. Once the addition was complete the ice-bath was removed and mixture stirred for 2 h at room temperature under N₂. The reaction mixture was diluted with water (150 mL) and extracted quickly with EtOAc (3 × 75 mL). The combined organic extracts were washed with water (100 mL), dried with anhydrous sodium sulfate and evaporated to afford the title compound **2.15** as a pale yellow oil (7.09 g, 92 %) which gradually solidified on standing at room temperature; mp = 82 – 83 °C; ν_{max} (neat) 3548, 3269, 2359, 1607, 1502, 1250, 1209, 1127, 1027, 585 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 2.79 (1H, s, acetylene-H), 3.78 (3H, s, OMe), 3.80 (3H, s, OMe), 3.81 (3H, s, OMe), 4.78 (1H, s, OH), 6.4 (1H, dd, J = 8.6, 2.3 Hz, Ar-H), 6.50 (1H, d, J = 2.3 Hz, Ar-H), 6.87 (2H, d, J = 8.8 Hz, Ar-H), 7.20 (1H, d, J = 8.5 Hz, Ar-H), 7.46 (2H, d, J = 8.8 Hz, Ar-H); δ_{C} (100 MHz, CDCl₃) 55.28, 55.43, 55.84, 73.56, 74.45, 86.14, 100.06, 103.96, 113.30, 125.04, 127.58, 129.15, 136.35, 157.80, 159.03, 160.81; HRMS (ESI) found $[\text{M}-\text{H}_2\text{O}+\text{H}]^+ = 281.1170$ C₁₈H₁₈O₄ requires $[\text{M}-\text{H}_2\text{O}+\text{H}]^+ = 281.1172$.

6.6 General procedure for synthesis of 1,1,3-triarylprop-2-yn-1-ols via a Sonogashira cross-coupling reaction

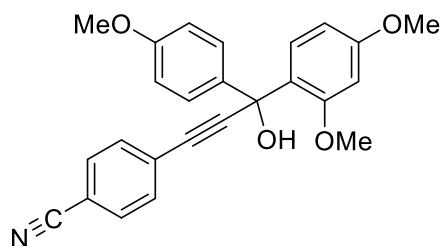
The requisite 1,1-diaryl prop-2-yn-1-ol (1.0 eq.), the appropriate aryl halide (1.0 eq.), copper(I) iodide (7.5 mol %), PPh₃ (15 mol %) and Pd(PPh₃)₄ (3 mol %) were added to an oven dried 3 neck flask under nitrogen and freshly distilled anhydrous Et₃N (7 mL/mmol) was added. The mixture was heated under reflux until TLC examination of the reaction mixture indicated no further change (up to 20 h). The cooled mixture was evaporated to dryness and the crude was diluted with DCM (75 mL), washed with water (200 mL) and neutralised with 2M aq. HCl (15 mL). The aqueous layer was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with water (100 mL), dried with anhydrous sodium sulfate and solvent evaporated under reduced pressure to afford the crude mixture that was eluted from silica to provide the pure product. The following compounds were obtained by using this method.

6.6.1 1-(2,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-3-(4-nitrophenyl)prop-2-yn-1-ol
2.1af



From 1-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)prop-2-yn-1-ol (3.20 g, 10.7 mmol) and 1-bromo-4-nitrobenzene (2.17 g, 10.7 mmol) after elution from silica with 20 % EtOAc/petroleum ether (bp. 40 – 60 °C) afford the title compound **2.1af** as a dark brown waxy solid (3.10 g, 69 %); mp = 54 – 56 °C; ν_{max} (neat) 3500, 2935, 2836, 2362, 1584, 1505, 1340, 1246, 1027, 855, 749, 587 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.81 (3H, s, OMe), 3.82 (3H, s, OMe), 3.83 (3H, s, OMe), 4.88 (1H, s, OH), 6.45 (1H, dd, J = 8.6 , 2.4 Hz, Ar-H), 6.54 (1H, d, J = 2.4 Hz, Ar-H), 6.88 – 6.92 (2H, m, Ar-H), 6.86 – 6.89 (2H, m, Ar-H), 7.27 (1H, d, J = 8.6 Hz, Ar-H), 7.38 – 7.42 (2H, m, Ar-H), 7.17 (1H, d, J = 8.6 Hz, Ar-H), 7.48 – 7.52 (2H, m, Ar-H), 7.58 – 7.62 (2H, m, Ar-H), 8.15 – 8.18 (2H, m, Ar-H); δ_{C} (100 MHz, CDCl_3) 55.31, 55.46, 55.90, 74.03, 84.24, 97.18, 100.10, 104.07, 113.44, 123.50, 124.88, 127.70, 129.05, 129.96, 132.47, 135.91, 147.09, 157.87, 159.18, 160.95; HRMS (ESI) found $[\text{M}-\text{H}_2\text{O}+\text{H}]^+ = 402.1336$ $\text{C}_{24}\text{H}_{21}\text{NO}_6$ requires $[\text{M}-\text{H}_2\text{O}+\text{H}]^+ = 402.1341$.

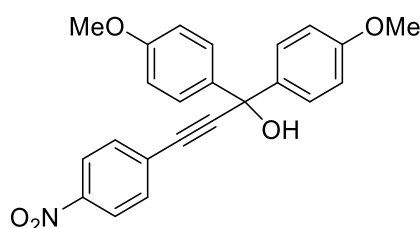
6.6.2 4-(3-(2,4-Dimethoxyphenyl)-3-hydroxy-3-(4-methoxyphenyl)prop-1-yn-1-yl)benzonitrile 2.1ag



From 1-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)prop-2-yn-1-ol (1.50 g, 5.03 mmol) and 4-iodobenzonitrile (1.15 g, 5.03 mmol) after elution from silica with 30 % EtOAc/petroleum ether (bp. 40 – 60 °C) afford the title compound **2.1ag** as a brown powder (1.96 g, 98 %); mp = 76 – 77 °C; ν_{max} (neat) 3655, 2980, 2889, 1603, 1382, 1250, 1157, 955, 834 cm^{-1} ; δ_{H} (400

MHz, CDCl₃) 3.81 (6H, s, 2 × OMe), 3.82 (3H, s, OMe), 4.87 (1H, s, OH), 6.45 (1H, dd, *J* = 8.6, 2.3 Hz, Ar-H), 6.53 (1H, d, *J* = 2.2 Hz, Ar-H), 6.89 (2H, d, *J* = 8.8 Hz, Ar-H), 7.17 (1H, d, *J* = 8.6 Hz, Ar-H), 7.49 (2H, d, *J* = 8.8 Hz, Ar-H), 7.53 – 7.60 (4H, m, Ar-H); δ_c (100 MHz, CDCl₃) 55.31, 55.46, 55.90, 74.01, 84.48, 96.27, 100.10, 104.06, 111.60, 113.41, 118.51, 124.97, 127.69, 127.96, 129.04, 131.93, 132.25, 136.02, 157.86, 159.14, 160.91; HRMS (ESI) found [M-H₂O+H]⁺ = 382.1435 C₂₅H₂₁NO₄ requires [M-H₂O+H]⁺ = 382.1643.

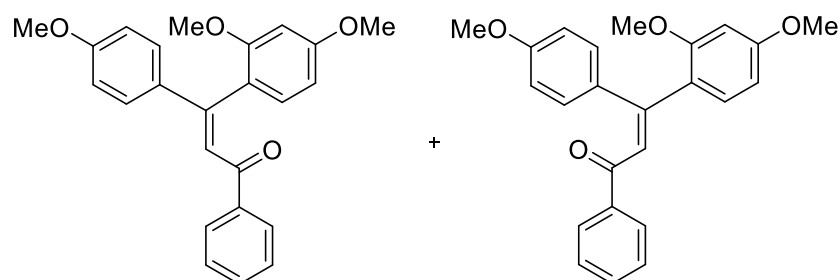
6.6.3 1,1-Bis(4-methoxyphenyl)-3-(4-nitrophenyl)prop-2-yn-1-ol 2.1ca



From 1,1-bis(4-methoxyphenyl)prop-2-yn-1-ol (2.00 g, 7.45 mmol) and 1-bromo-4-nitrobenzene (1.51 g, 7.45 mmol) after elution from silica with 20 % EtOAc/petroleum ether (bp. 40 – 60 °C) afford the title compound **2.1ca** as a dark brown oil (2.75 g, 95 %); ν_{max} (neat) 3500, 2940, 1592, 1517, 1340, 1237, 1171, 855, 775, 588 cm⁻¹; δ_H (400 MHz, CDCl₃) 2.85 (1H, s, OH), 3.81 (6H, s, 2 × OMe), 6.89 (4H, d, *J* = 8.6 Hz, Ar-H), 7.53 (4H, d, *J* = 8.6 Hz, Ar-H), 7.64 (2H, d, *J* = 8.6 Hz, Ar-H), 8.20 (2H, d, *J* = 8.6 Hz, Ar-H); δ_c (100 MHz, CDCl₃) 55.34, 74.24, 84.83, 97.41, 113.71, 123.59, 127.41, 129.45, 132.52, 136.75, 147.28, 159.30; HRMS (ESI) found [M-H₂O+H]⁺ = 372.1228 C₂₃H₁₉NO₅ requires [M-H₂O+H]⁺ = 372.1236.

6.7 Preparation of α,β-unsaturated ketones

6.7.1 Synthesis of *Z*- and *E*-3-(2,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one 3.25a and 3.25b

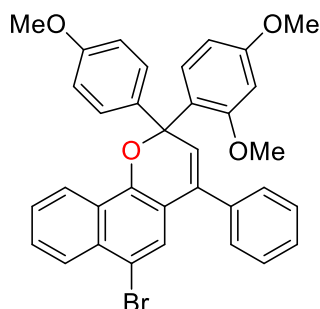


A stirred solution of 1-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol (3.80 g, 10.1 mmol), pyridinium 4-toluenesulfonate (PPTS) (0.13 g, 0.51 mmol) and trimethyl orthoformate (2.21 mL, 2.14 g, 20.2 mmol) in 1,2-dichloroethane (80 mL) was heated under reflux for 5 hours. Removal of the solvent from the cooled reaction mixture gave a dark brown gum which was eluted from silica with 30 % Et₂O/hexane to afford an inseparable mixture of the title ketones **3.25a** and **3.25b** (10⁺:1⁺) as a dark orange viscous gum (2.53 g, 67 %); ν_{max} (neat) 2932, 2836, 1657, 1504, 1247, 1207, 1029, 830, 543 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 3.52 (3H, s, OMe⁺), 3.71 (3H, s, OMe⁺), 3.75 (3H, s, OMe⁺), 3.79 (3H, s, OMe⁺), 3.835 (3H, s, OMe⁺), 3.842 (3H, s, OMe⁺), 6.37 (1H, d, J = 2.4 Hz, Ar-H⁺), 6.43 (1H, dd, J = 8.3, 2.4 Hz, Ar-H⁺), 6.47 (1H, dd, J = 8.5, 2.4 Hz, Ar-H⁺), 6.52 (1H, d, J = 2.2 Hz, Ar-H⁺), 6.69 – 6.73 (2H, m, Ar-H⁺), 6.85– 6.89 (2H, m, Ar-H⁺), 6.94 (1H, d, J = 8.3 Hz, Ar-H⁺), 6.97 (2H, s, Ar-H⁺), 7.06 (1H, s, C=C-H⁺), 7.08 – 7.10 (3H, m, Ar-H⁺), 7.14 (1H, s, C=C-H⁺), 7.34 – 7.39 (4H, m, Ar-H⁺), 7.44 – 7.49 (1H, m, Ar-H⁺), 7.89 – 7.91 (2H, m, Ar-H⁺), 7.91 – 7.93 (2H, m, Ar-H⁺); δ_{C} (100 MHz, CDCl₃) 55.14⁺, 55.24⁺, 55.29⁺, 55.36⁺, 55.44⁺, 55.72⁺, 98.72⁺, 99.21⁺, 104.30⁺, 113.11⁺, 113.72⁺, 121.05⁺, 122.39⁺, 125.34⁺, 125.83⁺, 127.89⁺, 128.13⁺, 128.21⁺, 128.48⁺, 128.87⁺, 129.36⁺, 130.84⁺, 131.68⁺, 132.12⁺, 132.32⁺, 132.60⁺, 133.94⁺, 138.87⁺, 150.39⁺, 157.39⁺, 159.41⁺, 160.51⁺, 161.03⁺, 192.26⁺, 193.85⁺.

6.8 General method for the synthesis of substituted 6-bromo-2H-naphtho[1,2-*b*]pyrans (6-bromo-2H-benzo[*h*]chromenes)

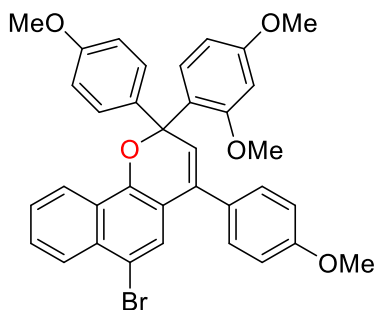
A stirred solution of the 4-bromo-1-naphthol (1.0 eq.) and the requisite 1,1,3-triaryl prop-2-yn-1-ol (1.0 eq.) in the presence of pyridinium 4-toluenesulfonate (PPTS) (5 mol %) and trimethyl orthoformate (2.0 eq.) in 1,2-dichloroethane (6 mL/mmol) was heated under reflux for up to 5 hours (until none of the prop-2-yn-1-ol remained by TLC examination of the reaction mixture). Removal of the solvent under reduced pressure from the cooled reaction mixture and gave either a dark red or green gum that was eluted from silica to afford the pure products. The following compounds were obtained by using this method.

6.8.1 6-Bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-4-phenyl-2H-benzo[*h*]chromene 3.1aa



From 1-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol (7.47 g, 19.9 mmol) and 4-bromo-1-naphthol (4.45 g, 19.9 mmol) after elution from silica with 80 % DCM/hexane to afford the title compound **3.1aa** as fluffy pale pink microcrystals (4.81 g, 42 %); mp = 86 – 88 °C; ν_{max} (neat) 1606, 1501, 1248, 1206, 1161, 1029, 827, 758, 699, 577 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.62 (3H, s, OMe), 3.76 (3H, s, OMe), 3.78 (3H, s, OMe), 6.43 (1H, s, 3-H), 6.45–6.48 (2H, m, Ar-H), 6.78–6.82 (2H, m, Ar-H), 7.41–7.48 (8H, m, Ar-H), 7.51–7.58 (2H, m, Ar-H), 7.65–7.67 (1H, m, Ar-H), 8.08–8.10 (1H, m, 7-H), 8.41–8.44 (1H, m, 10-H); δ_{C} (100 MHz, CDCl_3) 55.17, 55.32, 55.51, 82.29, 100.19, 103.70, 113.10, 113.21, 117.91, 122.82, 124.48, 126.23, 126.42, 126.80, 126.89, 127.06, 127.63, 127.89, 127.98, 128.21, 128.60, 128.78, 132.30, 134.27, 136.79, 138.21, 148.05, 157.23, 158.75, 160.52; HRMS (ESI) found $[\text{M}]^+$ 578.1086 $\text{C}_{34}\text{H}_{27}^{81}\text{BrO}_4$ requires $[\text{M}]^+$ 578.1093.

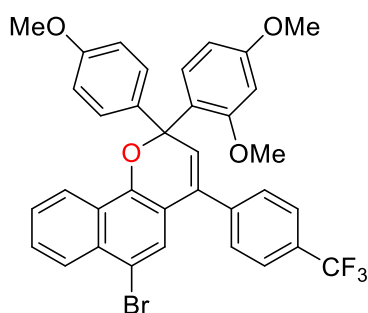
6.8.2 6-Bromo-2-(2,4-dimethoxyphenyl)-2,4-bis(4-methoxyphenyl)-2H-benzo[*h*]chromene 3.1ab



From 1-(2,4-dimethoxyphenyl)-1,3-bis(4-methoxyphenyl)prop-2-yn-1-ol (5.01 g, 12.4 mmol) and 4-bromo-1-naphthol (2.77 g, 12.4 mmol) after elution from silica with neat DCM to afford the title compound **3.1ab** as pale pink fluffy needles (3.66 g, 48 %); mp = 105 – 107 °C; ν_{max}

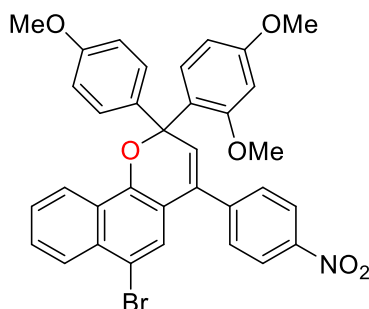
(neat) 1606, 1505, 1244, 1029, 826, 756, 532 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.60 (3H, s, OMe), 3.74 (3H, s, OMe), 3.76 (3H, s, OMe), 3.87 (3H, s, OMe), 6.36 (1H, s, 3-H), 6.44 – 6.47 (2H, m, Ar-H), 6.77 – 6.80 (2H, m, Ar-H), 6.97 – 7.01 (2H, m, Ar-H), 7.38 – 7.45 (4H, m, Ar-H), 7.48 (1H, s, 5-H), 7.51 – 7.58 (2H, m, Ar-H), 7.64 – 7.66 (1H, m, Ar-H), 8.07 – 8.10 (1H, m, 7-H), 8.40 – 8.43 (1H, m, 10-H); δ_{C} (100 MHz, CDCl_3) 55.16, 55.31, 55.37, 55.49, 82.27, 100.21, 103.70, 113.07, 113.13, 113.99, 118.16, 122.80, 124.60, 126.16, 126.86, 127.02, 127.55, 127.87, 128.18, 129.91, 130.53, 132.24, 133.78, 136.89, 148.07, 157.25, 158.72, 159.43, 160.48; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 609.1267$ $\text{C}_{35}\text{H}_{29}^{79}\text{BrO}_5$ requires $[\text{M}+\text{H}]^+ = 609.1276$.

6.8.3 6-Bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-4-(4-(trifluoromethyl)-phenyl)-2H-benzo[*h*]chromene 3.1ac



From 1-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-ol (4.80 g, 10.8 mmol) and 4-bromo-1-naphthol (2.41 g, 10.8 mmol) after elution from silica with 60 % DCM/hexane to afford the title compound **3.1ac** as colourless fluffy needles (3.37 g, 48 %); mp = 97 – 98°C; ν_{max} (neat) 1607, 1503, 1322, 1162, 1121, 1104, 1066, 1032, 828, 758 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.62 (3H, s, OMe), 3.76 (3H, s, OMe), 3.78 (3H, s, OMe), 6.45 – 6.46 (2H, m, Ar-H), 6.47 (1H, s, 3-H), 6.78 – 6.82 (2H, m, Ar-H), 7.37 (1H, s, 5-H), 7.40 – 7.43 (2H, m, Ar-H), 7.53 – 7.64 (5H, m, Ar-H), 7.72 (2H, d, $J = 8.1$ Hz, Ar-H), 8.09 – 8.11 (1H, m, 7-H), 8.41 – 8.43 (1H, m, 10-H); δ_{F} (376 MHz, CDCl_3) -62.5; δ_{C} (100 MHz, CDCl_3) 55.19, 55.34, 55.52, 82.32, 100.21, 103.81, 113.19, 113.45, 117.16, 122.81, 124.07, 124.18 (q, $J = 272.5$ Hz, CF_3), 125.62 (q, $J = 3.8$ Hz, $=\text{CH}-\text{C}-\text{CF}_3$), 126.26, 126.37, 126.47, 127.14, 127.87, 127.89, 128.05, 128.17, 129.10, 130.11 (q, $J = 32.5$ Hz, $\text{C}-\text{CF}_3$), 132.45, 133.23, 136.40, 141.95 (q, $J = 1.3$ Hz, $\text{C}-\text{CH}=\text{CH}-\text{C}-\text{CF}_3$), 148.12, 157.15, 158.88, 160.63; HRMS (ESI) found $[\text{M}]^+ = 646.0959$ $\text{C}_{35}\text{H}_{26}^{81}\text{BrF}_3\text{O}_4$ requires $[\text{M}]^+ = 646.0967$.

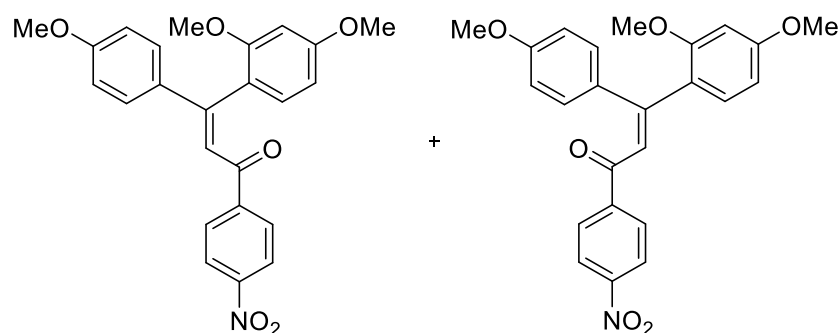
6.8.4 6-Bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-4-(4-nitrophenyl)-2H-benzo[*h*]chromene 3.1ad



From 1-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-3-(4-nitrophenyl)prop-2-yn-1-ol (1.50 g, 3.58 mmol) and 4-bromo-1-naphthol (0.80 g, 3.58 mmol) after elution from silica with 20 % EtOAc/petroleum ether (bp. 40 – 60 °C) afforded:

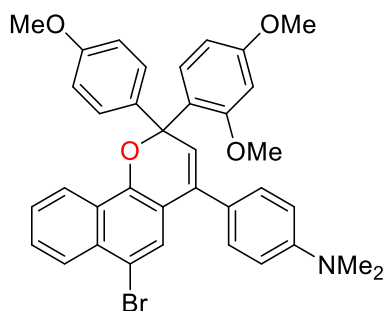
Fraction 1: the title compound **3.1ad** as an orange powder (0.76 g, 33 %); mp = 173 – 175 °C; ν_{max} (neat) 1596, 1504, 1342, 1248, 1025, 825, 754 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.63 (3H, s, OMe), 3.76 (3H, s, OMe), 3.77 (3H, s, OMe), 6.44 – 6.47 (2H, m, Ar-H), 6.52 (1H, s, 3-H), 6.80 (2H, d, J = 8.9 Hz, Ar-H), 7.32 (1H, s, 5-H), 7.40 (2H, d, J = 8.8 Hz, Ar-H), 7.54 – 7.64 (5H, m, Ar-H), 8.09 – 8.11 (1H, m, 7-H), 8.32 (2H, d, J = 8.7 Hz, Ar-H), 8.41 – 8.43 (1H, m, 10-H); δ_{C} (100 MHz, CDCl_3) 55.20, 55.35, 55.56, 82.34, 100.23, 103.89, 113.25, 113.62, 116.69, 122.82, 123.76, 123.98, 125.97, 126.36, 126.62, 127.20, 127.88, 128.08, 128.15, 128.95, 129.59, 132.54, 132.67, 136.11, 145.05, 147.56, 148.22, 157.13, 158.97, 160.71; HRMS (ESI) found $[\text{M}+\text{H}]^+$ 624.1017 $\text{C}_{34}\text{H}_{26}^{81}\text{BrNO}_6$ requires $[\text{M}+\text{H}]^+$ 624.1022.

Fraction 2: an inseparable mixture of the *Z*- and *E*- **3-(2,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-1-(4-nitrophenyl)prop-2-en-1-one 3.21a** and **3.21b** ($10^{\dagger}:1^{\dagger}$) as a dark orange viscous gum (0.34 g, 14 %):



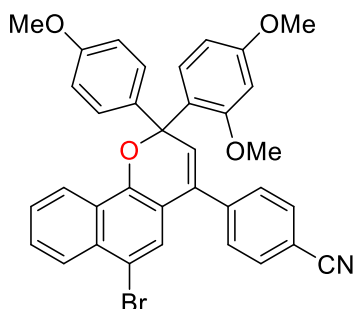
$\nu_{\max}$ (neat) 2950, 2820, 1658, 1600, 1510, 1342, 1265, 1207, 1165, 1035, 833, 715, 554 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.53 (3H, s, OMe^+), 3.72 (3H, s, OMe^+), 3.76 (3H, s, OMe^+), 3.76 (3H, s, OMe^+), 3.84 (3H, s, OMe^+), 3.85 (3H, s, OMe^+), 6.28 (1H, d, $J = 2.4$ Hz, Ar-H^+), 6.39 (1H, dd, $J = 8.3, 2.4$ Hz, Ar-H^+), 6.47 (1H, dd, $J = 8.5, 2.4$ Hz, Ar-H^+), 6.54 (1H, d, $J = 2.2$ Hz, Ar-H^+), 6.65 – 6.68 (2H, m, Ar-H^+), 6.86– 6.90 (3H, m, Ar-H^+), 6.92 (1H, s, $\text{C}=\text{C-H}^+$), 7.00 (1H, s, $\text{C}=\text{C-H}^+$), 7.01– 7.04 (3H, m, Ar-H^+), 7.33 – 7.36 (2H, m, Ar-H^+), 7.89 – 7.93 (2H, m, Ar-H^+), 7.93 – 7.94 (2H, m, Ar-H^+), 8.10 – 8.12 (2H, m, Ar-H^+), 8.12 – 8.15 (2H, m, Ar-H^+); δ_{C}^* (100 MHz, CDCl_3) 55.24, 55.36, 55.40, 98.60, 104.40, 113.86, 120.50, 121.75, 123.15, 129.25, 129.56, 132.16, 133.19, 144.02, 149.36, 152.59, 157.80, 160.98, 161.63, 191.52. * Only ^{13}C NMR signals stated for major isomer as some of the signals for the minor isomer were too weak to be identified.

6.8.5 4-(6-Bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-2H-benzo[*h*]chromen-4-yl)-*N,N*-dimethylaniline 3.1ae



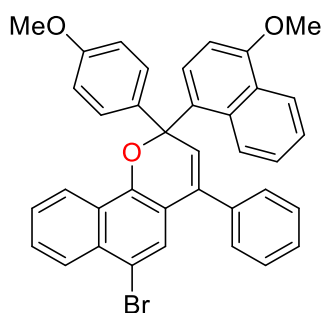
From 1-(2,4-dimethoxyphenyl)-3-(4-(dimethylamino)phenyl)-1-(4-methoxyphenyl)prop-2-yn-1-ol (1.85 g, 4.43 mmol) and 4-bromo-1-naphthol (0.98 g, 4.43 mmol) after elution from silica with 50 % DCM/petroleum ether (bp. 40 – 60 °C) to afford the title compound **5f** as a pale brown crystalline powder (1.51 g, 55 %); mp = 225 – 226 °C; $\nu_{\max}$ (neat) 2160, 2027, 1606, 1501, 1246, 1206, 1028, 820, 588 cm^{-1} ; δ_{H} (600 MHz, CDCl_3) 3.01 (6H, s, NMe_2), 3.59 (3H, s, OMe), 3.74 (3H, s, OMe), 3.75 (3H, s, OMe), 6.33 (1H, s, 3-H), 6.43 – 6.44 (2H, m, Ar-H), 6.77 (2H, d, $J = 8.8$ Hz, Ar-H), 6.79 (2H, d, $J = 8.6$ Hz, Ar-H), 7.34 (2H, d, $J = 8.6$ Hz, Ar-H), 7.42 (2H, d, $J = 8.8$ Hz, Ar-H), 7.49 – 7.54 (2H, m, Ar-H), 7.56 (1H, s, 5-H), 7.63 – 7.65 (1H, m, Ar-H), 8.07 (1H, d, $J = 8.3$ Hz, 7-H), 8.40 (1H, d, $J = 8.3$ Hz, 10-H); δ_{C} (150 MHz, CDCl_3) 40.54, 55.13, 55.27, 55.45, 82.28, 100.16, 103.60, 112.32, 113.00, 118.47, 122.79, 124.77, 125.26, 125.96, 126.03, 126.46, 126.96, 127.13, 127.40, 127.86, 128.22, 129.51, 132.15, 134.06, 137.10, 148.09, 150.27, 157.27, 158.64, 160.39; HRMS (ESI) found $[\text{M}+\text{H}]^+$ 622.1590 $\text{C}_{36}\text{H}_{32}^{81}\text{BrNO}_4$ requires $[\text{M}+\text{H}]^+$ 622.1593.

6.8.6 4-(6-Bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-2H-benzo[*h*]chromen-4-yl)benzonitrile 3.1af



From 4-(3-(2,4-dimethoxyphenyl)-3-hydroxy-3-(4-methoxyphenyl)prop-1-yn-1-yl)benzonitrile (1.10 g, 2.75 mmol) and 4-bromo-1-naphthol (0.61 g, 2.75 mmol) after elution from silica with 70 % DCM/petroleum ether (bp. 40 – 60 °C) to afford the title compound **3.1af** as a pale green crystalline powder (0.60 g, 36 %); mp = 128 – 129 °C; ν_{max} (neat) 2227, 1605, 1503, 1248, 1206, 1102, 1031, 827, 760, 557 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.61 (3H, s, OMe), 3.75 (3H, s, OMe), 3.76 (3H, s, OMe), 6.43 – 6.46 (2H, m, Ar-H), 6.47 (1H, s, 3-H), 6.79 (2H, d, J = 8.8 Hz, Ar-H), 7.32 (1H, s, 5-H), 7.39 (2H, m, Ar-H), 7.52 – 7.60 (5H, m, Ar-H), 7.74 (2H, d, J = 8.3 Hz, Ar-H), 8.08 – 8.10 (1H, m, 7-H), 8.39 – 8.42 (1H, m, 10-H); δ_{C} (100 MHz, CDCl_3) 55.19, 55.35, 55.55, 82.32, 100.23, 103.87, 111.77, 113.22, 113.56, 116.76, 118.77, 122.81, 123.84, 126.01, 126.37, 126.58, 127.17, 127.87, 128.03, 128.15, 128.62, 129.45, 132.50, 132.98, 136.19, 143.07, 148.21, 157.13, 158.94, 160.69; HRMS (ESI) found $[\text{M}+\text{H}]^+$ 604.1114 $\text{C}_{35}\text{H}_{26}^{81}\text{BrNO}_4$ requires $[\text{M}+\text{H}]^+$ 604.1123.

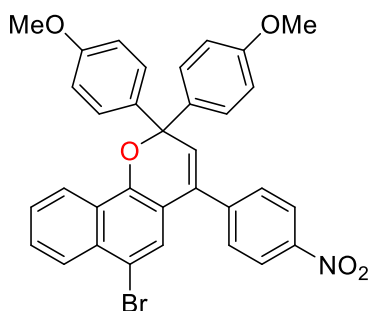
6.8.7 6-Bromo-2-(4-methoxynaphthalen-1-yl)-2-(4-methoxyphenyl)-4-phenyl-2H-benzo[*h*]chromene 3.1ah



From 1-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol (2.00 g, 5.07 mmol) and 4-bromo-1-naphthol (1.13 g, 5.07 mmol) after elution from silica with 20 %

DCM/petroleum ether (bp. 40 – 60 °C) to afford the title compound **3.1ah** as an off-white microcrystalline powder (1.24 g, 41 %); mp = 106 – 107 °C; ν_{max} (neat) 2359, 2339, 1582, 1508, 1245, 1170, 1029, 756, 691, 408 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.76 (3H, s, OMe), 3.97 (3H, s, OMe), 6.08 (1H, s, 3-H), 6.71 (1H, d, J = 8.2 Hz, Ar-H), 6.83 (2H, d, J = 9.0 Hz, Ar-H), 7.37 – 7.54 (12H, m, Ar-H), 7.74 (1H, d, J = 8.1 Hz, Ar-H), 8.02 (1H, d, J = 8.2 Hz, 7-H), 8.24 – 8.26 (1H, m, Ar-H), 8.29 – 8.35 (2H, m, Ar-H); δ_{C} (100 MHz, CDCl_3) 55.23, 55.47, 84.22, 101.91, 113.30, 113.70, 117.70, 122.50, 123.13, 124.73, 125.95, 126.15, 126.57, 126.77, 126.91, 126.95, 127.18, 127.23, 127.67, 127.72, 128.00, 128.23, 128.68, 128.71, 130.05, 131.59, 132.43, 134.89, 137.69, 137.78, 148.70, 156.03, 158.81; HRMS (ESI) found $[\text{M}+\text{H}]^+$ 599.1200 $\text{C}_{37}\text{H}_{27}^{79}\text{BrO}_3$ requires $[\text{M}+\text{H}]^+$ 599.1222.

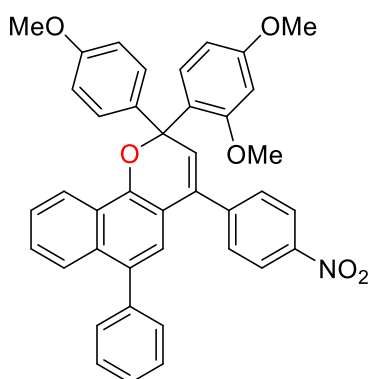
6.8.8 6-Bromo-2,2-bis(4-methoxyphenyl)-4-(4-nitrophenyl)-2H-benzo[*h*]chromene 3.1ai



From 1,1-bis(4-methoxyphenyl)-3-(4-nitrophenyl)prop-2-yn-1-ol (1.69 g, 4.34 mmol) and 4-bromo-1-naphthol (0.97 g, 4.34 mmol) after elution from silica with 60 % DCM/petroleum ether (bp. 40 – 60 °C) to afford the title compound **3.1ai** as a pale yellow powder (0.47 g, 40 %); mp = 245 – 246 °C; ν_{max} (neat) 2980, 1595, 1507, 1342, 1247, 1168, 1096, 1032, 978, 825, 751, 586 cm^{-1} ; δ_{H} (600 MHz, CDCl_3) 3.76 (6H, s, 2 × OMe), 6.21 (1H, s, 3-H), 6.83-6.86 (4H, m, Ar-H), 7.31 (1H, s, 5-H), 7.41 - 7.43 (4H, m, Ar-H), 7.55 - 7.61 (2H, m, Ar-H), 7.64 – 7.66 (2H, m, Ar-H), 8.09 – 8.10 (1H, m, 7-H), 8.31 – 8.33 (2H, m, Ar-H), 8.41 – 8.43 (1H, m, 10-H); δ_{C} (150 MHz, CDCl_3) 55.27, 83.00, 113.67, 113.83, 116.68, 122.81, 124.03, 125.94, 126.40, 126.75, 127.21, 128.16, 128.30, 128.95, 129.64, 132.70, 134.01, 136.28, 144.50, 147.76, 148.43, 159.20; HRMS (ESI) found $[\text{M}+\text{H}]^+$ 594.0891 $\text{C}_{33}\text{H}_{24}^{81}\text{BrNO}_5$ requires $[\text{M}+\text{H}]^+$ 594.0916.

126.26, 126.43, 127.63, 128.02, 128.26, 128.39, 128.86, 131.23, 131.94, 132.63, 133.24, 135.02, 137.39, 138.84, 147.51, 157.27, 158.60, 158.65, 160.42; HRMS (ESI) found $[M]^+ = 606.2396$ $C_{41}H_{34}O_5$ requires $[M]^+ = 606.2406$.

6.9.2 2-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-4-(4-nitrophenyl)-6-phenyl-2H-benzo[h]chromene 3.1dd



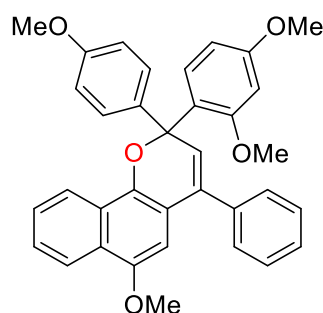
From 1-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-3-(4-nitrophenyl)prop-2-yn-1-ol (1.00 g, 2.38 mmol) and 4-phenyl-1-naphthol (0.53 g, 2.38 mmol) after elution from silica with 20 % EtOAc/petroleum ether (bp. 40 – 60 °C) to afford the title compound **3.1dd** as a bright yellow powder (0.74 g, 50 %); mp = 116 – 117 °C; $\nu_{\max}$ (neat) 2980, 1508, 1344, 1247, 1173, 1031, 827, 765, 700 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.64 (3H, s, OMe), 3.76 (3H, s, OMe), 3.78 (3H, s, OMe), 6.48 – 6.50 (2H, m, Ar-H), 6.53 (1H, s, 3-H), 6.82 (2H, d, $J = 8.8$ Hz, Ar-H), 6.98 (1H, s, 5-H), 7.34 – 7.46 (8H, m, Ar-H), 7.50 – 7.54 (1H, m, Ar-H), 7.65 (2H, d, $J = 8.8$ Hz, Ar-H), 7.68 – 7.70 (1H, m, Ar-H), 7.80 (1H, d, $J = 8.4$ Hz, 7-H), 8.27 (2H, d, $J = 8.8$ Hz, Ar-H), 8.48 (1H, d, $J = 8.4$ Hz, 10-H); δ_{C} (100 MHz, CDCl_3) 55.20, 55.35, 55.58, 82.08, 100.23, 103.93, 113.21, 114.99, 122.67, 123.41, 123.83, 124.31, 125.15, 125.75, 126.05, 126.82, 127.05, 128.01, 128.22, 128.24, 128.44, 129.65, 130.13, 132.64, 132.86, 133.46, 136.68, 140.46, 145.71, 147.35, 147.87, 157.15, 158.88, 160.63; HRMS (ESI) found $[M+H]^+ = 622.2222$ $C_{40}H_{31}NO_6$ requires $[M+H]^+ = 622.2229$.

6.10 General method for the synthesis of 6-methoxy-2H-naphtho[1,2-*b*]pyrans (6-methoxy-2H-benzo[*h*]chromenes)

A stirred solution of the 4-methoxy-1-naphthol (1.0 eq.) and the requisite 1,1,3-triaryl prop-2-yn-1-ol (1.0 eq.) in the presence of pyridinium 4-toluenesulfonate (PPTS) (5 mol %) and

trimethyl orthoformate (2.0 eq.) in 1,2-dichloroethane (6 mL/mmol) was heated under reflux for up to 5 hours until none of the prop-2-yn-1-ol remained by TLC examination of the reaction mixture. Removal of the solvent under reduced pressure from the cooled reaction mixture and gave a dark red/green gum that was eluted from silica to afford the pure products. The following compounds were obtained by using this method.

6.10.1 2-(2,4-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)-4-phenyl-2H-benzo[*h*]chromene 3.1ba

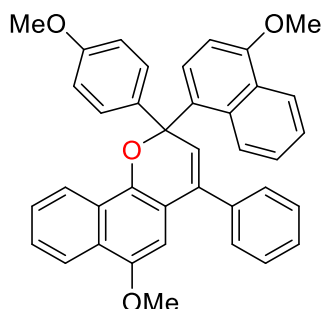


From 1-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol (2.00 g, 5.34 mmol) and 4-methoxy-1-naphthol (0.93 g, 5.34 mmol) after gradient elution from silica with 50 % DCM/petroleum ether (bp. 40 – 60 °C) → 60 % DCM/petroleum ether (bp. 40 – 60 °C) to afford:

Fraction 1: the title compound **3.1ba** as an off-white microcrystalline powder (1.57 g, 56 %); mp = 99 – 101 °C; ν_{max} (neat) 2931, 2834, 1605, 1455, 1380, 1207, 1097, 962, 832, 701, 574 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.62 (3H, s, OMe), 3.74 (3H, s, OMe), 3.76 (6H, s, 2 × OMe), 6.43 – 6.45 (2H, m, Ar-H), 6.44 (1H, s, 3-H), 6.51 (1H, s, 5-H), 6.76 – 6.79 (2H, m, Ar-H), 7.37 – 7.47 (6H, m, Ar-H), 7.50 – 7.53 (3H, m, Ar-H), 7.69 – 7.72 (1H, m, Ar-H), 8.13 (1H, d, J = 8.0 Hz, 7-H), 8.37 (1H, d, J = 8.0 Hz, 10-H); δ_{C} (100 MHz, CDCl_3) 55.15, 55.29, 55.49, 55.66, 81.35, 100.12, 101.68, 103.63, 112.95, 116.22, 121.87, 122.20, 124.93, 125.66, 125.85, 126.11, 126.78, 127.67, 127.90, 128.26, 128.34, 128.87, 135.27, 137.24, 139.02, 142.14, 149.03, 157.27, 158.58, 160.29; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 531.2160$ $\text{C}_{35}\text{H}_{30}\text{O}_5$ requires $[\text{M}+\text{H}]^+ = 531.2171$.

Fraction 2: the title compound **3.1ba** as a pale blue microcrystalline powder (0.54 g, 19 %) which had identical NMR spectroscopic data to fraction 1.

6.10.2 6-Methoxy-2-(4-methoxynaphthalen-1-yl)-2-(4-methoxyphenyl)-4-phenyl-2H-benzo[*h*]chromene 3.1bh



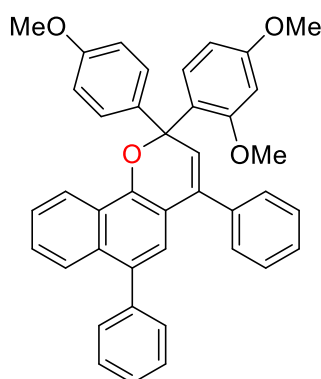
From 1-(4-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol (1.00 g, 2.54 mmol) and 4-methoxy-1-naphthol (0.44 g, 2.54 mmol) after gradient elution from silica with 10 % EtOAc/petroleum ether (bp. 60 – 80 °C) → 20 % EtOAc/petroleum ether (bp. 60 – 80 °C) to afford the title compound **3.1bh** as a beige powder (0.99 g, 71 %); mp = 143 – 145 °C; ν_{max} (neat) 3270, 1606, 1502, 1250, 1026, 831, 605 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.76 (3H, s, OMe), 3.77 (3H, s, OMe), 3.96 (3H, s, OMe), 6.09 (1H, s, 3-H), 6.56 (1H, s, 5-H), 6.70 (1H, d, J = 8.2 Hz, Ar-H), 6.80 – 6.83 (2H, m, Ar-H), 7.35 – 7.42 (5H, m, Ar-H), 7.43 – 7.50 (4H, m, Ar-H), 7.56 – 7.58 (2H, m, Ar-H), 7.74 (1H, d, J = 8.1 Hz, Ar-H), 8.05 – 8.09 (1H, m, Ar-H), 8.22 – 8.28 (2H, m, Ar-H), 8.39 – 8.43 (2H, m, Ar-H); δ_{C} (100 MHz, CDCl_3) 55.50, 55.43, 55.70, 83.30, 101.63, 101.90, 113.55, 115.99, 121.73, 122.37, 122.56, 124.63, 125.78, 125.81, 126.01, 126.03, 126.30, 126.91, 126.98, 127.40, 127.50, 127.95, 128.07, 128.44, 128.82, 130.69, 131.79, 136.00, 138.15, 138.60, 142.85, 149.05, 155.85, 158.65; HRMS (ESI) found $[\text{M}+\text{H}]^+$ 551.2218 $\text{C}_{38}\text{H}_{30}\text{O}_4$ requires $[\text{M}+\text{H}]^+$ 551.2222.

6.11 General method for the Suzuki cross-coupling reaction of 4-aryl-6-bromo-2H-naphtho[1,2-*b*]pyrans

A 4-aryl-6-bromo-2H-naphtho[1,2-*b*]pyran (1.0 eq.), arylboronic acid (1.5 – 3.0 eq.) and potassium fluoride (1.9 eq.) were dissolved in a mixture of EtOH and PhMe (1:1) (15 mL/mmol) and the mixture was degassed with N_2 for 20 minutes. $\text{Pd}(\text{PPh}_3)_4$ catalyst (5 mol %) was added to the reaction mixture and mixture was heated at reflux under N_2 for up to 20 h until no further change was noted by TLC examination of the reaction mixture. The cooled mixture was diluted with water (250 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (2 × 100 mL), dried with anhydrous sodium sulfate

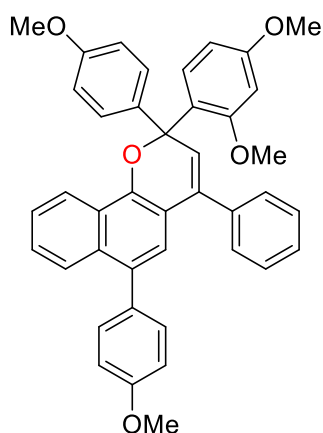
and the solvent evaporated under reduced pressure to afford the crude product that required further purification by flash chromatography to afford the pure target compound. The following naphthopyrans were obtained by using this protocol:

6.11.1 2-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-4,6-diphenyl-2H-benzo[*h*]chromene 4.1a



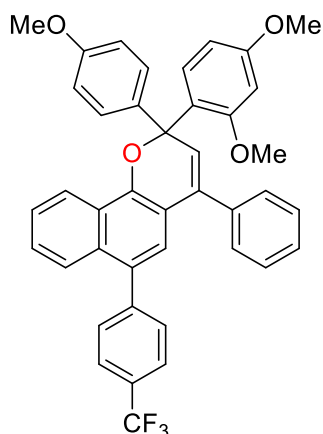
From 6-bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-4-phenyl-2H-benzo[*h*]-chromene (1.00 g, 1.73 mmol) and phenylboronic acid (0.32 g, 2.60 mmol) after elution from silica with 10 % EtOAc/petroleum ether (bp. 40 – 60 °C) to afford the title compound **4.1a** as an off-white microcrystalline powder (0.89 g, 89 %); mp = 84 – 87 °C; ν_{max} (neat) 1605, 1503, 1247, 1207, 1158, 1029, 972, 829, 771, 700, 579 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.61 (3H, s, OMe), 3.76 (3H, s, OMe), 3.78 (3H, s, OMe), 6.42 (1H, s, 3-H), 6.45 – 6.50 (2H, m, Ar-H), 6.79 – 6.81 (2H, m, Ar-H), 7.12 (1H, s, 5-H), 7.31 – 7.41 (9H, m, Ar-H), 7.46 – 7.50 (5H, m, Ar-H), 7.73 (1H, d, J = 8.5 Hz, Ar-H), 7.76 (1H, d, J = 8.4 Hz, 7-H), 8.47 – 8.49 (1H, m, 10-H); δ_{C} (100 MHz, CDCl_3) 55.17, 55.31, 55.52, 82.03, 100.21, 103.77, 113.06, 116.13, 122.68, 124.24, 125.06, 125.17, 125.34, 125.89, 126.35, 126.45, 126.77, 127.65, 128.02, 128.10, 128.26, 128.41, 128.85, 130.25, 132.31, 132.41, 134.98, 137.37, 138.80, 140.85, 147.73, 157.27, 158.66, 160.43; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 577.2365$ $\text{C}_{40}\text{H}_{32}\text{O}_4$ requires $[\text{M}+\text{H}]^+ = 577.2379$.

6.11.2 2-(2,4-Dimethoxyphenyl)-2,6-bis(4-methoxyphenyl)-4-phenyl-2H-benzo[*h*]chromene 4.1b



From 6-bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-4-phenyl-2H-benzo[*h*]chromene (1.00 g, 1.73 mmol) and 4-methoxyphenylboronic acid (0.40 g, 2.60 mmol) after elution from silica with 20 % EtOAc/hexane as a colourless gum that solidified when scratched with *n*-pentane and gave the title compound **4.1b** as off-white crystalline powder (0.76 g, 72 %). This compound had near identical physical and spectroscopic properties as compound **3.1ca**.

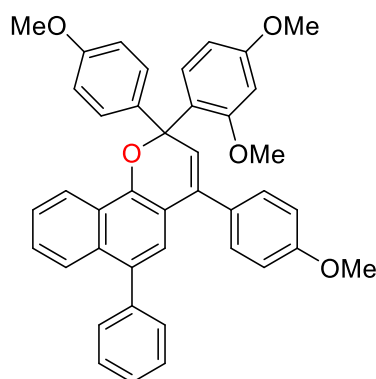
6.11.3 2-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-4-phenyl-6-(4-(trifluoromethyl)phenyl)-2H-benzo[*h*]chromene 4.1c



From 6-bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-4-phenyl-2H-benzo[*h*]chromene (1.00 g, 1.73 mmol) and (4-trifluoromethyl)phenylboronic acid (0.49 g, 2.60 mmol) after elution from silica with 20 % EtOAc/hexane to afford the title compound **4.1c** as a peach coloured microcrystalline powder (0.95 g, 85 %); mp = 53 – 56 °C; ν_{max} (neat) 1607, 1502,

1321, 1248, 1159, 1118, 1065, 829, 700, 578 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.63 (3H, s, OMe), 3.77 (3H, s, OMe), 3.79 (3H, s, OMe), 6.46 (1H, s, 3-H), 6.47 – 6.51 (2H, m, Ar-H), 6.80 – 6.84 (2H, m, Ar-H), 7.12 (1H, s, 5-H), 7.36 – 7.44 (4H, m, Ar-H), 7.47 – 7.54 (7H, m, Ar-H), 7.65 (2H, d, J = 8.1 Hz, Ar-H), 7.70 – 7.75 (2H, m, Ar-H), 8.51 (1H, d, J = 8.3 Hz, 10-H); δ_{F} (376 MHz, CDCl_3) -62.3; δ_{C} (100 MHz, CDCl_3) 55.18, 55.33, 55.53, 82.20, 100.19, 103.75, 113.08, 116.20, 122.87, 124.36 (q, J = 272 Hz, CF_3), 124.47, 124.86, 125.11 (q, J = 3.8 Hz, $=\text{CH}-\text{C}-\text{CF}_3$), 125.22, 125.37, 125.63, 126.63, 126.78, 127.80, 127.97, 128.26, 128.49, 128.80, 128.95 (q, J = 32.5 Hz, $\text{C}-\text{CF}_3$), 130.52, 130.75, 132.01, 134.76, 137.18, 138.59, 144.58 (q, J = 1.3 Hz, $\text{C}-\text{CH}=\text{CH}-\text{C}-\text{CF}_3$), 148.33, 157.26, 158.71, 160.49; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 645.2236$ $\text{C}_{41}\text{H}_{31}\text{F}_3\text{O}_4$ requires $[\text{M}+\text{H}]^+ = 645.2252$.

6.11.4 2-(2,4-Dimethoxyphenyl)-2,4-bis(4-methoxyphenyl)-6-phenyl-2H-benzo[*h*]chromene 4.1d

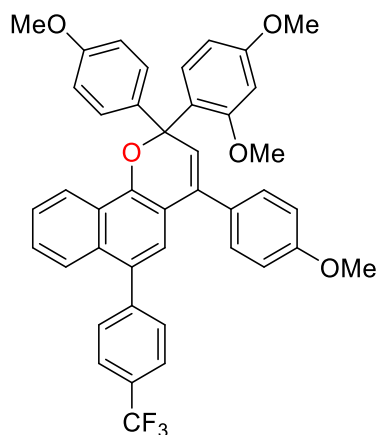


From 6-bromo-2-(2,4-dimethoxyphenyl)-2,4-bis(4-methoxyphenyl)-2H-benzo[*h*]chromene (1.00 g, 1.64 mmol) and phenylboronic acid (0.30 g, 2.46 mmol) after elution from silica with 30 % EtOAc/petroleum ether (bp. 40 – 60 °C) afforded the title compound **4.1d** as pale yellow microcrystalline powder (0.92 g, 92 %); mp = 101 – 103 °C; ν_{max} (neat) 1606, 1504, 1245, 1207, 1173, 1030, 828, 701 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.63 (3H, s, OMe), 3.77 (3H, s, OMe), 3.79 (3H, s, OMe), 3.84 (3H, s, OMe), 6.40 (1H, s, 3-H), 6.47 – 6.51 (2H, m, Ar-H), 6.80 – 6.83 (2H, m, Ar-H), 6.93 – 6.97 (2H, m, Ar-H), 7.16 (1H, s, 5-H), 7.33 – 7.45 (8H, m, Ar-H), 7.47 – 7.52 (3H, m, Ar-H), 7.75 (1H, d, J = 8.4 Hz, Ar-H), 7.79 (1H, d, J = 8.4 Hz, 7-H), 8.49 (1H, d, J = 7.9 Hz, 10-H); δ_{C} (100 MHz, CDCl_3) 55.17, 55.32, 55.52, 82.02, 100.19, 103.71, 113.03, 113.83, 116.38, 122.69, 124.34, 125.11, 125.18, 125.33, 125.77, 125.88, 126.33, 126.78, 127.99, 128.12, 128.28, 129.98, 130.27, 131.13, 132.26, 132.34, 134.49, 137.43, 140.89, 147.76, 157.26,

6.11.5 2-(2,4-Dimethoxyphenyl)-2,4,6-tris(4-methoxyphenyl)-2*H*-benzo[*h*]chromene 4.1e

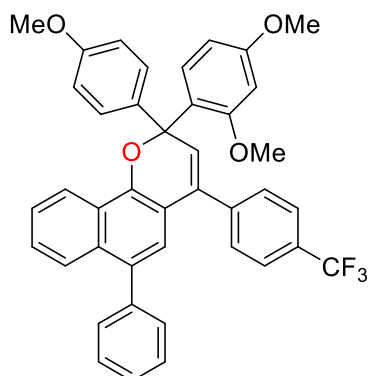
From 6-bromo-2-(2,4-dimethoxyphenyl)-2,4-bis(4-methoxyphenyl)-2*H*-benzo[*h*]chromene (1.00 g, 1.64 mmol) and (4-methoxyphenyl)boronic acid (0.37 g, 2.46 mmol) after elution from silica with 30 % EtOAc/petroleum ether (bp. 40 – 60 °C) to afford the title compound **4.1e** as a pale yellow microcrystalline powder (0.89 g, 86 %); mp = 110 – 112 °C; ν_{max} (neat) 1606, 1510, 1242, 1170, 1030, 828, 570 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.62 (3H, s, OMe), 3.76 (3H, s, OMe), 3.78 (3H, s, OMe), 3.84 (3H, s, OMe), 3.85 (3H, s, OMe), 6.39 (1H, s, 3-H), 6.47 – 6.50 (2H, m, Ar-H), 6.80 – 6.82 (2H, m, Ar-H), 6.93– 6.96 (4H, m, Ar-H), 7.13 (1H, s, 5-H), 7.29 – 7.31 (2H, m, Ar-H), 7.37 – 7.43 (3H, m, Ar-H), 7.47 – 7.50 (3H, m, Ar-H), 7.74 (1H, d, J = 8.4 Hz, Ar-H), 7.79 (1H, d, J = 8.3 Hz, 7-H), 8.47 – 8.49 (1H, m, 10-H); δ_{C} (100 MHz, CDCl_3) 55.16, 55.31, 55.51, 81.97, 100.20, 103.74, 113.02, 113.56, 113.82, 122.67, 124.27, 125.17, 125.20, 125.25, 125.74, 125.93, 126.22, 128.00, 128.26, 129.97, 131.18, 131.23, 131.88, 132.57, 133.29, 134.52, 137.48, 147.53, 157.28, 158.59, 158.63, 159.19, 160.38; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 637.2581$ $\text{C}_{42}\text{H}_{36}\text{O}_6$ requires $[\text{M}+\text{H}]^+ = 637.2590$.

6.11.6 2-(2,4-Dimethoxyphenyl)-2,4-bis(4-methoxyphenyl)-6-(4-(trifluoromethyl)phenyl)-2H-benzo[*h*]chromene 4.1f



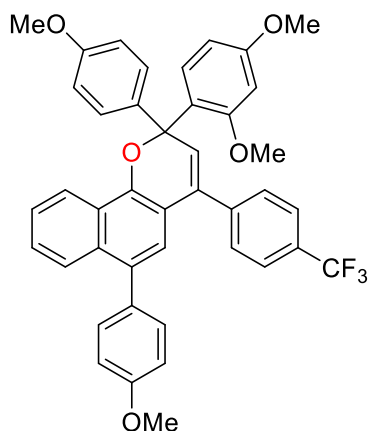
From 6-bromo-2-(2,4-dimethoxyphenyl)-2,4-bis(4-methoxyphenyl)-2H-benzo[*h*]chromene (1.00 g, 1.64 mmol) and (4-trifluoromethyl)phenylboronic acid (0.47 g, 2.46 mmol) after elution from silica with 20 % EtOAc/petroleum ether (bp. 40 – 60 °C) to afford the title compound **4.1f** as a colourless gum that solidified when scratched with *n*-pentane and gave a very pale yellow microcrystalline powder (0.81 g, 73 %); mp = 120 – 122 °C; ν_{max} (neat) 1608, 1504, 1323, 1247, 1121, 1031, 830, 768 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.62 (3H, s, OMe), 3.77 (3H, s, OMe), 3.78 (3H, s, OMe), 3.84 (3H, s, OMe), 6.40 (1H, s, 3-H), 6.46 – 6.50 (2H, m, Ar-H), 6.79 – 6.83 (2H, m, Ar-H), 6.93 – 6.96 (2H, m, Ar-H), 7.13 (1H, s, 5-H), 7.40 – 7.43 (3H, m, Ar-H), 7.44 – 7.51 (5H, m, Ar-H), 7.65 (2H, d, J = 8.1 Hz, Ar-H), 7.70 – 7.73 (2H, m, Ar-H), 8.49 (1H, d, J = 8.3 Hz, 10-H); δ_{F} (376 MHz, CDCl_3) -62.3; δ_{C} (100 MHz, CDCl_3) 55.17, 55.31, 55.51, 82.21, 100.21, 103.75, 113.06, 113.88, 116.44, 122.87, 124.36 (q, J = 272.0 Hz, $\underline{\text{C}}\text{F}_3$), 124.55, 124.99, 125.09 (q, J = 3.8 Hz, $\underline{\text{C}}\text{H}-\text{C}-\text{CF}_3$), 125.23, 125.34, 125.57, 125.93, 126.71, 127.95, 128.25, 128.93 (q, J = 32.5 Hz, $\underline{\text{C}}-\text{CF}_3$), 129.92, 130.51, 130.68, 130.91, 131.96, 134.26, 137.29, 144.64 (q, J = 1.2 Hz, $\underline{\text{C}}-\text{CH}=\text{CH}-\text{C}-\text{CF}_3$), 148.36, 157.28, 158.69, 159.30, 160.46; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 675.2347$ $\text{C}_{42}\text{H}_{33}\text{F}_3\text{O}_5$ requires $[\text{M}+\text{H}]^+ = 675.2358$.

6.11.7 2-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-6-phenyl-4-(4-(trifluoromethyl)phenyl)-2*H*-benzo[*h*]chromene 4.1g



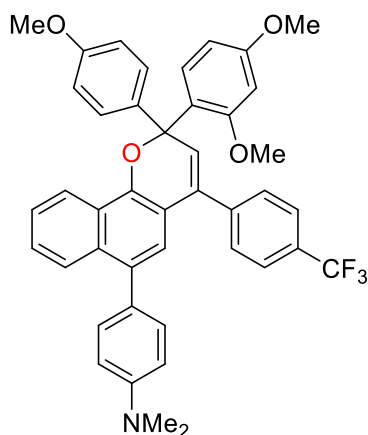
From 6-bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)-2*H*-benzo[*h*]chromene (0.80 g, 1.24 mmol) and phenylboronic acid (0.23 g, 1.85 mmol) after elution from silica with 10 % EtOAc/petroleum ether (bp. 40 – 60 °C) to afford the title compound **4.1g** as a pale yellow microcrystalline powder (0.65 g, 81 %); mp = 76 – 78 °C; ν_{max} (neat) 1606, 1503, 1322, 1249, 1121, 1066, 1031, 829, 702 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.63 (3H, s, OMe), 3.77 (3H, s, OMe), 3.79 (3H, s, OMe), 6.48 (1H, s, 3-H), 6.49 – 6.51 (2H, m, Ar-H), 6.80 – 6.84 (2H, m, Ar-H), 7.03 (1H, s, 5-H), 7.35 – 7.53 (9H, m, Ar-H), 7.59 – 7.61 (2H, m, Ar-H), 7.66 – 7.68 (2H, m, Ar-H), 7.71 (1H, d, J = 8.4 Hz, Ar-H), 7.78 (1H, d, J = 8.4 Hz, 7-H), 8.48 (1H, d, J = 8.3 Hz, 10-H); δ_{F} (376 MHz, CDCl_3) -62.5; δ_{C} (100 MHz, CDCl_3) 55.19, 55.33, 55.53, 82.06, 100.20, 103.83, 113.14, 115.41, 122.67, 123.68, 124.61, 125.13, 125.44 (q, J = 3.8 Hz, $=\underline{\text{C}}\text{H}-\text{C}-\text{CF}_3$), 125.59, 125.98, 126.62, 126.91 (q, J = 272 Hz, $\underline{\text{C}}\text{F}_3$), 126.95, 127.56, 127.99, 128.19, 128.24, 129.14, 129.78 (q, J = 32.5 Hz, $\underline{\text{C}}-\text{CF}_3$), 130.19, 132.56, 132.64, 133.97, 136.96, 140.62, 142.54 (q, J = 1.3 Hz, $\underline{\text{C}}-\text{CH}=\text{CH}-\text{C}-\text{CF}_3$), 147.77, 157.17, 158.78, 160.53; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 645.2244$ $\text{C}_{41}\text{H}_{31}\text{F}_3\text{O}_4$ requires $[\text{M}+\text{H}]^+ = 645.2252$.

**6.11.8 2-(2,4-Dimethoxyphenyl)-2,6-bis(4-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)-
2*H*-benzo[*h*]chromene 4.1h**



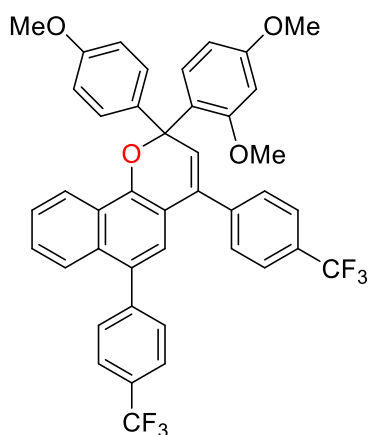
From 6-bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)-2*H*-benzo[*h*]chromene (0.80 g, 1.24 mmol) and (4-methoxyphenyl)boronic acid (0.28 g, 1.85 mmol) after elution from silica with 20 % EtOAc/petroleum ether (bp. 40 – 60 °C) to afford the title compound **4.1h** as a pale yellow gum that solidified when scratched with *n*-pentane and gave pale yellow microcrystalline powder (0.68 g, 81 %); mp = 99 – 101 °C; ν_{max} (neat) 1607, 1509, 1322, 1245, 1159, 1104, 1031, 972, 829, 768 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.63 (3H, s, OMe), 3.77 (3H, s, OMe), 3.79 (3H, s, OMe), 3.85 (3H, s, OMe), 6.48 (1H, s, 3-H), 6.48 – 6.51 (2H, m, Ar-H), 6.82 (2H, d, J = 8.8 Hz, Ar-H), 6.95 (2H, d, J = 8.6 Hz, Ar-H), 7.00 (1H, s, 5-H), 7.29 (2H, d, J = 8.6 Hz, Ar-H), 7.40 – 7.53 (4H, m, Ar-H), 7.59 – 7.61 (2H, m, Ar-H), 7.66 – 7.68 (2H, m, Ar-H), 7.71 (1H, d, J = 8.5 Hz, Ar-H), 7.79 (1H, d, J = 8.4 Hz, 7-H), 8.48 (1H, d, J = 8.2 Hz, 10-H); δ_{F} (376 MHz, CDCl_3) -62.4; δ_{C} (100 MHz, CDCl_3) 55.19, 55.32, 55.33, 55.53, 82.00, 100.20, 103.83, 113.13, 113.63, 114.81, 115.43, 116.02, 122.65, 123.64, 124.22 (q, J = 272.5 Hz, CF_3), 124.64, 125.15, 125.43 (q, J = 3.8 Hz, $=\text{CH}-\text{C}-\text{CF}_3$), 125.53, 126.04, 126.54, 127.54, 127.99, 128.24, 129.16, 129.60, 129.79 (q, J = 32.5 Hz, $\text{C}-\text{CF}_3$), 129.92, 131.18, 132.29, 132.78, 132.98, 134.01, 136.99, 142.58 (q, J = 1.2 Hz, $\text{C}-\text{CH}=\text{CH}-\text{C}-\text{CF}_3$), 147.56, 157.17, 158.70, 158.77, 160.52; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 675.2352$ $\text{C}_{42}\text{H}_{33}\text{F}_3\text{O}_5$ requires $[\text{M}+\text{H}]^+ = 675.2358$.

6.11.9 4-(2-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)-2*H*-benzo[*h*]chromen-6-yl)-*N,N*-dimethylaniline 4.1i



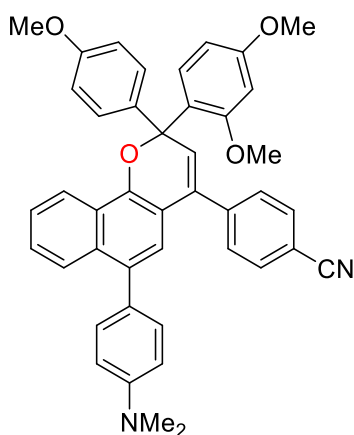
From 6-bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)-2*H*-benzo[*h*]chromene (0.35 g, 0.54 mmol) and 4-(dimethylamino)phenylboronic acid (0.22 g, 1.35 mmol) after elution from silica with 20 % EtOAc/petroleum ether (bp. 40 – 60 °C) to afford the title compound **4.1i** as a pale yellow microcrystalline powder (0.30 g, 80 %); mp = 227 – 228 °C; ν_{max} (neat) 2981, 1608, 1504, 1324, 1256, 1177, 1110, 1065, 1031, 971, 823, 767 cm^{-1} ; δ_{H} (600 MHz, CDCl_3) 2.97 (6H, s, NMe_2), 3.61 (3H, s, OMe), 3.75 (3H, s, OMe), 3.77 (3H, s, OMe), 6.46 (1H, s, 3-H), 6.46 – 6.49 (2H, m, Ar-H), 6.76 – 6.78 (2H, m, Ar-H), 6.79 – 6.82 (2H, m, Ar-H), 7.00 (1H, s, 5-H), 7.23 – 7.25 (2H, m, Ar-H), 7.37 – 7.40 (1H, m, Ar-H), 7.44 – 7.46 (2H, m, Ar-H), 7.47 – 7.49 (1H, m, Ar-H), 7.59 (2H, d, $J = 8.1$ Hz, Ar-H), 7.65 (2H, d, $J = 8.1$ Hz, Ar-H), 7.71 (1H, d, $J = 8.5$ Hz, Ar-H), 7.87 (1H, d, $J = 8.4$ Hz, 7-H), 8.46 (1H, d, $J = 8.4$ Hz, 10-H); δ_{F} (376 MHz, CDCl_3) -62.5; δ_{C} (150 MHz, CDCl_3) 40.61, 55.19, 55.33, 55.54, 81.94, 100.22, 103.87, 112.20, 113.14, 115.50, 122.60, 123.49, 124.26 (q, $J = 272.0$ Hz, CF_3), 124.78, 125.19, 125.40 (q, $J = 3.8$ Hz, $=\text{CH}-\text{C}-\text{CF}_3$), 126.31, 126.33, 127.40, 128.03, 128.25, 128.66, 129.20, 129.71 (q, $J = 32.5$ Hz, $\text{C}-\text{CF}_3$), 130.85, 132.90, 132.95, 133.97, 134.15, 137.11, 142.70 (q, $J = 1.3$ Hz, $\text{C}-\text{CH}=\text{CH}-\text{C}-\text{CF}_3$), 147.21, 149.59, 157.20, 158.77, 160.52; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 688.2666$ $\text{C}_{43}\text{H}_{36}\text{F}_3\text{NO}_4$ requires $[\text{M}+\text{H}]^+ = 688.2674$.

6.11.10 2-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-4,6-bis(4-(trifluoromethyl)phenyl)-2*H*-benzo[*h*]chromene 4.1j



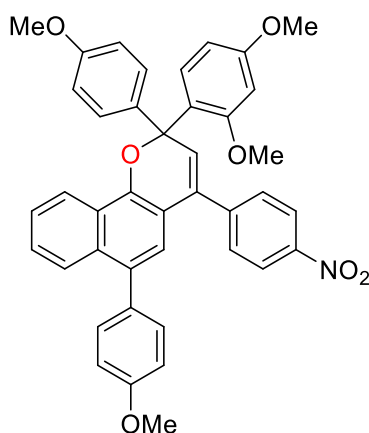
From 6-bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)-2*H*-benzo[*h*]chromene (0.80 g, 1.24 mmol) and (4-trifluoromethyl)phenylboronic acid (0.35 g, 1.85 mmol) after elution from silica with 20 % EtOAc/petroleum ether (bp. 40 – 60 °C) to afford the title compound **4.1j** as pale yellow gum that solidified when scratched with *n*-pentane and gave a white microcrystalline powder (0.79 g, 90 %); mp = 111 – 114 °C; ν_{max} (neat) 1608, 1503, 1321, 1160, 1105, 830, 768 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.64 (3H, s, OMe), 3.77 (3H, s, OMe), 3.79 (3H, s, OMe), 6.49 (1H, s, 3-H), 6.50 – 6.51 (2H, m, Ar-H), 6.82 – 6.85 (2H, m, Ar-H), 7.02 (1H, s, 5-H), 7.44 – 7.61 (8H, m, Ar-H), 7.66 – 7.73 (6H, m, Ar-H), 8.50 (1H, d, J = 8.4 Hz, 10-H); δ_{F} (376 MHz, CDCl_3) -62.4, -62.5; δ_{C} (150 MHz, CDCl_3) 55.19, 55.34, 55.55, 82.26, 100.24, 103.89, 113.20, 115.49, 122.87, 123.42, 123.88, 124.17 (q, J = 272.0 Hz, $\underline{\text{C}}\text{F}_3$), 124.34 (q, J = 272 Hz, $\underline{\text{C}}\text{F}_3$), 124.49, 125.07, 125.20 (q, J = 3.5 Hz, $=\underline{\text{C}}\text{H}-\text{C}-\text{CF}_3$), 125.48, 125.52 (q, J = 3.5 Hz, $=\underline{\text{C}}\text{H}-\text{C}-\text{CF}_3$), 125.86, 127.04, 127.79, 127.97, 128.23, 129.11, 129.15 (q, J = 32.5 Hz, $\underline{\text{C}}-\text{CF}_3$), 129.95 (q, J = 32.5 Hz, $\underline{\text{C}}-\text{CF}_3$), 130.48, 131.10, 132.20, 133.76, 136.82, 142.36 (q, J = 1.5 Hz, $\underline{\text{C}}-\text{CH}=\text{CH}-\text{C}-\text{CF}_3$), 144.36 (q, J = 1.5 Hz, $\underline{\text{C}}-\text{CH}=\text{CH}-\text{C}-\text{CF}_3$), 148.40, 157.21, 158.87, 160.63; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 713.2125$ $\text{C}_{42}\text{H}_{30}\text{F}_6\text{O}_4$ requires $[\text{M}+\text{H}]^+ = 713.2126$.

6.11.11 4-(2-(2,4-Dimethoxyphenyl)-6-(4-(dimethylamino)phenyl)-2-(4-methoxyphenyl)-2*H*-benzo[*h*]chromen-4-yl)benzonitrile 4.1k



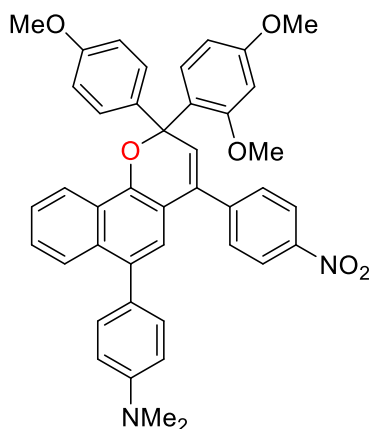
From 4-(6-bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-2*H*-benzo[*h*]chromen-4-yl)benzonitrile (100 mg, 0.165 mmol) and 4-(dimethylamino)phenylboronic acid (68.2 mg, 0.414 mmol) after elution from silica with 20 % EtOAc/petroleum ether (bp. 40 – 60 °C) to afford the title compound **4.1k** as a beige powder (0.10 g, 94 %); mp = 148 – 149 °C; ν_{max} (neat) 2845, 1897, 1607, 1504, 1249, 1208, 1161, 1033, 948, 824, 768, 446 cm^{-1} ; δ_{H} (600 MHz, CDCl_3) 2.98 (6H, s, NMe_2), 3.62 (3H, s, OMe), 3.76 (3H, s, OMe), 3.77 (3H, s, OMe), 6.46 (1H, s, 3-H), 6.47 – 6.48 (2H, m, Ar-H), 6.77 (2H, d, $J = 8.5$ Hz, Ar-H), 6.81 (2H, d, $J = 8.6$ Hz, Ar-H), 6.95 (1H, s, 5-H), 7.23 (2H, d, $J = 8.4$ Hz, Ar-H), 7.40 (1H, t, $J = 7.3$ Hz, Ar-H), 7.44 (2H, d, $J = 8.6$ Hz, Ar-H), 7.49 (1H, t, $J = 7.6$ Hz, Ar-H), 7.59 (2H, d, $J = 8.0$ Hz, Ar-H), 7.68 – 7.70 (3H, m, Ar-H), 7.87 (1H, d, $J = 8.4$ Hz, 7-H), 8.45 (1H, d, $J = 8.3$ Hz, 10-H); δ_{C} (100 MHz, CDCl_3) 40.61, 55.19, 55.34, 55.56, 81.92, 100.24, 103.92, 111.32, 112.20, 113.16, 115.10, 118.89, 122.59, 123.21, 124.54, 125.20, 125.51, 126.33, 126.45, 127.95, 128.02, 128.21, 128.51, 129.57, 130.80, 132.29, 132.99, 133.02, 133.91, 136.89, 143.87, 147.27, 149.62, 157.16, 158.81, 160.56; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 645.2745$ $\text{C}_{43}\text{H}_{36}\text{N}_2\text{O}_4$ requires $[\text{M}+\text{H}]^+ = 645.2753$.

6.11.12 2-(2,4-Dimethoxyphenyl)-2,6-bis(4-methoxyphenyl)-4-(4-nitrophenyl)-2H-benzo[*h*]chromene 4.1m



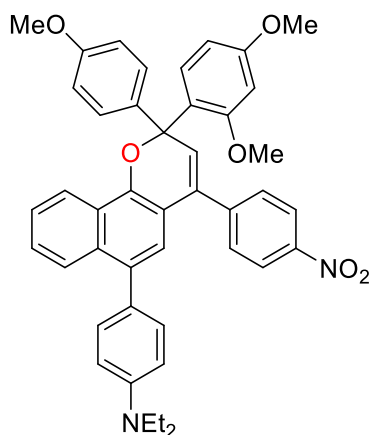
From 6-bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-4-(4-nitrophenyl)-2H-benzo[*h*]chromene (0.30 g, 0.48 mmol) and 4-methoxyphenylboronic acid (0.11 g, 0.72 mmol) after elution from silica with 20 % EtOAc/petroleum ether (bp. 60 – 80 °C) to afford the title compound **4.1m** as an orange oil that solidified on standing to give orange powder (0.20 g, 63 %); mp = 133 – 135 °C; ν_{max} (neat) 2930, 2834, 2361, 1607, 1511, 1344, 1244, 1101, 1030, 828, 710 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.64 (3H, s, OMe), 3.77 (3H, s, OMe), 3.79 (3H, s, OMe), 3.84 (3H, s, OMe), 6.48 – 6.50 (2H, m, Ar-H), 6.53 (1H, s, 3-H), 6.80 – 6.84 (2H, m, Ar-H), 6.93 – 6.97 (2H, m, Ar-H), 6.96 (1H, s, 5-H), 7.27 – 7.30 (2H, m, Ar-H), 7.41 – 7.47 (3H, m, Ar-H), 7.50 – 7.54 (1H, m, Ar-H), 7.64 – 7.67 (2H, m, Ar-H), 7.68 – 7.71 (1H, m, Ar-H), 7.80 (1H, d, J = 8.3 Hz, 7-H), 8.26 – 8.29 (2H, m, Ar-H), 8.47 (1H, d, J = 7.9 Hz, 10-H); δ_{C} (100 MHz, CDCl_3) 55.20, 55.33, 55.35, 55.57, 82.02, 100.22, 103.92, 113.19, 113.68, 115.00, 122.66, 123.35, 123.81, 124.32, 125.69, 126.10, 126.72, 128.00, 128.22, 128.41, 129.65, 131.12, 132.50, 132.81, 132.86, 133.49, 136.70, 145.77, 147.33, 147.64, 157.15, 158.76, 158.86, 160.61; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 652.2323$ $\text{C}_{41}\text{H}_{33}\text{NO}_7$ requires $[\text{M}+\text{H}]^+ = 652.2335$.

6.11.13 4-(2-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-4-(4-nitrophenyl)-2*H*-benzo[*h*]chromen-6-yl)-*N,N*-dimethylaniline 4.1n



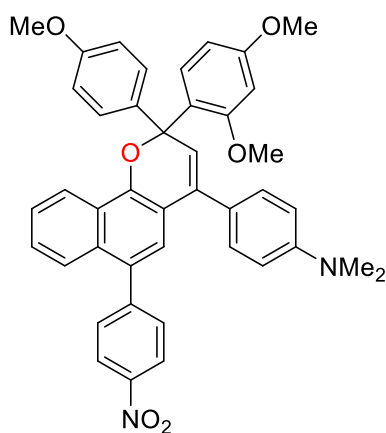
From 6-bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-4-(4-nitrophenyl)-2*H*-benzo[*h*]chromene (0.30 g, 0.48 mmol) and 4-(dimethylamino)phenylboronic acid (0.12 g, 0.72 mmol) after elution from silica with 20 % EtOAc/petroleum ether (bp. 40 – 60 °C) to afford the title compound **4.1n** as an orange oil that solidified when scratched with *n*-pentane and gave an orange powder (0.27 g, 85 %); mp = 126 – 128 °C; ν_{max} (neat) 2932, 2834, 2159, 1608, 1514, 1344, 1248, 823, 414 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 2.98 (6H, s, NMe_2), 3.64 (3H, s, OMe), 3.77 (3H, s, OMe), 3.79 (3H, s, OMe), 6.48 – 6.50 (2H, m, Ar-H), 6.53 (1H, s, 3-H), 6.77 – 6.83 (4H, m, Ar-H), 6.97 (1H, s, 5-H), 7.25 (2H, d, $J = 9.1$ Hz, Ar-H), 7.40 – 7.53 (4H, m, Ar-H), 7.65 (2H, d, $J = 8.6$ Hz, Ar-H), 7.70 (1H, d, $J = 9.2$ Hz, Ar-H), 7.89 (1H, d, $J = 8.4$ Hz, 7-H), 8.27 (2H, d, $J = 8.6$ Hz, Ar-H), 8.47 (1H, d, $J = 8.3$ Hz, 10-H); δ_{C} (100 MHz, CDCl_3) 40.62, 40.85, 55.20, 55.35, 55.57, 81.94, 100.22, 103.91, 112.22, 113.18, 115.06, 122.60, 123.20, 123.78, 124.42, 125.19, 125.57, 126.35, 126.51, 128.03, 128.23, 128.28, 128.45, 129.69, 130.79, 133.00, 133.11, 133.62, 136.79, 145.88, 147.27, 149.63, 157.15, 158.83, 160.58; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 665.2640$ $\text{C}_{42}\text{H}_{36}\text{N}_2\text{O}_6$ requires $[\text{M}+\text{H}]^+ = 655.2651$.

6.11.14 4-(2-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-4-(4-nitrophenyl)-2H-benzo[*h*]chromen-6-yl)-*N,N*-diethylaniline 4.1o



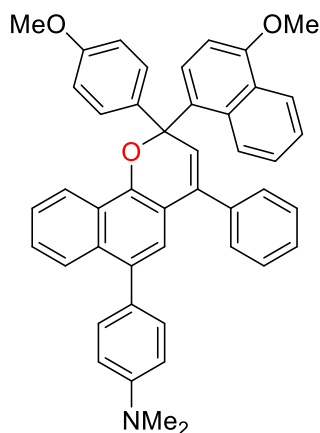
From 6-bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-4-(4-nitrophenyl)-2H-benzo[*h*]chromene (0.30 g, 0.51 mmol) and (4-(diethylamino)phenyl)boronic acid (0.24 g, 1.26 mmol) after elution from silica with 20 % EtOAc/petroleum ether (bp. 40 – 60 °C) to afford the title compound **4.1o** as an orange powder (0.30 g, 94 %); mp = 260 – 261 °C; ν_{max} (neat) 2962, 2359, 1606, 1519, 1347, 1252, 1174, 1159, 1036, 831 and 817 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 1.18 (6H, t, $J = 7.0$ Hz, NEt_2), 3.37 (4H, q, $J = 7.0$ Hz, NEt_2), 3.62 (3H, s, OMe), 3.75 (3H, s, OMe), 3.77 (3H, s, OMe), 6.47 – 6.49 (2H, m, Ar-H), 6.51 (1H, s, 3-H), 6.70 (2H, d, $J = 8.6$ Hz, Ar-H), 6.81 (2H, d, $J = 8.8$ Hz, Ar-H), 6.96 (1H, s, 5-H), 7.20 (2H, d, $J = 8.6$ Hz, Ar-H), 7.39 – 7.51 (4H, m, Ar-H), 7.65 (2H, d, $J = 8.6$ Hz, Ar-H), 7.70 (1H, d, $J = 9.2$ Hz, Ar-H), 7.93 (1H, d, $J = 8.4$ Hz, 7-H), 8.26 (2H, d, $J = 8.6$ Hz, Ar-H), 8.46 (1H, d, $J = 8.2$ Hz, 10-H), δ_{C} (100 MHz, CDCl_3) 12.68, 44.35, 55.19, 55.34, 55.57, 81.93, 100.25, 103.96, 111.29, 113.19, 115.06, 122.57, 123.12, 123.76, 124.50, 125.21, 125.52, 126.43, 126.46, 127.20, 128.05, 128.22, 129.70, 130.99, 133.05, 133.28, 133.66, 136.86, 145.93, 146.85, 147.15, 147.30, 157.17, 158.84, 160.59; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 693.2951$ $\text{C}_{44}\text{H}_{40}\text{N}_2\text{O}_6$ requires $[\text{M}+\text{H}]^+ = 693.2964$.

6.11.15 4-(2-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-6-(4-nitrophenyl)-2H-benzo[*h*]chromen-4-yl)-*N,N*-dimethylaniline 4.1p



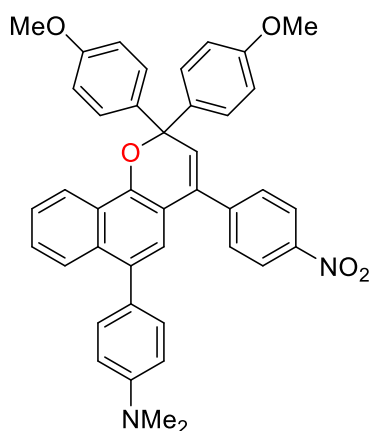
From 4-(6-bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-2H-benzo[*h*]chromen-4-yl)-*N,N*-dimethylaniline (0.40 g, 0.64 mmol) and 4-nitrophenylboronic acid (0.22 g, 1.29 mmol) after elution from silica with 20 % EtOAc/petroleum ether (bp. 60 – 80 °C) to afford the title compound **4.1p** as an orange powder (0.34 g, 79 %); mp = 154 – 155 °C; ν_{max} (neat) 1608, 1514, 1343, 1249, 1208, 1159, 1034, 829 and 767 cm^{-1} ; δ_{H} (600 MHz, CDCl_3) 3.00 (6H, s, NMe_2), 3.64 (3H, s, OMe), 3.78 (3H, s, OMe), 3.80 (3H, s, OMe), 6.41 (1H, s, 3-H), 6.48 – 6.50 (2H, m, Ar-H), 6.79 (2H, d, J = 8.6 Hz, Ar-H), 6.82 (2H, d, J = 8.7 Hz, Ar-H), 7.27 (1H, s, 5-H), 7.38 (2H, d, J = 8.5 Hz, Ar-H), 7.44 (1H, t, J = 7.4 Hz, Ar-H), 7.49 (2H, d, J = 8.6 Hz, Ar-H), 7.53 (1H, t, J = 7.7 Hz, Ar-H), 7.57 (2H, d, J = 8.5 Hz, Ar-H), 7.71 – 7.74 (2H, m, Ar-H), 8.27 (2H, d, J = 8.5 Hz, Ar-H), 8.53 (1H, d, J = 8.4 Hz, 10-H), δ_{C} (100 MHz, CDCl_3) 40.49, 55.15, 55.29, 55.48, 82.38, 100.16, 103.66, 112.22, 113.01, 116.81, 123.01, 123.44, 124.93, 125.02, 125.09, 129.19, 125.33, 125.64, 126.15, 126.88, 127.91, 128.26, 129.50, 129.54, 130.98, 131.53, 134.34, 137.35, 146.67, 148.03, 148.93, 150.18, 157.30, 158.65, 160.41; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 665.2644$ $\text{C}_{42}\text{H}_{36}\text{N}_2\text{O}_6$ requires $[\text{M}+\text{H}]^+ = 665.2651$.

6.11.16 4-(2-(4-Methoxynaphthalen-1-yl)-2-(4-methoxyphenyl)-4-phenyl-2H-benzo[*h*]chromen-6-yl)-*N,N*-dimethylaniline 4.1q



From 6-bromo-2-(4-methoxynaphthalen-1-yl)-2-(4-methoxyphenyl)-4-phenyl-2H-benzo[*h*]chromene (0.40 g, 0.67 mmol) and 4-(dimethylamino)phenylboronic acid (0.17 g, 1.00 mmol) after gradient elution from silica with 20 % EtOAc/petroleum ether (bp. 60 – 80 °C) → neat EtOAc to afford the title compound **4.1q** as beige powder (0.40 g, 95 %); mp = 188 – 191 °C; ν_{max} (neat) 2934, 1608, 1509, 1368, 1244, 1218, 1114. 982, 818, 771 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 2.98 (6H, s, NMe_2), 3.77 (3H, s, OMe), 3.97 (3H, s, OMe), 6.08 (1H, s, 3-H), 6.73 (1H, d, $J = 8.2$ Hz, Ar-H), 6.77 (2H, d, $J = 8.5$ Hz, Ar-H), 6.85 (2H, d, $J = 8.7$ Hz, Ar-H), 7.17 (1H, s, 5-H), 7.25 – 7.27 (2H, m, Ar-H), 7.29 – 7.43 (7H, m, Ar-H), 7.50 – 7.57 (4H, m, Ar-H), 7.78 – 7.83 (2H, m, Ar-H), 8.25 – 8.27 (1H, m, Ar-H), 8.37 (1H, d, $J = 8.0$ Hz, 10-H), 8.43 – 8.45 (1H, m, Ar-H); δ_{C} (100 MHz, CDCl_3) 40.65, 55.23, 55.46, 83.82, 101.96, 112.20, 113.63, 116.05, 122.40, 122.93, 124.03, 124.67, 125.13, 125.38, 125.87, 126.07, 126.19, 126.96, 127.23, 127.44, 127.83, 128.05, 128.46, 128.82, 128.85, 130.77, 130.87, 131.77, 132.62, 132.91, 135.73, 138.36, 138.50, 147.84, 149.51, 155.91, 158.68; HRMS (ESI) found $[\text{M}+\text{H}]^+$ 640.2844 $\text{C}_{45}\text{H}_{37}\text{NO}_3$ requires $[\text{M}+\text{H}]^+$ 640.2852.

6.11.17 4-(2,2-Bis(4-methoxyphenyl)-4-(4-nitrophenyl)-2H-benzo[*h*]chromen-6-yl)-*N,N*-dimethylaniline 4.1r

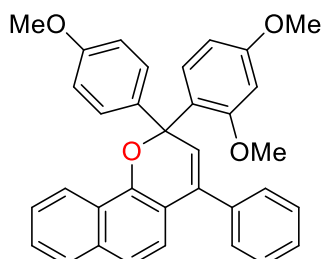


From 6-bromo-2,2-bis(4-methoxyphenyl)-4-(4-nitrophenyl)-2H-benzo[*h*]chromene (0.25 g, 0.42 mmol) and 4-(dimethylamino)phenylboronic acid (0.17 g, 1.05 mmol) after elution from silica with 20 % EtOAc/petroleum ether (bp. 40 – 60 °C) to afford the title compound **4.1r** as an orange powder (0.24 g, 90 %); mp = 149 – 150 °C; ν_{max} (neat) 2956, 2363, 2342, 1610, 1510, 1342, 1253, 1173, 830, 817, 770 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 2.97 (6H, s, NMe_2), 3.77 (6H, s, 2 $\times$ OMe), 6.20 (1H, s, 3-H), 6.77 (2H, d, J = 8.8 Hz, Ar-H), 6.84 – 6.88 (2H, m, Ar-H), 6.95 (1H, s, 5-H), 7.22 – 6.24 (2H, m, Ar-H), 7.39 – 7.43 (1H, m, Ar-H), 7.46 – 7.52 (5H, m, Ar-H), 7.65 – 7.68 (2H, m, Ar-H), 7.88 (1H, d, J = 8.4 Hz, 7-H), 8.25 – 8.27 (2H, m, Ar-H), 8.47 (1H, d, J = 7.9 Hz, 10-H); δ_{C} (100 MHz, CDCl_3) 40.60, 55.26, 82.53, 112.21, 113.60, 115.10, 122.58, 123.14, 123.83, 125.25, 125.69, 126.36, 126.74, 128.20, 128.30, 128.35, 129.72, 130.77, 133.15, 133.30, 134.90, 136.98, 145.33, 147.46, 147.49, 149.66, 159.05; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 635.2542$ $\text{C}_{41}\text{H}_{34}\text{N}_2\text{O}_5$ requires $[\text{M}+\text{H}]^+ = 635.2546$.

6.12 Synthesis of 2,2,4-triaryl substituted 2*H*-naphtho[1,2-*b*]pyran using heterogeneous conditions

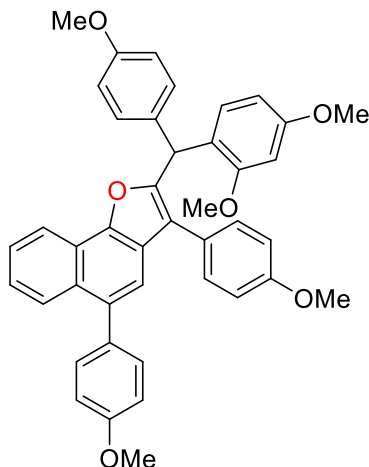
6.12.1 2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-4-phenyl-2*H*-benzo[*h*]chromene

3.1ea



A stirred solution of 1-naphthol (0.58 g, 4.01 mmol) and the 1-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol (1.50 g, 4.01 mmol) in PhMe (50 mL) was warmed to 50 °C. Aluminium oxide (activated, acidic, Brockmann I) (4.08g, 40.1 mmol) was added and the mixture refluxed for 3 h. The hot mixture was filtered and the spent alumina catalyst was washed with hot PhMe (3 × 50 mL). Evaporation of the solvent under reduced pressure gave a deep red gum that required gradient elution from silica with 10 % EtOAc/petroleum ether (bp. 40 – 60 °C) → 20 % EtOAc/petroleum ether (bp. 40 – 60 °C) to afford the title compound **3.1ea** as a pale green microcrystalline powder (0.34 g, 17 %); mp = 96 – 98 °C; $\nu_{\max}$ (neat) 3270, 1607, 1504, 1250, 1208, 1169, 1030, 963, 822, 629 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.61 (3H, s, OMe), 3.75 (3H, s, OMe), 3.77 (3H, s, OMe), 6.42 (1H, s, 3-H), 6.45 – 6.46 (2H, m, Ar-H), 6.79 (2H, d, J = 8.3 Hz, Ar-H), 7.16– 7.18 (1H, m, Ar-H), 7.26 – 7.29 (1H, m, Ar-H), 7.39 – 7.50 (9H, m, Ar-H), 7.72 (2H, d, J = 6.8 Hz, Ar-H), 8.41 (1H, d, J = 7.8 Hz, 10-H); δ_{C} (100 MHz, CDCl_3) 55.15, 55.30, 55.50, 81.88, 100.15, 103.68, 113.00, 116.73, 119.80, 122.46, 123.36, 124.96, 125.07, 125.43, 126.06, 126.26, 127.55, 127.67, 127.90, 128.24, 128.35, 128.91, 134.34, 135.12, 137.23, 138.90, 148.20, 157.19, 158.61, 160.35; HRMS (ESI) found $[\text{M}+\text{H}]^+$ 501.2067 $\text{C}_{34}\text{H}_{28}\text{O}_4$ requires $[\text{M}+\text{H}]^+$ 501.2066.

6.13 Ring-contraction of 2-(2,4-dimethoxyphenyl)-2,4,6-tris(4-methoxyphenyl)-2H-benzo[*h*]chromene to afford 2-((2,4-dimethoxyphenyl)(4-methoxyphenyl)methyl)-3,5-bis(4-methoxyphenyl)naphtho[1,2-*b*]furan 4.41

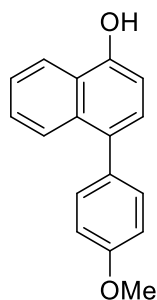


A mixture of 2-(2,4-dimethoxyphenyl)-2,4,6-tris(4-methoxyphenyl)-2H-benzo[*h*]chromene (100 mg, 0.157 mmol), 18-crown-6 (124 mg, 0.471 mmol), K₂CO₃ (32.6 mg, 0.236 mmol) in PhMe (3 mL) was heated at reflux under N₂ for 20 h. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in EtOAc (20 mL), washed with water (30 mL) and the aqueous layer extracted with EtOAc (2 × 10 mL). The combined organic layers were dried with anhydrous sodium sulfate and the solvent removed under reduced pressure to give orange oil that solidified with scratching and gave orange powder. Trituration from *n*-pentane gave the title compound **4.41** as white powder (50 mg, 50 %); mp = 129 – 132°C; ν_{max} (neat) 3000, 2880, 2400, 1609, 1511, 1244, 1030, 834, 765, 557 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 3.69 (3H, s, OMe), 3.79 (3H, s, OMe), 3.81 (3H, s, OMe), 3.87 (3H, s, OMe), 3.89 (3H, s, OMe), 6.13 (1H, s, methine-H), 6.46 (1H, d, *J* = 2.4 Hz, Ar-H), 6.50 (1H, dd, *J* = 8.5, 2.5 Hz, Ar-H), 6.83 (2H, d, *J* = 8.8 Hz, Ar-H), 6.99 – 7.04 (4H, m, Ar-H), 7.20 (2H, d, *J* = 8.6 Hz, Ar-H), 7.38 – 7.47 (6H, m, Ar-H), 7.54 – 7.60 (2H, m, Ar-H), 7.92 (1H, d, *J* = 8.5 Hz, Ar-H), 8.33 (1H, d, *J* = 8.0 Hz, Ar-H); δ_{C} (100 MHz, CDCl₃) 40.29, 55.23, 55.33, 55.35, 55.39, 55.55, 98.50, 104.35, 113.57, 113.62, 114.08, 118.50, 119.55, 120.40, 121.36, 123.17, 123.60, 124.75, 125.05, 125.92, 126.91, 129.71, 130.42, 130.86, 131.39, 133.71, 134.47, 135.42, 149.25, 153.83, 157.67, 157.98, 158.75, 158.79, 159.67; HRMS (ESI) found [M+H]⁺ 637.2509 C₄₂H₃₆O₆ requires [M+H]⁺ 637.2590

6.14 Procedure for the Suzuki cross-coupling to 4-bromo-1-naphthol

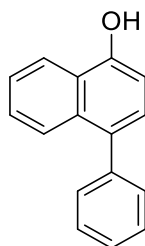
A mixture of 4-bromo-1-naphthol (1 eq.), arylboronic acid (1.5 eq.), NaOH (4 eq.) and Pd(OAc)₂ (2.7 mol %) in water (4.5 mL/mmol) was stirred in a closed flask at room temperature until TLC examination of the reaction mixture indicated no further change in composition (20 h). The suspension was neutralised with HCl (2M aq.) and then extracted into EtOAc (3 × 100 mL). The combined organic extracts were washed with water (200 mL), dried with anhydrous sodium sulfate and evaporated to afford the crude product that required further purification by flash chromatography to afford the pure target compound. The following 4-substituted 1-naphthols were obtained from 4-bromo-1-naphthol by using this protocol:

6.14.1 4-(4-Methoxyphenyl)naphthalen-1-ol **2.24a**



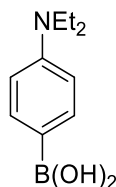
From (4-methoxyphenyl)boronic acid (3.07 g, 20.2 mmol) and 4-bromo-1-naphthol (3.00 g, 13.5 mmol) after gradient elution from silica with 10 % EtOAc/petroleum ether (bp. 40 – 60 °C) → 20 % EtOAc/petroleum ether (bp. 40 – 60 °C) to afford the title compound **2.24a** as a beige powder (1.57 g, 47 %); mp = 130 – 131 °C; ν_{max} (neat) 3309, 3057, 1579, 1343, 1230, 1044, 1019, 825, 785, 762, 419 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 3.90 (3H, s, OMe), 5.34 (1H, s, OH), 6.86 (1H, d, J = 7.6 Hz, 2H), 7.01 – 7.04 (2H, m, Ar-H), 7.24 (1H, d, J = 7.6 Hz, 3-H), 7.38 – 7.41 (2H, m, Ar-H), 7.43 – 7.53 (2H, m, 6-H, 7-H), 7.88 – 7.90 (1H, m, 5-H), 8.25 – 8.27 (1H, m, 8-H); δ_{C} (100 MHz, CDCl₃) 55.40, 108.19, 113.71, 121.82, 124.45, 125.14, 126.06, 126.48, 126.76, 131.27, 132.92, 132.92, 133.19, 150.67, 158.68; HRMS (ESI) found $[M+H]^+$ 251.1064 C₁₇H₁₄O₂ requires $[M+H]^+$ 251.1072.

6.14.2 4-Phenylnaphthalen-1-ol **2.24b**



From phenylboronic acid (2.87 g, 23.5 mmol) and 4-bromo-1-naphthol (3.50 g, 15.7 mmol) after elution from silica with 15 % EtOAc/petroleum ether (bp. 40 – 60 °C) to afford the title compound **2.24b** as a brown microcrystalline powder (1.62 g, 47 %); mp = 146 – 147 °C; ν_{max} (neat) 3325, 2980, 1509, 1343, 1244, 1175, 1031, 820, 760, 560 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.33 (1H, s, OH), 6.88 (1H, d, $J = 7.6$ Hz, 2-H), 7.27 (1H, d, $J = 7.4$ Hz, 3-H), 7.39 – 7.54 (7H, m, Ar-H), 7.88 – 7.90 (1H, m, 5-H), 8.26– 8.29 (1H, m, 8-H); δ_{C} (100 MHz, CDCl_3) 108.16, 121.84, 124.43, 125.19, 126.00, 126.57, 126.84, 126.94, 128.26, 130.28, 132.70, 133.29, 140.78, 150.91; HRMS (ESI) found $[\text{M}+\text{H}]^+$ 221.0966 $\text{C}_{16}\text{H}_{12}\text{O}$ requires $[\text{M}+\text{H}]^+$ 221.0966.

6.15 Preparation of 4-(diethylamino)phenylboronic acid **2.28**



A solution of 4-diethylaminophenylmagnesium bromide was prepared by the addition of 4-bromo-*N,N*-diethylaniline (4.00 g, 17.5 mmol) in dry THF (25 mL) to magnesium (0.469 g, 19.3 mmol) previously treated with iodine (50 mg), continuously stirred under N_2 . After 20 h of stirring at room temperature, the 4-diethylaminophenylmagnesium bromide solution was added dropwise to the solution of trimethyl borate (2.00 g, 19.3 mmol) in dry THF (25 mL) at -70 °C under N_2 . The ice bath was removed and the mixture stirred at room temperature under N_2 for 20 h. The resulting suspension was dissolved in aqueous HCl (6M, 10 mL) and then aqueous ammonia solution (~25 % v/v) was added to obtain a neutral pH. The resulting solution was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with water (100 mL), dried over magnesium sulfate. The solvent was reduced, petroleum ether (bp. 40 – 60 °C) added and the precipitate filtered to give the title compound **2.28** as a

dark blue powder (1.04 g, 31 %); mp = 229 – 230 °C; ν_{max} (neat) 3211, 2967, 2928, 1596, 1307, 1263, 1183, 1153, 748, 695 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 1.23 (6H, t, J = 6.4 Hz, $2 \times \text{CH}_3$), 3.45 (4H, q, J = 6.7 Hz, $2 \times \text{CH}_2$), 6.75 (2H, d, J = 7.8 Hz, Ar-H), 8.08 (2H, d, J = 7.8 Hz, Ar-H); δ_{C} (100 MHz, CDCl_3)[†] 12.64, 44.33, 110.51, 137.31, 150.59; HRMS (ESI) found $[\text{M}+\text{H}]^+ = 194.1346$ $\text{C}_{10}\text{H}_{16}\text{BNO}_2$ requires $[\text{M}+\text{H}]^+ = 194.1352$. [†] Note: one C atom, that directly attached to the boron atom, could not be readily identified from the routine ^{13}C NMR spectrum (see Chapter 2, section 2.4 and reference cited therein).

Chapter 7.0 Conclusions

A series of 1,1,3-triarylprop-2-yn-1-ols have been prepared in excellent yield by the addition of an arylacetylide, derived from the addition of *n*-butyllithium to either phenylacetylene, 4-methoxyphenylacetylene or 4-(trifluoromethyl)phenylacetylene, to substituted benzophenones. An alternative high yielding Sonogashira cross-coupling strategy between either 4-iodonitrobenzene or 4-iodobenzonitrile and 1-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)prop-2-yn-1-ol was employed to obtain 1,1,3-triarylprop-2-yn-1-ols bearing a nitro or nitrile function, respectively. The sp^3 hybridised C atom typically resonated in the narrow range of 73.6 – 74.3 ppm and was characteristic of the formation of these propynols.

The acid-catalysed condensation between either 4-methoxy-1-naphthol or 4-bromo-1-naphthol and the foregoing 1,1,3-triarylprop-2-yn-1-ols proceeded smoothly in moderate yield in refluxing 1,2-DCE containing $CH(OCH_3)_3$ and pyridinium *p*-toluenesulfonate to afford a series of 6-methoxy- and a series of 6-bromo- 4-aryl-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-2*H*-naphtho[1,2-*b*]pyrans. The chemical shift of 3-H resonated in the range of 6.33 – 6.52 ppm which strongly depended on the nature of the aryl group attached at C-4. The signal for 5-H mainly resonated in the range of 7.32 – 7.56 ppm for the 6-bromo substituents whereas the presence of the 6-methoxy substituent shifted 5-H upfield (ca. 6.5 ppm) resonating closer to 3-H. The sp^3 hybridised C atom (C-2) next to the pyran O atom usually resonated in the range of 81.4 – 84.2 ppm.

Replacement of the 6-bromo substituent of the foregoing 4-aryl-6-bromo-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-2*H*-naphtho[1,2-*b*]pyrans (late-stage coupling process) was achieved in routinely high yield by the Suzuki-Miyaura cross-coupling reaction with a range of arylboronic acids in the presence of $Pd(PPh_3)_4$ and KF in toluene:ethanol (1:1). The chemical shift of 5-H was found to be shifted upfield upon arylcoupling and resonated in the range of 6.95 – 7.27 ppm.

An alternative strategy to the late-stage introduction of the 6-aryl group was examined which required the preparation of 4-aryl-1-naphthols. Thus heating 4-bromo-1-naphthol with either phenyl- or 4-methoxyphenyl- boronic acid in tap water containing base and $Pd(OAc)_2$ gave 4-phenyl-1-naphthol (47 %) and 4-(4-methoxyphenyl)-1-naphthol (47 %), respectively. Heating

solutions of the 4-aryl-1-naphthols and the 1,1,3-triarylprop-2-yn-1-ols in 1,2-DCE containing $\text{CH}(\text{OCH}_3)_3$ and pyridinium *p*-toluenesulfonate gave directly coupled 2,2,4,6-tetraryl substituted 2*H*-naphtho[1,2-*b*]pyrans in moderate yield.

Heterogeneous reaction conditions were used to prepare a 2,2,4-triaryl substituted 2*H*-naphtho[1,2-*b*]pyran. Thus, the condensation reaction of a 1,1,3-triarylprop-2-yn-1-ol with a naphthol in a presence of an acidic alumina catalyst in toluene gave the 2,2,4-triaryl substituted 2*H*-naphtho[1,2-*b*]pyran in a poor yield (17 %).

Whilst the majority of the novel 4,6-diaryl-2-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-2*H*-naphtho[1,2-*b*]pyrans displayed a photochromic response generating weak pink / red hues (λ_{max} 486 – 538 nm with colourabilities in the range 4.9×10^1 to $1.06 \times 10^4 \text{ mol}^{-1}\text{dm}^3\text{cm}^{-1}$.) upon irradiation to a steady state. The best photochromic response was noted from the combination of a strongly electron-withdrawing 4-aryl moiety with an electron-donating 6-aryl unit; such a combination in the secondary chromophore resulted in opposition of the traditional donor-acceptor system in the photomerocyanine i.e. a cross-conjugated system was established upon irradiation. The stronger the electron withdrawing aryl group at C-4 the more persistent was the photogenerated colour $\text{NO}_2 > \text{CN} > \text{CF}_3$. Thermal bleaching rate constants were determined for the most persistent photomerocyanines and the photochromes with a *para*- NO_2 group on the aryl ring at C-4 possessed half-lives which ranged from 415 s to 1868 s.

Remarkably inverting the donor-acceptor properties of the 4- and 6- aryl groups, establishing a secondary chromophore which supported that of the photomerocyanine, resulted in complete loss of photochromism and instead lead to fluorescence.

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