Tetra-substituted Olefin Synthesis Using Palladium-Catalysed C-H Activation

A thesis presented for the degree of

DOCTOR OF PHILOSOPHY IN

ORGANIC CHEMISTRY

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To my family,

Declaration

I declare that all of the scientific work reported in this thesis is my own unless otherwise noted. None of this work has been submitted in any other application for a higher degree.

Laura Lopez Suarez

Acknowledgments

Firstly, I would like to thank Mike for the opportunity of joining his research group and work in this exciting project. Thanks for all your support and helpful advice.

I cannot forget my labmates, they made my time inside and outside the lab much easier and enjoyable. Thanks to Alastair, Alex, Naim, Lei, Didier, Stephan, Venu, Karsten, Donnie, Jenna, Scott, Feng Zhi, Kallol, Sang, Jen, Sarah and all the others. Special thanks go to Gemma and Graci from which I learnt a lot during the short time we worked together in the project.

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There are no words to thank how supportive my family has always been, thanks mama, papa, Loren, Montse, Josep and all the rest.

Thanks to Marc for believing in me so much and for being at my side, no matter the circumstances. It would not have been possible without you.

Abstract

In an effort to obtain more efficient and greener chemical transformations, a substantial amount of research interest has been directed towards the use of arene C-H bonds as functional groups. Hydroarylation of alkynes through direct functionalisation of C-H bonds has been studied in recent years leading to the development of high-yielding metal-mediated processes. The main aim of the current work is the addition of a third component in the hydroarylation of alkynes trough C-H activation, in order to achieve a second C-C bond formation.

Attempts at palladium-catalysed three-component reaction of unactivated indoles with alkynes and aryliodides are described. The three-component reaction was studied in the intermolecular mode with both aryliodides and the more reactive diaryliodonium salts. These latter regents are reactive arylating and oxidising agents and have been used in the direct arylation of indoles under mild conditions through a Pd^{II}-Pd^{IV} catalytic cycle. In both cases the three-component product was not obtained.

The intramolecular version of the reaction using alkyne-tethered indoles and diaryliodonium salts is also described. In this case the tandem process was successful, especially when using ethynylbenzyl indole derivatives, the *Z*-tetrasubstituted olefins could be selectively obtained under mild conditions. Finally, a low-yielding synthesis of chromenes from propargylaryl ethers and diaryliodonium salts is also discussed.

Abbreviations

Ac: acyl

ACS: american chemical society

Ar: aryl

atm.: atmosphere

Bn: benzyl

BQ: benzoquinone

brsm: (yield) based on recovered starting material

Bu: butyl

^{t}BuOK: potassium *tert*-butoxide

^{t}BuOOBz: *tert*-butyl benzoyl peroxide

Bz: benzoyl

^{o}C : degrees centigrades

cap: caprolactame

cat: catalytic

cod: 1,5-cyclooctadiene

coe: *cis*-cyclooctene

COX: cyclooxygenase

Cp: cyclopentyl

*m*CPBA: *meta*-chloroperoxybenzoic acid

Cy: cyclohexyl

p-cymene: 4-isopropyltoluene

DABCO: 1,4-diazabicyclo[2.2.2]octane

dba: dibenzylidenacetone

DBU: 1,8-diazabicyclo(5.4.0)undec-7-ene

DCC: *N,N'*-dicyclohexylcarbodiimide

DCE: 1,2-dichloroethane

DCM: dichloromethane

DEAD: diethylazodicarboxylate

DIPEA: diisoprpylethylamine

DMA: *N*,*N*-dimethylacetamide

DMAD: dimethyl acetylenedicarboxylate

DMAP: 4-dimethylamino pyridine

DME: dimethoxyethane

DMEDA: *N,N'*-dimethylethyldiamine

DMF: *N*,*N*-dimethylformamide

DMSO: dimethylsulfoxide

DOAc: deuterated acetic acid

dmpe: bis(dimethylphosphino)ethane

dppe: 1,2-bis(diphenylphosphino)ethane

dppf: 1,1'-bis(diphenylphosphino)ferrocene

dtbpy: 4, 4'-di-*tert*-butyl 2,2'-bipyridine

ee: enantiomeric excess

eq.: equivalent(s)

Et: ethyl

h: hour

HFIP: hexafluoro *iso*propanol

HOAc: acetic acid

HOTf: trifluoromethanesulfonic acid

HPMV: hetero-phosphomolybdovanadate

HPLC: high performance liquid chromatography

HRMS: high resolution mass spectrometry

5-HT : 5-hydroxytryptamine receptors (G protein-coupled receptors and ligand-gated ion channels)

Im.: imidazole

IMes: 1,3-bis(mesityl)imidazol-2-ylidene

IR: infrared spectroscopy

IS: internal standard

KIE: kinetic isotopic effect

L: ligand

LC-MS: liquid chromatography-mass spectrometry

M: metal

MeCN: acetonitrile

Mes: mesityl

MVK: methyl vinyl ketone

NEt$_3$: triethylamine

NHC: *N*-heterocylic carbene

NMP: *N*-methyl pyrrolidone

NMR: nuclear magnetic resonance

[O]: oxidant

OAc: acetate

OTf: trifluoromethane sulfonate (triflate)

P(^{t}Bu)$_3$: tri-*tert*-butylphosphine

PEPPSI-IPr: (1,3-diisopropylimidazol-2-ylidene)(3-chloropyridyl) palladium (II) dichloride
pfb: pentafluorobutyrate
pg.: page

Ph: phenyl

PKC: protein kinase C

Pr: propyl

^{i}PrOAc: *iso*-propylacetate

phen: phenanthroline

pin: pinacolate

PivOH: 2,2-Dimethylpropanoic acid (pivalic acid)

r.t.: room temperature

S$_E$Ar: electrophilic aromatic substitution

SEM: [2-(Trimethylsilyl)ethoxy]methyl

SET: single electron transfer

SM: starting material

SiMes: 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene

TBAB: tetra-nbutylammonium bromide

TBAF: tetra-nbutylammonium fluoride

TBTA: Tris[(1-benzyl-*1H*-1,2,3- triazol-4-yl)methyl] amine

TEMPO: (2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl

TFA: trifluoroacetic acid

THF: tetrahydrofuran

TLC: thin layer chromatography

TMS: trimethylsilyl

Ts: tosyl

UV: ultraviolet-visible spectroscopy

μw: microwave

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Chapter 1. Metal-Mediated C-H Bond Activation Reactions

1.1. Introduction and Aim

The Nobel Prize in Chemistry 2010 was awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their vast contribution to the palladium-catalysed cross-coupling reactions,[1] highlighting the enormous importance that these reactions have in the chemical community from the last quarter of the twentieth century. The term cross-coupling reaction refers to the metal-catalysed coupling of aryl and vinyl halides/triflates with organometallic reagents. This is one of the most straightforward methods for carbon-carbon (C-C) and carbon-heteroatom bond formation.[2] The continuous research in this field has led to the development of very robust coupling methods. Which have been widely used in both academic and industrial procedures for the synthesis of complex molecules.[3] However, the usual cross-coupling procedure has the drawback of pre-activate both partners. The installation of these activating groups involves extra synthetic steps and the generation of waste after the C-C bond formation. In order to improve the efficiency and sustainability of the process, a lot of effort has been focused in recent years in the metal-catalysed activation of aryl carbon-hydrogen (C-H) bonds in coupling reactions, i.e. the transformation of unactivated C-H bonds into more reactive C-M bonds. Although the coupling of two unactivated aryl C-H bonds has been achieved, an easier and more common approach is the use of one pre-activated partner and a simple unactivated arene, what is usually known as direct arylation when a new biaryl molecule is formed (Scheme 1.1.1). [4-8]

Cross-coupling reaction:

$$\mathrm{R\text{-}X} + \mathrm{M\text{-}R'} \xrightarrow{\text{catalyst}} \mathrm{R\text{-}R} + \mathrm{M\text{-}X}$$

R, R'= aryl, vinyl
X= Cl, Br, I, OTf
M= B, Sn, Si, Zn, Mg, etc.

Direct arylation reaction:

$$\mathrm{Ar\text{-}}\mathbf{H} + \mathrm{Ar\text{-}X} \xrightarrow{\text{catalyst}} \mathrm{Ar\text{-}Ar} + \mathrm{H\text{-}X}$$

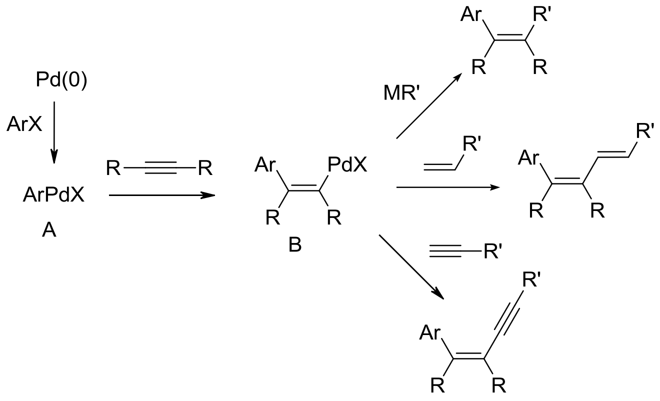
Ar=aryl
X= Cl, Br, I, OTf, B, Sn, Si, Zn, Mg, etc.

Scheme 1.1.1. Modern strategies for C-C bond formation.

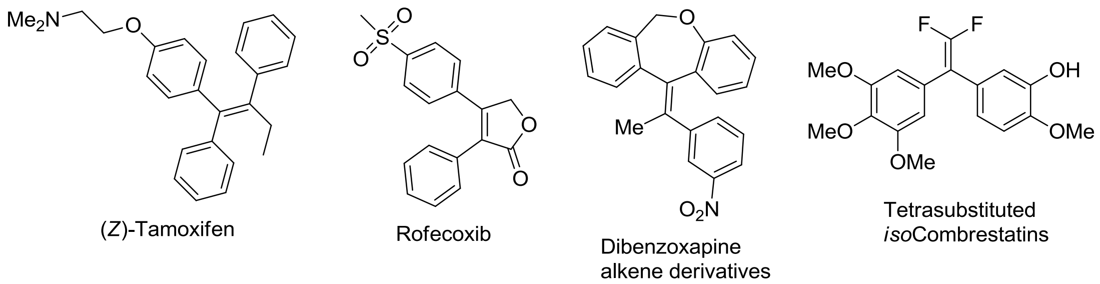
The main aim of this project is the use of unactivated arenes in a transition metal-catalysed domino coupling reactions in order to achieve interesting complex molecules in a straightforward way.

Metal-catalysed domino reactions in which two or more bonds are formed in one step have been deeply studied during the last decades in an effort to simplify the synthesis of complex molecules. An important and well precedented tandem reaction is the palladium-catalysed sequential three-component reaction between aryl halides, internal alkynes and various terminators, such as organometallic reagents, alkenes and terminal alkynes to afford the synthesis of tetra-substituted olefins[9] (Scheme 1.1.2). Tetra-substituted olefins having aryl group substituents are of interest for their photo-, electrochemical and biological properties.[10] Some important molecules containing tetra-substituted olefins in their structure are : (*Z*)-Tamoxifen, recognised by estrogen receptors, so can be useful for breast cancer treatment and prevention;[11] Rofecoxib, a COX-2 selective inhibitor has been used for rheumatic diseases and its possible activity against colon cancer is being studied;[12] Dibenzoxapine alkene derivatives were developed by researchers at Lilly pharmaceuticals as hormone receptor modulators;[13] tetra-substituted *iso*Combrestatins showed antitubullin activity for anticancer treatment (Scheme 1.1.3). [14]

The use of an unactivated arene in the synthesis of tetra-substituted olefins through the sequential difunctionalisation of alkynes represents an ambitious challenge to synthesise interesting olefins in a more direct one-pot procedure.



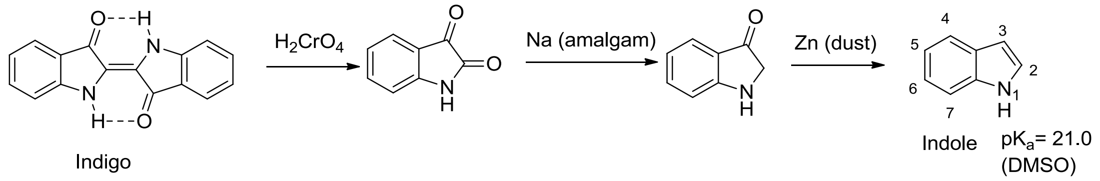
Scheme 1.1.2. Palladium-catalysed sequential three-component coupling of aryl halides, internal alkynes and various terminators. The key intermediate B is *living* and undergoes further coupling.[9]



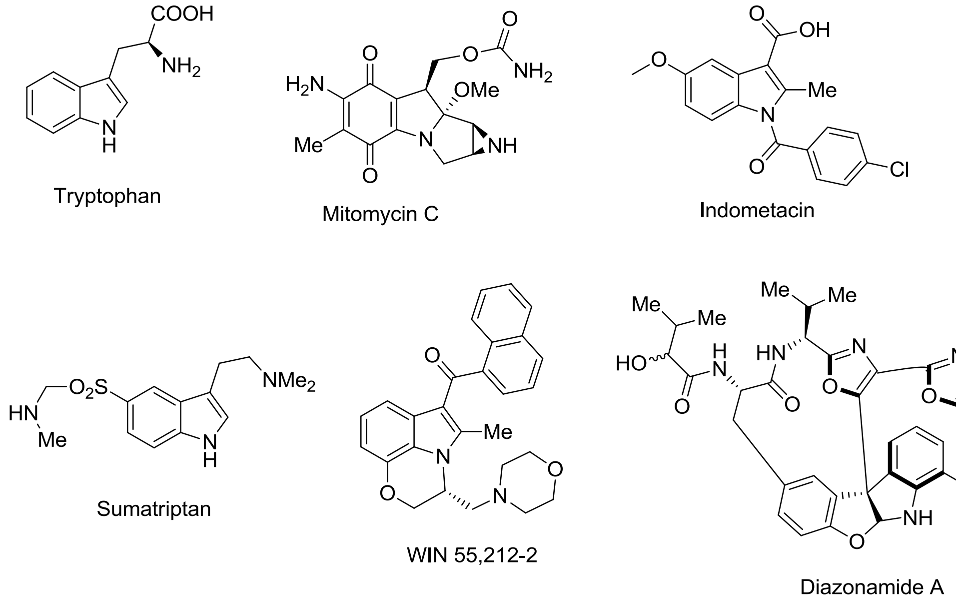
Scheme 1.1.3. Biologically active molecules containing tetra-substituted olefins.

Ideally, the use of a heterocylic arene would be advantageous in the tandem reaction as electron-rich nucleophilic arenes exhibit enhanced reactivity in direct arylations. The regioselectivity can be usually controlled by the electrophilic features of the heterocycle itself.[7] Among suitable heterocycle arenes, indole stands out as one of the most common moiety in natural products.[15]

Indole was first isolated from the widely used dye indigo by Baeyer and Knop in 1866.[16] They described indole as a white solid at room temperature and proposed its structure: a pyrrole ring fused to a benzene one (Scheme 1.1.4.). Since this first synthesis, by zinc reduction of isatin, an astonishing number of publications related to the synthesis and isolation of indole derivatives have emerged. The oldest and most known indole synthesis is the one developed by Fisher in 1883, from phenylhydrazines and aldehydes or ketones.[17] There are many other well known synthesis like the procedures developed by Bartoli[18] or Fukuyama.[19] Especially effective methods have been described using palladium catalysis[20] such as the Larock synthesis of indoles from *ortho*-iodo anilines and internal alkynes.[21] More recently, the direct arylation of indoles have attracted much attention.[22] It is not surprising indole derivatives are the centre of so many research efforts, keeping in mind that the indole moiety is present in an enormous number of important compounds, starting with the essential aminoacid tryptophan. Most indole alkaloids show interesting pharmacologically properties,[23] Mitomycin C which is thought to possess antitumor and chemotherapeutic properties.[24] Currently, a large number of drugs containing an indole centre can be found in the market or in clinical trials, for example: Indometacin: anti-inflamatory drug;[25] Sumatriptan (Imitrex): used for treatment of migraine;[26] WIN 55,212-2: cannabinoid receptor agonist that has potent analgesic effects,[27] and Diazonamide A: complex molecule with anticancer activity (Scheme 1.1.5). [28]



Scheme 1.1.4. First isolation of indole from indigo by Baeyer and co-workers.[16]



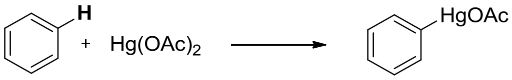
Scheme 1.1.5. Indole-containing biologically active compounds.

As the indole core is present in so many pharmaceutical and agrochemical compounds, the development of new efficient synthetic methods for its direct functionalisation is of great interest.

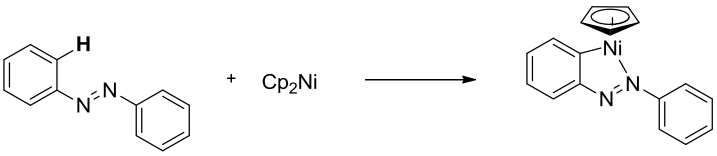
1.2. Metal-catalysed C-H Bond Activation

1.2.1. C-H Bond Activation Mechanisms

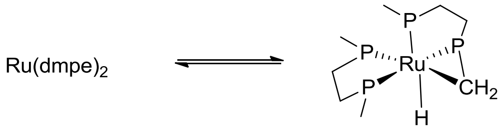
The main difficulty for the use of C-H bonds as a functional group is that they require high bond dissociation energies, for example 110 kcal/mol for H-C_6H_5.[29] Although the functionalisation of C-H bonds without the participation of metal compounds is widely known, the metal-mediated transformations of saturated and especially unsaturated hydrocarbons have emerged as a very powerful tool in organic synthesis in the last decades. The first example of C-H activation with a metal compound was described in 1898 by Dimroth using Hg (Scheme 1.2.1).[30] The reaction proceeds through a S_EAr mechanism using electrophilic $Hg(OAc)_2$ or $Hg(TFA)_2$ to afford arylmercury acetates. Since this early example, several C-H activation procedures with stochiometric amounts of metals have been reported. Kleiman and Dubeck described the cyclometalation of azobenzene with dicyclopentadienyl nickel in 1963. The azo moiety acts as an intramolecular chelating group (Scheme 1.2.2).[31] Shortly after, Chatt and Davidson found that $Ru(dmpe)_2$ spontaneously cyclometalates at the phosphorous methyl group being the first example of $C(sp^3)$-H bond cyclometalation (Scheme 1.2.3).[32]



Scheme 1.2.1. Formation of arylmercury acetates from benzene.[30]

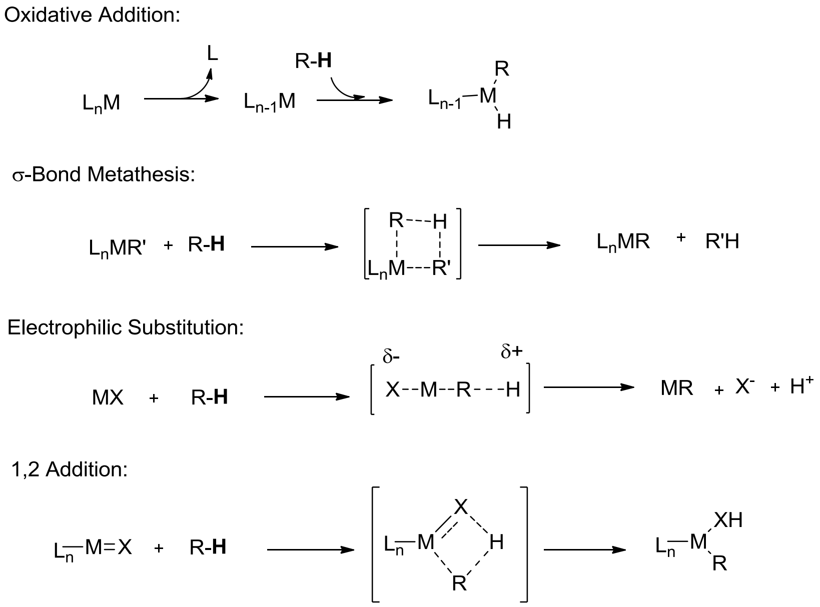


Scheme 1.2.2. Azobenzene cyclometalation with Cp_2Ni.[31]



Scheme 1.2.3. Cyclometalation of Ru(dmpe)$_2$.[32]

The studied reactions of unactivated C-H bonds with stoichiometric amounts of metal led to the identification of four main mechanisms for the transformation of C-H bonds into C-M bonds:[22, 33-35] oxidative addition, σ-bond metathesis, electrophilic substitution and 1,2 addition (Scheme 1.2.4).



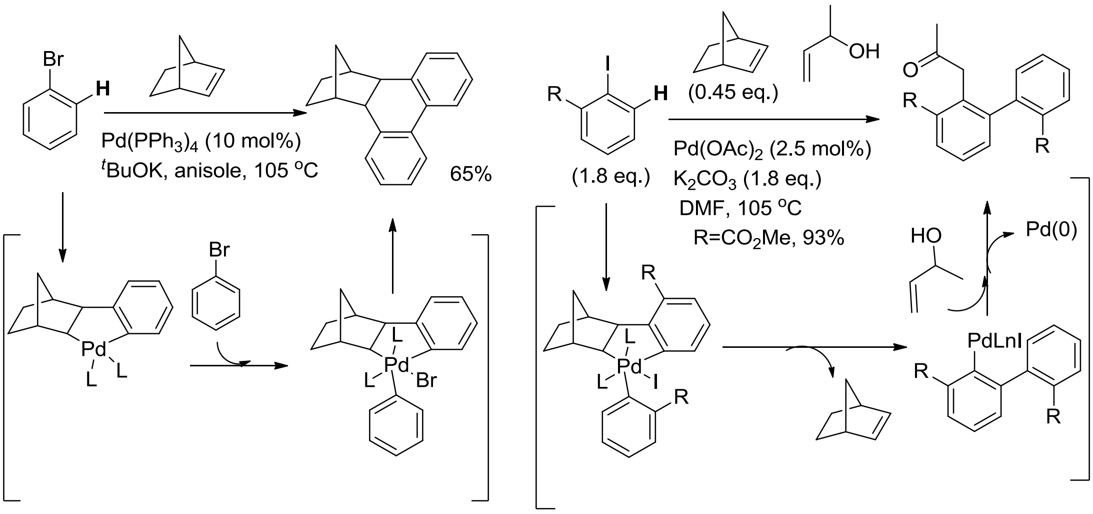
Scheme 1.2.4. C-H Activation Mechanisms.

Although the use of second-row transtition metals (especially Pd, Rh, Ru) for the functionalisation of C-H bonds has been known for about a century, its catalytic version has only been broadly explored for the past 30 years. A brief summary of the different metal-catalysed reactions through C-H activation for the formation of C-C bonds can be found in the next section. Direct functionalisation of indoles and the use of iodonium salts in C-H functionalisation reactions have especial impact in our investigation and are further discussed in following sections.

1.2.2. Recent Developments in Metal-Catalysed C-C Bond Formation through C-H Activation

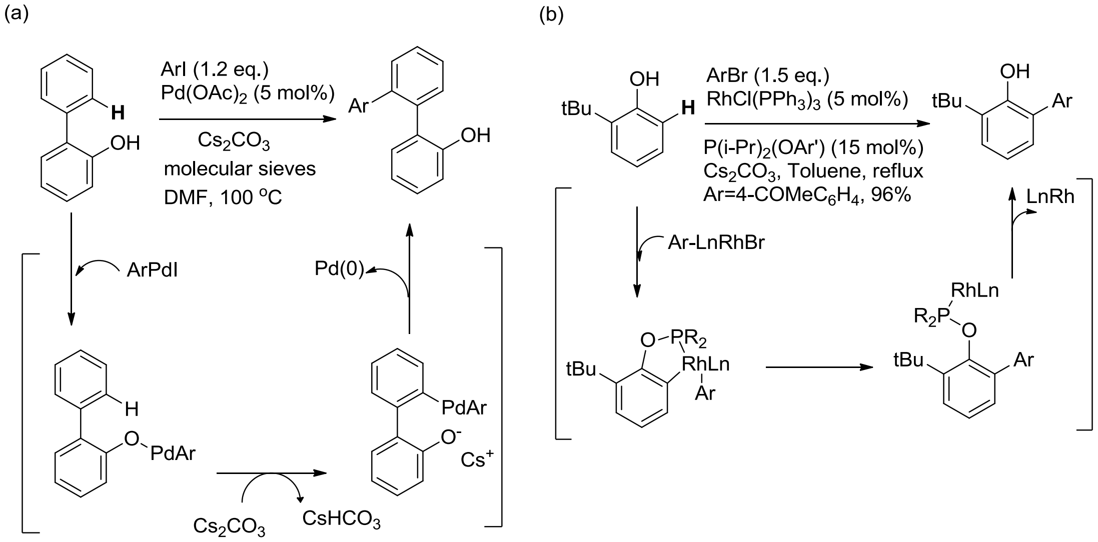
1.2.2.1. C-H Arylation

The preparation of biaryl molecules is of capital importance in organic chemistry due to their overwhelming presence in pharmaceutical products and biologically active compounds.[36] Consequently, a large amount of research has been focused on the development of metal-catalysed high-yielding methods for the arylation of unactivated arenes.[4, 34] One of the earliest examples reported is the direct arylation of aryl halides *via* a palladium-catalysed, norbornene-mediated, cascade reaction. First described by Catellani and Chiusoli in 1985.[37] de Mejiere also reported a similar system in which a multiple arylation takes place.[38] Later, it was noticed that in sterically strained systems, the presence of a second coupling partner could generate norbornene-free biaryl products (Scheme 1.2.5).[39]



Scheme 1.2.5. Catellani's norbornene-mediated arylations.[37]

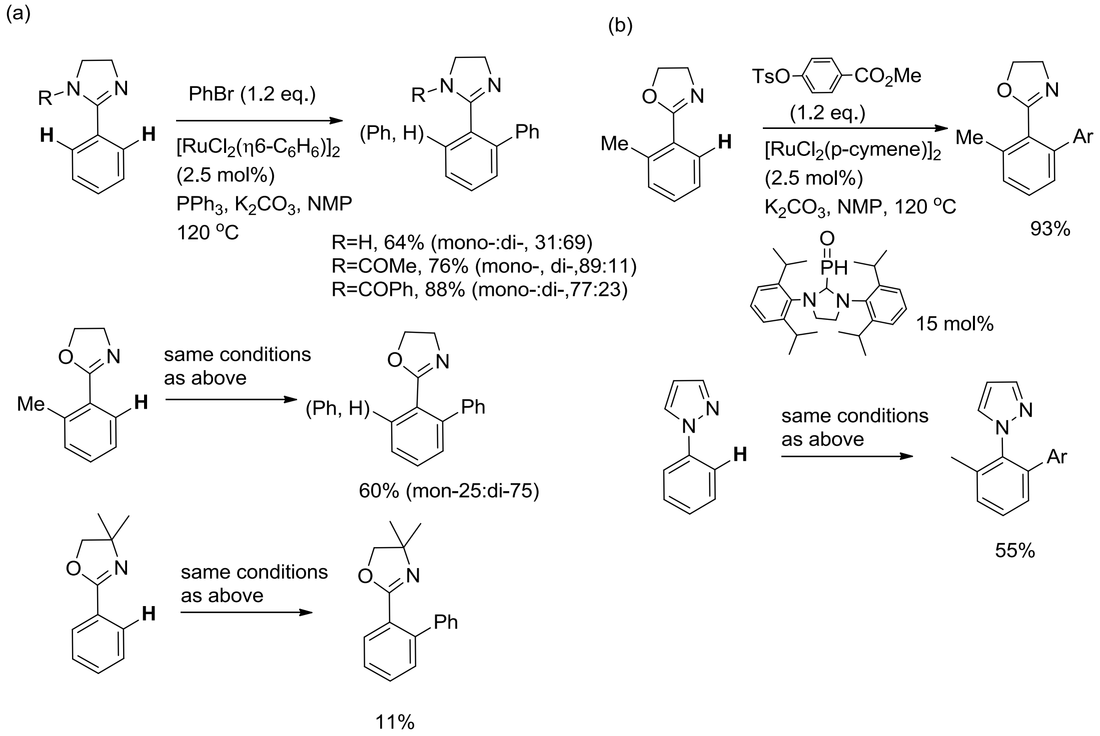
The use of arenes containing a directing group, which can coordinate the transtition-metal catalyst, is an excellent method for controlling the regioselectivity of the arylation reaction. The palladium-catalysed arylation of 2-phenylphenols and naphthols through an (aryl)(aryloxy)palladium (II) complex, reported by Miura *et. al.* represents a breakthrough in regioselective direct arylations.[40] Slightly later, Bedford and co-workers also reported the *ortho*-arylation of phenols, in this case using RhCl(PPh_3) as catalyst and phosphinites, P(*i*-Pr)$_2$(OAr), as co-catalysts.[41] The phosphinite coordinates with the hydroxyl and later with the Rh atom to direct the electrophilic substitution with Rh(III) species to the *ortho* position (Scheme 1.2.6).



Ar=4-OMeC$_6$H$_4$, 79%, monoarylated:diarylated, 7.8:1.0

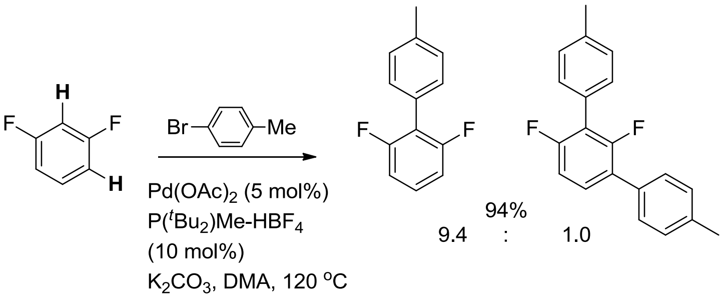
Scheme 1.2.6. Miura's (a) and Bedford's (b) strategies for the regioselective direct arylation of phenols.

Many other directing groups have been used for the intermolecular direct arylation of unactivated arenes and aryl halides as: arylmethanols, ketones, aldehydes, amides, imines, ethers, alkyls and phosphines.[4, 8] Interestingly, heteroaromatic compounds have also been used as directing groups in the arylation reactions. For instance, palladium and ruthenium catalysed arylations of 2-phenylpyridines with aryl halides or triflates have been reported.[42] 2-arylimidazolines, 2-aryloxazolines and 2-arylpyrazoles are also mono- or diarylated in the presence of a ruthenium (II) catalyst (Scheme 1.2.7).[43]



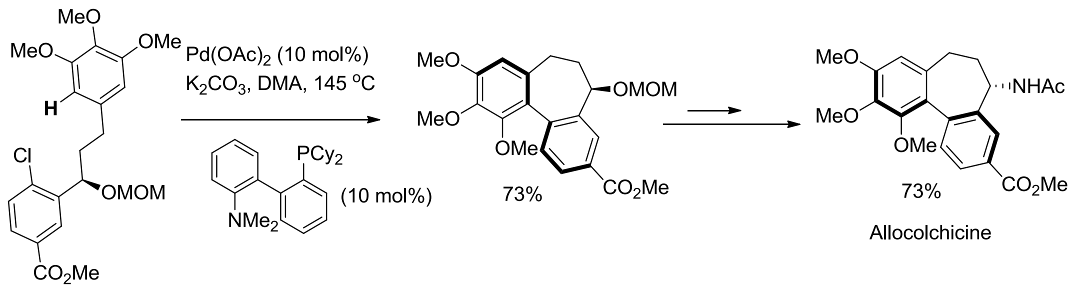
Scheme 1.2.7. Study of the *ortho*-arylation of 2-phenylimidazolines, 2-aryloxazolines and 2-arylpyraxoles by Oi and Inoue[42] (a) and Ackerman and co-workers[43] (b).

The intermolecular direct arylation of aromatic hydrocarbons in the absence of a coordinating group has been described by Fagnou and co-workers[44] for the direct arylation of electron-deficient fluoro-containing benzenes with arylhalides (Scheme 1.2.8).



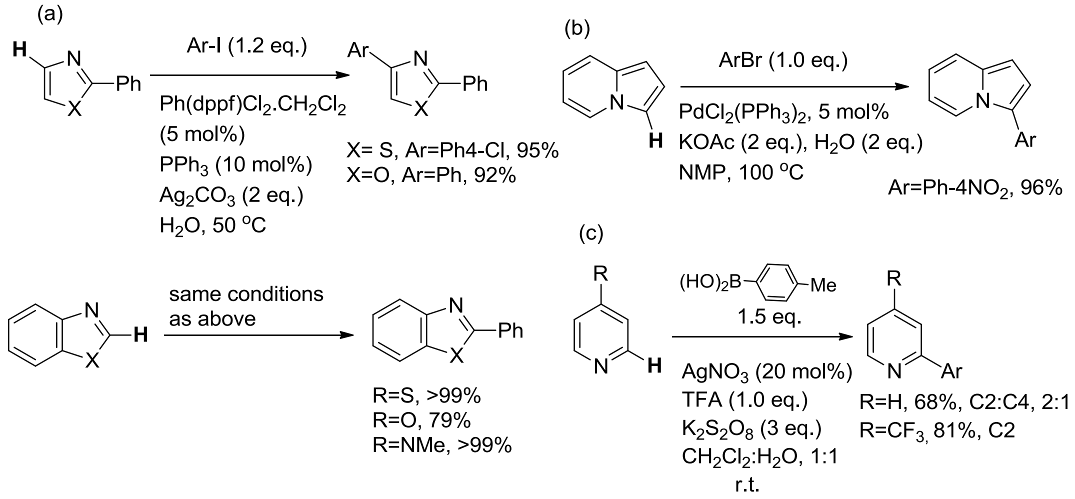
Scheme 1.2.8. Palladium-catalysed selective arylation of 1,3-difluorobenzene.[44]

Intramolecular direct arylation has been used for shorter synthesis of natural products, such as the formal synthesis of Allocolchicine[45] (Scheme 1.2.9) among others.[4]



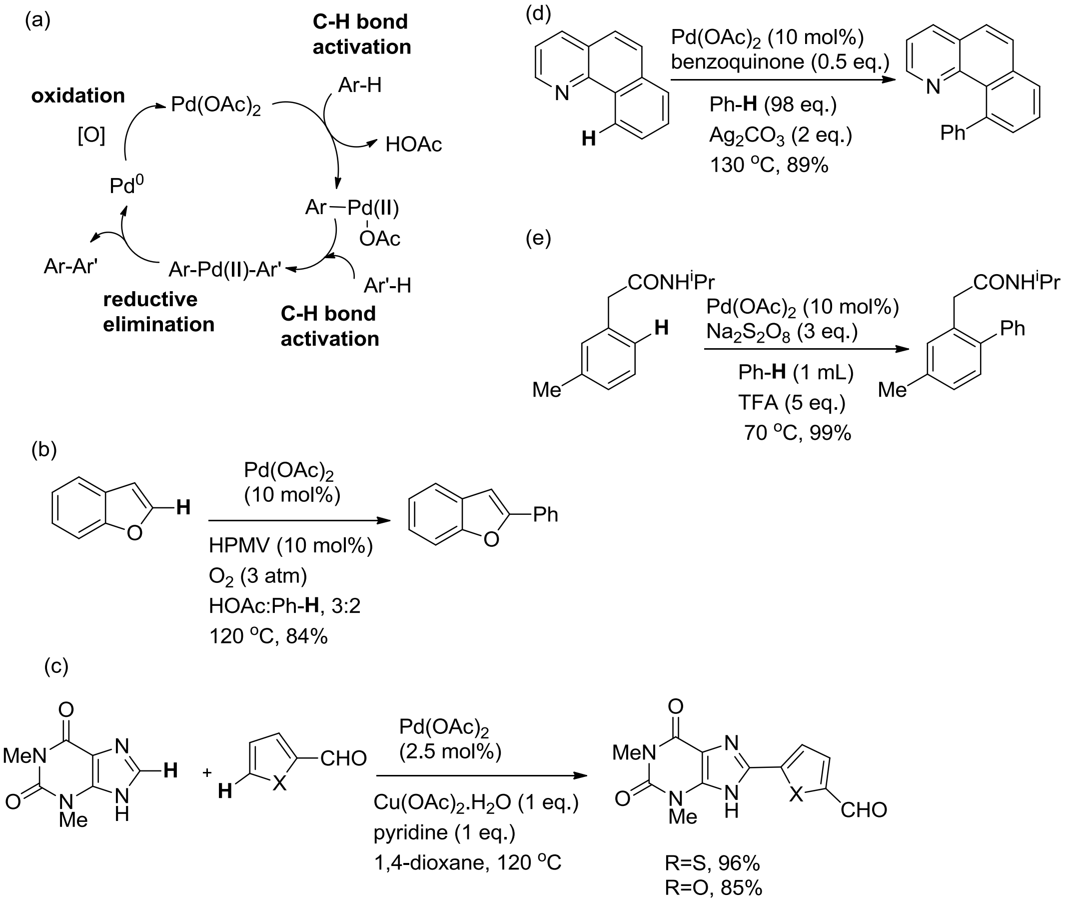
Scheme 1.2.9. Intramolecular direct arylation as a key step in the formal synthesis of Allocolchicine.[45]

The arylation of unactivated heterocyclic compounds represents a rapid way for the achievement of interesting compounds in medicinal chemistry. The regioselectivity of the reaction depends on the electronic properties of the heterocycle (Scheme 1.2.10).[46]



Scheme 1.2.10. Several examples of direct arylation of heterocycles: (a) Direct arylation on water under mild conditions reported by Greaney and co-workers.[47] (b) Direct aylation of indolizines with aryl bromides by Gevorgyan and co-workers.[48] (c) Room-temperature silver-catalysed direct arylation of electron-poor heterocylces with arylboronic acids by Baran and co-workers.[49]

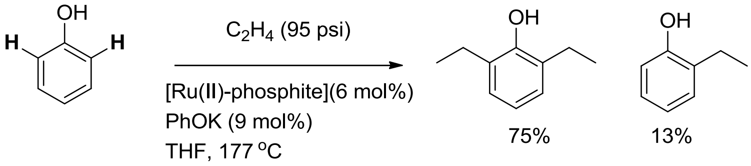
The palladium-catalysed oxidative cross-coupling of two unactivated arenes, also known as tandem direct arylation or cross dehydrogenative arylation, has emerged as a powerful direct method for the synthesis of biaryl motifs.[50] To control the regioselectivity, electron-rich arenes or arenes bearing a directing group are used. Choosing the right oxidant is of great importance for the reaction to proceed (Scheme 1.2.11).



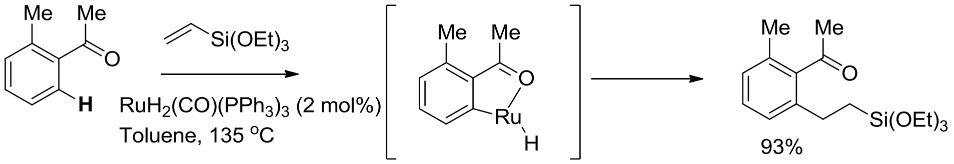
Scheme 1.2.11. Examples of palladium-catalysed oxidative cross-coupling of two arenes. (a) General mechanism.[50] (b) Procedure for the arylation of benzofurans and indoles with benzene derivatives by DeBoef and co-workers.[51] (c) Oxidative cross-coupling of heterocycles described by You and co-workers.[52] (d) Pyridine-directed tandem direct arylation reported by Sanford and co-workers.[53] (e) Amide-directed tandem direct arylation reported by Dong and co-workers.[54]

1.2.2.2. C-H Alkylation

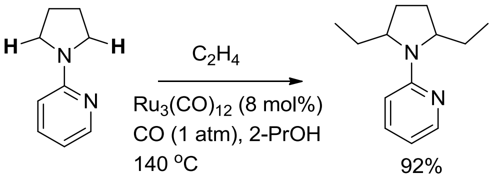
The catalytic addition of C-H bonds to alkenes is a very efficient method for the synthesis of new C-C bonds. One of the earliest examples is the dialkylation of phenols with ethylene reported by Lewis and Smith in 1986.[55] The process is catalysed by a Ru(II)-phosphite catalyst and the hydroxyl group is believed to act as a directing group as the alkenylation takes place exclusively at the *ortho* position (Scheme 1.2.12). Many alkenylation processes using an unactivated arene with a directing group have been reported to date, for instance the Murai group has got an important role in the development of efficient reactions. One of their first examples is the Ru catalysed *ortho*-alkylation of aryl ketones with terminal olefins (Scheme 1.2.13).[56] Murai also reported successful procedures using a wide range of directing groups as: esters, hydrazones, aldehydes, nitriles and heterocycles.[6] Another remarkable example from Murai and co-workers is the use of Ru catalysts for the alkylation of sp^3 C-H bonds from 2-*N*-pyridildialkylamines.[57] The reaction is thought to occur *via* the formation of a ruthenacycle by coordination with pyridine's nitrogen (Scheme 1.2.14).



Scheme 1.2.12. Early example of ruthenium-catalysed arene alkylation by Lewis and Smith.[55]

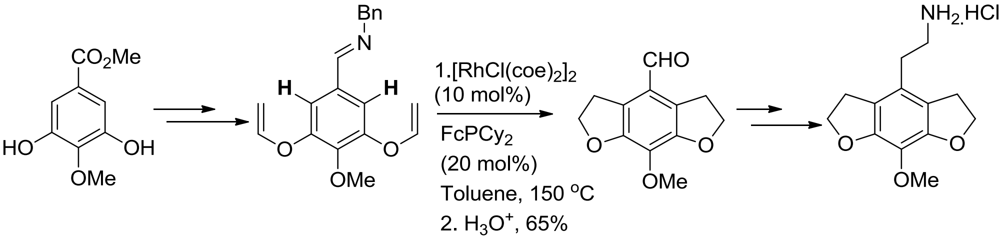


Scheme 1.2.13. Efficient ketone-directed alkylation reported by Murai and co-workers.[56]



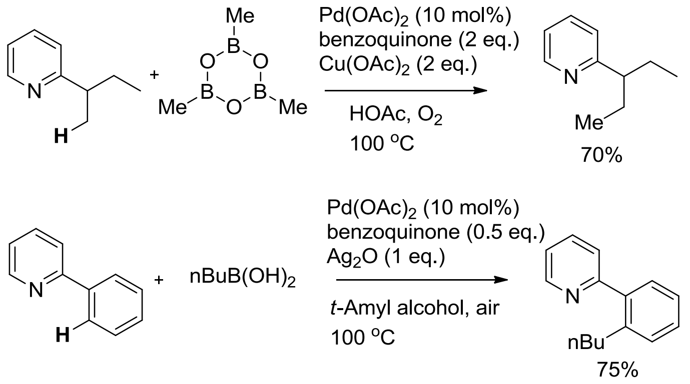
Scheme 1.2.14. Interesting example of pyridine-directed C(sp^3)-H bond alkylation.[57]

The intramolecular alkylation of alkene-tethered arenes has been used for the synthesis of interesting molecules as natural products, an example of it is the synthesis of a mescaline analogous reported by Ellman *et. al.* (Scheme 1.2.15).[58]



Scheme 1.2.15. Intramolecular arene alkylation used in the synthesis of Mescaline analogues.[58]

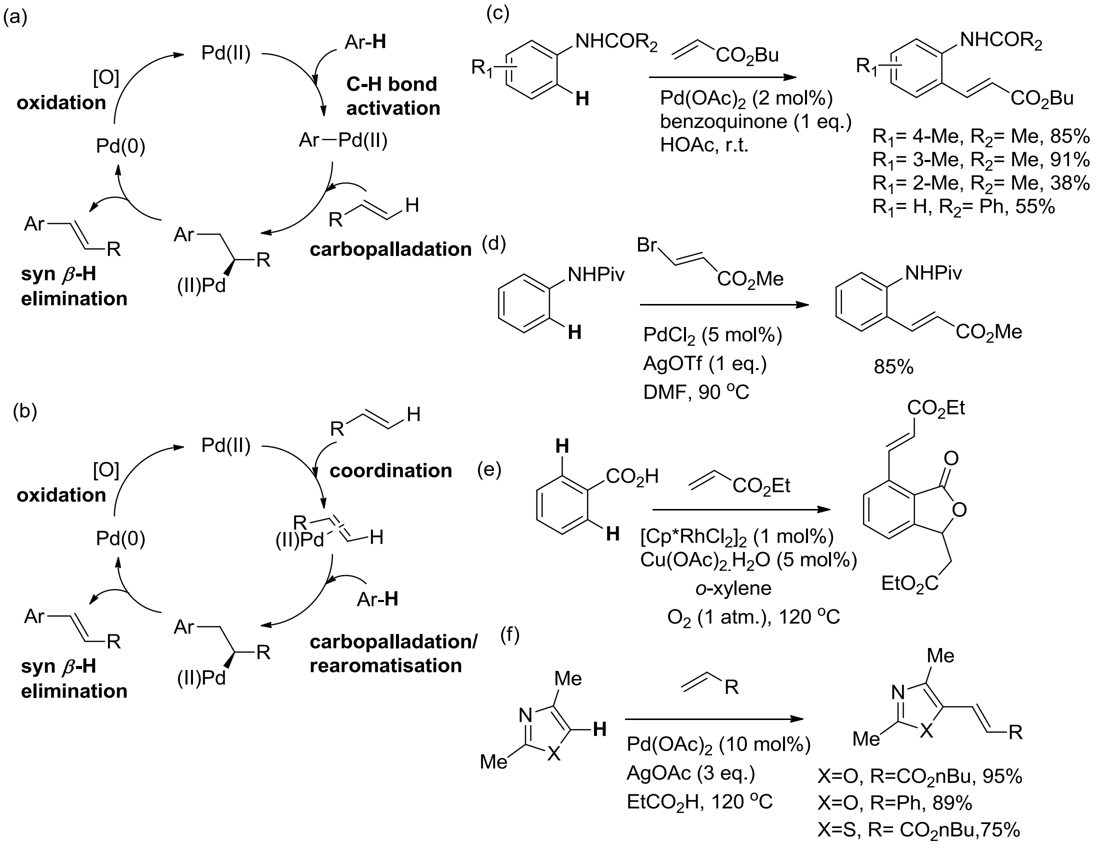
More recently several protocols have been developed for the alkylation of C(sp^2)-H bonds with alkyl boronic acids.[59] This procedure has also been employed in the pyridine- directed alkylation of C(sp^3)-H bonds (Scheme 1.2.16).



Scheme 1.2.16. sp^2 and sp^3 C-H alkylation with alkylboronates (or boronic acids) described by Chen *et. al.*[59]

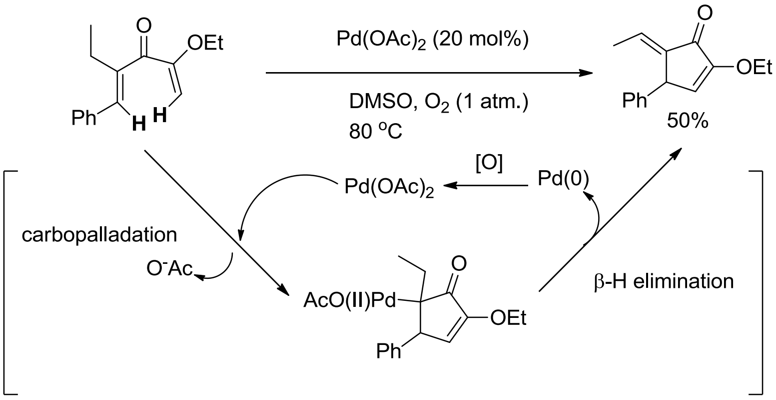
1.2.2.3. Heck-type C-H Alkenylation with Alkenes

The cross-coupling reaction between C(sp^2)-H bonds and alkenes can take place through a Heck-type mechanism leading to alkenylated products. In the late 60s Fujiwara and co-workers reported the formation of styrenes by the coupling of benzene derivatives and alkenes.[60] Since then, many efficient arene alkenylations catalysed by Pd salts in most of the cases, have been developed. There are two possible mechanisms generally applied for the transformation,[22, 50] in the first one (Scheme 1.2.17 (a)) an electrophilic palladation of the arene happens at the beginning leading to a σ-aryl-palladium intermediate that undergoes alkene carbopalladation followed by *β*-elimination to afford the alkene products. Pd(0) is reoxidised to Pd(II) by an oxidising agent present in the reaction. In an alternative pathway (Scheme 1.2.17 (b)) the alkene is previously coordinated with a Pd(II) catalyst, so its electrophilicity is higher and can be attacked by an electron-rich arene, subsequent *β*-elimination and Pd reoxidation complete the catalytic cycle. The use of several alkenes as arene coupling partners has been broadly used for the synthesis of interesting olefins (Scheme 1.2.17).[50, 61] The alkenylation process has been used, as well, in complex natural product synthesis, for example: (±)-claviciptic acid,[62] (+)-Austamide,[63] (+)-Dragmacidin F[64] or (±)-rhazinicine.[65] In these synthesis, the use of unactivated arenes avoided some steps, although stoichiometric amounts of metals were needed in the two first examples.



Scheme 1.2.17. (a), (b) General mechanisms for Heck-type alkenylation.[50] Several examples of catalytic alkenylation of arenes: (c) Alkenylation of anilides by deVries and co-workers.[66] (d) Alkenylation with 3-halide olefins by Daugulis and co-workers.[67] (e), (f) Double C-H activation of benzoic acids and alkenylation of heterocylcles by Miura *et. al.* [68]

Alkene-alkene coupling is less common but it has also been explored affording a few interesting protocols for the rapid synthesis of annulated products, for instance Tius *et. al.*[69] published an oxidative Heck variant of Nazarov reaction for the synthesis of cyclopentenone products (Scheme 1.2.18).

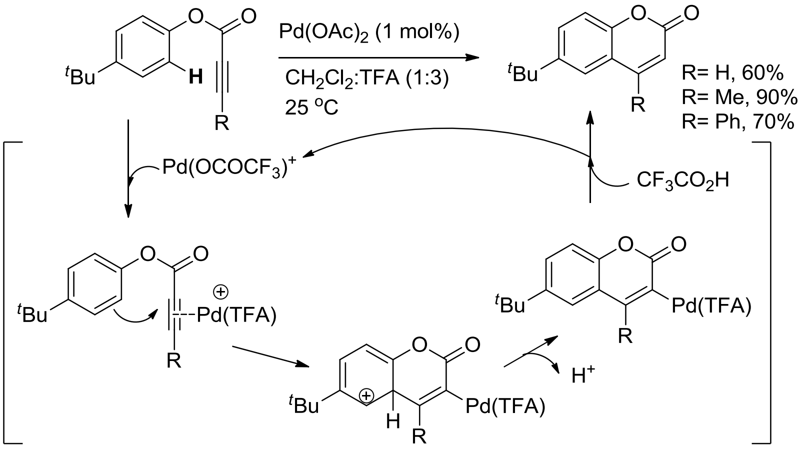


Scheme 1.2.18. Cyclopentenones from an intramolecular palladium-catalysed alkene-alkene coupling.[69]

1.2.2.4. *C-H Alkenylation through Hydroarylation of Alkynes*

The hydroarylation of alkynes is an efficient method for the synthesis of aromatic olefins. As shown in the case of the reaction of alkenes with unactivated arenes, there are two main mechanisms depending on whether arene metalation or alkyne metal coordination happens first.[70] If the arene metalation happens first, the σ-aryl-metal intermediate adds to the triple bond in a *syn* manner to form an arylvinyl metal hydride intermediate. The alkene product is formed after reductive elimination. The presence of a directing group is usually needed to afford good regioselectivities. On the other hand, if the triple bond coordinates first with the metal to form a highly electrophilic species, this is attacked by an electron-rich arene. The arylvinyl metal complex formed is protonated to form the aryl-alkene product.

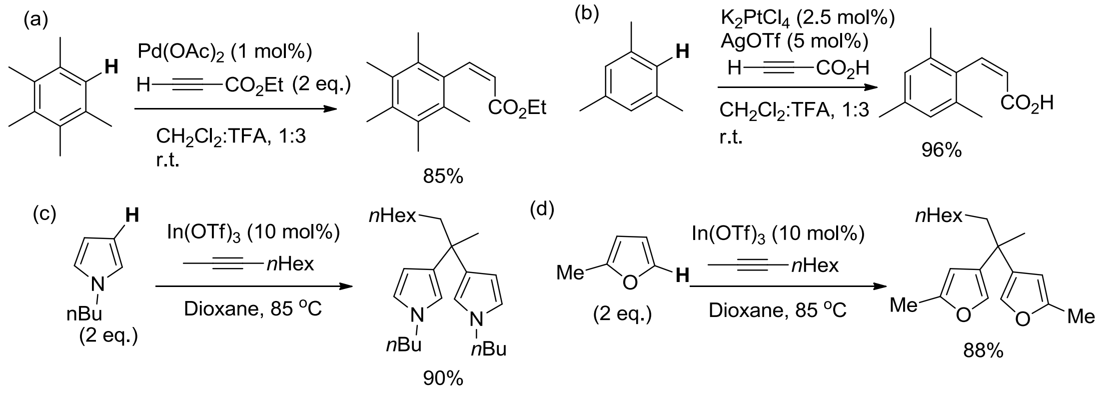
Fujiawara and co-workers were pioneers in the use of simple benzene derivatives including pentamethylbenzene or mesitylene in the palladium-catalysed hydroarylation of electron-poor terminal and internal alkynes.[71, 72] An intramolecular cyclisation of aryl propiolates was found to give coumarine derivatives through a 6-*endo* pathway. The reaction usually takes place under very mild conditions, high conversions are observed at r.t. in the presence of an acid. Initially, the mechanism was thought to undergo arene palladation first, but more recent mechanistic studies suggest than an electrophilic aromatic substitution mechanism is more likely (Scheme 1.2.19).[73] The reaction can be catalysed by Au[74] or Hf[75] catalysts as well. Similar intramolecular hydroarylations have been used for the obtainment of many interesting heterocycles as quinolinones, chromenes and dihydroquinolines.[70]



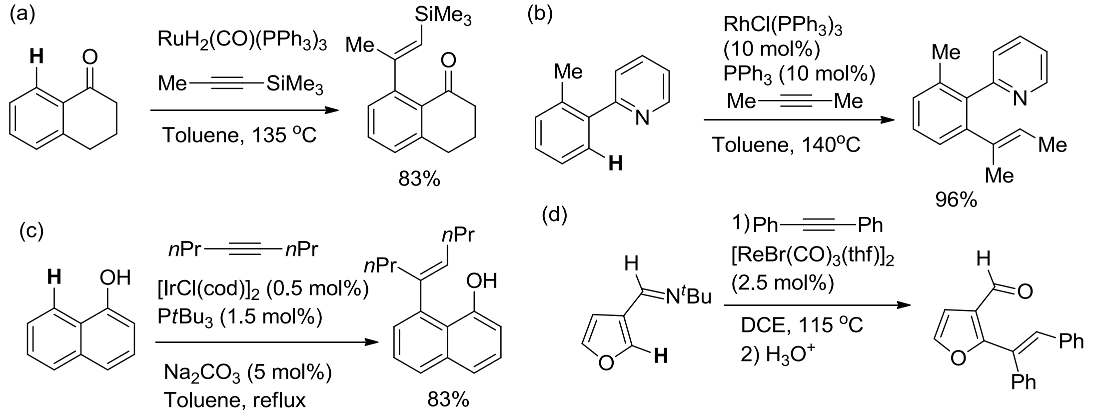
Scheme 1.2.19. Synthesis of coumarines through intramolecular hydroarylation of aryl alkynoates.[72]

The intermolecular version of the reaction between electron-rich benzene derivatives and electron-poor terminal or internal alkynes is also thought to proceed *via* alkyne triple bond activation with the palladium-catalyst. The hydroarylation also happens at low temperatures in an acid medium giving the products from the trans addition in a regio- and stereoselective manner in most cases (Scheme 1.2.20).[71] Several variations of the reaction have been reported, as the use of different metal catalysts and the employment of electron-rich heterocylces like pyrroles, indoles and furans.[70] In these cases, diaddition products have been reported depending on the nature of the alkyne (Scheme 1.2.20).

The intermolecular arylation of internal alkynes with arene rings containing a directing group is believed to undergo metalation of the aromatic group and selectively give the alkenylated product at the *ortho* position. Different catalysts and directing groups as 2-pyridine, ketones and hydroxyls have been used (Scheme 1.2.21).

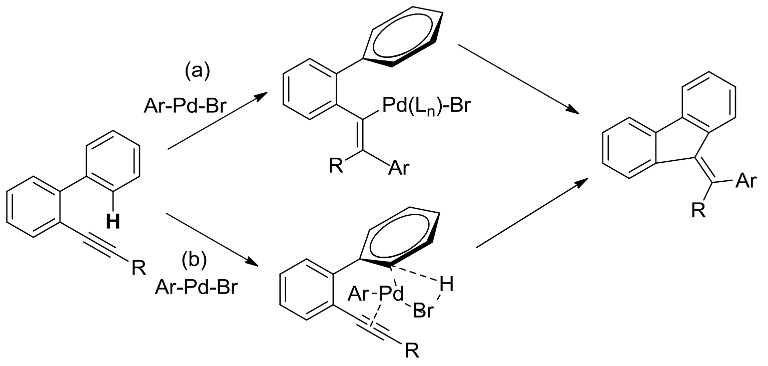


Scheme 1.2.20. Fujiwara[71] (a), Kitamura[76] (b) and Kawakami[77] (c) approaches to intermolecular hydroarylations.



Scheme 1.2.21. (a) Ketone[78], (b) 2-pyridine[79], (c) hydroxyl[80] and (d) imine[81] directed *ortho*-alkenylation of arenes.

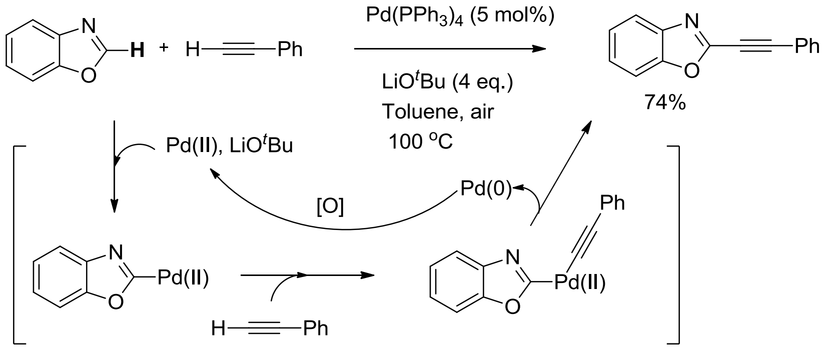
Recently, the synthesis of fluorenes, *via* a palladium-catalysed 5-*exo*-dig annulation of *o*-alkynylbiaryls, has been reported by Gevorgyan and co-workers.[82] This method represents an elegant way of directing the alkenylation to the *ortho* position of the triple bond by coordination with the aryl-palladium intermediate, giving the conjugated aromatic products in high yields and excellent regioselectivities. Furthermore, a tandem arylation/annulation reaction can take place by the addition of bromoarenes. The aryl bromide forms a σ-aryl-palladium intermediate that can interact firstly with the alkyne or the arene to afford the final product (Scheme 1.2.22).[83] This is a significant example of a sequential synthesis of tetra-substituted olefins through hydroarylation of an unactivated arene, our main aim.



Scheme 1.2.22. The two proposed routes for the arylation/annulation reaction: (a) regioselective carbopalladation of triple bond happens first; (b) direct insertion into the C-H bond by the arene-palladium intermediate coordinated to the alkyne happens first.

1.2.2.5. C-H Alkynylation

Recently, new methods have been discovered for the direct reaction of arenes with terminal or pre-functionalised alkynes. This procedure was developed to be a greener and reliable alternative to Sonogashira reactions. The main difficulty of the reaction is trying to reduce the formation of alkyne homocoupling byproducts. This transformation has mostly been applied to the alkynylation of heterocycles, one of the last reported examples is the reaction of several benzoxaxoles with terminal alkynes reported by Chang and co-workers (Scheme 1.2.23).[84]



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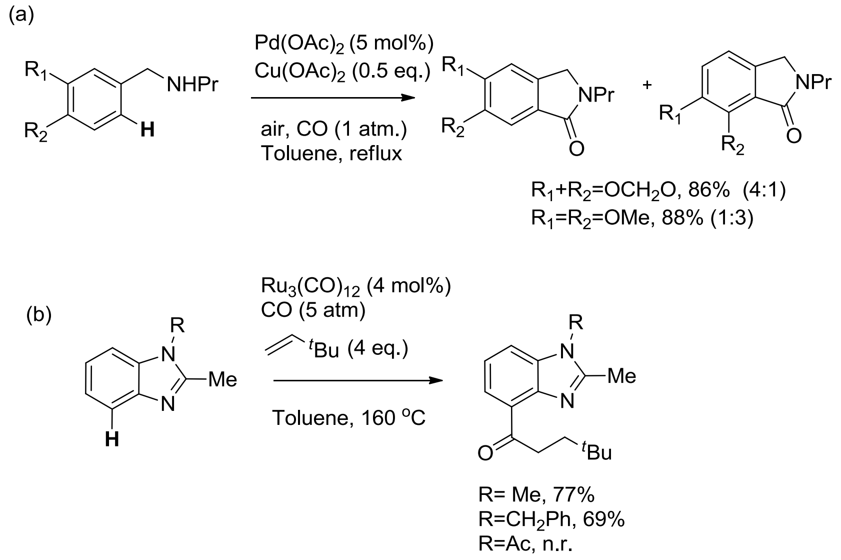
Scheme 1.2.23. Benzoxazole alkynylation.[84]

1.2.2.6. C-H Carbonylation

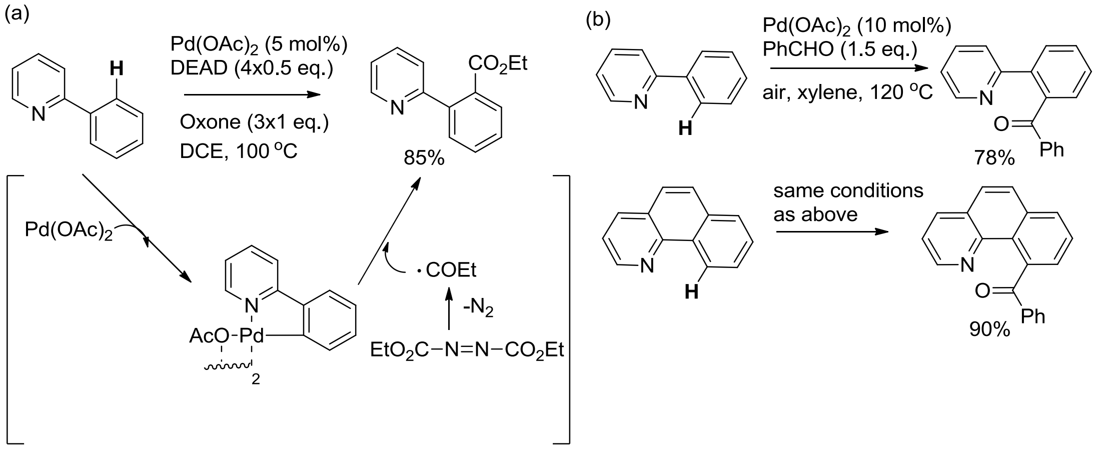
The metal-catalysed carbonylation of aromatic C-H bonds with CO has been well used in organic chemistry for the synthesis of interesting molecules. One early example is the intramolecular Pd-catalysed carbonylation of benzylamines described by Tokuda *et. al.*[85] The reaction afforded benzolactam derivatives in high yields when using both molecular O_2 or $Cu(OAc)_2$ as co-oxidants (Scheme 1.2.24).

The carbonylation of aryl C-H bonds with CO followed by alkylation with an alkene present in the reaction is a usual tandem procedure to obtain acylated products in one step. Murai and co-workers studied the carbonylation of several aryl imidazoles and benzimidazoles,[86] a wide range of olefins and functional groups are allowed in the reaction. The new C-C bond is formed exclusively at the α-position of the sp^2 nitrogen (Scheme 1.2.24).

More recently, the use of DEAD as a source of ethoxycarbonyl has been described as a new method for the obtainment of esters, avoiding the use of toxic CO.[87] The reaction is thought to proceed *via* the addition of ethoxycarbonyl radicals to cyclopalladacyclic intermediates. The coupling of simple aldehydes with unactivated arenes stands out as a novel and highly efficient carbonylation method (Scheme 1.2.25).[88]



Scheme 1.2.24. (a) Carbonylation of benzylamines by Tokuda *et. al*[85]. (b) Tandem carbonylation/arylation of benzimidazoles[86].

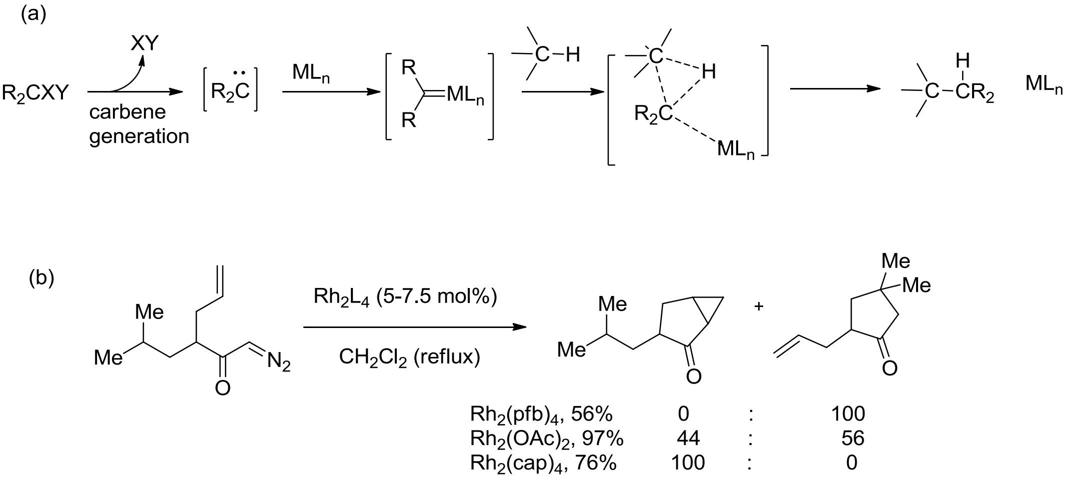


Scheme 1.2.25. Alternative carbonylation methods: (a) DEAD as ethoxycarbonyl source by Chan and co-workers.[87] (b) Direct acylation with aldehydes reported by Cheng and co-workers.[88]

1.2.2.7. Carbene insertion into C-H bonds

Diazoalkanes can provide carbenes either photochemically, thermally or by the use of a transition metal[89, 90]. The metal-catalysed insertion of carbenes into a C-H bond does not involve the formation of a carbon-metal σ-bond (i.e. not a truly C-H activation, Scheme 1.2.26 (a)) and the insertion occurs with retention of configuration. Although ligated copper, silver and gold (coinage metals) have been used,[91] copper and dirhodium catalysts are generally employed for the formation of metal carbenes. In the case of dirhodium (II) there is an additional stabilisation of the metal carbene provided by the second rhodium atom. Diazo esters and diazo amides are the most used substrates for catalytic C-H insertion due to their ease of formation and relative stability. The C-H insertion is thought to take place in a single step, so the cleavage of the carbon-hydrogen bond is concurrent with the formation of the carbene-carbon and carbene-hydrogen bond.[92] Ligands on the metal have been shown to have significant influence either in the chemoselectivity, regioselectivity, diastereoselectivity and enantioselectivity of the reaction.[90] For instance, changes in electrophilicity in the dirhodium catalyst control C-H insertion and cyclopropanation ratios in diazo ketone substrates (Scheme 1.2.26 (b)).[93] Although intramolecular C-

H insertion is generally used, recently also intermolecular examples have been reported using aryl and vinyldiazoacetates.[94]

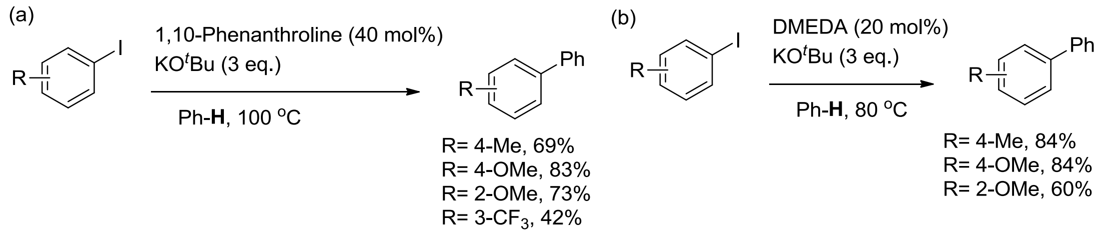


Scheme 1.2.26. (a) General mechanism of metal-mediated carbene insertion into C-H bonds.[90] (b) Effect of rhodium ligands in chemoselectivity.[93]

1.2.3. Metal-Free Functionalisation of C-H Bonds

An excellent tool for the functionalisation of unactivated arenes is the organo-SOMO (singly occupied molecular orbital) catalysis procedure, developed by MacMillan.[50] In this procedure, a chiral amine catalyst is used in the presence of a good oxidant (usually CAN: ceric (IV) ammonium nitrate or $[Fe(phen)_3]PF_6$) for the radical enantioselective arylation of aldehydes and unactivated arenes.

Very recently, other metal-free procedures for the direct arylation of aryl halides with arenes mediated by amines or heterocycles and potassium *tert*-butoxide have been reported by Itami,[95] Shi,[33] and Lei,[96] groups (Scheme 1.2.27). The authors hypothesised that the reaction involves radical intermediates generated from the reaction of aryl halides with KO^{t}Bu. Accordingly, when radical scavengers as TEMPO or 1,1-diphenylethylene were added to the reaction no arylation was observed.

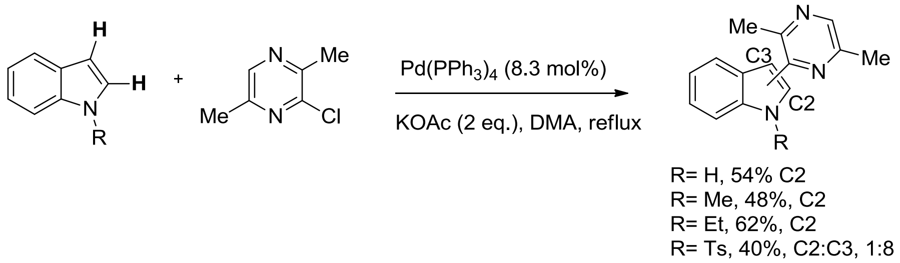


Scheme 1.2.27. Direct arylation reactions in the absence of transition-metals: (a) Use of 1,10-phenantroline as organocatalyst in the presence of KO^{t}Bu by Shi and co-workers.[.33] (b) Use of DMEDA reported by Lei and co-workers.[96]

1.3. Direct Functionalisation of Indole through C-H Activation

1.3.1. Direct Arylation of Indole

2- and 3-arylated indoles are common moieties in natural products, drugs and other industrially interesting compounds. It is not surprising then, that direct arylation of unactivated indoles has attracted a lot of research interest, especially in the last ten years. The first example of palladium-catalysed intermolecular arylation of indole was reported by Ohta and co-workers using chloropyrazines back in 1989.[97] It was observed that the regioselectivity was affected by the indole protecting group, so alkyl groups gave exclusively 2-arylated derivatives while 1-tosylindole afforded mixtures of 2- and 3-arylated products (Scheme 1.3.1).

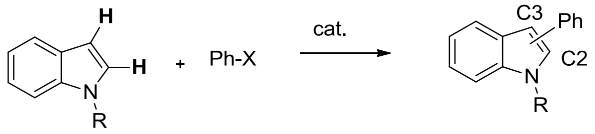


Scheme 1.3.1. Ohta's firt example of indole direct arylation.[97]

Since this early example, the unique electron-rich character of indole has offered the possibility of develop mild and regioselective arylation methods using all kind of activated arenes as well as unactivated ones. An extensive list of methods can be found in table 1.3.1.

Sames and co-workers (entries 1-3) were the first ones interested in improving the reaction explored before by Ohta. They studied the Pd(0)-catalysed coupling of iodoarenes to protected indoles. The use of very small loadings of $Pd(OAc)_2$ and

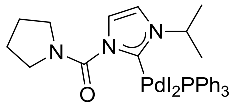
Table 1.3.1. Several methods used for the direct arylation of indoles.



Entry	*R*	*PhX (eq.)*	*Reaction Conditions*	*Yield (C2:C3)*
1[98]	Me	PhI (1.2)	$Pd(OAc)_2$ (0.5 mol%), PPh_3 (2 mol%), CsOAc (2 eq.), DMA (7.6 M), 125 °C, 24h.	88% (C2)
2[98]	Ph	PhI (1.2)	Same as above.	68% (C2)
3[98]	Ac	PhI (1.2)	Same as above.	0%
4[98]	MgCl/ TMEDA	PhBr (0.5)	$Pd(OAc)_2$ (2.5 mol%), IMes (2.5 mol%), CsOAc (2 eq.), Dioxane (0.1 M), 125 °C, 24h.	96% (1:67)
5[99]	H	PhI (1.2)	$[Rh(coe)_2Cl_2]_2$ (2.5 mol%), P[*p*-$(CF_{3)}C_6H_4]_3$ (15 mol%), CsOPiv (1.4 eq.), Dioxane (1.2 M), 120 °C, 18h.	82% (>50:1)
6[100]	SEM	PhI	PdNHC* (1.5 mol%), CsOAc (2 eq.), DMA (1.0 M), 125 °C	77% (C2)
8[101]	Me	Ph_2IBF_4 (2)	IMes$Pd(OAc)_2$ (5 mol%), HOAc, 25 °C, 18h.	89% (C2)
9[101]	H	Ph_2IBF_4 (2)	Same as above	81% (C2)
10[102]	Me	Ph_2OTf (1.1)	$Cu(OTf)_2$ (10 mol%), dtbpy (1 eq.), DCE (0.1 M), r.t., 24h.	72% (1:14)
11[102]	Ac	Ph_2OTf (1.1)	$Cu(OTf)_2$ (10 mol%), dtbpy (1 eq.), DCE (0.1 M), 60 °C, 24h	83% (9:1)
12[103]	Me	PhI (2)	$Pd(OAc)_2$ (5 mol%), Ag_2O (0.75 eq.), *o*-$NO_2C_6H_4COOH$ (1.5 eq.), DMF (0.5 M), 25 °C, 18h.	92% (C2)
13[104]	H	PhBr (1.2)	$Pd(OAc)_2$ (5 mol%), $BnBu_3NCl$ (20 mol%), K_2CO_3 (3 mol%), Toluene (0.25 M), 110 °C, 24h.	97 % (C3)
14[105]	Me	$PhB(OH)_2$ (1.5)	$Pd(OAc)_2$ (5 mol%), O_2 (1 atm.), HOAc (0.1 M), r.t., 8h.	77% (C2)
15[105]	H	$PhB(OH)_2$ (1.5)	Same as above	83% (C2)

16[106]	H	$PhBF_3K$ (1.25)	$Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (10 mol%), air, HOAc (0.1 M), r.t., 12h.	81% (C2)
17[107]	Me	$PhSi(OMe)_3$ (3 eq.)	$Pd(OAc)_2$ (10 mol%), Ag_2O (3 eq.), TBAF (3 eq.), EtOH:HOAc (4:0.5), r.t., 18h.	82% (C2)
18[108]	Ac	PhH (30)	$Pd(TFA)_2$ (5 mol%), 3-nitropyridine (10 mol%), CsOPiv (40 mol %), $Cu(OAc)_2$ (3 eq.), HOPiv, 140 ^{o}C, (μW), 5h.	84% (1:13.8)
19[108]	Ac	PhH (30)	$Pd(TFA)_2$ (2 mol%), 3-nitropyridine (10 mol%), CsOPiv (40 mol $Cu(OAc)_2$ (3 eq.), HOPiv, 140 ^{o}C, (μW), 5h.	63% (1:27)
20[109]	Ac	PhH (300)	$Pd(OAc)_2$ (25 mol%), Ag_2O (4 eq.), HOAc:PhH, 2:3, 120 ^{o}C	55% (3.6:1)
21[109]	Ac	PhH (300)	$Pd(OAc)_2$ (25 mol%), $Cu(OAc)_2$ (4 eq.), HOAc:PhH, 2:3, 120 ^{o}C	66% (1:4)
22[110]	SEM	PhH (300)	$Pd(OAc)_2$ (10 mol%), AgOAc (3 mol%), PhH (0.4 M), PivOH (2.5 eq.), 120 ^{o}C (μW), 3h.	69% (2.6:1)
23[111]	Me	Ph_2IOTs (2)	DMF (0.25 M), 100 ^{o}C, 22h.	64% (C3)

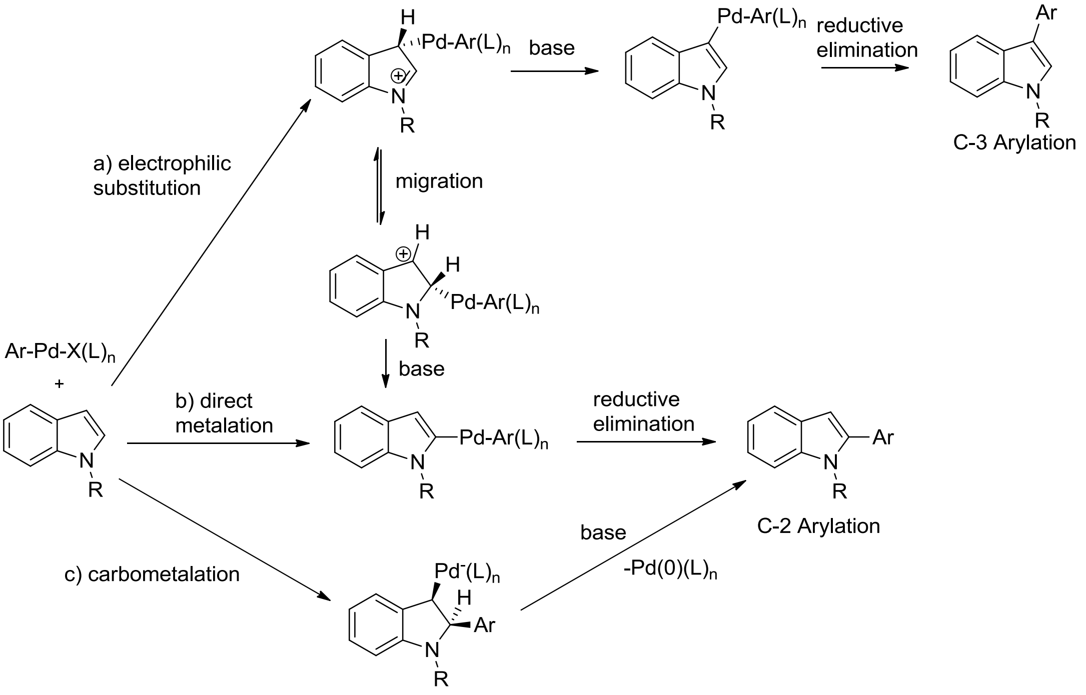
*PdNHC=



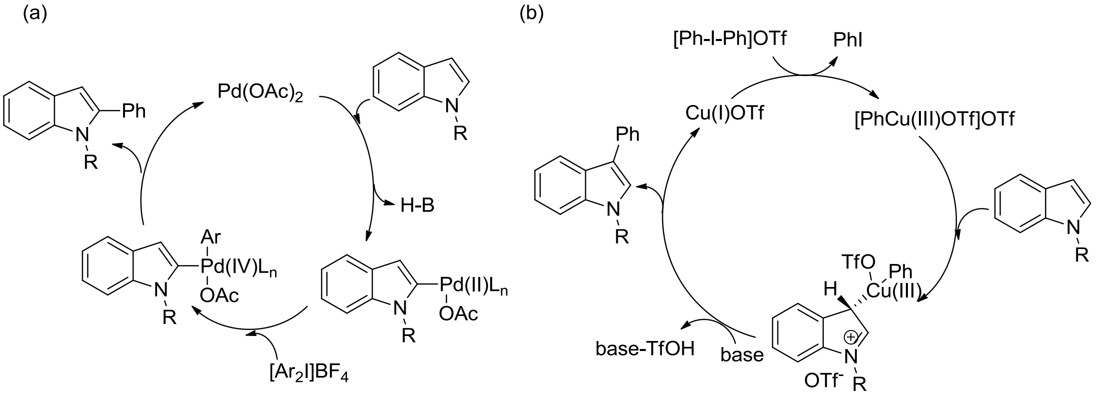
PPh_3 turned out to be crucial in order to achieve good yields and avoid the formation of biphenyl as a reaction byproduct. The employment of anhydrous CsOAc as base also enhanced the direct arylation process which afforded exclusively 2-arylated indoles.

The authors conducted a mechanistic investigation where three possible pathways were taken into account for the indole activation: a) electrophilic metalation followed by C3 to C2 palladium-migration, b) non-electrophilic metalation at the C2 position and c) Heck-type reaction (carbometalation) (Scheme 1.3.2). The direct metalation at C2 was refused as in the examples reported before a strong donating group in the indole ring was necessary.[112] Neither the Heck-type route seemed appropriate as it would involve an isomerisation step with a reversible α-hydride elimination through a palladium hydride-carbene intermediate,[113] which is not known for Pd species. The kinetic isotope effects at the 2- and 3-position of the indole substrate were calculated giving 1.2 and 1.6 (secondary KIE) values respectively. These values are in agreement with a electrophilic metalation at the C3 position (higher KIE) followed by a palladium 1,2-shift to the C2 position, probably due to the major stability of the palladium-carbon bond next to the nitrogen atom. With this mechanism in mind, the authors hypothesised that the use of bulky *N*-substituents in the indole would allow regioselective 3-arylation. That was confirmed by the use of indoles with *N*-Mg bulky complexes which afforded 3-phenyl indole when reacted with iodobenezene under the optimised conditions and even better regioselectivity could be achieved when using bromobenzene (Table 3.1.1., entry 4). The same group reported the use of rhodium catalysts in the direct arylation of protected and unprotected indoles as well as the arylation of SEM-protected indoles using Pd-NHC catalysts (entries 5 and 6).

A lot of research has been done in order to improve the conditions and amplify the scope of reagents suitable for the direct arylation of indoles. This has resulted in the development of efficient methods that can take place under very mild conditions. Sanford and co-workers first reported the selective 2-arylation of protected and free indoles at r.t. (Table 3.1.1, entries 8 and 9). It was reasoned that the electrophilic palladation of indole would be faster with electron-deficient $Pd(OAc)_2$ and the palladium intermediate could be further oxidised to Pd(IV) using diaryliodonium salts as both the aryl source and the oxidising agent (Scheme 1.3.3). Also Gaunt's group worked in this direction using diaryliodonium salts to obtain a very electrophilic Cu(III) intermediate from $Cu(OTf)_2$ (entries 10 and 11). They could control the regioselectivity of the arylation tunning the reaction conditions, so the reaction of free or methyl protected indoles gave the 3-arylated products at 35 ^{o}C. However, when using acetyl protected indoles, coordination of the acetyl group with the copper catalyst favoured the C3 to C2 migration. The 2-arylated indoles were obtained at 70 ^{o}C (Scheme 1.3.3).

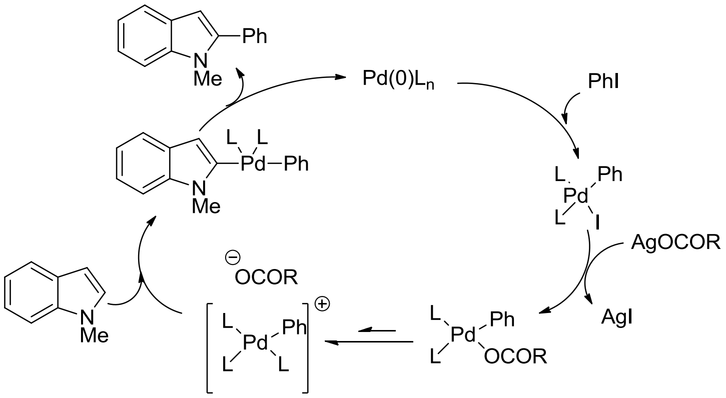


Scheme 1.3.2. Possible mechanisms for indole C-H activation proposed by Sames *et. al.*[98]



Scheme 1.3.3. Sanford's[101] (a) and Gaunt's[102] (b) strategies for the regioselective direct arylation of indoles with diaryliodonium salts.

Larrosa and co-workers developed a method where the arylation reaction took place at r.t., while it was still possible to use commercially available iodoarenes (entry 12). The use of silver oxide to remove iodide from the palladium-aryl intermediate together with a poorly coordinating carboxylate counterion (*o*-$NO_2C_6H_4COOH$) is thought to form a cationic highly electrophilic salt, which could undergo electrophilic palladation of indole. Reductive elimination affords the arylated product (Scheme 1.3.4).

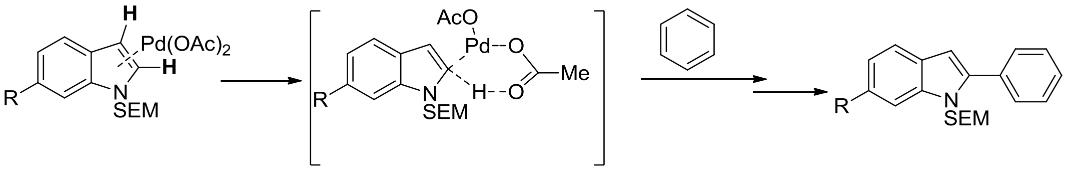


Scheme 1.3.4. Catalytic cycle proposed by Larrosa and co-workers for the direct arylation of indoles with iodoarenes.[103]

Besides Gaunt's elegant process for selective indole 3-arylation, other methods have been reported[114], from these, the work published by Rossi and co-workers (entry 13) represents a general route for the arylation of a wide range of free NH-indoles substituted or not at the 2-position. Either electron-rich or electron-poor bromoarenes are used, with a cheap catalyst system formed by $Pd(OAc)_2$ (1-5 mol%) and a lipophilic quaternary ammonium halide (4-20 mol%).

The use of boronic acids, potassium trifluoroborate salts and arylsiloxanes for the palladium-catalysed arylation of unactivated indoles also happened under very mild conditions (entries 14-17). The reactions were conducted in acidic media and in the presence of an oxidant to reoxidise the Pd(0) from the reductive elimination step to Pd(II) in order to restart the catalytic cycle with the electrophilic palladation of indole.

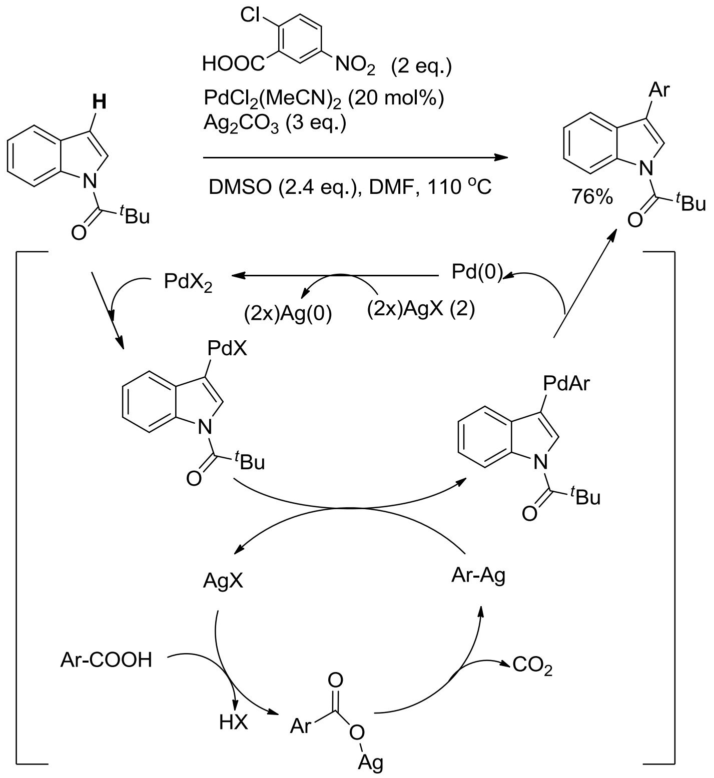
Interestingly, the oxidative cross-coupling of unactivated indoles and unactivated arenes has also been explored. Fagnou reported a high-yielding selective 3-arylation of acetylindoles with a large excess of benzene using electrophilic $Pd(TFA)_2$ catalyst in the presence of stoichiometric amounts of $Cu(OAc)_2$ under harsh conditions (140 ^{o}C µW, 5h, Table 3.1.1, entries 18-19). 3-nitropyridine and CsOPiv were necessary to enhance the reaction. Later, the authors reported that the regioselectivity outcome could be controled depending on the oxidant used. When AgOAc was the oxidant mainly 2-arylated products were obtained.[115] DeBoef's group also reported the arylation of indoles with benzene (solvent) and observed the oxidant-dependent change in regioselectivity of the reaction using $Cu(OAc)_2$ or AgOAc (entries 20 and 21). More recently, the same group also reported the 3-arylation of SEM protected indoles (entry 22). In that case, mechanistic studies were conducted in order to find out the route for indole and arene palladation. The generally accepted electrophilic aromatic route did not explain that the reaction with 6-NO_2-indole enhanced the obtainment of 2-arylated products. Computational studies showed that a concerted metalation-deprotonation mechanism[116] (CMD) for the palladation of both arenes is more in accordance with the observed experimental results. Also KIE studies with benzene and d_6-benzene resulted in high values (>4), in the presence or absence of acid (PivOH), indicating that the cleavage of benzene C-H bond is the rate-determining step in the reaction (Scheme 1.3.5).



Scheme 1.3.5. Concerted metalation-deprotonation (CMD) mechanism for the oxidative cross-coupling of SEM-indoles and benzene by DeBoef and co-workers.[110]

Finally, a very recent report by Ackermann and co-workers (entry 23) demonstrated that the 3-arylation of indoles is possible using diaryl iodonium tosylates in the absence of metal-catalysts when heating at 100 ^{o}C. Although no mechanistic explanation is showed in this report, other arylation procedures have been reported using diaryl iodonium salts in the absence of metal-catalysts and it would be discussed in following sections.

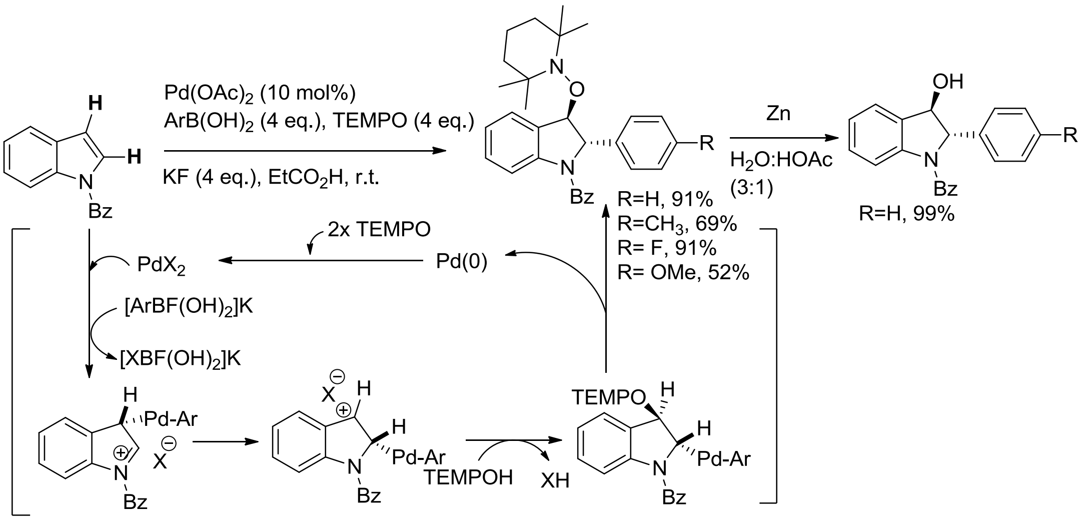
The use of benzoic acids as the arene source has also been reported as an efficient method for the synthesis of 3-aryl indoles by Larrosa and co-workers (Scheme 1.3.6).[117] In this procedure 2-substituted benzoic acids are used to afford a new carbon-carbon bond formation through a combined C-H activation/decarboxylation procedure.



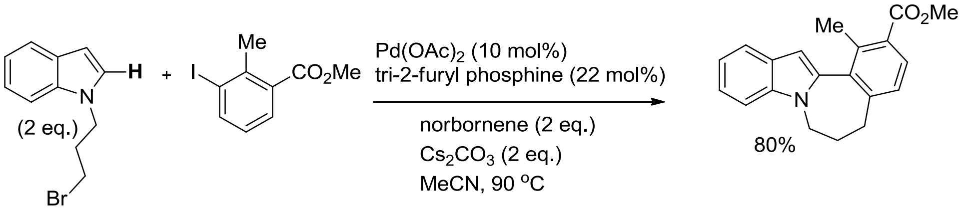
Scheme 1.3.6. Direct 3-arylation of indoles through a decarboxylative process.[117]

An impressive stereoselective tandem arylation/carboaminoxylation procedure was published by Studer *et. al.*[117] When TEMPO was used as oxidant in the direct arylation of indoles with aryl boronic acids, it was noticed that TEMPO could attack the cationic indole-palladium intermediate affording *anti* 2-aryl-3-TEMPO products which can easily be converted to the correspondent 2-aryl-3-hydroxyl indoles after treatment with Zn (Scheme 1.3.7).

Lautens and co-workers reported a very elegant norbornene-tandem alkylation/direct arylation process for the obtainment of annulated indoles from *N*-bromoalkyl indoles and aryl iodides (Scheme 1.3.8).[118] The ortho alkylation is thought to proceed *via* a Catellani mechanism, followed by the indole-arene coupling after norbornene expulsion through indole C2-H functionalisation.

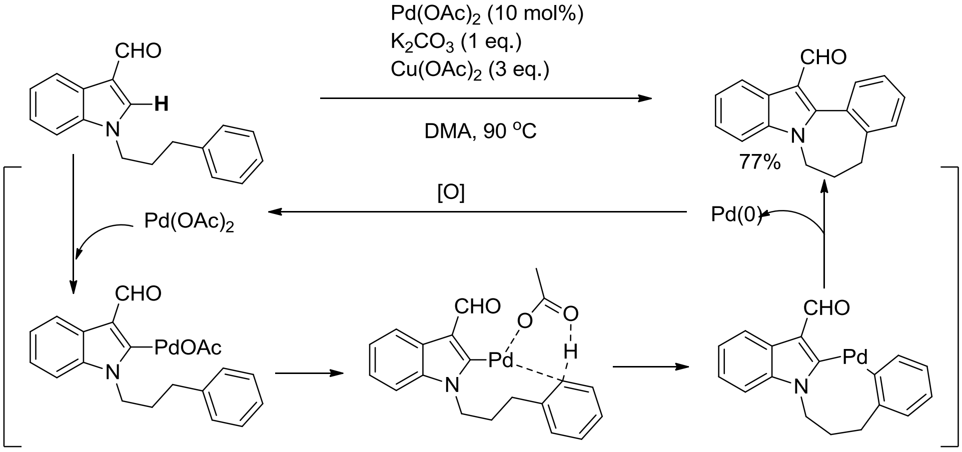


Scheme 1.3.7. Tandem arylation/carboaminoxylation of indoles.[117]



Scheme 1.3.8. Synthesis of annulated indoles through a tandem alkylation/direct arylation process.[118]

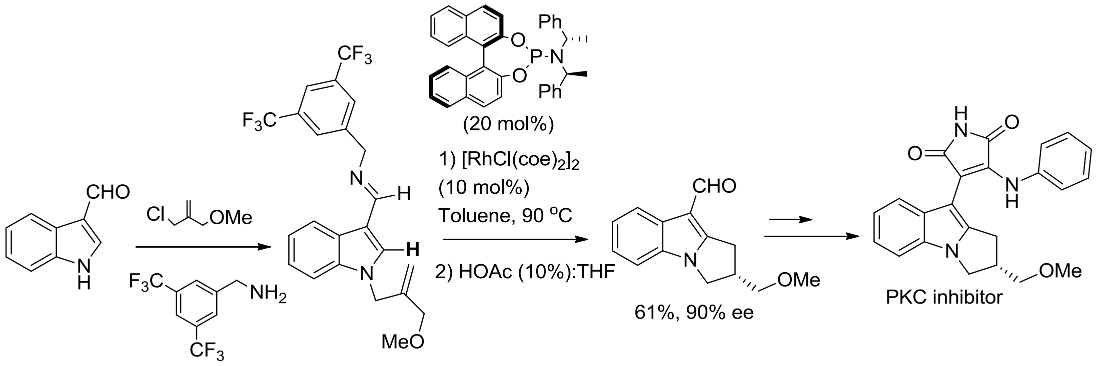
At the beginning of 2011 Greaney and co-workers reported a simpler intramolecular approach for the synthesis of annulated 3-substituted indoles involving the oxidative cross-coupling of indole with another unactivated arene (Scheeme 1.3.9).[119] This approach allowed the formation of 7- and 8-membered rings through the annulation of the arene-tethered indoles. Electron-withdrawing groups at the 3-position of the indole ring were needed to achieve high yields and avoid the formation of indole dimers.



Scheme 1.3.9. Intramolecular medium-ring indole annulation *via* an oxidative cross-coupling reaction.[119]

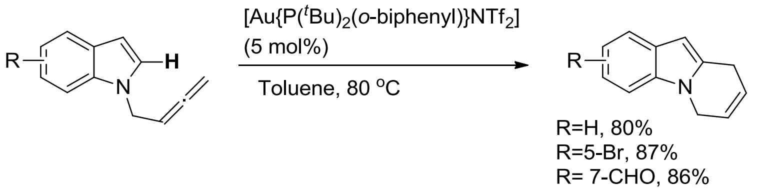
1.3.2. Direct (Carbon)-Alkylation of Indole

The intra- and intermolecular metal-catalysed alkylation of indoles through allylic substitution or by reaction with unactivated alkenes has been widely studied, especially its enantioselective version using chiral ligands.[120] An interesting intramolecular enantioselective Rh-catalysed alkene hydroarylation has been used for the synthesis of a PKC inhibitor by Bergman and Ellman (Scheme 1.3.9).[121] The reaction is directed by the *N*-benzyl imine group in the 3-position of indole, optimisation studies showed that two *meta*-trifluoromethyl groups as substituents in the benzene ring gave the best yield and ee when using a chiral phosphoramidite ligand.



Scheme 1.3.9. Synthesis of a PKC inhibitor by intramolecular enantioselective Rh-catalysed alkylation of indole.[121]

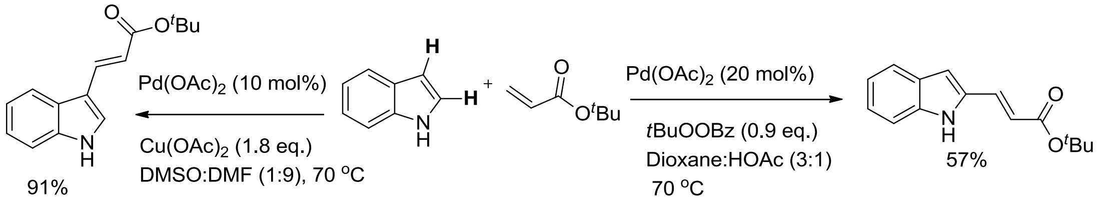
Very recently, the group of Barluenga described the gold-catalysed 6-*endo* annulations of allenylindoles (Scheme 1.3.10).[122] Besides the formation of pyrido[1,2*a*]-1H-indole derivatives, the 2-Me substituted substrates can undergo cyclotrimerisation through C3-H activation.



Scheme 1.3.10. Gold-catalysed annulation of indoles.

1.3.3. Heck-type Direct Alkenylation of Indole

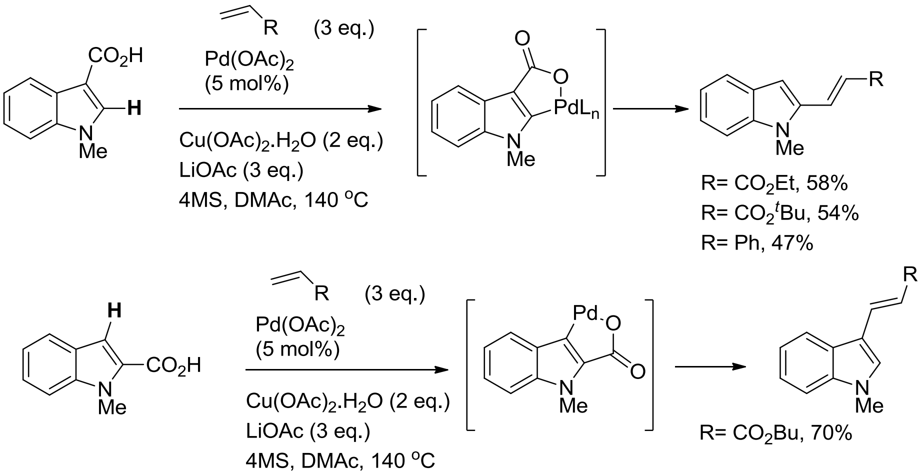
Numerous applications of oxidative Heck-type couplings of indoles and olefins have been reported.[61] Especially interesting is the Gaunt's research group work about the solvent-controlled regioselective alkenylation of indoles (Scheme 1.3.11).[123] The authors suggested that electrophilic palladation of free (NH)-indoles can be controlled by the solvent. Using a polar solvent as DMF and DMSO avoids the palladium migration from C3 to C2 in the indole ring, obtaining 3-functionalised products when $Pd(OAc)_2$ and $Cu(OAc)_2$ are used as catalyst and oxidant. However, when a weakly coordinating solvent as dioxane is used the palladium migration step is favoured and 2-alkenylated indoles are mostly obtained when the oxidant is *t*BuOOBz. The same group, later reported the regioselective alkenylation depending on the steric effect of indole *N*-substitution.[124]



Scheme 1.3.11. Solvent-controlled regioselective direct alkenylation of indoles.

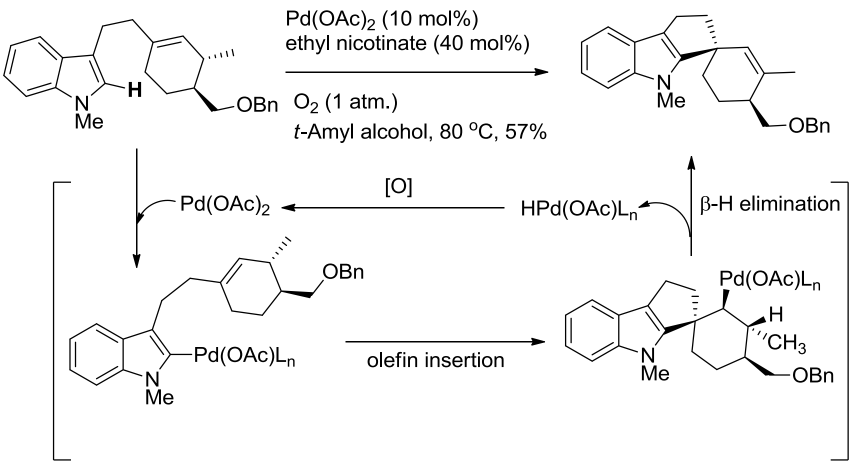
More recently, Carretero and co-workers have reported the $PdCl_2(MeCN)_2$ catalysed regioselective 2-alkenylation of *N*-(2-pyridyl)-sulfonyl indoles using $Cu(OAc)_2.H_2O$ as oxidant.[125] The pyridine group is thought to act as a directing group, coordinating the palladium intermadiates to selectively give the 2-substituted products. A wide range of olefins and indoles can be used in the reaction.

A smart way of controlling the alkenylation regioselectivity has been reported by Miura et. al.[126] It consists in the use of carboxylic acids as directing groups, decarboxylation of the acid occurs in the same step leading to the 2- or 3-alkenylated products (Scheme 1.3.12).



Scheme 1.3.12. Acid directed alkenylation of indoles.[126]

The intramolecular alkenylation of indoles has been used in the synthesis of important natural products as Ibogamine[127] and (+)-Austamide[63] with stoichiometric amounts of Pd. The remarkable catalytic version developed by Stoltz[128] allows the synthesis of annulated indoles in high-yields (Scheme 1.3.13). The reaction proceeds under oxygen atmosphere using $Pd(OAc)_2$ as catalyst and a pyridine as ligand, 3-ethyl nicotinate afforded the best yields. A mechanism where indole palladation happens first, followed by olefin migratory insertion and *β*-elimination is suggested according to the experimental evidence.

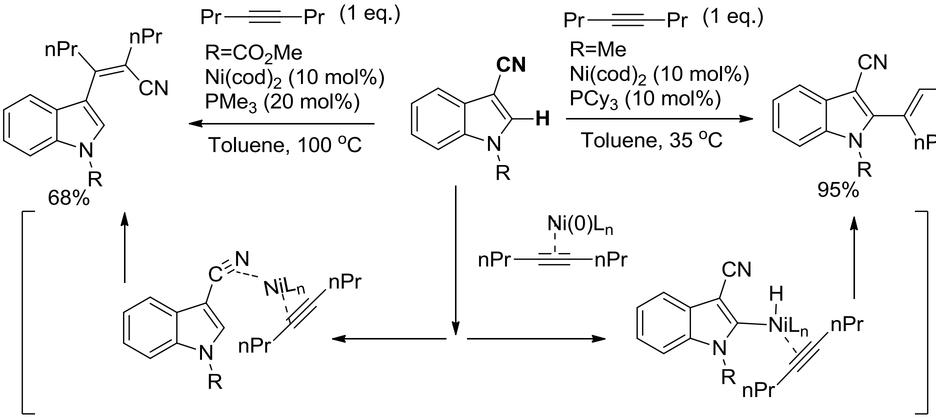


Scheme 1.3.13. Intramolecular oxidative annulation of indoles.[128]

1.3.4. Direct Alkenylation of Indole through Hydroarylation of Alkynes

Fujiwara and co-workers reported an early example of palladium-catalysed insertion of unactivated indoles into triple bonds.[129] The reaction proceeds under very mild conditions, usually r.t. in acetic acid, affording the *trans* addition products in most of the cases. Although the reaction was thought to undergo through indole palladation, later studies suggested than an electrophilic aromatic substitution mechanism was more likely.[73]

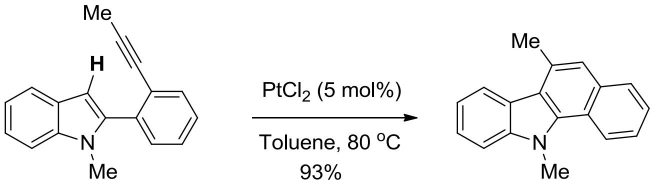
Hiyama's group analysed the synthesis of ethenes from *N*-protected-3-cyanoindoles and alkynes catalysed by Ni(0).[130] They found that depending on the phosphine ligand and *N*-substitution, the alkyne insertion could happen at the 2-position of indole or at the 3-position between indole ring and CN. When 1-acetyl-3-cyanoindole was used in the presence of PMe_3 as ligand, the Ar-CN bond was activated. Whereas, in the case of 1-methyl-3-cyanoindole in the presence of PCy_3, Ar-H was activated (Scheme 1.3.14). The reaction could happen at 35 °C when using electron-withdrawing groups in the 3-position. The alkyne insertion can also be extended to other heteroarenes as imidazoles, benzofuranes and thiazoles.



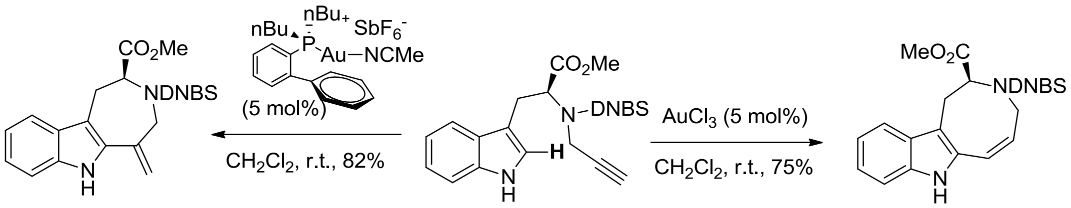
Scheme 1.3.14. Regioselective alkenylation of 3-cyanoindoles.[130]

The regioselective 2-alkenylation of indoles with alkynes catalysed by Rh(III) has recently been reported by Fagnou's group.[131] The reaction proceeds smoothly for a broad range of alkynes *via* a conceptually new cationic catalysis route.

The intramolecular hydroarylation reaction has been widely used for the synthesis of interesting indole derivatives. Fürstner and co-workers used their 6-*endo*-dig cyclisation of *o*-alkynyl biaryls catalysed by $PtCl_2$ for the synthesis of benzoannulated carbazoles that are known as antitumor agents (Scheme 1.3.15).[132] Echavarren and collaborators reported another interesting example, the Au-catalysed cyclisation of 3-alkyne-tethered indoles for the synthesis of 7- or 8-membered rings,[133] activating the C-H bond in the 2-indole position. Stereo- and regioselective products could be obtained depending on the Au catalyst used (Scheme 1.3.16). Also 2-allenyl indole products could be formed depending on the reaction conditions through an alternative elimination process.

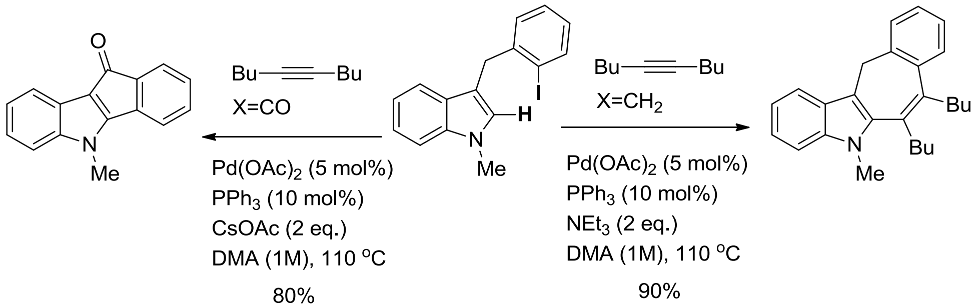


Scheme 1.3.15. Carbazole synthesis by 6-*endo*-dig cyclisation of *ortho*-alkyne 2-arylindoles.[132]



Scheme 1.3.16. 7-*exo*-dig and 8-*endo*-dig cyclisations of 3-alkyne-tethered indoles catalysed by Au(I) or Au(III).[133]

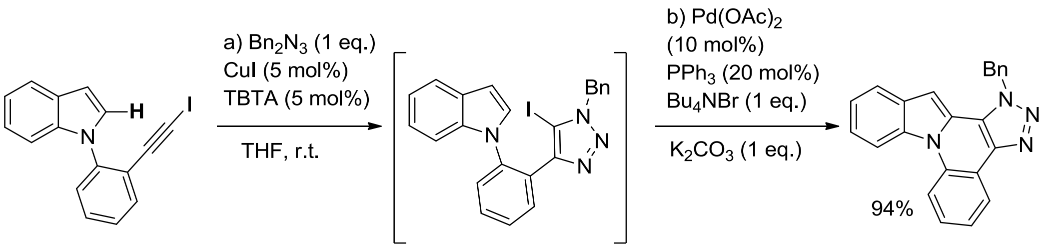
Since the start of our project, some tandem reactions involving the alkenylation of unactivated indoles with alkynes in the presence of a third reagent, have been developed leading to the obtainment of really interesting indole-fused tetra-substituted olefins. Miura and Jia have both presented very impressive synthesis of carbazoles by a tandem double C-H activation from indole and two alkyne molecules or from 2-phenylindole and an alkyne, respectively, and an unexpected rearrangement was observed also by Jiao's group in the palladium-catalysed reaction of indoles with internal alkynes.[134] Tetrahydroquinoline derivatives were generated under mild conditions using O_2 as oxidant. Gevorgyan *et. al.* recently published the synthesis of 7-membered rings from 3-(2-iodobenzyl)-indoles and alkynes. Intramolecular cyclisation happens when benzoyl substrates are employed whereas benzylindoles undergo alkyne insertion (Scheme 1.3.17).[135]



Scheme 1.3.17. Intramolecular cyclisation or alkyne insertion in the palladium-catalysed reaction of 3-(2-iodobenz(o)yl)-indoles with internal alkynes.[135]

Copper-catalysis has also been used for the obtainment of 6-membered annulated indoles,[136] from simple indoles and *ortho*-bromoaryl alkynes through initial *N*-

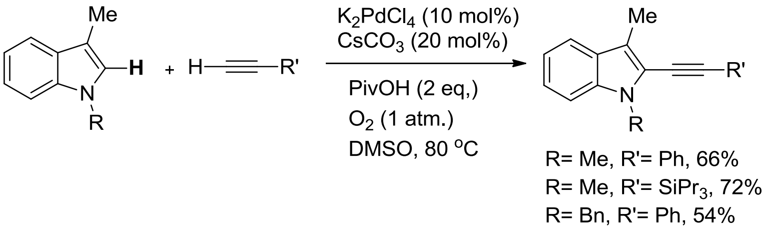
alkenylation. A very recently example is the synthesis of indole-fused triazoles by Lautens and co-workers.[137] *N*-aryl indoles containing *ortho*-iodoalkynes form 1,2,3-triazoles reacting with azides under copper-catalysis, the resulting activated triazole can undergo palladium-catalysed intramolecular coupling with the indole ring in the 2-position (Scheme 1.3.18). The two reactions can be performed in one-pot, without isolation of the intermediates.



Scheme 1.3.18. One-pot synthesis of indole fused triazoles through C-H activation.[137]

1.3.5. Direct Alkynylation of Indole

Recent articles have reported the alkynylation of unactivated indoles with alkynyl halides or alkynyliodonium salts,[138] however, Li and co-workers have recently described an oxidative Heck-Cassar-Sonogashira alkynylation from 1,3-disubstituted indoles and unactivated alkynes (Scheme 1.3.19).[139] The transformation allows a broad scope of alkynes although the indole substrate is quite restricted to 3-methyl substituted indoles.

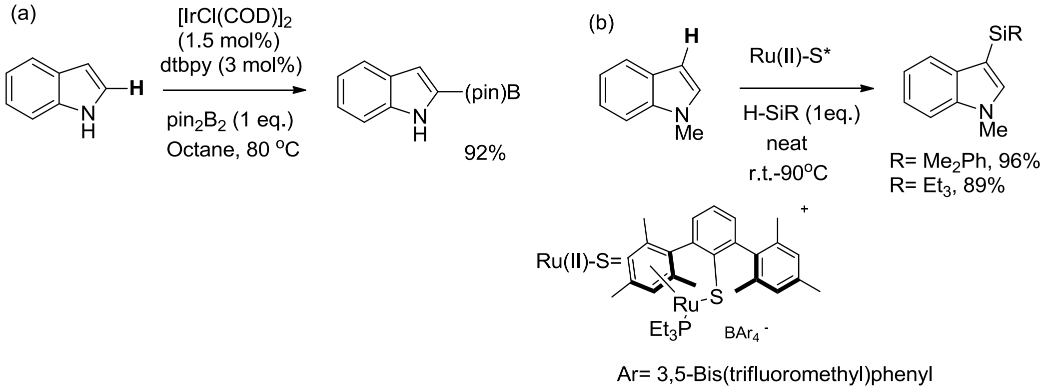


Scheme 1.3.19. Direct alkynylation of indoles with terminal alkynes.

1.3.6. C-Heteroatom Bond Formation through Indole C-H Activation

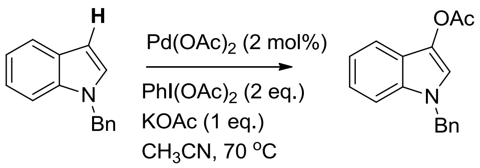
In addition to the formation of new C-C bonds, there are also examples of metal-catalysed coupling of unactivated indoles with heteroatoms.

An important example is the borylation of indoles. It has been stated that the coupling of many heterocycles with bis(pinacolato)diboron can take place under iridium catalysis (Scheme 1.3.20).[140] The synthesis of boronic esters is especially important as counterparts in Suzuki-Miyaura reactions. Likewise the synthesis of silyl indoles is also important an a very recent approach describes the regioselective 3-silylation of indoles with simple silanes using a thiolate Ru(II)-S complex as catalyst (Scheme 1.3.14).[141]



Scheme 1.3.20. (a) Direct boronylation by Miyaura and co-workers.[140] (b) Direct silylation by Tatsumi and co-workers.[141]

Eventually, also the regioselective 3-acetetoxylation of indoles has been analysed.[142] Recently, milder conditions have been reported by Kwong and co-workers using $Pd(OAc)_2$ as catalyst and diacetoxy iodobenzene (Scheme 1.3.21).[143]

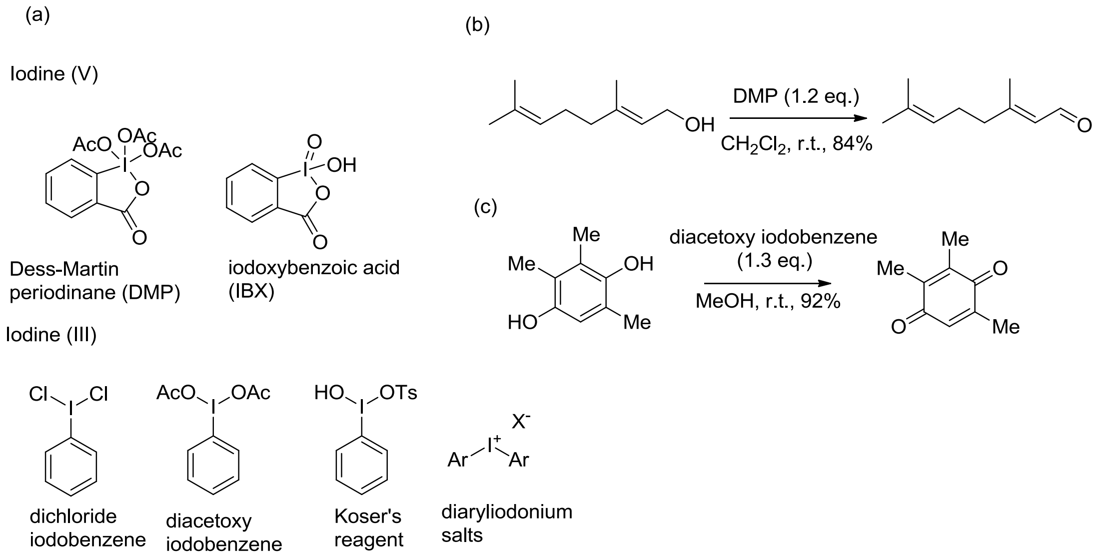


Scheme 1.3.21. Direct 3-acetoxylation of *N*-protected indoles.[143]

1.4. Hypervalent Iodine Compounds in C-H Activation

1.4.1. Definition and Use of Hypervalent Iodine Compounds

The best known hypervalent iodine compound is the Dess-Martin reagent, an extremely useful oxidant.[144] Most of the aromatic iodo(III) species are used as oxidants[145] like diacetoxy iodobenzene (or phenyliodine diacetate, PIDA) (Scheme 1.4.1). Other interesting compounds are (dichloroiodo)arenes, $ArICl_2$, usually solid and safe compounds which are an interesting alternative to toxic Cl_2 in chlorination reactions. Diaryliodonium salts, discovered by Hartmann and Meyer early in 1894,[146] are also an example of aromatic iodo(III) species. Some of them display biological activity or photochemical properties,[147] however they are mostly used in organic chemistry as arylating agents.[148] Their first syntheses involved at least two steps, but recent developments, especially from the group of Olofsson, afford the salts in a quick one-pot procedure from readily available starting materials,[149] making their use more attractive.

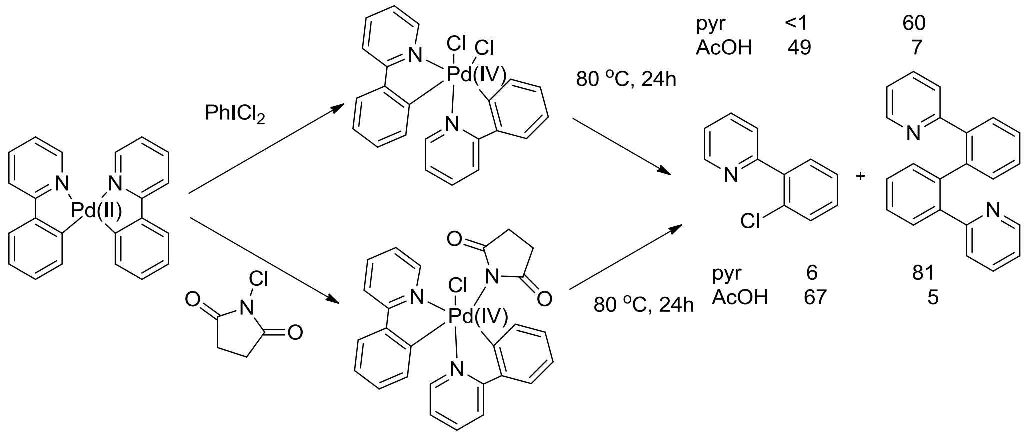


Scheme 1.4.1. (a) Representative examples of hypervalent iodine compounds. (b), (c) Examples of the use of hypervalent iodine compounds as oxidants.[144, 150]

Hypervalent iodine reagents have also been used in the metal-catalysed coupling of unactivated arenes, few representative examples are next discussed, with special mention to the work carried out by the group of Sanford.

1.4.2. Direct Chlorination with $PhICl_2$

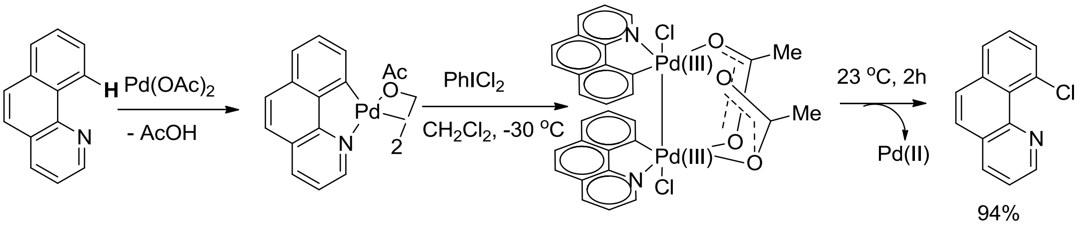
Sanford and co-workers developed a very efficient method for the palladium-catalysed chlorination of 2-aryl pyridines using both $PhICl_2$ and *N*-chorosuccinimide.[151] The stoichiometric study of the reaction led to the isolation of stable Pd(IV) complexes in both cases from $Pd(phpy)_2$ (Scheme 1.4.2). Their thermal decomposition afforded predominantly the new C-Cl bond formation product in acetic acid, whereas in pyridine the reductive elimination process led to C-C bond formation. When the same study was conducted with Pt instead of Pd, Pt(IV) compounds were also found in the reaction with $PtICl_2$, however when NCS was used as oxidant, bimetallic Pt(III)-Pt(III) complexes were isolated at r.t.[152]



Scheme 1.4.2. Formation of Pd(IV) complexes from $Pd(phpy)_2$ and thermal decomposition.[151]

Slightly later, Ritter and collaborators isolated Pd(III)-dimeric species when $PhICl_2$ reacted with the bimetallic Pd(II)-complex generated from $Pd(OAc)_2$ and benzo[*h*]quinoline.[153] The bimetallic Pd(III) species is formed under -30 °C and gives the 10-chloro-benzo[*h*]quinoline product when heating at r.t. *via* a concerted

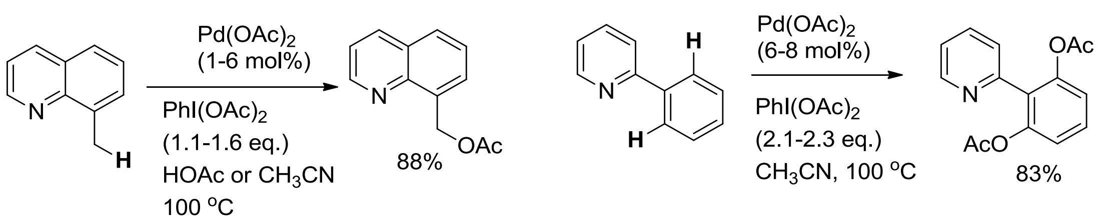
1,1-reductive elimination according to the observed experimental data (Scheme 1.4.3).



Scheme 1.4.3. Direct chlorination of benzo[*h*]quinoline, through a bimetallic Pd(III) complex.[153]

1.4.3. Direct Acetoxylation with PhI(OAc)$_2$

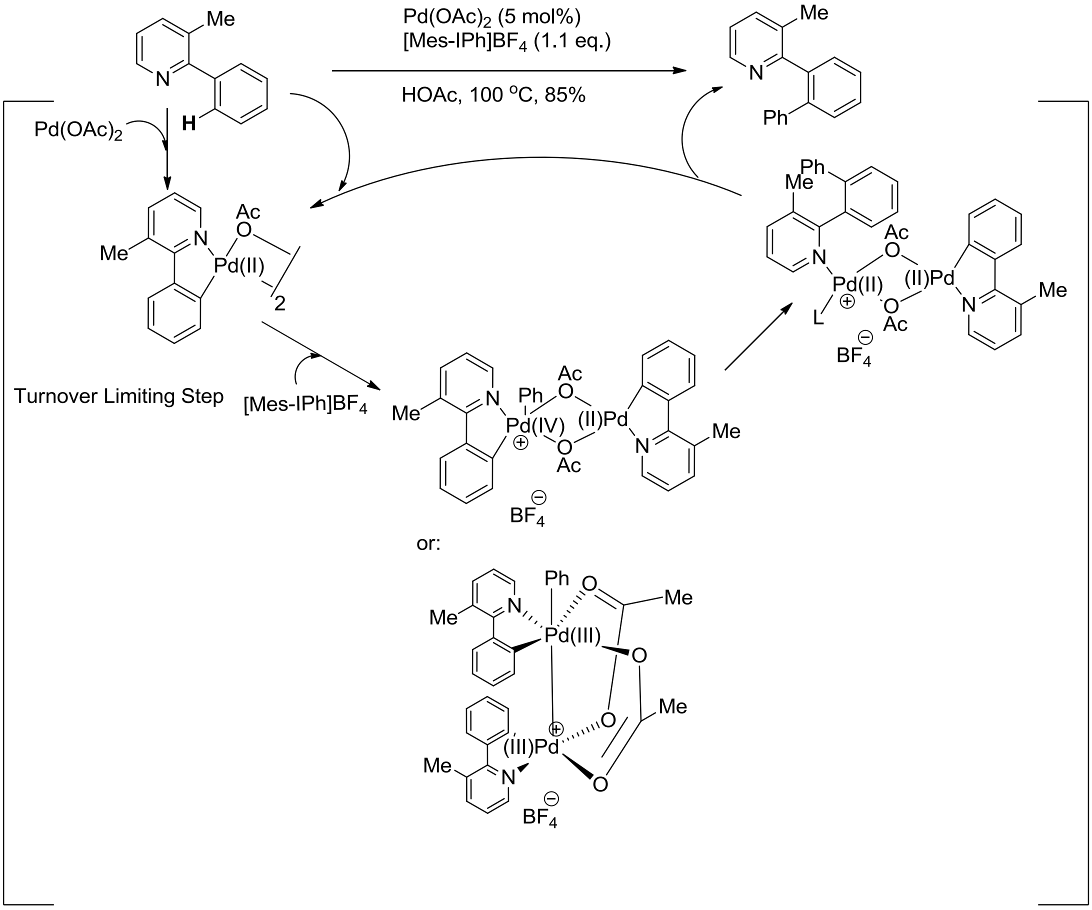
Diacetoxyiodobenzene is a powerful oxidant and it has been used in numerous palladium-catalysed oxidative coupling processes. Besides that, it has also been utilised for the acetoxylation of C(sp^2)-H and C(sp^3)-H bonds. Again, Sanford's group has thoroughly studied this reaction.[154] They found that when using several chelating groups, as pyridine, regioselective palladium-catalysed di- or monoacetoxylation smoothly took place depending on the amount of PhI(OAc)$_2$ employed. After several mechanistic investigations the authors propose the formation of a Pd(IV) intermediate that undergoes reductive elimination, through an ionic mechanism involving initial carboxylate dissociation, to afford the desired products (Scheme 1.4.4).



Scheme 1.4.4. Ligand-directed acetoxylation of unactivated C-H bonds with PhI(OAc)$_2$.[154]

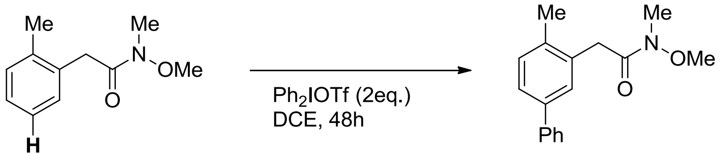
1.4.4. Direct Arylation with Diaryliodonium Salts

Besides the use of diaryiodonium salts for the regioselective direct arylation of indoles (Scheme 1.3.3, pg. 28), the group of Sanford has also used these compounds for the arylation of other systems. Recently, they reported the palladium-catalysed ligand-directed arylation of aryl and benzyl C-H bonds.[155] Careful mechanistic studies proved the existence of a bimetallic acetate-bridged intermediate. Interestingly, the dimer could be composed of Pd(II)-Pd(IV) centres or two Pd(III)-Pd(III) if the palladium atoms are close enough and there is significant bonding between them (Scheme 1.4.5).



Scheme 1.4.5. Suggested mechanism for the direct arylation of 2-arylpyridines with diaryliodonium salts.[155]

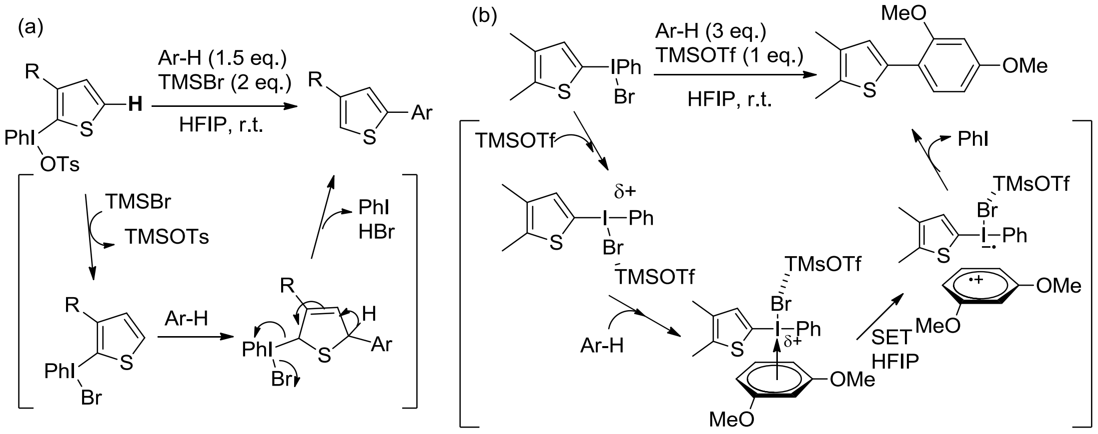
Also Gaunt and co-workers have reported the direct arylation of aromatic C-H bonds using diaryliodonium salts and copper catalysis. They reported the really unusual *meta*-selective direct arylation of arylamides following this procedure.[156] The reaction was thought to involve Cu(III) catalytic species (Scheme 1.3.3, pg. 28), however, very recently the authors found that the reaction can proceed without the presence of copper catalyst when the temperature is higher than 80 °C in the selective *meta* arylation of α-aryl carbonyl compounds (Scheme 1.4.6).[157] The mechanism for this metal-free transformation is still unknown, but they also observed the copper-free reaction happening in the para-arylation of anilines and phenols heating at 90 °C.[158] In this case a thermally dissociation (or copper catalyst induced dissociation) of the diaryliodonium salt counterion is hypothesised to give a highly electrophilic specie that can be attacked by an electron rich arene.



Catalyst	T	Yield
$Cu(OTf)_2$ 5 mol%	70	84
no catalyst	70	0
no catalyst	90	59

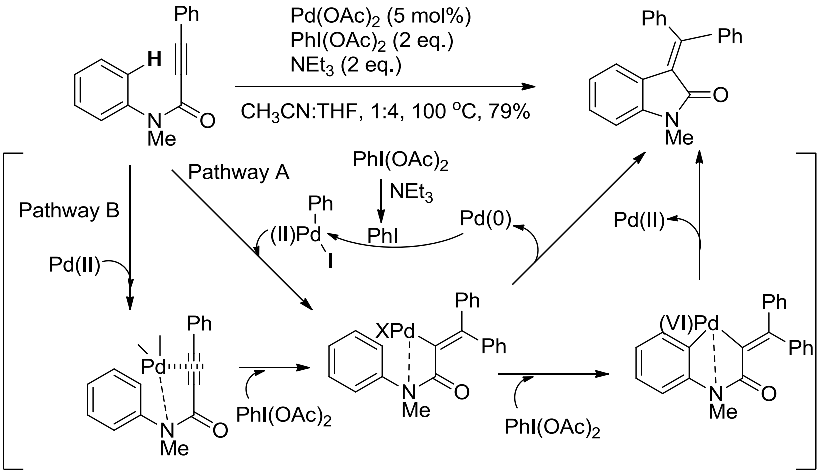
Scheme 1.4.6. Metal-free direct arylation of α-aryl carbonyl compounds with diaryliodonium triflates.[157]

Previous metal-free arylations with diaryliodonium salts were reported by Kita and co-workers. The direct arylation of α-thienyliodonium tosylate with several arenes is proposed to proceed *via* a formal hydroarylation with the unactivated arene acting as nuchleophile in the presence of TMSBr in hexafluoroisopropanol.[159] On the other hand, an *ipso* substitution of thienyliodonium bromides in the presence of TMSOTf is suggested to undergo a SET process (Scheme 1.4.7).[160]



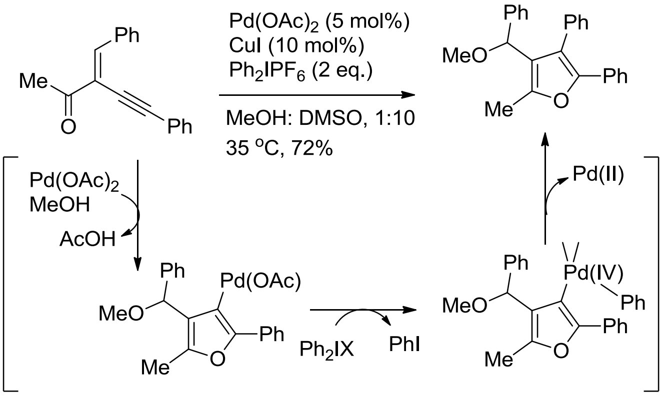
Scheme 1.4.7. Metal-free arylations with diaryliodonium salts.[159-160]

Iodonium salts have also been used in alkyne tandem reactions, a double functionalisation of alkynes involving C-H activation was reported by Li and co-workers. In this example, surprisingly, diacetoxyiodo arenes are used as the arylating agents. When they reacted with *N*-arylpropiolamides and catalytic amounts of $Pd(OAc)_2$, 3-(1-arylmethylene)oxindoles were obtained *via* hydroarylation of the alkyne and directed cyclisation.[161] Synthesis of this kind of oxindoles was reported before using aryliodides.[162] In Lei's example, the authors showed that in the presence of NEt_3, $PhI(OAc)_2$ decomposed to PhI. In the presence of PhI the reaction mechanism would be the already reported. However, the reaction can also take place in the absence of base (lower yields). Therefore, a second mechanism was proposed in which one equivalent of $PhI(OAc)_2$ is used for the arylation of the alkyne, the vinyl-palladium intermediate formed can be oxidised to Pd(IV) for a second equivalent of diacetoxyiodo benzene and finally cyclisation through C-H activation gives the final product (Scheme 1.4.8). The reaction also worked with diaryliodonium salts, in that case better yields were obtained when changing NEt_3 for NaOAc.



Scheme 1.4.8. 3-(1-arylmethylene)oxindoles by a tandem reaction with diacetoxyiodo arenes.[161]

More recently, Zhang and collaborators reported the palladium-catalysed synthesis of tetra-substituted furans from 2-(1-alkynyl)-2-alken-1-ones, alcohols (nuchleophile) and diaryliodonium salts.[163] The authors propose that after nuchleophilic attack and cyclisation, the vinyl-palladium intermediate can be trapped with the diaryliodonium salt to afford a Pd(IV) intermediate. Reductive elimination would afford the tetra-substituted furans (Scheme 1.4.9). Although the reaction needs the presence of CuI as co-catalyst, it proceeds under very mild conditions for a broad range of substrates.



Scheme 1.4.9. Use of diaryliodonium salts in a three-component domino reaction for the synthesis of tetra-substituted furanes.[163]

1.5. References

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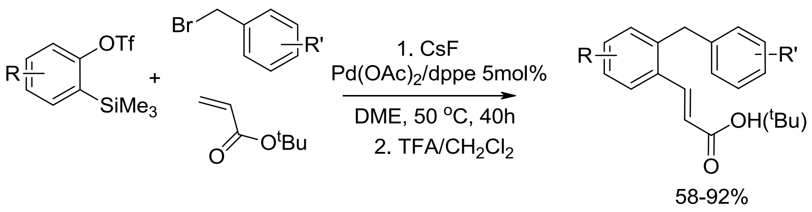
Chapter 2. Intermolecular Palladium-Catalysed Three-Component Reaction

2.1. Intermolecular Palladium-Catalysed Three-Component Reaction between Indoles, Alkynes and Aryl Iodides

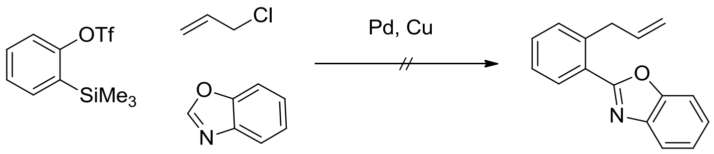
2.1.1. Introduction and Aims

Our group has done extensive work in the area of C-H activation. The main aim of the current project is to use C-H activation in metal-mediated tandem reactions to obtain complex molecules in an efficient way. One example of a palladium-catalysed tandem reaction developed in our group is the three-component coupling of benzyne[1] with benzyl bromides and acrylates (Scheme 2.1.1).[2]



Scheme 2.1.1. Three component reaction between benzyne, phenyl bromides and a Heck acceptor.[2]

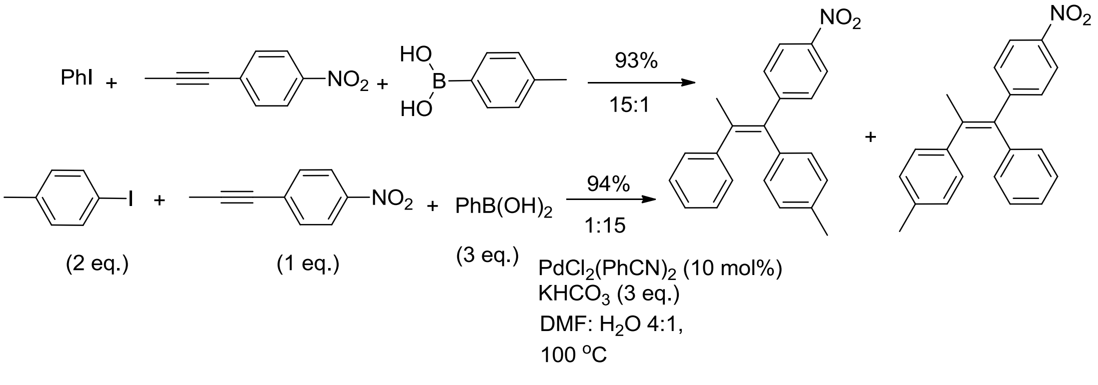
Based upon this work, we began a study of the palladium-catalysed three component reaction with benzyne, allyl chlorides and benzoxazole (Scheme 2.1.2). This approach would lead to the synthesis of interesting heterocycles in a simple manner through C-H activation at the C2 position of benzoxazole. Unfortunately, after several attempts the desired product was never obtained. No reaction involving the heterocycle was achieved as the highly reactive arynes reacted very quickly with themselves or the allyl moiety to give the corresponding annulated products. Therefore it was decided to replace the highly reactive arynes with alkynes.



Scheme 2.1.2. First aim: three-component reaction with benzyne, allyl halides and benzoxazole.

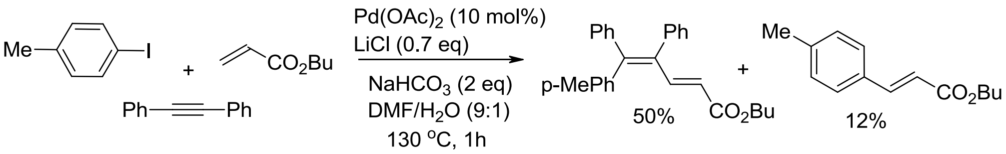
In the last few years palladium-catalysed sequential three-component couplings with alkynes have been reported. The palladium-catalysed reaction of alkynes with aryliodides proceeds through a vinyl-palladium intermediate that can be trapped with various terminators including organometallic reagents, alkenes and terminal alkynes (Chapter 1, Scheme 1.1.2, pg. 3).[3]

One example of a tandem reaction with internal alkynes is the three-component coupling reaction between aryliodides, alkynes and boronic acids published by Larock and co-workers.[4] The synthesis of tetra-substituted olefins from a regio- and stereoselective palladium-catalysed process was achieved. The regiochemistry is primarily controlled by steric effects, so the aryl group from the aryliodide favours the less hindered end of the alkyne, while the aryl group from the arylboronic acid favours the more hindered end of the alkyne. Electronic effects are also important and the aryl group from the arylboronic acid is more likely to add to the more electron-poor end of the alkyne (Scheme 2.1.3).



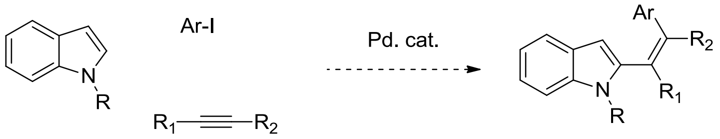
Scheme 2.1.3. Regioselectivity in the formation of tetra-substituted olefins from the palladium-catalysed three-component reaction of aryl iodides, boronic acids and internal alkynes.[4]

Also Miura and co-workers[3] performed a palladium-catalysed three-component reaction with aryliodides, internal alkynes and acrylates. In this case a large excess of the diarylacetylene is needed (4 eq.) for a good selectivity of the desired three-component reaction in front of the normal Mizoroki-Heck-type product (Scheme 2.1.4).



Scheme 2.1.4. The sequential three-component coupling of aryl iodides, diarylacetylenes and acrylates.[3]

The first aim of this project was to develop conditions for a three-component reaction of aryliodides with internal alkynes and a heterocycle which could undergo C-H activation to act as the terminator in a sequential palladium-catalysed process (Scheme 2.1.5). As explained in the first chapter (Chapter 1, pg. 4-5), indole is a very important heterocycle present in a large number of natural products and biologically active compounds and there are many reported examples of indole derivatives which undergo C-H functionalisation. For these reasons indole was thought to be a good choice for being the third component in the reaction study.

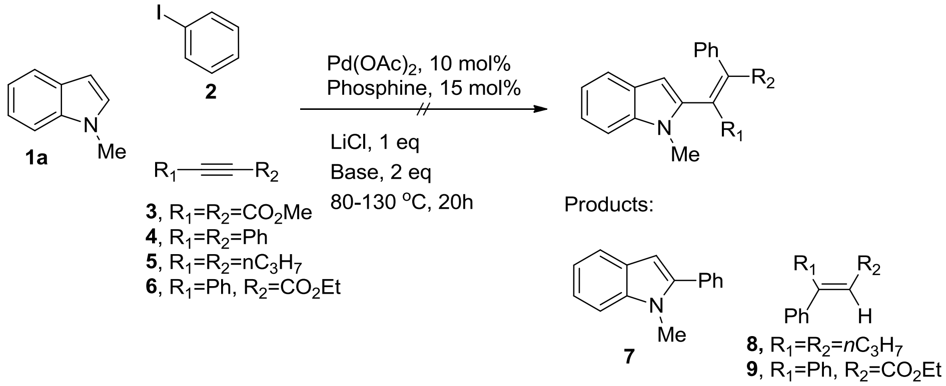


Scheme 2.1.5. Aimed palladium-catalysed three-component reaction of aryliodides with internal alkynes and indoles.

2.1.2. Results and Discussion

The study of the palladium-catalysed three-component reaction involving C-H activation of indole started by mixing 1-methyl-*1H*-indole and iodobenzene with an internal alkyne in excess as in Miura's[3] three-component reaction. The effect of adding different palladium-catalysts, phosphines, additives, bases and solvents in the reaction was studied and a summary of results can be found in Table 2.1.1.

Table 2.1.1. Attempts at palladium-catalysed three-component reaction between *N*-methylindole, internal alkynes and iodobenzene.



Entry	*Alkyne*	*Additive*	*PR₃*	*Base*	*Solvent*	*T (°C)*	*Results*
1[b]	**3**	LiCl	PPh_3	Ag_2CO_3	DMF:H_2O, 9:1	130	**7** (53%)[a] [35%][c]
2[b]	**4**	LiCl	PPh_3	Ag_2CO_3	DMF:H_2O, 9:1	130	Complex mixture, unreacted **1a**
3	**4**	LiCl	PPh_3	$NaHCO_3$	DMF:H_2O, 9:1	130	Complex mixture, unreacted **1a**
4	**4**	LiCl	PPh_3	Ag_2CO_3	DMF	80	Complex mixture, unreacted **1a**
5	**4**	LiCl	-	Ag_2CO_3	DMF	80	Complex mixture, unreacted **1a**
6	**4**	-	PPh_3	Ag_2CO_3	DMF	80	Complex mixture, unreacted **1a**

7	**5**	LiCl	PPh_3	Ag_2CO_3	DMF	130	**8** (76%)[a]
8	**5**	LiCl	PPh_3	Ag_2CO_3	DMF	80	**8** (55%)[a]
9	**5** (1 eq.)	LiCl	PPh_3	Ag_2CO_3	DMF	80	n.r.
10	**5** (2 eq.)	LiCl	PPh_3	Ag_2CO_3	DMF	80	**8** (68%)[a]
11	**5** (2 eq.)	-	PPh_3	Ag_2CO_3	DMF	80	**8** (58%)[a]
12[d]	**5**	-	-	Ag_2CO_3	DMF	130	**7** (5%)[a], **8** (67%)[a]
13[d]	**5**	LiCl	-	Ag_2CO_3	DMF	130	**8** (26%)[a]
14	**6**	LiCl	-	Ag_2CO_3	DMF	80	**9** (34%)[a]

Reaction conditions: *N*-methylindole, **1a** (0.5 mmol), **2** (0.5 mmol), alkyne (2 mmol), $Pd(OAc)_2$ (0.05 mmol), phosphine (0.075 mmol), LiCl (0.5 mmol), base (1 mmol), solvent (0.5 M) at 80 or 130°C for 20h. [a] Conversion calculated from ^1H NMR [b] 0.13 M [c] Isolated yield [d] $Pd(PPh_3)$ 5 mol%.

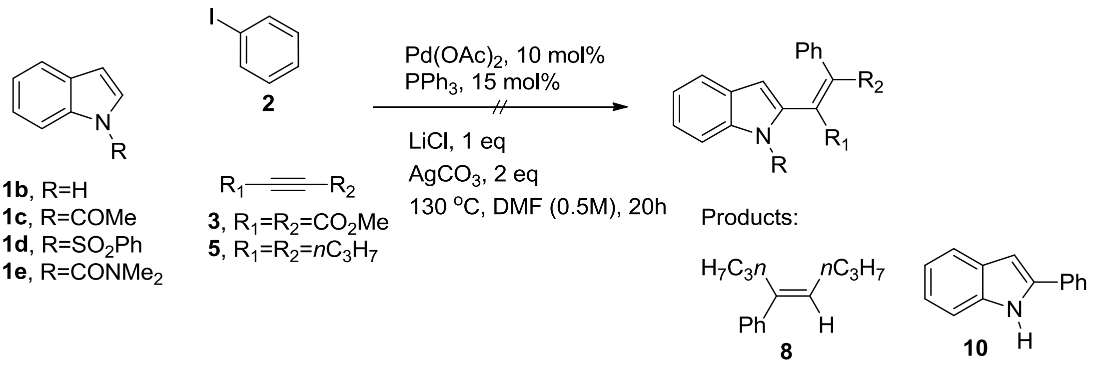
In the first experiments of the intermolecular reaction with 1-methylindole, a large excess of dimethyl acetylenedicarboxylate, **3**, was used (4 eq.). When the reaction was left 3 h at 130 °C there was still *N*-methylindole left, yet a new product was formed. ^1H NMR analysis of the crude identified the new compound as 1-methyl-2-phenylindole (**7**, 13% conversion). The good news was that under these conditions C-H activation of indole could be performed. However, no interaction with the acetylene was observed. If the reaction was heated for longer time, a maximum conversion of 53% was found after 20 h of reaction (Table 2.1.1, entry 1). Although there was still 1-methylindole left, no further advance was observed in the reaction (a silver mirror was formed inside the reaction tube). When the concentration was increased to 0.5 M in dry DMF the conversion after 20h went down to 35%. Exactly the same conversion was achieved when the temperature was brought down to 80°C or the reaction was conducted without phosphine ligand or with different amounts of alkyne. After these trials it seemed clear that DMAD was not playing any role in the reaction, so other internal alkynes were tried out.

It was surprising to find out that the same reaction conditions when using diphenylacetylene, **4**, gave no direct-arylation product as unreacted Me-indole was recovered, however a complex mixture of aromatics was seen by ^{1}H NMR. Unfortunately no clean product could be isolated, but it is likely that alkyne hydrophenylation and alkyne dimerisation happened (Table 2.1.1, entry 2). The same mixture of products was obtained when a different base as sodium hydrogencarbonate was used or in the absence of base. Reaction with or without water, phosphine ligand or additive (Table 2.1.1, entries 3 to 6) also resulted in a complex mixture with probably triphenylethene and the dimerisation-hydroarylation product[5] in it, whereas no indole contribution in the reaction was detected.

Similar results were found when using 4-octyne, **5**, as the internal acetylene. In this case reaction in DMF led to *(E)*-4-phenyloct-4-ene formation (Table 2.1.1, entry 7). Bringing down the temperature resulted in a lower conversion (Table 2.1.1, entry 8). When only one equivalent of octyne was used, starting materials were mostly recovered. The hydrophenylation reaction also worked when two equivalents were present in the mixture (Table 2.1.1, entry 10). The presence of the additive did not seem to be very important for the reaction to take place (Table 2.1.1., entry 11) and the same can be said for the phosphine. Similar conversions were obtained when no phosphine was used or when different ones were tried as dppe or $P(^tBu)_3$. No reaction involving indole was either seen when other solvents as DMSO, DMA, dioxane or toluene were used, only **8** was formed. Interestingly when tetrakis(triphenylphosphine)palladium (0) was used *(E)*-4-phenyloct-4-ene and also traces of 2-phenyl-1-methylindole were obtained (Table 2.1.1, entry 12) meaning that when the arylpalladium (II) inermediate is formed, there is a competition between carbopalladation of the alkyne and electrophilic palladation of the indole. When the reaction was repeated in the presence of LiCl no arylation product was seen and the conversion of the hydrophenylation product was lower (Table 2.1.1, entry 13). When other palladium catalysts such as $PdCl_2$ or Hermann-Beller palladacycle were used only **8** was generated.

Finally, when phenylpropionic acid ethylester was the internal alkyne used, only the hydrophenylation reaction happened (Table 1, entry 14).

Table 2.1.2. Attempts at palladium-catalysed three-component reaction between different *N*-protected indoles, internal alkynes and iodobenzene.



Entry	*Indole*	*Alkyne*	*Results*[a]
1	**1b**	**3**	**10** (35%) [15%][b]
2[c]	**1b**	**-**	**10** [16%][b]
3	**1b**	**5**	Complex mixture
4	**1c**	**3**	n.r.[d]
5	**1c**	**5**	**8** (28%)
6	**1d**	**3**	n.r.
7	**1d**	**5**	**8** (33%)
8	**1e**	**3**	n.r.
9	**1e**	**5**	**8** (28%)

Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), alkyne (2 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.075 mmol), LiCl (0.5 mmol), $AgCO_3$ (1 mmol), DMF (0.5 M) at 130°C for 20h. [a] Conversion calculated from ^1H NMR [b] Isolated yield [c] No alkyne [d] n.r.= no reaction, only starting materials recovered, some deprotection in the case of 1-acetylindole was observed.

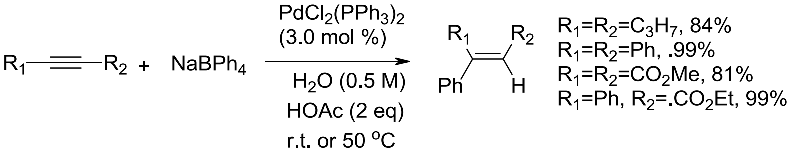
The three-component reaction was also tried out with other indole derivatives as shown in Table 2.1.2. When free indole, **1b**, was mixed with iodobenzene and DMAD, **3**, together with a catalytic amount of $Pd(OAc)_2$ in the specified conditions, 2-phenylindole was obtained in low yield. Repeating the reaction without alkyne lead to a major conversion of **10** (entries 1 and 2) but no full conversion was achieved and

performing the same reaction in the presence of 4-octyne only afforded some 4-phenyl-4-octene (entry 3). The hydrophenylation of octyne was also the only reaction taking place when using 1-acetylindole, **1c**, 1-phenylsulfonylindole, **1d**, or *N*,*N*-

dimethyl-1*H*-indole-1-carboxamide, **1e**, (entries 5, 7 and 9) while no arylation occurred when using dimethyl acetylenedicarboxylate.

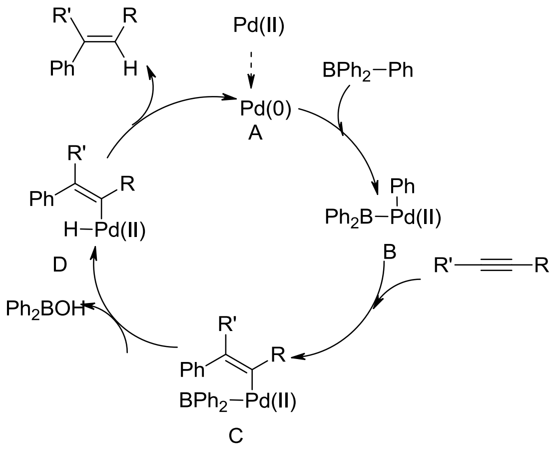
Looking at the results it seems like, except in the case of DMAD, the formation of a phenylpalladium intermediate, generated after iodobenzene oxidative insertion into Pd (0) species, undergoes carbopalladation of the alkyne faster than electrophilic palladation of indole. The formation of ethene products means that hydrolysis of the key vinylpalladium intermediate takes place before it can react with indole.

There are several procedures of selective palladium-catalysed hydrophenylation of alkynes in the literature. One example is the recently reported work from Hua and co-workers[6] (Scheme 2.1.7) where terminal and internal alkynes are phenylated using sodium tetraphenylborate in water.



Scheme 2.1.7. Palladium-catalysed hydrophenylation of alkynes.[6]

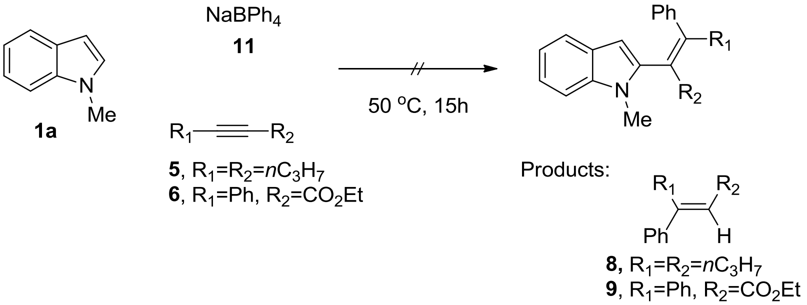
The authors propose a mechanism in which the alkyne is selectively inserted into the phenylpalladium intermediate. That gives a vinylpalladium species that undergoes a hydrolysis followed by reductive elimination to afford the alkene product (Scheme 2.1.8)



Scheme 2.1.8. Proposed mechanism for the hydrophenylation of alkynes by Hua and co-workers.[6]

The described reaction was repeated and 1-methyl-1*H*-indole was added to the mixture to study whether there is any change in the reaction; if the intermediate can be trapped with indole or if there is also competition between alkyne hydroarylation and indole arylation. Results are shown in Table 2.1.3.

Table 2.1.3. Attempts at palladium-catalysed three-component reaction between *N*-methylindole, ethyl-2-phenylpropiolate and sodium tetraphenylborate.



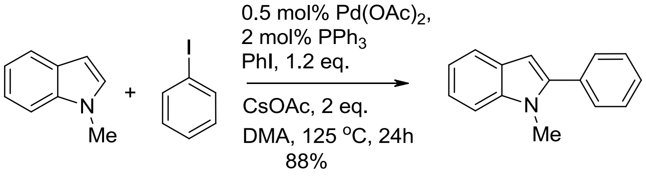
Entry	*1a*	*Alkyne*	*Pd cat. (mol%)*	*Solvent*	**Results**[a]
1	-	**6**	$PdCl_2(PPh_3)$, (3)	H_2O	**9** (99%)
2	1 eq.	**6**	$PdCl_2(PPh_3)$, (3)	H_2O	**9** (54%)
3	3 eq.	**6**	$PdCl_2(PPh_3)$, (3)	H_2O	**9** (34%)
4	1 eq.	**6**	$PdCl_2(PPh_3)$, (10)	Dioxane	**9** (35%)
5	1 eq.	**6**	$PdCl_2(PPh_3)$, (10)	MeCN	**9** (39%)
6	1 eq.	**6**	$PdCl_2(PPh_3)$, (10)	DMF	**9** (20%)

7	1 eq.	**6**	$PdCl_2(PPh_3)$, (10)	DMSO	**9** (57%)
8[b]	3 eq.	**6**	$PdCl_2(PPh_3)$, (3)	HOAc	**9** (49%)
9	1 eq.	**6**	$Pd(OAc)_2$, (3)	H_2O	**9** (13%)
10	1 eq.	**5**	$PdCl_2(PPh_3)$, (3)	H_2O	**8** (8%)

Reaction conditions: Alkyne (1.0 mmol), **1a** (1.0 to 3.0 mmol), HOAc (2 mmol), $NaBPh_4$ (0.3 mmol), Pd cat. (0.03 to 0.1 mmol) and solvent (2 mL), 50 °C, 15 h [a] Conversion calculated from ^1H NMR indicated between brackets [b] 1 eq. of $NaBPh_4$.

Adding indole to the reaction affected the conversion to ethyl-3-diphenyl acrylate, **9**, which was lower as higher quantities of indole were present in the mixture (Table 2.1.3., entries 1-3). However no other products were detected, so the hydrophenylation reaction was still the only significant pathway. Changing the solvent or increasing the catalyst loading did not afford any new compound (Table 2.1.3, entries 4-9).

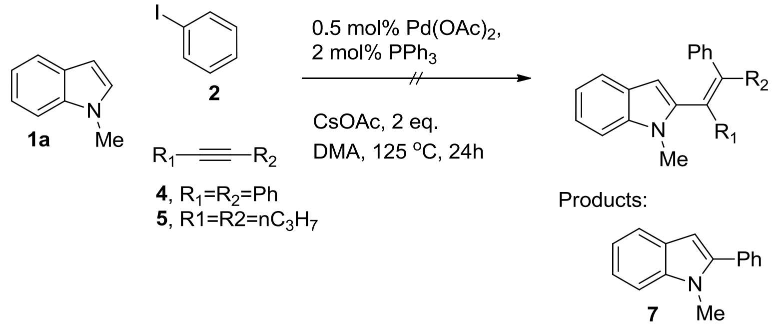
The effect of adding an internal alkyne to a literature indole direct arylation reaction to see whether the arylation process is affected was also studied. In the last few years a large quantity of direct arylation processes of indoles have been reported[7] (Chapter 1, pg. 25). Sames and co-workers[8] reported one of the first direct arylation of *N*-methylindole with different iodoarenes using only 0.5 mol% of $Pd(OAc)_2$ at 125 °C (Scheme 2.1.9).



Scheme 2.1.9. Palladium-catalysed arylation of 1-methylindole.[8]

In our hands, when one equivalent of diphenylacetylene, **4**, was added, conversion of the arylated product decreased dramatically (Table 2.1.4., entries 1 and 2). A big excess of the alkyne resulted in lower conversion of the 2-arylated indole product. The addition of 4-octyne absolutely suppressed any reaction and unreacted starting materials were recovered (Table 2.1.4, entries 3 to 5).

Table 2.1.4. Effect of adding internal alkynes in a reported direct palladium-catalysed arylation of 1-methyl indole.



Entry	*Alkyne (eq)*	*Results*[a]
1	-	**7**, (82%)
2	**4**, (1)	**7**, (23%)
3	**4**, (5)	**7**, (5%)
4	**5**, (1)	n.r.[b]
5	**5,** (5)	n.r.[b]

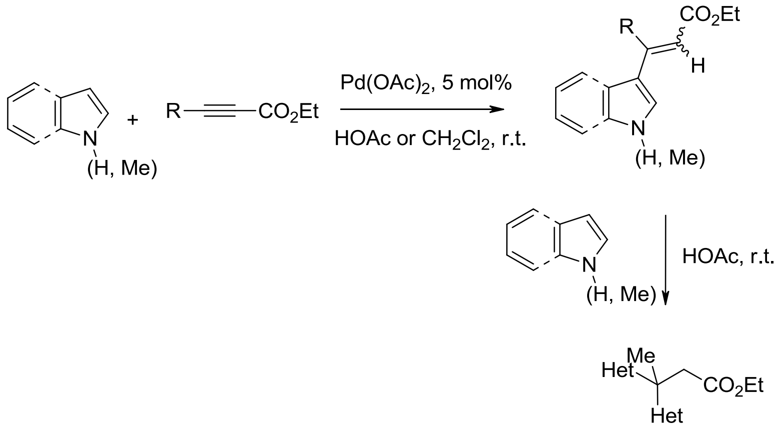
Reaction conditions: Alkyne (0.75-3.75 mmol), **1a** (0.75 mmol), **2** (0.9 mmol), CsOAc (1.5 mmol), $Pd(OAc)_2$ (0.004 mmol), PPh_3 (0.015 mmol), DMA (5 mL), 125 °C, 24h. [a] Conversion calculated from ^1H NMR indicated between brackets. [b] n.r.= no reaction, starting materials recovered.

The results shown in the last two tables show that either the hydrophenylation of alkynes or the direct arylation of indoles are affected in the case of adding a third component in the reaction. Contrary to what was firstly expected, the reactions are not messier leading to the formation of more products. Instead, the active life of the catalytic species seems to be reduced when the three components are mixed together resulting in the suppression of the literature pathways.

2.2. Intermolecular Palladium-Catalysed Three-Component Reaction between Indoles, Alkynes and Diaryliodonium Salts

2.2.1. Introduction and Aims

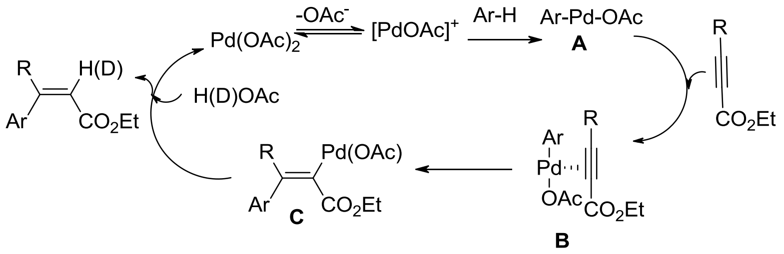
As shown in the previous section, depending on the reaction conditions it is possible to obtain either the phenylation of indole or the hydrophenylation of internal alkynes when a palladium catalyst is added to a mixture containing an indole derivative, internal alkyne and iodobenzene. However the desired three-component reaction was not detected, neither was the addition of indole to the triple bond. There are few precedents for intermolecular alkenylation of unactivated heterocycles, the first example is the work reported by Fujiwara and co-workers[9] where methylfuranes, pyrroles and indoles are selectively coupled to alkynoates in the presence of catalytic amounts of $Pd(OAc)_2$ at r.t. (Scheme 2.2.1).



Scheme 2.2.1. Palladium-catalysed addition of pyrroles and indoles to alkynes.[9]

In the case of indole or 1-methyl-*1H*-indole the reaction occurs at the 3-position predominantly. It is possible to have monoaddition or diaddition products depending on the reaction conditions and the substituents in the alkynoate. The reaction of pyrrole and ethyl phenylpropiolate with $Pd(OAc)_2$ (5 mol%) in DOAc resulted in

55% deuterium incorporation at the 2-vinyl position. This observation is in agreement with the presence of a vinylpalladium intermediate which can be protonated. Based on these results the authors suggested a mechanism in which the electrophilic substitution of the aromatic C-H bond by cationic Pd(II) species would form an arylpalladium intermediate that undergoes trans-insertion of the triple bond to afford the vinylpalladium complex (Scheme 2.2.2).

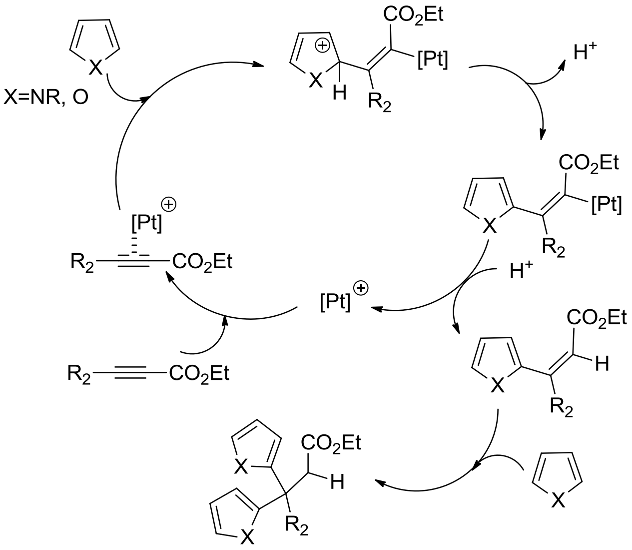


Scheme 2.2.2. First mechanism proposed for the palladium-catalysed hydroarylation of alkynes with pyrroles, furanes and indoles through electrophilic palladation of aromatic C-H.

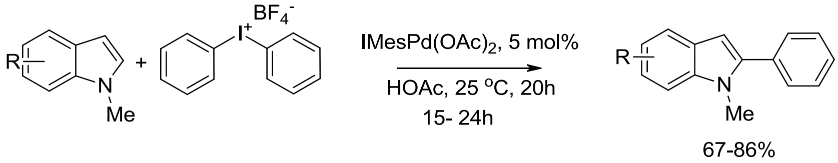
A few years later, further mechanistic studies on Fujiwara hydroarylation[10] were performed by Tunge and co-workers.[11] In these studies the authors argue that the palladium-catalysed hydroarylation of aryl alkynoates in trifluoroacetic acid is more likely to go through an electrophilic aromatic substitution mechanism rather than *via* C-H activation. In fact, the group of Fujiwara (Kitamura[12]) in the recently reported hydroarylation of alkynes with pyrroles and furans catalysed by Pt(II) suggested an electrophilic aromatic substitution mechanism (Scheme 2.2.3).

Even if the reaction proceeds via an electophilic aromatic substitution mechanism, a vinylpalladium intermediate is generated as well, which could undergo a second coupling reaction.

The reaction conditions used for Fujiwara hydroarylation of alkynes are very similar to the ones reported for the direct arylation of indole by Sanford and collaborators (Chapter 1, Scheme 1.3.3, pg. 28).[13] In this example the direct arylation of indole at the 2-position also happens at r.t. in HOAc with palladium catalysis. The key to the process is the use of diaryliodonium salts that have a double function as oxidants and arylating reagents. In this case a palladium intermediate in a high-oxidation state is supposed to be responsible for the smoothness of the process.

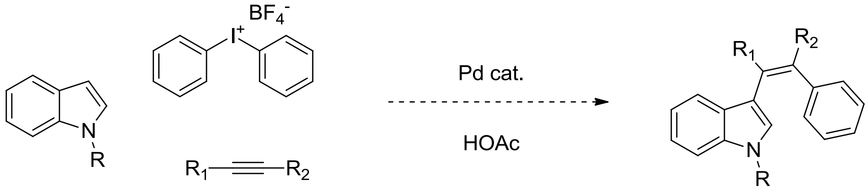


Scheme 2.2.3. Proposed mechanism for the platinium-catalysed hydroarylation of alkynes with pyrroles and furanes through electrophilic aromatic substitution.[12]



Scheme 2.2.4. Palladium-catalysed direct arylation of indole with diaryl iodonium salts.[13]

The next aim in the project was to analyse the result of mixing a catalytic amount of $Pd(OAc)_2$ with an indole derivative, an alkynoate (or other internal alkyne) and a diaryliodonium salt (Scheme 2.1.14). In very similar reaction conditions either the insertion of indole into a triple bound or the arylation of indole has been reported. So it was thought that it would be interesting to see which reaction would be favoured when mixing methylindole, an alkynoate and a diaryliodonium salt in these conditions. We also wanted to observe if the vinylpalladium intermediate can be trapped by the iodonium salt and whether there is any regoiselectivity between indole 2- and 3- position.

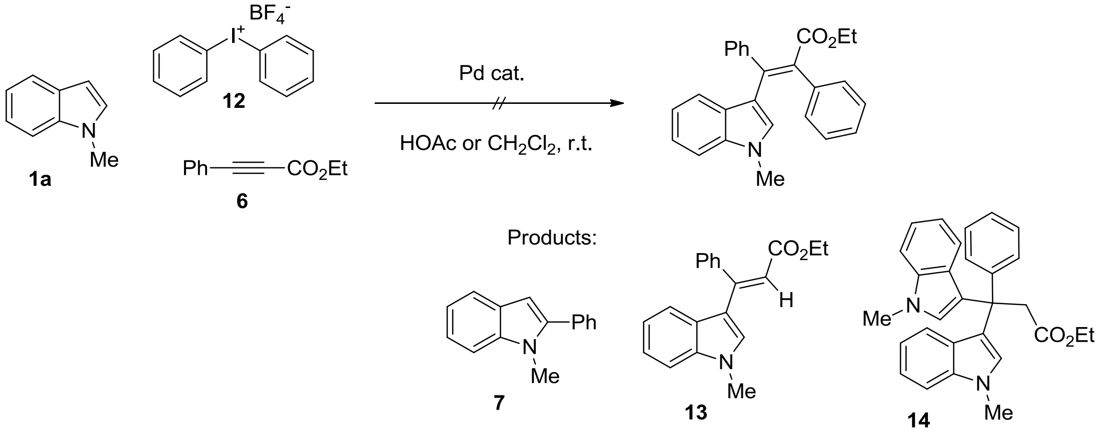


Scheme 2.2.5. Next aim: Palladium-catalysed three-component reaction between indoles, alkynes and diaryliodonium salts.

2.2.2. Results and discussion

The three-component reaction study started with the reaction between 1-methylindole, **1a**, diphenyliodonium tetrafluoroborate, **12**, and phenylpropinoic acid ethylester, **6**, as the internal alkyne in the presence of a palladium catalyst (Table 2.2.1.). Firstly, conditions for the indole arylation reported by Sanford *et. al.*[13] were reproduced without any alkyne, using $PdCl_2$ as catalyst (described to be better than $Pd(OAc)_2$ for this reaction) obtaining the 2-arylated indole as expected (Table 2.2.1, entry 1). Fujiwara's conditions[9] were also reproduced using $Pd(OAc)_2$ and ethyl phenylpropiolate, **6**, without iodonium salt, affording the monoaddition product and a small amount of the diaddition product (Table 2.2.1., entry 2). When the three components were placed together in acetic acid along with a catalytic quantity of $Pd(OAc)_2$ only *(2E)* ethyl 3-(1-methyl-3-indolyl)-3-phenyl-2-propenoate, **13**, was obtained (entry 3). Changes in the number of equivalents of each component did not alter the result and only **13** was obtained with small differences in conversion. When no palladium catalyst was present in the reaction only starting materials were recovered. Using bis(benzonitrile)palladium chloride as the catalyst gave the same result whereas $PdCl_2$ augmented the proportion of the diaddition product. However, when using $Pd(OAc)_2$ and LiCl as additive the reactivity was quite low and only **13** was detected (entries 4 to 6). Surprisingly, when the reaction was conducted in CH_2Cl_2 instead of HOAc, mixtures of 2-arylated indole and propenoate product were obtained, being the arylation product favoured (entry 7). These results expose the competition between the two reactions. The insertion of methylindole to the propiolate is preferred when the reaction is run under acidic conditions, this may be due just to solubility issues as the iodonium salt is not very soluble in acetic acid. But also because the protonation of the vinyl-Pd intermediate generated in the alkenylation of indole is favoured in acetic acid. When mixtures of HOAc and CH_2Cl_2 were used the propenoate product was again the only one detected, in contrast, no reaction took place when the reaction was performed under basic conditions using triethylamine as a solvent (Table 2.2.1. entries 8 to 10).

Table 2.2.1. Attempts at palladium-catalysed three-component reaction between 1-methyl-*1H*-indole, ethyl phenylpropiolate and diphenyliodonium tetrafluoroborate.



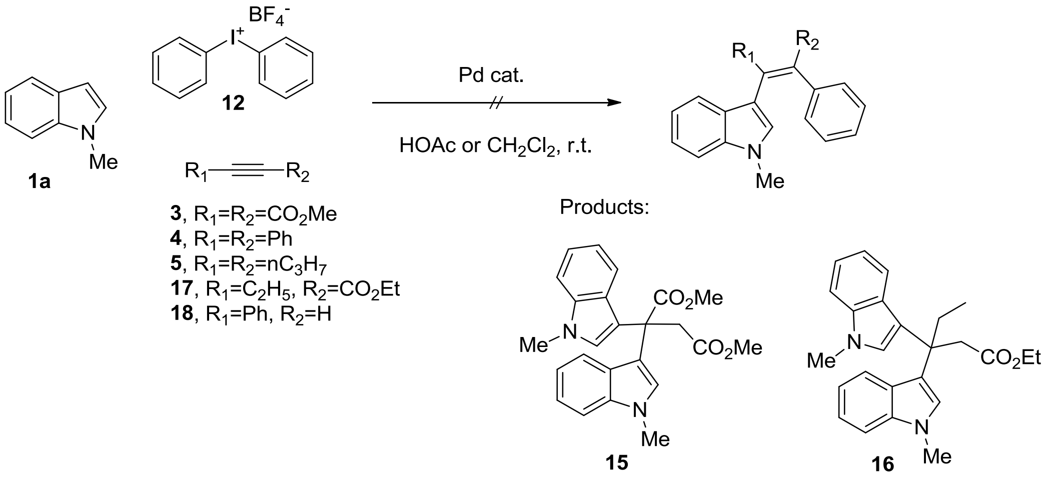
Entry	*Pd cat.*	*t (h)*	*Solvent*	*Results*[a]
1[b]	$PdCl_2$	15	HOAc	**7** (65%)
2[c]	$Pd(OAc)_2$	24	HOAc	**13** [67%][d], **14** [8%][d]
3	$Pd(OAc)_2$	20	HOAc	**13** (81%)
4	$Pd(C_6H_5CN)_2Cl_2$	20	HOAc	**13** (86%)
5	$PdCl_2$	20	HOAc	**13**:**14**, 3.5:1[e] (95%)
6	$Pd(OAc)_2$+ LiCl	20	HOAc	**13** (13%)
7[f]	$PdCl_2$	20	CH_2Cl_2	**7**:**13**, 5.2:1[e] (94%)
8	$Pd(C_6H_5CN)_2Cl_2$	20	AcOH:CH_2Cl_2 (9:1)	**13** (83%)
9	$Pd(C_6H_5CN)_2Cl_2$	20	AcOH:CH_2Cl_2 (1:1)	**13** (69%)
10	$Pd(OAc)_2$	20	Et_3N	n.r.[g]

Reaction conditions: **6** (0.25 mmol), **1a** (0.25 mmol), **12** (0.5 mmol), Pd catalyst (0.012 mmol), solvent (2 mL), r.t. (~ 20 ^oC), 15-24h. [a] Conversion calculated from ^1H NMR indicated between brackets [b] Reaction without alkyne [c] Reaction without iodonium salt, 2 eq. of *N*-methylindole used [d] Isolated yield [e] Ratio by ^1H NMR [f] 1 eq. of diphenyldiodonium tetrafluoroborate used [g] n.r.: no reaction, starting materials recovered.

The employment of other alkynes gave different results depending on the nature of the triple bond (Table 2.2.2.). When DMAD was used, only the double insertion of indole into the triple bond was observed, the best conversion was achieved with $PdCl_2$ (entries 1 to 3). No reaction was detected when using diphenylacetylene or 4-

octyne, although the reaction with diphenylacetylene in CH_2Cl_2 was quite messy, 1-methylindole was still the major product and noticeably the arylated product was not observed in any case (entries 4 to 7). No reaction happened either with ethyl pentynoate, although the alkenylation with methylindole in the absence of the iodonium salt worked well giving the diaddition product (entry 9). Finally, also a terminal alkyne was tried and no reaction happened in acetic acid but in CH_2Cl_2 the 2-arylated product **7** was obtained.

Table 2.2.2. Attempts at palladium-catalysed three-component reaction between *N*-methylindole, diphenyliodonium tetrafluoroborate and different alkynes.

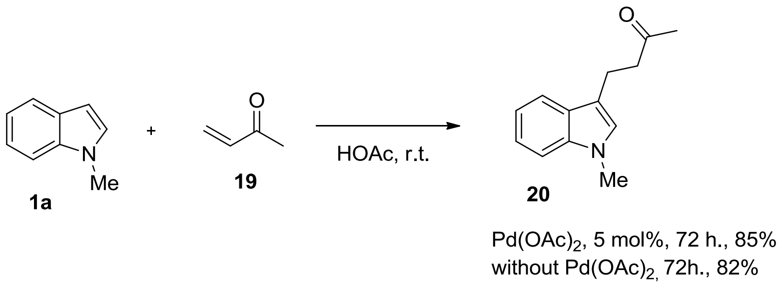


Entry	*Alkyne*	*Pd. Cat*	*T (°C)*	*t (h)*	*Solvent*	*Result*[a]
1	**3**	$Pd(OAc)_2$	r.t.	20	HOAc	**15** (15%)
2	**3**	$PdCl_2$	r.t.	30	HOAc	**15** (58%) [46%][b]
3	**3**	$PdCl_2$	r.t.	30	CH_2Cl_2	**15** (33%)
4	**4**	$Pd(OAc)_2$	r.t.	20	HOAc	n.r.[c]
5	**4**	$PdCl_2$	r.t.	20	HOAc	n.r.
6	**4**	$PdCl_2$	r.t.	20	CH_2Cl_2	Mostly **1a** left, but messy
7	**5**	$Pd(OAc)_2$	r.t.	20	HOAc	n.r.
8	**17**	$PdCl_2$	r.t.	20	HOAc	n.r.
9[d]	**17**	$PdCl_2$	r.t.	20	HOAc	**16** [56%][b]

10	**17**	$PdCl_2$	80	20	HOAc	n.r.
11	**17**	$PdCl_2$	r.t.	20	CH_2Cl_2	n.r.
12	**18**	$PdCl_2$	r.t.	20	HOAc	n.r.
13	**18**	$PdCl_2$	r.t.	20	CH_2Cl_2	**7**[21%]^b

Reaction conditions: Alkyne (0.25 mmol), **1a** (0.25 mmol), **12** (0.5 mmol), Pd catalyst (0.012 mmol), solvent (2 mL), r.t. (~ 20 °C), 20-30h. [a] Conversion calculated from ^{1}H NMR indicated between brackets [b] Isolated yield [c] n.r.= no reaction, starting materials recovered [d] No iodonium salt.

The alkenylation of indole was favoured when using acetic acid as solvent. Assuming that the reaction proceeds through electrophilic aromatic substitution, these conditions were used in the Friedel-Crafts reaction of 1-methylindole with Michael acceptors. Reaction of **1a** with methyl vinyl ketone in acetic acid and with $Pd(OAc)_2$ (5 mol%) afforded the desired product in 85% yield albeit the reaction was very slow. The reaction also worked without catalyst. (Scheme 2.2.6.).

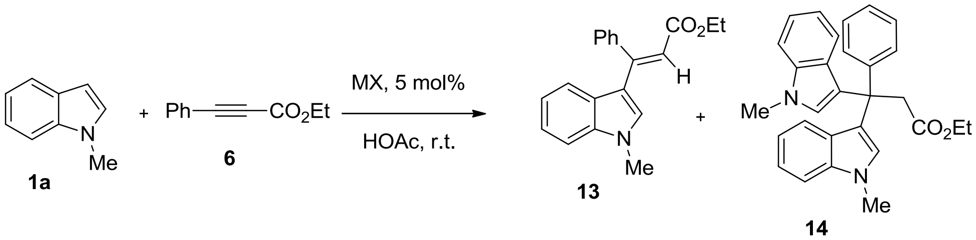


$Pd(OAc)_2$, 5 mol%, 72 h., 85%
without $Pd(OAc)_2$, 72h., 82%

Scheme 2.2.6. Friedel-Crafts reaction between 1-Methylindole and methylvinylketone.

Knowing that these conditions allow the Friedel-Crafts reaction to happen easily Fujiwara alkenylation was tried with different metal catalysts that can act as Lewis acids (Table 2.2.3.). The reaction between 1-methyl-*1H*-indole and ethyl phenylpropiolate afforded the diaddition product in low yield only when copper triflate was used as the catalyst (entry 3).

Table 2.2.3. Alkenylation of 1-methylindole with ethyl phenylpropiolate in the presence of various metal-catalysts.

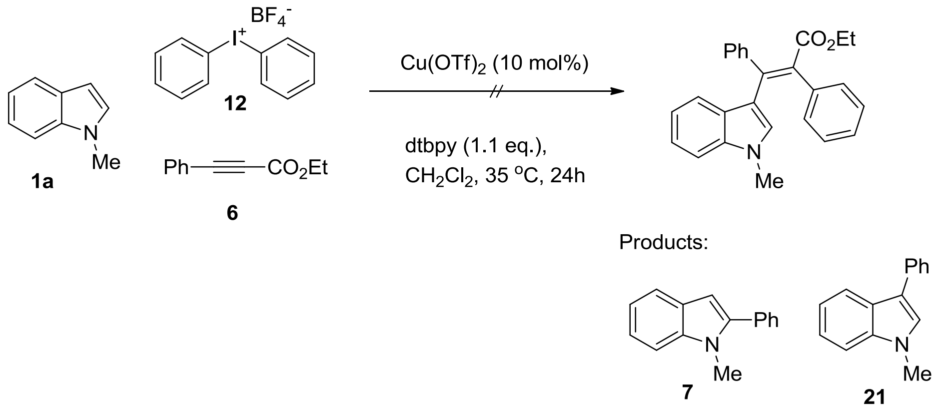


Entry	*Catalyst*	*Result*
1	AgOAc	n.r.[a]
2	CuI	n.r.[a]
3	$Cu(OTf)_2$	**14** [11%][b]
4	$FeCl_3.6H_2O$	n.r.[a]
5	$AlCl_3$	n.r.[a]
6	$Sc(OTf)_3$	n.r.[a]

Reaction conditions: **1a** (1 mmol), **6** (0.5 mmol), catalyst (0.05 mmol), HOAc (0.5 mL), r.t., 72 h [a] n.r.= no reaction, starting materials recovered [b] Isolated yield.

Copper triflate has recently been reported as a good catalyst for the direct arylation of indoles also with diaryliodonium salts, affording either 3- or 2-substituted products only by small differences in the reaction conditions.[14] The three-component reaction by introduction of a propiolate in the described procedure was also attempted (Table 2.2.4.). In that case the 3-arylated indole was selectively obtained even in the presence of the propiolate. No big changes in conversion were observed. The introduction of acid in the reaction had a curious effect, no changes were observed when the mixture was CH_2Cl_2:HOAc, 9:1, on the other hand when the ratio was 1:1, a mixture of 3-arylated and 2-arylated indoles was achieved (entries 4 and 5). The presence of acid seems to favour the 1,2-Pd migration from 3- to 2-position in indole. No alkenylated indole was detected when indole was mixed with ethyl phenylpropiolate under these conditions, this can be due to the presence of base (entry 6).

Table 2.2.4. Attempts at copper-catalysed three-component reaction between *N*-methylindole, diphenyliodonium tetrafluoroborate and ethyl phenylpropiolate.

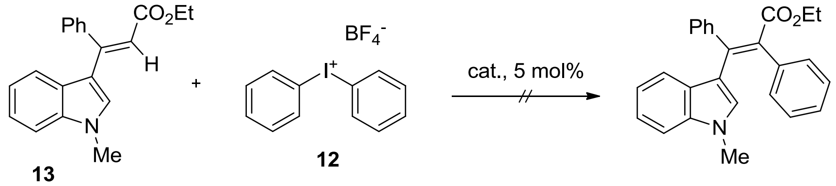


Entry	6 (eq.)	Solvent (0.1M)	Results[a]
1	-	CH_2Cl_2	**21** (94%) [64%][b]
2	**6** (1)	CH_2Cl_2	**21** (81%)
3	**6** (3)	CH_2Cl_2	**21** (79%)
4	**6** (1)	CH_2Cl_2:HOAc, 9:1	**21** (79%)
5	**6** (1)	CH_2Cl_2:HOAc, 1:1	**7**:**21**, (1:1.1)[c](42%)
6[d]	**6** (2)	CH_2Cl_2	n.r.[e]

Reaction conditions: **1a** (0.25 mmol), **12** (0.27 mmol), **6** (0.25 to 0.75 mmol), $Cu(OTf)_2$ (0.025 mmol), dtbpy [4,4'-di-*tert*-butylbipyridine] (0.27 mmol), solvent (2.5 mL). [a] Conversion calculated from ^1H NMR [b] Isolated yield [c] Ratio from ^1H NMR [d] No iodonium salt added [e] n.r.= no reaction, starting materials recovered.

The desired three-component reaction did not take place in any of the conditions tried so far. In order to observe if the reaction was actually possible with these substrates the palladium-catalysed reaction of *(2E)* ethyl 3-(1-methyl-3-indolyl)-3-phenyl-2-propenoate, **13**, with diphenyliodonium tetrafluoroborate was studied (Table 2.2.5.). The aim was to see whether it was possible to activate the alkene obtaining the vinylpalladium intermediate that could provide the tetrasubstituted olefin. No reaction happened when $Cu(OTf)_2$ was used as catalyst (entry 1). When $Pd(OAc)_2$ was used as catalyst at r.t. both in HOAc and CH_2Cl_2 the alkenoate starting material was still the major product in the final mixture, but a new product could be observed by ^1H NMR, attempts to isolate it were unsuccessful. When heating up the reaction in acetic acid, decarboxylation was observed leading to a complex mixture of products. No reaction was observed in DMF (entry 5). And although the reaction in DCE was completed in just 20 min. (no starting material left and palladium black deposition could be observed) the reaction was very messy and no clean product could be isolated. In this case, though, the masses of the desired product and the decarboxylated starting material were detected by HPLC/MS.

Table 2.2.5. Attempts at palladium-catalysed reaction of **13** with diphenyliodonium tetrafluoroborate.



Entry	*Catalyst*	*Solvent*	*T(°C)*	*t (h)*	*Results*
1	$Cu(OTf)_2$	CH_2Cl_2	35	20	n.r.[a]
2	$Pd(OAc)_2$	HOAc	r.t.	24	SM mostly but 14% conversion[b] new unknown product
3	$Pd(OAc)_2$	CH_2Cl_2	r.t.	20	SM mostly but 19% conversion[b] new unknown product
4	$Pd(OAc)_2$	HOAc	80	16	Decarboxylation happened leading to a complex mixture
5	$Pd(OAc)_2$	DMF	80	20	n.r.[a]
6	$Pd(OAc)_2$	DCE	70	0.3	Complex mixture

Reaction conditions: **13** (0.25 mmol), **12** (0.25 mmol), $Pd(OAc)_2$ (0.012 mmol), solvent (2.5 mL). [a] n.r.= no reaction, starting materials recovered [b] Converstion calculated from ^{1}H NMR.

2.3. Conclusions

The palladium-catalysed three-component reaction between indole derivatives, internal alkynes and iodobenzene has been studied. Several conditions were tried including the use of different Pd catalysts, solvents, temperatures, ligands, additives and bases. Unfortunately in none of the cases the three-component reaction took place. The direct arylation of indole derivative or the hydrophenylation of the alkyne were the only two reactions happening, no alkenylation of indole was observed.

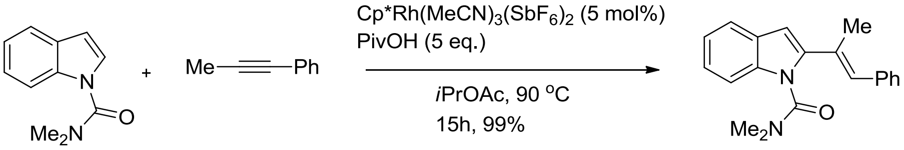
On the other hand, when using oxidative conditions and diphenyliodonium tetrafluoroborate as the arylating reagent, alkenylation of the indole was the major product when electron-poor alkynoates were used in acetic acid under mild conditions. Also the arylated indole product was obtained depending on the conditions and the alkyne used, especially when there was no acid present in the reaction. Friedel-Crafts reaction of methylindole with Michael acceptors happened easily in acetic acid but no alkenylation of the indole with ethyl phenylpropiolate took place when using other metal Lewis Acid catalysts except $Cu(OTf)_2$.

Finally, attempts to obtain the tetra-substituted olefin by the coupling of *(2E)* ethyl 3-(1-methyl-3-indolyl)-3-phenyl-2-propenoate, **13**, with diphenyliodonium tetrafluoroborate also failed, affording complex mixtures. When heating up the reaction decarboxylation could be observed. The mass of the desired product could be observed by HPLC/MS but unfortunately it could not be isolated.

2.4. Future Work

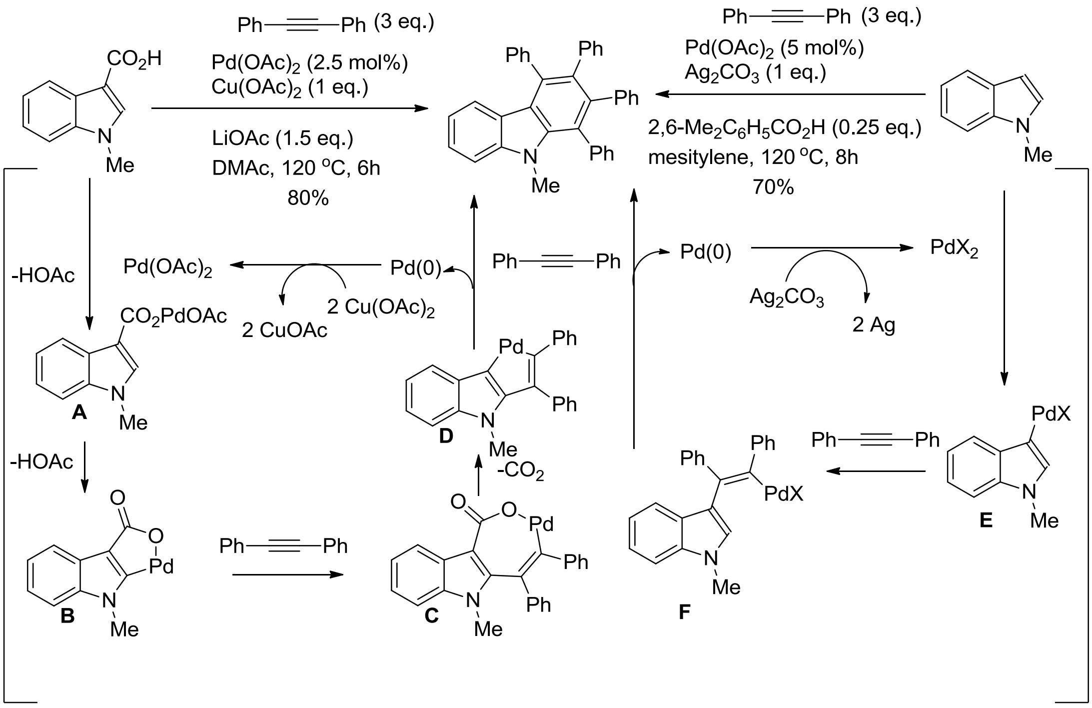
As the main aim of the current project has not been achieved yet, the future work is still focussed on performing intermolecular three-component reactions through C-H activation.

During the realisation of our studies other metal-catalysed methods for the alkenylation of indoles have been developed. For instance, recently, Fagnou and co-workers[15] reported the hydroarylation of alkynes with *N*,*N*-dimethyl-1*H*-indole-1-carboxamide through Rh(III) cationic catalysis (Scheme 2.4.1.)



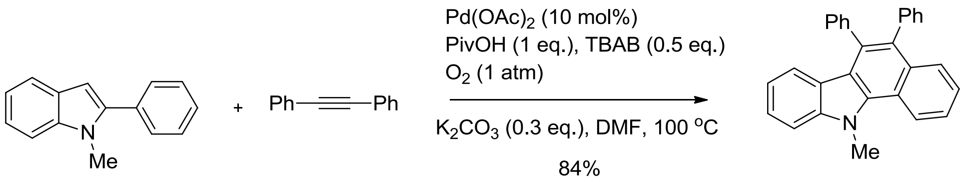
Scheme 2.4.1. Hydroarylation of alkynes with *N*,*N*-dimethyl-1*H*-indole-1-carboxamide through Rh(III) cationic catalysis.[15]

Also, more complicated systems including the activation of two aromatic C-H bonds in a single process have been reported. For instance, Miura and co-workers[16] described the synthesis of 1,2,3,4-tetra-substituted carbazoles from protected 3-carboxylic acid indoles or 3-H indoles and alkynes through a palladium-catalysed oxidative process. The suggested mechanism for 3-H indoles is thought to proceed via a direct palladation on the 3-position of indole followed by alkyne insertion to afford a vinylpalladium intermediate. Subsequent second alkyne insertion and reductive elimination leads to the carbazole product (Scheme 2.4.2.). The route to carbazoles from 3-carboxylic acid indoles is suggested to go through a palladacycle intermediate formed by palladium coordination to the acid and palladation at the C2 position of the indole.



Scheme 2.4.2. Palladium-catalysed synthesis of tetra-substituted carbazoles from 3-carboxylic acid methyl-1*H*-indole and methyl-1*H*-indole reported by Miura and co-workers.[16]

Another interesting example of oxidative palladium-catalysed process through the activation of two C-H bonds is the synthesis of benzo[α]carbazoles from diarylacetylenes and 1-methyl-2-aryl-1*H*-indoles described by Jiao and co-workers[17]. In this example molecular oxygen is used as oxidant (Scheme 2.4.3.).



Scheme 2.4.3. Palladium-catalysed oxidative cycloaromatisation of biaryls with alkynes.[17]

Methyl-1*H*-indole, diphenyl acetylene and a third component: diaryliodonium tetrafluoroborate, phenylboronic acid or *tert*-butylacrylate, were treated under the oxidative conditions described either by Miura or by Jiao, but the desired three-component product was not observed in any case.

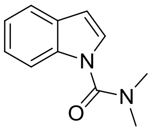
Nevertheless, the activation of C-H bonds in the indole motif is the aim of many investigations in recent years, as it can be an excellent synthetic route to interesting biologically active compounds. In that sense, the intermolecular three-component reaction of indole, alkynes and a third component remains as an interesting challenge and it is worthwhile to continue working in this direction.

2.5. Experimental Procedures

2.5.1. General considerations

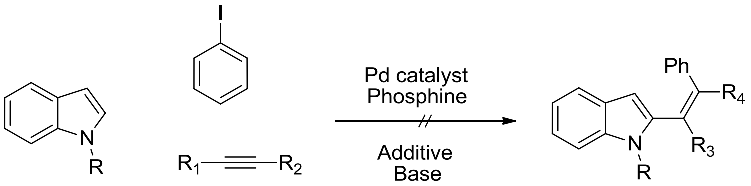
Chemicals were purchased from a chemical supplier and used as received unless otherwise stated. Palladium catalysts were purchased from Strem chemicals. Toluene, Diethyl ether, MeCN, DMF and THF were dried by passage through activated alumina columns using a solvent purification system from www.glasscontour.com or a PureSolv solvent purification system supplied by Innovative Technologies Inc. The rest of the solvents were purchased from reagent to HPLC grade. Distilled water was used in the reactions carried out in water as solvent. Melting point measurements were obtained from a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Jasco FT/IR 410 apparatus preparing the sample as a film on a NaCl tablet or as a solid solution mixed with KBr. ^{1}H-NMR, ^{19}F-NMR and ^{13}C-NMR spectra were recorded on a Brüker arx250 (250MHz) or on a Brüker dpx360 (360MHz) instrument from the University of Edinburgh with deuterated solvents. The following abbreviations have been used: δ (chemical shift, in ppm with TMS as reference), *J* (coupling constant), s (singlet), bs (broad singlet), d (doublet), dd (double doublet), ddd (double of doublet of doublet), t (triplet), dt (double triplet), td (triplet of doublets), tt (triplet of triplets), q (quartet), m (multiplet), quat (quaternary carbon). Low resolution mass spectrometry was performed in the Mass Spectrometry Service from the University of Edinburgh using a Finningan MAT 900 for EI method and Finningan LCQ for ESI method. Electrospray high resolution mass spectromety was perfomed by EPSRC National Mass Spectrometry Service Centre in Swansea. The data is recorded as the ionisation method followed by the calculated and measured masses. A Biotage 2.5 Initiator Microwave Synthesiser was used for some reactions as specified. Control of the reaction advance by TLC was performed on Merck 60F_{254} silica plates and visualized by UV light (λ=254 nm). The compounds were purified by wet flash chromatography using Merck Kieselgel 60 (particle size 35-70) silica under a positive pressure.

2.5.2. Experimental procedures and analytical data for the synthesised compounds



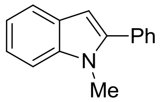
***N*,*N*-dimethyl-1*H*-indole-1-carboxamide, 1d**. Indole was protected with dimethylcarbamic chloride following the procedure described by Illi[18] as follows: indole (1.21 g, 10.32 mmol), tetrabutylammonium hydrogensulfate (340 mg, 1.05 mmol) and sodium hydroxide (1.17 g, 29.25 mmol) were weighed in a flask and dissolved in dry CH_2Cl_2 (40 mL). A condenser was attached to the flask and the system purged with N_2, finally dimethylcarbamic chloride was added dropwise *via* syringe and the mixture heated to reflux for 3h. No starting material was observed by TLC. The crude was diluted in CH_2Cl_2 (20 mL) and sat. $NaHCO_3$ solution (20 mL). The two layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (20 mL × 2) and the combined organic layers washed with brine (20 mL × 2), dried over $MgSO_4$, filtered and the solvent evaporated under vacuum. The crude was purified through a silica column (hexane: CH_2Cl_2, 4:6) obtaining 1.61 g of yellow prisms (87%). The spectroscopic data are in accordance with that reported in the literature.[18] **^{1}H NMR** (360 MHz, $CDCl_3$): δ 3.09 (6H, s), 6.60 (1H, dd, *J* = 3.6, 0.8 Hz), 7.20 (1H, td, *J* = 7.6, 1.1 Hz), 7.30 (1H, td, *J* = 8.1, 1.1 Hz), 7.32 (1H, d, *J* = 3.6 Hz), 7.61 (1H, d, *J* = 7.6 Hz), 7.66 (1H, dd, *J* = 8.1, 0.8 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 38.4 (2 × CH_3), 105.6 (CH), 113.4 (CH), 120.9 (CH), 121.7 (CH), 123.4 (CH), 126.2 (CH), 129.3 (quat), 135.4 (quat), 155.0 (CO).

Attempts at palladium-catalysed three-component reaction between methyl-*1H*-indole, internal alkynes and iodobenzene:

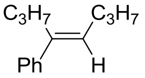


General procedure A: Ag_2CO_3 (275.5 mg, 1.0 mmol), LiCl (21 mg, 0.49 mmol), PPh_3 (18 mg, 0.08 mmol) and $Pd(OAc)_2$ (11 mg, 0.05 mmol) were added in a microwave vial. The tube was evacuated and filled with N_2 (× 3). Solvent was added, followed by the other reagents: indole derivative (0.50 mmol), alkyne (2.00 mmol) and Ph-I (55.7 μL, 0.50 mmol). The mixture was placed in a pre-heated oil bath and it was left to react at 130 °C for 20 h. After cooling down the reaction, the mixture was diluted with Et_2O and filtered through a pad of celite, washed with water (10 mL × 2) and brine (10 mL × 2). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The crude residue was analysed by NMR.

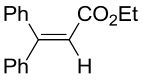
1-Methyl-2-phenyl-1*H*-indole, 7. The named product was obtained following the general procedure A using 1-methyl-1*H*-indole and dimethyl acetylenedicarboxylate. The crude was purified through a silica column (hexane:CH_2Cl_2, 8:2) affording 36 mg of a white solid (35%). The spectroscopic data are in accordance with the reported one.[13] **^{1}H NMR** (360 MHz, $CDCl_3$): δ 3.75 (3H, s), 6.56 (1H, s), 7.13 (1H, td, *J* = 7.8, 1.0 Hz), 7.25 (1H, td, *J* = 7.8, 1.6 Hz), 7.38 (1H, d , *J*= 8.2 Hz), 7.39-7.44 (1H, m), 7.47 (2H, t, *J*= 8.2 Hz), 7.50-7.53 (2H, m), 7.65 (1H, d, *J* = 7.8 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 31.3 (CH_3), 101.8 (CH), 109.8 (CH), 120.1 (CH), 120.6 (CH), 121.8 (CH), 127.9 (2 × CH), 128.1 (CH), 128.6 (2 × CH), 128.9 (quat), 131.9 (quat), 138.5 (quat), 141.7 (quat).



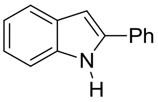
***(E)*-4-Phenyloct-4-ene, 8**. The product was obtained following the general procedure A when using 4-octyne as the alkyne. The spectroscopic data



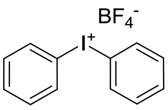
are in agreement with that previously reported.[6] ^{1}**H NMR** (360 MHz, $CDCl_3$): δ 0.87 (3H, t, *J* = 7.3 Hz), 0.96 (3H, t, *J* = 7.3 Hz), 1.36 (2H, q, *J* = 7.5 Hz), 1.47 (2H, q, *J* =7.5 Hz), 2.19 (2H, q, *J* = 6.9 Hz), 2.48 (2H, t, *J* = 7.5 Hz), 5.65 (1H, t, *J* = 7.5 Hz), 7.17-7.36 (5H, m); ^{13}**C NMR** (90 MHz, $CDCl_3$): δ 14.0 (2 × CH_3), 21.8 (CH_2), 22.8 (CH_2), 30.7 (CH_2), 31.8 (CH_2), 126.5 (CH), 128.1 (2 × CH), 129.2 (2 × CH), 140.10 (quat), 143.6 (quat).



Ethyl 3,3-diphenyl acrylate, 9. General procedure A with ethyl phenylpropiolate afforded the compound as a white solid (43 mg, 34% yield). ^{1}H NMR and ^{13}C NMR agree with that previously reported data.[6] ^{1}**H NMR** (360 MHz, $CDCl_3$): δ 1.12 (3H, t, *J* = 7.2 Hz), 4.05 (2H, q, *J* = 7.2 Hz), 6.37 (1H, s), 7.20-7.41 (10 H, m); ^{13}**C NMR** (90 MHz, $CDCl_3$): δ 18.8 (CH_3), 59.7 (CH_2), 117.4 (CH), 127.7 (2 × CH), 127.9 (CH), 128.1 (2 × CH), 129.0 (2 × CH), 129.4 (CH), 129.9 (2 × CH), 138.89 (quat), 140.8 (quat), 159.2 (quat), 165.8 (CO).



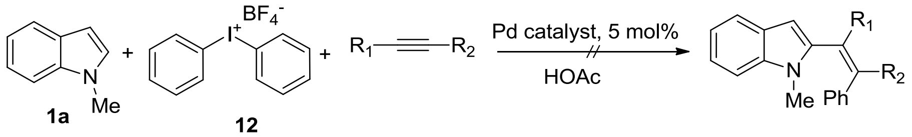
2-Phenyl-1*H*-indole, 10 When the general procedure A was applied to indole and dimethyl acetylenedicarboxylate and iodobenzene, the arylation of indole took place. 14 mg (15 % yield) of the product was obtained after purification through silica column (hexane:CH_2Cl_2, 9:1). NMR data are in accordance with that previously reported.[13] ^{1}**H NMR** (360 MHz, $CDCl_3$): δ 6.83 (1H, bs), 7.14 (1H, td, *J*= 7.5, 1.1 Hz), 7.21 (1H, ddd, *J*= 8.2, 7.1, 1.1 Hz), 7.33 (1H, tt, *J*= 7.5, 1.0 Hz), 7.40-7.47 (3H, m), 7.63-7.68 (2H, m), 8.33 (1H, bs); ^{13}**C NMR** (90 MHz, $CDCl_3$): δ 100.0 (CH), 110.9 (CH), 120.3 (CH), 120.7 (CH), 122.4 (CH), 125.1 (2 × CH), 127.7 (CH), 129.0 (2 × CH), 129.2 (quat), 132.4 (quat), 136.8 (quat), 137.9 (quat).



Diphenylidonium tetrafluoroborate, 12. The product was prepared from the commercially available diphenyliodonium bromide *via* oxidative anion metathesis using tetrafluoroboric acid, as described by Kazmierczak *et al.*[19] Diphenyliodonium bromide (2.03 g, 5.62

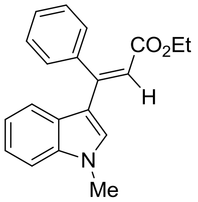
mmol) was suspended with stirring in MeOH (10 mL). HBF_4 (580 μL, 6.61 mmol), H_2O_2 (248 μL, 8.11 mmol) and cyclohexene (0.6 mL, 5.90 mmol) were also added and the mixture was refluxed until the bromide was dissolved, then heating continued for 15 min more. The solvent was removed under vacuum and the solid residue was triturated with Et_2O and filtered. Then it was further purified by crystallisation dissolving the solid in boiling CH_2Cl_2 and allowing to cool down. The white crystals were collected by filtration (95% yield). The spectroscopic data are in accordance with that previously reported.[20] **m.p.**: 134-136 (137-138 lit)[19] **^{1}H NMR** (250 MHz, DMSO-*d6*): δ 7.52 (4H, t, *J*= 7.8 Hz), 7.65 (2H, tt, *J*= 7.0, 1.0 Hz), 8.23 (4H, dd, *J*= 8.4, 1.0 Hz); **^{13}C NMR** (62 MHz, DMSO-*d6*): 117.1 (2 × quat), 131.6 (4 × CH), 135.0 (4 × CH); **^{19}F NMR** (141 MHz, DMSO-*d6*): δ [-150.53, -150.59].

Attempts at palladium-catalysed three-component reaction between 1-methyl-*1H*-indole, diphenyliodonium tetrafluoroborate and different alkynes:



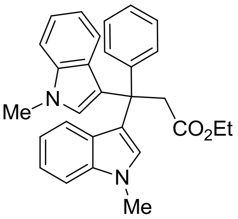
General procedure B: the general procedure described in Fujiwara hydroarylation[9] was followed. Pd catalyst (5 mol%) was weighed in a MW vial, the solvent was added (CH_2Cl_2, HOAc or mixtures, 2 mL) followed by methyl-1*H*-indole (31.5 μL, 0.25 mmol), the alkyne (0.25 mmol) and finally **12** (183 mg, 0.51 mmol). The mixture was stirred at r.t. for 20 h. Then CH_2Cl_2 was added (5 mL) and the crude was washed with sat. $NaHCO_3$ (5 mL × 2). The combined organic layers were dried over anh. $MgSO_4$, filtered and the solvent was evaporated under vacuum.

(2E) **Ethyl 3-(1-methyl-3-indolyl)-3-phenyl-2-propenoate, 13**. When the general procedure B was followed without the iodonium salt, the propenoate product was obtained. It was purified through a silica column eluting with hexane: CH_2Cl_2 mixtures (from 1:1 to 100%

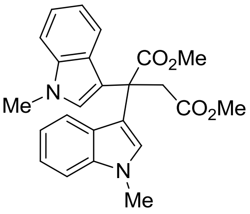


CH_2Cl_2). The product was further purified by recrystallisation in hot hexane obtaining a 52mg (68%) of a white solid. NMR data are according with literature values.[9] **^{1}H NMR** (360 MHz, $CDCl_3$): δ 1.30 (3H, t, *J* = 7.2 Hz), 3.71 (3H, s), 4.05 (2H, q, *J* =7.2 Hz), 6.55 (1H, s), 6.73 (1H, s), 7.24 (1H, ddd, *J*= 8.1, 6.9, 1.3 Hz), 7.29-7.35 (4H, m), 7.40-7.41 (3H, m), 7.85 (1H, d, *J* = 7.9 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 14.1 (CH_3), 33.1 (CH_3), 59.5 (CH_2), 109.9 (CH), 111.7 (CH), 117.2 (quat), 121.1 (CH), 121.1 (CH), 122.7 (CH), 125.6 (quat), 127.6 (CH), 127.7 (2 × CH), 128.8 (2 × CH), 133.6 (CH), 138.0 (quat), 140.4 (quat), 152.2 (quat), 166.9 (CO).

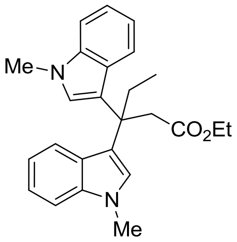
Ethyl 3,3-bis-(1-methyl-3-indolyl)-3-phenyl-2-propenoate, **14.** General procedure B afforded a small amount of the product when no iodonium salt was present in the mixture. 9 mg of a white solid where recovered after purification through silica column (8% yield). **m. p.**: 112-114 °C; **^{1}H NMR** (360 MHz, $CDCl_3$): δ 0.68 (3H, t, *J*= 7.2 Hz), 3.68-3.72 (8H, m), 3.82 (2H, s), 6.86-6.92 (4H, m), 7.11-7.16 (2H, m), 7.21-7.27 (7H, m), 7.50 (2H, d, *J* = 7.2 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 13.3 (CH_3), 32.7 (2 × CH_3), 46.4 (CH_2), 46.9 (quat), 59.7 (CH_2), 109.0 (2 × CH), 118.3 (2 × CH), 119.9 (quat), 120.9 (2 × CH), 122.0 (2 × CH), 125.9 (2 × quat), 127.0 (CH), 127.6 (2 × CH), 128.4 (2 × CH), 129.0 (2 × CH), 137.5 (2 × quat), 146.1 (2 × quat), 171.4 (CO); **IR** (KBr): 2983, 2924, 2821, 1712, 1479, 1448, 1327, 1247 cm^{-1}; **HRMS**: (ESI) calculated for $C_{29}H_{32}O_2N_3$ [MNH_4^+]: 454.2489, found: 454.2489.



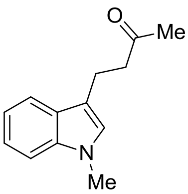
Dimethyl 2,2,-bis(1-methyl-3-indolyl)-succinate, 15. General procedure B with dimethyl acetylenedicarboxylate and $PdCl_2$ as catalyst afforded 46 mg of a white solid (46 % yield) after purification through a silica column eluting with mixtures hexane:CH_2Cl_2 (from 1:1 to 100% CH_2Cl_2). **m.p.**: 172-174 °C; **^{1}H NMR** (360 MHz, $CDCl_3$): δ 3.48 (3H, s), 3.69 (3H, s), 3.73 (8H, m), 6.85 (2H, t, *J* = 7.6 Hz), 7.09 (2H, t, *J* = 7.2 Hz), 7.22-7.26 (6H, m); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 32.8 (2 × CH_3), 42.3 (CH_2), 48.3 (quat), 51.3 (CH_3) 52.2 (CH_3), 109.1 (2 ×



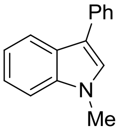
CH), 114.1 (2 × quat), 118.7 (2 × CH), 120.9 (2 × CH), 121.1 (2 × CH), 126.4 (2 × quat), 128.6 (2 × CH), 137.4 (2 × quat), 171.4 (CO), 173.6 (CO); **IR** (KBr): 2954, 2929, 2858, 1732, 1273 cm^{-1}; **HRMS:** (ESI) calculated for $C_{24}H_{29}O_4N_3$ [MNH_4^+]: 422.2074, found 422.2074.



Ethyl 3,3-bis-(1-methyl-3-indolyl)-3-phenyl-2-propenoate, **16.** When $PdCl_2$ was used as catalyst in the presence of 1-methyl-1*H*-indole and ethyl-2-pentynoate (without iodonium salt) under the general conditions from procedure B, the propenoate product was obtained as a white solid (54 mg, 56% yield) after silica column purification. **m. p.**: 178-180 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 0.77 (3H, t, *J*= 7.2 Hz), 0.78 (3H, t, *J*= 7.2 Hz), 2.58 (2H, q, *J*= 7.2 Hz), 3.29 (2H, s), 3.75 (2H, q, *J*= 7.2 Hz), 3.78 (6H, s), 6.80 (2H, t, *J*= 7.7 Hz), 7.00 (2H, s), 7.08 (2H, t, *J*= 7.7 Hz), 7.23 (4H, t, *J*= 7.7 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 9.0 (CH_3), 13.5 (CH_3), 30.1 (CH_2), 32.7 (2 × CH_3), 41.7 (quat), 42.2 (CH_2), 59.4 (CH_2), 108.1 (2 × CH), 118.8 (2 × CH), 119.7 (2 × quat), 120.9 (2 × CH), 121.2 (2 × CH), 126.8 (2 × CH), 126.9 (2 × quat), 137.6 (2 × quat), 171.6 (CO); **IR** (KBr): 2960, 2931, 1712, 1469, 1323, 1188 cm^{-1}; **HRMS**: (ESI) calculated for $C_{25}H_{32}O_2N_3$ [MNH_4^+]: 406.2486, found 406.2489.



4-(3-*N*-methylindolyl)-2-butanone, 20. A dried microwave vial was charged with 1-methyl-1*H*-indole (125 μL, 1 mmol), HOAc (0.5 mL), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and methylvinyl ketone (40.5 μL, 0.51 mmol). The vial was sealed and the mixture stirred at r.t. for 72 h. The crude was partitioned between H_2O and EtOAc (5 mL each), the aqueous phase was extracted twice with EtOAc (5 mL) and the combined organic layers washed with sat. $NaHCO_3$ (5 mL × 2) and brine (5 mL × 2), dried over anh. $MgSO_4$, filtered and solvent evaporated *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexane:EtOAc, 9:1) to afford 85 mg of tan solid (85%). The spectroscopic data are in agreement with the reported in the literature.[21] **^{1}H NMR** (360 MHz, $CDCl_3$): δ 2.18 (3H, s), 2.88 (2H, t, *J*= 7.4 Hz), 3.09 (2H, t, *J*= 7.4 Hz), 3.75 (3H, s), 6.88 (1H, s), 7.17 (1H, t, *J*= 7.5 Hz), 7.28 (1H, t, *J*= 7.5 Hz), 7.33 (1H, d, *J*= 7.9 Hz), 7.64 (1H, d, *J*= 7.9 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 19.1 (CH_3), 29.9 (CH_2), 32.4 (CH_2), 44.1 (CH_3), 109.1 (CH), 113.5 (quat), 118.6 (CH), 118.6 (CH), 120.4 (CH), 126.2 (CH), 127.4 (quat), 136.9 (quat), 208.6 (CO).



1-Methyl-3-phenyl-1*H*-indole, 21. The general procedure described by Phipps *et. al.*[14] was followed. Dtbpy (46 μL, 0.27 mmol) and $Cu(OTf)_2$ (9 mg, 0.025 mmol, previously dried at 100 °C under vacuum for 1h) and **12** (100 mg, 0.27 mmol) were added to a solution of methylindole (31.5 μL, 0.25 mmol) in anh. CH_2Cl_2 (2.5 mL). The reaction was stirred at 35 °C for 24 h. Then it was diluted with CH_2Cl_2 (10 mL) and washed with sat. solution of $NaHCO_3$ (10 mL). The aqueous layer was further extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over anh. $MgSO_4$ and the solvent evaporated *in vacuo*. The crude was purified through a silica column (hexane:CH_2Cl_2, 9:1) to afford the expected product as a colourless oil (33 mg, 64%). Spectroscopic data are in agreement with that previously reported one.[14] **^{1}H NMR** (360 MHz, $CDCl_3$): δ 3.79 (3H, s), 7.18 (1H, td, *J* = 7.0, 1.2 Hz0, 7.19 (1H,s), 7.22-7.29 (1H, m), 7.30 (1H, td, *J* = 7.0, 1.1 Hz), 7.35 (1H, d, *J*= 8.0 Hz), 7.47 (2H, t, *J*= 7.8 Hz), 7.71 (2H, dd, *J* = 7.8, 1.1 Hz), 8.01 (1H, d, *J* =8.0 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): 33.0 (CH_3), 109.5 (quat), 115.2 (CH), 119.9 (CH), 121.9 (CH), 125.6 (CH), 126.1 (2 × CH), 126.5 (2 × CH), 127.3 (quat), 128.7 (CH), 135.6 (quat), 137.4 (quat).

2.6. References

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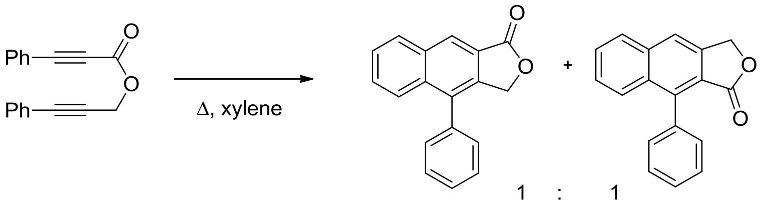
Chapter 3. Intramolecular Palladium-Catalysed Tandem Reactions

3.1. Palladium-Catalysed Tandem Reaction between Alkyne-Tethered Indoles and Diaryliodonium Salts

3.1.1. Introduction and Aims

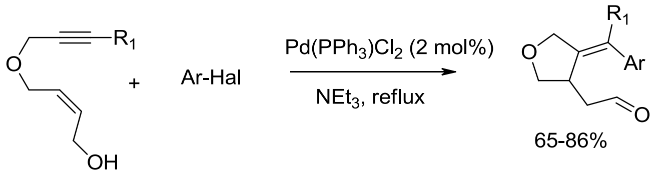
Previous attempts at intermolecular palladium-catalysed three-component reaction between indoles, alkynes and iodoarenes or diaryliodonium salts failed to give the desired tetra-subtituted olefins (See chapter 2). However, arylation of propiolates with unactivated indoles under Fujiwara's conditions[1] smoothly afforded the corresponding alkenoates or the diaddition products. So, it was hypothesised that making the second C-C bond forming step intramolecularly, by tethering an electrophile that could react with the vinylpalladium intermediate, would increase the chances of developing a successful process.

There are some examples in the literature of arylpropargyl arylpropiolate ester cyclisations, either by simple heating[2, 3] (Scheme 3.1.1), by photochemical reaction[4] or by a metal-mediated process.[5] Therefore, it is expected that the incorporation of an arylpropargyl or a cinnamyl group in the arylpropiolate ester would afford the corresponding lactone in the palladium-catalysed reaction with indoles.



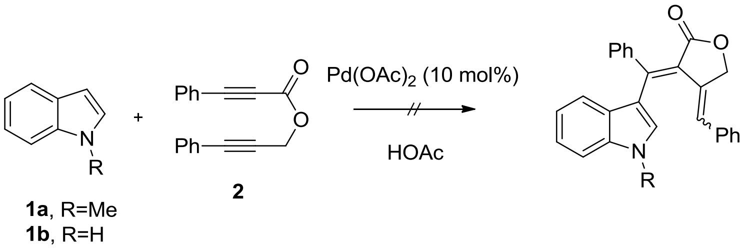
Scheme 3.1.1. Thermal cyclisation of arylpropargyl arylpropiolates described by Stevenson *et. al.*[2]

Also, the synthesis of tetra-substituted olefins through a palladium-catalysed tandem carbopalladation/cyclisation reaction between alkynylallyl alcohols and iodoarenes has been reported by Müller and co-workers.[6] In this case the vinylpalladium intermediate, generated after arylation of the triple bond, coordinates to the allyl moiety undergoing a cyclocarbopalladation which gives the final aldehydes after *β*-hydride elimination and enol-aldehyde tautomerism.



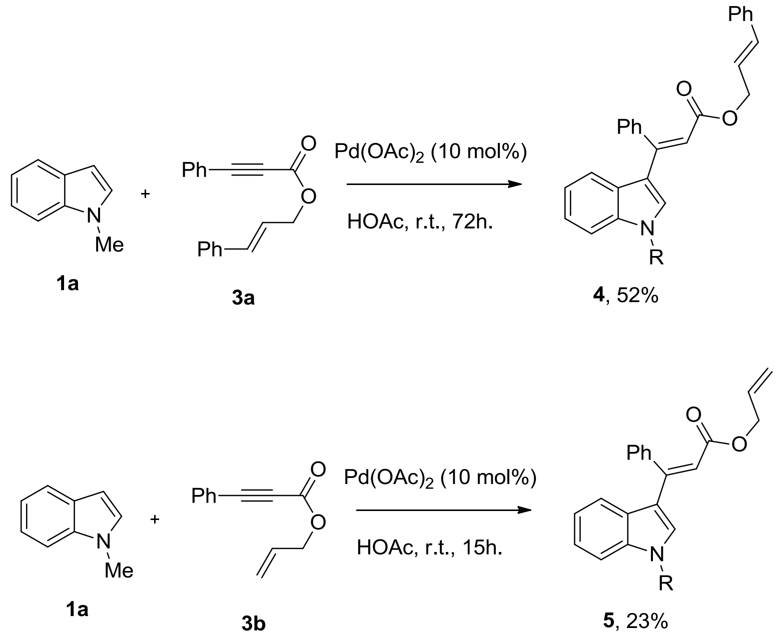
Scheme 3.1.2. Alkynylallyl alcohols Heck carbopalladation/cyclisation domino reaction.[6]

With these precedents of internal cyclisations it was thought that phenyl propiolates containing a tethered ynyl or allyl group could be used as the alkyne counterpart in our reaction study. These alkyne moieties, containing a second alkyne or alkene group in the molecule, could undergo indole insertion followed by intramolecular cyclisation. However, mixing phenylpropynoic acid phenylprop-2-ynyl ester, **2**, with indole in the presence of a catalytic amount of Pd(OAc)$_2$ did not afford the desired tandem reaction under diferent reaction conditions (Scheme 3.1.3). When the reaction was run in acid acetic as solvent, as in Fujiwara's reaction,[1] indole alkenylation was expected to take place. But when the reaction was runned either at r.t., higher temperatures or under microwave irradiation, only the unreacted indole was recovered. Unreacted propiolate was not isolated, neither were the expected lactones. Acetic acid may be acting as a nucleophile during the reaction attacking the propiolate or the lactone product[7] leading to its decomposition under the reaction conditions. No reaction happened either in different solvents or using other palladium, gold or rhodium catalysts.



Scheme 3.1.3. Attempt at palladium-catalysed tandem arylation/cyclisation reaction between indoles and phenylpropynoic acid 3-phenylprop-2-ynyl ester, **2**.

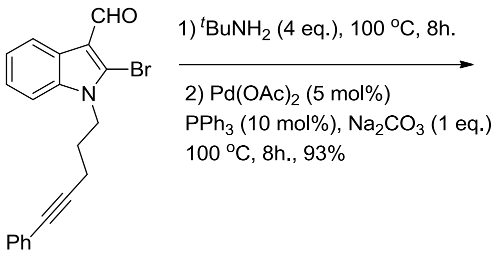
In the case of allyl derivatives, **3**, palladium-mediated insertion of indole into the triple bond was obtained when using Pd(OAc)$_2$ in acidic conditions, but a second C-C bond formation through an intramolecular cyclisation has not been achieved under many different conditions (Scheme 3.1.4).



Scheme 3.1.4. Attempts at palladium-catalysed tandem arylation/cyclisation reaction between indoles and phenylpropynoic acid 2-allyl esters, **3**.

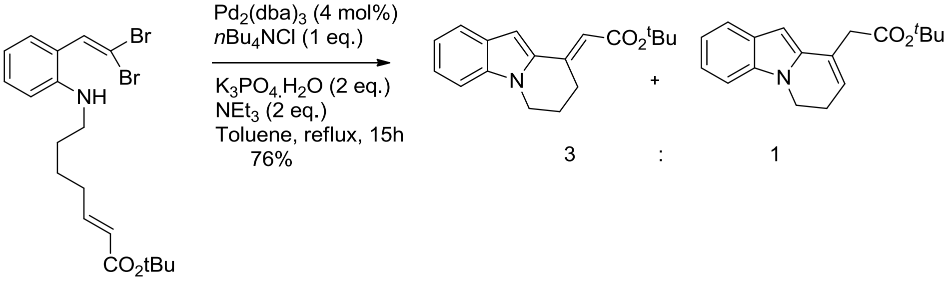
As the attempts tried so far for the intermolecular three-component reaction failed, as well as the attempts to trap the vinyl palladium intermediate with an intramolecular cyclisation with –ynyl or allyl propiolate esters, a new change in direction of the project was required. At this point it was thought that the installation of both C-H and alkyne components in the same molecule could facilitate the desired tandem alkyne difunctionalisation process.

There are few examples[8, 9] of alkyne tethered indoles yielding polycyclic indole products. Larock and co-workers[10] reported the powerful palladium-catalysed iminoannulation reaction of *N*-tethered triple bond 2-bromo-1*H*-indole-3-carboxaldehydes with tert-butyl amine to afford γ-carbolines in good to excellent yields (Scheme 3.1.5).



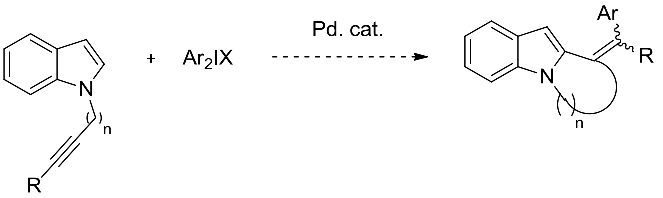
Scheme 3.1.5. Synthesis of annulated γ-carbolines from alkyne tethered 2-bromo-1*H*-indole-3-carboxaldehydes.[10]

Recently, more examples of *N*-annulated indoles have been reported[11], for instance Lautens and co-workers[12] published the synthesis of annulated indoles by their palladium-catalysed amination-Heck sequence procedure from *ortho*-*gem*-dibromovinylanilines (Scheme 3.1.6).



Scheme 3.1.6. Synthesis of annulated indoles from a tandem palladium-catalysed amination/Heck sequence.[12]

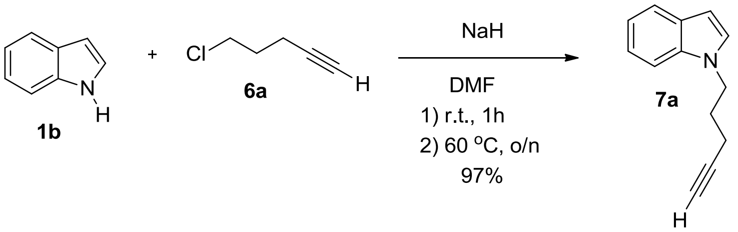
Based in these intramolecular palladium-catalysed tandem reactions, we hypothesised that the addition of diaryliodonium salts to alkyne-tethered indoles in the presence of a palladium catalyst, could be a plausible method for the synthesis of tricyclic derivatives containing a tetra-substituted olefin through indole C-H activation (Scheme 3.1.7).



Scheme 3.1.7. Next goal: synthesis of annulated indoles containing a tetrasubtituted olefin through indole C-H activation.

3.1.2. Results and discussion

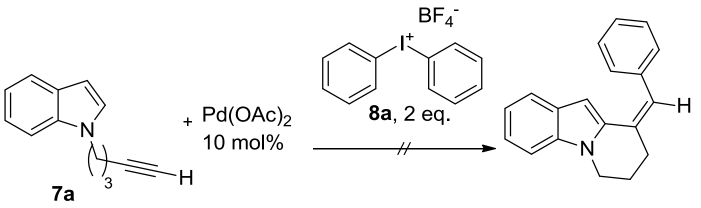
In order to synthesise starting materials, the *N*-alkylation of indole with the commercially available 5-chloro-1-pentyne was tried under several conditions. The alkylation procedure described by Larock *et al.*[10] for the synthesis of alkyne-tethered 2-bromo-*1H*-indole-3-carboxaldehydes was not successful when using plain indole, neither was the use of KOH[13] or nBuLi[14] as base. However, using NaH as base in DMF[15-17] with gentle heating, proved to be a good procedure for *N*-alkylation (Scheme 3.1.8).



Scheme 3.1.8.. *N*-alkylation of indole with 5-chloro-1-pentyne.

With **7a** in hand, its palladium-catalysed reaction with diphenyliodonium tetrafluoroborate was studied (Table 3.1.1). Firstly, **7a** was treated with 2 eq. of iodonium salt in the presence of $Pd(OAc)_2$ and another co-catalyst as CuI or $Cu(OAc)_2$ which could coordinate with the terminal alkyne (entries 1 to 3). NMR analysis of the crude residues showed unreacted starting material and a complex mixture of aromatic protons in which biphenyl and iodobenzene could be detected. The reaction did not work in the presence of acetic acid (entry 4) or with Larrosa's conditions for indole direct arylation,[18] instead biphenyl was mostly obtained (entry 5).

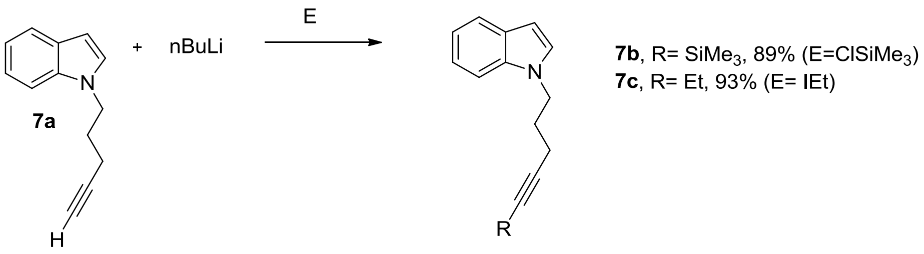
Table 3.1.1. Attempts at the palladium-catalysed reaction of 1-pent-4-ynyl-*1H*-indole with diphenyliodonium tetrafluoroborate.



Entry	*Additive*	*Solvent (0.25M)*	*T (°C)*	*t (h)*	*Results*
1	CuI, 10 mol%	CH_2Cl_2	1) r.t. 2) reflux	1)15 2)15	Unreacted **7a**[a]
2	CuI, 10 mol%, HOAc (2 eq.)	CH_2Cl_2	r.t.	15	Unreacted **7a**[a]
3	$Cu(OAc)_2$,10 mol%	CH_2Cl_2	1) r.t. 2) reflux	1)15 2)15	Unreacted **7a**[a]
4	-	HOAc:CH_2Cl_2, 1:1	1) r.t. 2) 50	1)15 2)15	Unreacted **7a**[a]
5	AgO, 2 eq.	DMF	1) r.t. 2) 50	1)15 2)15	Unreacted **7a**[a]

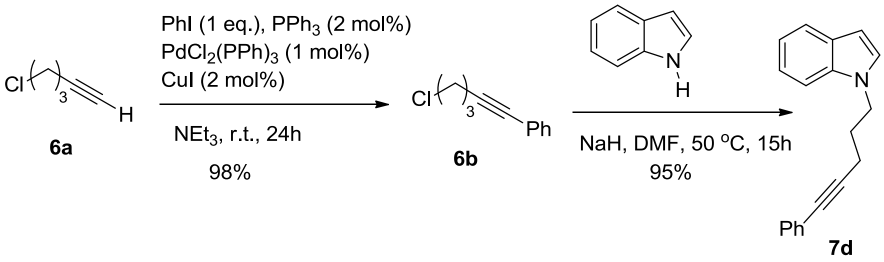
Reaction conditions: **7a** (0.25 mmol), **8a** (0.5 mmol), solvent (1 mL) [a] Unreacted starting material, a complex mixture of aromatic protons seen by ^{1}H NMR: biphenyl, PhI and other unknown compounds.

Internal alkynes were also synthesised to evaluate their reactivity. They were easily synthesised by reaction of 1-pent-4-ynyl-*1H*-indole, **7a**, with a strong base, nBuLi, in the presence of an electrophile (Scheme 3.1.9). [19]



Scheme 3.1.9. Synthesis of internal alkynes from **7a**.

In the case of the phenyl derivative, it was synthesised according to the general *N*-alkylation of indole with the previously functionalised chloropentyne **6b** (Scheme 3.1.10).

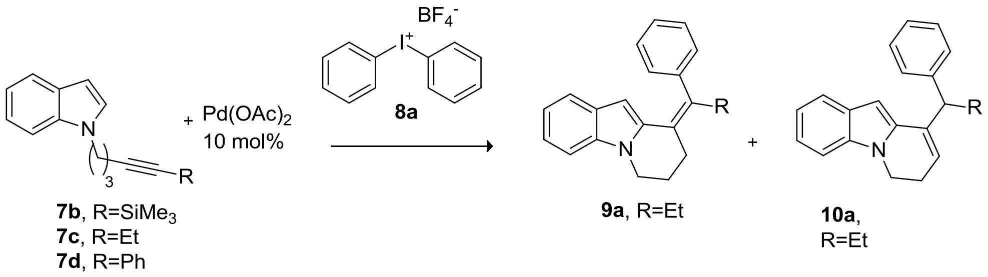


Scheme 3.1.10. Synthesis of phenyl derivative **7d**.

Attempts at the annulation reaction, with internal alkynes, started with the trimethylsilyl substrate, **7b**, which was mixed with $Pd(OAc)_2$ in the presence or absence of **8a** with HOAc or CH_2Cl_2 as solvent (Table 3.1.2, entries 1 to 7). Unfortunately, no reaction involving the alkyne-tethered indole was observed and complex mixtures of aromatic compounds could be seen by NMR. The same conditions with the phenyl substituted alkyne **7d** lead to complex mixtures, with unreacted starting material being the main component.

When substrate **7c** was tried in the reaction, heating at 50 ^{o}C, decomposition happened in HOAc. However in CH_2Cl_2 traces of a new product were detected by ^{1}H NMR and further transformation took place in toluene (entries 11-14). In this last experiment conversion of 31% of a new product in which the indole ring and the *N*-propyl chain could be observed by ^{1}H NMR. However, attempts to purify the compound in a silica gel column lead to a very messy mixture. The product could not be identified at this stage, but later comparison of the crude ^{1}H NMR with product **9a** (*vide infra*) confirmed it to be the same compound. Stoltz's conditions for oxidative annulation of 3-alkene-tethered indoles[20, 21] (Chapter 1, pg. 36) led to a single product **10a** in which the tetra-substituted double bond had migrated into the new formed cycle (entry 15). The presence of the migrated double bond could be easily seen by ^{1}H NMR as the proton from the alkene showed up as a characteristic triplet of doublets at 6.0 ppm. Although there was only one product detected, its purification turned out to be difficult by silica chromatography and several purifications were needed to obtain the pure product in low yield.

Table 3.1.2. Palladium-catalysed reaction of alkyne-tethered indoles with diphenyliodonium tetrafluoroborate.



Entry	*R*	*8a*	*Additive (mol%)*	*Solvent (0.25 M)*	*T (°C)*	*t (h)*	*Results*
1	SiMe$_3$	-	-	HOAc	50	15	Complex mixture, SM main compound
2	SiMe$_3$	2 eq.	-	HOAc	1) r.t. 2) 50	1) 15 2) 15	Mostly unreacted **7b**[a]
3	SiMe$_3$	2 eq.	CuI (10)	HOAc	1) r.t. 2) 50	1) 15 2) 15	Mostly unreacted **7b**[a]
4	SiMe$_3$	-	-	CH$_2$Cl$_2$	reflux	15	Mostly unreacted **7b**[a]
5	SiMe$_3$	2 eq.	CuI (10)	CH$_2$Cl$_2$	1) r.t. 2) reflux	1) 15 2) 15	Mostly unreacted **7b**[a]
6	SiMe$_3$	2 eq.	-	HOAc: CH$_2$Cl$_2$, 1:1	35	15	Mostly unreacted **7b**[a]
7	SiMe$_3$	-	-	DMF	50	15	Mostly unreacted **7b**[a]
8	Ph	2 eq.	-	HOAc	1) r.t. 2) 50	1) 15 2) 15	Complex mixture, **7d** main compound
9	Ph	2 eq.	CuI (10)	HOAc	1) r.t. 2) 50	1) 15 2) 15	Complex mixture, **7d** main compound

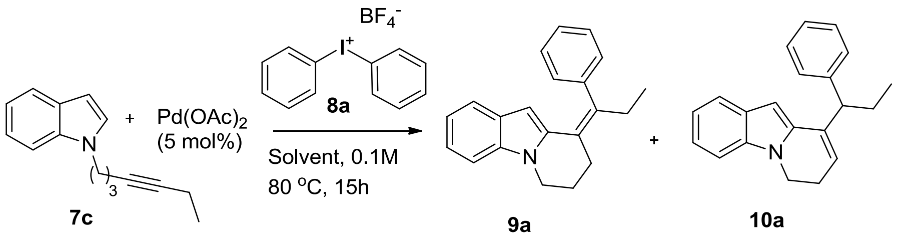
10	Ph	2 eq.	CuI (10)	CH_2:Cl_2	1) r.t. 2) reflux	1) 15 2) 15	Complex mixture, **7d** main compound
11	Et	2 eq.	-	HOAc	50	15	Decomp., complex mixture aromatics
12	Et	2 eq.	-	HOAc: CH_2Cl_2, 1:1	50	15	Decomp., complex mixture aromatics
13	Et	2 eq.	-	CH_2Cl_2	reflux (50)	15	Mostly **7c**, but traces new product
14	Et	2 eq.	-	Toluene	50	15	**7c** left, but new product **9a** (31%)^b
15^c	Et	1 eq.	-	^{t}Amyl alcohol: HOAc (4:1) (0.1 M)	80	15	**10a** [16%] ^{d}

Reaction conditions: **7** (0.25 mmol), Pd(OAc)$_2$ (0.025 mmol), **8a** (0.5 mmol), solvent (1 mL). ^{a} Complex mixture of aromatics, no reacted starting material observed but no desired product ^{b} Conversion calculated from ^{1}H NMR ^{c} 3-ethylnicotinate (0.1 mmol) added, reaction under O_2 atmosphere (O_2 balloon) ^{d} Isolated yield (SiO_2).

The formation of arylated indoles as byproducts in the reaction was not observed. That was surprising, as some of the conditions tried (Table 3.1.2, entries 2, 8 and 11) are very similar to the ones reported by Sanford *et al.*[22] for the room temperature direct arylation of indoles with diaryliodonium salts. Although the formation of the arylated products cannot be totally ruled out, because some degradation is observed in the experiments, their absence seems to indicate that electrophilic palladation on the alkyne-containing indole derivatives is not as easy as expected.

Nevertheless, the fact that small amounts of the desired product were obtained, even with the migration of the double bound, was very encouraging and further experiments were carried out in order to improve the formation of the annulation product. The reaction of **7c** with diphenyliodonium tetrafluoroborate, **8a**, was analysed under a broad range of different conditions, summarised in Table 3.1.3. Firstly, the reaction was done in the absence of oxygen as the iodonium salt should act as an oxidant itself. Pleasingly, the tandem reaction took place either under air or under N_2. The crude was slightly cleaner under N_2, but its purification was very difficult again, and variations such as the addition of NEt_3 (10 mol%) to the silica column did not help to obtain a cleaner product (entry 1). Increasing the amount of **8a** to 2 eq. did not improve the yield and the reaction was messier. Best results were attained between 1 and 1.2 eq. of iodonium salt in the reaction.

Table 3.1.3. Tandem palladium-catalysed reaction of 1-Hept-4-ynyl-*1H*-indole, **7c**, with **8a**.



Entry	*Ligand (mol%)*	*Solvent (0.1M)*	*Results*
1[a]	3-ethylnicotinate, (40)	^{t}Amylalcohol:HOAc (4:1)	**10a** [18%][b]
2	3-ethylnicotinate, (40)	^{t}Amylalcohol:HOAc (4:1)	**10a** [14%][b]
3	Pyridine, (40)	^{t}Amylalcohol:HOAc (4:1)	**10a** (31%)[c]
4	2-trimetylsilylpyridine, (40)	^{t}Amylalcohol:HOAc (4:1)	**10a** (17%)[c]
5	Quinoline (40)	^{t}Amylalcohol:HOAc (4:1)	**10a** (16%)[c]
6	1,10-phenantroline (10)	^{t}Amylalcohol:HOAc (4:1)	n.r.[d]
7[e]	3-ethylnicotinate, (10)	^{t}Amylalcohol:HOAc (4:1)	**10a** [42%][f]
8[e]	-	^{t}Amylalcohol:HOAc (4:1)	**10a** [51%][f]
9[e]	-	^{t}Amylalcohol	**10a** (21%)[c]
10[e]	-	HOAc	Traces, decomp.
11[e]	-	THF:HOAc (4:1)	**10a** [26%][f]
12[e]	-	Toluene:HOAc (4:1)	**10a** [26%][f]
13[e]	-	H_2O:HOAc (4:1)	n.r.[d]
14[g]	-	^{t}Amylalcohol:HOAc (4:1)	**9a**:**10a**, 1:1[h] [43%][f]
15[g]	-	^{t}Amylalcohol	**9a**:**10a**, 1:3[h] (43%)[c]

		HOAc (1 eq.)	
16[g]	-	^{t}Amylalcohol HOAc (5 eq.)	**9a**:**10a**, 1:1.1[h] (49%)[c]
17[g]	-	Toluene HOAc (1 eq.)	**9a**:**10a**, 1:1[h] (41%)[c]
18[e]	-	^{t}Amylalcohol:HCO_2H (4:1)	**9a**:**10a**, 1:1.1[h] (74%)[c]
19[e]	-	Toluene:HCO_2H (4:1)	**9a** [20%][f]
20[e, i]	-	^{t}Amylalcohol:HOAc (4:1)	**9a** [43%][f]

Reaction conditions: **7c** (0.25 mmol), Pd(OAc)$_2$ (0.012 mmol), **8a** (0.025 mmol), solvent (2.5 mL), 80 °C, 15h. [a] Pd(OAc)$_2$ [b] Isolated yield (SiO_2+10% NEt_3) [c] Reaction conversion calculated from ^{1}H NMR [d] n.r.= no reaction, starting material recovered [e] 1.2 eq. of **8a** used [f] Isolated yield (neutral AlO_3) [g] Reaction at 70 °C [h] Ratio from ^{1}H NMR [i] Reaction under μwaves irradiation, 10 min at 80 °C.

In Stoltz's procedure[20] the indole derivative was added last, when the reaction is at 80 °C. In the current reaction the addition order was not important and identical results were achieved when all the components were mixed at once.

Decreasing the palladium loading to 5 mol% (entry 2) did not compromise the reaction conversion, however the yield was still low and purification difficult, further decreasing to 1% resulted in a very slow reaction with most of **7a** unreacted after 24h. Other palladium catalysts did not improve yields, use of $PdCl_2$ resulted in very low conversion, $PdCl_2(NCPh)_2$ gave a mixture of the two isomers **9a** : **10a** (1:3) in low yield (26%). While other metal catalysts like chloro(1,5-cyclooctadiene)rhodium (I) dimer, indium trichloride or tris(norbornadiene)acetylacetonate iridium(III), among others, did not give the desired product and only starting material was recovered. No reaction happened in the absence of catalyst.

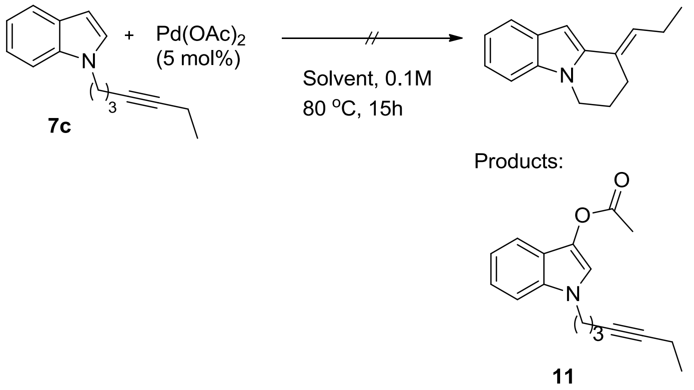
Other pyridine-based ligands led to low conversion (entries 3 to 5). The use of 1,10-phenanthroline suppressed the reaction, while decreasing the loading of 3-ethylniconinate to 10 mol% did not affect the result. However, better results were achieved with the ligandless variation and purification using neutral alumina (entry 8).

Migration of the double bond was also observed in the absence of acid, however in this case, no higher conversion than 25% was observed. The reaction stopped and leaving it for longer or at higher temperature only afforded a messier reaction. On the other hand, just traces of product could be detected when acetic acid was the solvent, with **7c** being the main compound in the mixture which was very dirty. Other solvents were tried in the reaction with the same quantity of acetic acid. Solvents such as THF and toluene gave the cyclohexene product in low yield, while the use of polar solvents as DMF, DMSO and H_2O resulted in no reaction happening and recovering of starting material (Table 3.1.3, entries 11-13).

Increasing the temperature did not improve yields and the reaction seemed to be messier. No reaction was observed at r.t., and very low conversion at 50 ^{o}C after 24 h. However, total starting material consumption took place at 70 ^{o}C, overnight. And surprisingly, not all the product suffered migration of the tetra-substituted double bond, so mixtures of the two isomers **9a** and **10a** were obtained. Unfortunately, yields continued to be low. Purification was tedious, with the best results obtained using neutral alumina, although more than one column was needed in most cases to get a pure compound and the two isomers could not be separated. No significant amounts of other compounds besides starting material or the annulated products were isolated. Low yields could be due to decomposition taking place in the reaction conditions or in the purification. In order to establish milder reaction conditions the amount of acetic acid present in the reaction was reduced to 1 or 5 eq. (entries 15-17), but reaction was not completed in 15h. or longer times, being stopped between 40-50% conversion. Employing formic acid instead of acetic acid in the reaction also worked and mitigated the migration of the double bond, though yields were still low. Finally, reducing the reaction time using microwave irradiation, led to the isolation of a single isomer, identified as **9a**. The proton in the indole 3-position resonated at 5.18 ppm in the ^{1}H NMR (entry 20).

Attempts at obtaining the annulated product in the absence of iodonium salt in the reaction were unsuccessful, even if using an oxidant in order to mimic the effect of iodonium salts to get a Pd^{II}/Pd^{IV} catalytic cycle (Table 3.1.4). In most of the cases only starting material was recovered, except when diacetoxyiodobenzene was used as oxidant,[23] in this case the 3-acetoxyindole derivative was obtained in poor yield together with another unidentified compound.

Table 3.1.4. Attempts at palladium-catalysed annulation of alkyne-tethered indoles.



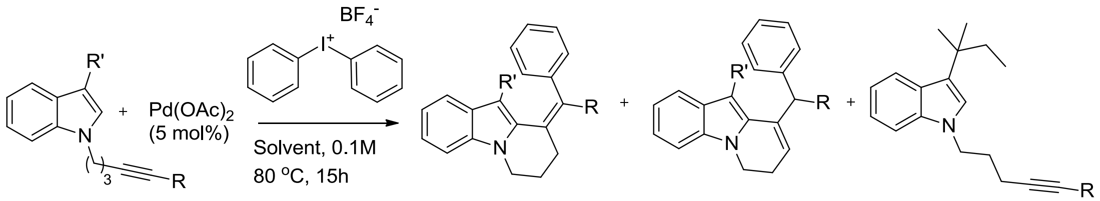
Entry	*Ligand*	*Solvent*	*Oxidant*	*Results*
1[a]	3-nicotinate, 40 mol%	^{t}Amylalcohol:HOAc (4:1)	-	n.r.[b]
2	-	^{t}Amylalcohol:HOAc (4:1)	-	n.r [b].
3	-	^{t}Amylalcohol:HOAc (4:1)	O_2 balloon	n.r.[b]
4	-	Toluene:HOAc (4:1)	O_2 balloon	n.r.[b]
5	-	^{t}Amylalcohol:HOAc (4:1)	BQ[c]	n.r.[b]
6	-	^{t}Amylalcohol:HOAc (4:1)	$PhI(OAc)_2$[d]	**11** [12%][e] + unknown product
7	-	Toluene:HOAc (4:1)	$PhI(OAc)_2$[d]	**11** [33%][e] + unknown product

Reaction conditions: **7c** (0.25 mmol), $Pd(OAc)_2$ (0.012 mmol), solvent (2.5 mL), 80 °C, 15h. [a] $Pd(OAc)_2$, 10 mol% [b] n.r.= no reaction, starting material recovered [c] BQ: benzoquinone (0.25 mmol) [d] $PhI(OAc)_2$ (0.3 mmol) [e] Isolated yield (SiO_2).

As the desired double functionalisation of alkyne through C-H activation of indole was accomplished, although in moderate yields, some other starting materials were prepared in order to study the scope of the transformation. The alkyne-tethered indole derivatives were prepared according to the general procedure described in Scheme 3.1.9. Palladium-catalysed oxidative conditions described by Ferreira *et.*

al.[20] applied to the free alkyne, **7a**, the trimethylsilyl derivative, **7b**, and the methylester derivative, **7e**, led to a complex mixture in which starting material could be detected, but no desired product was observed (Table 3.1.5, entries 1-3).

Table 3.1.5. Palladium-catalysed reaction of different substituted alkyne-tethered indoles with diphenyliodonium tetrafluoroborate.



7a, R'= H, R=H
7b, R'=H, R=SiMe$_3$
7d, R'=H, R=Ph
7e, R'=H, R=CO$_2$Me
7f, R'=H, R=COMe
7g, R'=H, R=Me
7h, R'=Me, R=Et
7i, R'=Me, R=Ph
7j, R'=H, R=4-NO$_2$Ph

9b, R=CO$_2$Me, R'=H

10b, R=CO$_2$Me, R'=H

12, R=Ph

Entry	*SM*	*Pd cat. (mol %)*	*Ligand (mol %)*	*Solvent*	*T (°C)*	*Results*
1	**7a**	Pd(OAc)$_2$ (10)	3-ethylnicotinate (40)	^{t}Amylalcohol:HOAc (4:1)	80	Complex mixture
2	**7b**	Pd(OAc)$_2$ (10)	3-ethylnicotinate (40)	^{t}Amylalcohol:HOAc (4:1)	80	Complex mixture, loss of SiMe$_3$, no desired product detected
3	**7e**	Pd(OAc)$_2$ (10)	3-ethylnicotinate (40)	^{t}Amylalcohol:HOAc (4:1)	80	Complex mixture, SM detected
4	**7e**	Pd(OAc)$_2$ (5)	-	^{t}Amylalcohol:HOAc (4:1)	80	**10b** [23%][a] and traces **9b**
5	**7e**	PdCl$_2$(NCPh)$_2$ (5)	-	^{t}Amylalcohol:HOAc (4:1)	80	**10b** [31%][a] and traces **9b**
6	**7e**	Pd(OAc)$_2$ (5)	-	CH$_3$CN	80	Complex mixture, **9b** and **10b** detected + unknown compounds

7	**7e**	Pd(OAc)$_2$ (5)	-	DMF	80	n.r.^{b}
8	**7e**	Pd(OAc)$_2$ (5)	-	^{t}Amylalcohol:HOAc (4:1)	70	**9b** :**10b**, 5:1^{e} [16%]^{c}
9	**7f**	Pd(OAc)$_2$ (5)	3-ethylnicotinate (40)	^{t}Amylalcohol:HOAc (4:1)	80	n.r.
10	**7g**	Pd(OAc)$_2$ (5)	-	^{t}Amylalcohol:HOAc (4:1)	80	Complex mixture
11	**7h**	Pd(OAc)$_2$ (5)	-	^{t}Amylalcohol:HOAc (4:1)	70	Mixture of two inseparable isomers
12	**7d**	Pd(OAc)$_2$ (5)	-	^{t}Amylalcohol:HOAc (4:1)	80	**12** [32%]^{a} + unreacted **7d**
13	**7i**	Pd(OAc)$_2$ (5)	-	^{t}Amylalcohol:HOAc (4:1)	80	n.r.
14	**7j**	Pd(OAc)$_2$ (5)	-	^{t}Amylalcohol:HOAc (4:1)	80	n.r.

Reaction conditions: **7** (0.25 mmol), Pd(OAc)$_2$ (0.012 mmol), **8a** (0.3 mmol), solvent (2.5 mL, 0.1M), 80 ^{o}C, 15h. ^{a} Isolated yield (SiO$_2$) ^{b} n.r.= no reaction, starting material recovered ^{c} Isolated yield (SiO$_2$ + 3% NEt$_3$) ^{d} Isolated yield (AlO$_3$) ^{e} Ratio from ^{1}H NMR.

In the case of the ester derivative, **7e**, the ligandless reaction afforded the expected product, being the cyclohexene isomer, **10b**, the main compound (entry 4). Several palladium catalysts were tried in these conditions, PdCl$_2$ gave low conversion, while no reaction took place using Pd(dppf)$_2$Cl$_2$.CH$_2$Cl$_2$ and PdCl$_2$(NCPh)$_2$ provided a slightly better yield. Solvent screening resulted in no better results, complex mixtures were obtained when using MeCN. No reaction happened when using polar solvents as DMF (entries 6 and 7). Bringing down the temperature to 70 ^{o}C suppressed the double bound migration (more than in the ethyl derivative, Table 3.1.3, entry 14) but yields continued to be quite low. Unexpectedly, when the ketone derivative was used, only starting material was recovered.

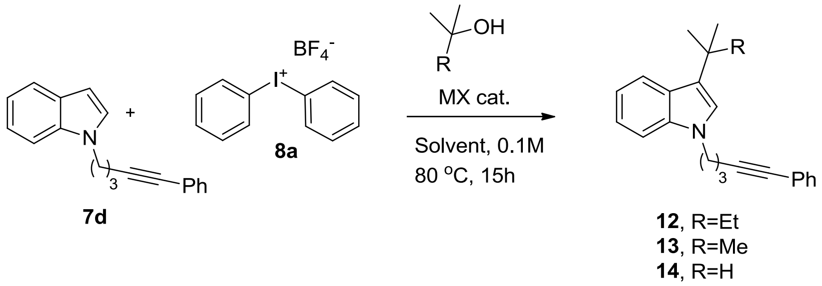
Reaction with **7g** was messier than the reaction with the ethyl derivative and the migrated alkene was the main compound, but the crude was very dirty and no clean product could be isolated. When using the 3-Me indole ethylalkyne no double bond migration was observed (no alkene protons seen by ^{1}H NMR) but the product was obtained as an inseparable mixture of two isomers.

Finally, no reaction between the diphenyliodonium salt and the indole was observed when the alkyne was substituted with a phenyl, **7d**. Instead, Friedel-Crafts reaction with *tert*-amylalcohol was observed in the 3-position of the indole (entry 12). When the 3-position was blocked with a methyl, then no reaction took place (entry 13). And finally, in order to examine the electronic effect in the phenyl substituent, an electron-withdrawing group was used, 4-NO_2. Only starting material was recovered in this case (entry 14).

The Friedel-Crafts reaction of indole with secondary and tertiary alcohols has been reported before.[24] However, there are no examples of palladium catalysts being used, except in the case of allyl alcohols which regioselectively provide 3-alkylated indoles in the presence of a $Pd(PPh_3)/BEt_3$ catalytic system.[25]

In order to understand this transformation, the reaction of **7d** with diphenyliodonium tetrafluoroborate (Table 3.1.5, entry 12) was repeated using only 1 eq. of *tert*-amyl alcohol in a toluene:HOAc, 4:1 solvent mixture (Table 3.1.6, entry 1). Surprisingly, the Friedel-Crafts reaction still took place, while no annulation reaction was observed. When the solvent system was toluene:HCO_2H, the reaction seemed even cleaner and the use of 2 equivalents of alcohol gave the best conversion. However, yields after purification were low. When the reaction was performed in a basic media, using triethylamine, only starting material was recovered, while using trifluoroethanol, a more acidic alcohol, led to no reaction. In absence of acid, the 3-alkylation of indole was also the only reaction happening, by contrast no reaction happened without diphenyliodonium salt or palladium catalyst. This fact could indicate that interaction of $Pd(OAc)_2$ with the diaryliodonium salt gives a palladium intermediate that acts as Lewis acid in the Fridel Crafts reaction. Actually, reducing the quantity of diphenyliodonium tetrafluoroborate in the mixture did not affect the Friedel-Crafts reaction and even better conversions were obtained with 20 mol%. However, full conversion was not obtained. Changing the palladium catalyst for a silver salt, lead to the 3-alkyl indole in similar yields (entries 9-11). No acid or iodonium salt were needed in the reaction and it also worked with secondary alcohols, albeit in low yield.

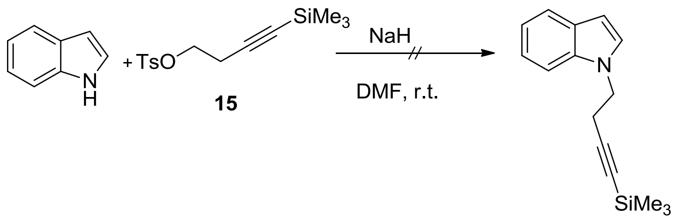
Table 3.1.6. Friedel-Crafts reaction of **7d** with alcohols.



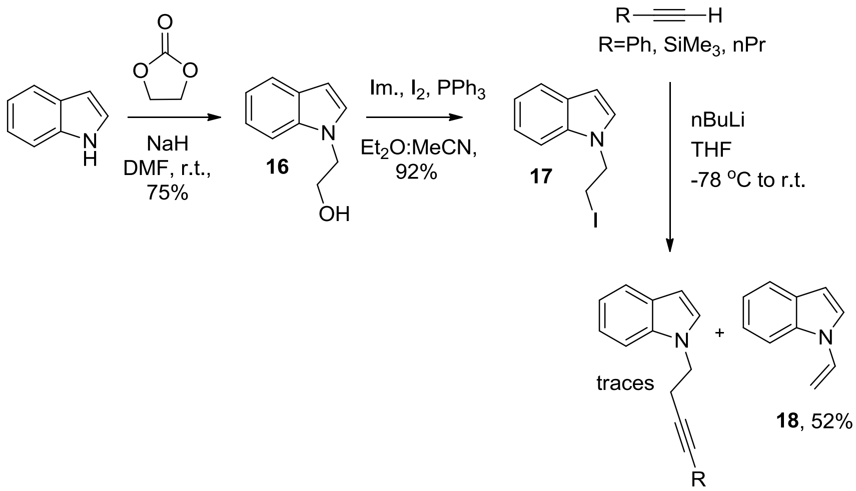
Entry	*cat. (mol %)*	*Ph$_2$IBF$_4$ (eq.)*	*Alcohol (eq.)*	*Solvent*	*Results*
1	Pd(OAc)$_2$ (5)	**8a** (1.2)	^{t}Amylalcohol (1)	Toluene:HOAc (4:1)	**12** (62%)[a]
2	Pd(OAc)$_2$ (5)	**8a** (1.2)	^{t}Amylalcohol (2)	Toluene:HOAc (4:1)	**12** (81%)[a] [32%][b]
3	Pd(OAc)$_2$ (5)	**8a** (1.2)	^{t}Amylalcohol (2.5)	Toluene:HOAc (4:1)	**12** (77%)[a] [31%][b]
4	Pd(OAc)$_2$ (5)	**8a** (1.2)	-	*t*-Amylalcohol:NEt$_3$ (4:1)	n.r.
5	Pd(OAc)$_2$ (5)	**8a** (1.2)	^{t}Amylalcohol (2)	Toluene	**12** [19%][b]
6	Pd(OAc)$_2$ (5)	-	^{t}Amylalcohol (2)	DCE (5 eq. HOAc)	n.r.[c]
7	-	**8a** (1.2)	^{t}Amylalcohol (2)	DCE (5 eq. HOAc)	n.r.[c]
8	Pd(OAc)$_2$ (5)	**8a** (20 mol%)	^{t}Amylalcohol (2)	DCE (5 eq. HOAc)	**12** [50%][b]
9	AgSO$_3$CF$_3$ (10)	-	^{t}Amylalcohol (2)	DCE	**12** [50%][b]
10	AgSO$_3$CF$_3$ (10)	-	^{t}Butanol (2)	DCE	**13** [53%][b]
11	AgSO$_3$CF$_3$ (10)	-	Isopropanol (2)	DCE	**14** [23%][b]

Reaction conditions: **7d** (0.25 mmol), Pd(OAc)$_2$ (0.012 mmol), **8a** (0.3 mmol), solvent (2.5 mL, 0.1M), 80 °C, 24h. [a] Conversion calculated from ^{1}H NMR [b] Isolated yield (SiO$_2$) [c] n.r.= no reaction, starting material recovered.

The Friedel-Crafts reaction was not observed with any other of the substrates used, indicating that the reaction is very sensitive to alkyne substitution. In the other reacting substrates, the major product came from the sequential difunctionalisation of the alkyne, however migration of the resulting alkene can happen giving the product as mixtures of isomers, yields were low and the reaction was quite messy. In order to see whether the five membered ring products were more stable to overcome the problems found in the reaction, the *N*-alkylation of indole with (4-trimethylsilyl-3-butyn-1-yl)-4-toluene sulfonate, **15**, was attempted (Scheme 3.1.11). Unfortunately, no desired product was formed and only indole was recovered. Probably elimination in the alkyne took place giving but-1-en-3-yne which is volatile and may have been lost in the reaction. Synthesis of the alkyne-tethered indole was also tried installing the leaving group in the indole and making it react with a terminal alkyne in basic media, but this also afforded mainly elimination product and only traces of the expected product were detected (Scheme 3.1.12).

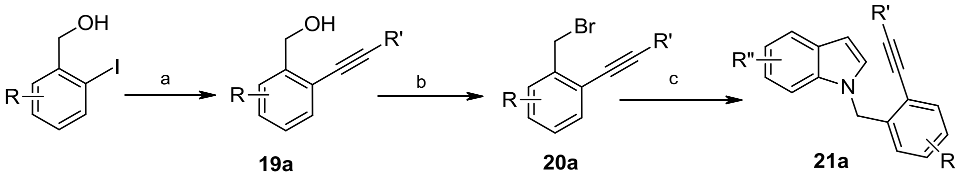


Scheme 3.1.11. Failed attempt to *N*-alkylation of indole with **15**.



Scheme 3.1.12. Attempts to synthesise ethynylindoles from **17**.

As the five-membered rings precursors could not be easily synthesised, ethynylbenzyl indoles were synthesised as they might provide more stable substrates and products for the reaction. The synthetic route is shown in Scheme 3.1.13, ethynylbenzyl halides are used as described by Sashida *et. al.*[26] Having the benzene group next to the alkyne would avoid the double bond migration in the annulated product. So, the products obtained should be more stable.



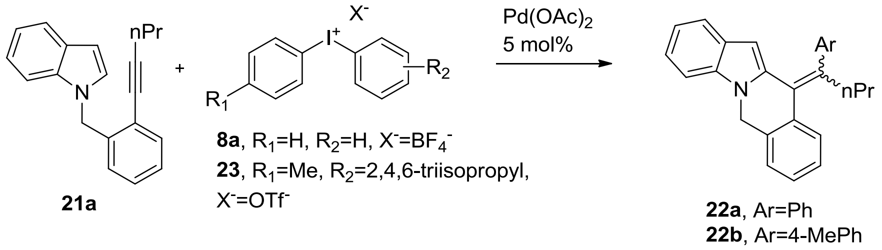
a) 1-pentyne (1.2 eq), $Pd(PPh_3)Cl_2$ (1 mol%), CuI (2 mol%), Toluene:Piperidine, 1:1, r.t.
b) PBr_3 (1.2 eq), pyridine (1.3 eq), $CHCl_3$, 0°C- r.t. c) Indole (1 eq), NaH (1.1 eq), DMF, r.t.

Scheme 3.1.13. Synthesis of 2-ethynylbenzyl indoles.

Treatment of **21a** with $Pd(OAc)_2$ and diaryliodonium tetrafluoroborate, **8a**, in mixtures of *tert*-amylalcohol, toluene or trifluoroethanol with acetic acid at 80 ^{o}C did in fact provide the desired annulated product **22a**, as a mixture of double bond *E*/*Z* isomers (Table 3.1.7, entries 1-4). The reaction, though, was messy and yields not very good. Interestingly, a better yield was achieved in trifluoroethanol in absence of acid (Table 3.1.7, entry 5). The mixtures of double bond isomers were very hard to separate by column chromatography. Fortunately, the major compound could be crystallised out by precipitation in CH_2Cl_2: hexane as a white solid. NMR characterisation of the product also showed the 3-indole proton being shielded to δ 5.8 ppm.

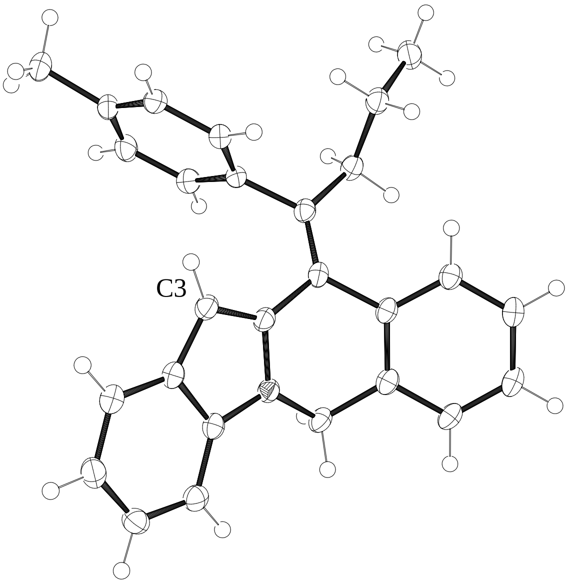
To unequivocally determine the product structure a crystal was grown from the p-methylphenyl derivative **22b** in toluene:nitromethane, affording crystalline needles to perform X-ray crystallography. The major compound was identified as the desired 6-membered ring annulated product, with *Z*-double bond geometry (Scheme 3.1.14). The X-ray structure could clarify that the rare shift of the proton in the 3-indole position is due to it pointing directly to the shielded zone of the aryl group. Obtaining this crystal structure was of capital importance as it allowed us to unambiguously assign the structure of all the cyclised products synthesised before where the 3-indole proton resonated at this characteristic point.

Table 3.1.7. Palladium-catalysed reaction of **21a** with diphenyliodonium salts.



Entry	*Diaryliodonium salt (1.2 eq.)*	*Solvent (0.1 M)*	*T (°C)*	*Results*
1	**8a**	^{t}Amylalcohol:HOAc (4:1)	80	***Z*-22a**:***E*-22a**, 1:1.3[a] (49%)[b]
2	**8a**	Toluene:HOAc (4:1)	80	***Z*-22a**:***E*-22a**, 1.7:1[a] [24%][c]
3	**23**	Toluene:HOAc (4:1)	80	***Z*-22b**:***E*-22b**, 1.6:1[a] [28%][c]
4	**8a**	CF_3CH_2OH:HOAc (4:1)	80	***Z*-22a**:***E*-22a**, 7.1:1 [23%][c]
5	**8a**	CF_3CH_2OH	80	***Z*-22a**:***E*-22a**, 5:1 [47%][c]
6	**8a**	CF_3CH_2OH	r.t.[d]	***Z*-22a** [57%][c]

Reaction conditions: **21a** (0.3 mmol), **8a** (or **23**) (0.36 mmol), $Pd(OAc)_2$ (0.015 mmol), solvent (3mL, 0.1M) at the specified temperature for 24 h. under N_2 atm. [a] Ratio from ^{1}H NMR [b] Conversion calculated from ^{1}H NMR [c] Isolated yield (SiO_2) [d] r.t. about 20 °C.

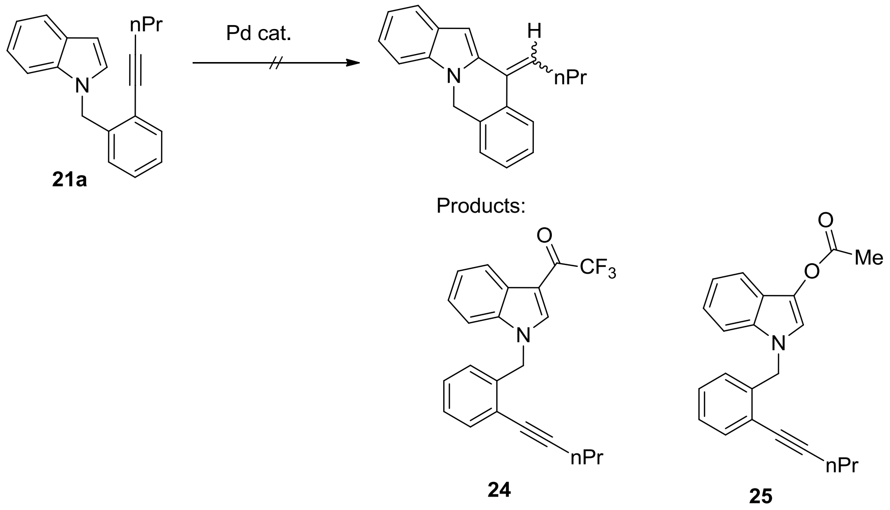


Scheme 3.1.14. X-ray structure of **Z-22b**. Thermal ellipsoids at 50% probability.

Surprisingly, reaction in trifluoroethanol was also successful at r.t. affording exclusively the *Z* isomer as a white crystalline solid in 57% yield (Table 3.1.7, entry 6).

The annulation reaction in the absence of diaryliodonium salts failed to happen (Table 3.1.8). Use of Fujiwara´s conditions[1] for arylation of propionic alkynes did not work and Friedel-Crafts reaction was observed when using trifluoroacetic acid (entry 4).[27, 28] Using oxidants in the reaction trying to mimic the diaryliodonium salt

Table 3.1.8. Attempts to obtain the cyclised product in the absence of diaryliodonium salts.



Entry	*Pd cat.* (*mol%*)	*ArX*	*Ligand* (*mol %*)	*Oxidant*	*Base*	*Solvent*	*T* (^{o}*C*)	*Results*
1	$Pd(OAc)_2$ (5)	-	-	-	-	CF_3CH_2OH (0.1 M)	80	n.r.[a]
2	$Pd(OAc)_2$(5)	-	-	-	-	Toluene:HOAc (4:1) (0.1 M)	100	n.r.[a]
3	$Pd(OAc)_2$ (10)	-	-	-	-	HOAc (0.2M)	r.t.[b]	n.r.[a]
4	$Pd(OAc)_2$ (10)	-	-	-	-	CH_2Cl_2:TFA, 3:1 (0.2M)	r.t.[b]	**24** [15%][c]
5	$Pd(CNMe)_4(BF_4)_2$ (5)	-	-	-	-	CF_3CH_2OH (0.1 M)	r.t.[b]	n.r.[a]

6	$Pd(OAc)_2$(5)	-	-	$Cu(OAc)_2$ (1 eq.)	-	CH_2Cl_2 (0.1 M)	r.t.^{b}	n.r.^{a}
7	$Pd(OAc)_2$(5)	-	-	BQ (1 eq.)	-	CH_2Cl_2 (0.1 M)	r.t.^{b}	n.r.^{a}
8	$Pd(OAc)_2$(5)	-	-	$PhI(OAc)_2$ (1 eq.)	-	CH_2Cl_2 (0.1 M)	r.t.^{b}	**25** [18%]^c
9	$Pd(OAc)_2$ (5)	PhI	PPh_3, (10)	-	-	Toluene (0.1M)	100	n.r.^{a}
10	$Pd(OAc)_2$ (5)	PhI	-	-	-	CF_3CH_2OH (0.1 M)	r.t.	n.r.^{a}
11	$Pd(OAc)_2$ (5)	-	di-Prpf, (7)	-	-	Toluene (0.5 M)	120	n.r.^{a}
12	$Pd(OAc)_2$ (5)	*p*Me PhBr	di-Prpf, (7)	-	DABCO (2 eq.)	NMP (0.5 M)	120	traces **22b**

Reaction conditions: **21a** (0.3 mmol), ArX (0.36 mmol), Pd cat. (0.015 to 0.03 mmol), solvent (3mL, 0.1M) at the specified temperature for 24 h. under N_2 atm. ^{a} n.r. = no reaction, starting material recovered ^{b} r.t. about 20 ^oC ^{c} Isolated yield (SiO_2).

oxidant effect did not work either (entries 6 to 8). In the case of using diacetoxyiodobenzene, acetylation could be observed in the 3-indole position (entry 8). No reaction either took place when using iodobenzene as arylating agent and when Gevorgyan's *o*-alkynylbyaryls annulation conditions[29] were tried (Chapter 1, pg. 19) no different product was observed in the absence of an arylating agent (entry 11), however traces of the expected product were found under their tetra-substituted olefins approach when *p*-bromotoluene and DABCO were present in the mixture (entry 12).

It was clear at this point that the diaryliodonium salt is playing a critical role in the tandem reaction. The next step was to study a wide range of conditions in order to improve yields. To accelerate the optimisation study, reactions were analysed by HPLC/MS using methylbenzoate as internal standard to provide accurate HPLC yields. Firstly, several palladium catalysts were tried in the reaction in CF_3CH_2OH at r.t., as under these mild conditions only the *Z*-isomer was obtained. Other palladium catalyst as $Pd(MeCN)_2Cl_2$, $Pd(C_5H_7O_2)_2$ and cationic palladium catalyst $Pd(NCMe)_4(BF_4)_2$ also performed well in the reaction (Table 3.1.9, entries 6-8).

Bulky catalysts showed no activity, the same happened with other metal catalysts as $FeCl_2$, $Rh(C_5H_7O_2)$ and $Ir(C_5H_7O_2)$ (Table 3.1.9, entries 10-13). No reaction took place either in the absence of catalyst.

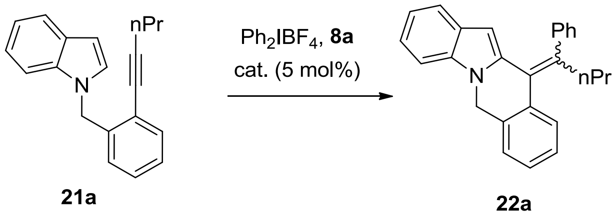
No big changes were observed in the reaction conversion when concentration was varied between 0.02 M and 0.5 M, with 0.1 M the concentration giving better yields. The same happened with the amount of diphenyliodonium tetrafluoroborate used in the reaction, several amounts were used in the reaction between 1 and 5 equivalents. The reaction turned out to be messier when using more than 1.5 eq. and best yields were obtained when the amount of iodonium salt was kept between 1 and 1.2 eq.

On the other hand, more noticeable yield improvements could be observed when testing several ligands in the reaction. Low yields were obtained when using phosphine ligands except in the case of the bulkier $P(o\mathrm{Tol})_3$ ligand (entries 14-16). No improvement was noticed when using nitrogen ligands as 1,10-phenanthroline and 3-ethyl nicotinate, however the use of carbene ligands Mes.HCl and especially the imidazolinium derivative SIMes.HCl in the presence of 1 eq. of LiO^tBu gave better yields (entries 17-20). Carbene ligands are strong σ-donors[30] which have been used in other palladium-catalysed C-H activation processes[22, 31] and in the hydroarylation of alkynes.[32] A base screening gave an improvement in yields when using NaO^tBu or Cs_2CO_3.[33] Slightly better yields were obtained when the reaction was done using moisture free ligand, base and iodonium salt.

When heating up the reaction, mixtures of *E*/*Z* products could be detected from 50 °C, however at 30 °C the *Z* isomer could still be selectively obtained and the reaction was quicker and cleaner using just a slightly excess of the iodonium salt (1.05 eq.) leading to ***Z*-22a** in an improved 78% yield in 8 h (entry 24).

Finally, a solvent screening established MeCN as the best choice, product could be obtained in only 2h in 93% yield. Also, an excellent yield was obtained when using CH_2Cl_2 as solvent but in this case a mixture of the two isomers was obtained. This mixture was purified through a SiO_2:$AgNO_3$ (10%)[34] column to get a small portion of the clean ***E*-22a** isomer, and the structure was confirmed by a NOESY NMR experiment (Scheme 3.1.15).

Table 3.1.9. Optimisation of palladium-catalysed reaction of **21a** with diphenyliodonium tetrafluoroborate, **8a**.

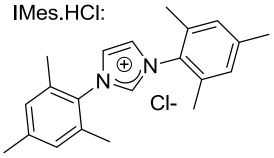


Entry	*Pd cat.* *(5 mol%)*	*8a (eq.)*	*Ligand (mol%)*	*Base (eq.)*	*Solvent (0.1M)*	*T (°C)*	*t (h)*	*Results*
1	$PdCl_2$	1.2	-	-	CF_3CH_2OH	r.t.[a]	24	Traces
2	$PdCl_2(CNPh)_2$	1.2	-	-	CF_3CH_2OH	r.t.[a]	24	**Z-22a** [40%][c]
3	$PdCl_2(PPh_3)_2$	1.2	-	-	CF_3CH_2OH	r.t.[a]	24	n.r.[d]
4	$Pd_2(dba)_3$	1.2	-	-	CF_3CH_2OH	r.t.[a]	24	**Z-22a** [10%][c]
5	PEPPSI	1.2	-	-	CF_3CH_2OH	r.t.[a]	24	**22a** (9)[b]
6	$PdCl_2(MeCN)_2$	1.2	-	-	CF_3CH_2OH	r.t.[a]	24	**Z-22a** [47%][c]
7	$Pd(C_5H_7O_2)_2$	1.2	-	-	CF_3CH_2OH	r.t.[a]	24	**Z-22a**:***E*-22a**, 8:1[e] [55%][c]
8	$Pd(CNMe)_4(BF_4)_2$	1.2	-	-	CF_3CH_2OH	r.t.[a]	24	**Z-22a**:***E*-22a**, 8.3:1[e] [53%][c]
9	Pdallyl[f]	1.2	-	-	CF_3CH_2OH	r.t.[a]	24	n.r.[d]
10	$FeCl_2$	1.2	-	-	CF_3CH_2OH	r.t.[a]	24	n.r.[d]
11	Rh (I) dimer[g]	1.2	-	-	CF_3CH_2OH	r.t.[a]	24	n.r.[d]
12	$Rh(C_5H_7O_2)_2$	1.2	-	-	CF_3CH_2OH	r.t.[a]	24	n.r.[d]
13	$Ir(C_5H_7O_2)_2$	1.2	-	-	CF_3CH_2OH	r.t.[a]	24	n.r.[d]
14	$Pd(OAc)_2$	1.2	PPh_3 (10)	-	CF_3CH_2OH	25	24	**22a** (12%)[b]
15	$Pd(OAc)_2$	1.2	dppe (10)	-	CF_3CH_2OH	25	24	**22a** (17%)[b]
16	$Pd(OAc)_2$	1.2	P(*o*Tol)$_3$ (10)	-	CF_3CH_2OH	25	24	**22a** (52%)[b]
17	$Pd(OAc)_2$	1.2	1,10-phen (10)	-	CF_3CH_2OH	25	24	**22a** (26%)[b]
18	$Pd(OAc)_2$	1.2	3-ethyl nicotinate (10)	-	CF_3CH_2OH	25	24	**22a** (35%)[b]
19	$Pd(OAc)_2$	1.2	IMes. HCl(10)	LiO^{t}Bu (1 eq.)	CF_3CH_2OH	r.t.[a]	24	**Z-22a** [46%][c]

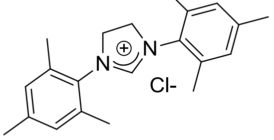
20	$Pd(OAc)_2$	1.2	SIMes.HCl, (10)	LiO^tBu (1 eq.)	CF_3CH_2OH	r.t.[a]	24	**Z-22a** [59%][c]
21	$Pd(OAc)_2$	1.2	SIMes.HCl, (10)	NaO^tBu (1 eq.)	CF_3CH_2OH	r.t.[a]	24	**Z-22a** (65%)[b]
22	$Pd(OAc)_2$	1.2	SIMes.HCl, (10)	KOAc	CF_3CH_2OH	r.t.[a]	24	**Z-22a** (40%)[b]
23	$Pd(OAc)_2$	1.2	SIMes.HCl, (10)	Cs_2CO_3 (1 eq.)	CF_3CH_2OH	r.t.[a]	24	**Z-22a** [62%][c]
24	$Pd(OAc)_2$	1.05	SIMes.HCl, (10)	Cs_2CO_3 (1 eq.)	CF_3CH_2OH	30	8	**Z-22a** [78%][c]
25	$Pd(OAc)_2$	1.05	SIMes.HCl, (10)	Cs_2CO_3 (1 eq.)	MeOH	30	24	**Z-22a** [79%][c]
26	$Pd(OAc)_2$	1.05	SIMes.HCl, (10)	Cs_2CO_3 (1 eq.)	DCE	30	24	**Z-22a**: ***E*-22a**, 1.3:1[e] [63%][c]
27	$Pd(OAc)_2$	1.05	SIMes.HCl, (10)	Cs_2CO_3 (1 eq.)	CH_2Cl_2	30	3	**Z-22a**: ***E*-22a**, 3:1[e] [92%][c]
28	$Pd(OAc)_2$	1.05	SIMes.HCl, (10)	Cs_2CO_3 (1 eq.)	MeCN	30	2	**Z-22a** [93%][c]
29	$Pd(OAc)_2$	1.05	SIMes.HCl, (10)	Cs_2CO_3 (1 eq.)	PhCl	30	2	**Z-22a** [86%][c]
30	$Pd(OAc)_2$	1.05	SIMes.HCl, (10)	-	MeCN	30	24	**Z-22a** [53%][c]
31	$Pd(OAc)_2$	1.05	-	Cs_2CO_3 (1 eq.)	MeCN	30	2	**Z-22a** [52%][c]

Reaction conditions: **21a** (0.3 mmol), **8a** (0.36 mmol or 0.32 mmol), $Pd(OAc)_2$ (0.015 mmol), solvent (3mL, 0.1M) at the specified temperature for 24 h (or specified time) under N_2 atm. [a] r.t. about 20 ^{o}C [b] HPLC yield [c] Isolated yield (SiO_2) [d] n.r.= no reaction, starting material recovered [e] Ratio from ^{1}H NMR [f] Allyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]Pd(II) [g] Chloro(1,5-cyclooctadiene)rhodium(I) dimer.

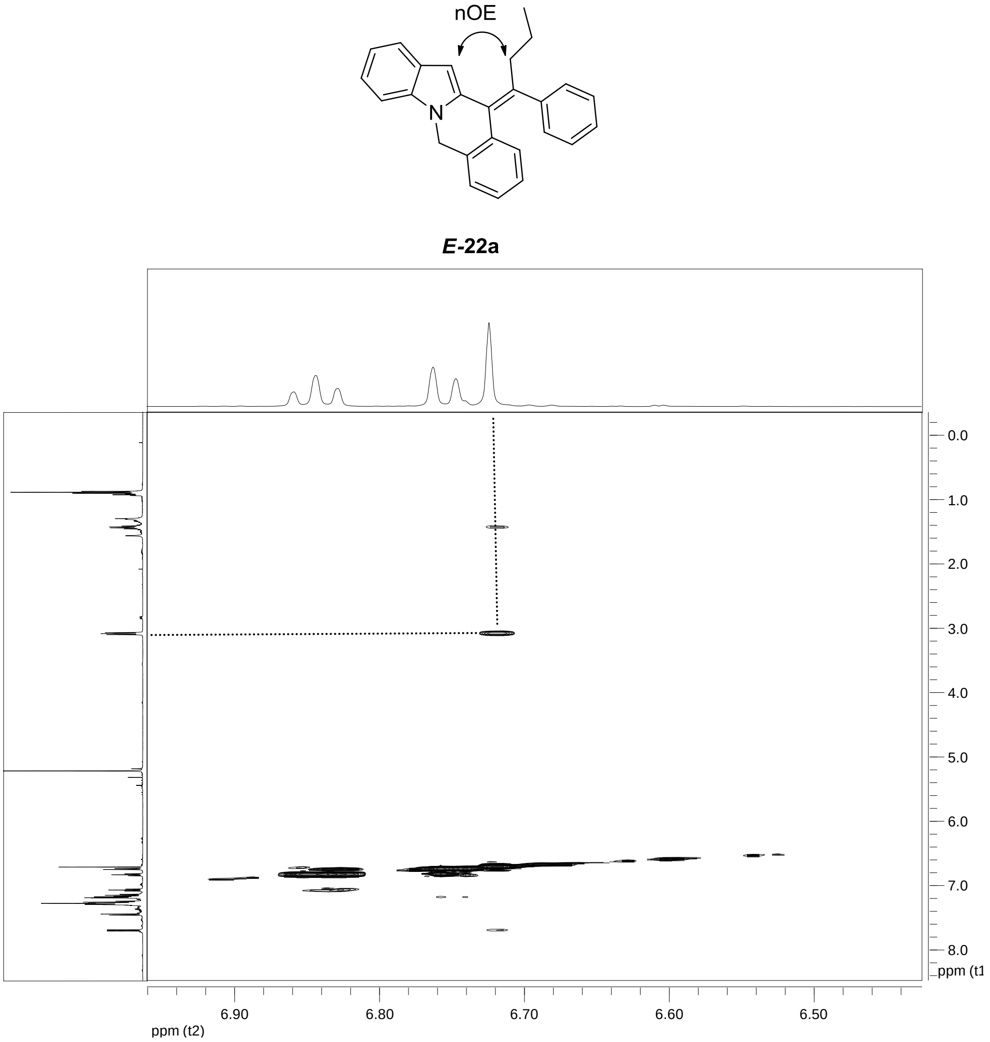
IMes.HCl:



SIMes.HCl:



Both base and ligand needed to be present in the reaction in order to obtain full conversion and good yields (entries 30 and 31). Different palladium loading was also studied in the reaction and best yields were obtained when using a 5 mol% loading. A ratio between the catalyst and ligand of $Pd(OAc)_2$:SIMes.HCl, 1:2 gave the best results when 1 eq. of Cs_2CO_3 was used. However the reaction with a 1:1 ratio also worked well with only slightly lower yield, so it is not clear if a monocarbene-palladium or a dicarbene-palladium complex is being formed. Although monocarbene complexes are thought to be more reactive,[30] hydroarylation of alkynes with heterocycles using dicarbene-palladium catalysts has also been reported.[35]

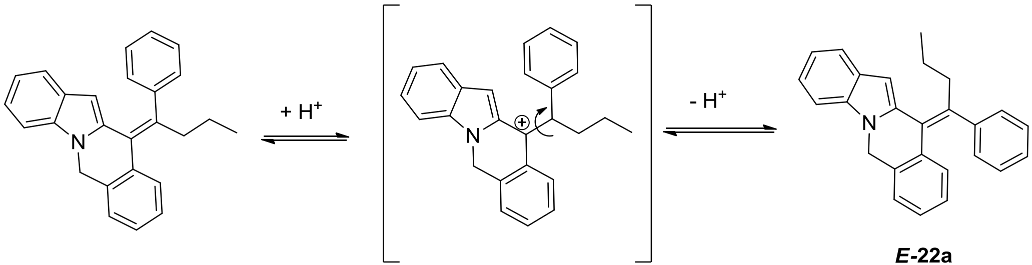


***E*-22a**

Scheme 3.1.15. ^{1}H NOESY NMR confirmation of ***E*-22a** structure.

With an optimised process in hand, the scope of the reaction was studied next (Table 3.1.10). 2-Ethynylbenzyl indoles were synthesised according the general steps showed in Scheme 3.1.13 (pg. 109). When performing the reaction using the 5-methoxyindole derivative **21b**, a lower yield was obtained in MeCN, whilst a good yield was still obtained in trifluoroethanol (83%) and chlorobenzene (88%), so chlorobenzene was chosen as the solvent to be used in general as its results seemed more reproducible.

Whilst only *Z*-isomer was observed in the crude of the reaction with **21b** (^{1}H NMR) some isomerisation could be seen after silica purification. To avoid that happening, the crude was adsorbed in SiO_2 + 3% NEt_3 just after filtration and purified through SiO_2 + 3% NEt_3. In these neutral conditions and keeping the water bath at 30 ^{o}C when evaporating solvent under vacuum it was possible to isolate the single ***Z*-22c** isomer. However, double bond isomerisation appeared to be very easy in solution and *Z/E* equilibration could be observed in $CDCl_3$ NMR samples in the course of a day. Once the *Z*-isomer was isolated as a white solid, however, it was very stable, showing no decomposition or interconversion after several months kept in a freezer. To establish whether the *Z*-selectivity was intrinsic to the reaction, exposure of a 2:1 *Z*/*E* mixture of **22a** to the precatalyst optimised reaction conditions in chlorobenzene gave no change in the isomer ratio over 24 h, indicating that the *Z*-isomer could be the kinetic product of the reaction and the easy *Z/E* interconversion observed in some solvents and when heating up the reaction could be explained due to the facile



Scheme 3.1.16. Possible mechanism for the *Z/E* alkene isomerisation in **22a**.

production of a tertiary cation, stabilised by both aromatic groups, indole and its benzyl substituent (Scheme 3.1.16).

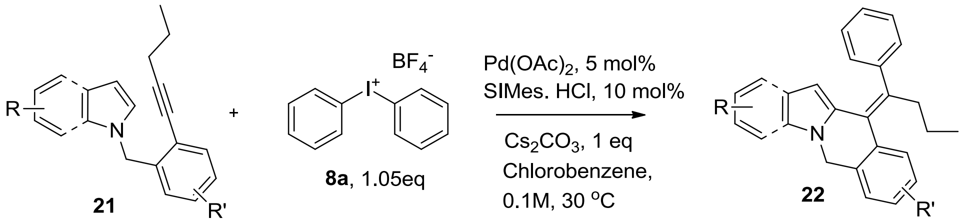
The use of the optimised mild conditions in different substituted indoles afforded the *Z*-isomer in most of the cases. The reaction worked well when using 3-methyl indole (entry 2). However, it did not work when using the carboxaldehyde substituent; this could be due either to its electron-withdrawing character or to steric impedance. When the reaction was heated up, low conversion could be detected but clean products could not be isolated. The same happened when using nitro substituents in the indole ring, suggesting that electron poor indoles are not good substrates, though a 5-ester derivative afforded the product in moderate yield albeit the reaction was not completed after 30 h reaction (entry 7).

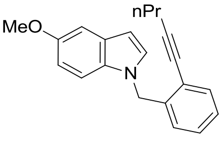
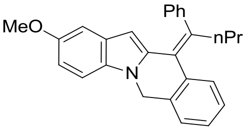
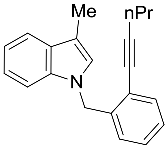
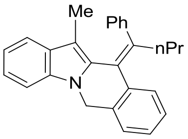
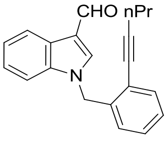
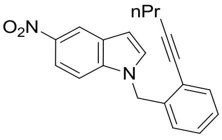
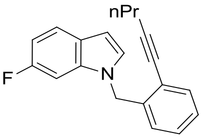
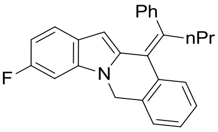
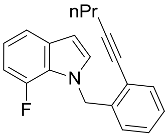
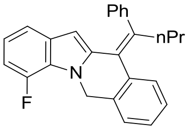
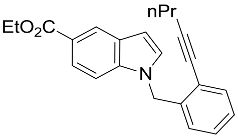
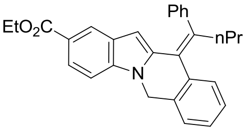
Surprisingly, no reaction happened when using the 7-azaindole derivative (entry 8). This could be explained if the two neighbor nitrogen atoms coordinate the palladium catalyst poisoning it for further reactivity.

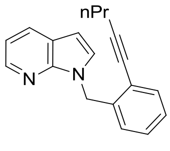
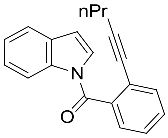
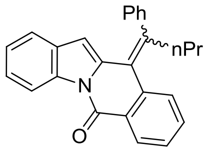
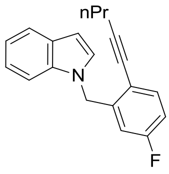
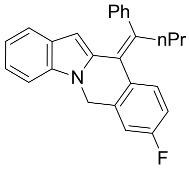
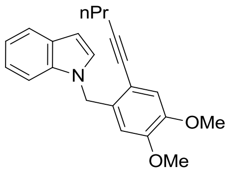
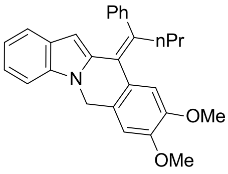
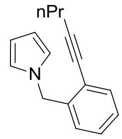
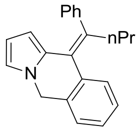
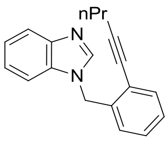
Unexpected reactivity was also detected when the benzoyl *N*-substituent was submitted to the reaction conditions. The reaction rate at 30 ^{o}C was very slow. When heating the reaction at 50 ^{o}C, 48h were needed for full conversion. Unfortunately, under these conditions the reaction turned messy and only 46% of the desired product could be isolated as an inseparable mixture of *E*/*Z* isomers (entry 9). Substituents in the benzyl ring were well tolerated, despite only a moderate yield was achieved in the case of the 3-fluoroderivative (entry 10).

Pleasingly, pyrrole could also be used in the reaction, and it was so reactive that the temperature had to be kept below 20 ^{o}C to obtain the product as a single isomer in a good 70% yield. On the other hand, benzimidazole did not react under these conditions.

Table 3.1.10. Scope of the tandem annulation/arylation reaction, indole and benzyl substituents.



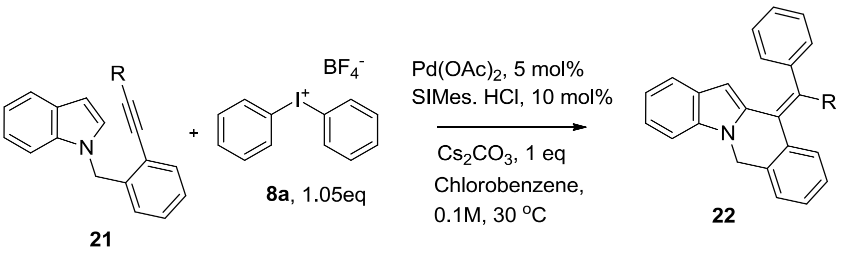
Entry	*Starting Material*	*t (h)*	*Product*	*Yield*[a]
1	 **21b**	4	 **22c**	88%
2	 **21c**	6	 **22d**	76%
3	 **21d**	48	n.r.[b]	0%
4	 **21e**	30	n.r.[b]	0%
5	 **21f**	7	 **22e**	78%
6	 **21g**	24	 **22f**	54%
7	 **21h**	30	 **22g**	52%

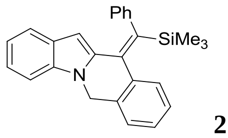
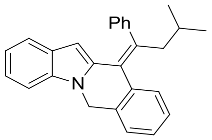
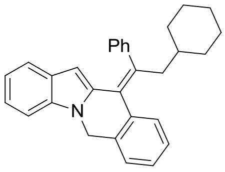
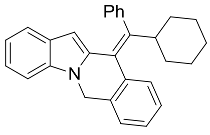
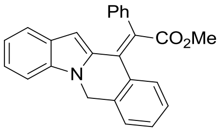
8	 **21i**	30	n.r.^{b}	0%
9^{c}	 **21j**	48	 *Z*-**22h**:*E*-**22h** (1:1.6)^{d}	46%
10	 **21k**	36	 **22i**	49%
11	 **21l**	7	 **22j**	78%
12^{e}	 **21m**	4	 **22k**	70%
13	 **21n**	36	n.r.	0%

Reaction conditions: **21** (0.3 mmol), **8a** (0.32 mmol), $Pd(OAc)_2$ (0.015 mmol), SIMes.HCl (0.03mmol), Cs_2CO_3 (0.3 mmol), chlorobenzene (3 mL). [a] Isolated yield (SiO_2+3% NEt_3), [b] n.r.= no reaction, starting material recovered, [c] T=50°C [d] Ratio from ^{1}H NMR [e] T=15-18°C.

Further changes in the alkyne substituent were then studied (Table 3.1.11). Lamentably, reaction with the free alkyne was very messy and although the desired product mass could be detected by HPLC/MS it was not possible to obtain the clean compound after purification. On the other hand, aliphatic substituents worked well, as expected, under the optimised experimental conditions (except in the case of the *N*, *N*-dimethylpropyne derivative, Table 3.1.11., entry 4). The propionate derivative gave also the tetra-substituted *Z*-olefin, with the proton in the 3-indole position resonating at 5.63 ppm in ^{1}H NMR, proving the high selectivity of the process.

Table 3.1.11. Scope of the tandem annulation/arylation reaction with different alkyne substituents.



Entry	*R*	*t (h)*	*Product*	*Yield*[a]
1	H, **21o**	6	Complex mixture	-
2	$SiMe_3$, **21p**	36	 **22l**	42%
3	$CH_2CH(CH_3)_2$, **21q**	7	 **22m**	68%
4	$CH_2N(CH_3)_2$, **21r**	36	n.r.[b]	0%
5	$CH_2(C_6H_{11})$, **21s**	8	 **22n**	71%
6	(C_6H_{11}), **21t**	15	 **22o**	71%
7	CO_2Me, **21u**	4	 **22p**	79%
8	*p*-MeC_6H_4, **21v**	36	Complex mixture	-

Reaction conditions: **21** (0.3 mmol), **8a** (0.32 mmol), $Pd(OAc)_2$ (0.015 mmol), SIMes.HCl (0.03mmol), Cs_2CO_3 (0.3 mmol), chlorobenzene (3 mL) [a] Isolated yield (SiO_2+3% NEt_3), [b] n.r. = no reaction, starting material recovered.

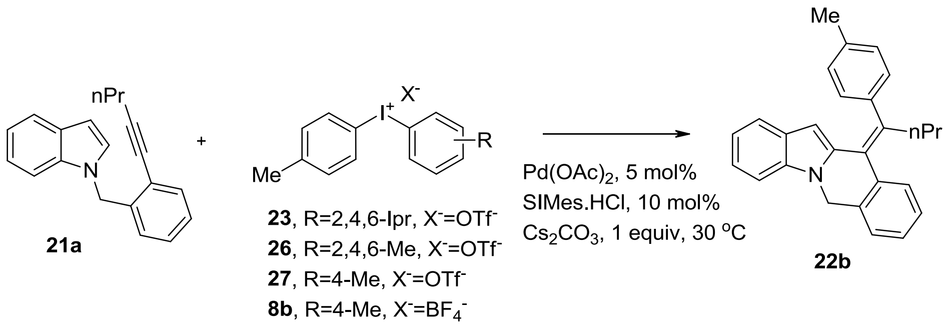
The reaction was messy when using aromatic substituents in the alkyne, in the case of 4-methylphenyl (entry 8) although the desired product could be detected, it was not possible to obtain it pure. Gevorgyan's conditions[29] on this substrate failed to give the annulated product in the absence of an aryl halide; however when PhBr and DABCO were present in the reaction at 120 °C the starting material was consumed after 12h to afford the tandem annulated/arylated product as a mixture of *E*/*Z* isomers, but no pure compound could be isolated as contained inseparable impurities.

When using different iodonium salts in the reaction other than diphenyliodonium tetrafluoroborate, the unsymmetrical, easily synthesised (4-methylphenyl)(2,4,6-triisopropylphenyl)iodonium triflate,[36] **23**, was first used with the successful **21a** substrate. Unexpectedly, its use in acetonitrile gave no reaction, while reaction was slow in trifluoroethanol giving a 50% of the desired product after 24h, slightly better yield was obtained under the optimised conditions using chlorobenzene as solvent, despite not giving full conversion either and being also quite slow. Changing the bulky triisopropyl substituents for 2,4,6-trimethyl led to an improvement in yield and conversion. However a more dramatic change could be seen when using symmetrical salts and no change in reactivity was observed between the tetrafluoroborate and triflate counteranions (Table 3.1.12, entries 5 and 6).

These good results encouraged us to examine the scope of symmetrical diaryliodonium salts, easily synthesized by the one-pot processes developed by Olofsson and co-workers.[37]

As with the para-methylphenyl, the use of di(ortho-methylphenyl)iodonium tetrafluoroborate gave the desired annulated product in good yield (Table 3.1.13, entry 1). The electron donating methoxy substituent worked well, but a mixture of inseparable *E*/*Z* isomers was obtained in this case, as well as when the aryl used was 2-thiophene, albeit in lower yield (entries 2 and 3).

Table 3.1.12. Exploring diaryliodonium salts in the reaction.



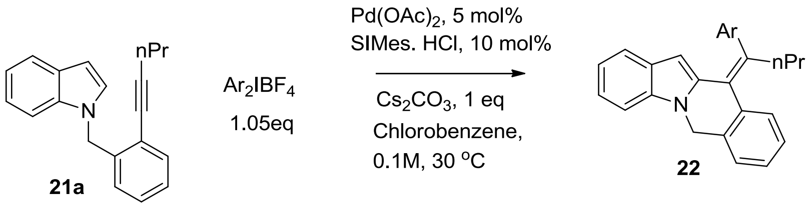
Entry	*Ar$_2$IX (1.05 eq.)*	*Solvent (0.1 M)*	*t (h)*	**Yield 22b**[a]
1	**23**	MeCN	24	n.r.[b]
2	**23**	CF_3CH_2OH	24	50%
3	**23**	Chlorobenzene	24	69%
4	**26**	Chlorobenzene	24	75%
5	**27**	Chlorobenzene	2	90%
6	**8b**	Chlorobenzene	2	90%

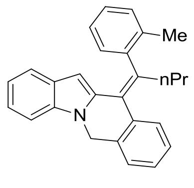
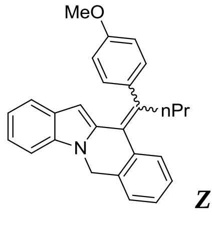
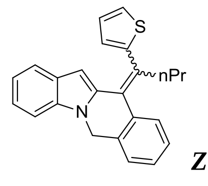
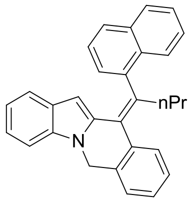
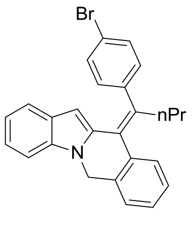
Reaction conditions: **21a** (0.3 mmol), Diaryl iodonium salt (0.32 mmol), $Pd(OAc)_2$ (0.015 mmol), SIMes.HCl (0.03mmol), Cs_2CO_3 (0.3 mmol), chlorobenzene (3 mL) [a] Isolated yield (SiO_2+3% NEt_3), [b] n.r.= no reaction, starting material recovered.

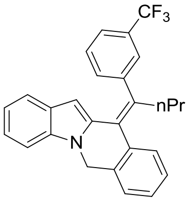
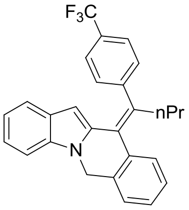
The bulkier 1-naphtyl derivative could be also used in the reaction but no full conversion was achieved. However, the use of para-bromo, para-trifluoromethyl and even meta-trifluoromethyl substituents in the phenyl ring performed very well in the tandem reaction (Table, 3.1.13, entries 5 to 7).

Further changes were made to the substrate structure in order to analyse the reaction's scope and selectivity. *N*-phenyl substituted indole derivatives were synthesised following the copper-catalysed method described by Verma and Larock (Scheme 3.1.17).[38] In a later paper, the copper-catalysed reaction with a benzotriazole based ligand is used for the synthesis of indolo[2,1*a*]isoquinolines in a tandem process from indoles and bromoarylalkynes (Scheme 3.1.18).[39]

Table 3.1.13. Scope of the tandem annulation/arylation reaction, with different diaryliodonium salts.



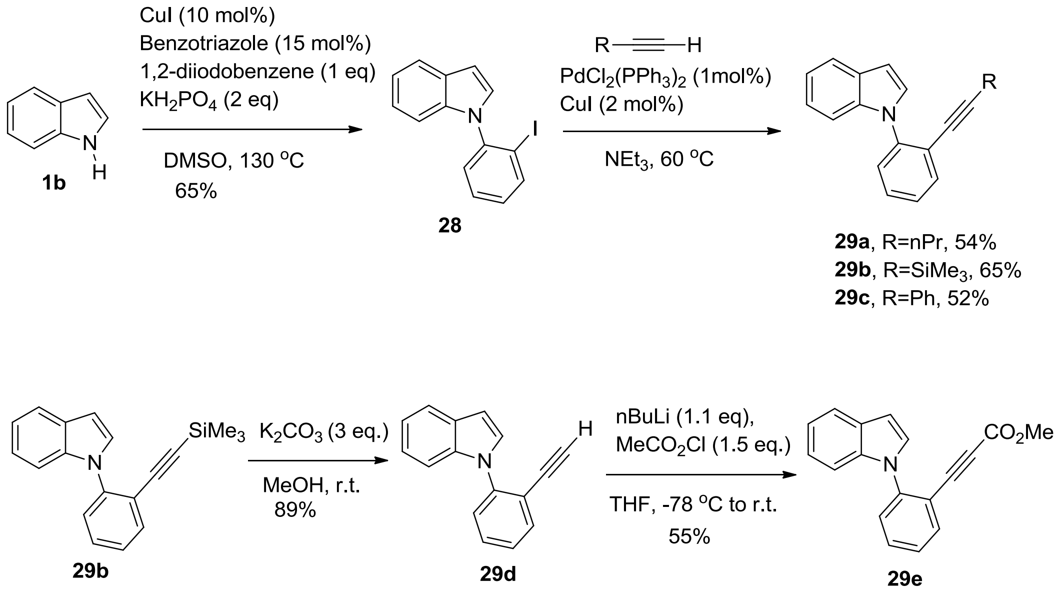
Entry	*Ar*	*t (h)*	*Product*	*Yield*[a]
1	2-Me, **8c**	3	 **22q**	83%
2	4-OMe, **8d**	3	 ***Z*-22r**:***E*-22r** (1:2)[b]	75%
3	2-thionyl, **8e**	3	 ***Z*-22s*E*-22s** (1:1.9)[b]	51%
4	1-naphtyl, **8f**	8	 **22t**	50%
5	4-Br, **8g**	4	 **22u**	81%

6	3-CF_3, **8h**	3	 **22v**	86%
7	4-CF_3, **8i**	2	 **22w**	88%

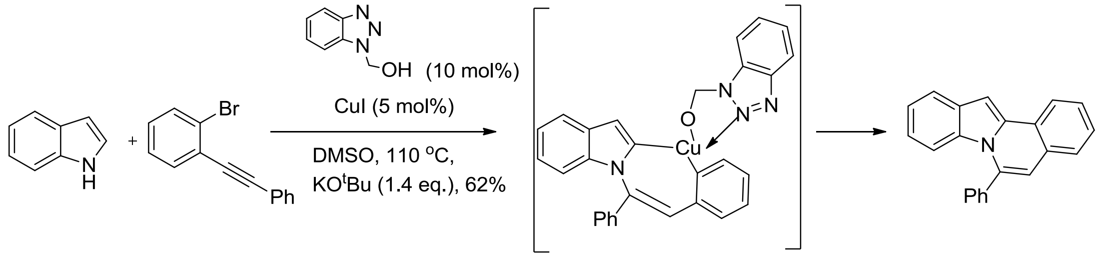
Reaction conditions: **21a** (0.3 mmol), Diaryl iodonium salt (0.32 mmol), $Pd(OAc)_2$ (0.015 mmol), SIMes.HCl (0.03mmol), Cs_2CO_3 (0.3 mmol), chlorobenzene (3 mL) [a] Isolated yield (SiO_2+3% NEt_3).

Applying the established method, the palladium-catalysed reaction of diphenyliodonium tetrafluoroborate with the 2-ynylphenylindole derivatives should afford the tetra-substituted olefin in a 5-*exo*-dig fashion, contrary to the 6-*endo* selectivity observed in Larock's process.

When **29a** was treated under the usual reaction conditions with diphenyliodonium tetrafluoroborate at 30 ^oC the reaction stopped at 50% conversion and no further conversion was achieved even if the reaction was left for longer. Increasing the temperature to 50 ^oC allowed the reaction to advance until completion and the desired product was obtained in 78% yield as a bright yellow solid after 15 h. The 5-*exo*-dig *Z*-alkene structure was assumed as the 3-indole proton resonated at 5.14 ppm by ^1H NMR. Indicating it was pointing to the shielded zone of the introduced phenyl ring (Table 3.1.14., entries 1 and 2).



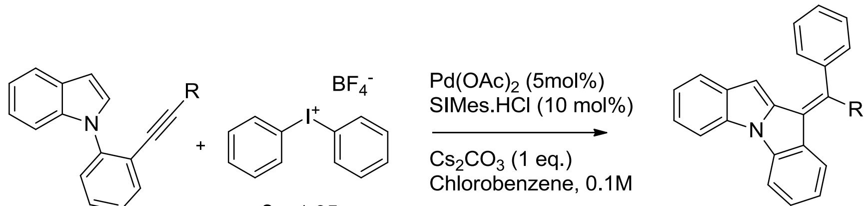
Scheme 3.1.17. Synthesis of 2-ynylphenylindole derivatives.



Scheme 3.1.18. Larock's copper-catalysed tandem hydroamination/direct arylation process.[39]

The reaction also worked well with trimethylsilyl as the alkyne substituent, when it was carried at 50 °C. Although the reaction was again very messy with the phenylacetylene derivative, **29c**, on this occasion the clean 5-membered ring product could be obtained in moderate yield. On the other hand the reaction with the free alkyne resulted also in a complex mixture and unfortunately no pure product could be isolated. Finally, the propiolate example selectively produced the *Z*-isomer 5-*exo*-dig product in good yield (entry 5).

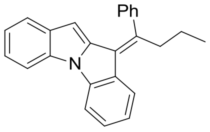
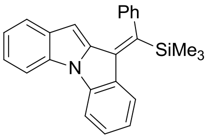
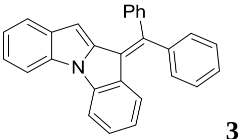
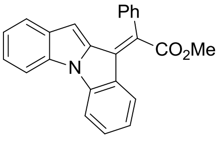
Table 3.1.14. Palladium-catalysed tandem annulation/arylation reaction with 2-ynylphenylindoles.



8a, 1.05 eq.

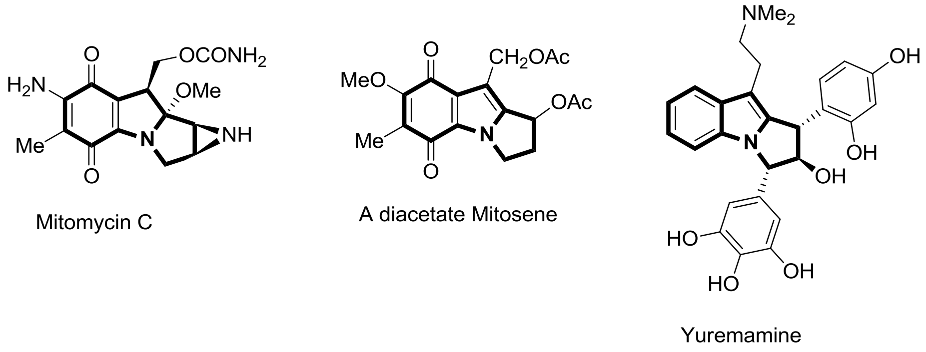
30

29a, R=nPr
29b, R=SiMe$_3$
29c, R=Ph
29e, R=CO$_2$Me

Entry	R	T (°C)	t (h)	Product	Yield[a]
1	nPr	30	24	 **30a**	50% conversion[b]
2	nPr	50	15	**30a**	78%
3	SiMe$_3$	50	24	 **30b**	67%
4	Ph	50	24	 **30c**	47%
5	CO$_2$Me	50	15	 **30d**	79%

Reaction conditions: **29** (0.3 mmol), **8a** (0.32 mmol), Pd(OAc)$_2$ (0.015 mmol), SIMes.HCl (0.03mmol), Cs$_2$CO$_3$ (0.3 mmol), chlorobenzene (3 mL), [a] Isolated yield (SiO$_2$+3% NEt$_3$) [b] Conversion calculated from ^{1}H NMR.

The synthesis of these products is of special importance as they contain the pyrrolo[1,2*a*]indole skeleton which is present in a large number of biologically active compounds. Mitomicyn alkaloids, particularly Mitomicyn C, are known for their antitumor activity.[40] Other compounds containing a mitosene skeleton have also shown activity against cancer.[41] Another example is Yuremamine, a phytoindole alkaloid which contains dimethyl tryptamine in its structure and has shown psychoactive effects[42] (Scheme 3.1.19).



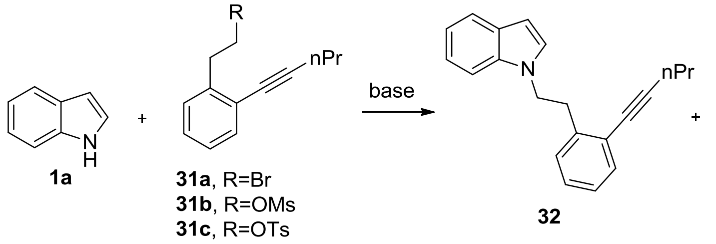
Scheme 3.1.19. Structure of biologically active compounds containing pyrrolo[1,2*a*]indole skeleton.

With the intention to discover if it was possible to obtain larger rings, the synthesis of an ethyl phenylindole derivative was attempted. Unfortunately, the usual synthesis from 2-(pent-1-ynylphenyl)-ethanol did not work as the indole *N*-alkylation with the corresponding bromide only afforded the elimination product **33** and no the alkylated product (Table 3.1.15, entry 1). Other alkylation procedures were tried as exposed in Table 3.1.15.

Phase-transfer procedures using TBAB[43, 44] failed to give a significant amount of alkylated indole, while small amounts of the product were obtained using a weaker base as Cs_2CO_3[45] having better results with the tosylated derivative rather than the mesilated one. Finally, the reaction of indole in the presence of KO^{t}Bu and 18-crown-6[44, 46] afforded the alkylated product, albeit in low yield (Table 3.1.15, entry 6).

When sufficient of **32** could finally be synthesised, its reaction with **8a** under the optimised reaction conditions at 50 ^{o}C, afforded the seven member ring product as a single isomer, the 3-indole proton resonating as a singlet at 5.69 ppm by ^{1}H NMR (Scheme 3.1.20).

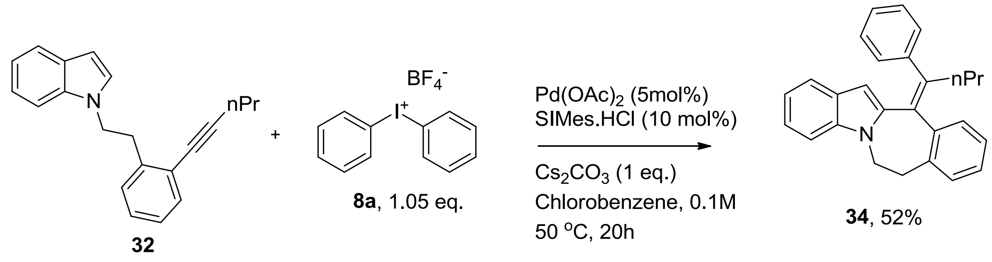
Table 3.1.15. Several indole *N*-alkylation methods for the synthesis of 1-[2-(2-Pent-1ynylphenyl)-ethyl]-*1H*-indole.



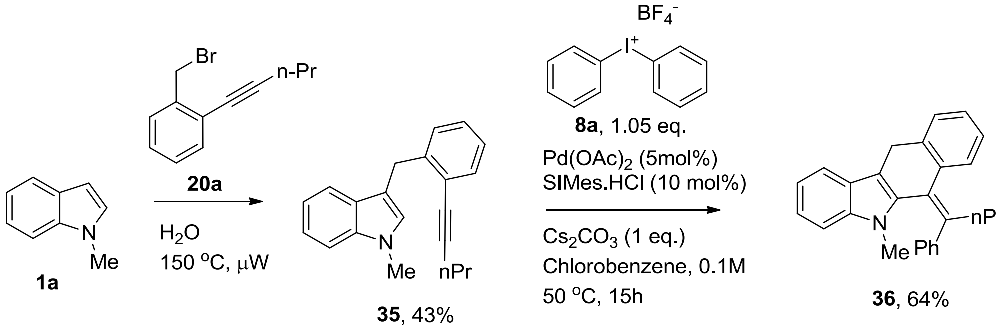
Entry	R (eq.)	Base (eq.)	Additives (eq.)	Solvent (M)	T (^{o}C)	Time (h)	Results
1	Br (1.2)	NaH (1.1)	-	DMF (0.5)	r.t.	a)1 b)3	**33** [89%][a]
2	OMs (1.2)	KOH (6.2)	TBAB (10%)	DMSO (0.8)	r.t.	1	**32** (traces), **33** (40%)[b]
3	OMs (1.2)	NaOH (1.1, 20%aq.)	TBAB (10%)	Toluene (1.8)	r.t.	24	**32** (traces), **33** (33%)[b],
4	OMs (1.5)	Cs_2CO_3 (1.5)	-	DMF (0.6)	r.t.	24	**32** [10%][a], **33** [52%][a]
5	OTs (2)	Cs_2CO_3 (1.5)	-	DMF (0.6)	r.t.	24	**32** [27%][a], **33** [86%][a]
6	OTs (1.1)	KO^{t}Bu (1.1)	18-crown-6 (10%)	Et_2O (0.5)	r.t.	20	**32** [33%][a], **33** [54%][a]

Reaction conditions: **1a** (0.45 mmol), **31** (0.5 mmol). [a] Isolated yield [b] Conversion calculated from ^{1}H NMR.

To further show the high versatility of the tandem reaction a carbazole derivative was formed from the 3-alkylated benzylylidene indole. The 3-alkylation of 1-methyl-*1H*-indole with 2-pent-1-ynylbenzyl bromide was achieved following the microwave Friedel-Crafts reaction described by Soriente and co-workers.[47] Treatment of substrate **35** with **8a** in the presence of a catalytic amount of $Pd(OAc)_2$ afforded the 2,3-annulated indole as a single compound when heating at 50 ^{o}C (Scheme 3.1.21). NOESY ^{1}H NMR showed no relation between *N*-methyl and the propyl group from the alkene, assuming the *Z*-isomer was the only one being formed under these mild conditions.

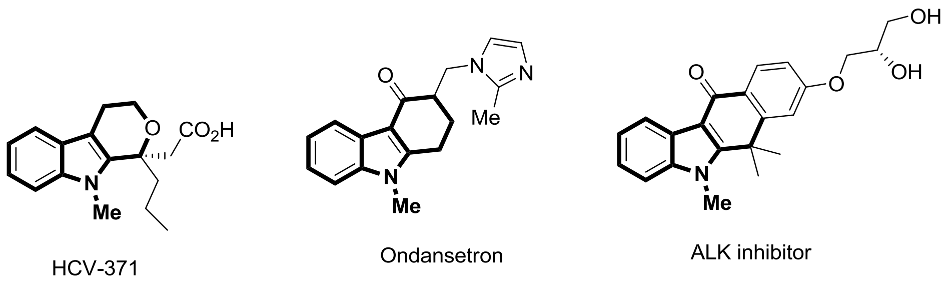


Scheme 3.1.20. Annulation tandem reaction between 1-[2-(2-Pent-1ynylphenyl)-ethyl]-*1H*-indole, **32**, and **8a**.



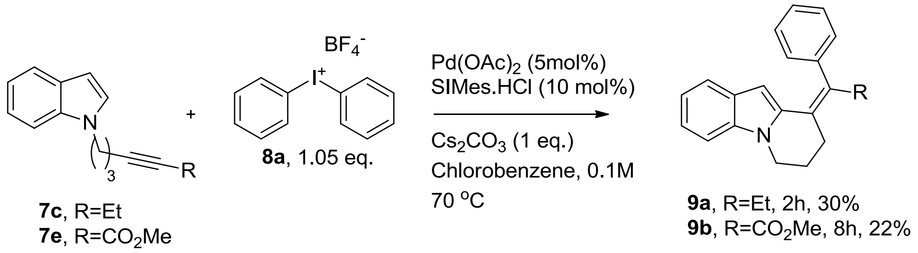
Scheme 3.1.21. Annulation tandem reaction to the synthesis of the carbazole derivative **36**.

The carbazole structure is present in many pharmacologically interesting molecules.[48] Our carbazole derivative is structurally similar to HCV-371: a very recently discovered inhibitor of hepatitis C virus;[49] or to Ondansetron: which belongs to a family of 5-HT$_3$ receptor antagonists with antiemetic activity.[50] A series of related structures have also been reported as anaplastic lymphoma kinase (ALK) inhibitors by Oikawa and co-workers.[51]



Scheme 3.1.22. Examples of carbazole derivatives with important biological activity.

When the optimised conditions were applied to the indole derivatives in which the alkyne was linked to the indole nitrogen through an aliphatic chain, **7b** and **7e**, no reaction took place at 30 or 50 °C. The reaction needed to be heated at 70 °C. At this temperature, total consumption of the starting material happened in a few hours, however only low yields of the expected products were obtained (Scheme 3.1.23). No migration of the double bond was observed probably due to the reaction being quicker, but yields were similarly low as the obtained before, indicating that decomposition may also be happening under these reaction conditions.



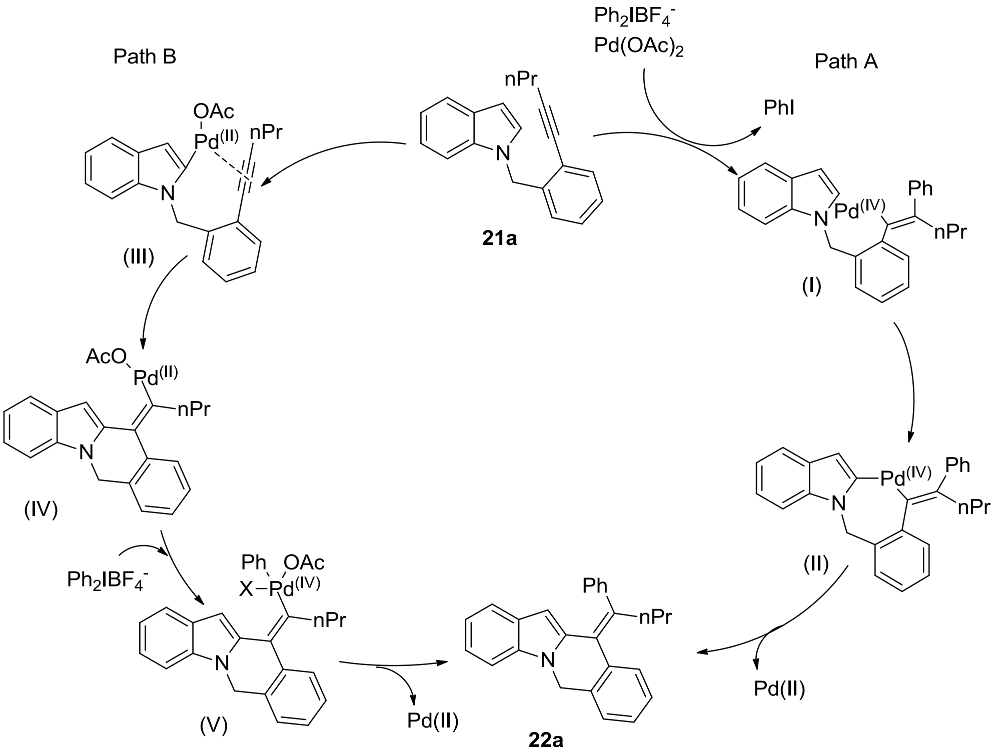
Scheme 3.1.23. Tandem reaction with aliphatic derivatives **7c** and **7e**.

Having studied the palladium-catalysed tandem annulation/arylation reaction between alkyne-tethered indoles and diaryliodonium salts, it can be seen that the reaction allows a broad substrate scope. Complex molecules can be easily synthesised through the formation of two new C-C bonds under mild conditions. Although moderate yields are obtained with some substrates, no significant quantities of byproducts other than starting material or annulated product were detected. In some cases traces (few mg) of other compounds were isolated but their structure could not be determined by NMR analysis, as messy spectra were obtained. However, analysis by HPLC/MS showed high molecular masses, which could be consistent with dimeric structures. Therefore, it is possible that indole-indole or indole-alkene dimeric structures are formed during the reaction and their decomposition may lead to low yields.

The next stage in the investigation was the proposal of a suitable mechanism. Several routes could be contemplated for the reaction, however obtaining the *Z*-isomer in most cases requires a stereoselective path in the formation of the tetra-substituted olefins.

The fact that no reaction is observed in the absence of the iodonium salt suggests that the arylating/oxidating agent is having an important role in the reaction. Although, traces of the annulated product from **21a** were obtained under Gevorgyan's conditions[29] when PhBr was present, no annulation took place without arylating agent (Table 3.1.8, entries 11 and 12).

With this information in hand a first path was suggested (Path A, Scheme 3.1.24) in which alkyne arylation may be happening first and then the vinylpalladium intermediate formed (I) can undergo intramolecular C-H bond activation at the indole 2-position (II).[52] As a iodonium salt is being used, a Pd(II)-Pd(IV) catalytic cycle is expected,[22, 53] so the alkyne carbopalladation must be done by a PhPd(OAc)X species.



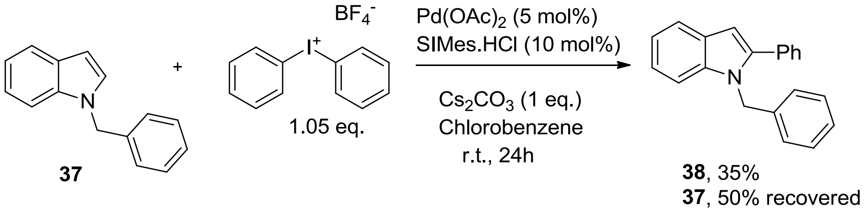
Scheme 3.1.24. Suggested mechanisms for the tandem indole C-H alkenylation/arylation reaction.

However, no previous alkyne hydroarylation with iodonium salts through this kind of Pd(IV) species has been reported. In order to afford the *Z*-alkene after the reduction elimination step, the carbopalladation should be regioselective.

Another plausible mechanism (Path B, Scheme 3.1.24) would be the electrophilic palladation of indole happening first (III) and consequent alkyne carbopalladation. Interaction of the palladium vinyl (IV) with the iodonium salt must oxidise the Pd(II) to a Pd(IV) species which can lead to the final tetra-substituted olefin after a reductive elimination step.

These proposed paths are simplifications of the main steps which could be taking place. Actually, the real palladium intermediates are not known at this stage. In their studies of palladium-catalysed ortho-arylation of 3-methyl-2-phenylpyridine through C-H activation using iodonium salts, Sandford and co-workers[54] conducted mechanistic studies that pointed to the existence of palladium dimers as catalytic species. In this specific example the dimer specie could both be either a Pd(IV) species attached to a bridging Pd(II) complex or it could be considered a Pd(III)-Pd(III) dimer if there is sufficient bonding between the two Pd centers (Chapter 1, pg. 44). So, in our case, probably complex Pd intermediates are present in the catalytic cycle and the electron rich σ-donating imidazolinium ligand used must have an important role in their formation and stabilisation.

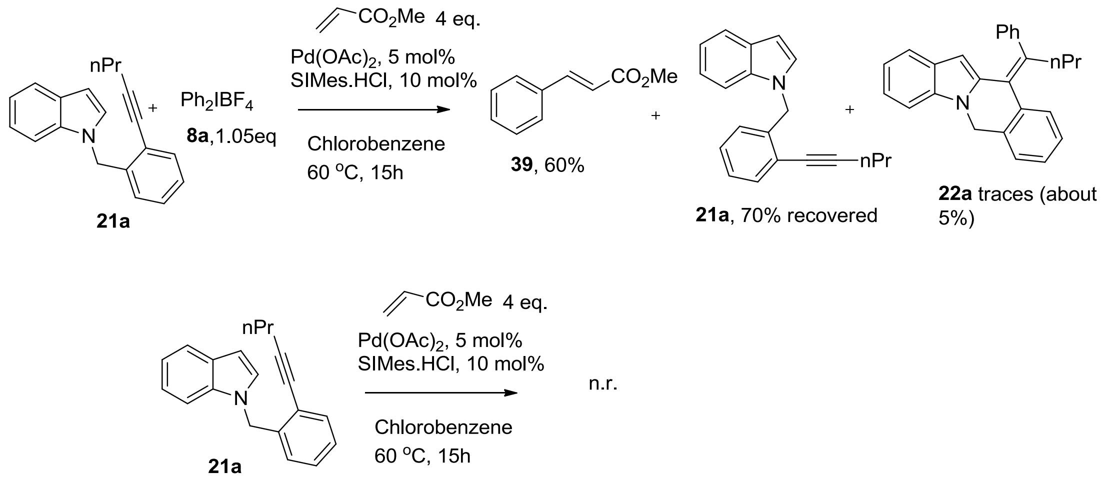
In order to see whether the electrophilic palladation of indole could be taking place under these reaction conditions, the direct arylation of the analogous benzylindole was attempted (Scheme 3.1.25). Under the usual reaction conditions the 2-arylated product could be isolated, albeit in low yield.



Scheme 3.1.25. Direct arylation of benzylindole under usual reaction conditions.

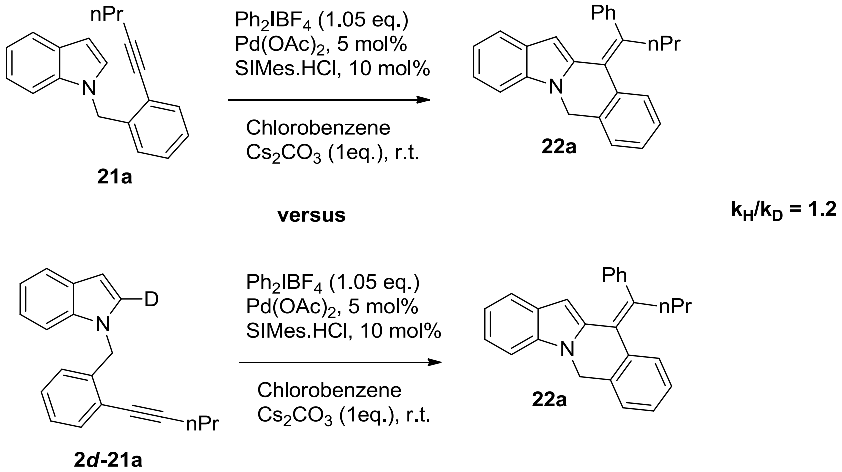
Unfortunately, attempts at trapping the possible metalated indole (III) with a Heck acceptor, using **21a** as starting material, introducing an excess of methyl acrylate in the reaction failed to give the alkenylated indole. Instead, Heck reaction with the iodonium salt took place (Sheme 3.1.26). Again no reaction happened in the absence of the iodonium salt.

The electron-rich indole is thought to be metalated first at its nucleophilic 3-position and undergo a 1,2-Pd migration to afford the 2-metallated indole.[16, 55] In the indole 2-position direct arylation reported by Sames and co-workers[16] KIE studies confirmed the electrophilic palladation pathway as the more likely to be. KIE for the C-2 position had a value of 1.2, too low for the cleavage of this bond to be involved in the rate-limiting step, in contrast KIE for C-3 position is 1.6 (secondary KIE).



Scheme 3.1.26. Attempts at trapping metalated indole (III) with a Heck acceptor.

To understand what could be the rate-determining step in the tandem reaction, H/D KIE studies were done. 2-Deuterated **21a** was synthesised. Response for the increment in the product formation (measured by SIM[56]) vs time during the first 30 min. (~20% conversion) was compared with the rate under the same conditions for the non-deuterated subtstrate giving a k_H/k_D of 1.2 for the 2-position (Scheme 3.1.27).



Scheme 3.1.27. KIE between **21a** and **2*d*-21a.**

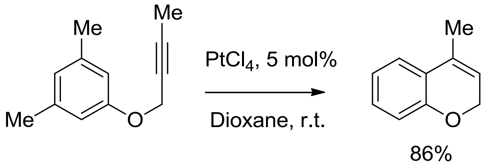
3-Deuterated **21a** was also synthesised and the same procedure was followed. Unfortunately, a linear plotting of response vs time was not obtained in this case, probably due to H/D exchange taking place. Though no deuterium loss was seen in the 3-deuterated starting material, after 30 min. reaction, ^{1}H NMR showed a 20% conversion of the tetra-substituted olefin product in which the H:D ratio at the indole 3-position was 1:1.

In conclusion, while the proposed path B (Scheme 3.1.24) would be in accordance with earlier mechanisms discussed in the direct arylation of indoles, this path does not fully support the experimental evidence, mainly because no annulation reaction has been detected in the absence of the iodononium salt. So, it seems to indicate the iodonium salt is having an important role in the early steps of the reaction, possibly forming a high oxidation state Pd(IV) complex. It can be reasoned that this oxidised Pd intermediate is actually the one undergoing the electrophilic attack to form a palladated indole intermediate which could then undergo either alkyne carbopalladation or reductive elimination to afford the 2-arylated indole derivative. However the fact that no direct arylation byproduct has been observed makes this option unlikely. That leads again to path A (Scheme 3.1.24) in which the high oxidation state Pd(IV) complex reacts with the alkyne first, giving a Pd(IV) vinyl intermediate (I). KIE value for indole 2-position does not rule out any of the paths as its value would fit in both mechanisms. KIE value for the 3-position would be more useful as a value higher than 1.5 would support path B. Although no specific reaction mechanism is known at this point of the investigation, the two paths discussed are currently under consideration based in the experimental evidence found up to the present moment.

3.2. Palladium-Catalysed Tandem Reaction between Propargyl Aryl Ethers and Diaryliodonium Salts

3.2.1. Introduction and Aims

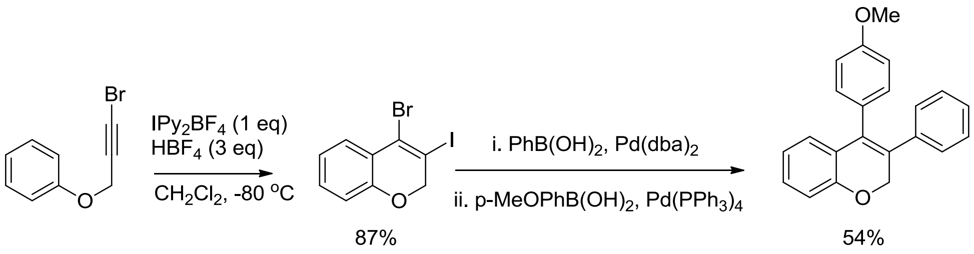
Since Fujiwara and co-workers[27, 28, 57] reported the synthesis of coumarins and quinolines through an intramolecular palladium-catalysed hydroarylation of alkynes, a lot of effort has been directed towards the development of mild and efficient methods to the synthesis of these compounds and derivatives.[58] For instance, Sames and collaborators[59, 60] reported the $PtCl_2$ and $PtCl_4$ cyclisation of propargyl aryl ethers, propargylamines and alkynoate esters which selectively afforded the corresponding 6-*endo* products. A broad scope of substrates including terminal and internal alkynes reacted well under mild conditions (Scheme 3.2.1).



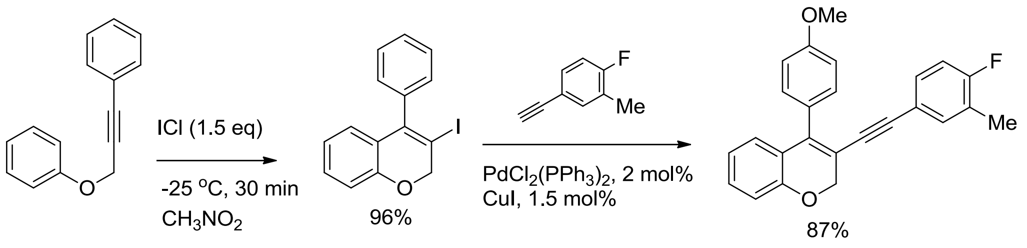
Scheme 3.2.1. $PtCl_4$ catalysed cyclisation of propargyl aryl ethers.[59,60]

Examples of the gold-catalysed reaction have also been reported[61] and further studies of the reaction mechanism done by Echavarren and co-workers[62] suggest cyclopropyl carbenes as probable intermediates.

Interestingly, in the recent years some groups have been investigating the intramolecular iodoarylation of alkynes to afford benzofused heterocycles. Barlengua and collaborators[63] used bis(pyridine)iodonium tetrafluoroborate as the source of iodonium ion to afford the iodo-cyclised products (Scheme 3.2.2), while Larock and co-workers use I_2 or ICl to perform the electrophilic cyclisation (Scheme 3.2.3).[64] The main advantage of the iodoarylation process is that the products obtained can be further elaborated by cross-coupling reactions.

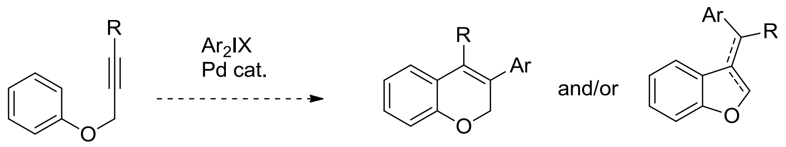


Scheme 3.2.2. Intramolecular iodoarylation of alkynes to afford benzofused heterocylces reported by Barlengua *et al.*[63]



Scheme 3.2.3. Intramolecular iodoarylation of alkynes to afford benzofused heterocylces reported by Larock *et al.*[64]

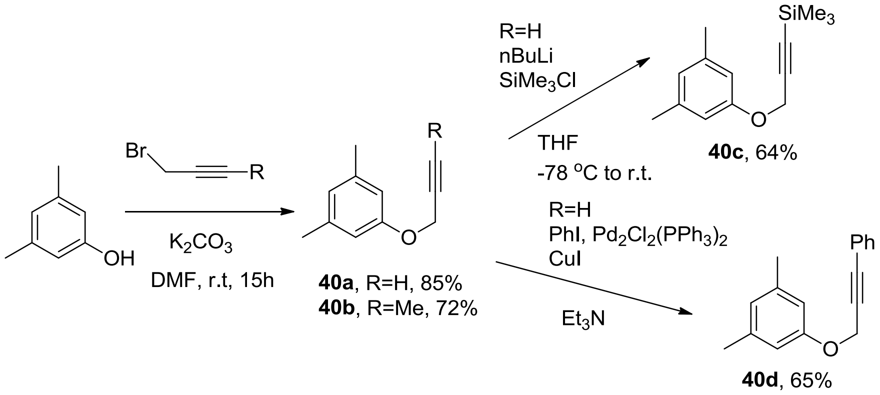
It would be interesting to see whether the tetrasubstituted olefins can be obtained in one pot through a palladium-catalysed tandem reaction between propargyl aryl ethers and diaryl iodonium salts (Scheme 3.2.4).



Scheme 3.2.4. Proposed palladium-catalysed tandem reaction between propargyl aryl ethers and diaryl iodonium salts.

3.2.2. Results and discussion

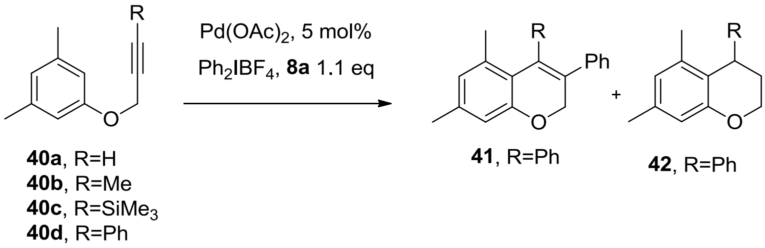
To start the reaction study some propargylic ethers were synthesised from the electron-rich 3,5-dimethylphenol, its reaction with a base and propargylbromide afforded the terminal alkyne.[59, 60] Which could be further transformed to an internal alkyne by reaction with electrophiles in basic media or by a Sonogashira reaction affording the desired materials in moderate to good yields, Scheme 3.2.5.



Scheme 3.2.5. Synthesis of propargyl aryl ethers from 3,5-dimethylphenol.

The Pd catalysed tandem reaction was first tried in acid media, the ethers were dissolved in toluene:HOAc mixtures and heated up in the presence of $Pd(OAc)_2$, with or without diphenyliodonium tetrafluorate (Table 3.2.1). In all cases no cyclisation happened in the absence of iodonium salt and starting materials were recovered. When iodonium salt was present in the reaction it led to complex mixtures containing biphenyl, unreacted starting materials and other unknown products in small amounts, except in the case of **40d** (entry 8), no starting material was left after 2 h reaction and a new product could be isolated in low yield. HPLC/MS and NMR analysis of the product was in accordance with the 6-*endo* cyclised product with phenyl insertion. Fujiwara's conditions[27] using TFA (entry 9) afforded the saturated benzopyran product as reported by Sames and co-workers.[59, 60]

Table 3.2.1. First attempts at palladium-catalysed tandem reaction of propargylaryl ethers and diaryliodonium salts.

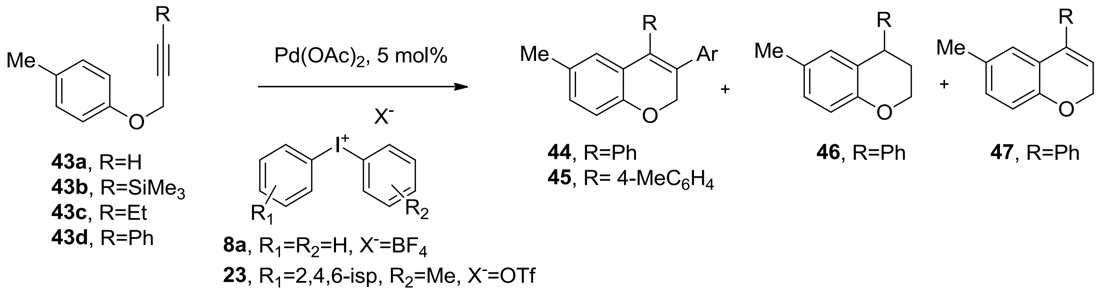


Entry	*R*	*Ph_2IBF_4*	*Solvent*	*T (°C)*	*t (h)*	*Results*
1	H	-	Toluene:HOAc, 4:1	70	8	n.r.[a]
2	H	1.1 eq.	Toluene:HOAc, 4:1	70	8	Complex mixture
3	Me	-	Toluene:HOAc, 4:1	70	8	n.r.
4	Me	-	Toluene:HOAc, 4:1	70	8	Complex mixture, biphenyl, starting material and other unknown products
5	$SiMe_3$	-	Toluene:HOAc, 4:1	80	16	Starting material and decomposition
6	$SiMe_3$	1.1 eq.	Toluene:HOAc, 4:1	80	16	Complex mixture
7	Ph	-	Toluene:HOAc, 4:1	80	16	n.r.
8	Ph	1.1 eq.	Toluene:HOAc, 4:1	80	1	**41** [19%][b]
9[c]	Ph	-	CH_2Cl_2:TFA, 3:1	r.t.	1	**42** [24%][b]

Reaction conditions: **40** (0.3 mmol), $Pd(OAc)_2$ (0.015 mmol), **8a** (0.33 mmol), Toluene/HOAc, 4/1 (3 mL), N_2 atm. [a] n.r= no reaction, starting materials recovered, [b] Isolated yield [c] 1.5 mL (0.2 M) of solvent.

Initial results were encouraging as some of the desired product could be formed when using **40d** as the starting material. However, yield was very low and a lot of decomposition seemed to be happening in the reaction. Further study of the reaction was carried out with 4-methylphenylether derivatives as it was thought that in the case of the 3,5 dimethyl derivative there could be some steric impedance in the cyclisation reaction. The synthesis of the 4-methylphenyl ether derivatives was also done as specified in scheme 3.2.5. A summary of results can be seen in Table 3.2.2. Reaction of the free alkyne, **43a**, derivative in Fujiwara's conditions[27] led to a complex mixture of compounds as well as in the heated reaction in toluene:HOAc (Table 3.2.2, entries 1 and 2). Also the reaction using **43b** was very messy and the expected product could not be isolated (entry 3). In the case of the ethyl substituent, **43c**, only traces of the desired product were detected when using toluene:HOAc, 4:1 as solvent at 80 ^{o}C. Using these experimental conditions in the case of the Ph substituent, **43d**, afforded the expected product in low yield (entry 5). Increasing the amount of iodonium salt in the reaction did not improve the yield and led to an even messier reaction (entry 6), whereas using a bulky unsymmetrical diaryliodonium salt, **23**, also afforded the desired product in low yield (entry 7). No reaction took place when using iodobenzene as the arylating agent or in the absence of iodonium salt (entries 8 and 9). Fujiwara's conditions[27] resulted in the saturated product, while use of HOAc instead of TFA led to no reaction (entries 10 and 11), but more surprisingly, the palladium-catalysed reaction in toluene:HOAc at r.t. in the presence of the iodonium salt **23** gave the cyclised product without tolyl insertion in the triple bond (entry 12). Although yields of the products are very low, the fact that three different products can selectively be formed just by small changes in the procedure was quite exciting. In order to better understand the effect of the acid in the achievement of the different products, several acids were tried in the reaction as can be seen in Table 3.2.3. The reaction in absence of acid yields very small amount of product (Table 3.2.3, entry 1), when a mild acid such as benzoic acid is present, a few milligrams of the disubstituted chromene are obtained (entry 2), larger amounts of the acid did not give better yields. Using strong acids as TFA and HOTf, only yielded the saturated benzopyran (entries 3 to 5).

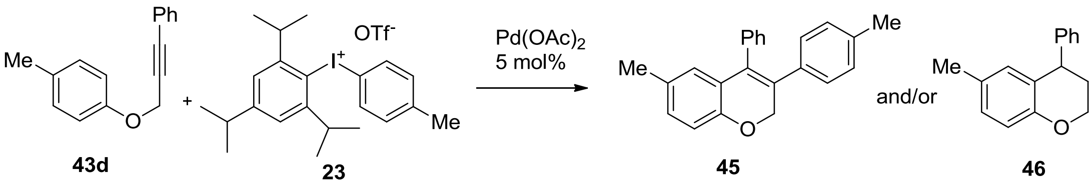
Table 3.2.2. Palladium-catalysed reaction of propargyl 4-methylphenyl ethers and diaryliodonium salts



Entry	R	Iodonium salt	Solvent	T (^{o}C)	t (h)	*Results*
1[a]	H	-	DCM:TFA, 3:1	r.t.	5	Complex mixture
2	H	**8a**	Toluene:AcOH, 4:1	80	5	Complex mixture
3	SiMe$_3$	**8a**	Toluene:AcOH, 4:1	80	5	Complex mixture
4	Et	**8a**	Toluene:AcOH, 4:1	80	3	Traces of product
5	Ph	**8a**	Toluene:HOAc, 4:1	80	3	**44** [31%][b]
6	Ph	**8a** (2eq)	Toluene:HOAc, 4:1	80	3	**44** [31%][b]
7	Ph	**23**	Toluene:HOAc, 4:1	80	1	**45** [23%][b]
8[d]	Ph	-	Toluene:HOAc, 4:1	80	1	n.r.[e]
9	Ph	-	Toluene:HOAc, 4:1	80	1	n.r.[e]
10[a]	Ph	-	DCM:TFA, 3:1	r.t	1	**46** [60%][b]
11[a]	Ph	-	DCM:HOAc, 3:1	r.t	1	n.r.[e]
12	Ph	**23**	Toluene:HOAc, 4:1	r.t	18	**47** [35%][b]

Reaction conditions: (0.3 mmol), Pd(OAc)$_2$ (0.015 mmol), Ph$_2$IBF$_4$ (0.33 mmol), Toluene/HOAc, 4/1 (3 mL), N$_2$ atm. [a] 1.5 mL (0.2 M) of solvent, [b] Isolated yield [c] Not isolated [d] PhI (0.33 mmol) under N$_2$ atm. [e] n.r.: no reaction, starting materials recovered.

Table 3.2.3. Acid effect in the palladium-catalysed reaction of propargyl 4-methylphenyl ethers and diaryliodonium salts



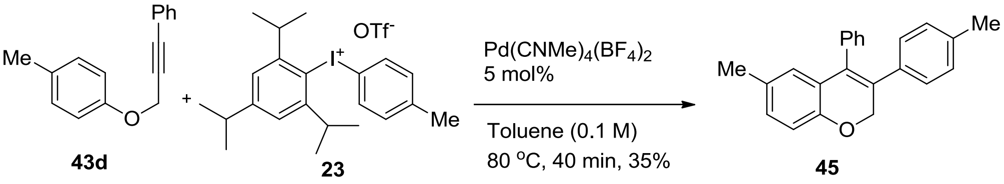
Entry	Solvent	T (^oC)	*Results*[a]
1	Toluene	80	**45** [8%]
2	Toluene:C_6H_5COOH (10 eq.)	80	**45** [22%]
3	Toluene:TFA, 4:1	80	**46** [28%]
4	Toluene:TFA (10 eq.)	80	**46** [43%]
5	Toluene:HOTf (10 eq.)	r.t.	**46** [40%] + unknown mixture of products
6	Toluene:HCOOH	80	**46** [16%]
7	Toluene:HCl (2 eq.)	80	Complex mixture, traces **45**
8	Toluene:HBF_4 (10 eq.)	80	Complex mixture, traces **45**
9	Toluene:HOAc (2 eq.)	80	**45** [11%]
10	Toluene:HOAc (5 eq.)	80	**45** [22%]

Reaction conditions: **43d** (0.3 mmol), $Pd(OAc)_2$ (0.015 mmol), **23** (0.36 mmol), solvent (3 mL), reactions stopped in 1h [a] Isolated yield.

The reduced product is also obtained with formic acid (entry 6) which is not a strong acid, however it is a known hydride donor and can effect the transition metal catalysed reduction of olefins and acetylenes.[65] Finally, reducing the amount of acid present in the reaction did not decrease the decomposition and similar low yields were obtained (entries 9 to 10).

The use of other solvents as tert-amylalcohol, trifluoroethanol, dichloroethane, ethyl acetate or DMF in the presence of 5 eq. of HOAc did not lead to any improvement in the reaction and in some cases complex mixtures of unknown complexes were obtained. Concentration was not very important and similar yield values were achieved with concentrations between 0.05 M and 0.5 M. When performing the reaction in toluene:HOAc, 4:1 at 50 °C ($Pd(OAc)_2$, 5 mol%), no evolution was seen after 5 h, traces of **45** and **47** were observed, together with recovered starting material.

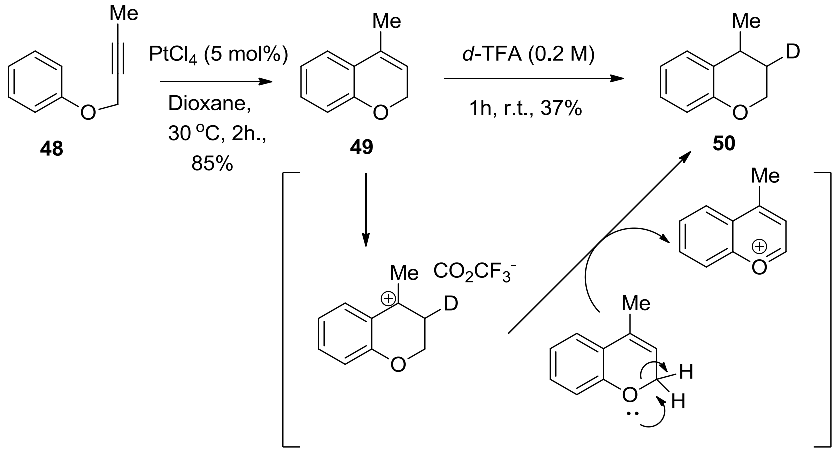
Recently the synthesis of dihydrocoumarin compounds from alkynals and arylboronic acids has been reported by Lu *et al.*[66] using cationic palladium species. The utilisation of tetrakisacetonitrile palladium tetrafluoroborate in the reaction yielded only 15% yield when the toluene:HOAc, 4:1 mixture was used as solvent and 35% yield without acid at 80 °C was achieved after just 40 min. reaction (Scheme 3.2.6).



Scheme 3.2.6. Tandem reaction catalysed with cationic palladium $Pd(CNMe)_4(BF_4)_2$.

Despite having isolated few interesting products, the results obtained indicated that either the propargylic aryl ethers or the chromene products are not stable in the conditions tried in the presence of the iodonium salts and a successful domino procedure could not been achieved. The fact that **45** is obtained at r.t., may indicate that the alkene in **47** can be activated to undergo arylation with the iodonium salt when heating. To prove this idea, the aryl chromene was heated together with $Pd(OAc)_2$ and **23** under the usual reaction conditions. A complex mixture was obtained after only 20 min. heating at 80 °C, from where **45** could be detected by ^1H NMR and HPLC/MS however no clean product could be isolated. Probably, **47** is being formed first in the reaction and then it reacts with the iodonium salt to afford **45**. However, the iodonium salt must be having an unknown more complex role as no conversion at all is observed without it in the reaction mixture.

On the other hand, formation of the reduced benzopyrans is also an interesting reaction. To see whether the reduction could happen only in the presence of TFA, chromene **47** was dissolved in distilled TFA under N_2 atmosphere and vigorously stirred for 1h., after that time no starting material was left and **46,** was isolated in 59% yield. To further study this reaction, 4-methyl-*2H*-chromene, **49**, was synthesised in a larger scale using Sames' procedure with $PtCl_4$.[59, 60] **49** was dissolved in deuterated TFA under N_2 atm. and stirred for 1h. at r.t. The corresponding 3-deuterated chromane was achieved in 37% yield (Scheme 3.2.7). This result points to the protonation of the double bond happening first, giving a tertiary carbocation, as expected by Markorvnikov's rule. The carbocation must be attacked by a hydride to give the final saturated compound. One possibility is the formation of a benzopyrylium cation as the source of hydrides.



Scheme 3.2.7. Possible mechanism for the reduction of chromenes in the presence of TFA.

This possible mechanism was proposed by Tilak and co-workers[67] for the formation of chromanes from 4-chromanols in perchloric acid. This path would only take place when using very strong acids as TFA or HOTf to undergo the protonation of the double bond in the chromene. The obtainment of the 3-deuterated product in less than 50% yield seems to support this path, however no pyrylium cation was isolated and higher yields were obtained when **43d** reacted under Fujiwara's conditions[27, 28, 57](Table 3.2.2, entry 12) as also reported by Sames and co-workers.[59, 60] The source of the hydride in this reaction is currently un-resolved and is the focus of further study in the group.

3. 3. Conclusions

Intramolecular approaches to the challenging three component reaction between indoles, alkynes and aryliodides have been studied.

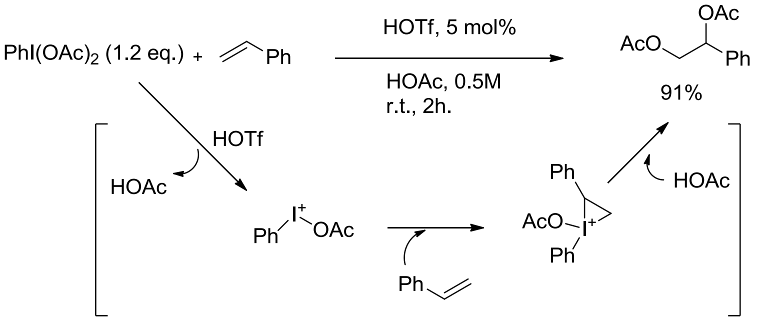
By installing a second alkyne or allyl moiety in an alkynoate molecule, the palladium-catalysed insertion of indole in the alkynoate triple bond was thought to be followed by an internal cyclisation, however several attempts under different reaction conditions failed to achieve the desired products.

A second approach, in which the reacting C-H bond and the alkyne were installed in the same molecule, was then studied. When the alkyne was tethered to the indole nitrogen atom through an aliphatic chain, the palladium-catalysed reaction with diphenyiodonium tetrafluoroborate led to the annulated products. Migration of the alkene into the new formed cycle was observed, depending on the reaction temperature. Reactions were messy and difficult to purify affording the tandem reaction products in low yields. Suppression of the possible alkene migration by introduction of a phenyl group next to the alkyne, resulted in the development of a successful procedure for the palladium-catalysed sequential difunctionalisation of alkynes through C-H activation of indole and arylation with iodonium salts. The procedure proved to be very robust allowing a broad substrate scope. Complex precious unknown molecules were synthesised over a simple route under very mild conditions. Furthermore, under these established conditions *Z*-alkenes were selectively obtained in most of the cases. Although the accurate mechanism for this transformation is not known yet, two possible mechanisms supported by the experimental evidence have been discussed.

Finally, synthesis of disubstituted chromenes by the palladium-catalysed tandem intramolecular cyclisation/arylation reaction of aryl propargyl ethers has also been studied. The desired alkyne difunctionalised products were achieved, although decomposition was observed leading to low yields.

3.4. Future Work

Very recently Gade and co-workers[68] published the HOTf catalysed dioxygenation of alkenes using $PhI(OAc)_2$, the rate determing step is thought to be the formation of a iodoso cationic intermediate, questioning the catalytic role of Pd or Cu species in examples reported before (Scheme 3.5.1).[69]

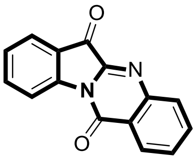


Scheme 3.5.1. Acid-catalysed dioxygenation of alkenes with $PhI(OAc)_2$.

Also, Gaunt and co-workers[70] observed that the copper-catalysed meta-selective direct arylation of α-aryl carbonyl compounds with diaryliodonium triflates, can be performed in the absence of copper when the temperature is higher than 80 °C (Chapter 1, Scheme 1.4.6, pg. 45).

The studied tandem reaction between ethynylbenzyl indoles and diaryliodonium salts did not work in the absence of palladium catalyst and is carried out under very mild and basic conditions, therefore the reaction is expected to proceed through a Pd high oxidation state.[53] However, the study of the reaction in the presence of acid additives or under higher temperatures could provide interesting data in order to achieve a more detailed mechanism. Studing the reaction of iodonium salts with alkynes would be also interesting for this aim. A more accurate knowledge about the mechanism could be crucial in order to succesfully achieve the intermolecular three-component reaction.

On the other hand, most of the dihydroindolo[1,2*b*]isoquinolines synthesised with the studied method are new and no exact use is known yet. Due to their highly conjugated system they could be tested as fluorescent compounds[71] or even as organic semiconductors.[72] They may also have some biological activity as they are carbon analogues of Tryptanthrin,[73] which is a very interesting molecule with anticancer,[74] antitrypanosomal,[75] and antimicrobial[76] activity (Scheme 3.5.2). In order to test our molecules against some viable targets, establishing collaboration with a biochemistry research group would be of great interest.



Tryptanthrin

Scheme 3.5.2. Chemical structure of Tryptanthrin.

Finally, the reaction of diaryliodonium salts with propargyl aryl ethers using the optimised conditions for the synthesis of annulated indoles did not afford clean products. Optimisation of the reaction, as well as studing the effect of different acids in the presence or absence of catalyst could provide interesting information.

3.5. Experimental Procedures

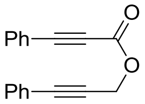
3.5.1. General considerations

Reagents were purchased and used without further purification unless otherwise noted. $Pd(OAc)_2$ was purchased from STREM Chemicals. Solvents used were ACS reagent or HPLC grade. Anhydrous solvents used: Toluene, Diethyl ether, MeCN, DMF, THF and Et_2O were dried by passage through activated alumina columns using a solvent purification system from Glasscontour or a PureSolv solvent purification system supplied by Innovative Technologies Inc. Melting point measurements were obtained from a Griffin melting point apparatus and are uncorrected. IR spectra were recorded either on a JASCO FT/IR 410 apparatus (preparing the sample as a film on a NaCl disc or as a solid solution mixed with KBr) or on a SHIMADZU IRAffinity-1 apparatus (neat compound). ^{1}H-NMR and ^{13}C NMR were recorded either on a Brüker Avance III 400MHz or on a Brüker Avance III 500 MHz instrument from the University of Edinburgh. The following abbreviations have been used: δ (chemical shift, in ppm with TMS as a reference), *J* (coupling constant), s (singlet), bs (broad singlet), d (doublet), dd (double doublet), ddd (doublet of double doublet), dt (double triplet), t (triplet), td (triplet of doublets), q (quartet), qd (quarted of doublets), quint (quintuplet), sext (sextet), sept (septet), septd (septet of doublets), m (multiplet), quat (quaternary carbon). HPLC/MS data was obtained from a 1200 Series Agilent Technologies apparatus with a WATERS Atlantis dC18.3µm (3.0x2.0 mm IS) column. High resolution mass spectrometry was performed by EPSRC National Mass Spectrometry Service Centre at Swansea or by The Mass Spectrometry Service in the University of Edinburgh using either of the following ionisation techniques: Electrical Ionisation (EI), Electrospray Ionisation (ESI) or Atmospheric-Pressure Chemical Ionisation (APCI). A Biotage 2.5 Initiator Microwave Synthesiser was used for some reactions as specified. Control of the reaction advance by TLC was performed on Merck $60F_{254}$ silica plates and visualised by UV light (λ=254 nm) or stained in anisaldehyde or potassium permanganate solution. The compounds were purified by wet flash chromatography using Merk

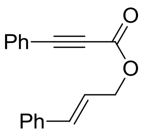
Kieselogel 60 silica (particle size 35-70) under positive pressure or Acros Aluminium oxide, neutral, Brockmann I (size 50-200) under atmospheric pressure.

3.5.2. Experimental procedures and analytical data for the synthesised compounds

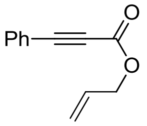
Phenylpropynoic acid 3-phenylprop-2-ynyl ester, 2. The product was synthesised according to the procedure reported by Wessig *et al*.[4] The synthesis of **2** is described as the general procedure for the ester synthesis. 3-phenylprop-2-yn-1-ol, (1.10 g, 7.56 mmol) and 3-phenylprop-2-ynoic acid, (0.99 g, 7.56 mmol) were placed in a two necked 250 mL flask along with catalytic DMAP (55 mg, 0.45 mmol). Anhydrous CH_2Cl_2 (76 mL) was added, the flask was purged with N_2 and the mixture cooled to 0 ^oC. DCC (1.55 g, 7.56 mmol) was dissolved in dry CH_2Cl_2 (76 mL) and added dropwise through a cannula under N_2 atm. to the first solution at 0 ^oC. A white precipitate started to form. After the addition the suspension was left to warm to r.t. and left stirring for 18 h. After this time it was filtered through a celite pad. The filtrate was washed with diluted HCl, 0.25 M (100 mL × 2) and sat. $NaHCO_3$ (100 mL × 2), then dried over $MgSO_4$ and the solvent evaporated under vacuum. The residue was purified through a silica column (hexane:CH_2Cl_2, 8:2) yielding 1.63 g (83%) of a yellowish solid. Spectroscopic data are in agreement with that previously reported.[4] **^{1}H NMR** (360 MHz, $CDCl_3$): δ 5.07 (2H, s), 7.30-7.40 (5H, m), 7.44-7.49 (3H, s), 7.59-7.61 (2H, m); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 54.1 (CH_2), 80.0. (quat), 81.9 (quat), 87.3 (quat), 87.4 (quat), 119.3 (quat), 121.9 (quat), 128.3 (2 × CH), 128.6 (2 × CH), 128.9 (CH), 130.8 (CH), 131.9 (2 × CH), 133.1 (2 × CH), 153.3 (CO).



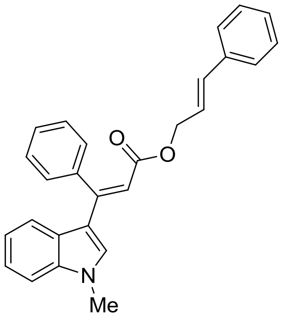
Phenylpropynoic acid (*E*)-3-phenylallyl ester, 3a. The product was synthesised following the same procedure for **2** from *(E)*-3-phenylprop-2-en-1-ol (1.01 g, 7.56 mmol) and 3-phenylprop-2-ynoic acid (1.1 g, 7.56 mmol) to afford 1.53 g (77%) of a colourless oil. The spectroscopic data are in



accordance with that reported before.[3] **^{1}H NMR** (360 MHz, $CDCl_3$): δ 4.91 (2H, dd, *J*= 6.6, 61.1 Hz), 6.35 (1H, dt, *J*= 15.9, 6.6 Hz), 6.74 (1H, d, *J*= 15.9 Hz), 7.26-7.48 (8H, m), 7.59-7.61 (2H, m); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 66.4 (CH_2), 80.4 (quat), 88.5 (quat), 119.4 (quat), 122.0 (CH), 126.6 (2 × CH), 128.2 (CH), 128.5 (2 × CH), 128.6 (2 × CH), 130.6 (CH), 132.9 (2 × CH), 135.2 (CH), 135.9 (quat), 153.7 (CO).



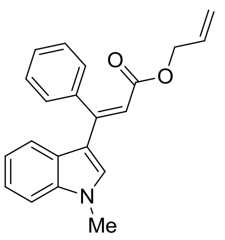
Phenylpropynoic acid allyl ester, 3b. Allyl alcohol (514 μL, 7.56 mmol) and 3-phenylprop-2-ynoic acid (1.11 g, 7.56 mmol) under the usual reaction conditions for the synthesis of **2** afforded 853 mg (61%) of the named product.[77] **^{1}H NMR** (360 MHz, $CDCl_3$): δ 4.63-4.64 (2H, m), 5.21 (1H, dd, *J*= 1.0, 10.4 Hz), 5.31 (1H, dd, *J*= 1.3, 17.2 Hz), 5.85-5.92 (1H, m), 7.28 (2H, d, *J*= 7.5 Hz), 7.35 (1H, t, *J*= 7.4 Hz), 7.49 (2H, d, *J*= 7.0 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 66.4 (CH_2), 80.4 (quat), 86.4 (quat), 119.3 (CH_2), 119.5 (quat), 128.5 (2 × CH), 130.6 (CH), 131.2 (CH), 132.9 (2 × CH), 153.6 (CO).



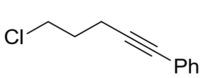
[*(E)*-phenylallyl] *(Z)*-3-(1-methylindolin-3-yl)-3-phenylprop-2-enoate, 4. Phenylpropynoic acid (*E*)-3-phenylallyl ester, **3a**, (65.6 mg, 0.25 mmol) was weighed in a microwave vial. HOAc (2.5 mL) was added followed by 1-methylindole (31.2 μL, 0.25 mmol) and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol). The mixture was stirred at r.t. for 72 h. H_2O (5 mL) was added and the solution extracted twice with EtOAc (5 mL). The combined organic layers were washed with sat. $NaHCO_3$ (5 mL × 2) and brine (5 mL × 2), dried over anh. $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified through a silica column (hexane:CH_2Cl_2, 8:2) to yield 51 mg (52%) of an orange gum. **^{1}H NMR** (360 MHz, $CDCl_3$): δ 3.71 (3H, s), 4.69 (2H, dd, *J*= 6.3, 1.0 Hz), 6.20 (1H, dt, *J*= 15.9, 6.3 Hz), 6.55 (1H, d, *J*= 15.9 Hz), 6.61 (1H, s), 6.74 (1H, s), 7.23-7.27 (2H, m), 7.31-7.39 (8H, m), 7.42-7.43 (3H, m), 7.86 (1H, d, *J*= 8.0 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 33.1 (CH_3), 64.5 (CH_2), 109.5 (CH), 112.3 (quat), 115.0 (CH), 120.0 (CH), 121.0 (CH), 121.9 (CH), 123.7 (CH), 126.6 (2 × CH), 127.8 (quat), 127.9 (CH), 128.2 (2 ×

CH), 128.5 (2 × CH), 129.0 (2 × CH), 129.2 (CH), 132.7 (CH), 133.6 (CH), 136.4 (quat), 136.9 (quat), 142.6 (quat), 150.9 (quat), 166.4 (CO); **IR** (neat): 3057, 2963, 2916, 1712, 1590, 1525, 1473, 1379, 1265 cm^{-1}; **HRMS**: (ESI) calculated for $C_{27}H_{24}O_2N$ [MH$^+$]: 394.1802, found: 394.1808.

Allyl *(Z)*-3-(1-methylindolin-3-yl)-3-phenyl-prop-2-enoate, 5. The procedure described for the synthesis of **4** was followed using phenylpropynoic acid allyl ester, **3b**, to afford 18 mg (23%) of a reddish gum.**^{1}H NMR** (360 MHz, $CDCl_3$): δ 3.71 (3H, s), 4.55 (2H, dt, *J*= 5.6, 1.2 Hz), 5.19 (1H, dd, *J*= 15.8, 1.2 Hz), 5.25 (1H, ddd, *J*= 15.8 2.9, 1.4 Hz), 5.83-5.91 (1H, m), 6.59 (1H, s), 6.73 (1H, s), 7.23-7.26 (1H, m), 7.31-7.35 (5H, m), 7.41-7.42 (3H, m), 7.85 (1H, d, *J*= 8.0 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 33.1 (CH_3), 64.4 (CH_2), 109.9 (CH), 111.1 (CH), 117.6 (CH_2), 121.0 (CH), 121.2 (CH), 122.8 (CH), 127.7 (2 × CH), 127.8 (CH), 128.8 (2 × CH), 128.9 (quat), 129.1 (quat), 132.7 (CH), 133.7 (CH), 138.1 (quat), 140.3 (quat), 152.8 (quat), 166.4 (CO); **IR** (neat): 3059, 2932, 1710, 1590, 1526, 1377, 1149, 1131 cm^{-1}; **HRMS**: (ESI) calculated for $C_{21}H_{20}O_2N$ [MH$^+$]: 318.1489, found: 318.1487.

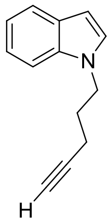


5-Chloro-1-phenylpent-1-yne, **6b**. The compound was prepared by a standard Sonogashira reaction from 5-chloro-1-pentyne and iodobenzene as reported by Larock *et al.*[78] The reaction conditions are described here as a representative procedure. An oven dried 150 mL flask, containing an stirring bar, was charged with PPh_3 (47 mg, 0.18 mmol), CuI (35 mg, 0.18 mmol) and $PdCl_2(PPh_3)_2$ (70.2 mg, 0.10 mmol). The flask was purged with N_2 and previously degassed NEt_3 (100 mL) was added, followed by 5-chloro-1-pentyne, **6a**, (1.00 mL, 19.5 mmol) and iodobenzene (2.18 mL, 19.5 mmol). The reaction was left to stir at r.t. under N_2 for 24 h. After this time, the crude was filtered through celite, eluting with CH_2Cl_2 (100 mL). H_2O (100 mL) was added. To the filtrate and the phases were separated. The organic layer was further washed with H_2O (50mL × 2) and brine (50 mL × 2), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was



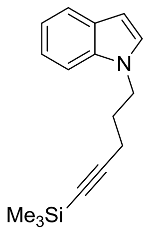
purified by wet silica chromatography (hexane:CH_2Cl_2, 9:1) to afford 3.42 g (98%) of a colourless oil. The spectroscopic data are in accordance with that previously reported.[78] **^{1}H NMR** (250 MHz, $CDCl_3$): δ 2.06 (2H, tt, *J*= 6.8, 6.4 Hz), 2.62 (2H, t, *J*= 6.8 Hz), 3.71 (2H, t, *J*= 6.4 Hz), 7.27-7.31 (3H, m), 7.28-7.42 (2H, m); **^{13}C NMR** (62.5 MHz, $CDCl_3$): 16.8 (CH_2), 31.2 (CH_2), 43.7 (CH_2), 81.49 (quat), 88.0 (quat), 123.6 (quat), 127.7 (CH),128.2 (2 × CH), 131.5 (2 × CH).

General procedure A: *N*-alkylation of indole. The following procedure[17] for the synthesis of **7a** is representative.

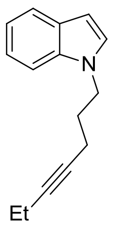


1-Pent-4-ynyl-*1H*-indole, 7a. Indole (1.97 g, 16.95 mmol) was weighed in an oven dry flask and dissolved with dry DMF (100 mL). NaH (60% dispersion in mineral oil, 819 mg, 20.41 mmol) was added portion wise and the mixture was left stirring for 1h at r.t. under N_2 atm. After this time 5-chloro-1-pentyne (2.1 mL, 20.02 mmol) dissolved in 8 mL of dry DMF was added dropwise and the resulting mixture was heated at 60 ^{o}C for 15 h. Then, about half of the solvent was evaporated *in vacuo*. Water (50 mL) and EtOAc (50 mL) were added and the two phases separated. The aqueous phase was extracted twice with EtOAc (50 mL × 2) and the combined organic phases washed with water (50 mL × 3) and brine (50 mL × 2), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica (hexane:CH_2Cl_2, 7:3) to afford the known product as 3.02g of a slightly yellow oil (97% yield).[79, 80] **^{1}H NMR** (360 MHz, $CDCl_3$): δ 2.05 (2H, t, *J*= 6.5 Hz), 2.08 (1H, t, *J*= 2.6 Hz), 2.18 (2H, td, *J*= 6.5, 2.6 Hz), 4.30 (2H, t, *J*= 6.7 Hz), 6.51 (1H, d, *J*= 2.8 Hz), 7.12 (1H, t, *J*= 7.5 Hz), 7.15 (1H, d, *J*= 2.8 Hz), 7.23 (1H, td, *J*= 7.5, 1.0 Hz), 7.39 (1H, d, *J*= 8.2 Hz), 7.65 (1H, d, *J*= 7.9 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 15.8 (CH_2), 28.7 (CH_2), 44.6 (CH_2), 69.6 (CH), 90.0 (quat), 101.2 (CH), 109.3 (CH), 119.3 (CH), 121.0 (CH), 121.5 (CH), 128.0 (CH), 128.6 (quat), 135.9 (quat).

General procedure B: internal alkyne derivatives synthesis. The following procedure described by Shimp *et. al.*[19] for the preparation of **7b** is representative.

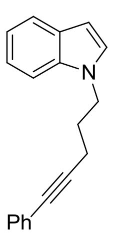


5-Indol-1-ylpent-1-ynyl(trimethyl)silane, 7b. 1-Pent-4-ynyl-*1H*-indole (1.05 g, 5.46 mmol) was weighed in an oven dried flask, dissolved in dry THF (25 mL), purged with N_2 and cooled to -78 ^{o}C in a dry ice:acetone bath. nBuLi (1.5 M, 5.5 mL, 8.19 mmol) was added dropwise *via* syringe for 30 min. After the addition the solution was allowed to warm to 0 ^{o}C for 2 h before cool it again to -78 ^{o}C. Then trimethylsilyl chloride (1.2 mL, 9.82 mmol) was added dropwise and the reaction was allowed to warm up to r.t. for 2h, after which time no SM was seen by TLC. EtOAc (20 mL) and H_2O (20 mL) were added, the layers were separated and the aqueous layer extracted twice with EtOAc (20 mL). The combined organic layers were washed with sat. aqueous solution of $NaHCO_3$ (25 mL × 2) and brine (25 mL × 2), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified through silica chromatography (hexane:Et_2O, 8:2 as eluent) to afford a colourless oil (1.24g, 89%). The compound is known and spectroscopic data are in agreement with that reported in the literature.[19] **^{1}H NMR** (360 MHz, $CDCl_3$): δ 0.32 (9H, s), 2.08 (2H, qd, *J*= 6.7, 0.7 Hz), 2.27 (2H, td, *J*= 6.7, 0.7 Hz), 4.34 (2H, t, *J*= 6.7 Hz), 6.59 (1H, dd, *J*= 3.1, 0.8 Hz), 7.19-7.23 (2H, m), 7.31 (1H, td, *J*= 7.8, 1.0 Hz), 7.48 (1H, dd, *J*= 8.2, 1.0 Hz), 7.73 (1H, dt, *J*= 7.9, 1.1 Hz) ppm **^{13}C NMR** (90 MHz, $CDCl_3$): δ 0.1 (3 × CH_3), 17.2 (CH_2), 28.8 (CH_2), 44.6 (CH_2), 86.0 (quat), 101.2 (CH), 105.7 (quat), 109.3 (CH), 119.3 (CH), 120.9 (CH), 121.4 (CH), 127.9 (CH), 128.6 (quat), 135.9 (quat).

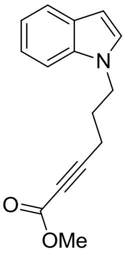


1-Hept-4-ynyl-*1H*-indole, 7c. The general procedure B was followed, using iodoethane as the electrophile. After its addition at -78 ^{o}C the reaction was allowed to warm up to r.t. for 2 h and then it was heated to 50 ^{o}C for 3 extra hours prior starting material consumption. Usual aqueous work up and purification (SiO_2, hexane:CH_2Cl_2, 8:2) afforded 1.15 g of a pale yellow oil (93% yield). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 1.21 (3H, t, *J*= 7.5 Hz), 2.00 (2H, p, *J*= 6.7 Hz), 2.12-2.17 (2H, m), 2.20-2.26 (2H, m), 4.28 (2H, t, *J*= 6.7 Hz), 6.50 (1H, d, *J*= 3.0 Hz), 7.11 (1H, t, *J*= 7.5 Hz), 7.15 (1H, d, *J*= 3.0 Hz), 7.22 (1H, t, *J*= 7.5 Hz), 7.40 (1H, d, *J*= 8.1 Hz), 7.64 (1H, d, *J*= 8.1 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 12.4 (CH_3), 14.3 (CH_2), 16.1 (CH_2), 29.2 (CH_2), 44.8 (CH_2), 77.9 (quat), 83.1 (quat), 101.0 (CH), 109.4 (CH), 119.2 (CH), 120.9 (CH), 121.3 (CH), 128.0 (CH), 128.6 (quat), 135.9 (quat); **IR** (neat): 2972, 2935, 2228, 1485, 1462, 1315, 1240 cm^{-1}; **HRMS**: (ESI) calculated for $C_{15}H_{18}N$ [MH$^+$]: 212.1434, found: 212.1434.

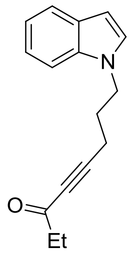
1-(5-Phenylpent-4-ynyl)-1*H*-indole, **7d**. The compound was prepared according to the general procedure A from indole (1.99 g, 17.0 mmol) and **6b** (3.56 g, 20.01 mmol) as a slightly orange oil (4.35g, 95% yield). **^{1}H NMR** (250 MHz, CDCl$_3$): δ 2.29 (2H, m), 2.56 (2H, t, *J*= 6.6 Hz), 4.52 (2H, t, *J*= 6.6 Hz), 6.68 (1H, dd, *J*= 3.1, 0.9 Hz), 7.26-7.42 (3H, m), 7.48-7.50 (3H, m), 7.58-7.64 (3H, m), 7.82 (1H, d, *J*= 7.8 Hz); **^{13}C NMR** (62.5 MHz, CDCl$_3$): δ 16.8 (CH$_2$), 28.9 (CH$_2$), 44.8 (CH$_2$), 81.8 (quat), 88.5 (quat), 101.2 (CH), 109.3 (CH), 119.3 (CH), 121.0 (CH), 121.4 (CH), 123.6 (quat), 127.8 (2 × CH), 128.0 (CH), 128.3 (2 × CH), 128.6 (quat), 131.6 (CH), 135.9 (quat); **IR** (neat): 2966, 2876, 2234, 1495, 1467, 1318 cm^{-1}; **HRMS**: (ESI) calculated for $C_{19}H_{18}N$ [MH$^+$]: 260.1361, found: 260.1366.



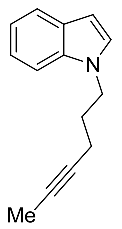
6-Indol-1-ylhex-2-ynic acid methyl ester, 7e. General procedure B for the synthesis of internal alkynes afforded 682 mg (77%) of colourless oil from **7a** (0.52 g, 2.83 mmol) and methyl chloroformate (400 µL, 5.04 mmol) **^{1}H NMR** (250 MHz, CDCl$_3$): 2.12 (2H, qd, *J*= 6.4, 1.2 Hz), 2.28 (2H, td, *J*= 6.4, 1.2 Hz), 3.79 (3H, s), 4.28 (2H, t, *J*= 6.5 Hz), 6.51 (1H, dd, *J*= 3.2, 0.8 Hz), 7.08-7.14 (2H, m), 7.22 (1H, td, *J*= 8.1, 1.2 Hz), 7.36 (1H, dd, *J*= 8.1, 0.9 Hz), 7.61-7.65 (1H, m); **^{13}C NMR** (90 MHz, CDCl$_3$): δ 15.9 (CH$_2$), 27.8 (CH$_2$), 44.5 (CH$_2$), 52.6 (CH$_3$), 73.8 (quat), 87.8 (quat), 101.5 (CH), 109.8 (CH), 119.4 (CH), 121.0 (CH), 121.6 (CH), 127.8 (CH), 128.7 (quat), 135.8 (quat), 153.9 (CO); **IR** (neat): 2951, 2235, 1713, 1479, 1463, 1435, 1354, 1334, 1257, 1172, 1078 cm^{-1}; **HRMS**: (ESI) calculated for $C_{15}H_{16}O_2N$ [MH$^+$]: 242.1176, found: 242.1178.



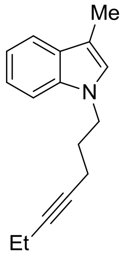
8-indol-1-yloct-4-yn-3-one, 7f. The desired product was obtained from **7a** (0.51 g, 2.79 mmol) and propionyl chloride (440 μL, 5.02 mmol) following the general procedure B as slightly orange oil (487 mg, 72% yield). **^{1}H NMR** (250 MHz, $CDCl_3$): 1.17 (3H, t, *J*= 7.4 Hz), 2.12 (2H, q, *J*= 6.5 Hz), 2.32 (2H, t, *J*= 6.5 Hz), 2.59 (2H, q, *J*= 7.4 Hz), 4.28 (2H, t, *J*= 6.5 Hz), 6.53 (1H, dd, *J*= 3.1, 0.8 Hz), 7.12 (1H, d, *J*= 3.1 Hz), 7.15 (1H, m), 7.24 (1H, m), 7.37 (1H, d, *J*= 8.2 Hz), 7.66 (1H, m); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 8.0 (CH_3), 16.3 (CH_2), 28.0 (CH_2), 38.8 (CH_2), 44.7 (CH_2), 81.4 (quat), 91.9 (quat), 101.5 (CH), 109.2 (CH), 119.4 (CH), 121.0 (CH), 121.6 (CH), 127.8 (CH), 126.6 (quat), 135.8 (quat), 188.4 (CO); **IR** (neat): 3051, 2978, 2937, 2876, 2210, 1672, 1462, 1176 cm^{-1}; **HRMS**: (ESI) calculated for $C_{16}H_{19}ON$ [MH^+]: 240.1383, found: 240.1380.



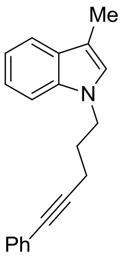
1-Hex-4-ynyl-1*H*-indole, 7g. Prepared according to the general procedure B from **7a** (0.52 g, 2.84 mmol) and iodomethane (320 μL, 5.12 mmol). Purification by flash chromatography (SiO_2, hexane:CH_2Cl_2, 9:1) gave 504 mg of a colourless oil (90% yield). **^{1}H NMR** (360 MHz, $CDCl_3$): 1.85 (3H, t, *J*= 2.5 Hz), 2.00 (2H, q, *J*= 6.8 Hz), 2.10-2.15 (2H, m), 4.27 (2H, t, *J*= 6.7 Hz), 6.51 (1H, dd, *J*= 3.1, 0.7 Hz), 7.12 (1H, ddd, *J*= 7.9, 7.1, 1.0 Hz), 7.15 (1H, d, *J*= 3.1 Hz), 7.22 (1H, ddd, *J*= 7.9, 7.1, 1.0 Hz), 7.39 (1H, dd, *J*= 8.1, 0.8 Hz), 7.65 (1H, dt, *J*= 8.1, 0.8 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 3.5 (CH_3), 16.1 (CH_2), 29.2 (CH_2), 44.9 (CH_2), 76.8 (quat), 77.7 (quat), 101.0 (CH), 109.3 (CH), 119.2 (CH), 120.9 (CH), 121.3 (CH), 128.0 (CH), 128.6 (quat), 135.9 (quat); **IR** (neat): 3055, 2918, 2856, 2233, 1610, 1462, 1315 cm^{-1}; **HRMS**: (ESI) calculated for $C_{14}H_{16}N$ [MH^+]: 198.1277, found: 198.1275.



1-Hept-4-ynyl-1*H*-3-methylindole, **7h**. General procedure A between 3-methylindole (1.01 g, 7.70 mmol) and 5-chloropentyne (0.96 mL, 9.20 mmol) afforded **1-hept-4-ynyl-*1H*-3-methylindole** as a colourless oil (1.68 g, 97% yield) after 15h at r.t. **^{1}H NMR** (360 MHz, $CDCl_3$): δ 2.03 (2H, td, *J*= 6.5, 0.5 Hz), 2.08 (1H, t, *J*= 2.6 Hz), 2.16-2.21 (2H, m), 2.35 (3H, d, *J*= 1.0 Hz), 4.24 (2H, t, *J*= 6.5 Hz), 6.92 (1H, d, *J*= 1.0 Hz), 7.13

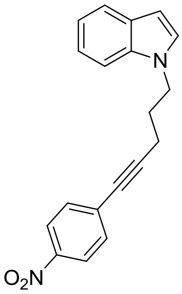


(1H, ddd, *J*= 7.8, 7.0, 1.0 Hz), 7.23 (1H, ddd, *J*= 8.2, 7.0, 0.9 Hz), 7.35 (1H, dt, *J*= 8.3, 0.9 Hz), 7.60 (1H, dt, *J*= 7.8, 1.1 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 9.5 (CH_3), 15.8 (CH_2), 28.8 (CH_2), 44.3 (CH_2), 69.4 (CH), 83.1 (quat), 109.1 (CH), 110.3 (quat), 118.6 (CH), 119.0 (CH), 121.4 (CH), 125.6 (CH), 128.8 (quat), 136.2 (quat); **IR** (neat): 3053, 2918, 2117, 1614, 1467, 1363, 1328 cm^{-1}; **HRMS**: (ESI) calculated for $C_{14}H_{16}N$ [MH$^+$]: 198.1277, found: 198.1274. General substitution reaction (procedure B) of 1-hept-4-ynyl-*1H*-3-methylindole (1.4 g, 7.34 mmol) with iodoethane in the presence of nBuLi afforded the desired product as a colourless oil (940 mg, 57%). **^{1}H NMR** (360 MHz, $CDCl_3$): 1.19 (3H, t, *J*= 7.5 Hz), 1.94-2.00 (2H, m), 2.13-2.18 (2H, m), 2.20-2.27 (2H, m), 2.34 (3H, d, *J*= 1.0 Hz), 4.21 (2H, t, *J*= 6.7 Hz), 6.91 (1H, d, *J*= 0.8 Hz), 7.11 (1H, td, *J*= 7.5, 1.5 Hz), 7.21 (1H, td, *J*= 7.5, 1.1 Hz), 7.35 (1H, d, *J*= 8.1 Hz), 7.58 (1H, dt, *J*= 8.1, 0.8 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 9.6 (CH_3), 12.4 (CH_3), 14.3 (CH_2), 16.2 (CH_2), 29.4 (CH_2), 44.5 (CH_2), 78.0 (quat), 82.9 (quat), 109.1 (CH), 110.1 (quat), 118.5 (CH), 119.0 (CH), 121.3 (CH), 125.6 (CH), 128.7 (quat), 136.3 (quat); **IR** (neat): 3053, 2970, 2933, 2916, 2117, 1614, 1467, 1363, 1328 cm^{-1}; **HRMS**: (ESI) calculated for $C_{16}H_{20}N$ [MH$^+$]: 226.1590, found: 226.1590.

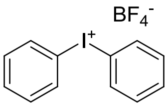


3-Methyl-1-(5-phenylpent-4-ynyl)-*1H*-indole, 7i. General procedure A with 3-methylindole (1.00 g, 7.62 mmol) and **6b** (1.63 g, 9.14 mmol) afforded the named product as a white solid (2.08 g, 86%). **m.p.**: 68-70 ^{o}C **^{1}H NMR** (360 MHz, $CDCl_3$): 2.10 (2H, m), 2.35 (3H, s), 2.39 (2H, t, *J*= 6.6 Hz), 4.29 (2H, t, *J*= 6.6 Hz), 6.95 (1H, s), 7.12 (1H, t, *J*= 7.5 Hz), 7.22 (1H, t, *J*= 7.5 Hz), 7.32-7.34 (3H, m), 7.38 (1H, d, *J*= 8.0 Hz), 7.44-7.47 (2H, m), 7.59 (1H, d, *J*= 8.0 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 9.6 (CH_3), 16.8 (CH_2), 29.1 (CH_2), 44.5 (CH_2), 81.7 (quat), 88.7 (quat), 109.2 (CH), 110.4 (quat), 118.6 (CH), 119.0 (CH), 121.4 (CH), 123.7 (quat), 125.6 (CH), 127.8 (CH), 128.3 (2 × CH), 128.8 (quat), 131.6 (2 × CH), 136.3 (quat); **IR** (neat): 3045, 2927, 2858, 2222, 1610, 1597, 1465, 1444, 1325, 1163 cm^{-1}; **HRMS**: (ESI) calculated for $C_{20}H_{20}N$ [MH$^+$]: 274.1590, found: 274.1586.

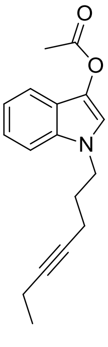
1-[5-(4-nitrophenyl)pent-4-ynyl]-*1H*-indole, 7. The named compound was synthesised using the general conditions for Sonogashira coupling (see synthesis of **6b**) from **7a** (505 mg, 2.73 mmol) and iodobenzene (365 µL, 3.28 mmol). 828 mg of a yellow solid was obtained after purification (hexane:CH_2Cl_2, 1:1 to CH_2Cl_2 100%) in 65% yield. **m.p.**: 76-78 °C **^{1}H NMR** (360 MHz, $CDCl_3$): 2.17 (2H, m), 2.43 (2H, t, *J*= 6.7 Hz), 4.33 (2H, t, *J*= 6.7 Hz), 6.53 (1H, dd, *J*= 3.1, 0.7 Hz), 7.11-7.15 (2H, s), 7.21-7.25 (1H, m), 7.40 (1H, dd, *J*= 8.0, 0.7 Hz), 7.53 (2H, dd, *J*= 6.6, 2.0 Hz), 7.65 (1H, d, *J*= 8.0 Hz), 8.18 (2H, dd, *J*= 7.2, 2.0 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 17.0 (CH_2), 28.7 (CH_2), 44.9 (CH_2), 80.3 (quat), 94.6 (quat), 101.4 (CH), 109.2 (CH), 119.4 (CH), 121.1 (CH), 121.6 (CH), 123.6 (2 × CH), 127.8 (CH), 128.7 (quat), 130.6 (quat), 132.3 (2 × CH), 135.9 (quat), 146.8 (quat); **IR** (neat): 2956, 2927, 2856, 2229, 1591, 1514, 1336, 1313, 1180 cm^{-1}; **HRMS**: (ESI) calculated for $C_{19}H_{17}O_2N_2$ [MH^+]: 305.1285, found: 305.1284.



Diphenyliodonium tetrafluoroborate, 8a. Synthesised by oxidative anion metathesis from the commercially available diphenyliodonium bromide and fluoroboric acid[81] (Chapter 2, pg. 84).

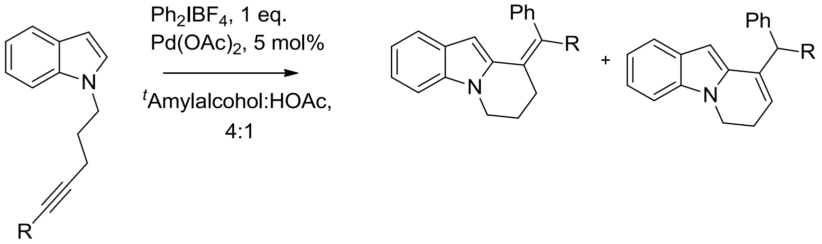


(1-Hept-4-ynylindol-3-yl) acetate, 11. **7c** (52.8 mg, 0.25 mmol) was weighed in a 5 mL dry reaction tube and dissolved in toluene:HOAc (4:1, 2.5 mL). To the solution, $Pd(OAc)_2$ (3 mg, 0.013 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) were added and the mixture was heated at 70 °C for 15h. After cooling down, the crude was filtered through a celite pad and usual aqueous work up was done. The combined organic layers were concentrated under vacuum. The residue was purified through a silica column (hexane:CH_2Cl_2, 1:1). 22.2 mg (33%) of a colourless oil were obtained together with an unknown compound. **^{1}H NMR** (360 MHz, $CDCl_3$): δ 1.16 (3H, t, *J*= 7.4 Hz), 1.97 (2H, m), 2.12-2.25 (4H, m), 2.35 (3H, s), 4.22 (2H, t, *J*= 6.8 Hz), 7.11 (1H, ddd, *J*= 8.1, 7.0, 0.9 Hz), 7.22 (1H, ddd, *J*= 8.1, 7.0, 1.0 Hz), 7.33



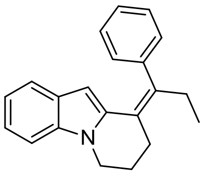
(1H, s), 7.35 (1H, dt, *J*= 8.1, 0.9 Hz), 7.54 (1H, dt, *J*= 8.1, 0.9 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): 12.4 (CH_3), 14.3 (CH_3), 16.1 (CH_2), 21.0 (CH_2), 29.3 (CH_2), 44.9 (CH_2), 77.8 (quat), 83.2 (quat), 109.4 (CH), 117.0 (CH), 117.6 (CH), 119.3 (CH), 120.2 (quat), 122.2 (CH), 129.3 (quat), 130.0 (quat), 168.6 (CO); **IR** (neat): 3055, 2976, 2305, 1747, 1469, 1367, 1265, 1213 cm^{-1}; **HRMS**: (ESI) calculated for $C_{17}H_{20}O_2N$ [MH$^+$]: 270.1489, found: 270.1489.

General procedure C: tandem annulation reaction between alkyne-tethered indoles and diaryliodonium salts



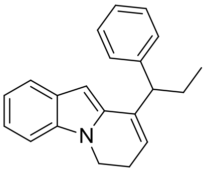
The alkyne-tethered indole (0.25 mmol) was weighed in a 5 mL reaction tube containing a stirring bar. The starting material was dissolved in the solvent mixture of *tert*-amylalcohol:acetic acid, 4:1 (3 mL), then $Pd(OAc)_2$ (2.8 mg, 0.012 mmol) was added, followed by **8a** (132 mg, 0.31 mmol). The tube was capped and placed in a pre-heated aluminium block at 80 °C. The reaction was stopped after 15 h by cooling it down. The crude was filtered through a celite pad, washing with EtOAc. H_2O (5 mL) was added and the two layers separated. The organic layer was further washed with H_2O (5 mL), sat. $NaHCO_3$ (5 mL × 2) and brine (5 mL × 2), dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The residue was purified through an alumina column eluting with hexane:CH_2Cl_2 mixtures to yield the products.

9-[1-Phenylbut-(*Z*)-ylidene]-6,7,8,9-tetrahydropyrido[1,2*a*]indole, 9a. 1-Hept-4-ynyl-*1H*-indole, **7c** (64 mg, 0.25 mmol) and **8a** (132mg, 0.30 mmol) afforded 31 mg of the cyclised product as a colourless oil (43% yield) when the reaction was conducted following the general procedure C, but under microwave irradiation for 10 min. **^{1}H NMR** (500 MHz, $CDCl_3$): 1.04 (3H, t, *J*= 7.5 Hz), 2.21 (2H, quint, *J*= 6.0 Hz), 2.55 (2H, q,

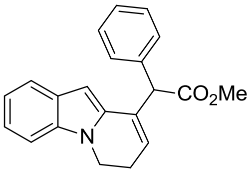


J= 7.5 Hz), 2.76 (2H, dd, *J*= 7.1, 5.2 Hz), 4.13 (2H, t, *J* = 6.0 Hz), 5.18 (1H, s), 6.96 (1H, t, *J*= 7.5 Hz), 7.09 (1H, td, *J*= 7.5, 1.0 Hz), 7.20-7.22 (3H, m), 7.25 (1H, d, *J*= 7.7 Hz), 7.33-7.42 (3H, m); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 12.3 (CH_3), 23.6 (CH_2), 26.1 (CH_2), 29.0 (CH_2), 42.3 (CH_2), 101.5 (CH), 108.5 (CH), 119.5 (CH), 120.2 (CH), 120.9 (CH), 123.4 (quat), 126.7 (CH), 127.5 (quat), 128.7 (2 × CH), 128.9 (2 × CH), 135.4 (quat), 135.9 (quat), 140.3 (quat), 144.3 (quat); **IR** (neat): 3057, 2962, 2931, 2872, 1458, 1315, 1263 cm^{-1}; **HRMS**: (EI) calculated for $C_{21}H_{22}N$ [MH^+]: 288.1747, found: 288.1745.

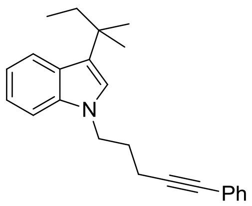
9-(1-Phenylpropyl)-6,7-dihydropyrido[1,2*a*]indole, 10a. Usual procedure C afforded 37 mg (51%) of a colourless oil from **7c** (64 mg, 0.25 mmol) and **8a** (132mg, 0.30 mmol) at 80 °C for 15h. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.04 (3H, t, *J* = 7.3 Hz), 1.90-2.07 (1H, m), 2.05-2.25 (1H, m), 2.67-2.70 (2H, m), 3.83 (1H, t, *J* = 7.5 Hz), 4.15 (2H, td, *J*= 7.1, 1.5 Hz), 6.01 (1H, td, *J* = 4.6, 1.0 Hz), 6.47 (1H, s), 7.11 (1H, ddd, *J* = 8.0, 6.9, 1.3 Hz), 7.21-7.31 (3H, m), 7.35-7.46 (4H, m), 7.60 (1H, dt, *J* = 8.0, 1.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 12.7 (CH_3), 24.3 (CH_2), 27.8 (CH_2), 39.4 (CH_2), 49.1 (CH), 98.3 (CH), 108.5 (CH), 119.3 (CH), 119.3 (CH), 120.6 (CH), 121.7 (CH), 126.2 (CH), 127.8 (2 × CH), 128.2 (quat), 128.2 (2 × CH), 135.0 (quat), 136.4 (quat), 136.6 (quat), 144.0 (quat); **IR** (neat): 3304, 3053, 2985, 2304, 1708, 1612, 1514, 1421 cm^{-1}; **HRMS**: (ESI) calculated for $C_{21}H_{22}N$ [MH^+]: 288.1747, found: 288.1750.



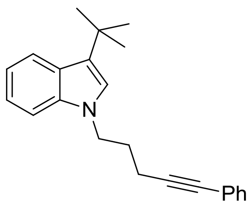
2-(6,7-Dihydropyrido[1,2*a*]indol-9-yl)-2-phenylacetic acid methyl ester, 10b. General procedure C for the palladium-catalysed tandem reaction of **7e** (60.9 mg, 0.25 mmol) and **8a** (133mg, 0.30 mmol) at 80 °C in *tert*-amyl alcohol:HOAc (4:1) afforded 13 mg of a yellow gum (16% yield).**^{1}H NMR** (360 MHz, $CDCl_3$): δ 2.64-2.70 (2H, m), 3.74 (3H, s), 4.07-4.12 (2H, m), 4.97 (1H, d, *J*= 1.3 Hz), 5.80 (1H, td, *J*= 4.6, 1.3 Hz), 6.42 (1H, s), 7.05 (1H, ddd, *J*= 8.0, 6.9, 1.2 Hz), 7.19 (1H, ddd, *J*= 8.0, 6.9, 1.2 Hz), 7.30-7.42 (6H, m), 7.54 (1H, dt, *J*= 7.9, 0.7 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 24.3 (CH_2), 39.3 (CH_2), 52.5 (CH), 53.6 (CH_3), 98.1 (CH),



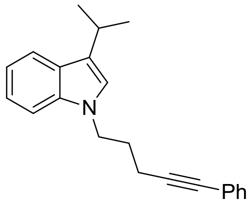
108.7 (CH), 119.6 (CH), 120.8 (CH), 122.1 (CH), 122.9 (CH), 127.6 (CH), 128.2 (quat), 128.6 (2 × CH), 128.8 (2 × CH), 129.9 (quat), 135.4 (quat), 136.4 (quat), 136.9 (quat), 172.5 (CO); **IR** (neat): 3061, 2922, 2854, 2250, 1735, 1454, 1313, 1201, 1155 cm^{-1}; **HRMS**: (ESI) calculated for $C_{21}H_{20}O_2N$ [MH$^+$]: 318.1489, found: 318.1490.



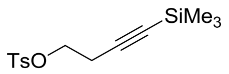
3-(1,1-Dimethylpropyl)-1-(5-phenylpent-4-ynyl)-1*H*-indole, 12. When the general annulation procedure C was applied to **7d** (64.5 mg, 0.25 mmol) no desired product was obtained. Instead, the Friedel-Crafts reaction with *tert*-amyl alcohol took place yielding 29 mg of **12** as a colourless oil after purification through a silica column (hexane:CH_2Cl_2, 8:2, 35% yield). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 0.73 (3H, t, *J* = 7.4 Hz), 1.41 (6H, s), 1.86 (2H, q, *J* = 7.4 Hz), 2.12 (2H, p, *J* = 6.5 Hz), 2.39 (2H, t, *J* = 6.5 Hz), 4.29 (2H, t, *J* = 6.8 Hz), 6.90 (1H, m), 7.08 (1H, t, *J* = 7.8 Hz), 7.20 (1H, t, *J* = 7.6 Hz), 7.31-7.33 (3H, m), 7.37 (1H, d, *J*= 8.1 Hz), 7.44 (2H, dd, *J*= 6.6, 3.1 Hz), 7.79 (1H, d, *J*= 8.1 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 9.4 (CH_3), 16.9 (CH_2), 28.3 (2 × CH_3), 28.9 (CH_2), 35.0 (quat), 35.0 (CH_2), 44.6 (CH_2), 81.7 (quat), 88.7 (quat), 109.5 (quat), 118.1 (CH), 120.9 (CH), 121.5 (CH), 123.5 (CH), 123.7 (quat), 124.8 (CH), 126.6 (quat), 127.8 (CH), 128.9 (2 × CH), 131.6 (2 × CH), 137.1 (quat); **IR** (neat): 3049, 2963, 2874, 2245, 1611, 1465, 1361 cm^{-1}; **HRMS**: (ESI) calculated for $C_{24}H_{28}N$ [MH$^+$]: 330.2216, found: 330.2223.



3-*tert*-Butyl-1-(5-phenylpent-4-ynyl)-1*H*-indole, 13. 1-(5-Phenylpent-4-ynyl)-1*H*-indole, **7d**, (78 mg, 0.3 mmol) was weighed in a dried 5 mL reaction tube and dissolved in DCE (3 mL), $AgSO_3CF_3$ (7.7 mg, 0.03 mmol) was added followed by tert-butanol (57 μL, 0.6 mmol). The tube was purged with N_2 and placed in a pre-heated aluminium bloc at 80 ^{o}C. The mixture was left for 24h before cooling it down, filter it through celite washing with CH_2Cl_2 and evaporate the solvent under vacuum. The residue was purified through a silica column (hexane:CH_2Cl_2 mixtures) to afford 50 mg of a colourless oil (53%). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 1.50 (9H, s), 2.14 (2H, quint, *J*= 6.8 Hz), 2.43 (2H, t, *J* = 6.8 Hz), 4.29 (2H, t, *J* = 6.8 Hz), 6.93 (1H, s), 7.14 (1H, td, *J* = 7.5, 1.2 Hz), 7.23 (1H, td, *J*= 7.5, 0.8 Hz), 7.33-7.36 (3H, m), 7.41 (1H, d, *J* = 8.1 Hz), 7.47 (2H, dd, *J*= 6.5, 3.1 Hz), 7.86 (1H, d, *J*= 8.0 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 16.9 (CH_2), 29.0 (CH_2), 30.9 (3 × H_3), 31.5 (quat), 44.6 (CH_2), 81.7 (quat), 88.7 (quat), 109.5 (quat), 118.2 (CH), 121.0 (CH), 121.4 (CH), 123.3 (CH), 123.7 (CH), 125.4 (quat), 126.5 (quat), 127.79 (CH), 128.3 (2 × CH), 131.6 (2 × CH), 137.1 (quat); **IR** (neat): 2959, 2866, 2244, 1490, 1480, 1467, 1361, 1234 cm^{-1}; **HRMS**: (ESI) calculated for $C_{23}H_{26}N$ [MH^+]: 316.2060, found: 316.2065.



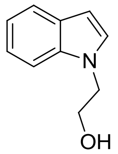
3-Isopropyl-1-(5-phenylpent-4-ynyl)-1*H*-indole, 14. Identical procedure as for the synthesis of **13** was used with isopropanol. to The named product was obtained as a colourless oil (21 mg, 23%). **^{1}H NMR** (360 MHz, $CDCl_3$): δ 1.36 (3H, s), 1.38 (3H, s), 2.11 (2H, quint, *J* = 6.8 Hz), 2.40 (2H, t, *J* = 6.8 Hz), 3.22 (1H, sept, *J*= 6.8), 4.28 (2H, t, *J*= 6.7 Hz), 6.92 (1H, s), 7.10 (1H, ddd, *J* = 8.1, 7.0, 1.0 Hz), 7.20 (1H, ddd, *J*= 8.1, 7.0, 1.0 Hz), 7.33-7.36 (3H, m), 7.41 (1H, d, *J* = 8.2 Hz), 7.47 (2H, dd, *J*= 6.5, 3.1 Hz), 7.86 (1H, d, *J*= 8.0 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 16.9 (CH_2), 29.0 (CH_2), 30.9 (2 × CH_3), 31.5 (CH), 44.6 (CH_2), 81.7 (quat), 88.7 (quat), 109.5 (quat), 118.2 (CH), 121.0 (CH), 121.4 (CH), 123.3 (CH), 123.7 (CH), 125.4 (quat), 126.5 (quat), 127.8 (CH), 128.3 (2 × CH), 131.6 (2 × CH), 137.1 (quat); **IR** (neat): 2959, 2866, 2236 1490, 1480, 1467, 1361, 1234 cm^{-1}; **HRMS**: (ESI) calculated for $C_{23}H_{26}N$ [MH^+]: 316.2060, found: 316.2065.



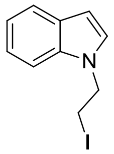
(4-Trimethylsilyl-3-butyn-1-yl)-4-toluene sulfonate, 15. 4-Trimethylsilyl-3-butyn-1-ol was prepared from 3-butyn-1-ol according to the procedure described by Davison *et. al.*[82] **^{1}H NMR** (360 MHz, $CDCl_3$): δ 0.16 (9H, s), 2.51 (2H, t, *J*= 6.2 Hz), 3.71 (2H, t, *J*= 6.2 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): δ 0.1 (3 × CH_3), 29.3 (CH_2), 60.9 (CH_2). 87.1 (quat), 103.3 (quat). Treatment of the alcohol with 4-toluenesulfonyl chloride in pyridine as solvent at r.t. afforded the known product as a colourless oil in 94% yield. Spectroscopic data are in agreement with that previously reported.[82] **^{1}H NMR** (360 MHz, $CDCl_3$): δ 0.12

(9H), 2.45 (3H, s), 2.59 (2H, t, *J*= 7.3 Hz), 4.08 (2H, t, *J*= 7.3 Hz), 7.35 (2H, d, *J*= 8.1 Hz), 7.80 (2H, d, *J*= 8.3 Hz); **^{13}C NMR** (90 MHz, $CDCl_3$): 0.1 (3 × CH_3), 20.7 (CH_3), 21.6 (CH_2), 67.5 (CH_2), 87.5 (quat), 100.3 (quat), 127.9 (2 × CH), 129.9 (2 × CH), 132.9 (CH), 144.9 (quat).

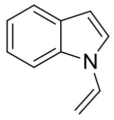
2-(Indol-1-yl)-1*H*-ethanol, **16**. The product was obtained from indole and ethylene carbonate[83]following the usual *N*-alkylation procedure with NaH. After the addition of ethylene carbonate the reaction was heated at 40 °C for 8h. A colourless oil was obtained after purification through silica column (hexane:CH_2Cl_2, 1:1, 75%). The spectroscopic data are in agreement with that reported in the literature.[84] **^{1}H NMR** (360 MHz, $CDCl_3$): δ 3.95 (2H, t, *J*= 5.1 Hz), 4.28 (2H, t, *J*= 5.2 Hz), 6.53 (1H, d, *J*= 3.1 Hz), 7.10-7.17 (2H, m), 7.23 (1H, td, *J*= 7.1, 1.1 Hz), 7.38 (1H, d, *J*= 8.0 Hz), 7.65 (1H, dt, *J*= 8.0, 0.7 Hz) ppm **^{13}C NMR** (90 MHz, $CDCl_3$): 48.7 (CH_2), 61.8 (CH_2), 101.4 (CH), 109.3 (CH), 119.5 (CH), 121.0 (CH), 121.6 (CH), 128.4 (CH), 128.5 (quat), 136.0 (quat).



1-(2-Iodoethyl)-1*H*-indole, **17**. Prepared from 2-(Indol-1-yl)-1*H*-ethanol through Appel reaction with I_2 and Im., following the procedure described by Jamison *et. al.*,[85] in 92% yield. Spectroscopic data are in accordance with that reported before.[86] **^{1}H NMR** (360 MHz): δ 3.44 (2H, t, *J*= 7.6 Hz), 4.52 (2H, t, *J*= 7.6 Hz), 6.92-6.96 (1H, m), 7.12-7.45 (4H, m), 7.79-7.85 (1H, m); **^{13}C NMR** (90 MHz): 8.2 (CH_2), 48.9 (CH_2), 102.0 (CH), 108.9 (CH), 119.8 (CH), 121.2 (CH), 121.9 (CH), 127.5 (CH), 128.7 (quat), 135.4 (quat).

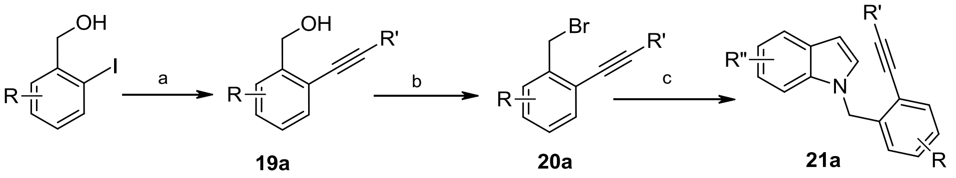


1-Vinyl-1*H*-indole, **18**. When 1-(2-iodoethyl)indole (700 mg, 2.59 mmol) was treated with trimethylsilylacetylene (285 μL, 2.05 mmol) and nBuLi (1.6 M, 1.25 mL, 2.03 mmol) under the general conditions for the synthesis of internal alkynes (general procedure B), *β*-elimination happened leading to *N*-vinylindole, 185 mg of a colurless oil were obtained (52% yield) after usual aqueous work up and purification (SiO_2, hexane:diethyl ether, 9:1). Spectroscopic data agree with literature values.[87] **^{1}H NMR** (360 MHz): δ 4.77 (1H, dd, *J*= 9.0, 0.5



Hz), 5.20 (1H, dd, *J*= 15.7, 0.6 Hz), 6.61-6.64 (1H, m), 7.15-7.18 (1H, m), 7.22-7.29 (2H, m), 7.41-7.43 (1H, m), 7.44-7.48 (1H, m), 7.63 (1H, d, *J*= 7.8 Hz); **^{13}C NMR** (90 MHz): 96.3 (CH_2), 104.9 (CH), 109.4 (CH), 120.8 (CH), 121.2 (CH), 122.7 (CH), 123.3 (CH), 129.1 (quat), 129.64 (CH), 135.5 (quat).

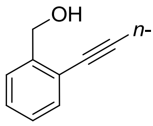
Synthesis of benzylylidene indoles



The starting materials were prepared *via*: a) Sonagashira coupling [1-pentyne (1.2 equiv), $Pd(PPh_3)Cl_2$ (1 mol%), CuI (2 mol%), toluene:piperidine, 1:1, r.t.]; b) bromination using the procedure of Sashida *et. al.*[26] for the synthesis of *o*-ethynylbenzyl bromides [PBr_3 (1.1 equiv), pyridine (1.3 equiv), $CHCl_3$, 0 ºC - r.t.]; c) indole *N*-alkylation [indole (1 equiv), NaH (1.1 equiv), DMF, r.t.].

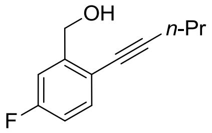
Representative procedure D: synthesis of 2-ethynylbenzyl alcohols (step a)

2-Pent-1-ynylbenzyl alcohol, 19a. 2-Iodobenzyl alcohol (1.01 g, 4.28 mmol) was weighed in a dried flask containing a stirrer bar. Piperidine and dry toluene (12 mL, 1:1) were added and the mixture was degassed with a stream of N_2 for 10 min. $Pd_2Cl_2(PPh_3)_2$ (28 mg, 0.04 mmol) and CuI (15 mg, 0.08 mmol) were then added. The flask was capped with a rubber septum and 1-pentyne (450 μL, 4.62 mmol) was added *via* syringe. The reaction was left stirring at r.t. (approx. 20 °C) under N_2 atmosphere for 6 h after which time no starting material was seen by TLC. Water and EtOAc were added (15 mL each) and the two layers separated. The aqueous layer was extracted twice with EtOAc (15 mL × 2) and the combined organic layers washed with sat. NH_4Cl aqueous solution (15 mL × 2) and brine (15 mL × 2). Drying over $MgSO_4$, filtration and concentration *in vacuo* gave a crude solid that was purified using silica gel column chromatography

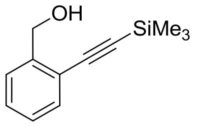


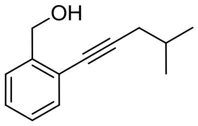
(hexane:CH_2Cl_2,, 1:1), affording 682 mg (93%) of a colourless oil. Spectroscopic data are in accordance with the literature values.[88] **^{1}H NMR** (500 MHz): δ 1.07 (3H, t, *J*= 7.4 Hz), 1.65 (2H, sext, *J*= 7.4 Hz), 2.44 (2H, t, *J*= 7.0 Hz), 4.80 (2H, d, *J*= 6.5 Hz), 7.22 (1H, td, *J*= 7.5, 1.3 Hz), 7.29 (1H, td, *J*= 7.5, 1.3 Hz), 7.39 (1H, dd, *J*= 7.6, 0.6 Hz), 7.41 (1H, dd, *J*= 7.6, 1.2 Hz); **^{13}C NMR** (125 MHz): δ 13.6 (CH_3), 21.5 (CH_2), 22.2 (CH_2), 64.3 (CH_2), 78.2 (quat), 95.3 (quat), 122.2 (quat), 127.2 (CH), 127.4 (CH), 127.9 (CH), 132.2 (CH), 142.4 (quat).

5-Fluoro-2-pent-1-ynylbenzyl alcohol, 19b. The product was synthesised through a Sonogashira coupling between 2-bromo-5-fluorobenzyl alcohol (199 mg, 0.97 mmol) and 1-pentyne (0.1 mL, 1.08 mmol). The general procedure D was followed but the reaction was carried out at 100 ºC (instead of r.t.) for 36 h. Aqueous work-up and purification afforded 93 mg of the product as colourless oil (50% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.05 (3H, t, *J*= 7.3 Hz), 1.63 (2H, sext, *J*= 7.3 Hz), 2.41 (2H, t, *J*= 7.0 Hz), 4.77 (2H, bs), 6.90 (1H, td, *J*= 8.4, 2.7 Hz), 7.14 (1H, dd, *J*= 8.4, 2.7 Hz), 7.35 (1H, dd, *J*= 8.4, 5.6 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.5 (CH_3), 21.4 (CH_2), 22.2 (CH_2), 63.5 (CH_2), 77.2 (quat), 95.0 (quat, d, $J_{C\text{-}F}$= 1.6 Hz), 113.9 (CH, d, $J_{C\text{-}F}$= 25.0 Hz), 114.1 (CH, d, $J_{C\text{-}F}$= 22.1 Hz), 117.6 (quat, d, $J_{C\text{-}F}$= 3.3 Hz), 133.7 (CH, d, $J_{C\text{-}F}$= 8.2 Hz), 145.1 (quat, d, $J_{C\text{-}F}$= 7.3 Hz), 162.2 (quat, d, $J_{C\text{-}F}$= 248.7 Hz); **IR** (neat): 3296(b), 2962, 2933, 1581, 1487, 1463, 1440, 1409, 1230, 1147, 1064, 1024 cm^{-1}; **HRMS:** (APCI) calculated for $C_{12}H_{17}ONF$ [MNH_4^+] : 210.1289, found: 210.1285.

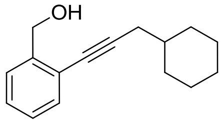


2-Trimethylsylyethynyllbenzyl alcohol, **19c**. Prepared according to the general procedure D in 86% yield (3.76 g) from 2-iodobenzyl alcohol (5 g, 21.4 mmol) after 8 h of reaction. The NMR spectroscopic data are in accordance with literature values.[26] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.27 (9H, s), 4.82 (2H, d, *J*= 5.5 Hz), 7.24 (1H, td, *J*= 7.5, 1.3 Hz), 7.33 (1H, td, *J*= 7.5, 1.3 Hz), 7.41 (1H, dd, *J*= 7.6, 0.8 Hz), 7.47 (1H, dd, *J*= 7.6, 0.8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -0.1 (3 × CH_3), 64.1 (CH_2), 99.6 (quat), 102.6 (quat), 121.1 (quat), 127.2 (CH), 127.3 (CH), 128.9 (CH), 132.4 (CH), 143.1 (quat).

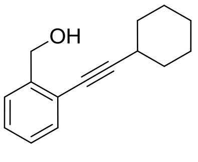




2-(4-Methylpent-1-ynyl)benzyl alcohol, 19d. Usual procedure D afforded 360 mg of a reddish oil (90% yield) from 2-iodobenzyl alcohol (499 mg, 2.13 mmol) after 15 h reaction.**^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.1 (6H, d, *J*= 6.6 Hz), 1.9 (1H, sept, *J*= 6.6 Hz), 2.4 (2H, d, *J*= 6.6 Hz), 4.8 (2H, d, *J*= 6.5 Hz), 7.2 (1H, td, *J*= 7.5, 1.4 Hz), 7.3 (1H, td, *J*= 7.5, 1.4 Hz), 7.4 (2H, dt, *J*= 7.5, 1.4 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.1 (2 × CH_3), 28.2 (CH), 28.7 (CH_2), 64.3 (CH_2), 79.0 (quat), 94.4 (quat), 122.2 (quat), 127.2 (CH), 127.4 (CH), 127.9 (CH), 132.3 (CH), 142.3 (quat); **IR**: 3302, 2956, 2926, 2902, 2180, 1660, 1579, 1485, 1463, 1450, 1220 cm^{-1}; **HRMS**: (EI) calculated for $C_{13}H_{16}O_1$: 188.1196, found: 188.1195.



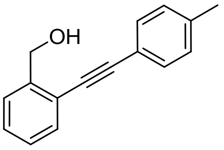
2-(3-Cyclohexylprop-1-ynyl)benzyl alcohol, 19e. 477 mg of the product were obtained as a colourless oil (98% yield) after 15 h reaction from Sonogashira coupling between 2-iodobenzyl alcohol (500 mg, 2.13 mmol) and 3-cyclohexyl-1-propyne (345 μL, 2.34 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.03-1.33 (5H, m), 1.65-1.89 (5H, m), 2.35 (2H, d, *J*= 6.6 Hz), 4.80 (2H, s), 7.22 (1H, td, *J*= 7.5, 1.5 Hz), 7.28 (1H, td, *J*= 7.5, 1.5 Hz), 7.38-7.42 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.1 (CH_2), 26.2 (2 × CH_2), 27.4 (CH_2), 32.8 (CH_2), 37.5 (CH), 64.3 (CH_2), 79.0 (quat), 94.4 (quat), 122.2 (quat), 127.2 (CH), 127.4 (CH), 128.9 (CH), 132.2 (CH), 142.3 (quat); **IR** (neat): 3352 (bs), 2920, 2848, 2220, 1448 cm^{-1}; **HRMS**: (EI) calculated for $C_{16}H_{20}O$ $[M^+]$: 228.1509, found: 228.1507.



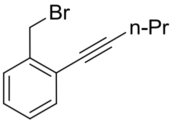
2-Cyclohexylethynylbenzyl alcohol, **19f**. The general procedure D afforded 356 mg of the product (78% yield) after 15 h from 2-iodobenzyl alcohol (499 mg, 2.13 mmol) and the corresponding alkyne. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.35-1.44 (3H, m), 1.52-1.58 (3H, m), 1.73-1.77 (2H, m), 1.88-1.91 (2H, m), 2.62-2.66 (1H, m), 4.80 (2H, s), 7.22 (1H, td, *J*= 7.4, 1.3 Hz), 7.29 (1H, dd, *J*= 7.4, 1.3 Hz), 7.37-7.42 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.8 (CH_2), 25.9 (2 × CH_2), 29.8 (CH), 32.7 (2 × CH_2), 64.4 (CH_2), 78.1

(quat), 99.7 (quat), 122.2 (quat), 127.2 (CH), 127.4 (CH), 127.9 (CH), 132.1 (CH), 142.4 (quat); **IR** (neat): 3354 (b), 2927, 2852, 2224, 1483, 1448, 1037, 1008 cm^{-1}; **HRMS:** (EI) calculated for $C_{15}H_{18}O$ [M^+]: 214.1352, found: 214.1353.

2-*p*-Tolylethynylbenzyl alcohol, **19g**. A white solid was obtained (850 mg, 90% yield) after 12 h reaction from 2-iodobenzyl alcohol (0.99 g, 4.26 mmol) and *p*-tolylacetylene (0.6 mL, 4.70 mmol). **m.p.:** 60-62 ^{o}C **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.38 (3H, s), 4.91 (2H, d, *J*= 6.4 Hz), 7.18 (2H, d, *J*= 7.9 Hz), 7.28 (1H, td, *J*= 7.5, 1.4 Hz), 7.35 (1H, td, *J*= 7.5, 1.4 Hz), 7.43-7.44 (2H, m), 7.46-7.48 (1H, m), 7.54 (1H, dd, *J*= 7.5, 1.3 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.5 (CH_3), 64.0 (CH_2), 86.0 (quat), 94.4 (quat), 119.8 (quat), 121.4 (quat), 127.2 (CH), 127.4 (CH), 128.5 (CH), 129.2 (2 × CH), 131.4 (2 × CH), 132.0 (CH), 138.7 (quat), 142.4 (quat); **IR** (neat): 3338 (bs), 3059, 2947, 2858, 2216, 1510, 1450; **HRMS:** (EI) calculated for $C_{16}H_{14}O_1$:222.1039, found: 222.1038.

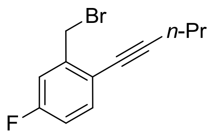


General procedure E: synthesis of 2-ethynylbenzyl bromides (step b)

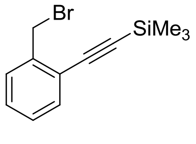


The synthesis of 2-ethynylbenzyl bromides was carried out using Sashida and co-workers' procedure[26]. The preparation of **2-pent-1-ynylbenzyl bromide**, **20a**, is described as an example. To a solution of 2-pent-1-ynylbenzyl alcohol, **19a**, (590 mg, 3.4 mmol) and pyridine (360 μL, 4.34 mmol) in $CHCl_3$ (3.4 mL) at 0 ºC was slowly added phosphorus tribromide (350 μL, 3.69 mmol). The mixture was left to react at r.t. for 2 h, and then poured into ice-water. The aqueous phase was extracted twice with CH_2Cl_2 (15 mL × 2) and the combined organic layer was washed with 5% H_2SO_4 (15 mL × 2), sat. $NaHCO_3$ (15 mL × 2), and brine (15 mL × 2). Then, it was dried with $MgSO_4$ and the solvent was evaporated under reduced pressure and the crude material purified using silica gel column chromatography (hexane:CH_2Cl_2, 9:1) to give 630 mg of a clear oil (79%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.09 (3H, t, *J*= 7.2 Hz), 1.68 (2H, sext. *J*= 7.2 Hz), 2.46 (2H, t, *J*= 7.2 Hz), 4.67 (2H, *s*), 7.21-7.27 (2H, m), 7.39-7.41 (2H, m); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.6 (CH_2), 22.1 (CH_2), 32.3 (CH_2), 77.8 (quat), 96.4 (quat), 124.0 (quat), 128.0 (CH), 128.3 (CH), 129.6 (CH), 132.5 (CH), 139.0 (quat); **IR** (neat): 2963, 2933, 2871, 2234, 1600, 1485, 1450, 1338, 1265, 1222 cm^{-1}; **HRMS**: (EI) calculated for $C_{12}H_{13}Br^{79}$ [M^+]: 236.0195, found: 236.0194.

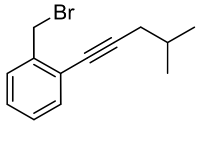
5-Fluoro-2-pent-1-ynylbenzyl bromide, **20b**. Starting from 5-fluoro-2-pent-1-ynylbenzyl alcohol (86 mg, 0.45 mmol), the general procedure E (2 h reaction time) gave 70.9 mf of the named product as a colourless oil (62% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.08 (3H, t, *J*= 7.2 Hz), 1.67 (2H, sext, *J*= 7.2 Hz), 2.44 (3H, t, *J*= 7.2 Hz), 4.61 (2H, s), 6.94 (1H, td, *J*= 8.4, 2.7 Hz), 7.12 (1H, dd, *J*= 8.9, 2.7 Hz), 7.38 (1H, dd, *J*= 8.9, 5.7 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.6 (CH_2), 22.1 (CH_2), 31.3 (CH_2, d, $J_{C\text{-}F}$= 1.7 Hz), 76.9 (quat), 96.0 (quat, d, $J_{C\text{-}F}$=1.6 Hz), 115.6 (CH, d, $J_{C\text{-}F}$= 21.9 Hz), 116.5 (CH, d, $J_{C\text{-}F}$= 22.7 Hz), 120.0 (quat, d, $J_{C\text{-}F}$= 3.4 Hz), 134.2 (CH, d, $J_{C\text{-}F}$= 8.3 Hz), 141.2 (quat, d, $J_{C\text{-}F}$= 7.9 Hz), 161.7 (quat, d, $J_{C\text{-}F}$= 249.2 Hz); **IR** (neat): 2958, 2933, 2908, 2837, 1604, 1502, 1463, 1438, 1382, 1259, 1153 cm^{-1}; **HRMS**: (EI) calculated for $C_{12}H_{12}Br^{79}F$: 254.0101, found: 254.0100.



2-Trimethylsylyethynyllbenzyl bromide, **20c**. Prepared according to the general procedure E (297 mg, 76% yield) after 4h reaction from **19c** (300 mg, 1.47 mmol). The NMR spectroscopic data are in accordance with literature values[26]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.29 (9H), 4.67 (2H, s), 7.23 (1H, td, *J*= 7.5, 1.5 Hz), 7.3 (1H, td, *J*= 7.5, 1.5 Hz), 7.41 (1H, dd, *J*= 7.5, 1.3 Hz), 7.46 (1H, dd, *J*= 7.5, 1.3 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -0.1 (3 × CH_3), 31.8 (CH_2), 100.3 (quat), 101.6 (quat), 121.9 (quat), 127.7 (CH), 128.2 (CH), 128.84 (CH), 132.5 (CH), 139.9 (quat).

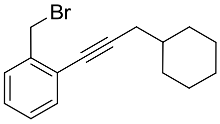


2-(4-Methylpent-1-ynyl)-benzyl bromide, **20d**. The named compound was obtained as colourless oil (293 mg, 71% yield) from 2-(4-Methylpent-1-ynyl)benzyl alcohol, **19d**, (310 mg, 1.65 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.10 (3H, s), 1.12 (3H, s), 2.00 (1H, sept, *J*= 6.6 Hz), 2.41 (2H, d, *J*= 6.6 Hz), 4.70 (2H, s), 7.23-7.29 (2H, m), 7.41-7.45 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.2 (2 × CH_3), 28.3 (CH), 28.3 (CH_2), 32.3 (CH_2), 78.6

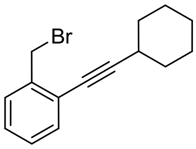


(quat), 95.4 (quat), 124.0 (quat), 127.9 (CH), 128.3 (CH), 129.5 (CH), 132.5 (CH), 138.9 (quat); **IR**: 2956, 2926, 2902, 2180, 1660, 1579, 1485, 1463, 1450, 1220; **HRMS**: (EI) calculated for $C_{13}H_{15}Br^{79}$:250.0352, found: 250.0353.

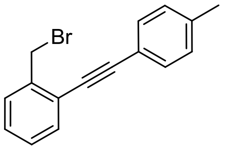
2-(3-Cyclohexylprop-1-ynyl)benzyl bromide, 20e. The general procedure E (8 h reaction time, 1.74 mmol scale) afforded 348 mg of the desired product (69% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.09-1.16 (3H, m), 1.25-1.31 (3H, m), 1.65-1.69 (1H, m), 1.74-1.77 (2H, m), 1.88-1.91 (2H, m), 2.38 (2H, d, *J*= 6.5 Hz), 4.67 (2H, s), 7.24 (2H, ddd, *J*= 7.4, 5.1, 1.7 Hz), 7.37-7.41 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.2 (2 × CH_2), 26.3 (CH_2), 27.5 (CH_2), 32.4 (CH_2), 32.8 (2 × CH_2), 37.5 (CH), 78.6 (quat), 95.5 (quat), 124.1 (quat), 127.9 (CH), 128.3 (CH), 129.6 (CH), 132.5 (CH), 139.0 (quat); **IR** (neat): 2922, 2850, 2222, 1485, 1448, 1263, 1220 cm^{-1}; **HRMS**: (ESI) calculated for $C_{16}H_{19}Br^{79}$ [M^+]:290.0665, found: 290.0662.



2-Cyclohexylethynylbenzyl bromide, **20f**. General procedure E (4h reaction time, 1.66 mmol scale) afforded 207 mg the desired product (45% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.37-1.40 (3H, m), 1.58-1.65 (2H, m), 1.76-1.82 (2H, m), 1.90-1.93 (2H, m), 2.66-2.71 (1H, m), 4.67 (2H, s), 7.22-7.25 (2H, m), 7.38-7.41 (2H, m); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 24.8 (CH_2), 25.9 (2 × CH_2), 29.8 (CH), 32.4 (2 × CH_2), 32.5 (CH_2), 77.7 (quat), 100.7 (quat), 124.1 (quat), 127.9 (CH), 128.3 (CH), 129.5 (CH), 132.4 (CH), 139.0 (quat); **IR** (neat): 2933, 2856, 2198, 1485, 1448, 1263, 1220, 1053 cm^{-1}; **HRMS**: (EI) calculated for $C_{15}H_{17}Br^{79}$ [MH^+]: 276.0508, found: 276.0508.



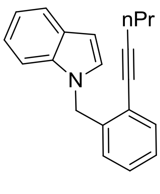
2-*p*-Tolylethynylbenzyl bromide, **20g**. General procedure E afforded the desired product as a colourless oil in 52% yield (1.19 g) from 2-*p*-tolylethynylbenzyl alcohol (933 mg, 4.2 mmol) after 5 h reaction. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.40 (3H, s), 4.76 (2H, s), 7.20 (2H, dd, *J*= 6.8, 1.2 Hz), 7.29-7.37 (2H, m), 7.44-7.46 (1H, m), 7.49 (2H, dd, *J*= 5.8,



1.5 Hz), 7.54-7.58 (1H, m); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 21.5 (CH_3), 32.1 (CH_2), 85.8 (quat), 95.4 (quat), 119.9 (quat), 123.5 (quat), 128.5 (CH), 128.6 (CH), 129.2 (2 × CH), 129.7 (CH), 131.5 (2 × CH), 132.4 (CH), 138.8 (quat), 139.1 (quat); **IR**: 3028, 2920, 2214, 1597, 1510, 1481, 1448, 1263, 1220 cm^{-1}; **HRMS**: (EI) calculated for $C_{16}H_{13}Br^{79}$: 284.0195, found: 290.0196.

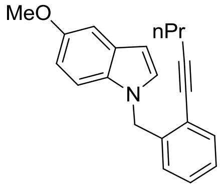
General procedure F: *N*-alkylation of indole derivatives with 2-ethynylbenzyl bromides[17] **(step c)**

The indole derivative (8.5 mmol) was weighed in an oven dried 100 mL round bottomed flask and dissolved in dry DMF (50 mL) under N_2 atmosphere. NaH (60% in mineral oil, 9.3 mmol) was added portion wise and the mixture was stirred for 1h at r.t. A solution of 2-ethynylbenzyl bromide (9.3 mmol) dissolved in DMF (5 mL) was then added via cannula under N_2. The reaction was left stirring for 3-15h until no indole starting material was seen by TLC. The mixture was then quenched with EtOAc (30 mL) and water (30 mL), and the two layers separated. The aqueous layer was extracted with EtOAc (30 mL × 2), and the combined organic layers washed with brine (30 mL × 2), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane:CH_2Cl_2 mixtures).

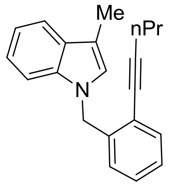


1-(2-Pent-1-ynylbenzyl)-*1H*-indole, **21a**. The general procedure F afforded 2.04 g of the named product (88% yield) as a colourless oil, solidifying on standing. **m.p.**: 36-38 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): 1.07 (3H, t, *J*= 7.5 Hz), 1.66 (2H, m), 2.46 (2H, t, *J*= 7.0 Hz), 5.49 (2H, s), 6.57 (1H, d, *J*= 3.0 Hz), 6.67 (1H, d, *J*= 8.0 Hz), 7.09-7.19 (5H, m), 7.31 (1H, d, *J*= 8.0 Hz), 7.45 (1H, d, *J*= 8.0 Hz), 7.66 (1H, d, *J*= 8.0 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.6 (CH_2), 22.2 (CH_2), 48.6 (CH_2), 78.2 (quat), 96.2 (quat), 101.6 (CH), 109.8 (CH), 119.5 (CH), 120.9 (CH), 121.6 (CH), 122.3 (quat), 126.4 (CH), 127.2 (CH), 128.0 (CH), 128.4 (CH), 128.5 (quat), 132.2 (CH), 136.4 (quat), 139.0 (quat) **IR** (neat): 3096, 2999, 2997, 2253, 1711, 1501, 1437 $^{cm-1}$; **HRMS**: (ESI) calculated for $C_{20}H_{20}N$ [MH^+]: 274.1590, found: 274.1596.

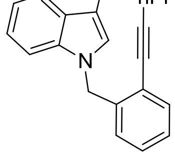
5-Methoxy-1-(2-pent-1-ynylbenzyl)-*1H*-indole, 21b. *N*-alkylation of 5-methoxyindole (206 mg, 1.41 mmol) with the corresponding bromide according to general procedure F, afforded 320 mg of a colourless oil (75%). **^{1}H NMR** (500 MHz, CDCl$_3$): δ 1.06 (3H, t, *J*= 7.4 Hz), 1.65 (2H, tt, *J*= 7.4, 7.0 Hz), 2.45 (2H, t, *J*= 7.0 Hz), 3.85 (3H, s), 5.44 (2H, s), 6.48 (1H, d, *J*= 2.7 Hz), 6.65 (1H, d, *J*= 7.7 Hz), 6.82 (1H, dd, *J*= 7.7, 2.7 Hz), 7.10-7.14 (3H, m), 7.18 (2H, d, *J*= 8.1 Hz), 7.44 (1H, d, *J*= 7.4 Hz); **^{13}C NMR** (150 MHz, CDCl$_3$): δ 13.6 (CH$_3$), 21.6 (CH$_2$), 22.2 (CH$_2$), 48.8 (CH$_2$), 55.9 (CH$_3$), 78.2 (quat), 96.2 (quat), 101.1 (CH), 102.5 (CH), 110.5 (CH), 112.0 (CH), 122.2 (quat), 126.3 (CH), 127.2 (CH), 128.0 (CH), 129.0 (quat), 129.0 (CH), 131.7 (quat), 132.2 (CH), 139.1 (quat), 154.1 (quat); **IR** (neat): 2965, 2837, 2252, 1623, 1488, 1449, 1239, 1151, 1033 cm^{-1}; **HRMS**: (ESI) calculated for C$_{21}$H$_{22}$ON [MH$^+$]: 304.1696, found: 304.1693.



3-Methyl-1-(2-pent-1-ynylbenzyl)-*1H*-indole, 21c. *N*-alkylation of 3-methylindole (288mg, 2.2 mmol) with 2-pent-1-ynylbenzyl bromide, **20a** (573 mg, 2.4 mmol) afforded 556 mg the desired product (88% yield). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.08 (3H, t, *J*= 7.3 Hz), 1.67 (2H, sext, *J*= 7.3 Hz), 2.36 (3H, d, *J*= 1.0 Hz), 2.46 (2H, t, *J*= 7.3 Hz), 5.43 (2H, s), 6.70 (1H, dd, *J*= 7.7, 0.6 Hz), 6.93 (1H, d, *J*= 1.0 Hz), 7.08-7.20 (4H, m), 7.26-7.28 (1H, m), 7.45 (1H, dd, *J*= 7.5, 1.0 Hz), 7.6 (1H, dd, *J*= 7.7, 2.0 Hz); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 9.6 (CH$_3$), 13.6 (CH$_3$), 21.6 (CH$_2$), 22.2 (CH$_2$), 48.2 (CH$_2$), 78.3 (quat), 96.1 (quat), 109.5 (CH), 110.8 (quat), 118.7 (CH), 118.9 (CH), 121.5 (CH), 122.2 (quat), 126.0 (CH), 126.5 (CH), 127.1 (CH), 128.0 (CH), 129.8 (quat), 132.1 (CH), 136.7 (quat), 139.3 (quat); **IR** (neat): 3056, 3030,2962, 2931, 2871, 2232, 1614, 1482, 1466, 1352, 1331 cm^{-1}; **HRMS**: (ESI) calculated for C$_{21}$H$_{22}$N [MH$^+$]: 288.1747, found: 288.1750.

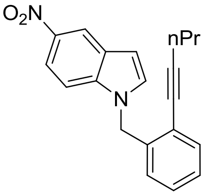


1-(2-Pent-1-ynylbenzyl)-*1H*-indole-3-carbaldehyde, 21d. A white solid was obtained (390 mg, 90% yield) after the *N*-alkylation of *1H*-indole-3-



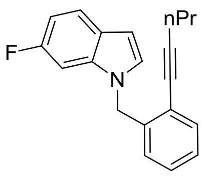
carbaldehyde (343 mg, 1.40 mmol) with 2-pent-1-ynylbenzyl bromide, **20a** (363 mg, 1.54 mmol) in 15 h reaction according to procedure F. **m.p.:** 44-46 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.99 (3H, t, *J*= 7.5 Hz), 1.57 (2H, tt, *J*= 7.5, 7.0 Hz), 2.37 (2H, t, *J*= 7.0 Hz), 5.50 (2H, s), 6.92 (1H, d, *J*= 7.5 Hz), 7.20 (1H, td, *J*= 8.0, 1.5 Hz), 7.27 (1H, td, *J*= 7.5, 1.0 Hz), 7.31-7.33 (2H, m), 7.38-7.40 (1H, m), 7.49 (1H, dd, *J*=7.5, 1.0 Hz), 7.72 (1H, s), 8.33 (1H, m), 10.00 (1H, s); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.5 (CH_2), 22.0 (CH_2), 49.4 (CH_2), 77.9 (quat), 96.7 (quat), 110.4 (CH), 118.4 (quat), 121.1 (CH), 123.0 (CH), 123.3 (quat), 124.1 (CH), 128.2 (CH), 125.4 (quat), 127.4 (CH), 128.2 (CH), 128.2 (CH), 132.7 (CH), 136.5 (CH), 137.6 (quat), 138.7 (quat), 184.6 (CHO); **IR** (neat): 2960, 2929, 2868, 2806, 2229, 1651, 1529, 1384 cm^{-1}; **HRMS**: (ESI) calculated for $C_{21}H_{20}ON$ [MH^{+}]: 302.1539, found: 302.1541.

5-Nitro-1-(2-pent-1-ynylbenzyl)-*1H*-indole, 21e. The alkylation of 5-nitroindole



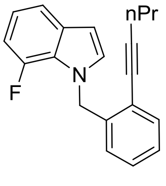
(204 mg, 1.23 mmol) with 2-pent-1-ynylbenzyl bromide (319 mg, 1.34 mmol) gave 219 mg of a solid yellow (56% yield) after 15 h reaction. **m.p.:** 70-72 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.04 (3H, t, *J*= 7.2 Hz), 1.59-1.65 (2H, m), 2.42 (2H, t, *J*= 6.8 Hz), 5.50 (2H, s), 6.73-6.76 (2H, m), 7.16 (1H, t, *J*= 7.5 Hz), 7.24 (1H, t, *J*= 7.5 Hz), 7.29 (1H, bs), 7.36 (1H, d, *J*= 9.0 Hz), 7.48 (1H, d, *J*= 7.5 Hz), 8.09 (1H, d, *J*= 9.0 Hz), 8.62 (1H, bs); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.5 (CH_2), 22.1 (CH_2), 49.1 (CH_2), 78.0 (quat), 96.6 (quat), 104.3 (CH), 109.7 (CH), 117.4 (CH), 118.2 (CH), 122.8 (quat), 126.6 (CH), 127.8 (quat), 127.9 (CH), 128.2 (CH), 131.5 (CH), 132.6 (CH), 137.4 (quat), 139.2 (quat), 141.7 (quat); **IR** (neat): 2962, 2923, 2863, 2225, 1579, 1515, 1477, 1450, 1401, 1331, 1068 cm^{-1}; **HRMS**: (ESI) calculated for $C_{20}H_{19}N_2O_2$ [MH^{+}]: 319.1441, found: 319.1444.

6-Fluoro-1-(2-pent-1-ynylbenzyl)-*1H*-indole, 21f. N-Alkylation of 6-fluoroindole

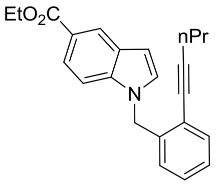


with 2-pent-1-ynylbenzyl bromide according to general procedure F (1.5 mmol scale) afforded **5d** (210 mg, 48%) as a pale brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.09 (3H, t, *J*= 7.4 Hz), 1.68 (2H, m), 2.48 (2H, t, *J*= 7.0 Hz), 5.44 (2H, s), 6.56 (1H, dd, *J*= 3.2, 0.7 Hz), 6.74 (1H, dd, *J*= 7.7, 0.7 Hz), 6.90 (1H, ddd, *J*= 9.7, 8.7, 2.2 Hz), 7.02 (1H, dd, *J*= 9.7, 2.2 Hz), 7.14-7.18 (2H, m), 7.22 (1H, td, *J*= 7.6, 1.3 Hz), 7.46 (1H, dd, *J*= 7.6, 1.3 Hz), 7.57 (1H, dd, *J*= 8.6, 5.4 Hz); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 13.6 (CH$_3$), 21.6 (CH$_2$), 22.2 (CH$_2$), 48.7 (CH$_2$), 78.2 (quat), 96.3 (CH, d, $J_{\text{C-F}}$= 26.2 Hz), 96.3 (quat), 101.8 (CH), 108.3 (CH, d, $J_{\text{C-F}}$= 24.4 Hz), 121.6 (CH, d, $J_{\text{C-F}}$= 10.0 Hz), 122.5 (quat), 125.0 (quat), 126.5 (CH), 127.4 (CH), 128.0 (CH), 128.8 (CH, d, $J_{\text{C-F}}$= 3.6 Hz), 132.3 (CH), 136.4 (quat, d, $J_{\text{C-F}}$= 23.4 Hz), 138.4 (quat), 159.8 (quat, d, $J_{\text{C-F}}$=237.4 Hz); **IR** (neat): 2962, 2872, 2231, 1620, 1487, 1465, 1452, 1330, 1251, 1166 cm^{-1}; **HRMS**: (APCI) calculated for $C_{20}H_{19}NF$ [MH$^+$]: 292.1496, found: 292.1500.

7-Fluoro-1-(2-pent-1-ynylbenzyl)-*1H*-indole, 21g. *N*-alkylation reaction of 7-indole following general procedure F (1.5 mmol scale) afforded 230 mg of a pale brown oil (53% yield) after 2 h reaction. The reaction flask was covered with aluminum foil as 7-fluoroindole is light sensitive. **^{1}H NMR** (500 MHz, CDCl$_3$): δ 1.05 (3H, t, *J*= 7.4 Hz), 1.64 (2H, tt, *J*= 7.4, 7.0 Hz), 2.43 (2H, t, *J*= 7.0 Hz), 5.66 (2H, s), 6.55 (1H, dd, *J*= 3.0, 2.4 Hz), 6.73 (1H, d, *J*= 7.4 Hz), 6.85 (1H, ddd, *J*= 12.8, 7.8, 0.6 Hz), 6.97-7.01 (1H, m), 7.11 (1H, d, *J*= 3.0 Hz), 7.13 (1H, td, *J*= 7.5, 1.4 Hz), 7.19 (1H, td, *J*= 7.5, 1.4 Hz), 7.39 (1H, d, *J*= 7.9 Hz), 7.44 (1H, dd, *J*= 7.6, 1.3 Hz); **^{13}C NMR** (125 MHz, CDCl$_3$): δ 13.6 (CH$_3$), 21.5 (CH$_2$), 21.2 (CH$_2$), 50.6 (CH$_2$), 78.3 (quat), 95.9 (quat), 102.6 (CH), 107.3 (CH, d, $J_{\text{C-F}}$= 18.0 Hz), 116.7 (CH, d, $J_{\text{C-F}}$= 3.5 Hz), 119.7 (CH, d, $J_{\text{C-F}}$= 6.5 Hz), 122.3 (CH), 124.4 (quat, d, $J_{\text{C-F}}$=9.4 Hz), 126.4 (quat), 127.2 (CH), 128.0 (CH), 129.7 (CH), 132.2 (CH), 135.6 (quat, d, $J_{\text{C-F}}$= 5.5 Hz), 139.8 (quat), 150.3 (quat, d, $J_{\text{C-F}}$= 243.8 Hz); **IR**: 2960, 2929, 2229, 1573, 1490, 1452, 1313, 1238, 1190, 1178, 1029 cm^{-1}; **HRMS**: (APCI) calculated for $C_{20}H_{19}NF$ [MH$^+$]: 292.1496, found: 292.1496.

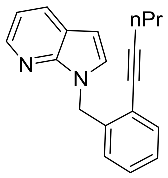


1-(2-Pent-1-ynylbenzyl)-*1H*-indole-5-carboxylic acid ethyl ester, 21h. The general *N*-alkylation reaction (procedure F) between *1H*-indole-5-carboxylic acid (502 mg, 3.10 mmol) and 2-pent-1-ynylbenzyl



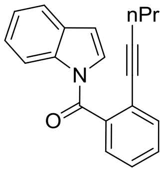
bromide, **20a** (1.62 g, 6.82 mmol) afforded the dialkylated product. The crude obtained after the usual aqueous work-up and solvent evaporation was dissolved in EtOH (50 mL) and LiOH (223 mg, 9.30 mmol) was added. The mixture was left stirring overnight and then the solvent was evaporated under vacuum. The crude was partitioned between EtOAc and water (15 mL each), the layers were separated and the aqueous one was further extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine (15 mL × 3), then dried over $MgSO_4$, filtered and the solvent evaporated. The residue was purified through flash chromatography on silica (hexane:CH_2Cl_2, 6:4) to give 396 mg of **5f** as a colourless oil (37% yield after two steps, 46% of 2-pent-1-ynylbenzyl alcohol was recovered). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.05 (3H, t, *J*= 7.4 Hz), 1.41 (3H, t, *J*= 7.1 Hz), 1.63 (2H, m), 2.43 (2H, t, *J*= 7.0 Hz), 4.39 (2H, q, *J*= 7.1 Hz), 5.49 (2H, s), 6.65 (1H, dd, *J*= 3.2, 0.7 Hz), 6.69 (1H, dd, *J*= 7.7, 0.7 Hz), 7.12 (1H, td, *J*= 7.7, 1.3 Hz), 7.18-7.22 (2H, m), 7.33 (1H, d, *J*= 8.7 Hz), 7.46 (1H, dd, *J*= 7.6, 1.1 Hz), 7.89 (1H, dd, *J*= 8.7, 1.6 Hz), 8.42 (1H, dd, *J*= 1.6, 0.4 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 14.5 (CH_3), 21.6 (CH_2), 22.2 (CH_2), 48.8 (CH_2), 60.5 (CH_2), 78.1 (quat), 96.4 (quat), 103.2 (CH), 109.4 (CH), 122.0 (quat), 122.6 (quat), 123.1 (CH), 123.9 (CH), 126.5 (CH), 127.5 (CH), 128.1 (CH), 128.1 (quat), 129.7 (CH), 132.3 (CH), 138.3 (quat), 138.8 (quat), 167.7 (CO); **IR** (neat): 2927, 2933, 2228, 1707, 1612, 1308, 1254, 1184 cm^{-1}; **HRMS**: (ESI) calculated for $C_{23}H_{24}O_2N$ [MH^+]: 346.1802, found: 346.1798.

1-(2-Pent-1-ynylbenzyl)-*1H*-7-azaindole, 21i. General procedure F afforded 320 mg of the named product as a colourless oil (67% yield) from 7-azaindole following general procedure F (1.7 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.03 (3H, t, *J*= 7.4 Hz), 1.60 (2H, m), 2.39 (2H, t, *J*= 7.0 Hz), 5.68 (2H, s), 6.48 (1H, d, *J*= 3.5 Hz), 6.92 (1H, dd, *J*= 7.5, 0.8 Hz), 7.08 (1H, dd, *J*= 7.8, 4.7 Hz), 7.14 (1H, td, *J*= 7.5, 1.5 Hz), 7.19 (1H, td, *J*= 7.5, 1.5 Hz), 7.23 (1H, d, *J*= 3.5 Hz), 7.44 (1H, dd, *J*= 7.5, 1.5 Hz), 7.93 (1H, dd, *J*= 7.6, 1.5 Hz), 8.36 (1H, dd, *J*= 4.7, 1.5 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.5 (CH_2), 22.2 (CH_2), 46.2 (CH_2), 78.4 (quat), 95.7 (quat), 99.9 (CH), 115.8 (CH), 120.4 (quat), 123.0 (quat), 127.3 (CH), 127.5 (CH), 127.9 (CH), 128.0 (CH), 128.7 (CH), 132.2 (CH), 139.2 (quat), 142.9 (CH), 147.8 (quat); **IR** (neat): 3053,

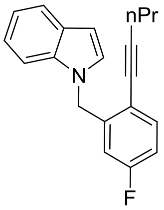


2962, 2932, 2871, 2232, 1690, 1594, 1571, 1510, 1486, 1450, 1265 cm^{-1} **HRMS**: (ESI) calculated for $C_{20}H_{19}N_2$ [MH$^+$]: 275.1543, found: 275.1544.

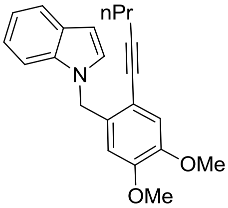
1-(2-Pent-1-ynylbenzoyl)-*1H*-indole, **21j**. The general *N*-alkylation procedure F between indole (996 mg, 8.5 mmol) and 2-iodobenzoyl chloride (2.48 g, 9.31 mmol) afforded the known product 1-(2-iodobenzoyl)-1H-indole[89] (2.12 g, 72% yield) as colourless prisms. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.61 (1H, d, *J*= 3.7 Hz), 6.95 (1H, bs), 7.24 (1H, td, *J*= 7.7, 2.0 Hz), 7.33 (1H, td, *J*= 7.7, 0.6 Hz), 7.40 (1H, t, *J*= 7.7 Hz), 7.44 (1H, dd, *J*= 7.7, 1.7 Hz), 7.51 (1H, td, *J*= 7.5, 1.0 Hz), 7.59 (1H, d, *J*= 7.7 Hz), 7.95 (1H, dd, *J*= 7.5, 1.0 Hz), 8.02 (1H, bs); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 92.5 (quat), 109.8 (CH), 121.0 (CH), 124.4 (CH), 125.3 (CH), 126.7 (CH), 128.3 (CH), 128.3 (CH), 131.1 (quat), 131.6 (CH), 135.4 (quat), 139.6 (CH), 141.1 (quat), 162.5 (CO). 1-(2-iodobenzoyl)-1H-indole (500 mg, 1.44 mmol) was weighed in a dry reaction tube with a screw cap. Diisopropylamine (5 mL) was added *via* syringe and the mixture was bubbled with N_2 for 10 min. Meanwhile $PdCl_2(PPh_3)_2$ (10 mg, 0.014 mmol) and CuI (5.3 mg, 0.028 mmol) were added followed by 1-pentyne (170 µL, 1.72 mmol). The mixture was purged with N_2, the tube was capped and heated up to 60 ºC. After 4 h of reaction the tube was left to cool down to r.t. and the content was filtered through a silica pad, eluting with EtOAc. The crude was concentrated and purified through a silica column (hexane:CH_2Cl_2, 6:4) giving 292 mg (71%) of a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.65 (3H, t, *J*= 7.4 Hz), 1.16 (2H, tt, *J*= 7.4, 6.9 Hz), 2.07 (2H, t, *J*= 6.9 Hz), 6.56 (1H, d, *J*= 3.5 Hz), 7.05 (1H, d, *J*= 3.5 Hz), 7.30 (1H, t, *J*= 7.5 Hz), 7.36 (1H, t, *J*= 7.5 Hz), 7.42 (1H, td, *J*= 1, 7.5 Hz), 7.47 (1H, td, *J*= 7.5, 1.4 Hz), 7.51 (2H, d, *J*= 7.6 Hz), 7.57 (1H, d, *J*= 7.6 Hz), 8.40 (1H, bs); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 13.1 (CH_3), 21.2 (CH_2), 21.5 (CH_2), 77.3 (quat), 96.1 (quat), 108.8 (CH), 116.4 (CH), 120.7 (CH), 122.3 (quat), 123.9 (CH), 124.9 (CH), 127.4 (CH), 127.5 (CH), 127.7 (CH), 130.3 (CH), 130.9 (quat), 132.3 (CH), 135.5 (quat), 137.9 (quat), 168.1 (CO); **IR** (neat): 2962, 2930, 2233, 1687, 1536, 1451, 1380, 1344, 1207 cm^{-1}; **HRMS**: (ESI) calculated for $C_{20}H_{18}ON$ [MH$^+$]: 288.1383, found: 288.1386.



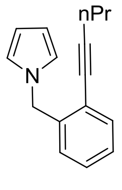
1-(5-Fluoro-2-pent-1-ynylbenzyl)-*1H*-indole, 21k. General procedure F for *N*-alkylation between indole and 5-fluoro-2-pent-1-ynylbenzyl bromide, **20b**, (1.2 mmol scale) gave 287 mg of the desired product (82%) after 4 h reaction. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.07 (3H, t, *J*= 7.4 Hz), 1.66 (2H, tt, *J*= 7.4, 7.0 Hz), 2.45 (2H, t, *J*= 7.0 Hz), 5.45 (2H, s), 6.33 (1H, dd, *J*= 8.4, 2.6 Hz), 6.58 (1H, d, *J*= 3.0 Hz), 6.87 (1H, td, *J*= 8.4, 2.6 Hz), 7.12 (1H, t, *J*= 7.3 Hz), 7.15 (1H, d, *J*= 3.2 Hz), 7.18 (1H, td, *J*= 7.7, 1.0 Hz), 7.27 (1H, d, *J*= 6.0 Hz), 7.42 (1H, dd, *J*= 8.4, 6.0 Hz), 7.67 (1H, d, *J*= 7.7 Hz); **^{13}C NMR:** (125 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.5 (CH_2), 22.2 (CH_2), 48.4 (CH_2), 77.3 (quat), 95.9 (quat), 102.1 (CH), 109.6 (CH), 113.6 (CH, d, J_{C-F}= 23.4 Hz), 114.5 (CH, d, J_{C-F}= 22.1 Hz), 118.1 (quat, d, J_{C-F}= 3.4 Hz), 119.7 (CH), 121.0 (CH), 121.9 (CH), 128.2 (CH), 128.6 (quat), 133.9 (CH, d, J_{C-F}= 8.2 Hz), 136.2 (quat), 141.9 (quat, d, J_{C-F}= 7.2 Hz), 162.3 (quat, d, J_{C-F}= 251.3 Hz); **IR** (neat): 2962, 2931, 2220, 1606, 1583, 1512, 1485, 1462, 1433, 1317, 1267, 1186 cm^{-1}; **HRMS**: (APCI) calculated for $C_{20}H_{19}NF$ [MH^+]: 292.1496, found: 292.1497.



1-(4,5-Dimethoxy-2-pent-1-ynylbenzyl)-*1H*-indole, 21l. This compound was prepared using an alternative ordering of the steps in the general procedure. Accordingly, 2-bromo-4,5-dimethoxybenzyl bromide[90] was synthesised first from 2-bromo-4,5-dimethoxybenzyl alcohol (1.01 g, 4.04 mmol) in 81% yield following the general bromination procedure E. **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 3.87 (3H, s), 3.88 (3H, s), 4.59 (2H, s), 6.93 (1H, s), 7.01 (1H, s); **^{13}C NMR** (400 MHz, $CDCl_3$): *δ* 34.1 (CH_2), 56.1 (CH_3), 56.2 (CH_3), 113.3 (CH), 114.9 (quat), 115.7 (CH), 128.8 (quat), 148.6 (quat), 149.9 (quat). Next, *N*-alkylation of indole with the corresponding bromide according to the general alkylation procedure F (2.92 mmol scale) afforded 758 mg of **1-(2-Bromo-4,5-dimethoxybenzyl)-*1H*-indole** as a white solid (75% yield). **m.p.:** 66-68 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.52 (3H, s), 3.86 (3H, s), 5.32 (2H, s), 6.16 (1H, s), 6.57 (1H, d, *J*= 3.1 Hz), 7.06 (1H, s), 7.11-7.14 (2H, m), 7.18-7.21 (1H, m), 7.29 (1H, d, *J*= 8.1 Hz), 7.66 (1H, d, *J*= 8.1 Hz); **^{13}C**



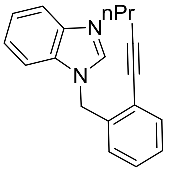
NMR (100 MHz, $CDCl_3$): δ 49.8 (CH_2), 55.8 (CH_3), 56.2 (CH_3), 102.0 (CH), 109.7 (CH), 111.1 (CH), 112.4 (quat), 115.5 (CH), 119.7 (CH), 120.1 (CH), 121.8 (CH), 128.1 (CH), 128.5 (quat), 128.7 (quat), 136.3 (quat), 148.8 (quat), 149.0 (quat); **IR** (neat): 3053, 3003, 2933, 2908, 1600, 1504, 1462, 1435, 1382, 1313, 1259, 1209, 1159 cm^{-1}; **HRMS**: (ESI) calculated for $C_{17}H_{17}O_2NBr^{79}$ [MH$^+$]: 346.0437, found: 346.0442. 1-(2-Bromo-4,5-dimethoxybenzyl)-*1H*-indole (400 mg, 1.15 mmol) was dissolved in diisopropylamine (14 mL) and bubbled with N_2 for 10 min. Meanwhile $Pd(OAc)_2$ (13.4 mg, 0.06 mmol), CuI (21 mg, 0.11 mmol), PPh_3 (60.2 mg, 0.23 mmol) and 1-pentyne (120 µL, 1.26 mmol) were added. The mixture was heated up to 100 ºC and left stirring under a N_2 atmosphere for 15 h. After this time the reaction was cooled down to r.t. and the crude material filtered through a silica pad eluting with EtOAc. The solvent was evaporated *in vacuo*. The residue was purified by flash chromatography on silica (hexane:EtOAc, 6:4) giving 188 mg of a colourless oil (51%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.05 (3H, t, *J*= 7.4 Hz), 1.64 (2H, m), 2.43 (2H, t, *J*= 7.0 Hz), 3.59 (3H, s), 3.86 (3H, s), 5.41 (2H, s), 6.30 (1H, s), 6.54 (1H, dd, *J*= 3.2, 0.8 Hz), 6.94 (1H, s), 7.1 (1H, ddd, *J*= 8.0, 7.0, 1.0 Hz), 7.15 (2H, d, *J*= 3.2 Hz), 7.18 (1H, td, *J*= 2.2, 1.1 Hz), 7.37 (1H, dd, *J*= 8.0, 0.8 Hz), 7.64 (1H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.7 (CH_3), 21.6 (CH_2), 22.3 (CH_2), 48.3 (CH_2), 55.7 (CH_3), 56.0 (CH_3), 78.3 (quat), 94.2 (quat), 101.6 (CH), 109.8 (CH), 110.0 (CH), 114.6 (CH), 114.7 (quat), 119.4 (CH), 120.9 (CH), 121.6 (CH), 128.2 (CH), 128.6 (quat), 132.0 (quat), 136.4 (quat), 148.0 (quat), 149.1 (quat); **IR** (neat): 2960, 2931, 2870, 2223, 1512, 1462, 1265, 1224, 1207 cm^{-1}; **HRMS**: (ESI) calculated for $C_{22}H_{24}O_2N$ [MH$^+$]: 334.1802, found: 334.1806.



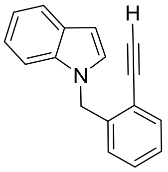
1-(2-Pent-1-ynylbenzyl)-*1H*-pyrrole, 21m. Alkylation of pyrrole and 2-pent-1-ynylbenzyl bromide using the general procedure F (3.70 mmol scale) afforded the desired product as colourless oil (458 mg, 55% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.07 (3H, t, *J*= 7.5 Hz), 1.67 (2H, tt, *J*= 7.5, 7.2 Hz), 2.46 (2H, t, *J*= 7.2 Hz), 5.23 (2H, s), 6.19 (2H, t, *J*= 2.0 Hz), 6.73 (2H, t, *J*= 2.0 Hz), 6.79 (1H, dd, *J*= 5.5, 3.7 Hz), 7.19 (2H, dd, *J*= 5.5, 3.7), 7.41 (1H, dd, *J*= 5.5, 3.7 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.6 (CH_2), 22.2 (CH_2), 51.8 (CH_2), 78.2 (quat), 95.7 (quat), 108.3 (2 × CH), 121.3 (2 × CH), 122.3

(quat), 126.7 (CH), 127.3 (CH), 128.1 (CH), 132.1 (CH), 139.9 (quat); **IR** (neat): 2963, 2931, 2231, 1708, 1496, 1450,1429, 1290, 1274, 1085 cm^{-1}; **HRMS**: (ESI) calculated for $C_{16}H_{18}N$ [MH$^+$]: 224.1434, found: 224.1436.

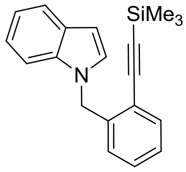
1-(2-Pent-1ynylbenzyl)-*1H*-benzimidazole, 21n. Benzimidazole was alkylated with 2-pent-1-ynylbenzyl bromide, **20a**, following the general procedure F (1.7 mmol scale) to furnish 307 mg of the product as a white solid (66% yield). **m.p.:** 64-66 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.03 (3H, t, *J*= 7.4 Hz), 1.62 (2H, tt, *J*= 7.4, 7.2 Hz), 2.42 (2H, t, *J*= 7.2 Hz), 5.49 (2H, s), 6.93 (1H, d, *J*= 7.0 Hz), 7.17 (1H, td, *J*= 7.6, 1.4 Hz), 7.22-7.29 (3H, m), 7.36 (1H, dd, *J*= 5.7, 2.0 Hz), 7.47 (1H, dd, *J*= 7.6, 1.4 Hz), 7.82 (1H, dd, *J*= 5.7, 2.0 Hz), 7.97 (1H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.5 (CH_2), 22.1 (CH_2), 47.4 (CH_2), 78.0 (quat), 96.7 (quat), 110.0 (CH), 120.3 (CH), 122.1 (CH), 122.9 (CH), 123.1 (quat), 127.2 (CH), 128.0 (CH), 128.1 (CH), 132.6 (CH), 134.0 (quat), 136.7 (quat), 143.4 (CH), 143.8 (quat); **IR** (neat): 2962, 2926, 2900, 2233, 1494, 1450, 1265, 1197 cm^{-1}; **HRMS**: (ESI) calculated for $C_{19}H_{19}N_2$: 275.1543, found: 275.1541.



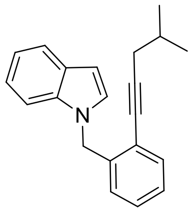
1-(2-ethynylbenzyl)-*1H*-indole, 21o. *N*-Alkylation of indole with 2-trimethylsylyethynylbenzyl bromide, **20c**, following the general procedure F (2.40 mmol scale) afforded 350 mg of a slightly brown solid (63% yield). Alkyne deprotection happened during the reaction due to the basic conditions. **m.p.**: 48-50 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.43 (1H, s), 5.52 (2H, s), 6.58 (1H, dd, *J*= 3.0, 0.5 Hz), 6.68 (1H, dd, *J*= 7.6, 0.5 Hz), 7.12 (1H, td, *J*= 7.6, 1.0 Hz), 7.16-7.19 (3H, m), 7.22 (1H, td, *J*= 7.5, 1.5 Hz), 7.29 (1H, td, *J*= 8.0, 0.5 Hz), 7.55 (1H, dd, *J*= 7.5, 1.5 Hz), 7.67 (1H, d, *J*= 7.5 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 48.3 (CH_2), 81.1 (quat), 82.8 (CH), 101.8 (CH), 109.7 (CH), 119.6 (CH), 120.2 (quat), 120.9 (CH), 121.7 (CH), 126.5 (CH), 127.3 (CH), 128.4 (CH), 128.6 (quat), 129.4 (CH), 132.8 (CH), 136.3 (quat), 139.9 (quat); **IR**: 3298, 3059, 3030, 2960, 2926, 2246, 1733, 1613, 1602, 1463, 1318 cm^{-1}; **HRMS**: (ESI) calculated for $C_{17}H_{14}N$ [MH$^+$]: 232.1121, found: 232.1122.



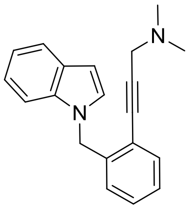
1-(2-Trimethylsilanylethynylbenzyl)-*1H*-indole, 21p. 2-Ethynylbenzyl-*1H*-indole (200 mg, 0.86 mmol) was weighed in an oven-dried flask and dissolved in dry THF (3 mL) under N_2 atmosphere. The flask was put in a -78 ºC dry ice/acetone bath and nBuLi (1.6 M, 650 μL, 1.04 mmol) was added dropwise during 15 min. The mixture was stirred 30 min. at -78 ºC and then 30 min. at r.t. After that it was cooled again at -78 ºC and trimethylsilyl chloride (165 μL, 1.29 mmol) was added dropwise *via* syringe. The reaction was left to warm up to r.t. during 2 h. After this time EtOAc and water (5 mL each) were added, the two phases were separated. The aqueous layer was further extracted with EtOAc (5 mL × 2), the combined organic layers were washed with brine (5 mL × 2), dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified through a silica column (hexane:CH_2Cl_2, 8:2) to give 258 mg of **5i** as a white solid (99%). **m.p.:**102-104 ºC **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.27 (9H, s), 5.49 (2H, s), 6.56 (1H, d, *J*= 2.5 Hz), 6.70 (1H, d, *J*= 7.1 Hz), 7.10-7.21 (5H, m), 7.32 (1H, dd, *J*= 8.1, 0.5 Hz), 7.51 (1H, dd, *J*= 7.6, 1.3 Hz), 7.66 (1H, d, *J*= 8.1 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ -0.1 (3 × CH_3), 48.4 (CH_2), 100.4 (quat), 101.7 (CH), 102.4 (quat), 109.8 (CH), 119.5 (CH), 120.9 (CH), 121.4 (quat), 121.7 (CH), 126.5 (CH), 127.2 (CH), 128.4 (CH), 128.6 (quat), 129.0 (CH), 132.5 (CH), 136.3 (quat), 139.6 (quat); **IR** (KBr): 3090, 2960, 2918, 2160, 1463, 1247 cm^{-1}; **HRMS**: (ESI) calculated for $C_{20}H_{22}NSi$ [MH^+]: 304.1516, found: 304.1520.



1-[2-(4-Methylpent-1-ynyl)-benzyl]-*1H*-indole, 21q. The usual alkylation procedure F (1.20 mmol scale) between indole and 2-(4-Methylpent-1-ynyl)benzyl bromide, **20d**, provided 335 mg of the desired product as a colourless (97% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.05 (3H, s), 1.07 (3H, s), 1.94 (1H, sept., *J*= 6.6 Hz), 2.38 (2H, d, *J*= 6.6 Hz), 5.49 (2H, s), 6.57 (1H, dd, *J*= 3.1, 0.7 Hz), 6.66 (1H, d, *J*= 7.7, 0.7 Hz), 7.08-7.13 (2H, m), 7.15-7.20 (3H, m), 7.31 (1H, dd, *J*= 8.1, 0.8 Hz), 7.46 (1H, dd, *J*= 7.6, 1.2 Hz), 7.66 (1H, ddd, J= 7.6, 1.2, 0.8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.1 (2 × CH_3), 28.2 (CH), 28.77 (CH_2), 48.6 (CH_2), 79.0 (quat),

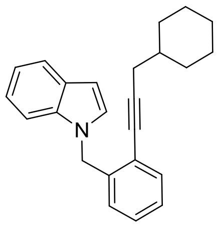


95.3 (quat), 101.6 (CH), 109.8 (CH), 119.5 (CH), 120.9 (CH), 121.6 (CH), 122.3 (quat), 126.4 (CH), 127.1 (CH), 128.0 (CH), 128.4 (CH), 128.6 (quat), 132.2 (CH), 136.4 (quat), 139.0 (quat); **IR**: 2957, 2924, 2904, 2868, 2220, 1512, 1483, 1462, 1450, 1317, 1178 cm^{-1}; **HRMS**: (ESI) calculated for $C_{21}H_{22}N$ [MH$^+$]: 288.1747, found: 288.1750.

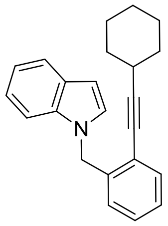


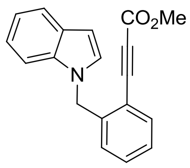
[3-(2-Indol-1-ylmethylphenyl)-prop-2-ynyl]-dimethyl amine, 21r. Order of the steps in the general procedure was altered. General procedure F, *N*-alkylation between indole and 2-iodobenzyl bromide (1.20 mmol scale) afforded 1-(2-iodobenzyl)-*1H*-indole[91] quantitatively. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.31 (2H, s), 6.48 (1H, dd, *J*= 7.7, 0.7 Hz), 6.60 (1H, d, *J*= 3.2 Hz), 6.96 (1H, td, *J*= 7.9, 1.6 Hz), 7.12-7.24 (5H, m), 7.68 (1H, d, *J*= 7.8, 1.0 Hz), 7.89 (1H, dd, *J*= 7.8, 1.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.1 (CH_2), 97.1 (quat), 102.1 (CH), 109.7 (CH), 119.7 (CH), 121.0 (CH), 121.9 (CH), 127.6 (CH), 128.3 (CH), 128.6 (quat), 128.7 (CH), 129.2 (CH), 136.2 (quat), 139.4 (CH), 139.5 (quat). The iodide (200 mg, 0.60 mmol) was weighed in a dry reaction tube and dissolved in Et_3N (2 mL), the mixture was bubbled with N_2 for 10 min. then $PdCl_2(PPh_3)_2$ (4.2 mg, 0.006 mmol), CuI (2.3 mg, 0.012 mmol) and *N,N*-dimethyl-2-propyn-1-amine (71 µL, 0.66 mmol) were added under N_2 atmosphere. The reaction was stirred for 15 h at r.t. then it was filtered through a silica pad, eluting with EtOAc and the solvent evaporated *in vacuo*. The crude was purified by flash chromatography on silica (hexane:CH_2Cl_2, 1:1) affording 160 mg of a colourless oil (92% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.38 (6H, s), 3.54 (2H, s), 5.51 (2H, s), 6.57 (1H, dd, *J*= 3.1, 0.7 Hz), 6.68 (1H, d, *J*= 7.7 Hz), 7.10-7.23 (5H, m), 7.30 (1H, d, *J*= 8.3 Hz), 7.51 (1H, dd, *J*= 7.6, 1.2 Hz), 7.66 (1H, dd, *J*= 7.3, 0.8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 44.3 (2 × CH_3), 48.6 (CH_2), 48.7 (CH_2), 82.7 (quat), 90.5 (quat), 101.7 (CH), 109.7 (CH), 119.5 (CH), 120.9 (CH), 121.4 (quat), 121.7 (CH), 126.5 (CH), 127.3 (CH), 128.3 (CH), 128.6 (CH), 132.5 (CH), 136.3 (quat), 139.1 (2 × quat); **IR** (neat): 2939, 2819, 2773, 2360, 1512, 1462, 1450, 1317, 1031 cm^{-1}; **HRMS**: (ESI) calculated for $C_{20}H_{21}N_2$ [MH$^+$]: 289.1699, found: 289.1698.

1-[2-(3-Cyclohexylprop-1-ynyl)-benzyl]-*1H*-indole, 21s. The general procedure F for the *N*-alkylation of indole and 2-(3-cyclohexylprop-1-ynyl)-benzyl bromide, **20e**, (0.73 mmol scale) afforded 158 mg (91%) of the desired product. ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 1.09-1.17 (3H, m), 1.18-1.32 (3H, m), 1.58-1.64 (1H, m), 1.71-1.76 (2H, m), 1.85-1.89 (2H, m), 2.37 (2H, d, *J*= 6.6 Hz), 5.48 (2H, s), 6.56 (1H, dd, *J*= 3.1, 0.8 Hz),6.68 (1H, d, *J*= 7.7 Hz), 7.08-7.13 (2H, m), 7.15-7.19 (3H, m), 7.31 (1H, dd, *J*= 8.1, 0.7 Hz), 7.45 (1H, dd, *J*= 7.6, 1.2 Hz), 7.66 (1H, d, *J*= 7.6 Hz); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 26.1 (2 × CH$_2$), 26.2 (CH$_2$), 27.4 (CH$_2$), 32.8 (2 × CH$_2$), 37.5 (CH), 48.6 (CH$_2$), 79.0 (quat), 95.3 (quat), 101.6 (CH), 109.8 (CH), 119.5 (CH), 120.9 (CH), 121.6 (CH), 122.4 (quat), 126.5 (CH), 127.2 (CH), 128.0 (CH), 128.4 (CH), 128.6 (quat), 132.2 (CH), 136.4 (quat), 138.9 (quat); **IR** (neat): 2920, 2848, 2220, 1612, 1512, 1483, 1462, 1448, 1350, 1317, 1192, 1178 cm^{-1}; **HRMS**: (ESI) calculated for $C_{24}H_{26}N$ [MH$^+$]: 328.2060, found: 328.2063.

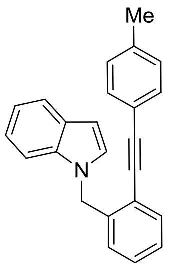


1-(2-Cyclohexylethynylbenzyl)-*1H*-indole, 21t. The general procedure F for the *N*-alkylation of indole and 2-cyclohexylethynylbenzyl bromide, **20f**, (0.67 mmol scale) gave 180 mg (86%) of a colourless oil. ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 1.34-1.42 (3H, m), 1.52-1.61 (3H, m), 1.73-1.80 (2H, m), 1.88-1.92 (2H, m), 2.64-2.70 (1H, m), 5.48 (2H, s), 6.57 (1H, dd, *J*= 3.1, 0.7 Hz), 6.68 (1H, d, *J*= 7.5 Hz), 7.08-7.13 (2H, m),7.16-7.20 (3H, m), 7.32 (1H, d, *J*= 8.1 Hz), 7.45 (1H, dd, *J*= 7.6, 1.2 Hz), 7.66 (1H, d, *J*= 7.6 Hz); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 24.9 (CH$_2$), 25.9 (2 × CH$_2$), 29.8 (CH), 32.7 (2 × CH$_2$), 48.6 (CH$_2$), 78.0 (quat), 100.5 (quat), 101.6 (CH), 109.8 (CH), 119.5 (CH), 120.9 (CH), 121.6 (CH), 122.3 (quat), 126.4 (CH), 127.2 (CH), 128.0 (CH), 128.4 (CH), 128.6 (quat), 132.1 (CH), 136.3 (quat), 138.9 (quat); **IR** (neat): 3055, 2927, 2852, 2223, 1512, 1483, 1462, 1448, 1350, 1317, 1178 cm^{-1}; **HRMS**: (ESI) calculated for $C_{23}H_{24}N$ [MH$^+$]: 314.1903, found: 314.1906.





2-(Indol-1-ylmethylphenyl)-propynoic acid methyl ester, 21u. 1-(2-ethynylbenzyl)-*1H*-indole, **21o**, (150 mg, 0.65 mmol) was weighed in a dry flask, dissolved in dry THF (2 mL) and purged with N$_2$. The flask was put in a -78 ºC dry ice/acetone bath and *n*-BuLi (1.6 M, 440 µL, 0.72 mmol) was added dropwise *via* syringe. After the addition the mixture was left for 30 min at -78 ºC and 30 min at r.t., then cooled again to -78 ºC when methyl chloroformate (60 µL, 0.78 mmol) was added dropwise. The final mixture was allowed to warm slowly to r.t. and left o/n. EtOAc and water (2 mL each) were added, the two phases were separated. The aqueous layer was further extracted with EtOAc (2mL × 2), the combined organic layers were washed with brine (2mL × 2), dried over MgSO$_4$, filtered and concentrated at reduced pressure. The residue was chromatographed on a silica column (hexane:CH$_2$Cl$_2$, 6:4) to give a white solid (143 mg, 76%). **m.p.:** 116-118 ºC **^{1}H NMR** (500 MHz, CDCl$_3$): δ 3.94 (3H, s), 5.62 (2H, s), 6.66 (1H, d, *J*= 3.1 Hz), 6.78-6.80 (1H, m), 7.20 (1H, td, *J*= 7.5, 1.0 Hz), 7.24-7.27 (2H, m), 7.33-7.36 (3H, m), 7.70-7.72 (1H, m), 7.74 (1H, d, *J*= 8.0 Hz); **^{13}C NMR** (150 MHz, CDCl$_3$): δ 48.3 (CH$_2$), 52.9 (CH$_3$), 83.6 (quat), 85.6 (quat), 102.1 (CH), 109.6 (CH), 117.6 (quat), 119.7 (CH), 121.0 (CH), 121.9 (CH), 126.8 (CH), 127.6 (CH), 128.4 (CH), 128.7 (quat), 131.3 (CH), 133.8 (CH), 136.3 (quat), 141.4 (quat), 154.2 (CO); **IR** (neat): 3182, 3153, 2988, 2224, 1705, 1515, 1427, 1298, 1203 cm^{-1}; **HRMS**: (ESI) calculated for C$_{19}$H$_{16}$O$_2$N [MH$^+$]: 290.1176, found: 290.1172.



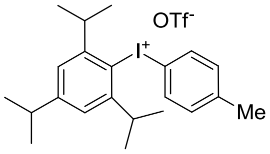
1-(2-*p*-Tolylethynylbenzyl)-*1H*-indole, 21v. General alkylation procedure F between indole and 2-*p*-tolylethynylbenzyl bromide, **20g**, (2.40 mmol scale) gave 548 mg (71%) of a slightly brown solid. **m.p.:** 62-64 ^{o}C; **^{1}H NMR** (500 MHz, CDCl$_3$): δ 2.39 (3H, s), 5.59 (2H, s), 6.58 (1H, dd, *J*= 3.4, 0.8 Hz), 6.72 (1H, dd, *J*= 7.8, 0.6 Hz), 7.13 (1H, ddd, *J*= 9.0, 7.1, 1.0 Hz), 7.15-7.20 (4H, m), 7.21 (1H, d, *J*= 3.1 Hz), 7.24 (1H, dd, *J*= 7.6, 1.2 Hz), 7.35 (1H, dd, *J*= 8.1, 0.8 Hz), 7.41 (2H, d, *J*= 8.1 Hz), 7.58 (1H, dd, *J*= 7.6, 1.0 Hz), 7.67-7.68 (1H, m); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.6 (CH$_3$), 48.6 (CH$_2$), 86.1 (quat), 95.2 (quat), 101.7 (CH), 109.7 (CH), 119.5 (CH), 119.7 (quat), 120.9 (CH), 121.6 (quat), 121.7 (CH), 126.6 (CH), 127.4 (CH), 128.5

(CH), 128.6 (quat), 128.6 (CH), 129.2 (2 × CH), 131.4 (2 × CH), 132.1 (CH), 136.3 (quat), 138.8 (quat), 139.0 (quat); **IR** (neat): 3053, 2984, 2924, 2215, 1612, 1511, 1463, 1318, 1265, 1182, 1012 cm^{-1}; **HRMS**: (ESI) calculated for $C_{24}H_{20}N$ [MH^+]: 322.1590, found: 322.1591.

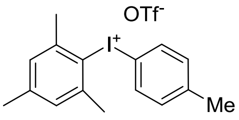
Synthesis of Diaryliodonium salts

Salts **23, 26, 27** were prepared from *p*-iodotoluene and the corresponding arene in the presence of mCPBA and HOTf as described by Olofsson and co-workers[92] as follows: *p*-iodotoluene (500 mg, 2.31 mmol) and mCPBA (~65%, 664 mg, 2.50 mmol) were weighed in a dry round bottomed flask and dissolved in dry CH_2Cl_2. The arene (2.50 mmol) was added to the mixture and it was cooled to 0 ^oC, then HOTf (400 µL, 4.6 mmol) was added dropwise *via* syringe and the colourless solution turned dark yellow or pale brown. The mixture was stirred at r.t. for 2 to 10h. The solvent was evaporated and the product was crystallised from diethyl ether. The solid obtained was dried in an oven at 100 ^oC under vacuum for at least 1h.

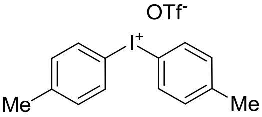
(4-Methylphenyl)(2,4,6-triisopropylphenyl) iodonium triflate, 23. Reaction between 1,3,5-trisisopropylbenzene and 4-iodotoluene under the described procedure afforded 630 mg of the product as a white crystalline solid in (64% yield). Spectroscopic data are in accordance with that reported in the literature.[36] **^{1}H NMR** (400 MHz, DMSO-*d6*): δ 1.28 (12H, d, *J*= 6.8 Hz), 1.31 (6H, d, *J*= 6.8 Hz), 2.41 (3H, s), 3.00 (1H, sept, *J*= 6.8 Hz), 3.30 (2H, sept, *J*= 6.8 Hz), 7.21 (2H, s), 7.27 (2H, d, *J*= 8.4 Hz), 7.59 (2H, d, *J*= 8.4 Hz); **^{13}C NMR** (100 MHz, DMSO-*d6*): δ 20.7 (CH_3), 23.5 (2 × CH_3), 24.0 (4 × CH_2), 33.3 (2 × CH), 38.5 (CH), 111.3 (quat), 121.2 (CF_3, q, *J*= 320.0 Hz), 123.23 (quat), 124.50 (2 × CH), 132.47 (2 × CH), 133.95 (2 × CH), 142.18 (quat), 151.02 (2 × quat), 154.10 (quat).



Phenyl(2,4,6-trimethylphenyl)iodonium triflate, 26. The same as for product **25** procedure between 1,3,5-trimethylbenzene and 4-iodotoluene afforded the product in 57% yield[93] **^{1}H NMR** (400 MHz, DMSO-*d6*): δ 2.29 (3H, s), 2.33 (3H, s), 2.59 (6H, s), 7.20 (2H, s), 7.30 (2H, d, *J*= 8.2 Hz), 7.86 (2H, d, *J*= 8.3 Hz); **^{13}C NMR** (100 MHz, DMSO-*d6*): δ 20.4 (CH_3), 20.7 (CH_3), 26.2 (2 × CH_3), 110.8 (2 × quat), 120.8 (CF_3, q, *J*= 320.5 Hz), 122.6 (2 × quat), 129.7 (2 × CH), 132.4 (2 × CH_3), 134.5 (2 × CH_3), 141.4 (2 × quat), 142.2 (quat), 144.9 (quat).

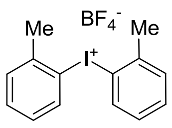


Bis(4-methylphenyl)iodonium tetrafluoroborate, 27. Reaction between toluene and 4-iodotoluene in the presence of mCPBA and HOTf afforded 908 mg of a white solid (52% yield).[92] **^{1}H NMR** (400 MHz, DMSO-*d6*): δ 2.33 (6H, s), 7.32 (4H, d, *J*= 8.1 Hz), 8.09 (4H, d, *J*= 8.1 Hz); **^{13}C NMR** (100 MHz, DMSO-*d6*): δ 20.7 (2 × CH_3), 112.9 (2 × quat), 120.6 (CF_3, q, $J_{C\text{-}F}$= 322.3 Hz), 132.2 (4 × CH), 134.9 (4 × CH), 142.38 (2 × quat).

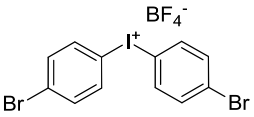


For the preparation of the symmetric diaryliodonium tetrafluoroborate salts **8c**, **8g**, **8h** and **8i** the one-pot procedure from the corresponding arylboronic acids and the aryl iodides described by Olofsson and co-workers[37] was used. mCPBA (66%, 584 mg, 2.20 mmol) was weighed in a dry flask and dissolved in dry CH_2Cl_2 (7.4 mL). The corresponding iodoarene (2.00 mmol) was added followed by $BF_3.Et_2O$ (628 μL, 5 mmol). The reaction was stirred at r.t for 30 min. and then cooled down to 0 ^oC, when the boronic acid was added portion wise (2.20 mmol). The final mixture was vigorously stirred for 15 min. and then filtered through a silica pad (4.40 g) eluting with CH_2Cl_2 (40 mL), this filtrate was separated and further column washing with CH_2Cl_2:MeOH, 20:1 (80 mL) afforded the product. The solvent was evaporated under vacuum and the filtrate was precipitated in Et_2O (7 mL) to obtain the pure iodonium tetrafluoroborate.

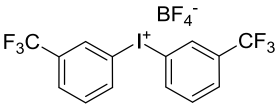
Bis(2-methylphenyl)iodonium tetrafluoroborate, 8c. The described procedure afforded 514 mg of the product (65% yield) as a pale yellow solid from 2-iodotoluene and 2-methylphenylboronic acid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.62 (6H, s), 7.25 (2H, td, *J*= 7.5, 1.3 Hz), 7.47 (2H, dd, *J*= 7.5, 1.3 Hz), 7.54 (2H, td, *J*= 7.5, 1.0 Hz), 7.98 (2H, dd, *J*= 7.5, 1.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.5 (2 × CH_3), 116.2 (2 × quat), 130.0 (2 × CH), 132.4 (2 × CH), 133.5 (2 × CH), 136.9 (2 × CH), 141.5 (2 × quat).



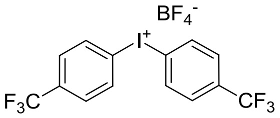
Bis(4-bromophenyl)iodonium tetrafluoroborate, 8g. The one-pot procedure afforded 750 mg of the iodonium salt (72% yield) as a white solid. **^{1}H NMR** (400 MHz, DMSO-*d6*): δ 7.76 (4H, d, *J*= 8.6 Hz), 8.17 (4H, d, *J*= 8.6 Hz); **^{13}C NMR** (100 MHz, DMSO-*d6*): δ 115.2 (2 × quat), 126.3 (2 × quat), 134.6 (4 × CH), 137.0 (4 × CH).



Bis(3-trifluoromethylphenyl)iodonium tetrafluoroborate, 8h. Olofsson's procedure afforded 867 mg of a white solid in 86% yield. The oxidation step was left for 1h, before adding 3-trifluoromethylphenylboronic acid at 0 °C and the reaction was left to warm to r.t. for 30 min. The product was extracted as usual. **^{1}H NMR** (400 MHz, DMSO-*d6*): δ 7.79 (2H, t, *J*= 8.0 Hz), 8.07 (2H, d, *J*= 8.0 Hz), 8.61 (2H, d *J*= 8.0 Hz), 8.82 (2H, s); **^{13}C NMR** (100 MHz, DMSO-*d6*): δ 117.1 (2 × quat), 122.8 (2 × CF_3, q, $J_{C\text{-}F}$= 271.7 Hz), 129.0 (2 × CH, q, $J_{C\text{-}F}$= 3.6 Hz), 131.4 (2 × quat, q, $J_{C\text{-}F}$= 32.6 Hz), 131.9 (2 × CH, q, $J_{C\text{-}F}$= 3.6 Hz), 132.7 (2 × CH), 139.3 (2 × CH).



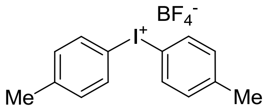
Bis(4-trifluoromethylphenyl)iodonium tetrafluoroborate, 8i. Olofsson's procedure afforded 645 mg of the product (69% yield) as a white solid. The oxidation step was left for 1h, before adding 4-trifluoromethylphenylboronic acid at 0 °C and the reaction was left to warm to r.t. for 30 min. **^{1}H NMR** (400 MHz, DMSO-*d6*): δ 7.95 (4H, d, *J*= 8.2 Hz), 8.51 (4H, d, *J*= 8.2 Hz); **^{13}C NMR** (100 MHz, DMSO-*d6*): δ 120.9 (2 ×



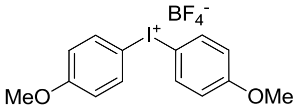
quat), 123.3 (2 × CF_3, q, J_{C-F}= 271.6 Hz), 128.5 (4 × CH, q, J_{C-F}= 3.5 Hz), 132.2 (2 × quat, q, J_{C-F}= 32.6 Hz), 136.2 (4 × CH).

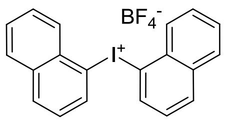
The synthesis of the electron-rich diaryliodonium salts **8b**, **8d**, **8f**, was done following the special procedure described by Oloffsson and co-workers.[37] mCPBA (~66%, 590 mg, 2.20 mmol) and iodoarene (2.00 mmol) were weighed in 30 mL dry reaction tube and dissolved in CH_2Cl_2 (7 mL) then the tube was capped with a rubber septum and heated at 80 ^oC for 10 min. After that it was cooled down and put in a -78 ^oC dry ice/acetone bath. Meanwhile, the arylboronic acid (2.20 mmol) was dissolved in CH_2Cl_2 (7 mL) and cooled to 0 ^oC, borontrifluoride diethyl ether (628 μL, 5 mmol) was added dropwise to the solution before being transferred *via* cannula to the tube at -78 ^oC. The final mixture was left 30 min at -78 ^oC and left to warm up to r.t., then the product was isolated filtering through a silica pad.

Bis(4-methylphenyl)iodonium tetrafluoroborate, 8b. Reaction of 4-iodomethylbenzene and 4-methylphenylboronic acid in the presence of mCPBA and borontrifluoride afforded 507 mg of **2b** (64% yield) as a white solid after purification. **^{1}H NMR** (400 MHz, DMSO-*d6*): δ 2.33 (6H, s), 7.32 (4H, d, *J*= 8.1 Hz), 8.08 (4H, d, *J*= 8.1 Hz); **^{13}C NMR** (100 MHz, DMSO-*d6*): δ 20.8 (2 × CH_3), 113.0 (2 × quat), 132.2 (4 × CH), 134.9 (4 × CH), 142.4 (2 × quat).

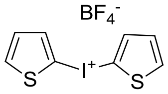


Bis(4-methoxylphenyl)iodonium tetrafluoroborate, 8d. Usual procedure afforded 530 mg of a grey solid (62% yield). **^{1}H NMR** (500 MHz, DMSO-*d6*): δ 3.79 (6H, s), 7.06 (4H, dd, *J*= 8.9, 1.8 Hz), 8.12 (4H,dd, *J*= 8.9, 1.8 Hz); **^{13}C NMR** (125 MHz, DMSO-*d6*): δ 55.6 (2 × CH_3), 105.9 (2 × quat), 117.3 (4 × CH), 136.8 (4 × CH), 161.8 (2 × quat).

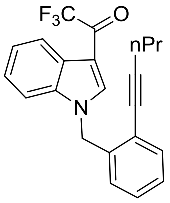




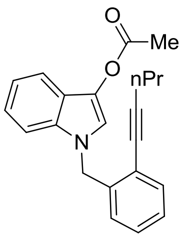
Bis(1-naphtyl)iodonium tetrafluoroborate, 8f. 224 mf of a grey solid were obtained (24% yield) after Olofsson's special one-pot procedure for electron rich boronic acids. **^{1}H NMR** (500 MHz, DMSO-*d6*): δ 7.57 (2H, t, *J*= 7.5 Hz), 7.68 (2H, t, *J*= 7.5 Hz), 7.81 (2H, td, *J*= 8.0, 1.0 Hz), 8.01 (2H, d, *J*= 8.0 Hz), 8.21 (2H, d, *J*= 8.3 Hz), 8.49 (2H, d, *J*= 8.3 Hz), 8.88 (2H, d, *J*= 6.9 Hz); **^{13}C NMR** (125 MHz, DMSO-*d6*): δ 119.1 (2 × quat), 127.4 (2 × CH), 127.9 (2 × CH), 128.8 (2 × CH), 129.4 (2 CH), 129.6 (2 × CH), 130.8 (2 × quat), 133.3 (2 × CH), 134.1 (2 × quat), 137.2 (2 × CH).



Bis(2-thiophene)iodonium tetrafluoroborate, 8e. The product was synthesised following Ochiai and co-workers[94] procedure from 2-(diacetoxyiodo)thiophene. Yellow solid prepared following the procedure described by Yamaguchi *et. al.*[95] from 2-iodothiophene and sodium perborate tetrahydrate in acetic acid in 41% yield. **^{1}H NMR** (400 MHz, DMSO-*d6*): δ 2.06 (6H, s), 7.14 (1H, dd, *J*= 5.3, 3.8 Hz), 7.64 (1H, dd, *J*= 5.3, 1.1 Hz), 7.78 (1H, dd, *J*= 3.8, 1.1 Hz); **^{13}C NMR** (100 MHz, DMSO-*d6*): δ 20.3 (2 × CH_3), 106.2 (quat), 128.6 (CH), 134.8 (CH), 139.1 (CH), 177.0 (2 × CO). 2-thiopheneboronic acid (102 mg, 0.81 mmol) was dissolved in CH_2Cl_2 (12 mL) and cooled to 0 ^oC. Then borontrifluoride dietheylether (111 μL, 0.90 mmol) was added dropwise. After 10 min. a solution of 2-(diacetoxyiodo)thiophene in CH_2Cl_2 (0.80 mmol in 2 mL) was added dropwise *via* cannula and the mixture was allowed to warm to r.t. for 2h. After these time a saturated solution of $NaBF_4$ (13 mL) was added and the resulting solution was stirred vigorously for 30 min. Then water (10 mL) and CH_2Cl_2 (5 mL) were added and the two layers separated. The aqueous layer was further extracted with CH_2Cl_2 (10 mL × 2) and the combined organic layers washed with brine (10 mL × 2), dried over $MgSO_4$, filtered and the solvent evaporated under vacuum. To the residue Et_2O was added (3 mL) and the precipitated solid was filtered and dried at 100 ^oC under vacuum for 1h. 230 mg of a yellow solid (76%) were obtained. **^{1}H NMR** (400 MHz, DMSO-*d6*): δ 7.16 (2H, dd, *J*= 5.3, 3.8 Hz), 7.95 (2H, dd, *J*= 5.3, 1.3 Hz), 8.05 (2H, dd, *J*= 3.8, 1.3 Hz); **^{13}C NMR** (100 MHz, DMSO-*d6*): δ 99.6 (2 × quat), 130.6 (2 × CH), 139.2 (2 × CH), 142.2 (2 × CH).



2,2,2-Trifluoro-1-[1-[(2-pent-1-ynylbenzyl)indol-3-yl]ethanone, **24**. 1-(2-pent-1-ynylbenzyl)-*1H*-indole (82.4 mg, 0.30 mmol) was weighed in a 5 mL dried reaction tube containing a stirring bar. CH_2Cl_2 (2.2 mL) and trifluoroacetic acid (0.8 mL) were added, followed by $Pd(OAc)_2$ (6.7 mg, 0.03 mmol). The tube was flushed with N_2 and the mixture stirred at r.t. for 5h, after which time no starting material was left. The crude was partitioned between H_2O and CH_2Cl_2 and the aqueous phase further extracted twice with CH_2Cl_2. The combined organic layers were washed twice with sat. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under vacuum. Purification through a silica column (hexane:CH_2Cl_2, 1:1) afforded a small amount of the unexpected product as a colourless oil (17 mg, 15%). **^{1}H NMR** (500 MHz, $CDCl_3$): 1.03 (3H, t, *J*= 7.0 Hz), 1.6 (2H, m), 2.41 (2H, t, *J*= 7.0 Hz), 5.54 (2H, s), 6.94 (1H, d, *J*= 8.0 Hz), 7.22 (1H, td, *J*= 7.5, 1.5 Hz), 7.28 (1H, td, *J*= 7.5, 1.5 Hz), 7.34-7.39 (2H, m), 7.42 (1H, d, *J*= 8.0 Hz), 7.50 (1H, dd, *J*= 7.5, 1.0 Hz), 8.04 (1H, d, *J*= 1.5), 8.43 (1H, dd, *J*= 7.5, 1.7 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.5 (CH_2), 22.1 (CH_2), 49.9 (CH_2), 77.9 (quat), 97.0 (quat), 109.8 (quat), 110.8 (CH), 117.0 (CF_3, q, *J*= 293.0 Hz), 122.7 (CH), 123.2 (quat), 124.0 (CH), 124.6 (CH), 127.0 (quat), 127.2 (CH), 128.3 (CH), 126.3 (CH), 132.8 (CH), 135.9 (quat), 136.9 (quat), 138.0 (quat), 174.9 (CO, $J_{C\text{-}F}$= 34.9 Hz); **IR** (neat): 2927, 2925, 2180, 1670, 1527, 1465, 1392, 1286, 1174, 1136 cm^{-1}; **HRMS**: (ESI) calculated for $C_{22}H_{19}ONF_3$: 370.1413, found: 370.1415.

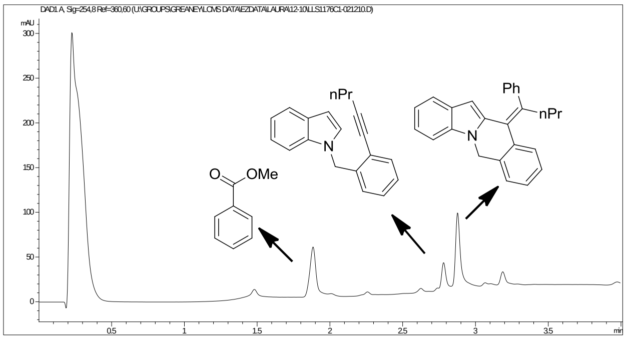


[1-[(2-pent-1-ynylphenyl)methyl]indol-3-yl] acetic acid methyl ester, 25. 1-(2-pent-1-ynylbenzyl)-*1H*-indole (82.4 mg, 0.30 mmol) was weighed in a 5 mL dried reaction tube containing a stirrer bar. Chlorobenzene (3 mL) was added, followed by $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) and diacetoxyiodobenzene (97 mg, 0.31 mmol). The tube was flushed with N_2 and placed in a pre-heated aluminium bloc at 30 ^oC. No starting material was seen by TLC after 8 h. Usual aqueous work up and purification (SiO_2, hexane:CH_2Cl_2) afforded a colourless oil in low yield (18 mg, 18%). **^{1}H NMR** (500 MHz, $CDCl_3$): 1.06 (3H, t, *J*= 7.4 Hz), 1.65 (2H, tt, *J*= 7.4, 7.0 Hz), 2.35

(3H, s), 2.44 (2H, t, *J*= 7.0 Hz), 5.43 (2H, s), 6.75 (1H, d *J*= 7.8 Hz), 7.10-7.14 (2H, m), 7.17-7.20 (2H, m), 7.29 (1H, d, *J*= 8.3 Hz), 7.37 (1H, s), 7.44 (1H, dd, *J*= 8.3, 1.5 Hz), 7.57 (1H, d, *J*= 7.9 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.0 (CH_3), 21.6 (CH_2), 22.2 (CH_2), 48.6 (CH_2), 78.2 (quat), 96.3 (quat), 109.8 (CH), 117.5 (CH), 117.6 (CH), 119.5 (CH), 120.3 (quat), 122.5 (CH), 126.5 (CH), 127.3 (CH), 128.0 (CH), 129.0 (quat), 129.7 (quat), 132.2 (CH), 133.4 (quat), 138.6 (quat), 168.5 (CO); **IR** (neat): 3053, 2985, 2304, 1745, 1614, 1467 cm^{-1}; **HRMS**: (ESI) calculated for $C_{22}H_{22}O_2N$ [MH^+]: 332.1645, found: 332.1648.

Reaction optimisation

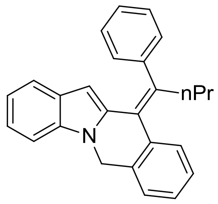
In order to accelerate the optimisation process the crudes were analysed by HPLC/MS using an internal standard (IS) to calculate yields. Methyl benzoate was used as internal standard, the relation between the peak areas in the UV spectra and concentration of IS and product was determined by a calibration table. During the optimisation process trifluoroethanol was used as solvent in most cases, which was not seen by UV. To analyse crudes, 92.2 µL (0.73 mmol) of methyl benzoate were added to the reaction solution from where 100 µL were taken into a 5mL volumetric flask adding DMSO to complete the volume. The 5mL solution was further diluted taking 50 µL in a 2mL volumetric flask adding MeOH to complete the volume and an aliquot of this final diluted solution was injected in the HPLC/MS apparatus. This procedure permitted rapid access to accurate HPLC yields so optimised reaction conditions could be developed quicker.



HPLC trace showing the presence of IS, starting material and product in a reaction crude.

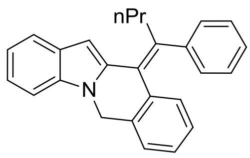
General procedure G: tandem annulation reaction between alkyne-tethered indoles and diaryliodonium salts.

Cs_2CO_3, SIMes.HCl and the diaryliodonium salt were dried in an oven at 100 ºC under vacuum for 1 h prior to the reaction. The alkyne-tethered indole (0.30 mmol) was weighed in a 5 mL glass screwed cap vial (previously dried in the oven at 100 ºC) and dissolved in chlorobenzene (3 mL, ACS reagent grade). Cs_2CO_3 (98 mg, 0.3 mmol), SIMes.HCl (10.2 mg, 0.03 mmol), $PdOAc_2$ (3.4 mg, 0.015 mmol) and the diaryliodonium salt (0.32 mmol) were added in this order and the mixture was flushed with N_2. The vial was capped and put into an aluminium bloc previously heated at 30 ºC. The reaction was followed by TLC until no starting material remained. The mixture was then diluted with toluene and filtered through a silica + 3% Et_3N pad, eluting with toluene. To the filtrate was added some silica + 3% Et_3N and the solvent evaporated under vacuum in a rotary evaporator (water bath at 30 ºC). The product adsorbed on silica was purified through a silica + 3% Et_3N column eluting with hexane:CH_2Cl_2 mixtures.



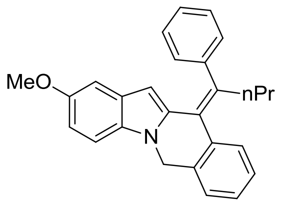
11-[1-Phenylbut-(*Z*)-ylidene]-6,11-dihydroindolo[1,2*b*]isoquinoline, *Z*-22a. White solid (90 mg, 86% yield) from **21a**, and **8a** according to general procedure G. **m.p.:** 188-190 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.87 (3H, t, *J*= 7.0 Hz), 1.46 (2H, m), 2.80 (2H, t, *J*= 8.0 Hz), 5.16 (2H, s), 5.45 (1H, s), 6.95 (1H, td, *J*= 7.5, 1.0 Hz), 7.11 (1H, td, *J*= 8.0, 1.5 Hz), 7.17 (1H, d, *J*= 1.5 Hz), 7.19 (1H, d, *J*= 1.5 Hz), 7.28-7.42 (8H, m), 7.68 (1H, d, *J*= 7.5 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.0 (CH_3), 21.7 (CH_2), 38.3 (CH_2), 45.4 (CH_2), 100.5 (CH), 108.2 (CH), 119.1 (CH), 120.6 (CH), 120.8 (CH), 125.4 (quat), 126.3 (CH), 126.7 (CH), 126.8 (CH), 126.9 (CH), 128.2 (2 × CH), 128.4 (quat), 128.7 (CH), 128.8 (2 × CH), 134.6 (2 × quat), 135.4 (quat), 136.7 (quat), 142.6 (quat), 143.2 (quat); **IR** (KBr): 2954, 2925, 2865, 1452, 1385, 1368, 1264 cm^{-1}; **HRMS**: (ESI) calculated for $C_{26}H_{24}N$ [MH^+]: 350.1903, found: 350.1906.

11-[1-Phenylbut-(*E*)-ylidene]-6,11-dihydroindolo[1,2*b*]isoquinoline, *E*-**22a**.



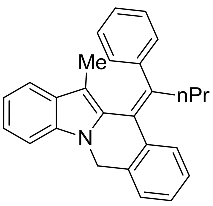
Reaction of **21a** with **8a** using the general procedure G but with CH_2Cl_2 as reaction solvent gave 97 mg of **7a** as a mixture of isomers (92% yield, *Z*:*E*, 3:1). Further purification through a silica + 10% $AgNO_3$[34] column enabled partial separation of the minor *E* isomer for characterisation purposes. 22 mg (22 %) of the *E* isomer was obtained as a slightly yellow gum. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.86 (3H, t, *J*= 7.3 Hz), 1.41 (2H, m), 3.05-3.08 (2H, m), 5.20 (2H, s), 6.69 (1H, s), 6.73 (1H, d, *J*= 7.9 Hz), 6.82 (1H,t, *J*= 7.6 Hz), 7.05 (1H, t, *J*= 7.4 Hz), 7.12-7.15 (1H, m), 7.17 (2H, d, *J*= 6.5 Hz), 7.23-7.29 (5H, m), 7.44 (1H, d, *J*= 8.1 Hz), 7.68 (1H, d, *J*= 8.1 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 13.8 (CH_3), 21.5 (CH_2), 37.2 (CH_2), 45.5 (CH_2), 100.1 (CH), 108.5 (CH), 119.5 (CH), 120.7 (CH), 121.3 (CH), 125.1 (quat), 125.6 (CH), 125.9 (CH), 126.1 (CH), 126.7 (CH), 128.1 (2 × CH), 128.4 (quat), 129.4 (2 × CH), 129.9 (CH), 134.0 (quat), 135.1 (quat), 136.0 (quat), 136.1 (quat), 142.4 (quat), 142.9 (quat); **IR** (neat): 2933, 2947, 2858, 1421, 1265 cm^{-1}; **HRMS**: (ESI) calculated for $C_{26}H_{24}N$ [MH^+]: 350.1903, found: 350.1901.

2-Methoxy-11-[1-Phenylbut-(*Z*)-ylidene]-6,11-dihydroindolo[1,2*b*]isoquinoline,



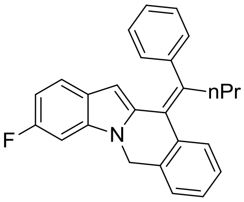
22c. White solid (100 mg, 88% yield) from **21b** and **8a** according to general procedure G. **m.p.:** 192-194 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.87 (3H, t, *J*= 7.0 Hz), 1.42-1.55 (2H, m), 2.77-2.88 (2H, m), 3.75 (3H, s), 5.11 (2H, s), 5.32 (1H, s), 6.76 (1H, s), 6.77 (1H, dd, *J*= 9.0, 2.5 Hz), 7.17-7.21 (3H, m), 7.30-7.41 (6H, m), 7.68 (1H, dd, *J*= 8.0, 1.0 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.0 (CH_3), 21.7 (CH_2), 38.4 (CH_2), 45.5 (CH_2), 55.8 (CH_3), 100.2 (CH), 102.2 (CH), 108.9 (CH), 111.2 (CH), 125.4 (quat), 126.3 (CH), 126.7 (CH), 126.8 (CH), 126.8 (CH), 128.2 (2 × CH), 128.6 (quat), 128.7 (CH), 128.8 (2 × CH), 130.1 (quat), 134.6 (quat), 135.3 (quat), 137.2 (quat), 142.7 (quat), 143.0 (quat), 153.8 (quat); **IR** (neat): 2956, 2933, 1620, 1482, 1217, 1152, 1034, 786 cm^{-1}; **HRMS**: (ESI) calculated for $C_{27}H_{26}O_1N_1$: 380.2009, found: 380.2008.

12-Methyl-11-[1-Phenylbut-(*Z*)-ylidene]-6,11-dihydroindolo[1,2*b*]isoquinoline,



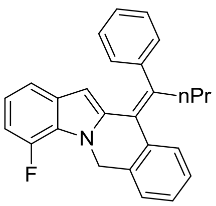
22d. Yellow solid (83 mg, 76% yield) from **21c**, and **8a** according to general procedure G. **m.p.**: 158-160 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.70 (3H, t, *J*= 7.3 Hz), 1.07-1.19 (1H, m), 1.23-1.33 (1H, m), 1.38 (3H, s), 2.69-2.82 (1H, m), 3.17-3.30 (1H, m), 5.06-5.18 (1H, m), 5.23-5.26 (1H, m), 6.98 (1H, td, *J*= 8.0, 1.0 Hz), 7.13-7.24 (7H, m), 7.29-7.37 (4H, m), 7.64-7.65 (1H, d, *J*= 7.0 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 9.1 (CH_3), 13.3 (CH_3), 21.5 (CH_2), 35.6 (CH_2), 45.8 (CH_2), 106.4 (quat), 107.9 (CH), 118.2 (CH), 118.9 (CH), 120.8 (CH), 125.9 (CH), 126.2 (quat), 126.4 (2 × CH), 126.6 (CH), 128.0 (2 × CH), 128.3 (CH), 129.1 (quat), 129.2 (2 × CH), 133.9 (quat), 135.2 (quat), 135.7 (quat), 137.4 (quat), 142.0 (quat), 142.6 (quat); **IR** (neat): 2953, 2906, 2858, 1490, 1465, 1444, 1375, 1247, 1028 cm^{-1}; **HRMS**: (ESI) calculated for $C_{26}H_{24}N$ [MH^+]: 350.1903, found: 350.1906.

3-Fluoro-11-[1-Phenylbut-(*Z*)-ylidene]-6,11-dihydroindolo[1,2*b*]isoquinoline,

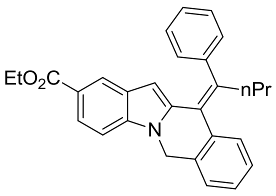


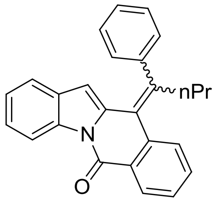
22e. White solid (86 mg, 78% yield) from **21f** and **8a** according to general procedure G. **m.p.:** 74-76 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.87 (3H, t, *J*= 7.3 Hz), 1.42-1.50 (2H, m), 2.77-2.80 (2H, m), 5.08 (2H, s), 5.37 (1H, s), 6.71 (1H, ddd, *J*= 9.7, 8.7, 2.3 Hz), 6.98 (1H, dd, *J*= 9.7, 2.3 Hz), 7.16-7.19 (3H, m), 7.31-7.41 (6H, m), 7.68 (1H, d, *J*= 7.7 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 14.0 (CH_3), 21.7 (CH_2), 38.3 (CH_2), 45.6 (CH_2), 94.8 (CH, d, $J_{C\text{-}F}$= 26.2 Hz), 100.4 (CH), 107.8 (CH, d, $J_{C\text{-}F}$= 24.2 Hz), 121.2 (CH, d, $J_{C\text{-}F}$= 9.9 Hz), 125.0 (quat, d, $J_{C\text{-}F}$= 38.9 Hz), 126.3 (CH), 126.9 (2 × CH), 127.0 (CH), 127.5 (quat), 128.2 (2 × CH), 128.7 (CH), 128.8 (2 × CH), 134.2 (quat), 134.5 (quat, d, $J_{C\text{-}F}$= 12.1 Hz), 135.3 (quat), 137.2 (quat, $J_{C\text{-}F}$= 3.7 Hz), 142.6 (quat), 143.2 (quat), 159.4 (quat, d, $J_{C\text{-}F}$= 235.6 Hz); **IR** (neat): 3054, 2985, 1421, 1265 cm^{-1}; **HRMS**: (APCI) calculated for $C_{26}H_{23}NF$ [MH^+]: 368.1809, found: 368.1811.

4-Fluoro-11-[1-Phenylbut-(*Z*)-ylidene]-6,11-dihydroindolo[1,2*b*]isoquinoline, 22f. Reddish gum (60 mg, 54% yield) from **21g** and **8a** according to general procedure G. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.86 (3H, t, *J*= 7.3 Hz), 1.41-1.49 (2H, m), 2.79-2.82 (2H, m), 5.43 (1H, d, *J*= 2.4 Hz), 5.46 (2H, s), 6.71-6.83 (3H, m), 7.02 (1H, d, *J*= 7.8 Hz), 7.18 (1H, t, *J*= 1.4 Hz), 7.20 (1H, d, *J*= 1.6 Hz), 7.31-7.30 (3H, m), 7.39 (1H, td, *J*= 7.7, 1.4 Hz), 7.42 (1H, td, *J*= 7.4, 1.0 Hz), 7.68 (1H, d, *J*= 7.7 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 13.9 (CH_3), 21.6 (CH_2), 38.2 (CH_2), 47.8 (CH_2, d, $J_{C\text{-}F}$= 6.5 Hz), 101.4 (CH, d, $J_{C\text{-}F}$= 6.0 Hz), 106.4 (CH, d, $J_{C\text{-}F}$= 72.2 Hz), 116.4 (CH, d, $J_{C\text{-}F}$= 3.2 Hz), 119.1 (CH, d, $J_{C\text{-}F}$= 6.6 Hz), 122.6 (quat, d, *J*= 9.0 Hz), 125.1 (quat), 126.3 (CH), 126.8 (CH), 126.9 (CH), 127.0 (CH), 128.2 (2 × CH), 128.5 (CH), 128.7 (2 × CH), 132.1 (quat), 132.1 (quat), 135.1 (quat, d, $J_{C\text{-}F}$= 5.5 Hz), 138.1 (quat), 142.4 (quat), 143.8 (quat), 149.7 (quat, d, $J_{C\text{-}F}$= 248.1 Hz); **IR** (neat): 2960, 2931, 2872, 1691, 1578, 1492, 1442, 1263, 1236 cm^{-1}; **HRMS**: (APCI) calculated for $C_{26}H_{23}NF$ [MH^+]: 368.1809, found: 368.1804.



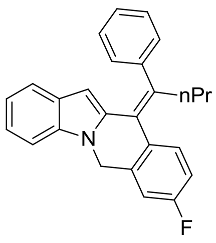
11-[1-Phenylbut-(*Z*)-ylidene]-6,11-dihydroindolo[1,2*b*]isoquinoline-2-carboxylic acid ethyl ester, 22g. 66 mg of a white solid (52% yield) (17% SM recovered, brsm yield = 63%) were obtained from **21h**, and **8a** after 30 h reaction time (17% SM recovered, brsm yield = 63%). **m.p.**: 112-114 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (3H, t, *J*= 6.5 Hz), 1.38 (3H, t, *J*= 7.2 Hz), 1.43-1.53 (2H, m), 2.79-2.83 (2H, m), 4.34 (2H, q, *J*= 7.1 Hz), 5.18 (2H, s), 5.50 (1H, s), 7.18 (2H, dd, *J*= 7.7, 1.7 Hz), 7.31-7.43 (7H, m), 7.70 (1H, d, *J*= 7.7 Hz), 7.84 (1H, dd, *J*= 8.7, 1.7 Hz), 8.06 (1H, d, *J*= 1.2 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 14.4 (CH_3), 21.6 (CH_2), 38.3 (CH_2), 45.6 (CH_2), 60.4 (CH_2), 101.7 (CH), 107.9 (CH), 121.5 (quat), 122.3 (CH), 123.5 (CH), 125.0 (quat), 126.4 (CH), 127.0 (2 × CH), 127.1 (CH), 127.9 (quat), 128.3 (2 × CH), 128.7 (3 × CH), 134.1 (quat), 135.1 (quat), 136.9 (quat), 138.0 (quat), 142.3 (quat), 144.3 (quat), 167.8 (CO) **IR** (neat): 2958, 2870, 1701, 1608, 1444, 1354, 1300, 1249, 1165, 1085 cm^{-1}; **HRMS**: (ESI) calculated for $C_{29}H_{28}O_2N$ [MH^+]: 422.2115, found: 422.2115.





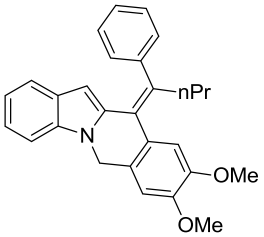
11-[1-Phenyl-but-(Z)-ylidene]-11*H*-indolo[1,2-*b*]isoquinolin-6-one, *Z*-22h and **11-[1-Phenyl-but-(*E*)-ylidene]-11*H*-indolo[1,2-*b*]isoquinolin-6-one, *E*-22h**. A light yellow gum (50 mg, 46% yield, $Z_{(a)}$:$E_{(b)}$ ratio = 1:1.6) was obtained from **21j** and **8a** (48 h at 50 ºC). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.94 ($3H_a$, t, *J*= 7.3 Hz), 0.94 ($3H_b$, t, *J*= 7.3 Hz), 1.51-1.61 ($2H_a$, $2H_b$, m), 2.76-2.79 ($2H_a$, m), 2.90-2.93 ($2H_b$, m), 5.37 ($1H_a$, s), 6.79 ($1H_b$, d, *J*= 8.0 Hz), 6.85 ($1H_b$, s), 7.01 ($1H_b$, ddd, *J*= 8.0, 7.3, 1.5 Hz), 7.10-7.15 ($1H_a$ $3H_b$, m), 7.19 ($1H_a$, t, *J*= 7.9 Hz), 7.24-7.31 ($4H_b$, m), 7.34 ($2H_a$, t, *J*= 7.5Hz), 7.38-7.45 ($3H_a$, $1H_b$, m), 7.54 ($1H_a$, t, *J*= 7.5 Hz), 7.64-7.67 ($2H_a$, $1H_b$, m), 7.80 ($1H_a$, d, *J*= 7.8 Hz), 8.26 ($1H_b$, dd, *J*= 7.8, 1.1 Hz), 8.41 ($1H_a$, dd, *J*= 7.8, 1.1 Hz), 8.55 ($1H_a$, dd, *J*= 8.2, 0.8 Hz), 8.66 ($1H_b$, dd, *J*= 8.2, 0.8 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.0 (CH_3), 14.1 (CH_3), 21.5 (CH_2), 21.9 (CH_2), 39.1 (CH_2), 40.0 (CH_2), 108.4 (CH), 108.6 (CH), 115.9 (CH), 116.1 (CH), 120.3 (CH), 120.5 (CH), 122.1 (quat), 122.7 (quat), 123.8 (CH), 124.1 (CH), 124.5 (CH), 125.0 (CH), 127.0 (CH), 127.3 (CH), 127.4 (CH), 127.9 (2 × CH), 128.0 (CH) 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.6 (2 × CH), 128.7 (2 × CH), 128.8 (CH), 128.9 (2 × CH), 129.2 (quat), 129.3 (quat), 129.6 (CH), 130.7 (CH), 131.6 (quat), 134.8 (quat), 134.4 (quat), 134.9 (quat), 135.1 (quat), 135.1 (quat), 136.6 (quat), 137.4 (quat), 142.9 (quat) 143.0 (quat), 148.0 (quat), 148.6 (quat), 161.7 (CO), 162.1 (CO); **IR** (neat): 3059, 2985, 1687, 1421, 1265 cm^{-1}; **HRMS**: (ESI) calculated for $C_{26}H_{22}ON$ [MH^+]: 364.1696, found: 364.1697.

8-Fluoro-11-[1-Phenylbut-(*Z*)-ylidene]-6,11-dihydroindolo[1,2*b*]isoquinoline,22i.

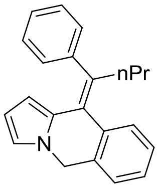


54 mg of a white solid (49% yield) were obtained from **21k**, and **8a** according to the general procedure G (62% brsm, 43% SM recovered). **m.p.:** 138-140 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.87 (3H, t, *J*= 7.3Hz), 1.42-1.49 (2H, m), 2.75-2.78 (2H, m), 5.13 (2H, s), 5.40 (1H, s), 6.97 (1H, t, *J*= 7.5 Hz), 7.06-7.18 (5H, m), 7.29-7.37 (5H, m), 7.65 (1H, dd, *J*= 8.5, 5.5 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.0 (CH_3), 21.6 (CH_2), 38.3 (CH_2), 45.2 (CH_2), 100.7 (CH), 108.2 (CH), 113.3 (CH, d, $J_{C\text{-}F}$= 22.2 Hz), 113.7 (CH, d, $J_{C\text{-}F}$= 21.3 Hz), 119.3 (CH), 120.7 (CH), 121.0 (CH), 124.5 (quat), 126.9 (CH), 128.2 (2 × CH), 128.4 (quat), 128.8 (2 × CH), 130.4 (CH,

d, $J_{C\text{-}F}$= 8.7 Hz), 131.4 (quat, d, $J_{C\text{-}F}$= 3.3 Hz), 134.6 (quat), 134.4 (quat), 136.8 (quat, d, $J_{C\text{-}F}$= 7.6 Hz), 142.4 (quat), 143.1 (quat), 161.3 (quat, d, $J_{C\text{-}F}$= 247.6 Hz); **IR** (neat): 2958. 2870, 1614, 1581, 1492, 1450, 1238 cm^{-1}; **HRMS**: (ESI) calculated for $C_{26}H_{23}NF$ [MH^+]: 368.1809, found: 368.1813.

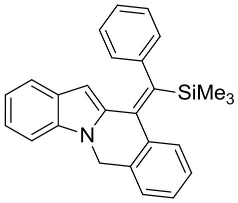


8,9-Dimethoxy-11-[1-Phenylbut-(*Z*)-ylidene]-6,11-dihydroindolo[1,2*b*]isoquinoline, 22j. Tan solid in 78% yield from **21l** and **8a** (96 mg). **m.p.:** 148-150 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.91 (3H, t, *J*= 7.3 Hz), 1.52-1.56 (2H, m), 2.78-2.81 (2H, m), 3.96 (3H, s), 3.97 (3H, s), 5.10 (2H, s), 5.39 (1H, s), 6.92 (1H, s), 6.95 (1H, t, *J*= 7.5 Hz), 7.10 (1H, t, *J*= 7.5 Hz), 7.18-7.19 (2H, m), 7.23 (1H, s), 7.28-7.37 (5H, m); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.2 (CH_3), 21.9 (CH_2), 38.9 (CH_2), 45.0 (CH_2), 56.0 (CH_3), 56.1 (CH_3), 101.3 (CH), 108.2 (CH), 109.4 (CH), 112.1 (CH), 119.1 (CH), 120.6 (CH), 120.8 (CH), 125.2 (quat), 126.8 (CH), 127.3 (quat), 127.7 (quat), 128.2 (2 × CH), 128.3 (quat), 128.9 (2 × CH), 134.6 (quat), 136.7 (quat), 141.9 (quat), 142.9 (quat), 147.2 (quat), 147.9 (quat); **IR** (neat): 2959, 2931, 1608, 1514, 1454, 1315, 1213, 1117cm^{-1}; **HRMS**: (ESI) calculated for $C_{28}H_{28}O_2N$ [MH^+]: 410.2115, found: 410.2112.



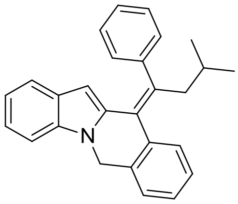
10-[1-Phenylbut-(*Z*)-ylidene]-5,10-dihydropyrrolo[1,2*b*]isoquinoline, 22k. White solid in 70% yield from **21m** and **8a** (63 mg, reaction temperature was maintained between 15-18 ºC for 2 h to avoid double bond isomerisation). **m.p.:** 148-150 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.86 (3H, t, *J*= 7.3 Hz), 1.45 (2H, m), 2.72-2.76 (2H, m), 4.96 (2H, s), 5.05 (1H, dd, *J*= 3.7, 1.5 Hz), 5.82 (1H, dd, *J*= 3.7, 2.7 Hz), 6.59 (1H, dd, *J*= 2.7, 1.5 Hz), 7.17-7.19 (2H, m), 7.26-7.32 (3H, m), 7.33-7.38 (3H, m), 7.65 (1H, d, *J*= 7.6 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.0 (CH_3), 21.8 (CH_2), 38.3 (CH_2), 49.1 (CH_2), 107.6 (CH), 107.9 (CH), 117.9 (CH), 125.2 (quat), 126.0 (CH), 126.5 (2 × CH), 126.6 (CH), 128.1 (2 × CH), 128.6 (CH), 129.0 (2 × CH), 130.5 (quat), 134.6 (quat), 135.8 (quat), 139.4 (quat), 143.2 (quat); **IR** (neat): 2954, 2924, 2868, 1490, 1475, 1458, 1436, 1082 cm^{-1}; **HRMS**: (ESI) calculated for $C_{22}H_{22}N$ [MH$^+$]: 300.1747, found: 300.1750.

11-[1-Phenyl-1-trimethylsilanylmeth-(*E*)-ylidene]-6,11-dihydro-



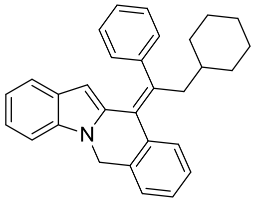
indolo[1,2*b*]isoquinoline, 22l. 48 of a white solid (42% yield) were obtained from **21p** and **8a** following general procedure G (36h reaction time, 42% of SM recovered, 71% brsm). **m.p.:** 158-160 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.07 (9H, s), 5.18 (2H, s), 5.23 (1H, s), 6.96 (1H, td, *J*= 7.5, 1.0 Hz), 7.0 (2H, dd, *J*= 7.5, 1.0 Hz), 7.14 (1H, ddd, *J*= 8.1, 7.0, 1.1 Hz), 7.27-7.38 (8H, m), 7.78 (1H, dd, *J*= 6.8, 1.9 Hz); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 1.2 (3 × CH_3), 45.2 (CH_2), 101.9 (CH), 108.5 (CH), 119.3 (CH), 121.0 (CH), 121.4 (CH), 125.7 (CH), 125.9 (CH), 126.7 (CH), 127.9 (2 × CH), 127.9 (CH), 128.2 (quat), 128.4 (2 × CH), 128.9 (CH), 134.0 (quat), 134.6 (quat), 136.4 (quat), 137.1 (quat), 138.7 (quat), 144.9 (quat), 145.4 (quat) **IR** (neat): 3059, 3016, 2947, 1583, 1483, 1446, 1317, 1250, 1199 cm^{-1}; **HRMS**: (APCI) calculated for $C_{26}H_{26}NSi$ [MH$^+$]: 380.1829, found: 380.1830.

11-[3-Methyl-1-phenyl-but-(Z)-ylidene]-6,11-dihydro-indolo[1,2-*b*]isoquinoline,



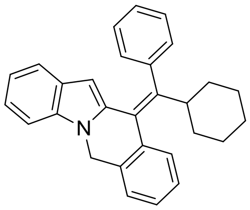
22m. Reaction between **21q** and **8a** afforded 73 mg of a white solid (67%) under the normal reaction conditions from general procedure G. **m.p.:** 176-178 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.76 (3H, s), 0.77 (3H, s), 1.49 (1H, sept., *J*= 6.9 Hz), 2.86 (2H, d, *J*= 6.9 Hz), 5.15 (2H, s), 5.36 (1H, m), 6.95 (1H, ddd, *J*= 7.9, 7.2, 0.9 Hz), 7.11 (1H, ddd, *J*= 7.9, 7.2, 0.9 Hz), 7.19 (2H, dd, *J*= 7.7, 1.7 Hz), 7.28-7.33 (6H, m), 7.36 (1H, td, *J*= 7.4, 1.4 Hz), 7.40 (1H, dd, *J*= 8.4, 0.7 Hz), 7.73 (1H, d, *J*= 7.7 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.2 (2 × CH_3), 286.0 (CH), 44.1 (CH_2), 45.4 (CH_2), 100.3 (CH), 108.2 (CH), 119.1 (CH), 120.7 (CH), 120.7 (CH), 126.3 (CH), 126.4 (quat), 126.7 (CH), 126.7 (CH), 126.8 (CH), 128.1 (2 × CH), 128.4 (quat), 128.9 (2 × CH), 129.2 (CH), 134.5 (quat), 134.9 (quat), 135.7 (quat), 136.9 (quat), 142.1 (quat), 142.2 (quat); **IR** (neat): 2947, 2924, 2862, 1541, 1460, 1444, 1365, 1315, 1238 cm^{-1}; **HRMS**: (ESI) calculated for $C_{27}H_{26}N$ [MH$^+$]: 364.2060, found: 364.2062.

11-[2-Cyclohexyl-1-phenyleth-(Z)-ylidene]-6,11-dihydro-indolo[1,2-*b*]isoquinoline, 22n.

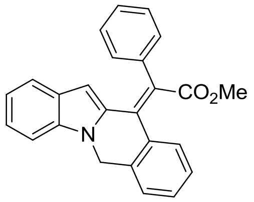


86 mg of a white solid (71% yield, 8 h reaction) from **21s**, and **8a**. **m.p.:** 156-158 ºC; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.71-0.78 (2H, m), 1.00-1.03 (3H, m), 1.14-1.22 (1H, m), 1.51-1.54 (3H, m), 1.60-1.62 (2H, m), 2.86 (2H, d, *J*= 7.0 Hz), 5.14 (2H, s), 5.34 (1H, s), 6.93-6.96 (1H, m), 7.10 (1H, ddd, *J*= 8.1, 7.0, 1.1 Hz), 7.17 (2H, dd, *J*= 7.6, 1.8 Hz), 7.27-7.32 (6H, m), 7.36 (1H, td, *J*= 7.6, 1.3 Hz), 7.40 (1H, d, *J*= 7.4 Hz), 7.72 (1H, d, *J*= 7.7 Hz); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 26.0 (2 × CH$_2$), 26.3 (CH$_2$), 33.0 (2 × CH$_2$), 35.3 (CH), 42.6 (CH$_2$), 45.5 (CH$_2$), 100.2 (CH), 108.2 (CH), 119.1 (CH), 120.6 (CH), 120.7 (CH), 126.3 (CH), 126.5 (quat), 126.7 (3 × CH), 128.1 (2 × CH), 128.4 (quat), 128.9 (2 × CH), 129.1 (CH), 134.5 (quat), 134.9 (quat), 135.8 (quat), 136.9 (quat), 141.7 (quat), 142.4 (quat) **IR** (neat): 2924, 1475, 1448, 1421, 1350, 1315, 1263, 1236, 1165 cm^{-1}; **HRMS**: (ESI) calculated for $C_{30}H_{30}N$ [MH$^+$]: 404.2373, found: 404.2373.

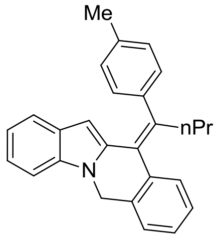
11-[1-Cyclohexyl-1-phenylmeth-(Z)-ylidene]-6,11-dihydro-indolo[1,2-*b*]isoquinoline, 22o.



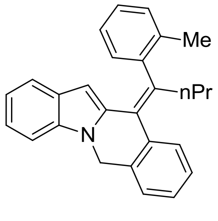
White solid in 71% yield (83 mg) from **21t** and **8a** (8 h reaction time). **m.p.:** 228-230 ºC; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.25-1.33 (5H, m), 1.59-1.61 (1H, m), 1.72-1.74 (2H, m), 1.82-1.83 (2H, m), 3.21-3.26 (1H, m), 5.14 (2H, s), 5.20 (1H, d, *J*= 0.7 Hz), 6.93 (1H, ddd, *J*= 7.5, 7.1, 0.9 Hz), 7.07-7.10 (3H, m), 7.24-7.26 (1H, m), 7.29-7.34 (5H, m), 7.38 (1H, td, *J*= 7.5, 1.4 Hz), 7.41 (1H, d, *J*= 7.5 Hz), 7.66 (1H, d, *J*= 6.9 Hz); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 25.8 (CH$_2$), 26.1 (2 × CH$_2$), 32.2 (2 × CH$_2$), 42.3 (CH), 45.4 (CH$_2$), 100.6 (CH), 108.2 (CH), 119.0 (CH), 120.60 (CH), 120.7 (CH), 125.0 (quat), 126.4 (CH), 126.7 (CH), 126.8 (CH), 126.9 (CH), 127.7 (2 × CH), 128.4 (quat), 128.5 (CH), 129.7 (2 × CH), 134.4 (quat), 134.8 (quat), 135.3 (quat), 136.8 (quat), 140.2 (quat), 147.9 (quat); **IR** (neat): 2929, 2850, 1487, 1448, 1317, 1238 cm^{-1}; **HRMS**: (ESI) calculated for $C_{29}H_{28}N$ [MH$^+$]: 390.2216, found: 390.2210.



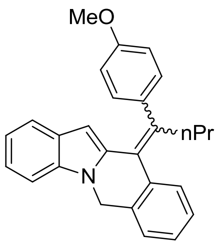
[6*H*-Indolo[1,2-*b*]isoquinolin-(11*E*)-ylidene]-phenylacetic acid methyl ester, 22p. Yellow solid in 79% (87 mg) from **21u** and **8a** (4 h reaction time). **m.p.:** 190-192 ºC; **^{1}H NMR** (500 MHz, CDCl$_3$): δ 3.68 (3H, s), 5.27 (2H, s), 5.63 (1H, s), 7.01 (1H, t, *J*= 7.8 Hz), 7.17-7.21 (1H, m), 7.32-7.44 (8H, m), 7.47-7.49 (2H, m), 7.69 (1H, dd, *J*= 7.6, 1.1 Hz); **^{13}C NMR** (150 MHz, CDCl$_3$): 42.3 (CH$_2$), 52.4 (CH$_3$), 102.8 (CH), 108.7 (CH), 119.9 (CH), 121.3 (CH), 122.1 (CH), 126.6 (CH), 126.9 (CH), 127.3 (CH), 128.0 (quat), 128.3 (CH), 128.4 (CH), 128.7 (2 × CH), 129.5 (2 × CH), 129.9 (quat), 131.9 (quat), 133.2 (quat), 133.3 (quat), 133.3 (quat), 135.4 (quat), 136.7 (quat), 170.4 (CO); **IR** (neat): 3053, 2947, 1724, 1448, 1435, 1319, 1261, 1215, 1132 cm^{-1}; **HRMS**: (ESI) calculated for $C_{25}H_{20}O_2N$ [MH$^+$]: 366.1489, found: 366.1489.



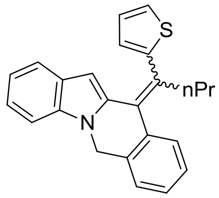
11-[1-*p*-Tolylbut-(Z)-ylidene]-6,11-dihydro-indolo[1,2-*b*]isoquinoline, 22b. White solid in 90% yield (98 mg) from **21a** and **8b**. **m.p.:** 190-192 ºC **^{1}H NMR** (500 MHz, CDCl$_3$): δ 0.86 (3H, t, *J*= 7.3 Hz), 1.46 (2H, sext, *J*= 7.3 Hz), 2.39 (3H, s), 2.78 (2H, m), 5.15 (2H, s), 5.47 (1H, s), 6.96 (1H, td, *J*= 7.7, 0.9 Hz), 7.07 (2H, d, *J*= 8.0 Hz), 7.11 (1H, td, *J*= 7.2, 1.2 Hz), 7.15 (2H, d, *J*= 7.7 Hz), 7.30-7.33 (3H, m), 7.37 (1H, dt, *J*= 7.5, 1.4 Hz), 7.40 (1H, d, *J*= 7.5 Hz), 7.67 (1H, dd, *J*= 7.7, 0.8 Hz); **^{13}C NMR** (150 MHz, CDCl$_3$): δ 13.9 (CH$_3$), 21.3 (CH$_3$), 31.6 (CH$_2$), 38.4 (CH$_2$), 45.4 (CH$_2$), 100.4 (CH), 108.2 (CH), 119.1 (CH), 120.6 (CH), 120.7 (CH), 125.3 (quat), 126.3 (CH), 126.7 (CH), 126.8 (CH), 128.4 (quat), 128.6 (2 × CH), 128.7 (CH), 128.9 (2 × CH), 134.6 (2 × quat), 135.5 (quat), 136.3 (quat), 136.8 (quat), 139.6 (quat), 143.3 (quat); **IR** (neat): 2904, 1496, 1452, 1280, 1195, 1033, 1022 cm^{-1}; **HRMS**: (ESI) calculated for $C_{27}H_{26}N$ [MH$^+$]: 364.2060, found: 364.2066.



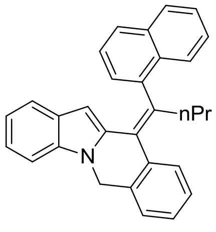
11-[1-*o*-Tolylbut-(Z)-ylidene]-6,11-dihydro-indolo[1,2-*b*]isoquinoline, 22q. 90 mg of a light brown oil (83% yield) were afforded from **21a** and **8c** after 3 h according to general procedure G. **^{1}H NMR** (500 MHz, CDCl$_3$): δ 0.91 (3H, t, *J*= 7.3 Hz), 1.47-1.62 (2H, m), 2.07 (3H, s), 2.57-2.63 (1H, m), 2.88-2.92 (1H, m), 5.10 (1H, d, *J*= 14.6 Hz), 5.20 (1H, d, *J*= 14.6 Hz), 5.34 (1H, s), 6.96 (1H, t, *J*= 7.4 Hz), 7.11 (1H, t, *J*= 7.5 Hz), 7.16-7.18 (2H, m), 7.24 (1H, d, *J*= 3.4 Hz), 7.25 (1H, d, *J*= 3.8 Hz), 7.29-7.35 (3H, m), 7.39 (1H, d, *J*= 7.5 Hz), 7.42 (1H, d, *J*= 7.9 Hz), 7.7 (1H, d, *J*= 7.6 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.3 (CH_3), 19.3 (CH_3), 21.7 (CH_2), 38.1 (CH_2), 45.3 (CH_2), 100.0 (CH), 108.2 (CH), 119.1 (CH), 120.7 (CH), 120.8 (CH), 125.5 (CH), 125.7 (quat), 126.3 (CH), 126.8 (CH), 126.9 (CH), 127.0 (CH), 128.7 (CH), 129.2 (CH), 129.7 (quat), 130.3 (CH), 134.5 (quat), 134.6 (quat), 134.8 (quat), 135.2 (quat), 136.6 (quat), 141.7 (quat), 142.0 (quat); **IR** (neat): 2956, 2857, 1612, 1597, 1454, 1317, 1234, 1141cm^{-1}; **HRMS**: (ESI) calculated for $C_{27}H_{26}N$ [MH^+]: 364.2060, found: 364.2062.



11-[1-(4-Methoxyphenyl)but-(Z)-ylidene]-6,11-dihydro-indolo[1,2-*b*]isoquinoline, *Z*-22r and **11-[1-(4-Methoxyphenyl)but-(*E*)-ylidene]-6,11-dihydro-indolo[1,2-*b*]isoquinoline, *E*-22r**. White solid (86 mg, 75%, $Z_{(a)}$:$E_{(b)}$ = 1:2) from **21a** and **8d**. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.84 (3H_b, t, *J*= 7.3 Hz), 0.86 (3H_a, t, *J*= 7.3 Hz), 1.35-1.43 (2H_b, m), 1.43-1.49 (2H_a, m), 2.77-2.80 (2H_a, m), 3.02-3.05 (2H_b, m), 3.81 (3H_b, s), 3.84 (3H_a, s), 5.15 (2H_a, s), 5.18 (2H_b, s), 5.49 (1H_a, s), 6.66 (1H_b, s), 6.76 (1H_b, d, *J*= 7.9 Hz), 6.80 (2H_b, d, *J*= 8.7 Hz), 6.85 (1H_b, t, *J*= 7.6 Hz), 6.89 (2H_a, d, *J*= 8.7 Hz), 6.95-6.98 (1H_a, m), 7.03-7.13 (2H_a, 4H_b, m), 7.16-7.18 (2H_a, m), 7.21-7.24 (1H_b, m), 7.27 (1H_b, d, *J*= 8.8 Hz), 7.30-7.34 (2H_a, m), 7.37 (1H_a, td, *J*= 1.4, 7.6 Hz), 7.40 (1H_a, d, *J*= 7.7 Hz), 7.42 (1H_b, d, *J*= 8.3 Hz), 7.66 (1H_a, d, *J*= 7.1 Hz), 7.67 (1H_b, d, *J*= 7.9 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.8 (CH_3), 13.9 (CH_3), 21.5 (CH_2), 21.7 (CH_2), 37.2 (CH_2), 38.5 (CH_2), 45.4 (CH_2), 45.5 (CH_2), 55.2 (CH_3), 55.2 (CH_3), 100.1 (CH), 100.4 (CH), 108.2 (CH), 108.4 (CH), 113.5 (2 × CH), 113.6 (2 × CH), 119.1 (CH), 119.5 (CH), 120.6 (CH), 120.7 (2 × CH), 121.2 (CH), 124.9 (CH), 125.6 (CH), 125.8 (CH), 126.2 (CH), 126.3 (CH), 126.7 (CH), 126.8 (CH), 128.4 (quat) 128.5 (quat), 128.7 (quat), 129.9 (2 × CH), 130.1 (CH), 130.6 (2 × CH), 134.1 (quat), 134.5 (quat), 134.60 (quat), 134.9 (quat), 135.0 (quat), 135.5 (quat), 136.3 (quat), 136.4 (quat), 136.2 (quat), 136.8 (quat), 136.8 (quat), 142.5 (quat), 143.0 (quat), 158.4 (2 × quat); **IR** (neat): 2956, 2933, 2873, 1604, 1508, 1465, 1448, 1246, 1178 cm^{-1}; **HRMS**: (ESI) calculated for $C_{27}H_{26}ON$ [MH$^+$]: 380.2009, found: 380.2017.



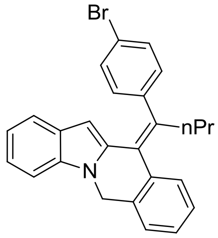
11-[1-Thiophen-2-ylbut-(Z)-ylidene]-6,11-dihydro-indolo[1,2-*b*]isoquinoline, Z-22s and **11-[1-Thiophen-2-ylbut-(*E*)-ylidene]-6,11-dihydro-indolo[1,2-*b*]isoquinoline, *E*-22s**. 54 mg of a pale yellow solid (51 % yield, $Z_{(a)}$:$E_{(b)}$ = 1:1.9) from **21a** and **8e** according to general procedure G. **^{1}H NMR** (500 MHz, CDCl$_3$): δ 0.91 ($3H_a$, t, *J*= 7.3 Hz), 0.97 ($3H_b$, t, *J*= 7.3 Hz), 1.57-1.67 ($2H_a$, $2H_b$, m), 2.76-2.79 ($2H_a$, m), 2.95-2.98 ($2H_b$, m), 5.17 ($2H_a$, s), 5.19 ($2H_b$, s), 5.82 ($1H_a$, s), 6.66 ($1H_b$, s), 6.78 ($1H_b$, dd, *J*= 1.0, 3.4 Hz), 6.90-6.92 ($1H_b$, $1H_a$, m), 6.95 ($1H_b$, t, *J*= 7.6 Hz), 7.00 ($1H_a$, t, J= 7.5 Hz), 7.02 ($1H_a$, t, *J*= 3.4, 5.0 Hz), 7.07 ($1H_b$, d, *J*= 7.9 Hz), 7.11-7.16 ($1H_a$, $2H_b$, m), 7.22-7.26 ($4H_a$, $1H_b$, m), 7.29-7.43 ($2H_a$, $3H_b$), 7.65-7.68 ($1H_{a,}$ $1H_b$, m); **^{13}C NMR** (125 MHz, CDCl$_3$): δ 13.8 (2 × CH$_3$), 22.0 (2 × CH$_2$), 38.4 (CH$_2$), 38.9 (CH$_2$), 45.4 (2 × CH$_2$), 100.2 (CH), 100.3 (CH), 108.3 (CH), 108.5 (CH), 119.3 (CH), 119.6 (CH), 120.8 (2 × CH), 121.1 (CH), 121.5 (CH), 124.9 (CH), 125.2 (CH), 125.3 (quat), 125.7 (CH), 126.3 (2 × CH), 126.4 (CH), 126.7 (3 × CH), 126.8 (CH), 127.1 (CH), 127.2 (CH), 127.2 (quat), 127.9 (quat), 128.2 (quat), 128.4 (quat), 128.5 (quat), 128.6 (CH), 128.7 (quat), 129.0 (quat), 129.5 (CH), 134.2 (quat), 134.7 (quat), 134.9 (quat), 135.1 (quat), 135.5 (quat), 136.1 (quat), 143.5 (quat), 144.7 (quat); **IR** (neat): 2953, 2926, 2868, 1722, 1674, 1610, 1448, 1371, 1354, 1240 cm^{-1}; **HRMS**: (ESI) calculated for $C_{24}H_{22}NS$ [MH$^+$]: 356.1468, found: 356.1465.



11-[1-Naphthalen-1-ylbut-(Z)-ylidene]-6,11-dihydro-indolo[1,2-*b*]isoquinoline, 22t. 60 mg of a pale brown solid (50 % yield, 64% yield brsm) were achieved from **21a** and **8f**. **m.p.:** 94-96 ºC; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.86 (3H, t, *J*= 7.3 Hz), 1.40-1.51 (2H, m), 2.72-2-88 (1H, m), 2.98-3.04 (1H, m), 5.18 (3H, bs), 6.85 (1H, t, , *J*= 7.1 Hz), 7.05 (1H, td, *J*= 7.0, 1.0 Hz), 7.11 (1H, d, *J*= 7.9 Hz), 7.26-7.30 (2H, m), 7.35-7.40 (2H, m), 7.43-7.49 (4H, m), 7.82-7.88 (3H, m), 7.92

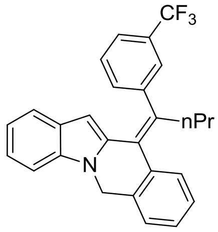
(1H, d, *J*= 8.3 Hz); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 14.2 (CH$_3$), 22.5 (CH$_2$), 38.9 (CH$_2$), 45.4 (CH$_2$), 100.2 (CH), 108.1 (CH), 119.0 (CH), 120.6 (CH), 120.8 (CH), 125.2 (CH), 125.3 (CH), 125.7 (CH), 126.0 (CH), 126.4 (2 × CH), 126.9 (CH), 127.1 (CH), 127.2 (quat), 127.3 (CH), 128.3 (quat), 128.5 (CH), 128.7 (CH), 131.6 (quat), 133.7 (quat), 134.5 (quat), 134.6 (quat), 135.4 (quat), 136.4 (quat), 140.0 (quat), 141.2 (quat); **IR** (neat): 3055, 2956, 2868, 1612, 1589, 1504, 1479, 1446, 1317, 1234, 1141 cm^{-1}; **HRMS**: (ESI) calculated for C$_{30}$H$_{26}$N [MH$^+$]: 400.2060, found: 400.2054.

11-[1-(4-Bromophenyl)but-(Z)-ylidene]-6,11-dihydro-indolo[1,2-*b*]isoquinoline,



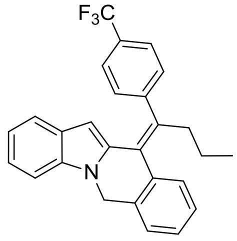
22u. White solid in 81 % yield (105 mg) from **21a** and **8g**. **m.p.:** 170-172 ºC; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.85 (3H, t, *J*= 7.3 Hz), 1.41 (2H, m), 2.76-2.80 (2H, m), 5.15 (2H, s), 5.46 (1H, s), 6.98 (1H, t, *J*= 7.4 Hz), 7.07 (2H, d, *J*= 8.2 Hz), 7.13 (1H, t, *J*= 7.4 Hz), 7.32-7.42 (5H, m), 7.47 (2H, d, *J*= 8.2 Hz), 7.66 (1H, d, *J*= 7.5 Hz); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 13.9 (CH$_3$), 21.6 (CH$_2$), 38.0 (CH$_2$), 45.4 (CH$_2$), 100.7 (CH), 108.3 (CH), 119.3 (CH), 120.8 (quat), 120.8 (CH), 121.1 (CH), 125.9 (quat), 126.4 (CH), 126.8 (CH), 127.0 (CH), 128.3 (quat), 128.6 (CH), 130.7 (2 × CH), 131.4 (2 × CH), 134.6 (quat), 134.7 (quat), 135.1 (quat), 135.3 (quat), 141.5 (quat), 141.6 (quat) **IR** (neat): 2957, 2870, 1485, 1452, 1319, 1240, 1009 cm^{-1}; **HRMS**: (ESI) calculated for C$_{26}$H$_{23}$NBr^{79} [MH$^+$]: 428.1008, found: 428.1011.

11-[1-(3-Trifluoromethylphenyl)but-(Z)-ylidene]-6,11-dihydro-

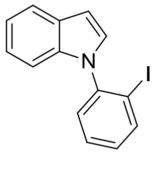


indolo[1,2*b*]isoquinoline, 22v.White solid in 86% yield (108 mg) from **21a** and **8h**. **m.p.:** 128-130 ºC; **^{1}H NMR** (500 MHz, CDCl$_3$): δ 0.88 (3H, t, *J*= 7.3 Hz), 1.39-1.46 (2H, m), 2.80-2.83 (2H, m), 5.17 (2H, s), 5.33 (1H, s), 6.97 (1H, t, *J*= 7.4 Hz), 7.13 (1H, m), 7.29-7.35 (4H, m), 7.38-7.44 (3H, m), 7.53 (1H, s), 7.58 (1H, d, *J*= 7.8 Hz), 7.68 (1H, d, *J*= 7.5 Hz); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 13.9 (CH$_3$), 21.7 (CH$_2$), 38.0 (CH$_2$), 45.4 (CH$_2$), 100.7 (CH), 108.3 (CH), 119.3 (CH), 120.3 (CF$_3$, q, $J_{C\text{-}F}$= 263 Hz), 120.8 (CH), 121.1 (CH), 123.7 (CH, q, $J_{C\text{-}F}$= 3.7 Hz), 124.5

(quat, q, $J_{C\text{-}F}$= 4.5 Hz), 125.6 (CH, q, $J_{C\text{-}F}$= 3.7 Hz), 126.4 (CH), 126.8 (CH), 127.2 (CH), 128.3 (quat), 128.6 (CH), 128.7 (CH), 130.6 (quat, q, $J_{C\text{-}F}$= 32.2 Hz), 132.6 (CH), 134.6 (quat), 134.7 (quat), 135.0 (quat), 136.0 (quat), 141.1 (quat), 143.3 (quat); **IR** (neat): 2966, 2941, 2883, 1589, 1454, 1332, 1319, 1165, 1107, 1070 cm^{-1}; **HRMS**: (ESI) calculated for $C_{27}H_{23}NF_3$ [MH$^+$]: 418.1777, found: 418.1776.

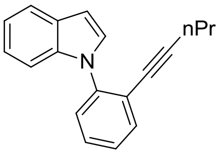


11-[1-(*p*-Trifluoromethylphenyl)but-(Z)-ylidene]-6,11-dihydro-indolo[1,2*b*]isoquinoline, 22w. General procedure G afforded 110 mg of a white solid in 88 % yield when **21a** reacted with bis(4-trifluoromethanephenyl)iodonium tetrafluoroborate, **8i**. **m.p.:** 166-168 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (3H, t, *J*= 7.3 Hz), 1.38-1.46 (2H, m), 2.80-2.83 (2H, m), 5.17 (2H, s), 5.37 (1H, s), 6.98 (1H, td, *J*= 7.2, 0.5 Hz), 7.13 (1H, ddd, *J*= 8.2, 7.2, 1.1 Hz), 7.31-7.35 (5H, m), 7.39 (1H, td, *J*= 7.5, 1.3 Hz), 7.43 (1H, d, *J*= 7.4 Hz), 7.61 (2H, d, *J*= 8.0 Hz), 7.68 (1H, d, *J*= 7.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 21.6 (CH_2), 37.9 (CH_2), 45.4 (CH_2), 100.8 (CH), 108.3 (CH), 119.4 (CH), 120.8 (CH), 121.2 (CH), 125.6 (2 × CH, q, *J*= 3.7 Hz), 126.1 (quat), 126.4 (CH), 124.3 (CF_3, q, $J_{C\text{-}F}$= 272.0 Hz), 126.8 (CH), 127.2 (CH), 128.2 (quat), 128.6 (CH), 129.0 (quat, q, $J_{C\text{-}F}$= 32.3 Hz), 129.4 (2 × CH), 134.6 (quat), 134.7 (quat), 134.9 (quat), 136.1 (quat), 141.3 (quat), 146.5 (quat); **IR** (neat): 2960, 2931, 2873, 1610, 1450, 1282, 1163, 1074, 1066 cm^{-1}; **HRMS**: (ESI) calculated for $C_{27}H_{23}NF_3$ [MH$^+$]: 418.1777, found: 418.1770.

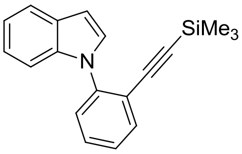


1-(2-Iodophenyl)-*1H*-indole, **28**. Synthesised from indole and 1,2-diiodobenzene using CuI as catalyst in the presence of benzotriazole as described by Verma *et. al.*[38] in 66% after 30 h at 120 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.71 (1H, dd, *J*= 3.2, 0.8 Hz), 7.05 (1H, dd, *J*= 7.6, 1.6 Hz), 7.18-7.21 (4H, m), 7.40 (1H, dd, *J*= 7.6, 1.6 Hz), 7.49 (1H, td, *J*= 7.6, 1.4 Hz), 7.70-7.72 (1H, m), 8.04 (1H, dd, *J*= 8.0, 1.4 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 97.6 (quat), 103.1 (CH), 110.7 (CH), 120.2 (CH), 120.9 (CH), 122.3 (CH), 128.4 (CH), 128.5 (CH), 129.2 (CH), 129.4 (CH), 129.9 (CH), 136.7 (quat), 140.2 (quat), 142.0 (quat).

General procedure H: Sonogashira coupling.

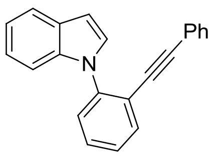


1-(2-Pent-1-ynylphenyl)-*1H*-indole, 29a. The named product was synthesised by a Sonogashira coupling from 1-(2-iodophenyl)-*1H*-indole (180 mg, 1.57 mmol) and 1-pentyne. The coupling conditions are described as a representative procedure[78, 80]: the aryliodide was dissolved in Et_3N (5 mL) bubbled with N_2 for 10 min. and $PdCl_2(PPh_3)_2$ (4.3 mg, 0.006 mmol), CuI (2.3 mg, 0.012 mmol) and 1-pentyne (190 µL, 1.89 mmol) were added. The mixture was heated at 60 ºC for 20 h. Then the crude was filtered through a silica pad, eluting with EtOAc and the solvent was evaporated under vacuum. The residue was purified through a silica column (hexane:CH_2Cl_2, 8:2) affording 220 mg of colourless oil (54% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.75 (3H, t, *J*= 7.4 Hz), 1.31 (2H, tt, *J*= 7.4, 7.0 Hz), 2.13 (2H, t, *J*= 7.0 Hz), 6.64 (1H, d, *J*= 3.2 Hz), 7.14 (1H, td, *J*= 7.4, 1.1 Hz), 7.18 (1H, td, *J*= 8.0, 1.5 Hz), 7.30 (1H, dd, *J*= 8.7, 1.0 Hz), 7.34 (1H, dd, *J*= 7.6, 1.6 Hz), 7.38-7.44 (3H, m), 7.58 (1H, dd, *J*= 7.7, 1.4 Hz), 7.67 (1H, d, *J*= 7.2 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.3 (CH_3), 21.4 (CH_2), 21.6 (CH_2), 77.3 (quat), 95.8 (quat), 102.5 (CH), 111.0 (CH), 120.0 (CH), 120.7 (CH), 121.6 (quat), 121.8 (CH), 126.9 (CH), 127.0 (CH), 128.3 (CH), 128.8 (quat), 129.0 (CH), 133.6 (CH), 136.5 (quat), 140.6 (quat); **IR** (neat): 2960, 2931, 2870, 2230, 1514, 1492, 1458, 1330, 1211, 1136, 1012 cm^{-1}; **HRMS**: (APCI) calculated for $C_{19}H_{18}N$ [MH$^+$]: 260.1434, found: 260.1439.

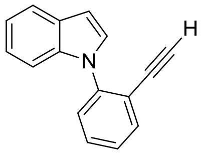


2-(2-Indol-1-ylphenyl)ethynyl-trimethylsilane, 29b. The described procedure H afforded 450 mg of a colourless oil (65% yield) from **28** and trimethylsilylacetylene after 24h at 60 ^{o}C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ -0.03 (9H, s), 6.64 (1H, d, *J*= 3.2 Hz), 7.13-7.20 (2H, m), 7.30-7.36 (2H, m), 7.41 (1H, d, *J*= 3.2), 7.44-7.46 (2H, m), 7.63 (1H, dd, *J*= 7.7, 0.7 Hz), 7.67 (1H, d, *J*= 7.7 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ -0.6 (3 × CH_3), 100.4 (quat), 101.3 (quat), 102.6 (CH), 111.1 (CH), 120.0 (CH), 120.6 (quat), 120.7 (CH), 121.8 (CH), 126.9 (2 × CH), 128.8 (quat), 128.9 (CH), 129.3 (CH), 133.7 (CH), 136.4 (quat), 141.3 (quat); **IR** (neat): 3052, 2958, 2898, 2161, 1596, 1587, 1515, 1491, 1459, 1308, 1235, 1137 cm^{-1}; **HRMS**: (ESI) calculated for $C_{19}H_{20}N_1Si_1$ [MH$^+$]: 290.1360, found: 290.1363.

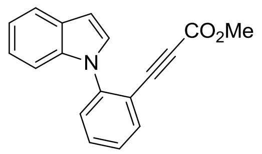
1-[2-(2-Phenylethynyl)phenyl]-*1H*-indole, 29c. Usual Sonogashira coupling (procedure H) between **28** and iodobenzene (r.t., 15 h) afforded 240 mg of an orange oil (52% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.71 (1H, dd, *J*= 3.2, 0.6 Hz), 7.08 (2H, dd, *J*= 8.1, 1.5 Hz), 7.16-7.24 (5H, m), 7.36-7.38 (1H, m), 7.40 (1H, td, *J*= 7.5, 1.5 Hz), 7.46-7.53 (3H, m), 7.71 (2H, dd, *J*= 7.8, 1.1 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 85.2 (quat), 94.5 (quat), 102.8 (CH), 111.1 (CH), 120.1 (CH), 120.8 (CH), 120.9 (quat), 122.0 (CH), 122.7 (quat), 127.0 (CH), 127.1 (CH), 128.1 (2 × CH), 128.4 (CH), 128.8 (quat), 129.1 (2 × CH), 131.4 (2 × CH), 133.4 (CH), 136.5 (quat), 140.7 (quat); **IR** (neat): 3043, 2877, 2812, 2218, 1593, 1496, 1483, 1458, 1330 cm^{-1}; **HRMS**: (ESI) calculated for $C_{22}H_{16}N$ [MH$^+$]: 294.1277, found: 294.1281.



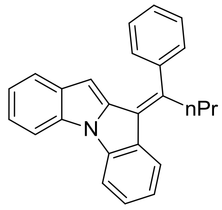
1-(2-Ethynylphenyl)-*1H*-indole, 29d. The named product was prepared from **29b** following the procedure described by Xu and co-workers[96]. **29b** (350 mg, 1.20 mmol) was weighed in a 50 mL round bottomed flask containing a stirrer and dissolved in MeOH (35 mL). K_2CO_3 (500 mg, 3.61 mmol) was added and the mixture was vigorously stirred at r.t. for 3 h. The solvent was evaporated and usual aqueous work up and purification (SiO2, hexane:EtOAc, 9:1) afforded 230 mg (89%) of a brownish oil. The spectroscopic data are in accordance with that reported in the literature.[9] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.03 (1H, s), 6.69 (1H, d, *J*= 3.3 Hz), 7.06-7.22 (2H, m), 7.32-7.48 (5H, m), 7.67-7.71 (2H, m); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 80.1 (quat), 82.3 (CH), 102.9 (CH), 110.8 (CH), 119.6 (quat), 120.3 (CH), 120.9 (CH), 122.0 (CH), 127.0 (CH), 127.2 (CH), 128.7 (quat), 129.0 (CH), 129.7 (CH), 134.5 (CH), 136.5 (quat), 141.2 (quat).



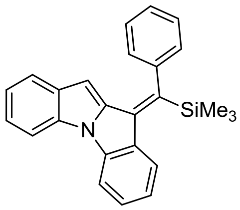
3-(2-Indol-1-ylphenyl)prop-2-ynoic acid methyl ester, 29e. 1-(2-Ethynylphenyl)-*1H*-indole, **29d** (130 mg, 0.60 mmol) was weighed in an oven-dried flask, sealed with a rubber septum and purged with N_2. Dry THF (5 mL) was added and the solution was cooled down to -78 ^{o}C in a dry ice/acetone bath. nBuLi (510 µL, 1.4 M, 0.71 mmol) was added dropwise and the yellow solution was allowed to warm up to r.t. for 1h. Then it was cooled again at -78 ^{o}C and methyl chloroformate (70 µL, 0.91 mmol) was carefully added *via* µsyringe. The pale yellow solution was left to slowly warm up at r.t. and left stirring overnight. Then EtOAc (5 mL) and H_2O (5 mL) were slowly added. The two layers were separated and the aqueous one further extracted twice with EtOAc. The combined organic layers were washed twice with brine, dried over anh. $MgSO_4$, filtered and evaporated under vacuum. The crude was chromatographed (SiO_2, hexane:CH_2Cl_2 mixtures) to afford 91 mg of a white solid (55%). **m.p.:** 108-110 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.70 (3H, s), 6.71 (1H, dd, *J*= 3.3, 0.7 Hz), 7.16-7.23 (2H, m), 7.34 (1H, dd, *J*= 8.1, 0.9 Hz), 7.41 (1H, td, *J*= 7.5, 1.5 Hz), 7.43 (1H, d, *J*= 3.3 Hz), 7.53-7.61 (2H, m), 7.67-7.69 (1H, m), 7.77 (1H, dd, *J*= 7.8, 1.3 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 52.8 (CH_3), 83.0 (quat), 84.5 (quat), 103.8 (CH), 110.6 (CH), 116.8 (quat), 120.6 (CH), 121.1 (CH), 122.3 (CH), 126.9 (CH), 127.0 (CH), 128.8 (CH), 129.1 (quat), 131.5 (CH), 135.3 (CH), 136.3 (quat), 142.0 (quat), 153.9 (CO). **IR** (neat): 3070, 3010, 2220, 1703, 1494, 1456, 1427, 1298, 1263, 1201 cm^{-1}; **HRMS**: (ESI) calculated for $C_{18}H_{14}O_2N$ [MH$^+$]: 276.1019, found: 276.1022.



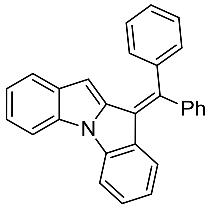
10-[1-Phenylbut-(*Z*)-ylidene]-*10H*-indolo[1,2*a*]indole, 30a. The general procedure G for the tandem annulation/arylation reaction was followed, but heating at 50 ^{o}C afforded 79 mg of a yellow solid (78% yield) from **29a** and **8a**. **m.p.:** 130-132 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.09 (3H, t, *J*= 7.3 Hz) ,1.73 (2H, sext, *J*= 7.4 Hz), 2.97-3.00 (2H, m), 5.14 (1H, s), 7.04 (1H, td, *J*= 7.6, 1.0 Hz), 7.16 (1H, td, *J*= 7.6, 1.0 Hz), 7.20 (1H, ddd, *J*= 8.2, 7.2, 1.0 Hz), 7.34-7.37 (3H, m), 7.40 (1H,t d, *J*= 7.8, 1.0 Hz), 7.48 (1H, *J*= 4.7, 1.9 Hz), 7.52-7.55 (2H, m), 7.60 (1H, d, *J*= 7.8 Hz), 7.67 (1H, dd, *J*= 8.2, 0.6 Hz), 7.83 (1H, d, *J*= 7.7 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.3 (CH_3),



21.0 (CH_2), 38.5 (CH_2), 98.4 (CH), 110.4 (CH), 110.5 (CH), 120.5 (CH), 121.5 (CH), 122.3 (CH), 122.4 (CH), 124.5 (quat), 125.0 (CH), 127.7 (2 × CH), 127.8 (CH), 128.4 (CH), 129.4 (2 × CH), 130.7 (quat), 131.2 (quat), 132.9 (quat), 140.9 (quat), 141.0 (quat), 143.8 (quat), 145.2 (quat); **IR** (neat): 3059, 2953, 2929, 2870, 1599, 1489, 1469, 1450, 1328, 1230 cm^{-1}; **HRMS**: (ESI) calculated for $C_{25}H_{22}N$ [MH^+]: 336.1747, found: 336.1746.

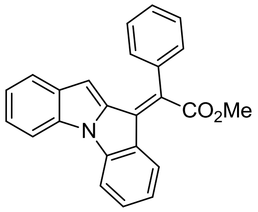


[(*E*)-Indolo[1,2*a*]indol-11-ylidene(phenyl)methyl]-trimethylsilane, 30b. 73 mg of a yellow solid (67%) were obtained from **29b** and **8a** according to general procedure G (50 °C, 24 h). **m.p.:** 136-138 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.31 (9H, s), 4.88 (1H, s), 7.03 (1H, t, *J*= 7.3 Hz), 7.09 (2H, dd, *J*= 7.0, 1.0 Hz), 7.13 (1H, td, *J*= 7.5, 0.5 Hz), 7.22 (1H, td, *J*= 8.0, 0.5 Hz), 7.33 (1H, d, *J*= 8.0 Hz), 7.37-7.43 (2H, m), 7.50 (2H, t, *J*= 7.7 Hz), 7.55 (1H, d, *J*= 7.7 Hz), 7.63 (1H, d, *J*= 7.9 Hz), 7.89 (1H, d, *J*= 7.9 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 0.1 (3 × CH_3), 101.9 (CH), 110.5 (2 × CH), 120.5 (CH), 121.7 (CH), 122.1 (CH), 123.3 (CH), 125.7 (CH), 126.1 (2 × CH), 126.2 (CH), 129.1 (CH), 129.6 (2 × CH), 130.7 (quat), 131.1 (quat), 132.9 (quat), 136.8 (quat), 140.7 (quat), 141.5 (quat), 145.7 (quat), 146.2 (quat); **IR** (neat): 3055, 2953, 2895, 1602, 1489, 1471, 1321, 1247, 1232 cm^{-1}; **HRMS**: (ESI) calculated for $C_{25}H_{24}NSi$ [MH^+]: 366.1673, found: 366.1678.



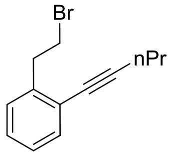
11-Benzhydrylideneindolo[1,2*a*]indole, 30c. 50 mg of a yellow solid (47% yield) were obtained from **29c** and **8a** following general procedure G (50 °C, 24 h). **m.p.:** 200-202 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.78 (1H, s), 6.77-6.80 (2H, m), 7.08-7.12 (1H, m), 7.24-7.32 (3H, m), 7.44-7.56 (11H, m), 7.70 (1H, dd, *J*= 8.2, 0.7 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 99.2 (CH), 110.4 (CH), 110.6 (CH), 120.7 (CH), 121.8 (CH), 121.9 (CH), 123.0 (CH), 125.1 (CH), 125.4 (quat), 128.1 (quat), 128.2 (CH), 128.4 (CH), 128.6 (quat), 128.7 (CH), 128.8 (2 × CH), 129.1 (2 × CH), 129.2 (2 × CH), 129.7 (2 × CH), 132.9 (quat), 140.9 (quat), 141.1 (quat), 141.5 (quat), 141.9 (quat), 142.6 (quat); **IR** (neat): 3049, 3024, 1600, 1487, 1470, 1431, 1323cm^{-1}; **HRMS**: (ESI) calculated for $C_{28}H_{20}N$ [MH^+]: 370.1590, found: 370.1597.

(2E)-2-Indolo[1,2*a*]indol-11-ylidene-2-phenylacetic acid methyl ester, 30d.



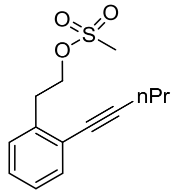
General procedure G afforded 83 mg of a reddish gum (79% yield) after heating at 50 °C overnight. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.91 (3H, s), 5.47 (1H, s), 7.05-7.09 (1H, m), 7.12 (1H, td, *J*= 8.3, 1.3 Hz), 7.27 (1H, td, *J*= 8.3, 1.3 Hz), 7.38 (1H, d, *J*= 8.0 Hz), 7.43 (1H, td, *J*= 7.8, 1.0 Hz), 7.50-7.57 (6H, m), 7.63 (1H, dd, *J*= 8.2, 1.0 Hz), 8.03 (1H, d, *J*= 7.9 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 52.5 (CH_3), 103.7 (CH), 110.5 (CH), 110.6 (CH), 121.0 (CH), 122.4 (CH), 122.7 (CH), 124.3 (CH), 126.2 (CH), 128.5 (2 × CH), 128.8 (CH), 128.9 (quat), 129.0 (quat), 129.5 (2 × CH), 130.6 (CH), 131.5 (quat), 131.7 (quat), 132.7 (quat), 137.6 (quat), 139.4 (quat), 141.4 (quat), 168.3 (CO); **IR** (neat): 3057, 2922, 2854, 1716, 1604, 1489, 1473, 1282 cm^{-1}; **HRMS**: (ESI) calculated for $C_{24}H_{18}O_2N$ [MH$^+$]: 352.1332, found: 352.1341.

1-(2-Bromoethyl)-2-pent-1-ynylbenzene, **31a.**

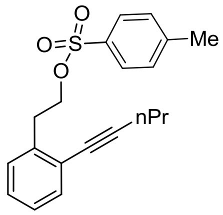


2-iodophenyl ethanol was synthesised by reduction of the commercially available 2-iodophenylacetic acid with sodium borohydride as described by Buchwald and Minatti.[97] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.01 (2H, t, *J*= 6.6 Hz), 3.85 (2H, t, *J*= 6.2 Hz), 6.92 (1H, td, *J*= 7.2, 2.0 Hz), 7.24-7.31 (2H, m), 7.83 (1H, dd, *J*= 7.9, 0.5 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 43.4 (CH_2), 62.3 (CH_2), 100.7 (quat), 128.3 (CH), 128.4 (CH), 130.3 (quat), 139.6 (CH), 141.1 (CH). Sonogashira coupling according to the general procedure H for benzyl alcohols and alkynes, afforded 2-(pent-1-ynylphenyl)-ethanol in 83% yield from 2-(2-iodophenyl)-ethanol (2.00 mmol) and pentyne (1.1 equiv.) as a colourless oil. Spectroscopic data are in agreement with that reported in the literature.[88] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.06 (3H, t, *J*= 7.4 Hz), 1.64 (2H, m), 2.42 (2H, t, *J*= 7.0 Hz), 3.05 (2H, t, *J*= 6.6 Hz), 3.89 (2H, t, *J*= 6.6 Hz), 7.16 (1H, m), 7.22 (2H, m), 7.41 (1H, d, *J*= 7.4 Hz); **^{13}C NMR** (100 MHz), $CDCl_3$): δ 13.5 (CH_3), 21.5 (CH_2), 22.3 (CH_2), 38.0 (CH_2), 62.9 (CH_2), 79.1 (quat), 94.2 (quat), 123.9 (quat), 126.3 (CH), 127.6 (CH), 129.5 (CH), 132.4 (CH), 140.0 (quat). Usual bromination (general procedure E) of 2-(pent-1-ynylphenyl)-ethanol using Sashida and co-workers' method,[26] (1.50 mmol scale) achieved 192 mg of a colourless oil (51% yield) after 1 h reaction. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.08 (3H, t, *J*= 7.4 Hz), 1.66 (2H, tt, *J*= 7.0, 7.4 Hz), 2.44 (2H, t, *J*= 7.0 Hz), 3.31 (2H, t, *J*= 7.8 Hz), 3.62 (2H, t, *J*= 7.8 Hz), 7.17-7.24 (3H, m), 7.40 (1H, d, *J*= 7.4 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.5 (CH_2), 22.3 (CH_2), 31.9 (CH_2), 38.5 (CH_2), 78.6 (quat), 94.7 (quat), 123.7 (quat), 126.9 (CH), 127.7 (CH), 129.3 (CH), 132.4 (CH), 140.5 (quat); **IR** (neat): 2962, 2931, 2870, 2210, 1483, 1446, 1213 cm^{-1}; **HRMS**: (EI) calculated for $C_{13}H_{15}Br^{79}$: 250.0352, found: 250.0350.

Methylsulfonic acid 2-(2-pent-1-ynylphenyl)ethyl ester, 31b. The procedure described by Minatti *et. al.*[97] was followed. 2-(pent-1-ynylphenyl)-ethanol (188 mg, 1.00 mmol) was dissolved in dry CH_2Cl_2 (1.5 mL). NEt_3 (320 μL, 2.31 mmol) was added and the solution was cooled at 0 °C in an ice bath. MsCl (95 μL, 1.22 mmol) was added dropwise and the mixture allowed to warm to r.t. during 2h. 220 mg (83%) of a colourless oil was obtained after usual aqueous work up and purification through a silica column (hexane: EtOAc, 8:2)**.** **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.06 (3H, t, *J*= 7.6 Hz), 1.65 (2H, m), 2.43 (2H, t, *J*= 7.0 Hz), 2.82 (3H, s), 3.22 (2H, t, *J*= 7.0 Hz), 4.47 (2H, t, *J*= 7.0 Hz), 7.17-7.23 (2H, m), 7.41 (2H, d, *J*= 7.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.5 (CH_2), 22.2 (CH_2), 34.6 (CH_2), 37.1 (CH_3), 69.4 (CH_2), 78.5 (quat), 95.0 (quat), 123.9 (quat), 127.0 (CH), 127.8 (CH), 129.8 (CH), 132.5 (CH), 137.7 (quat); **IR** (neat): 2962, 2935, 2231, 1448, 1354, 1210, 952cm^{-1}; **HRMS**: (EI) calculated for $C_{14}H_{18}O_3S$: 266.0971, found: 266.0971.

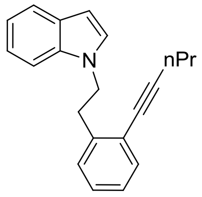


Toluene-4-sulfonic acid 2-(2-pent-1-ynylphenyl)-ethyl ester, 31c. 2-**(**pent-1-ynylphenyl)-ethanol (370 mg, 1.51 mmol) was dissolved in dry CH_2Cl_2 (2 mL) at r.t., DABCO (350 mg, 3.12 mmol) and *p*-toluenesulfonyl chloride (440 mg, 2.31 mmol) were added and the mixture was left stirring for 5 h. Usual aqueous work up and purification through a silica column (hexane: EtOAc, 1:1) afforded 514 mg of the protected alcohol as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.02 (3H, t, *J*= 7.4 Hz), 1.58 (2H, tt, *J*= 7.0, 7.4 Hz), 2.35 (2H, t, *J*= 7.0 Hz), 2.43 (3H, s), 3.12 (2H,

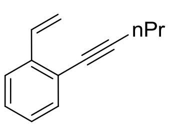


t, J= 7.2 Hz), 4.26 (2H, t, J= 7.2 Hz), 7.10-7.17 (3H, m), 7.27 (2H, d, J= 8.0 Hz), 7.31 (1H, dd, J= 7.0, 2.0 Hz), 7.68 (2H, d, J= 8.3 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.4 (CH_3), 21.6 (CH_2), 22.2 (CH_2), 34.3 (CH_2), 69.6 (CH_2), 78.5 (quat), 94.8 (quat), 123.8 (quat), 126.8 (CH), 127.7 (CH), 127.8 (2 × CH), 129.7 (3 × CH), 132.3 (CH), 133.1 (quat), 137.6 (quat), 144.5 (quat); **IR**: 2964, 2231, 1554, 1544, 1406, 1361, 1195 cm^{-1}; **HRMS**: (EI) calculated for $C_{20}H_{22}O_3S$ [M^+]: 342.1284, found: 342.1287.

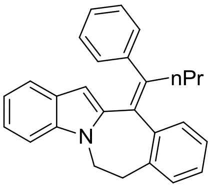
1-[2-(2-Pent-1ynylphenyl)-ethyl]-*1H*-indole. 32. The method described by Guida and Mathre[12] for *N*-indole alkylation was followed. To a stirred solution of 18-crown-6 (29 mg, 0.11 mmol) in dry diethyl ether (2 mL), potassium tert-butoxide (123 mg, 1.11 mmol) and indole (118 mg, 1.01 mmol) were added in one portion. The mixture was purged with N_2 and stirred for 1 h at r.t. After this time toluene-4-sulfonic acid 2-(pent-1-ynylphenyl)-ethyl ester (398 mg, 1.16 mmol) dissolved in diethyl ether (2 mL) was added dropwise through a cannula under N_2 atm. The mixture was left to react at r.t. for 20 h. Water (2 mL) and Et_2O (2 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (2 mL × 2) and the combined organic solution was washed with brine (2 mL × 2), dried ($MgSO_4$), filtered and evaporated under vacuum. The crude was purified through a silica column (hexane:CH_2Cl_2, 8:2) to afford 95 mg of the desired product as a colourless oil (33% yield, 54% elimination product obtained). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.08 (3H, t, J= 7.4 Hz), 1.67 (2H, tt, J= 7.0, 7.4 Hz), 2.45 (2H, t, J= 7.0 Hz), 3.27 (2H, t, J= 7.5 Hz), 4.39 (2H, t, J= 7.5 Hz), 6.45 (1H, d, J= 3.1 Hz), 6.96 (1H, d, J= 3.1 Hz), 7.00 (1H, dd, J= 6.5, 1.5 Hz), 7.11 (1H, t, J= 7.4 Hz), 7.14 (1H, dd, J= 7.4, 1.5 Hz), 7.17 (1H, dd, J= 7.4, 1.5 Hz), 7.20 (1H, t, J= 7.0 Hz), 7.44 (2H, d, J= 8.2 Hz), 7.63 (1H, d, J= 7.9 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.7 (CH_3), 21.6 (CH_2), 22.3 (CH_2), 35.9 (CH_2), 45.0 (CH_2), 79.0 (quat), 94.3 (quat), 101.0 (CH), 109.4 (CH), 119.2 (CH), 120.9 (CH), 121.3 (CH), 123.7 (quat), 126.6 (CH), 127.8 (2 × CH), 128.6 (quat), 129.3 (CH), 132.5 (CH), 135.9 (quat), 140.0 (quat); **IR** (neat): 3051, 2962,



2872, 2231, 1485, 1265 cm^{-1}; **HRMS**: (ESI) calculated for $C_{21}H_{22}N$ [MH^{+}]: 288.1747, found: 288.1741.

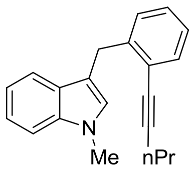


1-pent-1-ynyl-2-vinylbenzene, 33. Usual *N*-alkylation (general procedure F) failed to give the desired alkylated indole and the elimination product was mostly obtained in all cases. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.07 (3H, t, *J*= 7.4 Hz), 1.66 (2H, m), 2.45 (2H, t, *J*= 7.0 Hz), 5.32 (1H, dd, *J*= 11.0, 1.1 Hz), 5.79 (1H, dd, *J*= 17.1, 1.1 Hz), 7.17 (1H, td, *J*= 7.5, 1.1 Hz), 7.20-7.26 (2H, m), 7.39 (1H, dd, *J*= 7.6, 1.2 Hz), 7.55 (1H, dd, *J*= 7.6, 0.7 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.6 (CH_2), 22.3 (CH_2), 79.0 (quat), 95.1 (quat), 115.0 (CH), 122.8 (quat), 124.4 (CH_2), 127.4 (CH), 127.6 (CH), 132.5 (CH), 135.2 (CH), 138.8 (quat); **IR** (neat): 3053, 2964, 2873, 1770, 1483, 1448 cm^{-1}; **HRMS**: (EI) calculated for $C_{13}H_{13}$ [M-H^{+}]: 169.1012, found: 169.1011.

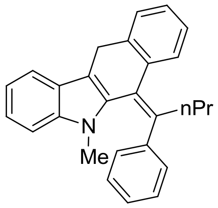


11-[1-Phenylbut-(*Z*)-ylidene]-6,11-dihydro-*5H*-4b-aza-dibenzo[*a,f*]azulene, 34. White solid in 52% yield (57 mg) from **32** and **8a** according to general procedure G (50 ºC for 20 h). **m.p.:** 194-196 ºC; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.68 (3H, t, *J*= 7.3 Hz), 1.07-1.14 (1H, m), 1.23-1.29 (1H, m), 2.43-2.49 (1H, m), 2.66-2.72 (1H, m), 3.11 (1H, dt, *J*= 14.0, 3.4 Hz), 3.91 (1H, td, *J*= 14.0, 3.4 Hz), 4.15 (1H, td, *J*= 14.0, 3.4 Hz), 4.49 (1H, dt, *J*= 14.0, 3.4 Hz), 5.69 (1H, s), 6.94 (1H, t, *J*= 7.8 Hz), 7.04-7.07 (1H, m), 7.18-7.20 (2H, m), 7.20-7.23 (3H, m), 7.24-7.27 (4H, m), 7.33-7.35 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 20.6 (CH_2), 31.2 (CH_2), 36.4 (CH_2), 46.3 (CH_2), 103.2 (CH), 108.6 (CH), 119.3 (CH), 120.2 (CH), 120.7 (CH), 125.3 (quat), 126.4 (CH), 126.7 (CH), 127.5 (CH), 127.6 (quat), 127.8 (CH), 127.9 (2 × CH), 128.2 (quat), 128.5 (CH), 129.0 (2 × CH), 129.0 (quat), 137.0 (quat), 137.1 (quat), 138.1 (quat), 141.1 (quat), 142.0 (quat), 143.1 (quat); **IR** (neat): 2958, 2925, 2870, 1487, 1454, 1350, 1313, 1261 cm^{-1}; **HRMS**: (EI) calculated for $C_{27}H_{26}N$ [MH^{+}]: 364.2060, found: 364.2059

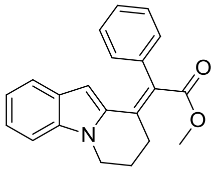
1-Methyl-3-(2-pent-1-ynylbenzyl)-*1H*-indole, 35. The Friedel-Crafts reaction between indole and benzylbromides described by De Rosa and Soriente[47] was followed for the synthesis of this compound. Methylindole (75 μL, 0.61 mmol) and 2-pent-1-ynylbenzyl bromide (117 mg, 0.5 mmol) were added to a 5 mL biotage microwave tube, deionised water (1mL) was added, the tube was capped and placed in the microwave cavity were it was heated at 150 °C under microwave irradiation for 10 min. After the vial was cooled down EtOAc (1 mL) was added and usual aqueous work up was done. The resulting crude was purified by a silica column (hexane:CH$_2$Cl$_2$. 95:5) affording 61 mg (43%) of the product. **^{1}H NMR** (500 MHz, CDCl$_3$): δ 1.02 (3H, t, *J*= 7.4 Hz), 1.61 (2H, tt, *J*= 7.4, 7.0 Hz), 2.42 (2H, t, *J*= 7.0 Hz), 3.74 (3H, s), 4.27 (2H, s), 6.80 (1H, s), 7.06-7.09 (1H, m), 7.11-7.18 (3H, m), 7.21 (1H, t, *J*= 7.0 Hz), 7.29 (1H, d, *J*= 8.1 Hz), 7.42 (1H, dd, *J*= 7.1, 1.8 Hz), 7.58 (1H, d, *J*= 8.1 Hz); **^{13}C NMR** (125 MHz, CDCl$_3$): δ 13.5 (CH$_3$), 21.6 (CH$_2$), 22.3 (CH$_2$), 29.7 (CH$_3$), 39.6 (CH$_2$), 79.6 (quat), 94.4 (quat), 109.0 (CH), 113.8 (quat), 118.7 (CH), 119.3 (CH), 121.4 (CH), 123.7 (quat), 125.6 (CH), 127.2 (CH), 127.6 (CH), 128.0 (quat), 128.8 (CH), 132.0 (CH), 137.1 (quat), 143.1 (quat); **IR** (neat): 2960, 2931, 2872, 2233, 1560, 1473, 1448, 1373 cm^{-1}; **HRMS**: (ESI) calculated for C$_{21}$H$_{22}$N [MH^{+}]: 288.1747, found: 288.1743.



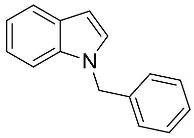
5-Methyl-6-[1-phenylbut-(Z)-ylidene]-6,11-dihydro-5*H*-benzo[*b*]carbazole, 36. Pale yellow solid in 64 % yield (70 mg) from **35** and **8a** according to general procedure G, but at 50 °C for 5 h. **m.p.:** 128-130 °C; **^{1}H NMR** (500 MHz, CDCl$_3$): δ 0.66 (3H, t, *J*= 7.3 Hz), 1.07-1.13 (1H, m), 1.26-1.28 (1H, m), 2.74 (3H, s), 2.74-2.78 (1H, s), 3.25-3.31 (1H, m), 4.05 (1H, s), 4.07 (1H, s), 6.98-7.00 (1H, m), 7.07-7.11 (3H, m), 7.18-7.25 (6H, m), 7.43 (1H, d, *J*= 7.0 Hz), 7.57-7.59 (1H, m), 7.64 (1H, dd, *J*= 7.4, 1.0 Hz); **^{13}C NMR** (125 MHz, CDCl$_3$): δ 13.2 (CH$_3$), 21.7 (CH$_2$), 28.9 (CH$_2$), 30.9 (CH$_3$), 35.7 (CH$_2$), 109.5 (CH), 111.9 (quat), 117.7 (CH), 119.0 (CH), 120.9 (CH), 124.6 (CH), 125.8 (quat), 125.9 (CH), 126.2 (quat), 126.0 (CH), 127.9 (CH), 128.0 (2 × CH), 128.4 (CH), 129.3 (2 × CH), 137.6 (quat), 138.4 (quat), 138.5 (quat), 139.0



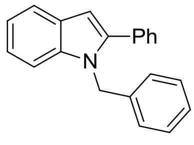
(quat), 140.0 (quat), 142.3 (quat); **IR** (neat): 2954, 1635, 1554, 1544, 1442, 1409, 1373 cm^{-1}; **HRMS**: (ESI) calculated for $C_{27}H_{26}N$ [MH$^+$]: 364.2060, found: 364.2060.



2-(6,7,8,9-Tetrahydropyrido[1,2*a*]indol-9-*(E)*-ylidene)-2-phenylacetic acid methyl ester, 9b. Usual procedure G for the palladium-catalysed tandem reaction at 70 ^{o}C afforded 21 mg of a yellow gum (22% yield) after 8h reaction. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.21-2.26 (2H, m), 3.08-3.10 (2H, m), 3.73 (3H, s), 4.14-4.16 (2H, m), 5.38 (1H, s), 6.99 (1H, ddd, *J*= 8.1, 7.0, 1.1 Hz), 7.16 (1H, ddd, *J*= 8.1, 7.0, 1.1 Hz), 7.24 (1H, d, *J*= 8.3, 0.8 Hz), 7.28-7.31 (3H, m), 7.33-7.42 (3H, m); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 23.2 (CH_2), 28.3 (CH_2), 42.3 (CH_2), 52.0 (CH_3), 105.5 (CH), 109.0 (CH), 120.1 (CH), 121.3 (CH), 122.8 (CH), 127.1 (quat), 127.8 (CH), 128.8 (quat), 129.1 (2 × CH), 129.5 (2 × CH), 133.3 (quat), 136.1 (quat), 137.2 (quat), 138.9 (quat), 169.1 (CO); **IR** (neat): 2956, 2926, 2858, 1716, 1602, 1456, 1240, 1234cm^{-1}; **HRMS**: (ESI) calculated for $C_{21}H_{20}O_2N$ [MH$^+$]: 318.1489, found, 318.1493.

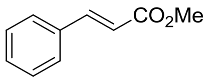


1-Benzyl-*1H*-indole, 37. General procedure F for indole *N*-alkylation with benzylbromide yielded the known product as colourless oil (61%).[98] **^{1}H NMR** (400 MHz): δ 5.38 (2H, s), 6.55 (1H, dd, *J*= 3.1, 0.8 Hz), 7.10-7.32 (9H, m), 7.63-7.66 (1H, m); **^{13}C NMR** (100 MHz): δ 50.1 (CH_2), 101.7 (CH), 109.7 (CH), 119.5 (CH), 120.9 (CH), 121.7 (CH), 126.7 (quat), 126.8 (2 × CH), 127.6 (CH), 128.2 (CH), 128.7 (2 × CH), 136.3 (quat), 137.5 (quat).



1-Benzyl-*1H*-2-phenylindole, 38. General tandem reaction G conditions afforded 30 mg of the 2-phenylated compound (35%) after 20h. at r.t. (50% of unreacted **37** recovered). Spectroscopic data are in agreement with that previously reported.[98] **^{1}H NMR** (400 MHz): δ 5.40 (2H, s), 6.70 (1H, s), 7.06 (2H, d, *J*= 7.0 Hz), 7.13-7.34 (9H, m), 7.48 (2H, dd, *J*= 7.9, 1.6 Hz), 7.71=7.72 (1H, m); **^{13}C NMR** (100 MHz): δ 47.7 (CH_2), 102.3 (CH), 110.5

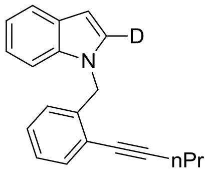
(CH), 120.1 (CH), 120.5 (CH), 121.9 (CH), 125.9 (2 × CH), 127.1 (CH), 128.0 (CH), 128.5 (2 × CH), 128.7 (2 × CH), 129.2 (2 × CH), 132.7 (2 × quat), 138.0 (quat), 138.2 (quat), 141.8 (quat).



(*E*)-3-Phenylprop-2-enoic acid methyl ester, 39. Methyl acrylate (110 μL, 1.2 mmol) was added to the usual tandem reaction (general procedure G) between **21a** and **8a**. The reaction was heated at 60 °C for 15 h. 32 mg of **39** were obtained (60%) after usual purification (SiO_2+ 3% Et_3N, hexane:CH_2Cl_2, 8:2 to 1:1).[99] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.81 (3H, s), 6.45 (1H, d, *J*= 16.0 Hz), 7.38-7.39 (3H, m), 7.51-7.53 (2H, m), 7.70 (1H, d, *J*= 16.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 51.7 (CH_3), 117.8 (CH), 128.0 (2 × CH), 128.9 (2 × CH), 130.3 (CH), 134.3 (quat), 144.8 (CH), 167.4 (quat).

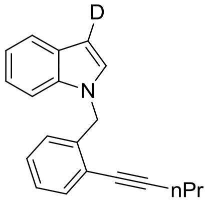
Kinetic Isotope Effect (KIE) studies

KIEs were determined by studying the initial rate of reactions for 1-(2-pent-1-ynylbenzyl)-*1H*- indole, **21a,** 2-deutero-1-(2-pent-1-ynylbenzyl)-*1H*-indole, ***2d*-21a**, and 3-deutero-1-(2-pent-1-ynylbenzyl)-*1H*-indole**, *3d*-21a**. The deuterated starting materials were synthesised as follows:



2-Deutero-1-(2-pent-1-ynylbenzyl)-*1H*-indole, *2d*-21a. 2*d*-Indole was synthesised from 1-(phenylsulfonyl)-indole according to the procedure described by Maresh *et al.*[100]. Incorporation of deuterium was measured as > 98% by ^{1}H NMR. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.57 (1H, s), 7.13 (1H, ddd, *J*= 8.0, 7.1, 1.1 Hz), 7.21 (1H, ddd, *J*= 8.0, 7.1, 1.1 Hz), 7.41 (1H, dd, *J*= 8.0, 1.0 Hz), 7.66 (1H, dd, *J*= 8.0, 1.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 109.0 (CH), 113.5 (CH), 120.9 (CH), 121.7 (CH), 127.2 (quat, t, J_{C-D}= 19.8 Hz), 127.4 (CH), 136.2 (quat), 138.9 (quat). 2*d*-Indole (330 mg, 2.81 mmol) was dissolved in dry DMF (9 mL) under N_2 atmosphere and NaH (60%, 3.11 mmol) was added portion wise at r.t. The mixture was stirred for 1 h, after this time 2-pent-1-ynylbenzyl bromide (3.12 mmol dissolved in 4 mL of dry DMF) was added dropwise. Monitoring by TLC showed no starting material left after 4 h. EtOAc and water (10 mL each) were added and the solvent was partially evaporated before adding more EtOAc and water (10 mL) and the two layers were separated. The aqueous phase was extracted twice with EtOAc (5 mL) and the combined organic layers were washed with brine (5 mL × 2), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the crude was purified through silica column (Hexane:CH_2Cl_2, 8:2) affording 655 mg of the named product as a colourless oil (85% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.06 (3H, t, *J*= 7.4 Hz), 1.65 (2H, tt, *J*= 7.4, 7.0 Hz), 2.45 (2H, t, *J*= 7.0 Hz), 5.48 (2H, s), 6.56 (1H, s), 6.67 (1H, d, 7.8 Hz), 7.08-7.13 (2H, m), 7.15-7.20 (2H, m), 7.31 (1H, d, *J*= 8.1 Hz), 7.45 (1H, dd, *J*= 7.7, 1.0 Hz), 7.66 (1H, d, *J*= 7.7 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.6 (CH_2), 22.2 (CH_2), 48.5 (CH_2), 78.2 (quat), 96.2 (quat), 101.4 (CH), 109.8 (CH), 119.5 (CH), 120.9 (CH), 121.6 (CH), 122.3 (quat), 126.4 (CH), 127.2 (CH), 128.0 (CH), 128.2 (quat, t, $J_{C\text{-}D}$= 20.5 Hz), 128.6 (quat), 132.2 (CH), 136.3 (quat), 139.0 (quat); **IR** (neat): 2964, 2231, 1541, 1460, 1406, 1265, 1012cm^{-1}; **HRMS**: (APCI) calculated for $C_{20}H_{19}{}^2H_1N$ [MH^+]: 275.1653, found: 275, 1647.

3-Deutero-1-(2-pent-1-ynylbenzyl)-*1H*-indole, *3d*-21a. 1-(2-Pent-1-ynylbenzyl)-*1H*-indole, **21a** (100 mg, 0.37 mmol) was weighed in a microwave vial and D_2O (1 mL) and CD_3OD (1mL) added together with DCl (0.01 M)[16, 101] and the mixture heated at 150 ºC under microwave irradiation for 30 min. After cooling to r.t. the residue was extracted with hexane (5 mL × 3), the combined organic layers were dried over anh. Na_2SO_4, filtered and the solvent evaporated under reduced pressure to afford a pale orange oil in 91% yield (93 mg). Incorporation of deuterium was measured > 97% by ^{1}H NMR. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.06 (3H, t, *J*= 7.4 Hz), 1.65 (2H, tt, *J*= 7.4, 7.0 Hz), 2.45 (2H, t, *J*= 7.0 Hz), 5.48 (2H, s), 6.67 (1H, d, 7.7 Hz), 7.08-7.13 (2H, m), 7.15-7.19 (3H, m), 7.31 (1H, d, *J*= 8.1 Hz), 7.45 (1H, dd, *J*= 7.8, 1.0 Hz), 7.66 (1H, d, *J*= 7.8 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.6 (CH_2), 22.2 (CH_2), 48.6 (CH_2), 78.2 (quat), 96.2 (quat), 101.4 (quat, t, $J_{C\text{-}D}$= 26.2 Hz), 109.8 (CH), 119.5 (CH), 120.9 (CH), 121.6 (CH), 122.3 (quat), 126.4 (CH), 127.2 (CH), 128.0 (CH), 128.3 (CH), 128.5 (quat), 132.2 (CH), 136.4 (quat),



139.0 (quat); **IR** (neat): 2962, 2936, 2873, 2231, 1483, 1461, 1429, 1329 cm^{-1}; **HRMS**: (EI) calculated for $C_{20}H_{19}{}^{2}H_{1}N$ [MH^{+}]: 275.1650, found: 275, 1649.

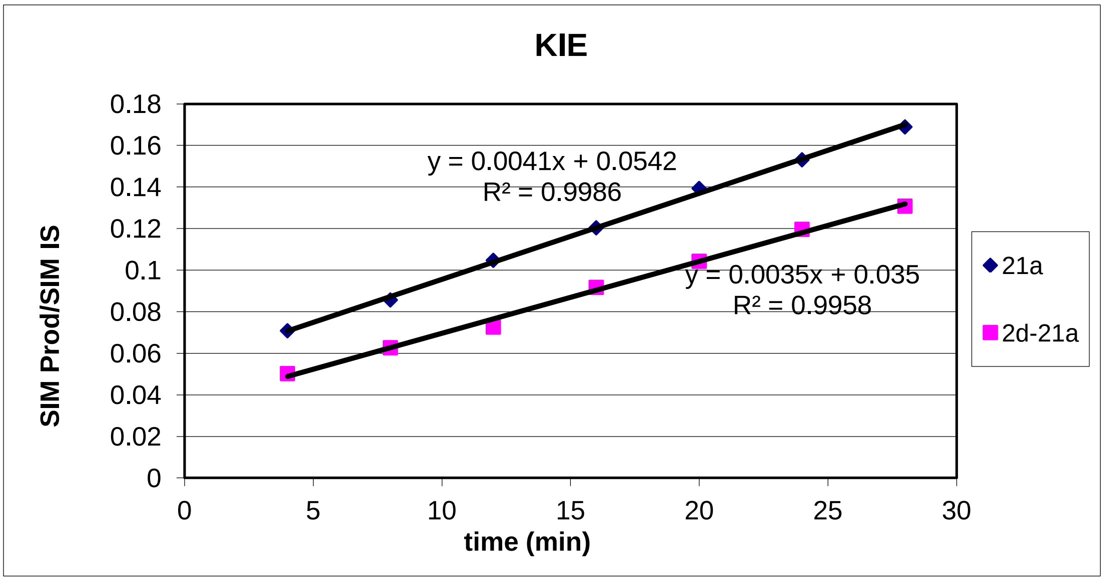
For the KIE experiments the general procedure was used: **21a** (82 mg, 0.30 mmol) was weighed in an oven-dried 5 mL vial, dissolved in 3 mL of chlorobenzene and then Cs_2CO_3 (98 mg, 0.30 mmol), SIMes.HCl (10.2 mg, 0.03 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) and diphenyliodonium tetrafluoroborate (116mg, 0.32 mmol) were added in this order and the mixture was flushed with N_2. The vial was capped and put into an aluminium bloc at 20 ºC (the vial was not heated in order to slow down the reaction and make it easier to follow). During the first half an hour of the reaction aliquots of 50 µL were taken every 4 min. Each aliquot was dissolved in 2 mL of DMSO containing 0.002M of benzanilide (used as Internal Standard) and then MeOH was added until a final volume of 10 mL in a volumetric flask (final [IS]= 0.0004). Every sample was analysed using HPLC/MS and the response was measured by Single Ion Monitoring (SIM).[56] The comparison between SIM of the product being formed and SIM of the internal standard gave a response vs time rate of the reaction. Three different kinetic experiments were done and the rate represented comes from the average data of the three runs.

Time (min)	SIM Prod/SIM IS (i)	SIM Prod/SIM IS (ii)	SIM Prod/SIM IS (iii)	Average
4	0.064565419	0.075597673	0.072477683	0.070880259
8	0.074861166	0.087512677	0.09473584	0.085703228
12	0.089929217	0.114318842	0.110074207	0.104774089
16	0.11605677	0.121721737	0.123452228	0.120410245
20	0.132013869	0.13911516	0.146913759	0.139347596
24	0.141504644	0.163390948	0.154556341	0.153150645
28	0.158149378	0.175954253	0.172782273	0.168961968

Exactly the same procedure was followed using the 2-deuterated substrate ***2d*-21a**

Time (min)	SIM Prod/SIM IS (i)	SIM Prod/SIM IS (ii)	SIM Prod/SIM IS (iii)	Average
4	0.057184782	0.050831516	0.042782923	0.050266407
8	0.052079604	0.070364242	0.065702653	0.0627155
12	0.074748186	0.079299271	0.063962703	0.072670053
16	0.09072035	0.080839404	0.103733762	0.091764505
20	0.097119972	0.107556504	0.108276724	0.104317733
24	0.110460093	0.129079515	0.119525546	0.119688385
28	0.122846136	0.135727089	0.133946523	0.130839916

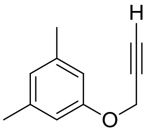
Finally the two reaction rates where compared giving a $\mathbf{k_H/k_D}$ = 1.2



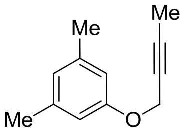
The same procedure was followed for ***3d*-21a**. However, a non-linear relationship was observed when plotting product formation response against time. This can be due to H/D exchange taking place during the sampling phase of the reaction. ^{1}H NMR of the crude reaction mixture after 30 min showed a 20% conversion, with the product having a H:D ratio of 1:1 at the indole C3-position.

General procedure I: synthesis of arylpropargyl ethers. The following procedure described by Sames and co-workers[59, 60] was followed, preparation of **40a** is representative.

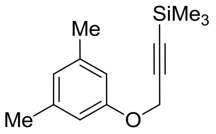
1,3-Dimethyl-5-prop-2-ynoxybenzene, 40a. 3,5-Dimethylphenol (2.02 g, 16.33 mmol) was weighed in a dry flask and dissolved in DMF (100 mL). Then K_2CO_3 was added and the flask was purged with N_2. Propargylbromide (80% solution in toluene, 2.73 mL, 24.63 mmol) was added *via* syringe and the mixture was left to react at r.t. for 4 h. About three quarters of the solvent was evaporated under reduced pressure and the residue was partitioned between water and ether (100 mL each). The layers were separated, the aqueous layer was further extracted with ether (50 mL × 2) and the combined organic layers were washed with sat. $NaHCO_3$ (50 mL × 2) and brine solution (50 mL × 2), dried over anh. $MgSO_4$, filtered and the solvent evaporated under vacuum. The crude was purified through a silica column (hexane:diethyl ether, 1:1) affording 2.22 g of a colourless oil (85% yield). NMR data are according with literature values.[102] **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.31 (6H, s), 2.52 (1H, t, *J*= 2.4 Hz), 4.67 (2H, d, *J*= 2.4 Hz), 6.62 (2H, s), 6.66 (1H, s); **^{13}C NMR** (100MHz, $CDCl_3$): δ 21.4 (2 × CH_3), 55.6 (CH_2), 75.2 (CH), 78.8 (quat), 112.5 (2 × CH), 123.3 (CH), 139.2 (2 × quat), 157.5 (quat).



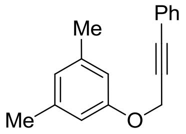
1-But-2-ynoxy-3,5-dimethyl-benzene, **40b.** Prepared according to the general procedure I using 1-bromo-2-butyne (221 μL, 2.45 mmol). After flash chromatography purification (hexane:diethyl ether 1:1) 200 mg (72%) of colourless oil was obtained. Spectroscopic data is in accordance with the reported in the literature.[59] **^{1}H NMR** (500MHz, $CDCl_3$): δ 1.87 (3H, t, *J*= 2.3 Hz), 2.29 (6H, s), 4.61 (2H, q, *J*= 2.3 Hz), 6.59 (2H, s), 6.62 (1H, s); **^{13}C NMR** (100MHz, $CDCl_3$): δ 3.8 (CH_3), 21.5 (2 × CH_3), 56.2 (CH_2), 74.2 (quat), 83.4 (quat), 112.5 (2 × CH), 123.0 (CH), 139.2 (2 × quat), 157.9 (quat).



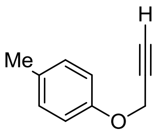
3-(3,5-Dimethylphenoxy)prop-1-ynyl-trimethylsilane, 40c. 1,3-Dimethyl-5-prop-2-ynoxybenzene (600 mg, 3.70 mmol) was weighed in a dry flask, purged with N_2 and dissolved in dry THF (6 mL). The flask was cooled down to -78 ^{o}C in a dry ice:acetone bath and nBuLi (1.5 M, 2.7 mL, 4.11 mol) was added dropwise. The mixture was left stirred for 30 min at this temperature and chlorotrimetylsilane (570 µL, 4.50 mmol) was slowly added *via* syringe, then the reaction was allowed to warm up to r.t. for 1.5 h when no starting material was left. Water and diethyl ether (10 mL each) were carefully added and the two layers separated. The aqueous layer was further extracted with ether (5 mL × 2) and the combined organic layers were washed with brine solution (5 mL × 2), dried over anh. $MgSO_4$, filtered and the solvent evaporated under vacuum. The crude was purified through a silica column (hexane: diethyl ether, 1:1) affording 730 mg of a colourless oil (85% yield). **^{1}H NMR** (400MHz, $CDCl_3$): δ 0.18 (9H, s), 2.29 (6H, s), 4.63 (2H, s), 6.61 (2H, s), 6.63 (1H, s); **^{13}C NMR** (100MHz, $CDCl_3$): δ -0.3 (3 × CH_3), 21.4 (2 × CH_3), 56.7 (CH_2), 92.5 (quat), 100.4 (quat), 112.7 (2 × CH), 123.1 (CH), 139.1 (2 × quat), 157.9 (quat); **IR** (neat): 3018, 2959, 2919, 2860, 2179, 1595, 1471, 1368, 1293, 1151 cm^{-1}; **HRMS:** (ESI) calculated for $C_{14}H_{21}OSi$ [MH^+]: 233.1356, found: 233.1354.



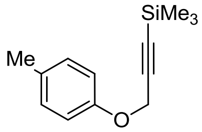
1,3-Dimethyl-5-(3-phenylprop-2-ynoxy)benzene, **40d**. The product was obtained after a Sonogashira reaction. 1,3-Dimethyl-5-prop-2-ynoxybenzene (500 mg, 3.11 mmol) was weighed in a dry flask and dissolved in Et_3N (10 mL) the mixture was bubbled with N_2 for 10 min while $PdCl_2(PPh_3)_2$ (22 mg, 0.03 mmol) and CuI (11.8 mg, 0.06 mmol) were weighed and added to the mixture, finally PhI (380 µL, 3.41 mmol) was added under N_2 atmosphere and the reaction was stirred for 15 h at r.t., then filtered through a pad of celite, washing with EtOAc and the solvent evaporated under vacuum. The residue was purified through a silica column affording 470 mg of a colourless oil (64% yield). The product is known and the spectroscopic data agree with that previously reported[102]. **^{1}H NMR** (500MHz, $CDCl_3$): δ 2.31 (6H, s), 4.88 (2H, s), 6.65 (1H, s), 6.68 (2H, s), 7.30-7.32 (3H, m), 7.43 (1H, d, *J*= 2.5 Hz), 7.45 (1H, d, *J*= 1.5 Hz) ppm **^{13}C NMR** (125MHz, $CDCl_3$): δ 21.5 (2 × CH_3), 56.5 (CH_2), 84.2 (quat), 86.9 (quat),



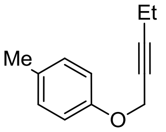
112.7 (2 × CH), 122.4 (quat), 123.2 (CH), 128.3 (2 × CH), 128.6 (CH), 131.8 (2 × CH), 139.2 (2 × quat), 157.9 (quat).



1-Methyl-4-prop-2-ynoxybenzene, **43a**. General procedure I for the synthesis of arylpropargyl ethers afforded 2.14 g of the desired product (90% yield) from p-cresol and propargylbromide. The spectroscopic data are in accordance with that reported before.[64] **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.30 (3H), 2.50 (1H, t, *J*= 2.4 Hz), 4.67 (2H, d, *J*= 2.4 Hz), 6.87-6.90 (2H, m), 7.08-7.12 (2H, m); **^{13}C NMR** (100MHz, $CDCl_3$): δ 20.5 (CH_3), 55.9 (CH_2), 75.3 (CH), 78.8 (quat), 114.8 (2 × CH), 129.9 (2 × CH), 130.9 (quat), 155.4 (quat).

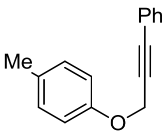


[3-(4-Methylphenoxy)prop-1-ynyl]-trimetylsilane, 43b. The same procedure for the synthesis of **40c** was followed. The product was obtained as 420 mg of a colourless oil (52% yield). **^{1}H NMR** (400MHz, $CDCl_3$): δ 0.17 (9H, s), 2.29 (3H, s), 4.64 (2H, s), 6.86-6.88 (2H, m), 7.07-7.09 (2H, m); **^{13}C NMR** (100MHz, $CDCl_3$): δ -0.3 (3 × CH_3), 20.5 (CH_3), 56.9 (CH_2), 92.4 (quat), 100.3 (quat), 114.9 (2 × CH), 129.8 (2 × CH), 130.7 (quat), 155.8 (quat); **IR** (neat): 3031, 2959, 2923, 2899, 2862, 2178, 1612, 1586, 1510, 1294, 1251 cm^{-1}; **HRMS**: (ESI) calculated for $C_{13}H_{22}O_1N_1Si_1$: 236.1465, found: 236.1466.



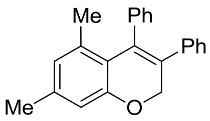
1-Methyl-4-pent-2-ynoxybenzene, 43c. The same procedure for the synthesis of **40c** was followed to afford 348 mg of the named product (54% yield) from **43a** and iodoethane. **^{1}H NMR** (500MHz, $CDCl_3$): δ 1.14 (3H, t, *J*= 7.5 Hz), 2.24 (2H, qt, *J*= 7.5, 2.0 Hz), 2.29 (3H, s), 4.64 (2H, t, *J*= 2.0 Hz), 6.87 (2H, d, *J*= 8.5 Hz), 7.09 (2H, d, *J*= 8.5 Hz); **^{13}C NMR** (125MHz, $CDCl_3$): δ 12.5 (CH_3), 13.6 (CH_2), 20.5 (CH_3), 55.5 (CH_2), 74.4 (quat), 89.3 (quat), 114.7 (2 × CH), 129.8 (2 × CH), 130.4 (quat), 155.7 (quat); **IR** (neat): 3030, 2977, 2937, 2874, 2230,1611, 1585, 1510, 1217 cm^{-1}; **HRMS**: (ESI) calculated for $C_{12}H_{14}O_1$: 174.1039, found: 174.1038.

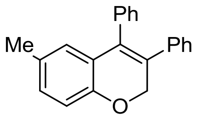
1-Methyl-4-(3-phenylprop-2-ynoxy)benzene, **43d**. Synthesised from **43a** and iodobenzene after usual Sonogashira coupling in 98% yield. The spectroscopic data are in accordance with the previously reported.[64] **^{1}H NMR** (500MHz, CDCl$_3$): δ 2.30 (3H, s), 4.89 (2H, s), 6.94 (2H, dd, *J*= 6.7, 2.70 Hz), 7.11 (2H, d, *J*= 8.2 Hz), 7.28-7.34 (3H, m), 7.44 (2H, dd, *J*= 7.6, 1.9 Hz); **^{13}C NMR** (125MHz, CDCl$_3$): δ 20.5 (CH$_3$), 56.8 (CH$_2$), 84.1 (quat), 87.0 (quat), 114.9 (2 × CH), 122.4 (quat), 128.3 (2 × CH), 128.6 (CH), 129.9 (2 × CH), 130.7 (quat), 131.8 (2 × CH), 155.7 (quat).



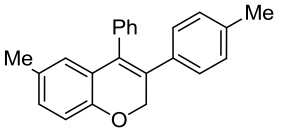
General procedure J: synthesis of chromenes. The following procedure for the synthesis of **41** is representative.

5,7-Dimethyl-3,4-diphenyl-2H-chromene, **41**. 1,3-dimethyl-5-(3-phenylprop-2-ynoxy)benzene, **40d**, (70.8 mg, 0.30 mmol) was weighed in an oven dried reaction tube, dissolved in toluene:HOAc, 4:1 mixture (3 mL), Pd(OAc)$_2$ (3.4 mg, 0.015 mmol) was added followed by diphenyliodonium tetrafluoroborate, **8a**. The tube was flushed with N$_2$, sealed and placed in a pre-heated bath at 80 ^{o}C for 1h. The crude was filtered through a celite pad, H$_2$O (5 mL) and CH$_2$Cl$_2$ (5 mL) were added and the phases were separated, the aqueous phase was extracted with CH$_2$Cl$_2$ (5 mL × 2) and the combined organic layers washed with sat. NaHCO$_3$ solution (5 mL × 3) and brine (5 mL × 2), dried over anh. MgSO$_4$, filtered and concentrated *in vacuo*. Silica column purification (hexane: CH$_2$Cl$_2$, 8:2) afforded 18 mg of a colourless oil (19% yield). **^{1}H NMR** (500MHz, CDCl$_3$): δ 1.59 (3H, s), 2.30 (3H, s), 4.82 (2H, s), 6.55 (1H, s), 6.72 (1H, s), 6.91 (2H, dd, *J*= 7.9, 1.6 Hz), 7.03-7.05 (2H, m), 7.11-7.14 (3H, m), 7.18 (1H, d, *J*= 2.0 Hz), 7.19 (2H, d, *J*= 2.0 Hz); **^{13}C NMR** (125MHz, CDCl$_3$): δ 21.2 (CH$_3$), 22.2 (CH$_3$), 69.6 (CH$_2$), 114.2 (CH), 122.3 (quat), 126.4 (CH), 126.5 (CH), 126.7 (CH), 127.8 (2 × CH), 128.0 (2 × CH), 128.5 (2 × CH), 130.2 (quat), 130.3 (2 × CH), 133.4 (quat), 136.4 (quat), 138.9 (quat), 139.1 (quat), 139.5 (quat), 155.7 (quat); **IR** (neat): 3020, 2920, 2852, 1604, 1492, 1444, 1282 cm^{-1}; **HRMS**: (ESI) calculated for C$_{13}$H$_{21}$O [MH$^+$]: 213.1587, found: 213.1584.

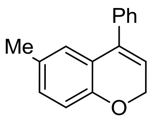




6-Methyl-3,4-diphenyl-2H-chromene, **44**. The general procedure J was followed. 1-Methyl-4-(3-phenylprop-2-ynoxy)benzene, **43d**, (67.0 mg, 0.30 mmol) in dry toluene:HOAc mixture, 4:1 (3 mL) with $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) and **8a** (132.3 mg, 0.36 mmol) were used. The disubstituted product was obtained as 28 mg of a colourless gum (31%) after usual aqueous work up and purification (SiO_2, hexane:CH_2Cl_2, 8:2). **^{1}H NMR** (500MHz, $CDCl_3$): δ 2.17 (3H, s), 5.07 (2H, s), 6.62 (1H, d, *J*= 1.5 Hz), 6.84 (1H, d, *J*= 8.0 Hz), 6.96-6.99 (3H, m), 7.11-7.14 (5H, m), 7.27-7.28 (3H, m); **^{13}C NMR** (125MHz, $CDCl_3$): δ 20.8 (CH_3), 69.6 (CH_2), 115.5 (CH), 125.1 (quat), 126.8 (CH), 126.9 (CH), 127.1 (CH), 127.9 (2 × CH), 128.2 (4 × CH), 129.5 (CH), 129.8 (quat), 130.6 (quat), 130.7 (2 × CH), 132.9 (quat), 137.0 (quat), 138.2 (quat), 151.6 (quat); **IR** (neat): 3057, 2924, 1732, 1496, 1265 cm^{-1}; **HRMS**: (APCI) calculated for $C_{22}H_{17}O$: 297.1274, found: 297.1274.

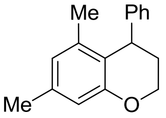


6-Methyl-4-phenyl-3-(p-methylphenyl)-2H-chromene, **45**. The product was obtained as a white gum (21.6 mg, 23% yield) from **43d** and **23** following general procedure J. **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.16 (3H, s), 2.25 (3H, s), 5.05 (2H, s), 6.6 (1H, d, *J*= 2.0 Hz), 6.83 (1H, d, *J*= 8.0 Hz), 6.86-6.88 (2H, m), 6.93-6.95 (3H, m), 7.11-7.14 (2H, m), 7.23-7.29 (3H, m); **^{13}C NMR** (100MHz, $CDCl_3$): δ 20.8 (CH_3), 21.2 (CH_3), 69.7 (CH_2), 115.5 (CH), 125.2 (quat), 126.7 (CH), 127.0 (CH), 128.0 (2 × CH), 128.2 (2 × CH), 128.6 (2 × CH), 129.3 (CH), 129.7 (quat), 130.5 (quat), 130.7 (2 × CH), 132.4 (quat), 135.2 (quat), 136.6 (quat), 137.2 (quat), 151.5 (quat); **IR** (neat): 3051, 2924, 2856, 1720, 1600, 1494, 1444, 1265 cm^{-1}; **HRMS**: (APCI) calculated for $C_{23}H_{19}O$: 311.1430, found: 311.1431.

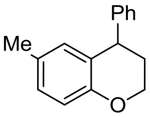


6-Methyl-4-phenyl-2H-chromene, **47**. When reacting **43d** and **23** according to the general procedure J but at r.t. instead of heating at 80 ^{o}C, the 4-substituted chromene was obtained without arylation in the 3-position after 16 h reaction. Usual aqueous work up and purification (SiO_2, hexane: diethyl ether, 8:2) afforded 23 mg of a coulourless oil (35% yield). NMR data are in agreement with that reported by Eguchi *et. al.*[103] ^{1}**H NMR** (400MHz, $CDCl_3$): δ 2.2 (3H, s), 4.82 (2H, d, *J*= 4.0 Hz), 5.80 (1H, t, *J*= 4.0 Hz), 6.80-6.82 (2H, m), 6.97 (1H, dd, *J*= 8.0, 1.6 Hz), 7.34-7.44 (5H, m); ^{13}**C NMR** (100MHz, $CDCl_3$): δ 20.7 (CH_3), 65.2 (CH_2), 115.9 (CH), 120.1 (CH), 123.5 (quat), 126.2 (CH), 127.7 (CH), 128.4 (2 × CH), 128.6 (2 × CH), 129.6 (CH), 130.4 (quat), 137.4 (quat), 138.4 (quat), 152.5 (quat).

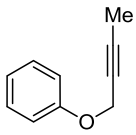
5,7-Dimethyl-4-phenyl-chromane, **42**. 1,3-dimethyl-5-(3-phenylprop-2-ynoxy)benzene, **40d**, (70.8 mg, 0.30 mmol) was weighed in an oven dried reaction tube containing a stirring bar, dissolved in CH_2Cl_2:TFA, 3:1 mixture (1.5 mL), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) was added followed by diphenyliodonium tetrafluoroborate (121.3 mg, 0.33 mmol). The tube was sealed and the mixture stirred at r.t. for 1h. The crude was filtered through a celite pad, H_2O (5 mL) and CH_2Cl_2 (5 mL) were added and the phases separated, the aqueous phase was extracted with CH_2Cl_2 (5 mL × 2) and the combined organic layers washed with sat. $NaHCO_3$ solution (5 mL × 3) and brine (5 mL × 2), dried over anh. $MgSO_4$, filtered and concentrated *in vacuo*. Silica column purification (hexane: CH_2Cl_2, 8:2) afforded 17 mg of a white solid (24% yield), spectroscopic data agree with that previously reported.[60] ^{1}**H NMR** (500MHz, $CDCl_3$): δ 1.92 (3H, s), 1.96 (1H, dd, *J*= 10.7, 1.9), 2.30 (3H, s), 2.34-2.42 (1H, m), 3.93 (1H, td, *J*= 10.7, 1.9), 4.11-4.13 (1H, m), 4.16 (1H, d, *J*= 5.0 Hz), 6.59 (1H, s), 6.62 (1H, s), 7.09 (2H, d, *J*= 7.6 Hz), 7.20 (1H, t, *J*= 7.3 Hz), 7.28 (2H, t, *J*= 7.5 Hz); ^{13}**C NMR** (125MHz, $CDCl_3$): *δ* 18.9 (CH_3), 21.0 (CH_3), 31.1 (CH_2), 37.5 (CH), 61.1 (CH_2), 114.9 (CH), 118.7 (quat), 123.3 (CH), 126.1 (CH), 128.3 (2 × CH), 128.3 (2 × CH), 137.5 (quat), 138.0 (quat), 145.4 (quat), 155.1 (quat).



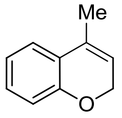
6-Methyl-4-phenylchromane, 46. **43d** (66.7 mg, 0.30 mmol) was weighed in an oven dried reaction tube containing a stirring bar, dissolved in CH_2Cl_2:TFA, 3:1 mixture (1.5 mL), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) was added followed by **23** (205.3 mg, 0.36 mmol). The tube was sealed and the mixture stirred at r.t. for 1h. Usual aqueous work up and purification (SiO_2, hexane:CH_2Cl_2, 8:2) as described for the synthesis of **42** afforded 40 mg of the



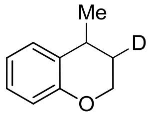
product as a colourless oil (60% yield). The reaction in the absence of the iodonium salt also afforded the reduced benzopyran in the same yield (59%).[59]**^{1}H NMR** (500MHz, $CDCl_3$): δ 2.04-3.00 (1H, m), 2.16 (3H, s), 2.27-2.33 (1H, m), 4.13-4.17 (3H, m), 6.65 (1H, d, *J*= 1.6 Hz), 6.77 (1H, d, *J*= 8.3 Hz), 6.94 (1H, dd, *J*= 8.3, 2.1 Hz), 7.14-7.15 (2H, m), 7.22-7.25 (2H, m), 7.31 (2H, t, *J*= 7.4 Hz); **^{13}C NMR** (125MHz, $CDCl_3$): δ 20.5 (CH_3), 31.8 (CH), 41.0 (CH_2), 63.7 (CH_2), 116.5 (CH), 124.0 (quat), 126.4 (CH), 128.4 (2 × CH), 128.6 (CH), 128.7 (2 × CH), 129.5 (quat), 130.8 (CH), 145.8 (quat), 152.9 (quat).



But-2-ynoxybenzene, **48**. Obtained from phenol (500 mg, 5.30 mmol) and 1-bromo-2-butyne (557 µL, 6.36 mmol) as 635 mg of a colourless oil (82% yield) following the general procedure I. Spectroscopic data are in accordance with that reported before[60]. **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.87 (3H, t, *J*= 2.3 Hz), 4.65 (2H, q, *J*= 2.3 Hz), 6.97-7.00 (3H, m), 7.30 (2H, dd, *J*= 9.0, 7.1 Hz); **^{13}C NMR** (100MHz, $CDCl_3$): δ 3.7 (CH_3), 56.3 (CH_2), 114.8 (2 × CH), 121.2 (CH), 129.4 (2 × CH), 157.8 (quat).



4-Methyl-*2H*-chromene, **49**. The $PtCl_4$ catalysed cyclisation of **48** reported by Sames and co-workers[59, 60] at r.t. in dioxane afforded a colourless oil in 85% yield. NMR data agree with that one reported before.[60] **^{1}H NMR** (400MHz, $CDCl_3$): δ 2.03 (3H, dd, *J*= 3.3, 1.7 Hz), 4.74-4.76 (2H, m), 5.57-5.59 (1H, m), 6.80 (1H, dd, *J*= 8.0, 1.1 Hz), 6.91 (1H, td, *J*= 7.5, 1.1 Hz), 7.11-7.16 (2H, m); **^{13}C NMR** (100MHz, $CDCl_3$): δ 17.9 (CH_3), 65.4 (CH_2), 115.7 (CH), 118.4 (CH), 121.1 (CH), 123.5 (CH), 124.3 (quat), 128.9 (CH), 130.2 (quat), 154.1 (quat).



3-deuterio-4-methyl-chromane, **50**. 4-Methyl-*2H*-chromene, **49**, (100 mg, 0.68 mmol) was weighed in a dry 5 mL reaction tube, deuterated trifluoroacetic acid was slowly added (3.4 mL) and the solution turned pink. The tube was flushed with N_2 and the reaction was left at r.t. for 1h with vigorous stirring. The crude was partitioned between H_2O (5 mL) and EtOAc

(5 mL). The two phases were separated and the aqueous layer further extracted with EtOAc (5 mL × 2). The combined organic layers were washed with sat. $NaHCO_3$ (5 mL × 2), dried over anh. $MgSO_4$, filtered and concentrated under vacuum. The filtrate was chromatographed (SiO_2, hexane:Et_2O, 9:1) to afford 38 mg of a colourless oil (37%). **^{1}H NMR** (400MHz, $CDCl_3$): δ 1.34 (3H, d, *J*= 7.0 Hz), 2.95 (1H, quint, *J*= 6.4 Hz), 4.14-4.24 (3H, m), 6.79 (1H, d, *J*= 8.2 Hz), 6.87 (1H, t, *J*= 7.4 Hz), 7.06-7.13 (1H, m), 7.14-7.16 (1H, m); **^{13}C NMR** (100MHz, $CDCl_3$): δ 22.2 (CH_3), 28.4 (CH), 29.9 (CHD, t, $J_{C\text{-}D}$= 19.2 Hz), 63.8 (CH_2), 116.7 (CH), 120.2 (CH), 127.1 (CH), 127.6 (quat), 128.5 (CH), 154.3 (quat); **IR** (neat): 2960, 2873, 1575, 1483, 1444, 1303, 1256, 1239, 1047 cm^{-1}; **HRMS**: (EI) calculated for $C_{10}H_{11}{}^2HO$ [M^+]: 149.0945, found: 149.0943.

3.6. References

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Appendix: Published Article