Development of New Carbon-Carbon Bond-Forming Strategies: Formation and Reactivity of sp^3-*gem*-Organodimetallic Palladium(II)/MR_n Alkane Intermediates (MR_n=Dialkylalumino, Trialkylstannyl)

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Author's Declaration for Electronic Submission of a Thesis

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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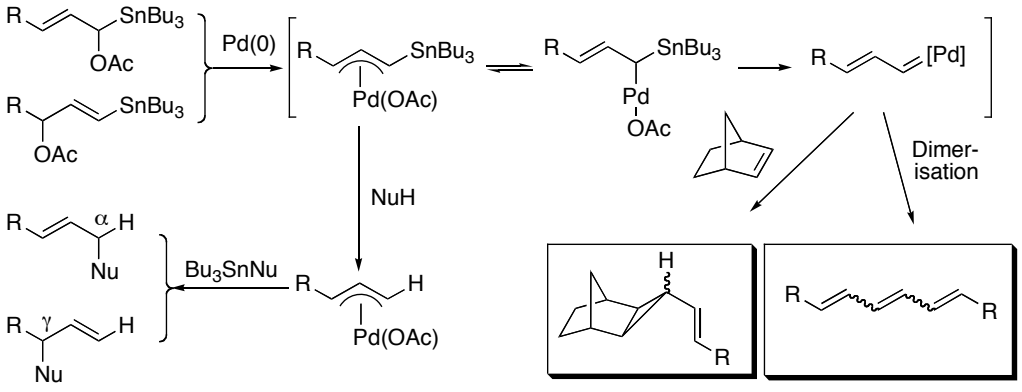
Abstract

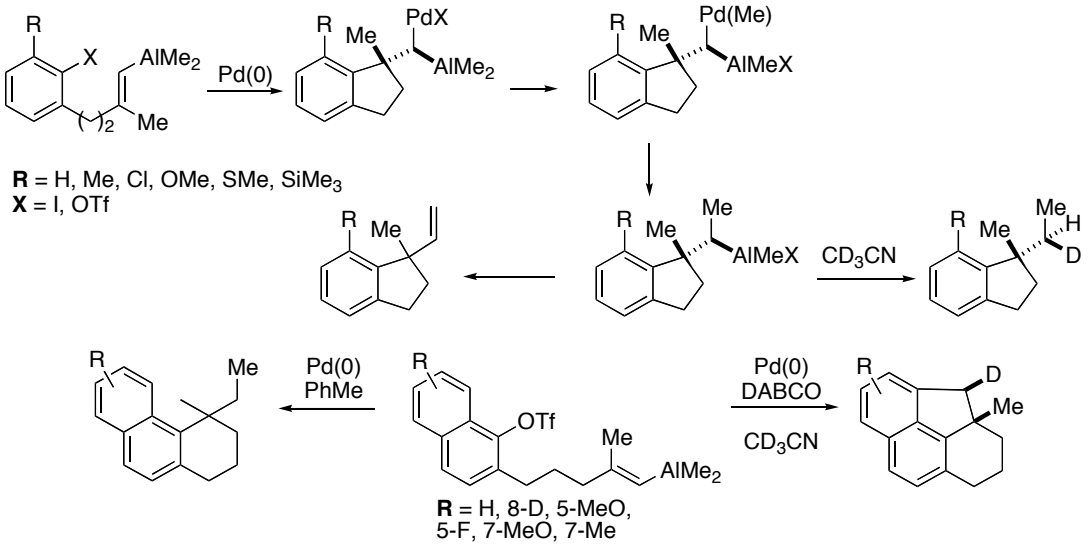
Investigation of the catalytic formation, reactivity and synthetic scope of *gem*-organodimetallic palladio(II)/main group metal (main group metal = tributylstannyl, dialkylalumino) alkane species has been carried out. Insight was expanded regarding the inter- and intramolecular reactivity of vinylmetallic reagents in presence of transition metal catalysts. New Pd-catalysed methodologies for carbon-carbon bond formation were developed, such as cyclopropanation of strained olefins, as well as tandem vinylalane arylation/1,2-methyl transfer and 1,2-diarylation.

On the one hand, geminal π-allylpalladio(II)/tributylstannylalkane intermediates are produced by oxidative addition of Pd(0) catalysts to α-tributylstannylpropenyl acetate derivatives. They adopt ambiphilic behaviour depending on the transition metal pre-catalyst, presence or absence of phosphine ligands, and reaction temperature. In presence of $Pd(PPh_3)_4$ with additional bidentate ligand, the carbenoid reactivity of these *gem*-organobismetallic species is exposed by reaction with dimethyl malonate. Deuterium-labeling studies demonstrated sequential functionalisation of the C-Sn and C-Pd bonds. Conversely, phosphine-free catalyst $Pd(dba)_2$ uncovers metal-carbene reactivity, and dimerisation and strained alkene cyclopropanation reactions are observed. The nature of the palladium catalyst controls the reactivity of the carbenoid species. Finally, $[Rh(COD)Cl]_2$ catalytically activates the alkenylstannane moiety, leaving the allylic acetate leaving group available for further transformations.



On the other hand, *gem*-disubstituted trifluoromethanesulfonyloxy- and iodopalladio(II)/ dialkylaluminoneopentane species are generated by intramolecular migratory insertion of 2,2-

disubstituted-1-butenyldialkylalanes with σ-arylpalladium(II) triflate and iodide intermediates. Using excess Lewis-basic 1,4-diazabicyclo[2.2.2]octane, electron-rich tris(*p*-methoxyphenyl)phosphine ligand and acetonitrile as solvent, tandem arylation/1,2-alkyl migration from aluminum to carbon affords 7-substituted-1-ethyl-1-methylindanes containing an all-carbon quaternary stereogenic centre in good yields. This reaction is tolerant of 6-aryl methyl ethers, thioethers and trimethylsilanes. Deuterium labeling established that protiodealumination of the key neopentyl(methyl)aluminum triflate intermediate is caused by the acetonitrile solvent. The organodimetallic species in that study were shown to be configurationally stable, hence the stereospecificity of the process that proceeds via carbopalladation, transmetalation and reductive elimination of an alkylpalladium(II) intermediate.



When applied to 1-naphthyl triflate-tethered vinylalanes, the same reaction conditions mediate stereospecific 1,2-diarylation, leading to 2,3,3a,4-tetrahydro-1*H*-cyclopenta[*def*]phenanthrenes in excellent yields. The influence of DABCO, tether length and solvent polarity was studied. Selective tandem arylation/1,2-methyl migration could also be achieved in non-polar solvent in absence of Lewis base. While steric properties took precedence over electronic considerations when inducing product selection, preagostic C-H•••Pd interactions were postulated to facilitate 1,3-metal migration in the production of 1*H*-cyclopenta[*def*]phenanthrene derivatives.

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First and foremost, I wish to warmly acknowledge Prof. Eric Fillion for patiently steering me towards the methodical way of conducting scientifically sound research; for teaching me to funnel my – much too wild and untamed, sometimes – imagination and creativity in a useful way, leading to valid conclusions; for chairing demanding weekly group meetings that have incommensurable educational value; and finally, for greatly widening my musical horizons. Oh! and thanks for patiently bearing my Guy Mongrain-type humour.

I would like to thank Prof. John P. Wolfe for acting as external examiner for this *Ph. D.* thesis, as well as my committee members, past and present: Profs. J. Michael Chong, Gary Dmitrienko, Russell Rodrigo, Marcel Schlaf and William Tam. Your valuable input into my research, and the graduate courses you taught, have been precious. You contributed to whatever success I will have in my career.

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The euphemism "last but not least" really does not do justice to my significant other, Karine Villeneuve, and her amazing contribution to my achievements. In her case, one should rather say "last but actually first." Without you, without your patience and without your love, I would not have become the chemist and the man I am. *Merci Karine*.

Dedication

I wish, with this *Ph. D.* thesis, to pay homage to the significant people who made organic chemistry, science and life a constant, pleasant, and renewed challenge for me.

To Dr. Patrick Draper (Champlain Regional College, Lennoxville, QC, Canada), whose obvious passion for teaching Organic Chemistry first planted the seeds;

To Prof. William W. Ogilvie (University of Ottawa, ON, Canada), who first made experimental organic chemistry an exciting science to me, and who convinced me to leave physical electrochemistry to others;

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Finally, to my parents, for they purchased a piano when I was five years old, and figured out how to, somehow, afford those thirteen years of music lessons.

Music has surely taught me discipline, perseverance, resilience, and the ability to repeatedly perform the same pieces over and over. Sounds like scientific methodology.

To all, thanks. Now it's payback time, so here's to you.

Table of Contents

List of Figures

List of Schemes

List of Tables

List of Equations

List of Abbreviations

Ac	acetyl
acac	acetylacetonate
ACCN	azobis(cyclohexanecarbonitrile)
AIBN	azobis(isobutyronitrile)
Ar	aryl
BBN	borabicyclo[3.3.1]nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
bp	boiling point
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
18-C-6	18-crown-6
COD	cycloocta-1,5-diene
Cp	cyclopentadienyl
Cy	cyclohexyl
d	day
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DIPEA	diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DOSP	*N*-(*p*-dodecylphenylsulfonyl)prolinate
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppm	(diphenylphosphino)methane
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
equiv	equivalent
Et	ethyl
EtOAc	ethyl acetate
FBW	Fritsch-Buttenberg-Wichell
GC-MS	tandem gas chromatography-mass spectrometry
gem	geminal
HMDS	*N*,*N*-bis(trimethylsilyl)amide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Imid	imidazole
JMOD	*J*-modulated ^{13}C-decoupled NMR
KIE	kinetic isotope effect
L	ligand
M	mole per litre

M	metal
m	meta
M.S.	molecular sieves
Me	methyl
MeCN	acetonitrile
MEPY	methyl 2-oxopyrrolidine-5-carboxylate
MOM	methoxymethyl
MOMCl	chloromethyl methyl ether
MOP	2-(diphenylphosphino)-2'-methoxy-1,1'-binaphthyl
mp	melting point
Ms	methanesulfonyl
N/A	non available
N/R	no reaction
NB	norbornene, bicyclo[2.2.1]hept-2-ene
NBS	*N*-bromosuccinimide
ND	norbornadiene, bicyclo[2.2.1]hepta-2,5-diene
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nu	nucleophile
O	ortho
P	para
PCC	pyridinium chlorochromate
PE	petroleum ether 30-60
pfp	pentafluorophenyl
PhCN	benzonitrile
Piv	trimethylacetyl
PMB	*p*-methoxybenzyl
PMP	1,2,2,6,6-pentamethylpiperidine
Py	pyridine
quant	quantitative
R	alkyl
RedAl	sodium bis(2-methoxyethoxy)aluminate
SM	starting material
TBAAc	tetra-*n*-butylammonium acetate
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMPP	tris(*p*-methoxyphenyl)phosphine
TMS	trimethylsilyl
TMTHF	2,2,5,5-tetrahmethyltetrahydrofuran
TON	turnover number
Ts	*p*-toluenesulfonyl (tosyl)
vic	vicinal
Vitride™	sodium bis(2-methoxyethoxy)aluminate

Chapter 1 – Introduction: Organometallic Reagents and Intermediates in Carbon-Carbon Formation

1.1 Synthetic Relevance of Carbon-Carbon Bond Formation

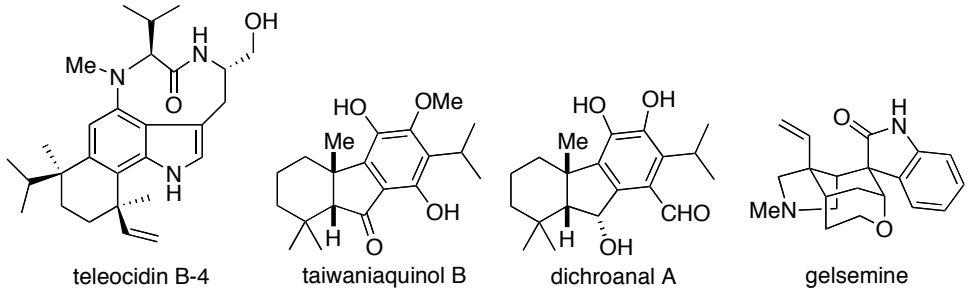
Devising strategies that generate molecular complexity from simple reagents is an important area of research in organic chemistry. Thinking with a sustainable development perspective – meeting the needs of the present without compromising the ability of future generations to meet their own needs[1] – the synthetic chemist must bear key objectives in mind when developing a new reaction technology. High productivity, low metal content in the final product, potential catalyst recycling, low energy consumption, mild reaction conditions, low waste generation and environmentally safe solvents are all important components of a so-called green reaction.

Among the plethora of synthetic transformations under study by the organic community, the efficient formation of carbon-carbon (C-C) bonds has attracted considerable attention in the recent decades. Transition metal-catalysed C-C bond forming reactions, such as the Heck and cross-coupling reactions, as well as metal carbenoid C-H insertion and cyclopropanation reactions, have become weapons par excellence in the synthetic chemist's arsenal. Their ability to unite "two sophisticated moieties under mild conditions" has made them especially attractive on the industrial scale.[2] As well, synthetic approaches based on *gem*-organodimetallic species are known to mediate C-C bond formation. In the case of heterodimetallic reagents, bismetallic reagents can allow diastereoselective transformations, due to the distinct reactivity of the individual metals. Finally, treatment of vinylmetallic species with electrophiles has been observed to trigger 1,2-metallate rearrangement, concomitant with C-C bond formation, leaving a new organometallic residue to achieve further functionalisation. In the following sections, these carbon-carbon bond formation technologies, in parallel with their relevance to the research endeavour presented in this thesis, will be reviewed.

1.2 Transition Metal-catalysed Stereoselective Formation of All-carbon Quaternary Stereogenic Centres

An especially challenging transformation is the C-C bond-forming construction of all-carbon quaternary stereocentres with maximum control over diastereo- and enantioselectivity, in linear or benzocyclic systems. Several natural products, displaying an array of biological activities, possess carbobenzocyclic frameworks incorporating a benzylic quaternary all-carbon stereocentre: among others, the teleocidins, taiwaniaquinols and dichroanals, as well as alkaloids such as gelsemine (Figure 1.1).

Figure 1.1: Natural products containing all-carbon benzylic quaternary carbons

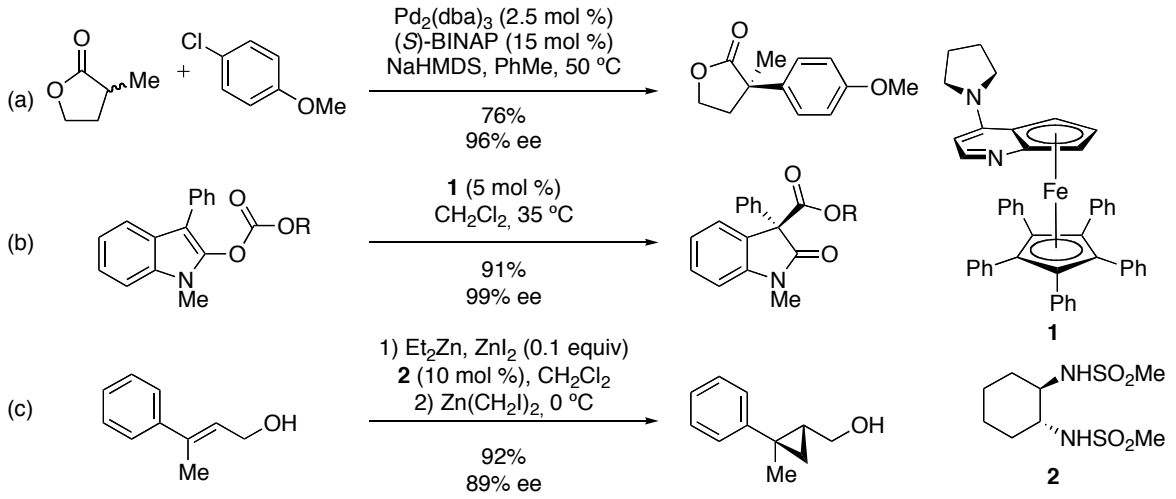


teleocidin B-4 taiwaniaquinol B dichroanal A gelsemine

Approaches based on transition metal catalysis or organocatalysis have provided a partial solution to this synthetic demand. In a 2004 edition of the *Proceedings of the National Academy of Science* entirely devoted to recent advances in asymmetric organic synthesis, Douglas and Overman[3] have identified the Hartwig α-arylation of lactones, ketones and oxindoles (Scheme 1.1a),[4] the Fu chiral 4-aminopyridine-catalysed carboxylation of oxindoles (Scheme 1.1b),[5] and the zinc carbenoid-promoted asymmetric cyclopropanation of styrene-derived trisubstituted alkenols[6] (Scheme 1.1c) as the few methods then available for the creation of chirally pure benzylic all-carbon quaternary stereogenic centres. Since then, the Fillion group has published the copper-catalysed enantioselective addition of dialkylzinc reagents to 5-[1-arylethylidene] Meldrum's acid electrophiles,[7] and Hoveyda's group has reported Cu-catalysed addition of dialkylzincs to nitroalkenes.[8] Common to those strategies is

their discrimination of the prochiral faces of an achiral, planar sp^2 alkene system, while building a carbon-carbon bond at the sterically congested benzylic position.

Scheme 1.1: Chiral all-carbon benzylic quaternary centre formation



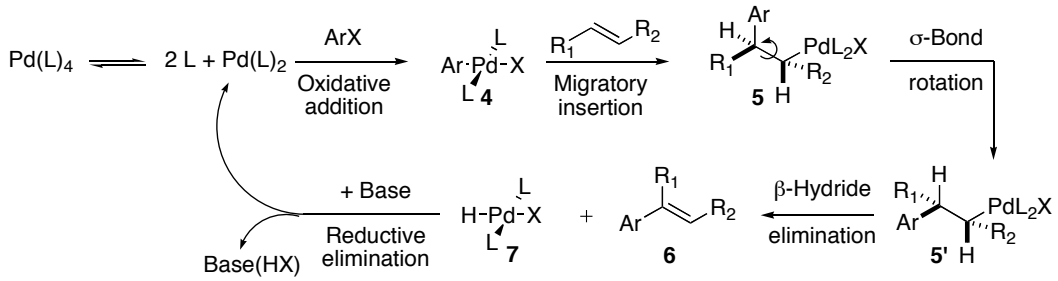
1.2.1 The Mizoroki-Heck Reaction

1.2.1.1 Historical and Mechanistic Considerations

The Pd-catalysed Mizoroki[9]-Heck[10] reaction was discovered shortly after the pioneering report, by Fitton *et al.*,[11] of the X-ray structure of the complex obtained by oxidative addition of iodobenzene to $Pd(PPh_3)_4$, bis(triphenylphosphino)phenylpalladium(II) iodide. Mizoroki and Heck independently reported the $Pd(OAc)_2$-catalysed union between iodoarene and acrylic ester or styrene derivatives. Heck's concluding statement regarding this reaction's synthetic value was premonitory: "In spite of some limitations, the organic halide olefinic substitution reaction should prove to be a useful synthetic reaction." In general, the Heck reaction unites an aryl or alkenyl halide or sulfonate with an olefin, in the presence of palladium(0) catalysts, forming a C-C bond between the two fragments.[12] Although many reviews have been written on the Heck reaction,[13] the elementary steps will be summarised herein (Scheme 1.2). Following oxidative addition of the halide or sulfonate to the short-lived 14-electron Pd(0) species, migratory insertion of the olefin into the resulting σ-aryl or -alkenylpalladium(II) species **4** affords σ-alkylpalladium(II) species **5**. This key intermediate then undergoes C-C

bond rotation allowing *syn* β-hydride elimination to proceed, hence forming the unsaturated C-C bond and generating a palladium(II) salt, by-product **7**. The base promotes reductive elimination of Pd(0), regenerating the 14-electron catalyst, with concomitant formation of the conjugate acid salt. Importantly, the *syn* migratory insertion featured in the Heck reaction makes it stereospecific. That is, an (*E*)-olefin will lead to the opposite diastereomer from the Heck product obtained in the reaction of a (*Z*)-alkene with the same aryl or alkenyl halide. Thereby, the configurational stability of the C-Pd bond has been inferred.

Scheme 1.2: Heck reaction mechanism



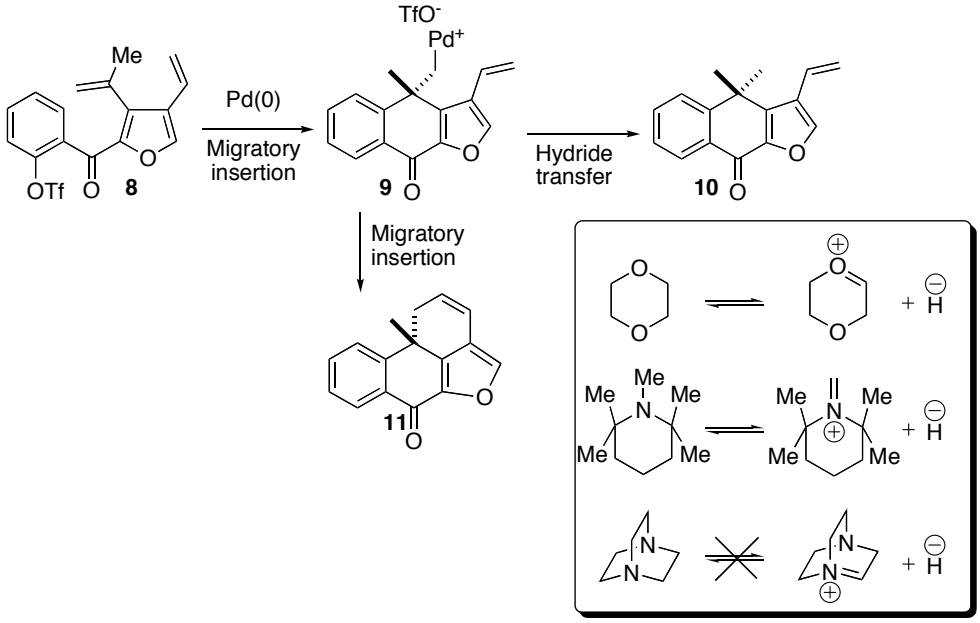
1.2.1.2 Optimisation of the Heck Reaction

Recent advances in the Heck reaction involve new reaction media, such as ionic liquids or water as solvents,[14] and fine-tuning of the pre-catalyst by altering ligands, the ultimate objective being to increase the catalyst turnover number, while maintaining optimal product yield. Pincer-type, phosphine-free catalysts are becoming the new potency standard for high turnover rates in the Heck reaction.[15]

It was recently found that employing 1,4-diazabicyclo[2.2.2]octane (DABCO) as base also generates high turnover rates in the Heck reaction,[16] as well as many other Pd-catalysed cross-coupling reactions.[17] While studying polyene cyclisations, Keay and co-workers have found that DABCO is an excellent substitute for the expensive yet widely used 1,2,2,6,6-pentamethylpiperidine (PMP) in intramolecular asymmetric Heck reactions (see section 1.2.1.3). En route to the natural product xestoquinone, they demonstrated that the reduced cyclisation product **10**, displaying a *gem*-dimethyl motif, arose from hydride transfer to neopentylic alkylpalladium(II) species **9**, followed by reductive elimination of Pd(0) and

formation of the C-H bond (Scheme 1.3). They demonstrated that d_8-1,4-dioxane as well as 1-(trideuteriomethyl)-2,2,6,6-tetramethylpiperidine (d_3-PMP) were hydride sources in this process. They surmised that hydride transfer was occurring via the corresponding oxonium or iminium species. To eliminate these hydride sources, they replaced 1,4-dioxane by toluene and PMP by DABCO, allowing for the exclusive formation of biscyclised product **11**.[18] Indeed, DABCO cannot transfer a hydride via the corresponding bridgehead iminium intermediate, for this would violate Bredt's rule.[19]

Scheme 1.3: Comparison of DABCO and PMP in polyene cyclisations



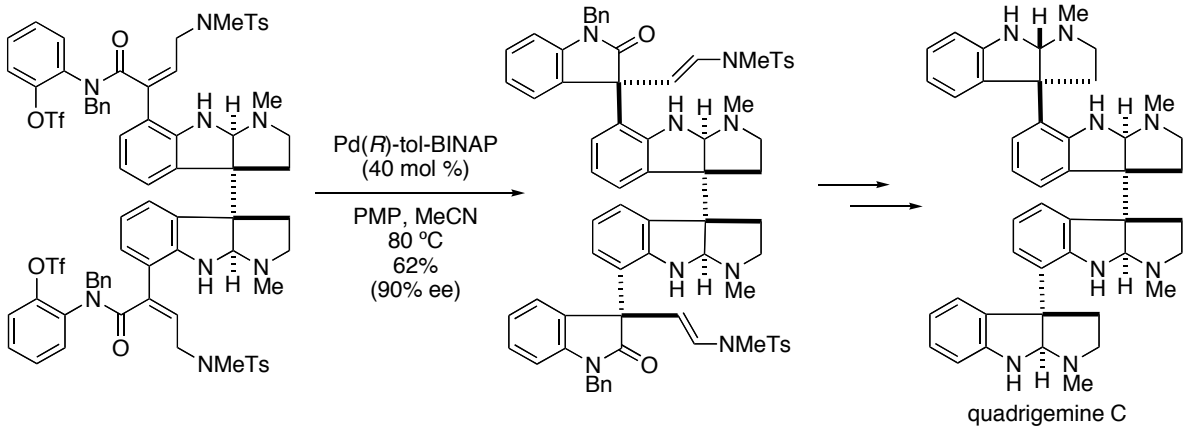
1.2.1.3 The Enantioselective Intramolecular Heck Reaction

Since their infancy in the late 1980s, the Shibasaki[20]-Overman[21] refinements of the Heck reaction have led to the establishment of an intramolecular cyclisation reaction, forming benzylic all-carbon quaternary centres enantioselectively. So far, the asymmetric Heck reaction remains the catalytic method with the widest scope for this purpose. Although the structural factors maximising enantioselectivity have yet to be fully rationalised, an examination of reaction parameters such as base, Pd catalysts, ligand structure, halide scavengers and other additives is provided in the review by Overman and Dounay.[22] As well, Overman and Watson have recently reported their thorough studies on diastereoselective asymmetric intramolecular

double Heck reactions of aryl triflates, forming two vicinal all-carbon quaternary stereogenic centres.[23]

In 2003, applications of the Heck reaction to the enantioselective construction of tertiary and quaternary all-carbon benzylic stereocentres by intramolecular cyclisation of prochiral substrates, in the context of total synthesis of complex molecules, were reviewed. By then, at least 22 such examples were censused in the literature.[22] For example, asymmetric Heck methodology has been showcased by the Overman group in the total sythesis of the polypyrrolidinoindoline alkaloid quadrigemine C in 2002.[24] The key stage of their work involved a double Heck reaction creating two benzylic all-carbon quaternary stereogenic centres in 90% enantiomeric excess (ee) and 62% overall yield (Scheme 1.4). Recently, Overman *et al*. also disclosed their discoveries en route to the alkaloid gelsemine, containing a benzylic all-carbon quaternary stereogenic centre, successively synthesised via the enantioselective Overman-Heck methodology.[25] Of importance, a scalemic total synthesis of dichroanal (Figure 1.1) centred upon an intramolecular Heck cyclisation to construct the all-carbon benzylic quaternary centre was recently published.[26]

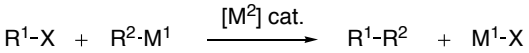
Scheme 1.4: Asymmetric Heck reaction in the Overman synthesis of quadrigemine C



1.2.2 Palladium-Catalysed Cross-Coupling Reactions

The stoichiometric reaction of organometallic species with an aryl or alkyl halide or sulfonate in the presence of a transition metal catalyst (typically Pd or Ni) is known as cross-coupling. As reviewed by Nicolaou, transition metal-catalysed cross-coupling reactions have been utilised extensively for key C-C bond forming events in the context of complex molecule total synthesis.[27] Due to its ease of handling and well-established reactivity, Pd-based catalysis has gained in popularity. Among the organometallic species known to transmetalate with Pd(II), organoaluminum[28] and -alanate,[29] -zirconium,[30] -zinc[31] and -zincate,[32] -silicon and -siliconate,[33] -boron and -boronate,[34] -stannane[35] and -germane[36] reagents have led to widely applicable and commonly used C-C bond formation methods (Scheme 1.5). The Stille cross-coupling of sterically encumbered vinyltributylstannanes often leads to the *cine* substitution product, wherein C-C bond formation occurs α- to the stannane C-Sn bond. This phenomenon will be covered in more detail in section 1.3.4.

Scheme 1.5: Transition-metal catalysed cross-coupling reactions



R1: aryl, alkyl, alkenyl
R2: H, alkyl, alkenyl, aryl
M1: MgX (Kumada), AlR_2, ZrR_2X, ZnX (Negishi), SiR_3 (Hiyama), $Si(OR)_3$, $B(OR)_2$ (Suzuki), BR_2, BX_2, SnR_3 (Stille), GeR_2, Cu(alkynyl) (Sonogashira)
M2: Ni(0), Pd(0), Cu(I)

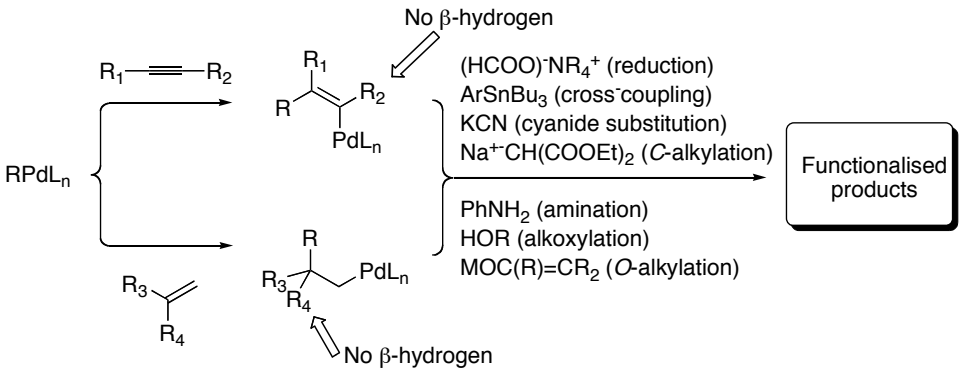
The transition metal-catalysed coupling of $C(sp^3)$-$C(sp^3)$ centres, prone to potential side-reactions due to the presence of β-hydrogens, still remains a redoubtable challenge. Of late, much work has been devoted to solve this issue. As reviewed by Cárdenas in 2003,[37] switching from less selective Grignard reagents to more compatible organozinc and organoboron species, Pd- or Ni-catalysed reactions have displayed accrued functional group tolerance. Much knowledge still remains to be gained, although the *B*-alkyl Suzuki coupling, mediated by *B*-alkyl-9-borabicyclo[3.3.1]nonanes, is gaining popularity.[38]

1.2.3 σ-Alkylpalladium(II) Functionalisation Cascades Based on Carbopalladation

Recalling section 1.2.1, intramolecular migratory insertion of σ-arylpalladium(II) species into highly substituted olefins presents a strategy for the construction of benzylic quaternary centres. As reviewed by Negishi *et al.*, after initial C-C bond-forming carbopalladation, the resulting σ-alkyl- or -alkenylpalladium(II) intermediate can take part in further functionalisation (Scheme 1.6). Diverse strategies such as reduction, cross-coupling, substitution with nitriles, enolate *C*- or *O*-alkylation, amination, imination, amidation, alkoxylation and phenoxylation have been realised.[39] Alternatively, migratory insertion of the σ-alkyl- or -alkenylpalladium(II) intermediate with an olefin results in a Heck process.

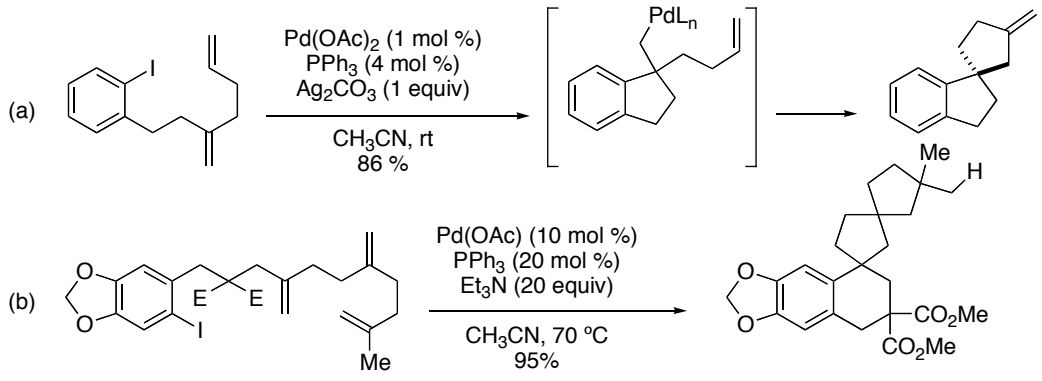
For an efficient functionalisation strategy, the β-hydride elimination pathway must be greatly slowed down until the termination step. For that purpose, two major tactics can be employed, namely migratory insertion of alkynes and *gem*-disubstitution of the alkene counterpart. For neither internal nor terminal alkynes is a β-hydride found in synclinal orientation with the C-Pd(II) bond following carbopalladation, so the resulting alkenylpalladium(II) can be further decorated using one of the previously mentioned strategies. Conversely, migratory insertion of 2,2-disubstituted-1-alkenes with an arylpalladium(II) intermediate leads to a neopentylic alkylpalladium(II) species, with which no β-hydride can possibly interefere. Hence, successful trapping can ensue, leading to maximum molecular complexity from simple building blocks.

Scheme 1.6: σ-Alkylpalladium(II) functionalisation strategies



Furthermore, in the presence of an internal double bond, intramolecular migratory insertion is the basis for polyene cyclisations.[40] Following sequential olefin migratory insertions into C-Pd(II) bonds, β-hydride elimination affords the exocyclic double bond, and base-promoted reductive elimination allows catalytic cycle completion. This approach has been used to synthesise spirobenzocyclic compounds (Scheme 1.7a) as well as linear-fused spirocyclic ring systems (Scheme 1.7b), bearing an all-carbon benzylic quaternary stereogenic centre. The application of Pd-catalysed polyene cyclisation has been showcased in the racemic total synthesis of scopalducic acid A.[41]

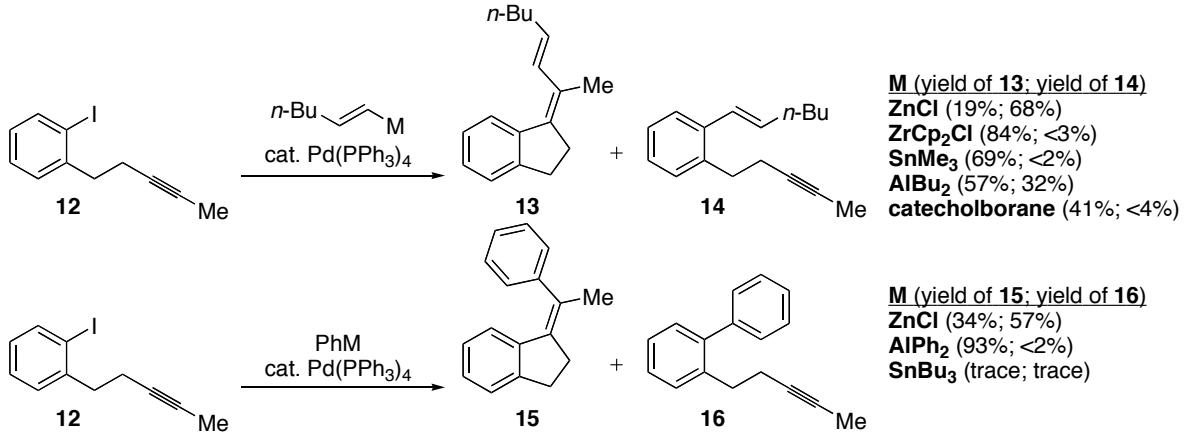
Scheme 1.7: Palladium-catalysed polyene cyclisation



Transmetalation of organometallic reagents with a palladium(II) intermediate also presents an avenue for C_{alkyl}-Pd(II) bond functionalisation. To ensure a successful strategy, carbopalladation must be faster than the C-C bond forming transmetalation cascade-terminating step, otherwise the major products observed are cross-coupled products **14** or **16**

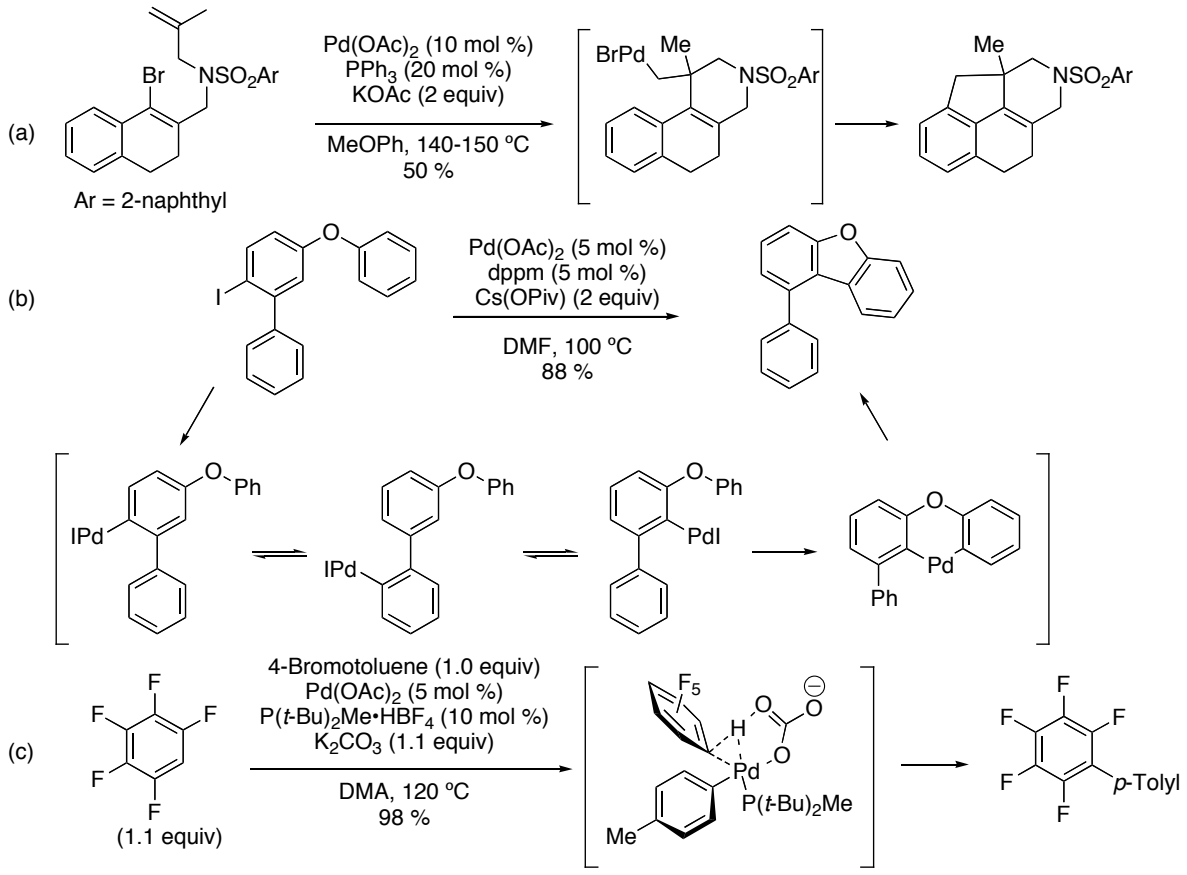
(Scheme 1.8). While Negishi noted organozincs to be disappointing overall, "highly satisfactory results may be obtainable with organometals containing Sn and Zr for alkenylation, Sn for alkynylation, and Al for arylation."[39]

Scheme 1.8: Functionalisation of a σ-alkylpalladium(II) intermediate via transmetalation



Arene substitution is another avenue for C-Pd(II) bond functionalisation that is gaining in popularity and versatility for the construction of C-C bonds. While the first such example merely demonstrated the dimerisation of π-compounds,[42] synthetically significant examples of this strategy were published by Grigg (Scheme 1.9a),[43] Larock (Scheme 1.9b),[44] Echavarren,[45] and Fagnou (Scheme 1.9c).[46] Since the overall process forms a sigma bond between two sp^2-hybridised carbon atoms, a transformation that has traditionally been brought about by organic halides and organometallic transmetalating partners,[47] arene migratory insertion is more and more commonly termed "direct arylation" of σ-arylpalladium(II) species. Fagnou *et al*. have recently proposed "a concerted metalation of the fluoroarene and H-transfer to either a carbonate or bromide ligand on the catalyst" to explain the mechanism at play in direct arylations,[48] much in line with Echavarren's proposal of a rate-determining proton abstraction.[49]

Scheme 1.9: Direct arylation of σ-alkylpalladium(II) intermediates



In addition to the Heck and cross-coupling strategies, transition metal-catalysed carbon-carbon bond formation sometimes involves the intermediacy of metal carbenes. The next section reviews aspects bearing relevance to this thesis.

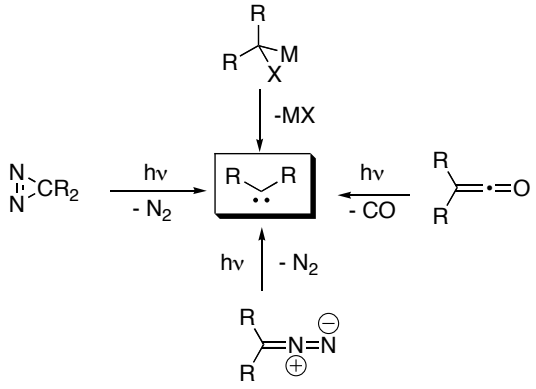
1.3 Carbenes: Formation and Reactivity

1.3.1 Historical and General Considerations

Carbenes are six-electron species that exist either in the singlet (paired electrons, sp^2-hybridised) or triplet (diradical, sp^3-hybridised) state. They adopt an electrophilic behaviour,

reacting with another carbene molecule or carbene precursor to undergo dimerisation, with double and triple bonds to form cyclopropanes and cyclopropenes via [2+1] cheletropic cycloaddition, and with heteroatom lone pairs to form ylides. Free carbenes also undergo C-H insertion reactions. Historically, free carbenes have been generated either by photochemical decomposition of diazoalkanes, ketenes or diazenes. α-Elimination of metal halide from a metal carbenoid is another avenue for the generation of free carbenes (Scheme 1.10).[50]

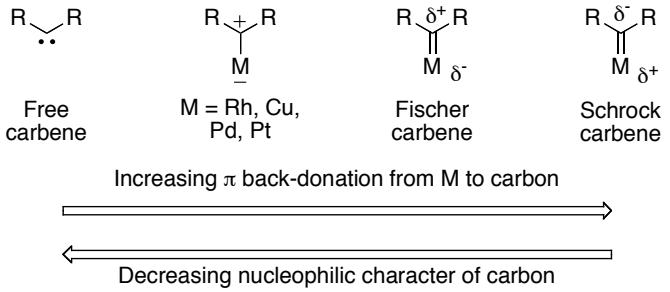
Scheme 1.10: Generation of free carbenes



Since non-stabilised, or free, carbenes are highly reactive species, they generally display poor selectivity. It is thus desirable to stabilise the carbene, which is effected by sharing its lone pair electrons with an empty transition metal d-orbital; simultaneously, back-donation of the metal's electrons into the carbene's empty p-orbital produces a metal carbene complex. Such complexes can have different types of reactivities based on the electronic properties of the metal to which the carbene is associated (Figure 1.2). High-valent, electron-depleted metal complexes (typically titanium(IV), chromium(VI), molybdenum(VI) and tungsten(VI), for example) produce so-called Fischer carbenes, whose reactivity is electrophilic and carbonyl-like, undergoing addition of nucleophiles either in a direct (1,2) or conjugate (1,4) fashion. Conversely, electron-rich metal complexes of Mo and Ru, among others, yield Schrock carbene complexes, whose reactivity is entirely different than Fischer carbenes – their carbene carbon typically adds to electrophiles. The Nobel Prize-winning Ru- and Mo-catalysed olefin and acetylene metathesis reaction, occurring via a series of [2+2] cycloadditions, is brought about by the intermediacy of Schrock carbenes. Zaragoza-Dörwald has pointed out that, nowadays, the division between the two types of complexes may be overemphasised, as it is no

longer possible to predict the metal carbene reactivity based exclusively on the nature of the metal.[51]

Figure 1.2: Metal-carbene structure-activity relationship[51]

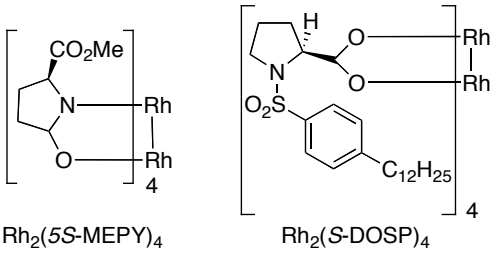


1.3.2 Rh-, Cu- and Pd-Catalysed Cyclopropanation Reactions

Cyclopropanation reactions mediated by transition metal-stabilised carbenes have been effected through copper-, palladium- and rhodium-catalysed decomposition of diazoalkanes. Cyclopropanation of styrene derivatives,[52] as well as strained[53] and electron-deficient[54] olefins are best accomplished by palladium(II) catalysts such as $Pd(OAc)_2$, $PdCl_2$, and $Pd(PhCN)_2Cl_2$. Such reactions are most successful for intramolecular cases or using the simplest diazoalkanes, such as diazomethane.[55] Moreover, cyclopropanations have led to marginal enantioselectivity using Pd(0) or Pd(II) catalysts[56] although diastereoselectivity is high in many cases.[55]

For enantioselective cyclopropanations, best results are obtained with the complementary rhodium(I) catalysts, which allow inter- and intramolecular reactions, including enantioselective methodologies, to be carried out selectively. Doyle's[57] as well as Davies'[58] research groups have rendered enantioselective applications of this technology wide in scope and highly efficient by using potent catalysts based upon the proline scaffold. Specifically, Doyle's catalyst utilises the 5*S*-MEPY carboxamidate framework whereas Davies' catalyst comprises a long-chain dodecyl-*N*-sulfonylprolinate (*S*-DOSP), soluble in pentane even at –78 ºC (Figure 1.3), allowing the performance of extremely selective reactions.

Figure 1.3: Doyle's MEPY and Davies' DOSP ligands



Rh_2(*5S*-MEPY)$_4$ Rh_2(*S*-DOSP)$_4$

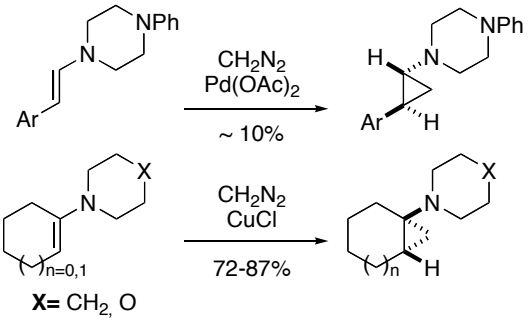
Davies and co-workers have provided numerous applications of vinyl-stabilised diazoalkanes. In the presence of the Rh_2(*S*-DOSP)$_4$ catalyst, the resulting Rh-vinylcarbenoid undergoes highly enantio- and diastereoselective cyclopropanation with alkenes and dienes. As well, these catalysts allow for efficient and stereoselective C-H insertions, along with Si-H, N-H and O-H insertions, to take place. However, due to the unfriendly nature and sometimes non-trivial synthesis and manipulation of diazoalkane compounds, the industrial application of these important C-C bond forming reactions is hampered.

Palladium-catalysed cyclopropanation reactions display a reactivity pattern that sets them, in most cases, in a separate niche from their rhodium- and copper-catalysed counterparts. For instance, Tomilov *et al.*[55] emphasised that, unlike Pd, Cu catalysts will effect cyclopropanation of olefins with a wide range of nature and degree of substitution. However, copper complexes tend to be over-reduced by diazomethane, leading to metallic copper, which vigorously decomposes diazomethane and affords reduced yields of [2+1] adduct. Products of competitive reaction rates between CH_2N_2 and cyclohexene or bicyclo[2.2.1]hept-2-ene and two different metal catalysts, $Pd(PhCN)_2Cl_2$ and $Cu(acac)_2$, have been compared by Tomilov. Strikingly, whereas the $Cu(acac)_2$ allowed cyclopropanation of both alkenes at similar rates, leading to 1:1 mixtures, $Pd(PhCN)_2Cl_2$ was especially reactive with the strained alkene, favouring norbornene over cyclohexene by two orders of magnitude.

Both chemoselectivity and functional group tolerance will now be compared and contrasted for Pd and Cu catalysts. When the reaction is catalysed by Pd salts, it has been established that terminal olefins are more readily cyclopropanated than their internal counterparts. Further, with Pd catalysts, the C-C double bond in alkyl vinyl ethers undergoes cyclopropanation at

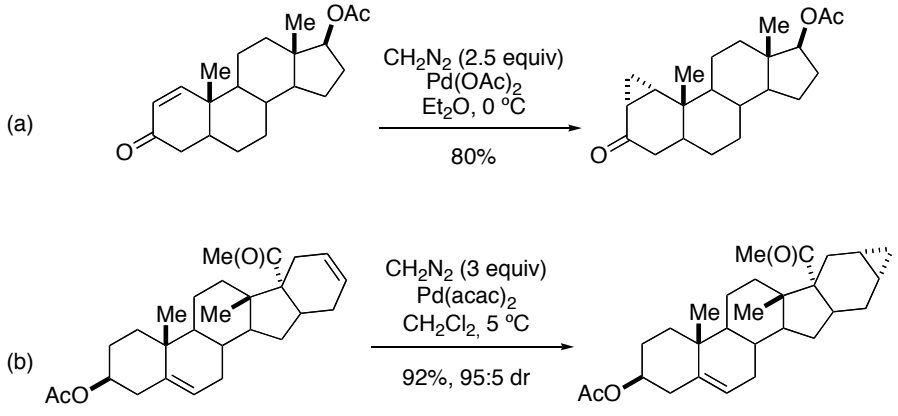
unproductively slow rates, synthetically speaking, contrasting with allyl ethers, alcohols and amines. Interestingly, with Cu catalysts, allyl halides undergo both cyclopropanation and methylene insertion into the carbon-halogen bond, unlike Pd catalysts, which mediate neither reaction.[59] Contrary to copper catalysts, enamines are barely reactive with CH_2N_2 in the presence of $Pd(OAc)_2$ (Scheme 1.11).

Scheme 1.11: Transition metal-catalysed cyclopropanation of enamines



Of note, the metal-catalysed cyclopropanation of α,β-unsaturated carbonyl compounds is the almost exclusive domain of palladium, yet the usual steric limitations apply: 1,2-disubstituted acrylate derivatives are generally tolerated, contrary to their 1,1-disubstituted equivalents. Cyclohexenone and -pentenone systems successfully undergo cyclopropanation with diazomethane (Scheme 1.12a), with complete diastereoselectivity in the example presented. As well, a disubstituted olefin is cyclopropanated faster than a trisubstituted one (Scheme 1.12b).

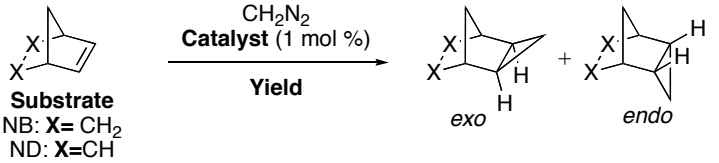
Scheme 1.12: Pd-catalysed cyclopropanation of cyclic alkenes



The superior *exo*-diastereoselectivity of the methylenation of norbornene derivatives in the presence of CH_2N_2 and Pd salts (Table 1.1), compared with Cu and Rh salts, is noteworthy. This selectivity was associated by Tomilov *et al*. with the ability of norbornenes to form initially coordinated π-complexes with the metal, subsequently reacting with diazomethane.[55] This coordination is sensitive to electron density of the π-bond, which is greater on the *exo*-face of the bicyclo[2.2.1] system.[60] In comparison, with copper and rhodium carbenes, the double bond was demonstrated to undergo attack by the metal carbene. Contrary to the more polarised Pd^{II}-diazomethane complexes, Cu and Rh carbenes are nearly neutral species. As a result, the interaction of the carbene centre with the double bond is less sensitive to electronic factors and Rh- and Cu-carbene complexes react partially at the *endo* face of norbornene.

The greater reactivity of Pd^{II}/CH_2N_2 with strained olefins compared with the simple cycloalkenes is also caused by the latter's higher ground state energy due to *endo*-deformation of the vinylic hydrogen atoms, that is, the angle of deviation of the C-H bonds from the C-CH=CH-C plane, which varies between 3º and 5º. Hence, the less strained cyclopentene and -hexene derivatives react more reluctantly with CH_2N_2 under palladium catalysis than bicyclo[2.2.1]alkenes.

Table 1.1: Metal-catalysed cyclopropanation of norbornene and norbornadiene



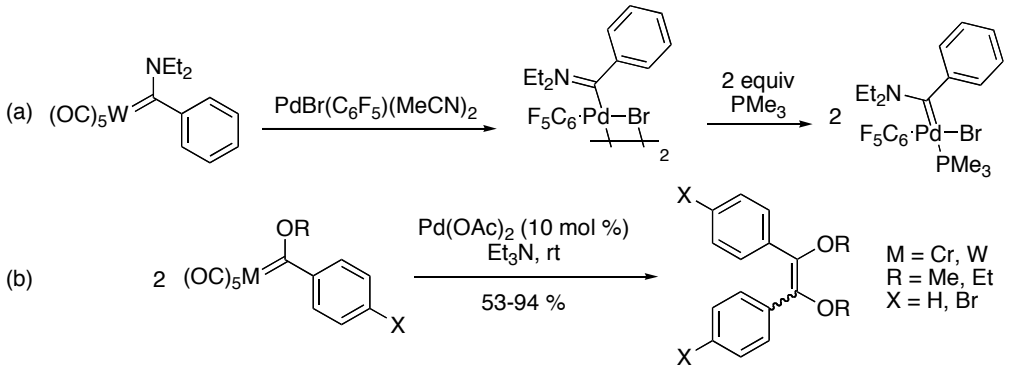
Entry	Substrate	Catalyst	*Exo-endo* ratio	Yield (%)
1	NB	$Pd(acac)_2$	100:0	87
2	NB	$Pd(OAc)_2$	100:0	78
3	NB	$Pd(PhCN)_2Cl_2$	100:0	81
4	NB	$Cu(acac)_2$	97:3	38
5	NB	$Rh_2(OCO_2CF_3)_4$	90:10	18
6	ND	$Pd(acac)_2$	99:1	52
7	ND	$Pd(OAc)_2$	99:1	48
8	ND	$Pd(PhCN)_2Cl_2$	99:1	54
9	ND	$Cu(acac)_2$	64:36	36
10	ND	$Rh(OCO_2CF_3)_4$	58:42	19

1.3.3 Formation and Reactivity of Pd-carbene Intermediates

Much research has been conducted in order to discover new metal carbenoid precursors. In particular, palladium-carbene complexes have been made accessible via other approaches, both stoichiometric and catalytic, which will be discussed herein.

Albéniz and co-workers have demonstrated that tungsten Fischer carbene complexes transmetalate with bis(acetonitrile)pentafluorophenylpalladium(II) bromide to yield the corresponding palladium carbene complex whose intermediacy was also inferred by observation of hydrolysis and pentafluorophenyl migratory insertion products (Scheme 1.13).[61] This strategy is restricted due to the need for stoichiometric amounts of tungsten precursor complex. Similarly, the dimerisation of chromium(0) alkylidenes was shown to be catalysed by $Pd(OAc)_2$ via the corresponding palladium carbene.[62] Sierra *et al.* recently pointed out that chromium, molybdenum and tungsten Fischer carbene complexes undergo this carbene transmetalation reaction not only with palladium but also with rhodium, nickel and copper.[63]

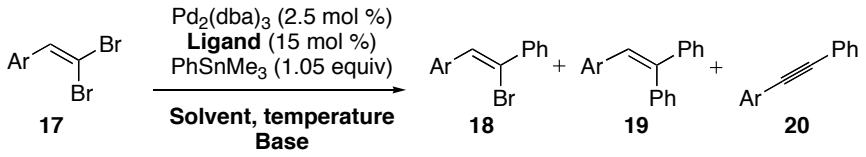
Scheme 1.13: Generation of Pd carbenes by transmetalation with metal-carbene complexes



Palladium carbene intermediates have been proposed in a variety of Pd-catalysed processes.[64] Particular examples of relevance to this thesis are now presented. Shen and Wang have observed that the Stille reaction of 1,1-dibromo-1-alkenes with aryl- and alkenyltin reagents produces different outcomes depending on the reaction conditions.[65] When less polar solvents (1,4-dioxane or toluene) and electron-poor tri-(2-furyl)phosphine (TFP) are employed, the

expected (*Z*)-bromoolefin is obtained stereoselectively (Table 1.2, entries 1-2). *A contrario*, when Stille reactions are conducted using *N*,*N*-dimethylformamide (DMF) with strongly electron-donating tris(*p*-methoxyphenyl)phosphine (TMPP), the resulting alkynes can be obtained selectively (entries 5-6). The electron-poor TFP ligand was shown by Farina to be responsible for a rate acceleration of transmetalation in the proposed Stille cross-coupling mechanism, most markedly in non-polar solvents.[66] Employing the electron-rich TMPP in highly dipolar DMF solvent impedes transmetalation. Under those conditions, palladium-carbenoid formation can occur due to accrued electron density on the Pd centre (Scheme 1.14) through the Fritsch-Buttenberg-Wichell rearrangement, or by elimination of the hydrobromide salt of diisopropylethylamine (DIPEA), as proposed by Shen and Wang. Of note, using toluene as non-polar solvent (entry 3, Table 1.2) with the TMPP ligand led exclusively to recovered **17**, as both processes were shut down.

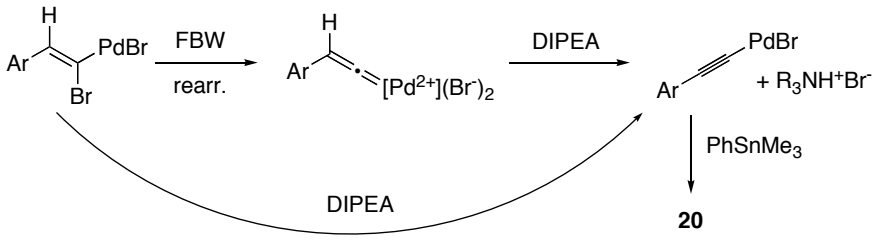
Table 1.2: Stille reaction of 1,1-dibromo-2-aryl-1-alkenes



Ar = 4-(CO_2Me)Ph

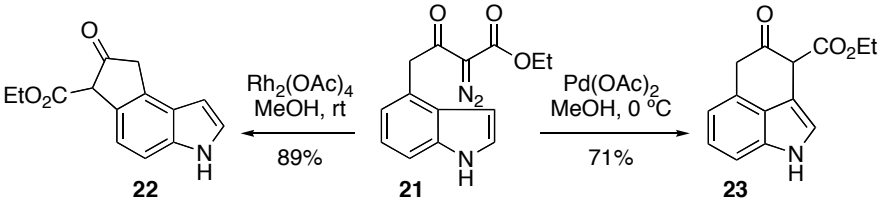
Entry	Ligand	Solvent	Temp. (ºC)	Base	Ratio (**17**:**18**:**19**:**20**)	Yield (%)
1	TFP	PhMe	100	---	0:92:8:0	98
2	TFP	1,4-Dioxane	100	---	0:90:10:0	93
3	TMPP	PhMe	100	---	100:0:0:0	N/A
4	TFP	MeCN	100	---	46:27:7:21	N/D
5	TFP	DMF	80	DIPEA	0:0:0:100	91
6	TMPP	DMF	80	DIPEA	0:0:0:100	88

Scheme 1.14: Proposed FBW rearrangement in diarylacetylene formation



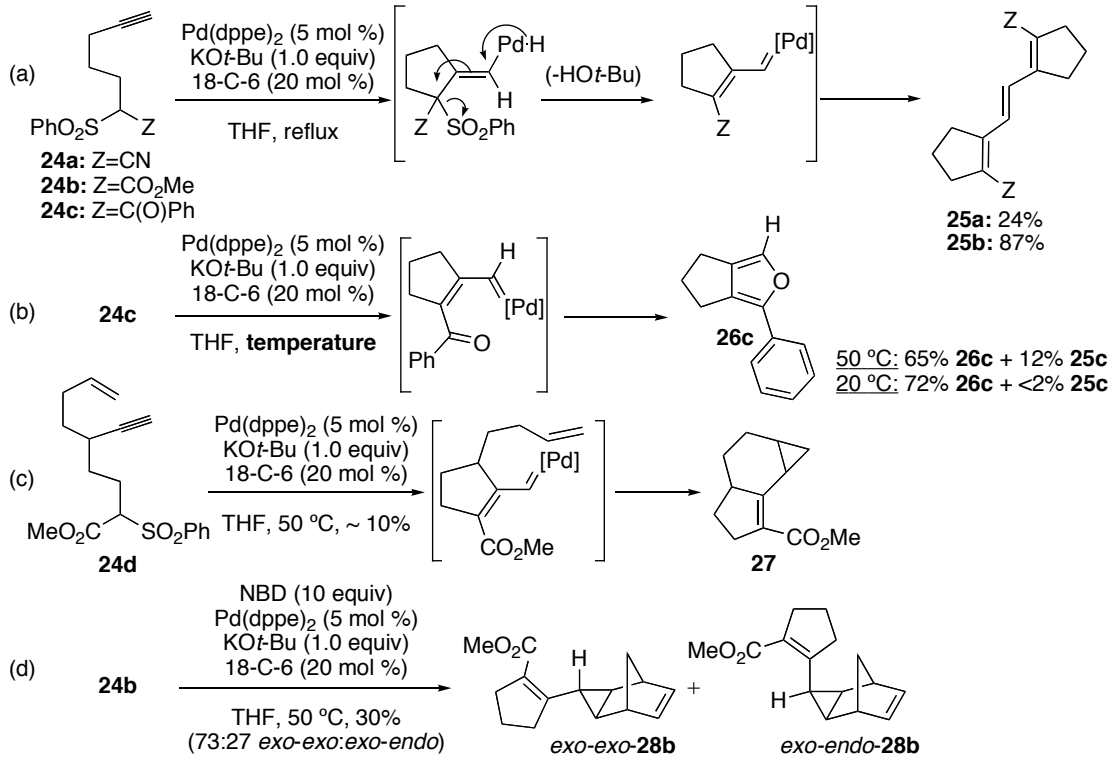
The group of Matsumoto has observed that different diazocarbonyl decomposition products were obtained upon treatment of ethyl 2-diazo-4-(4-indolyl)-3-oxobutanoate **21** with either $Rh_2(OAc)_4$ or $Pd(OAc)_2$ catalysts (Scheme 1.15).[67] When the indole nitrogen was unsubstituted, the regioselectivity was most striking. Indole-C_5-H insertion was favoured for rhodium, contrasting with C_3-H insertion with palladium. While C_{alkyl}-H insertion was already studied in the late 1980s, this constituted but the second example of Pd-carbene insertion into a $C(sp^2)$-H bond.[68]

Scheme 1.15: Pd-catalysed formation of the hapalindole ring system



Balme and co-workers also presented a novel approach to palladium alkylidene intermediates.[69] Intramolecular Pd-catalysed cyclisation of the potassium enolates of α-sulfonyl-ε-acetylenic nitrile **24a** and ester **24b** led to the corresponding dimerised unsaturated esters and nitriles **25**, in which the phenylsulfinate had undergone elimination (Scheme 1.16a). They surmised that products **25** arose from a Pd-carbene intermediate. In order to demonstrate its intermediacy, they submitted the corresponding α-sulfonyl-ε-acetylenic ketone **24c** to the same reaction conditions. In that case, a mixture of ketone dimer **25c** and furan **26c** was isolated (Scheme 1.16b). Reaction of metal carbenoids with carbonyl lone pair electrons results in a 1,3-dipole that tautomerises to the corresponding furan, so the contents of the product mixture attested to a Pd-carbene intermediate.[70] Finally, whereas intramolecular cyclopropanation yielded minute amounts (10%, mixture of four products) of the expected cyclopropane **27** (Scheme 1.16c), intermolecular cyclopropanation with norbornadiene lead to a 73:27 mixture of *exo-exo* and *exo-endo* cyclopropane diastereomers **28b** (Scheme 1.16d) when performing slow addition of the enolate to a solution of $Pd(dppe)_2$ and ten-fold ND excess.

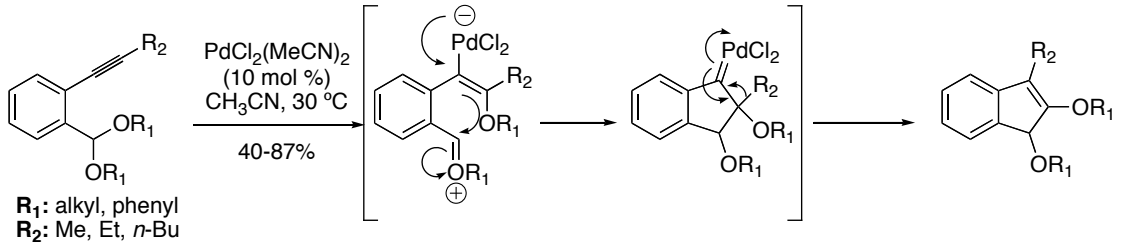
Scheme 1.16: Palladium carbenes by conjugate elimination of potassium phenylsulfinate



Norbornene and other strained alkene derivatives have also undergone acylcyclopropanation under a protocol developed by Murai *et al.*, wherein an oxa-π-allylpalladium(II) intermediate is generated by oxidative addition of a Pd(0) catalyst to acetonyl ethyl carbonate.[71] The authors proposed the involvement of a palladium carbene, although that pathway was not thoroughly demonstrated. This work is further discussed in section 2.1.2.

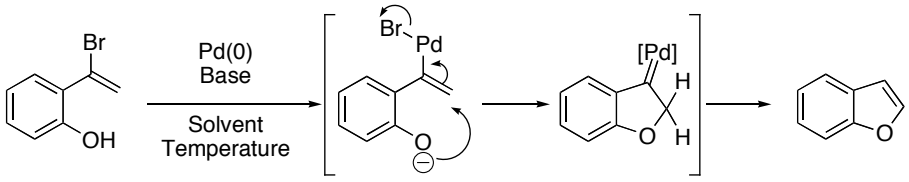
Lastly, Yamamoto and co-workers recently published an interesting palladium-catalysed carboalkoxylation of 2-alkynylbenzaldehyde dimethyl acetals that appears to involve a Pd-carbene intermediate (Scheme 1.17).[72] An alkoxide was proposed to attack the Pd(II)-complexed alkyne, leading to a β-alkoxyalkenylpalladium(II) intermediate, which then alkylated the latent oxonium electrophile, leading to a palladium(II) carbene. That intermediate undergoes a 1,2-alkyl shift followed by carbon-carbon bond formation, affording the indenol ether products.

Scheme 1.17: Indenol ether formation from 2-alkynylbenzaldehyde dialkyl acetals



Somewhat similar in approach, unpublished results from the Fillion laboratories show that benzofuran synthesis is possible via an intermediate Pd carbene, generated by intramolecular addition of a phenoxide nucleophile onto a vinylpalladium(II) bromide intermediate (Scheme 1.18). The product was then obtained by 1,3-hydride shift followed by reductive elimination of Pd(0). Yields and reproducibility for this method were plagued by the propensity of benzofuran to undergo polymerisation, side-reactions under the reaction conditions, and unstability of the starting material.[73]

Scheme 1.18: Pd carbenes in the Fillion/Fishlock synthesis of benzofurans

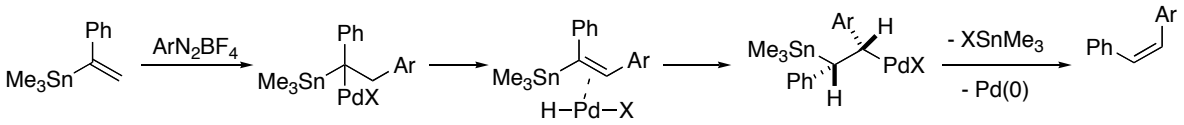


1.3.4 Cine Substitution in the Stille Cross-coupling Reaction

Especially relevant to the research programme presented in this thesis is the proposed involvement of a Pd carbene intermediate in the *cine* substitution occurring during Stille cross-coupling of bulky α-substituted alkenylstannanes. Putting this phenomenon in a historical perspective, Kikukawa and co-workers noticed prevailing substitution at the α-position of 1-phenyl-1-trimethylstannylethene in an attempted Stille coupling with aryldiazonium tetrafluoroborates. Formation of the *cis*-stilbene derivative was first explained by a sequence of steps involving carbopalladation of the vinylstannane by an arylpalladium(II) halide, followed by β-hydride elimination, hydropalladation of the diarylvinylstannane with reversal of

regiochemistry, and finally, destannapalladation, affording the trimethylstannyl halide with concomitant regeneration of the palladium catalyst (Scheme 1.19).[74]

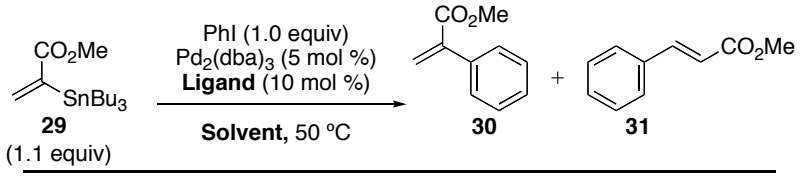
Scheme 1.19: Kikukawa's proposed *cine* substitution mechanism



A few years thereafter, two research groups proposed an alternative to Kikukawa's mechanistic hypothesis. Indeed, Kikukawa's diarylvinylstannane intermediate was never observed or isolated from the reaction. Busacca and co-workers systematically studied the anomalous Stille reactions of methyl α-(tributylstannyl)acrylate **29** and provided further evidence for a Pd carbene intermediate.[75] It was found that a 254:1 ratio of *cine* product, cinnamyl ester **31**, versus the expected Stille product, atropic acid ester **30**, was obtained using the $Pd_2(dba)_3/AsPh_3$ (1:4 Pd:ligand) catalyst system in tetrahydrofuran (THF) with iodobenzene as substrate at 50 ºC. In control experiments, neither conversion from *cine* product **31** to Stille product **30** nor the opposite transformation was observed. As well, α-stannane **29** was shown not to convert to the β-derivative under the reactions conditions. Of note, polar solvents mediated formation of greater amounts of **31** while still favouring the *cine* adduct **30** (Table 1.3, entry 2) whereas combinations of less polar THF or benzene solvent with ligands more electron-poor than triphenylphosphine (entry 6) favoured **31**.

2,2-Dideuterio-1-tributylstannylacrylate d_2-**29** was prepared, and led to methyl 2,3-dideuteriocinnamate d_2-**31** in 59% overall yield (Scheme 1.20). Based on the observed 1,2-deuterium shift and the previous optimisation studies, a new mechanism was proposed. Whereas transmetalation of phenylpalladium(II) iodide with α-stannylacrylate **29** would lead to normal product d_2-**30**, migratory insertion of σ-arylpalladium(II) would lead to a *gem*-bismetallic intermediate, methyl 1-iodopalladio-2-dideuterio-3-phenyl-1-tributylstannylpropanoate **32**. The latter could undergo deiodotributylstannylation to palladium acylcarbene intermediate **33**, from which 1,3-deuteride shift would afford **34**. Reductive elimination of deuteride from the latter would provide the labeled *cine* product d_2-**31**.

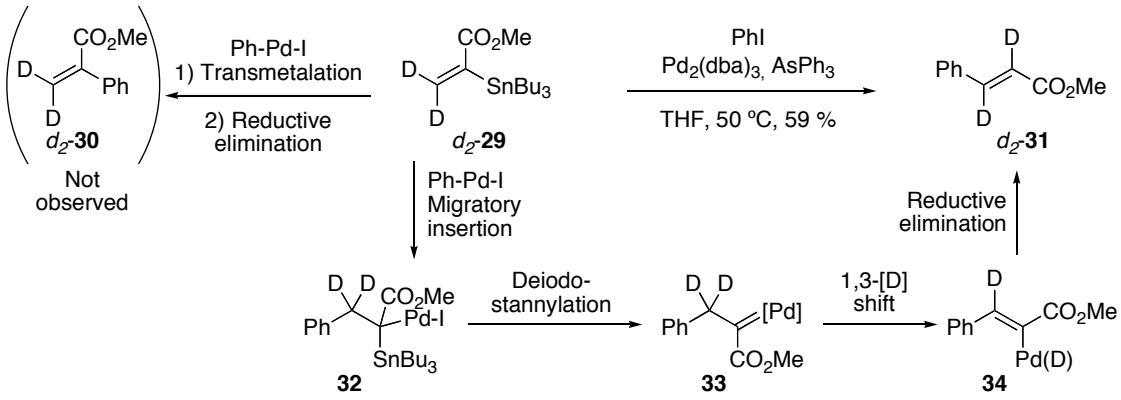
Table 1.3: Solvent and ligand effects in Busacca's mechanistic study of *cine* substitution



Entry	Ligand	Solvent	Ratio (**30**:**31**)[a]
1	None	THF	1:5.4
2	$AsPh_3$	NMP	1:4.3
3	$AsPh_3$ + Et_3N	PhH	1:55
4	$AsPh_3$	PhH	1:213
5	$AsPh_3$	THF	1:254
6	PPh_3	THF	N/R
7	P(pfp)Ph_2	THF	<1:300
8	P(2-furyl)$_3$	THF	<1:300

[a] Determined by GC-MS. [b] NMP = *N*-methylpyrrolidinone; pfp = pentafluorophenyl.

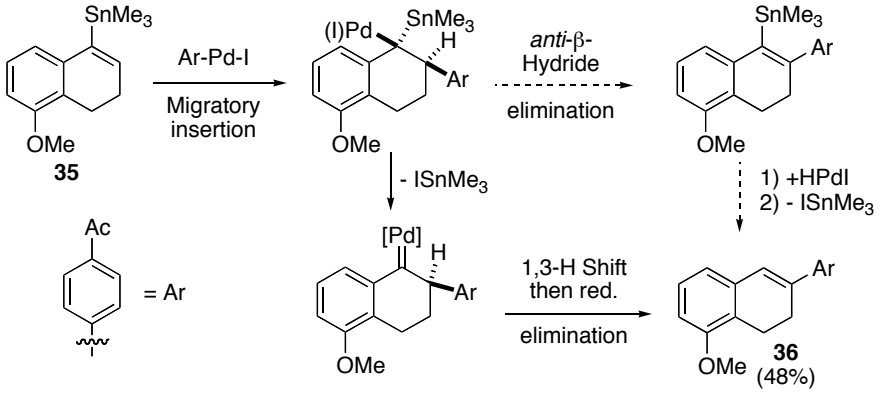
Scheme 1.20: Deuterium-labeling studies of *cine* substitution by Busacca *et al.*



Scrutinising the work of Busacca *et al.*, Farina and Hossain[76] remarked that not only deuterium incorporation but also regiochemistry could be explained in Kikukawa's terms using Busacca's acyclic system. To build further evidence towards Busacca's proposal, Farina conceived a cyclic system, for which Kikukawa's proposed β-hydride elimination/hydropalladation would necessitate *anti*-hydride elimination.[77] Although uncommon, *anti*-β-hydride elimination[78] was described as "a theoretically disfavoured pathway, which has nonetheless been invoked previously" to explain certain Pd-catalysed reactions. Strongly supporting Busacca's mechanism,

with cyclic 1-(trimethylstannyl)-5-methoxy-3,4-dihydronaphthalene **35**, Farina observed the exclusive formation of the 2-aryl-5-methoxy-3,4-dihydronaphthalene **36** (Scheme 1.21).

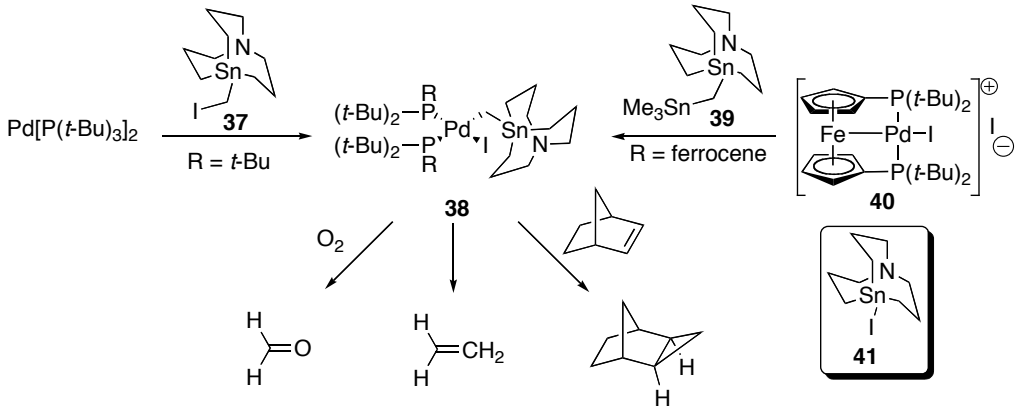
Scheme 1.21: Farina's cyclic system for the study of the *cine* substitution mechanism



As stated by Fillion and Taylor in 2003: "The synthetic importance of the Stille coupling demands that the *cine*-substitution mechanism be clearly established."[79] In order to definitively close the argument, iodomethylstannatrane **37** was synthesised. For this simplified substrate,[80] the putative palladium carbene 1,3-hydride shift would be inaccessible. The observation of typical reactivity for metal carbenes, namely cyclopropanation and dimerisation, should therefore be possible.

When the decomposition of iodomethylstannatrane was achieved in the presence of 25 mol % $Pd[P(t\text{-}Bu)_3]_2$ in C_6D_6, nuclear magnetic resonance (NMR) experiments showed the formation of ethylene; this product was attributed to methylene carbenoid dimerisation (Scheme 1.22). Gratifyingly, when the same decomposition was carried out in presence of five equivalents of norbornene, the corresponding *exo*-[2+1] cycloadduct was formed in 64% yield.[81] Fillion's further observation of formaldehyde was in agreement with McCrindle's oxidation of chloromethylpalladium(II) chloride carbenoid complexes to CH_2O under an air atmosphere.[82] In all those experiments, iodostannatrane by-product **41** was generated stoichiometrically, as evidenced by ^{1}H and ^{119}Sn NMR. Lastly, the 1-iodopalladio-1-trialkylstannylmethane intermediate could also be derived by stoichiometric transmetalation of trimethylstannylmethylstannatrane **39** with palladium(II) iodide complex **40**, rationally designed to induce *cis*-conformation in the resulting complex **38**.

Scheme 1.22: Fillion's evidence for a Pd carbenoid in the *cine* substitution mechanism



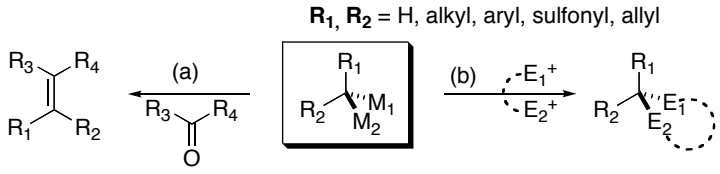
Such extensive evidence gathering has lead to wide acceptance of the Busacca-Farina mechanism for the *cine* substitution in the Stille cross-coupling of sterically demanding vinylstannane reagents. Furthermore, it has central consequences to this thesis research proposal, expanding fundamental knowledge. The work of Busacca, Farina and Fillion establishes carbopalladation of σ-alkyl and -arylpalladium(II) intermediates into alkenylmetallic reagents as means of producing *gem*-disubstituted halopalladio(II)/trialkylstannylalkane intermediates. Those approaches involved substoichiometric amounts of Pd, thereby demonstrating the feasibility of a catalytic cycle.

Recalling section 1.2.1.3, which discussed the overwhelming importance of the intramolecular Heck reaction for the synthesis of all-carbon benzylic quaternary stereogenic centres, it remains to be explored whether a union of the two aforementioned processes, migratory insertion and dehalopalladation of a *gem*-dimetallic intermediate, would permit the synthesis of highly functionalised molecules. Before such a research project is undertaken, it is valuable to look whether similar approaches have been realised thus far in organic synthetic method discovery.

1.4 Geminal Dimetallic Reactive Intermediates

Marek and Normant have reviewed the synthesis and reactivity of sp^3 *gem*-disubstituted organodimetallic reagents.[83] As well, Normant has provided an account of their synthetic application in the elaboration of di- or trisubstituted linear molecules.[84] *gem*-Organobismetallic reagents, more specifically 1,1-dilithioalkanes, have been first reported by Wittig in 1944,[85] and the application of their homologues in olefination reactions of aldehydes and ketones have been known ever since. Examples include the Tebbe[86] and Petasis[87] methylenation agents, as well as the Nozaki[88] and Lombardo,[89] Takai-Utimoto,[90] Nysted[91] or Peterson[92] olefination reagents (Scheme 1.23a). Worthy of note is that most of those olefination reagents are heterodimetallic, that is, they contain two different metallic partners.

Scheme 1.23: *gem*-Organobismetallic reagents in organic synthesis



(a) Olefination reagents

M_1 = $TiClCp_2$, **M_2** = $AlMe_2$ (Tebbe, Petasis)
M_1 = $TiClCp_2$, **M_2** = ZnX (Nozaki, Lombardo)
M_1 = **M_2** = CrX_2, ZnX (Takai, Utimoto, Nysted)
M_1 = Li, **M_2** = $SiMe_3$ (Peterson)

(b) Dialkylating agents

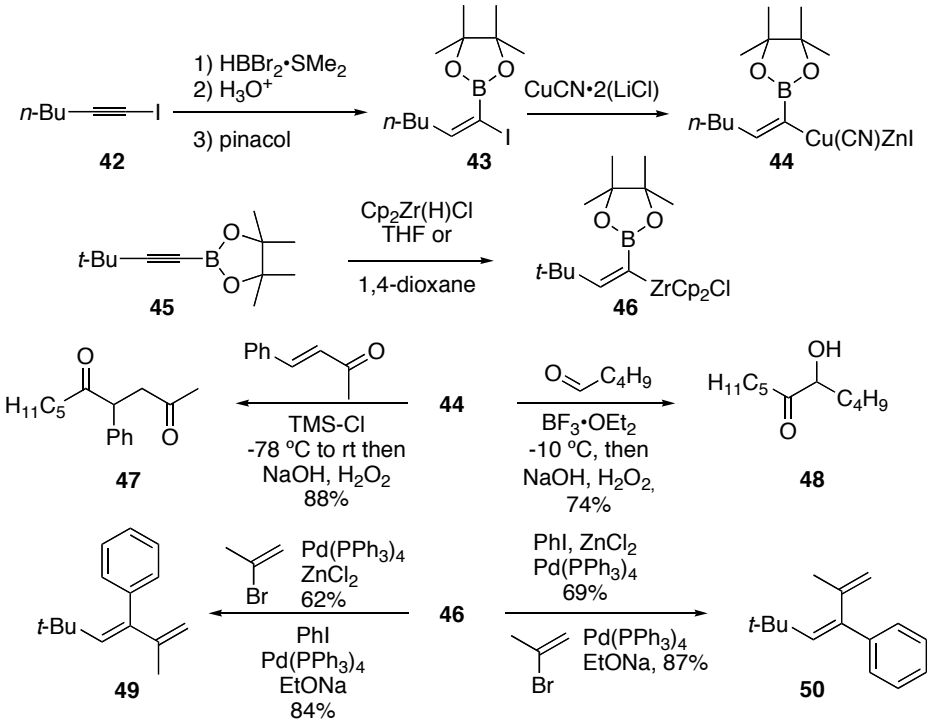
M_1 = **M_2** = Li
M_1 = **M_2** = MgX
M_1 = BR_2, **M_2** = Li
M_1 = BR_2, **M_2** = ZnX
M_1 = BR_2, **M_2** = $ZrCp_2Cl$

Conversely, lithium-, magnesium- and boron-based *gem*-organobismetallic reagents, either homo- or heterodimetallic, have been utilised for sequential functionalisation of their carbon-metal bonds with electrophiles. In the case of tethered, unsymmetrical electrophiles, for instance 1,n-alkyl dihalides (n>2), in presence of heterodimetallic intermediates, this methodology has led to the formation of carbocycles bearing all-carbon tertiary and quaternary stereocentres (Scheme 1.23b). Diasteroselectivities achieved in sequential electrophile incorporation are typically modest. As well, a drawback to those methods is the strongly basic conditions and the cryogenic temperatures often necessary for the stoichiometric generation of

the *gem*-dimetallic species. As well, the resulting dimetallic is itself a strong base that displays incompatibility with certain organic functional groups.

The synthesis and reactivity of the corresponding sp^2-hybridised *gem*-organodimetallic alkanes was reviewed by Marek.[93] Again, it was demonstrated that they behave as bis-nucleophilic synthons, and in the case of heterodimetallic species, the distinct reactivity of their carbon-metal bonds can be used to mediate sequential carbon-carbon bond formation. For instance, Knochel has reported that *gem*-boriocuprioalkene **44** can be reacted in a multitude of schemes.[94] Shown in Scheme 1.24 are the conjugate addition of **44** to benzylideneacetone and the BF_3•OEt_2-promoted addition to pentanal, followed by oxidation of the carbon-boron bond to the enol, which tautomerises to ketones **47** or **48**. *gem*-Boriozirconioalkenyl species **46**, very similar to **44**, can be prepared by hydrozirconation of the alkynylboronate **45**. The advantage of this approach is the high functional group tolerance of the latter reaction combined with the ease of preparation of the alkynylpinacolborane reagent.[95] The more reactive vinylzirconium species can be used to effect further functionalisation. For example, iodinolysis provided the resulting (*E*)-iodovinylboronic esters. Alternatively, the two distinct carbon-metal bonds can be put to contribution in Pd-catalysed cross-couplings. Depending on their order of performance, sequential Negishi and Suzuki cross-couplings stereospecifically led to diastereomeric 1,3-dienic compounds **49** and **50** in good yields for the two steps.

Scheme 1.24: Formation of reactivity of 1,1-boriozincio- and 1,1-boriozirconioalkenes



Importantly, the *gem*-organobismetallic reagents reviewed by Marek and Normant display a *bis*-nucleophilic reactivity. However, despite their synthetic potential, they all require the stoichiometric formation and reaction of the bismetallic species.

1.5 Research Objectives

This research undertaking is directed at the catalytic formation and reactivity of geminal palladium(II)/main group metal organobismetallic species. At the outset, strategies for the formation of geminal dimetallic halopalladio(II)/main group metal alkane intermediates will be explored. It is envisaged that the resulting *gem*-dimetallic alkane will adopt a distinct behaviour from the known bis-nucleophilic "geminated" organodimetallic synthetic intermediates discussed by Marek and Normant. Altering both the transition and main-group metal partners should tune the reactivity of the bismetallic complex. Foremost, based on the

intervention of a low-valent transition metal, a catalytic cycle, better suited for sustainable development, is expected.

Once those reactivity patterns are established, synthetic applications are desirable. Should the bismetallic complex adopt carbenoid behaviour, standard carbene reactivity is expected, namely olefin cyclopropanation, dimerisation and C-H insertion processes. Ultimately, new carbon-carbon bond forming methods, whose applications may well be yet unknown, will be passed on to the synthetic organic community.

1.6 Thesis Statement

This *Ph. D.* thesis presents the development of catalytic routes to geminal dimetallic palladium(II)/trialkylstannyl and dialkylalumino alkane complexes, the exploitation of the distinct reactivity and the synthetic relevance of those organodimetallic intermediates.

It is shown herein that oxidative addition of Pd(0) complexes to 1-tributylstannyl-2-propenyl acetates leads to *gem*-dimetallic allylpalladio(II)/tributylstannylalkane intermediates. The ambiphilic nature of those intermediates is then demonstrated. Electron-rich phosphine ligands exposed their nucleophilic behaviour in the presence of Brønsted acids. As well, how phosphine-free palladium catalysts induce reactivity upheaval, leading to palladium-alkenylcarbene species that take part in dimerisation and strained alkene cyclopropanation reactions, is shown. Finally, the dramatic effect upon the outcome of the transformation exerted by the transition metal catalyst (Pd^0 versus Rh^I) used to activate an ambiphilic synthon is showcased.

This thesis also demonstrates that *gem*-organodimetallic (pseudo)halopalladio(II)/ dialkylaluminoneopentane intermediates are accessed via intramolecular carbopalladation of 2,2-disubstituted-1-alkenyldialkylalane species. Sequential, stereospecific functionalisation of two organometallic bonds, C-Al and C-Pd is accomplished in a tandem three carbon-carbon bond-forming arylation/1,2-alkyl migration sequence. It is shown that reaction parameters such

as tether length, Lewis-basic additive, solvent, phosphine ligands, aryl substitution pattern as well as the very nature of the substrate (aryl versus naphthyl halide or pseudohalide) determine not only the reaction outcome but also the mechanism whereby formation of benzo- and naphthocyclic products takes place.

Chapter 2 – Formation and Reactivity of sp^3-*gem*-π-Allylpalladio(II)/Tributylstannylalkane Intermediates

2.1 Introduction

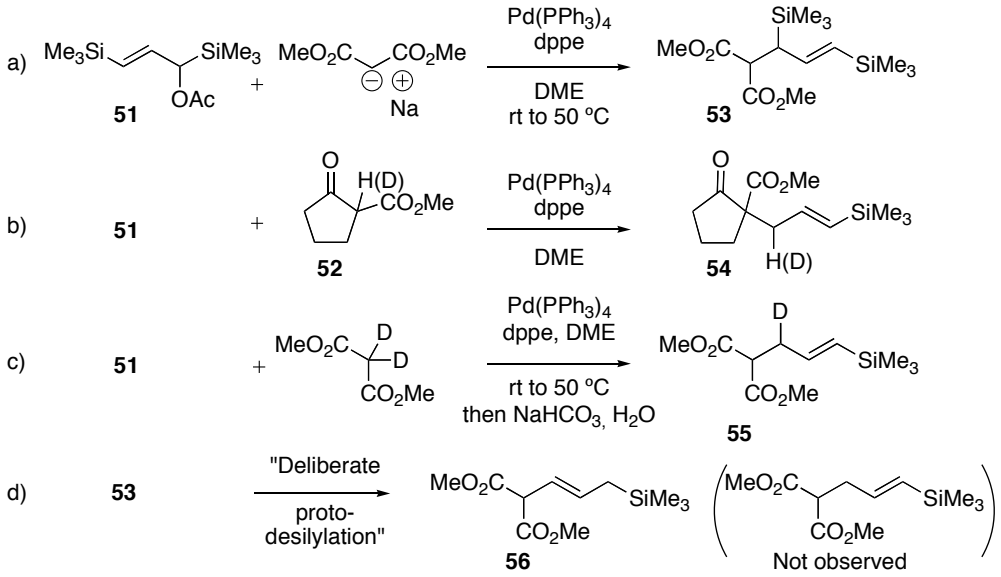
As shown in section 1.3.4, the Fillion laboratories have contributed to the body of evidence for *gem*-organodimetallic iodopalladio(II)/trialkylstannylalkane intermediates, shedding light on the reaction mechanism for the competing *cine* substitution pathway of Stille cross-coupling reactions involving 1-substituted-1-alkenylstannanes. The intermediacy of Pd/Sn carbenoid species was inferred from reactivity such as dimerisation, strained alkene cyclopropanation and oxidation. Methylene transfer agents, iodomethyltrialkylstannanes were employed, where the trialkyl- constituent was either stannatrane, trimethyl- or tributylstannane.

Extension of this new alkylidene transfer strategy to the formation and reactivity of vinyl-stabilised carbenoid intermediates would complement the available methods based on diazoalkane decomposition by metal salts. To widen its scope, not only carbene dimerisation and [2+1] cheletropic reactions but also C-H insertion reactions should be achieved with the same substrate, by simply altering the transition metal catalyst.

2.1.1 α-Deacetoxysilylation

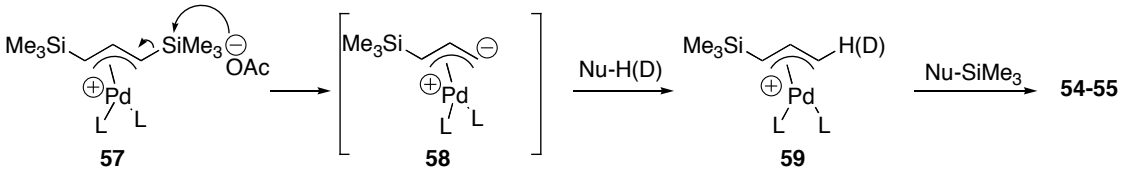
Surveying the literature, in 1983, Trost and Self disclosed a Pd-catalysed formal malonate C-H insertion process utilising α,γ-bis(trimethylsilyl)allyl acetate **51**.[96] When nucleophiles such as 2-carbomethoxycyclopentanone **52** and dimethyl malonate were first treated with NaH then with **51**, the expected allylic substitution products were isolated (Scheme 2.1b), retaining both silanes. Contrariwise, when neutral reaction conditions were employed, an apparent C-H insertion product was obtained, as evidenced by deuterium labeling. It is noteworthy that yields were not reported for the transformations referred to therein, nor were the full experimental procedures delineated. The authors ascertained that products and starting materials were inert to protiodesilylation, and that $AcOSiMe_3$ was therefore eliminated prior to allylic alkylation. Moreover, "deliberate proto-desilylation" of **53**, for which no experimental conditions were specified, yielded allylic silane **56** instead of the expected vinyl(mono)silane (Scheme 2.1d).

Scheme 2.1: Pd-catalysed allylic substitution of 1,3-bis(trimethylsilyl)prop-2-enyl acetate



Based on the available evidence, the apparent C-H insertion adducts **54-55** were explained with the intervention of Pd-stabilised vinylcarbenoid species **58** (Scheme 2.2). After oxidative addition of the allylic acetate **51** to Pd(0), the acetate displaces a trimethylsilyl substituent, leaving vinylcarbenoid intermediate **58**. The latter adopts nucleophilic behaviour in the presence of the Brønsted-acidic malonate or β-ketoester, abstracting a proton, thereby releasing a silylketene acetal nucleophile, which reacts with the allylpalladium(II) complex, forming the C-C bond and regenerating the catalyst.[97] Only one alkenysilane regioisomer was reported in each case.

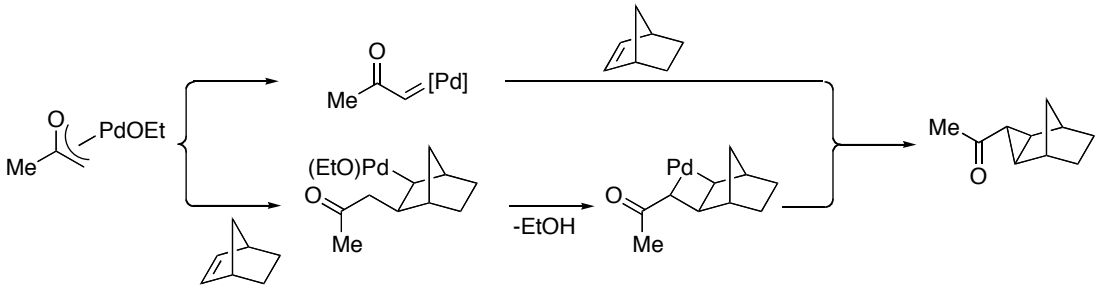
Scheme 2.2: Proposed mechanism for Pd-stabilised vinylcarbene generation



2.1.2 Oxa-π-allyl Approach

Murai and co-workers have suggested that an oxa-π-allylpalladium(II) intermediate, catalytically generated from acetonyl ethyl carbonate in the presence of $Pd(PPh_3)_4$ in DMF at 120 ºC, gave rise to a Pd carbene in the cyclopropanation of bicyclo[2.2.1]heptane derivatives (Scheme 2.3).[71] The authors also proposed a carbopalladation of norbornene to explain the acylcyclopropane products, but their experimental evidence negated neither pathway. To the author's knowledge, Trost's and Murai's reports are the only ones suggesting Pd-stabilised carbenes are formed from π-allyl intermediates.

Scheme 2.3: Oxa-π-allylpalladium(II) approach to a Pd-carbene intermediate

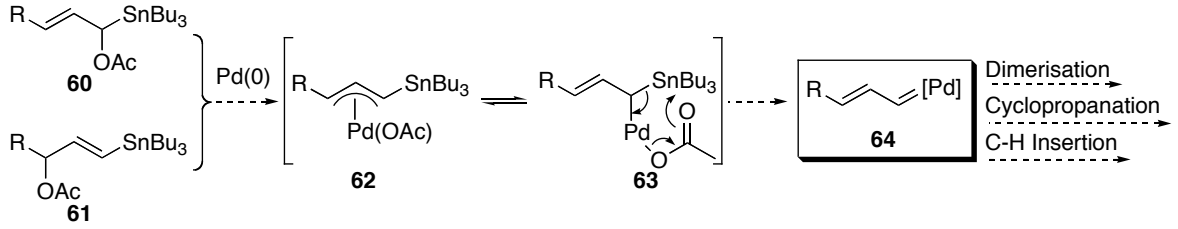


2.1.3 Research Outline

The Pd-complexed vinylcarbene described by Trost and Self was reminiscent of a nucleophilic metal carbene in its failure to undergo typical carbene reactions. As well, Trost was unable to trap the putative vinylcarbenoid by nucleophilic addition to aldehydes, and since his preliminary report, no further investigation was published. Deeper study of the formation and reactivity of Pd-stabilised vinylcarbenes is therefore required. Stannanes are known to transmetalate more readily than the corresponding silanes. It was surmised that the combination of Fillion's dehalostannylation approach to Pd carbenoid intermediates with Trost's report would furnish an alternate entry into Pd vinylcarbenes, from α-tributylstannyl allylpalladium(II) derivatives (Scheme 2.4). Treatment of either substrate, **60** or **61**, with a

Pd(0) catalyst would provide a common π-allylpalladium(II) acetate **62**, in equilibrium with σ-allyl **63**. The latter would collapse to Pd-stabilised vinylcarbene **64** following deacetoxystannylation. The reactivity of the resulting palladium-stabilised vinylcarbene species would then be investigated: it was expected to take part in standard carbene reactions, namely dimerisation, alkene [2+1] cheletropic cycloadditions, as well as C-H insertion.

Scheme 2.4: Research proposal



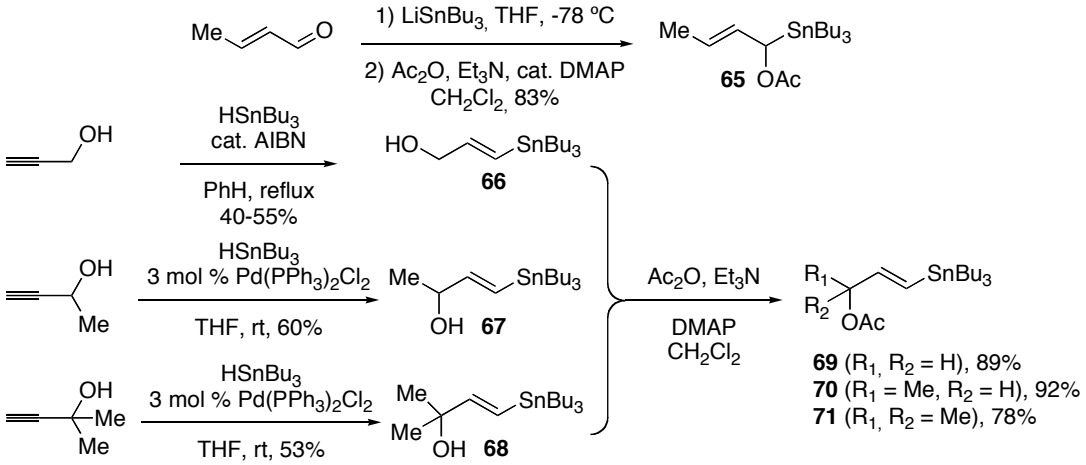
2.2 Allylation of Dimethyl Malonate

To supplement the studies by Trost, unsymmetrical alkyl-substituted substrates were prepared from commercially available starting materials (Scheme 2.5). Addition of lithium tributylstannide onto crotonaldehyde, followed by acetylation gave **65** in 83% yield for the reported procedure.[98] Addition of $HSnBu_3$ to 2-propyn-1-ol typically provided the (*E*)-stannylalkenol **66** in 40-55% yields.[99] Palladium-catalysed hydrostannylation of β-alkynols[100] provided access to β-tributylstannylalkenols **67** and **68**. Alcohols **66**-**68** were then acetylated to yield substrates **69**-**71**.

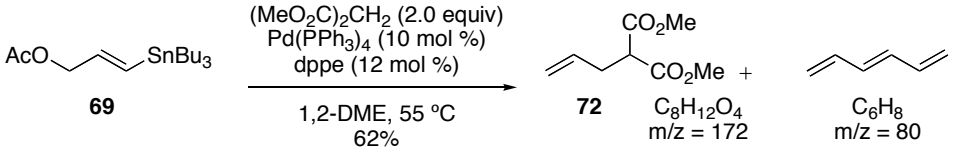
The reaction conditions described by Trost and Self were first applied to the reaction of propenyl substrate **69** with dimethyl malonate (Equation 2.1). Upon heating in the presence of 10 mol % $Pd(PPh_3)_4$, 12 mol % dppe[101] and 2.0 equiv of $(MeO_2C)_2CH_2$, at 55 ºC in 1,2-dimethoxyethane (DME), complete consumption of the stannylated starting material was observed by TLC after one h. Gas chromatographic/mass spectrometric (GC-MS) analysis of the crude composition revealed a product of the expected molecular mass corresponding to

malonate addition onto **69** (m/z = 172) with loss of $AcOSnBu_3$. As well, peaks of low retention times, attributed to species of molecular ion (80) corresponding to dimerised vinylcarbene products, were seen. While analysis by ^1H NMR of the concentrated mixture did not show the volatile hexatrienes, the characteristic peaks for dimethyl (2-propenyl)malonate **72** were displayed, and the latter could be isolated in 62% yield after column chromatography.

Scheme 2.5: Preparation of propenyl and butenyl substrates for the malonate studies



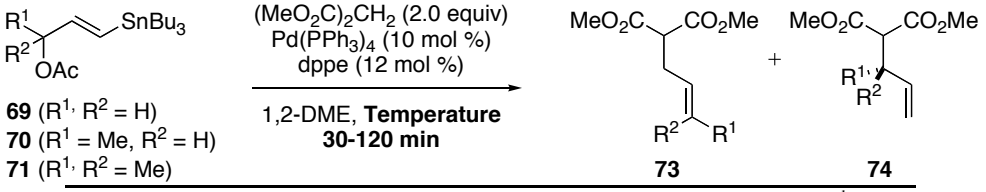
Equation 2.1: Initial results with dimethyl malonate



Encouraged by that initial result, alkenyl acetates **65**, **70** and **71** were then submitted to the same reaction conditions (Table 2.1). Mixtures of inseparable linear and branched allylated malonate **73** and **74** were isolated, with similar ratios arising from stannanes **65** and **70** (entries 2 and 3). As before, yield-limiting dimerisation to volatile 2,4,6-octatrienes was evidenced by GC-MS analysis. Finally, *gem*-dimethyl substrate **71** would not form a π-allylpalladium(II) complex, despite prolonged heating to reflux (entries 4-5), and starting material was quantitatively recovered. Heating to 55 ºC was required for malonate reaction with **70**; at 40 ºC, 6% of regioisomer mixture was isolated, and at 23 ºC, only dimerised products were

observed following TLC analysis (entries 6-7). When phosphine-free $Pd(dba)_2$ replaced $Pd(PPh_3)_4$ and dppe (entry 8), substrate **70** was quantitatively consumed, yet only dimerised products were seen by GC-MS analysis of the crude mixture.

Table 2.1: Pd-catalysed allylation of dimethyl malonate with deacetoxystannylation



69 (R^1, R^2 = H)
70 (R^1 = Me, R^2 = H)
71 (R^1, R^2 = Me)

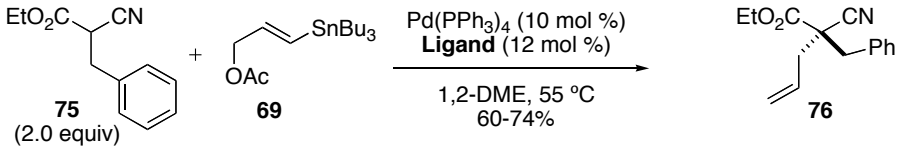
73 **74**

Entry	Substrate	Temperature (ºC)	Products (ratio)[a]	Yield[b] (%)
1	**69**	55	**72** (N/A)	62
2	**65**	55	**73**:**74** (68:32)	53
3	**70**	55	**73**:**74** (62:38)	31
4	**71**	55	N/A	N/R
5	**71**	85	N/A[c,d]	N/R[d]
6	**70**	40	**73**:**74** (61:39)	6
7	**70**	rt	N/A[d]	N/A[d]
8[e]	**70**	55	N/A[d]	N/R[d]

[a] Determined by ^{1}H NMR. [b] Isolated yield of regioisomer mixture.
[c] For 20 h. [d] No product detected. [e] Using 10 mol % $Pd(dba)_2$.

An extension of this C-C bond forming methodology to all-carbon quaternary stereocentre construction was demonstrated using ethyl 2-cyano-3-phenylpropanoate **75** (Scheme 2.6). Utilising dppe as ligand, 60% yield of allylated product **76** was obtained. Reaction yield could further be increased to 74% by substituting (*S*)-BINAP for dppe, but no enantiomeric excess was observed in this unoptimised reaction.

Scheme 2.6: Quaternary stereocentre formation by Pd-catalysed malonate allylation

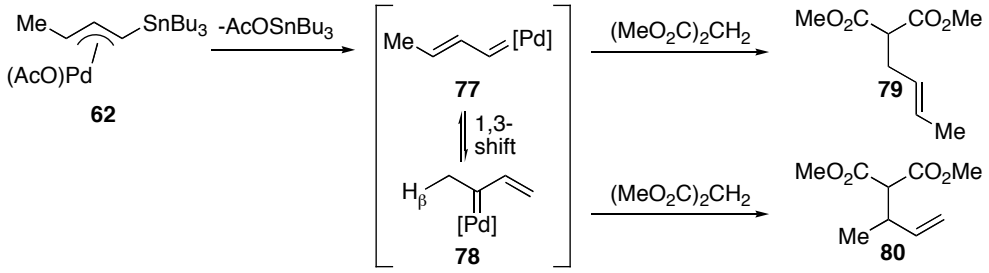


75 (2.0 equiv) **69** **76**

To rationalise the observed reactivity, a mechanistic hypothesis was proposed. The mixture of linear and branched allylation products may arise from vinyl-substituted palladium carbene **77**, followed by 1,3-carbene shift leading to vinyl-stabilised metal carbene **78**.[102] Then, C-H bond insertion would lead to the observed reaction products, linear **79** and branched **80**. The

presence of β-hydrides on Pd carbene **78** was expected to lead to the observation of side-processes.

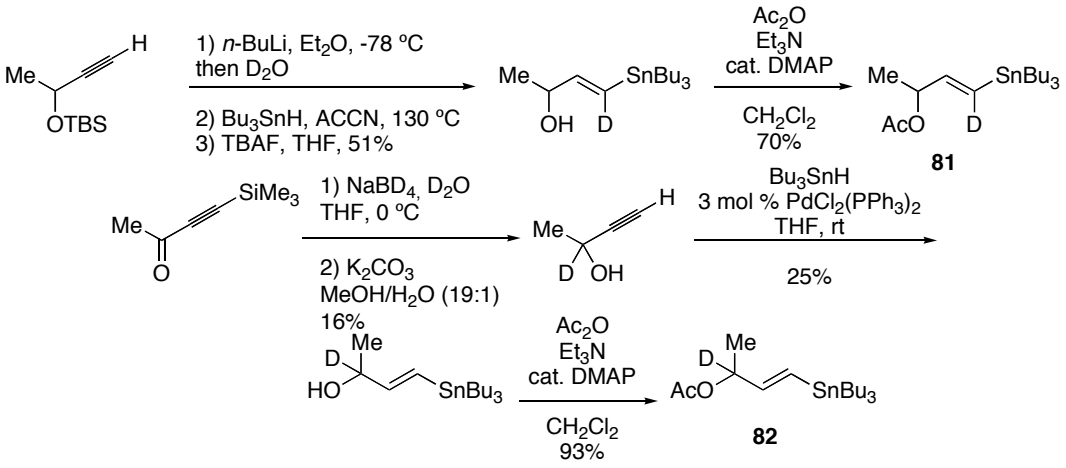
Scheme 2.7: Mechanistic working hypothesis



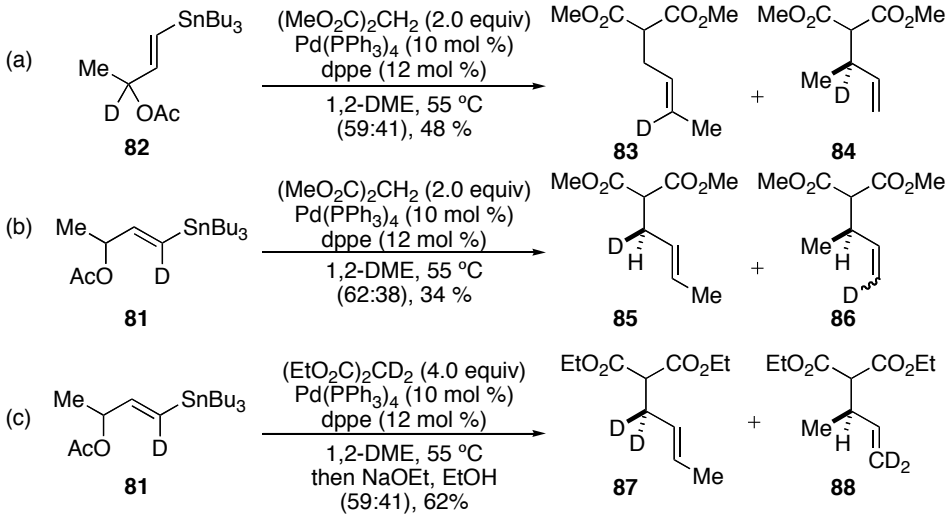
Deuterium labeling would shed light on the intervention of a 1,3-shift. Indeed, if it were the actual pathway, label scrambling should take place, leading to common products from α- and γ-labeled substrates, perhaps even altering product ratios due to kinetic isotope effects.

Deuterium-labeled analogues of **70** were thus prepared as described in Scheme 2.8, to probe Pd [1,3]-carbene shift. Efficient alkyne deuteriation (>99% *D*-incorporation) occurred using 2-(*tert*-butyldimethylsilyloxy)-3-butyne. ACCN-Initiated radical hydrostannation was conducted according to the literature procedure,[103] followed by TBAF desilylation and acetylation, to yield 4-deuterio substrate **81**. In order to label the carbinol position, 4-trimethylsilyl-3-butyn-2-one was reduced with $NaBD_4$ in anhydrous THF containing D_2O. After protiodesilylation of the terminal alkyne with K_2CO_3 in methanol, distillation of the volatile alkynol under reduced pressure, hydrostannation and acetylation, 2-deuterio substrate **82** was obtained. Overall, both acetates were produced with >98% *D*-incorporation.

Scheme 2.8: Preparation of deuterium-labeled substrates



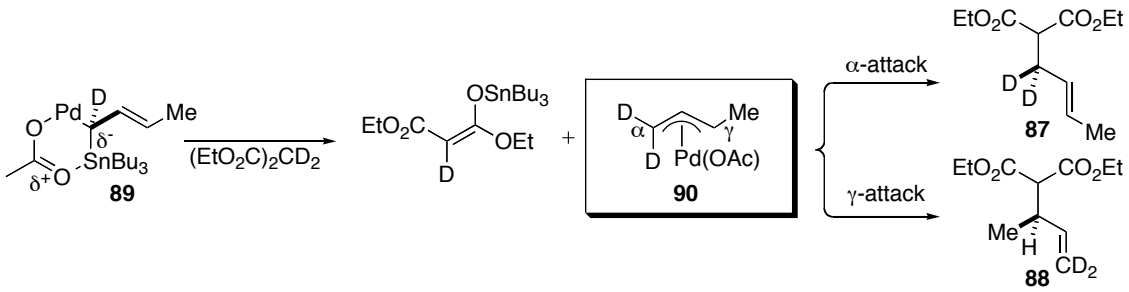
Scheme 2.9: Deuterium-labeling experiments



The substrates were then reacted with dimethyl malonate. Comparing integration values with the parent compounds, ^{1}H NMR was used to identify reaction products, confirmed by ^{2}H NMR. From the 4-deuterio stannane **81**, the expected product mixture was obtained in a 62:38 ratio (**85**:**86**) and 34% combined yield of the regioisomer mixture (>99% D incorporation, Scheme 2.9b). The experiment with **82** yielded **83** and **84**, in a 59:41 ratio, 48% yield and quantitative deuteriation (Scheme 2.9a). Lastly, reaction of 4-deuterio substrate **81** in the presence of 4.0 equiv of d_2-diethyl malonate and 10 mol % of the usual $Pd(PPh_3)_4$/dppe catalytic system, followed by back-exchange of the acidic deuterons with EtOH in the presence of NaOEt, gave

a 59:41 ratio of **87** and **88** (86-89% deuteriation, 62% yield, Scheme 2.9c). The ratios of linear and branched products were essentially similar in the labeling experiments. The absence of isotopic scrambling negated the intervention of a Pd-carbene [1,3]-shift.An updated mechanistic proposal is shown in Scheme 2.10. *gem*-Organobismetallic vinylcarbenoid species **89** is proposed, its nucleophilic nature conceivably enhanced through acetate complexation. After protiodestannylation (deuteriodestannylation), π-allylpalladium(II) complex **90** is released, along with the resulting stannylketene acetal; this path is supported by protonation regioselectivity. Since no malonate allylic substitution took place when $Pd(dba)_2$ was used as catalyst, electron-rich palladium(II) species are likely intermediates.

Scheme 2.10: Proposed reaction mechanism



The ratio of observed products directly correlates with steric interactions experienced with the α- or γ-substituents of **90**, leading to **87** and **88**, respectively. Steric influence upon nucleophilic attack on allylpalladium(II) complexes is substantiated in the literature in the absence of bulky ligands,[104] and is mirrored in the ratio of linear to branched products observed. Despite forcing reaction conditions (Table 2.1, entries 4-5), no reaction was observed with *gem*-dimethyl substrate **71**, designed to augment steric interactions in **90**. Plausibly, the 1,1,3-trisubstituted allylic acetate **71** experienced too much steric repulsion for Pd(0) to form the π-complex, leading to starting material recovery.

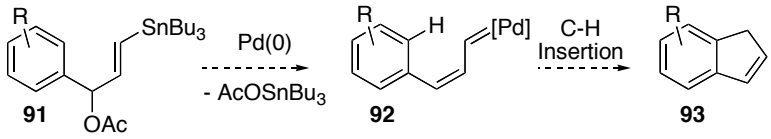
2.3 Dimerisation and C-H Insertion Reactions

In the previous section, a method for the formation of *gem*-dimetallic intermediates, involving oxidative addition of a palladium(0) complex to 1- and 3-tributylstannyl-2-alkenyl acetates, was established. The carbenoid nature of allylpalladio(II)/tributylstannylalkane species was inferred by observing sequential reaction of their C-M bonds in a nucleophilic (C-Sn) and electrophilic (C-Pd) manner. Expanding the reactivity of the carbenoid species **89** thus formed to typical carbene reactions warranted further investigation. Among the expected cyclopropanation, insertion and dimerisation reactions, the latter were tackled first.

2.3.1 Substrate Synthesis and Initial Results

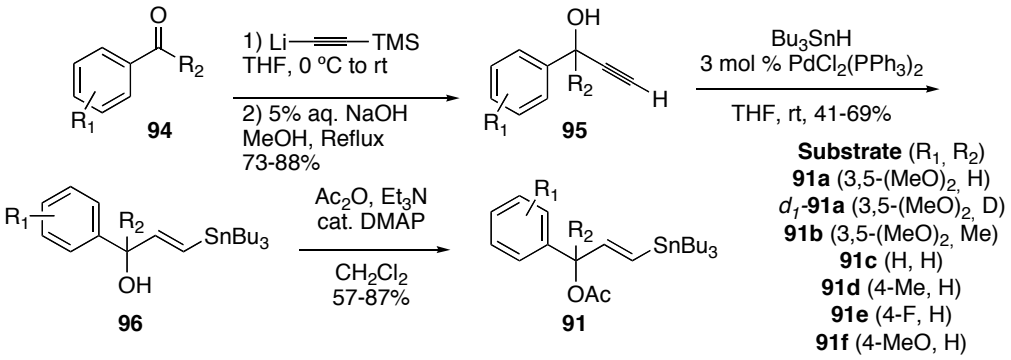
Previously, dimer formation was inferred from GC-MS evidence, yet dimers were never isolated due to volatility issues. Hence, heavier substrates **91a-f**, incorporating an aryl framework substituted with electron-donating or -withdrawing groups, were designed with a two-pronged objective: to provide a C_{aryl}-H bond for the proposed Pd-stabilised vinylcarbene to insert into, and to afford products whose higher molecular weight would simplify isolation.

Scheme 2.11: Proposed intramolecular C-H insertion reaction



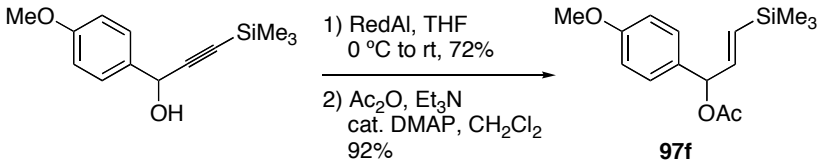
Substrates **91** would arise from Pd-catalysed hydrostannylation of 1-aryl-2-propyn-1-ols **95**, in turn derived from the addition of an acetylene surrogate to benzaldehyde, following a one-pot transformation established in the Fillion laboratories. 3,5-Dimethoxyacetophenone **94b** was the electrophile utilised to synthesise substrate **91b**. For the synthesis of *d*-**91a** (R_2=D), 1-deuterio(3,5-dimethoxyphenyl)methanal (*d*-**94a**) was used as electrophile (Scheme 2.12).

Scheme 2.12: Aryl substrates synthesis



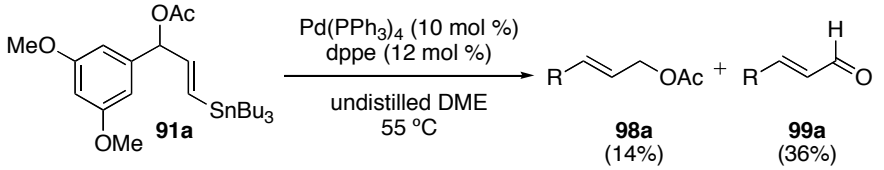
For comparison, vinylsilane **97f** was also prepared from the trimethylsilylalkynol, via stereoselective reduction followed by alcohol activation, as described in Scheme 2.13.

Scheme 2.13: Vinylsilane synthesis



With substrate **91a** in hand, C_{aryl}-H insertion studies were commenced. In undistilled DME, protiodestannylation side-product **98a** was isolated in 14% yield after 90 min, along with 36% of 3,5-dimethoxycinnamaldehyde **99a** (Equation 2.2). Although counter-productive as for C-H insertion, the isolation of **99a** demonstrated reaction of a palladium vinylcarbenoid species with oxygen.[82]

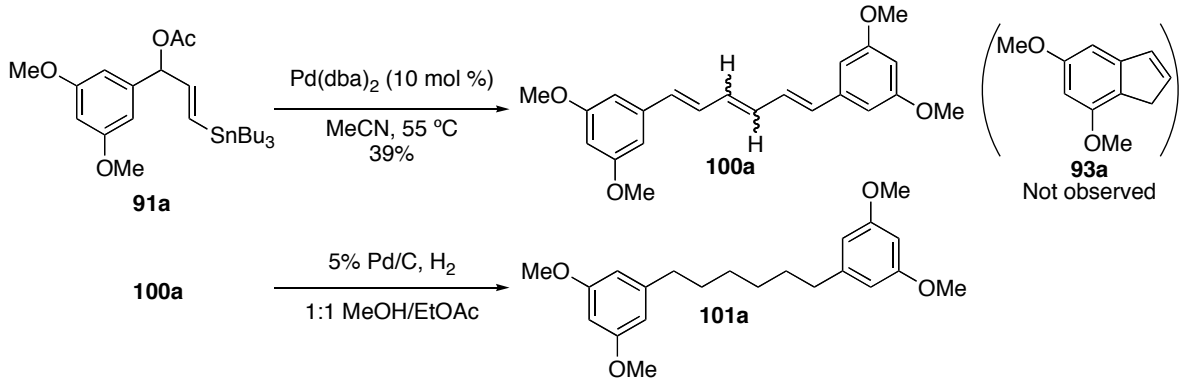
Equation 2.2: Reaction in undistilled DME



Using dry and oxygen-free solvent, C-H insertion studies were pursued. Disappointingly, utilising substrate **91a** under the previously employed conditions ($Pd(PPh_3)_4$/dppe, DME), the reaction produced only dimeric product **100a** in 53% yield with no detectable indene C-H

insertion product **93a**. That reaction was sluggish, taking 14 h to reach completion at 55 ºC. To render the palladium-carbene complex more electrophilic and favour C-H insertion, $Pd(dba)_2$ was used as catalyst in absence of phosphine, in either DME or acetonitrile (MeCN) as solvents, at 55 ºC. In 1,2-dimethoxyethane, dimerisation was sluggish, albeit clean, and none of the previous by-products were formed. In MeCN, it was a delight to observe complete and rapid conversion by TLC analysis. The dimeric structure was supported by GC-MS (m/z = 352) and ^{1}H NMR analysis of the crude reaction mixture, from which **100a** was isolated in 39% yield. Dimerised 1,6-diaryl-1,3,5-hexatrienes **100a** comprised double bond diastereoisomers in a 2:1 mixture that made structure determination ambiguous. Further substantiating structural assignment, hydrogenation of **100a** yielded exclusively 1,6-bis(3,5-dimethoxyphenyl)hexane **101a**, which showed the expected three aliphatic CH_2 signals by ^{13}C JMOD NMR. Thereby, it was conclusively established that only head-to-head diastereomeric dimers were formed, with no branched product to attest of a potential 1,3-carbene shift.

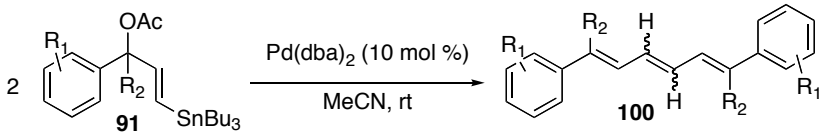
Scheme 2.14: Initial attempts at C_{aryl}-H insertion



Decreasing reaction temperature from 55 ºC to ambient, dimerisation was found to proceed in 30 min using 10 mol % $Pd(dba)_2$ in acetonitrile. The scope of the dimerisation process was explored, using substrates **91a-e** (Table 2.2). With 3,5-disubstituted arenes **91a** and **91b**, better yields of dimer were obtained than with phenyl substrate **91c** (entries 1-3). Substituents at the aryl-4 position, whether electron-rich or electron-poor, had a detrimental effect on reaction efficiency (entries 4-5). Insoluble materials were systematically observed in the last two

reaction mixtures, after a few min of stirring. The outcome was similar using a 9:1 $MeCN/CH_2Cl_2$ solvent mixture, attempting to increase solubility.

Table 2.2: Scope of the dimerisation reaction



Entry	Substrate	R_1	R_2	Yield (%)[a]
1	**91a**	3,5-(MeO)	H	78
2	**91b**	3,5-(MeO)	Me	92
3	**91c**	H	H	64
4	**91d**	4-Me	H	26
5	**91e**	4-F	H	22

[a]Isolated yield after column chromatography, averaged over at least two runs.

p-Methoxy-substituted stannane **91f** was also synthesised from *p*-anisaldehyde, yet complete decomposition occurred after less than one day of storage at 4 ºC. In contrast, vinylsilane **97f** was stable to storage at rt and to silica gel. Moreover, upon heating at 55 ºC in MeCN for 24 h, in the presence of 10 mol % $Pd(dba)_2$, ^1H NMR and TLC analysis indicated no formation of new products from vinylsilane **97f**. It was thus verified that tributylstannane substrates are more reactive than the corresponding trimethylsilanes.

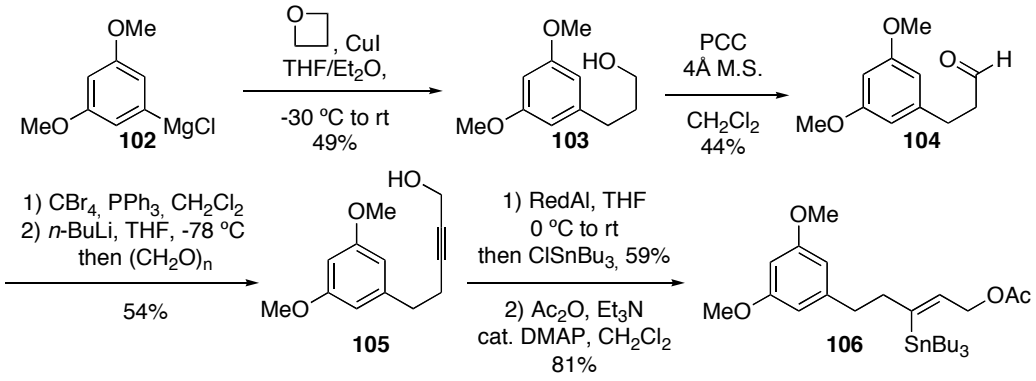
2.3.2 Second-generation Intramolecular C(sp^2)-H Insertion Substrates

In no dimerisation reaction cited above did C_{aryl}-H insertion compete with dimerisation to **100**. This hinted that, compared with intermolecular dimerisation, formation of the required (*Z*)-olefin necessary for intramolecular C-H insertion was disfavoured. For cyclisation to evade (*E*)-to-(*Z*) isomerisation, the Pd carbene should be disubstituted.

Thus, second-generation C_{aryl}-H insertion substrate **106** was synthesised (Scheme 2.15). 3,5-Dimethoxyphenylmagnesium chloride **102** was treated with oxetane in the presence of CuI[105] to afford the 1-propanol derivative in 49% yield and 59% conversion from the arylmagnesium chloride. Following PCC oxidation, Corey-Fuchs homologation[106] and intercepting the lithioacetylene with paraformaldehyde furnished alkynol **105**. The latter was stereoselectively

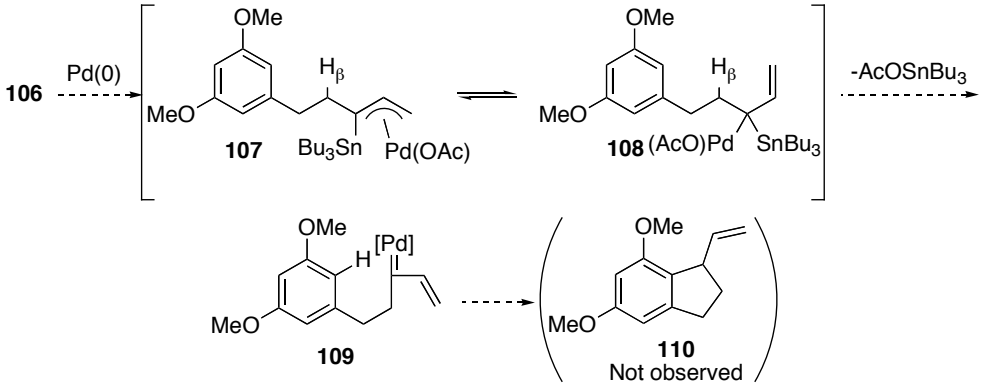
converted to the (*Z*)-trisubstituted stannylalkenol, via hydroxy-directed Vitride™ reduction and stannylation, which was acetylated to afford substrate **106**.

Scheme 2.15: Synthesis of second-generation C_{aryl}-H insertion substrates



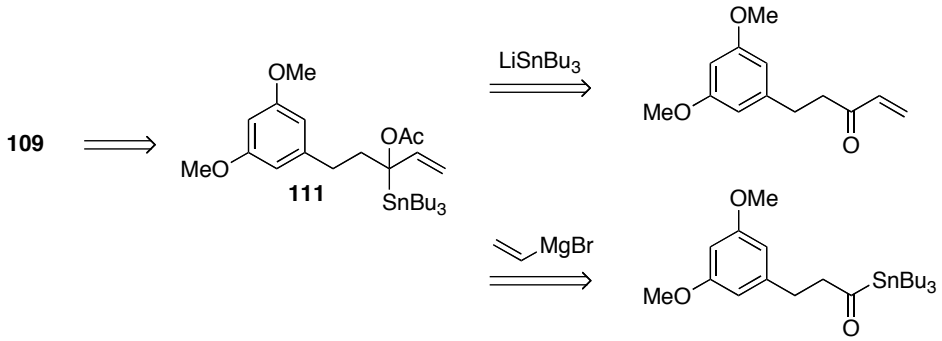
The C_{aryl}-H insertion studies were resumed using this second-generation cyclisation precursor. Utilising the previously productive $Pd(dba)_2$ or $Pd(PPh_3)_4$ catalysts in solvents such as toluene, DMF or MeCN, at 55 ºC for up to 24 h, no reaction was observed. Upon increasing reaction temperatures up to 110 ºC, extensive decomposition to intractable mixtures was found to occur. Displacement of the acetate leaving group by an S_N2' process gives rise to allylpalladium(II) complexes, with inversion of configuration.[107] In the case of **106**, olefin pre-complexation would be hampered by the bulky tributylstannane that would also cause steric hindrance with the nucleophilic Pd(0), precluding π-allylpalladium(II) complex **107** formation. If complexes **107** or **108** had actually been formed, then β-hydride elimination would have become a competing pathway with deacetoxystannylation. Yet no products derived from that process were detected.

Scheme 2.16: Rationalisation of second-generation substrate results



In light of the aforementioned results, the Pd-stabilised vinylcarbene precursors examined so far have not mediated intramolecular C-H insertion reactions. The two major reasons for this were: first, the inability to form a (*Z*)-palladium-stabilised carbene intermediate; second, the requirement that π-allylpalladium(II) intermediate formation occurs with S_N2' displacement, which is sterically hindered by the tributylstannanyl group. A solution may lie in substrate **111**, precursor to carbene **109**, and for which π-allyl complex formation may occur more readily due to reduced steric interactions leading to the desired allylpalladium(II) complexes **107** and **108** (Scheme 2.17). Substrate **109** has yet to be synthesised.

Scheme 2.17: Alternate routes to vinyl-stabilised Pd-carbene 109



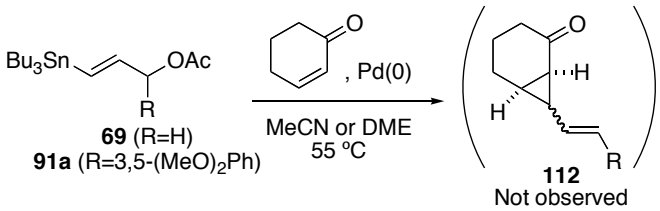
2.4 Cyclopropanation Reactions

Based on the previous observation of dimerised products, indicative of a vinyl-stabilised Pd-carbene intermediate, application of the same intermediates towards cyclopropanation reactions was next attempted. Tomilov's review of metal-catalysed diazomethane reactions[55] demonstrated that the Pd(II)/diazomethane system most effectively cyclopropanates electron-deficient as well as strained olefins. Research was therefore engaged in those two directions.

2.4.1 Transition Metal-catalysed Functionalisation of α,β-Unsaturated Carbonyl Compounds

Using unsubstituted alkenylstannane **69** under conditions previously shown to lead to Pd-carbenoid intermediates, the vinylcyclopropanation of cyclohex-2-en-1-one was studied. To a mixture of three to up to ten equiv of α,β-unsaturated ketone, heated to 55 ºC in either DME or MeCN in the presence of $Pd(PPh_3)_4$ (10 mol %) and dppe (12 mol %), was added substrate **69** over a range of addition times (2 min to 1 h). In all cases, ^1H NMR analysis of the crude mixture did show stoichiometric formation of tributyltin acetate along with recovered cyclohexenone and starting material disappearance. Again, GC-MS suggested the formation of hexatriene products, yet none of the previously characterised cyclohexanone bicyclo[4.1.0]heptanone adduct **112** was observed.[108] The reaction of aryl-substituted carbene precursor **91a** in the presence of 10 mol % $Pd(dba)_2$ and 3.0 equiv of cyclohexenone in MeCN (55 ºC) also failed to provide vinylcyclopropane products.

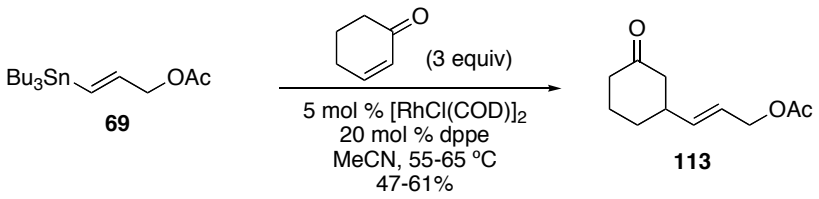
Scheme 2.18: Expected Pd-catalysed vinylcyclopropanation of cyclohex-2-en-1-one



This negative outcome indicated the nature of the carbenoid species in the work presented herein to be different from that intervening in the Pd(II)/CH_2N_2 cyclopropanation of enones and other electron-depleted olefins. To effect cyclopropanation, ruthenium[109] and rhodium[110] complexes, reported to form π-allyl complexes, were examined.

Initial attempts were made with ruthenium(II) complexes $RuClCp(PPh_3)_2$ and $RuCl_2(PPh_3)_3$ in the cyclopropanation reaction in MeCN at 55 ºC, yet no starting material consumption was observed after 24 h by TLC and ^{1}H NMR analysis. Pleasingly, using the rhodium source $[RhCl(COD)]_2$ in presence of a two-fold excess of dppe, quantitative conversion to a product more polar than cyclohexenone was observed. By ^{1}H NMR, comparison of the signals with the known **112** showed that the latter vinylcyclopropane was not formed in the reaction. Upon purification by flash chromatography, a 47-61% yield of allylic acetate **113** was obtained (Equation 2.3).

Equation 2.3: Reactivity of stannane 69 in presence of catalytic $[RhCl(COD)]_2$

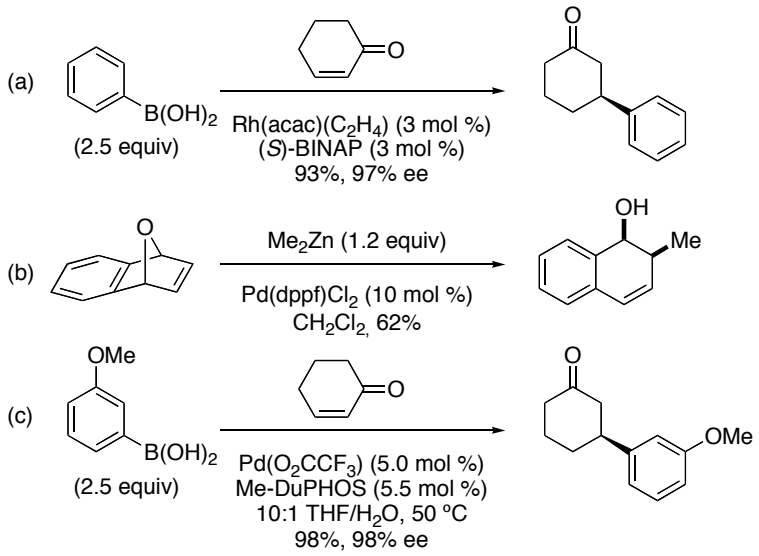


Similar reactivity, involving transmetalation of an organometallic fragment with a transition metal catalyst (Pd or Rh), has received attention, of late (Scheme 2.19). Metal-catalysed conjugate addition, or more formally, C-C bond formation via addition of the organotransition metal species, to an enone[111] or strained allyl ether[112] electrophile takes place via the corresponding organopalladium or –rhodium species.

Conjugate addition of vinylstannanes, in presence of Rh(I) catalysts, has been reported by the groups of Oi and Hayashi,[113] albeit with more reactive aryltrimethylstannane reagents. Utilising less reactive tributyltin counterparts, lower isolated yields were observed. Furthermore, in their work, alkenyltributylstannanes gave lowered yields of cyclohexenone adduct (20-40%).

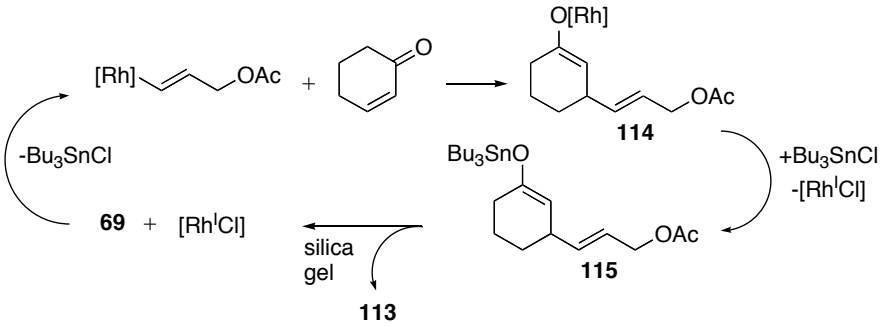
Presenting significant yield improvement over Oi and Hayashi's work, the results shown in Equation 2.3 deserved further investigation.

Scheme 2.19: Transmetalation-based approaches to C-C bond formation



By analogy, it is proposed that the adduct **113** arises from addition of the functionalised vinylrhodium moiety to cyclohexenone, thereby forming oxyallylrhodium(I) **114**. The rhodium(I) enolate intermediate undergoes transmetalation with Bu_3SnCl to afford tributylstannyl enol ether **115** and regenerate the Rh(I) catalyst (Scheme 2.20).

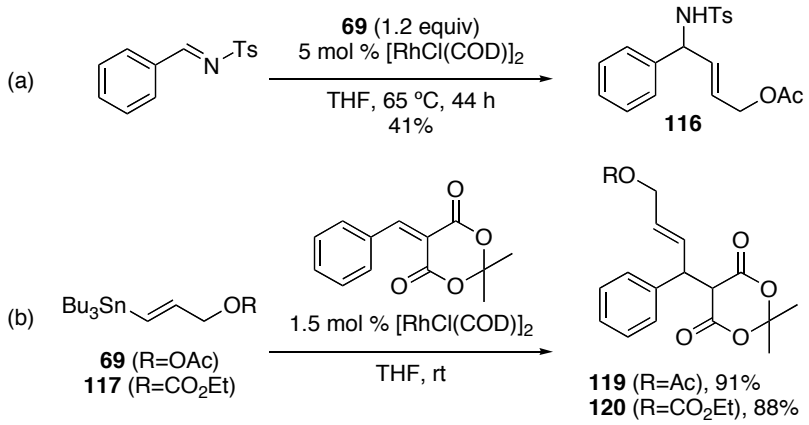
Scheme 2.20: Proposed mechanism for the formation of propenyl acetate 113



Exploratory work showed this unoptimised reaction also forms a functionalised *N*-tosyl benzylamine derivative (Scheme 2.21a). Moreover, Fillion group colleagues demonstrated that

alkenyltributylstannane **69** and its ethyl carbonate relative **117** also add at ambient temperature to alkylidene Meldrum's acids in excellent yields (Scheme 2.21b).[114] In both reactions, a tertiary benzylic stereocentre and a new carbon-carbon bond are generated.

Scheme 2.21: Scope of the Rh(I)-catalysed nucleophilic addition of stannane 69



Having explored the reactivity of the vinylmetallic species derived from **69**, it was demonstrated that altering the transition metal catalyst modulates reactivity of the vinylstannane. In the future, combination of the reactivity of the tributylstannyl enol ether (**115**, Scheme 2.20), *N*-tosylamide or ketene acetal intermediates in an intramolecular fashion with the residual allylic acetate or carbonate, may allow development of intramolecular carbon-carbon bond forming reactions.

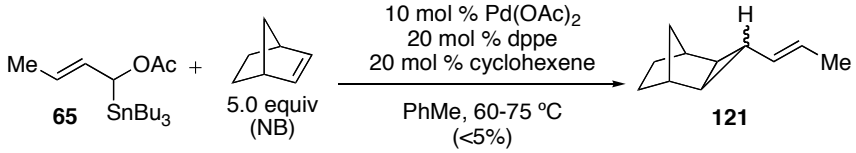
2.4.2 Intermolecular Pd-catalysed Cyclopropanation of Strained Alkenes

2.4.2.1 Initial Results and Stereochemical Study of the Products

Keeping in line with the established reactivity of palladium in cyclopropanations,[55] attention was then focused on intermolecular [2+1] cycloadditions with strained alkene partners. The reactivity of acetate **65** was first explored in the presence of norbornene (NB). Combining Pd(0) pre-catalysts ($Pd(PPh_3)_4$ or $Pd_2(dba)_3$) with 1,2-(diphenylphosphino)ethane, the desired cyclopropane product was not formed. Only dimerised product and $AcOSnBu_3$ were evidenced by GC-MS and crude NMR analysis. However, employing Sato's catalyst system, 1:2:2

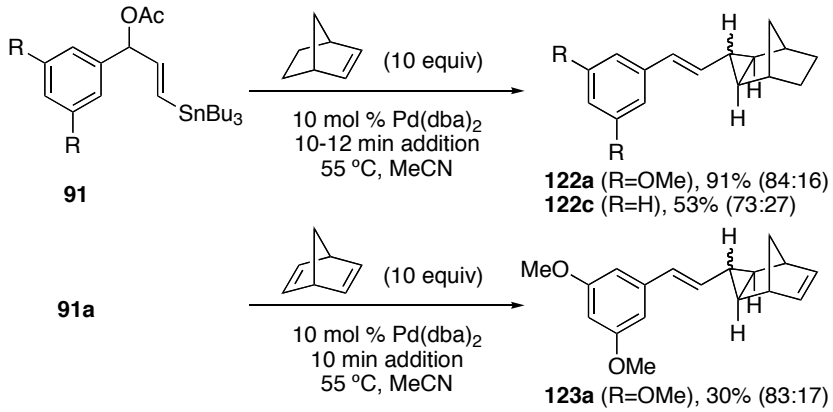
$Pd(OAc)_2$/dppe/cyclohexene,[115] the corresponding *exo*-(3-propenyl)tricyclo[3.2.1.$0^{2,4}$]octane **121** could be isolated in trace amount, and be matched with the published ^1H NMR data (Equation 2.4).[116] Comparison of GC-MS retention times, molecular ion and fragmentation pattern confirmed the absence of cyclopropane **121** in previous runs.

Equation 2.4: Initial norbornene cyclopropanation result



In order to facilitate product isolation, the study of Pd-catalysed norbornene cyclopropanation was pursued using the previously described aryl-substituted acetates **91**. Using phenyl-substituted **91c**, the previously successful conditions for Pd carbene formation were revisited. In order to hamper carbene dimerisation, slower addition was attempted. A solution of substrate in MeCN (0.15 M) was manually added over 12 min, corresponding to one drop every five seconds, to a solution of $Pd(dba)_2$ (10 mol %) and norbornene (10 equiv) in MeCN (0.15 M) maintained at 55 ºC. Under those initial conditions, in 45 min, a 53% yield (73:27 diastereomeric ratio, dr) of the desired vinylcyclopropane was isolated. Similarly, using **91a**, product **122a (**84:16 dr, 91% yield) was isolated when running the reaction in presence of 10 equiv of NB (Scheme 2.22). Of note, of the possible four diastereomers incorporating a *trans*-alkene, only two were observed.

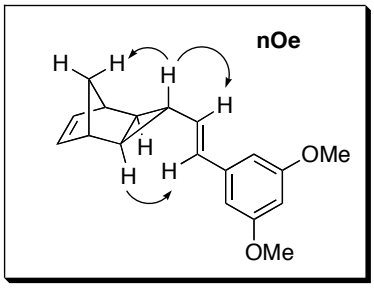
Scheme 2.22: Cyclopropanation with substrates 91: initial results



The observed enhancement of reactivity using phosphine-free $Pd(dba)_2$ instead of the $[Pd(PPh_3)_4$/dppe] system, has precedent. Hegedus has demonstrated that for π-allylpalladium(II) acetates to participate in Stille reactions, $Pd(dba)_2$ and LiCl (3 equiv) in DMF at 60 ºC are required.[117] In their study, added phosphine impeded the reaction. Likewise, Farina's mechanistic studies of the Stille cross-coupling reaction suggested a rate-determining transmetalation step based on the rate acceleration witnessed when using electron-poor phosphine ligands such as tfp.[66] The above experimental observation therefore suggests a rate-limiting deacetoxystannation step producing a Pd-carbene intermediate.

3,5-Dimethoxyphenyl stannane **91a** was further submitted to the cyclopropanation reaction in presence of 10 equiv of norbornadiene (ND), using the conditions described above (Scheme 2.22). The corresponding product **123a** was isolated in 30% yield (83:17 dr), with no detectable bis-cycloadduct. The methoxy substituents greatly eased purification of the final product mixture, so that pure samples of the major diastereomer could be secured. Using nuclear Overhauser effect (nOe) NMR studies, the structure was confirmed to be the *anti-exo* [2+1] cycloadduct (Figure 2.1). Since the other diastereomer differed by the chemical shift and coupling constant of the allylic, cyclopropyl-bridgehead proton, it was assumed to be the *syn-exo* vinylcyclopropane. Therefore, cyclopropanation occurs exclusively from the *exo*-face of the strained bicyclic system.

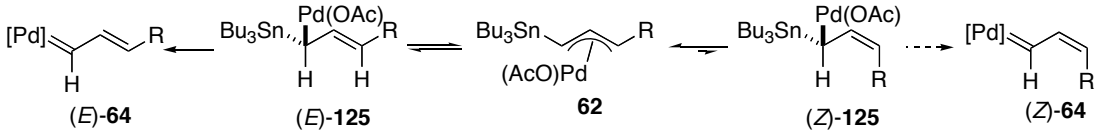
Figure 2.1: Nuclear Overhauser effect study for the major diastereomer of 123a



The isolation and stereochemical identity of **123a** are of utmost significance. The complete *exo* diastereoselectivity lends further credence to a Pd-carbene intermediate conducting vinylcyclopropanation, based on the stereochemical studies discussed by Tomilov (*c.f.* Section

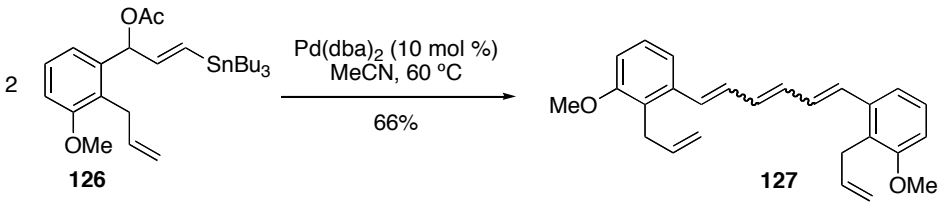
1.3.2). Moreover, the absence of any (*Z*)-olefin in the vinylcyclopropane products **122-123** provides further support for the postulated explanation for the failure of intramolecular C_{aryl}-H insertion reactions (section 2.3.1). The formation of dimetallic π-allylpalladium(II) intermediate **62** (Scheme 2.23) can lead to two distinct *gem*-dimetallic σ-allyl species **125**. Based on allylic strain arguments, (*E*)-**125** is favoured and leads to the corresponding (*E*)-carbene, (*E*)-**64**. As a consequence, in order to react Pd-stabilised vinylcarbenes via intramolecular approaches, alternate tactics, such as forcing the olefin in the (*Z*)-geometry using a cyclic system, will be necessary.

Scheme 2.23: Stereochemical rationale revisited



For instance, substrate **126** was designed to intercept a vinylcarbenoid intermediate in an intramolecular fashion (Scheme 2.24). However, upon submitting it to the conditions previously shown to lead to Pd-carbene intermediate formation, heating to 60 ºC in presence of $Pd(dba)_2$ in MeCN, the only product isolated was dimer **127**. One would believe that an *ortho*-allyl substituent would override the unfavourable (*Z*)-geometry, by complexation of the olefin with Pd, and mediate intramolecular cyclopropanation. The exclusive isolation of dimerised **127** in 66% yield illustrates lower reactivity towards unstrained alkenes. Thereby, the propensity of **62** to undergo dimerisation faster than any competing C-C bond-forming event is illustrated.

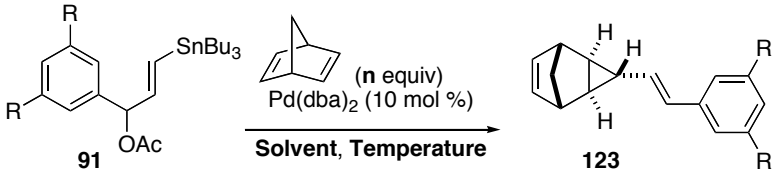
Scheme 2.24: Attempted intramolecular cyclopropanation



2.4.2.2 Scope and Limitations of the Vinylcyclopropanation Reaction

To better understand the intermolecular carbene cheletropic [2+1] reaction, efforts were then devoted to the optimisation of its reaction parameters. Upon decreasing reaction temperature, and adding a substrate solution dropwise over 45-60 min with a syringe pump, diastereoselectivity increased (Table 2.3, entries 1-3). At rt in MeCN, carbon-carbon bond forming cyclopropanation of norbornadiene is rate-limiting, for it made no difference whether the substrate was added in one portion (entry 4) or over an hour period (entry 3). In the previous four cases, dimerised products **100c** were observed, and following the reaction summarised in entry 4, 31% yield of dimer **100c** was isolated. Solvent polarity and Lewis-basicity exerted an influence upon diastereoselection. In polar, Lewis-basic acetonitrile, best diastereoselectivity was achieved (87:13, entry 2), while in polar, non-coordinating chlorinated solvents, intermediate diastereoselectivities were observed (entries 5-6). In comparison, non-polar, non-coordinating toluene gave rise to marginal stereoselection (entry 7). Finally, product purification was greatly facilitated using three equivalents of alkene instead of ten, with no yield erosion (entries 5 and 8). In dichloromethane, no dimer was detected, so despite lower diastereoselection, this solvent was chosen to study the scope of the [2+1] cycloaddition reaction.

Table 2.3: Optimisation of norbornadiene vinylcyclopropanation

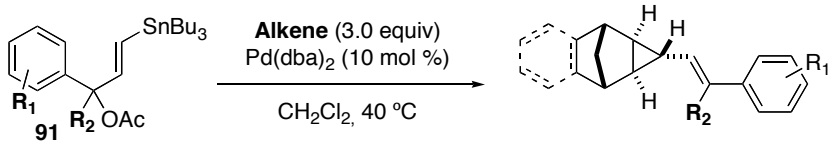


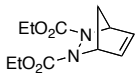
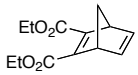
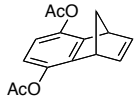
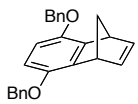
Entry	Substrate (R)	*n*	Solvent	Temperature (ºC)	Yield (%)[a]	dr[b]
1	**91a** (OMe)	10	MeCN	55[c]	30	83:17
2	**91a** (OMe)	10	MeCN	45[c]	27	87:13
3	**91c** (H)	10	MeCN	23[c]	44	93:7
4	**91c** (H)	10	MeCN	23	43	93:7
5	**91a** (OMe)	10	CH_2Cl_2	40	56	76:24
6	**91a** (OMe)	10	$(CH_2Cl)_2$	40	44	79:21
7	**91a** (OMe)	10	PhMe	40	21	57:43
8	**91a** (OMe)	3.0	CH_2Cl_2	40	55	71:29

[a] Isolated yield of diastereomer mixture after column chromatography.
[b] Determined by ^{1}H NMR by integration of allylic cyclopropyl protons.
[c] Slow addition of substrate (0.15 M) to $Pd(dba)_2$ + ND in MeCN (0.15 M) over 45-60 min via syringe pump.

When the benzylic hydrogen was labeled by deuteriation, d_1-**123a** was obtained with no detectable scrambling (Table 2.4, entry 3). A benzylic methyl substituent was tolerated, as similar yields were observed (entries 4-5), compared to the unsubstituted substrate (entries 1-2). Electron-donating *para*-methyl (entry 5) diminished diastereoselection compared with electron-withdrawing *para*-fluoro (entry 6), using bicyclo[2.2.1]hepta-1,4-diene. Overall, using ND and NB, diastereoselectivity ranged from 66:34 to 94:6 (entries 1-8).

Table 2.4: Scope of the vinylcyclopropanation reaction



Entry	Substrate	R_1	R_2	Alkene	Product (yield/%)[a]	dr[b]
1	**91a**	3,5-$(MeO)_2$	H	ND	**123a** (55)	71:29
2	**91a**	3,5-$(MeO)_2$	H	NB	**123a** (48)	94:6
3	d_1-**91a**	3,5-$(MeO)_2$	D	ND	d_1-**123a** (69)	78:22
4	**91b**	3,5-$(MeO)_2$	Me	ND	**123b** (58)	73:27
5	**91b**	3,5-$(MeO)_2$	Me	NB	**122b** (67)	68:32
6	**91d**	4-Me	H	ND	**123d** (59)	66:34
7	**91e**	4-F	H	ND	**123e** (79)	75:25
8	**91e**	4-F	H	NB	**122e** (85)	80:20
9	**91e**	4-F	H	 **128**	N/A[c]	N/A[c]
10	**91e**	4-F	H	 **129**	**130e** (21)	90:10
11	**91e**	4-F	H	 **131**	**132e** (56)	91:9
12	**91e**	4-F	H	 **133**	**134e** (51)	85:15

[a] Isolated yield of diastereomer mixture after column chromatography, averaged over at least two runs. [b] Determined by ^{1}H NMR by integration of allylic cyclopropyl protons. [c] Only **91e** and **128** observed after 48 h at 40 ºC.

Functional group tolerance was assessed using substrate **91e**. No reaction was observed with bis-carbamate **128**, and only starting materials were observed after 48 h. Electron-attracting

ester groups lowered the olefin π-reactivity but promoted stereodifferentiation, hence providing cyclopropanes **130e** with 90:10 dr (entry 10). Finally, both aryl ester and ether functionalities were tolerated (entries 11-12), yielding cyclopropanes **132e** and **134e** in 56 and 51% yields, respectively. In those two cases, repeated chromatography was required to secure pure cyclopropanes, affecting yields.

From the previous survey, reactivity trends can be extracted. First, solvent polarity influences diastereoselectivity; diastereomer ratios were generally higher in acetonitrile than in chlorinated solvents, which in turn gave better dr than toluene. Beyond polarity, Lewis basic MeCN not only improved selectivity, but also greatly eased dimerisation, necessitating slow addition for cyclopropanation to predominate. One can hypothesise that in MeCN, solvent molecules displace dibenzylideneacetone ligands, which does not occur in dichloroalkanes or toluene. Nevertheless, the reasoning behind diastereoselectivity enhancement in MeCN deserves further investigation.

As for electronic effects upon dimerisation, direct conjugation of the palladium carbene with the arene (4-F, 4-Me, compared with 4-H) is detrimental to isolated yields, plagued by side-reactions leading to the formation of unidentified insoluble materials. However, the 3,5-dimethoxyarenes favour higher yields. Further study of 3,5-disubstitution with electron-withdrawing groups may shed light on the reaction.

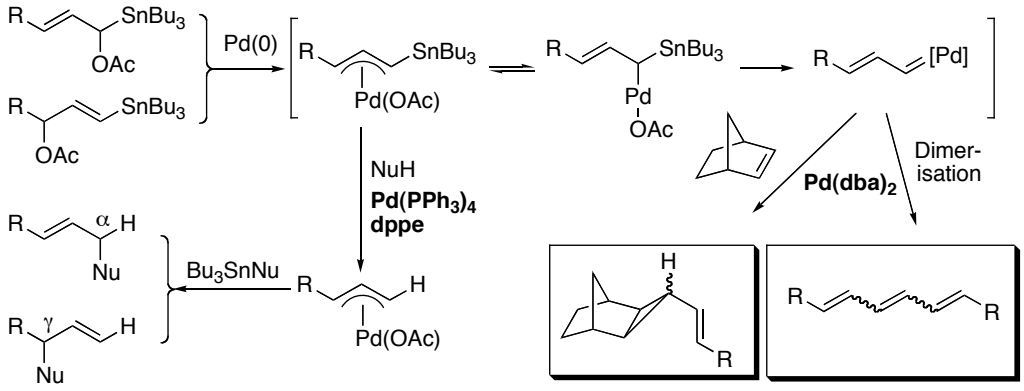
Conversely, direct aryl substituent conjugation with the metal carbene affected cyclopropane production. Compared with the 4-Me substrate, there were 20% yield increases with the 4-F and the 3,5-(MeO) substrates **91e** and **91a**, respectively electron-withdrawing and poorly electron-donating towards the carbene centre. Thus, an electron-rich Pd-carbene intermediate leads to more side-reactions than its electron-poor counterpart. This assertion is also supported by the ability of $Pd(dba)_2$ to promote cyclopropanation reactions, contrary to [$Pd(PPh_3)_4$/dppe].

2.5 Summary and Outlook

2.5.1 Conclusions

Oxidative addition of Pd(0) complexes to 1-tributylstannyl-2-propenyl acetates was verified as a route to *gem*-dimetallic allylpalladio(II)/tributylstannylalkane intermediates.[118] The ambiphilic nature of those species was investigated. They were found to display basic reactivity in the presence of Brønsted-acidic dialkyl malonates. The tributylstannylketene acetal thus formed reacted with π-allylpalladium(II) intermediates in nucleophilic allylic substitution reactions, and the ratio of regioisomeric products paralleled steric interactions. Nucleophilic behaviour required electron-rich ligands on the Pd catalyst, while phosphine-free $Pd(dba)_2$ upturned reactivity. The overall catalytic process exemplified sequential functionalisation of two distinct carbon-metal bonds (Scheme 2.25).

Scheme 2.25: Formation and reactivity of allylpalladium(II)/tributylstannylalkane *gem*-dimetallic species



Furthermore, the electrophilic carbenoid nature of allylpalladio(II)/tributylstannylalkane intermediates was demonstrated in their dimerisation and strained alkene cyclopropanation reactions. Further support was provided by the stoichiometric formation of tributyltin acetate and the absence of cyclopropanation with $Pd(PPh_3)_4$/dppe. In the long run, these discoveries could pave the way to the obviation of diazo compounds in the generation of metal carbenes.

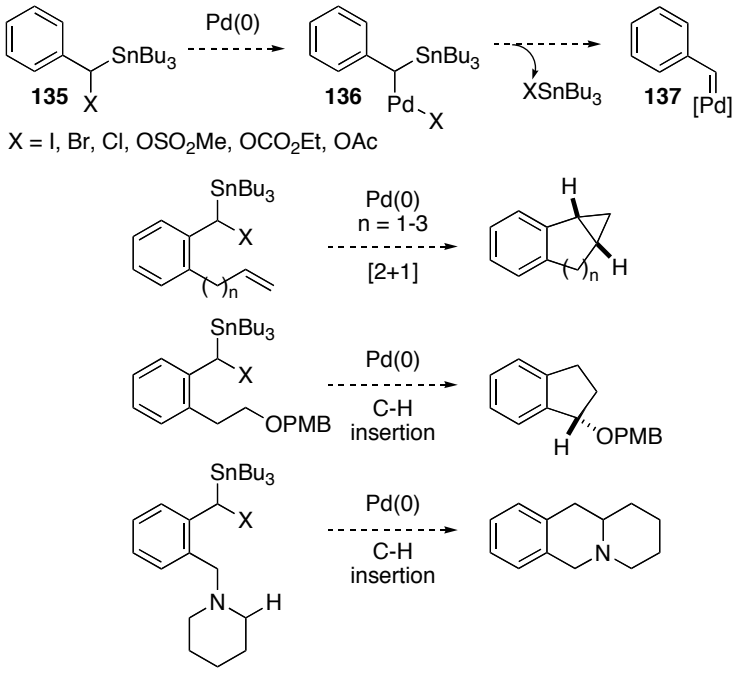
Finally, selective activation of either the vinylstananne or allylic acetate moiety was achieved by careful choice of transition metal. Palladium(0) catalysts led to π-allyl complexes that ultimately allowed carbon-metal bond bis-functionalisation. Conversely, rhodium(I) catalyst $[RhCl(COD)]_2$ produced selective vinylstannane activation for conjugate addition reactions to take place, and the residual allylic acetate present in the products is available for further transformation.

2.5.2 Outlook and Future Direction

The results presented herein have established the absence of 1,3-metal shift for vinyl-stabilised Pd-carbene species. Although it facilitated π-allyl complex formation, the resulting vinyl substituent rendered intramolecular carbene reactions unfeasible. This limitation must stimulate further examination of Pd/Sn *gem*-organodimetallic species, keeping with the successful deacetoxystannylation strategy, leading to Pd-carbene intermediates.

Negishi has demonstrated that benzylpalladium(II) halides are accessible via oxidative addition of Pd(0) to benzylic chlorides, bromides, mesylates, carbonates and acetates, albeit with diminished efficiency for the latter.[119] α-Alkoxystannanes can be generated using the method of Still by addition of lithium tributylstannide to benzaldehydes, followed by *O*-activation.[120] Combination of the two methods could lead to *gem*-organodimetallic halopalladio(II)/ tributylstannylalkane species **136** that may collapse with dehalostannylation to an aryl-stabilised palladium carbene **137** (Scheme 2.26).

Scheme 2.26: Intramolecular reactions of *gem*-benzylpalladio(II)/tributylstannylalkane intermediates



Since the establishment of the carbenoid behaviour of other sp^2-carbon-stabilised Pd-carbene species, it is reasonable to believe similar reactivity, namely dimerisation and cyclopropanation reactions, could be achieved with benzylic counterparts. Moreover, these species may take part in intramolecular C-H insertion and [2+1] cycloaddition reactions, due to decreased geometrical constraint. Then, the full synthetic potential of Pd-carbene species may be unleashed.

2.6 Experimental Section

2.6.1 General Experimental Methods

Substrate Preparation

Reactions were carried out in flame-dried glassware under an atmosphere of nitrogen unless otherwise mentioned. Palladium-catalysed reactions, including hydrostannylations, were carried under an argon atmosphere. Benzene and 1,2-dimethoxyethane (DME) were distilled from Na/benzophenone. Tetrahydrofuran (THF), diethyl ether (Et_2O), 1,2-dichloroethane (DCE), dichloromethane and acetonitrile were dried and purified from a solvent system by the published procedure.[121] Et_3N and *i*-Pr_2NH were freshly distilled under N_2 from CaH_2. Methanol (HPLC grade), ethanol, ethyl acetate, 5% Pd/C, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, 1,2-(diphenylphosphino)ethane, (*S*)-BINAP, norbornene (NB), norbornadiene (ND), trimethylsilylacetylene, Ac_2O, bis(tributyltin) oxide, 2-propyn-1-ol, 3-butyn-2-ol, 3-phenylprop-2-yn-1-ol, dimethyl malonate, diethyl malonate-d_2 and crotonaldehyde were used as received from commercial sources. Cyclohex-2-en-1-one was obtained from commercial sources and freshly distilled under reduced pressure before use. $Pd(dba)_2$ was prepared as reported.[122] The preparation of tributylstannane, adapted from the literature, is herein described.[123]

For work-ups and treatments, aqueous solutions were prepared using de-ionised water. The following abbreviations are used throughout: NH_4Cl sat. (saturated aqueous ammonium chloride), brine (saturated aqueous sodium chloride), 5% or 10% HCl (5% and 10% (w/v) aqueous HCl), 5% or 15% NaOH (5 and 15% aqueous NaOH).

Characterisation Methods

For nuclear magnetic resonance (NMR), the residual ^1H shift in $CDCl_3$ (7.26 ppm) was used as the internal reference for ^1H NMR, $CDCl_3$ (77.0 ppm) for ^{13}C NMR, and $CHCl_3$ (7.26 ppm) for

^{2}H NMR. Coupling constants are reported in Hertz. The following abbreviations were used to denote multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, br s = broad singlet. Unless specified otherwise, the quoted *J*-values refer to C-H coupling constants. High-resolution mass spectra (HRMS) were performed at the University of Waterloo by Dr. Richard W. Smith. Low-resolution (LRMS) spectra were recorded on a Hewlett Packard G1800A GCD system fitted with a 30 m X 0.25 mm HP5 column; injector temperature: 250 ºC; temperature program: initial 70 ºC for 2 min; heating rate 10 ºC/min for 18 min; final temperature 250 ºC for 10 min.

Reactions were monitored by thin-layer chromatography (TLC) on commercial silica pre-coated plates with a particle size of 60 Å. Developed plates were viewed under a UV lamp as well as by staining with *p*-anisaldehye, $KMnO_4$ or cerium ammonium molybdate solutions. Flash chromatography was performed using 230-400 mesh silica gel. Solvent systems were usually made of ethyl acetate (EtOAc) or diethyl ether and petroleum ether 30-60 (PE) or hexanes compositions. In certain cases, mixtures of EtOAc and toluene (PhMe) were also used as eluent.

2.6.1.1 Preparation of Tributylstannane (Bu_3SnH)

Bis(tributyltin) oxide (68.5 g, 115 mmol, 1.00 equiv) was diluted with EtOH (150 mL) under Ar. Finely powdered $NaBH_4$ (3.26 g, 86.1 mmol, 0.75 equiv) was then added in one portion at rt to the stirred solution, and the resulting milky suspension was stirred vigorously for 2 h. Then, it was sequentially quenched by the dropwise addition of H_2O (until no H_2 evolution), stirred for 3 min, and then by further addition of NH_4Cl sat. (until no H_2 evolution). The mixture was diluted with enough H_2O to completely dissolve residual boron salts, and EtOH was removed by rotary evaporation. The aqueous layer was extracted with PE (500 mL, 300 mL, 100 mL), the combined organic portions washed with brine (1X), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting clear colourless oil was then distilled (Kugelröhr, bp = 85–90 ºC at 0.8 mm Hg) using a pre-heated bath, to give 52.2 g (179 mmol) of $HSnBu_3$ (78%) as a clear colourless oil, transferred into base-washed, oven-dried brown bottles under Ar and stored at 4 ºC.

2.6.2 General Procedures

2.6.2.1 Acetylation of Allylic Alcohols

To a solution of stannylated allylic alcohol (1.0 equiv), 4-dimethylaminopyridine (5 mol %), and triethylamine (1.5 equiv) in dichloromethane (0.25 M in alcohol) was added Ac_2O (1.2 equiv) via syringe at rt, and the resulting mixture was stirred for 30 min (monitored by TLC) after which time, starting material was completely consumed. The reaction was quenched by the addition of NH_4Cl sat. The solvent was then removed by rotary evaporation, and the aqueous phase was extracted (3X) with EtOAc. The combined organic layers are washed with NH_4Cl sat. (1X) and brine (1X), dried (Na_2SO_4), concentrated under reduced pressure and purified by flash chromatography.

2.6.2.2 Pd-Catalysed Malonate Allylation

In an oven-dried Schlenk tube were loaded $Pd(PPh_3)_4$ (58 mg, 0.050 mmol, 10 mol %) and 1,2-(diphenylphosphino)ethane (24 mg, 0.060 mmol, 12 mol %) under an argon atmosphere, followed by 1,2-dimethoxyethane (2 mL) and dimethyl malonate (114 μL, 1.00 mmol, 2.0 equiv). The mixture was stirred for 5 min, after which the substrate (0.50 mmol, 1.0 equiv) was syringed in, rinsing with 3X 1 mL of DME. The Schlenk tube was sealed and immersed in an oil bath pre-heated to 55 ºC, and the reaction was allowed to stir for the specified time. Upon completion (TLC monitoring), the reaction mixture was concentrated to dryness by rotary evaporation, analyzed by ^1H NMR, and used as such for chromatographic purification (5% EtOAc/PE).

2.6.2.3 Hydrostannylation of Alkynols[124]

A solution of propargyl alcohol (1.00 equiv) in THF (0.25 M) was treated with $PdCl_2(PPh_3)_2$ (3 mol %) under Ar. Tributyltin hydride (1.20 equiv) was then slowly added dropwise into the resulting yellow suspension at rt (rapidly evolves, with heat dissipation, into a dark orange then amber solution). The resulting near-black solution was stirred for 10 to 60 min (TLC monitoring). Upon reaction completion (adding more $HSnBu_3$ if necessary), THF was stripped

off under reduced pressure and the resulting black residue was purified by flash chromatography.

2.6.2.4 Formation of 1-Aryl-2-propyn-1-ols

A solution of trimethylsilylacetylene (1.20 equiv) in THF (0.3 M) was cooled to 0 ºC under argon and treated dropwise with a 2.4 M hexanes solution of butyllithium (1.15 equiv) and stirred for 30 min in the ice bath. The carbonyl compound (neat for liquids, as a 0.5 M THF solution for solids, 1.00 equiv) was added to the acetylide solution at 0 ºC. The solution was maintained at 0 ºC for 10 min, allowed to warm up to rt, and stirred until TLC analysis indicated complete electrophile consumption. The reaction was quenched with 1.0 M NaOH (2.5 mL per mmol substrate) and methanol (2.5 mL per mmol). After heating to reflux the resulting solution for 30 min, the volatile organics were removed on a rotary evaporator, and the aqueous phase was extracted (3X) with CH_2Cl_2. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated. The corresponding alkynol was purified on a short plug of silica gel.

2.6.2.5 Pd-Catalysed Dimerisation

In an oven-dried 20-mL scintillation vial was loaded the starting alkenyl acetate (0.30 mmol, 1.0 equiv) in 3.0 mL dry MeCN under argon. To this solution was added $Pd(dba)_2$ (16 mg, 0.030 mmol, 10 mol %) and the resulting solution was stirred for the time and at the temperature specified below. Upon extensive formation of Pd black (TLC monitoring for completion), the reaction mixture was treated with 100-200 mg of 10% potassium fluoride on silica gel[125] and stirred for 30 min, after which the solvent was removed by rotary evaporation. Purification by flash chromatography was then effected by loading the solid thus obtained on a silica gel column. Following purification, a non-quantified mixture of double-bond (*E*,*E*,*E*)- and (*E*,*Z*,*E*)-isomers was obtained, which isomerised over several weeks to the *(E,E,E)*-isomer when left in the solid state at rt in presence of light.

2.6.2.6 Pd-Catalysed Strained Alkene Cyclopropanation, Dropwise Addition

In an oven-dried round-bottom flask were loaded $Pd(dba)_2$ (16 mg, 0.030 mmol, 10 mol %), the strained alkene (0.90 mmol, 10 equiv) and 2.0 mL dry MeCN under an argon atmosphere. The resulting purple suspension was brought to the temperature specified and stirred for 5-10 min, until an orange solution was obtained. The substrate (0.30 mmol, 1.0 equiv) in MeCN (1.0 mL) was then syringed in dropwise over a total period of time as specified, rinsing with 2X 0.5 mL of MeCN. The reaction was allowed to stir under Ar at the temperature and for the time specified below. After reaction completion, as monitored by TLC, the black reaction mixture was partially concentrated by rotary evaporation, and loaded as a dichloromethane solution onto a silica gel column for flash chromatographic purification.

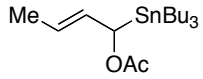
2.6.2.7 Pd-Catalysed Strained Alkene Cyclopropanation in CH_2Cl_2

In an oven-dried Schlenk tube were loaded $Pd(dba)_2$ (16 mg, 0.030 mmol, 10 mol %), the strained alkene (0.90 mmol, 3.0 equiv) and 2.0 mL dry CH_2Cl_2 under an argon atmosphere. The resulting purple-black suspension was stirred at rt until colour and solubility changes were observed, typically to an orange-red solution. The substrate (0.30 mmol, 1.0 equiv) was then syringed in, rinsing with 4x 0.5 mL of CH_2Cl_2. The Schlenk tube was sealed and immersed in an oil bath pre-heated to 40 ºC, and the reaction was allowed to stir for the time specified below. After reaction completion, as monitored by TLC, the black reaction mixture was partially concentrated by rotary evaporation, and loaded as a dichloromethane solution onto a silica gel column for flash chromatographic purification.

2.6.3 Characterisation Data

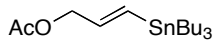
2.6.3.1 Synthesis of Vinylstannanes 65, 69-71

Synthesis of (*E*)-1-tributylstannylbut-2-enyl ethanoate[98] (65)



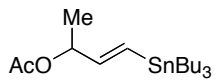
Prepared in 81% yield from (*E*)-crotonaldehyde as described. Freshly prepared and distilled $HSnBu_3$ were required to ensure high yield and reproducibility.

Synthesis of (*E*)-3-Tributylstannylprop-2-enyl ethanoate[126] (69)



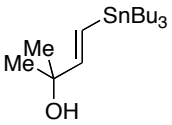
Prepared in 89% yield by acetylation of the previously reported alcohol[99] via General Procedure 2.6.2.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (1H, d, J = 19.1 Hz, $J_{Sn\text{-}H}$ = 65.8 Hz), 6.01 (1H, dt, J = 19.1, 5.2 Hz), 4.55 (2H, d, J = 4.8 Hz), 2.07 (3H, s), 1.53-1.41 (6H, m), 1.28 (6H, sext, J = 7.2 Hz), 0.92-0.84 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 141.5, 133.0, 67.7, 29.0 ($J_{Sn\text{-}C}$ = 20.6 Hz), 27.2 ($J_{Sn\text{-}C}$ = 55.0 Hz), 21.0, 13.6, 9.4 ($J_{Sn\text{-}C}$ = 344, 330 Hz); HRMS (EI) Calcd. for $C_{13}H_{25}O_2Sn$ $(M - Bu)^+$: 329.0871. Found: 329.0867.

Synthesis of (*E*)-4-Tributylstannylbut-3-en-2-yl ethanoate (70)



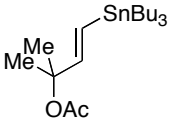
Prepared from the known (*E*)-4-tributylstannylbut-3-en-2-ol[100] in 92% yield as per General Procedure 2.6.2.1. Purified by flash chromatography (5% EtOAc/PE). Faint tan oil, crystallises to low-melting yellow needles; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (1H, dd, J = 19.8, 1.0 Hz), 5.95 (1H, dd, J = 19.9, 5.2 Hz), 5.34-5.26 (1H, m), 2.06 (3H, s), 1.51-1.43 (6H, m), 1.38-1.22 (6H, m), 1.29 (3H, d, J = 6.6 Hz), 0.91-0.86 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 146.9, 129.5, 73.1, 29.0 ($J_{Sn\text{-}C}$ = 20 Hz), 27.2 ($J_{Sn\text{-}C}$ = 52 Hz), 21.4, 19.9, 13.7, 9.4 ($J_{Sn\text{-}C}$ = 344, 330 Hz); HRMS (EI) Calcd. for $C_{14}H_{27}O_2Sn$ $(M - Bu)^+$: 343.1028. Found: 343.1017.

Synthesis of (*E*)-4-Tributylstannyl-2-methylbut-3-en-2-yl ethanoate (71)



(*E*)-4-Tributylstannyl-2-methylbut-3-en-2-ol

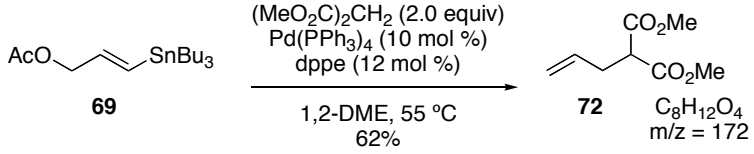
Prepared in 53% yield (7.14 g, 19.0 mmol) by $PdCl_2[P(o\text{-tolyl})_3]_2$-catalysed hydrostannation of 2-methyl-3-butyn-2-ol (36.0 mmol), as reported in the literature procedure.[100] All characterisation data were in agreement with those published.



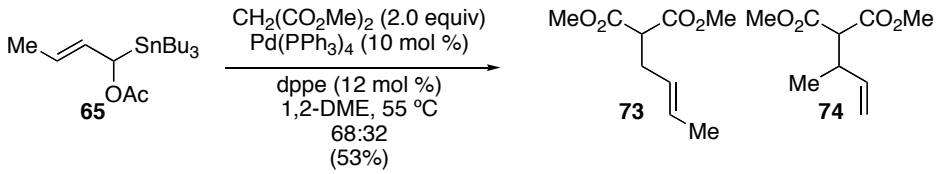
(*E*)-4-Tributylstannyl-2-methylbut-3-en-2-yl ethanoate (71)

Prepared by acetylation of the parent butenol (7.14 g, 19.0 mmol), as per General Procedure 2.6.2.1, altered by using 1.5 equiv of DMAP instead of Et_3N and stirring for 18 h. Following purification by flash chromatography (3% EtOAc/PE), the title compound was isolated as a clear colourless oil (6.21 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (1H, d, J = 19.4 Hz, $J_{Sn\text{-}H}$ = 64.0 Hz), 6.04 (1H, d, J = 19.6 Hz, $J_{Sn\text{-}H}$ = 34.5 Hz), 1.99 (3H, s), 1.50 (6H, s), 1.51-1.20 (12H, m), 0.95-0.84 (15H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 151.7, 125.0, 82.0, 29.0 ($J_{Sn\text{-}C}$ = 20.6 Hz), 27.2 ($J_{Sn\text{-}C}$ = 52 Hz), 26.5, 22.3, 13.7, 9.5 ($J_{Sn\text{-}C}$ = 342, 328 Hz).

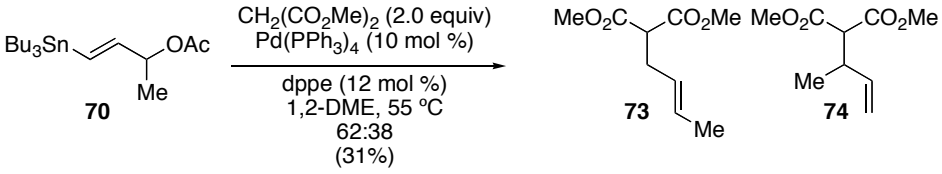
2.6.3.2 Pd-Catalysed Allylation of Dimethyl Malonate



Following General Procedure 2.6.2.2 using 152 mg of subtrate **69** (0.40 mmol) and heating for 60 min at 55 °C, **72** was obtained in 62% yield, with characterisation data matching those already published.[127]

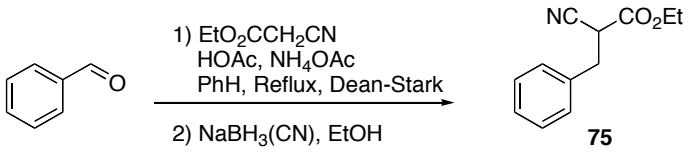


Following General Procedure 2.6.2.2 using 101 mg of substrate **65** (0.25 mmol) and heating for 30 min at 55 ºC, a 68:32 mixture of **73**:**74** was isolated in 53% yield, evidenced by integration of the characteristic ^{1}H NMR signals reported for the individual compounds.[128]



Following General Procedure 2.6.2.2 using 202 mg of substrate **70** (0.50 mmol) and heating for 30 min at 55 ºC, a 62:38 mixture of **73**:**74** was obtained in 31% yield, as evidenced by integration of the characteristic ^{1}H NMR signals, comparing with the published characterisation data for the separate compounds.[128] Also obtained in 6% isolated yield (61:39 mixture of **73**:**74**) when running the reaction at 40 ºC following General Procedure 2.6.2.2. These products were not observed when running the reaction at rt.

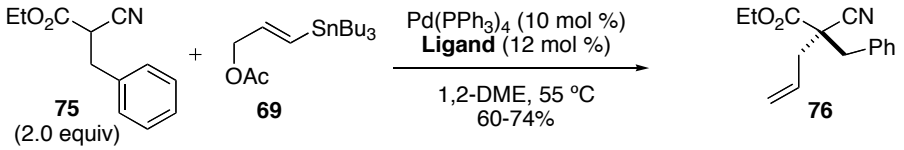
2.6.3.3 Pd-Catalysed Allylation of Cyanoacetate 75



Ethyl 2-cyano-3-phenylpropionate 75

To a solution of benzaldehyde (2.54 mL, 25.0 mmol, 1.0 equiv) and ethyl cyanoacetate (2.9 mL, 28 mmol, 1.1 equiv) in dry benzene (35 mL) were successively added acetic acid (1.1 mL, 20.0 mmol, 0.80 equiv) and ammonium acetate (1.16 g, 15.0 mmol, 0.60 equiv), and the resuting mixture was heated to reflux for 45 min under Dean-Stark conditions. After this time, 0.45 mL H_2O had collected (0.40 mL theoretical), and TLC indicated complete benzaldehyde consumption. The reaction mixture was diluted with 100 mL EtOAc and washed successively

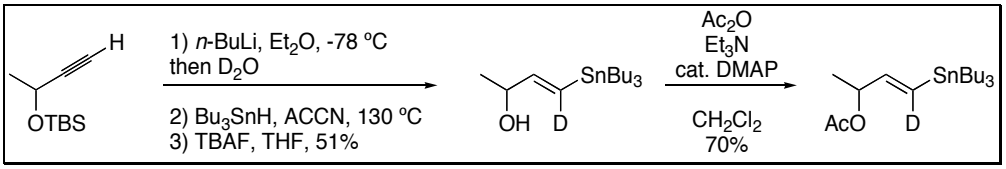
with $NaHCO_3$ (2X) and brine (1X), dried over Na_2SO_4, filtered and concentrated to dryness. The crude white pasty solid was redissolved in EtOH (100 mL) and treated with $NaBH_3(CN)$ under N_2. The resulting solution was stirred for 40 h (unoptimised) then quenched with NH_4Cl (40 mL) and H_2O (40 mL). Most of the EtOH was removed by rotary evaporation, and the aqueous layer was extracted with ether (3X). The combined organics were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated to dryness by rotary evaporation. Following purification by flash chromatography (10% EtOAc/PE), the title compound was obtained as a clear colourless oil (3.32 g, 65%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (5H, m), 4.24 (2H, q, *J* = 7.2 Hz), 3.72 (1H, dd, *J* = 8.4, 5.9 Hz), 3.28 (1H, dd, *J* = 13.9, 5.9 Hz), 3.23 (1H, dd, *J* = 13.8, 8.4 Hz), 1.26 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 135.2, 128.9, 128.8, 127.7, 116.1, 62.8, 39.6, 35.6, 13.8. LRMS (EI) Calcd. for $C_{12}H_{13}NO_2$: 203. Found: 203 (M^+), 158 $(M\text{-}EtO)^+$.



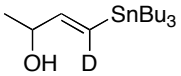
Ethyl 2-benzyl-2-cyanopent-4-enoate 76

Following General Procedure 2.6.2.2 using 152 mg of substrate **69** (0.40 mmol), replacing malonate with cyanoacetate derivative **75** (163 mg; 0.80 mmol, 2.0 equiv) and heating for 16 h (unoptimised) at 55 ºC, the title compound was isolated in 60% using dppe and 74% using (*S*)-BINAP as ligand. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.27 (5H, m), 5.85 (1H, ddt, *J* = 17.3, 9.8, 7.3 Hz), 5.32-5.22 (2H, m), 4.15 (2H, q, *J* = 7.1 Hz), 3.20 (1H, d, *J* = 13.6 Hz), 3.07 (1H, d, *J* = 13.5 Hz), 2.75 (1H, dd, *J* = 13.7, 7.4 Hz), 2.57 (1H, dd, *J* = 13.8, 7.0 Hz), 1.16 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 134.0, 130.5, 129.9, 128.5, 127.8, 121.0, 118.5, 62.6, 51.2, 42.5, 41.3, 13.9. LRMS (EI) Calcd. for $C_{15}H_{17}NO_2$: 243. Found: 243 (M^+), 202 $(M\text{-}CH_2CH{=}CH_2)^+$.

2.6.3.4 Preparation of Deuterium-Labeled Substrates 81-82



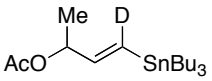
Synthesis of (*E*)-4-tributylstannyl-4-deuterio-3-propen-2-yl ethanoate (81)



(*E*)-4-Tributylstannyl-4-deuterio-3-buten-2-ol

The known TBS-protected alkynol[103] (3.5 g, 19.0 mmol) was diluted in dry Et_2O (80 mL) and cooled to –78 ºC under argon atmosphere. The solution was treated carefully with *n*-BuLi (2.4 M in hexanes, 10.3 mL, 24.7 mmol) and stirred at –78 ºC for 30 min, at 0 ºC for 60 min, then D_2O (8 mL) was added at that temperature. The resulting hetereogeneous mixture was stirred for 2 h while gradually reaching ambient temperature. Sat'd NH_4Cl was then added (50 mL) and the aqueous layer was extracted with Et_2O (3X). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness. The resulting clear colourless liquid was used as such in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.51 (1H, q, *J* = 6.5 Hz), 1.42 (3H, d, *J* = 6.5 Hz), 0.91 (9H, s), 0.13 (3H, s), 0.12 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.8, 25.8, 25.3, 18.2, -4.7, -5.0; one signal missing for the *D*-alkynyl carbon. Hydrostannation was effected following the literature procedure for the parent, unlabeled compound.[103] A neat mixture of the TBS-detuerioalkyne (19.0 mmol) and Bu_3SnH (7.1 mL, 26.6 mmol, 1.4 equiv) was treated with 100 mg of azo-bis(cyclohexanecarbonitrile) (ACCN) with stirring, and gradually heated to 130 ºC under argon for 2 h. After TLC analysis indicated reaction completion, the crude compound was cooled to 0 ºC, diluted with THF and treated with a 1.0 M TBAF solution (34.2 mL, 34.2 mmol, 1.8 equiv) over 5 min. The solution was stirred at rt for 40 h, after which TLC indicated completion. The reaction mixture was quenched with aqueous NH_4Cl, then the volatile components were removed under reduced pressure. The residue was extracted (3X) with CH_2Cl_2, the combined organic layers were washed once with NH_4Cl, and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Following

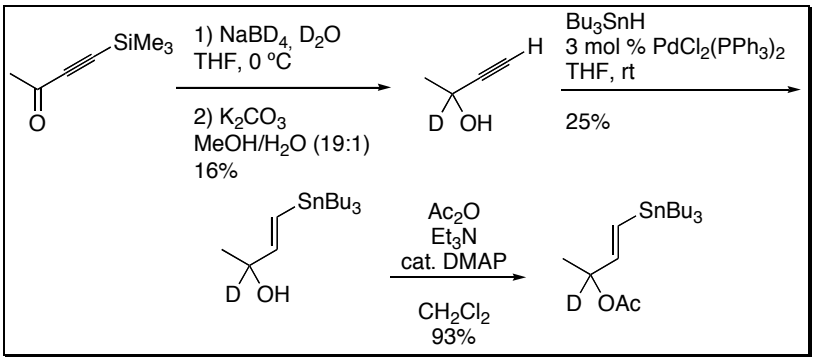
purification by flash chromatography (2% then 5% EtOAc/PE), the title compound was isolated (3.5 g; 51%) as a clear colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (1H, dq, *J* = 2.6, 2.6 Hz, J_{Sn-H} = 63.4 Hz), 4.22 (1H, ddq, *J* = 6.2, 3.8, 3.2 Hz), 1.87 (1H, br d, *J* = 3.7 Hz), 1.53-1.25 (12H, m), 1.24 (3H, d, *J* = 6.4 Hz), 0.87 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 126.0 (**C**-D, t, J_{C-D} = 21.8 Hz), 71.2 (J_{Sn-C} = 62.0), 29.0 (J_{Sn-C} = 20.4 Hz), 27.2 (J_{Sn-C} = 54.6 Hz), 23.0, 13.6, 9.3 (J_{Sn-C} = 342, 328 Hz).

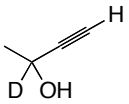


(*E*)-4-Tributylstannyl-4-deuterio-3-buten-2-yl ethanoate 81

Obtained by acetylation of the corresponding tributylstannylalkenol-*d* following General Procedure 2.6.2.1, to afford the title compound (2.76 g, 70%) as a clear colourless liquid after flash chromatography (0% then 2% then 3% EtOAc/PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (1H, br s, J_{Sn-H} = 61.8 Hz), 5.30 (1H, dq, *J* = 6.3, 6.3 Hz), 2.06 (3H, s), 1.56-1.41 (6H, m), 1.36-1.23 (6H, m), 1.29 (3H, d, *J* = 6.7 Hz), 0.88 (15H, t, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 146.9, 129.1 (**C**-D, t, J_{C-D} = 22 Hz), 73.0, 29.0 (J_{Sn-C} = 20.6 Hz), 27.2 (J_{Sn-C} = 54.6 Hz), 21.4, 19.9, 13.7, 9.4 (J_{Sn-C} = 346, 330 Hz); HRMS (EI) Calcd. for $C_{14}H_{26}DO_2Sn$ $(M - Bu)^+$: 344.1090. Found: 344.1093.

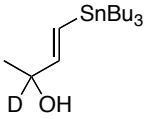
Synthesis of (*E*)-4-tributylstannyl-2-deuterio-3-propen-2-yl ethanoate (82)





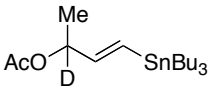
2-Deuterio-3-butyn-2-ol[129]

4-(Trimethylsilyl)-3-butyn-2-one (3.29 g ; 23.5 mmol) was diluted in dry THF (40 mL) and D_2O (3 mL). The solution was cooled to 0 ºC under N_2 and treated with $NaBD_4$ (660 mg, 15.8 mmol) portion-wise. The resulting mixture was allowed to react at 0 ºC for 2 h and at rt for 4 h. The reaction was quenched with careful addition of water then saturated NH_4Cl solution. The volatile components were evaporated *in vacuo* (T_{bath} = 25 ºC), then the aqueous layer was extracted with CH_2Cl_2 (3X). The organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness, to provide a light yellow liquid, which was used as such in the deprotection step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (1H, br s), 1.44 (3H, s), 0.17 (9H, s). The crude TMS-alkynol-*d* was dissolved in 55 mL of MeOH and 5 mL of water, treated with K_2CO_3 (2 g), and heated to reflux for 30 min. The methanol was distilled off under atmospheric pressure, then the residue was diluted with brine and cooled to ~10 ºC. The cold solution was extracted with ether (3X), followed by washing the combined organic extracts with brine (1X), dried ($MgSO_4$), filtering and concentrating by rotary evaporation (T_{bath} < 25 ºC). The residue was transferred in a round-bottom flask for atmospheric distillation of residual methanol and ether, and the product was then distilled under reduced pressure ($bp^{20\ mm\ Hg}$ = 40-42 ºC; lit bp = 108-111 ºC). The title compound was thus isolated (259 mg; 16% yield over 2 steps) as a clear colourless oil, for which characterisation data were in agreement with those published.



(*E*)-4-Tributylstannyl-2-deuterio-3-propen-2-ol

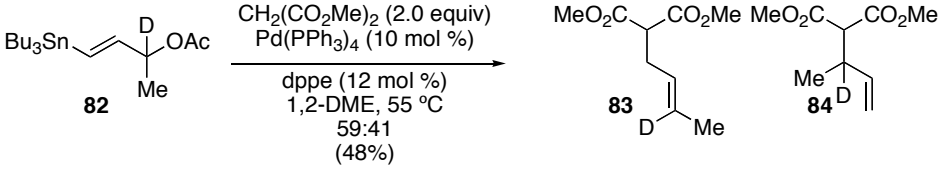
Produced by hydrostannation of the corresponding alkynol following General Procedure 2.6.2.3. The title compound (325 mg, 25%) was obtained as a dark tan oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (1H, d, J = 19.1 Hz, J_{Sn-H} = 70.6 Hz), 6.04 (1H, d, J = 19.2 Hz, J_{Sn-H} = 51.4 Hz), 1.56-1.24 (13H, m), 1.26 (3H, s), 0.80 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 126.5, 70.8 (**C**-D, t, J_{C-D} = 21.8 Hz), 29.2 (J_{Sn-C} = 4.8 Hz), 27.3 (J_{Sn-C} = 67.0 Hz), 22.9, 13.6, 9.4 (J_{Sn-C} = 342, 328 Hz).



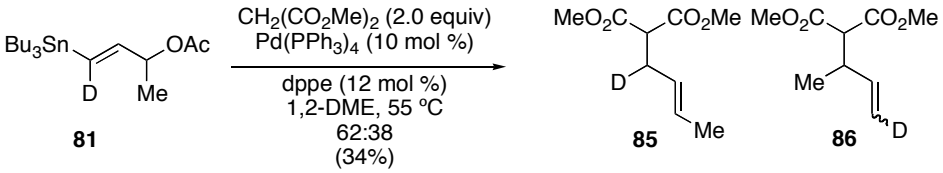
(*E*)-4-Tributylstannyl-2-deuterio-3-propen-2-yl ethanoate 82

Synthesised as a clear colourless oil (268 mg, 93%) by acetylation of the corresponding stannyl alkenol following General Procedure 2.6.2.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (1H, d, J = 19.2 Hz, $J_{Sn\text{-}H}$ = 69.8, 66.8 Hz), 5.92 (1H, d, J = 19.2 Hz, $J_{Sn\text{-}H}$ = 63.2, 61.0 Hz), 2.03 (3H, s), 1.55-1.23 (12H, m), 1.27 (3H, s), 0.93-0.82 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 146.9 ($J_{Sn\text{-}C}$ = 6.4 Hz), 129.4 ($J_{Sn\text{-}C}$ = 368, 350 Hz), 72.7 (**C**-D, t, $J_{C\text{-}D}$ = 22.8 Hz), 29.1 ($J_{Sn\text{-}C}$ = 20.6 Hz), 27.1 ($J_{Sn\text{-}C}$ = 54.8 Hz), 21.3, 19.8, 13.6, 9.4 ($J_{Sn\text{-}C}$ = 346, 330 Hz); HRMS (EI) Calcd. for $C_{14}H_{26}DO_2Sn$ $(M - Bu)^+$: 344.1090. Found: 344.1092.

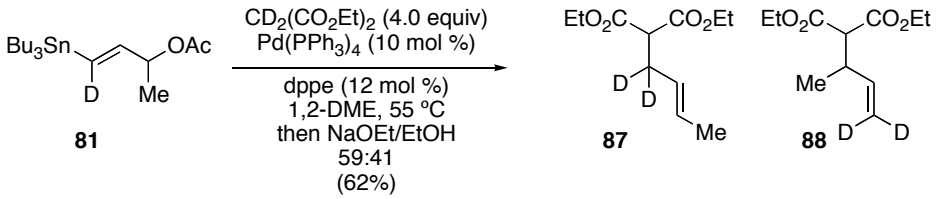
2.6.3.5 Pd-Catalysed Allylation of Deuterium-Labeled Substrates 81-82



Following General Procedure 2.6.2.2 on 168 mg of subtrate **82** (0.416 mmol) and heating for 60 min at 55 ºC, a 48% yield of 59:41 mixture (**83**:**84**) was obtained, whose characterisation data matched those already published for the parent compounds.[128] ^{2}H NMR (46.7 MHz, $CHCl_3$) δ 5.65-5.55 (m), 2.94 (m). LRMS (EI) Calcd. for $C_9H_{13}DO_4$: 187. Found: 187.



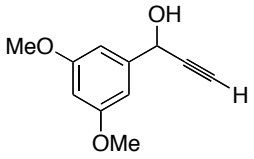
Following General Procedure 2.6.2.2 with 202 mg of subtrate **81** (0.50 mmol) and heating for 90 min at 55 ºC, a 34% yield of 62:38 mixture (**85**:**86**) was obtained, whose characterisation data matched those already published for the parent compounds.[128] ^{2}H NMR (46.7 MHz, $CHCl_3$) δ 5.25-5.02 (m), 2.55 (m). LRMS (EI) Calcd. for $C_9H_{13}DO_4$: 187. Found: 187.



Following General Procedure 2.6.2.2 using 4.0 equiv of diethyl malonate-d_2 (0.30 mL, 2.0 mmol) and 202 mg of subtrate **81** (0.50 mmol) and heating for 3 h at 55 ºC, a 62% yield of 59:41 mixture (**87**:**88**) was obtained, after purification by flash chromatography. The product thus obtained was treated with NaOEt in EtOH (from 100 mg Na in 20 mL EtOH, 2 mL), and stirred for 6 h. Then, the crude mixture was poured into 1% aqueous HCl and extracted with CH_2Cl_2 (3X). The organic layers were dried over $MgSO_4$, filtered and concentrated to dryness, to afford the same mixture of products, whose characterisation data matched those already published for the parent compound.[127] ^{1}H NMR (500 MHz, $CDCl_3$) (major isomer, **87**) δ 5.57 (1H, dq, *J* = 15.2, 6.5 Hz), 5.38 (1H, br d, *J* = 15.2 Hz), 4.23 (4H, q, *J* = 7.0 Hz), 3.41 (1H, s), 2.65-2.56 (0.14H, m, residual allylic 2H, 86%-*D*), 1.64 (3H, dd, *J* = 6.4, 0.6 Hz), 1.31-1.24 (6H, m); (minor isomer, **88**) δ 5.81-5.74 (1H, m), 5.10-5.00 (0.11H, m, residual vinyl H, 89%-*D*), 4.21 (4H, q, *J* = 6.9 Hz), 3.35-3.31 (1H, m), 2.95 (1H, quint, *J* = 6.8 Hz), 1.31-1.24 (6H, m), 1.15 (3H, dd, *J* = 6.6, 6.5 Hz); ^{2}H NMR (46.7 MHz, $CHCl_3$) (combined mixture) δ 5.10-4.98 (m), 2.53 (br s). LRMS (EI) Calcd. for $C_{11}H_{16}D_2O_4$: 216. Found: 216.

2.6.3.6 Preparation of Aryl Substrates 91

Synthesis of (*E*)-3-tributylstannyl-1-(3,5-dimethoxyphenyl)-2-propenyl ethanoate (91a)

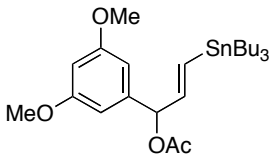


1-(3,5-Dimethoxyphenyl)prop-2-yn-1-ol 95a

Prepared in 73% yield as per General Procedure 2.6.2.4 from 3,5-dimethoxybenzaldehyde.[1] Purified by flash chromatography (100% CH_2Cl_2), to furnish a light yellow oil; ^{1}H NMR (300

[1] 3,5-Dimethoxybenzaldehyde was synthesised in 79% yield by the action of 3,5-dimethoxyphenylmagnesium chloride (prepared by refluxing the aryl chloride (5.0 g) with 5 equiv of

MHz, $CDCl_3$) δ 6.71 (2H, d, *J* = 2.1 Hz), 6.43 (1H, t, *J* = 2.2 Hz), 5.40 (1H, br s), 3.80 (6H, s), 2.66 (1H, d, *J* = 2.2 Hz), 2.04 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 142.3, 104.5, 100.6, 83.3, 74.8, 64.4, 55.4. LRMS (EI) Calcd. for $C_{11}H_{12}O_3$: 192. Found: 192 (M^+).

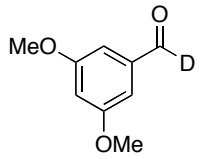


(*E*)- 3-Tributylstannyl-1-(3,5-dimethoxyphenyl)prop-2-enyl ethanoate 91a

(*E*)-1-(3,5-Dimethoxyphenyl)-3-tributylstannylprop-2-en-1-ol **96a** was prepared in 51% yield as per General Procedure 2.6.2.3, and purified by flash chromatography (5% then 10% EtOAc in PE), giving a yellow oil contaminated with 11% of the α-regioisomer, taken as such to the next step. Alkenol acetylation as per General Procedure 2.6.2.1 then afforded a 57% yield of the title acetate, after purification by flash chromatography (5% then 10% EtOAc in PE). Light yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (2H, d, *J* = 2.2 Hz), 6.39 (1H, d, *J* = 2.2 Hz), 6.25 (1H, dd, *J* = 19.0, 1.0 Hz), 6.15, (1H, d, *J* = 5.7 Hz), 6.05 (1H, dd, *J* = 18.9, 5.2 Hz), 3.78 (6H, s), 2.12 (3H, s), 1.52-1.42 (6H, m), 1.28 (6H, dq, *J* = 7.3, 7.3 Hz), 0.91-0.83 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 160.7, 144.6, 141.6, 131.3, 105.1, 99.8, 78.2, 55.2, 29.0 (J_{Sn-C} = 21.0 Hz), 27.2 (J_{Sn-C} = 54.0 Hz), 21.3, 13.6, 9.4 (J_{Sn-C} = 346, 330 Hz); LRMS (EI) Calcd. for $C_{25}H_{42}O_4Sn$: 526. Found: 526, 469 $(M - Bu)^+$.

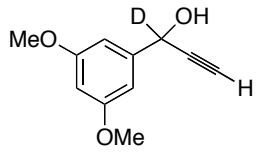
Mg metal and 0.1 mL 1,2-dibromoethane in THF (1.0 M) for 16 h) upon DMF (2.0 equiv) at 0 ºC followed by standard NH_4Cl/EtOAc extractive work-up.

Synthesis of (*E*)-3-tributylstannyl-1-deuterio-1-(3,5-dimethoxyphenyl)-2-propenyl ethanoate (*d*$_1$-1f)



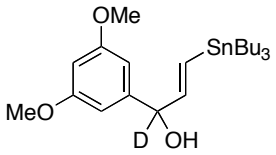
Deuterio-(3,5-dimethoxyphenyl)methanal *d*-94a

Sodium borodeuteride/I_2 reduction of 3,5-dimethoxybenzoic acid (4.00 g, 22.0 mmol) following the reported procedure,[130] and purification by flash chromatography (40% then 60% Et_2O in hexanes) gave 1,1-dideuterio-(3,5-dimethoxyphenyl)methanol in 48% yield (1.8 g). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (2H, d, J = 2.3 Hz), 6.41 (1H, t, J = 2.3 Hz), 3.82 (6H, s), 1.58 (1H, br s). PCC oxidation of the corresponding benzyl alcohol (1.8 g, 10.6 mmol), followed by gravity filtration through Celite, eluting with Et_2O, the filtrate was concentrated to dryness and purified by short column chromatography (20% EtOAc/hexanes), to furnish a clear tan oil which solidified upon standing to a beige solid (62%, 1.10 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (2H, d, J = 1.7 Hz), 6.69 (1H, br s), 3.83 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5 (O=**C**D, t, $J_{C\text{-}D}$ = 26.8 Hz), 161.2, 138.3 (t, $J_{C\text{-}D}$ = 3.5 Hz), 107.1, 107.1, 55.5. LRMS (EI) Calcd. for $C_9H_9DO_3$: 167. Found: 167 (M^+), 137 $[M\text{-}C(=O)D]^+$.



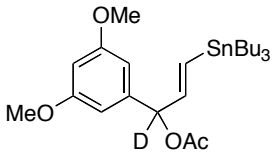
1-Deuterio-1-(3,5-dimethoxyphenyl)prop-2-yn-1-ol *d*-95a

Prepared as per General Procedure 2.6.2.4 from *d*-**94a**. Purified by flash chromatography (15% EtOAc/hexanes) to afford a light tan liquid (992 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (2H, d, J = 2.3 Hz), 6.43 (1H, t, J = 2.3 Hz), 3.80 (6H, s), 2.65 (1H, s), 2.32 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 142.4, 104.5, 100.5, 83.4, 74.6, 63.9 (**C**D_2OH, t, $J_{C\text{-}D}$ = 22.7 Hz), 55.3. LRMS (EI) Calcd. for $C_{11}H_{11}DO_3$: 193. Found: 193.



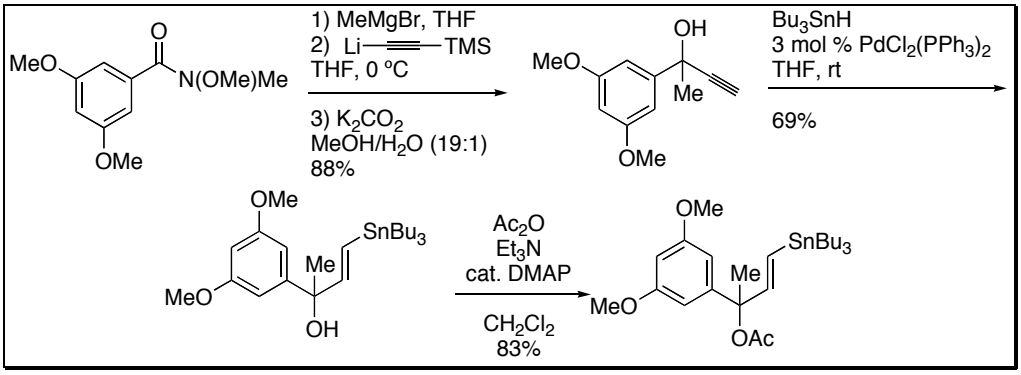
(*E*)-1-Deuterio-3-tributylstannyl-1-(3,5-dimethoxyphenyl)prop-2-en-1-ol *d*-96a

Prepared in 47% yield (1.16 g) as per General Procedure 2.6.2.3 from the alkynol. Purified by flash chromatography (0% then 5% then 10% then 15% EtOAc in PE), to furnish the title compound as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (2H, d, J = 2.3 Hz), 6.38 (1H, t, J = 2.4 Hz), 6.31 (1H, d, J = 19.0 Hz), 6.14 (1H, d, J = 19.0 Hz), 3.79 (6H, s), 1.93 (1H, s), 1.55-1.43 (6H, m), 1.29 (6H, sext, J = 7.3 Hz), 0.95-0.84 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 149.2, 145.3, 128.8, 104.2, 99.7, 55.3, 29.2 ($J_{Sn\text{-}C}$ = 20.6 Hz), 27.7 (**C**D, t, $J_{C\text{-}D}$ = 18.6 Hz), 13.7, 9.5 ($J_{Sn\text{-}C}$ = 344, 330 Hz).

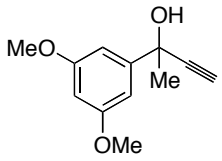


(*E*)- 1-Deuterio-3-tributylstannyl-1-(3,5-dimethoxyphenyl)prop-2-enyl ethanoate *d*-94a

The title compound was synthesised following General Procedure 2.6.2.1, and was purified by flash chromatography (5% EtOAc in PE), to provide 1.02 g (81%) of material. Clear colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.49 (2H, d, J = 2.3 Hz), 6.39 (1H, d, J = 2.2 Hz), 6.25 (1H, dd, J = 19.0, 1.0 Hz, $J_{Sn\text{-}H}$ = 68.4 Hz), 6.06 (1H, d, J = 19.1 Hz, $J_{Sn\text{-}H}$ = 60.2 Hz), 3.78 (6H, s), 2.12 (3H, s), 1.51-1.22 (12H, m), 0.91-0.83 (15H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 160.8, 144.6, 141.5, 131.4 ($J_{Sn\text{-}C}$ = 356, 338 Hz), 105.1, 99.8, 77.8 (**C**D, t, $J_{C\text{-}D}$ = 22.1 Hz), 55.3, 55.2, 29.0 ($J_{Sn\text{-}C}$ = 21.0 Hz), 27.2 ($J_{Sn\text{-}C}$ = 53.8 Hz), 21.3, 13.6, 9.5 ($J_{Sn\text{-}C}$ = 344, 328 Hz); LRMS (EI) Calcd. for $C_{25}H_{41}DO_4Sn$: 527. Found: 527, 470 $(M - Bu)^+$.



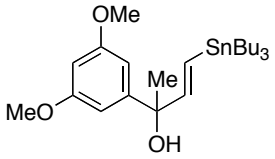
Synthesis of (*E*)-4-tributylstannyl-2-(3,5-dimethoxyphenyl)-3-buten-2-yl ethanoate (91b)



2-(3,5-Dimethoxyphenyl)-3-butyn-2-ol 95b[131]

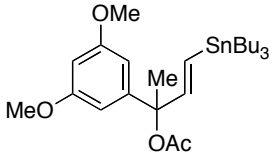
A solution of *N*-methoxy-*N*-methyl-3,5-dimethoxybenzamide (3.6 g, 16.0 mmol) in dry THF (125 mL) was cooled to 0 ºC, and treated with a 3.0 M ether solution of MeMgBr (8.0 mL, 24.0 mmol, 1.5 equiv). After stirring for 1 h at 0 ºC, the reaction mixture was quenched by transferring via cannula into a stirring biphasic mixture of ether (100 mL) and 5% aq. HCl (100 mL). The aqueous layer was then extracted with ether, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. This afforded a light yellow oil that crystallised to an off-white solid, whose spectral properties were in agreement with commercially available 3,5-dimethoxyacetophenone. 1-Lithio-2-trimethylsilylacetylene was formed as per the literature procedure[132] in 80 mL dry ether. To this anion, maintained at 0 ºC, was added the acetophenone derivative **94b** as a solid (+5 mL ether to rinse the flask). The reaction mixture was allowed to gradually reach rt and stirred for 16.5 h, after which it was quenched with saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc, and the combined organics were washed with brine (1X), dried over $MgSO_4$ and concentrated to dryness, to afford a clear colourless oil, which was redissolved in MeOH (100 mL) and H_2O (5 mL). To this solution was added K_2CO_3 (12.3 g, 89.1 mmol, 5.6 equiv) and the reaction mixture was allowed to stir for 90 min at rt then diluted with H_2O (100 mL). The aqueous layer was extracted (3X EtOAc), then the organics were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated to dryness. The crude orange oil was purified by flash

chromatography (25% EtOAc/hexanes) to afford the title compound as a clear colourless oil (2.9 g, 88% over 3 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (2H, d, J = 2.2 Hz), 6.40 (1H, t, J = 2.2 Hz), 3.80 (6H, s), 2.65 (1H, s), 2.43 (1H, s), 1.77 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 147.6, 103.2, 99.7, 87.2, 72.9, 69.9, 55.4, 33.0. LRMS (EI) Calcd. for $C_{12}H_{14}O_3$: 206. Found: 206 (M^+), 191 $(M\text{-}CH_3)^+$.



(*E*)-4-Tributylstannyl-2-(3,5-dimethoxyphenyl)-3-buten-2-ol 96b

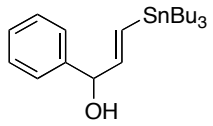
The title compound was made by hydrostannylation (General Procedure 2.6.2.3) in 69% yield (4.8 g), as a light yellow liquid, following purification by flash chromatography (0% then 5% then 10% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (2H, d, J = 2.3 Hz), 6.35 (1H, t, J = 2.2 Hz), 6.32-6.12 (2H, m), 3.78 (6H, s), 2.03 (1H, s), 1.61 (3H, s), 1.55-1.44 (6H, m), 1.29 (6H, sext, J = 7.3 Hz), 0.94-0.84 (15H, m); ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 160.6, 153.5, 149.5, 124.6 ($J_{Sn\text{-}C}$ = 360, 346 Hz), 103.5, 98.7, 76.1, 55.2, 29.2, 29.0, ($J_{Sn\text{-}C}$ = 20 Hz), 27.2 ($J_{Sn\text{-}C}$ = 54 Hz), 13.7, 9.5 ($J_{Sn\text{-}C}$ = 344, 330 Hz).



(*E*)-4-Tributylstannyl-2-(3,5-dimethoxyphenyl)-3-buten-2-yl ethanoate 94b

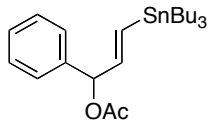
The title ester was synthesised via General Procedure 2.6.2.1 in 83% yield (4.31 g), isolated as a light yellow low-melting solid following flash chromatography (5% then 10% Et_2O/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.51 (2H, d, J = 2.2 Hz), 6.35 (1H, t, J = 2.2 Hz), 6.32 (1H, d, J = 19.4 Hz), 6.26 (1H, d, J = 19.4 Hz), 3.77 (6H, s), 2.07 (3H, s), 1.84 (3H, s), 1.52-1.27 (12H, m), 0.93-0.86 (15H, m); ^{13}C NMR (125 MHz, JMOD, $CDCl_3$) δ 169.1, 160.5, 149.8 ($J_{Sn\text{-}C}$ = 8.2 Hz), 146.7, 127.6 ($J_{Sn\text{-}C}$ = 364, 348 Hz), 103.9, 98.4, 84.3, 55.2, 29.0, ($J_{Sn\text{-}C}$ = 21.2 Hz), 27.2 ($J_{Sn\text{-}C}$ = 54.4 Hz), 25.4, 22.2, 13.6, 9.5 ($J_{Sn\text{-}C}$ = 344, 330 Hz). LRMS (EI) Calcd. for $C_{22}H_{35}O_4Sn$ $(M - Bu)^+$: 483. Found: 483, 424 $[M - (2X\ Bu)]^+$.

Synthesis of (*E*)-3-tributylstannyl-1-phenyl-2-propenyl ethanoate (91c)



(*E*)-1-Phenyl-3-tributylstannylprop-2-en-1-ol[133] 96c

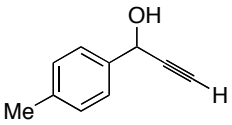
Prepared in 41% yield from 1-phenylprop-2-yn-1-ol[134] as per General Procedure 2.6.2.3. Purified by flash chromatography (0% then 2% then 5% EtOAc in PE). Light yellow oil.



(*E*)-1-Phenyl-3-tributylstannylprop-2-enyl ethanoate 91c

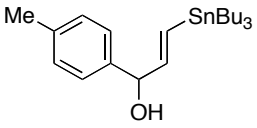
Prepared in 87% yield as per General Procedure 2.6.2.1. Purified by flash chromatography (0% then 2% then 5% EtOAc in PE). Clear colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.27 (5H, m), 6.27 (1H, dd, J = 19.3, 1.0 Hz), 6.25 (1H, dd, J = 4.8, 0.9 Hz), 6.09 (1H, dd, J = 19.4, 4.7 Hz), 2.11 (3H, s), 1.50-1.42 (6H, m), 1.28 (6H, dq, J = 7.1, 7.1 Hz), 0.92-0.84 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 144.9, 139.3, 131.1, 128.4, 127.9, 127.3, 78.3, 29.0 ($J_{Sn\text{-}C}$ = 20.8 Hz), 27.2 ($J_{Sn\text{-}C}$ = 54.2 Hz), 21.3, 13.6, 9.5 ($J_{Sn\text{-}C}$ = 344, 328 Hz).

Synthesis of (*E*)-3-tributylstannyl-1-(4-methylphenyl)-2-propenyl ethanoate (91d)



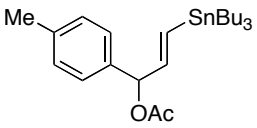
1-(4-Methylphenyl)prop-2-yn-1-ol[135] 95d

Prepared as per General Procedure 2.6.2.4 from TMS-acetylene and 4-methylbenzaldehyde, and carried as such to the hydrostannation, without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (2H, d, J = 7.9 Hz), 7.20 (2H, d, J = 7.8 Hz), 5.43 (1H, br d, J = 4.9 Hz), 2.66 (1H, d, J = 2.1 Hz), 2.36 (3H, s), 2.18 (1H, d, J = 6.1 Hz).



(*E*)-1-(4-Methylphenyl)-3-tributylstannylprop-2-en-1-ol 96d

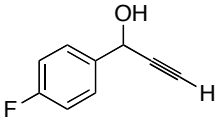
The 4-Me alkynol was hydrostannylated according to General Procedure 2.6.2.3, to provide the title compound as a yellow oil following flash chromatographic purification (0% then 5% Et_2O/hexanes), and furnish 3.5 g of the title compound (48% yield over 2 steps). ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (2H, d, J = 8.0 Hz), 7.16 (2H, d, J = 8.1 Hz), 6.30 (1H, dd, J = 19.0, 0.9 Hz, J_{Sn-H} = 68.2 Hz), 6.17 (1H, dd, J = 19.1, 4.9 Hz, J_{Sn-H} = 70.0, 60.4 Hz), 5.14 (1H, br t, J = 4.1 Hz), 2.35 (3H, s), 1.99 (1H, d, J = 3.9 Hz), 1.53-1.21 (12H, m), 0.98-0.88 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 139.9, 137.2, 129.1, 128.2, 126.4, 77.4 29.1 (J_{Sn-C} = 20.6 Hz), 27.2 (J_{Sn-C} = 55.0 Hz), 21.2, 13.7, 9.5 (J_{Sn-C} = 344, 330 Hz).



(*E*)-1-(4-Methylphenyl)-3-tributylstannylprop-2-enyl ethanoate (91d)

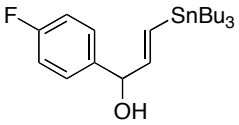
The title compound was prepared according to General Procedure 2.6.2.1, to provide 2.67 g (70%) of a light yellow oil, following flash chromatographic purification (5% Et_2O/hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (2H, d, J = 8.1 Hz), 7.17 (2H, d, J = 8.1 Hz), 6.25 (1H, dd, J = 19.2, 1.1 Hz, J_{Sn-H} = 64.2, 61.0 Hz), 6.24 (1H, d, J = 5.3 Hz), 6.09 (1H, dd, J = 19.2, 5.3 Hz), 2.36 (3H, s), 2.11 (3H, s), 1.53-1.25 (12H, m), 0.97-0.85 (15H, m); ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 169.9, 145.0, 137.7, 136.3, 130.7, 129.1, 127.3, 78.1 (J_{Sn-C} = 62 Hz), 29.0 (J_{Sn-C} = 20), 27.2 (J_{Sn-C} = 54), 21.3, 21.1, 13.6, 9.4 (J_{Sn-C} = 344, 328).

Synthesis of (*E*)-3-tributylstannyl-1-(4-fluorophenyl)-2-propenyl ethanoate (91e)



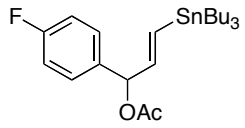
1-(4-Fluorophenyl)prop-2-yn-1-ol 95e

Prepared as per General Procedure 2.6.2.4 from TMS-acetylene and 4-fluorobenzaldehyde, and taken as such to the hydrostannation without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (2H, ddd, *J* = 8.5, 5.3, 1.6 Hz), 7.07 (2H, ddd, *J* = 8.6, 8.6, 2.0 Hz), 5.45 (1H, d, *J* = 1.8 Hz), 2.68 (1H, d, *J* = 2.2 Hz), 2.14 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7 (d, $J_{C\text{-}F}$ = 246 Hz), 135.8 (d, $J_{C\text{-}F}$ = 3.4 Hz), 128.5 (d, $J_{C\text{-}F}$ = 8.4 Hz), 115.5 (d, $J_{C\text{-}F}$ = 21.3 Hz), 83.3, 75.1, 63.7. HRMS (EI) Calcd. for C_9H_7OF: 150.0481. Found: 150.0481.



(*E*)-1-(4-Fluorophenyl)-3-tributylstannylprop-2-en-1-ol 96e

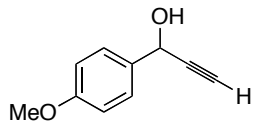
The title compound was prepared in 35% yield over 2 steps (2.9 g) from 4-fluorobenzaldehyde, after hydrostannylation as per General Procedure 2.6.2.3. Purified by filtration through a plug of silica gel (0% then 20% Et_2O in hexanes), followed by flash chromatography of the residue (5% then 15% Et_2O/hexanes), to furnish a light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (2H, ddd, *J* = 8.5, 5.5, 2.0 Hz), 7.03 (2H, ddd, *J* = 8.7, 8.6, 2.1 Hz), 6.29 (1H, dd, *J* = 19.0, 0.9 Hz, $J_{Sn\text{-}H}$ = 66.4 Hz), 6.14 (1H, dd, *J* = 19.0, 5.2 Hz, $J_{Sn\text{-}H}$ = 61.6, 59.2 Hz), 5.16 (1H, t, *J* = 4.3 Hz), 2.01 (1H, d, *J* = 3.8 Hz), 1.54-1.43 (6H, m), 1.31 (6H, sext, *J* = 7.3 Hz), 0.93-0.83 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2 (d, $J_{C\text{-}F}$ = 246 Hz), 149.3, 138.5 (d, $J_{C\text{-}F}$ = 3.1 Hz), 128.9, 128.0 (d, $J_{C\text{-}F}$ = 8.1 Hz), 115.2, (d, $J_{C\text{-}F}$ = 21.4 Hz), 76.9, 29.0 ($J_{Sn\text{-}C}$ = 20.6 Hz), 27.2 ($J_{Sn\text{-}C}$ = 54.6 Hz), 13.7, 9.5 ($J_{Sn\text{-}C}$ = 346, 330 Hz).



(*E*)-1-(4-Fluorophenyl)-3-tributylstannylprop-2-enyl ethanoate 91e

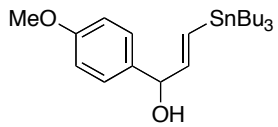
Prepared by following General Procedure 2.6.2.1. Purified by flash chromatography (5% Et_2O/hexanes), and obtained (2.77 g, 87%) as a clear colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (2H, ddd, J = 8.7, 5.4, 2.0 Hz), 7.03 (2H, ddd, J = 8.8, 8.7, 2.1 Hz), 6.23 (1H, dd, J = 19.2, 1.0 Hz, J_{Sn-H} = 67.8, 65.4 Hz), 6.20 (1H, d, J = 5.3 Hz), 6.08 (1H, dd, J = 19.3, 4.7 Hz, J_{Sn-H} = 61.2, 58.8 Hz), 2.11 (3H, s), 1.52-1.41 (6H, m), 1.31 (6H, sext, J = 7.1 Hz), 0.93-0.80 (15H, m); ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 169.8, 162.4 (d, J_{C-F} = 247 Hz), 144.8 (J_{Sn-C} = 4.1 Hz), 135.1 (d, J_{C-F} = 3.1 Hz), 131.4, 129.0 (d, J_{C-F} = 8.2 Hz), 115.2 (d, J_{C-F} = 21.5 Hz), 78.0 (J_{Sn-C} = 63.8 Hz), 29.0 (J_{Sn-C} = 20.8 Hz), 27.1 (J_{Sn-C} = 54.6 Hz), 21.2, 13.6, 9.5 (J_{Sn-C} = 346, 330 Hz); LRMS (EI) Calcd. for $C_{23}H_{37}FO_2Sn$: 484. Found: 484, 427 $(M - Bu)^+$.

Synthesis of (*E*)-3-tributylstannyl-1-(4-methoxyphenyl)-2-propenyl ethanoate (91f)



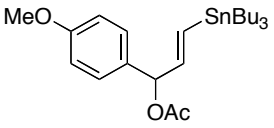
1-(4-Methoxyphenyl)prop-2-yn-1-ol 95f

Prepared in 87% yield as per General Procedure 2.6.2.4. The yellow oil thus obtained was taken to the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (2H, dd, J = 8.7, 1.9 Hz), 6.91 (2H, dd, J = 8.7, 2.2 Hz), 5.42 (1H, br d, J = 3.3 Hz), 3.82 (3H, s), 2.67 (1H, d, J = 2.2 Hz), 2.11 (1H, d, J = 5.6 Hz).



(*E*)-1-(4-Methoxyphenyl)-3-tributylstannylprop-2-en-1-ol 96f

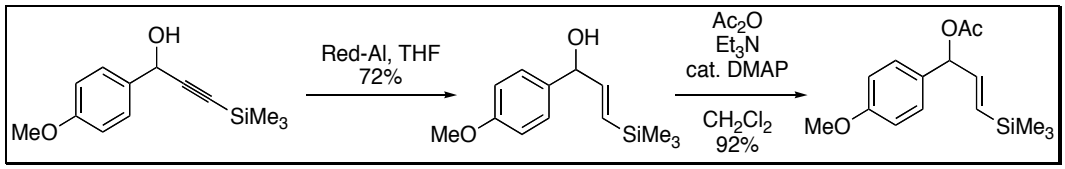
Prepared in 50% yield as per General Procedure 2.6.2.3. Purified by flash chromatography (0% then 1% then 5% then 10% EtOAc in PE), and the tan oil was taken as such to the next step.

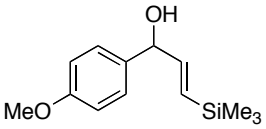


(*E*)-1-(4-Methoxyphenyl)-3-tributylstannylprop-2-enyl ethanoate 91f

Prepared in 76% yield as per General Procedure 2.6.2.1. Purified by flash chromatography on Et_3N-pretreated silica gel (0% then 1% then 5% then 10% EtOAc in PE). Light yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (2H, dd, *J* = 8.5, 2.0 Hz), 6.86 (2H, dd, *J* = 8.7, 2.1 Hz), 6.21 (1H, d, *J* = 4.8 Hz), 6.20 (1H, dd, *J* = 19.3, 0.9, $J_{Sn\text{-}H}$ = 60.2 Hz), 6.08 (1H, dd, *J* = 19.3, 4.3 Hz, $J_{Sn\text{-}H}$ = 62.6 Hz), 3.80 (3H, s), 2.09 (3H, s), 1.54-1.22 (12H, m), 0.93-0.83 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 159.4, 145.1, 131.4, 130.6, 128.9, 113.8, 77.9, 55.2, 29.0, 27.2, 21.3, 13.7, 9.5. Decomposed upon standing as the neat liquid at 4 ºC for 16 h.

Synthesis of (*E*)-1-(4-Methoxyphenyl)-3-trimethylsilylprop-2-enyl ethanoate (97f)

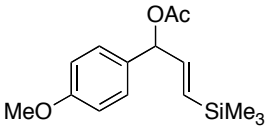




3-Trimethylsilyl-1-(4-methoxyphenyl)-2-propen-1-ol[136]

RedAl™ (65 wt.% in PhMe, 5.2 mL; 17.4 mmol) was diluted in 35 mL of dry THF and cooled to 0 ºC. Then, (3-(4-methoxyphenyl)-3-hydroxy-1-propynyl)trimethylsilane (2.04 g; 8.68 mmol) was added dropwise (gas evolution!) and quantitatively transferred rinsing with 2X 3 mL dry THF. Following addition, the reaction was allowed to reach rt and stirred for 4 h at that temperature. Following completion (TLC monitoring), the reaction was carefully quenched by dropwise addition of 2 mL of 15% aqueous NaOH. After gas evolution had subsided, the heterogeneous mixture was diluted with ether and filtered through a pad of Celite, which was rinsed with ether. The organic layer was collected and washed (3X) with brine. The aqueous layer was back-extracted with ether (1X) then the organic layers were pooled, dried over

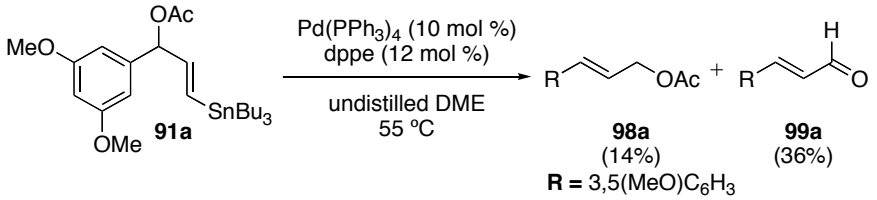
Na_2SO_4, filtered and concentrated to dryness. The crude composition was purified by flash chromatography (15% EtOAc/PE) to furnish the title compound as a clear colourless oil (1.56 g; 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (2H, dd, *J* = 8.7, 1.9 Hz), 6.89 (2H, dd, *J* = 8.7, 2.0 Hz), 6.21 (1H, dd, *J* = 18.6, 5.0 Hz), 5.98 (1H, dd, *J* = 18.7, 1.4 Hz), 5.13 (1H, br t, *J* = 3.9 Hz), 3.80 (3H, s), 2.00 (1H, d, *J* = 3.7 Hz), 0.08 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 147.3, 134.9, 129.5, 127.8, 113.9, 76.3, 55.2, -1.3. LRMS (EI) Calcd. for $C_{13}H_{20}O_2Si$: 236. Found: 236 (M^+), 221 $(M\text{-}CH_3)^+$.



(*E*)-1-(4-Methoxyphenyl)-3-trimethylsilylprop-2-enyl ethanoate 97f

Prepared in 92% yield (1.69 g) by acetylation of the previously obtained TMS-alkenol, according to General Procedure 2.6.2.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.7 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 6.21 (1H, d, *J* = 5.0 Hz), 6.13 (1H, dd, *J* = 18.4, 4.8 Hz), 5.88 (1H, d, *J* = 18.4 Hz), 3.81 (3H, s), 2.10 (3H, s), 0.07 (9H, s); ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 170.0, 159.4, 143.0, 131.4, 131.1, 128.9, 113.9, 77.1, 55.2, 21.3, -1.4. HRMS (EI) Calcd. for $C_{15}H_{22}O_3Si$: 278.1338. Found: 278.1329.

2.6.3.7 Pd-Catalysed Dimerisation

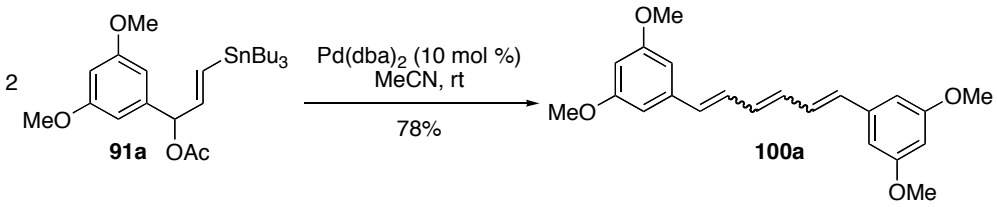


Reaction of Stannane 91a in Undistilled DME

3,5-Dimethoxycinnamyl Acetate 98a and 3,5-Dimethoxycinnamaldehyde 99a

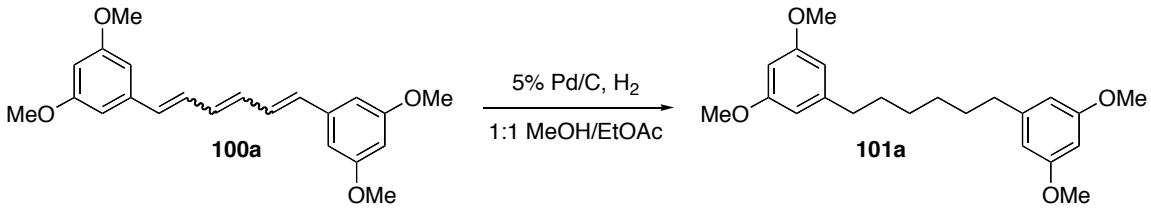
1,2-Dimethoxyethane was used as received from the commercial source, without drying or deoxygenating. In a Schlenk tube was loaded substrate **91a** (131 mg, 0.25 mmol, 1.0 equiv) and 2.5 mL DME under Ar, followed by $Pd(PPh_3)_4$ (29 mg, 0.025 mmol, 10 mol %) and dppe

(12 mg, 0.030 mmol, 12 mol %) and DME (2.5 mL). The resulting solution was allowed to stir in the sealed vessel for 2 h at 55 ºC, after which TLC indicated reaction completion. Following flash chromatography (10% then 15% EtOAc/PE), the two title products were isolated. **3,5-Dimethoxycinnamyl Ethanoate 98a** (8.5 mg, 14%) R_f 0.19 (10% EtOAc/PE), white film; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (1H, d, *J* = 16.0 Hz), 6.55 (2H, d, *J* = 2.3 Hz), 6.39 (1H, t, *J* = 2.3 Hz), 6.26 (1H, dt, *J* = 15.8, 6.6 Hz), 4.71 (2H, dd, *J* = 6.5, 1.1 Hz), 3.79 (6H, s); LRMS (EI) Calcd. for $C_{13}H_{16}O_4$: 236. Found: 236. **3,5-Dimethoxycinnamaldehyde 99a** (17.1 mg, 36%) R_f 0.14 (10% EtOAc/PE), white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (1H, d, *J* = 7.7 Hz), 7.40 (1H, d, *J* = 15.9 Hz), 6.70 (2H, d, *J* = 2.4 Hz), 6.72-6.67 (1H, m), 6.55 (1H, t, *J* = 2.3 Hz), 3.83 (6H, s); LRMS (EI) Calcd. for $C_{11}H_{12}O_3$: 192. Found: 192.



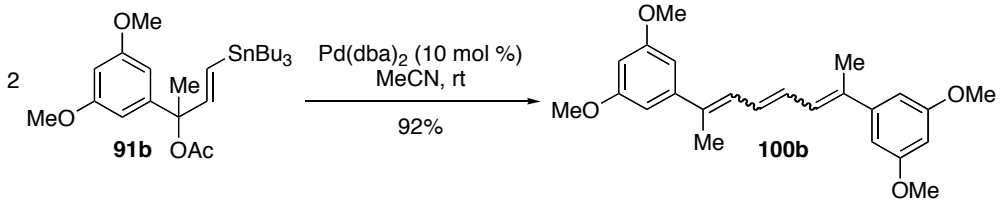
1,6-bis(3,5-Dimethoxyphenyl)-1,3,5-hexatriene 100a

As described in General Procedure 2.6.2.5 at a reaction temperature of 55 ºC, using stannane **91a**. The reaction was conducted in a tightly sealed vial, to furnish the title compound (17 mg, 39%) as a yellow solid following purification by flash chromatography (10% then 15% EtOAc/ hexanes). This compound was also obtained in 78% yield when following General Procedure 2.6.2.5 without deviation. Data for the (*E*,*E*,*E*)-compound: Mp (CH_2Cl_2): 139.5-141.5 ºC. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 (4H, d, *J* = 8.1 Hz), 7.12 (4H, d, *J* = 7.9 Hz), 6.83 (ddd, 2H, *J* = 15.5, 7.1, 3.2 Hz), 6.56 (2H, d, *J* = 15.5 Hz), 6.48 (2H, dd, *J* = 7.0, 3.0 Hz), 2.34 (6H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.4, 134.7, 133.3, 132.4, 129.4, 128.3, 126.3, 21.3; HRMS (EI) Calcd. for $C_{22}H_{24}O_4$: 352.1675. Found: 352.1669.



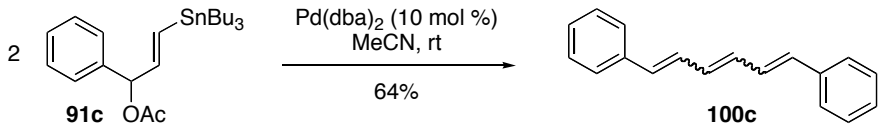
1,6-bis(3,5-Dimethoxyphenyl)hexane 101a

To further prove its structure by derivatisation, the diastereomeric mixture of dimerised products **100a** (17 mg; 0.048 mmol) was suspended in 2.5 mL MeOH and 2.5 mL EtOAc and purged with N_2 three times by evacuating the solution (water aspirator, 2 min) and back-filling with N_2. The suspension was then treated with 15 mg 5% Pd/C and purged with H_2 as described above (three times), and stirred vigorously for 1.7 h. The black mixture was then purged with N_2, filtered on silica gel in a Pasteur pipette, and the filtrate was concentrated to dryness, to afford the title compound as a clear colourless liquid that solidified to white crystals after prolonged storage at 4 ºC. Mp (hexanes): 32.5-33.5 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.34 (4H, d, *J* = 2.2 Hz), 6.29 (2H, t, *J* = 2.2 Hz), 3.78 (12H, s), 2.54 (4H, dd, *J* = 7.8, 7.5 Hz), 1.67-1.54 (4H, m), 1.39-1.32 (4H, m); ^{13}C NMR ($CDCl_3$, JMOD, 75 MHz) δ 160.6, 145.3, 106.4, 97.5, 55.2, 36.2, 31.2, 29.1; HRMS (EI) Calcd. for $C_{22}H_{30}O_4$: 358.2144. Found: 358.2137.



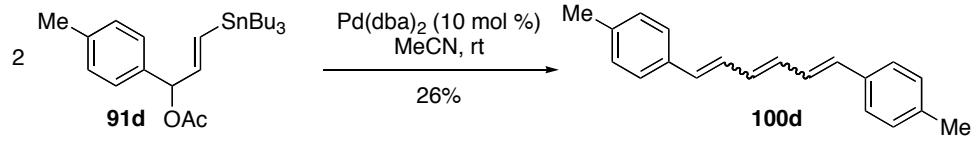
2,7-bis(3,5-Dimethoxyphenyl)-2,4,6-octatriene 100b

As described in General Procedure 2.6.2.5, using substrate **91b**, the reaction afforded the title compound in 92% yield after purification by column chromatography (8% Et_2O/PE). Data for the (*E*,*E*,*E*)-compound: Yellow viscous oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.74-6.35 (10H, m), 3.84-3.77 (12H, m), 2.20-2.02 (6H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) (peaks for the major isomer given) δ 160.6, 145.1, 136.3, 130.3, 127.8, 103.9, 99.1, 55.3, 16.2; HRMS (EI) Calcd. for $C_{24}H_{28}O_4$: 380.1988. Found: 380.1990.



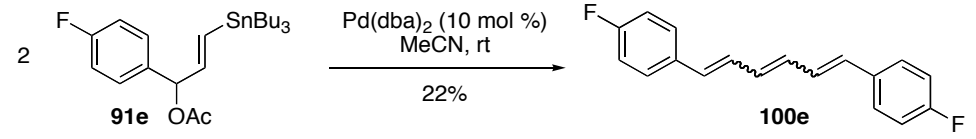
1,6-Diphenyl-1,3,5-hexatriene 100c[137]

As described in General Procedure 2.6.2.5, using substrate **91c**, the reaction afforded the title compound in 64% yield after purification by column chromatography (2% Et_2O/PE). ^1H NMR data were in agreement with those published for the (*E*,*E*,*E*)-compound: Yellow needles; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.43 (4H, d, *J* = 7.5 Hz), 7.33 (4H, t, *J* = 7.4 Hz), 7.24 (2H, t, *J* = 7.3 Hz), 6.90 (2H, ddd, *J* = 15.5, 7.0, 3.0 Hz), 6.61 (2H, d, *J* = 15.5 Hz), 6.53 (2H, dd, *J* = 7.0, 2.9 Hz); ^{13}C NMR ($CDCl_3$, JMOD, 125 MHz) δ 137.4, 133.6, 132.7, 129.1, 128.6, 127.5, 126.4.



1,6-bis(4-Methylphenyl)-1,3,5-hexatriene 100d[138]

As described in General Procedure 2.6.2.5, using substrate **91d**, the reaction afforded the title compound in 26% yield after purification by column chromatography (0 then 5% Et_2O/PE). Data for the (*E*,*E*,*E*)-compound: Yellow glassy solid. Mp (CH_2Cl_2): 184.0-186.5 ºC. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31 (4H, d, *J* = 8.1 Hz), 7.12 (4H, d, *J* = 7.9 Hz), 6.83 (ddd, 2H, *J* = 15.5, 7.1, 3.2 Hz), 6.56 (2H, d, *J* = 15.5 Hz), 6.48 (2H, dd, *J* = 7.0, 3.0 Hz), 2.34 (6H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.4, 134.7, 133.3, 132.4, 129.4, 128.3, 126.3, 21.3. HRMS (EI) Calcd. for $C_{20}H_{20}$: 260.1565. Found: 260.1573.

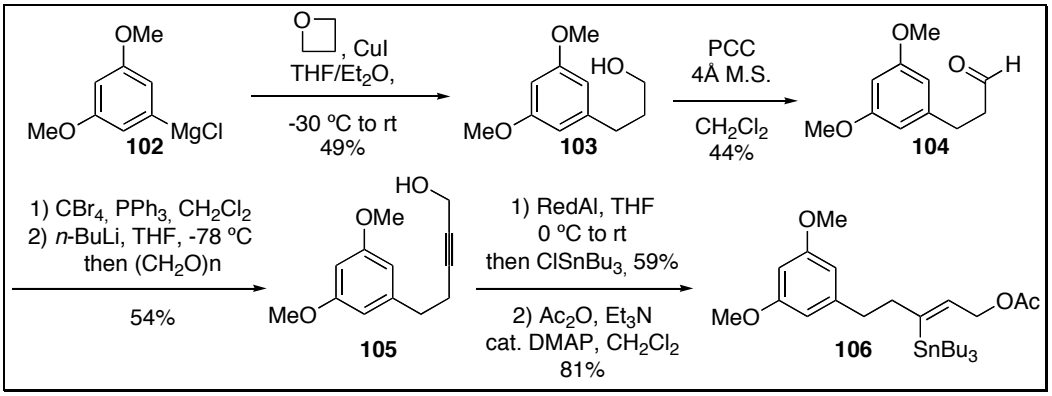


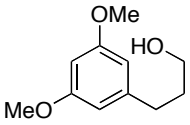
1,6-bis(4-Fluorophenyl)-1,3,5-hexatriene 100e[138]

As described in General Procedure 2.6.2.5, using substrate **91e**, the reaction afforded the title compound in 22% yield after purification by column chromatography (5% Et_2O/PE). Data for the (*E*,*E*,*E*)-compound: White solid. Mp (CH_2Cl_2): 209.5-212.0 ºC. ^1H NMR ($CDCl_3$, 500

MHz) δ 7.37 (4H, dd, J = 8.5, 5.6 Hz), 7.01 (4H, t, J = 8.6 Hz), 6.78 (ddd, 2H, J = 15.4, 6.9, 2.9 Hz), 6.55 (2H, d, J = 15.4 Hz), 6.49 (2H, dd, J = 6.9, 2.8 Hz); ^{13}C NMR ($CDCl_3$, JMOD, 125 MHz) δ 162.2 (d, $J_{C\text{-}F}$ = 246 Hz), 133.5 (d, $J_{C\text{-}F}$ = 3.5 Hz), 133.3, 131.4, 128.8, 127.8 (d, $J_{C\text{-}F}$ = 8.0 Hz), 115.6 (d, $J_{C\text{-}F}$ = 21.6 Hz); HRMS (EI) Calcd. for $C_{18}H_{14}F_2$: 268.1064. Found: 268.1074.

2.6.3.8 Preparation of Second-Generation Substrate 106

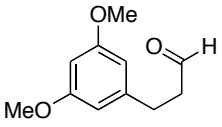




3-(3,5-Dimethoxyphenyl)propan-1-ol 103

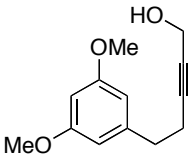
An oven-dried round-bottom flask was loaded successively with Mg metal (766 mg, 31.9 mmol, 1.1 equiv) and 1,2-dibromoethane (0.1 mL) in THF (15 mL) under Ar. The grey suspension was stirred for 5 min whereupon 3,5-dimethoxychlorobenzene (5.00 g, 29.0 mmol, 1.0 equiv) was added all at once. The reaction mixture was heated to reflux for 15 h. The Grignard reagent thus prepared was cooled to rt and transferred via cannula onto a stirred suspension of CuI (5.52 g, 29.0 mmol, 1.0 equiv) and oxetane (2.1 mL, 32 mmol, 1.1 equiv) in Et_2O (105 mL) while cooling to –30 ºC, over 30 min. After addition was complete, the reaction mixture was allowed to reach rt, at which temperature it was stirred for 40 h. The reaction was quenched with 100 mL 9:1 (NH_4Cl sat.: aq. NH_3). Most volatiles were removed by rotary evaporation, and the aqueous phase was extracted with 2X (1:1 EtOAc/hexanes). The

combined organics were washed successively with 9:1 (NH_4Cl sat.: aq. NH_3) (1X), H_2O (1X), brine (1X), dried over $MgSO_4$, filtered, and concentrated to dryness. Analysis by ^1H NMR of the crude mixture indicated 59% conversion. The product was purified by flash chromatography (2% MeOH/CH_2Cl_2) to afford the title compound as a light orange oil (2.76 g, 49%). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.36 (2H, t, *J* = 2.3 Hz), 6.31 (1H, t, *J* = 2.3 Hz), 3.78 (6H, s), 3.68 (2H, t, *J* = 6.4 Hz), 2.66 (2H, dd, *J* = 8.0, 7.4 Hz), 1.88 (dt, *J* = 7.5, 6.4 Hz), 1.31 (1H, br s).



3-(3,5-Dimethoxyphenyl)propanal 104

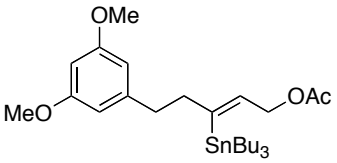
A suspension of alcohol **103** (2.76 g, 14.1 mmol) and 4Å molecular sieves (2.8 g, 100 wt.%) in CH_2Cl_2 was treated with PCC (3.33 g, 15.5 mmol, 1.1 equiv) in one portion. The resulting reaction mixture, which turned brown instantly, was stirred at rt for 50 min, whereupon TLC indicated reaction completion. The crude mixture was filtered through a pad of silica gel, eluting with CH_2Cl_2, and the crude product was then purified by flash chromatography (15% then 20% EtOAc/PE) to afford the title compound as a dark tan liquid (1.19 g, 44%). ^1H NMR ($CDCl_3$, 300 MHz) δ 9.80 (1H, d, *J* = 1.4 Hz), 6.35 (2H, d, *J* = 2.2 Hz), 6.30 (1H, t, *J* = 2.2 Hz), 3.76 (6H, s), 2.92-2.84 (2H, m), 2.75 (2H, dt, *J* = 8.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.4, 160.9, 142.7, 106.3, 98.0, 55.2, 45.0, 28.3. LRMS (EI) Calcd. for $C_{11}H_{14}O_3$: 194. Found: 194 (M^+), 165 [M-CH(=O)]$^+$.



5-(3,5-Dimethoxyphenyl)pent-2-yn-1-ol 105

CBr_4 (2.18 g, 6.56 mmol, 1.07 equiv) was added to PPh_3 (3.44 g, 13.1 mmol, 2.15 equiv) in CH_2Cl_2 (50 mL) under N_2 and the resulting orange solution was stirred for 15 min. Then, aldehyde **104** (1.19 g, 6.12 mmol, 1.00 equiv) was added as a CH_2Cl_2 solution (10 then 2X5 mL) via cannula. The reaction was stirred at rt for 2h, after which further CBr_4 (218 mg, 0.10

equiv) and PPh_3 (344 mg, 0.20 equiv) were added, which drove the reaction to completion after a further 30 min of stirring (TLC monitoring). The solvent was removed under reduced pressure, and the residue was triturated in 15% EtOAc/PE (60 mL) for 15 min. The slurry was filtered over silica gel, washed thoroughly with 15% EtOAc/PE, and the filtrate was concentrated to dryness. The intermediate dibromoalkene was carried on to the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.41 (1H, t, *J* = 7.1 Hz), 6.35-6.32 (3H, m), 3.79 (6H, s), 2.68 (2H, dd, *J* = 7.9, 7.4 Hz), 2.41 (2H, dt, *J* = 7.8, 7.4 Hz). The dibromide (6.12 mmol) was dissolved in THF (25 mL), flushed with Ar, cooled to –78 ºC and treated with a hexanes solution of *n*-BuLi (2.4 M, 5.5 mL, 13.0 mmol, 2.1 equiv) dropwise. After 30 min at that temperature, powdered $(CH_2O)_n$ was added as a solid. The white suspension was stirred at –78 ºC for 15 min and allowed to warm up to 0 ºC. After 1 h at 0 ºC, the reaction mixture was quenched with $NaHCO_3$ (20 mL) and diluted with ether. The organic layer was washed with brine (1X), dried over Na_2SO_4, filtered and concentrated to dryness. The crude alkynol was then purified by flash chromatography (33% EtOAc/PE) to afford the title compound as a viscous, light tan oil (787 mg, 54%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.38 (2H, d, *J* = 2.3 Hz), 6.33 (1H, t, *J* = 2.3 Hz), 4.24 (2H, t, *J* = 2.1 Hz), 3.78 (6H, s), 2.77 (2H, t, *J* = 7.6 Hz), 2.50 (2H, tt, *J* = 7.5, 2.1 Hz), 1.50 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.7, 142.9, 106.5, 98.2, 85.6, 79.1, 55.2, 51.3, 35.2, 20.7. LRMS (EI) Calcd. for $C_{13}H_{16}O_3$: 220. Found: 220 (M^+), 189 ($M\text{-}CH_2OH^+$)



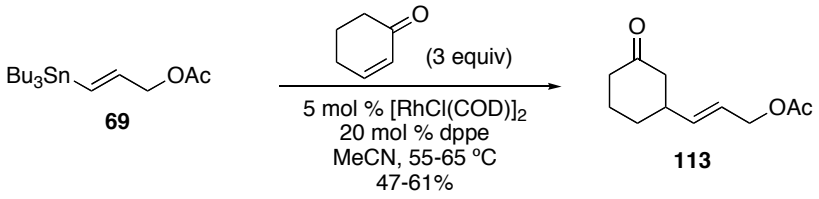
3-Tributystannyl-5-(3,5-dimethoxyphenyl)pent-2-enyl ethanoate 106

Alkynol **105** (787 mg, 3.36 mmol, 1.00 equiv) was dissolved in 10 mL THF and cooled to 0 ºC under N_2. To this solution was added RedAl™ (65 wt.% in PhMe, 1.06 mL, 3.53 mmol, 1.05 equiv) over 5 min. The reaction was allowed to reach rt and stirred for 3 h at that temperature. Bu_3SnCl (1.82 mL, 6.72 mmol, 2.00 equiv) was then added, and the reaction mixture was allowed to stir for 18 h at rt. It was carefully quenched with H_2O (20 mL) and stirred vigorously for 10 min with 20 mL EtOAc, filtered through Celite washing with EtOAc, and the

organic layer thus obtained was further washed with brine (1X), dried ($MgSO_4$), filtered and concentrated to dryness. Following purification by flash chromatography (5% then 15% EtOAc/PE), the title compound was isolated as a light yellow oil (1.01 g, 59%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.32 (2H, d, *J* = 2.2 Hz), 6.32-6.23 (3H, m), 4.06 (2H, t, *J* = 5.9 Hz), 3.78 (6H, s), 2.62-2.45 (4H, m), 1.55-1.29 (12H, m), 1.13 (1H, t, *J* = 5.7 Hz), 0.94-0.86 (15H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.7, 148.2, 144.3, 138.9, 106.4, 97.7, 65.0, 55.1, 29.2, 27.4, 17.5, 13.6. The alkenol (1.01 g, 1.97 mmol, 1.0 equiv) was acetylated following General Procedure 2.6.2.1. The crude product was then purified over a plug of silica gel (15% EtOAc/PE) to afford the title compound as a clear colourless oil (887 mg, 81%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.33 (2H, d, *J* = 2.2 Hz), 6.31 (1H, t, *J* = 2.3 Hz), 6.22 (1H, t, *J* = 7.1 Hz), 4.47 (2H, d, *J* = 7.1 Hz, J_{Sn-H} = 5.8 Hz), 3.78 (6H, s), 2.62-2.46 (4H, m), 2.06 (3H, s), 1.56-1.45 (6H, m), 1.32 (6H, sext, *J* = 6.8 Hz), 1.02-0.95 (6H, m), 0.90 (9H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.8, 160.7, 151.9, 144.2, 133.8, 106.4, 97.8, 66.4, 55.2, 42.5, 37.0, 29.1, 27.4, 21.0, 13.6, 10.4.

Upon heating substrate **106** with 10 mol % $Pd(dba)_2$ in MeCN (0.050 M) for 2.5 h, an intractable mixture was obtained. Using PhMe as solvent and 10 mol % $Pd(dba)_2$, from 55 to 80 ºC, no rxn occurred and only starting materials were observed after 20 h. Using $Pd(dba)_2$ in DMF (55 to 110 ºC), no reaction was observed. Finally, using $Pd(PPh_3)_4$ in MeCN (55 ºC, 24 h), starting material was also recovered.

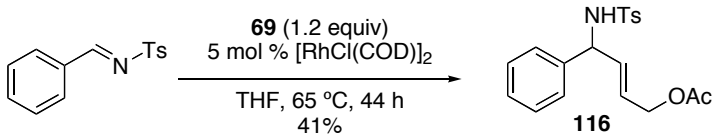
2.6.3.9 Rh-Catalysed Conjugate Addition Reactions



(*E*)-3-(3-Oxocyclohexyl)-2-propenyl ethanoate 113

In a Schlenk tube were suspended $[RhCl(COD)]_2$ (7.4 mg, 0.015 mmol, 10 mol % Rh) and dppe (24 mg, 0.060 mmol, 20 mol %) in 2.5 mL MeCN under Ar. The mixture was stirred until a deep orange solution was obtained then freshly distilled cyclohexenone (87 μL, 0.90 mmol,

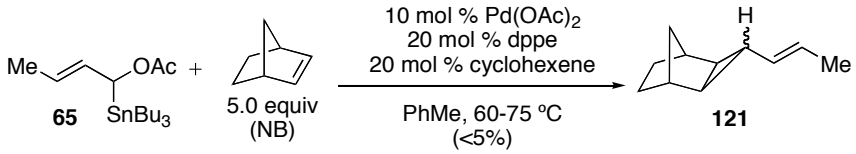
3.0 equiv) was added via microsyringe. The reaction mixture was immersed in a 55 ºC oil bath, then substrate **69** (114 mg, 0.30 mmol, 1.0 equiv) in MeCN (1.5 + 0.5 mL rinse) was syringed in dropwise over 12 min. After sealing the reaction vessel, the reaction was allowed to stir for a further 10 min, whereupon all starting material was consumed by TLC analysis. After partial concentration under reduced pressure, the crude material was loaded onto silica gel for purification by flash chromatography (15% then 33% EtOAc/PE) to afford the title compound as a golden oil (28 mg, 47%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.73 (1H, dd, *J* = 15.6, 6.2 Hz), 5.57 (1H, dtd, *J* = 15.6, 5.9, 0.9 Hz), 4.52 (2H, d, *J* = 6.1 Hz), 2.80-1.60 (9H, m), 2.07 (3H, s); ^{13}C NMR ($CDCl_3$, JMOD, 75 MHz) δ 210.5, 170.7, 138.0, 123.4, 64.7, 46.9, 41.1, 41.0, 30.9, 24.8, 20.9. LRMS (EI) Calcd. for $C_{11}H_{16}O_3$: 196. Found: 137 (M-OC(O)CH_3^+).



(*E*)-{[(4-Methylphenyl)sulfonyl]amino}-4-phenyl-2-butenyl ethanoate 116

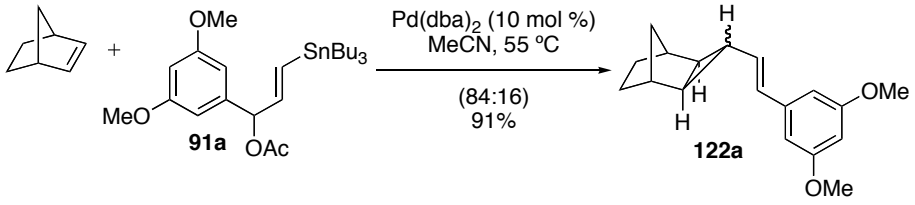
In a dry box were added 7.4 mg $[RhCl(COD)]_2$ (0.015 mmol, 10 mol % Rh) into a Schlenk tube under N_2. Outside the box, under Ar, were successively added stannane **69** (136 mg, 0.36 mmol, 1.2 equiv) and *N*-tosylbenzylideneimine (73 mg, 0.30 mmol, 1.0 equiv) followed by THF (1.5 mL). The reaction vessel was sealed, immersed in an oil bath at 65 ºC and allowed to stir for 44 h. The isolated product thus formed was isolated following partial concentration of the reaction mixture and flash chromatography (25% EtOAc/PE), to provide the title compound as a cream-coloured paste (44 mg, 41%). Starting *N*-tosylimine (unquantified) was also isolated. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61 (2H, d, *J* = 8.3 Hz), 7.28-7.18 (5H, m), 7.12-7.06 (2H, m), 5.74 (1H, ddt, *J* = 15.5, 6.0, 1.1 Hz), 5.59 (1H, dtd, *J* = 15.5, 5.6, 1.0 Hz), 5.30 (1H, d, *J* = 7.5 Hz), 4.94 (1H, t, *J* = 6.6 Hz), 4.41 (2H, d, *J* = 5.6 Hz), 2.38 (3H, s), 2.02 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 143.2, 139.0, 137.5, 132.7, 129.3, 128.6, 127.8, 127.1, 127.0, 126.5, 63.7, 58.8, 21.4, 20.8.

2.6.3.10 Pd-Catalysed Cyclopropanation of Strained Alkenes



***exo*-(3-propenyl)tricyclo[3.2.1.0^{2,4}]octane[116] 121**

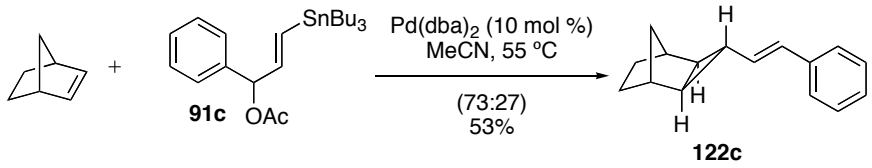
A suspension of $Pd(OAc)_2$ (6.7 mg, 0.030 mmol, 10 mol %) and dppe (24 mg, 0.060 mmol, 20 mol %) in PhMe (2.0 mL) was heated to 60 ºC under Ar for 15 min until a yellow suspension was obtained. At rt, a solution of NB (141 mg, 1.50 mmol, 5.0 equiv) and substrate **65** (121 mg, 0.30 mmol, 1.0 equiv) in 1.0 mL PhMe was added via cannula. The Schlenk tube was resealed and the reaction was stirred at 60 ºC for 15 h. Since there remained starting material, according to TLC analysis, the reaction temperature was increased to 75 ºC, and the reaction was allowed to proceed at that temperature for a further 23 h. Upon cooling to rt, the reaction medium was filtered through a short pad of silica, eluting with 8% EtOAc/PE. The crude product was purified by flash chromatography (100% PE) to produce the title compound (<2 mg, <5% yield) as a clear colourless fragrant oil that matched the ^{1}H NMR data previously reported.



(*E*)-*exo*-3-[2-(3,5-Dimethoxyphenyl)ethenyl]tricyclo[3.2.1.0^{2,4}]octane 122a

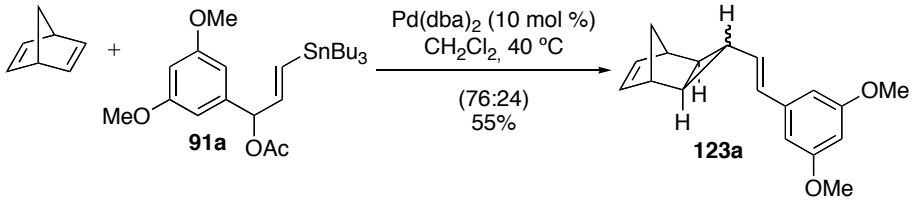
Obtained in 91% yield and 84:16 dr from substrate **91a** following the General Procedure 2.6.2.6, as a clear colourless oil after purification by column chromatography (5% Et_2O/hexanes), as a light yellow waxy film. When following General Procedure 2.6.2.7, this compound was isolated in 94:6 dr and 48% yield. Further purification by flash chromatography (5% Et_2O/hexanes) allowed the isolation of an analytical sample of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (2H, d, *J* = 2.2 Hz), 6.32 (1H, d, *J* = 15.3 Hz), 6.29 (1H, t, *J* = 2.3 Hz), 5.65 (1H, dd, *J* = 15.6, 9.1 Hz), 3.78 (6H, s), 2.36 (2H, br s), 1.55-1.43 (2H, m), 1.31-1.22 (3H, m), 1.02 (1H, dt, *J* = 10.6, 1.9 Hz), 0.92-0.87 (2H, m), 0.68 (1H, d, *J* = 10.5 Hz); ^{13}C

NMR (75 MHz, JMOD, $CDCl_3$) δ 160.8, 133.9, 133.6, 127.1, 103.7, 98.8, 55.3, 36.0, 29.4, 28.4, 25.2, 17.7. HRMS (EI) Calcd. for $C_{18}H_{22}O_2$: 270.1620. Found: 270.1626.



(*E*)-*exo*-3-[2-Phenylethenyl]tricyclo[3.2.1.0^{2,4}]oct-6-ene[139] **122c**

Obtained in 53% yield and 73:27 dr from substrate **91c** following the General Procedure 2.6.2.6, as a clear colourless oil. Characterisation data were in agreement with those reported. Following the General Procedure 2.6.2.6 at rt, the title compound was obtained in 44% and 93:7 dr. When following General Procedure 2.6.2.7 at rt, using MeCN as solvent, the title compound was isolated in 43% yield and 93:7 dr.

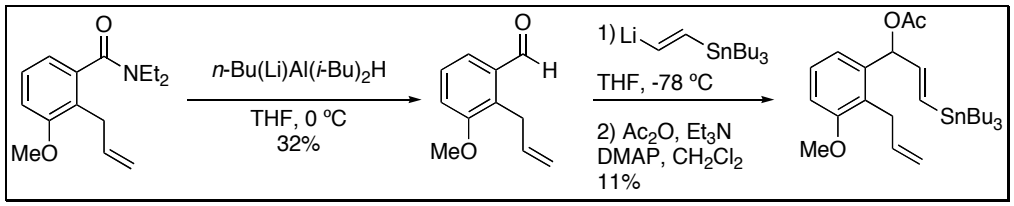


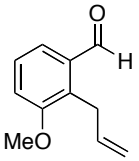
(*E*)-*exo*-3-[2-(3,5-Dimethoxyphenyl)ethenyl]tricyclo[3.2.1.0^{2,4}]oct-6-ene 123a

Obtained in 30% yield and 83:17 dr from substrate **91a** following the General Procedure 2.6.2.6, as a clear colourless oil, after purification by flash chromatography (5% EtOAc/hexanes). Also obtained in 27% yield and 87:13 dr at 45 ºC. Further purification by preparative plate chromatography (5% EtOAc/hexanes) allowed the isolation of an analytical sample of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (2H, d, *J* = 2.2 Hz), 6.40 (2H, t, *J* = 1.6 Hz), 6.33 (1H, d, *J* = 16.0 Hz), 6.31 (1H, t, *J* = 2.3 Hz), 5.79 (1H, dd, *J* = 15.7, 9.0 Hz), 3.78 (6H, s), 2.89 (2H, br s), 2.60 (1H, dt, *J* = 9.0, 2.4 Hz), 1.23 (1H, d, *J* = 9.2 Hz), 1.20 (2H, d, *J* = 2.0 Hz), 0.89 (1H, d, *J* = 9.3 Hz); ^{13}C NMR (125 MHz, JMOD, $CDCl_3$) δ 160.8, 140.5, 139.7, 132.4, 126.8, 103.8, 99.0, 55.3, 41.8, 38.9, 35.4, 31.2. HRMS (EI) Calcd. for $C_{18}H_{20}O_2$: 268.1463. Found: 268.1471. When using different reaction solvents, this compound was also obtained in the yields and diastereomer ratios reported in Table 2.3, when

following General Procedure 2.6.2.7.

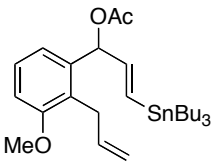
Synthesis of (*E*)-3-tributylstannyl-1-[3-methoxy-2-(2-propenyl)phenyl]-2-propenyl ethanoate (126)





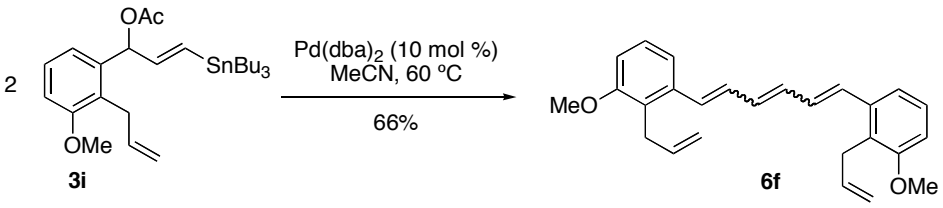
3-Methoxy-2-(2-propenyl)benzaldehyde

Neat Dibal-H (1.90 mL, 10.6 mmol, 1.05 equiv) was diluted in 10 mL THF, cooled to 0 ºC and treated drop-wise with a hexane solution of *n*-BuLi (2.4 M, 4.4 mL, 10.6 mmol, 1.05 equiv),[140] and the resulting clear colourless solution was stirred at 0 ºC for 30 min and added via cannula to a solution of *N*,*N*-diethyl 3-methoxy-2-(2-propenyl)benzamide[141] (2.5 g, 10.1 mmol) in dry THF (35 mL), cooled to 0 ºC under argon. The resulting solution was stirred for 1 h at 0 ºC and 20 h at rt. The reaction mixture was quenched by the careful addition of 10% aqueous HCl (100 mL), and stirred until two clear layers were obtained. The organic layer was separated, and the aqueous phase was further extracted with EtOAc (1X). The combined organics were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated to dryness. By ^{1}H NMR, the crude contained 65% aldehyde and 35% starting amide. Following purification by flash chromatography (10% EtOAc/PE), the desired aldehyde was isolated as a clear colourless oil (562 mg, 32%). Spectral data were in agreement with those previously reported.[142]



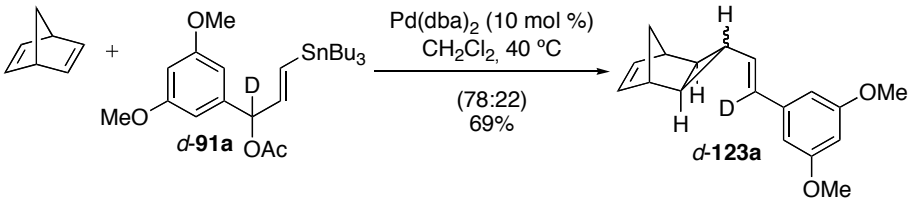
(*E*)-3-Tributylstannyl-1-[3-methoxy-2-(2-propenyl)phenyl]-2-propenyl ethanoate 126

1,2-bis-(Tributylstannyl)ethylene (2.51 g, 4.15 mmol, 1.30 equiv) was dissolved in dry THF (12 mL) and cooled to –78 ºC under Ar. A hexanes solution of *n*-BuLi (2.4 M, 1.60 mL, 3.83 mmol, 1.20 equiv) was syringed in, and the resulting solution was stirred at –78 ºC for 1 h.[143] To the vinyllithium solution was added a solution of aldehyde in THF (4 + 2 + 1 mL) via cannula. After 15 min at –78 ºC, the reaction mixture was allowed to warm up to rt and stirred for 15 h. The reaction mixture was quenched by adding 15 mL of saturated NH_4Cl solution. The organic layer was separated, and the aqueous residue was further extracted with EtOAc. The organic extracts were combined and washed with brine (1X), dried over $MgSO_4$, filtered and concentrated to dryness. The tin by-products were removed by column chromatography (5% then 10% then 15% EtOAc), and the stannylalkenol was isolated as an inseparable mixture with the aldehyde starting material. This mixture was carried through to the next step. Acetylation was performed according to General Procedure 2.6.2.1, to provide, after purification by column chromatography (5% EtOAc/hexanes), the title compound as a clear colourless oil (239 mg, 11% from the benzaldehyde). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (1H, t, *J* = 8.0 Hz), 7.03 (1H, d, *J* = 7.9 Hz), 6.85 (1H, d, *J* = 8.1 Hz), 6.48 (1H, dt, *J* = 4.2, 4.0 Hz), 6.18 (1H, d, *J* = 19.5 Hz), 6.10 (1H, dd, *J* = 19.1, 3.9 Hz), 6.04-5.91 (1H, m), 4.98 (1H, dd, *J* = 8.2, 1.6 Hz), 4.94 (1H, dd, *J* = 15.1, 1.8 Hz), 3.82 (3H, s), 3.55 (2H, d, *J* = 5.8 Hz), 2.09 (3H, s), 1.58-1.44 (6H, m), 1.30 (6H, sext, 7.2 Hz), 0.93-0.88 (15H, m); ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 169.8, 157.5, 144.8 (J_{Sn-C} = 6.8 Hz), 138.8, 136.5, 130.6 (J_{Sn-C} = 358, 344 Hz), 127.1, 126.6, 120.0, 114.7, 110.0, 75.0 (J_{Sn-C} = 63.2 Hz), 55.6, 29.7, 29.0, (J_{Sn-C} = 20.6 Hz), 27.1 (J_{Sn-C} = 54.2 Hz), 21.2, 13.6, 9.4 (J_{Sn-C} = 344, 328 Hz). LRMS (EI) Calcd. for $C_{23}H_{35}O_3Sn$ $(M - Bu)^+$: 479. Found: 479.



1,6-bis(3-Methoxy-2-(2-propenyl)phenyl)-1,3,5-hexatriene 127

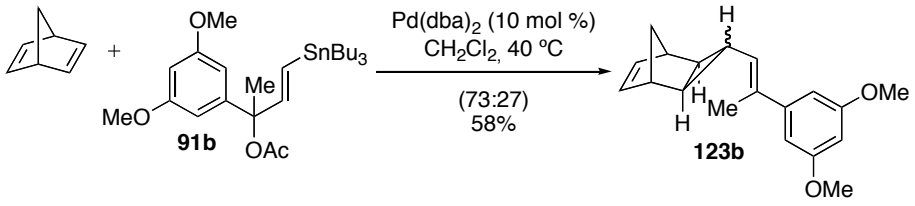
To a suspension of $Pd(dba)_2$ (8.0 mg, 0.015 mmol, 10 mol %) in MeCN (1.5 mL), heated to 60 ºC in an oven-dried round-bottom flask equipped with a condenser, was manually added a solution of stannane **126** (79.0 mg; 0.148 mmol; 1.0 equiv) in 1.0 mL MeCN over 12 min, in a dropwise fashion. After stirring for 75 min (TLC monitoring), the crude mixture was concentrated and purified by flash chromatography (3% then 5% EtOAc/PE) to provide the title compound, predominantly the (*E*,*E*,*E*)-isomer, as a yellow waxy solid (18.2 mg; 66%). Mp (CH_2Cl_2): 151.0-152.0 ºC. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.20-7.15 (4H, m), 6.82-6.77 (6H, m), 6.55-6.52 (2H, m), 5.95 (2H, ddd, *J* = 16.0, 10.2, 5.7 Hz), 4.99 (2H, dd, *J* = 10.1, 1.5 Hz), 4.92 (2H, dd, *J* = 17.1, 1.6 Hz), 3.82 (6H, s), 3.53 (4H, d, *J* = 5.6 Hz); ^{13}C NMR ($CDCl_3$, JMOD, 125 MHz) δ 157.6, 137.6, 136.5, 133.9, 131.0, 130.3, 127.0, 125.8, 117.9, 114.8, 109.6, 55.8, 29.6; HRMS (EI) Calcd. for $C_{26}H_{28}O_2$: 372.2098. Found: 372.2094.



(*E*)-*exo*-3-[2-Deuterio-2-(3,5-dimethoxyphenyl)ethenyl]tricyclo[3.2.1.0^{2,4}]oct-6-ene *d*-123a

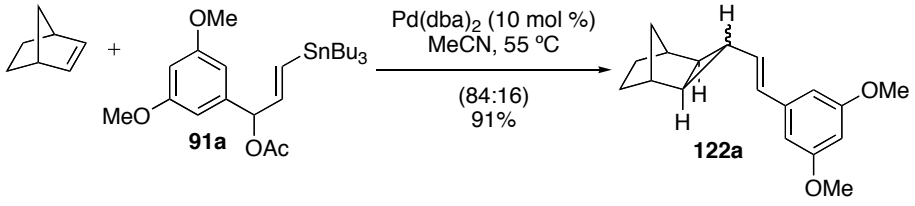
Following General Procedure 2.6.2.7 using 158 mg substrate *d*-**91a** (0.30 mmol), after heating to 40 ºC for 18 h, the title compound (55.7 mg, 69%, 79:21 dr) was obtained as a clear colourless wax after purification by flash chromatography (5% Et_2O/PE). Further purification by flash chromatography (5% Et_2O/PE) afforded an analytical sample of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (2H, d, *J* = 2.3 Hz), 6.40 (2H, dd, *J* = 1.6 Hz), 6.31 (1H, t, *J* = 2.2 Hz), 5.79 (1H, d, *J* = 9.0 Hz), 3.78 (6H, s), 2.89 (2H, br s), 2.60 (1H, dt, *J* = 9.0, 2.4 Hz), 1.23 (1H, d, *J* = 9.2 Hz), 1.20 (2H, d, *J* = 2.0 Hz), 0.89 (1H, d, *J* = 9.3 Hz); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 160.8, 140.5, 139.7, 132.4, 126.8 (t, $J_{C\text{-}D}$ = 19 Hz), 103.8, 99.0, 55.3, 41.8, 38.9, 35.4, 31.2. HRMS (EI) Calcd. for $C_{18}H_{19}DO_2$: 269.1526. Found: 269.1524.



(*E*)-*exo*-3-[2-(3,5-Dimethoxyphenyl)prop-1-enyl]tricyclo[3.2.1.0^{2,4}]oct-6-ene 123b

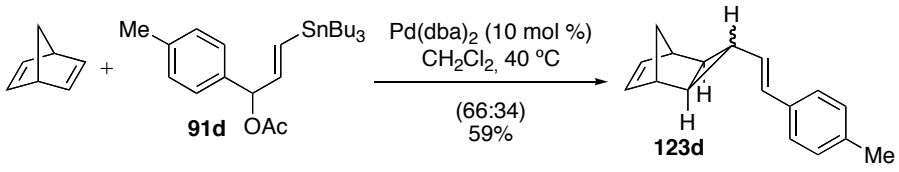
Following the general procedure using 162 mg substrate **91b** (0.30 mmol), after heating to 40 ºC for 20 h, after column chromatography (5% Et_2O/hexanes) the title compound (49 mg, 58%, 73:27 dr) was obtained as a clear colourless oil. An analytical sample, (95:5 dr) was obtained by repeated flash chromatography (5% Et_2O/PE), which had the following spectral properties: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (2H, d, *J* = 2.1 Hz), 6.40 (2H, br), 6.33 (1H, t, *J* = 2.2 Hz), 5.26 (1H, d, *J* = 9.6 Hz), 3.78 (6H, s), 2.90 (2H, br s), 2.71 (1H, dt, *J* = 9.6, 2.4 Hz), 2.13 (3H, s), 1.28 (1H, d, *J* = 9.3 Hz), 1.14 (2H, d, *J* = 1.8 Hz), 0.94 (1H, d, *J* = 9.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 145.9, 140.5, 132.2, 129.8, 103.9, 98.4, 55.3, 41.9, 39.0, 32.2, 31.2, 16.5. HRMS (EI) Calcd. for $C_{19}H_{22}O_2$: 282.1620. Found: 282.1625.



(*E*)-*exo*-3-[2-(3,5-Dimethoxyphenyl)prop-1-enyl]tricyclo[3.2.1.0^{2,4}]octane 122b

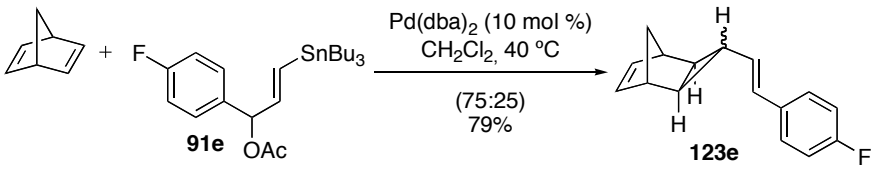
Following the general procedure using 162 mg substrate **91b** (0.30 mmol), after heating to 40 ºC for 19 h, the title compound was obtained as an inseparable mixture of diastereomers (57.3 mg, 67%, 68:34 dr), following purification by column chromatography (5% Et_2O/hexanes), as a clear colourless oil. Data for the major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (2H, d, *J* = 2.3 Hz), 6.33 (1H, t, *J* = 2.3 Hz), 5.12 (1H, dd, *J* = 10.0, 1.1 Hz), 2.37 (2H, br s), 2.09 (3H, d, *J* = 1.1 Hz), 1.60 (1H, dt, *J* = 9.5, 2.5 Hz) 1.50-1.46 (2H, m), 1.30-1.25 (2H, m), 1.08

(1H, dd, *J* = 10.5, 0.8 Hz), 0.85 (2H, d, *J* = 2.2 Hz), 0.70 (1H, d, *J* = 10.5 Hz); ^{13}C NMR (125 MHz, JMOD, $CDCl_3$) δ 160.5, 137.0, 132.8, 104.5, 103.7, 98.3, 55.3, 36.1, 29.5, 28.5, 25.1, 16.3, 14.4. HRMS (EI) Calcd. for $C_{19}H_{24}O_2$: 284.1776. Found: 284.1779.



(*E*)-*exo*-3-[2-(4-Methylphenyl)ethenyl]tricyclo[3.2.1.0^{2,4}]oct-6-ene 123d

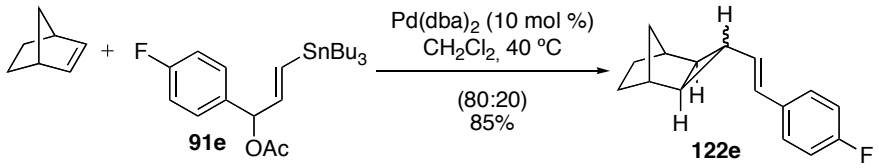
According to the general procedure using 144 mg substrate **91d** (0.30 mmol), after heating to 40 ºC for 16 h, following column chromatography (5% Et_2O/hexanes), the title compound (40 mg, 59%, 66:34 dr) was obtained as a light yellow pasty solid, as an inseparable mixture of diastereomers. Data for the major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (2H, d, *J* = 8.0 Hz), 7.08 (2H, d, *J* = 8.0 Hz), 6.40 (2H, t, *J* = 1.6 Hz), 6.36 (1H, d, *J* = 15.8 Hz), 5.74 (1H, dd, *J* = 15.8, 9.0 Hz), 2.89 (2H, br s), 2.60 (1H, dt, *J* = 9.0, 2.4 Hz), 2.31 (3H, s), 1.25 (1H, d, *J* = 8.7 Hz), 1.18 (2H, d, *J* = 2.1 Hz), 0.93 (1H, d, *J* = 9.3 Hz); ^{13}C NMR (125 MHz, JMOD, $CDCl_3$) δ 140.5, 136.4, 134.9, 130.7, 129.2, 126.7, 125.6, 41.8, 38.9, 35.5, 31.0, 21.1. HRMS (EI) Calcd. for $C_{17}H_{18}$: 222.1409. Found: 222.1408.



(*E*)-*exo*-3-[2-(4-Fluorophenyl)ethenyl]tricyclo[3.2.1.0^{2,4}]oct-6-ene 123e

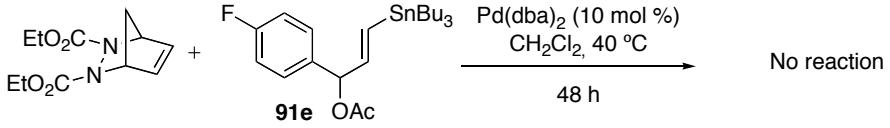
According to the general procedure using 145 mg substrate **91e** (0.30 mmol), after heating to 40 ºC for 16 h and purifying by flash chromatography (5% Et_2O/hexanes), the title compound (53 mg, 79%, 75:25 dr) was obtained as an inseparable diastereomer mixture, as a clear colourless liquid. Characterisation data for the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (2H, ddd, *J* = 8.7, 5.5, 2.1 Hz), 6.95 (2H, ddd, *J* = 8.7, 8.7, 1.9 Hz), 6.41 (2H, t, *J* = 1.6 Hz), 6.35 (1H, d, *J* = 15.8 Hz), 5.71 (1H, dd, *J* = 15.8, 9.0 Hz), 2.89 (2H, br s), 2.60 (1H, dt, *J* = 9.0, 2.4 Hz), 1.23 (1H, d, *J* = 9.3 Hz), 1.18 (2H, d, *J* = 2.1 Hz), 0.94 (1H, d, *J* = 9.3 Hz); ^{13}C

NMR (125 MHz, JMOD, $CDCl_3$) δ 161.7 (d, $J_{C\text{-}F}$ = 246 Hz), 140.5, 133.8 (d, $J_{C\text{-}F}$ = 3.4 Hz), 131.4 (d, $J_{C\text{-}F}$ = 1.8 Hz), 127.0 (d, $J_{C\text{-}F}$ = 7.9 Hz), 125.6, 115.3 (d, $J_{C\text{-}F}$ = 21.6 Hz), 41.8, 38.9, 35.4, 31.1. HRMS (EI) Calcd. for $C_{16}H_{15}F$: 226.1158. Found: 226.1154.

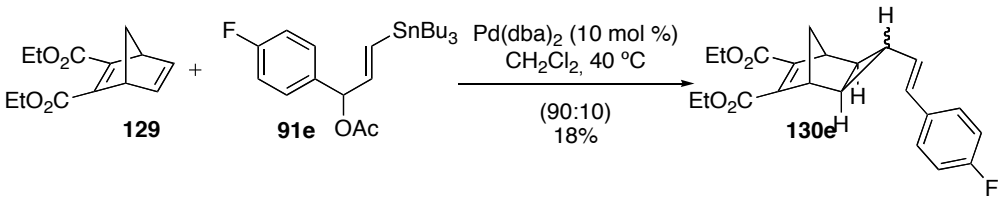


(*E*)-*exo*-3-[2-(4-Fluorophenyl)ethenyl]tricyclo[3.2.1.0^{2,4}]octane 122e

According to the general procedure using 145 mg substrate **91e** (0.30 mmol), after heating to 40 ºC for 16 h, working up as described and purifying by flash chromatography (5% Et_2O/hexanes), the title compound (53 mg, 79%, 75:25 dr) was obtained as an inseparable diastereomer mixture, as a clear colourless wax. Data for the major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (2H, ddd, *J* = 8.7, 5.5, 2.1 Hz), 6.94 (2H, ddd, *J* = 8.7, 8.7, 1.8 Hz), 6.35 (1H, d, *J* = 15.8 Hz), 5.58 (1H, dd, *J* = 15.8, 9.0 Hz), 2.36 (2H, br s), 1.51 (1H, dt, *J* = 9.1, 2.5 Hz), 1.50-1.44 (2H, m), 1.31-1.25 (2H, m), 1.00 (1H, d, *J* = 7.7 Hz), 0.89 (2H, d, *J* = 2.2 Hz), 0.69 (1H, d, *J* = 10.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6 (d, $J_{C\text{-}F}$ = 244 Hz), 132.6 (d, $J_{C\text{-}F}$ = 1.8 Hz), 126.9 (d, $J_{C\text{-}F}$ = 7.7 Hz), 126.9, 126.0, 115.3 (d, $J_{C\text{-}F}$ = 21.7 Hz), 36.0, 29.4, 28.4, 25.1, 17.7. HRMS (EI) Calcd. for $C_{16}H_{17}F$: 228.1314. Found: 228.1312.

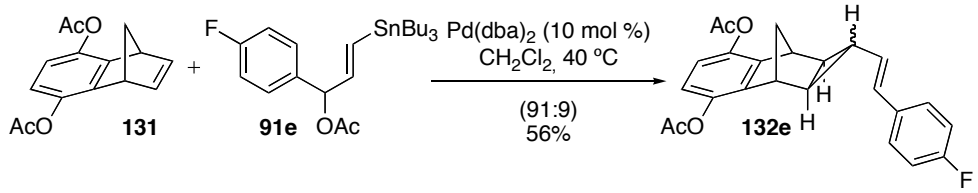


According to the general procedure using 145 mg substrate (0.30 mmol), after heating to 40 ºC for 48 h, concentration to dryness and ^{1}H NMR analysis indicated only starting stannane **91e** and alkene **128**[144] were present.



(*E*)-*exo*-6-[2-(4-Fluorophenyl)ethenyl]-2,3-bis(carboethoxy)tricyclo[3.2.1.0^{5,7}]oct-2-ene 130e

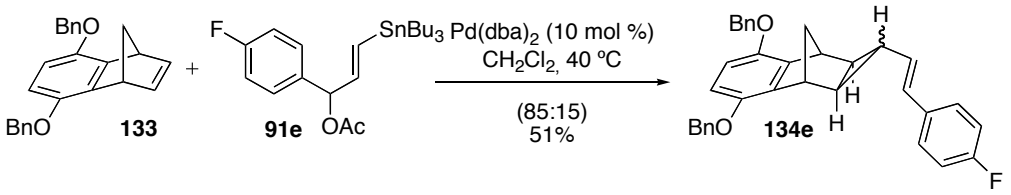
Following the general procedure using 242 mg substrate **91e** (0.50 mmol) and 590 mg diester **129**[145] (2.50 mmol, 5.0 equiv), after heating to 40 ºC for 44 h and purifying by flash chromatography (15% then 25% Et_2O/hexanes), the title compound (38.1 mg, 21%, 90:10 dr) was obtained as clear colourless droplets. Data for the major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (2H, ddd, *J* = 8.6, 5.4, 2.1 Hz), 6.96 (2H, ddd, *J* = 8.7, 8.7, 2.0 Hz), 6.38 (1H, d, *J* = 15.9 Hz), 5.72 (1H, dd, *J* = 15.8, 8.7 Hz), 4.25 (4H, q, *J* = 7.2 Hz), 3.36 (2H, br s), 2.71 (1H, dt, *J* = 8.7, 2.4 Hz), 1.56 (2H, br s), 1.32 (6H, t, *J* = 7.1 Hz), 1.40-1.20 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 161.9 (d, $J_{C\text{-}F}$ = 245 Hz), 149.0, 133.4 ($J_{C\text{-}F}$ = 3.4 Hz), 130.0 ($J_{C\text{-}F}$ = 2.2 Hz), 127.2 ($J_{C\text{-}F}$ = 7.9 Hz), 126.9, 115.4 ($J_{C\text{-}F}$ = 21.6 Hz), 61.0, 45.8, 37.2, 34.9, 30.8, 14.2. HRMS (EI) Calcd. for $C_{22}H_{22}FO_4$: 370.1580. Found: 370.1575.



5,8-bis(Acetoxy)-1,4-dihydro-1,4-methanonaphthalene 4-fluorophenyl [2+1] cycloadduct 132e

Following the general procedure using 145 mg substrate **91e** (0.30 mmol) and 232 mg diacetate **131**[146] (0.90 mmol, 3.0 equiv), after heating to 40 ºC for 15 h, the crude mixture was purified by flash chromatography (15% then 25% Et_2O/hexanes). Excess alkene impurities were removed by a second flash chromatography (2.5% EtOAc/PhMe), to furnish the title compound (66 mg, 56%, 91:9 dr) as a light yellow wax. Data for the major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.17 (2H, m), 6.93 (2H, ddd, *J* = 8.7, 8.7, 2.0 Hz), 76.76 (2H, s), 6.36 (1H, d, *J* = 15.8 Hz), 5.66 (2H, dd, *J* = 15.8, 8.8 Hz), 3.43 (2H, br s), 2.52 (1H, dt, *J* =

8.8, 2.5 Hz), 2.34 (1H, d, J = 6.0 Hz), 2.32 (6H, s), 1.57 (1H, d, J = 10.2 Hz), 1.41 (2H, d, J = 2.3 Hz), 1.31 (1H, d, J = 10.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 161.2 (d, $J_{C\text{-}F}$ = 240 Hz), 143.5, 141.9, 133.5 (d, $J_{C\text{-}F}$ = 3.3 Hz), 130.2 (d, $J_{C\text{-}F}$ = 2.1 Hz), 128.9 (d, $J_{C\text{-}F}$ = 4.7 Hz), 128.3 (d, $J_{C\text{-}F}$ = 12.9 Hz), 127.0 (d, $J_{C\text{-}F}$ = 7.9 Hz), 126.4, 119.7, 115.3 (d, $J_{C\text{-}F}$ = 21.6 Hz), 40.9, 38.3, 30.6, 28.3, 20.8. HRMS (EI) Calcd. for $C_{24}H_{21}FO_4$: 392.1424. Found: 392.1409.



5,8-bis(Benzyloxy)-1,4-dihydro-1,4-methanonaphthalene 4-fluorophenyl [2+1] cycloadduct 134e

Following the general procedure using 145 mg substrate **91e** (0.30 mmol) and 319 mg bis-benzyl ether **133**[2] (0.90 mmol; 3.0 equiv), after heating to 40 ºC for 12 h, the crude mixture was purified by flash chromatography (0% then 5% Et_2O/PE). Excess alkene impurities were removed by a second flash chromatography (5% Et_2O/PE) to afford the title compound (75.3 mg, 51%, 85:15 dr) as a light yellow gummy oil. Data for the major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (4H, d, J = 7.3 Hz), 7.42 (4H, t, J = 7.2 Hz), 7.34 (2H, d, J = 7.1 Hz), 7.23 (2H, dd, J = 8.4, 5.6 Hz), 6.97 (2H, dd, J = 8.7, 8.6 Hz), 6.67 (2H, s), 6.38 (1H, d, J = 15.8 Hz), 5.70 (1H, dd, J = 15.8, 8.8 Hz), 5.10-5.00 (4H, m), 3.72 (2H, br s), 2.57 (1H, d, J = 8.7 Hz), 1.56 (1H, d, J = 8.6 Hz), 1.30-1.23 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8 (d, $J_{C\text{-}F}$ = 244 Hz), 147.7, 140.4, 137.8, 133.8, 130.7, 128.5, 127.8, 127.4 (d, $J_{C\text{-}F}$ = 2.9 Hz), 127.3, 127.1 (d, $J_{C\text{-}F}$ = 8.0 Hz), 126.2, 115.4 (d, $J_{C\text{-}F}$ = 29.6 Hz), 112.2, 71.5, 40.1, 38.5, 31.4, 29.6. HRMS (EI) Calcd. for $C_{34}H_{29}FO_2$: 488.2152. Found: 488.2144.

[2] Yang, Y.-C.; Luh, T.-Y. *J. Org. Chem.* **2003**, *68*, 9870-9873. Synthesised as described in the literature procedure for the 4-bromobenzyl compound, from the 1:1 cyclopentadiene/benzoquinone cycloadduct (Oda, M. *et al. Org. Synth*. CV 9, 186).

Chapter 3 – Formation and Reactivity of Neopentylic sp^3-*gem*-Organodimetallic Trifluoromethanesulfonyloxy- and Iodopalladio(II)/Dialkylaluminoalkane Intermediates

3.1 Introduction

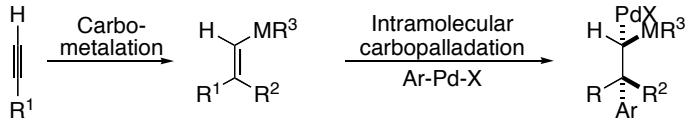
Following demonstration of the carbenoid reactivity of *gem*-palladio(II)/trialkylstannylalkane intermediates, supplementary catalytic routes to *gem*-dimetallic species incorporating a palladium(II) intermediate are desirable, to augment fundamental knowledge about these species and to discover new applications. The approach developed in this chapter involves sequential carbometalation of a terminal alkyne and leads to neopentylic *gem*-(pseudo)halopalladio(II)/dialkylaluminoalkane species.

3.1.1 Sequential Carbometalations

Building on the trialkylstannylalkyl halide and α-tributylstannylpropenyl acetate oxidative addition strategies previously presented, the carbopalladation of stereodefined vinylmetallic species using σ-arylpalladium(II) halides and sulfonates was envisaged as a further approach towards *gem*-organodimetallic σ-alkylpalladium(II)/main group metal intermediates. Based on Chapter 2, synthetic applications exploiting those species' carbenoid behaviour, namely intramolecular C-H insertion reactions, as well as competing dimerisation may be expected. Should they display configurational stability, sequential diastereoselective functionalisation of their carbon-metal bonds should take place.

In order to increase the synthetic value of this approach, its reaction parameters need to be controlled. First, carbopalladation should take place in an intramolecular fashion, using an (*E*)-trisubstituted alkenylmetallic partner, in order to avoid competing inter- and intramolecular cross-coupling pathways. Carbopalladation of a trisubstituted alkenylmetallic reagent would lead to neopentylic *gem*-halopalladio(II)/main group metal organodimetallic species, thus precluding competing β-hydride elimination (Scheme 3.1).

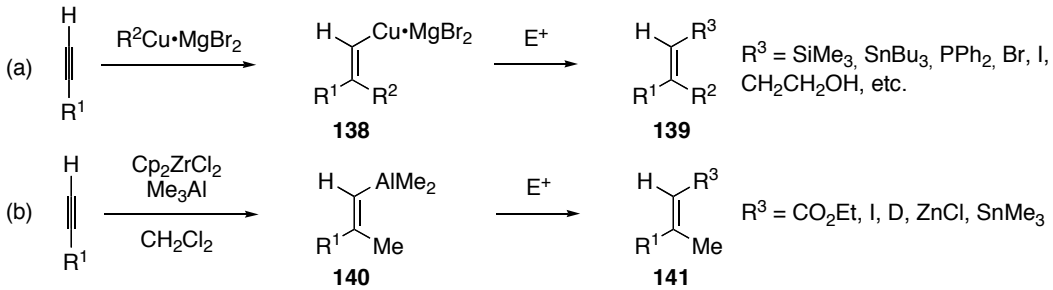
Scheme 3.1: General approach to neopentylic *gem*-organodimetallic palladium(II)/M species (M= main group metal)



*3.1.2 (*E*)-Trisubstituted Vinylmetallic Reagents*

There exist few methodologies for providing (*E*)-2,2-disubstituted-1-alkenylmetallic species. Terminal alkyne carbocupration as well as carboalumination, along with silylcupration,[147] essentially constitute the only such weapons. *syn*-Carbocupration of terminal acetylenes[148] leads to an (*E*)-trisubstituted alkenylcopper intermediate **138** that can be further functionalised by treatment with electrophiles (Scheme 3.2a). Yet among all carbocuprations, methylcupration is notoriously sluggish and therefore, less synthetically useful. This limitation can usually be circumvented with methylalumination of terminal alkynes, popularised by Negishi (Scheme 3.2b).[149] The resulting (*E*)-trisubstituted alkenylalane **140** has been utilised in various transmetalation protocols leading to carbon-carbon bond formation: addition to enones via the organocuprate,[150] organozinc formation for subsequent cross-coupling,[151] and reaction with Me_3SnCl to give vinyltrimethylstannanes.[152] The carboalumination reaction is limited to the addition of Me_3Al across a terminal alkyne, since attempts with the higher trialkylaluminums lead to competing hydro- and alkylalumination.[153] Thus, methylalumination and carbocupration of terminal alkynes are complementary.

Scheme 3.2: Stereoselective (*E*)-trisubstituted alkenylmetal formation

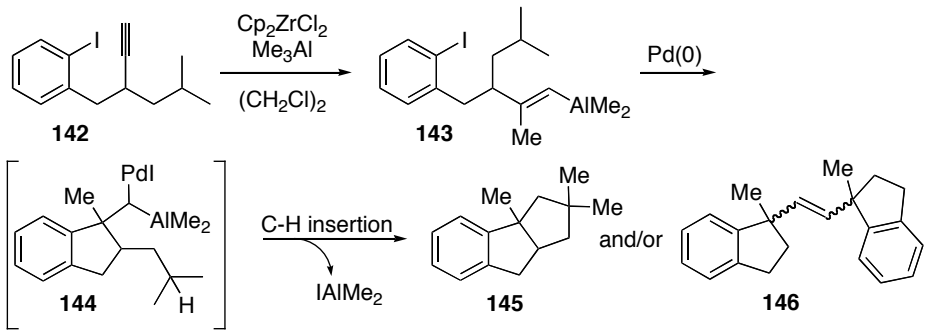


3.1.3 Initial Results

3.1.3.1 Preliminary Studies with 3-[(2-Iodophenyl)methyl]-5-methylhex-1-yne

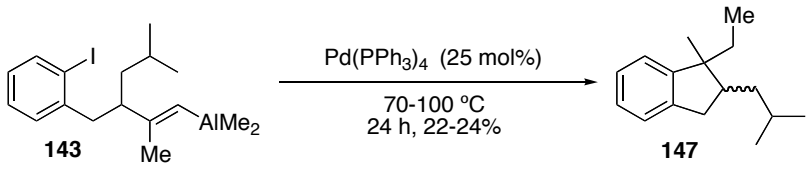
It was initially envisaged that intramolecular migratory insertion of (*E*)-2,2-disubstituted-1-alkenyltrimethylalane **143** into a σ-arylpalladium(II) iodide should lead to neopentylic dimetallic σ-alkylpalladium(II) species **144**. Concomitant with loss of iododimethylalane, the latter was expected to display carbenoid reactivity and undergo 1,5-C_{alkyl}-H insertion with the tethered isopropyl group (Scheme 3.3). Dimerised carbene side-products **146** were also expected based upon the previously delineated reactivity of *gem*-dimetallic palladio(II)/trialkylstannylalkane species (Chapter 2).

Scheme 3.3: Expected reactivity



Former laboratory colleague Rebekah J. Carson established that, from vinylalane **143**, using $Pd(PPh_3)_4$ (25 mol %) in either THF or PhMe at temperatures ranging between 70 and 100 ºC, neither tricycle **145** nor dimeric species **146** was detected. Instead, the major reaction product, albeit in low yields, was an inseparable 1:1 mixture of diastereomeric bicycles **147** containing a benzylic ethyl substituent (Equation 3.1), as ascertained through NMR and GC-MS studies.[154,155] No products derived from typical Pd-carbene reactivity were observed.

Equation 3.1: Observed reactivity of the vinylalane derived from 4-(2-iodophenyl)but-1-yne



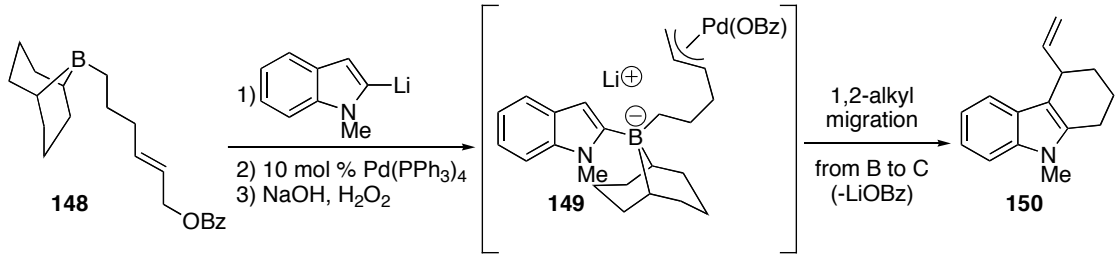
Of significance, formation of the 1,1-dialkyl indane framework was promising for the approach based on intramolecular (*E*)-2,2-disubstituted-1-alkenyldimethylalane carbopalladation. In this unexpected outcome, three carbon-carbon bonds were formed, yielding an all-carbon benzylic quaternary stereogenic centre. This domino process deserved further attention, formally constituting a $C(sp^3)$-$C(sp^3)$ cross-coupling reaction taking place at the sterically demanding neopentylic position.

3.1.3.2 C-C Bond-Forming 1,2-Alkyl Migration Initiated by Pd(II) Electrophiles

The observed reactivity bears analogy with the 1,2-metallate rearrangement.[156] Upon presentation of α-heteroalkenylmetal "ate" species with electrophiles, 1,2-ligand migration occurs from the hypervalent metal to carbon, and affords a carbon-carbon σ-bond. Still, to the best of the author's knowledge, few cases of Pd(II) electrophilic species triggering 1,2-migration from a main group metal are documented.[157]

Terashima and co-workers reported the intramolecular reaction of trialkyl-(1-methyl-2-indolyl)borates with allylpalladium(II) benzoates.[158] Hydroboration of 2,5-hexadienyl acetate led to mixed trialkylborane **148**, which was coupled with 2-lithio-1-methylindole to furnish the corresponding hypervalent lithium 2-indolylborate reagent. Upon treatment with catalytic amounts of $Pd(PPh_3)_4$, C-C bond forming indole addition to the allylpalladium(II) benzoate electrophile took place via intermediate **149**. Oxidative work-up allowed for the isolation of 2,3,4,9-tetrahydro-1*H*-carbazole **150** (Scheme 3.4). This specific case of 1,2-alkyl migration from boron to carbon allowed intramolecular cyclisation.

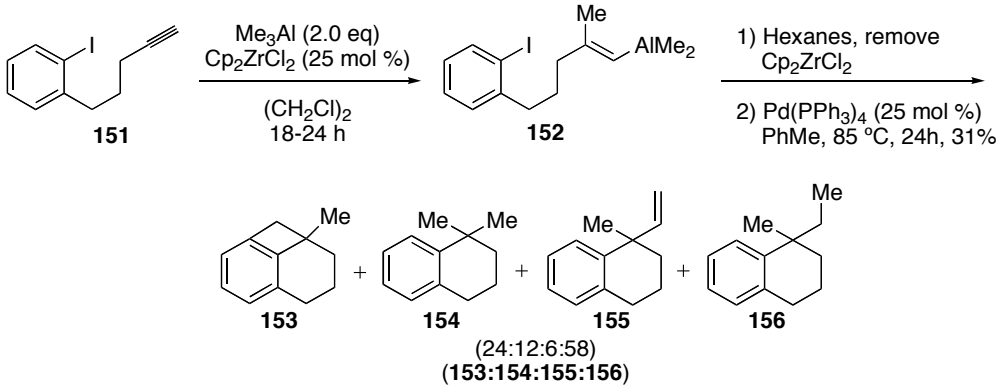
Scheme 3.4: 1,2-Alkyl migration from boron to carbon initiated by a Pd(II) electrophile



3.1.3.3 Sequential Carbometalation of 5-(2-Iodophenyl)-pent-1-yne

To study this multiple carbon-carbon bond-forming scheme, simplified substrate **151** was prepared.[154] With this alkynyl-tethered aryl iodide, diastereomer formation upon cyclisation was precluded, thereby facilitating product analysis and reaction optimisation. After subjecting 5-(2-iodophenyl)-1-pentyne **151** to Negishi methylalumination, the resulting (*E*)-2,2-disubstituted-1-alkenyldimethylalane **152** was treated with 25 mol % $Pd(PPh_3)_4$ and heated to 85 ºC for 24 h in a sealed Schlenk tube. Following aqueous work-up, an inseparable 24:12:6:58 mixture composed of products **153**, **154**, **155** and **156** was isolated in 31% overall yield (Scheme 3.5).

Scheme 3.5: Initial results with 5-(2-iodophenyl)pent-1-yne



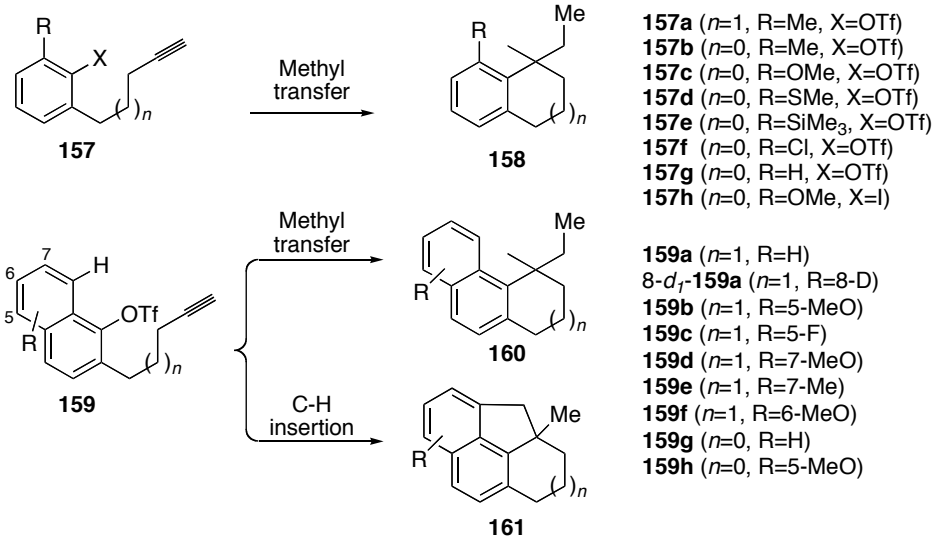
Synthesis of 1-ethenyl-1-methyl-1,2,3,4-tetrahydronaphthalene **155** via an alternate route (see section 3.6.3.1), as part of a joint endeavour with Fillion and Carson who respectively prepared **154** and **156**, allowed comparison of NMR and GC-MS evidence, so that the structures of **154**-

156 could unambiguously be assigned. Tricycle **153** was fortuitously separated from the product mixture, and its structure identified by ^{1}H NMR before decomposition.

Tetralins **155** and **156** were especially noteworthy for their incorporation of a supplementary carbon atom, presumably arising from trimethylaluminum. Conversely, benzocyclobutane **153** was proposed to arise from Pd-catalysed arylation of a Pd/Al carbenoid species analogous to **144**, and its strain energy could be causing extensive decomposition at the temperature of 85 ºC, thus lowering the yield.

In order to selectively optimise each Pd-catalysed carbon-carbon bond-forming process, methyl migration or 1,2-diarylation, competing pathways should be restricted. Hence, third-generation cyclisation substrates **157** and **159** were designed (Scheme 3.6). First, 2,6-disubstitution on aryl trifluoromethanesulfonates **157** would prohibit competing C_{aryl}-H insertion and allow the exclusive study of the ligand transfer reaction. Second, the 1-naphthalenyl triflate scaffold **159** would furnish a 1,5-C_{aryl}-H bond to study the arylation reaction, leading to stable cyclopentane ring products. For naphthalene **159**, development of reaction conditions to access either reaction pathway from the same alkenylalane intermediate constituted the ultimate objective.

Scheme 3.6: Third-generation 1-aryl and 1-naphthyl triflate cyclisation precursors



157a (*n*=1, R=Me, X=OTf)
157b (*n*=0, R=Me, X=OTf)
157c (*n*=0, R=OMe, X=OTf)
157d (*n*=0, R=SMe, X=OTf)
157e (*n*=0, R=$SiMe_3$, X=OTf)
157f (*n*=0, R=Cl, X=OTf)
157g (*n*=0, R=H, X=OTf)
157h (*n*=0, R=OMe, X=I)

159a (*n*=1, R=H)
8-d_1-**159a** (*n*=1, R=8-D)
159b (*n*=1, R=5-MeO)
159c (*n*=1, R=5-F)
159d (*n*=1, R=7-MeO)
159e (*n*=1, R=7-Me)
159f (*n*=1, R=6-MeO)
159g (*n*=0, R=H)
159h (*n*=0, R=5-MeO)

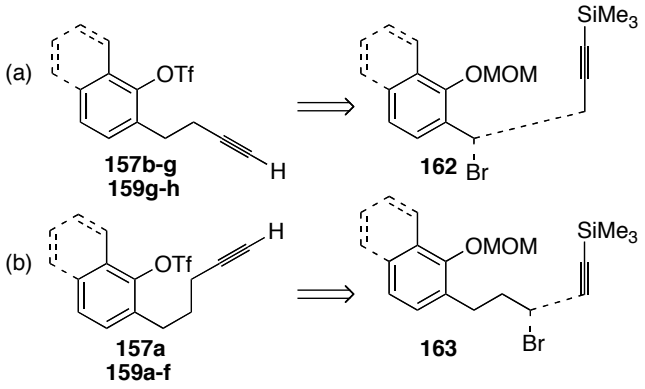
3.2 Preparation of Third-Generation Substrates

Third-generation intramolecular reaction substrates incorporated both electrophilic (aryl triflate) and nucleophilic (terminal alkyne) termini, posing new challenges in the course of their synthesis. This section describes bond formation discoveries made throughout their preparation.

3.2.1 Retrosynthetic Analysis

Using aryl triflates instead of the original iodides would simplify substrate synthesis, as limited iodoarenes are commercially available. Retrosynthetically, trifluoromethanesulfonylation would precede late-stage global deprotection. Indane-ring precursors **157b-g** would arise from displacement by (1-lithioprop-2-yn-3-yl)trimethylsilane of the key benzylic bromide intermediate **162** (Scheme 3.7a). The methoxymethyl (MOM) group was selected to mask the phenol proton due to its ability to not only survive under strongly basic or nucleophilic conditions but also to direct *ortho*-lithiation.[159] Following the synthetic path developed by Carson and Fillion,[154] tetrahydronaphthalene- and tetrahydrophenanthrene-ring precursors **157a** and **159a-f** should arise from 3-aryl- or 3-naphthyl-1-bromopropane derivatives **163** via nucleophilic displacement with TMS-acetylene (Scheme 3.7b).

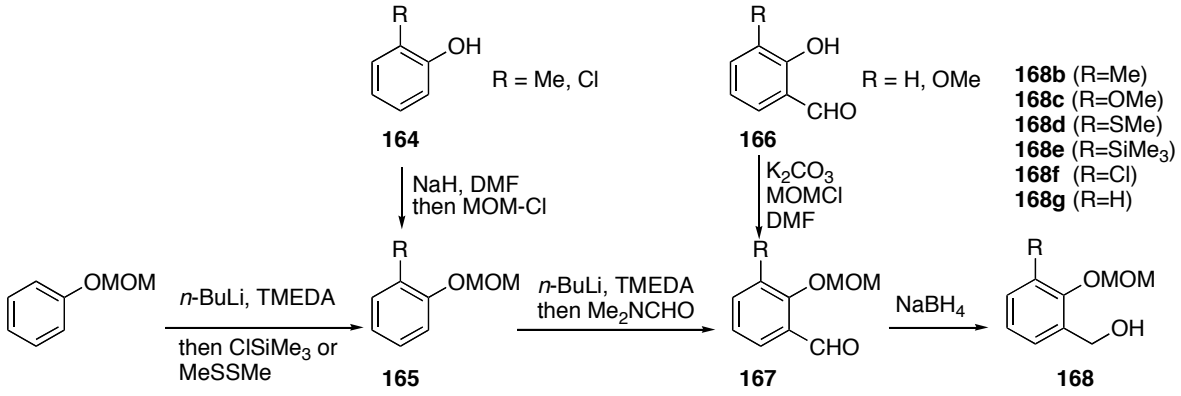
Scheme 3.7: Retrosynthetic analysis of substrates 157 and 159



3.2.2 Preparation of Butynyl-tethered Aryl Triflates and Iodide

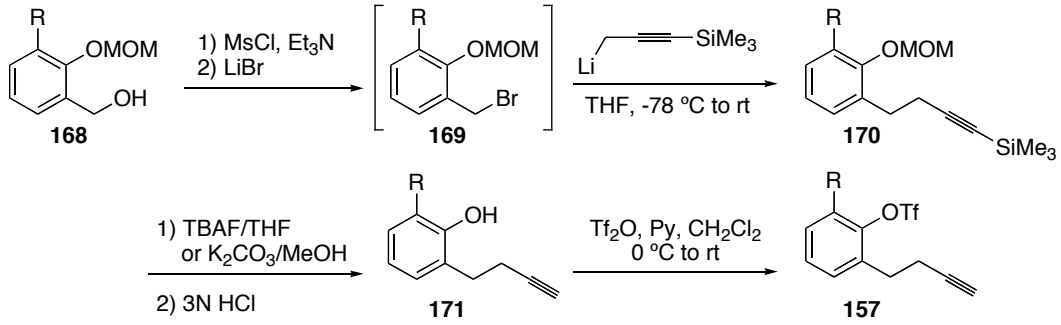
Benzylic alcohols for homologation with 1-propynyl-1-trimethylsilane were synthetically accessed in a few steps from inexpensive phenol starting materials. As described in Scheme 3.8, commercially available *o*-cresol and *o*-chlorophenol **164b,f** were methoxymethylated using MOM-Cl and NaH in DMF. Conversely, 2-thiomethyl- and 2-trimethylsilanylphenyl methoxymethyl ethers **165d-e**, formed from methoxymethyl phenyl ether via the *ortho*-lithiation procedure, were generously provided by Prof. Eric Fillion. MOM-Acetals **165b,d-f** were then transformed into benzaldehydes **167** following interception of the 3-substituted-2-methoxymethoxyaryllithiums with *N*,*N*-dimethylformamide. Salicylaldehyde and *o*-vanillin (**166c,g**) were *O*-methoxymethylated to furnish benzaldehydes **167c,g**. Finally, subsequent reduction to arylmethanols **168b-g** was achieved using $NaBH_4$ (Scheme 3.8).

Scheme 3.8: Synthesis of 2,3-disubstituted arylmethanols



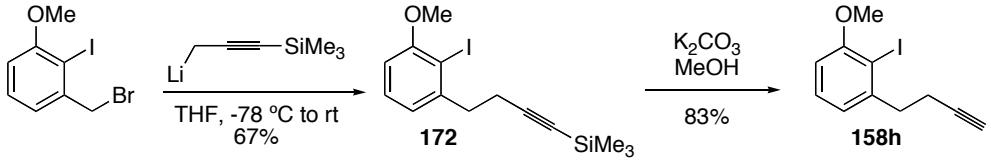
Benzyl alcohols were converted, via their mesylates, into bromides **169** that were used *in situ* for propyne homologation.[160] Following stepwise exposure of the alkynyl and phenoxyl protons, trifluoromethanesulfonylation yielded the butynyl-tethered substrates **157b-h** and **159h** (Scheme 3.9). Co-worker Anna A. Remorova synthesised unsubstituted naphthyl triflate **159g** as part of a collaborative effort.[161]

Scheme 3.9: Synthesis of 4-arylbut-1-ynes 157b-h



Synthesis of the aryl iodide was achieved from the known 3-methoxy-2-iodobenzyl bromide[162] following side-chain installation and protiodesilylation (Scheme 3.10).

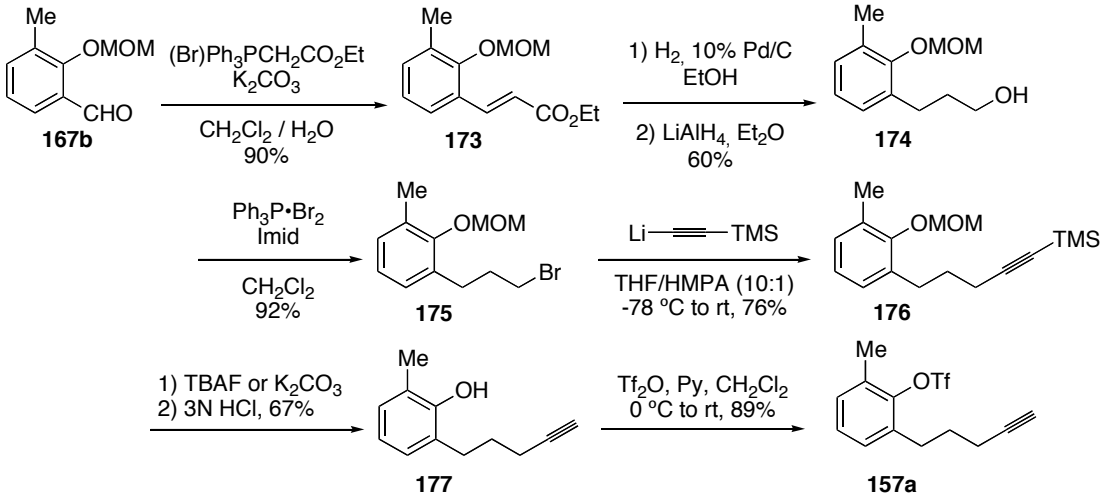
Scheme 3.10: Synthesis of aryl iodide 158h



3.2.3 Preparation of Pentynyl-tethered Aryl Triflate 157a

A route to propanol **174** from the corresponding benzaldehyde **167b** was designed. Transformation to the saturated alcohol was effected by C-C bond-forming stabilised Wittig reaction, Pd-catalysed hydrogenation to the 3-arylpropanoate followed by $LiAlH_4$ reduction (Scheme 3.11). From there, bromination with $Ph_3P{\bullet}Br_2$ in imidazole-buffered CH_2Cl_2 preceded nucleophilic displacement with lithiated TMS-acetylene. Following deprotection and triflation, aryl triflate **157a** was obtained in 23% overall yield from benzaldehyde **167b**.

Scheme 3.11: Synthesis of pentynyl-tethered 2,6-disubstituted aryl triflate 157a



3.2.4 Synthesis of Pentynyl-tethered Naphthyl Triflates 159a-e

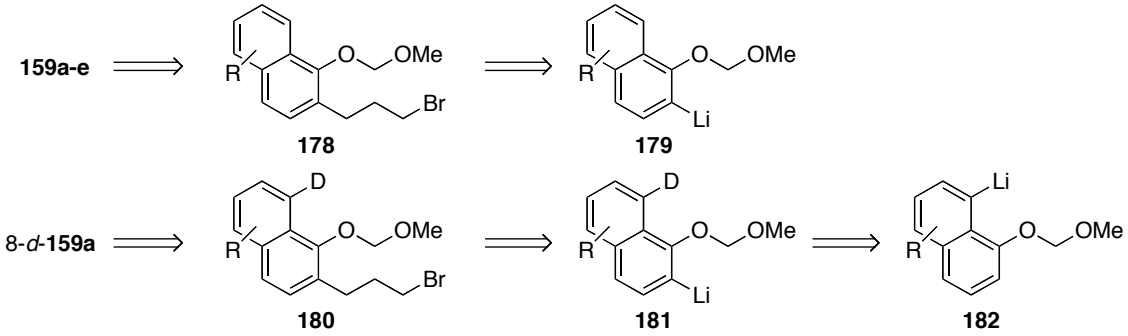
Preparation of unsubstituted naphthyl triflate **159a** first met with issues associated with the original synthetic route, developed by Carson on 100-mg scale, involving Jones oxidation of 2-(4-pentynyl)-1,2-dihydronaphthalen-1-ol. On multi-gram scale, the oxidation endpoint could not easily be monitored, neither by visual colour inspection, nor by thin-layer chromatography, and oxidative ring-coupled products were obtained instead of the expected 2-substituted-1-naphthol.[163] The alternate route utilised by Carson for an 5-arylpent-1-yne substrate, involving boron trifluoride-mediated opening of oxetane by aryllithiums, led to myriad side-products in presence of the naphthalene. Gratifyingly, the synthetic sequence previously disclosed, from benzaldehydes to pentynyl-tethered aryl triflate substrates, proved also suitable for the synthesis of naphthyl-tethered 1-pentynes. In some cases, the synthesis of 3-naphthyl-1-propanols or their precursors proved substantially challenging, so insight gained through their preparation is herein described.

3.2.4.1 Synthesis of Unsubstituted Substrates 159a and 8-*d*-159a

Naphthalenyl triflates **159a-e** would be accessed from 3-(1-methoxymethoxy-2-naphthyl)-1-bromopropanes **178**. *ortho*-Formylation of 1-methoxymethoxynaphthalenes should occur favourably over the possibly competing *peri*-substitution, to furnish 2-naphthaldehyde

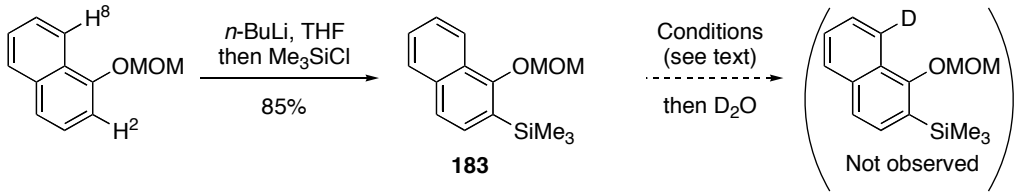
derivatives regioselectively (Scheme 3.12). Nonetheless, regioselective *peri*-metalation conditions were also sought, for they would allow entry into 8-*d*-**159a** for deuterium labeling studies.

Scheme 3.12: Expected functionalisation of 1-methoxymethoxynaphthalenes by *ortho*- and *peri*-lithiation



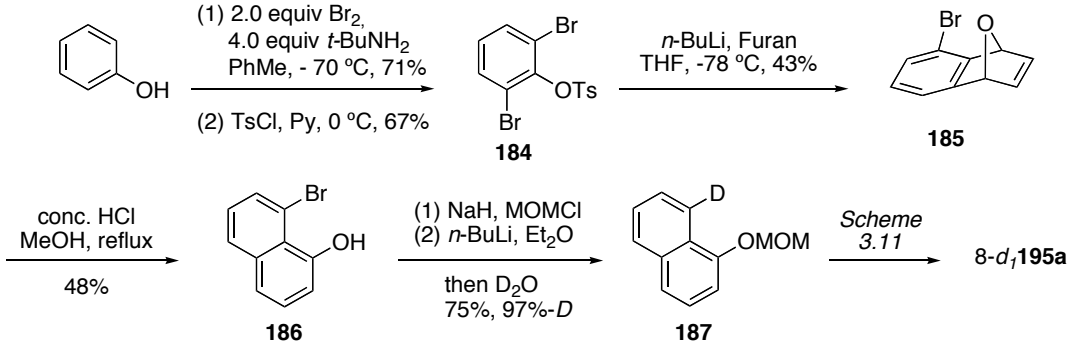
Substrate **159a** was synthesised following the same steps described in Scheme 3.11, starting from the known 1-methoxymethoxy-2-naphthaldehyde.[164] Forays into the desired *peri*-lithiation proved troublesome. There exist but scarce reports on *peri*-functionalisation of the 8-position of naphthalene rings via an organolithium species. Mitigated success was obtained by Clayden and co-workers in *peri*-carboxylation of methyl 1-naphthyl ether (35% yield, *t*-BuLi, cyclohexane, 26 h),[165] so it was hoped that the more strongly directing MOM group would allow for the 8-lithionaphthalene anion to form. In order to favour regioselection, the 2-hydrogen could be protected as the naphthyl trimethylsilane.[166] However, despite varying the solvent (THF, Et_2O, hexanes) and organolithium base (*sec*-BuLi, *n*-BuLi, *t*-BuLi), in presence or absence of TMEDA, only unlabeled (1-methoxymethoxy-2-naphthyl)trimethylsilane **183** was recovered after D_2O quench. Therefore, the route to 8-*d*-**159a** was redesigned, taking advantage of published synthetic methods to access substituted 1-naphthols.

Scheme 3.13: Preliminary study of methoxymethyl 1-naphthyl ether *peri*-lithiation



8-Bromo-1-naphthol was reported by Batt *et al*. to be the major regioisomer (9:1) of Brønsted acid-catalysed isomerisation of 5-bromo-1,4-epoxy-1,4-dihydronaphthalene.[167] The 3-bromo-1-benzyne precursor, 2,6-dibromophenyl tosylate **184** was obtained in two steps from phenol via bis-*ortho*-bromination following the published method,[168] followed by tosylation. Disappointingly, the acid-catalysed oxabicycle isomerisation gave a 66:34 mixture of 8- and 5-bromo-1-naphthols, contrasting with the authors' claim. Nevertheless, the regioisomers were easily separated by flash chromatography, and **186** was isolated in 48% yield. MOM-Protection was followed by lithium-bromide exchange and deuteriodemetalation, to afford the desired 8-deuterio-1-methoxymethoxynaphthalene **187** in 75% yield from 8-bromo-1-naphthol **186**, with 97% deuterium incorporation (Scheme 3.14).

Scheme 3.14: Synthesis of 8-deuterionaphthyl ether 187 towards 8-*d*-**159a**

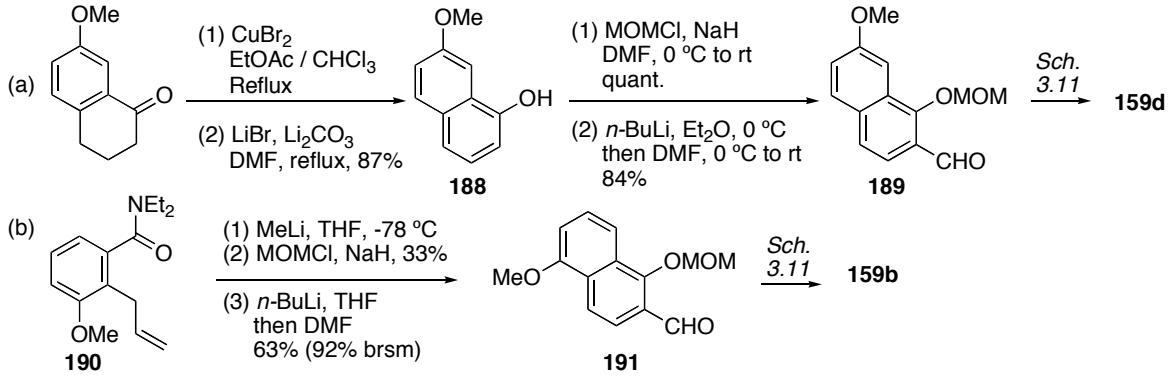


On this key intermediate, *ortho*-lithiation occurred exclusively at the naphthalene 2-position, without erosion of deuterium content. Hence, 1-naphthyl triflate 8-*d*-**159a** could be synthesised from the corresponding 2-naphthaldehyde, following the route previously described.

3.2.4.2 Synthesis of 5- and 7-Methoxy Substrates 159b,d

Taking advantage of the report by Banerjee, 7-methoxy-1-naphthol was synthesised from 7-methoxy-1-tetralone via sequential α-bromination/dehydrobromination, to yield the target material in 87% yield (Scheme 3.15a)[169] that was then elaborated into **159d** following the previously presented steps. Anionic cyclisation, as per Snieckus' report, provided access to 5-methoxy-1-naphthol[170] necessary for the synthesis of 5-methoxy-1-naphthyl triflate substrates, **159b** (Scheme 3.15b).

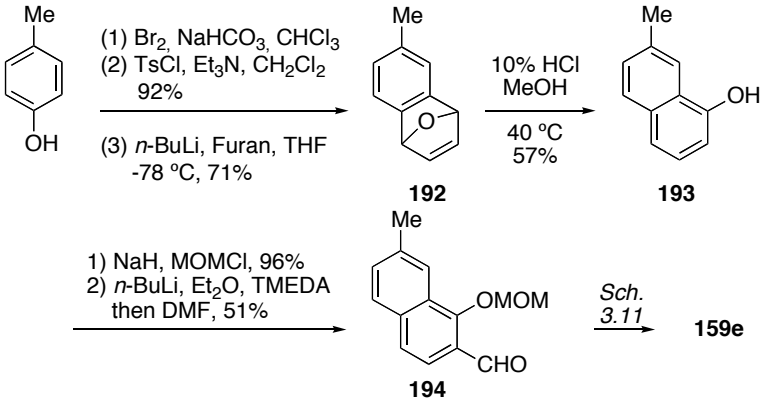
Scheme 3.15: Synthesis of substrates 159b and 159d



3.2.4.3 Synthesis of 7-Methyl Substrate 159e

The 7-methyl-1-naphthol intermediate **193** could be obtained after reoptimisation of the acid-catalysed isomerisation procedure reported by Gaviña,[171] from the corresponding oxabicycle **192** (Scheme 3.16). At reflux in methanol, a 67:33 ratio of regioisomers was initially obtained. Decreasing the isomerisation reaction temperature to 40 ºC, a crude 74:26 mixture of 7- *vs*. 6-methyl-1-naphthol isomers was isolated, enriched to 85:15 and 57% isolated yield by trituration in petroleum ether. Methoxymethyl etherification followed by *ortho*-formylation gave crystalline 2-naphthaldehyde **194** whose regiopurity was enhanced to 95:5 after two recrystallisations. From there, the synthesis of 7-methyl 1-naphthyl triflate substrate **159e** followed the previously outlined route.

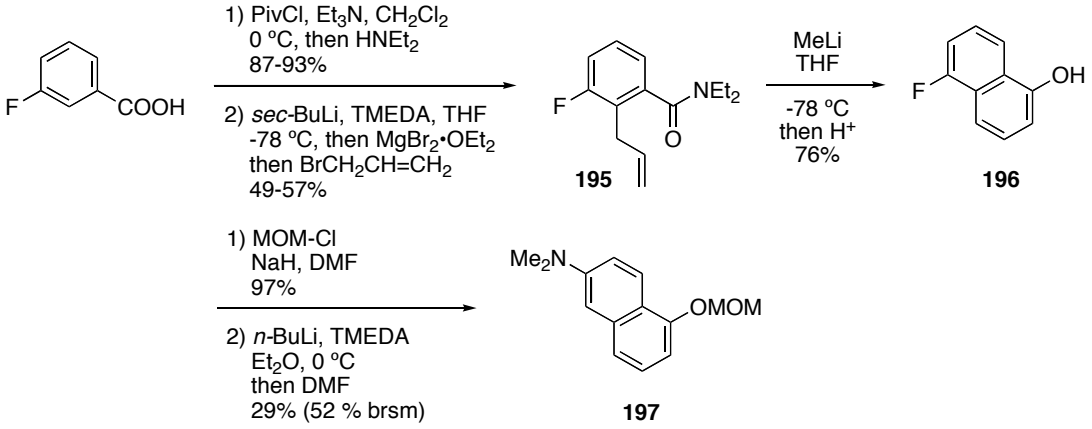
Scheme 3.16: Synthesis of substrate 159e



3.2.4.4 Synthesis of 5-Fluoro Substrate 159c

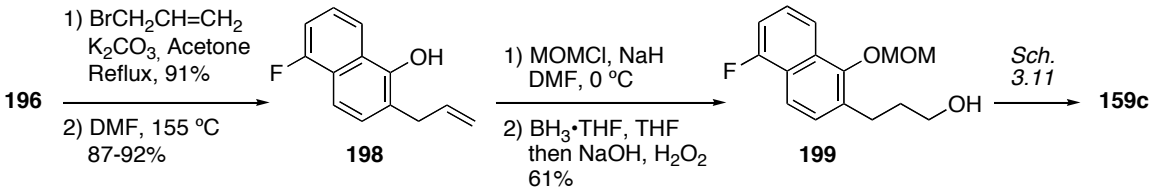
Snieckus' anionic cyclisation method was applied to *N*,*N*-diethyl-3-fluoro-2-(2-propenyl)benzamide **195** for the synthesis of 5-fluoro-1-naphthol. As presented in Scheme 3.17, up to 76% yield of 5-fluoro-1-naphthol was obtained after carefully adjusting the quenched reaction mixture to pH ~ 1, and optimising the MeLi equivalency (1.2 instead of 2.2 equiv) to prevent side-reactions. Unexpectedly, with the MOM ether, *ortho*-lithiation conditions gave rise to a pitch black reaction mixture from which, after quenching with DMF, a major product was isolated in 29% yield along with 23% of recovered starting MOM-acetal. The former was determined to be the defluorinated 6-(*N*,*N*-dimethyl)aminonaphthalene **197**.

Scheme 3.17: Attempted *ortho*-formylation of 5-fluoro-1-naphthyl methoxymethyl ether



Based on a recent medicinal chemistry report, the synthesis of 3-(5-fluoro-1-methoxymethoxy-2-naphthyl)-1-propanol was achieved.[172] Using 5-fluoro-1-naphthol **196**, *O*-allylation followed by Claisen rearrangement in DMF under reflux furnished the 2-allyl-5-fluoro-1-naphthol **198** in excellent yield. Protection of the 1-naphthyloxy proton was followed by hydroboration-oxidation, affording the key propanol intermediate **199**, from which completion of the 5-fluoro substrate **159c** could be completed.

Scheme 3.18: Synthesis of 3-(5-Fluoro-1-methoxymethoxy-2-naphthyl)-1-propanol



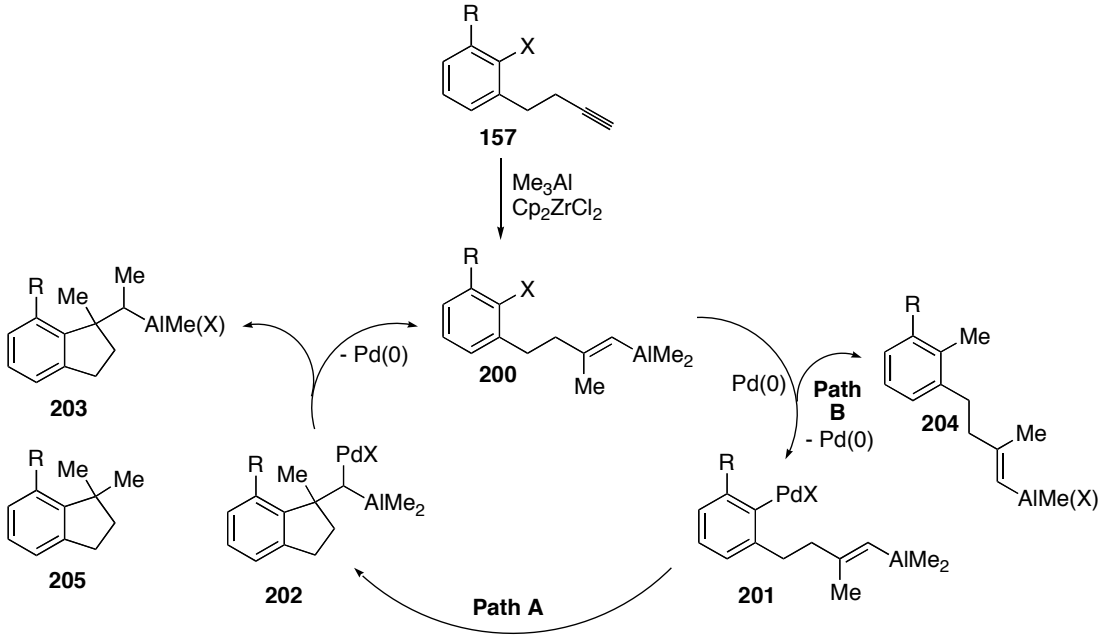
3.3 Study of the Pd-Catalysed 1,2-Ligand Migration

3.3.1 Optimisation Studies

With ready access to substrates **157** and **159**, the study of intramolecular Pd-catalysed reactions of (*E*)-2,2-disubstituted-1-alkenydimethylalanes was resumed. Using 2,6-disubstituted aryl triflates **157**, following methylalumination, the resulting vinylalane-tethered triflates and iodide **200** would be treated with a palladium(0) catalyst. After oxidative addition of the aryl triflate or iodide to palladium(0), the alkenyl should then undergo intramolecular migratory insertion with the arylpalladium(II) species **201**, giving rise to *gem*-dimetallic **202**. From the latter, 1,2-ligand migration should take place, forming a carbon-carbon bond at the neopentyl position, and regenerating the Pd(0) catalyst. The residual dialkylaluminum (pseudo)halide **203** could then be further functionalised through reaction with electrophiles (Scheme 3.19).

Efforts should be invested to control the reactivity of the σ-arylpalladium(II) species **201** that can either take part in intramolecular migratory insertion to yield **202** (path A), or intermolecular methyl cross-coupling, leading to arene **204** (path B). Adventitious hydride sources should be eliminated, as in the previously cited work by Keay; otherwise, *gem*-dimethyl side-products such as **205** may be observed in the course of benzylic all-carbon quaternary stereocentre formation.[18]

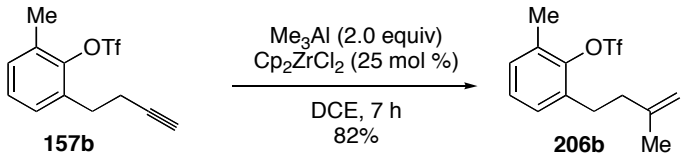
Scheme 3.19: Proposed sequential carbometalations



Studies of the Heck reaction have demonstrated the stereospecificity of olefin carbopalladation by σ-arylpalladium(II) species, leading to configurationally stable σ-alkylpalladium(II) intermediates. Should the C-Al bond also be configurationally stable, then stereospecific formation of two adjacent stereocentres, including an all-carbon benzylic centre, could take place in a catalytic fashion. In fact, Eisch has studied the configurational stability of organoaluminum intermediates, and found that in presence of a Lewis basic additive, they reacted stereospecifically with deuterium sources. However, in absence of Lewis base, organoalanes epimerised readily, leading to 50:50 diastereomer mixtures following D_2O quench.[173]

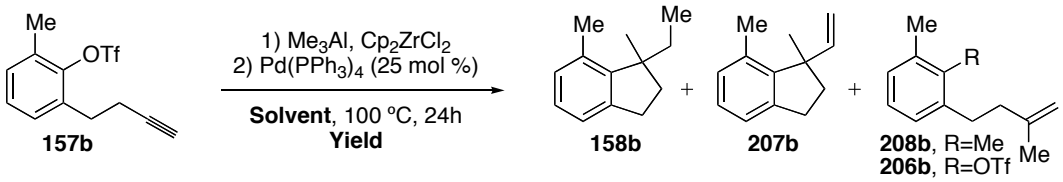
It was first ascertained whether methylalumination of **195b** following Negishi's conditions proceeded without interference with the aryl trifluoromethanesulfonate. Indeed, 2,2-disubstituted alkene **206b** was isolated in 82% yield upon applying the classical Negishi conditions (Equation 3.2). This result was encouraging, for when this study was commenced, there existed no precedent for methylalumination in presence of aryl triflates.

Equation 3.2: Methylalumination of 2-(3-butynyl)-6-methylphenyl triflate 157b



In a typical run, following evaporation of the volatile reaction components, the crude organoalane was used without removal of the zirconocene catalyst by slurrying with hexanes, as Cp_2ZrCl_2 was found to have no effect upon the reaction course. Upon redissolving the crude alane in benzene and treating with 25 mol % of $Pd(PPh_3)_4$ followed by heating to 100 ºC for 24 h in a sealed Schlenk tube, the expected 1-ethyl-1,7-dimethylindane **158b** was isolated, albeit in 1% yield for the overall process (Table 3.1, entry 1). Product **158b** was contaminated with 44% of inseparable methyl-vinyl indane **207b**. Using non-polar PhH as reaction solvent, the reaction produced twice as much methyl cross-coupling by-product **208b** than desired **158b**. Of significance for further diastereoselective C-Al bond functionalisation, Lewis-basic Et_3N was also suitable as reaction solvent, and eradicated side-product **207b** formation, although the isolated yield was 3% (entry 2). Solvent survey revealed that Lewis-basic DME led to somewhat better yields and decreased amounts of side-product **208b** (entry 4). In the absence of triethylamine, isolated products contained 10-44% methyl-vinyl side-product, and yields hovered below 20% (entries 1-5). The identity of **207b** was inferred from hydrogenation of the mixture (H_2, 5% Pd/C, EtOAc) yielding pure **158b**. In 1,4-dioxane, the vinylalane intermediate was not entirely consumed, and unreacted triflate **206b** was also observed (entry 5). Using acetonitrile, an encouraging 42% yield of indane **158b**, as a 90:10 mixture with **207b**, was isolated (entry 6).

Table 3.1: Initial solvent screening

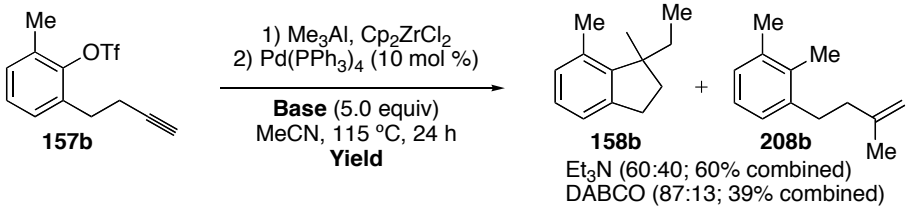


Entry	Solvent	Ratio[a] (**158**:**208**)	Ratio[a] (**158**:**207**)	Yield[c] (%)
1	PhH	33:67	56:44	1
2	Et_3N	N/A	>99:1	3
3	DMF	52:48	68:32	7
4	DME	83:17	82:18	16
5	1,4-Dioxane	64:36[b]	84:16	12
6	MeCN	86:14	90:10	42

[a] Determined by ^{1}H NMR. [b] Ratio of unreacted **206b** not taken.
[c] Isolated yield of mixture of **158b** and **207b**, for a single experiment.

Subsequent optimisation was conducted in partnership with Rebekah J. Carson, using a reaction temperature of 115 °C. Catalyst loading was successfully decreased to 10 mol % without yield erosion. Aiming at minimising competing intermolecular cross-coupling while preserving the stereochemical integrity of the C-Al bond, Lewis-basic additives were explored. It was found that whereas excess triethylamine (5.0 equiv) led to a 60:40 **158b**:**208b** ratio, DABCO lead to a 87:13 mixture of the same products, in 39% combined yield (Equation 3.3). Crude NMR spectra were noticeably cleaner using DABCO; this base, devoid of transferable hydrides, was consequently carried through the catalyst study.

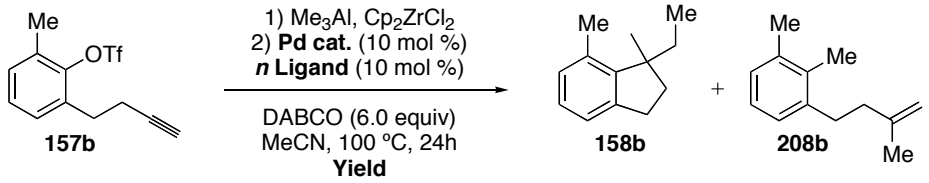
Equation 3.3: Lewis base exploration



Using $Pd_2(dba)_3$ as palladium source, the performance of several phosphine ligands was evaluated. As found by Carson, neither electron-rich and bulky trialkylphosphines (P(*t*-Bu)$_3$ or PCy_3), nor bidentate ligands (dppe, dppp, dppb, dppf) afforded significant conversion to the desired product. Combinations of protiodealuminated triflate **206**, methyl cross-coupled product **208**, *gem*-dimethyl **205** or decomposition were typical.[154] Electron-poor triphenylarsine

gave no conversion, and only triflate **206b** was observed (Table 3.2, entry 1). Tris(*p*-methoxyphenyl)phosphine, shown to ameliorate carbopalladation kinetics of an arylpalladium(II) bromide,[174] turned out to be the ligand par excellence for this process (entry 2), which requires migratory insertion of a sterically demanding and electron-deficient 2,2-disubstituted-1-alkenylalane. Since the absence of dba in the crude composition indicated side-reactions with the enone ligands, $Pd_2(dba)_3$ was deemed unsuitable as pre-catalyst. Switching to $Pd[(p\text{-}MeOPh)_3]_2Cl_2$ along with equimolar Et_3N to reduce Pd^{II} *in situ*, the reaction stalled at 85% conversion with the coordinatively unsaturated catalyst (entry 3). Gratifyingly, indane **158b** was isolated in 67% yield, as the sole product with >99% conversion when the coordinatively saturated tetrakis(phosphino) complex was used (entry 4).

Table 3.2: Palladium catalyst optimisation

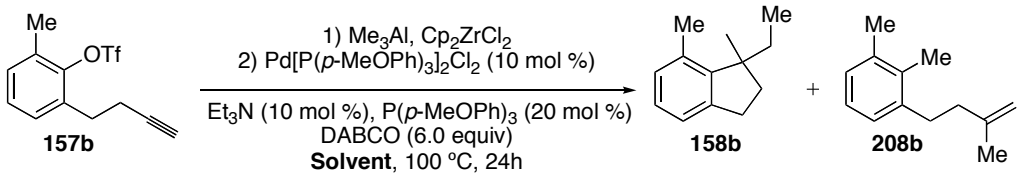


Entry	Catalyst	Ligand	*n*	Ratio (**158**:**208**)[a]	Yield (%)[b]
1	$Pd_2(dba)_3$	$AsPh_3$	4	N/A[c]	N/A[d]
2	$Pd_2(dba)_3$	$P(p\text{-}MeOPh)_3$	4	>99:1	54
3	$Pd[P(p\text{-}MeOPh)_3]_2Cl_2$	---	---	85:15	42
4	$Pd[P(p\text{-}MeOPh)_3]_2Cl_2$	$P(p\text{-}MeOPh)_3$	2	>99:1	67

[a] Determined by ^1H NMR. [b] Isolated yield of **158**. [c] Product **206b** exclusively observed.
[d] Yield of unwanted **206b** not taken.

The preliminary solvent survey was revisited using this optimised catalyst. Aprotic, non-polar and non-coordinating solvents, DCE and PhMe, were found to provide substantial amounts of cross-coupling product **208b** (Table 3.3, entries 1-2). Lewis-basic ethereal solvents improved the ratios of methyl-transfer vs. cross-coupled adducts as well as yields (entries 3-4). Optimal solvent polarity and Lewis basicity were afforded by MeCN (entry 5), in which no detectable amounts of **208b** were observed by ^1H NMR analysis of the crude composition. This optimal behaviour was not translated in PhCN (entry 6), whose high boiling point also made made isolation and purification cumbersome.

Table 3.3: Solvent optimisation

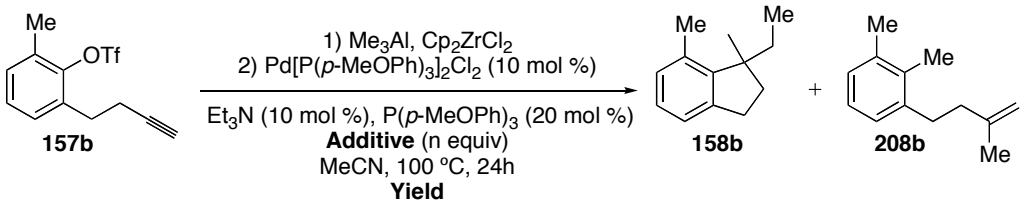


Entry	Solvent	Ratio (**158**:**208**)[a]	Yield (%)[b]
1	DCE	30:70	N/A[c]
2	PhMe	67:33	45
3	DME	90:10	58
4	1,4-dioxane	90:10	48
5	MeCN	>99:1	67
6	PhCN	52:48	28

[a] Determined by ^{1}H NMR. [b] Isolated yield of **158**.
[c] Yield not taken.

Finally, using MeCN as solvent in conjunction with the optimised Pd source, an assessment of Lewis-basic additives revealed that the ratio of methyl transfer **158b** to methyl cross-coupling product **208b** obtained in absence of additive (73:27, Table 3.4, entry 1) was worsened by pre-forming the cesium fluoroaluminate (entry 2), affording nearly equimolar amounts of **158b** and **208b**. Alkoxy- or fluorometalate complexes accelerate transmetalation in metal-catalysed cross-coupling reactions.[175] In this case, a less selective process favoured intermolecular methyl cross-coupling at the expense of 1,2-methyl migration. The addition of excess triethylamine gave a better ratio of 94:6 (entry 3), yet product **158b** was generated concomitantly with 8% of methyl-vinyl side-product **207b**. Employing a six-fold excess of DABCO (entry 4) eradicated the latter side-product and produced high isolated yields of **158b** and clean ^{1}H NMR spectra for the crude mixture. Another strongly nucleophilic Lewis base, DMAP, was inadequate to promote this process, whereas DBU gave messy mixtures as well as incomplete conversion (entries 5-6).

Table 3.4: Lewis base optimisation



Entry	Additive	*n*	Ratio (**158**:**208**)[a]	Yield (%)[b]
1	---	---	73:27	15
2	CsF	1.0	55:45	17
3	Et_3N	6.0	94:6[c]	56
4	DABCO	6.0	>99:1	67
5	DMAP	6.0	77:23	18
6	DBU	6.0	67:33[d]	N/A

[a] Determined by ^{1}H NMR. [b] Isolated yield of **158**.
[c] Contaminated with 8% **207b**. [d] Reaction went to 78% conversion.

3.3.2 Scope of the 1,2-Ligand Migration Reaction

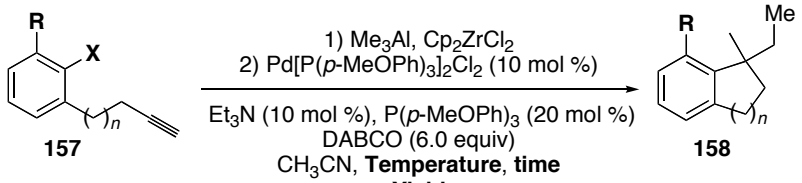
3.3.2.1 Carbocyclic Methyl-Transfer Products

Using the optimised protocol, the scope of the 1,2-ligand migration reaction was then determined, utilising tetrahydronaphthalene and indane precursors **157a-h**. The results are shown in Table 3.5, wherein entries 3-4 are Carson's contribution. Compared to the five-membered ring product **158b**, obtained in 67% isolated yield, six-membered methyl-transfer **158a** was only identified by its ^{1}H NMR ethyl group signature (δ 0.70, t, J = 7.5 Hz) in the crude reaction mixture. Despite varying reaction time and temperature, it was generated along with several side-products, and resisted isolation in pure form (entries 1-2). This contrasts with Carson's successful formation of the 7-isopropyl tetrahydronaphthalene analogue **rjc4**, in 35% yield (entry 4). Although higher temperatures and longer reaction times were required, the sterically bulky and electron-rich isopropyl group was tolerated, at the expense of the formation of considerable amounts of cross-coupled products competing with tetrahydronaphthalene formation (50:50).

Functional group tolerance at the aryl 6-position was explored. Methyl ether, thioether[176] and trimethylsilane substrates **157c-e** gave methyl-transfer indanes **158c-e** in 53-63% yields (entries 5-8). Interference from the methyl thioether led to unusually high proportions of *gem*-

dimethyl side-product **205d**. Aryl chloride **157f** likely underwent activation by the Pd catalyst, giving the desired product in only 26% yield. The crude reaction mixture was highly complex, and evidence of decomposition was seen upon purification. The catalyst based upon electron-rich tris(*p*-methoxyphenyl)phosphine was also less suited to aryl iodide **157h** since yield suffered erosion (compare entries 10 and 5). Finally, the necessity of substituting the aryl 6-position was demonstrated by the cumbersome isolation of 1-ethyl-1-methylindane **158g** from a multitude of unidentifiable side-products in 6% yield (entry 9).[177]

Table 3.5: Summary of the methyl transfer reaction

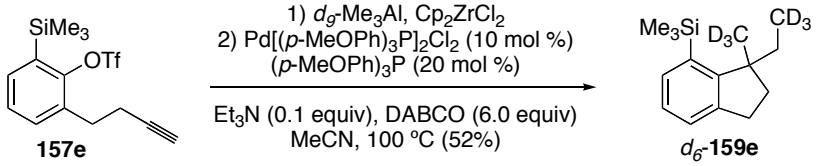


Entry	Alkyne	R	*n*	X	Temperature (ºC)	Time (h)	Yield (%)[a]
1	**157a**	Me	2	OTf	100-120	24-48	N/A[b]
2	**157b**	Me	1	OTf	100	24	67 (**158b**)
3	**rjc1**	*i*-Pr	1	OTf	120	72	54[c] (**rjc3**)
4	**rjc2**	*i*-Pr	2	OTf	120	72	35[c] (**rjc4**)
5	**157c**	OMe	1	OTf	100	24	53 (**158c**)
6	**157d**	SMe	1	OTf	120	72	63[d,e] (**158d**)
7	**157e**	$SiMe_3$	1	OTf	100	18	53 (**158e**)
8	**157f**	Cl	1	OTf	100	24	26 (**158f**)
9	**157g**	H	1	OTf	100	24	6 (**158g**)
10	**157h**	OMe	1	I	100	18	40 (**158c**)

[a] Isolated yield of **158**, typically an average of two runs. [b] Complex mixture.
[c] R. J. Carson's result. [d] Contaminated with 18% *gem*-dimethyl product **205d**. [e] J. M. Goll's result.

The origin of the supplementary methyl group was verified by submitting terminal alkyne **157c** to methylalumination with d_9-Me_3Al, followed by Pd-catalysed 1,2-ligand migration conditions. Hexadeuteriated indane d_6-**158c** was isolated in 52% yield, thereby confirming that two of the three new C-C bonds originate from the organoalane species (Equation 3.4).

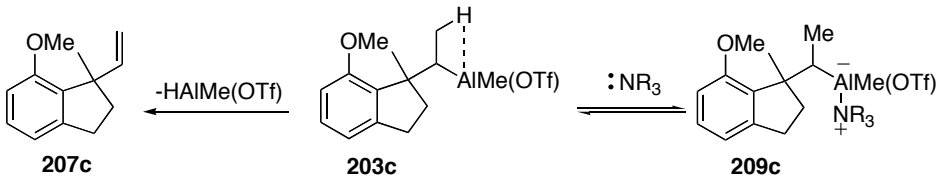
Equation 3.4: Reaction of alkyne 157e with $(D_3C)_3Al$



3.3.2.2 Configurational Stability of Organometallic Intermediates

Side-product **207c** is plausibly formed through dehydrometalation of neopentylic dialkylaluminum triflate **203c** (Scheme 3.20). As shown by Eisch, in absence of additive, a hydride can align favourably with the main group metal's empty p-orbital, leading to dehydroalumination.[173] *A contrario*, Lewis base complexation retards this competing pathway. The superior performance of DABCO over Et_3N can be explained by the better availability of the nitrogen lone pair in the 1,4-diaza[2.2.2]bicyclic system.[178]

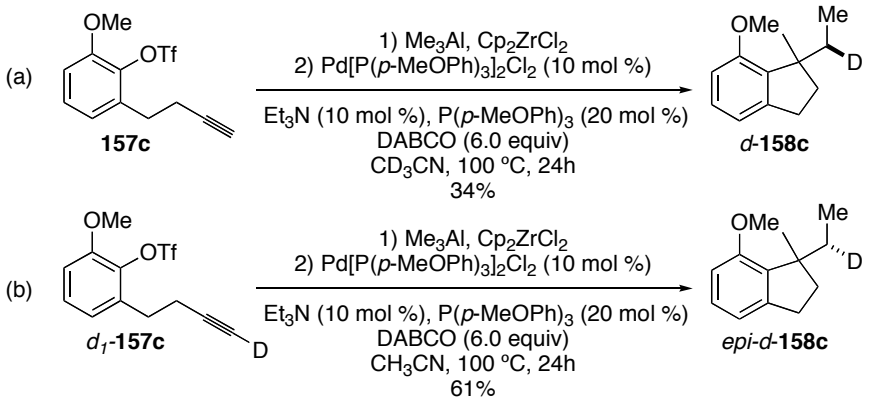
Scheme 3.20: Support for a dialkylaluminum triflate intermediate



Reaction with deuterium-labeled solvent provided further credence for dialkylaluminum triflate **203c**. It was found that rigorously degassed d_3-MeCN and glove-box techniques were *sine qua non* requirements to produce deuteriated indane *d*-**158c**. Only under those conditions was deuteriodemetalation at the neopentylic position observed. Furthermore, one sole product stereoisomer was isolated, as attested by ^1H, ^2H and ^{13}C NMR spectroscopy (Equation 3.5a). To gather information on the configurational stability of the C-Al bond, the labeled alkyne *d*-**157c** was also prepared.[179] Delightfully, upon submitting *d*-**157c** to the sequential carbometalation reaction conditions, the epimeric indane product, *epi-d*-**158c**, was obtained as a sole diastereomer (Equation 3.5b). These observations were confirmed by Anna A. Remorova for two more substrates, **157b** and **159g**. Hence, the generality of this stereospecific C-C bond-forming process was demonstrated.[161]

In this study, yields for reactions run in deuterium-labeled solvent were consistently lower, principally affected by greater 1,2,3-trialkylarene **208** formation. Further investigations are reported in section 3.4.2.3.

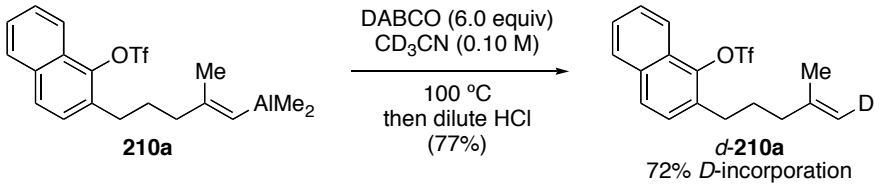
Equation 3.5: Stereospecificity of the sequential carbometalations



Not only providing strong support for dialkylaluminum triflate **203** intermediacy in the production of methyl-transfer products **158**, these results also demonstrated the configurational stability of *gem*-organobismetallic σ-alkylpalladium(II)/ trialkylaluminum intermediates.

Alkenylalane stability under the reaction conditions was also examined. When **210a** was heated in presence of DABCO (6.0 equiv) for 24 h at 100 ºC in CD_3CN, *d*-**210a** was recovered in 77% yield, and 72% *D*-incorporation after acid treatment (Equation 3.6). While the deuterium incorporation value appears sizeable, the relative rate of protiodealumination is deduced to be much smaller than that of vinylalane carbopalladation of the σ-arylpalladium(II) complex, given the large excess of deuterium source. From this, it is inferred that the resulting sp^3-hybridised neopentyl(dimethyl)alane participates in methyl transfer prior to protiodealumination. Otherwise, the reproducible isolation of methyl transfer products from vinylalanes such as **210a** in the presence of Pd(0) would be difficult to explain.

Equation 3.6: Stability of the vinylalane under the reaction conditions



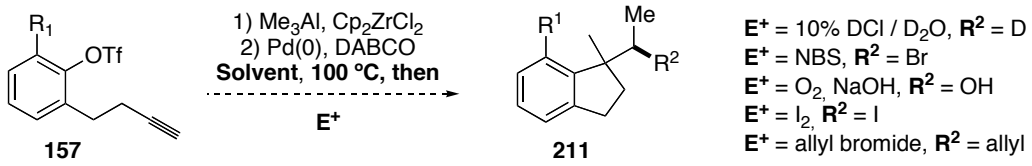
3.3.2.3 Methyl-Transfer Reaction Scope Expansion

Having shown tolerance of alkyl, ether, thioether and silane substituents at the aryl 6-position, further scope expansion would involve: functionalising the neopentylic dialkylalane **203** in electrophilic dealumination processes; broadening the span of transferable groups from aluminum; and effecting methyl transfer by intramolecular reaction of (*E*)-2-monosubstituted-1-alkenyldimethylalanes, thus forming a tertiary benzylic centre.

3.3.2.3.1 Dialkylaluminum Triflate Functionalisation Attempts

First, reaction of the neopentylic C-Al bond with electrophiles was attempted, in order to generate a fourth bond stereospecifically in a single synthetic operation. Switching from acetonitrile to a non Brønsted-acidic solvent should maintain the integrity of the neopentylic C-Al bond until an electrophile is added (Scheme 3.21).

Scheme 3.21: Electrophile incorporation



In partnership with Anna A. Remorova, a series of rigorously dried and degassed solvents (THF, 1,4-dioxane, DME, PhH and PhMe) was examined. For instance, when employing benzene as solvent and quenching the reaction with 10% DCl/D_2O, the cyclised methyl-transfer product **159g** was obtained albeit with only partial *D*-incorporation (39%-*D*) and in 11% yield.[177] Of note, aromatic solvents favoured cross-coupling product **208** in relation to methyl-transfer **159** (Table 3.1 and Table 3.3). This constituted a severe limitation, for when any other solvent than benzene was utilised, no incorporation took place at the neopentylic position following 10% DCl/D_2O treatment.

As shown earlier, premature protiodealumination took place in MeCN. It was hypothesised that another nitrile solvent, devoid of reasonable Brønsted acidity, would preserve the integrity of the C-Al bond. However, utilising pivalonitrile as solvent did not mediate cyclisation of **157**.

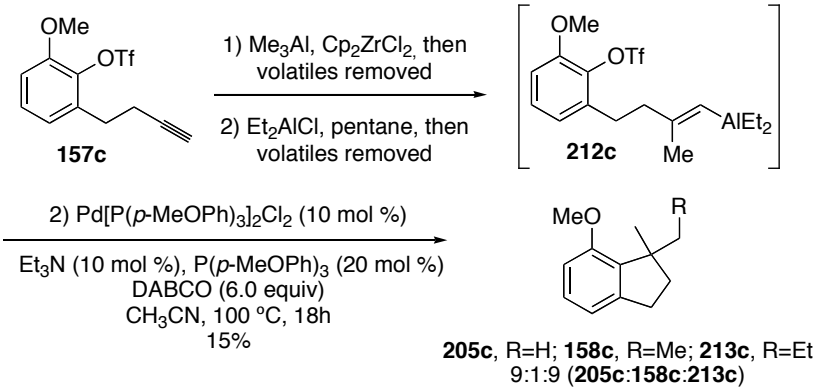
Likewise, although the use of benzonitrile or 2,2,5,5-tetramethyltetrahydrofuran (TMTHF), a THF surrogate with no transferable hydride,[18] led to the cyclised product in low conversions, no electrophile incorporation took place. In last resort, it was hoped that the addition of ethyl cyanoacetate as a mild electrophile during the Pd-catalysed reaction would lead to *in situ* C-Al bond carboxylation. Dismayingly, adding 5 to 10 equiv Mander's reagent to the reaction mixture (in pivalonitrile, TMTHF or PhMe) prevented cyclisation, affording only quenched vinylalane **206** after 24 h at 100 ºC.

This disappointing outcome may be explained by the low nucleophilicity of dialkylaluminum triflates, combined with the sterically congested neopentylic environment. In the future, transmetalation of either the dialkylaluminum triflate or vinylalane to organozinc or -cuprate species, more effective for C-C bond formation, may solve this issue.

3.3.2.3.2 Preliminary Results: Ethyl-Transfer Reaction

Tackling the second challenge, that is, expansion of the scope of transferable groups from Al, competing hydroalumination and alkylalumination must be avoided. Thus, alternate access to 2,2-disubstituted-1-alkenyldialkylalane species, wherein the alkyl is anything but a methyl group, was explored. Methylalumination of **157c** led to the intermediate 2,2-disubstituted-1-alkenyldimethylalane **200c**, which, upon treatment with 20 equiv of Et_2AlCl in pentane for 1 h followed by *in vacuo* removal of excess volatiles, led to the putative 2,2-disubstituted-1-alkenyldiethylalane **212c**. Submitting the latter to the optimised carbopalladation conditions, an inseparable mixture of three products, in which *gem*-dimethyl **205c** and ethyl-transfer **213c** were major and equimolar (Equation 3.7), was obtained in 15% combined yield. The conditions required to effect aluminum ligand disproportionation limited the method to a proof of concept. Chlorodemethylation of the aryl ether and further side-reactions may be promoted by the large excess of Lewis acid, although no phenol protons were evidenced by ^{1}H NMR examination of the crude mixture.

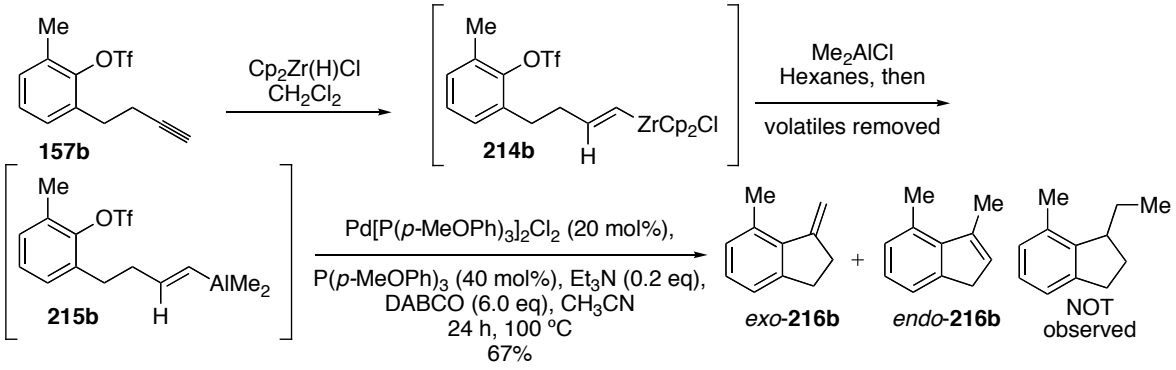
Equation 3.7: Pd-Catalysed ethyl transfer reaction



3.3.2.3.3 Pd-Catalysed Reaction of an (*E*)-1-Alkenyldimethylalane

To probe the necessity of forming a quaternary benzylic carbon in the 1,2-methyl migration, (*E*)-vinylalane **215b** was obtained via hydrozirconation of alkyne **157b** followed by transmetalation with Me_2AlCl, according to the protocol by Carr and Schwartz.[180] Submitting 2-monosubstituted-1-alkenyldimethylalane **215b** to the optimised reaction conditions afforded none of the expected 1,2-ligand migration adduct. Rather, an isomer mixture of 7-methyl-1-methyleneindane (*exo*-**216b**) and 1,7-dimethyl-1-indene (*endo*-**216b**) was isolated in 67% yield (Equation 3.8).

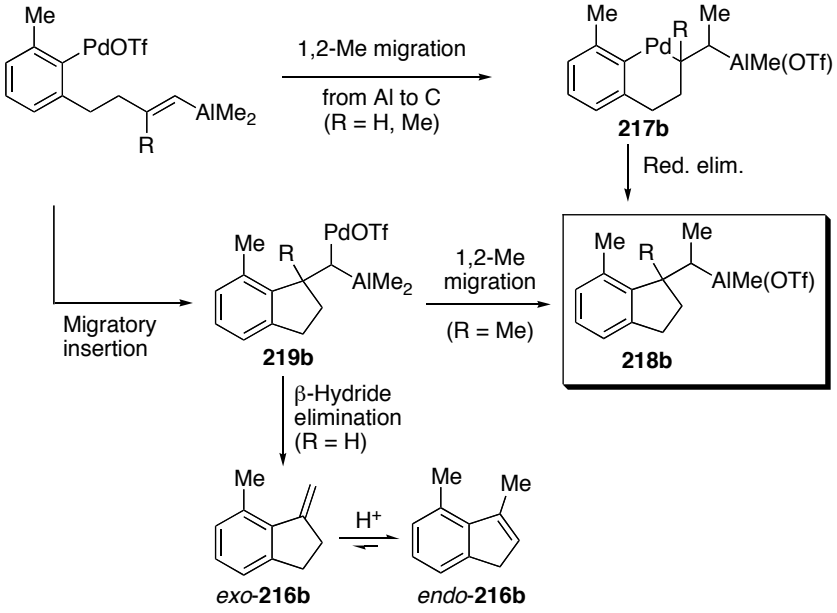
Equation 3.8: Pd-Catalysed reaction of 2-monosubstituted (*E*)-1-alkenyldimethylalane



3.3.2.3.4 Mechanistic Significance

The latter two equations convey key mechanistic information. As presented in Scheme 3.22, two pathways are available between the σ-arylpalladium(II) triflate and the resulting dialkylaluminum triflate **218**.

Scheme 3.22: Plausible *gem* or *vic*-organodimetallic intermediates



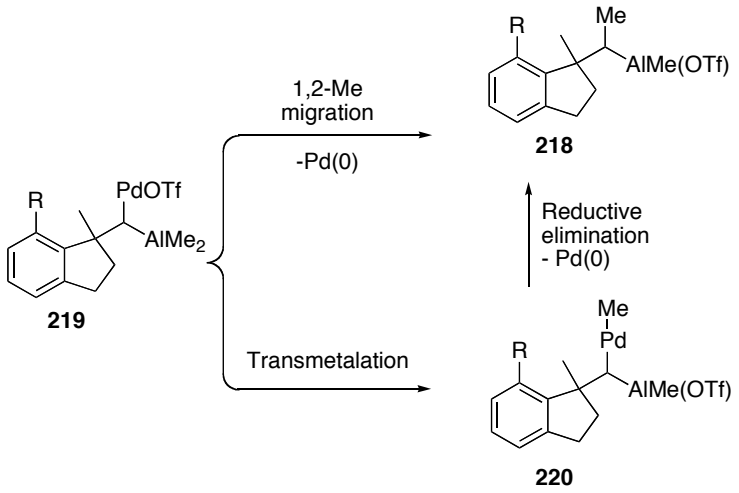
First, as per Terashima,[158] a Pd(II) electrophile can initiate 1,2-ligand migration from aluminum to carbon, leading to a palladacyclohexene intermediate, vicinal dimetallic **217**. From there, reductive elimination of Pd(0) allows arylation. Conversely, one can envisage migratory insertion of the vinylmetallic moiety into the σ-arylpalladium(II) complex, yielding geminal dimetallic **219**. From the latter intermediate, 1,2-ligand migration can take place via two possible pathways, to be discussed below.

The reaction of (*E*)-alkenyldimethylalane shown in Equation 3.8 strongly suggests that the migratory insertion pathway is followed. Indeed, the mixture of methyleneindane and methylindene products **216** likely arise through β-hydride elimination of a σ-alkylpalladium(II) triflate, obtained after carbopalladation of the alkenyldimethylalane. Should a vicinal dimetallic intermediate have been at play, the isolated products would rather have been akin to

218 (R=H), and no reasonable pathway could then have lead to indenes **216**. Moreover, the less successful formation of tetrahydronaphthalene systems in Table 3.5 presented above may be caused by the relatively more demanding 6-*exo*-trig migratory insertion, compared to 5-*exo*-trig cyclisation.[181] Intermolecular cross-coupling then becomes a more kinetically favoured pathway. Moreover, that electron-rich tris(*p*-methoxyphenyl)phosphine improves methyl transfer yields also supports a migratory insertion key step.[174] Low isolated yields of methyl-transfer **158** in presence of DMAP, CsF or in absence of additive (Table 3.4) may be due to increased oligomerisation, that is, enhanced intramolecular alkenyl cross-coupling with the aryl triflate. The superior performance of sp^3-hybridised trialkylamines, favouring the intramolecular carbopalladation process, has yet to be rationalised.

For geminal neopentylic organodimetallic species **219**, there exist two plausible C-C bond-forming paths accessible for subsequent 1,2-ligand migration from aluminum to carbon. Methyl transmetalation, affording geminal methylpalladium(II) neopentyl(methyl)aluminum triflate **220** can be envisaged. From there, reductive elimination would construct the carbon-carbon bond and regenerate the palladium(0) catalyst. Alternatively, intramolecular nucleophilic displacement of a palladium(II) triflate[182] is also possible, producing a Pd(0) leaving group and common dialkylaluminum triflate species **218** (Scheme 3.23).

Scheme 3.23: 1,2-Methyl migration manifold

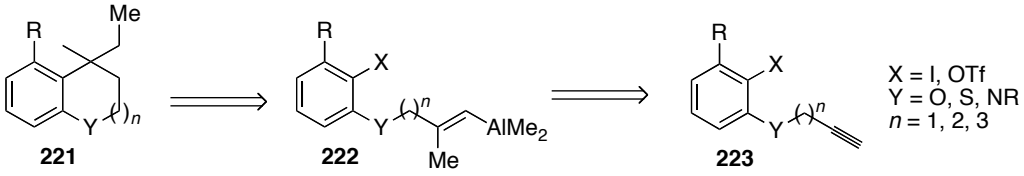


Of importance, the observation of equimolar amounts of *gem*-dimethyl and methyl-*n*-propyl-substituted products **205c** and **213c** in the reaction of alkenyldiethylalane **212c** with Pd(0) suggests intermediate **220** is intervening. Product **205c** likely arises from reductive elimination of a hydridopalladium(II)neopentane intermediate. With the presented data, the possibility of methyl migration taking place via an intramolecular nucleophilic displacement (S_Ni) cannot be ruled out. However, stereochemical analysis of a deuterium-labeled 1,2,3,4-tetrahydrophenanthrene provided conclusive evidence against the latter pathway, to be discussed in section 3.4.2.3.

3.3.2.4 Heterocyclic Methyl-Transfer Products

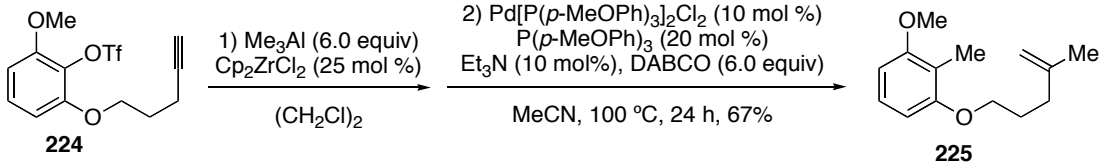
To expand the synthetic scope of the previously delineated intramolecular reaction of 2,2-disubstituted-1-alkenyldimethylalanes with aryl triflates and iodides, heterocycle formation was envisaged. Benzofurans, chromans, 2,3,4,5-tetrahydro-1-benzoxepines (Y = O, *n* = 0-2), 2,3-dihydrothiobenzofurans (X = S, *n* = 0) as well as indolines and 1,2,3,4-tetrahydroquinolines (Y = N, *n* = 0, 1) incorporating a benzylic quaternary stereocentre should be accessible using the recently developed reaction from parent alkynes **223** (Scheme 3.24).

Scheme 3.24: Heterocycle formation via Pd-catalysed intramolecular arylation of 2,2-disubstituted-1-alkenylalanes



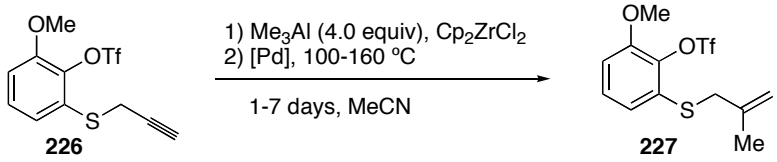
Although Negishi methylalumination of the shorter-tethered aryl (3-butynyl) and (2-propynyl) ethers was not successful, methylalumination of (4-pentynyl) aryl ether **224** proceeded smoothly in presence of excess Me_3Al (6.0 equiv). Subsequent treatment of the intermediate alkenylalane with Pd exclusively produced **225** in 67% yield, with no evidence of the desired benzoxepine.

Scheme 3.25: Attempted cyclisation of 4-pentynyl-tethered aryl ether 224



Attempts at the methylalumination of alkynes tethered to various nitrogen-based functional groups (sulfonamide, *N*-benzyl or free amine) led to either S-N bond cleavage or decomposition. With regards to benzothioethers, even though Negishi carboalumination took place as reported[183] with aryl propargyl thioether **226**, triflate **227** was recovered after heating with Pd for prolonged times at elevated temperatures (Scheme 3.26). Thus, formation of heterocycles containing an ethyl-methyl-substituted benzylic all-carbon quaternary centre using the recently developed methodology was aborted.

Scheme 3.26: Attempted cyclisation of aryl thioether-tethered vinylalane 226



3.3.3 Conclusions

In this section, a novel approach to geminal organodimetallic Pd/Al species, based on migratory insertion of σ-arylpalladium(II) complexes into (*E*)-2,2-disubstituted-1-alkenylalanes, was disclosed. Optimisation of the tandem catalytic intramolecular arylation/1,2-methyl migration reaction of neopentylic species was presented. Electron-rich triarylphosphine ligands, Lewis-basic solvent and excess trialkylamine were necessitated for optimal yields of methyl-transfer products. This process was better suited to the formation of 7-substituted-1-ethyl-1-methylindanes than the parent tetrahydronaphthalenes. Aryl methyl ether, thioether and trimethylsilane functionalities were tolerated at the aryl 6-position, unlike an aryl

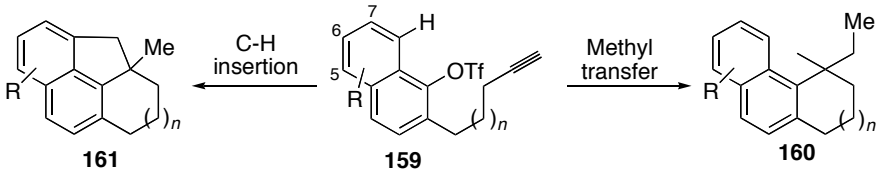
chloride. Competing intramolecular cross-coupling processes led to yield erosion in the formation of tetralin products.

Deuterium-labeling experiments revealed that stereospecific C-C bond formation takes place through sequential functionalisation of two carbon-metal bonds. Intermediacy of neopentylic (pseudo)halopalladio(II)/dialkylaluminoalkane species was inferred, also based on competing β-hydride elimination in absence of Lewis base as well as 1,4-arylation of the aryl 6-position. Moreover, experimental data suggest 1,2-methyl migration occurs through transmetalation of a neopentyl(dimethyl)alane species with neopentylpalladium(II) triflate, followed by reductive elimination. Finally, preliminary scope expansion studies exemplified the challenge of transferring alkyl groups that contain β-hydrogen atoms.

3.4 Study of the Pd-Catalysed 1,2-Diarylation of σ-Arylpalladium(II) Species

In the previous section were delineated the applicability and limitations of the intramolecular reaction of 2,2-disubstituted-1-alkenyldimethylalanes with aryl triflates and iodide **157**. Application of these findings to naphthalenyl triflate substrates **159** could potentially lead to mixtures of products, namely methyl-migrated **160** as well as 1,2-diarylated **161** (Scheme 3.27). The determination of reaction conditions to effect selective transformation of terminal alkynes **159** into either polycyclic product constitutes the final achievement of this thesis. Studying the effects of electronic substitution of the naphthalene ring should help understand the mechanistic pathway followed during the formal 1,5-C_{aryl}-H insertion process.

Scheme 3.27: Selective formation of 1,2,3,4-tetrahydrophenanthrenes or 3a-methyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*def*]phenanthrenes from alkynyl-tethered 1-naphthyl triflates

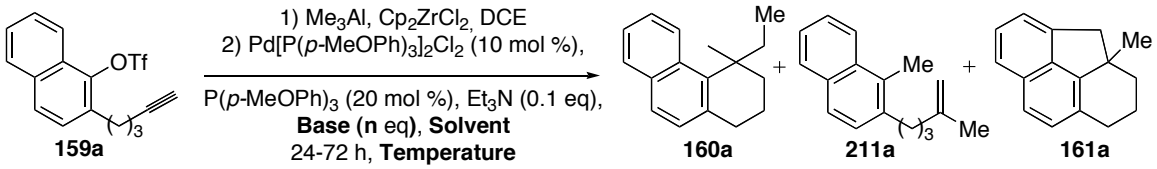


159a (*n*=1, R=H)
8-d_1-**159a** (*n*=1, R=8-D)
159b (*n*=1, R=5-MeO)
159c (*n*=1, R=5-F)
159d (*n*=1, R=7-MeO)
159e (*n*=1, R=7-Me)
159f (*n*=1, R=6-MeO)
159g (*n*=0, R=H)
159h (*n*=0, R=5-MeO)

3.4.1 Scope of the 1,2-Diarylation and Methyl-transfer Processes

Rather unexpectedly, using the previously optimised conditions (6.0 equiv of DABCO, MeCN, 100 ºC, 24 h) with unsubstituted naphthalene substrate **159a**, selective formation of tetracycle **161a** over methyl-transfer **160a** (95:5) was observed in 82% isolated yield (Table 3.6, entry 1). This result contrasted with the study presented above (section 3.3.2), wherein the same conditions mediated methyl transfer. A significant solvent effect was observed: PhMe (entry 2) gave seven times more 1,2-methyl transfer than polar, coordinating MeCN at 100 ºC. However, increasing reaction temperature in MeCN did not affect product ratios (120 ºC, entry 3). When the amount of DABCO was decreased to 1.5 equiv, formation of the cross-coupling side-product **211a** increased at the expense of the desired tetracyclic product **161a** (entry 4). Nearly equimolar mixtures of methyl-transfer **160a** and methyl cross-coupling **211a** were obtained using less than 1.5 equiv DABCO (entries 5-7), and isolated yields were unaffected. The nature of the trialkylamine also influenced the outcome, since using 1.5 to 6.0 equiv of Et_3N in place of DABCO produced methyl-transfer tricycle **160a** as the sole cyclised product (entries 8-9). Of significance, by altering the solvent and catalyst, either 1,2-diarylation or 1,2-ligand migration selectively took place.

Table 3.6: Effect of reaction variables upon product distribution



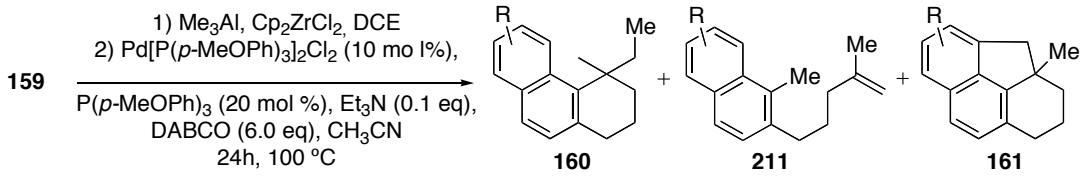
159a **160a** **211a** **161a**

Entry	Solvent	Temperature (ºC)	*n*	Base	Ratio (**160**:**211**:**161**)[a,b]	Yield (%)[b,c]
1	MeCN	100	6.0	DABCO	5:<1:95	82
2	PhMe	100	6.0	DABCO	36:1:63	35
3	MeCN	120	6.0	DABCO	6:<1:94	76
4	MeCN	120	1.5	DABCO	55:30:15	27
5	MeCN	120	1.0	DABCO	51:49:<1	29
6	MeCN	120	0.5	DABCO	50:50:<1	29
7	MeCN	120	0	DABCO	45:55:<1	27
8	MeCN	100	6.0	Et_3N	37:63:<1	13
9	MeCN	100	1.5	Et_3N	38:62:<1	16

[a] Determined by ^1H NMR analysis of the crude mixture. [b] Average of two runs for most entries.
[c] Combined yield of inseparable compounds **160** and **161**.

The range of applicability of tetracycle formation was then tested by submitting the substituted naphthalenes **159** to reaction in MeCN at 100 ºC with excess DABCO. The results summarised in Table 3.7 also comprise Anna A. Remorova's contribution (entries 8-10). Triflate **159b**, substituted with an electron-donating group at the 5-position, provided diarylated product **161b** in excellent yield and selectivity (entry 2). At higher reaction temperature (120 ºC), the reaction was less selective, producing more of the 1-methylnaphthalene side-product (entry 3). Replacing the 5-naphthyl methyl ether by a fluoride had little influence on product ratios although extensive decomposition became evident during purification, accounting for the low yield of **161c** (entry 4). On the contrary, substituting the naphthalene 6- or 7-position with an electron-donating ether detrimentally affected selectivity in comparison to the 5-position (entries 8 and 5), as triflates **159f** and **159d** yielded a **160**:**161** ratio of 17:83 and 32:68, respectively. 7-Methyl-substituted triflate **159e** afforded **160e** as the exclusive cyclised product (entry 6). Proportionally to their steric encumbrance, substituents at the 7-position increased formation of cross-coupled **211** (entries 1, 5 and 6). Also, highest ratio of tetracycle:tricycle production was observed with substrates containing the highest-field C^8 values (entries 2, 4, 1 and 8).

Table 3.7: Scope of the Pd-catalysed 1,2-diarylation reaction



	R	*n*	Ratio[a] **160**:**161**	Ratio[a] (**160**+**161**):**211**	Yield[b] (%)	δ C[8] (ppm)[c]	δ H[8] (ppm)[c]
1	H (**159a**)	1	5:95	>99:1	82	121.2	8.18
2	5-OMe (**159b**)	1	2:98	>99:1	91	113.3	7.66
3[d]	5-OMe (**159b**)	1	11:89	70:30	54	113.3	7.66
4	5-F (**159c**)	1	4:96	95:5	25	117.2	7.86
5	7-OMe (**159d**)	1	32:68	82:18	70	120.2	7.39
6	7-Me (**159e**)	1	>99:1	64:36	42	99.6	7.86
7	8-D (8-*d*-**159a**)	1	78:22[e]	72:28	38	120.9	8.18
8	6-OMe (**159f**)	1	17:83	>99:1	74	122.7	7.98
9	H (**159g**)	0	>99:1	>99:1	71	121.3	8.10
10	5-OMe (**159h**)	0	>99:1	>99:1	90	113.4	7.65

[a] Determined by analysis of the ^{1}H NMR of the crude mixture. [b] Isolated yield of **160** and **161**.
[c] Determined by 2D-NMR (COSY, HMQC) analysis. [d] Step 2 was run at 120 °C.
[e] Tricycle 8-*d*-**160a** contained 9% of dehydroaluminated product.

Replacement of the 8-hydrogen by a deuterium on the substrate demonstrated an isotope effect. Carbocyclisation of 8-*d*-**159a** led mainly to tricycle 8-*d*-**160a** and cross-coupled product 8-*d*-**211a** (entry 7).[184] Whereas the 8-deuterium was still borne by product 8-*d*-**160a**, no deuterium label was found on tetracycle **161a**. Finally, tether length also influenced product distribution. Although ethyl-methyl substituted products **160g**-**h** were obtained in excellent yields, no diarylation product **161** was detected from butynyl-tethered substrates **159g**-**h** (entries 9-10).

3.4.2 Mechanistic Discussion

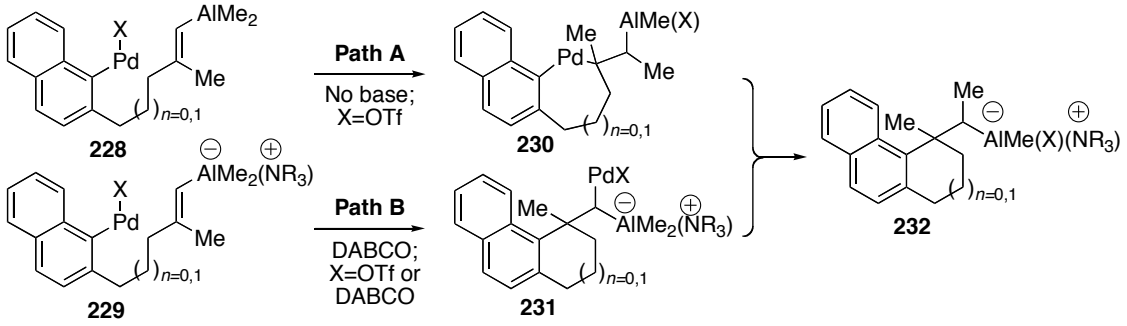
In this sub-section, rationalisation of experimental data leads to the presentation of reaction pathways accounting for the formation of tricycle **160** in competition with tetracycle **161**.

3.4.2.1 Tandem Arylation/1,2-Methyl Migration Path

As presented in Scheme 3.28, 1,2-migration of the methyl group from aluminum to carbon triggered by σ-naphthylpalladium(II) triflate species would produce *vic*-dimetallic

palladacycloheptene **230** that would reductively eliminate to **232**.[158] Alternatively, migratory insertion of the alkenylalane into the σ-naphthylpalladium(II) complex would generate *gem*-dimetallic species **231**, which would then undergo 1,2-methyl migration from aluminum to carbon with concomitant regeneration of Pd(0), leading to **232**.

Scheme 3.28: Methyl migration pathways



The observation by Remorova of exclusively 1,2-methyl migration cyclopentanaphthalene products **161g-h** in high yields suggests that **231** ($n = 0$) is a key intermediate. Faster 5-*exo*-trig than 6-*exo*-trig carbopalladation[181] (path B), as well as the ease of formation of 6- versus 7-membered ring palladacycles[185] from **229** (path A) could both adequately explain the courses followed by σ-naphthylpalladium(II) intermediates in presence of complexing DABCO. Indeed, Lewis acid-base interaction between the aluminum centre and DABCO is suggested to enhance alkene migratory insertion aptitudes. In the result summarised in entry 3 of Table 3.6, the olefin would insert more readily in the C-Pd(II) bond of **229a** to furnish dimetallic intermediate **231a** (path B), selectively resulting in 1,2-diarylation product **161a**. Contrariwise, in the absence of DABCO (entry 7), formation of 7-membered ring palladacycle **230a** would occur faster than migratory insertion of 1,2,2-trisubstituted electron-deficient alkenylalane **228a**, leading to **160a** as the sole cyclised product (path A). Conceivably, carbocyclisation becomes slow enough without DABCO for the relative rate of intermolecular transmetalation to compete with that of palladacycloheptene formation, leading to equimolar amounts of **160a** and by-product **211a**.

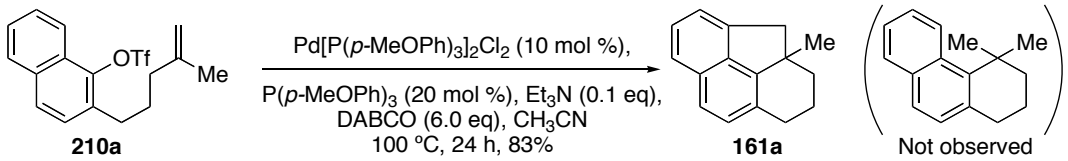
In light of the above proposals, *vic*-dimetallic intermediate **230** cannot reasonably explain formation of tetracycle **161**. Therefore, alternative mechanistic avenues leading to **161** via

gem-dimetallic **231** were investigated. Namely, Pd-carbene, electrophilic aromatic substitution (S_EAr) and carbopalladation pathways are proposed and discussed in the following section.

3.4.2.2 1,2-Diarylation Mechanistic Pathways

To assess the intermediacy of Pd-carbene species leading to tetracycle **161**, 2,2-disubstituted alkene **210a** was treated with the optimised palladium catalyst and 6.0 equiv of DABCO. If desulfonylalumination gave rise to a hypothetical Pd-carbene intermediate, either starting material or *gem*-dimethyl side-product should be observed in the absence of alane. Quite surprisingly, tetracycle **161a** was isolated in 83% yield – identical to Table 3.7, entry 1. This constituted evidence against alane involvement in any arylation process. Moreover, that unlabeled tetracycle **161a** is isolated after reaction of *d*-**159a** (Table 3.7, entry 7) signifies the second arylation does not proceed via carbene C_{aryl}-H insertion. Further data against Pd-carbene involvement were gathered from reactions conducted in CD_3CN, to be discussed below.

Equation 3.9: Reaction of (2,2-disubstituted-1-pentenyl)-tethered triflate 210a



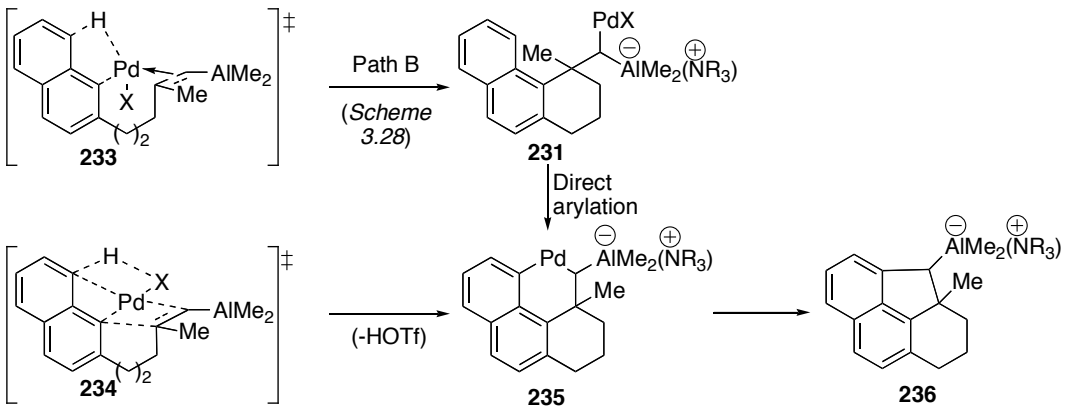
Other pathways were explored in order to explain the second arylation leading to closure of the fourth ring. Electrophilic aromatic substitution was eliminated based on the strongly differing ratios of 1,2-diarylation observed for 5- and 7-MeO substrates **159b** and **159d**, as well as the similar ratios obtained for electron-rich 5-MeO (**159b**), electron-poor 5-F (**159c**) and unsubstituted **159a**. In fact, Lewis-basic DABCO should rather decrease reactivity of the electrophile, so that S_EAr would be disfavoured and lead to excess methyl transfer compared to 1,2-diarylation. On the other hand, arene carbopalladation[44] was also discarded, for the KIE observed was poorly compatible with a C-C bond-forming rate-determining event.

The relationship between the electronic properties of the naphthyl ring in the ground state, conveyed by ^{1}H and ^{13}C NMR data of substrates **159a-h**, and product composition was scrutinised. No correspondence was found between δ (H^{8}) and the ratio of tetracycle **161** to methyl-transfer **160** and cross-coupling **211**. However, correlation with NMR chemical shifts of C^{8} was notable; specifically, a shielded C^{8} favoured **161** over **160** and **211** (Table 3.7, entries 1, 2, 4 and 8). The qualitative isotope effect observed with 8-*d*-**159a** may be indicative of a C-H•••Pd interaction facilitating migratory insertion in the transition state and deserved further scrutiny.

Aullón and Alvarez have proposed that synergistic enhancement of the Lewis acidity of square planar Pd(II) complexes is caused by a proton occupying an axial position, which then allows coordination of the olefin with the metal's second axially-oriented empty valence orbital.[186] Accordingly, migratory insertion to *gem*-dimetallic **231** could proceed from such a hexacoordinated species via **233** (Scheme 3.29). Direct arylation of the resulting neopentylic C-Pd(II) bond would subsequently provide **236** via palladacyclic intermediate **235**. Based on computational studies by Dedieu,[187] and experimental work by the groups of Echavarren[49] and Fagnou,[48] concerted migratory insertion/proton abstraction transition state **234** leading directly to **235** is also conceivable. Reductive elimination of palladium would then furnish **236**.

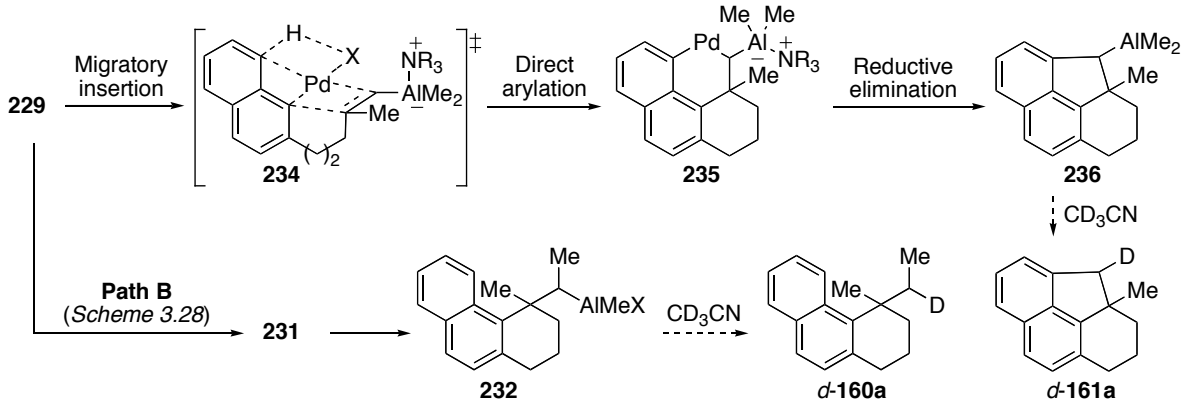
The electronic properties of C^{8} and their influence on reaction selectivity are better taken into account by transition state **234** than **233**. An electron-rich C^{8} favours direct arylation to **235**, as ratios of **161**:**160** decrease proportionally to C^{8} shielding: 5-MeO>5-F>5-H>6-MeO (δ 113.3, 117.2, 121.2 and 122.7, respectively).

Scheme 3.29: Proposed pathways and transition states for 1,2-diarylation (phosphine ligands omitted for clarity



Furthermore, sterically congested transition state **234**, in which palladium is partially bonded to C^8, also rationalises the trend of increasingly bulky 7-substituents (entries 1, 4-5 in Table 3.7) leading to decreased tetracycle formation. How the sequence 7-H>7-OMe>7-Me precisely parallels increasing steric demand of the 7-substituent is noteworthy. Experimental data also suggest the steric properties of the 7-substituent override the electronic properties of the C^8-H bond. Indeed, the most shielded C^8 in that series was 7-Me (99.6 ppm), followed by 7-MeO (120.2 ppm) and 7-H (121.2 ppm). This contrasts with the ratio of **161** to **160** (<1:99, 68:32, 95:5) observed experimentally with the corresponding substrates. The relative energy of transition state **234** in presence of a bulky 7-substituent increases so that rates of intermolecular cross-coupling or methyl transfer, via either *vic*- or *gem*-dimetallic intermediates **231** or **232**, become energetically competitive, and lead to side-products **160** and **211**. Likewise, at higher temperatures, as in the case of **159b** at 120 ºC, the reactants have enough energy to access competing pathways to tetracyclisation, lowering selectivity.

Scheme 3.30: Proposed reaction manifold (phosphine ligands omitted for clarity)



The concerted carbopalladation/proton abstraction transition state **234** implies significant charge separation. In the experimental work by Echavarren and Fagnou, dipolar aprotic solvents (DMF and DMA) are required for arylation. This further agrees with the observed vinylalane 1,2-diarylation solvent effect, whereby PhMe lead to seven times more methyl transfer than MeCN. Furthermore, rate-influencing proton abstraction is in line with the absence of tetrayclic product **161** without at least 1.5 equiv of DABCO.

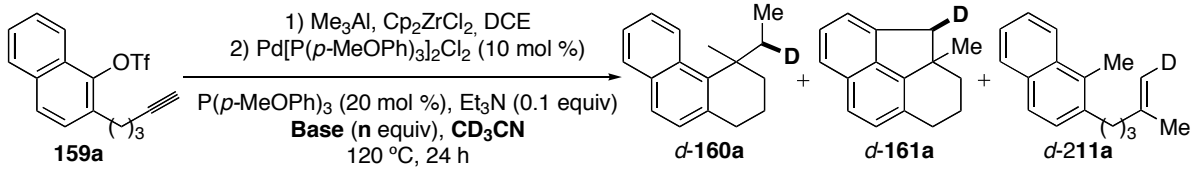
In addition, this transition state rationalises the kinetic isotope effect induced by substituting H^8 with deuterium. The stronger C-D bond is more reluctant than its unlabeled counterpart, as far as activation energy is concerned, to take part in concerted bond breakage-bond formation[50] leading to direct arylation via transition state **234**. Slower alkenylalane 1,2-diarylation in presence of a C^8-D substituent thus allows for higher proportions of products arising from the competing methyl-transfer and cross-coupling pathways to be produced. A computational study by Dedieu and Mota recently suggested that 1,3-arylpalladium(II) shifts preferentially proceed through Pd^{IV} transition states.[188] In the case presented herein, concerted oxidative addition of the naphthylpalladium(II) triflate to the C-H bond would lead to a palladacyclic intermediate. The latter would undergo reductive elimination of triflic acid, as well as C-C bond-forming cyclopentane ring closure, leading to neopentyl(dimethyl)alane **236**. The Pd^{IV} pathway also rationalises the solvent polarity and isotopic substitution effects noted previously.

For completion of the mechanistic picture, isotope labeling was summoned to assess both stereospecificity and confirm C-Al bond integrity during the process.

3.4.2.3 Deuterium-Labeling Studies

The intermediacy of neopentylic alanes **236** and **232** in the synthesis of **161** and **160**, respectively, was confirmed in a series of reactions with alkyne **159a** in CD_3CN at 120 ºC (Table 3.8). In the absence of DABCO, methyl-transfer *d*-**160a** was the sole cyclised product along with side-product *d*-**211a** (45:55) in 27% isolated yield (entry 1). The outcome was similar upon using excess Et_3N (64:36, 28% yield, entry 2). Not only did these results parallel those obtained in CH_3CN, previously presented, but reaction intermediate **232** was also confirmed. Subsequently, conclusive evidence for intermediate **236** arose from reaction in presence of 6.0 equiv DABCO, whereby a 29:13:58 ratio favouring methyl cross-coupling *d*-**211a** over tricycle *d*-**160a** and tetracycle *d*-**161a** was obtained (entry 3). This contrasted strongly with the composition obtained in CH_3CN under otherwise identical conditions (6:<1:94, 76% yield, Table 3.6, entry 3). Doubling the amounts of DABCO to 12 equiv in the Pd-catalysed reaction did not affect the amount of competing cross-coupling, although equimolar *d*-**160a** and *d*-**161a** were now generated (entry 4). In those reactions, the *D*-incorporation was similar for each product, in particular 82-83% in entry 4.

Table 3.8: Reaction with alkyne 159a in CD_3CN



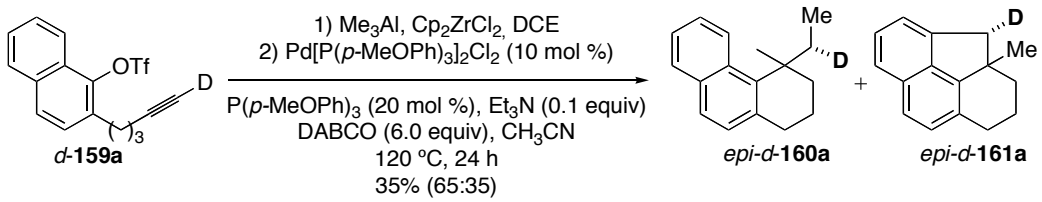
	Base	*n*	Ratio[a,b] (*d*-**160**:*d*-**161**:*d*-**211**)	Yield[b,c] (%)
1	N/A	0	45:<1:55	27
2	Et_3N	6.0	64:<1:36	28
3	DABCO	6.0	29:13:58	36
4	DABCO	12	24:22:54	36

[a] Determined by analysis of the ^1H NMR of the crude mixture.
[b] Average of two runs.
[c] Isolated yield of inseparable d_1-**160a** and d_1-**161a**.

Ultimately, label incorporation decisively ruled out a palladium-carbene intermediate in the 1,2-diarylation. The presence of deuterium at the benzylic position in *d*-**161a** implies that the C-Al bond was intact throughout the entire process, and hence, that no desulfonylalumination and Pd-carbene formation occurred. Therefore, the organodimetallic species bears a spectator C-Al bond that could be used in reactions with electrophiles.

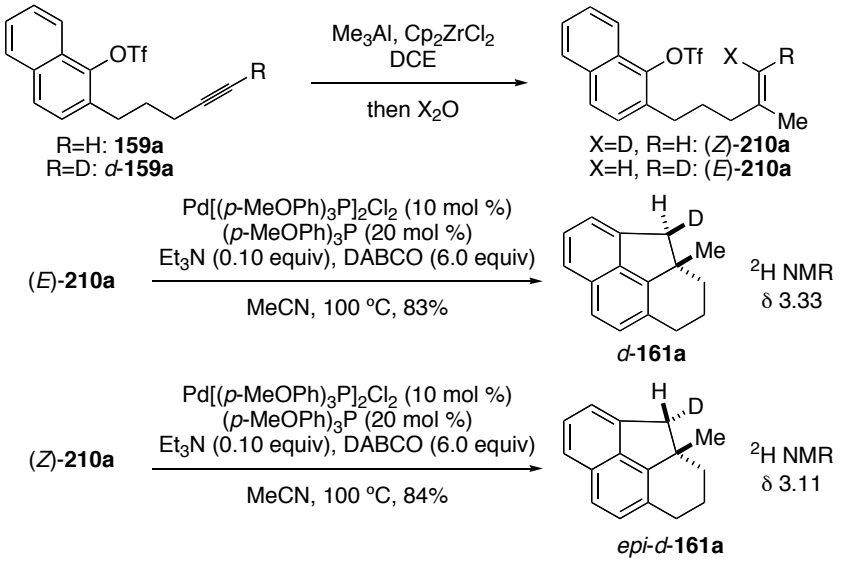
Moreover, that the 1,2-diarylation proceeds stereospecifically was established by reacting deuteriated acetylene *d*-**159a** in CH_3CN using the optimised conditions, from which a 65:35 ratio of tricycle *epi-d*-**160a** vs. *epi-d*-**161a** was isolated in 35% yield (Equation 3.10). Recalling the reaction of the parent **159** (Table 3.6, entry 3) that selectively produced tetracycle **161a** (76% yield), a secondary kinetic isotope effect might discriminate between reaction pathways. A proton-deuterium exchange intervening at C^8 would explain the similarity in the ratios of tricycle:tetracycle observed in Table 3.7, entry 7 (78:22) and Table 3.8, entry 3 (29:13). However, C^8 bore no label after reaction in CD_3CN, ruling out this process. So far, only speculation could be attempted to explain this.

Equation 3.10: Reaction of alkyne *d*-159a in CH_3CN



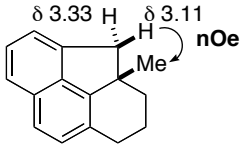
The fate of the C-Al bond in acetonitrile-induced protiodealumination was established. Authentic samples of diastereomeric tetracycles *d*-**161a** and *epi-d*-**161a** were synthesised independently from the corresponding (*Z*)- and (*E*)-deuteriopentene-tethered naphthyl triflates **210a** (Scheme 3.31). Their relative stereochemistry was deduced based on the stereospecific double carbopalladation used in their production. Thereby, chemical shifts of benzocyclopentane protons could unambiguously be assigned.

Scheme 3.31: Authentic samples of deuteriated tetraycles 161a



Then, bearing in mind the ^{2}H NMR chemical shifts of the epimeric deuterium-labeled compounds obtained by double Heck cyclisation, nOe studies were performed on the parent tetracycle **161a**. By observation of methyl signal enhancement upon irradiating the proton at 3.11 ppm, a *syn*-relationship with the benzylic methyl substituent was inferred (Figure 3.1). Absence of nOe between the other proton (δ 3.33) and the methyl group confirmed this assignment.

Figure 3.1: nOe Study of tetracycle 161a

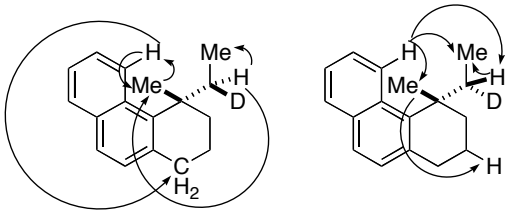


In consequence, the stereochemical outcome of the intramolecular reaction may only be achieved by successive steps involving retention of configuration. Indeed, olefin carbopalladation has been demonstrated by Overman *et al.* to occur in a concerted fashion, stereospecifically with respect to the alkene.[189] Then, second arylation of the sp^3-*gem*-dimetallic species can only take place with retention for each organometallic bond. Consequently, deuteriodealumination of the configurationally stable neopentyl(methyl)aluminum triflate **236**

affords a sole diastereomer of *d*-**161a**, with overall retention of the *syn* relationship between C-Al and C-Me bonds established in the methylalumination step (Scheme 3.30).

Extensive nOe studies on both deuterium-labeled diastereomeric tetrahydrophenanthrenes *d*-**160a** and *epi-d*-**160a** allowed to assess relative stereochemistry (Figure 3.2). For *d*-**160a**, strong signal enhancement of the benzylic CH_3 (singlet, 1.64) was observed upon irradiating the naphthyl H_8 (doublet, 8.18 ppm) as well as the exocyclic neopentyl proton (quartet, 1.91 ppm). Key to stereochemical assignment, the opposite diastereomer *epi-d*-**160a** displayed no nOe with the quaternary methyl group (singlet, 1.62 ppm) upon irradiation of the neopentylic proton (quartet, 2.29 ppm). It is noteworthy that the sample with the most deshielded neopentyl proton (*epi-d*-**160a**) also displayed stronger nOe with the naphthalene H^8, that is, the proton closer to the naphthalene experienced the stronger ring-induced diamagnetic deshielding.

Figure 3.2: nOe Study of tricycles *d*-160a and *epi-d*-160a

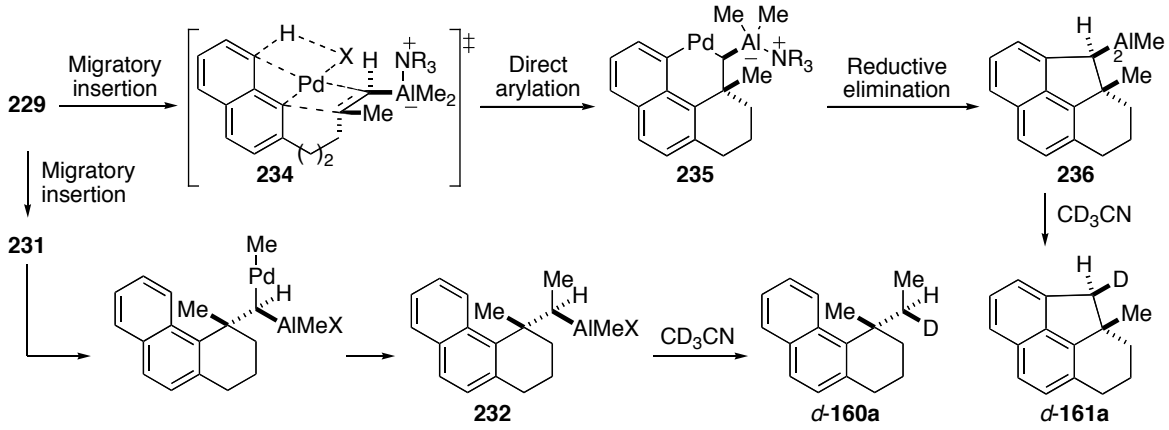


d-**160a**
δ_H 1.91; δ_D 2.31

epi-d-**160a**
δ_H 2.29; δ_D 1.95

Of utmost importance, the latter stereochemical assignment strongly supports the previous proposal (*c.f.* section 3.3.2.3.3) that the mechanistic pathway to methyl transfer first involves migratory insertion of the naphthylpalladium(II) σ-complex into the 2,2-disubstituted-1-alkenylalane. Subsequent transmetalation of a methyl group from Al to Pd, followed by reductive elimination, affords the carbon-carbon bond between the sp^3-hybridised centres. Whereas naphthylpalladium(II) insertion occurs in a *syn* fashion with respect to the olefin, transmetalation of an aluminum ligand takes place with retention of configuration. If the alternate path discussed in section 3.3.2.3.4, namely 1,2-metallate rearrangement, had intervened during methyl migration, inversion of configuration would have taken place. Moreover, the observation of a sole diastereomeric product demonstrates the configurational stability of the C-Al over the entire three C-C bond-forming process.

Scheme 3.32: Proposed mechanism for stereospecific formation of *d*-160 and *d*-161



In Scheme 3.32 is summarised the insight gleaned from studies of the electronic and steric effects of the naphthalene ring as well as from isotopic labeling. Worthy of note is the inferred involvement of neopentylic geminal pseudohalopalladio(II)/trialkylalane intermediates, **235** and **231** en route to **161** and **160**, respectively. The sequence of events regarding deuterium incorporation from the alane is suggested to take place after methyl transfer, in the case of formation of *d*-**160a**. Else, neither methyl migration nor observed stereospecificity would make sense. However, regarding diastereomerically pure labeled tetracycle *d*-**161a** formation, deuteriodealumination could take place at any stage of the course of action.

3.4.3 X-Ray Crystallographic Studies

X-Ray diffraction of a model Pd complex provided further evidence for electronic effects in transition structure **234** as well as the role played by the C^8-H(D) bond in the arylation step, by examining the nature of the ground state C^8-H•••Pd^{II} interaction. σ-Naphthylpalladium(II) complex **237** was synthesised from 1-iodonaphthalene and a stoichiometric quantity of $Pd(PPh_3)_4$ (Equation 3.11). By ^{1}H NMR spectroscopy, a 0.69 ppm downfield shift was observed for H^8 (8.14 → 8.83 ppm). X-Ray crystallography confirmed that, in the solid state, the Pd and H^8 atoms are in close contact, with a distance of 2.74Å and C^8-H^8•••Pd angle of 113°.

Equation 3.11: Preparation of bis(triphenylphosphino)-1-naphthylpalladium(II) iodide

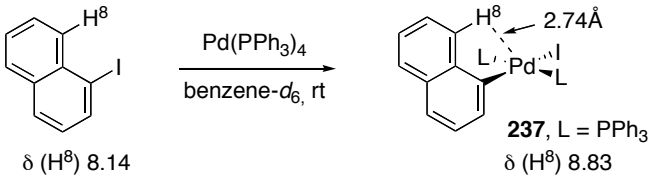
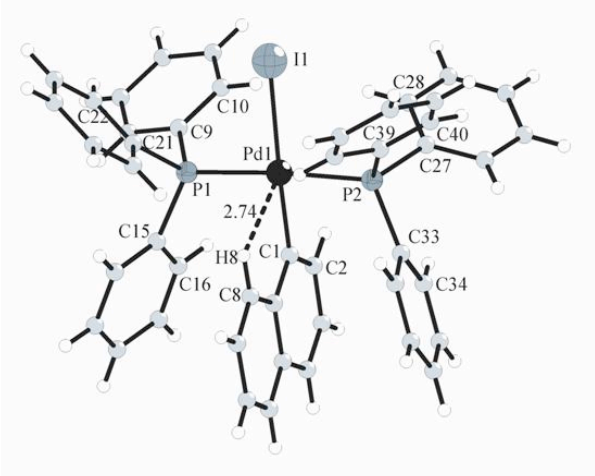


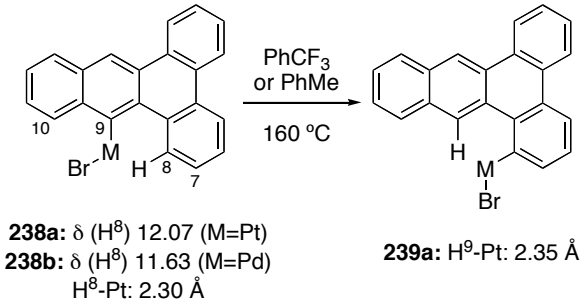
Figure 3.3: X-Ray crystallographic structure of *trans*-bis(triphenylphosphino)-1-naphthylpalladium(II) iodide



These experimental data correlate with the range of chemical shifts and bond lengths, albeit not with bond angle values, recently compiled by Ellman[190] and Crabtree[191] for preagostic C-H•••M interactions. Their studies aimed at bridging discrepancies between the well-established terminology and structural and spectroscopic data for "agostic C-H•••M interactions" and "X-H•••M hydrogen bonds", compared to the more loosely used "remote", "pregostic" and "preagostic" terminology utilised in intermediate cases. In general, ^{1}H NMR downfield shifts (0.3–1.6 ppm) are the signature of preagostic interactions, in contrast to the upfield-shifted agostic [C-H]•••M organometallic complexes. Of note, proton coupling to NMR-active metals is observed for agostic [C-H]•••M complexes, contrary to preagostic species. Finally, relatively long M•••H distances (2.3–2.9 Å) and large C-H•••M angles (130–170º) contrasted with the 1.8–2.2 Å and 90-130º values associated with preagostic and agostic interactions, respectively.

Recently, Singh and Sharp reported similar downfield shifts for analogous 9-bromodibenz[*a*,*c*]anthracenepalladium(II) and -platinum(II) complexes (Scheme 3.33). The chemical shift for the "bay" proton (H^8) of 9-bromodibenz[*a*,*c*]anthracene in the ground state was 9.40 ppm. After oxidative addition to M(0), values for δ (H^8) in the *trans*-complexes **238** were 11.63 (M=Pd) and 12.07 (M=Pt) ppm, deshielded by 2.2–2.7 ppm. Upon heating in a sealed tube at 160 ºC, the complexes underwent 1,4-metal shift, confirmed by X-ray crystallography of product **239a**. Importantly, in both **238a** and **239a** were H–Pt^{II} distances typical of a preagostic C-H•••Pt interaction. 1,4-Platinum shift rate dependence upon solvent polarity – three times faster in polar $PhCF_3$ than PhMe – was also noteworthy. Their study suggested contribution of preagostic C-H•••M^{II} (M=Pd, Pt) interactions during 1,4-metal shift processes.[192]

Scheme 3.33: Dibenz[*a*,*c*]anthracenemetal(II) complexes: pre-agostic interaction and 1,4-metal shift (PEt_3 ligands omitted for clarity)



238a: δ (H^8) 12.07 (M=Pt)
238b: δ (H^8) 11.63 (M=Pd)
H^8-Pt: 2.30 Å

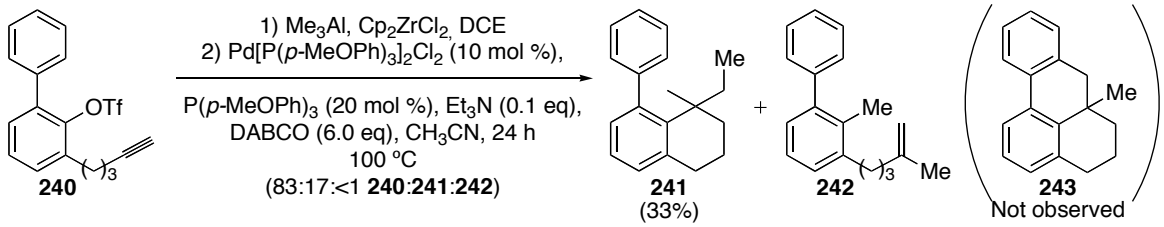
239a: H^9-Pt: 2.35 Å

Therefore, the preagostic C-H•••Pd^{II} interaction surmised in the ground state for 1-naphthylpalladium(II) iodide complex **237** correlates with the reactivity observed in solution for 2,2-disubstituted-1-alkenyldimethylalanes **159** in presence of naphthylpalladium(II) triflates. The reaction of **159**, via transition structure **234**, herein implies a 1,3-Pd shift during vinylalane migratory insertion leading to palladacyclohexene **235**, explaining the formation of 3a-methyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*def*]phenanthrene **161**.

Seeking further experimental correlation, 3-(4-pentynyl)-1,1'-biphen-2-yl triflate **240** was synthesised from 3-phenyl-2-hydroxybenzaldehyde[193] using the method delineated in Scheme 3.11. Upon reaction under optimised conditions, however, only methyl-migration and methyl

cross-coupling products were observed. Whereas tetralin derivative **241** was isolated in 33% yield, no formation of 1,2-diarylation analogue **243** was evident (Equation 3.12).

Equation 3.12: Attempted 1,2-diarylation to six-membered ring product 243



Furthermore, ^{1}H NMR studies of 2-phenylphenylpalladium(II) iodide **244**, obtained from 2-iodo-1,1'-biphenyl (1.5 equiv) and $Pd(PPh_3)_4$ in C_6D_6 at rt, showed signal overlap between starting material, triphenylphosphine and the palladium(II) complex. However, no significant deshielding was apparent, suggesting no C-H•••Pd^{II} interaction. This correlates with the reaction outcome from Equation 3.12, wherein 1,2-diarylation was expected to take place through 1,4-Pd^{II} shift, as demonstrated by Singh and Sharp. Whereas their system was geometrically restricted, further degrees of freedom may be accessible to biphenyl triflate **240**, especially under the reaction conditions, hence the absence of **243** despite using optimised 1,2-diarylation procedures.

3.4.4 Conclusions

In summary, experimental conditions that effect selective transformation of 2-alkynyl-tethered 1-naphthyl triflates **159** into methyl-transfer 1,2,3,4-tetrahydrophenanthrenes **160** or 1,2-diarylation 3a-methyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*def*]phenanthrenes **161** were developed. Solvent polarity, tether length, aluminum-centre complexation with DABCO and the intrinsic electronic and steric properties of the naphthalene ring were all found to affect reaction outcome.

Formation of 1,2,3,4-tetrahydrophenanthrenes **160** takes places favourably in non-polar toluene while polar acetonitrile favours tetracyclic product **161**. Whereas butynyl-tethered substrates

afforded none of the tetracyclised products, their pentynyl congeners could produce either 1,2-diarylated **161** or methyl-transfer monoarylated **160** depending on reaction conditions. In the absence of Lewis base, palladacyclic intermediates, whose formation competes with intermolecular methyl cross-coupling, lead to exclusively methyl-migration tricycle **160**. When employing DABCO, migratory insertion of the sterically demanding, electron-enriched 2,2-disubstituted-1-alkenyldimethylalane leads to neopentylic *gem*-dimetallic Pd/Al intermediates **235** and **232**, in the course of 1,2-diarylation and methyl-transfer product formation, respectively.

Steric and electronic considerations of the naphthalene ring lead to the proposal of concerted migratory insertion/proton transfer transition state **234**. Preagostic C^8-H•••Pd^{II} interactions, more pronounced for an electron-rich naphthalene C^8, were found to favour 1,2-diarylation. *A contrario*, the steric interactions induced by bulky naphthalene 7-substituents overrode electronic parameters and lead to selection between the methyl-transfer and direct arylation paths. Both reaction processes were determined to take place stereospecifically, and the configurational stability of C-M bonds (M=Al, Pd) was thus inferred. Dependence of product ratio upon solvent polarity and isotopic labeling at C^8 lead to the suggestion of a transition state involving a palladium(IV) species. Also, examination of the stereochemistry of the final products suggested that migratory insertion was followed by transmetalation of a methyl ligand between aluminum and palladium, followed by reductive elimination.

3.5 Summary and Outlook

3.5.1 General Conclusions

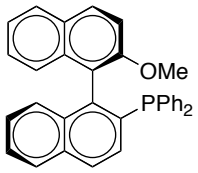
In this chapter, both geminal and vicinal iodopalladio(II) and sulfonyloxypalladio(II) dialkylaluminoalkane species were shown to be accessible when reacting 2,2-disubstituted-1-alkenylalanes in an intramolecular fashion with aryl and naphthyl triflates. Demonstration of

the configurational stability of neopentylic carbon-aluminum and carbon-palladium bonds during these processes bettered the understanding of those organometallic species. Taking advantage of their reactivity, synthetic applications were developed, namely stereospecific Pd-catalysed three-carbon-carbon bond-forming 1,2-alkyl migration as well as 1,2-diarylation of 1-naphthyl triflates. Ultimately, these methods exemplified the discovery of new reactivity patterns, triggered by σ-arylpalladium(II) (pseudo)halides, for readily accessible 2,2-disubstituted-1-alkenyldimethylalane species.

3.5.2 Future Direction

The intramolecular reactivity of 2,2-disubstituted-1-alkenyldimethylalanes with aryl triflates was established. To further expand the scope of the reaction, the enantioselective formation of the quaternary all-carbon benzylic stereocentre should be attempted. In Carson's work, no cyclisation was observed when using achiral bidentate phopshines. Since those ligands constitute the chiral framework par excellence in asymmetric Pd-catalysed transformations, alternate solutions should involve electron-rich triarylphosphines, successful in the current work. An example of such chiral, electron-rich monodentate ligand is Hayashi's MOP scaffold.[194]

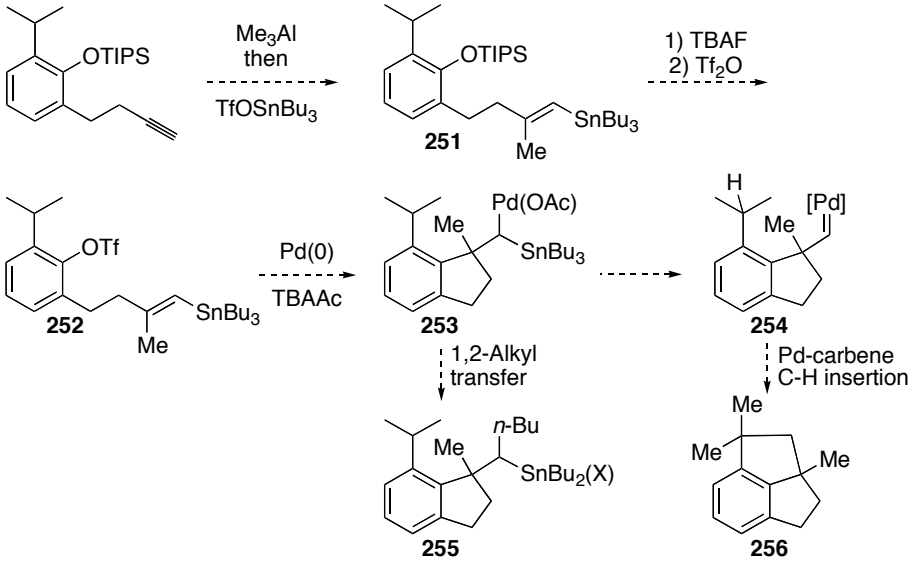
Figure 3.4: Chiral monodentate MOP ligand



Also, the knowledge acquired in the second chapter regarding geminal acetoxypalladio(II) tributylstannylalkane species could be fused with the migratory insertion approach delineated in the present chapter (Scheme 3.34). Intramolecular carbopalladation of 2,2-disubstituted-1-alkenyltrialkylstannanes **252** may lead to neopentylic *gem*-organobismetallic Pd/Sn carbenoid species. The former substrates could be synthesised from essentially similar synthetic intermediates described in Scheme 2.8, by using a silyl-based phenol protective group, stable

to strong bases and nucleophiles, but cleaved upon fluoride treatment, to which vinylstannanes have been observed to be stable (section 2.2). Terminal alkyne carbometalation would furnish a variety of reaction substrates, of which **252** represents a specific example.

Scheme 3.34: Intramolecular reaction of a 2,2-disubstituted-1-alkenyltributylstannane with an aryl triflate



An external source of acetate, such as the tetra-*n*-butylammonium salt, may be required as a reaction additive to facilitate destannylation and access the carbene manifold. Whether these intermediates could be selectively funnelled towards either the Pd-carbene or ligand-transfer pathway remains to be discovered.

3.6 Experimental Section

3.6.1 General Experimental Methods

Substrate Preparation

Preparative reactions were conducted in flame- or oven-dried glassware under a nitrogen atmosphere unless mentioned otherwise. Dry tetrahydrofuran (THF), diethyl ether (Et_2O), hexanes, dichloromethane (CH_2Cl_2), dichloroethane [$(CH_2Cl)_2$], acetonitrile (MeCN) and toluene (PhMe) were dried and purified from a solvent system by the published procedure.[121] Benzene (PhH) was distilled from Na/benzophenone, while pentane, Et_3N, tetramethylethylenediamine (TMEDA) and pyridine were distilled from CaH_2 under N_2. Hexamethylphosphoramide (HMPA), dimethylformamide (DMF), dimethyl sulfoxide (DMSO) were distilled from CaH_2 under water aspirator vacuum (10-15 mm Hg), while DBU was distilled from CaH_2 under high vacuum (0.3 mm Hg). Following distillation, pentane, TMEDA, pyridine, HMPA, DMF and DMSO were stored in oven-dried Schlenk flasks under Ar. Commercial methanol (MeOH), ethanol (EtOH) (HPLC-grade) and acetone (reagent-grade) were used without further purification.

Chloromethyl methyl ether (MOM-Cl) was prepared on 2-mole scale from decanoyl chloride, according to Chong and Shen.[195] Trifluoromethanesulfonic (triflic) anhydride (Tf_2O) was prepared from 50 g of commercially available triflic acid, according to the *Organic Syntheses* procedure by Stang and Dueber.[196]

For aqueous work-ups, solutions were prepared using deionised water. The following short-hand forms are used: "NH_4Cl", saturated ammonium chloride solution; "$NaHCO_3$", saturated sodium bicarbonate solution; "brine", saturated sodium chloride solution.

Pd-Catalysed Reactions of 2,2-Disubstituted-1-alkenylalanes

All key step reactions were carried out in oven-dried Schlenk glassware using standard Schlenk techniques. Operations were also performed in a nitrogen atmosphere dry-box wherein oxygen and moisture levels were below 5 and 1 ppm, respectively. Hexanes and toluene were dried and purified from a solvent system by the published procedure.[121] Benzene was distilled from Na/benzophenone, while $(CH_2Cl)_2$, Et_3N, CH_3CN, CD_3CN, pivalonitrile and 2,2,5,5-tetramethyltetrahydrofuran were distilled from CaH_2 under N_2. All anhydrous solvents as well as triethylamine were degassed (three freeze-pump-thaw cycles) and stored in oven-dried Schlenk flasks, then transferred to oven-dried Wheaton bottles that were kept and handled in a dry-box. Trialkylaluminum reagents were handled as neat liquids in the dry-box, unless mentioned otherwise. d_9-Trimethylaluminum was prepared according to the procedure outlined below. DABCO was azeotropically dried three times with benzene and stored in a dry-box. P(*p*-MeOPh)$_3$ was commercially available. Pd[P(*p*MeOPh)$_3$]$_2$Cl$_2$ was prepared according to the literature procedure[197] from Pd(PhCN)$_2$Cl$_2$ on a 1.0 mmol scale and stored in a dry-box; the bright yellow complex thus prepared afforded reproducible results until it turned clumpy (typically after 6 weeks) and to a dull yellow colour.

Characterisation Methods

FT-Infrared spectra were run using neat liquids between sodium chloride plates, unless otherwise mentioned. For nuclear magnetic resonance (NMR), the residual ^{1}H shift in $CDCl_3$ (7.26 ppm), acetone-d_6 (2.04 ppm) or PhH-d_6 (7.15 ppm) was used as the internal reference. Likewise, $CDCl_3$ (7.26 ppm) was used as the internal reference for ^{2}H NMR while $CDCl_3$ (77.0 ppm) was used as the internal reference for ^{13}C NMR. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br s = broad singlet, dt = doublet of triplets, dq = doublet of quartets, tt = triplet of triplets. Unless specified otherwise, the quoted *J*-values refer to C-H coupling constants. High resolution mass spectra (HRMS) were performed at the University of Waterloo by Dr. Richard W. Smith, or by the Mass Spectrometry Laboratory, Department of Chemistry, University of Toronto. Elementary analyses were performed at Canadian Microanalytical Service Ltd., Delta, BC, Canada.

Reactions were monitored by thin-layer chromatography (TLC) on commercial silica glass-backed pre-coated plates with a particle size of 60 Å. Developed plates were viewed under a UV lamp and by staining with *p*-anisaldehyde, $KMnO_4$ or cerium ammonium molybdate solutions. Tandem gas chromatography-mass spectrometry (GCMS) was also used to monitor reactions, employing a Hewlett Packard G1800A GCD system fitted with a 30 m X 0.25 mm HP5 column; injector temperature: 250 ºC; temperature program: initial 70 ºC for 2 min; heating rate 10 ºC/min for 18 min; final temperature 250 ºC for 10 min. Flash chromatography was performed using 230-400 mesh silica gel. Mixtures of dichloromethane (CH_2Cl_2), diethyl ether (Et_2O) or ethyl acetate (EtOAc) in 35-60 petroleum ether (PE) or hexanes were used as eluent systems, as specified.

3.6.1.1 Preparation of Tri(d_3-methyl)aluminum[198]

A Schlenk tube was loaded with aluminum powder (4.02 g, 148.9 mmol, 6.0 equiv) and iodine (42 mg, 0.165 mmol). d_3-Iodomethane (10.8 g, 74.5 mmol, 3.0 equiv) was then added via syringe, and the reaction vessel was sealed and immersed in an oil bath at 55 ºC while stirring vigorously for 40 h. The resulting black mixture was cooled to rt and treated with triethylaluminum (6.8 mL, 49.6 mmol, 2.0 equiv) via syringe in one portion (moderately exothermic reaction). The reaction medium was sonicated for 30-45 min and the Schlenk tube was then fitted with a 30-cm Vigreux column and short-path distillation apparatus, insulated by means of layers of aluminum foil. The closed system was flushed with Ar via three evacuation-backfill cycles. The reaction mixture was evacuated in a similar way, and distilled under reduced pressure (water aspirator, KOH trap), applying external heat by means of an oil bath set between 135 and 145 ºC. d_9-Trimethylaluminum (bp = 46-52 ºC@ 25 mm Hg; clear colourless liquid) was thus collected in an oven-dried Schlenk tube (570 mg, 25%) that was cooled in an ethanol/dry ice bath at -70 ºC, and stored under N_2 at –18 ºC in a dry box.

After the distillation was complete, the following quenching operations were undertaken to dismantle the system and quench the pyrophoric reaction mixture without incident. The system was closed, flushed with air via three evacuation-backfill cycles, after which the whole

distillation apparatus was taken apart and set aside at the back of the fume hood. The content of the Schlenk tube was diluted with dry PhMe (10 mL) and poured into 400 mL of undistilled toluene while stirring. This rinsing was repeated four more times. The resulting trialkylaluminum/PhMe solution was then quenched carefully by the successive, dropwise addition of isopropanol, ethanol, water and 5% aqueous HCl.

3.6.2 General Procedures

3.6.2.1 Sodium Borohydride Reduction

A methanol or ethanol solution (0.4 M) of the crude aldehyde was cooled to 0 ºC under N_2, and powdered $NaBH_4$ (1.0 equiv) was added in a portionwise fashion. The reaction was allowed to stir for 1 h (TLC analysis) and water was cautiously added until no more hydrogen was evolved. The alcohol solvent was removed by rotary evaporation, and the benzyl alcohol was extracted from the aqueous layer with CH_2Cl_2 (3X). The combined organics were sequentially washed with water (1X) and brine (1X), dried over $MgSO_4$, filtered and concentrated by rotary evaporation.

3.6.2.2 TMS-Propynylation of Benzylic Alcohols

Due to the unstability of the benzylic bromides, this procedure was carried out without isolation of intermediates. A dry Et_2O solution (0.33 M) of benzyl alcohol and dry Et_3N (1.2 equiv) was cooled to –78 ºC under argon, and treated dropwise with MsCl (1.1 equiv). The reaction was allowed to stir at –78 ºC (15 min) then warmed to 0 ºC and stirred for 1 h. The heterogeneous mixture was then treated with anhydrous LiBr (3.0 equiv; flame-dried 3X *in vacuo*), stirred for a further 30 min at 0 ºC then 30 min at rt. In a separate flask, *n*-BuLi (hexanes solution, 1.5 equiv) was added dropwise to a dry THF solution (0.55 M) of TMS-propyne (1.5 equiv) while cooling at –78 ºC.[160] The resulting mixture was stirred 20 min at –78 ºC, 20 min at –20 ºC and cooled back to –78 ºC. It was maintained at that temperature until the benzyl bromide was prepared. The supernatant ether layer from the benzyl bromide suspension was transferred onto the propargylic anion via cannula. Then, the solids were washed with dry Et_2O and the supernatant transferred via cannula into the anion solution; this trituration process

was carried three times. The reaction was left to stir at –78 ºC for 1 h, and then warmed up to rt whereupon it was deemed complete after stirring for the time specified, as determined by TLC analysis. The reaction was quenched with NH_4Cl (100 mL), and most volatiles were removed by rotary evaporation. The aqueous phase was extracted with ether (3X), and the combined organics were washed sequentially with NH_4Cl (1X) and brine (1X), dried over $MgSO_4$, filtered and concentrated by rotary evaporation.

3.6.2.3 Alkyne Protiodesilylation

A MeOH/CH_2Cl_2 solution (4:1, 0.2 M globally) of TMS-alkyne was treated with a saturating amount of K_2CO_3 and stirred vigorously at rt (6 h). The volatiles were thoroughly removed *in vacuo*, and the solids were then triturated with ether (15 min). After filtration through Celite and concentration by rotary evaporation, the alkyne was typically pure enough to carry on to the next step without purification.

3.6.2.4 Hydrolysis of MOM Acetals

The MOM-substituted aryl alkyne was dissolved in 1:1:1 MeOH, reagent-grade acetone and 3N aqueous HCl (total concentration = 0.12 M) and stirred at rt for 14 h (TLC monitoring). Upon completion, the volatiles were removed under reduced pressure, and the residue partitioned between water and CH_2Cl_2. The aqueous phase was extracted (4X total) with dichloromethane, dried (Na_2SO_4), filtered and concentrated to dryness to afford the corresponding 2-(4-pentynyl)-1-naphthol. The latter, due to its propensity to decompose, was rediluted in dry CH_2Cl_2 for use in the triflation step.

3.6.2.5 1-Naphthol Triflation

To a stirred solution of naphthol derivative (0.20 M) in dry CH_2Cl_2, cooled to 0 ºC, was added dry pyridine (6.0 equiv) followed by dropwise injection of Tf_2O (1.2 equiv). The dark red mixture was allowed to warm up to rt while stirring for 1 h (TLC monitoring). The reaction was quenched with 10% aqueous HCl. Dichloromethane was evaporated and the residue was extracted (3X) with Et_2O or EtOAc. The combined extracts were then washed (3X) with 10% HCl, brine (1X), dried ($MgSO_4$), filtered and concentrated to dryness. The dark oil was eluted

through a short silica plug (10% EtOAc/PE), concentrated to dryness then purified by column chromatography. For electron-rich naphthyl triflates, analytically pure samples could be secured after careful purification by column chromatography using mixtures of toluene/hexanes as eluent.

3.6.2.6 *ortho*-Lithiation/Formylation[199]

Under argon, TMEDA (1.00 equiv) was added dropwise to a hexanes solution of *n*-BuLi (1.02 equiv) at 0 ºC, then the methoxymethoxyphenol derivative, azeotropically dried with PhH (3X), was added via cannula (diluted with a minimum amount of hexanes, then two small volumes of hexanes to rinse). The resulting suspension was stirred at 0 ºC for 60 min, then dry DMF (1.3 equiv) was carefully injected at 0 ºC, and the reaction was allowed to stir 30 min at rt. Upon completion (TLC monitoring), the reaction was poured onto ice containing 5 mL concentrated HCl and extracted immediately with hexanes. The pH of the aqueous phase was adjusted to 2 and further extracted with hexanes/Et_2O (19:1, 3 x 100 mL). The combined organics were washed with $NaHCO_3$ (1X), H_2O (1X), and brine (1X), dried over $MgSO_4$, filtered and concentrated under reduced pressure.

3.6.2.7 Biphasic Stabilised Wittig Homologation[200]

To a solution of benzaldehyde (1.00 equiv) in CH_2Cl_2 and deionised H_2O (1:1, total concentration = 0.25 M) were successively added K_2CO_3 (2.00 equiv) and (carboxymethyl)methylphosphonium bromide (1.15 equiv). The resulting biphasic mixture was vigorously stirred for 14 h, and analysed for completion by GC-MS. The organic layer was separated, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated until solids crashed out. The crude reaction mixture was triturated with 10-20% EtOAc/PE for 15 min, filtered through silica gel eluting with 10-20% EtOAc/PE, and concentrated to dryness, to afford the β-aryl acrylate derivative in an *E*/*Z* mixture which was used as such in the hydrogenation step.

3.6.2.8 Hydrogenation of β-Aryl Acrylate Esters

The β-aryl acrylate was redissolved in MeOH or EtOAc (0.25 M), and evacuated (10-15 mm Hg), then back-filled with N_2 three times. 5% Pd/C (10 wt.% based on starting alkene) was then added, and the black mixture was evacuated (10-15 mm Hg) and back-filled with H_2 gas (balloon). The heterogeneous mixture was stirred vigorously for 4-6 h (monitored by GC-MS). Upon completion, the mixture was purged with N_2 as described above (2X) and filtered through Celite, concentrated to dryness, and then the crude product was eluted through a short plug of silica gel (EtOAc) to afford the pure 3-arylpropanoate derivatives.

3.6.2.9 Lithium Aluminum Hydride Reduction

To a suspension of $LiAlH_4$ (1.0 equiv) in dry THF (0.20 M) under Ar, cooled to 0 ºC, was added a solution of the ester in THF (1.0 M) via cannula, dropwise. The resulting grey mixture was warmed to rt, and analyzed by TLC. After completion was reached, the reaction was cooled back to 0 ºC, and carefully quenched successively with H_2O (1.00 mL per g $LiAlH_4$), 15% aqueous NaOH (1.00 mL per g $LiAlH_4$) then H_2O (3.00 mL per g $LiAlH_4$). After stirring the salts for 15 min at rt, the mixture was poured into triple the volume of Et_2O, stirred for 20 min then filtered through Celite eluting with Et_2O. The solution was concentrated to dryness to afford the corresponding 3-aryl-1-propanol derivative.

3.6.2.10 Bromination of Primary Alcohol

To a solution of PPh_3 (1.15 equiv) and imidazole (2.00 equiv) in dry CH_2Cl_2 (0.20 M) under N_2 was added Br_2 (1.14 equiv) dropwise while cooling in an ice bath. Should the orange colour of bromine persist, a crystal of PPh_3 can be added to ensure quantitative conversion of Br_2 into Br_2•PPh_3. A solution of the primary alcohol in CH_2Cl_2 (1.0 M) was then injected dropwise to the phosphonium salt mixture, which was allowed to warm to rt. After 1 h (TLC monitoring), then reaction was quenched with NH_4Cl, the layers separated, and the aqueous phase was extracted (2X) with CH_2Cl_2. The combined organic layers were then washed with NH_4Cl, dried (Na_2SO_4), filtered and the solvents removed under reduced pressure. The solids were triturated with 10-20% EtOAc/PE for 15 min, filtered through silica gel eluting with 10-20% EtOAc/PE, and concentrated to dryness, to afford the pure primary alkyl bromide.

3.6.2.11 Ethynylation of Alkyl Bromide

A solution of TMS-acetylene (1.5 equiv) in dry THF (0.20 M), cooled to 0 ºC under Ar, was injected dropwise with *n*-BuLi (solution in hexanes, 1.4 equiv). The yellow solution was then stirred for 20-30 min, and transferred via cannula to a solution of alkyl bromide in THF/HMPA (8:1) while maintaining at –78 ºC. After 1 h at that temperature, the reaction was allowed to reach rt and stirred until completion was attained (TLC monitoring). The reaction was quenched with of 1.0 M aqueous NaOH (50 mL) and methanol (50 mL). The orange mixture was then either stirred for 14 h at rt or heated to reflux, open to the air, for 30 min. The volatiles were then removed under reduced pressure, and H_2O was added (100 mL). The aqueous phase was extracted (3X) with 10% EtOAc/PE; the combined organics were washed 3-5 times with H_2O, brine (1X), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting liquid was then purified by flash chromatography to afford the corresponding 5-aryl-1-pentyne derivatives.

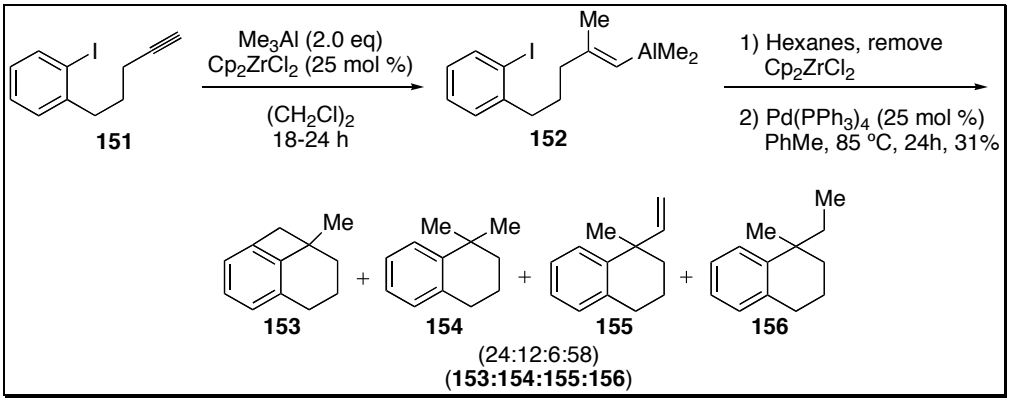
3.6.2.12 Sequential Carboalumination/Carbopalladation

An oven-dried Schlenk tube was loaded with Cp_2ZrCl_2 (25 mol %) followed by the alkynyl triflate (1.0 equiv). In a dry box, this mixture was dissolved using 1,2-dichloroethane (0.15 M), then neat Me_3Al (2.0 equiv) was added dropwise via syringe. The resulting lemon-yellow mixture was allowed to stir for 15-20 h in a sealed Schlenk tube, after which, the volatiles were removed *in vacuo* (0.05-0.10 mm Hg) while placing the reaction vessel in an oil bath (50-75 °C) for 1 h (4 h for methoxy- and fluoro-substituted substrates). In the dry box, a mixture of $Pd[P(p\text{-}MeOPh)_3]_2Cl_2$ (10 mol %), $P(p\text{-}MeOPh)_3$ (20 mol %) and triethylamine (0.10 equiv) was suspended in CH_3CN (0.4 M) in a vial, and heated gently until dissolution resulted. The warm, light orange mixture was then added to a mixture of the crude alane and DABCO (6.0 equiv), and quantitatively transferred CH_3CN, bringing the total concentration to 0.10 M. The Schlenk tube was sealed and placed in an oil bath at 100 ºC for 24 h, unless otherwise specified. Upon completion, the reaction was cooled to ambient temperature and quenched by the careful addition of H_2O (2.0 mL), stirring 10 min then diluting with 5% aqueous HCl (15 mL). The products were extracted with dichloromethane (3 x 10 mL) and washed with 5% HCl

(1X 5 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered over Celite eluting with dichloromethane and concentrated under reduced pressure. The resulting crude gum was purified by flash chromatography (100% hexanes or PE for non-functionalised substrates, or 10% CH_2Cl_2/PE for methyl ether substrates) to allow the collection of all non-polar components and ratio determination. Second flash chromatography afforded the title compounds in the reported isolated yields.

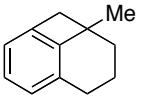
3.6.3 Experimental Procedures and Characterisation Data

3.6.3.1 Initial Results with 5-(2-Iodophenyl)pent-1-yne and Synthesis of 1-Ethenyl-1-methyl-1,2,3,4-tetrahydronaphthalene 155



To an oven-dried Schlenk tube was added Cp_2ZrCl_2 (31.9 mg, 0.109 mmol, 25 mol %) followed by alkyne **151** (118 mg, 0.435 mmol) and dichloroethane (3.0 mL). The resulting solution was degassed twice by applying vacuum (water aspirator, KOH trap) for one min then refilling with argon. In a dry box, trimethylaluminum (83 μL, 0.870 mmol) was added via syringe. The resulting lemon-yellow mixture was allowed to stir for 18 h in the sealed Schlenk tube, after which, the volatiles were removed in vacuo (0.1 mm Hg) while placing the reaction vessel in a warm bath (40 °C) for 1 h. The Schlenk tube was refilled with Ar, and hexanes were added (1.5 mL). The suspension was sonicated for two min, and the solids were allowed to settle. The supernatant was transferred into another oven-dried Schlenk tube via cannula. The solids were washed twice more (2X 1.0 mL hexanes). The yellow vinylalane solution was then

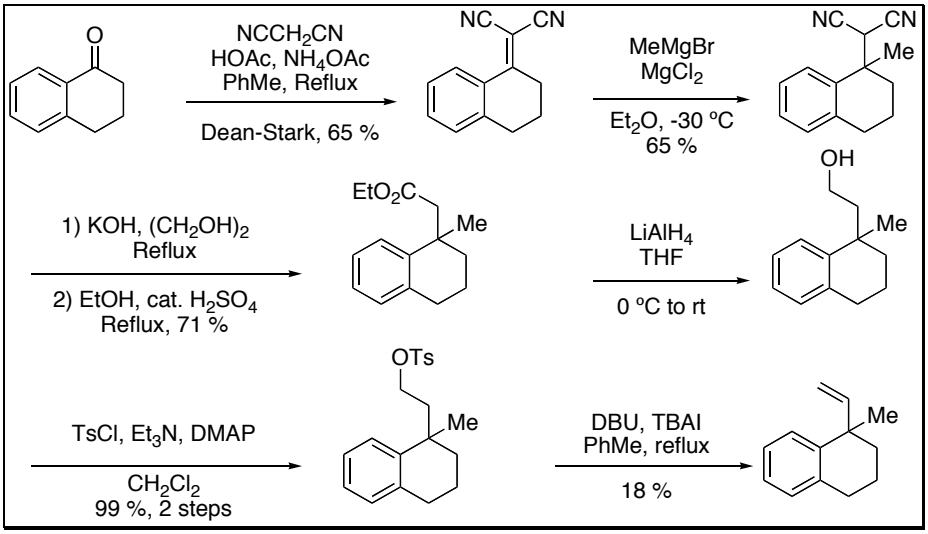
concentrated to dryness under high vacuum (0.1 mm Hg, 15 min, 40 °C). The Schlenk tube was refilled with Ar and loaded with $Pd(PPh_3)_4$ (126 mg, 0.109 mmol, 25 mol %) and toluene (4.4 mL). The resulting mixture was purged with Ar three times as described above. The Schlenk tube was refilled with Ar, resealed and placed in an oil bath at 85°C for 24 h. Upon completion, the reaction was cooled to ambient temperature and quenched by sequential addition of 1 mL of ethanol and 10 mL of 5% HCl. The products were extracted with EtOAc (3 x 10 mL) and washed with 5% HCl (1X 5 mL) and brine. The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude product was purified over a pad of silica gel using pentane as the eluent. ^{1}H NMR and GC-MS were used to determine the ratio of products in the resulting clear colourless liquid (23.7 mg, 31%). The independent synthesis and characterisation data of **154** and **156** are delineated in Carson's thesis.[154] Of note, bicycle **155** was not formed at 70 °C, and tricycle **153** not detected when the reaction was carried out at 100 °C or in the presence of Cp_2ZrCl_2.

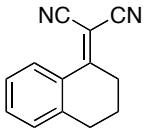


1a-Methyl-1a,2,3,4-tetrahydro-1*H*-cyclobuta[*de*]naphthalene 153

Clear colourless liquid; R_f 0.78 (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.07 (3H, m), 3.54-3.46 (2H, q_{AB}), 2.75 (2H, app t, J = 6.9 Hz), 2.02-1.97 (1H, m), 1.76-1.72 (2H, m), 1.67-1.58 (1H, m), 1.41 (3H, s). Decomposed upon standing.

Independent Synthesis of 1-Methyl-1-ethenyl-1,2,3,4-tetrahydronaphthalene 155

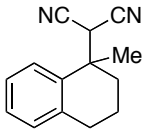




2-(2,3-Dihydronaphthalen-4(*1H*)-ylidene)malononitrile[201]

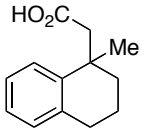
The title compound was prepared following the literature method using the following quantities of reagents: α-tetralone (freshly distilled (140 ºC @ 10 mm Hg); 7.3 mL; 54.5 mmol; 1.0 equiv), malononitrile (recrystallised from $CHCl_3$; 3.96 g; 60.0 mmol; 1.1 equiv), NH_4OAc (2.5 g; 32.7 mmol; 0.6 equiv) and acetic acid (2.5 mL; 43.6 mmol; 0.8 equiv) in dry toluene (60 mL). The mixture was heated to reflux for 14 h, whereupon TLC indicated reaction completion. After cooling to rt, the mixture was partitioned between EtOAc (200 mL) and H_2O (100 mL). The organic extracts were washed with $NaHCO_3$ (1X), brine (1X), dried over $MgSO_4$, filtered and concentrated by rotary evaporation. After filtration through a plug of silica gel (40% EtOAc/hexanes) and partial concentration of the filtrate, the crystals thus obtained were filtered off and washed sequentially with cold EtOH and petroleum ether, to afford 6.92 g (1 crop, 65%) of the title compound as corn-yellow crystals. Mp (EtOAc/hexanes): 109.5-110.3 ºC (lit. mp: 115.3-117.8 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (1H, d, *J* = 7.9 Hz), 7.50 (1H, t, *J* = 7.5 Hz), 7.35 (1H, t, *J* = 7.7 Hz), 7.29 (1H, d, *J* = 7.7 Hz), 3.03 (2H, t, *J* = 6.4

Hz), 2.89 (2H, t, J = 6.2 Hz), 2.01 (2H, quint, J = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 141.9, 133.6, 129.9, 129.4, 127.9, 126.8, 113.8, 113.3, 32.9, 29.6, 22.0.



(1-Methyl-1,2,3,4-tetrahydronaphthalenyl)malononitrile

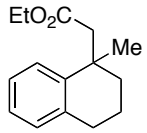
Under high vacuum, $MgCl_2$•$6H_2O$ (5.00 g; 24.6 mmol; 1.0 equiv) was extensively flame-dried *in vacuo*, and the flask was refilled with Ar. The cyanoalkylidene compound (4.78 g; 24.6 mmol; 1.0 equiv) was introduced, and Et_2O (100 mL) was added. The heterogeneous mixture was cooled to –20 ºC then MeMgBr (13.9 mL of a 3.0M ether solution; 41.8 mmol; 1.7 equiv) was syringed in over 5 min. After stirring for 30 min at that temperature, the reaction was allowed to reach rt. After 45 min, 100 mL NH_4Cl was added (carefully) followed by 100 mL H_2O. The organic layer was separated, and the aqueous layer was further extracted with Et_2O (2X). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated by rotary evaporation. Following purification by flash chromatography (10% EtOAc/PE), the title compound was isolated as a clear colourless oil (3.37 g; 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (1H, d, J = 6.8 Hz), 7.29-7.23 (2H, m), 7.19 (1H, d, J = 6.9 Hz), 4.11 (1H, s), 2.96-2.84 (2H, m), 2.20 (1H, ddd, J = 10.2, 3.0, 2.1 Hz), 2.10-1.95 (2H, m), 1.94-1.85 (1H, m), 1.64 (3H, s); ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 137.4, 136.7, 130.2, 128.0, 126.8, 125.9, 112.3, 112.1, 41.3, 36.0, 34.6, 29.7, 27.4, 19.0; HRMS (EI) Calcd. for $C_{14}H_{14}N_2$: 210.1157. Found: 210.1149.



2-(1-Methyl-1,2,3,4-tetrahydronaphthalenyl)-1-ethanoic acid

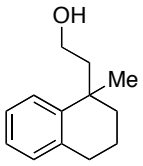
The dicyano compound (2.99 g; 14.2 mmol) was dissolved in ethylene glycol (40 mL). KOH (23.9 g; 426 mmol; 30 equiv) was added, and the mixture was heated to reflux open to the air for 16 h followed by cooling to ambient temperature, whereupon neither starting material nor

amide intermediate was observed by ^{1}H NMR analysis of an aliquot (10% HCl/Et_2O mini work-up). The reaction mixture was diluted with 20 mL water, and poured into 300 mL ice-cold 10% aq. HCl. The aqueous layer was extracted twice with Et_2O (100 mL) and once with EtOAc (75 mL), then the combined organic layers were washed with brine (3X 75 mL), dried ($MgSO_4$), filtered and concentrated by rotary evaporation. The crude carboxylic acid, obtained as a purple oil, was taken as such to the next step without further characterisation. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (1H, d, *J* = 7.7 Hz), 7.18-7.01 (3H, m), 2.76 (2H, t, *J* = 6.2 Hz), 2.69 (1H, d, *J* = 14.0 Hz), 2.60 (1H, d, *J* = 14.0 Hz), 2.14-2.01 (1H, m), 1.86-1.76 (2H, m), 1.72-1.61 (1H, m), 1.40 (3H, s).



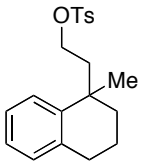
Ethyl 2-(1-methyl-1,2,3,4-tetrahydronaphthalenyl)-1-ethanoate

The parent carboxylic acid (14.2 mmol) was dissolved in 120 mL absolute EtOH and heated to reflux under N_2 in the presence of 2.5 mL concentrated H_2SO_4 for 3.5 h. After cooling to rt, the pH was adjusted to 8 by adding 1.0 M aqueous K_2CO_3 portionwise. Volatiles were removed under reduced pressure, and the residue was partitioned between EtOAc and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to dryness. The title compound (2.35 g, 71% over two steps) was obtained after purification by flash chromatography (5% EtOAc/PE) as a clear colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.01 (4H, m), 4.03 (2H, q, *J* = 7.2 Hz), 2.76 (2H, t, *J* = 6.5 Hz), 2.65 (1H, d, *J* = 13.8 Hz), 2.55 (1H, d, *J* = 13.9 Hz), 2.06 (1H, dddd, *J* = 9.5, 9.5, 3.7, 3.5 Hz), 1.88-1.74 (2H, m), 1.64 (1H, dddd, 8.2, 7.9, 3.5, 3.0 Hz), 1.38 (3H, s), 1.15 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 143.5, 136.5, 129.2, 126.5, 125.8, 125.7, 59.9, 47.4, 36.5, 35.7, 30.4, 29.7, 19.4, 14.1; HRMS (EI) Calcd. for $C_{15}H_{20}O_2$: 232.1463. Found: 232.1457.



2-(1-Methyl-1,2,3,4-tetrahydronaphthalenyl)ethan-1-ol[202]

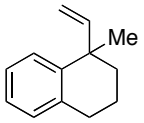
To a suspension of $LiAlH_4$ (227 mg; 6.00 mmol; 1.2 equiv) in 20 mL of dry THF, cooled to 0 ºC under Ar, was added a solution of ethyl ester (1.16 g; 5.00 mmol; 1.0 equiv) in THF (5 mL) via cannula. The grey suspension was allowed to stir for 45 min at rt (TLC monitoring) and cooled back to 0 ºC. The reaction was quenched by the dropwise and careful addition of 0.23 mL H_2O, 0.23 mL 15% aqueous NaOH, then 0.69 mL H_2O. The mixture was diluted with 75 mL ether and stirred for 15 min, filtered through Celite, and concentrated to dryness. Purification by column chromatography (15% EtOAc/PE) afforded the title alcohol as a colourless viscous oil, which was taken as such to the subsequent step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (1H, d, *J* = 7.7 Hz), 7.08 (1H, dt, *J* = 6.1, 1.8 Hz), 7.09-7.00 (2H, m), 3.66 (1H, ddd, *J* = 10.0, 5.7, 5.7 Hz), 3.54 (1H, ddd, *J* = 9.1, 6.1, 6.0 Hz), 2.73 (2H, t, *J* = 6.9 Hz), 2.05-1.54 (6H, m), 1.27 (3H, s), 1.11 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 136.6, 129.2, 126.6, 125.8, 125.4, 59.9, 45.8, 36.0, 35.9, 30.8, 30.5, 19.5; HRMS (EI) Calcd. for $C_{13}H_{18}O$: 190.1358. Found: 190.1351.



1-Methyl-1-[2-(4-toluenesulfonyloxy)ethoxy]-1,2,3,4-tetrahydronaphthalene[202]

To a solution of the primary alcohol (951 mg; 5.00 mmol) in CH_2Cl_2 (20 mL), were added successively DMAP (733 mg; 6.00 mmol; 1.2 equiv) then tosyl chloride (1.05 g; 5.50 mmol; 1.1 equiv) at rt. The reaction mixture was allowed to stir at that temperature for 16 h, after which TLC analysis revealed reaction completion. The mixture was quenched with $NaHCO_3$ and extracted with EtOAc (100 mL). The organic layer was successively washed with $NaHCO_3$ (2X), NH_4Cl (2X) and brine, dried ($MgSO_4$), filtered and concentrated to dryness. Following purification by flash chromatography (5% EtOAc/PE), there was obtained the title compound as a clear colourless oil (1.70 g; 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 7.7 Hz),

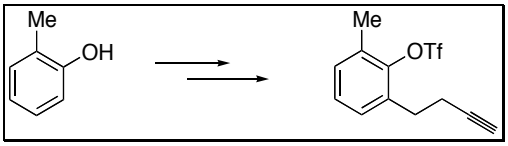
7.29 (2H, d, *J* = 8.0 Hz), 7.08-7.00 (4H, m), 4.05 (1H, ddd, *J* = 9.8, 9.0, 6.1 Hz), 3.93 (1H, ddd, *J* = 9.8, 9.0, 5.9 Hz) 2.68-2.62 (2H, m), 2.43 (3H, s), 2.13 (1H, ddd, *J* = 9.0, 8.6, 6.0 Hz), 1.94 (1H, ddd, *J* = 8.9, 8.8, 6.1 Hz), 1.75-1.53 (4H, m), 1.22 (3H, s); ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 144.5, 142.6, 136.5, 133.1, 129.7, 129.3, 127.7, 126.2, 126.0, 125.6, 68.0, 41.3, 35.8, 35.7, 30.6, 30.3, 21.5, 19.2; HRMS (EI) Calcd. for $C_{20}H_{24}O_3S$: 344.1446. Found: 344.1447.

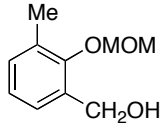


1-Ethenyl-1-methyl-1,2,3,4-tetrahydronaphthalene 155

The tosylate (250 mg; 0.725 mmol) was dissolved in dry PhMe (7 mL). Tetra-*n*-butylammonium iodide (27 mg; 0.073 mmol; 0.10 equiv) and DBU (0.54 mL; 3.6 mmol; 5.0 equiv) were successively added, and the resulting solution was brought to reflux under N_2 and stirred at that temperature for 5 h, whereupon TLC showed reaction completion. The crude mixture was diluted with hexanes (60 mL), and washed successively with H_2O (1X), 1M HCl (3X) and brine, dried ($MgSO_4$), filtered over silica gel (hexanes) and concentrated by rotary evaporation. Purification by flash chromatography (100% PE) afforded the title compound as a clear colourless oil (18% yield, 23 mg). R_f 0.52 (100% PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.06 (4H, m), 5.94 (1H, dd, *J* = 17.3, 10.5 Hz), 5.02 (1H, dd, *J* = 10.5, 1.4 Hz), 4.82 (1H, dd, *J* = 17.3, 1.4 Hz), 2.77 (2H, app t, *J* = 6.2 Hz), 1.85-1.63 (4H, m), 1.39 (3H, s); ^{13}C (75 MHz, $CDCl_3$) δ 148.8, 142.2, 136.7, 129.1, 128.4, 125.7, 125.6, 112.0, 40.9, 37.5, 30.3, 28.2, 19.3; HRMS (EI) Calcd. for $C_{13}H_{16}$: 172.1252. Found: 172.1248.

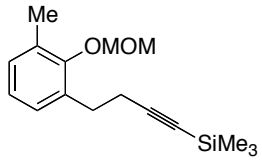
3.6.3.2 Synthesis of 2-(3-Butynyl)-6-methylphenyl Trifluoromethanesulfonate 157b





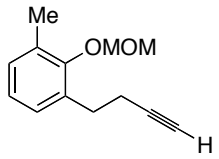
2-Methoxymethoxy-3-methylbenzyl alcohol[203]

The title alcohol was prepared by borohydride reduction, according to General Procedure 3.6.2.1, from 15.15 g (84.1 mmol) of the known 2-methoxymethoxy-3-methylbenzaldehyde,[204] to afford 14.7 g (96%) of the title compound, as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (1H, dd, *J* = 7.4, 0.9 Hz), 7.17 (1H, dd, *J* = 7.5, 0.9 Hz), 7.05 (1H, dd, *J* = 7.5, 7.5 Hz), 5.01 (2H, s), 4.62 (2H, s), 3.64 (3H, s), 2.9-2.1 (1H, br s), 2.28 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 134.4, 131.0, 130.8, 127.7, 124.7, 99.2, 60.9, 57.2, 16.6. HRMS (EI) Calcd. for $C_{10}H_{14}O_3$: 182.0943. Found: 182.0944.



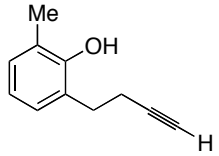
4-[(2-Methoxymethoxy-3-methylphenyl)butynyl]trimethylsilane

Prepared according to General Procedure 3.6.2.2, from 4.1 g (100 mmol) of the corresponding benzyl alcohol, and purified by flash chromatography (2% EtOAc/hexanes) to afford 4.1 g of the title compound as an orange oil in 66% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07-6.91 (3H, m), 4.95 (2H, s), 3.60 (3H, s), 2.87 (2H, t, *J* = 7.9 Hz), 2.49 (2H, t, *J* = 8.0 Hz), 2.24 (3H, s), 0.12 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 133.8, 131.1, 129.6, 128.0, 124.2, 107.1, 99.5, 84.9, 57.3, 30.0, 21.0, 17.0, 0.09; HRMS (EI) Calcd. for $C_{15}H_{21}O_2Si$ ($M^+ - CH_3$): 261.1305. Found: 261.1314.



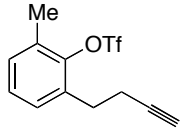
4-(2-Methoxymethoxy-3-methylphenyl)but-1-yne

Prepared according to General Procedure 3.6.2.3, from 10.1 g (36.5 mmol) of parent alkynyl(trimethyl)silane. The crude material thus obtained was used as such in the subsequent step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (2H, d, *J* = 7.7 Hz), 7.01-6.95 (1H, m), 5.00 (2H, s), 3.62 (3H, s), 2.91 (2H, dd, *J* = 8.0, 7.6 Hz), 2.50 (2H, dt, *J* = 7.8, 2.6 Hz), 2.29 (3H, s), 1.97 (1H, t, *J* = 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 133.6, 131.1, 129.7, 127.8, 124.3, 99.5, 84.2, 68.5, 57.3, 29.9, 19.5, 17.0.



2-(But-3-ynyl)-6-methylphenol

Prepared according to General Procedure 3.6.2.4, from the parent MOM ether. Due to its instability, the material thus obtained (5.1 g; 87% yield over 2 steps) was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (2H, d, *J* = 7.5 Hz), 6.78 (1H, t, *J* = 7.6 Hz), 4.86 (1H, br s), 2.85 (2H, t, *J* = 7.3 Hz), 2.49 (2H, dt, *J* = 7.2, 2.6 Hz), 2.23 (3H, s), 2.00 (1H, t, *J* = 2.5 Hz).

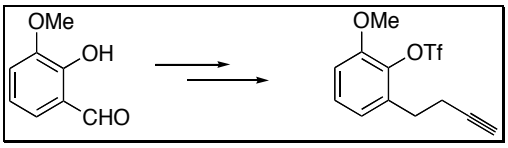


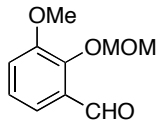
2-(But-3-ynyl)-6-methylphenyl trifluoromethanesulfonate[177]

Obtained via General Procedure 3.6.2.5, after purification by column chromatography (5% EtOAc/hexanes) in 83% yield (7.7 g). Clear colourless liquid; R_f 0.29 (3% EtOAc/pentane); IR (neat) 3306, 2122 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.13 (3H, m), 2.99 (2H, t, *J* = 7.4 Hz), 2.51 (2H, dt, *J* = 7.4, 2.6 Hz), 2.40 (3H, s), 1.97 (1H, t, *J* = 2.6 Hz); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 146.1, 133.7, 131.8, 130.8, 129.0, 128.2, 119.6 (q, $J_{C\text{-}F}$ = 315 Hz), 82.8, 69.36, 29.4, 18.9, 17.3; Anal. Calcd. for $C_{12}H_{11}F_3O_3S$: C, 49.31; H, 3.79. Found: C, 49.07; H, 3.95.

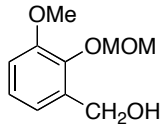
3.6.3.3 Synthesis of 2-(3-Butynyl)-6-methoxyphenyl Trifluoromethanesulfonate 157c





2-Methoxymethoxy-3-methoxybenzaldehyde[205]

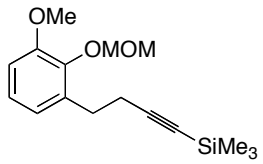
o-Vanillin (12.2 g; 80.0 mmol) and anhydrous K_2CO_3 (16.6 g; 120 mmol; 1.50 equiv) were slurried in DMF (100 mL) and cooled to 0 ºC. MOM-Cl (6.5 mL; 82.0 mmol; 1.02 equiv) was then added dropwise. The reaction was stirred for 16 h in the gradually warming ice-water bath. A further portion of MOM-Cl was added (1.0 mL; total 98.8 mmol; total 1.24 equiv) to drive the reaction to completion, whereupon the reaction mixture was poured into H_2O (250 mL), and the product was extracted with 3 portions of 10% EtOAc/hexanes. The combined organics were washed with 1.0 M K_2CO_3 twice and brine (once), dried over Na_2SO_4, filtered and concentrated by rotary evaporation. The title compound was obtained as a clear liquid that solidified to a white solid (15.2 g; 97%); spectral data were identical to the reported values.



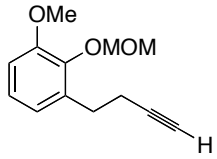
2-Methoxymethoxy-3-methoxybenzyl alcohol[206]

The title compound was obtained following General Procedure 3.6.2.1, from 15.2 g (77.5 mmol) of the corresponding benzaldehyde, as a white solid (15.2 g; 99%); NMR data was identical to that reported by Yamaguchi *et al.* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (1H, t, *J* =

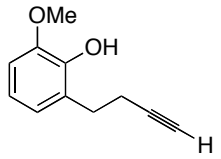
7.9 Hz), 6.93 (1H, dd, *J* = 7.7, 1.3 Hz), 6.88 (1H, dd, *J* = 8.1, 1.1 Hz), 5.09 (2H, s), 4.63 (2H, s), 3.83 (3H, s), 3.57 (3H, s).



4-[(2-Methoxymethoxy-3-methoxyphenyl)but-1-ynyl]trimethylsilane: Following General Procedure 3.6.2.2, from 15.2 g (76.7 mmol) of the corresponding benzyl alcohol, after column chromatography , the title compound was produced as a golden oil (16.5 g; 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (1H, t, *J* = 7.9 Hz), 6.80 (1H, d, *J* = 8.3 Hz), 6.77 (1H, d, *J* = 8.4 Hz), 5.09 (2H, s), 3.81 (3H, s), 3.72 (3H, s), 2.90 (2H, t, *J* = 7.8 Hz), 2.50 (2H, t, *J* = 7.8 Hz), 0.12 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 144.3, 134.8, 124.0, 122.2, 110.6, 107.2, 99.0, 84.8, 57.4, 55.7, 29.8, 21.0, 14.2, 0.1; HRMS (EI) Calcd. for $C_{16}H_{24}O_3Si$: 292.1495. Found: 292.1493.

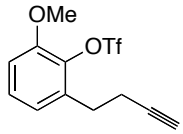


4-(2-Methoxymethoxy-3-methoxyphenyl)but-1-yne: Protiodesilylation according to General Procedure 3.6.2.3, on 56.8 mmol scale, gave a dark orange liquid (10.6 g; 85%) identified as the title compound, which was carried on to the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (1H, t, *J* = 7.9 Hz), 6.82 (1H, d, *J* = 7.5 Hz), 6.78 (1H, d, *J* = 8.0 Hz), 5.08 (2H, s), 3.81 (3H, s), 3.58 (3H, s), 2.92 (2H, t, *J* = 7.8 Hz), 2.49 (2H, dt, *J* = 8.0, 2.6 Hz), 1.95 (1H, t, *J* = 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 144.2, 134.4, 123.9, 121.8, 110.5, 98.8, 84.0, 68.4, 57.2, 55.5, 29.5, 19.3; HRMS (EI) Calcd. for $C_{13}H_{16}O_3$: 220.1099. Found: 220.1097.



2-(But-3-ynyl)-6-methoxyphenol

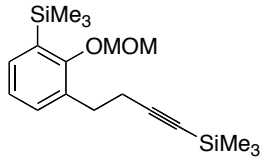
Acid-catalysed hydrolysis (General Procedure 3.6.2.4) of the corresponding MOM acetal (10.6 g; 48.1 mmol) gave a dark brown oil after usual work-up. Column chromatography (15% EtOAc/hexanes) afforded the title compound as a light orange oil (7.5 g; 88%). The phenol was taken to the triflation step with minimal characterisation. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89-6.72 (3H, m), 5.72 (1H, br s), 3.86 (3H, s), 2.87 (2H, t, *J* = 7.6 Hz), 2.49 (2H, dt, *J* = 7.6, 2.6 Hz), 1.94 (1H, t, *J* = 2.6 Hz).



2-(But-3-ynyl)-6-methoxyphenyl trifluoromethanesulfonate

Prepared via phenol triflation according to General Procedure 3.6.2.5, on 2.5 g (14.2 mmol) scale, after purification by column chromatography (7.5% EtOAc in hexanes) in 87% yield (3.8 g). Clear colourless liquid; R_f 0.41 (5% EtOAc/PE); IR (neat) 3303, 2122 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.23 (1H, m), 6.95 (1H, d, *J* = 7.4 Hz), 6.91 (H, d, *J* = 8.4 Hz), 3.89 (3H, s), 2.94 (2H, t, *J* = 7.4 Hz), 2.51 (2H, dt, *J* = 7.4, 2.6 Hz), 1.98 (1H, t, *J* = 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 137.3, 134.3, 128.4, 122.1, 118.7 (q, $J_{C\text{-}F}$ = 315 Hz), 111.2, 82.7, 69.4, 56.0, 28.9, 18.8; Anal. Calcd. for $C_{12}H_{11}F_3O_4S$: C, 46.76; H, 3.60. Found: C, 47.15; H, 3.73.

3.6.3.4 Synthesis of [2-(3-Butynyl)-6-(trimethylsilyl)]phenyl Trifluoromethanesulfonate 157e

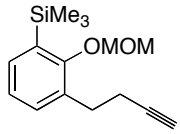


4-[(2-Methoxymethoxy-3-(trimethylsilyl)phenyl)but-1-ynyl]trimethylsilane

The corresponding benzyl alcohol[3] (14.9 g, 62.0 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (150 mL), cooled to 0 ºC and injected sequentially with Et_3N (17.3 mL, 2.0 equiv) and MsCl (5.3 mL, 68.2, 1.1 equiv) in a dropwise fashion over 7 min. The resulting heterogeneous mixture was then allowed to stir for 45 min in the ice-water bath, whereupon completion was observed by TLC analysis. The crude mixture was diluted with 150 mL CH_2Cl_2 and sequentially washed with H_2O (1X), 10% aq. HCl (3X), $NaHCO_3$ (3X) and brine (1X). The organic portion was dried over $MgSO_4$, filtered and concentrated to dryness (T_{bath} < 35 ºC). The resulting orange liquid (17.5 g, 88%) was dissolved in THF (150 mL) and cooled to 0 ºC under Ar. Meanwhile, the lithium anion of TMS-propyne was prepared by the dropwise addition of a pentane solution of *t*-BuLi (1.40 M, 53.1 mL, 74.4 mmol, 1.2 equiv) to a solution of TMS-propyne (11.0 mL, 74.4 mmol, 1.2 equiv) and TMEDA (46.8 mL, 310 mmol, 5.0 equiv) in THF (50 mL) under Ar at –45 ºC. The deprotonation was allowed to stir for 2 h at –45 ºC, and then cooled to –78 ºC. The ice-cold benzylic mesylate solution prepared previously was treated in one portion with triply flame-dried LiBr (18.3 g, 211 mmol, 3.4 equiv) under Ar and stirred for 5 min at that temperature. The anion solution was then transferred via cannula over the freshly prepared benzylic bromide THF solution, and the resulting dark reaction mixture was allowed to stir for 2 h at –78 ºC. Following reaction completion (TLC monitoring), the mixture was allowed to reach 0 ºC and quenched with brine. The volatile components were removed by rotary evaporation, and the aqueous layer was acidified to pH ~ 6 and extracted with three portions of 9:1 hexanes/EtOAc. The combined organics were sequentially washed with 10% aq. HCl (1X), $NaHCO_3$ (1X) and brine (1X), dried over $MgSO_4$, filtered and concentrated to dryness. Following purification over a short column of silica gel (5% EtOAc/hexanes), the title compound was obtained as a light yellow oil (12.8 g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ

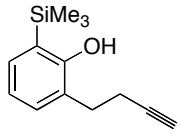
[3] (2-Methoxymethoxy-3-trimethylsilylphenyl)methanol was generously provided by Prof. Eric Fillion.

7.31-7.27 (2H, m), 7.05 (1H, dd, *J* = 7.4, 7.4 Hz), 5.18 (2H, s), 3.66 (3H, s), 2.93 (2H, t, *J* = 8.0 Hz), 2.51 (2H, t, *J* = 7.5 Hz), 0.28 (9H, s), 0.12 (9H, s).



4-(2-Methoxymethoxy-3-(trimethylsilyl)phenyl)-1-butyne

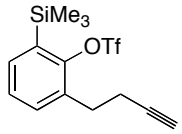
To a solution of the alkynylsilane (12.8 g, 38.3 mmol) in methanol (150 mL) and CH_2Cl_2 (100 mL) was added a saturating amount of $K_2CO_3 \bullet H_2O$, and the suspension was vigorously stirred at rt for 5.5 h. The volatiles were removed by rotary evaporation and the crude product was triturated with Et_2O (300 mL), dried over $MgSO_4$ and filtered over Celite. Following concentration to dryness, the crude product was isolated as an orange oil (10.9 g, quant.) and carried as such to the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.27 (2H, m), 7.05 (1H, dd, *J* = 8.1, 8.0 Hz), 4.95 (2H, s), 3.72 (3H, s), 2.95 (2H, t, *J* = 8.0 Hz), 2.49 (2H, dt, *J* = 7.5, 2.6 Hz), 1.96 (1H, t, *J* = 2.6 Hz), 0.28 (9H, s).



2-(3-Butynyl)-3-trimethylsilylphenol

To a solution of MOM ether (10.1 g, 38.3 mmol) in MeOH (100 mL) and acetone (100 mL) was added 2 mL of 37% HCl. The resulting solution was left to stir at rt for 15 h, after which TLC analysis indicated the presence of desilylated phenol and desired compound. The reaction was adjusted to pH ~ 8 by the careful addition of $NaHCO_3$ solution. The volatiles were removed by rotary evaporation and the aqueous layer was extracted with Et_2O (3X). The combined organics were washed with brine (1X) and dried over $MgSO_4$, filtered and concentrated to dryness. ^{1}H NMR Analysis of the crude mixture indicated a ratio of 50:50 between desilylated and silylated material. Following purification by column chromatography (3% EtOAc/PE), the title phenol was obtained as a light yellow oil (1.7 g, 42%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (1H, dd, *J* = 7.0, 1.4 Hz), 7.13 (1H, dd, *J* = 7.3, 1.2 Hz), 6.90 (1H, dd, *J* =

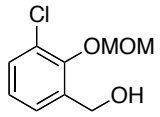
7.3, 7.3 H), 5.35 (1H, br s), 2.83 (2H, t, *J* = 7.0 Hz), 2.49 (2H, dt, *J* = 6.9, 2.5 Hz), 2.04 (1H, t, *J* = 2.5 Hz), 0.30 (9H, s).



[2-(3-Butynyl)-6-(trimethylsilyl)]phenyl trifluoromethanesulfonate 157e

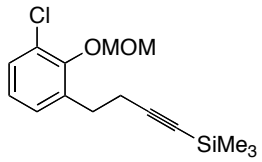
Obtained via General Procedure 3.6.2.5, and purified by flash chromatography (10% CH_2Cl_2/PE) to afford the title compound as a clear colourless liquid; R_f 0.21 (5% CH_2Cl_2/PE); IR (neat) 3309, 2122, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46-7.30 (3H, m), 3.00 (2H, t, *J* = 7.5 Hz), 2.50 (2H, dt, *J* = 7.5, 2.7 Hz), 1.98 (1H, t, *J* = 2.7 Hz), 0.40 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 135.4, 135.2, 133.7, 132.5, 128.1, 119.6 (q, $J_{C\text{-}F}$ = 310 Hz), 82.9, 69.2, 29.4, 19.0, 0.1; Anal. Calcd. for $C_{14}H_{17}F_3O_3SSi$: C, 47.99; H, 4.89. Found: C, 48.29; H, 4.87.

3.6.3.5 Synthesis of 2-(3-Butynyl)-6-chlorophenyl Trifluoromethanesulfonate 157f



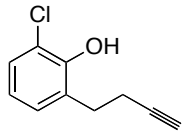
3-Chloro-2-methoxymethoxybenzyl alcohol

Obtained by reduction of the known aldehyde[204] (8.1 g, 46.9 mmol) following General Procedure 3.6.2.1 to furnish the alcohol as a yellow oil (7.6 g, 80%) after column chromatography (10% then 33% EtOAc/PE). ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (1H, dd, *J* = 7.9, 1.5 Hz), 7.29 (1H, dd, *J* = 7.6, 1.6 Hz), 7.10 (1H, dd, *J* = 7.8, 7.8 Hz), 5.14 (2H, s), 4.65 (2H, s), 3.64 (3H, s), 3.10 (1H, br s).



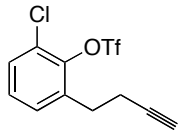
4-[(3-Chloro-2-methoxymethoxyphenyl)butynyl]trimethylsilane

Synthesised following General Procedure 3.6.2.2 using the alcohol (7.6 g, 37.5 mmol) to give the title alkynylsilane (9.8 g, 88%) following column chromatography (5% EtOAc/PE) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.25 (1H, m), 7.14 (1H, d, *J* = 7.4 Hz), 6.99 (1H, dd, *J* = 7.8, 7.8 Hz), 5.10 (2H, s), 3.63 (3H, s), 2.93 (2H, t, *J* = 7.6 Hz), 2.53 (2H, t, *J* = 7.5 Hz), 0.13 (9H, s).



2-(3-Butynyl)-6-chlorophenol

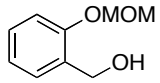
The TMS-alkyne (9.8 g, 33.0 mmol) was successively deprotected following General Procedure 3.6.2.3 and 3.6.2.4, without intermediate purification, to furnish the title phenol (4.73 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (1H, dd, *J* = 8.1, 1.1 Hz), 7.07 (1H, d, *J* = 7.3 Hz), 6.79 (1H, dd, *J* = 7.8, 7.8 Hz), 5.60 (1H, br s), 2.88 (2H, t, *J* = 7.4 Hz), 2.50 (2H, dt, *J* = 7.6, 2.6), 1.94 (1H, t, *J* = 2.6 Hz).



2-(3-Butynyl)-6-chlorophenyl trifluoromethanesulfonate 157f

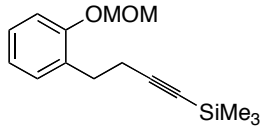
Following General Procedure 3.6.2.5, the title compound was obtained as a light yellow oil in 88% yield after purification by flash chromatography (10% EtOAc/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (1H, dd, *J* = 7.7, 1.9 Hz), 7.33-7.22 (2H, m), 3.00 (2H, t, *J* = 7.3 Hz), 2.52 (2H, dt, *J* = 7.3, 2.5 Hz), 1.97 (1H, t, *J* = 2.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 135.9, 129.7, 129.6, 128.9, 127.8, 118.5 (q, $J_{C\text{-}F}$ = 319 Hz), 82.2, 69.8, 29.5, 18.7; HRMS (EI) Calcd. for $C_{11}H_8ClO_3F_3$: 311.9835. Found: 311.9829.

3.6.3.6 Synthesis of 2-(3-Butynyl)phenyl Trifluoromethanesulfonate 157g



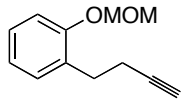
2-Methoxymethoxybenzyl alcohol

o-Salicylaldehyde (6.4 mL g; 60 mmol) and anhydrous K_2CO_3 (20.7 g, 150 mmol, 2.5 equiv) were slurried in DMF (75 mL) and cooled to 0 ºC. MOM-Cl (8.2 mL, 108 mmol, 1.8 equiv) was then added dropwise. The reaction was stirred for 3 h in the gradually warming ice-water bath. A further portion of MOM-Cl was added (2.0 mL) to drive the reaction to completion, whereupon the reaction mixture was poured into H_2O (250 mL), and the product was extracted with 3 125 mL portions of hexanes. The combined organics were washed with H_2O twice and brine (1X), dried over Na_2SO_4, filtered and concentrated by rotary evaporation. The title compound was obtained as a clear liquid that was taken as such into the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.59 (1H, s), 7.82 (1H, dd, *J* = 7.7, 1.8 Hz), 7.52 (1H, ddd, *J* = 8.5, 7.4, 1.9 Hz), 7.22 (1H, dd, *J* = 8.3, 7.9 Hz), 7.07 (1H, dd, *J* = 7.6, 7.5 Hz), 5.29 (2H, s), 3.51 (3H, s). Borohydride reduction of the benzaldehyde, after General Procedure 3.6.2.1 provided the title alcohol (8.7 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (1H, dd, *J* = 8.4, 1.4 Hz), 7.29-7.23 (1H, m), 7.10 (1H, d, *J* = 8.1 Hz), 7.01 (1H, dt, *J*= 7.4, 0.9 Hz), 5.24 (2H, s), 4.67 (2H, s), 3.49 (3H, s), 2.6-1.8 (1H, br s).



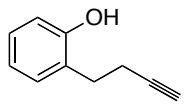
[4-(2-Methoxymethoxyphenyl)butyn-1-ynl]trimethylsilane

Following General Procedure 3.6.2.2 using 2-methoxymethoxybenzyl alcohol (8.79 g, 51.7 mmol), the title compound was obtained as a light yellow oil (9.5 g, 70%) following column chromatography (5% Et_2O/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (1H, d, *J* = 7.3 Hz), 7.14 (1H, d, *J* = 7.0 Hz), 7.04 (1H, d, *J* = 8.1 Hz), 6.91 (1H, dd, *J* = 7.7, 7.0 Hz), 5.33 (2H, s), 3.70 (3H, s), 2.85 (2H, t, *J* = 7.5 Hz), 2.48 (2H, t, *J* = 7.8 Hz), 0.12 (9H, s).



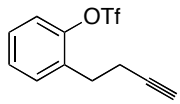
4-(2-Methoxymethoxyphenyl)but-1-yne

Protiodesilylation of the alkynylsilane (9.5 g, 36.2 mmol) was carried according to General Procedure 3.6.2.3 to furnish the terminal alkyne (4.7, 75%) after purification by flash chromatography (2% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (1H, d, *J* = 7.8 Hz), 7.15 (1H, d, *J* = 7.0 Hz), 7.05 (1H, d, *J* = 8.1 Hz), 6.93 (1H, dd, *J* = 7.8, 6.9 Hz), 5.19 (2H, s), 3.47 (3H, s), 2.87 (2H, t, *J* = 7.6 Hz), 2.47 (2H, dt, *J* = 7.8, 2.6 Hz), 1.95 (1H, t, *J* = 2.6 Hz).



2-(3-Butynyl)phenol

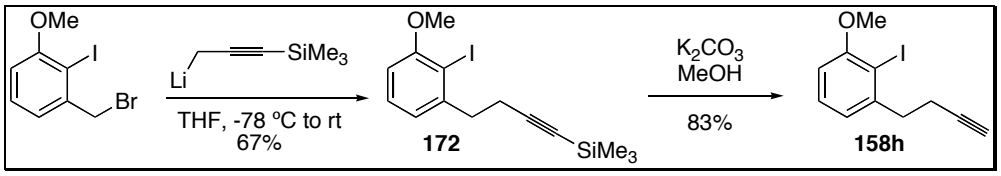
The title alcohol (2.2 g, 55%) was obtained following acetal hydrolysis as per General Procedure 3.6.2.4 following flash chromatography (5% then 10% EtOAc/hexanes) as a light orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (1H, dd, *J* = 8.6, 1.3 Hz), 7.11 (1H, dd, *J* = 7.7, 1.7 Hz), 6.88 (1H, ddd, *J* = 7.4, 7.4, 1.8 Hz), 6.78 (1H, d, *J* = 7.8 Hz), 5.09 (1H, br s), 2.86 (2H, t, *J* = 7.4 Hz), 2.52 (2H, dt, *J* = 7.3, 2.6 Hz), 2.00 (1H, t, *J* = 2 .6 Hz).

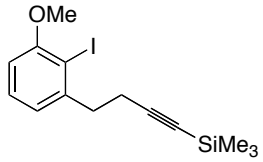


2-(3-Butynyl)phenyl trifluoromethanesulfonate

Obtained by triflation of the phenol (2.6 g, 17.8 mmol), following General Procedure 3.6.2.5, following flash chromatography (10% EtOAc/hexanes). 3.3 g, 80% yield; clear colourless liquid; R_f 0.26 (5% CH_2Cl_2/PE); IR (neat) 3303, 2120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.24 (4H, m), 2.97 (2H, t, *J* = 7.3 Hz), 2.52 (2H, dt, *J* = 7.3, 2.6 Hz), 1.97 (1H, t, *J* = 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 133.0, 131.5, 128.5, 128.4, 121.4, 118.6 (q, $J_{C\text{-}F}$ = 310 Hz), 82.7, 69.7, 29.0, 18.9.

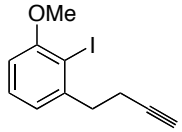
3.6.3.7 Synthesis of 1-(3-Butynyl)-2-iodo-3-methoxybenzene 158h





[4-(2-Iodo-3-methoxyphenyl)-1-butynyl]trimethylsilane 172

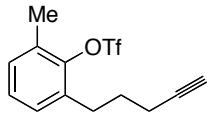
Obtained from the known benzylic bromide[162] in 67% yield following General Procedure 3.6.2.2 for the generation of the propynyllithium (1.05 equiv). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (1H, t, *J* = 7.9 Hz), 6.91 (1H, dd, *J* = 7.6, 1.3 Hz), 6.68 (1H, dd, *J* = 8.1, 1.3 Hz), 3.88 (3H, s), 3.01 (2H, t, *J* = 7.5 Hz), 2.51 (2H, t, *J* = 7.6 Hz), 0.14 (9H, s).



1-(3-Butynyl)-2-iodo-3-methoxybenzene 158h

Clear colourless oil; R_f 0.15 (5% CH_2Cl_2/PE); IR (neat): 3293, 2361 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (1H, app t, *J* = 7.8 Hz), 6.91 (1H, dd, *J* = 7.6, 1.1 Hz), 6.69 (1H, dd, *J* = 8.2, 1.1 Hz), 3.88 (3H, s), 3.03 (2H, t, *J* = 7.5 Hz), 2.50 (2H, dt, *J* = 7.5, 2.6 Hz), 1.99 (1H, t, *J* = 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1, 144.6, 128.9, 122.3, 108.9, 92.5, 83.3, 69.0, 56.5, 40.0, 19.0. HRMS Calcd. For $C_{11}H_{11}OI$: 285.9855. Found: 285.9861.

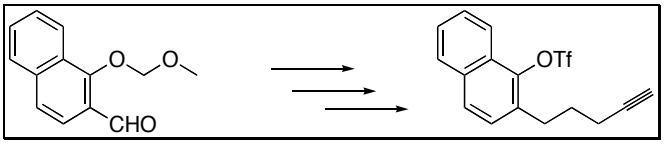
3.6.3.8 2-(4-Pentynyl)-6-methylphenyl Trifluoromethanesulfonate 157a

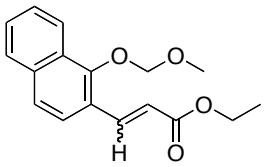


2-(4-Pentynyl)-6-methylphenyl trifluoromethanesulfonate 157a

Clear colourless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.03 (3H, m), 2.86 (2H, t, *J* = 7.6 Hz), 2.39 (3H, s), 2.21 (2H, dt, *J* = 7.5, 2.4 Hz), 1.99 (1H, t, *J* = 2.4 Hz), 1.84 (2H, quint, *J* = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 134.9, 131.8, 130.3, 128.9, 128.2, 118.6 (q, $J_{C\text{-}F}$ = 315 Hz), 83.5, 69.0, 29.3, 28.6, 18.0, 17.2, 17.2. Anal. Calcd. for $C_{13}H_{13}F_3O_3S$: C, 50.98; H, 4.28. Found: C, 50.68; H, 4.27.

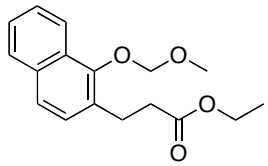
3.6.3.9 Synthesis of 2-(4-Pentynyl)naphthyl Trifluoromethanesulfonate 159a





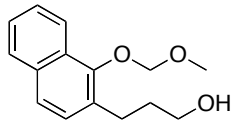
Ethyl (*E*)-3-(1-methoxymethoxy-2-naphthyl)-prop-2-enoate

Obtained as a 91:9 *E*:*Z* mixture in 87% yield using (carboethoxy)methylphosphonium bromide as Wittig salt and 1-methoxymethoxy-2-naphthaldehyde,[164] following General Procedure 3.6.2.7. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, peaks for the major diastereomer given): δ 8.28 (1H, d, *J* = 16.2 Hz), 8.17-8.14 (1H, m), 7.84 (1H, m), 7.68-7.50 (4H, m), 6.52 (1H, d, *J* = 16.2 Hz), 5.21 (2H, s), 4.29 (2H, q, *J* = 7.1 Hz), 3.74 (3H, s), 1.36 (3H, t, *J* = 7.2 Hz). The mixture of diastereomers was used as such in the next step. HRMS (EI) Calcd. for $C_{17}H_{18}O_4$: 286.1205. Found: 286.1192.



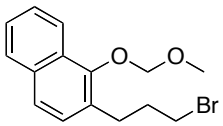
Ethyl 3-(1-methoxymethoxy-2-naphthyl)-propanoate

Obtained in 94% yield following General Procedure 3.6.2.8, using EtOH as solvent. Fragrant olive-green oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (1H, d, *J* = 8.6 Hz), 7.81 (1H, d, *J* = 8.7 Hz), 7.59 (1H, d, *J* = 8.4 Hz), 7.50 (1H, ddd, *J* = 8.2, 8.1, 1.4 Hz), 7.45 (1H, ddd, *J* = 7.9, 7.6, 1.3 Hz), 7.33 (1H, d, *J* = 8.4 Hz), 5.18 (2H, s), 4.15 (2H, q, *J* = 7.1 Hz), 3.70 (3H, s), 3.19 (2H, dd, *J* = 8.4, 7.7 Hz), 2.71 (2H, dd, *J* = 8.3, 7.7 Hz), 1.24 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 151.3, 133.9, 129.4, 128.3, 127.9, 127.7, 126.0, 125.6, 124.5, 122.1, 100.3, 60.3, 57.6, 35.2, 26.0, 14.2; HRMS (EI) Calcd. for $C_{17}H_{20}O_4$: 288.1362. Found: 288.1355.



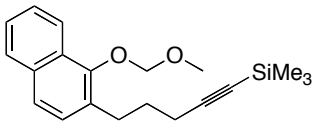
3-(1-Methoxymethoxy-2-naphthyl)-1-propanol

Obtained in 96% yield following General Procedure 3.6.2.9, as an orange syrupy oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (1H, d, *J* = 8.2 Hz), 7.81 (1H, d, *J* = 8.5 Hz), 7.61 (1H, d, *J* = 8.4 Hz), 7.51 (1H, ddd, *J* = 8.5, 8.0, 1.3 Hz), 7.45 (1H, ddd, *J* = 8.6, 8.3, 1.2 Hz), 7.33 (1H, d, *J* = 8.5 Hz), 5.18 (2H, s), 3.70 (3H, s), 3.62 (2H, br q), 2.98 (2H, t, *J* = 7.3 Hz), 2.09 (1H, br s), 2.00-1.91 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 133.7, 130.2, 128.2, 128.0, 127.9, 126.1, 125.5, 124.7, 122.0, 100.4, 61.5, 57.8, 33.3, 25.9; HRMS (EI) Calcd. for $C_{15}H_{18}O_3$: 246.1256. Found: 246.1254.

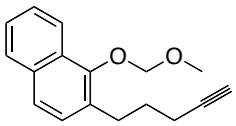


3-(1-Methoxymethoxy-2-naphthyl)-1-propyl bromide

Synthesised in 87% yield following General Procedure 3.6.2.10, as a clear colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (1H, d, *J* = 8.2 Hz), 7.82 (1H, d, *J* = 7.6 Hz), 7.60 (1H, d, *J* = 8.4 Hz), 7.51 (1H, ddd, *J* = 8.6, 8.4, 1.0 Hz), 7.45 (1H, dd, *J* = 8.7, 8.2 Hz), 7.33 (1H, d, *J* = 8.4 Hz), 5.17 (2H, s), 3.70 (3H, s), 3.47 (2H, t, *J* = 6.6 Hz), 3.02 (2H, t, *J* = 7.3 Hz), 2.27 (2H, dt, *J* = 7.6, 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 133.9, 129.4, 128.4, 128.0, 127.9, 126.1, 125.6, 124.5, 122.1, 100.3, 57.7, 33.6, 33.5, 29.0; HRMS (EI) Calcd. for $C_{15}H_{17}O_2Br$: 308.0412. Found: 308.0420.

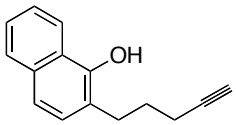


5-(1-Methoxymethoxy-2-naphthyl)-1-pentynyl(trimethyl)silane: Obtained in 81% yield following General Procedure 3.6.2.11, modified as follows: after completion of the TMS-ethynylation reaction, NH_4Cl was added, THF was removed under reduced pressure, and the mixture was extracted (3X) with 10% EtOAc/PE. The combined organic extracts were washed with brine (4X), dried (Na_2SO_4), filtered and concentrated to dryness. After purification by flash chromatography (5% EtOAc/PE), there was obtained the title compound as a light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (1H, d, *J* = 8.2 Hz), 7.81 (1H, d, *J* = 7.7 Hz), 7.59 (1H, d, *J* = 8.4 Hz), 7.50-7.44 (2H, m), 7.33 (1H, d, *J* = 8.4 Hz), 5.16 (2H, s), 3.70 (3H, s), 2.95 (2H, dd, *J* = 7.8, 7.7 Hz), 2.32 (2H, t, *J* = 7.1 Hz), 1.92 (2H, dt, *J* = 7.6, 7.2 Hz), 0.16 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 133.7, 130.4, 128.5, 127.8, 126.0, 125.5, 124.4, 122.2, 107.2, 100.3, 84.9, 68.6, 57.7, 29.5, 19.8, 0.17; HRMS (EI) Calcd. for $C_{20}H_{26}O_2Si$: 326.1702. Found: 326.1687.



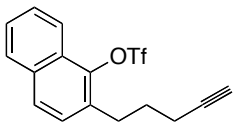
2-(4-Pentynyl)-1-methoxymethoxynaphthalene

The title compound was obtained in quantitative yield from 5-(1-Methoxymethoxy-2-naphthyl)-1-pentynyl(trimethyl)silane by K_2CO_3 in MeOH desilylation (General Procedure 3.6.2.3, 13 h, rt), as a light orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (1H, d, *J* = 8.2 Hz), 7.81 (1H, d, *J* = 7.5 Hz), 7.59 (1H, d, *J* = 8.4 Hz), 7.51 (1H, ddd, *J* = 7.9, 7.9, 1.0 Hz), 7.47-7.42 (1H, m), 7.33 (1H, d, *J* = 8.4 Hz), 5.16 (2H, s), 3.70 (3H, s), 2.97 (2H, dd, *J* = 7.9, 7.6 Hz), 2.28 (2H, dt, *J* = 7.0, 2.5 Hz), 2.00 (1H, t, *J* = 2.6 Hz), 1.96 (2H, dt, *J* = 7.7, 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 133.8, 130.3, 128.5, 128.1, 127.9, 126.0, 125.5, 124.4, 122.1, 100.3, 84.3, 68.6, 57.7, 29.5, 29.4, 18.3; HRMS (EI) Calcd. for $C_{17}H_{18}O_2$: 254.1307. Found: 254.1312.



2-(4-Pentynyl)-1-naphthalenol

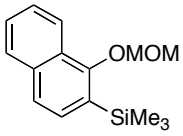
Obtained in quantitative yield from 2-(4-pentynyl)-1-methoxymethoxynaphthalene by acid hydrolysis following General Procedure 3.6.2.4, as an orange oil that solidified to light orange needles. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (1H, dd, *J* = 9.0, 1.6 Hz), 7.79 (1H, dd, *J* = 7.7, 1.9 Hz), 7.50 (1H, dt, *J* = 7.8, 1.9 Hz), 7.47 (1H, dd, *J* = 7.8, 1.6 Hz), 7.42 (1H, d, *J* = 8.4 Hz), 7.26 (1H, d, *J* = 8.4 Hz), 5.56 (1H, br, s), 2.95 (1H, t, *J* = 7.2 Hz), 2.27 (2H, dt, *J* = 6.6, 2.6 Hz), 2.16 (1H, t, *J* = 2.6 Hz), 1.95 (2H, quint, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 185.1, 150.8, 135.2, 133.7, 133.7, 132.3, 132.1, 126.6, 126.1, 83.3, 69.4, 28.7, 26.7, 18.1.



2-(4-Pentynyl)-1-naphthyl trifluoromethanesulfonate

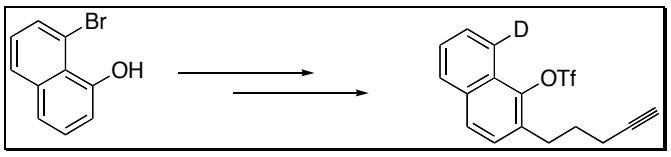
Obtained in 59% yield from the corresponding naphthol following General Procedure 3.6.2.5. Characterisation data were in agreement with those reported elsewhere.[177]

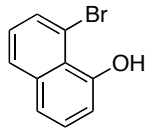
3.6.3.10 Synthesis of 8-Deuterio-2-(4-pentynyl)naphtyl Trifluoromethanesulfonate *d*-159a



Trimethyl(1-methoxymethoxynaphth-2-yl)silane 183

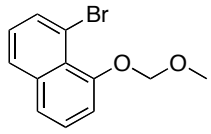
This procedure is based on that by Larock *et al.*[207] To a solution of MOM ether (7.83 g, 41.6 mmol, 1.0 equiv) in THF (200 mL) was added *n*-BuLi (2.4 M in hexanes, 20.9 mL, 50.1 mmol, 1.2 equiv) over 7 min while cooling the reaction by means of an ice-water bath. The resulting black suspension was allowed to reach rt and to stir for 1 h, whereupon it had turned to an olive green suspension. The reaction mixture was cooled back to 0 ºC, and freshly distilled Me_3SiCl (8.0 mL, 62.4 mmol, 1.5 equiv) was added dropwise. The reaction mixture was allowed to warm up to rt, stirred at that temperature for 30 min, and the resulting golden yellow solution was quenched with NH_4Cl (100 mL). Volatiles were removed under reduced pressure, and the aqueous layer was extracted (3X) with 25% EtOAc/hexanes. The combined organics were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated to dryness. Purification was done by short-path distillation under reduced pressure ($bp^{0.7\ mm\ Hg}$ = 115-135 ºC) to afford the title compound as a light yellow oil (9.25 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28-8.21 (1H, m), 7.87-7.79 (1H, m), 7.63 (1H, d, *J* = 8.1 Hz), 7.51 (1H, d, *J* = 8.4 Hz), 7.54-7.46 (2H, m), 5.17 (2H, s), 3.71 (3H, s), 0.41 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 136.0, 130.9, 127.8, 127.8, 126.5, 125.8, 123.8, 122.9, 100.8, 57.6, 0.00. LRMS (EI) Calcd. for $C_{15}H_{20}O_2Si$: 260. Found: 260 (M^+), 215 ($M\text{-}CH_2OCH_3^+$).





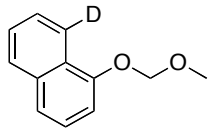
8-Bromo-1-naphthol[167]

Obtained as a crystalline white solid in 48% yield (3.26 g) by following the oxabicycle isomerisation literature procedure, then purifying by flash chromatography (5% EtOAc/PE). Mp (EtOAc/PE): 51.5-53.0 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (1H, s), 7.78 (1H, dd, *J* = 8.2, 0.9 Hz), 7.63 (1H, dd, *J* = 7.5, 1.0 Hz), 7.45-7.35 (2H, m), 7.22 (1H, t, *J* = 7.8 Hz), 7.08 (1H, dd, *J* 6.8, 2.1 Hz); ^{13}C NMR (JMOD 75 MHz, $CDCl_3$) δ 152.6, 137.0, 131.5, 129.3, 127.5, 125.9, 121.2, 120.5, 115.1, 113.2; HRMS (EI) Calcd. for $C_{10}H_7BrO$: 221.9680. Found: 221.9684.



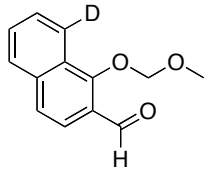
8-Bromo-1-methoxymethoxyaphthalene

Solid NaH (700 mg, 17.5 mmol, 60% in oil, 1.2 equiv) was washed free of oil with PE (3 times) and suspended in dry DMF (20 mL). To the cooled white slurry was added a solution of 8-bromo-1-naphthol (3.26 g, 14.6 mmol, 1.0 equiv) in dry DMF (6 mL then two 3-mL rinses) drop-wise via cannula. After hydrogen evolution had subsided, chloromethyl methyl ether (1.66 mL, 21.9 mmol, 1.5 equiv) was added at 0 ºC, and the resulting white slurry was allowed to reach rt and monitored by TLC. Upon completion, the mixture was quenched with 5% aq. NaOH solution (50 mL), diluted with water and extracted with 5% EtOAc/PE (3X). The organic phases were combined and washed (3X) with H_2O (3X), brine (1X) and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the crude oil was taken as such to the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (1H, dd, *J* = 7.5, 1.1 Hz), 7.75 (1H, dd, *J* 8.2, 0.8 Hz), 7.51 (1H, dd, *J* = 8.2, 0.7 Hz), 7.39 (1H, t, *J* = 7.9 Hz), 7.25-7.18 (2H, m), 5.33 (2H, s), 3.60 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 137.0, 133.1, 128.1, 126.5, 126.2, 124.0, 122.7, 116.5, 111.5, 95.1, 56.5; HRMS (EI) Calcd. for $C_{12}H_{11}BrO_2$: 265.9942. Found: 265.9938.



8-Deuterio-1-methoxymethoxynaphthalene

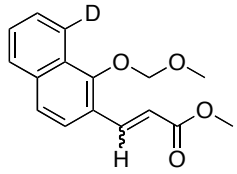
A solution of 8-bromo-1-methoxymethoxynaphthalene (14.6 mmol) in dry Et_2O (100 mL) was cooled to 0 ºC under Ar for the dropwise addition of a hexanes solution of *n*-BuLi (6.7 mL; 16.1 mmol; 1.1 equiv). After stirring at rt for 60 min (blue then light brown solution), the reaction was cooled back to 0 ºC and injected with 2.5 mL D_2O. The resulting light yellow solution was vigorously stirred for 16 h at rt then NH_4Cl was added, the layers separated, and the aqueous layer further extracted with Et_2O (1X). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. Following flash chromatography (5% Et_2O/PE), the title compound was obtained as a light yellow oil (2.0 g; 75% over 2 steps; 97%-D incorporation). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.84 (1H, m), 7.55-7.51 (3H, m), 7.42 (1H, t, J = 7.9 Hz), 7.14 (1H, d, J = 7.6 Hz), 5.43 (2H, s), 3.59 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 134.5, 127.5, 126.3, 125.8, 125.2, 121.6 (t, $J_{C\text{-}D}$ = 24.8 Hz), 121.3, 107.8, 94.7, 56.2; HRMS (EI) Calcd. for $C_{12}H_{11}DO_2$: 189.0900. Found: 189.0901.



8-Deuterio-1-methoxymethoxy-2-naphthaldehyde

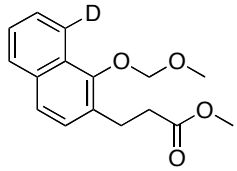
The MOM acetal (2.0 g, 10.6 mmol) was diluted in dry THF (50 mL) and cooled to 0 ºC under Ar. A hexanes solution of *n*-BuLi (5.3 mL, 12.7 mmol, 1.2 equiv) was injected slowly. The reaction was stirred at 0 ºC until an olive-green suspension was obtained, then at ambient temperature for 60 min, whereupon it was cooled back to 0 ºC. Dry DMF (1.5 mL, 21.2 mmol, 2.0 equiv) was then carefully added, the reaction was allowed to reach temperature and stirred for 20 min. Then, it was quenched carefully with NH_4Cl (75 mL) and further diluted with H_2O. The aqueous phase was extracted with Et_2O (3X). The combined organics were washed with

NH_4Cl (3X), and brine (1X), dried over $MgSO_4$ and concentrated to dryness. The crude mixture was purified by flash chromatography (5% then 15% EtOAc/PE) to provide the title compound as a yellow solid (1.43 g; 62%; 97%-D incorporation). Mp ($CHCl_3$): 48.0-49.0 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.5 (1H, s), 7.86 (1H, d, J = 8.6 Hz), 7.83 (1H, d, J = 8.1 Hz), 7.66-7.54 (3H, m), 5.26 (2H, s), 3.63 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.2, 159.3, 137.8, 129.2, 128.2, 127.8, 126.7, 124.8, 123.1 (t, $J_{C\text{-}D}$ = 24.9 Hz), 122.5, 101.7, 58.0; HRMS (EI) Calcd. for $C_{13}H_{11}DO_3$: 217.0849. Found: 217.0846.



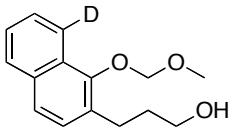
Methyl (*E*)-3-(8-deuterio-1-methoxymethoxy-2-naphthyl)-prop-2-enoate

Obtained as a 91:9 *E*:*Z* mixture using (carbomethoxy)methylphosphonium bromide as Wittig salt and 8-deuterio-1-methoxymethoxy-2-naphthaldehyde, following General Procedure 3.6.2.7. Clear yellow-greenish oil; ^{1}H NMR (300 MHz, $CDCl_3$, peaks for the major diastereomer reported) δ 8.29 (1H, d, J = 16.2 Hz), 7.84-7.50 (5H, m), 6.52 (1H, d, J = 16.2 Hz), 5.21 (2H, s), 3.84 (3H, s), 3.73 (3H, s); HRMS (EI) Calcd. for $C_{16}H_{15}DO_4$: 273.1111. Found: 273.1120.



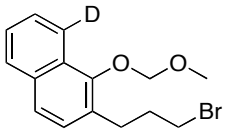
Methyl 3-(8-deuterio-1-methoxymethoxy-2-naphthyl)-propanoate

Synthesised following General Procedure 3.6.2.8 using EtOAc as solvent, and 4 h as reaction time, as a light yellow oil after purification over a short column of silica gel (100% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (1H, dd, J = 7.8, 1.5 Hz), 7.59 (1H, d, J = 8.4 Hz), 7.50-7.41 (2H, m), 7.32 (1H, d, J = 8.5 Hz), 5.18 (2H, s), 3.69 (3H, s), 3.20 (2H, dd, J = 8.5, 7.6 Hz), 2.73 (2H, dd, J = 8.4, 7.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 151.3, 133.9, 129.3, 128.3, 127.9, 127.7, 126.0, 125.6, 124.5, 121.8 (t, $J_{C\text{-}D}$ = 24.0 Hz), 100.3, 57.7, 51.6, 35.0, 26.0; HRMS (EI) Calcd. for $C_{16}H_{17}DO_4$: 275.1268. Found: 275.1262.



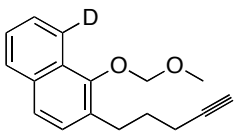
3-(8-Deuterio-1-methoxymethoxy-2-naphthyl)-1-propanol

Prepared from the corresponding methyl ester, following General Procedure 3.6.2.9 as a clear colourless oil (1.42 g; 88% yield over 3 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (1H, d, J = 7.9 Hz), 7.61 (1H, d, J = 8.4 Hz), 7.49 (1H, t, J = 6.5 Hz), 7.46-7.42 (1H, m), 7.32 (1H, d, J = 8.4 Hz), 5.18 (2H, s), 3.69 (3H, s), 3.62 (2H, t, J = 6.0 Hz), 2.98 (2H, t, J = 7.6 Hz), 2.17 (1H, br s), 1.95 (2H, quint, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 133.7, 130.2, 128.2, 128.0, 127.9, 125.9, 124.6, 121.7 (t, $J_{C\text{-}D}$ = 22.7 Hz), 100.4, 61.6, 57.8, 33.3, 29.8, 26.0; HRMS (EI) Calcd. for $C_{15}H_{17}DO_3$: 247.1319. Found: 247.1327.



3-(8-Deuterio-1-methoxymethoxy-2-naphthyl)-1-propyl bromide

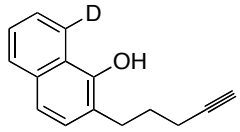
Obtained as a clear colourless oil following General Procedure 3.6.2.10, and taken as is to the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (1H, dd, J = 8.1, 0.9 Hz), 7.61(1H, d, J = 8.4 Hz), 7.53-7.47 (1H, m), 7.47 (1H, t, J = 7.9 Hz), 7.34 (1H, d, J = 8.4 Hz), 5.18 (2H, s), 3.71 (3H, s), 3.48 (2H, t, J = 6.6 Hz), 3.03 (2H, dd, J = 7.6 Hz), 2.28 (2H, quint, J = 6.7 Hz); ^{13}C NMR (JMOD, 125 MHz, $CDCl_3$) δ 151.2, 133.8, 129.4, 128.3, 128.0, 127.9, 126.0, 125.6, 124.5, 121.8 (t, $J_{C\text{-}D}$ = 24.6 Hz), 100.3, 57.7, 33.6, 33.5, 29.0; HRMS (EI) Calcd. for $C_{15}H_{16}DBrO_2$: 309.0473. Found: 309.0479.



1-(8-Deuterio-1-methoxymethoxy-2-naphthyl)-4-pentyne

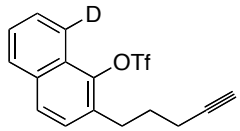
Obtained from the primary alkyl bromide following General Procedure 3.6.2.11, as a light yellow oil (0.49 g; 33% yield over 2 steps) following purification by flash chromatography

(5% EtOAc/PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (1H, dd, *J* = 7.9, 1.2 Hz), 7.59 (1H, d, *J* = 8.4 Hz), 7.51-7.46 (1H, m), 7.44 (1H, t, *J* = 7.2 Hz), 7.34 (1H, d, *J* = 8.4 Hz), 5.17 (2H, s), 3.70 (3H, s), 2.98 (2H, dd, *J* = 8.0, 7.6 Hz), 2.29 (2H, dt, *J* = 7.0, 2.6 Hz), 2.01 (1H, t, *J* = 2.6 Hz), 1.94 (2H, quint, *J* = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 133.8, 130.3, 128.4, 128.1, 127.9, 125.9, 125.5, 124.4, 121.9 (t, $J_{C\text{-}D}$ = 24.4 Hz), 100.3, 84.3, 68.6, 57.7, 29.5, 29.4, 18.3.



8-Deuterio-2-(4-pentyn-1-yl)-1-naphthol

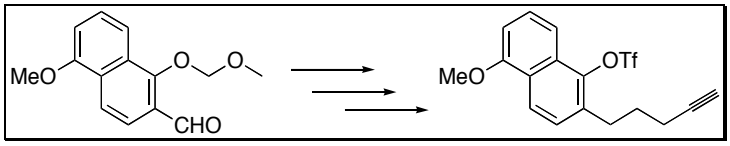
Obtained from the corresponding MOM acetal following General Procedure 3.6.2.4, as an orange oil that solidified to a yellowish solid (417 mg; quantitative). Mp ($CHCl_3$): 65.0-66.0 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (1H, d, *J* = 7.9 Hz), 7.49-7.46 (1H, m), 7.45 (1H, t, *J* = 7.9 Hz), 7.40 (1H, d, *J* = 8.4 Hz), 7.24 (1H, d, *J* = 8.4 Hz), 5.54 (1H, br s), 2.94 (2H, t, *J* = 7.2 Hz), 2.25 (2H, dt, *J* = 6.6, 2.5 Hz), 2.14 (1H, t, *J* = 2.5 Hz), 1.92 (2H, quint, *J* = 6.9 Hz).

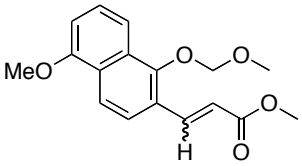


8-Deuterio-2-(4-pentyn-1-yl)-1-naphthalenyl trifluoromethanesulfonate d^{8}**-159a**

Triflation of the corresponding naphthalenol (417 mg; 1.97 mmol), according to General Procedure 3.6.2.5, followed by purification by column chromatography (2% Et_2O/PE) afforded the title compound as a clear colourless oil (453 mg; 67%), which solidified to yellow needles below 20 ºC; IR (neat) 3306, 2120, 1955 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (0.04H, d, *J* = 8.6 Hz), 7.85 (1H, d, *J* = 8.5 Hz), 7.81 (1H, dd, *J* = 8.1, 0.8 Hz), 7.59 (1H, d, *J* = 6.7 Hz), 7.54 (1H, dd, *J* = 8.1, 7.0 Hz), 7.41 (1H, d, *J* = 8.5 Hz), 3.02 (2H, dd, *J* = 7.8, 7.8 Hz), 2.25 (2H, dt, *J* = 7.0, 2.6 Hz), 2.00 (1H, t, *J* = 2.6 Hz), 1.93 (2H, dt, *J* = 7.9, 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.3, 133.7, 132.0, 128.6, 127.8, 127.7, 127.6, 127.1, 126.6, 121.3 (trace, residual C^{8}-H), 121.0 (t, $C_{Ar}D$, $J_{C\text{-}D}$ = 24 Hz), 118.8 (q, CF_3, $J_{C\text{-}F}$ = 318 Hz), 83.4, 69.1, 29.4, 28.7, 18.1. HRMS (EI) Calcd. for $C_{16}H_{12}DF_3O_3S$: 343.0600. Found: 343.0590.

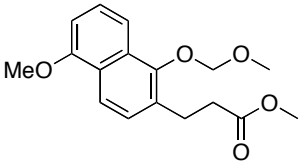
3.6.3.11 Synthesis of 5-Methoxy-2-(4-Pentynyl)naphtyl Trifluoromethanesulfonate 159b





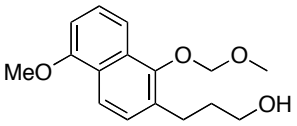
Methyl (*E*)-3-(5-methoxy-1-methoxymethoxy-2-naphthyl)-prop-2-enoate

Obtained as a 87:13 *E*:*Z* mixture from the known 5-methoxy-1-(methoxymethoxy)-2-naphthaldehyde,[208] following General Procedure 3.6.2.7; the mixture of diastereomers was carried on to the next step. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, peaks for the major diastereomer reported): δ 8.28 (1H, d, *J* = 16.2 Hz), 8.04 (1H, d, *J* = 9.0 Hz), 7.71 (1H, d, *J* = 8.5 Hz), 7.62 (1H, d, *J* = 8.9 Hz), 7.45 (1H, t, *J* = 8.2 Hz), 6.88 (1H, d, *J* = 7.8 Hz), 6.53 (1H, d, *J* = 16.2 Hz), 5.18 (2H, s), 4.00 (3H, s), 3.83 (3H, s), 3.72 (3H, s). HRMS (EI) Calcd. for $C_{17}H_{18}O_5$: 302.1154. Found: 302.1145.



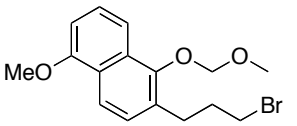
Methyl 3-(5-methoxy-1-methoxymethoxy-2-naphthyl)-propanoate

Obtained in 97% yield after purification over a short column of silica gel (100% EtOAc) over two steps following General Procedure 3.6.2.8, using MeOH as solvent. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (1H, d, *J* = 8.7 Hz), 7.60 (1H, d, *J* = 8.5 Hz), 7.40 (1H, t, *J* = 8.0 Hz), 7.30 (1H, d, *J* = 8.7 Hz), 6.79 (1H, d, *J* = 7.7 Hz), 5.15 (2H, s), 3.99 (3H, s), 3.68 (3H, s), 3.18 (2H, dd, *J* = 8.3, 7.8 Hz), 2.72 (2H, dd, *J* = 8.4, 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 155.7, 151.1, 130.0, 129.5, 126.9, 126.2, 126.0, 118.6, 114.3, 103.6, 100.3, 57.6, 55.5, 51.6, 34.9, 26.0; HRMS (EI) Calcd. for $C_{17}H_{20}O_5$: 304.1311. Found: 304.1316.



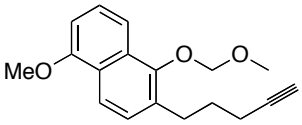
3-(5-Methoxy-1-methoxymethoxy-2-naphthyl)-1-propanol

Obtained following General Procedure 3.6.2.9, as a white solid; mp ($CHCl_3$) 60.5-63.5 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (1H, d, *J* = 8.7 Hz), 7.62 (1H, d, *J* = 8.5 Hz), 7.41 (1H, dd, *J* = 8.4, 8.1 Hz), 7.31 (1H, d, *J* = 8.7 Hz), 6.80 (1H, d, *J* = 7.6 Hz), 5.16 (2H, s), 3.99 (3H, s), 3.69 (3H, s), 3.60 (2H, dt, *J* = 6.0, 6.0 Hz); 2.98 (2H, t, *J* = 7.3 Hz), 2.06 (1H, t, *J* = 6.0 Hz), 1.95 (2H, dt, *J* = 7.2, 6.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 150.8, 130.8, 129.4, 127.2, 126.2, 125.8, 118.8, 114.3, 103.6, 100.5, 61.5, 57.8, 55.6, 33.3, 26.0; HRMS (EI) Calcd. for $C_{16}H_{20}O_4$: 276.1362. Found: 276.1362.



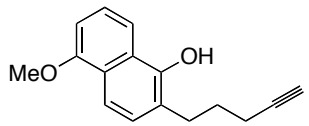
3-(5-Methoxy-1-methoxymethoxy-2-naphthyl)-1-bromopropane

Obtained following General Procedure 3.6.2.10, as a viscous colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (1H, d, *J* = 8.6 Hz), 7.65 (1H, d, *J* = 8.5 Hz), 7.43 (1H, t, *J* = 8.1 Hz), 7.36-7.31 (1H, m), 6.82 (1H, d, *J* = 7.6 Hz), 5.17 (2H, s), 4.01 (3H, s), 3.71 (3H, s), 3.48 (2H, t, *J* = 6.6 Hz), 3.03 (2H, dd, *J* = 7.8, 7.2 Hz), 2.28 (2H, dt, *J* = 7.6, 6.8 Hz); HRMS (EI) Calcd. for $C_{16}H_{19}O_3Br$: 338.0518. Found: 338.0521.



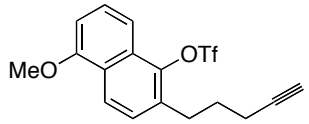
2-(4-Pentynyl)-5-methoxy-1-methoxymethoxynaphthalene

Obtained from the corresponding alkyl bromide following General Procedure 3.6.2.11 and carried as such into the hydrolysis reaction.



2-(4-Pentynyl)-5-methoxynaphthalen-1-ol

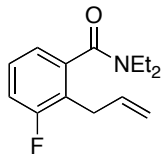
Obtained in 48% yield over five steps following General Procedure 3.6.2.4 from the corresponding MOM acetal, after flash chromatography (10% then 20% Et_2O/PE) as a white solid. Mp ($CHCl_3$) 89.0-89.5 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (1H, d, *J* = 8.5 Hz), 7.71 (1H, d, *J* = 8.4 Hz), 7.39 (1H, d, *J* = 7.9 Hz), 7.22 (1H, d, *J* = 8.6 Hz), 6.81 (1H, d, *J* = 7.7 Hz), 5.49 (1H, s), 3.99 (3H, s), 2.92 (2H, t, *J* = 7.2 Hz), 2.23 (2H, dt, *J* = 6.7, 2.3 Hz), 2.12 (1H, t, *J* = 2.3 Hz), 1.92 (2H, quint, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 148.5, 127.3, 125.5, 125.4, 120.7, 120.7, 114.4, 113.3, 103.7, 84.4, 69.6, 55.5, 28.5, 28.0, 17.4.



2-(4-Pentynyl)-5-methoxy-1-naphthalenyl trifluoromethanesulfonate 159b

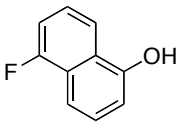
Obtained in 80% yield from the corresponding naphthol following General Procedure 3.6.2.5. Clear colourless viscous oil; IR (CH_2Cl_2) 3302, 2113 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (1H, d, *J* = 8.7 Hz), 7.66 (1H, d, *J* = 8.6 Hz), 7.55 (1H, t, *J* = 7.9 Hz), 7.39 (1H, d, *J* = 8.7 Hz), 6.86 (1H, d, *J* = 7.8 Hz), 4.00 (3H, s), 3.07-3.02 (2H, m), 2.28 (2H, dt, *J* = 7.0, 2.6 Hz), 2.03 (1H, t, *J* = 2.6 Hz), 1.95 (2H, dt, *J* = 7.5, 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 142.2, 132.5, 128.3, 128.0, 126.8, 125.9, 122.9, 118.9 (q, *J* = 318 Hz), 113.3, 104.6, 83.4, 69.1, 55.6, 29.4, 28.7, 18.1; HRMS (EI) Calcd. for $C_{17}H_{15}F_3O_4S$: 372.0643. Found: 372.0638.

3.6.3.12 Synthesis of 5-Fluoro-2-(4-Pentynyl)naphtyl Trifluoromethanesulfonate 159c



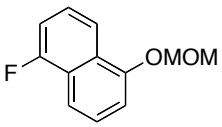
***N*,*N*-Diethyl 3-fluoro-2-(2-propenyl)benzamide**

The known *N*,*N*-diethyl 3-fluorobenzamide[209] was prepared (16.40 g, 92%) on 107 mmol scale, by the action of diethylamine upon the mixed anhydride of 3-fluorobenzoic and pivalic acid, and distilled under reduced pressure ($bp^{0.75\ mm\ Hg}$ = 90-91 ºC). This benzamide (9.76 g, 50.0 mmol, 1.0 equiv) was dissolved in THF (200 mL) and cooled to –78 ºC under Ar. To the clear solution were successively added TMEDA (8.3 mL, 55.0 mmol, 1.1 equiv) followed by a cyclohexane solution of *sec*-BuLi (1.4 M, 39.3 mL, 55.0 mmol, 1.1 equiv) over 10 min. The resulting mixture was maintained below –70 ºC while stirring for 50 min. An Et_2O solution of $MgBr_2$•OEt_2 (150 mmol, 3.0 equiv), prepared in the usual fashion,[210] was then added via cannula, and the resulting suspension was stirred outside the ethanol/dry ice bath for 15 min, cooled back to –78 ºC and treated with freshly distilled allyl bromide (10.8 mL, 125 mmol, 2.5 equiv). The reaction mixture was allowed to gradually reach rt while in the ethanol/dry ice bath, and stirred for 18 h. It was quenched with NH_4Cl (100 mL), most volatiles were evaporated under reduced pressure. The aqueous layer was extracted with EtOAc (3X), and the combined organics were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated to dryness. The crude product was purified by flash chromatography (25% EtOAc/PE) to afford the title compound as a light orange oil (10.0 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (1H, dt, *J* = 8.0, 5.3 Hz), 7.04 (1H, ddd, *J* = 8.2, 8.2, 1.1 Hz), 6.97 (1H, dd, *J* = 7.6, 0.9 Hz), 5.90 (1H, dddd, *J* = 16.7, 10.2, 6.4, 6.4 Hz), 5.08-4.98 (2H, m), 3.90-3.70 (1H, m), 3.40 (1H, d, *J* = 6.2 Hz), 3.40-3.25 (2H, m), 3.07 (2H, ddd, *J* = 9.9, 7.0, 3.0 Hz), 1.25 (3H, t, *J* = 7.1 Hz), 1.04 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1 (d, $J_{C\text{-}F}$ = 3.0 Hz), 161.3 (d, $J_{C\text{-}F}$ = 246 Hz), 139.0 (d, $J_{C\text{-}F}$ = 4.1 Hz), 135.0, 127.9 (d, $J_{C\text{-}F}$ = 8.6 Hz), 123.9 (d, $J_{C\text{-}F}$ = 17.3 Hz), 121.3 (d, $J_{C\text{-}F}$ = 3.5 Hz), 115.9, 115.6 (d, $J_{C\text{-}F}$ = 22.4 Hz), 43.0, 38.7, 30.7, 30.7, 13.8, 12.7.



5-Fluoro-1-naphthol[211]

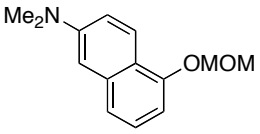
The procedure was adapted from that by Snieckus.[170] To a –78 ºC solution of the allyl benzamide just prepared (8.3 g, 35.3 mmol, 1.0 equiv) in THF (150 mL), was added an ether solution of MeLi (1.6 M, 26.5 mL, 42.3 mmol, 1.2 equiv) dropwise over 7 min. The dark reaction mixture was stirred at –78 ºC for 30 min, then allowed to reach rt and stirred at that temperature for 1 h. TLC analysis indicated complete starting material consumption, so the reaction was quenched with NH_4Cl and H_2O (1:1). The organic layer was separated and set aside. The aqueous layer was acidified to pH ~ 1 using 3N HCl and extracted with Et_2O (2X 100 mL) and CH_2Cl_2 (1X 100 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated to dryness. The crude product thus obtained had identical characterisation data to those published, and was used as such in the next step. Beige crystalline solid; mp (Et_2O/PE) 122.0-123.0 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (1H, d, *J* = 8.5 Hz), 7.69 (1H, d, *J* = 8.4 Hz), 7.44-7.34 (2H, m), 7.16 (1H, dd, *J* = 10.5, 7.7 Hz), 6.87 (1H, d, *J* = 7.5 Hz), 5.37 (1H, br s).



5-Fluoro-1-naphthyl methoxymethyl ether

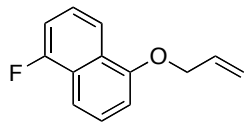
Sodium hydride (60% in oil, 1.06 g, 26.5 mmol, 1.3 equiv) was washed free of oil with PE (3X 15 mL) and suspended in 60 mL dry DMF, in a flame-dried round-bottom flask under N_2. This suspension was cooled to 0 ºC and treated portionwise with 5-fluoro-1-naphthol (3.3 g, 20 mmol, 1.0 equiv). After H_2 evolution had subsided, the resulting solution was treated dropwise with MOMCl (2.3 mL, 30.6 mmol, 1.5 equiv). After warming the reaction mixture to rt, the reaction was monitored by TLC; upon completion, it was quenched by the addition of 5% NaOH (100 mL) and extracted (3X) with 10% Et_2O/pentane. The combined organic layers were washed with 5% NaOH (1X) and brine (1X), dried (Na_2SO_4) and concentrated to dryness

(T_{bath} < 35 ºC). Following purification by flash chromatography (0% then 5% Et_2O/PE), the title compound was isolated as a clear colourless oil (3.89 g, 97%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (1H, d, *J* = 8.4 Hz)), 7.74 (1H, d, *J* = 8.4 Hz), 7.42 (1H, dt, *J* = 8.5, 8.4 Hz), 7.37 (1H, dt, *J* = 8.4, 8.4 Hz), 7.18 (1H, d, *J* = 8.6 Hz), 7.15 (1H, d, *J* = 8.1 Hz), 5.40 (2H, s), 3.55 (3H, s). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 158.7 (d, $J_{C\text{-}F}$ = 249 Hz), 128.9, 126.4, 125.0 (d, $J_{C\text{-}F}$ = 8.4 Hz), 117.8 (d, $J_{C\text{-}F}$ = 4.1 Hz), 113.9 (d, $J_{C\text{-}F}$ = 5.6 Hz), 110.7, 109.9 (d, $J_{C\text{-}F}$ = 19.7 Hz), 108.7, 105.0, 94.8, 56.3.



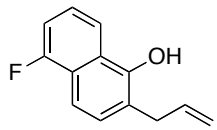
5-(Methoxymethoxy)-2-*N*,*N*-dimethylaminonaphthalene

To a solution of MOM ether (3.89 g, 19.8 mmol, 1.0 equiv) in Et_2O (40 mL) and TMEDA (3.6 mL, 23.8 mmol, 1.2 equiv), cooled to 0 ºC under Ar, was slowly added a hexanes solution of *n*-BuLi (9.9 mL, 2.4 M, 23.8 mmol, 1.2 equiv). After maintaining the black reaction mixture at 0 ºC for 15 min, it was allowed to stir at rt for 1.8 h, and cooled back to 0 ºC for the dropwise injection of DMF. The reaction was allowed to stir at rt for 6 h, and quenched with NH_4Cl. The aqueous layer was extracted (3X) with EtOAc. The combined organic extracts were washed successively with 5% HCl (2X) and brine (1X), dried ($MgSO_4$) and concentrated by rotary evaporation. Analysis by ^1H NMR of the crude mixture showed 54% of the title compound and 46% starting material. Following purification by column chromatography (5% then 10% EtOAc/PE), some starting material (912 mg, 23%) was recovered. Further elution provided the title compound (1.6 g, 29%, 52% brsm) as a fluorescent yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (1H, d, *J* = 9.3 Hz), 7.33-7.25 (2H, m), 7.15 (1H, d, *J* = 8.8 Hz), 6.91 (1H, br s), 6.82 (1H, d, *J* = 7.1 Hz), 5.37 (2H, s), 3.54 (3H, s), 3.06 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 148.9, 136.2, 126.3, 122.8, 119.9, 118.9, 115.5, 106.3, 104.4, 94.6, 56.2, 40.8. LRMS (EI) Calcd. for $C_{14}H_{17}NO_2$: 231. Found: 231 (M^+).



5-Fluoro-1-naphthyl 2-propenyl ether

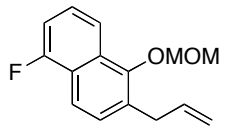
5-Fluoro-1-naphthol (35.3 mmol) was dissolved in HPLC-grade acetone (150 mL), treated successively with K_2CO_3 (9.75 g, 70.6 mmol, 2.0 equiv) and allyl bromide (6.1 mL, 70.6 mmol, 2.0 equiv) and brought to reflux under N_2. The resulting slurry was stirred at reflux temperature for 1.75 h, after which TLC indicated completion. The acetone solvent was removed *in vacuo*, and the residue was triturated with Et_2O (100 mL) and filtered through a pad of Celite. The filtrate was concentrated to dryness and purified by flash chromatography (5% EtOAc/PE) to afford the title ether as a light yellow oil (4.9 g, 69%).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (1H, d, *J* = 8.5 Hz), 7.69 (1H, d, *J* = 8.5 Hz), 7.42 (1H, dt, *J* = 8.4, 8.2 Hz), 7.38 (1H, t, *J* = 8.2 Hz), 717 (1H, ddd, *J* = 10.6, 7.7, 0.8 Hz), 6.87 (1H, d, *J* = 7.7 Hz), 6.18 (1H, dddd, *J* = 17.2, 10.4, 5.3, 5.2 Hz), 5.53 (1H, ddd, *J* = 17.2, 1.6, 1.5 Hz), 5.36 (1H, ddd, *J* = 10.5, 1.4, 1.4 Hz), 4.73 (2H, dt, *J* = 5.1, 1.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6 (d, $J_{C\text{-}F}$ = 249 Hz), 154.1 (d, $J_{C\text{-}F}$ = 4.1 Hz), 133.0, 126.3, 126.2, 124.8 (d, $J_{C\text{-}F}$ = 17.3 Hz), 124.7 (d, $J_{C\text{-}F}$ = 8.3 Hz), 118.0 (d, $J_{C\text{-}F}$ = 4.1 Hz), 117.5, 112.7 (d, $J_{C\text{-}F}$ = 5.7 Hz), 110.1 (d, $J_{C\text{-}F}$ = 19.7 Hz), 105.9, 69.0.



5-Fluoro-2-(2-propenyl)-1-naphthol

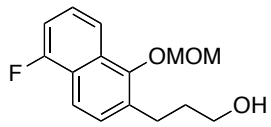
The allyl ether (4.9 g, 24.4 mmol) was dissolved in dry DMF (50 mL), and brought to reflux under N_2. After 6 h at that temperature, the reaction mixture was cooled down to rt. The solvent was removed by rotary evaporation (0.5 mm Hg, 50 ºC bath) then the crude oil was purified by flash chromatography (5 then 10% EtOAc/hexanes) to afford the rearranged product (4.5 g, 92%) as an orange liquid that crystallised upon standing. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (1H, d, *J* = 8.5 Hz), 7.66 (1H, d, *J* = 8.5 Hz), 7.38 (1H, dt, *J* = 8.1, 5.5 Hz), 7.28 (1H, d, *J* = 8.5 Hz), 7.13 (1H, dd, *J* = 10.7, 7.6 Hz), 6.08 (1H, dddd, *J* = 17.5, 9.8, 6.2, 6.2 Hz), 5.62 (1H, br s), 5.32-5.23 (2H, m), 3.59 (2H, dt, *J* = 6.2, 1.5 Hz); ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 158.7

(d, $J_{C\text{-}F}$ = 249 Hz), 149.6, 135.8, 128.8 (d, $J_{C\text{-}F}$ = 1.0 Hz), 126.41 (d, $J_{C\text{-}F}$ = 8.5 Hz), 125.0 (d, $J_{C\text{-}F}$ = 8.4 Hz), 124.2 (d, $J_{C\text{-}F}$ = 18.6 Hz), 118.8, 117.3 (d, $J_{C\text{-}F}$ = 4.4 Hz), 117.3, 112.9 (d, $J_{C\text{-}F}$ = 5.5 Hz), 109.3 (d, $J_{C\text{-}F}$ = 19.6 Hz), 35.8.



5-Fluoro-2-(2-propenyl)-1-naphthyl methoxymethyl ether

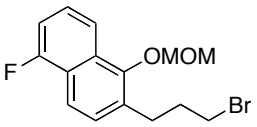
NaH (60% in oil, 1.22 g, 31 mmol, 1.4 equiv) was washed free of oil with PE (3X 15 mL) and was then suspended in dry DMF (60 mL) under N_2. To the cooled suspension (0 ºC) was added the naphthol derivative (4.4 g, 22 mmol, 1.0 equiv) portionwise as a solid. After H_2 evolution had subsided, the green solution was stirred for a further 15 min, cooled to 0 ºC and treated with MOMCl (2.5 mL, 33 mmol, 1.5 equiv) dropwise. The cream-coloured suspension was then stirred at 0 ºC for 1 h, whereupon TLC indicated reaction completion. The mixture was quenched with H_2O (50 mL) and the aqueous phase was extracted (3X) with 19:1 PE/Et_2O. The combined organics were successively washed with H_2O (3X) and brine (1X), dried over $MgSO_4$, filtered and concentrated to dryness. The MOM ether was used without further purification in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 7.8 Hz), 7.87 (1H, d, *J* = 8.0 Hz), 7.46-7.37 (2H, m), 7.14 (1H, dd, *J* = 10.6, 7.8 Hz), 6.04 (1H, dddd, *J* = 15.8, 9.2, 6.4, 6.3 Hz), 5.16 (2H, s), 5.15-5.13 (1H, m), 5.12-5.07 (1H, m), 3.70 (3H, s), 3.66 (2H, d, *J* = 6.4 Hz).



3-(5-Fluoro-1-methoxymethoxy-2-naphthyl)-1-propanol

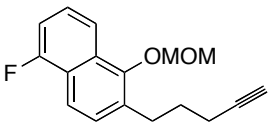
The alkene (21.8 mmol) was dissolved in THF (60 mL) and treated with BH_3•THF (1.0 M in THF, 24.0 mL, 24.0 mmol, 1.1 equiv) after which a mildly exothermic reaction was witnessed. After stirring the reaction for 1 h, TLC indicated completion, so it was quenched by the sequential, careful addition of 2.5 mL H_2O, 3.0 mL aqueous 3N NaOH and 3.0 mL 30% H_2O_2 solution. The mixture was allowed to stir for 1 h, whereupon water (50 mL) and brine (50 mL)

were added and the layers were separated. The organic phase was further extracted (2X) with EtOAc then the combined organics were washed with brine (1X), dried ($MgSO_4$), filtered and concentrated to dryness under reduced pressure. Following column chromatography (20 then 50% EtOAc/PE), the title alcohol was obtained (3.52 g, 61%) as a salmon-coloured oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (1H, d, *J* = 8.9 Hz), 7.82 (1H, d, *J* = 8.9 Hz), 7.45-7.37 (2H, m), 7.11 (1H, dd, *J* = 10.4, 8.1 Hz), 5.16 (2H, s), 3.69 (3H, s), 3.62 (2H, t, *J* = 6.0 Hz), 2.98 (2H, t, *J* = 7.5 Hz), 2.15 (1H, br s), 1.95 (2H, dt, *J* = 7.1, 6.2 Hz); ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 159.0 (d, $J_{C\text{-}F}$ = 249 Hz), 150.9 (d, $J_{C\text{-}F}$ = 4.1 Hz, 131.5, 130.0 (d, $J_{C\text{-}F}$ = 4.7 Hz), 128.5, 125.8 (d, $J_{C\text{-}F}$ = 8.5 Hz), 123.9 (d, $J_{C\text{-}F}$ = 17.1 Hz), 117.9 (d, $J_{C\text{-}F}$ = 4.1 Hz), 117.2 (d, $J_{C\text{-}F}$ = 5.5 Hz), 109.2 (d, $J_{C\text{-}F}$ = 19.7 Hz), 100.5, 61.6, 57.8, 33.2, 26.1.



3-(5-Fluoro-1-methoxymethoxy-2-naphthyl)-1-bromopropane

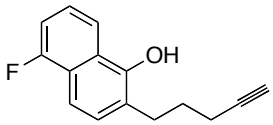
Bromination was conducted after General Procedure 3.6.2.10 using the alcohol (3.52 g, 13.3 mmol), to afford the title bromide as a light yellow liquid that was utilised as such in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (1H, d, *J* = 8.5 Hz), 7.83 (1H, d, *J* = 8.5 Hz), 7.42 (1H, dt, *J* = 7.9, 5.5 Hz), 7.39 (1H, d, *J* = 8.6 Hz), 7.11 (1H, dd, *J* = 10.4, 7.8 Hz), 5.16 (2H, s), 3.70 (3H, s), 3.46 (2H, t, *J* = 6.6 Hz), 3.05-2.98 (2H, m), 2.26 (2H, dt, *J*= 7.1, 6.6 Hz).



5-(5-Fluoro-1-methoxymethoxy-2-naphthyl)-1-pentyne

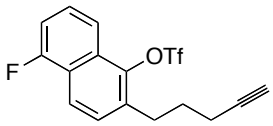
Following General Procedure 3.6.2.11 using the propyl bromide just prepared (13.3 mmol), the title alkyne was obtained after purification by column chromatography (2.5% EtOAc/PE) as a clear colourless oil (2.6 g, 72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (1H, d, *J* = 8.5 Hz), 7.84 (1H, d, *J* = 8.5 Hz), 7.41 (1H, dd, *J* = 7.7, 5.5 Hz), 7.40 (1H, d, *J* = 8.6 Hz), 7.11 (1H, ddd, *J* = 10.5, 7.6, 0.7 Hz), 5.15 (2H, s), 3.69 (3H, s), 2.98 (2H, dd, *J* = 7.7, 7.4 Hz), 2.28 (2H, dt, *J* = 7.0, 2.6 Hz), 2.02 (1H, t, *J* = 2.6 Hz), 1.93 (2H, dt, *J* = 7.7, 7.0 Hz); ^{13}C NMR (125 MHz,

JMOD, $CDCl_3$) δ 159.0 (d, $J_{C\text{-}F}$ = 250 Hz), 151.0 (d, $J_{C\text{-}F}$ = 4.0 Hz), 131.5, 130.2 (d, $J_{C\text{-}F}$ = 4.8 Hz), 128.5, 125.7 (d, $J_{C\text{-}F}$ = 8.6 Hz), 123.9 (d, $J_{C\text{-}F}$ = 16.9 Hz), 118.0 (d, $J_{C\text{-}F}$ = 4.3 Hz), 117.0 (d, $J_{C\text{-}F}$ = 5.4 Hz), 109.1 (d, $J_{C\text{-}F}$ = 19.4 Hz), 100.4, 84.2, 68.8, 57.8, 29.4, 29.3, 18.3.



2-(4-Pentynyl)-5-fluoro-1-naphthol

The title compound was obtained by deprotection of the corresponding MOM ether (2.6 g, 9.55 mmol) following General Procedure 3.6.2.4, as an off-white solid (2.08 g, 95%) that was used as is in the triflation step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (1H, d, *J* = 8.5 Hz), 7.65 (1H, d, *J* = 8.6 Hz), 7.39 (1H, dt, *J* = 7.7, 5.5 Hz), 7.29 (1H, d, *J* = 8.6 Hz), 7.11 (1H, ddd, *J* = 10.6, 7.6, 0.8 Hz), 5.61 (1H, br s), 2.94 (2H, t, *J* = 7.2 Hz), 2.25 (2H, dt, *J* = 6.6, 2.6 Hz), 2.16 (1H, t, *J* = 2.6 Hz), 1.93 (2H, quint, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 158.8 (d, $J_{C\text{-}F}$ = 248 Hz), 148.7 (d, $J_{C\text{-}F}$ = 4.4 Hz), 128.5, 126.2 (d, $J_{C\text{-}F}$ = 5.5 Hz), 125.0 (d, $J_{C\text{-}F}$ = 8.4 Hz), 123.6 (d, $J_{C\text{-}F}$ = 17.7 Hz), 120.9, 117.2 (d, $J_{C\text{-}F}$ = 4.0 Hz), 113.0 (d, $J_{C\text{-}F}$ = 5.5 Hz), 109.3 (d, $J_{C\text{-}F}$ = 19.8 Hz), 84.2, 69.9, 28.3, 27.9, 17.3.

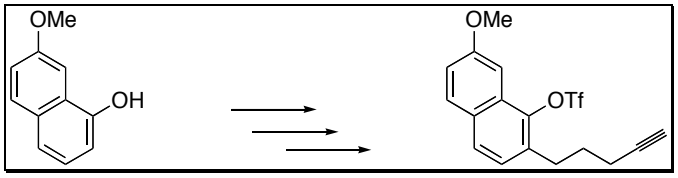


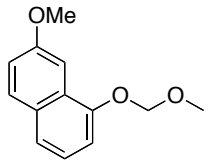
5-Fluoro-2-(4-Pentynyl)naphthyl trifluoromethanesulfonate 159c

Triflation was conducted using the previously prepared naphthol (1.00 g, 4.38 mmol) following General Procedure 3.6.2.5. The crude product was purified over a plug of silica gel (10% EtOAc/PE) to afford the title triflate as a clear colourless oil (1.51 g, 95%). IR (neat) 3307, 2120 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (1H, d, *J* = 8.7 Hz), 7.86 (1H, d, *J* = 8.6 Hz), 7.55 (1H, ddd, *J* = 8.6, 7.8, 5.4 Hz), 7.48 (1H, d, *J* = 8.7 Hz), 7.22 (1H, ddd, *J* = 10.1, 7.8, 0.7 Hz), 3.06 (2H, dd, *J* = 7.9, 7.8 Hz), 2.28 (2H, dt, *J* = 7.0, 2.6 Hz), 2.03 (1H, t, *J* = 2.6 Hz), 1.98-1.93 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5 (d, $J_{C\text{-}F}$ = 253 Hz), 142.0 (d, $J_{C\text{-}F}$ = 5.0 Hz), 133.3 (d, $J_{C\text{-}F}$ = 0.9 Hz), 128.7 (d, $J_{C\text{-}F}$ = 4.5 Hz), 128.2 (d, $J_{C\text{-}F}$ = 1.0 Hz), 127.7 (d, $J_{C\text{-}F}$ = 8.6 Hz), 124.1 (d, $J_{C\text{-}F}$ = 18.0 Hz), 121.4 (d, $J_{C\text{-}F}$ = 5.6 Hz), 118.7 (q, $J_{C\text{-}F}$ = 320 Hz), 117.2 (d,

$J_{C\text{-}F}$ = 4.1 Hz), 110.4 (d, $J_{C\text{-}F}$ = 19.7 Hz), 83.2, 69.3, 29.4, 28.6, 18.1. HRMS (EI) Calcd. for $C_{16}H_{12}F_4O_3S$: 360.0443. Found: 360.0449.

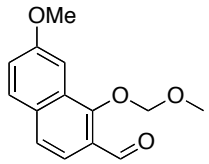
3.6.3.13 Synthesis of 7-Methoxy-2-(4-Pentynyl)naphthyl Trifluoromethanesulfonate 159d





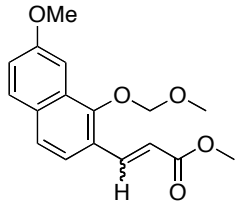
7-Methoxy-1-methoxymethoxynaphthalene

Solid NaH (2.38 g, 59.4 mmol, 60% in oil, 1.2 equiv) was washed free of oil with PE (3X) and suspended in dry DMF (80 mL). To the cooled white slurry was added a solution of 7-methoxy-1-naphthol[169] (8.62 g, 49.5 mmol, 1.0 equiv) in dry THF (20 mL then 2X 5-mL rinses), dropwise via cannula. After hydrogen evolution had subsided, chloromethyl methyl ether (5.6 mL, 74.2 mmol, 1.5 equiv) was added to the coloured solution at 0 ºC, and the resulting white slurry was allowed to reach rt and monitored by TLC. Upon completion, the mixture was quenched with 5% aq. NaOH solution (50 mL), diluted with water and extracted with PE (3X). The organic phases were combined and washed (3X) with 5% NaOH, H_2O (1X), brine (1X) and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the crude oil was passed through a short silica gel column (10% EtOAc/PE) to afford the title compound (10.5 g, quantitative) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (1H, d, J = 8.9 Hz), 7.55 (1H, d, J = 2.6 Hz), 7.43 (1H, d, J = 8.1 Hz), 7.24 (1H, t, J = 7.9 Hz), 7.18 (1H, dd, J = 8.9, 2.6 Hz), 7.10 (1H, d, J = 7.7 Hz), 5.40 (2H, s), 3.96 (3H, s), 3.57 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 152.0, 129.9, 129.1, 126.7, 123.3, 121.1, 118.9, 108.5, 100.1, 94.8, 56.1, 55.3; HRMS (EI) Calcd. for $C_{13}H_{14}O_3$: 218.0943. Found: 218.0939.



7-Methoxy-1-methoxymethoxy-2-naphthaldehyde

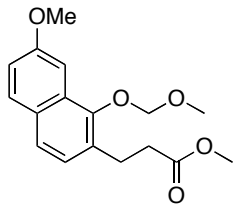
The MOM acetal (5.5 g, 27.2 mmol) was diluted in dry Et_2O (55 mL; 10% wt. with respect to the substrate) and cooled to 0 ºC under Ar. Dry TMEDA (9.0 mL, 59.8 mmol, 2.2 equiv) was injected via syringe, followed by dropwise addition of *n*-BuLi solution in hexanes (12.0 mL, 29.9 mmol, 1.1 equiv) over 5 min. After 5 min, whereupon a blood-red suspension was observed, the reaction was stirred at ambient temperature for 90 min, following which it was cooled back to 0 ºC. DMF (4.6 mL, 59.8 mmol, 2.2 equiv) was then carefully added, the reaction allowed to reach temperature and controlled by TLC. Upon completion, it was quenched carefully with NH_4Cl (50 mL), further diluted with H_2O and transferred to a separatory funnel. The organic layer was separated, and the aqueous phase was extracted twice with EtOAc. The combined organics were washed with 5% HCl (2X), water (1X) and brine, dried over $MgSO_4$ and concentrated to dryness. The resulting solids were triturated with warm (8:1 hexanes/EtOAc), cooled to 0 ºC and filtered off. After drying, the title compound was obtained as yellow crystals (5.61 g, 84%). Mp (EtOAc/hexanes): 59.0-59.5 ºC. ^{1}H NMR (300 MHz, acetone-d_6) δ 10.46 (1H, s), 7.91 (1H, d, *J* =8.9 Hz), 7.74-7.65 (2H, m), 7.63 (1H, d, 2.5 Hz), 7.34 (1H, dd, *J* = 8.9, 2.5 Hz), 5.36 (2H, s), 3.98 (3H, s), 3.66 (3H, s); ^{13}C NMR (75 MHz, acetone-d_6) δ 189.6, 158.6, 158.2, 133.2, 129.7, 129.4, 126.0, 124.4, 121.6, 119.8, 101.7, 101.6, 57.2, 54.8; HRMS (EI) Calcd. for $C_{14}H_{14}O_4$: 246.0892. Found: 246.0899.



Methyl (*E*)-3-(7-methoxy-1-methoxymethoxy-2-naphthyl)-prop-2-enoate

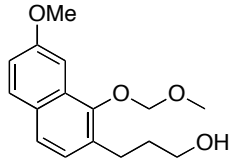
Obtained as a 89:11 *E*:*Z* mixture from 7-methoxy-1-(methoxymethoxy)-2-naphthaldehyde, following General Procedure 3.6.2.7; the mixture of diastereomers was carried on to the next

step. Fluorescent orange oil; ^{1}H NMR (300 MHz, $CDCl_3$, peaks for the major diastereomer given): δ 8.26 (1H, d, *J* =16.1 Hz), 7.72 (1H, d, *J* = 8.9 Hz), 7.58-7.47 (3H, m), 7.19 (1H, dd, *J* = 8.9, 2.5 Hz), 6.51 (1H, d, *J* = 16.2 Hz), 5.19 (2H, s), 3.95 (3H, s), 3.83 (3H, s), 3.73 (3H, 3). HRMS (EI) Calcd. for $C_{17}H_{18}O_5$: 302.1154. Found: 302.1160.



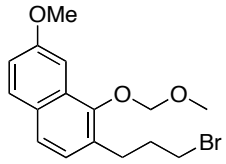
Methyl 3-(7-methoxy-1-methoxymethoxy-2-naphthyl)-propanoate

Synthesised following General Procedure 3.6.2.8, using MeOH as solvent; after purification over a short column of silica gel (100% EtOAc), the title ester was obtained as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (1H, d, *J* =8.9 Hz), 7.51 (1H, d, *J* = 8.4 Hz), 7.38 (1H, d, *J* = 2.3 Hz), 7.17 (1H, d, *J* = 8.4 Hz), 7.11 (1H, dd, *J* = 8.9, 2.5 Hz), 5.16 (2H, s), 3.94 (3H, s), 3.70 (3H, s), 3.69 (3H, s), 3.17 (2H, dd, *J* = 8.4, 7.7 Hz), 2.71 (2H, dd, *J* = 8.5, 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 158.0, 150.4, 129.8, 129.5, 129.4, 129.4, 125.2, 124.3, 118.3, 100.4, 100.0, 57.6, 55.2, 51.6, 34.9, 26.0; HRMS (EI) Calcd. for $C_{17}H_{20}O_5$: 304.1311. Found: 304.1317.



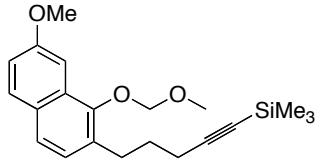
3-(7-Methoxy-1-methoxymethoxy-2-naphthyl)-1-propanol

Obtained following General Procedure 3.6.2.9, as a thick yellowish syrup (4.98 g, 79% yield) over the three steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (1H, d, *J* = 8.9 Hz), 7.52 (1H, d, *J* = 8.4 Hz), 7.39 (1H, d, *J* = 2.3 Hz), 7.17 (1H, d, *J* = 8.4 Hz), 7.11 (1H, dd, *J* = 8.9, 2.5 Hz), 5.16 (2H, s), 3.94 (3H, s), 3.71 (3H, s), 3.61 (2H, t, *J* = 6.1 Hz), 2.95 (2H, t, *J* = 7.4 Hz), 2.01 (1H, br s), 1.94 (2H, dt, *J* = 7.0, 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 150.2, 130.7, 129.5, 129.4, 129.2, 125.6, 124.4, 118.2, 100.5, 100.2, 61.5, 57.8, 55.2, 33.3, 26.1; HRMS (EI) Calcd. for $C_{16}H_{20}O_4$: 276.1362. Found: 276.1362.



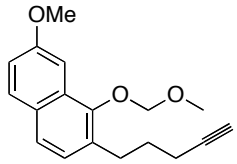
3-(7-Methoxy-1-methoxymethoxy-2-naphthyl)-1-bromopropane

Obtained following General Procedure 3.6.2.10, as a clear colourless liquid in 82% yield (5.0 g); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (1H, d, *J* = 8.9 Hz), 7.53 (1H, d, *J* = 8.3 Hz), 7.41 (1H, d, *J* = 2.4 Hz), 7.18 (1H, d, *J* = 8.4 Hz), 7.12 (1H, dd, *J* = 8.9, 2.6 Hz), 5.16 (2H, s), 3.94 (3H, s), 3.71 (3H, s), 3.46 (2H, t, *J* = 6.6 Hz), 3.00 (2H, m), 2.26 (2H, dt, *J* = 7.9, 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 150.4, 129.9, 129.5, 129.5, 129.3, 125.6, 124.3, 118.3, 100.5, 100.1, 57.7, 55.3, 33.6, 33.5, 29.0; HRMS (EI) Calcd. for $C_{16}H_{19}O_3Br$: 338.0518. Found: 338.0515.



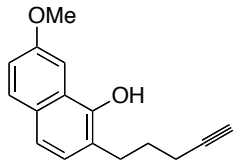
5-(7-Methoxy-1-methoxymethoxy-2-naphthyl)-1-pentynyl(trimethyl)silane

Obtained following General Procedure 3.6.2.11, modified as follows: after completion of the TMS-ethynylation reaction, NH_4Cl was added, THF was removed under reduced pressure, and the mixture was extracted (3X) with 10% EtOAc/PE. The combined organic extracts were washed (4X) with brine, dried (Na_2SO_4), filtered and concentrated to dryness. After purification by flash chromatography (3% then 10% EtOAc/PE), the title compound was obtained as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (1H, d, *J* = 8.9 Hz), 7.51 (1H, d, *J* = 8.4 Hz), 7.42 (1H, d, *J* = 2.4 Hz), 7.19 (1H, d, *J* = 8.3 Hz), 7.11 (1H, dd, *J* = 8.9, 2.5 Hz), 5.15 (2H, s), 3.94 (3H, s), 3.71 (3H, s), 2.92 (2H, dd, *J* = 7.9, 7.6 Hz), 2.31 (2H, t, *J* = 7.1 Hz), 1.91 (2H, dt, *J* = 7.8, 7.1 Hz), 0.16 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 150.3, 130.9, 129.5, 129.4, 129.2, 125.7, 124.1, 118.2, 107.2, 100.5, 100.1, 84.8, 57.6, 55.2, 29.6, 29.6, 19.8, 0.2; HRMS (EI) Calcd. for $C_{21}H_{28}O_3Si$: 356.1808. Found: 356.1808.



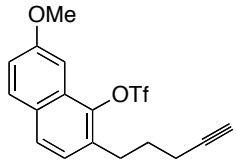
2-(4-Pentynyl)-5-methoxy-1-methoxymethoxynaphthalene

Prepared from the pentynylsilane via protiodesilylation by excess K_2CO_3 in MeOH (General Procedure 3.6.2.3, reflux, 90 min). The volatiles were removed by rotary evaporation, and the residue was slurried in ether (200 mL), filtered on Celite, then washed with $NaHCO_3$ (1X) and brine (1X), dried and concentrated under reduced pressure to afford the title compound as a red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (1H, d, *J* = 8.9 Hz), 7.52 (1H, d, *J* = 8.4 Hz), 7.42 (1H, d, *J* = 2.5 Hz), 7.18 (1H, d, *J* = 8.4 Hz), 7.11 (1H, dd, *J* = 8.9, 2.6 Hz), 5.15 (2H, s), 3.94 (3H, s), 3.71 (3H, s), 2.94 (2H, dd, *J* = 7.6, 6.2 Hz), 2.27 (2H, dt, *J* = 7.1, 2.6 Hz), 2.00 (1H, t, *J* = 2.6 Hz), 1.92 (2H, dt, *J* = 7.8, 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 150.3, 130.7, 129.5, 129.4, 129.2, 125.6, 124.1, 118.2, 100.5, 100.0, 84.3, 68.6, 57.6, 55.2, 29.4, 18.3; HRMS (EI) Calcd. for $C_{18}H_{20}O_3$: 284.1412. Found: 284.1411.



2-(4-Pentynyl)-7-methoxynaphthalen-1-ol

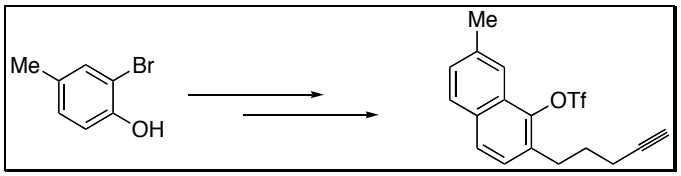
Obtained in 99% yield over three steps following General Procedure 3.6.2.4 from the corresponding MOM acetal as a red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (1H, d, *J* = 8.9 Hz), 7.48 (1H, d, *J* = 2.4 Hz), 7.35 (1H, d, *J* = 8.3 Hz), 7.12 (1H, dd, *J* = 8.9, 2.5 Hz), 7.10 (1H, d, *J* = 8.3 Hz), 5.52 (1H, br s), 3.95 (3H, s), 2.93 (2H, t, *J* = 7.1 Hz), 2.25 (2H, dt, *J* = 6.6, 2.6 Hz), 2.17 (1H, t, *J* = 2.6 Hz), 1.92 (2H, quint, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 147.9, 129.1, 128.9, 125.5, 120.3, 118.4, 99.9, 84.4, 69.8, 55.3, 28.5, 27.9, 17.4.

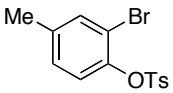


7-Methoxy-2-(4-pentynyl)-1-naphthalenyl trifluoromethanesulfonate 159d

Synthesised from the corresponding naphthol (2.25 g; 9.36 mmol) after General Procedure 3.6.2.5. Following flash chromatography (2.5% Et_2O/hexanes), the title compound was obtained as a light yellow oil (2.25 g; 64%); IR (neat) 3304, 2120 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (1H, d, *J* = 8.9 Hz), 7.72 (1H, d, *J* = 8.2 Hz), 7.39 (1H, d, *J* = 2.2 Hz), 7.26 (1H, d, *J* = 8.4 Hz), 7.18 (1H, dd, *J* = 9.0 Hz, 2.4 Hz), 3.95 (3H, s), 3.05-3.02 (2H, m), 2.28 (2H, dt, *J* = 7.0, 2.6 Hz), 2.04 (1H, t, *J* = 2.6 Hz), 1.95 (2H, dt, *J* = 7.5, 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 141.8, 132.5, 129.4, 129.2, 128.4, 128.2, 125.2, 119.7, 118.7 (q, $J_{C\text{-}F}$ = 318 Hz), 99.6, 83.5, 69.1, 55.3, 29.4, 28.7, 18.1; HRMS (EI) Calcd. for $C_{17}H_{15}F_3O_4S$: 372.0643. Found: 372.0645.

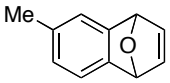
3.6.3.14 Synthesis of 7-Methyl-2-(4-Pentynyl)naphtyl Trifluoromethanesulfonate 159e





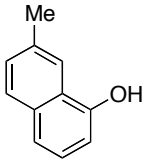
2-Bromo-4-methyl-1-tosylate[212]

Prepared according to the literature procedure on 100 mmol scale, recrystallised from boiling EtOAc, to obtain the title compound as white sticks (29.94 g, 88%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (2H, d, *J* = 8.3 Hz), 7.33 (1H, s), 7.32 (2H, d, *J* = 8.0 Hz), 7.20 (1H, d, *J* = 8.4 Hz), 7.07 (1H, dd, *J* = 8.3, 1.8 Hz), 2.46 (3H, s), 2.31 (3H, s); ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 145.5, 144.7, 138.4, 134.1, 132.8, 129.7, 129.1, 128.7, 123.6, 116.1, 21.7, 20.6.



6-Methyl-1,4-epoxy-1,4-dihydronaphthalene[213]

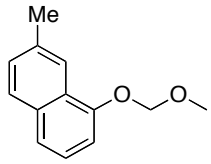
A solution of bromotosylate (6.82 g; 20.0 mmol) in THF (150 mL) and furan (14.5 mL; 200 mmol; 10.0 equiv) was cooled to –78 ºC under argon. The resulting white suspension was treated with *n*-BuLi (2.4 M in hexanes; 9.2 mL; 22.0 mmol; 1.1 equiv) over 5 min, left to react at that temperature for 15 min then allowed to reach rt. After 2 h (TLC monitoring), the brown reaction solution had attained completion, and was quenched with $NaHCO_3$, followed by removal of the volatiles by rotary evaporation. The aqueous layer was extracted (3X) with Et_2O, the combined organics were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated to dryness. Purification was effected by first eluting through a plug of silica (20% Et_2O/PE) and concentrating the filtrate to dryness, followed by flash chromatography (0% then 15% PhMe/PE) to afford the title compound as a tan oil (2.24 g; 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (1H, d, *J* = 7.8 Hz), 7.10 (1H, s), 7.04-6.99 (2H, m), 6.77 (1H, d, *J* = 7.2 Hz), 5.78 (2H, d, *J* = 4.6 Hz), 2.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 146.0, 143.2, 142.7, 134.7, 125.0, 121.6, 119.9, 82.3, 82.2, 21.3; HRMS (EI) Calcd. for $C_{11}H_{10}O$: 158.0732. Found: 158.0736.



7-Methyl-1-naphthol[171]

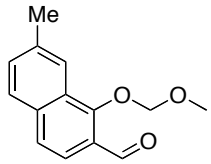
The literature procedure was modified such that the crude mixture of regioisomers was slightly bettered. Isomerisation was performed as described by Gil and co-workers, in MeOH (HPLC grade) at 40 ºC for 16 h. The crude 74:26 mixture of 7- to 6-methyl regioisomers was improved to 92:8 by repeated triturations with warm PE, to afford 4.24 g (57%) of the title compound as off-white crystals. Peaks for the major regioisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (1H, s), 7.73 (1H, d, *J* = 8.4 Hz), 7.41 (1H, d, 8.3 Hz), 7.33 (1H, dd, *J* = 8.4, 1.6 Hz), 7.25 (1H, dd, *J* = 7.6, 1.8 Hz), 6.79 (1H, d, *J* = 7.7 Hz), 7.14 (1H, br s), 2.54 (3H, s); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 150.8, 135.0, 133.0, 128.7, 127.6, 124.8, 124.3, 120.5, 120.3, 108.7, 21.9; HRMS (EI) Calcd. for $C_{11}H_{10}O$: 158.0732. Found: 158.0731.



7-Methyl-1-methoxymethoxynaphthalene

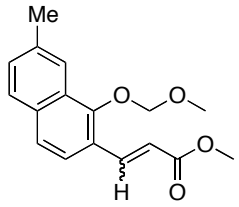
Solid NaH (1.52 g, 37.9 mmol, 60% in oil, 1.2 equiv) was washed free of oil with PE (3 times) and suspended in dry DMF (80 mL). To the cooled white slurry was added a solution of 7-methyl-1-naphthol (4.99 g, 31.5 mmol, 1.0 equiv) in dry DMF (10 mL then two 5-mL rinses) drop-wise via cannula. After hydrogen evolution had subsided, chloromethyl methyl ether (3.6 mL, 47.2 mmol, 1.5 equiv) was added to the yellow-green suspension at 0 ºC, and the resulting white slurry was allowed to reach rt and monitored by TLC. Upon completion (10 min), the mixture was quenched with 5% aq. NaOH solution (50 mL), diluted with water and extracted with 5% EtOAc/PE (3X). The organic phases were combined and washed with H_2O (3X), brine (1X) and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the crude oil was purified by flash chromatography (2% EtOAc/PE) to afford the title compound (6.1 g, 96%) as a clear colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (1H, br s), 7.72 (1H d, J = 8.7 Hz), 7.46 (1H, d, J = 8.2 Hz), 7.37-7.30 (2H, m), 7.08 (1H, d, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 135.0, 132.8, 128.5, 127.4, 125.9, 124.9, 121.2, 120.8, 107.9, 94.7, 56.2, 21.9; HRMS (EI) Calcd. for $C_{13}H_{14}O_2$: 202.0994. Found: 202.0989.



7-Methyl-1-methoxymethoxy-2-naphthaldehyde

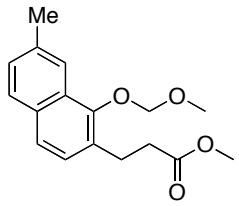
The MOM acetal (6.1 g, 30.2 mmol) was diluted in dry Et_2O (60 mL; 10% wt. with respect to the substrate, IMPORTANT!) and cooled to 0 ºC under Ar. Dry TMEDA (5.5 mL, 36.2 mmol, 1.2 equiv) was injected via syringe, followed by dropwise addition of *n*-BuLi solution in hexanes (15.1 mL, 36.2 mmol, 1.2 equiv) over 5 min. After 5 min at 0 ºC, the reaction was

stirred at ambient temperature for 90 min, whereupon it was cooled back to 0 ºC. DMF (4.7 mL, 60.4 mmol, 2.0 equiv) was then carefully added, the reaction was allowed to reach temperature and stirred for 18 h. Upon completion (TLC), it was quenched carefully with NH_4Cl (75 mL) and further diluted with H_2O. The aqueous phase was extracted three times with Et_2O. The combined organics were washed with NH_4Cl (3X), and brine (1X), dried over $MgSO_4$ and concentrated to dryness. The resulting yellow solid was recrystallised from MeOH (59% yield, 88:12 7- to 6-methyl ratio) followed by a second recrystallisation (MeOH) to afford 3.53 g of light tan crystals (51%, 95:5 regioisomeric mixture). Mp (MeOH): 67.5-68.0 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.5 (1H, s), 7.96 (1H, br s), 7.79 (1H, d, *J* = 8.6 Hz), 7.75 (1H, d, *J* = 8.4 Hz), 7.61 (1H, d, *J* = 8.6 Hz), 7.45 (1H, dd, *J* = 8.4, 1.5 Hz), 5.27 (2H, s), 3.65 (3H, s), 2.55 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 158.8, 136.8, 136.2, 131.4, 128.1, 128.0, 125.7, 124.6, 122.2, 121.6, 101.7, 58.1, 21.9; HRMS (EI) Calcd. for $C_{14}H_{14}O_3$: 230.0943. Found: 230.0941.



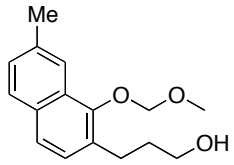
Methyl (*E*)-[3-(7-methyl-1-methoxymethoxy-2-naphthyl)]prop-2-enoate

Obtained as a 88:12 *E*:*Z* mixture using (carbomethoxy)methylphosphonium bromide as Wittig salt and 7-methyl-1-methoxymethoxy-2-naphthaldehyde, following General Procedure 3.6.2.7. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, peaks for the major diastereomer given): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (1H, d, *J* = 16.2 Hz), 7.90 (1H, br s), 7.72 (1H, d, *J* = 8.3 Hz), 7.58 (2H, m), 7.36 (1H, dd, *J* = 8.3, 1.6 Hz), 6.50 (1H, d, *J* = 16.2 Hz), 5.19 (2H, s), 3.83 (3H, s), 3.74 (3H, s), 2.54 (3H, s). HRMS (EI) Calcd. for $C_{17}H_{18}O_4$: 286.1205. Found: 286.1200.



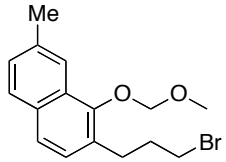
Methyl 3-(7-methyl-1-methoxymethoxy-2-naphthyl)-1-propanoate

Synthesised following General Procedure 3.6.2.8, using EtOAc as solvent, and purified over a short column of silica gel (100% EtOAc). Yellow viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (1H, br s), 7.71 (1H, d, *J* = 8.3 Hz), 7.55 (1H, d, *J* = 8.4 Hz), 7.28 (1H, dd, *J* = 8.4, 1.6 Hz), 7.24 (1H, d, *J* = 8.5 Hz), 5.17 (2H, s), 3.70 (3H, s), 3.69 (3H, s), 3.18 (2H, dd, *J* = 8.4, 7.7 Hz), 2.72 (2H, dd, *J* = 8.4, 7.7 Hz), 2.53 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 150.8, 135.8, 132.3, 129.4, 128.5, 127.9, 127.8, 126.8, 124.3, 121.0, 100.2, 57.6, 51.8, 35.0, 26.0, 22.1; HRMS (EI) Calcd. for $C_{17}H_{20}O_4$: 288.1362. Found: 288.1360.



3-(7-Methyl-1-methoxymethoxy-2-naphthyl)-1-propanol

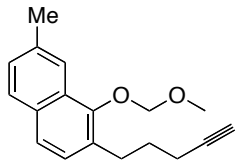
Obtained following General Procedure 3.6.2.9, as thick clear oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (1H, br s), 7.71 (1H, d, *J* = 8.3 Hz), 7.56 (1H, d, *J* = 8.4 Hz), 7.30-7.27 (1H, m), 7.25 (1H, d, *J* = 8.6 Hz), 5.17 (2H, s), 3.70 (3H, s), 3.61 (2H, t, *J* = 6.1 Hz), 2.97 (2H, t, *J* = 7.4 Hz), 2.53 (3H, s), 1.99-1.90 (2H, m), 1.88-1.81 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 135.9, 132.1, 130.2, 128.4, 127.8, 127.8, 127.1, 124.5, 121.0, 100.4, 61.6, 57.8, 33.3, 26.0, 22.1; HRMS (EI) Calcd. for $C_{16}H_{20}O_3$: 260.1412. Found: 260.1420.



3-(7-Methyl-1-methoxymethoxy-2-naphthyl)-1-propyl bromide

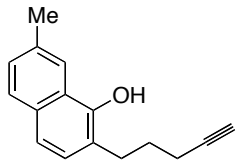
Obtained in 81% yield over 4 steps, following General Procedure 3.6.2.10, as a clear colourless oil ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (1H, br s), 7.71 (1H, d, *J* = 8.3 Hz), 7.55 (1H, d, *J* = 8.4

Hz), 7.34-7.24 (2H, m), 5.16 (2H, s), 3.70 (3H, s), 3.46 (2H, t, *J* = 6.6 Hz), 3.01 (2H, dd, *J* = 7.7, 7.3 Hz), 2.53 (3H, s), 2.26 (2H, dt, *J* = 7.8, 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 135.9, 132.2, 129.5, 128.5, 127.8, 127.8, 127.1, 124.3, 121.0, 100.3, 57.7, 33.6, 33.5, 29.0, 22.1; HRMS (EI) Calcd. for $C_{16}H_{19}BrO_2$: 322.0568. Found: 322.0573.



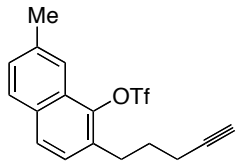
1-(7-Methyl-1-methoxymethoxy-2-naphthyl)-4-pentyne

Obtained from the corresponding alkyl bromide following General Procedure 3.6.2.11, after purification by flash chromatography (3% then 5% EtOAc/PE) as a clear colourless oil (2.7 g; 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (1H, br s), 7.71 (1H, d, *J* = 8.3 Hz), 7.54 (1H, d, *J* = 8.4 Hz), 7.31 (1H, dd, *J* = 8.2, 1.7 Hz), 7.28 (1H, d, *J* = 8.4 Hz), 5.16 (2H, s), 3.71 (3H, s), 3.02-2.95 (2H, m), 2.53 (3H, s), 2.27 (2H, dt, *J* = 7.0, 2.6 Hz), 2.00 (1H, t, *J* = 2.6 Hz), 1.93 (2H, dt, *J* = 7.7, 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 135.7, 132.1, 130.3, 128.6, 127.8, 127.7, 127.1, 124.1, 121.0, 100.2, 84.4, 68.6, 57.7, 29.5, 29.4, 22.1, 18.3; HRMS (EI) Calcd. for $C_{18}H_{20}O_2$: 268.1463. Found: 268.1467.



7-Methyl-2-(4-pentyn-1-yl)-1-naphthol

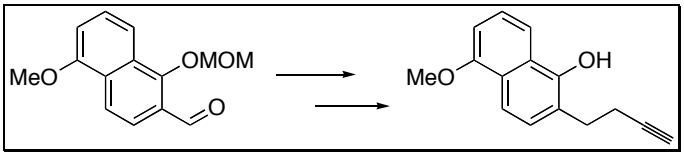
Prepared following General Procedure 3.6.2.4 from the corresponding MOM acetal as an off-white solid. Mp ($CHCl_3$): 61.5-62.5 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (1H, s), 7.69 (1H, d, *J* = 8.3 Hz), 7.37 (1H, d, *J* = 8.3 Hz), 7.29 (1H, dd, *J* = 8.3, 1.1 Hz), 7.17 (1H, d, *J* = 8.3 Hz), 5.50 (1H, br s), 2.93 (2H, t, *J* = 7.2 Hz), 2.54 (3H, s), 2.25 (2H, dt, *J* = 6.7, 2.6 Hz), 2.14 (1H, t, *J* = 2.6 Hz), 1.92 (2H, quint, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 135.1, 131.7, 127.8, 127.5, 127.1, 124.6, 120.2, 120.1, 119.9, 84.4, 69.7, 28.5, 28.0, 21.9, 17.4.

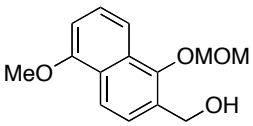


7-Methyl-2-(4-pentynyl)-1-naphthalenyl trifluoromethanesulfonate 159e

The 1-naphthol (2.27 g; 10.1 mmol) was derivatised according to General Procedure 3.6.2.5. After column chromatography (2.5% Et_2O/PE), the title compound was obtained (2.24 g; 62%) as a clear colourless oil, which solidified to colourless needles below 20 ºC. This compound was constituted of a 95:5 mixture of 7- and 6-methyl regioisomers, used as such; IR (neat) 3306 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (1H, s), 7.76 (1H, d, *J* = 8.5 Hz), 7.75 (1H, d, *J* = 8.4 Hz), 7.39-7.33 (2H, m), 3.04 (2H, t, *J* = 7.8 Hz), 2.57 (3H, s), 2.28 (2H, dt, *J* = 7.0, 2.6 Hz), 1.95 (2H, tt, *J* = 7.7, 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 137.8, 132.0, 131.9, 128.8, 128.3, 127.9, 127.6, 127.3, 120.2, 118.7 (1C, q, CF_3, *J* = 318 Hz), 83.4, 69.1, 29.4, 28.7, 22.1, 18.1. HRMS (EI) Calcd. for $C_{17}H_{15}F_3O_3S$: 356.0694. Found: 356.0699.

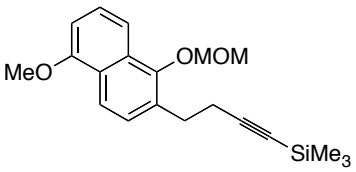
Synthesis of 2-(3-Butynyl)-5-methoxy-1-naphthol





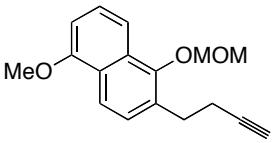
(5-Methoxy-1-methoxymethoxy-2-naphthyl)methanol

Obtained in 49% yield from the previously described 2-naphthaldehyde, following General Procedure 3.6.2.1, as a clear colourless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (1H, d, *J* = 8.6 Hz), 7.56 (1H, d, *J* = 8.5 Hz), 7.48 (1H, d, *J* = 8.6 Hz), 7.43 (1H, t, *J* = 8.5 Hz), 6.84 (1H, d, *J* = 7.6 Hz), 5.17 (2H, s), 4.79 (2H, d, *J* = 6.7 Hz), 4.00 (3H, s), 3.69 (3H, s), 3.09 (1H, t, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 151.6, 130.8, 12.1, 127.0, 126.9, 126.4, 119.2, 114.1, 104.2, 99.9, 60.8, 57.6, 55.6. HRMS (EI) Calcd. for $C_{14}H_{16}O_4$: 248.1049. Found: 248.1047.



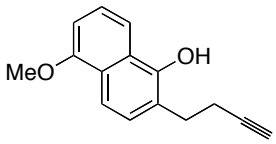
[4-(5-Methoxy-1-methoxymethoxy-2-naphthyl)-1-butynyl]trimethylsilane

Synthesised in 98% yield (3.13 g) from 2.32 g of the corresponding 2-naphthylmethanol, according to General Procedure 3.6.2.2, as a clear colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (1H, d, *J* = 8.6 Hz), 7.61 (1H, d, *J* = 8.5 Hz), 7.40 (1H, t, *J*= 8.2 Hz), 7.36 (1H, d, *J* = 8.6 Hz), 6.79 (1H, d, *J* = 7.6 Hz), 5.15 (2H, s), 3.99 (3H, s), 3.69 (3H, s), 3.08 (2H, t, *J* = 7.7 Hz), 2.59 (2H, t, *J* = 7.7 Hz), 0.14 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 150.9, 130.2, 129.5, 127.3, 126.1, 118.4, 114.4, 107.0, 103.7, 100.3, 100.3, 85.0, 57.6, 55.5, 29.8, 21.2, 0.08. HRMS (EI) Calcd. for $C_{20}H_{26}O_3Si$: 342.1651. Found: 342.1657.



4-(5-Methoxy-1-methoxymethoxy-2-naphthyl)-1-butyne

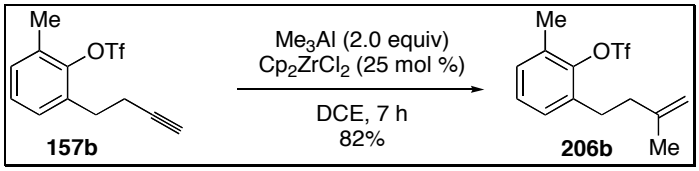
The alkynylsilane (3.13 g, 9.14 mmol, 1.0 equiv) was dissolved in 25 mL THF and treated at 0 ºC with a THF solution of TBAF (1.0M, 10.1 mL, 10.1 mmol, 1.1 equiv). After usual work-up, the title compound was isolated as a yellow oil, and taken as such to the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (1H, d, *J* = 8.6 Hz), 7.61 (1H, d, *J* = 8.5 Hz), 7.40 (1H, t, *J* = 7.9 Hz), 7.35 (1H, d, *J* = 8.6 Hz), 6.80 (1H, d, *J* = 7.6 Hz), 5.16 (2H, s), 3.99 (3H, s), 3.69 (3H, s), 3.10 (2H, t, *J* = 7.8 Hz), 2.58 (2H, dt, *J* = 7.9, 2.5 Hz), 1.98 (1H, t, *J* = 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 151.0, 130.0, 129.5, 127.0, 126.2, 126.1, 118.5, 114.4, 103.7, 100.3, 84.1, 68.7, 57.7, 55.5, 29.7, 19.6. HRMS (EI) Calcd. for $C_{17}H_{18}O_3$: 270.1256. Found: 270.1249.



4-(5-Methoxy-1-methoxymethoxy-2-naphthyl)-1-butyne

The MOM acetal was hydrolysed as per General Procedure 3.6.2.4 in 86% yield over 2 steps (1.79 g), as a clear colourless, viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (1H, d, *J* = 8.6 Hz), 7.68 (1H, d, *J* = 8.5 Hz), 7.39 (1H, dd, *J* = 8.4, 7.8 Hz), 7.26-7.22 (1H, m), 6.81 (1H, d, *J* = 7.6 Hz), 5.65 (1H, br s), 3.99 (3H, s), 3.04 (2H, t, *J* = 7.1 Hz), 2.59 (2H, dt, *J* = 7.0, 2.6 Hz), 2.06 (1H, t, *J* = 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 148.6, 127.4, 125.9, 125.8, 125.5, 121.2, 114.8, 113.1, 103.8, 84.5, 69.6, 55.5, 29.8, 19.6. This synthetic intermediate was then passed on to Anna A. Remorova, who carried out the triflation reaction and the subsequent studies.

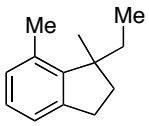
3.6.3.15 Methylalumination of Butynyl-tethered Triflate 157b



2(2-Methylbut-1-en-4-yl)-6-methylphenyl trifluoromethanesulfonate 206b

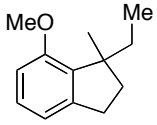
An oven-dried Schlenk tube was loaded with Cp_2ZrCl_2 (14.5 mg, 0.050 mmol, 25 mol %) followed by 1,2-dichloroethane (0.5 mL), then a hexanes solution of Me_3Al (2.0M, 0.20 mL, 2.0 equiv) was added dropwise via syringe. The resulting lemon-yellow mixture was allowed to stir for 10 min, after which the substrate **157b** was added via cannula as a DCE solution (1.0 mL). The resulting yellow reaction mixture was allowed to stir for 7 h in a sealed Schlenk tube, whereupon it was diluted with wet CH_2Cl_2 and cautiously poured into 1M aqueous NaOH. The aqueous phase was extracted with CH_2Cl_2 (2X 10 mL), and the combined organics were then washed with brine (1X), dried over $MgSO_4$ and concentrated to dryness. Following purification by flash chromatography (1% EtOAc/PE), the title compound was isolated as a clear colourless liquid (50 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.08 (3H, m), 4.72 (2H, d, *J* = 14.2 Hz), 2.86 (2H, dd, *J* = 8.4, 5.5 Hz), 2.38 (3H, s), 2.30 (2H, dd, *J* = 8.6, 7.6 Hz), 1.76 (3H, s).

3.6.3.16 Tandem Arylation/1,2-Methyl Migration Products 158



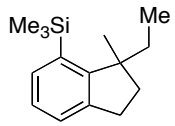
1-Ethyl-1,7-dimethylindane 158b

Following General Procedure 3.6.2.12. Clear colourless liquid; R_f 0.72 (100% PE); IR (neat) 3066, 3014, 2960, 2875, 1588, 1461, 1379, 771, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15-6.79 (3H, m), 2.84 (2H, app t, *J* = 7.4 Hz), 2.36 (3H, s), 2.07 (1H, ddd, *J* = 12.6, 7.7, 7.5 Hz), 1.80-1.67 (3H, m), 1.31 (3H, s), 0.83 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 129.0, 126.4, 122.3, 49.3, 38.0, 32.1, 30.2, 25.6, 19.4, 9.4; HRMS (EI) Calcd. for $C_{13}H_{18}$: 174.1409. Found: 174.1411.



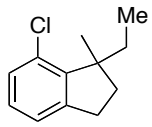
1-Ethyl-7-methoxy-1-methylindane 158c

Following General Procedure 3.6.2.12, using 3.0 equiv of Me_3Al for methylalumination to reach completion. The carbopalladation step was carried out for 18 h at 100 °C. Clear colourless liquid; R_f 0.29 (100% petroleum ether 30-60); IR (neat) 3064, 2957, 1588, 1478, 1377, 1296, 1258, 1169, 1078, 778, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (1H, app t, *J* = 7.7 Hz), 6.81 (1H, d, *J* = 7.8 Hz), 6.69 (1H, d, *J* = 8.0 Hz), 3.80 (3H, s), 2.86 (2H, app t, *J* = 7.5 Hz), 2.05 (1H, ddd, *J* = 12.7, 7.7, 7.5 Hz), 1.83-1.70 (3H, m), 1.34 (3H, s), 0.81 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 145.6, 137.3, 127.7, 117.0, 108.5, 54.9, 49.0, 37.6, 32.1, 30.9, 25.5, 9.5; Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.17; H, 9.71.



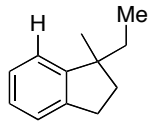
(3-Ethyl-3-methyl-2,3-dihydro-1*H*-4-indenyl)(trimethyl)silane 158e

Following General Procedure 3.6.2.12. Clear colourless liquid; R_f 0.68 (100% PE); IR (neat) 3066, 3014, 2958, 1639, 1460, 1402, 1250, 1127, 838, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (1H, d, *J* = 7.3 Hz), 7.22 (1H, d, *J* = 7.3 Hz), 7.13 (1H, app t, *J* = 7.4 Hz), 2.86 (2H, app t, *J* = 7.3 Hz), 2.01 (1H, ddd, *J* = 12.4, 7.2, 7.1 Hz), 1.82-1.62 (3H, m), 1.32 (3H, s), 0.91 (3H, t, *J* = 7.5 Hz), 0.40 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 143.1, 134.1, 134.1, 125.9, 125.4, 49.9, 38.2, 32.5, 30.3, 25.2, 9.6, 2.6; HRMS (EI) Calcd. for $C_{15}H_{24}Si$: 232.1647. Found: 232.1642.



7-Chloro-1-ethyl-1-methylindane 158f

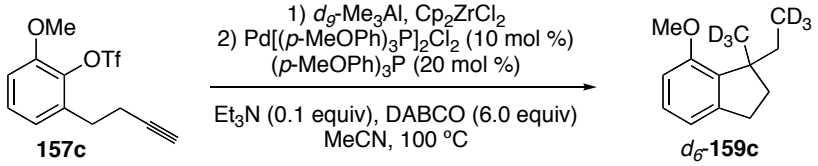
Following General Procedure 3.6.2.12. Clear colourless liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.13-7.05 (3H, m), 2.88 (2H, t, *J* = 7.8 Hz), 2.11 (1H, dt, *J* = 12.9, 7.8 Hz), 1.99 (1H, dq, *J* = 13.9, 7.3 Hz), 1.83-1.66 (2H, m), 1.38 (3H, s), 0.81 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 146.1, 130.9, 128.0, 127.8, 123.1, 50.3, 37.6, 31.7, 30.5, 25.5, 9.4; HRMS (EI) Calcd. for $C_{12}H_{15}Cl$: 194.0862. Found: 194.0864.



1-Ethyl-1-methylindane[214] **158g**

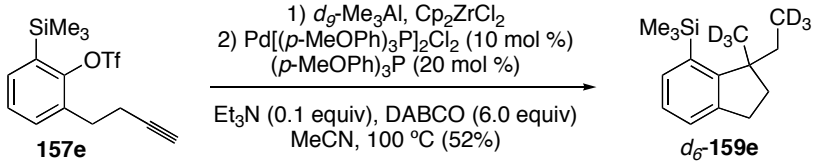
Following General Procedure 3.6.2.12. Clear colourless liquid; R_f 0.69 (5% CH_2Cl_2/PE); ^1H NMR (300 MHz, $CDCl_3$) δ 7.19-7.10 (4H, m), 2.87 (2H, app t, *J* = 7.3 Hz), 2.01 (1H, ddd, *J* = 12.7, 7.0, 6.9 Hz), 1.81 (1H, ddd, *J* = 12.5, 7.7, 7.6 Hz), 1.62-1.53 (2H, m), 1.22 (3H, s), 0.83 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 143.3, 126.1, 126.0, 124.4, 122.7, 38.0, 33.6, 30.2, 26.2, 9.3.

3.6.3.17 Reactions using d_9-Me_3Al



7-Methoxy-1-(2,2,2-trideuterioethyl)-1-(1,1,1-trideuteriomethyl)indane d_6-**159c**

Following General Procedure 3.6.2.12 using substrate **157e** (154 mg, 0.50 mmol) and $(D_3C)_3Al$ (162 μL, 1.50 mmol, 3.0 equiv). The methylalumination was left to stir for 40 h. After usual work-up and purification by flash chromatography (100% PE), the title compound was isolated as a clear colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (1H, dd, *J* = 7.7 Hz), 6.80 (1H, dd, *J* = 7.4, 0.7 Hz), 6.68 (1H, d, *J* = 8.1 Hz), 3.81 (3H, s), 2.87 (2H, t, *J* = 7.6 Hz), 2.04 (1H, dt, *J* = 12.9, 7.2 Hz), 1.81 (1H, d, *J* = 13.5 Hz), 1.80-1.70 (1H, m), 1.70 (1H, d, *J* = 13.2 Hz). ^{2}H NMR (44.1 MHz, $CHCl_3$) δ 1.28 (3D, s), 0.75 (3D, t, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CHCl_3$) δ 156.8, 145.6, 137.3, 127.6, 117.0, 108.5, 55.0, 49.0, 37.6, 31.8 (1C, t, **CD_3**, *J* = Hz), 30.9, 9.5 (one resonance for CD_3 missing); LRMS (EI) Calcd. for $C_{13}H_{12}D_6O$: 196. Found: 196 (M^+), 178 (M-CD_3^+), 164 (M-CH_2CD_3).



[3-(2,2,2-Trideuterioethyl)-3-(1,1,1-trideuteriomethyl)-2,3-dihydro-1*H*-4-indenyl](trimethyl)silane d_6-**159e**

Following General Procedure 3.6.2.12 using substrate **157e** (140 mg, 0.40 mmol) and $(D_3C)_3Al$ (87 μL, 0.80 mmol, 2.0 equiv). After usual work-up and purification by flash chromatography (100% PE), the title compound was isolated as a clear colourless oil (50 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (1H, d, *J* = 7.1 Hz), 7.23 (1H, d, *J* = 7.3 Hz), 7.14 (1H, dd, *J* = 7.4 Hz), 2.87 (2H, t, *J* = 7.3 Hz), 1.99 (1H, ddd, *J* = 12.4, 5.3, 5.2 Hz), 1.78 (1H, d, *J* = 13.5 Hz), 1.80-1.68 (1H, m), 1.62 (1H, d, *J* = 13.6 Hz), 0.39 (9H, s). ^{2}H NMR (75.6 MHz, $CHCl_3$) δ 1.32

(3D, s), 0.90 (3D, s); LRMS (EI) Calcd. for $C_{15}H_{18}D_6Si$: 238. Found: 238 (M^+), 223 ($M\text{-}CH_3^+$), 220 ($M\text{-}CD_3^+$), 206 ($M\text{-}CH_2CD_3^+$).

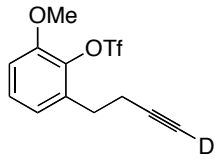
3.6.3.18 Synthesis of Deuterium-Labeled Terminal Alkynes

Terminal Alkyne Deuteriation

A solution of terminal alkyne (1.0 equiv) in dry THF (0.20 M solution) was cooled to 0 ºC. *n*-BuLi (1.07 equiv) was added dropwise at 0 ºC and the reaction was stirred for 20 min at this temperature. Then D_2O (1 mL per mmol) was added and the reaction mixture was stirred for another 20 min at 0 ºC, after which, brine was added to the flask and the resulting solution was transferred into a separatory funnel. The aqueous layer was extracted three times with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated by rotary evaporation. Following purification by flash chromatography, the D-incorporation was >99% by ^1H NMR.

Phenol (Naphthol) Deprotection in the Presence of a D-Alkyne[215]

Amberlyst 15 resin (0.50 g per mmol) was added to a solution of the MOM-protected alcohol (1.0 equiv) in MeOH/THF (1:1, 0.075 M total concentration) at rt. The reaction mixture was stirred vigorously under nitrogen for 3 days. After the reaction completion (monitored by TLC), the brown suspension was filtered through Celite two times washing with hexanes and dichloromethane. Due to the instability of the product, the alcohol thus obtained was taken as such to the triflation step, using the General Procedure 3.6.2.5, as described previously, to afford analytically pure cyclisation substrates.

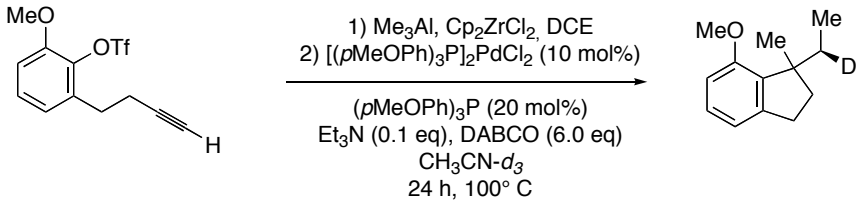


2-(4-Deuteriobut-3-ynyl)-6-methoxyphenyl trifluoromethanesulfonate *d*-157c

Obtained following the procedures cited above, as a clear colourless liquid; IR (neat) 2593 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.23 (1H, m), 6.95 (1H, d, J = 7.8 Hz), 6.91 (1H, d, J = 7.3 Hz), 3.89 (3H, s), 2.94 (2H, t, J = 7.4 Hz), 2.51 (2H, t, J = 7.4 Hz); ^{13}C NMR (75 MHz,

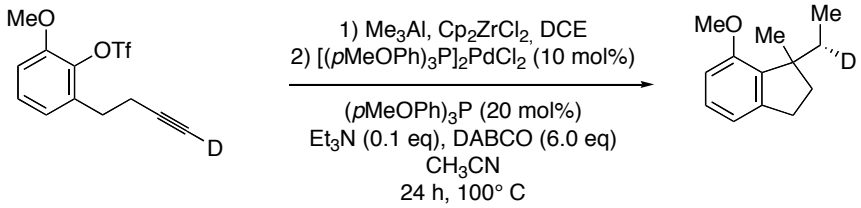
$CDCl_3$) δ 151.2, 137.3, 1343, 128.4, 125.1, 122.1, 118.7 (q, J = 319 Hz), 111.2, 82.2 (t, $J_{C\text{-}D}$ = 7.4 Hz), 69.1 (t, $J_{C\text{-}D}$ = 38 Hz), 55.9, 28.9, 18.8; HRMS (EI) Calcd. for $C_{12}H_{10}DF_3O_4S$: 309.0393. Found: 309.0389.

3.6.3.19 Synthesis of Diastereomeric Deuterium-Labeled Indanes 158c



1-(1-Deuteroethyl)-7-methoxy-1-methylindane *d*-158c

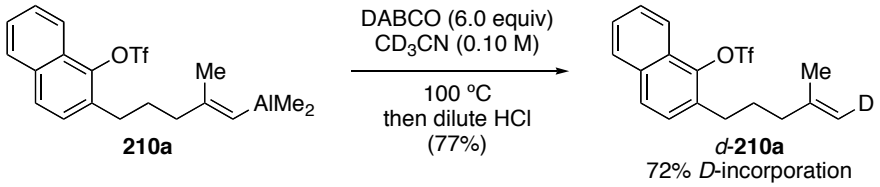
Following General Procedure 3.6.2.12 using CD_3CN as solvent. Clear colourless liquid; IR (neat) 2360, 2330 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (1H, app t, J = 7.7 Hz), 6.81 (1H, d, J = 7.8 Hz), 6.69 (1H, d, J = 8.0 Hz), 3.80 (3H, s), 2.86 (2H, app t, J = 7.5 Hz), 2.05 (1H, ddd, J = 12.7, 7.7, 7.5 Hz), 1.92 - 1.70 (2H, m), 1.34 (3H, s), 0.81 (3H, d, J = 7.5 Hz); ^2H NMR (77 MHz, $CHCl_3$) δ 1.83 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 145.6, 137.3, 127.7, 117.1, 108.5, 55.0, 49.0, 37.6, 31.8 (t, $J_{C\text{-}D}$ = 18.7 Hz), 30.9, 25.5, 9.5; HRMS (EI) Calcd. for $C_{13}H_{17}DO$: 191.1419. Found: 191.1412.



1-(1-Deuteroethyl)-7-methoxy-1-methylindane *epi-d*-158c

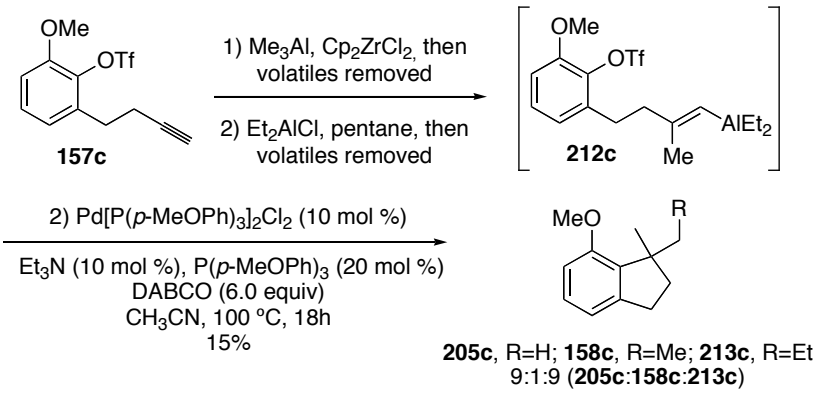
Clear colourless liquid; IR (neat) 2138 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (1H, app t, J = 7.7 Hz), 6.81 (1H, d, J = 7.8 Hz), 6.69 (1H, d, J = 8.0 Hz), 3.81 (3H, s), 2.87 (2H, ddd, J = 7.5, 7.5, 3.8 Hz), 2.06 (1H, ddd, J = 12.7, 7.7, 7.5 Hz), 1.85-1.75 (1H, m), 1.75-1.71 (1H, m), 1.33 (3H, s), 0.80 (3H, d, J = 7.5 Hz); ^2H NMR (77 MHz, $CHCl_3$) δ 1.71 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 145.6, 137.3, 127.7, 117.1, 108.5, 55.0, 48.9, 37.6, 31.7 (t, $J_{C\text{-}D}$ = 19.3 Hz), 30.9, 25.4, 9.4; HRMS (EI) Calcd. for $C_{13}H_{17}DO$: 191.1419. Found: 191.1417.

3.6.3.20 Vinylalane 210a Stability to Reaction Conditions



An oven-dried Schlenk tube was loaded with Cp_2ZrCl_2 (14.6 mg, 0.050 mmol, 25 mol %) followed by alkynyl triflate **159a** (68 mg, 0.20 mmol, 1.0 equiv). In a dry box, this mixture was dissolved using 1,2-dichloroethane (1.5 mL), then neat Me_3Al (38 μL, 0.40 mmol, 2.0 equiv) was added dropwise via syringe. The resulting lemon-yellow mixture was allowed to stir for 20 h in a sealed Schlenk tube, after which, the volatiles were removed *in vacuo* (0.05-0.10 mm Hg) while placing the reaction vessel in an oil bath (50 °C) for 1 h. In the dry-box, DABCO (135 mg, 1.20 mmol, 6.0 equiv) was added, followed by CD_3CN (2.0 mL), bringing the final concentration to 0.10 M. The Schlenk tube was resealed and immersed in an oil bath set to 100 ºC, and allowed to stir for 24 h. Then, the reaction mixture was allowed to reach rt, and carefully quenched by the dropwise addition of 5% HCl was added. After gas evolution had subsided, the aqueous phase was extracted with dichloromethane (3X). The combined organics were washed with brine (1X), dried over Na_2SO_4, filtered and concentrated to dryness. The crude compound was then purified over a short silica gel column (10% CH_2Cl_2/PE), to furnish the alkene *d*-**211**, for which deuterium incorporation was determined to be 72% by integration of the vinylic protons (55.5 mg, 77%). Complete characterisation data for the fully labeled compound, obtained by quenching the carboalumination with D_2O, are reported on page 231.

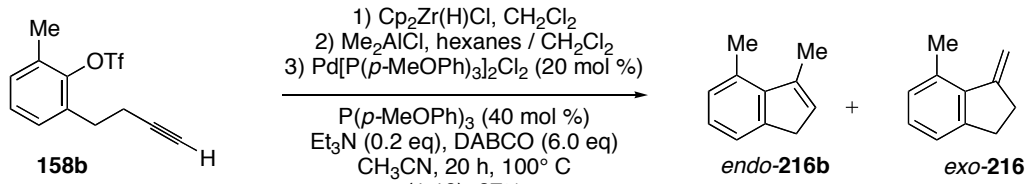
3.6.3.21 Ethyl Transfer Reaction



An oven-dried Schlenk tube was loaded with Cp_2ZrCl_2 (29 mg, 0.10 mmol, 25 mol %) followed by DCE (1.5 mL). To the stirring suspension was added a hexanes solution of Me_3Al (2.0 M, 0.60 mL, 1.20 mmol, 4.0 equiv), and the lemon-yellow solution was then stirred for 5 min. Substrate **157c** (123 mg, 0.40 mmol, 1.0 equiv) was then added as a DCE solution (1.5 mL) via cannula. The reaction mixture was allowed to stir for 20 h in the sealed Schlenk tube, after which, the volatiles were removed *in vacuo* (0.05-0.10 mm Hg) while placing the reaction vessel in an oil bath (50 °C) for 1 h. To the residue was added pentane (0.8 mL) and the suspension was sonicated in the sealed Schlenk tube for 5-10 min, after which a heterogeneous yellow suspension was obtained. In the dry-box, Et_2AlCl (1.00 mL, 8.00 mmol, 20 equiv) was added, and the ligand disproportionation was allowed to stir at rt for 1 h, whereupon the excess volatiles were carefully removed by vacuum distillation (0.10 mm Hg, 80 ºC). In the dry box, a mixture of $Pd[(p\text{-}MeOPh)_3P]_2Cl_2$ (36 mg, 0.040 mmol, 10 mol %), $P(p\text{-}MeOPh)_3$ (28 mg, 0.080 mmol, 20 mol %) and Et_3N (6.0 μL, 0.040 mmol) was suspended in 1.0 mL MeCN in a vial, and heated gently until dissolution resulted, and a slight colour change from yellow to light orange was observed. The warm mixture was then added to a mixture of the crude alane and DABCO (270 mg, 2.40 mmol, 6.0 equiv), and quantitatively transferred using with a further 3.0 mL MeCN. The Schlenk tube was sealed and placed in an oil bath at 100 ºC for 19 h. The reaction was cooled to ambient temperature and quenched by the careful addition of H_2O (2.0 mL), stirring 10 min then diluting with 5% aqueous HCl (15 mL). The products were extracted with dichloromethane (3 x 10 mL) and washed with 5% HCl (1X 5 mL). The combined organics were dried with anhydrous $MgSO_4$, filtered over Celite and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (100% PE) to

afford an inseparable mixture of products, whose characteristic signals were integrated by ^{1}H NMR to allow for ratio determination. By GC-MS analysis, the three reaction products were ascertained based on M^+ and fragmentation patterns.

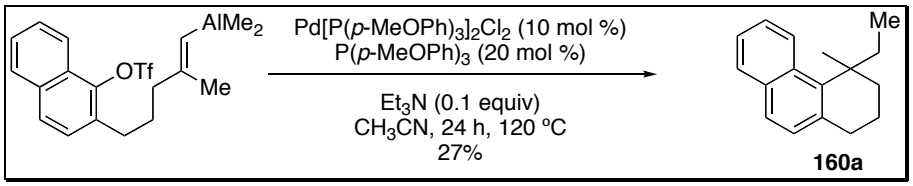
3.6.3.22 Tandem Hydrozirconation/Transmetalation/Carbopalladation



In a dry box, an oven-dried Schlenk tube was loaded with $Cp_2Zr(H)Cl$ (95%, 83 mg, 0.31 mmol, 1.03 equiv). Under Ar, Schwartz's reagent was then suspended in 1.5 mL anhydrous CH_2Cl_2 (0.5 mL) and treated with a solution of alkynyl triflate **157b** (88 mg, 0.30 mmol, 1.00 equiv) in CH_2Cl_2 (0.5 mL, followed by two 0.25 mL rinses) via cannula. The resulting lemon-yellow mixture was allowed to stir for 7.5 h (TLC monitoring) in a sealed Schlenk tube. Under Ar, the mixture was then treated with Me_2AlCl (0.31 mL, 1.0 M solution in hexanes, 0.31 mmol, 1.03 equiv), the Schlenk tube was resealed and the heterogenous mixture was stirred for 16 h at ambient temperature. The volatiles were carefully removed *in vacuo* (0.05 mm Hg) while placing the reaction vessel in a warm water bath (40 °C) for 1 h. In the dry box, a mixture of $Pd[(p\text{-}MeOPh)_3P]_2Cl_2$ (52 mg, 0.060 mmol, 20 mol %), $P(p\text{-}MeOPh)_3$ (42 mg, 0.120 mmol) and Et_3N (8.4 μL, 0.060 mmol) was suspended in 1.0 mL MeCN in a vial, and heated gently until dissolution resulted, and a slight colour change from yellow to light orange was observed. The warm mixture was then added to a mixture of the crude alane and DABCO (202 mg, 1.80 mmol, 6.0 equiv), and quantitatively transferred using with a further 2.0 mL MeCN. The Schlenk tube was sealed and placed in an oil bath at 100 ºC for 20 h. The reaction was cooled to ambient temperature and quenched by the careful addition of H_2O (2.0 mL), stirring 10 min then diluting with 5% aqueous HCl (15 mL). The products were extracted with dichloromethane (3 x 10 mL) and washed with 5% HCl (1X 5 mL). The combined organics were dried with anhydrous $MgSO_4$, filtered over Celite and concentrated under reduced pressure. The resulting crude gum was purified by flash chomatography (100% PE) to afford an inseparable mixture of indanyl products *endo*-**216b** and *exo*-**216b** in a ratio of 1:19 (29 mg;

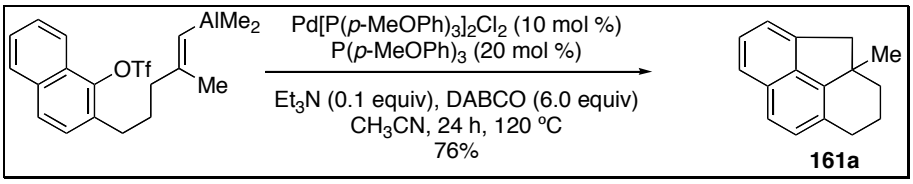
67%). Clear colourless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-6.99 (3H, m), 5.40 (1H, t, *J* = 2.1 Hz), 5.22 (1H, t, *J* = 2.1 Hz), 2.96 (2H, dd, *J* = 7.9, 6.1 Hz), 2.84-2.78 (2H, m), 2.51 (3H, s). During ^{13}C acquisition, in $CDCl_3$, *exo*-**216b** isomerised to the known endocyclic olefin isomer.[216]

3.6.3.23 Scope of the 1,2-Diarylation Reaction



4-Ethyl-4-methyl-1,2,3,4-tetrahydrophenanthrene (160a)[154]

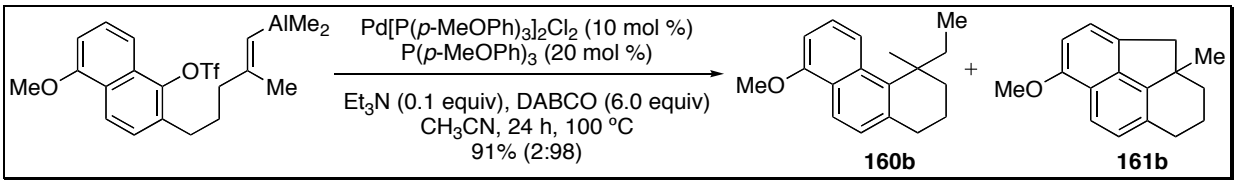
Isolated as a clear colourless oil in 27% yield by following the general procedure from **159a**, omitting DABCO and heating to 120 ºC for 24 h; characterisation data were in agreement with the values reported by Carson. IR (neat) 3048, 2930, 2871, 1621, 1605, 1511, 1461, 1382, 808, 787, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (1H, d, *J* = 8.5 Hz), 7.75 (1H, dd, *J* = 7.5, 1.9 Hz), 7.55 (1H, d, *J* = 8.4 Hz), 7.42–7.32 (2H, m), 7.15, (1H, d, *J* = 8.4 Hz), 2.83-2.98 (2H, m), 2.31 (1H, dq, *J* = 14.9, 7.5 Hz), 2.01-1.76 (4H, m), 1.60 (3H, s), 1.60-1.55 (1H, m), 0.64 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 136.1, 133.5, 132.6, 129.3, 128.6, 126.5, 126.1, 124.5, 123.9, 39.8, 38.5, 34.3, 33.1, 28.2, 19.0, 9.0. HRMS (EI) Calcd for $C_{17}H_{20}$: 224.1565. Found: 224.1560.



3a-Methyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*def*]phenanthrene (161a)[154]

Obtained in 76% yield from **159a** using the general procedure, as a clear colourless liquid; characterisation data were in agreement with the values reported by Carson. IR (neat) 3034, 2935, 1640, 1610, 1492, 1453 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 8.2 Hz), 7.53 (1H, d, *J* = 8.3 Hz), 7.39 (1H, dd, *J* = 8.2, 6.9 Hz), 7.25 (1H, d, *J* = 6.5 Hz), 7.22 (1H, d, *J*

= 8.3 Hz), 3.30 (1H, d, *J* = 15.8 Hz), 3.10 (1H, d, *J* = 15.9 Hz), 3.00 (1H, dd, *J* = 17.5, 8.2 Hz), 2.69 (1H, ddd, *J* = 17.4, 8.7, 8.7 Hz), 2.24 (1H, m), 2.17-1.94 (2H, m), 1.73 (1H, ddd, *J* = 12.7, 12.3, 4.3 Hz), 1.34 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 142.5, 136.7, 129.7, 128.4, 128.1, 127.2, 122.9, 122.2, 120.0, 47.8, 42.3, 34.0, 27.9, 24.7, 19.8; HRMS (EI) Calcd. for $C_{16}H_{16}$: 208.1252. Found: 208.1252.

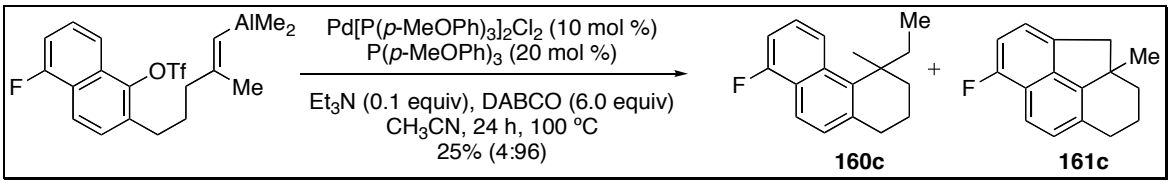


4-Ethyl-8-methoxy-4-methyl-1,2,3,4-tetrahydrophenanthrene (160b)

Obtained as a 2:98 mixture with **4b** following the general procedure, in 91% yield from **159b**. Upon flash chromatography (5% CH_2Cl_2/PE), an analytical sample was obtained as a clear colourless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (1H, d, *J* = 8.6 Hz), 7.94 (1H, d, *J* = 8.9), 7.31 (1H, dd, *J* = 8.6 Hz), 7.15 (1H, d, *J* = 8.6 Hz), 6.74 (1H, d, *J* = 7.6 Hz), 3.97 (3H, s), 2.93-2.86 (2H, m), 2.31 (1H, dq, *J* = 7.5, 7.3 Hz), 1.97 (1H, m), 1.89 (1H, dq, *J* = 7.5, 7.3 Hz), 1.83-1.78 (2H, m), 1.54 (3H, s), 0.64 (3H, d, *J* = 7.5 Hz); HRMS (EI) Calcd. for $C_{18}H_{22}O$: 254.1671. Found: 254.1674. The reaction did not produce enough of this minor component for acquiring a ^{13}C NMR spectrum.

7-Methoxy-3a-methyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*def*]phenanthrene (161b)

Obtained as a 98:2 mixture with **160b**, following the general procedure, in 91% yield from **159b**. Upon flash chromatography (5% CH_2Cl_2/PE), an analytical sample was obtained as a white solid, mp = 95.0-98.0 ºC (CH_2Cl_2/PE); IR (CH_2Cl_2) 3112, 3065, 2936, 1601, 1501, 1449, 1426, 1404, 1284, 1224, 1144, 1086 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (1H, d, *J* = 8.4 Hz), 7.20 (1H, d, *J* = 8.4 Hz), 7.15 (1H, d, *J* = 7.4 Hz), 6.72 (1H, d, *J* = 7.4 Hz), 3.98 (3H, s), 3.22 (1H, dd, *J* = 15.4, 0.7 Hz), 3.05 (1H, d, *J* = 15.4 Hz), 2.99 (1H, ddd, *J* = 17.5, 8.1, 1.3 Hz), 2.72-2.63 (1H, m), 2.23 (1H, m), 2.09 (1H, ddd, *J* = 12.4, 4.4, 3.0 Hz), 2.05-1.99 (1H, m), 1.73 (1H, dt, *J* = 12.8, 4.4 Hz), 1.32 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 148.2, 138.0, 134.2, 129.1, 127.3, 121.6, 119.9, 118.5, 105.3, 55.7, 47.1, 43.0, 34.1, 27.9, 24.7, 19.8; HRMS (EI) Calcd. for $C_{17}H_{18}O$: 238.1358. Found: 238.1354.

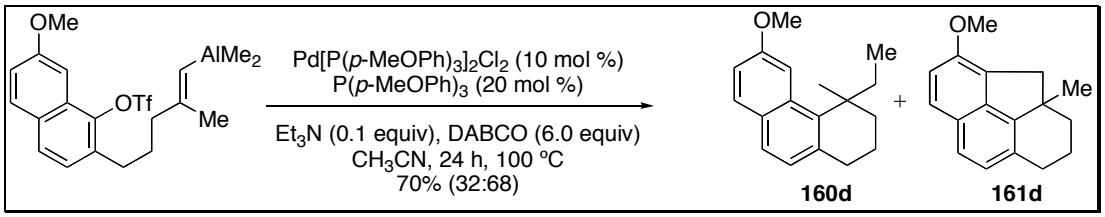


4-Ethyl-8-fluoro-4-methyl-1,2,3,4-tetrahydrophenanthrene (160c)

Obtained as a 4:96 mixture with **161c**, following the general procedure, in 25% yield from **159c**. Upon flash chromatography (100% PE), an analytical sample was obtained as a clear colourless liquid; IR (neat) 3131, 3065, 2934, 2874, 1632, 1608, 1510, 1242, 1165, 797, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (1H, d, J = 8.9 Hz), 7.88 (1H, d, J = 8.6 Hz), 7.36-7.27 (1H, dt, J = 8.2, 7.2 Hz), 7.23 (1H, d, J = 8.6 Hz), 7.03 (1H, dd, J = 10.0, 7.8 Hz), 2.96-2.90 (2H, m), 2.29 (1H, dq, J = 14.8, 7.4 Hz), 1.99 (ddd, J = 13.1, 9.7, 3.8 Hz), 1.90 (dq, J = 14.5, 7.3 Hz), 1.85-1.75 (2H, m), 1.61 (3H, s), 0.65 (3H, d, J = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4 (d, $J_{C\text{-}F}$ = 249 Hz), 139.0, 137.3, 134.2, 129.0, 124.0 (d, $J_{C\text{-}F}$ = 9.0 Hz), 123.7 (d, $J_{C\text{-}F}$ = 15.4 Hz), 122.0 (d, $J_{C\text{-}F}$ = 4.3 Hz), 118.3 (d, $J_{C\text{-}F}$ = 8.2 Hz), 107.5 (d, $J_{C\text{-}F}$ = 19.8 Hz); HRMS (EI) Calcd. for $C_{17}H_{19}F$: 242.1471. Found: 242.1475.

7-Fluoro-3a-methyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*def*]phenanthrene (161c)

Obtained as a 96:4 mixture with **160c**, following the general procedure, in 25% yield from **159c**. Upon flash chromatography (100% PE), an analytical sample was obtained as a clear colourless oil; IR (neat) 3112, 2936, 1642, 1612, 1502, 1428, 1408, 1281, 1223, 1189, 1133 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (1H, d, J = 8.4 Hz), 7.26 (1H, d, J = 8.4 Hz), 7.14 (1H, dd, J = 7.4, 3.8 Hz), 7.03 (1H, dd, J = 11.6, 7.5 Hz), 3.26 (1H, d, J = 15.7 Hz), 3.06 (1H, d, J = 16.2 Hz), 3.01 (1H, ddd, J = 17.7, 8.9, 7.6 Hz), 2.76-2.67 (1H, m), 2.33-1.98 (3H, m), 1.74 (1H, ddd, J = 13.0, 12.4, 4.4 Hz), 1.34 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8 (d, $J_{C\text{-}F}$ = 251 Hz), 149.3 (d, $J_{C\text{-}F}$ = 3.0 Hz), 139.3 (d, $J_{C\text{-}F}$ = 7.2 Hz), 137.7 (d, $J_{C\text{-}F}$ = 3.6 Hz), 129.5, 128.4, 119.8 (d, $J_{C\text{-}F}$ = 7.3 Hz), 120.3 (d, $J_{C\text{-}F}$ = 19.4 Hz), 117.0, 110.8 (d, $J_{C\text{-}F}$ = 20.8 Hz), 47.2, 43.2, 33.9, 27.8, 24.6, 19.6; HRMS (EI) Calcd. for $C_{16}H_{15}F$: 226.1158. Found: 226.1163.

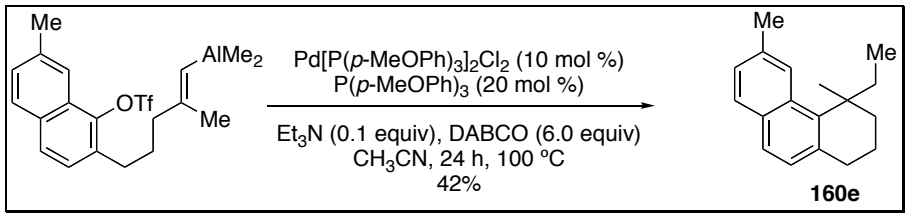


4-Ethyl-6-methoxy-4-methyl-1,2,3,4-tetrahydrophenanthrene (160d)

Obtained as a 32:68 mixture with **161d**, following the general procedure, in 70% yield from **159d**. Upon flash chromatography (5% CH_2Cl_2/PE), an analytical sample was obtained as a clear colourless liquid; IR (CH_2Cl_2) 3049, 2935, 2873, 1624, 1516, 1460, 1381, 1265, 1228, 1213, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (1H, d, *J* =2.3 Hz), 7.69 (1H, d, *J* = 8.9 Hz), 7.51 (1H, d, *J* = 8.3 Hz), 7.09 (1H, dd, *J* = 8.9, 2.4 Hz), 7.05 (1H, d, *J* = 8.5 Hz), 3.94 (3H, s), 2.95-2.88 (2H, m), 2.37 (1H, dq, *J* = 7.5, 7.3 Hz), 2.00-1.75 (4H, m), 1.64 (3H, s), 1.62-1.56 (1H, m), 0.69 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 137.5, 136.8, 133.5, 130.5, 128.8, 126.5, 126.2, 115.5, 106.4, 55.2, 40.0, 38.4, 34.0, 33.2, 27.7, 19.1, 9.1; HRMS (EI) Calcd. for $C_{18}H_{22}O$: 254.1671. Found: 254.1675.

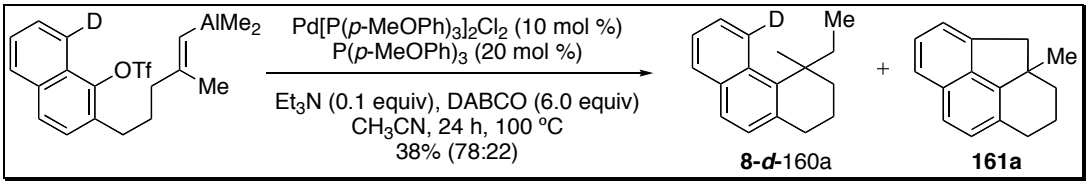
5-Methoxy-3a-methyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*def*]phenanthrene (161d)

Obtained as a 68:32 mixture with **160d**, following the general procedure, in 70% yield from **159d**. Upon flash chromatography (2% Et_2O/PE), a sample enriched in **161d**, containing all the characteristic peaks, was obtained as a light yellow liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (1H, d, *J* = 8.7 Hz), 7.48 (1H, d, *J* = 8.3 Hz), 7.14 (1H, d, *J* = 8.7 Hz), 7.08 (1H, d, *J* = 8.4 Hz), 3.99 (3H, s), 3.37 (1H, d, *J* = 15.7 Hz), 3.10 (1H, d, *J* = 15.8 Hz), 2.99 (1H, dd, *J* = 17.6, 7.8 Hz), 2.73-2.65 (1H, m), 2.30-2.00 (3H, m), 1.73 (1H, dd, *J* = 12.9, 4.5 Hz), 1.34 (3H, s); HRMS (EI) Calcd. for $C_{17}H_{18}O$: 238.1358. Found: 238.1363.



4-Ethyl-4,6-dimethyl-1,2,3,4-tetrahydrophenanthrene (160e)

Obtained in 42% yield from **159e** following the general procedure, after column chromatography (100% PE) as a clear colourless liquid; IR (neat) 3045, 2932, 2868, 1626, 1515, 1460, 1379, 833 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (1H, s), 7.67 (1H, d, *J* = 8.3), 7.53 (1H, d, *J* = 8.3 Hz), 7.21 (1H, d, *J* = 8.3 Hz), 7.10 (1H, d, *J* = 8.3 Hz), 2.94-2.90 (2H, m), 2.54 (3H, s), 2.33 (1H, dq, *J* = 14.4, 7.4 Hz), 1.99-1.81 (4H, m), 1.53 (3H, s), 1.52-1.28 (1H, m), 0.64 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 136.1, 133.8, 132.8, 131.7, 129.1, 127.8, 126.2, 125.9, 125.4, 39.9, 38.5, 34.3, 33.2, 28.2, 22.5, 19.1, 9.1; HRMS (EI) Calcd. for $C_{18}H_{22}$: 238.1722. Found: 238.1725.

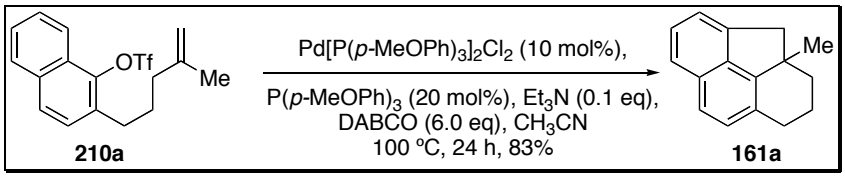


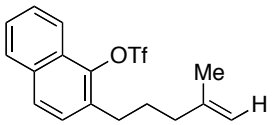
5-Deuterio-4-ethyl-4-methyl-1,2,3,4-tetrahydrophenanthrene (d^8-160a)

Obtained as a 78:22 mixture with **161a**, following the general procedure, in 38% yield, from d^8-**159a**. Upon flash chromatography (100% PE), an analytical sample was obtained as a clear colourless liquid; IR (neat) 3049, 2962, 2932, 2872, 2200, 1502, 1465, 1379, 836, 793 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (1H, dd, *J* = 7.7, 1.8 Hz), 7.56 (1H, d, *J* = 8.4 Hz), 7.42-7.33 (2H, m), 7.16 (1H, d, *J* = 8.4 Hz), 3.00-2.82 (2H, m), 2.31 (1H, dq, *J* = 14.4, 7.5 Hz), 2.03-1.77 (4H, m), 1.62 (3H, s), 1.61-1.57 (1H, m), 0.66 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 136.1, 133.6, 132.5, 129.3, 128.6, 126.5, 125.8 (t, $J_{C\text{-}D}$ = 23 Hz), 124.4, 123.9, 39.8, 38.5, 34.3, 33.1, 28.2, 19.0, 9.0; HRMS Calcd for $C_{17}H_{19}D$: 225.1628, Found: 225.1627.

3a-Methyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*def*]phenanthrene (159a)

Produced as a 22:78 mixture with d^8-**160a**, following the general procedure, in 38% yield from d^8-**159a**. Following analysis of the crude mixture, ^{1}H NMR signals for **161a** overlapped with those of analytically pure material obtained from **159a** as described previously.





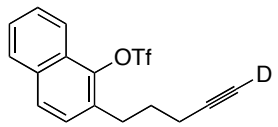
2-(4-Methyl-4-pentenyl)-1-naphthyl trifluoromethanesulfonate 210a

An oven-dried Schlenk tube was loaded with Cp_2ZrCl_2 (45 mg, 0.154 mmol, 25 mol %) followed by the alkynyl triflate (211 mg, 0.616 mmol, 1.00 equiv). In a dry box, this mixture was dissolved using 1,2-dichloroethane (4.5 mL), then neat Me_3Al (120 μL, 1.23 mmol, 2.00 equiv) was added dropwise via syringe. The resulting lemon-yellow mixture was allowed to stir for 18 h in a sealed Schlenk tube, after which it was diluted with wet CH_2Cl_2 and cautiously poured over 5% aqueous HCl. After gas evolution had subsided, the organic products were extracted into CH_2Cl_2 (3X 10 mL). The combined organics were washed successively with 5% HCl (1X) and H_2O (1X), dried (Na_2SO_4), filtered, and concentrated to dryness. Flash chromatography (2% EtOAc/PE) provided the title compound (211 mg, 95%) as a clear colourless liquid. IR (neat) 3073, 2961, 2933, 2868, 1406 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (1H, d, *J* = 8.5 Hz), 7.87 (1H, d, *J* = 8.0 Hz), 7.82 (1H, d, *J* = 8.5 Hz), 7.65 (1H, ddd, *J* = 7.4, 7.1, 0.9 Hz), 7.55 (1H, ddd, *J* = 7.2, 7.1, 0.9 Hz), 7.43 (1H, d, *J* = 8.3 Hz), 4.80 (2H, d, *J* = 11.4 Hz), 2.96 (2H, dd, *J* = 7.8 Hz), 2.17 (2H, t, *J* = 7.4 Hz), 1.91 (dt, 2H, *J* = 8.2, 8.1 Hz), 1.80 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 142.3, 133.6, 132.9, 128.5, 127.8, 127.7, 127.6, 127.4, 127.1, 126.5, 125.8, 125.2, 127.2, 118.7 (1C, q, *J* = 318 Hz), 110.5, 37.5, 30.0, 28.0, 22.2; HRMS (EI) Calcd. for $C_{17}H_{17}F_3O_3S$: 358.0850. Found: 358.0843.

3a-Methyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*def*]phenanthrene (161a)[154]

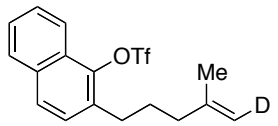
In the dry box, a mixture of $Pd[P(p\text{-}MeOPh)_3]_2Cl_2$ (27 mg, 0.031 mmol, 10 mol %), $P(p\text{-}MeOPh)_3$ (22 mg, 0.061 mmol, 20 mol %) and triethylamine (4.3 μL, 0.031 mmol, 0.10 equiv) was suspended in CH_3CN (1.0 mL) in a Schlenk tube, and heated gently until dissolution resulted. To this light orange mixture was then added a mixture of DABCO (6.0 equiv) and triflate **210a**, quantitatively transferred using CH_3CN (2.1 mL), bringing the total concentration to 0.10 M. The Schlenk tube was sealed and placed in an oil bath at 100 ºC for 24 h. Upon completion, the reaction was cooled to ambient temperature and poured into 5% aqueous HCl (15 mL). The products were extracted with dichloromethane (3 x 10 mL) and washed with 5% HCl (1X 5 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered over Celite eluting with dichloromethane and concentrated under reduced pressure. The resulting crude gum was purified by flash chromatography (100% PE) to produce the title compound in 83% yield from **210a** as a clear colourless liquid; characterisation data were in agreement with those by Carson.

3.6.3.24 Synthesis of Diastereomeric Deuterium-Labeled Tricycles *d*-160 and Tetracycles *d*-161



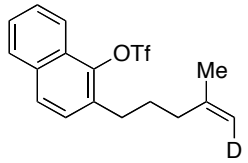
2-(5-Deuteriopent-4-ynyl)-1-naphthalenyl trifluoromethanesulfonate *d*-159a

Obtained after the procedures cited in section 3.6.3.18, as a clear colourless oil; IR (neat) 2594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (1H, d, J = 8.5 Hz), 7.87 (1H, d, J = 8.1 Hz), 7.82 (1H, d, J = 8.5 Hz), 7.63 (1H, ddd, J = 7.1, 7.0, 1.2 Hz), 7.55 (1H, ddd, J = 7.1, 7.0, 1.2 Hz), 7.42 (1H, d, J = 8.5 Hz), 3.05 (2H, dd, J = 8.0, 8.0 Hz), 2.27 (2H, t, J = 7.0 Hz), 1.95 (2H, dt, J = 15.4, 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.3, 133.7, 132.0, 128.6, 127.8, 127.7, 127.7, 127.2, 126.6, 121.3, 118.7 (q, J = 318 Hz), 82.9 (t, $J_{C\text{-}D}$ = 7.3 Hz), 68.9 (t, $J_{C\text{-}D}$ = 38 Hz), 29.4, 28.7, 18.1; HRMS (EI) Calcd. for $C_{16}H_{12}DF_3O_3S$: 343.0600. Found: 343.0599.



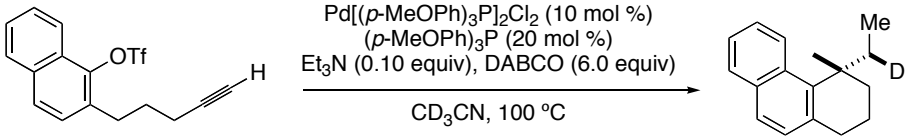
2-((*E*)-5-Deuterio-4-methylpent-4-enyl)naphth-1-yl trifluoromethanesulfonate

Obtained from **159a** (200 mg, 0.584 mmol) following methylalumination as described in the first half of General Procedure 3.6.2.12. After carefully quenching with D_2O (5 mL per mmol substrate), and extractive work-up as described, purification by flash chromatography (3% CH_2Cl_2/PE) gave the title alkene (180 mg, 86%) as a clear colourless oil; IR (neat) 2355 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (1H, d, *J* = 8.5 Hz), 7.86 (1H, d, *J* = 8.0 Hz), 7.81 (1H, d, *J* = 8.5 Hz), 7.62 (1H, ddd, *J* = 7.4, 7.1, 0.9 Hz), 7.54 (1H, ddd, *J* = 7.2, 7.1, 0.9 Hz), 7.42 (1H, d, *J* = 8.3 Hz), 4.69 (1H, s), 2.90 (2H, dd, *J* = 7.8 Hz), 2.10 (2H, t, *J* = 7.4 Hz), 1.85 (dt, 2H, *J* = 8.2, 8.1 Hz), 1.73 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 142.2, 133.5, 132.8, 128.5, 127.8, 127.7, 127.6, 127.1, 126.4, 121.2, 118.7 (q, $J_{C\text{-}F}$ = 318 Hz), 110.2 (t, $J_{C\text{-}D}$ = 23.7 Hz), 37.4, 30.0, 27.9, 22.2; HRMS (EI) Calcd. for $C_{17}H_{16}DF_3O_3S$: 359.0913. Found: 359.0913.



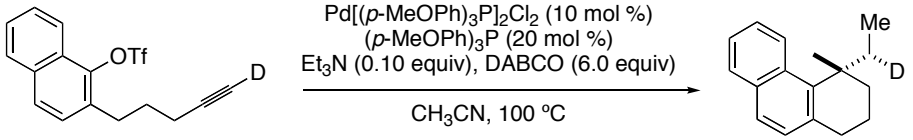
2-((*Z*)-5-Deuterio-4-methylpent-4-enyl)naphth-1-yl trifluoromethanesulfonate

Obtained from *d*-**159a** (98 mg, 0.284 mmol) following methylalumination as outlined in the first half of General Procedure 3.6.2.12. After carefully quenching with 5% HCl and extractive work-up as described, purification by flash chromatography (2% EtOAc/PE) gave the title alkene (87 mg, 85%) as a clear colourless oil; IR (neat) 2355 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (1H, d, *J* = 8.5 Hz), 7.86 (1H, d, *J* = 8.0 Hz), 7.81 (1H, d, *J* = 8.5 Hz), 7.63 (1H, ddd, *J* = 7.4, 7.1, 0.9 Hz), 7.59 (1H, ddd, *J* = 7.2, 7.1, 0.9 Hz), 7.41 (1H, d, *J* = 8.3 Hz), 4.74 (1H, s), 2.90 (2H, dd, *J* = 7.8 Hz), 2.11 (2H, t, *J* = 7.4 Hz), 1.85 (dt, 2H, *J* = 8.2, 8.1 Hz), 1.73 (3H, d, *J* = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 142.2, 133.5, 132.8, 128.5, 127.8, 127.7, 127.6, 127.1, 126.5, 121.2, 118.7 (q, $J_{C\text{-}F}$ = 318 Hz), 110.2 (t, $J_{C\text{-}D}$ = 23.7 Hz), 37.4, 30.0, 27.9, 22.2; HRMS (EI) Calcd. for $C_{17}H_{16}DF_3O_3S$: 359.0913. Found: 359.0913.



4-(1-Deuterioethyl)-4-methyl-1,2,3,4-tetrahydrophenanthrene (*d*-160a)

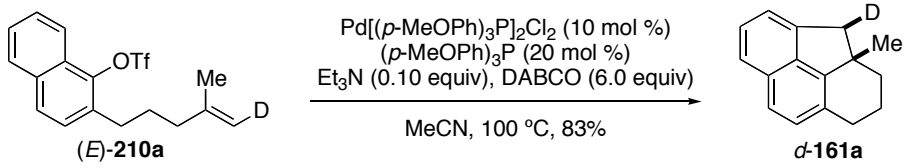
Obtained as per General Procedure 3.6.2.12 using CD_3CN on 0.40 mmol scale, following purification by column chromatography (100% PE). Repeated column chromatography (100% PE) provided an analytical sample, having the following properties. Clear colourless liquid; IR (neat) 3046, 2931, 2872, 2179, 1641, 1605, 1510, 1459, 1381 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.38 (1H, d, *J* = 8.6 Hz), 7.78 (1H, dd, *J* = 7.9, 1.4), 7.58 (1H, d, *J* = 8.3 Hz), 7.43 (1H, ddd, *J* = 8.6, 8.5, 1.7 Hz), 7.38 (1H, ddd, *J* = 8.0, 7.7, 1.1 Hz), 7.18 (1H, d, *J* = 8.3 Hz), 2.96-2.91 (2H, m), 2.00-1.97 (1H, m), 1.91 (1H, qt, *J* = 7.3, <1 Hz), 1.86-1.82 (2H, m), 1.64 (3H, s), 0.66 (3H, d, *J* = 7.4 Hz); ^2H NMR (77 MHz, $CHCl_3$) δ 2.31 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 136.1, 133.6, 132.6, 129.3, 128.6, 126.5, 126.1, 124.6, 123.9, 39.9, 38.5, 33.9 ($J_{C\text{-}D}$ = 18.8 Hz), 33.1, 28.2, 19.0, 8.9; HRMS (EI) Calcd. for $C_{17}H_{19}D$: 225.1628. Found: 225.1635.



4-(1-Deuterioethyl)-4-methyl-1,2,3,4-tetrahydrophenanthrene (*epi-d*-160a)

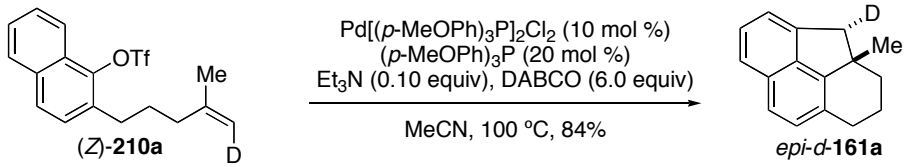
Obtained as per General Procedure 3.6.2.12 on 0.30 mmol scale, following purification by column chromatography (100% PE). Repeated column chromatography (100% PE) provided an analytical sample, having the following properties. Clear colourless liquid; IR (neat) 3048, 2933, 2872, 2133, 1620, 1605, 1510, 1458, 1381 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.38 (1H, d, *J* = 8.6 Hz), 7.78 (1H, dd, *J* = 7.9, 1.4), 7.58 (1H, d, *J* = 8.3 Hz), 7.43 (1H, ddd, *J* = 8.6, 8.5, 1.7 Hz), 7.38 (1H, ddd, *J* = 8.0, 7.7, 1.1 Hz), 7.18 (1H, d, *J* = 8.3 Hz), 2.96-2.82 (2H, m), 2.29 (1H, q, *J* = 7.5 Hz), 2.01-1.94 (1H, m), 1.86-1.80 (2H, m), 1.62 (3H, s), 1.61-1.57 (1H, m), 0.66 (3H, d, *J* = 7.4 Hz); ^2H NMR (77 MHz, $CHCl_3$) δ 1.95 (m); ^{13}C NMR (125 MHz, $CDCl_3$)

δ 139.0, 136.1, 133.6, 132.6, 129.3, 128.6, 126.5, 126.1, 124.6, 123.9, 39.9, 38.5, 33.9 (t, $J_{C\text{-}D}$ = 18.8 Hz), 33.1, 28.2, 19.0, 8.9; HRMS (EI) Calcd. for $C_{17}H_{19}D$: 225.1628. Found: 225.1635.



4-Deuterio-3a-methyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*def*]phenanthrene (*d*-161a)

The title compound was formed as outlined in the second part of General Procedure 3.6.2.12, from 176 mg alkene (*E*)-**210a** (0.490 mmol, 1.00 equiv). Following usual extractive work-up and purification by column chromatography (100% PE), tetracycle *d*-**161a** was obtained (85 mg, 83%) as a clear colourless liquid; IR (neat) 2179 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59-7.51 (2H, m), 7.39 (1H, dd, *J* = 6.9, 6.9 Hz), 7.26-7.20 (2H, m), 3.09 (1H, s), 2.96 (1H, ddd, *J* = 17.3, 8.1 Hz), 2.74-2.66 (1H, m), 2.24-2.04 (3H, m), 1.78-1.72 (1H, m), 1.33 (3H, s); ^2H NMR (77 MHz, $CHCl_3$) δ 3.33 (d, *J* = 3.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 142.4, 136.7, 129.7, 128.4, 128.1, 127.2, 122.9, 122.2, 120.0, 47.5 (t, $J_{C\text{-}D}$ = 20 Hz), 42.2, 34.0, 27.8, 24.7, 19.8; HRMS (EI) Calcd. for $C_{16}H_{15}D$: 209.1315. Found: 209.1315.

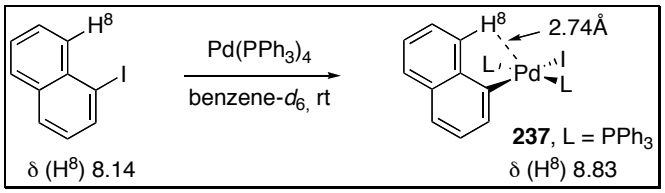


4-Deuterio-3a-methyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*def*]phenanthrene (*epi-d*-161a)

The title compound was synthesised as described in the second part of General Procedure 3.6.2.12, from 78 mg alkene (*Z*)-**210a** (0.217 mmol, 1.00 equiv). Following usual extractive work-up and purification by column chromatography (100% PE), tetracycle *epi-d*-**161a** was obtained (38 mg, 84%) as a clear colourless liquid; IR (neat) 2181 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (1H, d, *J* = 8.2 Hz), 7.55 (1H, d, *J* = 8.3 Hz), 7.39 (1H, dd, *J* = 6.9, 6.9 Hz), 7.27 (1H, d, *J* = 8.6 Hz), 7.23 (1H, d, *J* = 8.3 Hz), 3.30 (1H, s), 2.99 (1H, ddd, *J* = 17.3, 8.1

Hz), 2.77-2.68 (1H, m), 2.26-1.98 (3H, m), 1.79 (1H, ddd, J = 12.7, 12.5, 4.4 Hz), 1.36 (3H, s); ^{2}H NMR (77 MHz, $CHCl_3$) δ 3.11 (d, J = 3.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 142.5, 136.7, 129.7, 128.4, 128.1, 127.2, 122.9, 122.2, 120.1, 47.5 (t, $J_{C\text{-}D}$ = 20 Hz), 42.3, 33.9, 27.9, 24.7, 19.8; HRMS (EI) Calcd. for $C_{16}H_{15}D$: 209.1315. Found: 209.1308.

3.6.3.25 Synthesis and X-Ray Crystallography of *trans*-bis(triphenylphosphino)-1-naphthylpalladium(II) iodide



***trans*-Bis(triphenylphosphino)-1-naphthylpalladium(II) iodide 237**

An oven-dried Schlenk tube was loaded with 1-iodonaphthalene (5.9 μL, 0.040 mmol) and benzene (1.5 mL) under Ar, sealed and transferred to a dry box, wherein $Pd(PPh_3)_4$ (46 mg, 0.040 mmol) was added. The reaction mixture was stirred in the resealed tube for three days at room temperature then evaporated to dryness in a small vial in the dry box. Light yellow crystals (yield not recorded) suitable for X-ray analysis were obtained by recrystallisation from boiling benzene (about 2 mL).

NMR Experiment

In a vacuum-dried resealable NMR tube was dissolved under nitrogen $Pd(PPh_3)_4$ (23 mg; 0.020 mmol) in 0.60 mL PhH-d_6 at room temperature. A t_0 NMR spectrum was acquired then 1-iodonaphthalene (4.4 μL; 0.030 mmol; 1.5 equiv) was added via microsyringe. The resulting yellow solution was aged at room temperature in the dark, and analyzed periodically by ^{1}H and ^{31}P NMR. Deshielding of H^8 (8.14 to 8.83 ppm, Δδ = 0.79 ppm) was observed upon forming Pd(II) complex **15**, as well as shielding of H^3 (6.68 to 6.43 ppm, Δδ = - 0.25 ppm). By ^{31}P

NMR, the initial signal (26.7 ppm) gradually fades down to be replaced by two upfield signals (25.2 ppm, major and 25.0 ppm, minor).

Figure 1. ^{1}H NMR (300 MHz) of (a) 1.5 equiv 1-iodonaphthalene in PhH-d_6 at t_0; (b) after addition of 1.0 equiv $Pd(PPh_3)_4$ at t_1 = 3 min; (c) t_2 = 0.50 h; (d) t_3 = 2.25 h; (e) t_4 = 17.75 h; (f) t_5 = 122 h. Signal at 8.83 ppm, termed $H^{8'}$, is attributed to deshielded H^8 in Pd(II) complex **15**.

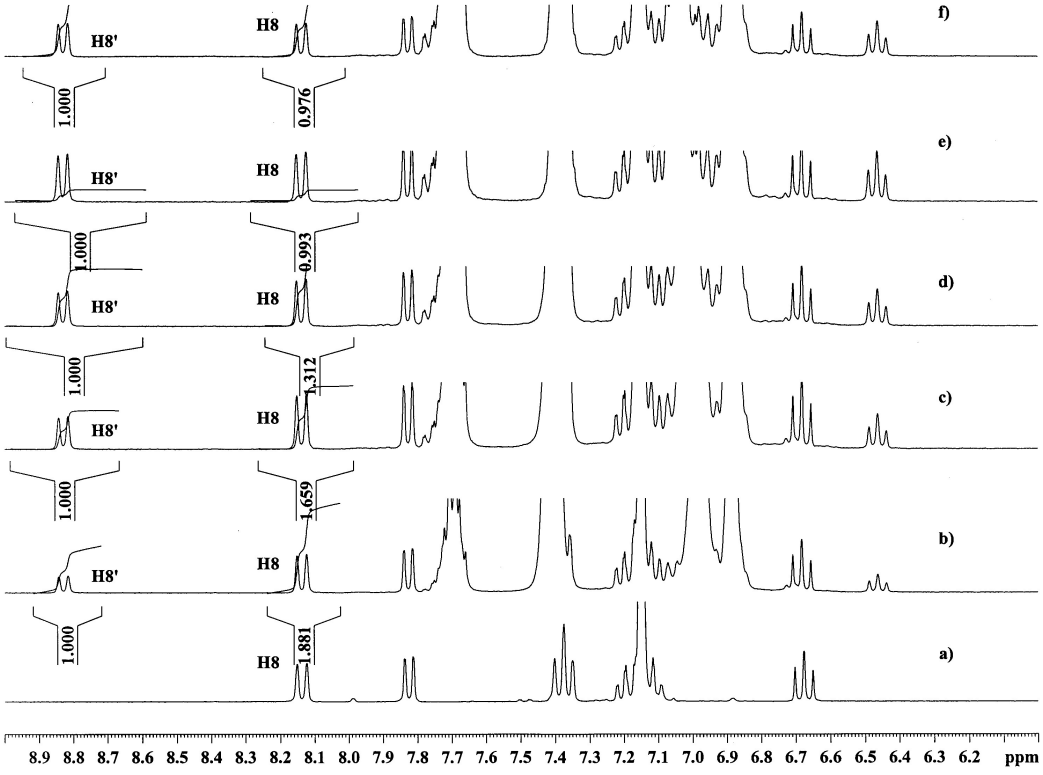


Figure 2. ^{31}P NMR (79.1 MHz) of (a) 1.0 equiv $Pd(PPh_3)_4$ in PhH-d_6 at t_0; (b) t_1 = 5 min after adding 1.5 equiv 1-iodonaphthalene; (c) t_2 = 32.25 h; (d) t_3 = 40.25 h.

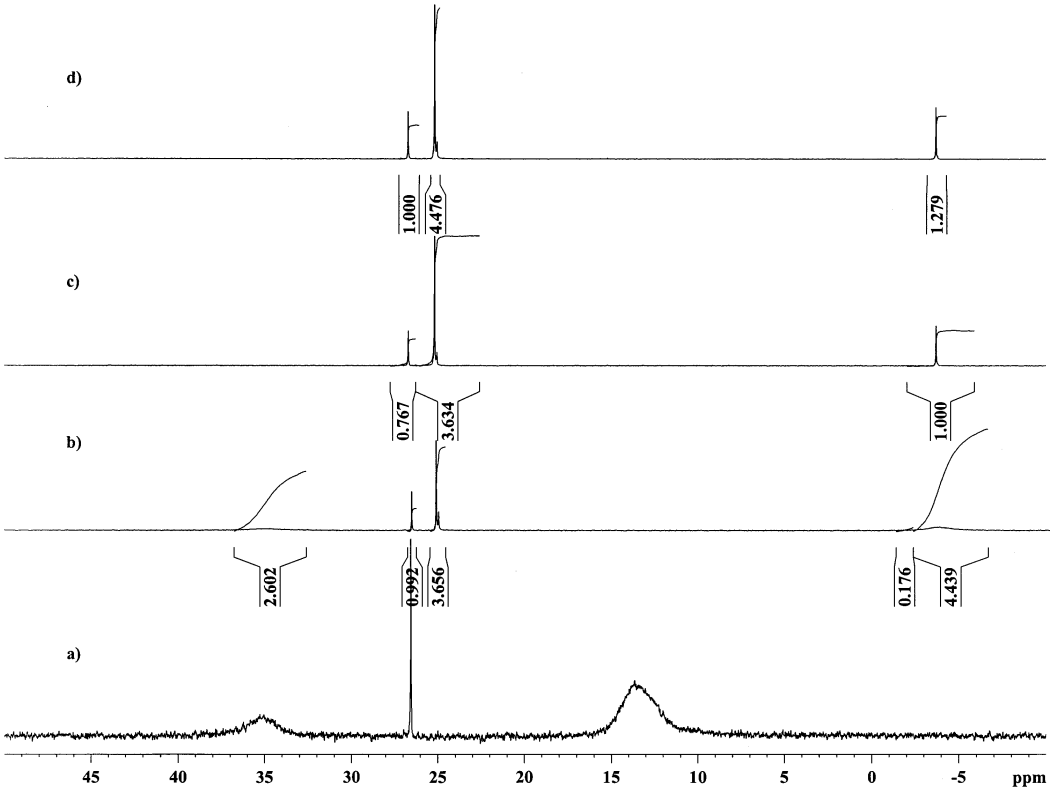


Table 1. Crystal data and structure refinement for ef1315m.

Identification code	ef1315m
Empirical formula	$C_{46}H_{37}IP_2Pd$
Formula weight	885.00
Temperature	180(1) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 11.9735(4) Å alpha = 90° b = 29.1706(10) Å beta = 101.228(1)° c = 11.1652(4) Å gamma = 90°
Volume, Z	3825.1(2) Å^3, 4
Density (calculated)	1.537 Mg/m^3
Absorption coefficient	1.408 mm^{-1}
F(000)	1768
Crystal size	0.36 x 0.23 x 0.20 mm
Θ range for data collection	1.73 to 30.03°
Limiting indices	$-16 \le h \le 16$, $-41 \le k \le 41$, $-15 \le l \le$
Reflections collected	45738
Independent reflections	11186 (R_{int} = 0.0326)
Completeness to Θ = 30.03°	100.0 %
Absorption correction	Integration
Max. and min. transmission	0.775 and 0.637
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11186 / 0 / 455
Goodness-of-fit on F^2	1.367
Final R indices [I>2σ(I)]	R1 = 0.0240, wR2 = 0.0553
R indices (all data)	R1 = 0.0278, wR2 = 0.0560
Largest diff. peak and hole	0.790 and -0.445 eÅ^{-3}

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [Å^2 x 10^3] for ef1315m. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Pd(1)	948(1)	1427(1)	5137(1)	20(1)
I(1)	1108(1)	2061(1)	3421(1)	29(1)
P(1)	-1034(1)	1457(1)	4702(1)	21(1)
P(2)	2919(1)	1362(1)	5680(1)	22(1)
C(1)	858(1)	929(1)	6375(1)	22(1)
C(2)	820(1)	474(1)	6038(2)	28(1)
C(3)	772(2)	121(1)	6893(2)	33(1)
C(4)	773(2)	223(1)	8079(2)	33(1)
C(4A)	820(1)	686(1)	8487(2)	27(1)
C(5)	864(2)	801(1)	9725(2)	35(1)
C(6)	935(2)	1248(1)	10097(2)	40(1)
C(7)	957(2)	1604(1)	9254(2)	35(1)
C(8)	920(1)	1502(1)	8046(2)	28(1)
C(8A)	855(1)	1042(1)	7615(1)	23(1)
C(9)	-1715(1)	1215(1)	3233(1)	22(1)
C(10)	-1092(1)	1114(1)	2333(1)	26(1)
C(11)	-1636(2)	948(1)	1203(2)	31(1)
C(12)	-2799(2)	882(1)	963(2)	34(1)
C(13)	-3426(2)	979(1)	1848(2)	33(1)
C(14)	-2891(1)	1143(1)	2981(2)	27(1)
C(15)	-1802(1)	1159(1)	5737(1)	24(1)
C(16)	-1863(1)	682(1)	5682(2)	30(1)
C(17)	-2391(2)	437(1)	6470(2)	36(1)
C(18)	-2880(2)	666(1)	7327(2)	43(1)
C(19)	-2840(2)	1135(1)	7380(2)	45(1)
C(20)	-2294(2)	1383(1)	6598(2)	35(1)
C(21)	-1547(1)	2046(1)	4669(1)	22(1)
C(22)	-2353(1)	2224(1)	3719(2)	28(1)
C(23)	-2694(2)	2677(1)	3741(2)	36(1)
C(24)	-2233(2)	2956(1)	4714(2)	36(1)
C(25)	-1431(2)	2786(1)	5658(2)	35(1)
C(26)	-1080(1)	2333(1)	5636(2)	32(1)
C(27)	3495(1)	1017(1)	4576(1)	26(1)
C(28)	2864(1)	961(1)	3401(2)	30(1)
C(29)	3269(2)	689(1)	2558(2)	36(1)
C(30)	4292(2)	460(1)	2893(2)	34(1)
C(31)	4932(2)	514(1)	4053(2)	35(1)
C(32)	4544(1)	794(1)	4888(2)	31(1)
C(33)	3480(1)	1078(1)	7132(1)	25(1)
C(34)	3461(1)	600(1)	7210(2)	28(1)
C(35)	3756(1)	381(1)	8327(2)	35(1)
C(36)	4074(2)	636(1)	9382(2)	44(1)
C(37)	4090(2)	1105(1)	9315(2)	50(1)
C(38)	3805(2)	1329(1)	8203(2)	37(1)
C(39)	3680(1)	1907(1)	5829(2)	29(1)
C(40)	4734(2)	1961(1)	5505(2)	40(1)
C(41)	5303(2)	2377(1)	5705(2)	51(1)
C(42)	4835(2)	2735(1)	6225(2)	53(1)
C(43)	3788(2)	2687(1)	6553(2)	53(1)
C(44)	3206(2)	2274(1)	6345(2)	40(1)

Table 3. Bond lengths [Å] and angles [°] for ef1315m.

Pd(1)-C(1)	2.0223(15)	Pd(1)-P(2)	2.3279(4)
Pd(1)-P(1)	2.3291(4)	Pd(1)-I(1)	2.69785(16)
P(1)-C(21)	1.8238(15)	P(1)-C(9)	1.8258(15)
P(1)-C(15)	1.8297(15)	P(2)-C(39)	1.8215(16)
P(2)-C(27)	1.8270(16)	P(2)-C(33)	1.8284(16)
C(1)-C(2)	1.378(2)	C(1)-C(8A)	1.424(2)
C(2)-C(3)	1.413(2)	C(3)-C(4)	1.357(2)
C(4)-C(4A)	1.422(2)	C(4A)-C(5)	1.414(2)
C(4A)-C(8A)	1.431(2)	C(5)-C(6)	1.368(3)
C(6)-C(7)	1.405(3)	C(7)-C(8)	1.374(2)
C(8)-C(8A)	1.422(2)	C(9)-C(10)	1.395(2)
C(9)-C(14)	1.397(2)	C(10)-C(11)	1.389(2)
C(11)-C(12)	1.379(2)	C(12)-C(13)	1.382(2)
C(13)-C(14)	1.386(2)	C(15)-C(20)	1.386(2)
C(15)-C(16)	1.395(2)	C(16)-C(17)	1.379(2)
C(17)-C(18)	1.386(3)	C(18)-C(19)	1.371(3)
C(19)-C(20)	1.391(2)	C(21)-C(22)	1.388(2)
C(21)-C(26)	1.395(2)	C(22)-C(23)	1.384(2)
C(23)-C(24)	1.383(2)	C(24)-C(25)	1.374(2)
C(25)-C(26)	1.387(2)	C(27)-C(28)	1.390(2)
C(27)-C(32)	1.396(2)	C(28)-C(29)	1.390(2)
C(29)-C(30)	1.380(2)	C(30)-C(31)	1.380(3)
C(31)-C(32)	1.386(2)	C(33)-C(38)	1.392(2)
C(33)-C(34)	1.398(2)	C(34)-C(35)	1.384(2)
C(35)-C(36)	1.383(3)	C(36)-C(37)	1.370(3)
C(37)-C(38)	1.385(3)	C(39)-C(40)	1.388(2)
C(39)-C(44)	1.390(2)	C(40)-C(41)	1.389(3)
C(41)-C(42)	1.367(3)	C(42)-C(43)	1.380(3)
C(43)-C(44)	1.387(3)		

C(1)-Pd(1)-P(2)	87.16(4)	C(1)-Pd(1)-P(1)	88.96(4)
P(2)-Pd(1)-P(1)	176.087(14)	C(1)-Pd(1)-I(1)	177.32(4)
P(2)-Pd(1)-I(1)	91.822(10)	P(1)-Pd(1)-I(1)	92.078(10)
C(21)-P(1)-C(9)	104.85(7)	C(21)-P(1)-C(15)	104.57(7)
C(9)-P(1)-C(15)	101.10(7)	C(21)-P(1)-Pd(1)	111.44(5)
C(9)-P(1)-Pd(1)	115.55(5)	C(15)-P(1)-Pd(1)	117.85(5)
C(39)-P(2)-C(27)	107.13(7)	C(39)-P(2)-C(33)	102.92(7)
C(27)-P(2)-C(33)	103.11(7)	C(39)-P(2)-Pd(1)	114.64(5)
C(27)-P(2)-Pd(1)	111.44(5)	C(33)-P(2)-Pd(1)	116.48(5)
C(2)-C(1)-C(8A)	118.89(14)	C(2)-C(1)-Pd(1)	120.52(11)
C(8A)-C(1)-Pd(1)	120.58(10)	C(1)-C(2)-C(3)	121.35(15)
C(4)-C(3)-C(2)	120.50(15)	C(3)-C(4)-C(4A)	120.85(15)
C(5)-C(4A)-C(4)	121.97(15)	C(5)-C(4A)-C(8A)	119.53(15)
C(4)-C(4A)-C(8A)	118.48(15)	C(6)-C(5)-C(4A)	120.77(16)
C(5)-C(6)-C(7)	120.64(16)	C(8)-C(7)-C(6)	119.81(16)
C(7)-C(8)-C(8A)	121.72(15)	C(8)-C(8A)-C(1)	122.53(14)
C(8)-C(8A)-C(4A)	117.51(14)	C(1)-C(8A)-C(4A)	119.93(14)
C(10)-C(9)-C(14)	118.88(14)	C(10)-C(9)-P(1)	121.36(11)
C(14)-C(9)-P(1)	119.72(12)	C(11)-C(10)-C(9)	120.32(15)
C(12)-C(11)-C(10)	120.19(16)	C(11)-C(12)-C(13)	120.05(15)
C(12)-C(13)-C(14)	120.29(16)	C(13)-C(14)-C(9)	120.27(15)
C(20)-C(15)-C(16)	118.37(14)	C(20)-C(15)-P(1)	123.27(12)
C(16)-C(15)-P(1)	118.33(12)	C(17)-C(16)-C(15)	121.09(16)
C(16)-C(17)-C(18)	119.89(16)	C(19)-C(18)-C(17)	119.65(17)
C(18)-C(19)-C(20)	120.66(18)	C(15)-C(20)-C(19)	120.33(16)

C(22)-C(21)-C(26)	118.79(14)	C(22)-C(21)-P(1)	123.32(12)
C(26)-C(21)-P(1)	117.87(12)	C(23)-C(22)-C(21)	120.46(15)
C(24)-C(23)-C(22)	120.09(16)	C(25)-C(24)-C(23)	120.17(16)
C(24)-C(25)-C(26)	119.95(16)	C(25)-C(26)-C(21)	120.53(15)
C(28)-C(27)-C(32)	118.55(15)	C(28)-C(27)-P(2)	119.59(12)
C(32)-C(27)-P(2)	121.84(12)	C(29)-C(28)-C(27)	120.59(15)
C(30)-C(29)-C(28)	120.07(16)	C(31)-C(30)-C(29)	120.04(16)
C(30)-C(31)-C(32)	120.06(16)	C(31)-C(32)-C(27)	120.65(16)
C(38)-C(33)-C(34)	118.45(15)	C(38)-C(33)-P(2)	121.10(13)
C(34)-C(33)-P(2)	120.02(12)	C(35)-C(34)-C(33)	120.80(16)
C(36)-C(35)-C(34)	119.89(17)	C(37)-C(36)-C(35)	119.72(17)
C(36)-C(37)-C(38)	121.06(18)	C(37)-C(38)-C(33)	120.07(17)
C(40)-C(39)-C(44)	119.04(16)	C(40)-C(39)-P(2)	122.60(14)
C(44)-C(39)-P(2)	118.28(13)	C(39)-C(40)-C(41)	119.98(19)
C(42)-C(41)-C(40)	120.53(19)	C(41)-C(42)-C(43)	120.23(19)
C(42)-C(43)-C(44)	119.8(2)	C(43)-C(44)-C(39)	120.44(18)

Symmetry transformations used to generate equivalent atoms:

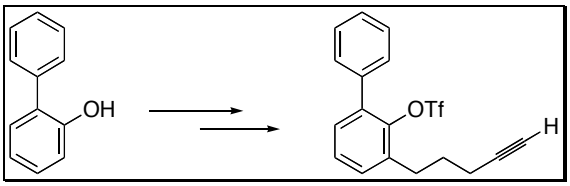
Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for ef1315m.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

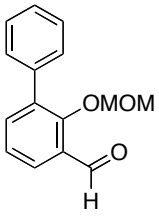
	U11	U22	U33	U23	U13	U12
Pd(1)	19(1)	20(1)	19(1)	2(1)	2(1)	1(1)
I(1)	31(1)	27(1)	29(1)	8(1)	4(1)	-1(1)
P(1)	20(1)	20(1)	21(1)	0(1)	3(1)	0(1)
P(2)	20(1)	24(1)	22(1)	1(1)	3(1)	1(1)
C(1)	21(1)	21(1)	24(1)	0(1)	3(1)	1(1)
C(2)	31(1)	24(1)	29(1)	-1(1)	2(1)	1(1)
C(3)	36(1)	21(1)	40(1)	2(1)	3(1)	-1(1)
C(4)	35(1)	26(1)	38(1)	10(1)	8(1)	0(1)
C(4A)	26(1)	29(1)	28(1)	6(1)	8(1)	1(1)
C(5)	40(1)	40(1)	28(1)	8(1)	12(1)	2(1)
C(6)	49(1)	47(1)	27(1)	-2(1)	14(1)	5(1)
C(7)	44(1)	31(1)	31(1)	-5(1)	11(1)	4(1)
C(8)	31(1)	26(1)	27(1)	1(1)	7(1)	2(1)
C(8A)	22(1)	23(1)	25(1)	3(1)	5(1)	2(1)
C(9)	26(1)	18(1)	23(1)	0(1)	3(1)	0(1)
C(10)	29(1)	21(1)	27(1)	1(1)	7(1)	1(1)
C(11)	43(1)	24(1)	26(1)	-2(1)	10(1)	-1(1)
C(12)	46(1)	29(1)	24(1)	-1(1)	2(1)	-10(1)
C(13)	31(1)	36(1)	30(1)	3(1)	-1(1)	-11(1)
C(14)	28(1)	29(1)	25(1)	0(1)	4(1)	-4(1)
C(15)	21(1)	25(1)	24(1)	3(1)	2(1)	-1(1)
C(16)	30(1)	26(1)	34(1)	2(1)	8(1)	0(1)
C(17)	41(1)	29(1)	39(1)	7(1)	8(1)	-7(1)
C(18)	53(1)	46(1)	32(1)	3(1)	15(1)	-18(1)
C(19)	60(1)	45(1)	38(1)	-11(1)	26(1)	-14(1)
C(20)	44(1)	31(1)	32(1)	-5(1)	14(1)	-6(1)
C(21)	22(1)	20(1)	26(1)	0(1)	6(1)	-1(1)
C(22)	34(1)	24(1)	25(1)	-1(1)	1(1)	1(1)
C(23)	46(1)	28(1)	30(1)	5(1)	-1(1)	7(1)
C(24)	46(1)	21(1)	41(1)	1(1)	5(1)	3(1)
C(25)	40(1)	25(1)	38(1)	-7(1)	0(1)	-2(1)
C(26)	32(1)	26(1)	33(1)	-3(1)	-3(1)	2(1)
C(27)	26(1)	27(1)	26(1)	3(1)	8(1)	0(1)
C(28)	27(1)	35(1)	29(1)	-1(1)	5(1)	4(1)
C(29)	39(1)	40(1)	28(1)	-5(1)	7(1)	2(1)
C(30)	38(1)	31(1)	39(1)	-3(1)	20(1)	0(1)
C(31)	30(1)	36(1)	41(1)	6(1)	14(1)	7(1)
C(32)	27(1)	38(1)	30(1)	2(1)	6(1)	3(1)
C(33)	20(1)	30(1)	24(1)	1(1)	3(1)	3(1)
C(34)	26(1)	30(1)	28(1)	1(1)	7(1)	5(1)
C(35)	32(1)	37(1)	36(1)	10(1)	9(1)	9(1)
C(36)	46(1)	56(1)	28(1)	11(1)	0(1)	9(1)
C(37)	62(1)	55(1)	26(1)	-3(1)	-9(1)	3(1)
C(38)	40(1)	36(1)	31(1)	-3(1)	-4(1)	1(1)
C(39)	26(1)	28(1)	30(1)	4(1)	1(1)	-3(1)
C(40)	34(1)	40(1)	47(1)	2(1)	12(1)	-6(1)
C(41)	38(1)	49(1)	68(1)	8(1)	12(1)	-15(1)
C(42)	46(1)	34(1)	73(2)	9(1)	-5(1)	-14(1)
C(43)	47(1)	32(1)	76(2)	-7(1)	3(1)	-3(1)
C(44)	32(1)	32(1)	57(1)	-4(1)	7(1)	-2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for ef1315m.

	x	y	z	U(eq)
H(2)	826	396	5213	34
H(3)	740	-190	6637	39
H(4)	741	-18	8645	39
H(5)	843	564	10306	42
H(6)	971	1319	10934	48
H(7)	996	1914	9518	42
H(10)	-290	1159	2493	31
H(11)	-1206	880	595	37
H(12)	-3169	770	188	40
H(13)	-4227	933	1680	40
H(14)	-3326	1206	3588	33
H(16)	-1536	523	5091	36
H(17)	-2419	112	6426	43
H(18)	-3240	498	7875	51
H(19)	-3188	1292	7957	54
H(20)	-2260	1708	6655	41
H(22)	-2673	2034	3050	34
H(23)	-3244	2797	3086	43
H(24)	-2473	3266	4729	43
H(25)	-1116	2978	6326	42
H(26)	-518	2218	6285	38
H(28)	2150	1111	3172	36
H(29)	2842	659	1750	43
H(30)	4554	265	2325	41
H(31)	5640	360	4280	42
H(32)	4996	835	5680	38
H(34)	3243	423	6488	34
H(35)	3740	56	8369	42
H(36)	4282	487	10149	53
H(37)	4299	1280	10042	60
H(38)	3832	1654	8172	44
H(40)	5066	1713	5145	47
H(41)	6023	2413	5480	61
H(42)	5232	3018	6360	64
H(43)	3467	2935	6920	63
H(44)	2479	2243	6557	48
H(8)	934(14)	1750(6)	7435(16)	30(5)

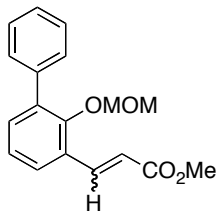
3.6.3.26 Synthesis of 3-(5-Pentynyl)-1,1'-biphen-2-yl Trifluoromethanesulfonate 240





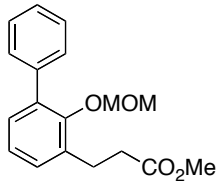
3-Phenyl-2-methoxymethoxybenzaldehyde

To a solution of the known salicylaldehyde[193] (40.0 mmol) in dry DMF (80 mL) was added K_2CO_3 (13.8 g, 100 mmol, 2.5 equiv) and the slurry was stirred at rt for 30 min. Then, it was cooled to 0 ºC for the injection of MOM-Cl (4.6 mL, 60.0 mmol, 1.5 equiv). After 15 min at 0 ºC, the reaction was allowed to stir at rt for 18 days. Although incomplete by TLC (unoptimised), the reaction was quenched by diluting with water (200 mL) and ether (150 mL). The aqueous layer was twice more extracted with ether, and the combined organics were successively washed with water (3 times) and brine, dried over $MgSO_4$, filtered and concentrated to dryness. After flash chromatography (2% then 5% then 10% EtOAc/PE), there was obtained 4.4 g (45%) of the title compound as light yellow oil, which was taken to the next step without further characterisation. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.50 (1H, s), 7.88 (1H, dd, *J* = 7.7, 1.8 Hz), 7.62 (1H, dd, *J* = 7.6, 1.9 Hz), 7.58-7.40 (5H, m), 7.34 (1H, t, *J* = 7.6 Hz), 4.72 (2H, s), 3.27 (3H, s).



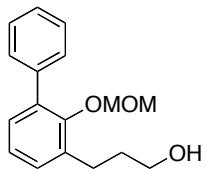
Methyl (*E*)-3-(3-Phenyl-2-methoxymethoxyphenyl)-2-propenoate

Obtained as a 84:6 *E*:*Z* mixture using (carbomethoxy)methylphosphonium bromide as Wittig salt, following General Procedure 3.6.2.7. Clear colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$, peaks for the major diastereomer reported) δ 8.16 (1H, d, *J* = 16.2 Hz), 7.59-7.32 (7H, m), 7.22 (1H, t, *J* = 7.9 Hz), 6.49 (1H, d, *J* = 16.2 Hz), 4.62 (2H, s), 3.81 (3H, s), 3.23 (3H, s); HRMS (EI) Calcd. for $C_{18}H_{18}O_4$: 298.1205. Found: 298.1203.



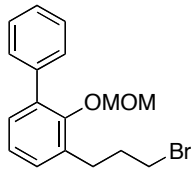
Methyl 3-(3-Phenyl-2-methoxymethoxyphenyl)propanoate

Obtained following General Procedure 3.6.2.8 using (1:1) EtOAc/MeOH as solvent, and 4 h as reaction time, after purification over a short column of silica gel (100% EtOAc), as a clear colourless oil (5.0 g, 91% over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (2H, dt, *J* = 7.0, 1.6 Hz), 7.40 (2H, tt, *J* = 7.0, 1.6 Hz), 7.34-7.30 (1H, m), 7.24-7.18 (2H, m), 7.13 (1H, t, *J* = 7.7 Hz), 4.54 (2H, s), 3.70 (3H, s), 3.28 (3H, s), 3.08 (2H, dd, *J* = 8.4, 7.6 Hz), 2.74 (2H, dd, *J* = 8.5, 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 153.2, 139.0, 135.2, 134.3, 129.6, 129.2, 129.2, 128.3, 127.1, 124.4, 99.4, 57.2, 51.6, 34.7, 26.1; HRMS (EI) Calcd. for $C_{18}H_{20}O_4$: 300.1362. Found: 300.1366.



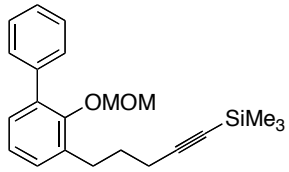
3-(3-Phenyl-2-methoxymethoxyphenyl)-1-propanol

Prepared from the corresponding methyl ester, following General Procedure 3.6.2.9 as a clear colourless oil that was carried on to the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 7.6 Hz), 7.41 (2H, t, *J* = 7.4 Hz), 7.35-7.32 (1H, m), 7.22-7.11 (3H, m), 4.54 (2H, s), 3.67 (2H, q, *J* = 6.0 Hz), 3.26 (3H, s), 2.86 (2H, t, *J* = 7.3 Hz), 2.13 (1H, t, *J* = 6.0 Hz), 1.94 (2H, dt, *J* = 6.8, 6.6 Hz); ^{13}C NMR (JMOD, 75 MHz, $CDCl_3$) δ 152.8, 139.0, 135.3, 135.2, 129.5, 129.3, 129.1, 128.3, 127.1, 124.6, 99.4, 61.6, 57.4, 33.5, 26.1; HRMS (EI) Calcd. for $C_{17}H_{20}O_3$: 272.1412. Found: 272.1416.



3-(3-Phenyl-2-methoxymethoxyphenyl)-1-bromopropane

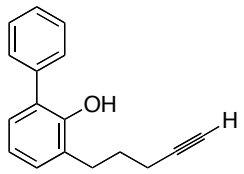
Obtained as a clear colourless oil following General Procedure 3.6.2.10, and taken as is to the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (2H, dd, *J* = 8.0, 1.6 Hz), 7.40 (2H, tt, *J* 8.0, 1.3 Hz), 7.35-7.30 (1H, m), 7.23-7.13 (3H, m), 4.55 (2H, s), 3.50 (2H, t, *J* = 6.7 Hz), 3.27 (3H, s), 2.91 (2H, dd, *J* = 7.8, 7.2 Hz), 2.27 (2H, dt, *J* = 7.6, 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 139.1, 135.3, 134.5, 129.5, 129.5, 129.3, 128.3, 127.1, 124.4, 99.4, 57.3, 33.6, 33.4, 29.2; HRMS (EI) Calcd. for $C_{17}H_{19}BrO_2$: 334.0568. Found: 334.0574.



5-(3-Phenyl-2-methoxymethoxyphenyl)-1-pentynyl)trimethylsilane

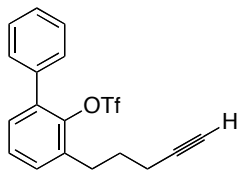
Obtained following General Procedure 3.6.2.11, modified as follows: after completion of the TMS-ethynylation reaction, NH_4Cl was added, THF was removed under reduced pressure, and

the mixture was extracted (3X) with 10% EtOAc/hexanes. The combined organic extracts were washed with H_2O (3X) and brine, dried (Na_2SO_4), filtered and concentrated to dryness. After purification by flash chromatography (5% EtOAc/PE), the title compound was obtained as a light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 7.6 Hz), 7.40 (2H, t, *J* = 7.6 Hz), 7.34-7.28 (1H, m), 7.19-7.11 (3H, m), 4.55 (2H, s), 3.24 (3H, s), 2.83 (2H, dd, *J* = 7.7, 7.7 Hz), 2.33 (2H, t, *J* = 7.2 Hz), 1.92 (2H, dt, *J* = 7.5, 7.1 Hz), 0.16 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 139.2, 135.4, 135.2, 129.4, 129.3, 129.1, 128.2, 126.9, 124.2, 107.2, 99.3, 84.7, 57.1, 29.5, 29.3, 19.7, 0.08; HRMS (EI) Calcd. for $C_{22}H_{28}O_2Si$: 352.1859. Found: 352.1855.



2-(4-Pentyn-1-yl)-6-phenylphenol

Obtained from the pentynylsilane via protiodesilylation by saturating amounts of K_2CO_3 in MeOH (General Procedure 3.6.2.5, reflux, 60 min). The volatiles were removed by rotary evaporation, and the residue was slurried in ether (80 mL) and stirred for 10 min. Following filtration on silica gel and concentration of the filtrate to dryness, the crude MOM acetal was hydrolysed following General Procedure 3.6.2.4, and obtained as a yellow oil (3.5 g, 89% over 5 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.38 (5H, m), 7.15 (1H, d, *J* = 7.8 Hz), 7.09 (1H, d, *J* = 7.5 Hz), 6.92 (1H, t, *J* = 7.5 Hz), 5.29 (1H, s), 2.80 (2H, t, *J* = 7.5 Hz), 2.26 (2H, t, *J* = 7.0 Hz), 2.00 (1H, br s), 1.90 (2H, dt, *J* = 7.6, 7.1 Hz).

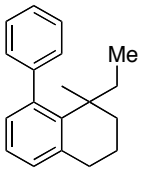


2-(4-Pentyn-1-yl)-6-phenylphenyl trifluoromethanesulfonate 240

Obtained in 55% yield from the corresponding phenol following General Procedure 3.6.2.5 (3.02 g) as a clear colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.42 (5H, m), 7.40-7.37

(1H, m), 7.36 (1H, dd, J = 7.3, 2.3 Hz), 7.30 (1H, dd, J = 7.1, 2.3 Hz), 2.98 (2H, dd, J = 8.0, 7.8 Hz), 2.33 (2H, dt, J = 7.0, 2.6 Hz), 2.05 (1H, t, J = 2.6 Hz), 1.99 (2H, dt, J = 7.9, 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 136.5, 136.4, 135.6, 130.3, 130.2, 129.4, 128.4, 128.3, 128.1, 118.0 (q, $J_{C\text{-}F}$ = 318 Hz), 83.4, 69.1, 29.6, 28.7, 18.1; HRMS (EI) Calcd. for $C_{18}H_{15}O_3F_3S$: 368.0694. Found: 368.0692.

3.6.3.27 Attempted 1,2-Diarylation with 240



1-Ethyl-1-methyl-8-phenyl-1,2,3,4-tetrahydronaphthalene

Following General Procedure 3.6.2.12, the title compound was obtained in 33% yield following repeated column chromatography (100% PE), as a clear colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.25 (5H, m), 7.10 (1H, dd, J = 7.8, 2.2 Hz), 7.05 (1H, d, J = 7.6 Hz), 6.81 (1H, dd, J = 6.9, 2.1 Hz), 2.90 (2H, t, J = 6.4 Hz), 1.90-1.76 (2H, m), 1.49 (1H, dq, J = 14.2, 7.2 Hz), 1.45-1.20 (2H, m), 1.28 (1H, dq, J = 14.2, 7.2 Hz), 1.22 (3H, s), 0.65 (3H, t, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 142.7, 142.1, 138.0, 130.5, 130.4, 129.2, 129.1, 127.2, 126.7, 126.3, 124.3, 38.9, 37.7, 33.5, 32.3, 30.3, 18.9, 9.0; HRMS (EI) Calcd. for $C_{19}H_{22}$: 250.1722.

3.6.3.28 Synthesis and X-Ray Crystallography of *trans*-bis(triphenylphosphino)-1,1'-biphen-2-ylpalladium(II) iodide 244

A flame-dried round-bottom flask was loaded with $Pd(PPh_3)_4$ (70.5 mg, 0.061 mmol, 1.00 equiv) under Ar, and dissolved in 4 mL benzene. Then, 2-iodobiphenyl (16.2 μL, 0.092 mmol, 1.5 equiv) was added via micro-syringe. The reaction mixture was stirred for three days at room temperature, whereupon a white powder had precipitated out. The reaction mixture was concentrated by rotary evaporation and triturated with Et_2O (3 mL). After decanting the

supernatant, the solids thus obtained were first recrystallised by diffusion of cyclohexane into a $CHCl_3$ solution. The solids were isolated by filtration, and crystals suitable for X-ray crystallographic analysis were subsequently grown by slow diffusion of Et_2O into a CH_2Cl_2 solution, at 4 ºC. The crystallographic structure of complex **244** could not be solved.

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