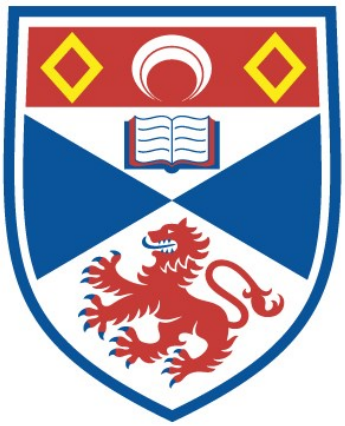
Internal alkynes in rhodium-catalysed, semi-intramolecular [2+2+2] cycloadditions

John M. Halford-McGuff

A thesis submitted for the degree of PhD
at the
University of St Andrews



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“You live and learn. At any rate, you live.” – Douglas Adams

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0.2. Publications

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J. M. Halford-McGuff, A. M. Z. Slawin, and A. J. B. Watson, *ACS Catal.*, 2023, **13**, 3463–3470.
J. M. Halford-McGuff, D. B. Cordes, and A. J. B. Watson, *Chem. Commun.*, 2023, **59**, 7759–7762.
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0.3. Acknowledgements

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Research Data

Research data underpinning this thesis are available at https://doi.org/10.17630/e4061ad1-adf2-4104-9450-e985b828f1cf.

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PhDs aren't easy, particularly if you decide to go into organic synthesis. The hours are long, the work is difficult, at times tedious, and Reviewer 2 is never impressed and always wants more so that is why it is important that you undertake a PhD with the best people around you.

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0.4. Abbreviations

Ac	Acetyl
acac	Acetylacetonate
atm	Atmosphere
ATR	Attenuated total reflectance
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
BIPHEP	2,2′-Bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bz	Benzoyl
c-Pr	Cyclopropyl
CAN	Ceric ammonium nitrate
COD	1,5-Cyclooctadiene
COE	Cyclooctene
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
CS	Chelation score
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
dan	1,8-Diaminonaphthalene
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
de	Diastereomeric excess
DHF	Dihydrofuran
DIFLUORPHOS	5,5'-Bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole
DIPEA	*N*,*N*-Di-*iso*-propylethylamine
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DPEPhos	Bis[(2-diphenylphosphino)phenyl] ether
dppb	1,4-Bis(diphenylphosphino)butane
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppm	Methylenebis(diphenylphosphine)
dppp	1,3-Bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTBM-SEGPHOS	5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
dtbpf	1,1′-Bis(di-*tert*-butylphosphino)ferrocene
ee	Enantiomeric excess
EI	Electron impact
er	Enantiomeric ratio
es	Enantiosepecificity
ESI	Electrospray Ionisation
Et	Ethyl
ETH	Ethylene
EWG	Electron-withdrawing group

Fc	Ferrocenyl
h	Hour
[H^-]	Reduction
HD	Hoffmann degradation
HRMS	High resolution mass spectrometry
HSB	Hexasubstituted benzene
i-	*ipso*-
i-Pr	*iso*-Propyl
ImH	1*H*-Imidazole
IR	Infrared
L	Ligand
LB	Lewis base
m-	*meta*-
Me	Methyl
MEK	Methyl ethyl ketone (butanone)
MIDA	*N*-Methyliminodiacetic acid
mins	minutes
mol	Mole
n-Bu	*n*-Butyl
n-Hex	*n*-Hexyl
neop	Neopentylglycol
NMR	Nuclear magnetic resonance
[O]	Oxidation
o-	*ortho*-
p-	*para*-
Xyl	Xylene
PCC	Pyridinium chlorochromate
PDB	Protodeboronation
Ph	Phenyl
pin	Pinacolato
ppb	Parts per billion
ppm	Parts per million
pyr	Pyridine
rac	Racemic
rr	Regiomeric ratio
RT	Room temperature
RTO	Rhodium turnover
S	Solvent
s	Second
(SC)XRD	(Single crystal) X-ray diffraction
SEGPHOS	5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
SMCC	Suzuki-Miyaura cross coupling
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
SR	Sandmeyer reaction
t-Bu	*tert*-Butyl
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TDB	Taft-Dubois parameter
Tf	Triflyl
TFA	Trifluoroacetic acid

THF	Tetrahydrofuran
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
TMS	Trimethylsilyl
tol	Tolyl
Ts	Tosyl
VT	Variable tempeature
WCA	Weakly coordinating anion
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	Dicyclohexyl[2′,4′,6′-tris(propan-2-yl)[1,1′-biphenyl]-2-yl]phosphane
σ	Hammett Parameter

0.5. Abstract

Transition-metal catalysed [2+2+2] cycloadditions are an atom-economic method to generate highly complex arenes in a single step and can be classified into one of three categories depending on the number of molecules involved. The synthetic utility of the bimolecular (or semi-intramolecular) reaction is hampered by poor reactivity when the monoalkyne component is internal. This limitation is often described in the literature as an electronic effect in nature with little in the way of mechanistic evidence offered. This is the so-called “internal alkyne problem”.

The research reported herein details the full analysis of the limitations of this reaction, developing a rhodium-based manifold that can be generally applied to a variety of monoalkynes. It was found, in apparent disagreement with the literature, that the electronic nature of the monoalkyne was not a good predictor for the success of a reaction. Instead, the steric environment of the alkyne correlated much more strongly with the reaction outcome, with sterically encumbered alkynes performing significantly poorer than their unhindered counterparts. The apparent electronic effect was examined and as found to be an artifact of coordination, wherein the electron-withdrawing groups often contained an atom capable of acting as a secondary coordinating group, enhancing binding to the metal centre thus increasing reactivity.

Finally, the scope of the reaction was explored with a wide variety of functional groups being tolerated yielding highly complex benzene cores. This methodology was further extended to the use of borylated alkynes, which allowed for the synthesis of complex molecules with a valuable functional handle. Lastly, these borylated arenes were applied to the synthesis of benzoxaboroles, a moiety with an ever-growing presence in the pharmaceutical sector.

1.0. Chapter 1: Introduction

1.1. Aromatic Rings

Aromatic rings are hugely important. The prototypical aromatic, benzene, was first isolated in 1825 by Michael Faraday[1] and was the subject of much investigation. Through careful analysis, it was determined that the structure was C_6H_6, implying either a maximum of four degrees of unsaturation (*e.g.* a linear carbon chain with an alkyne and two alkenes), a maximum of six ring junctions, or some combination thereof.[2, 3] A number of the chemical characteristics further complicated the structural characterisation of the molecule. The addition of benzene to bromine did not suppress the strong red colour of bromine significantly (a classic test for unsaturation), leading to the conclusion that there are no double/triple bonds in the molecule.[4] However, the proposed high degree of cyclicisation required to satisfy the chemical formula with so few carbons led to some outlandish suggestions for the structure.

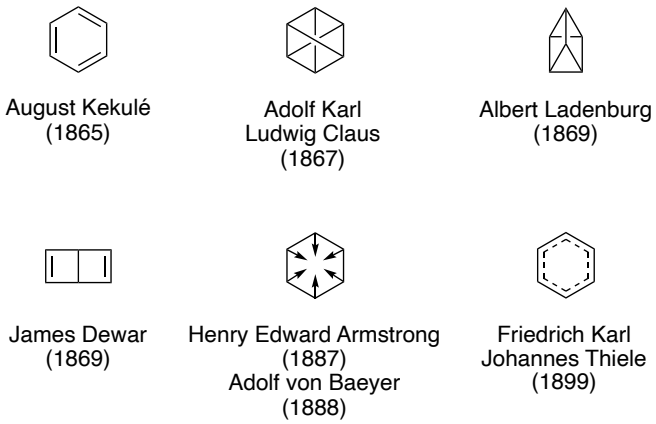


Figure 1.1: Proposed structures of benzene.

In **Figure 1.1**, a selection of the proposed structures is shown. By this point in history, the tetravalent nature of carbon had been disclosed by both Archibald Scott Couper and August Kekulé (although Coupar's work faced delays in publication leading to credit widely been given solely to Kekulé).[5-10] There are two clear regimes observed: (1) those structures wherein the structural formula can be explained through polycyclism, (2) those structures where high degrees of unsaturation are required. The Kekulé structure proposed in 1865 caused a great stir in the chemical community on publication, sparking debate on what the correct structure was.[11] Adolf Karl Ludwig Claus dismissed this structure, namely due to the resistance of benzene to addition reactions compared to other unsaturated compounds, proposing the tetracycle as the correct structure.[12] A similar explanation was proposed by Ladenburg wherein the prismatic isomer shown was proposed.[13] An interesting suggestion was Dewar's unsaturated bicycle (although he agreed with the Kekulé structure), known as Dewar benzene.[14, 15] Unlike Claus's structure, this is synthetically accessible and has been shown to be highly unstable with a half-life of approximately two days, decomposing readily into benzene.[16-18] The other two structures proposed by Armstrong and von Baeyer and also by Thiele nod towards the possibility of the resonant structure of benzene. Whilst von Baeyer and Armstrong proposed the excess electrons that would occupy the double bonds resided in the centre of the cyclohexane (as opposed to being localised in π bonding orbitals), Thiele hypothesised (correctly) that the double bonds were in a superposition of states across the carbocyclic scaffold.[19-23]

Aromatic rings offer a great number of helpful properties for chemical synthesis. The chemistry of these molecules is very well studied and is highly predictable, such as reactions as old as the Friedel-Crafts reaction[24, 25] and the Sandmeyer reaction.[26-29] For this reason, a wide variety of highly derivatised benzene cores are commercially available, providing a useful starting point for chemical synthesis. It is estimated that 80% of drug molecules contain an aromatic ring, possibly due to this convenience.[30]

The ubiquity of complex benzene rings leads to a notable overrepresentation of certain substitution patterns. It is evident that the more complex a substitution pattern, the higher number of isomers are possible. **Figure 1.2** shows all possible isomers of *n*-substituted benzenes, of note, is how quickly structural complexity increases; the number of possible isomers increases faster than even *n*! (for $n \leq 4$).

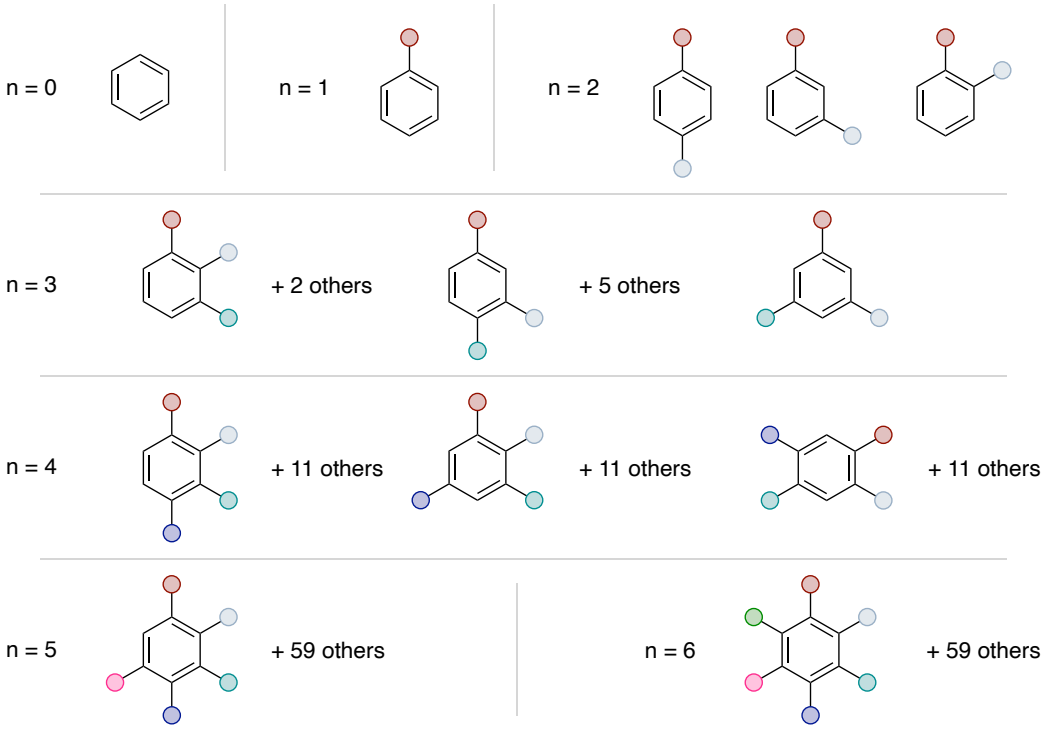
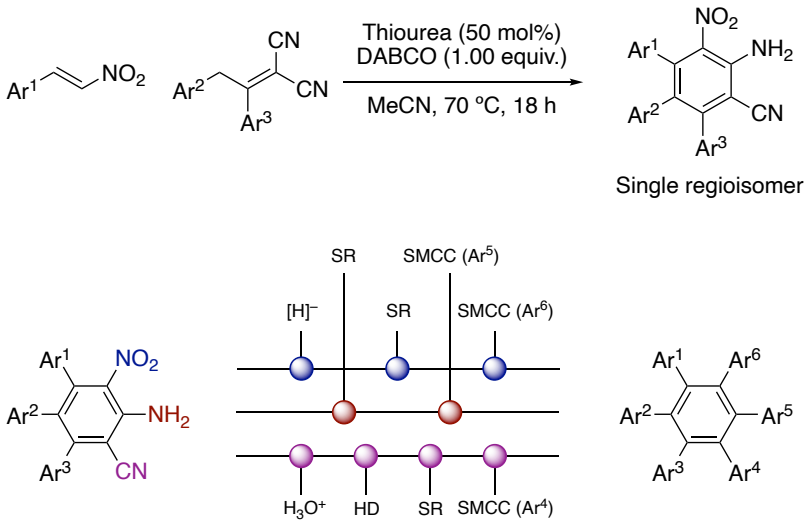


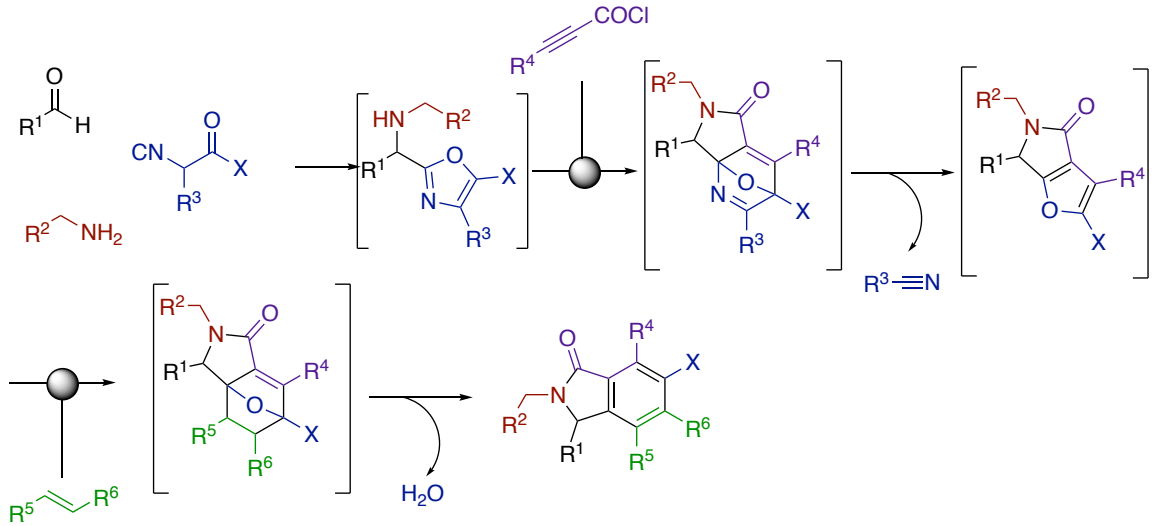
Figure 1.2: Possible isomers of *n*-substituted benzene cores.

Synthesis of hexasubstituted benzenes (HSB) with complete regioselectivity (so-called non-statistical) is a challenge. However, these products are of interest in various fields including supermolecular[31-36] and even medicinal chemistry.[37] Examples of statistical methods for their synthesis include Diels-Alder reactions,[38, 39] cyclotrimerisations,[40-42] and Pd-catalysed cross coupling reactions.[43-45] Non-statistical methods are more challenging: a recent disclosure by Tsogoeva and coworkers[46] (Scheme 1.1), reminiscent of a reaction manifold earlier by Zheng *et. al,*[47] utilises a Michael addition-intramolecular cyclisation-oxidation domino cascade to yield a hexasubstituted benzene which can undergo orthogonal functional group interconversions to generate halides for Suzuki-Miyaura cross couplings. Thus, hexaarylbenzenes, a moiety sought after for applications in multiple fields of materials chemistry, can be synthesised.[48-51]



Scheme 1.1: Non-statistical synthesis of hexasubstituted benzenes and orthogonal FGIs towards hexaarylbenzenes. (SR = Sandmeyer reaction; SMCC = Suzuki-Miyaura Cross Coupling; HD = Hoffmann degradation).

Another approach was published by Zhu and coworkers.[52] This reaction regime employs a number of well-studied steps to generate complex HSBs: (1) An interrupted Ugi multicomponent reaction[53-55] earlier disclosed by Zhu and coworkers;[56] (2) A condensation–Diels-Alder–retro-Diels-Alder cascade with the intermediate oxazole;[57-59] (3) A second Diels-Alder–fragmentation cascade with the addition of a second dienophile (*via* an intermediate oxabicyclo[2.2.1]heptane) yields the desired HSB in a modular fashion in high yields.[60-64]

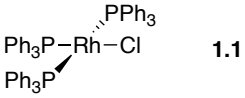


Scheme 1.2: Synthesis of HSBs by Zhu and coworkers.

The evident disadvantage of this method is the step intensity. However, an aforementioned methodology can generate these products in a single step: cyclotrimerisations in the form of [2+2+2] cycloadditions.

1.2. Rhodium Catalysis and [2+2+2] Cycloadditions

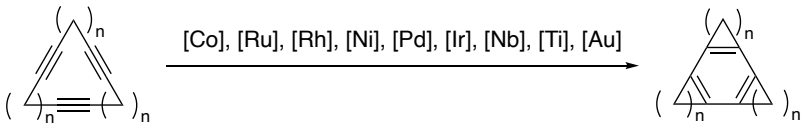
Rhodium is amongst the rarest metals on the planet, with crustal concentrations being estimated to be around 1 ppb.[65] This high rarity leads to high cost, but it is an exceptionally versatile material for a wide variety of chemical processes. For instance, Wilkinson's catalyst (**1.1**), is an effective complex for hydrogenating alkenes, alkynes, and a myriad of alkene hydrofunctionalisation reactions.[66-68] Wilkinson's catalyst is able to perform these reactions due the Rh(I) centre being a 16-electron complex, making it coordinatively unsaturated and able to accept a 2-electron ligand (such as hydrogen or an alkene).



1.1

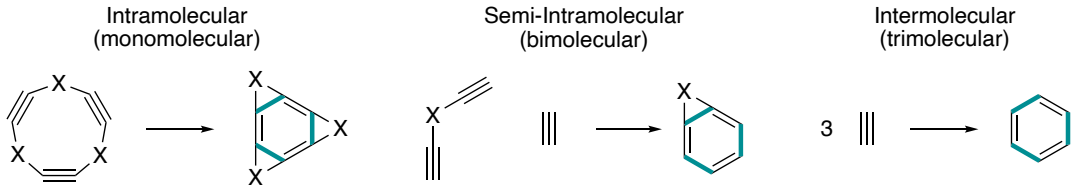
Figure 1.3: Structure of Wilkinson's catalyst.

Most pertinent to the work presented herein is the propensity for Rh(I) to catalyse [2+2+2] cycloaddition chemistry. Metal-based [2+2+2] reactions were first discovered by Walter Reppe and coworkers in 1948 wherein the preparation of benzene was reported *via* the cyclotrimerisation of acetylene under high pressure using nickel(II) catalysis.[69] Since these early discoveries, the use of a variety of metals are known to promote these transformations.[70-73]



Scheme 1.4: General scheme for metal-catalysed [2+2+2] cycloadditions.[70-73]

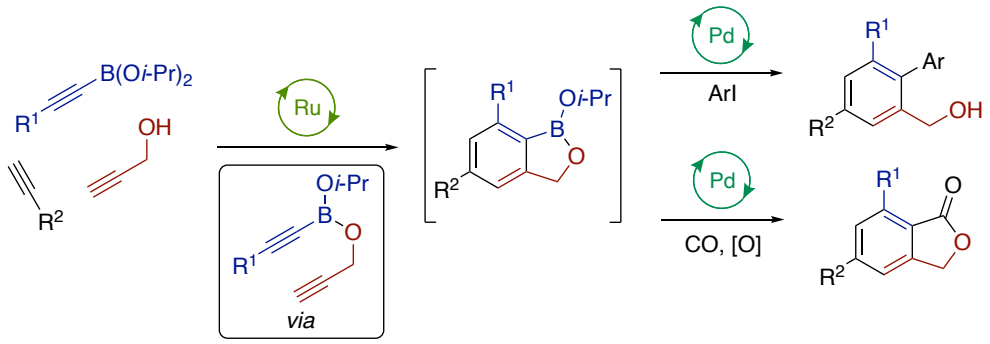
There are three distinct classes of [2+2+2] cycloaddition, determined by the number of alkyne-containing molecules that undergo the cyclisation. These are shown in **Scheme 1.5**: (1) The intramolecular (or monomolecular), wherein all three alkynes are present in the same molecule; (2) The semi-intramolecular (or bimolecular), involving the reaction of a diyne and a monoalkyne; (3) The intermolecular (or trimolecular) reaction where three independent alkynes cyclise to form a benzene core.



Scheme 1.5: Classes of [2+2+2] cycloaddition.

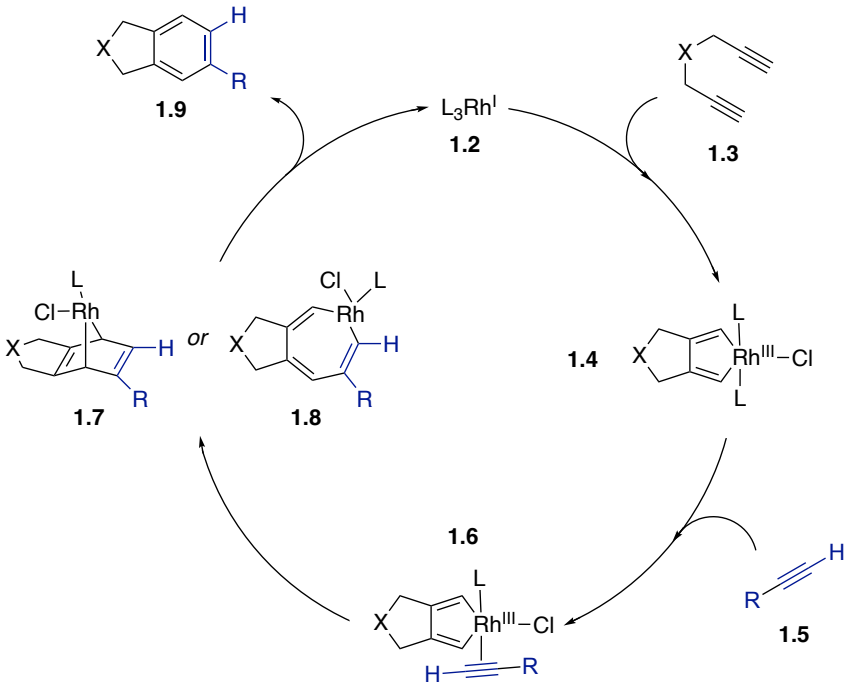
Each of these reactions has its advantages and drawbacks. For instance, the intramolecular reaction is the most reliable, often offering excellent regioselectivity and chemoselectivity, however the synthesis of the starting materials can be somewhat challenging and is, by definition, not a modular process. The intermolecular [2+2+2] on the other hand yields complex benzene cores with maximal modularity. However, chemoselectivity and regioselectivity is conversely challenging.[74] The semi-intramolecular cyclisation balances these attributes allowing for control of the chemoselectivity through kinetic means whilst also using relatively accessible starting materials that are relatively uncomplicated. It should be noted that methods have been developed to overcome some of the control issues regarding the

intermolecular [2+2+2]. For instance, elegant work by Yamamoto *et al.* utilises alkyne boronic esters as a templating group for a propargylic alcohol, generating a diyne *in situ*, allowing for the [2+2+2] to proceed with high chemoselectivity.[75, 76] The products generated are then functionalised using palladium catalysis, either through oxidative carbonylation or Suzuki-Miyaura cross coupling (**Scheme 1.6**). Of note in these processes is the prevalence of terminal propargylic alcohols to control regioselectivity. When an unsymmetrical diyne is used, a terminal monoalkyne tends to react in such a way that steric interactions are minimised.[77]



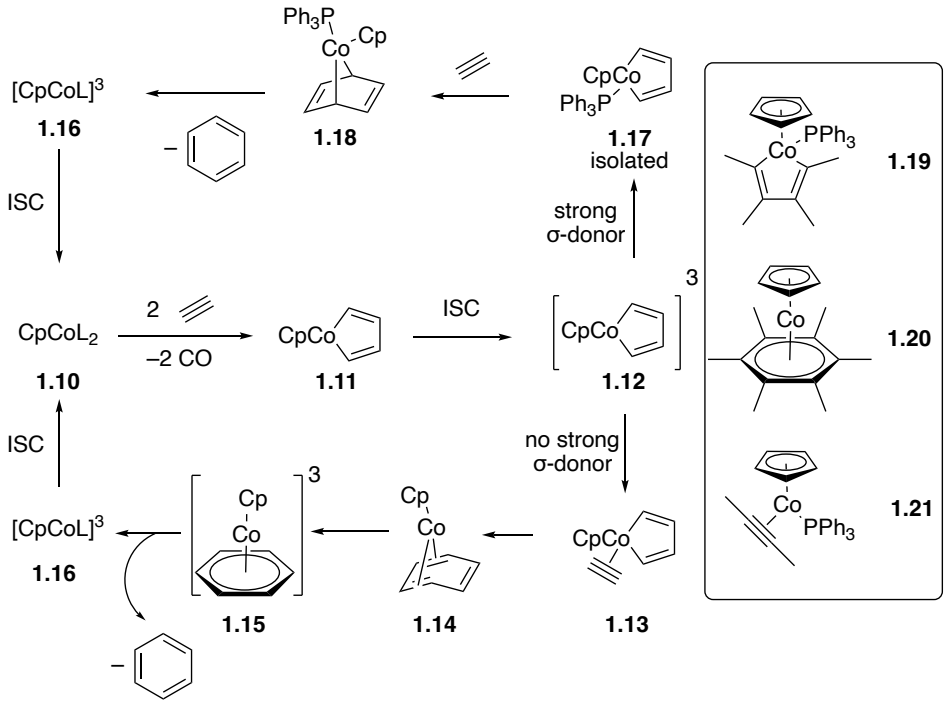
Scheme 1.6: Yamamoto's strategy for chemo- and regioselective intermolecular [2+2+2] cycloadditions.

Mechanistically, there are two simplified pathways that are accepted for the transition-metal catalysed [2+2+2] cycloadditions. Unfortunately, detection of many of these intermediates using NMR spectroscopy is not possible due to the presence of paramagnetic metal centres. Similarly, their isolation is difficult due to their inherent instability. Thus, quantum chemical calculations have been extensively employed to garner mechanistic rationale. However, the exact mechanistic pathway has been shown to depend on a variety of factors including: the choice of metal, ligand, and the nature of the alkynes.[70] In **Scheme 1.7**, Rh^{I} is used as an example; first, the resting state Rh^{I} catalyst (**1.2**) undergoes an oxidative cyclisation with the diyne (**1.3**) to yield the rhodacyclopentadiene (**1.4**), as determined by computational chemistry.[78] After ligand exchange with an alkyne (**1.5**), complex **1.6** may undergo either a [4+2]/Diels-Alder reaction to yield **1.7** or an alkyne insertion reaction giving **1.8**.[78] After reductive elimination, the desired product (**1.9**) is returned along with the resting state catalyst (**1.2**).[78]



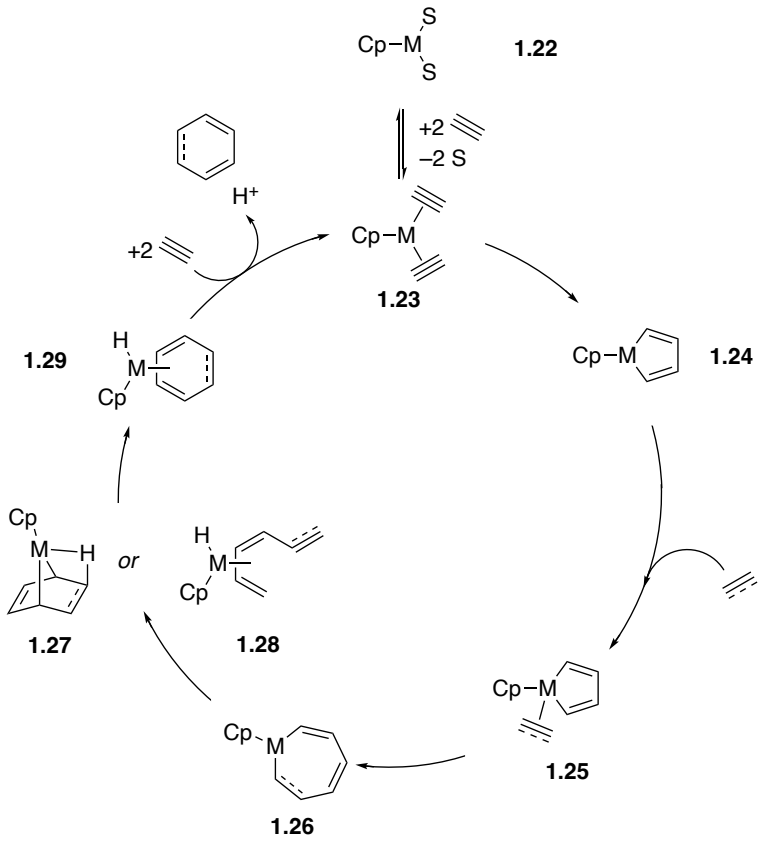
Scheme 1.7: Generally accepted, simplified mechanistic pathways for semi-intramolecular [2+2+2] cycloadditions (ligands omitted for clarity).

However, a study published by Agenet *et al.* isolated intermediates in the cobalt-catalysed [2+2+2] reaction of acetylene (**Scheme 1.8**).[79] The work presented precluded the presence of the cycloheptametallocycle intermediate and also showed that the reaction mechanism is dependent on whether a strong σ-donor is present.[79] When present, the cobalt-norbornadiene intermediate (**1.18**) is operative, when absent, an η^4 complex forms (**1.14**).[79] After elimination of benzene, the triplet-state cobalt (**1.16**) undergoes intersystem crossing to yield the singlet state catalyst (**1.10**).[79] A number of interesting intermediates were isolated and characterised in this study including the phosphine ligated cobaltocycle **1.17** and its derivative **1.19**, along with the hexamethylbenzene sandwich complex **1.20** and Co-alkyne complex **1.21**. These were amongst the first reports of isolation of such complexes. [79]



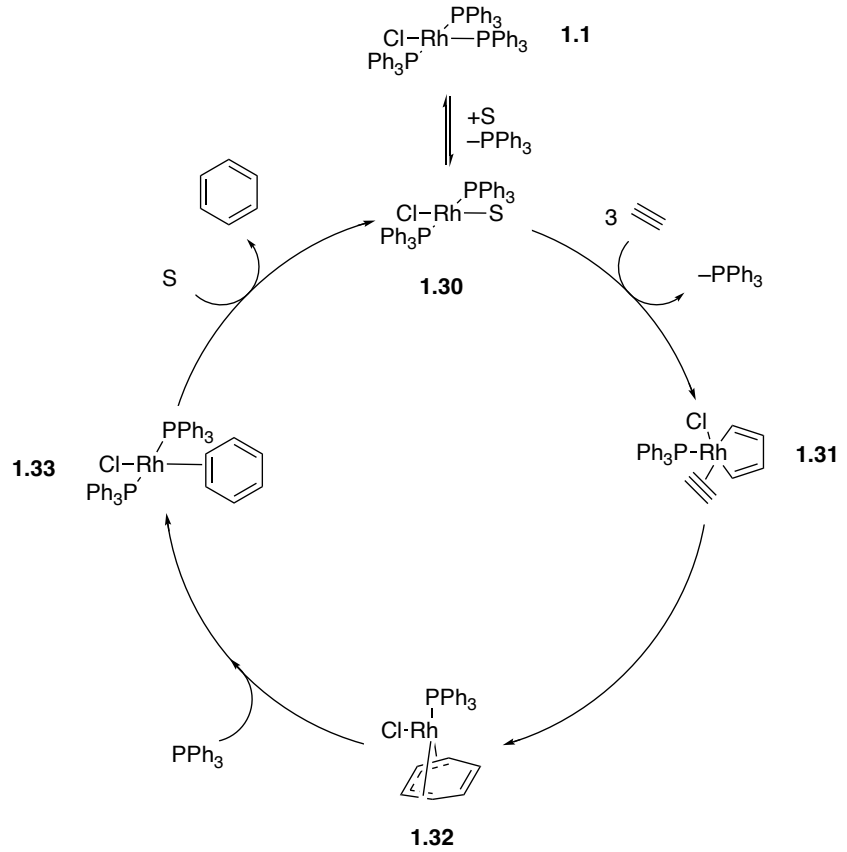
Scheme 1.8: Agenet *et al.*'s proposed catalytic cycle for cobalt-catalysed [2+2+2] cycloaddition.

Similarly, a separate pair of computational studies of ruthenium- and cobalt-catalysed reactions agreed with many intermediates (**Scheme 1.9**). The key difference was the mechanism of the incorporation of the third 2π component.[80, 81] First, alkyne coordination (**1.23**) followed by oxidative cyclisation yields the metallocyclopentadiene, **1.24**. This undergoes a coordination event followed by alkene insertion to yield metallocycloheptadiene **1.26** which either forms the metallonorbornene (**1.27**) or the triene (**1.28**) depending on the nature of the alkene.[80, 81] The triene (**1.28**) undergoes thermal, disrotatory 6π-electrocyclisation and **1.27** does a retro-cheletropic cycloaddition to yield the desired product.[80]



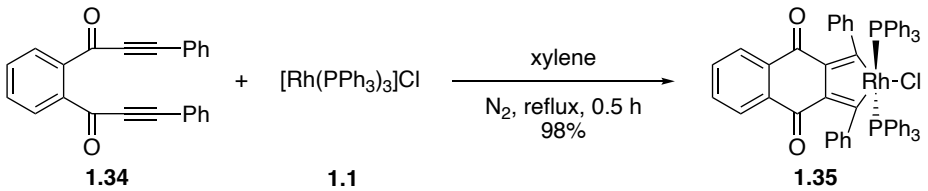
Scheme 1.9: Theoretical studies on Ru- and Co-catalysed [2+2+2] cycloadditions of acetylene and ethylene. M=Co^{I}/Ru^{II} + weakly coordinating anion; S = Solvent.

Finally, a theoretical study performed by Solà and coworkers focussed on the rhodium-catalysed [2+2+2] cyclotrimerisation of acetylene with Wilkinson's catalyst (**Scheme 1.10**).[82] The mechanism proposed in this paper yields the rhodocyclopentadiene through previously described routes which is a coordinatively unsaturated 16-electron complex, the formation of which is rate-determining (as corroborated by virtually all other theoretical studies[71, 77-89]). A molecule of acetylene coordinates to this complex yielding **1.31** and then undergoes an addition into the π-system leading to an η^4-complex with a six-membered arene (**1.32**).[82] Reductive elimination yields the benzene bound catalyst, **1.33**, which dissociates benzene and regenerates the catalyst **1.30**.[82]



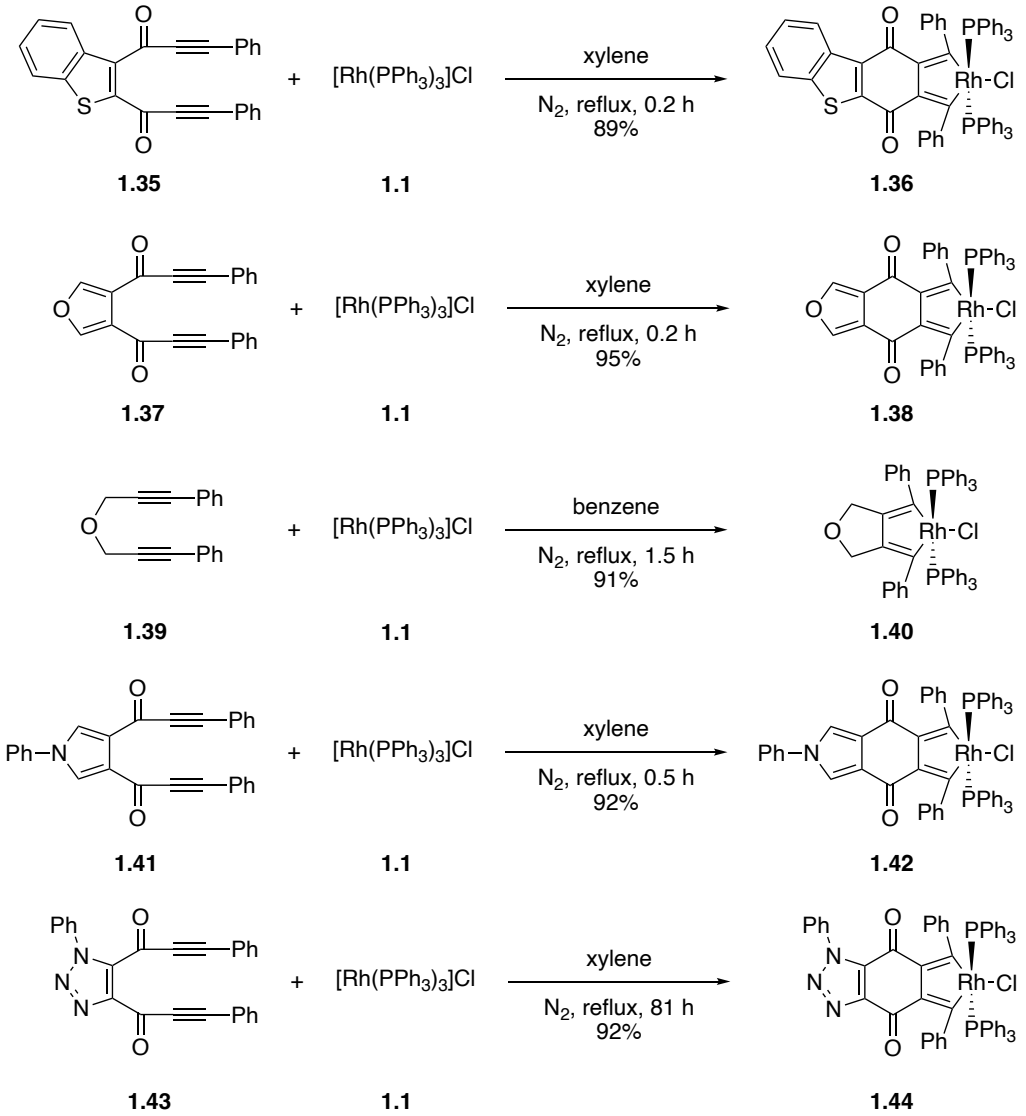
Scheme 1.10: Solà and coworkers' examination of [2+2+2] cycloadditions of acetylene using Wilkinson's catalyst. S = Solvent.

In terms of experimental evidence, in 1974, Müller and coworkers isolated and obtained the crystal structure of the rhodacyclic intermediate formed from the reaction between Wilkinson's catalyst and diyne **1.34** (**Scheme 1.11**).[90, 91] It was found that the rhodium complex exhibits a distorted trigonal bipyramidal structure and – most pertinently to this section – the metallocycle is essentially coplanar to the rest of the molecule implying that the structure is truly bound as a metallocyclopentadiene and not as an η^4-complex.[90, 91]



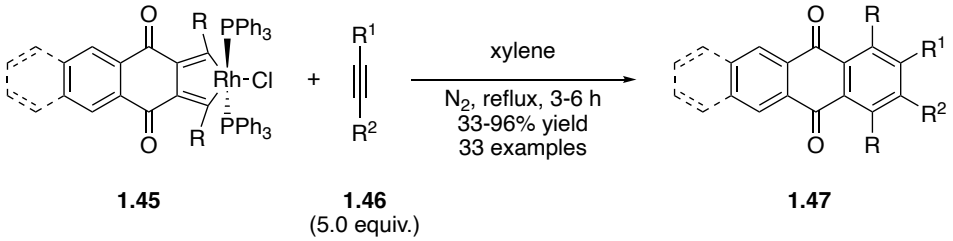
Scheme 1.11: Müller and coworkers' isolation of a rhodacyclopentadiene.

Müller and coworkers synthesised a variety of these rhodium complexes in a series of studies (**Scheme 1.12**), yielding rhodaheterocycles such as benzothiophenes (**1.36**),[92] furans (**1.38**),[93] tetrahydrofurans (**1.40**),[94] pyrroles (**1.42**),[95] and triazoles (**1.44**).[96 91] The formation of other metal complexes was also attempted. The analogous platinum and iridium complexes form in comparatively good yields (albeit lower than rhodium).[97] Isolation of the corresponding nickel complex was possible, though the metallocycle proved very unstable and prone to polymerisation. Iron and palladium may also form the desired complex but the desired products were not isolated.[97]



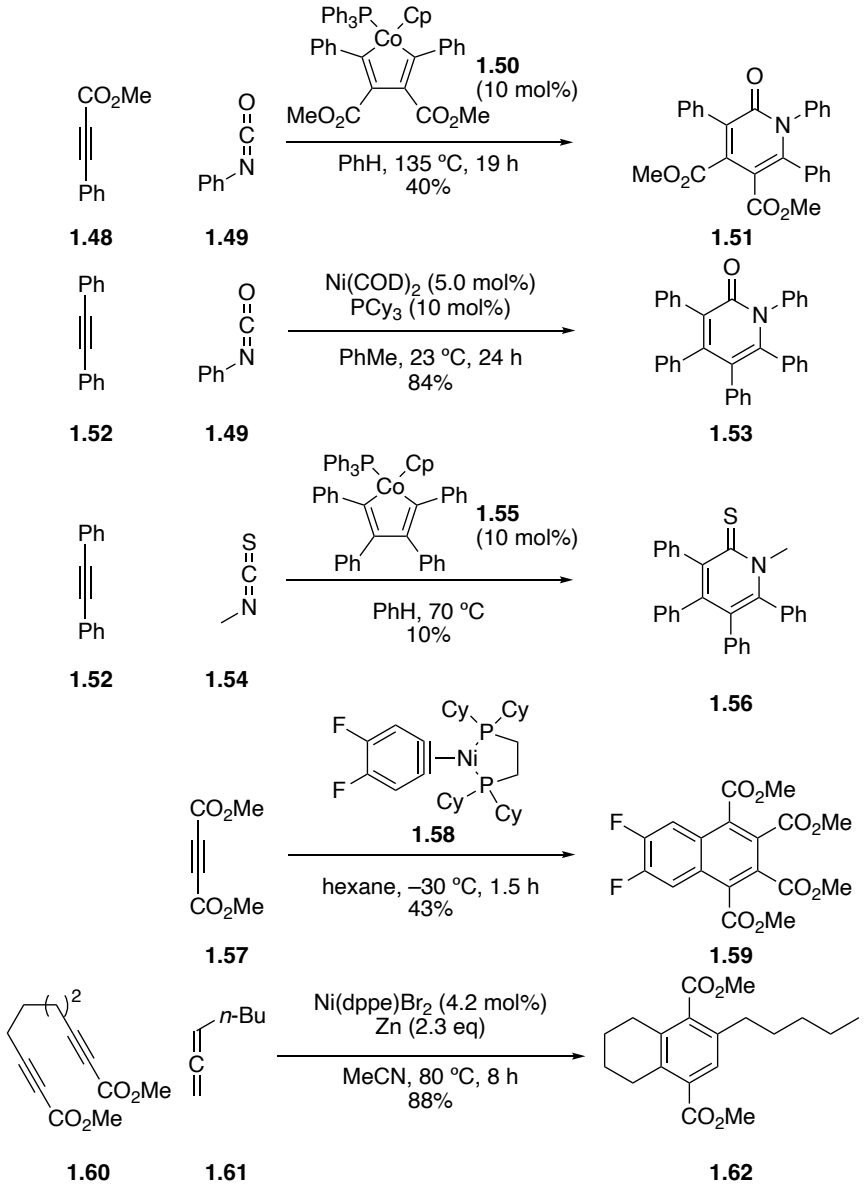
Scheme 1.12: Formation of various rhodacycles through oxidative cyclisation.

Müller and coworkers then showed that this preformed complex (**1.45**) may react with an array of alkynes to yield arenes in moderate to excellent yield (**Scheme 1.13**). In some cases, it is not necessary to use the preformed complex as a reactant and instead, the rhodium source can be simply mixed with the diyne and the alkyne to yield the desired anthroquinone derivatives (**1.47**).[97-99] This process implies that the rhodacycle (**1.45**) is an intermediate in the [2+2+2] cycloaddition process.



Scheme 1.13: Müller and coworkers' synthesis of arenes through reaction of rhodacycles with alkynes.

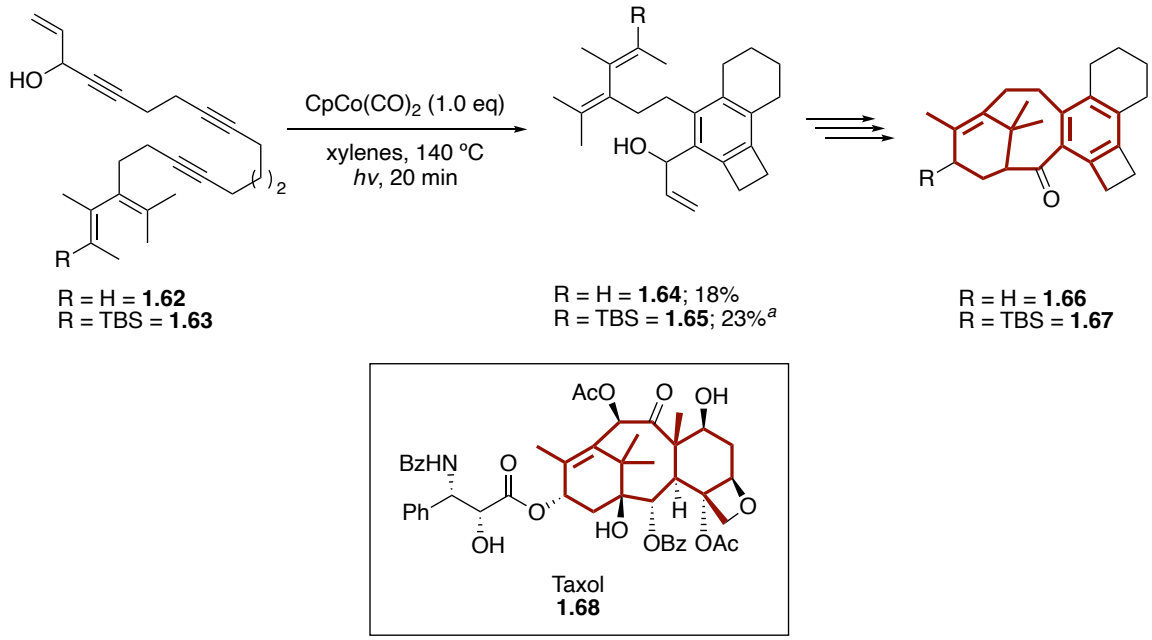
In a general sense, a variety of 2π components are amenable to [2+2+2] cycloadditions (**Scheme 1.14**) with various metals. Reports exist of the use of isocyanates such as **1.49** under reaction conditions with either cobalt or nickel catalysis yielding functionalised pyridone derivatives (**1.51** and **1.53**).[100, 101] Isothiocyanates (**1.54**) have also been used in a similar way to isocyanates to yield thiopyridones (**1.56**) with an unusual cobaltocycle catalyst (**1.55**) albeit with poor yield.[102, 103] An interesting example of arynes was demonstrated using a stoichiometric amount of a premade nickel aryne complex (**1.58**) to yield the hexasubstituted benzene core of **1.59**.[104] Lastly, allenes such as 1,2-hexadiene (**1.61**) are capable of reacting with diynes to yield the relevant benzene derivative — of note is the allene only reacting through the terminus followed by a tautomerisation to yield the aromatic system (**1.62**).[105]



Scheme 1.14: Use of non-alkyne 2π components in generic transition metal-mediated [2+2+2] cycloadditions.

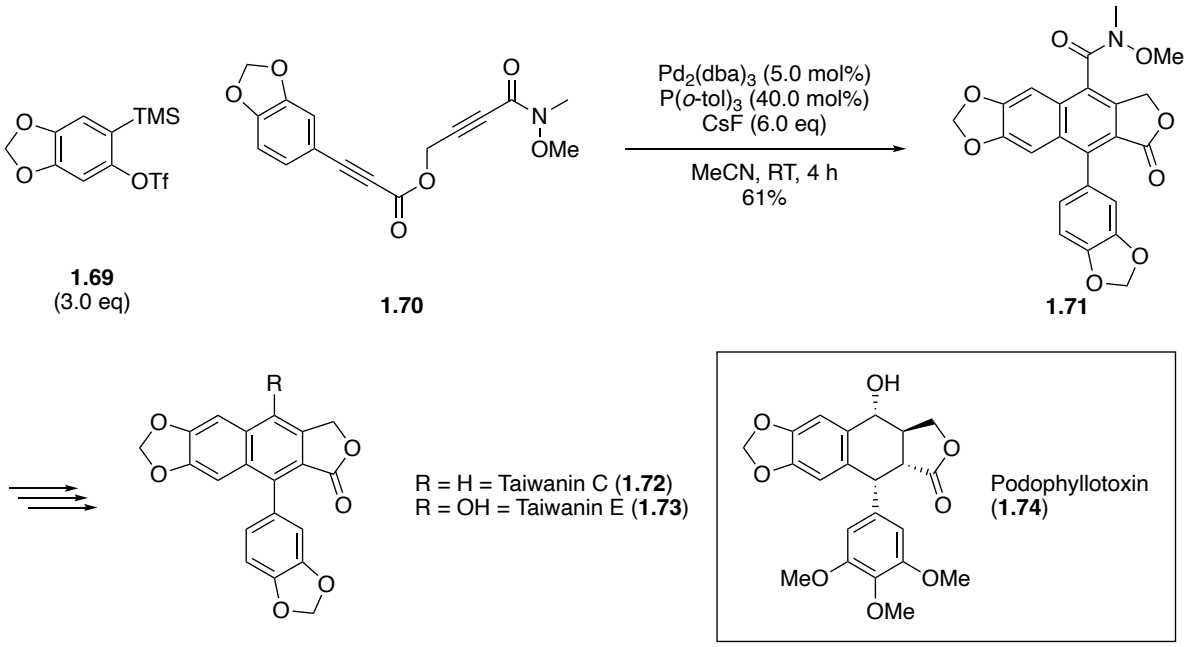
Further to the range of possible substrates, the reaction also typically exhibits high functional group tolerance, a trait highly valued in the synthesis of natural products and bioactive molecules. For instance, Malacria and coworkers (**Scheme 1.15**) employed both a cobalt-mediated and cobalt-catalysed [2+2+2]-cycloaddition to form part of the major ring system of

taxanes **1.66** and **1.67**, structures with the same 6-8-6-ring structure as taxol (**1.68**).[106] The importance of these structures is due to the broad application of taxol as an anticancer medication.[107-109] Due to their highly challenging syntheses, ways to prepare these compounds and their derivatives are highly valued.[110-112]



Scheme 1.15: Malacria and coworkers' syntheses of taxanes. [a]$CpCo(CO)_2$ (5.0 mol%).

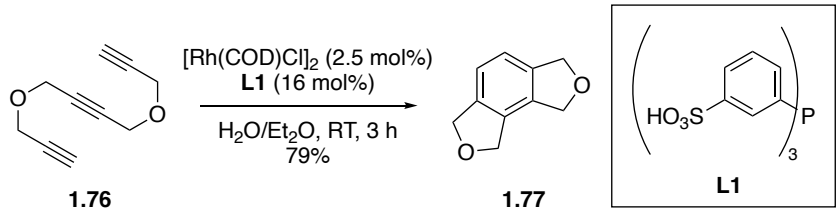
A notable example of the use of arynes in total synthesis is Sato, Tamura, and Mori's synthesis of Taiwanins using a palladium-catalysed [2+2+2] process between aryne precursor **1.69** and diyne **1.70**.[113] Taiwanins are structurally related to podophyllotoxin, a treatment for human papilloma virus infections, and they share many of the same traits in terms of bioactivity.[114, 115] The process described by Sato *et al.* provided a rapid and convergent synthesis of these molecules, with several facile points of diversification.[113]



Scheme 1.16: Sato, Tamura, and Mori's syntheses of the advanced intermediate of the Taiwanin natural products.

1.3. Rhodium-Catalysed [2+2+2] Cycloadditions

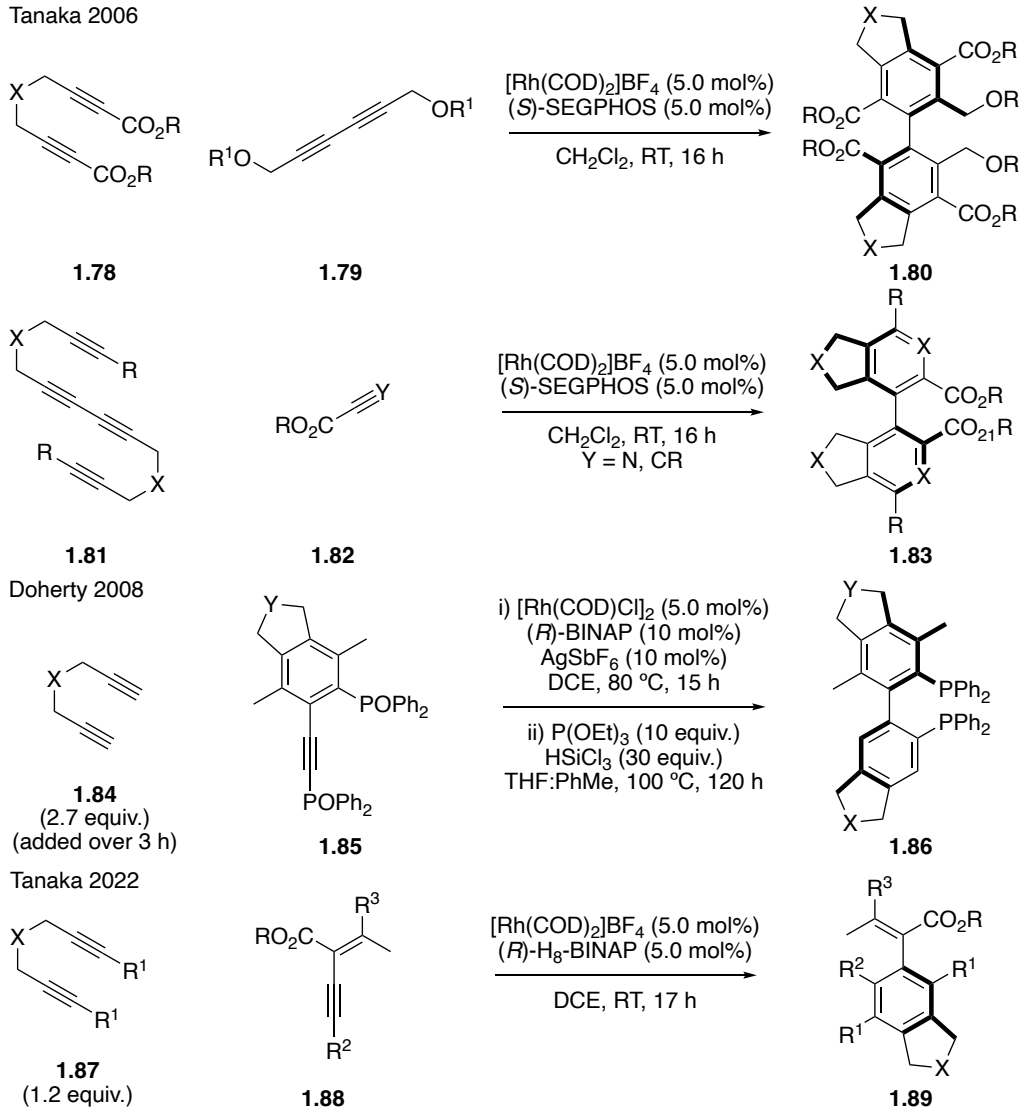
Numerous conditions for Rh-catalysed [2+2+2] cycloadditions have been developed. Kinoshita *et al.* have shown that the use of a water soluble analogue of Wilkinson's catalyst allows for the performance of the reaction in biphasic systems permitting the facile recovery of both products and catalyst *via* extraction.[116] Further applications of water soluble catalysts include work by Tsai and coworkers, wherein a sulfonate substituted bipyridine allows for the semi-intramolecular [2+2+2] to occur in water, including some internal alkynes (*vide infra)*.[117] Similarly, highly substituted fluorene derivatives have been synthesised through Rh-catalysed [2+2+2] by Kotora and coworkers utilising Wilkinson's catalyst (*vide infra)*.[118] It is evident that most Rh-catalysed processes require ligand, adding further cost to the process — this lead to the development of conditions by Tanaka and coworkers, wherein Hünig's base acts as the ligand, a cheap alternative to phosphines (*vide infra)*.[119] Highly appealing processes have also been developed utilising $[Rh(COD)Cl]_2$ as the catalytic system, without the requirement for pnictogen-based ligands.[120]



Scheme 1.17: Rhodium-catalysed, biphasic, intramolecular [2+2+2] using a water-soluble catalyst system developed by Kinoshira *et al*.

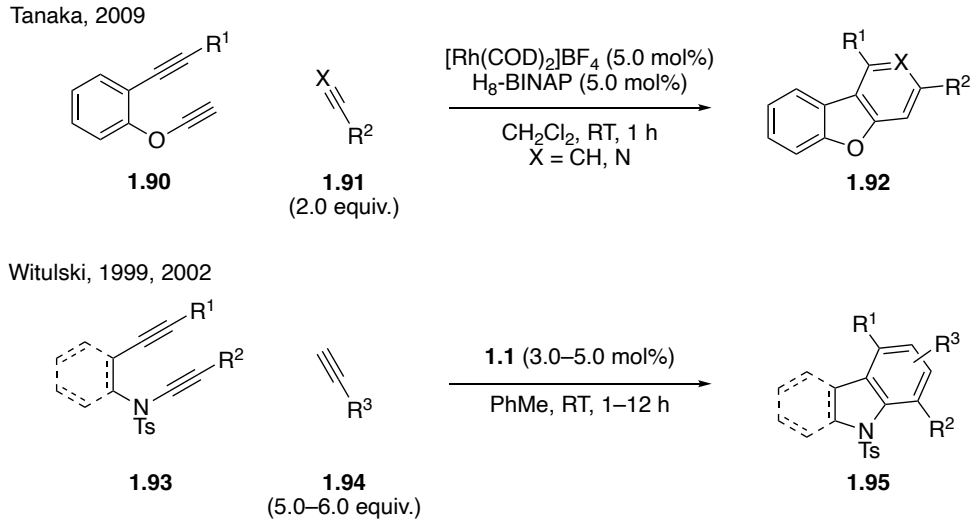
Trialkyne [2+2+2] cycloadditions have also been applied extensively within asymmetric synthesis, particularly by Tanaka.[121-132] Selected examples are shown in **Scheme 1.18**. In 2006, Tanaka and coworkers demonstrated that enantioenriched biaryls (**1.80**) can be synthesised

through enantioselective [2+2+2] cycloadditions between 1,6-diynes (**1.78**) and 1,2-diynes (**1.79**), as well as through [2+2+2] of tetraynes (**1.81**) and nitriles or alkynes (**1.82**).[122] Doherty and coworkers utilised a similar manifold (although through two separate [2+2+2] steps) to generate axially chiral bisphosphine oxides which can be reduced to the corresponding phosphines, allowing a convenient route to complex chiral ligands (**1.83**).[125] Finally, Tanaka and coworkers have demonstrated that eneyne esters (**1.88**) can undergo atroposelective [2+2+2] cycloadditions to generate axially chiral styrene carboxylate derivatives (**1.87**).[132] This work was supplemented by theoretical studies which showed that chelation through the ester carbonyl was vital in controlling the stereochemical outcome of the reaction.[132]



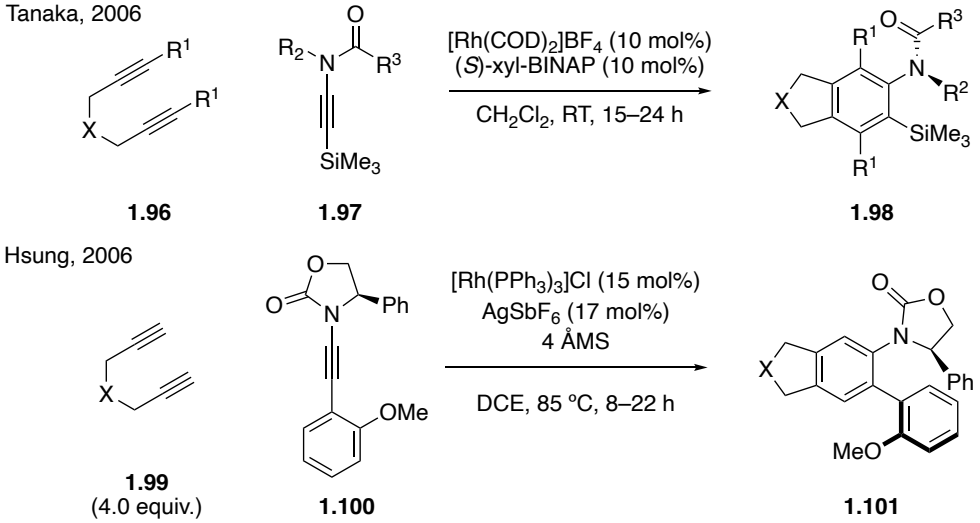
Scheme 1.18: Examples of asymmetric trialkyne [2+2+2] cycloadditions.

Further rhodium-catalysed processes are not limited to conventional alkynes. For instance, work performed by Tanaka[133] and by Witulski[134-136] employed both ynols and ynamines, respectively, to generate complex heterocycles. Tanaka's procedure utilises a Rh^{I}-bisphosphine manifold to react an ynol-bearing diyne (**1.90**) with either alkynes or nitriles (**1.91**) to yield complex (aza)benzofurans (**1.92**).[133] Witulski has performed the corresponding work with ynamides (**1.93**) to yield both complex carbazoles and indolines (**1.94**) with Wilkinson's catalyst.[134, 135]



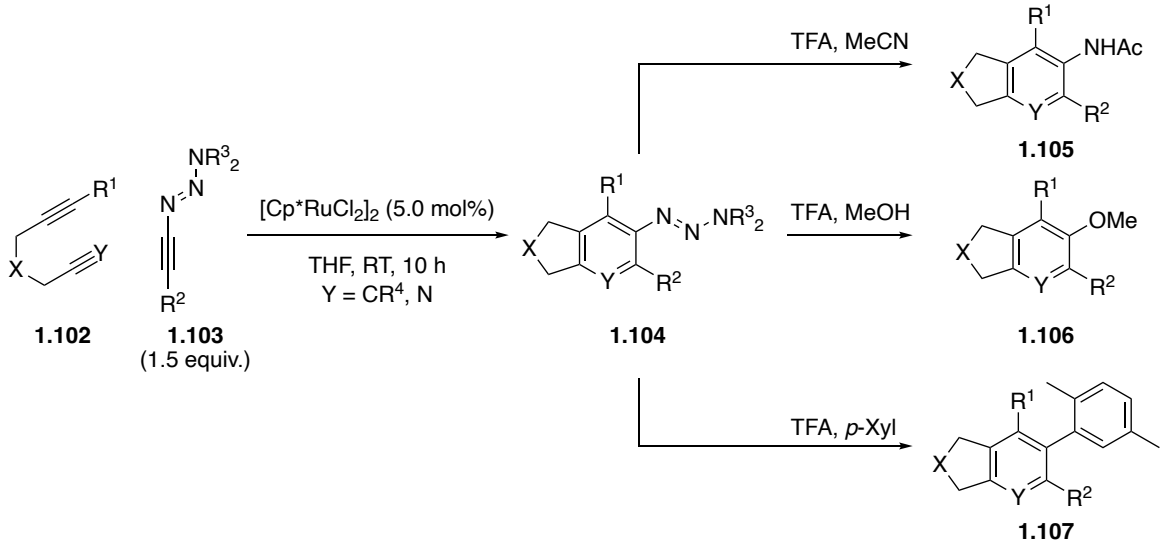
Scheme 1.19: Early efforts towards heteroatom substituted alkynes in [2+2+2] cycloadditions.

Ynamides have also been frequently utilised as the monoalkyne component. Early work was performed in 2006 by the groups of Tanaka[137] and Hsung[138] in the field of asymmetric synthesis (**Scheme 1.20**). Both groups sought to construct axially chiral aniline derivatives through different means. Tanaka and coworkers utilised a chiral bisphosphine derivative to induce enantioselectivity in the [2+2+2] cycloaddition between diynes (**1.96**) and internal alkynyl amides (**1.97**), yielding axially chiral amides (**1.98**).[137] Whereas the Hsung group opted for chiral auxiliary based alkynes (**1.100**), yielding atropisomeric biaryls (**1.101**) through transfer of chirality.[137, 138]



Scheme 1.20: Early examples of ynamine monoalkynes in [2+2+2] cycloadditions.

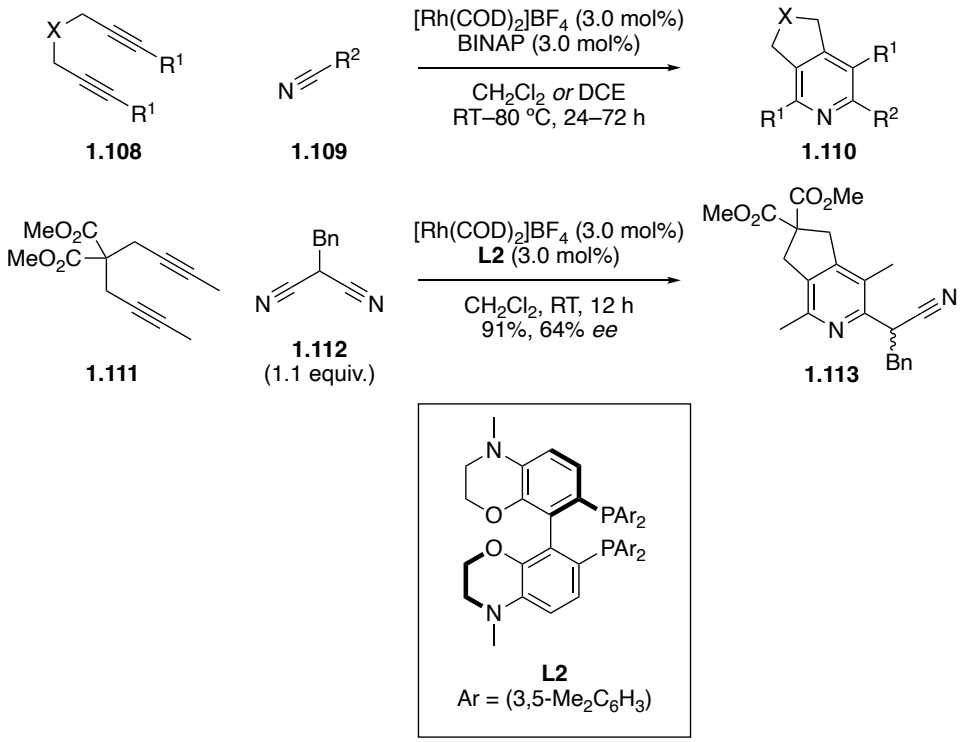
The synthetic utility of this method using ynamine derivatives has been greatly explored, from various groups including those of Anderson,[139] Malacria,[140] and Cramer[141] groups using Rh^{I}, Co^{I}, and Ru^{II} catalysis, respectively. The Cramer group's methodology is particularly noteworthy (**Scheme 1.21**); a semi-intramolecular [2+2+2] occurs between a diyne (**1.102**) and an alkynyl triazene (**1.103**) to yield a triazobenzene (**1.104**). The triazo group is easily displaced by a nucleophile under acidic conditions, adding another point of diversification. Examples shown below include a Ritter-type product (**1.105**), methanolysis (**1.106**) and the Friedel-Crafts product (**1.107**).[141]



Scheme 1.21: Cramer's synthesis of densely functionalised triazobenzenes and the subsequent displacement with a nucleophile.

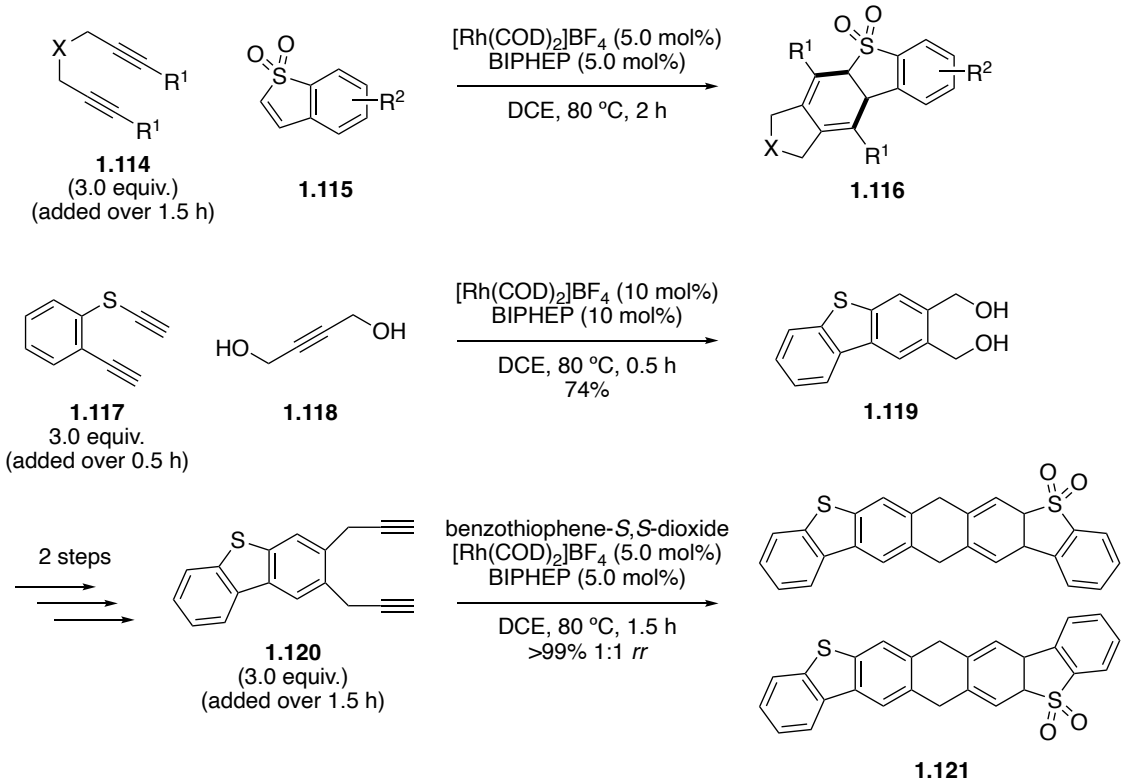
As discussed previously, alkynes are not the only component amenable to [2+2+2] cycloadditions. Whilst alkynes are overall most common, Rh catalysts can engage allenes (with the Roglans group being particularly prevalent in this field),[142-144] nitriles,[71, 145, 146] alkenes,[147-153] and even carbonyls.[154-156]

An example of a nitrile [2+2+2] is shown in **Scheme 1.22**. In this work, Tanaka and coworkers employed standard [2+2+2] conditions to generate complex pyridine derivatives (**1.110**) from diynes (**1.108**).[146] This work included the use of nitrile derivatives such as acrylonitrile, which were found to only react through the cyanide moiety, allowing for retention of the alkene. Furthermore, malononitrile derivatives could be used with only monocoupling observed. This opens the door to desymmetrative [2+2+2]; thus, prochiral malononitrile derivative (**1.112**) was subjected to the reaction conditions yielding the desired product (**1.113**) in excellent yield and modest enantioselectivity.[146]



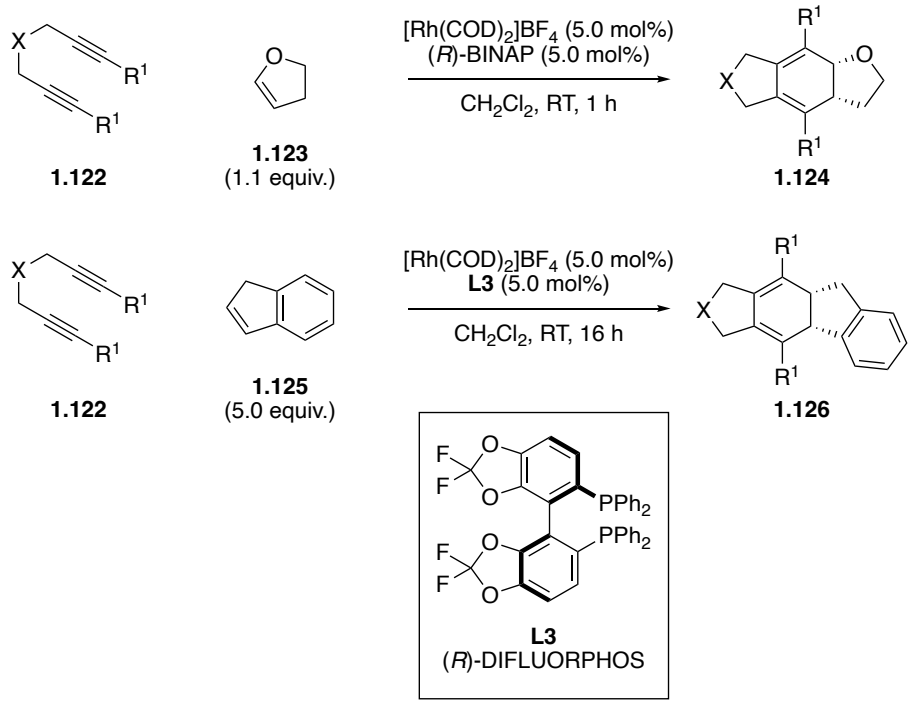
Scheme 1.22: Examples of nitriles in [2+2+2] cycloadditions published by Tanaka and coworkers.

Alkenes are highly important substrates in [2+2+2] cycloadditions. Whilst they are typically more resistant to reactivity, the products possess stereogenic centres. An *s-cis*-1,3-diene is also produced, an ideal partner for subsequent Diels-Alder cycloadditions. Early examples of alkene [2+2+2] cycloadditions were published by the groups of Shibata and Tanaka.[147-153] Shibata reported the diyne [2+2+2] with benzothiophene-*S*,*S*-dioxides (**1.115**) using a Rh^{I}–bisphosphine manifold.[147] This methodology was applied to numerous diynes (**1.114**) and benzothiophene-*S*,*S*-dioxide derivatives (**1.116**) with excellent functional group tolerance including the successful application of halides (Cl and Br) and boronic esters (Bpin). This was eventually extended in the same paper to the synthesis of polyaromatic scaffolds bearing both thiophene and *S*,*S*-thiopehenedioxides (**1.121**) through the sequence shown in **Scheme 1.23**.[147]



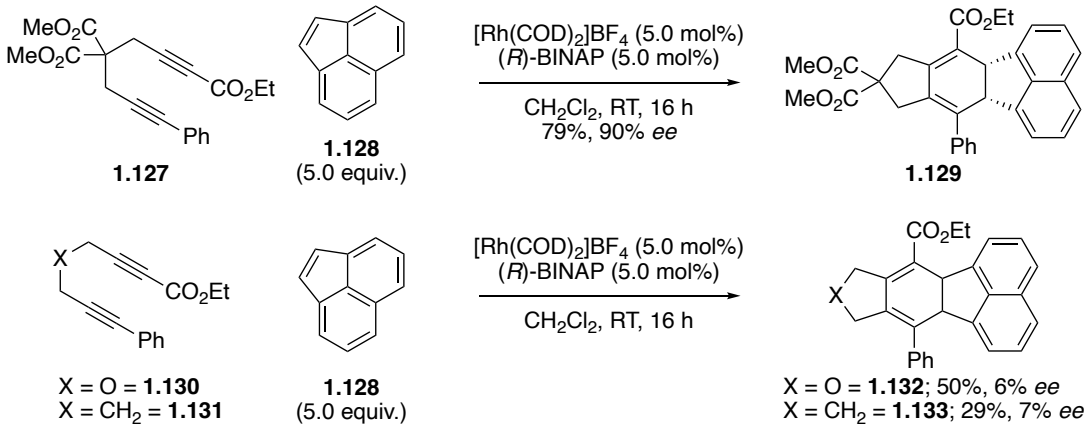
Scheme 1.23: Shibata's alkene [2+2+2] and applications to extended aromatics.

Tanaka then performed a similar reaction (**Scheme 1.24**), asymmetrically, utilising BINAP or DIFLUORPHOS (**L3**) as the chiral ligand depending on whether DHF (**1.123**) or indene (**1.125**) were used as the coupling partner (**Scheme 1.24**).[157] Whilst THF derivatives (**1.124**) were produced in excellent yields and enantioselectivities (up to 97%, up to >99% *ee*), the reactions with indene were less active (**1.126**), with the reaction time extended (1 h *vs* 16 h) and the yields and enantioselectivities significantly reduced. Furthermore, issues with Diels-Alder cycloadditions between DHF and the products were observed in some cases.[157]



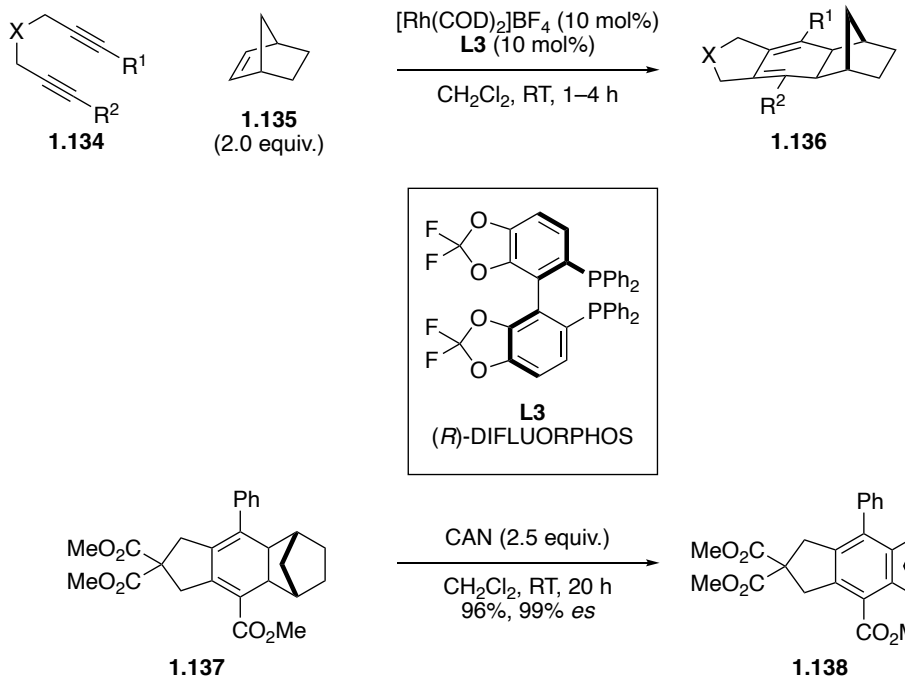
Scheme 1.24: Tanaka's asymmetric diyne-alkene [2+2+2] cycloaddition.

Tanaka and coworkers in 2018 extended this methodology to acenaphthylene derivatives (**Scheme 1.25**).[158] It was found that, unlike indene derivatives, Thorpe-Ingold effects on the diyne are very important predictors for enantioselectivity.[158, 159] For instance, malonyl derivative (**1.127**) exhibits good reactivity and high enantioenrichment on reaction with acenaphthylene (**1.128**) to yield **1.129**; however, replacement of the malonate with an ether or methylene linkage (**1.130** or **1.131**) results in an near racemic product in either **1.132** or **1.133**.[158]



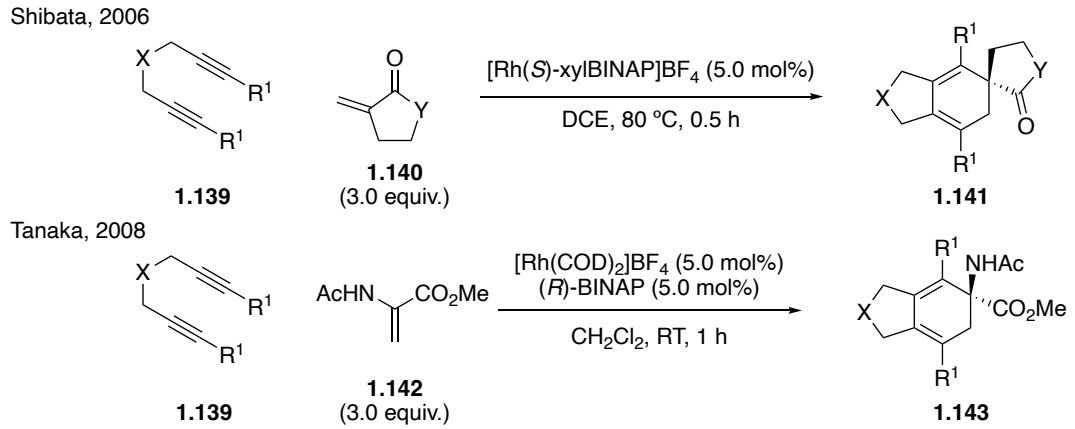
Scheme 1.25: Tanaka's enantioselective [2+2+2] cycloaddition of diynes and acenaphthylene derivatives and the sensitivity towards the Thorpe-Ingold effect.

This work is similar to work published previously by Shibata (**Scheme 1.26**), wherein a diyne (**1.134**) is reacted with norbornene (**1.135**) to generate chiral 1,3-cyclohexadienes (**1.136**) with a modest scope disclosed (10 examples).[149] Overall, fair yields and excellent enantioselectivities (up to 93%, up to 99% *ee*) were observed. The products could be aromatised to yield benzene derivates (**1.137**) bearing a chiral element in the bicycle with very little erosion in enantiomeric excess observed. [149]



Scheme 1.26: Shibata's asymmetric diyne-alkene [2+2+2] cycloaddition and its application to aromatised materials (relative stereochemistry shown).

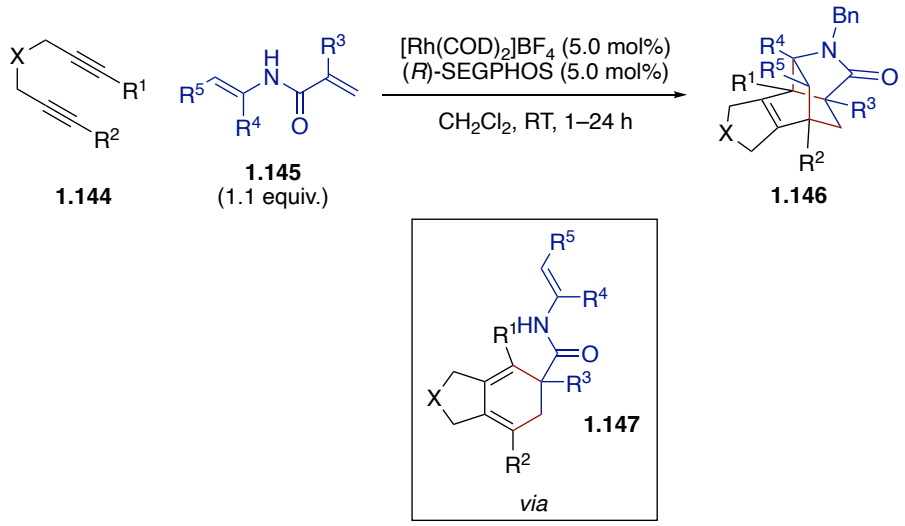
Further examples of alkenes in diyne [2+2+2] were published by Shibata in 2006 and Tanaka in 2008 (**Scheme 1.27**). Shibata utilised exocyclic methylene lactones (**1.139**) which, upon reaction with diynes (**1.138**), generate enantioenriched spirocycles (**1.140**) in excellent yields and enantioselectivities (up to 94%, up to 99% *ee*).[160] This method is appealing as the stereocentres are quaternary carbons, an often cited challenge in asymmetric synthesis, and the reaction is very fast, reaching completion in 30 minutes.[160] Tanaka and coworkers utilised a similar methodology, using protected dehydroalanines (**1.142**) and a Rh^{I}-chiral bisphosphine manifold to produce complex, chiral, unnatural amino acid derivatives with quaternary stereocentres (**1.143**).[151] In this case, the terminal methylene was found to be essential for reaction success, with substitution at that position shutting down reactivity.[151]



Scheme 1.27: Shibata and Tanaka's enantioselective methylene-diyne [2+2+2] cycloaddition yielding 1,3-cyclohexadiene derivatives with quaternary stereogenic centres.

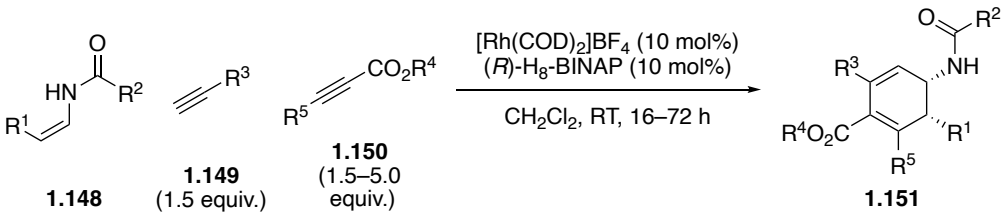
Tanaka extended this work in 2011 (**Scheme 1.28**) — *N*-vinylacrylamide derivatives (**1.145**) were utilised, allowing for an intramolecular Diels-Alder cycloaddition to occur efficiently *via*

the triene intermediate **1.147**.[150] This yields highly complex polycycles (**1.146**) in a controlled manner, enantioselectively.[150] This has also been performed in a fully intermolecular sense, allowing for the highly modular synthesis of these scaffolds.[150] As was noted before, substitution at the methylene is not tolerated at the [2+2+2] stage, which allows for a high degree of chemoselectivity between cycloaddition steps.[150]



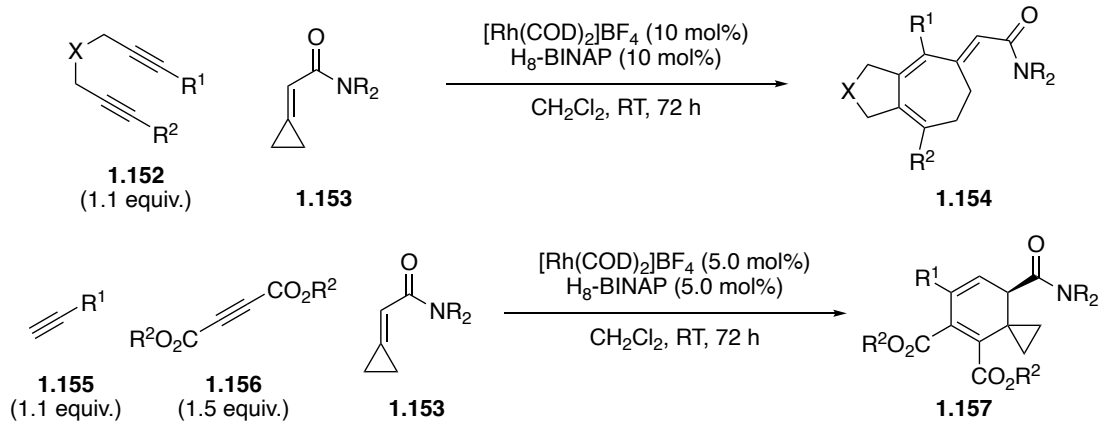
Scheme 1.28: Tanaka's enantioselective diyne-alkene [2+2+2]-Diels-Alder cascade to yield enantioenriched polycycles (*N*-vinylacrylamide component highlighted in blue and new bonds highlighted in red for clarity).

A study on alkenes in diyne-alkene [2+2+2] has been recently published by Tanaka in 2022 (**Scheme 1.29**).[161] Two monoalkynes (**1.149** and **1.150**) and an enamide (**1.148**) are cyclised enantioselectively using Rh^I catalysis to generate complex cyclohexadienes (**1.151**) with a high degree of chemo-, enantio-, and regioselectivity.[161] The reaction was studied computationally with enamide coordination identified as the first step, and secondary coordination through the carbonyl moiety being found to be an important interaction.[161] Coordination and oxidative cyclisation of the remaining two alkynes was found to be rate determining.[161]



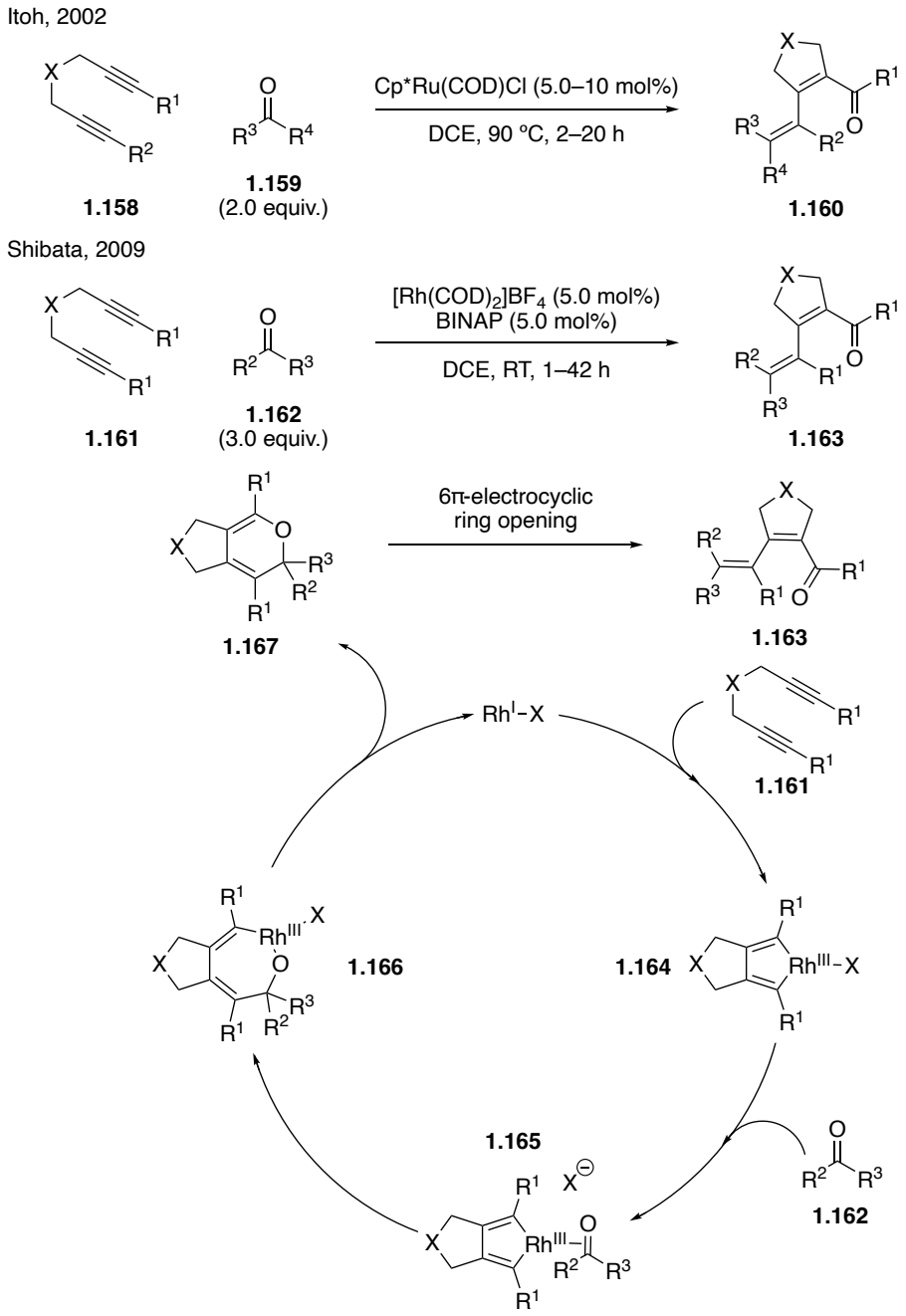
Scheme 1.29: Tanaka's enantioselective trimolecular [2+2+2] yielding enantioenriched amine-substituted 1,3-cyclohexadiene.

Since Tsuji's seminal work, cyclopropanes are well understood to undergo ring opening to the corresponding η^3-allyl system under suitable conditions in the presence of a metal.[162] Tanaka and coworkers (**Scheme 1.30**) utilised cyclopropylidene amides (**1.153**) as coupling partners with diynes (**1.152**) in a [2+2+2] cycloaddition to yield cycloheptadienes (**1.154**).[163] This process was also rendered trimolecular; with an interesting difference in reactivity. When fully intermolecular, ring opening of the cyclopropane is not observed and, instead, enantioenriched cyclohexadienes (**1.157**) are observed in high yield and enantioselectivity.[163]



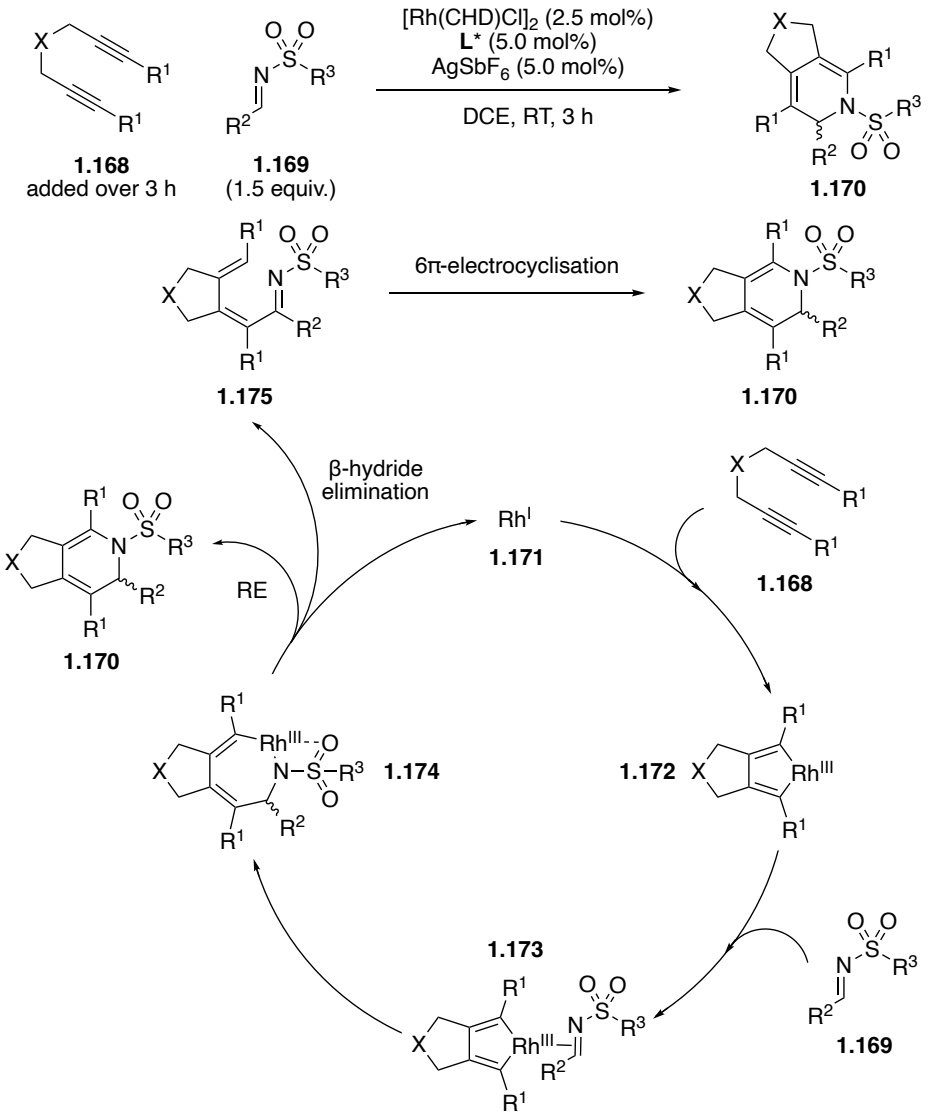
Scheme 1.29: Tanaka's [2+2+2] of cyclopropylidene amides and the difference in reactivity between trimolecular and bimolecular reactions.

Carbonyls are well known substrates in [2+2+2] cycloadditions. However, the process is more commonly performed using Ru catalysis (**Scheme 1.31**),[156, 164] although the engagement of Rh^{I} catalytic manifolds with carbonyls is well documented.[154, 155] Itoh and coworkers reported the cycloaddition of diynes (**1.158**) and activated carbonyls (**1.159**, i.e., pyruvate derived ketones) in the presence of a Ru catalyst to yield *α*,β,*γ*-unsaturated ketones (**1.160**). The same transformation was applied to Rh^{I} catalysis by Shibata and coworkers utilising symmetrical diynes (**1.161**) and carbonyls (**1.162**) to yield the same class of products (**1.163**).[156, 164] The products are somewhat different if one naïvely predicts the [2+2+2] product; a catalytic cycle for the Shibata process is shown in **Scheme 1.31**. First, the Rh^{I} catalyst undergoes the expected oxidative cyclisation to yield the Rh^{III} rhodacycle (**1.164**). After a ligand exchange with a ketone (**1.165**), a nucleophilic addition occurs to yield rhodadihydrooxepine (**1.166**) which yields a 2*H*-pyran (**1.167**) and the starting Rh^{I} catalyst after reductive elimination.[156, 164] This 2*H*-pyran (**1.167**) is unstable, and undergoes a 6π-electrocyclic ring opening to reveal the *α*,β,*γ*-unsaturated ketone (**1.163**).[156, 164]



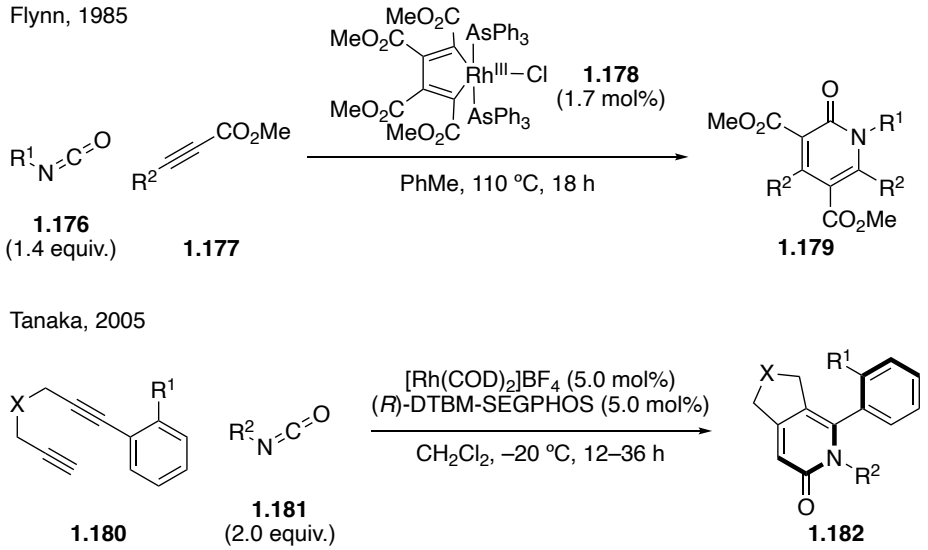
Scheme 1.31: Carbonyl diyne [2+2+2] cycloadditions under Ru^{II} and Rh^{I} catalysis. Catalytic cycle for the formation of **1.163**.

Nevertheless, rearrangements are not guaranteed to occur. A report by Amatore *et al.* has shown that sulfonylimines (**1.169**) can be used as 2π-components in [2+2+2] cycloadditions, expanding on work published by Adak *et al*. wherein 2-pyridyl hydrazones are used as directing groups (**Scheme 1.32**).[165, 166] In this case, electrocyclic ring opening was suppressed and a chiral ligand was used to generate enantioenriched dihydropyridines (**1.170**). A slight mechanistic subtlety is the possibility of facile β-hydride elimination which leads to the corresponding acyclic product (**1.175**). This can undergo a 6π-electrocyclisation to yield the desired product (**1.170**); however, the lack of chiral Rh^{I}-L means that this process is not likely to result in an enantioenriched species. The presence of often highly enantioenriched products indicates that this β-hydride elimination process is not operative.



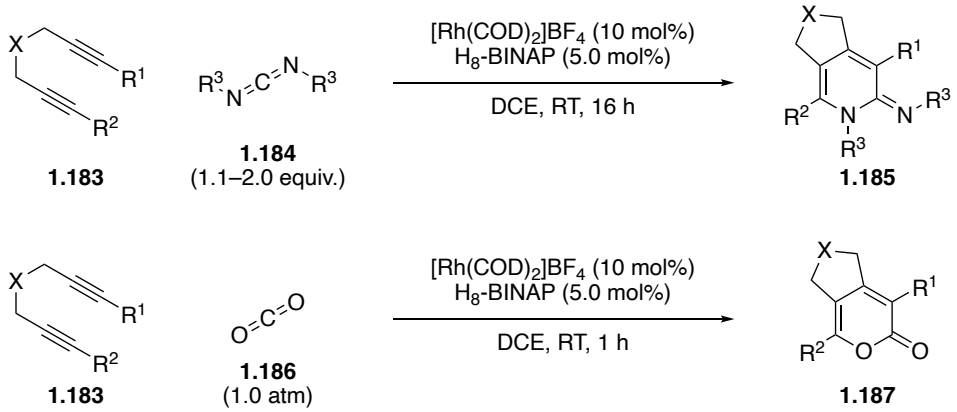
Scheme 1.32: Amatore's diyne-sulfonylimine [2+2+2] and the mechanism of formation of **1.170** (WCA not shown for clarity).

The use of isocyanates has been disclosed in this reaction to generate 2-pyridones. At first, Ru^{II} based systems were developed by Yamamoto *et al.* and offered useful access to these molecules, this was followed by Rh^{I} by Tanaka.[167-169] The very first example of Rh^{I}-catalysed [2+2+2] with isocyanates (**1.176**) and alkynes (**1.177**) was disclosed by Flynn *et al.* utilising an unusual isolable rhodacycle catalyst (**1.178**) developed by Collman and coworkers, although the yields are very low.[170, 171] Furthering this work, Tanaka and coworkers employed a chiral bisphosphine ligand in order to generate axially chiral 2-pyridones (**1.182**) using a more conventional diyne (**1.180**) and isocyanate (**1.181**) framework with massively improved yields as opposed to Flynn *et al.*'s report.[169]



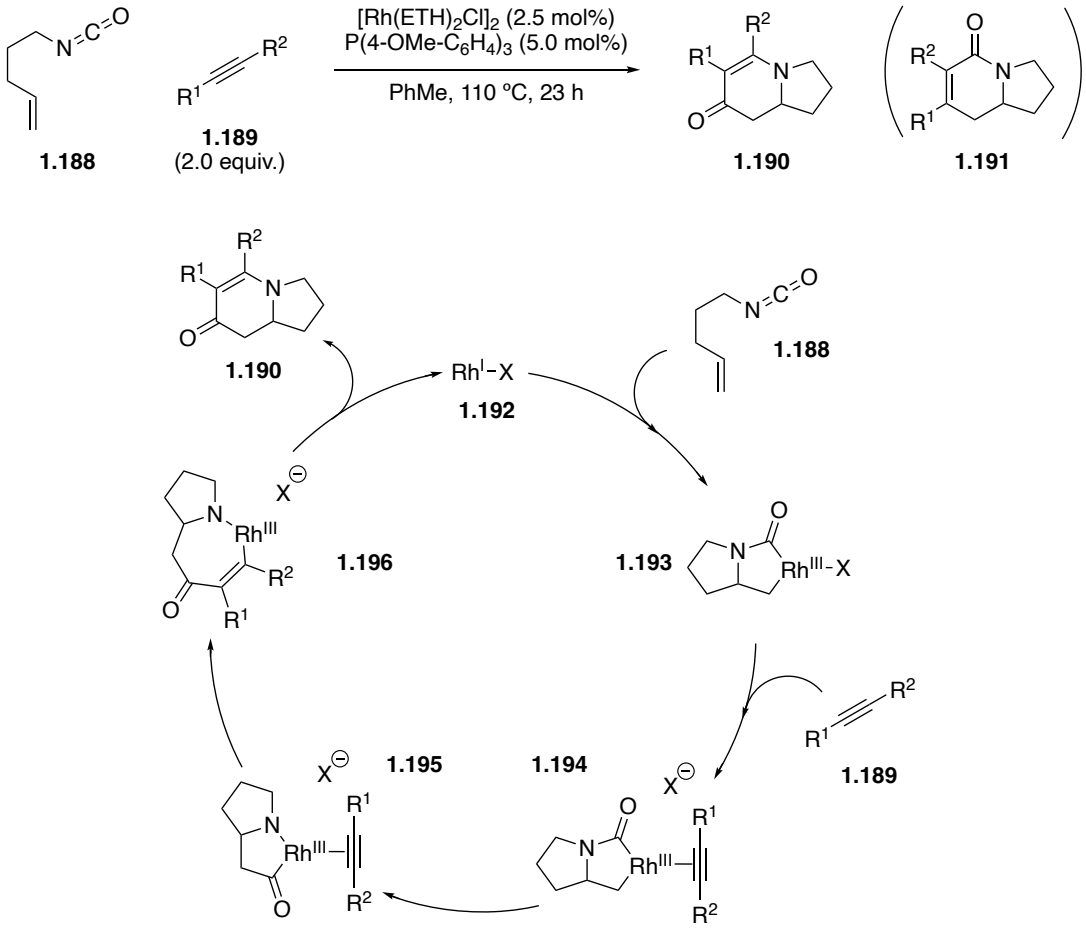
Scheme 1.33: An early example of [2+2+2] of alkynes and isocyanates and a more recent asymmetric example.

Tanaka has further applied carbodiimides and carbon dioxide in [2+2+2] cycloadditions to yield either 2*H*-pyridinyl imines (**1.185**) or 2*H*-pyran-2-ones (**1.187**) (**Scheme 1.34**).[172] In order to prevent issues with chemoselectivity, only symmetrical carbodiimides (**1.184**) are utilised; however, good yields are observed with excellent regioselectivity (where applicable). [172] This also extends to carbon dioxide (**1.186**) where yields are good but regioselectivity is poor (where applicable).[172] Attempts to render this process either axially or point enantioselective through chiral ligands yielded the desired products, albeit with lower yields and poor enantioselectivity. [172]



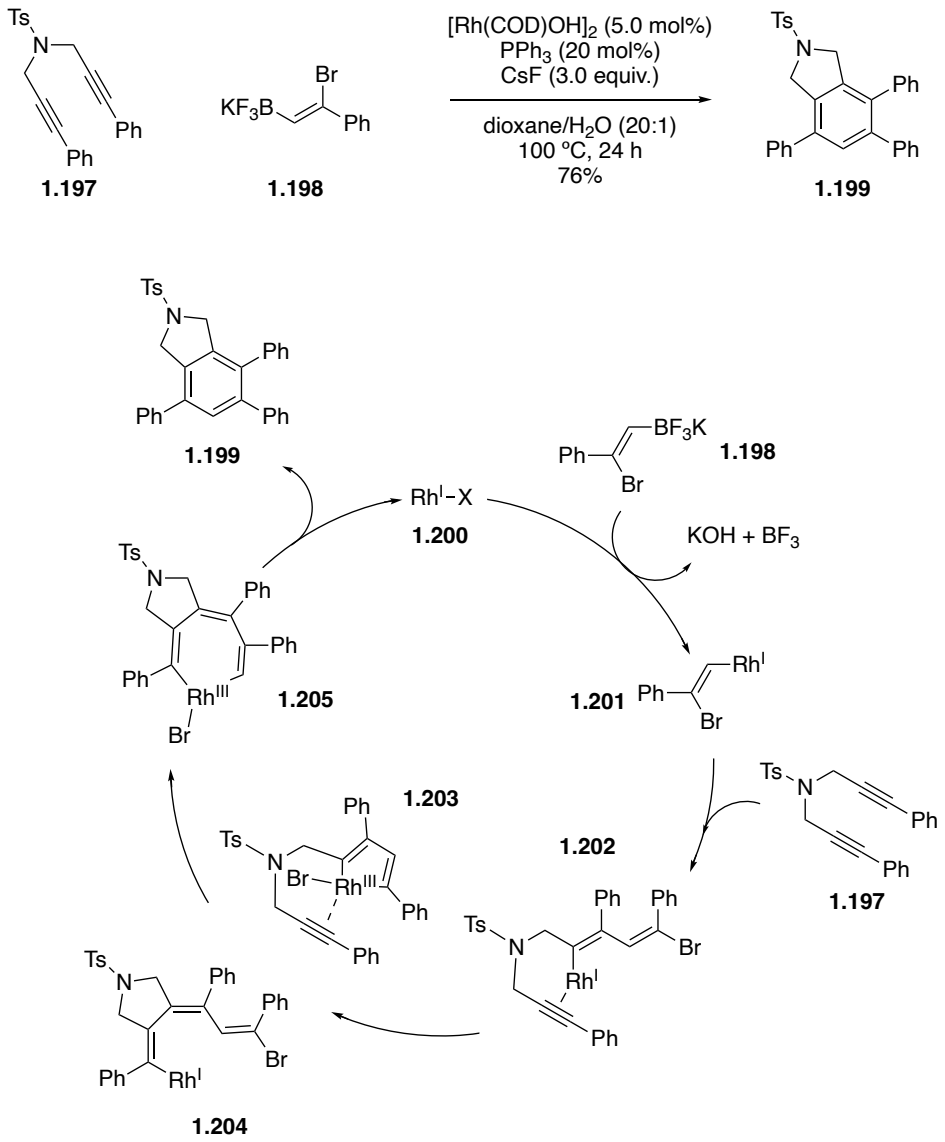
Scheme 1.34: Examples of [2+2+2] with diynes and carbodiimides or carbon dioxide.

Diyne components can also be swapped out for other unsaturated moieties. Yu and Rovis utilised alkenyl isocyanates (**1.189**) in place of diynes to couple to monoalkynes (**Scheme 1.35**).[173] Of note in this mechanism is a fast migratory insertion (**1.194 → 1.195**) which selects for the ketone (**1.190**) product rather than the amide product (**1.191**), which would result from the direct [2+2+2] cycloaddition.[173] When unsymmetrical aryl alkynes were used, regioselectivity was high and favoured minimising steric interactions.[173]



Scheme 1.35: Rovis and Yu's [2+2+2] of alkenyl isocyanates and alkynes.

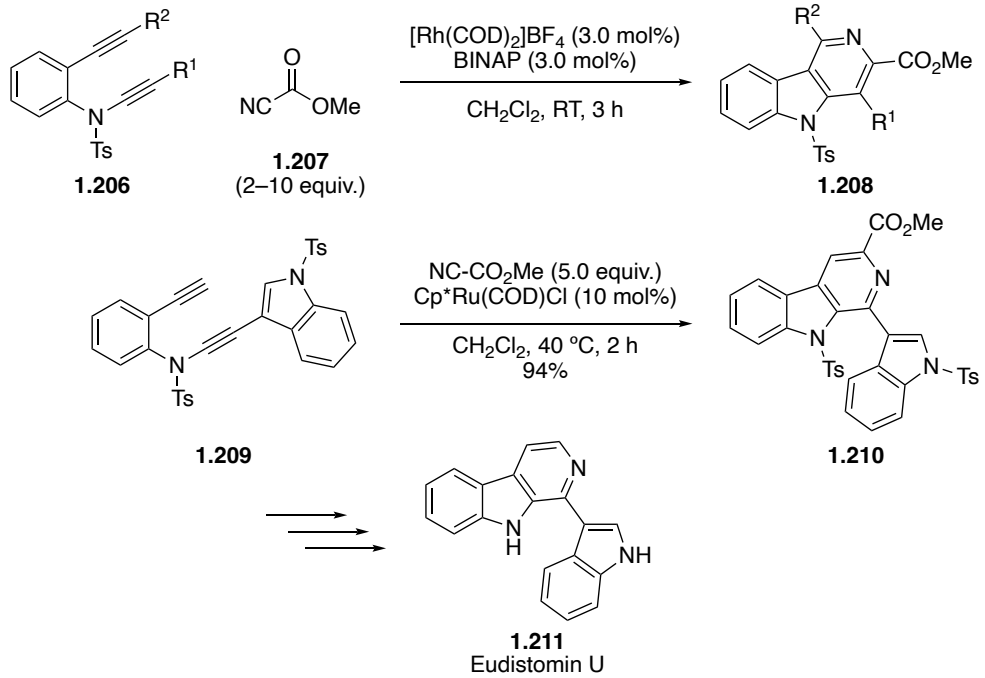
A mechanistically distinct transformation has been developed by Tong and coworkers, which generates identical products to a [2+2+2] through a slightly different mechanism (**Scheme 1.36**).[174] The postulated mechanism proceeds with transmetallation of the vinyltrifluoroborate (**1.198**) to the Rh^{I} (**1.200**) to generate a vinylrhodium(I) species (**1.201**). This undergoes a carborhodation process (**1.202**) with the diyne with two possible pathways from this point: (1) a second carborhodation (**1.204**) or (2) oxidative addition (**1.203**).[174] These intermediates undergo carborhodation or oxidative addition respectively to generate a rhodacycloheptatriene (**1.205**) which can undergo reductive elimination to generate the desired product (**1.199**) and to regenerate the Rh^{I} catalyst.[174]



Scheme 1.36: Rhodium-catalysed formal [2+2+2] cycloaddition of bromovinyltrifluoroborates and diynes.

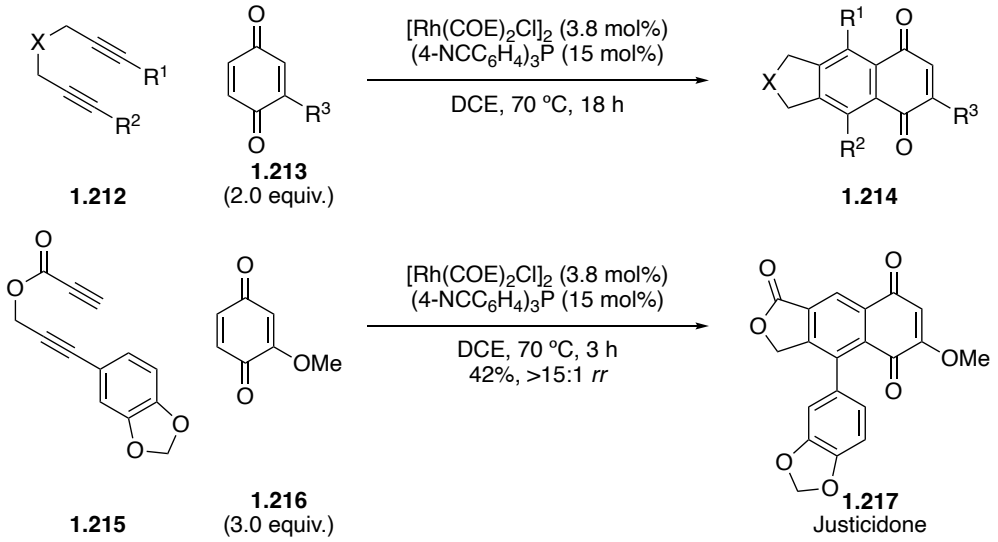
1.4. Rhodium-Catalysed [2+2+2] Cycloadditions in Natural Product Synthesis

Due to the reaction's high chemoselectivity and functional group tolerance, Rh-catalysed [2+2+2] cycloadditions are used extensively in natural product synthesis. For instance, Witulski (**Scheme 1.37**) utilised ynamide based diynes (**1.206**) and developed a Rh^{I} and Ru^{II} set of conditions for their cycloaddition with nitriles (**1.207**) to yield azacarbazoles (**1.208**). These conditions were then applied to the synthesis of the natural product eudistomin U (**1.211**) although Ru^{II} was found to be the more efficient catalyst.[175]



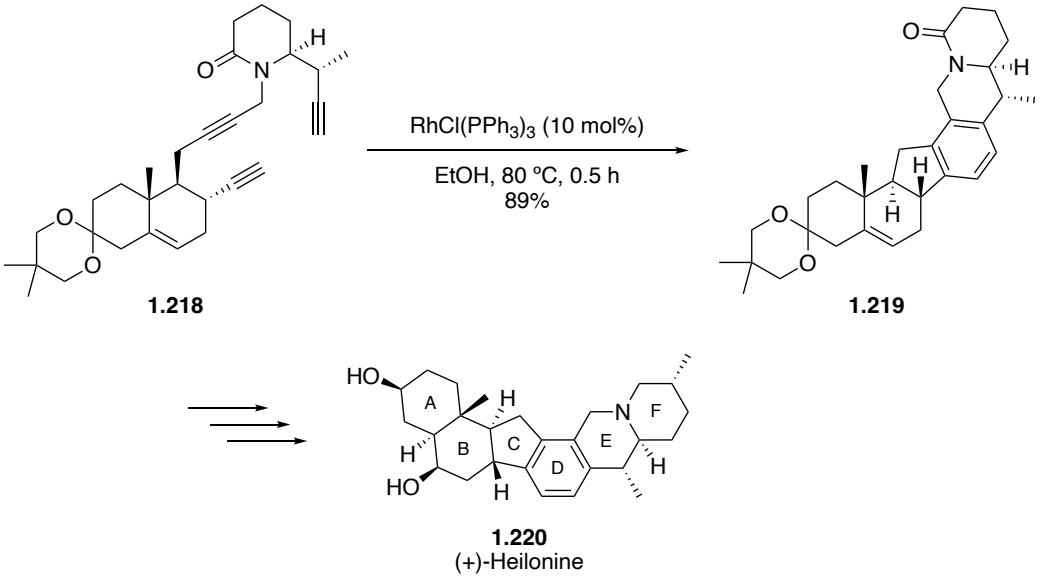
Scheme 1.37: Witulski's conditions for the [2+2+2] of diynes and nitriles and its application to the synthesis of eudistomin U.

Wood *et al*. (**Scheme 1.38**) utilised a more conventional diyne manifold (**1.215**) to couple with a benzoquinone derivative (**1.216**), generating the anti-Leishmanial natural product justicidone (**1.217**) in modest yield but exceptional regiocontrol.[176-178] In the same publication, the authors prepared a series of derivatives of the same molecule and compared their biological activity against *Trypanosoma cruzi*, a parasite which leads to Chagas disease.[179]



Scheme 1.38: Wood *et al.*'s rhodium-catalysed [2+2+2] of diynes and benzoquinones and its subsequent application within the synthesis of justicidone.

A recent example from Cassaidy and Rawal (**Scheme 1.39**) demonstrates the use of rhodium to catalyse the [2+2+2] reaction to yield an advanced intermediate (**1.219**) in the synthesis of (+)-heilonine (**1.220**).[180] The trialkyne coupling generates the central benzene core of (+)-heilonine, whilst simultaneously forming the C and E rings of the molecule. This process led to no erosion in enantioenrichment as well as no deprotection of the ketal nor migration of the double bond, highlighting the synthetic utility of this reaction.

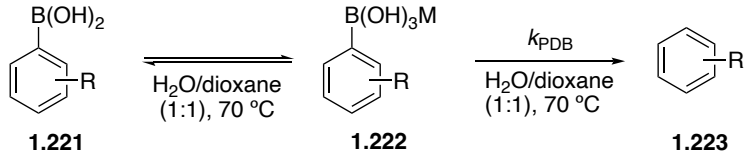


Scheme 1.39: Cassaidy and Rawal's [2+2+2] strategy in the synthesis of (+)-heilonine.

1.5. Organoboron Compounds and their Use in [2+2+2] Cycloadditions

[2+2+2] cycloadditions typically exhibit high functional group tolerance.[70, 72-74, 181-187] This goes hand-in-hand with organoboron chemistry. Organoboron molecules are very important for a variety of transition metal-catalysed reactions including the Suzuki-Miyaura cross-coupling, Chan-Lam reaction, and Hayashi conjugate addition (although a number of transition metal-free reactions with organoborons are also known, e.g. Petasis reaction, Brown allylation, etc.). However, organoboron compounds can be unstable, suffering from various pathways of

degradation with protodeboronation (PDB) being the most common. PDB involves the replacement of the boron moiety by a proton with loss of a borate derivative. Seminal work performed by Lloyd-Jones and coworkers investigated the rates and mechanisms of PDB.[188, 189] To show this, the approximate half-lives of various (hetero)arylboronic acids are listed in **Scheme 1.40**. As can be seen, a general trend is noted with electron-deficient rings becoming more unstable and heteroaromatic boronic acids, such as 2-pyridyl, also exhibiting short half-lives.[188-190]

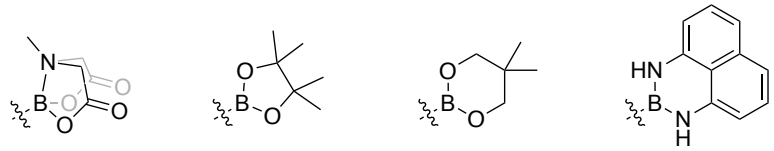


1.221 **1.222** **1.223**

R	~$t_{0.5}$
H	6 months
3-F	7 months
3,5-F_2	3 months
3,4,5-F_3	7 weeks
2,3,4-F_3	39 mins
2,3,4,5-F_4	3 mins
2,3,4,5,6-F_5	2.6 ms
2-pyridyl	25 s
5-thiazolyl	48 s
1-methyl-1*H*-pyrazol-5-yl	63 mins
1*H*-pyrazol-5-yl	169 mins

Scheme 1.40: Half-lives of various (hetero)aryl boronic acids in solution.

This is particularly problematic for the Suzuki-Miyaura cross coupling, which almost always requires some form of aqueous base except under very specific conditions.[191-193] Many solutions to this have been proposed; some have sought to utilise alternative elements to serve as more stable nucleophiles. For instance, work from the Willis group using sulfinate salts as nucleophiles in palladium-catalysed cross couplings.[190, 194-196] Others have employed protected organoborons which can be either coupled directly,[197, 198] or can be hydrolysed *in situ*, releasing a small amount of unstable organoboron at a time which can undergo the desired Suzuki-Miyaura coupling.[190, 199-201] Of particular note (**Figure 1.4**) are *N*-methyliminodiacetic acid (MIDA, **1.224**), pinacol (pin, **1.225**), neopentylglycol (neop, **1.226**) and 1,8-diaminonaphthalene (dan, **1.227**) boronic esters and amides which will be discussed below, with particular focus on their roles in Suzuki-Miyaura cross coupling reactions.

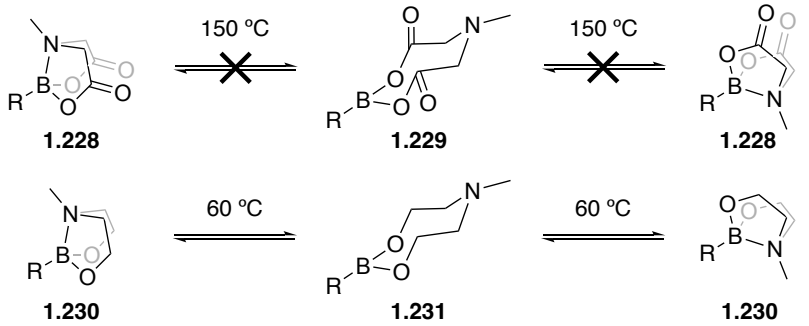


BMIDA **1.224** Bpin **1.225** Bneop **1.226** Bdan **1.227**

Figure 1.4: Examples of protected boronic acids

BMIDAs, first disclosed by Mancilla *et al.*,[202] are protected through coordination of a pendant nitrogen lone pair into the empty *p*-orbital of the boron, preventing an incoming nucleophile from generating a tetrahedral boronate, which can then undergo PDB or transmetallation (leaving aside arguments of whether boronate/oxo-palladium pathway is operative).[203-206]

BMIDAs (**1.228**) are structurally similar to *N*-methyldiethanolamine (**1.230**) counterparts. However, the acid moiety grants increased stability, even at high temperature, as evidenced by variable temperature (VT) NMR experiments, which show that dissociation of the nitrogen is not observed (**Scheme 1.41**).[202, 207, 208] MIDA groups can be cleaved by the addition of base to reveal a boronic acid; a technique particularly researched by the Burke group who have used this technique for iterative cross-couplings to synthesise complex scaffolds.[208-214]



Scheme 1.41: Conformational stability of BMIDAs and BMDEA esters.

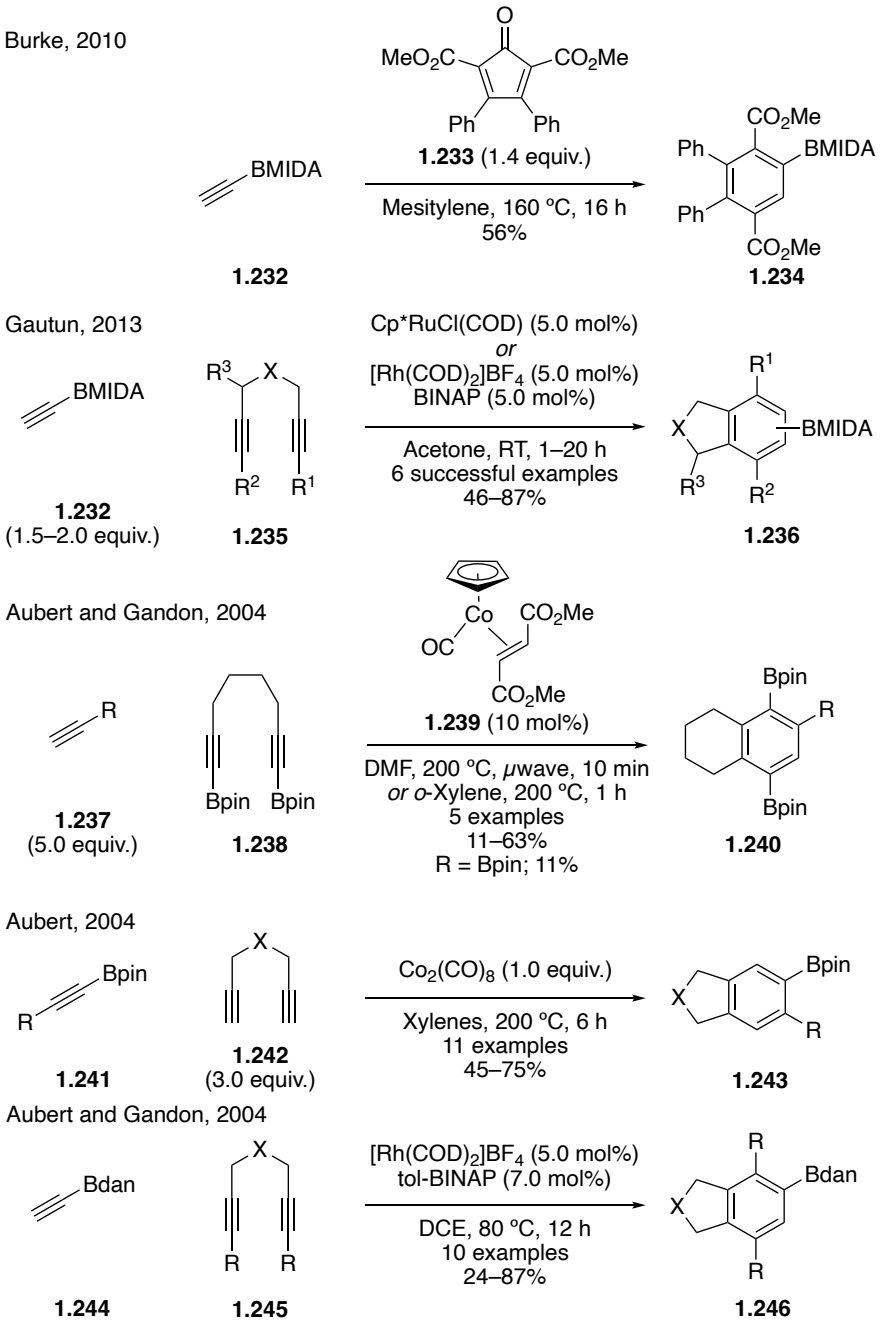
Bpin (and Bneop, however due to the increased prevalence of Bpin, Bneop will not be discussed in detail) esters are very commonly found protected organoboron compounds, which tend to react sluggishly compared to the free boronic acid.[206, 208, 215-217] This is thought to be due to the conjugation of the oxygen lone pair into the *p*-orbital on boron.[206, 208, 215-217] Similarly, these groups have been extensively examined by the Watson group for chemoselective cross couplings of boronic acids in the presence of pinacol esters.[218-220] Bpin esters have also been demonstrated to undergo direct transmetallation under anhydrous Suzuki-Miyaura conditions.[191, 192]

Finally, Bdan amides are unusual for boronic acid protecting groups in that they are not cleaved by aqueous base, but rather acid.[221-223] As is the case of Bpins, the stability is enhanced due to conjugation of the amines' lone pairs into the vacant *p*-orbital on boron.[217, 222] These molecules have been used in iterative cross couplings, as with BMIDAs, but also are known to undergo direct cross coupling under suitable conditions.[197, 221]

Whilst other boron protecting groups are available, the aforementioned examples were selected due their precedent in the literature with respect to [2+2+2] cycloadditions. Burke and coworkers (**Scheme 1.42**) demonstrated that ethynyl BMIDA (**1.232**) can undergo a formal [2+2+2] cycloaddition through a Diels-Alder-cheletropic reaction cascade to generate a functionally dense benzene core (**1.234**) in 2010.[224] The scope of this reaction was expanded in 2013 using a more conventional transition metal-catalysed [2+2+2] cycloaddition using either a Ru or Rh manifold to give arenes (**1.236**) with a key limitation being the use of only ethynyl BMIDA (**1.232**).[225]

Alkynyl Bneop and Bpin esters have been shown to undergo [2+2+2] cyclisations using stoichiometric or substoichiometric amounts of transition metals. Aubert and Gandon have shown that ethynyl Bpin (**1.241**) can undergo the reaction using a Vollhardt type Co^{I}-catalyst (**1.239**),[226] and Michelet and Ratovelomanana-Vidal have demonstrated that Bneop and Bpins are successfully cyclised using Ir catalysis.[227] In a separate publication, Aubert and coworkers have reported that the [2+2+2] reaction of alkynyl Bpins (**1.241**) can be performed by stoichiometric pretreatment of the requisite monoalkyne with dicobalt octacarbonyl.[228]

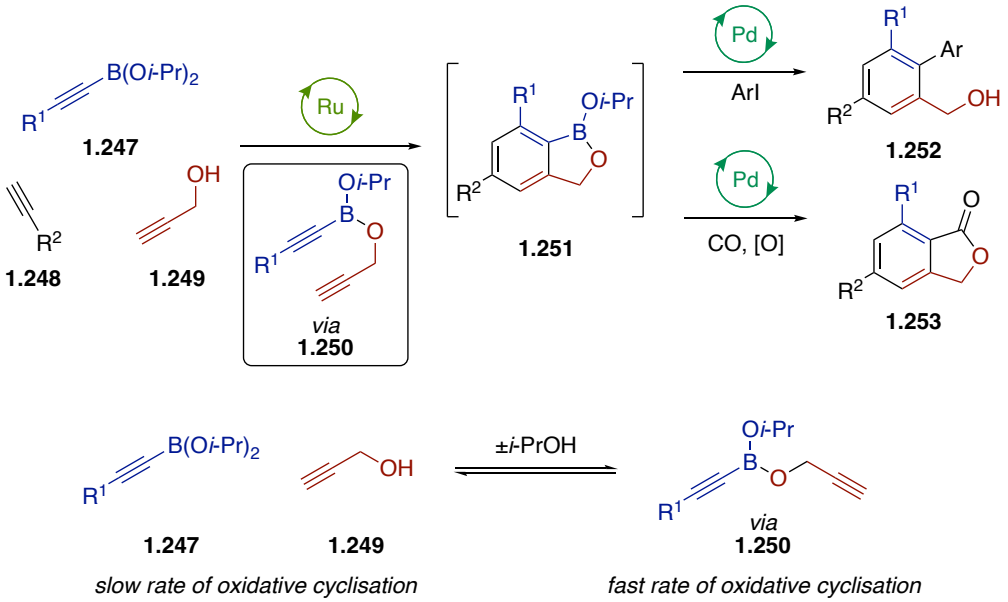
Finally, Aubert and Gandon have also established that ethynyl Bdan (**1.244**) is also a competent monoalkyne in [2+2+2] cycloadditions.[226] Interestingly, there were observations that ethynyltrifluoroborate salts are incompatible towards the Co^{I}-mediated processes due to oxidation to catalytically inactive Co^{III} species.[226] Ethynyl BMIDA was also unreactive though no oxidation products were noted.[226]



Scheme 1.42: Examples of alkynylorganoborons in [2+2+2] cycloadditions.

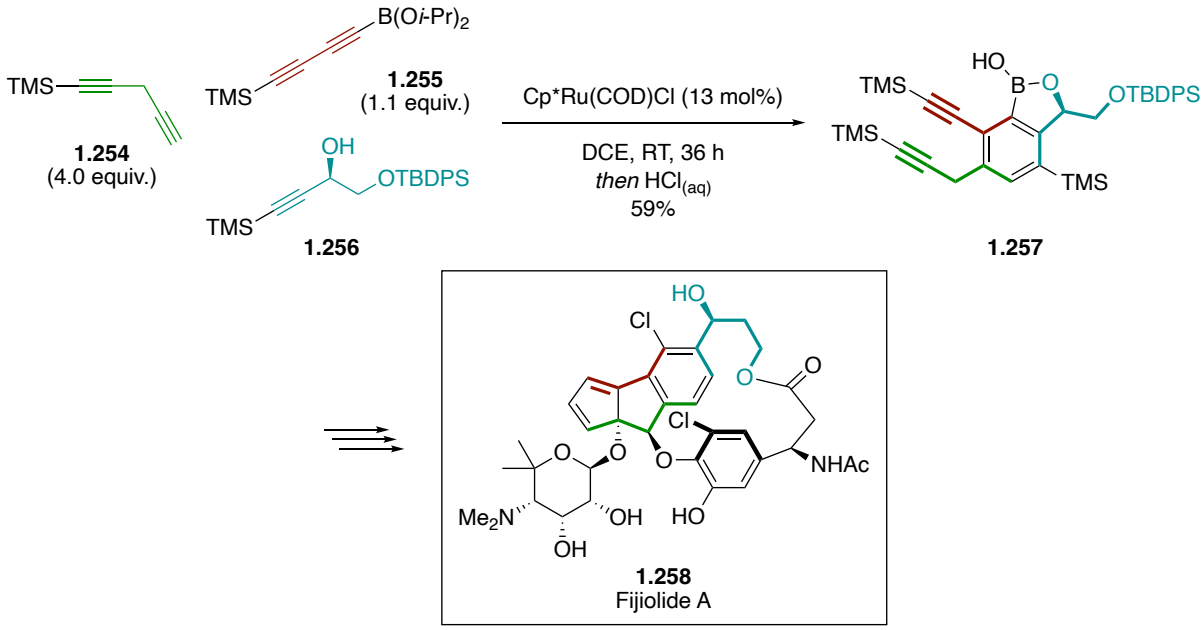
Whilst comparatively rare, dialkyl boronic esters have been implemented in [2+2+2] cycloadditions. Aforementioned elegant work performed by Yamamoto and coworkers (**Schemes 1.6** and **1.43**) utilised boron speciation events between the dialkyl ester (**1.247**) and a propargylic alcohol (**1.249**) to generate a mixed ester *in situ* (**1.250**).[75, 76] This nascent 1,6-diyne is able to successfully engage a Ru^{II} catalyst at a much-enhanced rate compared to the free alkynes, commencing a cycle of a [2+2+2] cycloaddition. This work is impactful in a

number of ways: (1) it features dialkyne formation through boron templation, (2) it is a rare example of a trimolecular [2+2+2] cycloaddition with high regio- and chemoselectivity,[74] (3) whilst the products are not isolated as the benzoxaborole (**1.251**) (they are subject to either oxidative carbonylation to yield **1.253** or Suzuki-Miyaura cross coupling to give **1.252**), this class of molecules are an emerging motif in drug discovery, with [2+2+2] cycloadditions offering a mild and convenient route to complex derivatives.[229-232]



Scheme 1.43: Yamamoto's trimolecular [2+2+2] utilising temporary boron tethering and the subsequent SMCC or lactonisation.

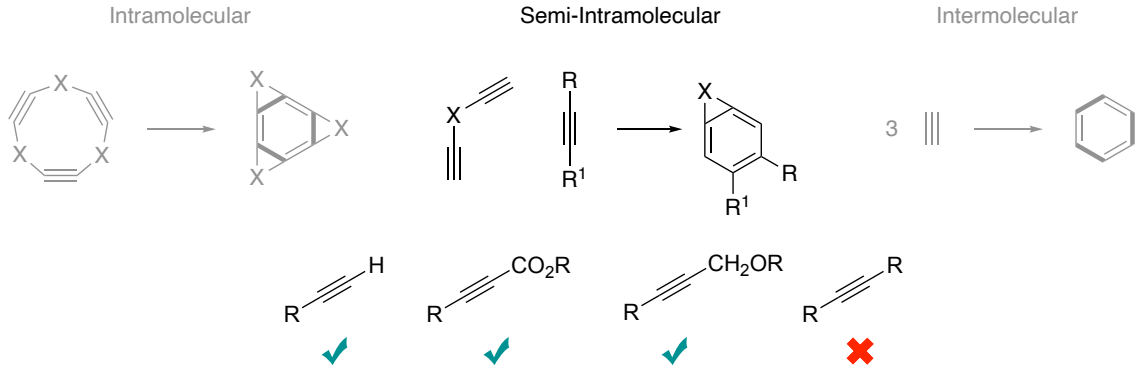
After Yamamoto's work on boron-templating [2+2+2], the Cramer group (**Scheme 1.44**) employed this methodology as an effective way to generate the core structure of the natural product fijiolide A (**1.258**).[233] The chiral propargylic alcohol (**1.256**) templates with the boronic ester (**1.255**), forming the diyne *in situ*. This undergoes the standard cycloaddition with the stoichiometrically biased 1,4-diyne (**1.254**) to yield the desired product (**1.257**).[233] Excellent chemoselectivity is offered as a consequence of the boron templating and regioselectivity is offered through steric repulsion differences between the trimethylsilylethynyl group *vs* the trimethylsilyl group. [233] Excellent chemoselectivity in the case of the diynes is also offered, assumedly through a mechanism similar to that described by Yamamoto and coworkers. [77, 233]



Scheme 1.44: Cramer's application of boron templated [2+2+2] in the synthesis of fijioilide A.

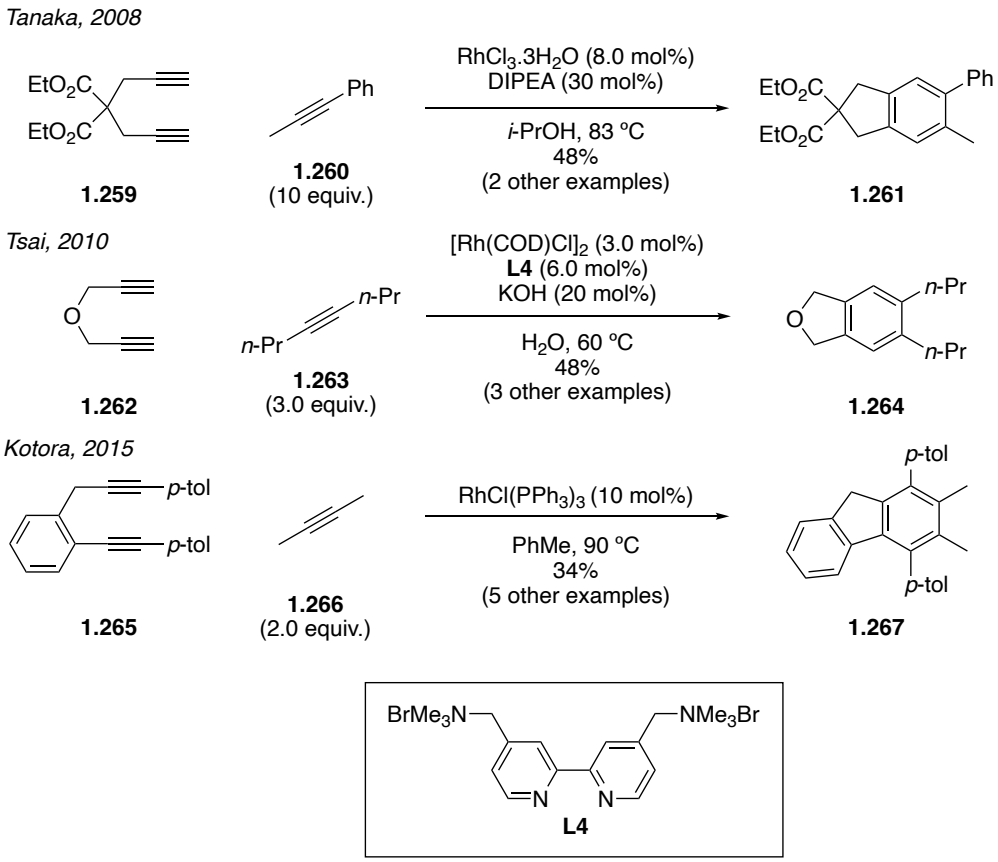
1.6. The Internal Alkyne Problem in Semi-Intramolecular [2+2+2] Cycloadditions

Upon examining the literature with respect to the semi-intramolecular [2+2+2], terminal alkynes are the most commonly seen monoalkyne component. When internal monoalkynes are used, they are broadly derivatives of propiolate esters/propargyl alcohols (**Scheme 1.45**). Henceforth, the term activated alkyne will be used to refer to these derivatives (an explanation of this terminology will be described in **Section 3.4**). Similarly, activated dialkynes exist for which unactivated internal alkynes may be employed. These dialkynes are typically structurally biased in such a way that they may undergo thermal [4+2] cycloadditions and will thus not be considered.[234-238]



Scheme 1.45: Propiolate derivative overrepresentation.

If the literature search is limited to solely rhodium catalysis (although this problem does exist for other metal catalysts but it is less apparent with some metals, e.g., cobalt), the only examples of internal unactivated alkynes used in the relevant reactions are shown in **Scheme 1.46**.[108–110]



Scheme 1.46: Rhodium-catalysed unactivated dialkyne-unactivated monoalkyne [2+2+2] cycloadditions.

What is evident is that yields are typically low and, generally, the monoalkynes are typically sterically undemanding. Further to this, there is a prevailing dogma in the literature that electron poor alkynes react preferentially to electron rich species. When examining the general catalytic cycle (**Scheme 1.7**), the Rh(III) centre (**1.7** or **1.8**) is, at this point, electron deficient. Thus, binding towards electron rich monoalkynes should, in fact, be preferred.

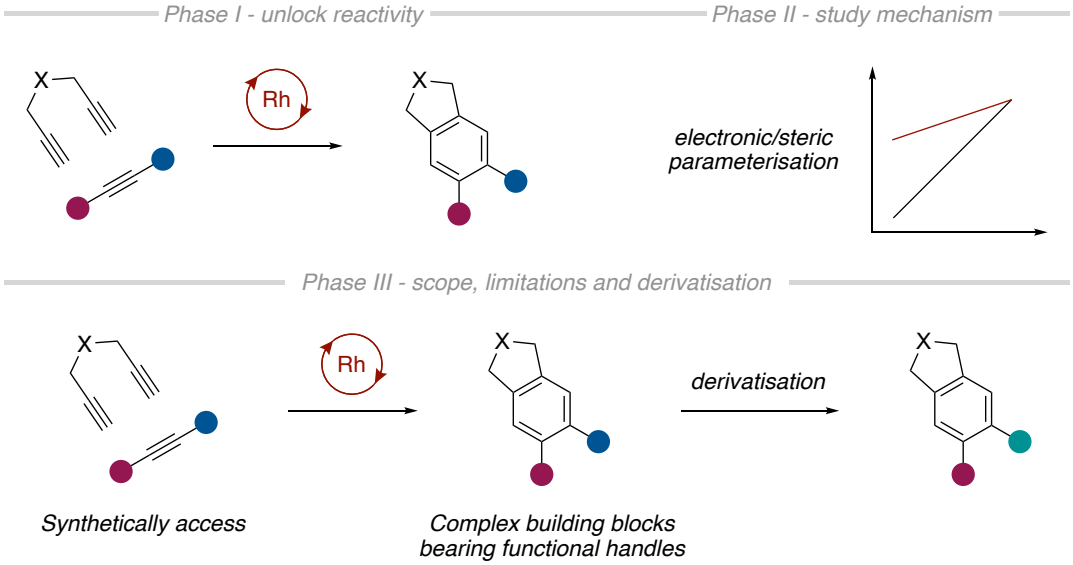
2.0. Research Outline

The apparent inconsistency between electronic preference and reaction mechanism prompted the initial investigation into this reaction. This leads to the main goals of the project which will be delineated in the following chapters:

(1) Develop conditions that allow for the use of internal alkynes in a general sense in semi-intramolecular [2+2+2] cycloadditions. Optimising with respect to metal, ligand, stoichiometry, solvent temperature, and, if needs be, addition rate. It should be noted that the conditions developed may be commercially unviable; however, the information gleaned may be essential for development of future reactions.

(2) Use these conditions to study the reaction with respect to electronics of the beginning monoalkyne. Failing to find any strong evidence for electronic bias, other factors will be examined. Naturally, sterics should be scrutinised due to the regiochemical observations noted by Yamamoto and coworkers.[77] Furthermore, the effects of the ester and alcohol groups that are so prevalent in the literature will be investigated.

(3) Utilising the information attained from the mechanistic investigations, the scope of the reaction will be examined. Functional group tolerance will be assessed and then the reaction scope will be expanded towards borylated alkynes to generate complex organoborons. These complex products can be subjected to standard organoboron transformations including Suzuki-Miyaura cross couplings, Chan-Lam reactions, Brown oxidations, and Hayashi-Miyaura reactions.

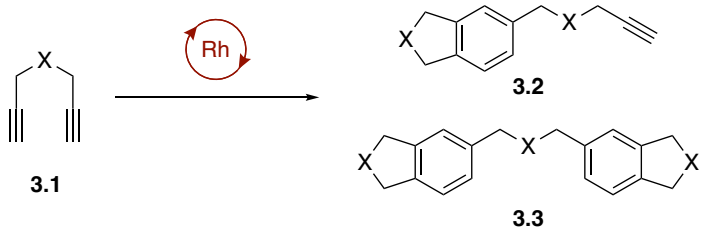


Scheme 2.1: Outline of planned research campaign with relevant phases.

3.0. Chapter 2: Optimisation and Mechanistic Investigations

3.1. Reaction optimisation

In order to examine the reaction with respect to electronics, reaction conditions must be developed that allow for the successful and general application of internal alkynes in [2+2+2] cycloadditions. As with most reactions, the choice of catalyst, solvent, temperature, etc. are all possible choices for optimisation; however, an additional parameter is required for this reaction, which is addition rate. Slow addition of the diyne component was often a required, as otherwise, homodimer- (**3.2**) and trimerisation (**3.3**) of this reaction component occurs (**Scheme 3.1**). Indeed, the requirement to control addition rate is commonly observed throughout the literature (e.g., Shibata *et al.*'s [2+2+2] of diynes and benzothiophene-*S*,*S*-dioxides).[147]

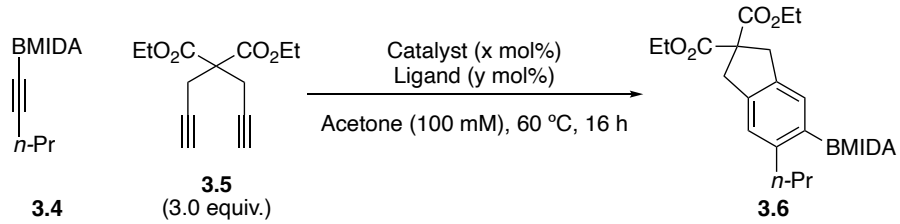


Scheme 3.1: Homodimer- and trimerisation of dialkyne.

Choice of catalyst

[2+2+2] cycloadditions can be performed by a great number of metals with various advantages and disadvantages.[239] A number of different metal catalysts were selected using manifolds which are present in the literature.[224-228] A model system was selected using a BMIDA bearing alkyne (**3.4**) and malonate diyne (**3.5**). The origin of this choice of monoalkyne, is due to the desired to apply this reaction to borylated molecules in the future. The results are shown in **Table 3.1**. As can be seen, essentially all catalytic systems perform poorly with yields ≤10% across the board, and only trace amounts of product observed with iridium and cobalt systems. Of note is the apparent importance in selection of ligand and pre-catalyst. When comparing different rhodium sources, Wilkinson's catalyst (entry 4) offered only trace product whereas the use of a BINAP-rhodium catalytic system (entry 3) yielded 10% yield by NMR spectroscopy. However, the use of a different rhodium precatalyst (entry 5) returned only trace reactivity. Thus the $[Rh(COD)(NCMe)_2]BF_4$–BINAP system was taken forward.

Table 3.1: Catalyst selection



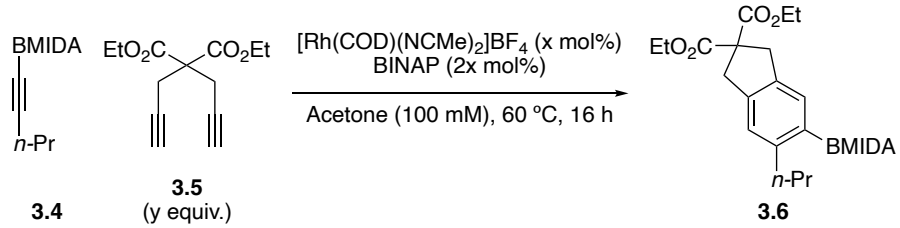
3.4 **3.5** (3.0 equiv.) **3.6**

Entry	Catalyst (x mol%)	Ligand (y mol%)	Yield (%)[a]
1	[Ru(COD)Cp*]Cl (5.0)	0	7
2	$[Ir(COD)Cl]_2$ (5.0)	0	<5
3	$[Rh(COD)(NCMe)_2]BF_4$ (5.0)	BINAP (10.0)	10
4	$[Rh(PPh_3)_3]Cl$ (5.0)	0	<5[b]
5	$(acac)Rh(C_2H_4)_2$ (5.0)	BINAP (10.0)	<5

[a]Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.
[b]Performed in ethanol.

Next, the loading of catalyst was examined. What became obvious, was that as the loading of catalyst increased, the reaction became much more successful. This was only evident up to 20 mol% of the Rh catalyst however (entry 4). After this point, the solution appeared to become heterogeneous, thus reducing reaction efficiency. In order to counteract this, the reaction was performed at high loadings (entries 6–8) at decreased concentration; however, the reactivity was not rescued. The similarity in yield in entries 6 and 7 implied that concentration likely did not have a significant role at these high loadings. Entries 9–12 show a near twofold increase in yield is observed when slow addition of the dialkyne was employed, a factor which was also examined below.

Table 3.2: Catalyst loading



3.4 **3.5** (y equiv.) **3.6**

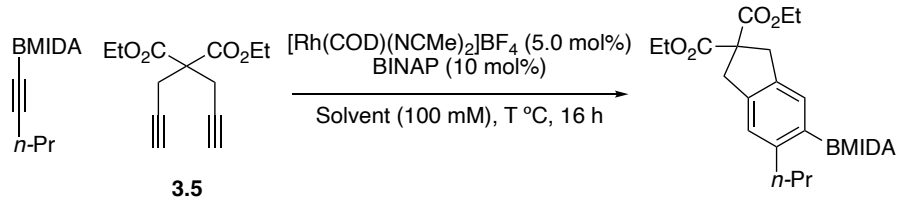
Entry	(x mol%)	(y equiv.)	Yield (%)[a]
1	5	3.0	10
2	10	3.0	14
3	15	3.0	31
4	20	3.0	43
5	30	3.0	39
6	50	3.0	27
7	50	3.0	28[b]
8	100	3.0	29[b]
9	5	6.0	10[c]
10	10	6.0	37[c]
11	15	6.0	63[c]
12	20	6.0	80[c]

[a]Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.
[b]Performed at 50 mM.

Choice of solvent and temperature

A variety of solvents were tested with acetone emerging as a frontrunner overall, outcompeting other commonly employed solvents in [2+2+2] cycloadditions including DCE, DMSO, and MEK. A temperature screen of the reaction in acetone revealed that maximal reactivity was observed at 60 ºC and 70 ºC. 60 ºC was taken onwards due to the lower energy requirement but also due to concerns about superheating the solvent. Of note, is the fact that acetone itself is able to be a competent partner in [2+2+2] cycloadditions. Systems reacting in this way typically employ nickel catalysts;[240-242] however, reports exist using either ruthenium[164, 243, 244] and rhodium catalysis (see **Scheme 1.31**, **1.163**).[156, 245, 246] These products were only detected in trace amounts in this optimisation.

Table 3.3: Solvent/temperature selection



3.4 **3.5** (3.0 equiv.) **3.6**

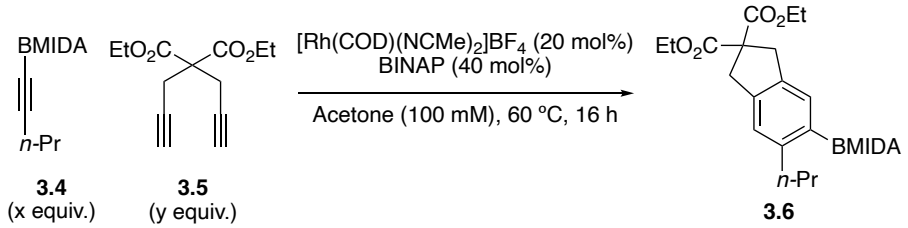
Entry	Solvent	Temperature (ºC)	Yield (%)[a]
1	Acetone	60	10
2	DCE	60	<5
3	DMSO	100	<5
4	DMSO	140	<5
5	MEK	90	30[b]
6	Acetone	RT	17[b]
7	Acetone	50	25[b]
8	Acetone	60	50[b]
9	Acetone	70	50[b]

[a]Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.
[b]Performed using 20 mol% $[Rh(COD)(NCMe)_2]BF_4$ and 40 mol% BINAP.

Choice of reactant stoichiometry and addition rate

The stoichiometry of the alkyne components was next examined. First, the monoalkyne component was varied with little success observed when compared to the high equivalence of dialkyne (entries 1–3). It was noted that increasing the dialkyne component equivalents yielded a smooth increase in yield (entries 4–8) which plateaus at 6.0 equiv. We hypothesise that this plateauing is due to excess homodimers and trimers leading to heterogeneity.

Table 3.4: Mono/dialkyne stoichiometry



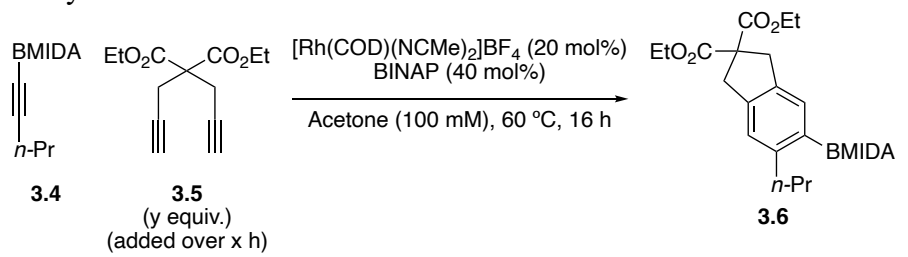
3.4 (x equiv.) **3.5** (y equiv.) **3.6**

Entry	x (equiv.)	y (equiv.)	Yield (%)[a]
1	1.0	1.0	25
2	3.0	1.0	27[b]
3	5.0	1.0	29[b]
4	1.0	2.0	23
5	1.0	3.0	43
6	1.0	4.0	52
7	1.0	5.0	56
8	1.0	6.0	63
9	1.0	7.0	58
10	1.0	8.0	50
11	1.0	9.0	59

[a]Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.
[b]Performed using 10 mol% $[Rh(COD)(NCMe)_2]BF_4$.

Next the addition rate was examined with 6.0 equiv. of dialkyne. At a 15 h addition rate, a maximal yield of 80% was observed. 20 h may be expected to follow the trend, yielding the desired product at an even higher yield; however, diminished yields were observed. It can be postulated at this point that the lower yield was due to catalyst degradation/deactivation pathway which may occur off-cycle.

Table 3.5: Dialkyne addition rate



3.4 **3.5** (y equiv.) (added over x h) **3.6**

Entry	x (h)	Yield (%)[a]
1	5	54
2	10	63
3	15	80
4	20	52

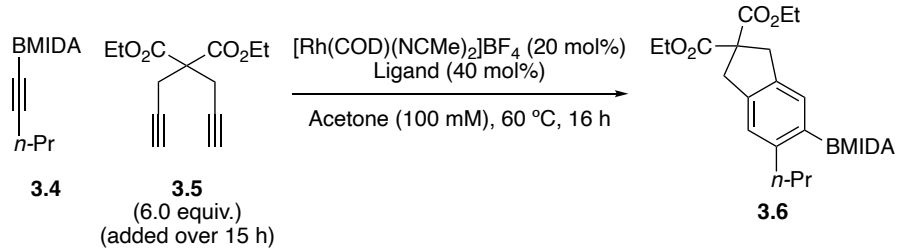
[a]Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

Reoptimisation of ligand and robustness

With the optimised conditions in hand, a secondary ligand screen was performed to ascertain whether any further product could be obtained through ligand selection. A variety of phosphine ligands were selected with the ligands offering poorer yields than BINAP. Overall, it appears that bisphosphines are essential, as when monophosphines are used (entries 8, 10–12), no reaction was observed. The importance of bisphosphine ligands has been previously described

in other publications; however, it is not mechanistically clear why the preference was so strong.[160]

Table 3.6: Ligand selection



Entry	Ligand	Yield (%)[a]
1	DPEPhos	33
2	Xantphos	<5
3	dppp	44
4	dppe	<5
5	SEGPHOS	<5
6	dtbpf	<5
7	dppf	50
8	tBu$_3$P.HBF$_4$	NR
9	dppm	NR
10	PPh$_3$	NR
11	SPhos	NR
12	XPhos	NR
13	BINAP	80
14	dppb[b]	55
15	(*S*)-(−)-TolBINAP	61
16	(*R*)-SEGPHOS	34
17	(*R*)-DIFLUORPHOS	<5
18	-	<5
19	BINAP[c]	21

[a]Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.
[b][Rh(dppb)(COD)]BF$_4$ (20.0 mol%), dppb (20.0 mol%) as catalyst.
[c][Rh(COD)Cl]$_2$ (10.0 mol%) used as Rh source.

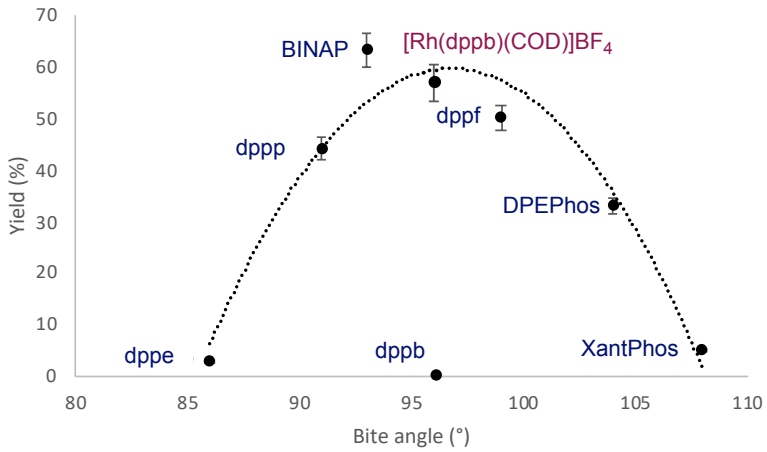


Figure 3.1: Apparent yield vs phosphine bite angle dependence.

An interesting observation is the apparent dependence of the bite angle of various bisphosphines and reaction efficiency. Plotting the yield of the reaction *vs* the bite angle yields a clear maximum at around 95º. dppb as a ligand falls in this area; however, this is a poor ligand for this reaction. In the reaction using dppb a distinct lack of colour change was noted, implying no Rh-P coordination. Comparing the $^{31}P\{^{1}H\}$ NMR spectra of the Rh source with either dppb or BINAP showed that after stirring for 30 mins at 60 ºC, in the case of BINAP, no free ligand was observed with only trace amounts of BINAP oxide observed and a vast majority being Rh bound as evidenced by the formation of a doublet from coupling to ^{103}Rh (100% abundant, I = ½).[247] When the experiment was performed with dppb, a sizable amount of the ligand complexed with the catalyst but a considerable amount of free ligand remained in solution and a larger amount of oxidation was also observed. We rationalise that the restricted rotation of the BINAP ligand enables more facile complex formation whereas the flexible butylene backbone of dppb offers significantly more degrees of freedom, prohibiting the formation of the desired bidentate complex. Of note, when the premade Rh-dppb complex was used in the reaction (**Table 3.6**, **Entry 14**), reactivity was rescued, although BINAP still remains the best ligand.

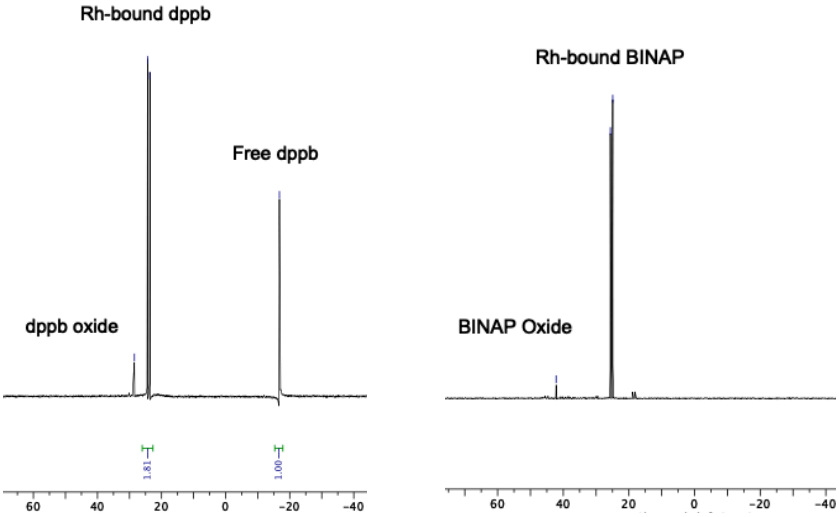
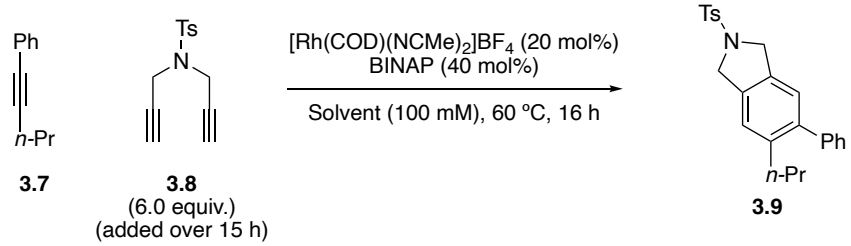


Figure 3.2: [Rh(COD)(NCMe)$_2$]BF_4 + phosphine ligand (1:1) in d_6-acetone after heating to 60 ºC for 10 minutes. No free BINAP observed; however, large amount of dppb observed.

As a final step, the reaction was subjected to a small robustness screen. First, the response of the reaction to different atmospheres was measured. No difference was observed between argon and nitrogen atmospheres; however, pleasingly, only a small decrease was observed when the reaction was performed under air in spite of the high likelihood of oxidation of BINAP, particularly in the presence of a rhodium catalyst.[248] The use of degassed solvent did not appear to be required, with no change in yield observed, even using acetone with no drying treatments. Of note was that the use of DCE offers significantly reduced yield (postulated to be due to poor solvating effects); however, the doping of acetone as an additive appears to regain the desired reactivity. Finally, attempting to use this system with no phosphine ligand added only gave limited amounts of product.

Table 3.7: Reaction robustness



3.7 **3.8** (6.0 equiv.) (added over 15 h) **3.9**

Entry	Solvent	Degassed	Atmosphere	Yield (%)[a]
1	Acetone (dry)	Y	N_2	>99
2	Acetone (dry)	Y	Ar	>99
3	Acetone (dry)	Y	Air	89
4	Acetone (dry)	N	N_2	>99
5	Acetone (wet)	N	N_2	>99
6	DCE (dry)	N	N_2	68
7	Acetone (dry)	Y	N_2	9[b]
8	DCE (dry) + Acetone (5.0 equiv.)	N	N_2	73
9	DCE (dry) + Acetone (10.0 equiv.)	N	N_2	81

[a]Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.
[b]Phenylpropyne as monoalkyne. No ligand added.

3.2. Examination of Electronic Parameters

With reaction conditions in hand, the reaction efficiency was examined as a function of the electronic nature of the monoalkyne.

The electronic nature of the monoalkyne was determined through examining the Hammett parameters of substituents on the benzene ring and this was compared to the reaction yield in a fashion similar to work by the Gilmour group.[249, 250] The reaction efficiency was simply determined by the yield of the reaction as no side reactions were observed in this methodology (i.e., no cyclotrimerisation of monoalkyne was observed, therefore if 50% of monoalkyne is consumed to yield the desired product, 50% of the monoalkyne was remaining at the end of the reaction).

In dissensus with the literature, no clear trend was observed in either dialkyne regime. If there were a preference for electron-poor alkynes, a tilting of the graph up towards more positive σ values would be expected.

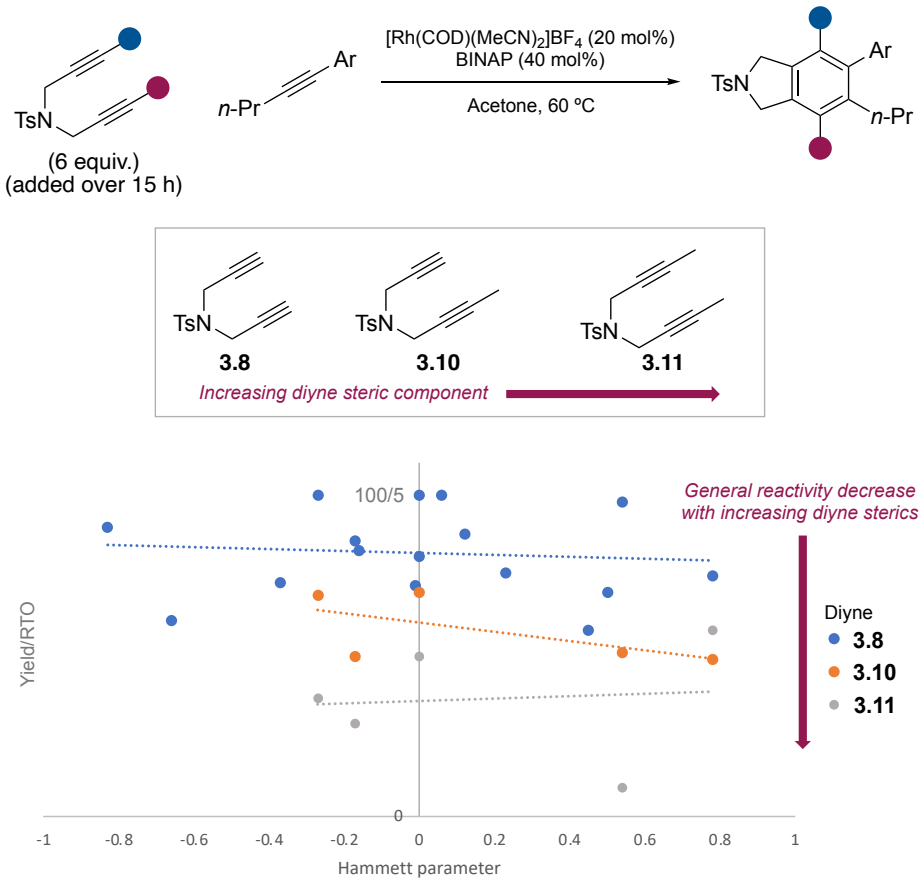


Figure 3.3: Electronic investigations of internal alkyne [2+2+2] with dialkynes **3.8**, **3.10**, **3.11**. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

The results of these analyses are shown in **Figure 3.3**. It was evident that no clear relationship was present. The graphs show that little electronic preference was observed. In apparent opposition to the literature,[122, 123, 251, 252] several electronically rich/neutral alkynes react better than their electron-deficient analogues. A further detail of note was the overall decrease in reactivity as steric environment on dialkyne was increased. Details of substrates and yields will be reported in **Section 4.1**. This investigation was further expanded (**Figure 3.4**) to two other dialkynes, including malonate derivative (**3.5**) and octadiyne (**3.12**) with similar observations noted.

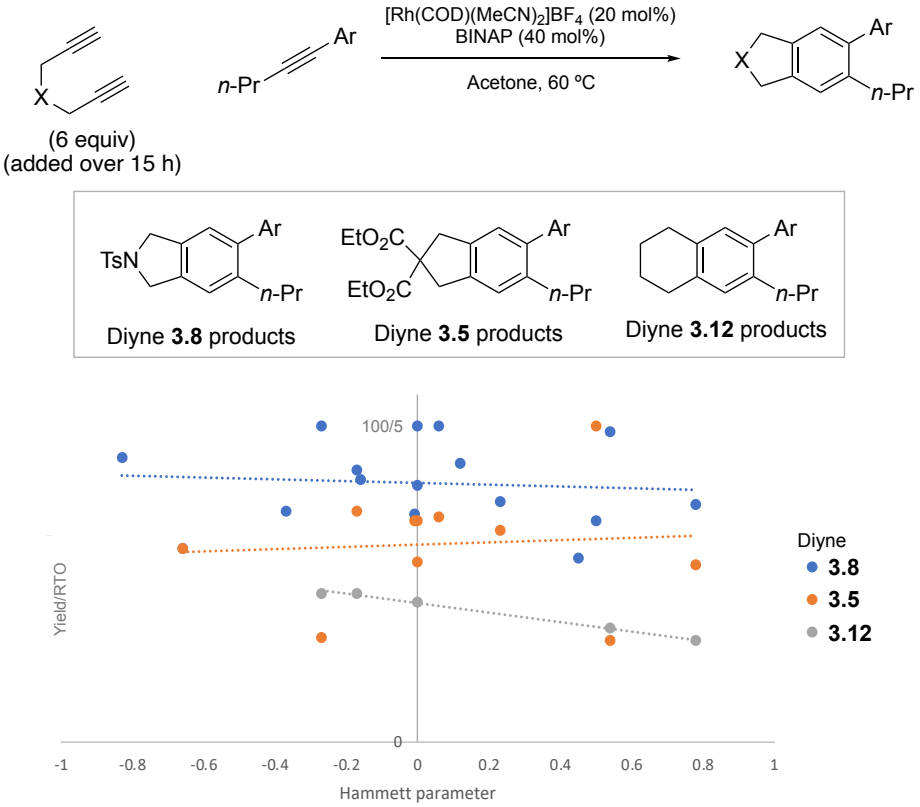
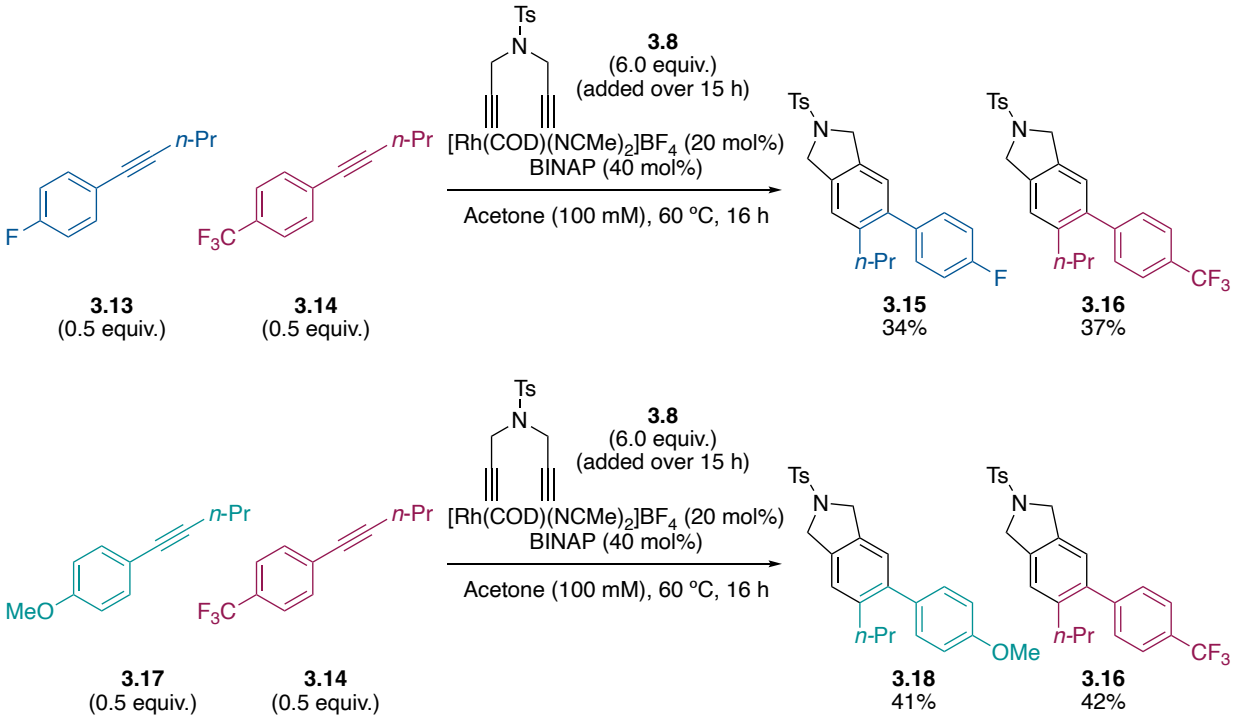


Figure 3.4: Electronic investigations of internal alkyne [2+2+2] with dialkynes **3.5**, **3.8**, **3.12**. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

To further test the apparent conclusion that electronic discrimination was unlikely, competition experiments were carried out (**Scheme 3.2**). Using the same conditions as optimised, 0.5 equiv of **3.13** bearing a weakly electron-withdrawing *p*-F and 0.5 equiv of **3.14** with a strong withdrawing *p*-CF_3 group, essentially 1:1 product formation of **3.15** and **3.16** was observed. Starker still was when the same experiment was performed with **3.14** *vs* **3.17** containing an electron rich alkyne as a function of the *p*-OMe group. A similar result was observed in that near 1:1 of **3.16** vs **3.18** product formation occurred. This type of experiment was repeated several times with various alkynes and the product distribution was noted (**Figure 3.5**).



Scheme 3.2: Initial competition experiments between alkynes in [2+2+2] cycloadditions. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

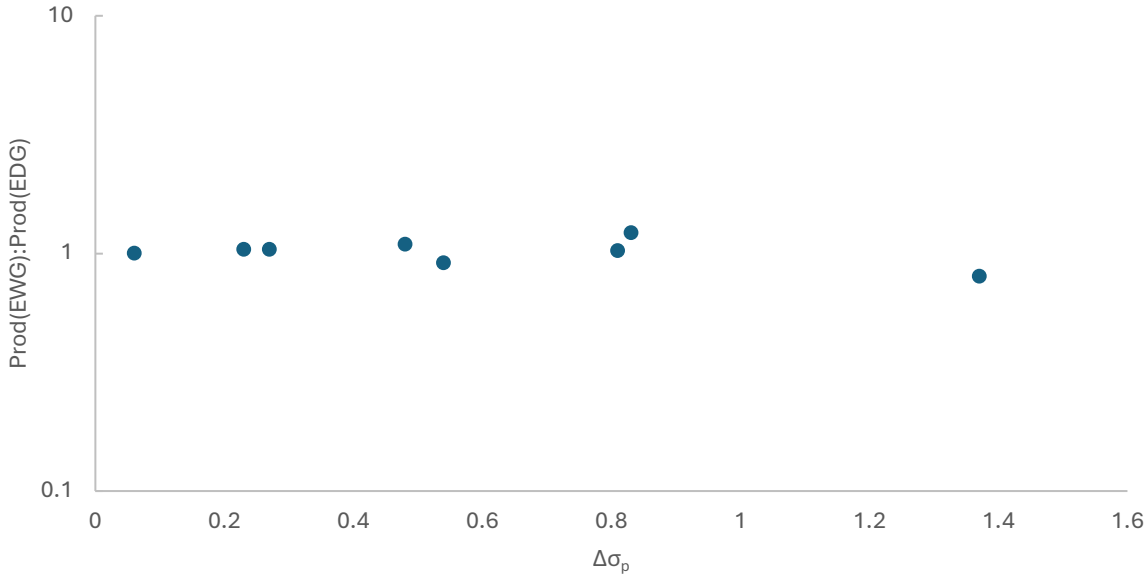


Figure 3.5: Product distribution (favouring electron deficient) as a function of difference of Hammett parameter ($\Delta\sigma_p$). Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

As can be seen from **Figure 3.5**, very little deviation from a 1:1 product distribution was observed. It can be inferred that this means that the reaction does not exhibit a significant preference in terms of electronics. To further support this, a time study was performed of the reactions shown in **Scheme 3.2** in order to ascertain whether the products form at equal rates or if one forms significantly faster. The results of these experiments are shown in **Figure 3.6** and it can be seen that the product ratio was approximately constant throughout the reaction period, further suggesting that electronics are not a strong predictor of the reaction efficiency.

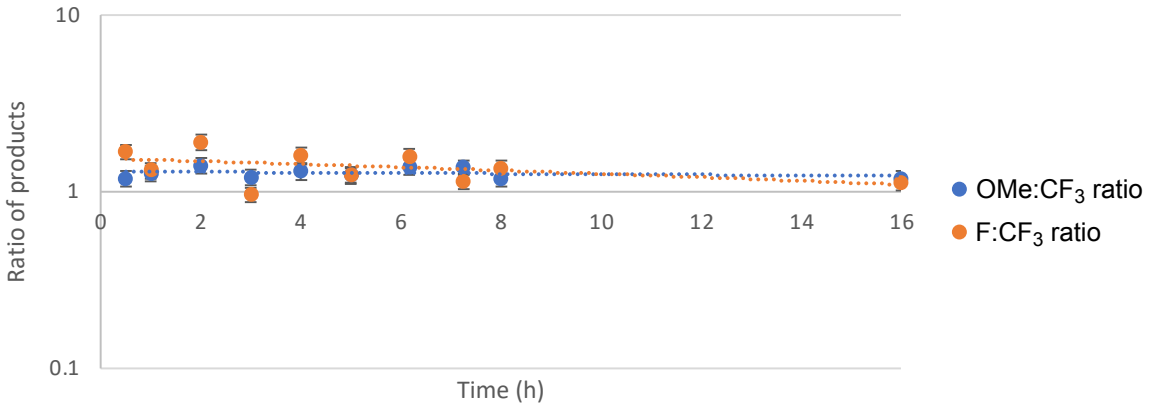


Figure 3.6: Product distribution during a competition experiment over time. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

In conclusion, little evidence was found that shows that electronic effects determine reaction success. Examining the Hammett parameters and looking at the reaction rate has shown that electronically poor internal alkynes do not offer better reactivity than their electron neutral/rich counterparts. Competition studies have demonstrated that alkynes of differing electronic natures were not significantly discriminated between during the reaction and were consumed at a similar rate throughout the reaction. A final observation was noted when examining the yield *vs* Hammett parameter. Though electron-poor preference was still not observed, increasing the steric bulk of the dialkyne component led to overall decreased yields, possibly hinting at a dependence of reactivity.

3.3. Examination of Steric Parameters

Steric parameters were analysed through synthesising a variety of monoalkynes with different steric demands. A key assumption made is that electronic effects are negligible thus they can be ignored, based on the findings reported in **Section 3.1**.

In the first instance, the same optimised conditions were utilised and the yield of the reaction was measured with respect to the sum of the monoalkyne A-values. What was immediately apparent was that when steric demands were low, the yield of the reaction plateaus at ≥95% before dropping off linearly as larger substituents are appended. This implied a correlation with the reaction efficiency and steric demands.

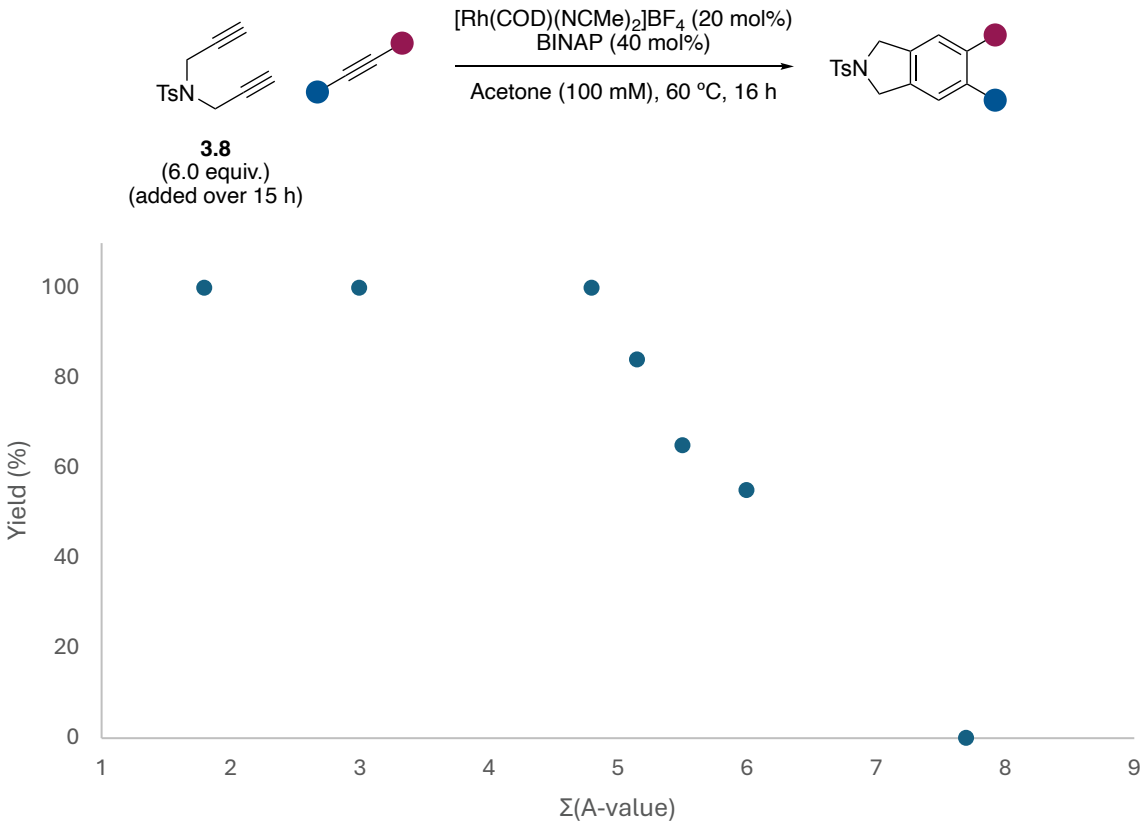


Figure 3.7: Initial investigation between reaction efficiency and steric environment. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

To further probe this correlation, the y-axis was reparameterised to rhodium turnovers (RTO). This reparameterisation serves two important roles: firstly, the number obtained was now independent of rhodium catalyst loading, secondly, this allowed for the extraction of data related to small alkynes since they would plateau otherwise. Constructing this graph revealed that the reaction was indeed inversely proportional to total steric parameter in a linear fashion. Three different steric parameters were use: A-value, Taft-Dubois (increased by 10 for ease of graphical depiction) and ΔG_{GA} and the same trend is observed for all. It should be noted that attempts were made to model the behaviour of internal dialkynes; however, this was not successful.

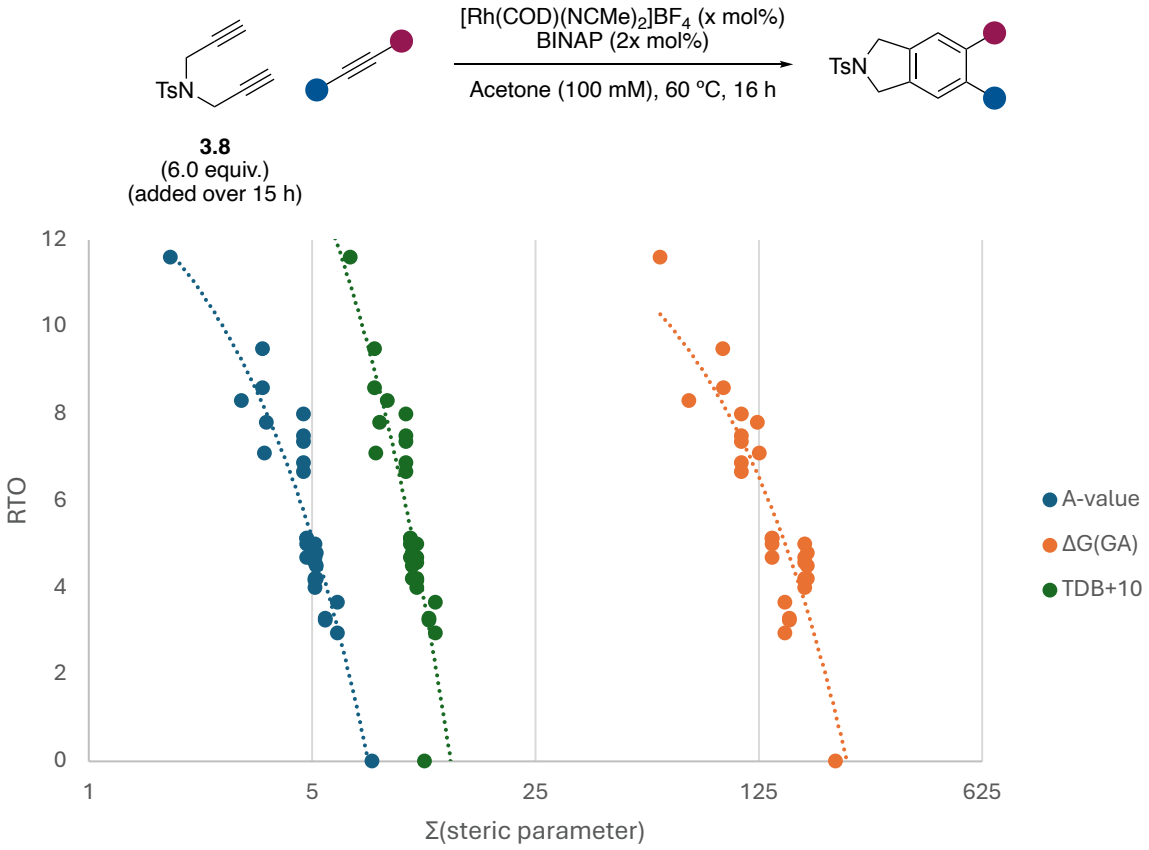
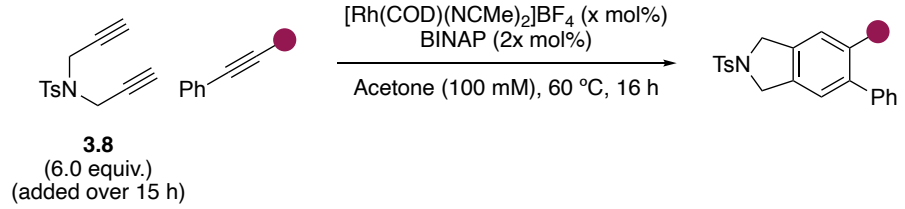


Figure 3.8: RTO against sum of steric parameters. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

This relationship is at the heart of the internal alkyne problem. Focussing particularly on A-values, any internal alkyne will likely have an A-value ≥3.4 (since A_{Me} = 1.7) yielding only around 9 RTOs. However, what is more likely is an alkyne will have a total A-value of around 5, giving around 5 RTOs. Therefore, in order to obtain quantitative yields 20 mol% rhodium catalyst is required.

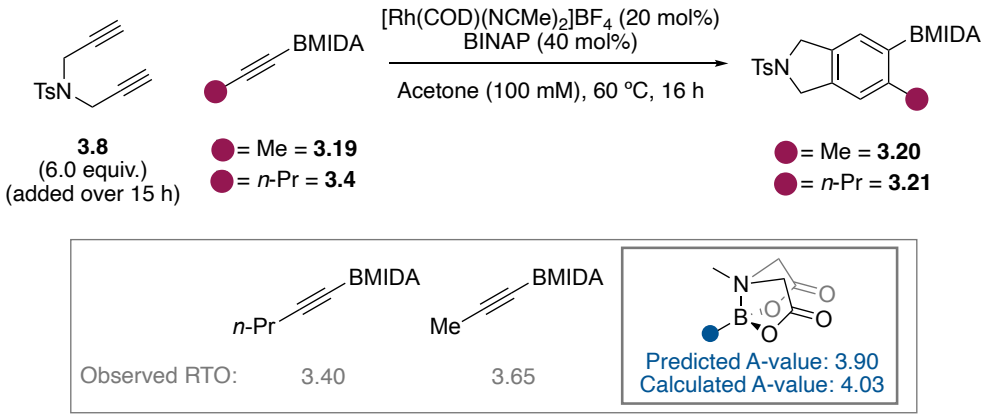
The reverse relationship was also true, in that steric parameters could be determined from reaction efficiency. **Scheme 3.3** shows the RTO value of various substituents and how the A-value can be predicted from this number. These values correspond well with literature values, although, it should be noted that overestimation appears to occur. This is likely due to the fact that A-values are determined from cyclohexane derivatives and thus are not a perfect measure of steric bulk.



●	CF_3	*i*-Pr	$SiMe_3$	Ph
Observed RTO:	*4.44*	*4.50*	*3.28*	*2.95*
Predicted A-value:	*2.34*	*2.31*	*2.91*	*3.07*
Literature A-value:	*2.10*	*2.15*	*2.50*	*3.00*

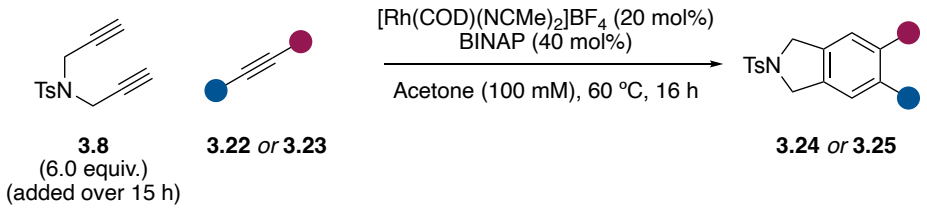
Scheme 3.3: Determination of A-value of compounds from [2+2+2] RTO and comparison to literature. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

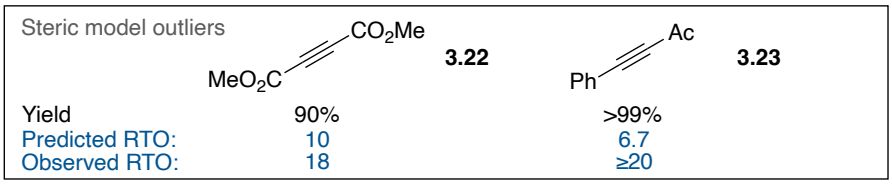
For instance, the aforementioned boronic acid *N*-methyliminodiacetic acid esters (BMIDA esters) are an important class of protected boronic acids, which are very stable and thus can be used in many reactions without degradation.[208] However, their steric parameters (unlike other boronic esters[253]) are unknown. Calculating back from observed reaction yield (and thus RTO, **Scheme 3.4**) one can determine that the BMIDA group has an A-value of around 4.11. This is in good agreement with the value that can be predicted from crystallography (3.90).[254]



Scheme 3.4: Determination of an unknown A-value from [2+2+2] RTO. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

In **Figure 3.8** two data points have been removed. The compounds corresponding to these points exhibit significantly inflated RTO than would be expected. These are highlighted in **Scheme 3.5**. Each of these compounds (**3.23** and **3.24**) undergo the reaction around twice as efficiently compared to what would be expected from their steric parameters. What is important to note is that these compounds are structurally similar to those substrates that are prevalent the literature (as described in **Scheme 1.45**). These molecules contain an electron deficient alkyne; however, from **Section 3.2**, the electronic nature of the monoalkyne is not correlated with yield: thus, there must be another effect leading to this enhanced reactivity. The most obvious structural feature is the Lewis basic oxygen atoms. Hence, the role of potential of coordinating groups was explored.





Scheme 3.5: Steric model outliers with their yields, predicted RTO and their observed RTO. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

3.4. Examination of Chelation Effects

In order to probe the importance of adjacent Lewis basic groups a selection of molecules was procured which are sterically similar around the monoalkyne but possess different oxygen containing moieties. The same reaction was performed at different catalyst loadings and the response of product formation was measured. There were four possible scenarios possible indicating different behaviours (illustrated **Figure 3.9**):

A. If product yield was the same as the control, then the Lewis basic group had no effect.
B. If yield resisted the lowering in catalyst loading, then the Lewis basic group was enhancing reactivity.
C. If yield decreased at a greater rate than the control, then (by some mechanism) the Lewis base decreases reactivity.
D. The final scenario is when no clear trend can be observed.

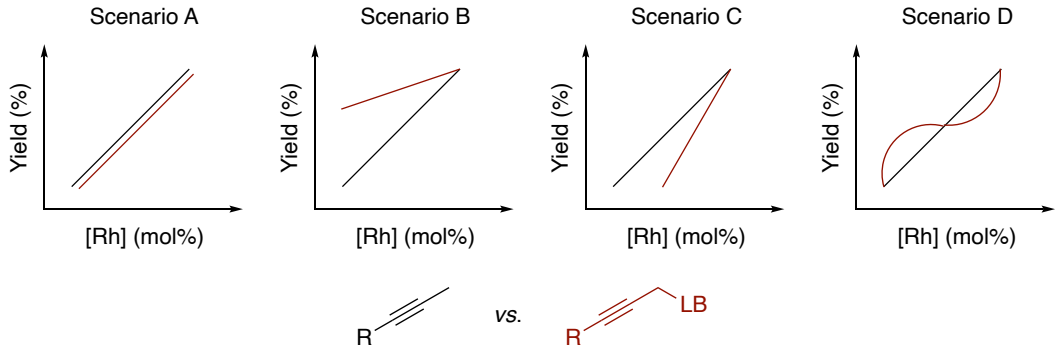
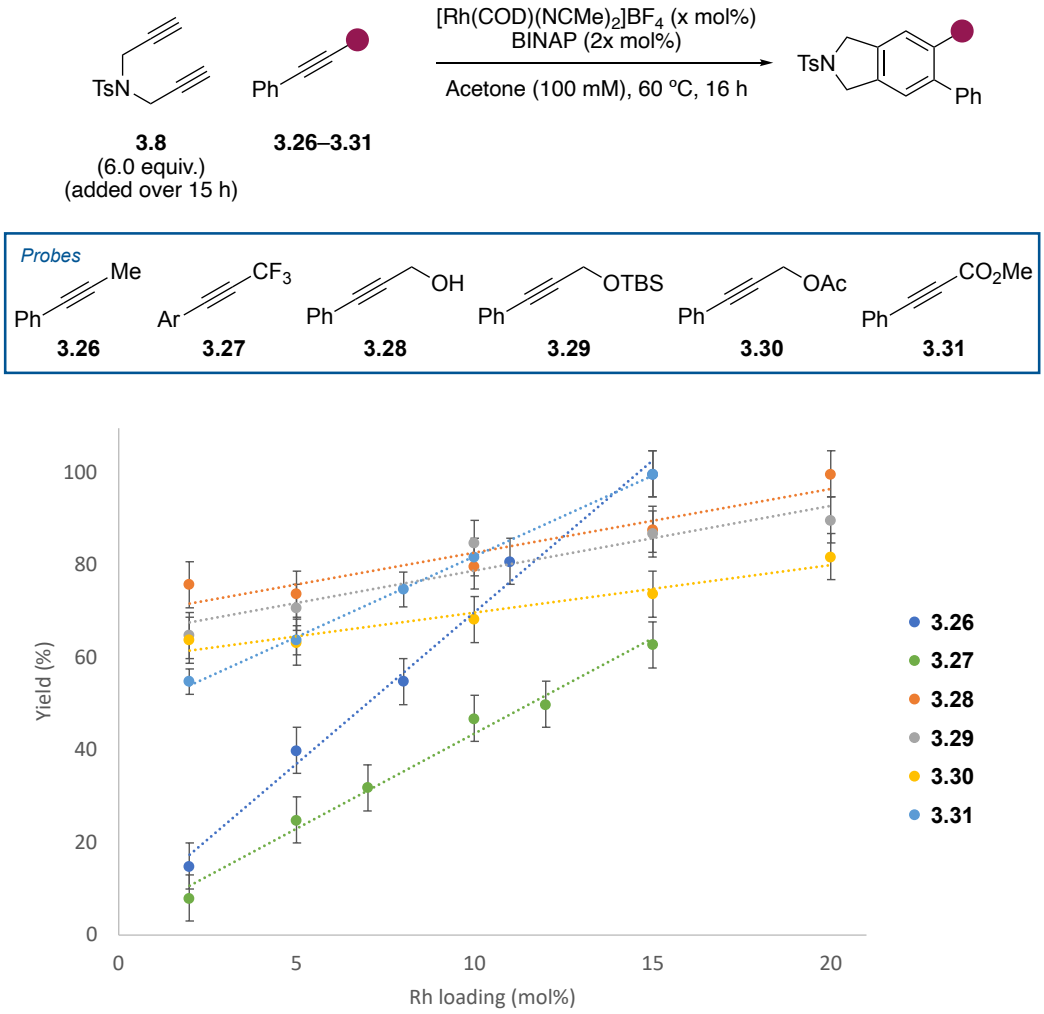
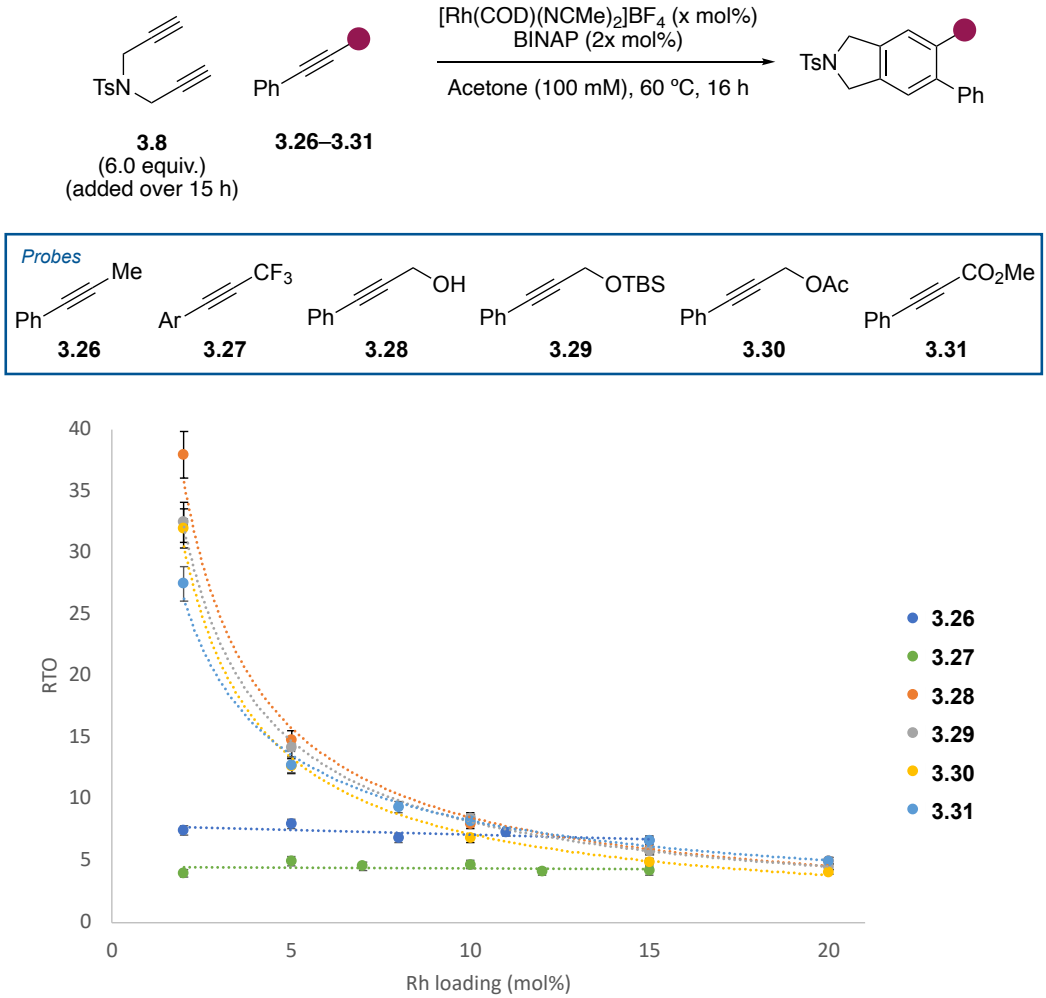


Figure 3.9: Possible scenarios observed when testing effect of Lewis basic groups.



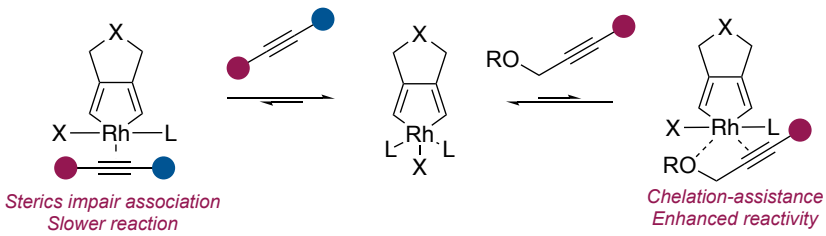
Scheme 3.6: Study of potential chelating groups in [2+2+2] cycloadditions. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard. Ar = 4-biphenyl.

From **Scheme 3.6,** it is obvious that scenario B was operative, this implied that the Lewis basic group indeed enhanced reactivity quite significantly. Even at 2 mol% catalyst, **3.28–3.31** all gave product formations in excess of 50%. Another way to express this data is in terms of RTOs. Of note is that alkynes **3.26** and **3.27** gave virtually the same number of turnovers at all catalyst loadings (**Scheme 3.7**) loadings, however alkynes **3.28–3.31** exhibit increasingly inflated RTOs as the catalyst loading is lowered. Alkyne **3.27** appeared to trend downwards; however, this was actually due to catalytic activity plateauing at higher catalyst loadings (*i.e.* this substrate gives 7 RTOs but at loadings >15%, this will give >100% product formation, thus the RTOs max out at ~6.7 at 15 mol% and 5 at 20 mol%).



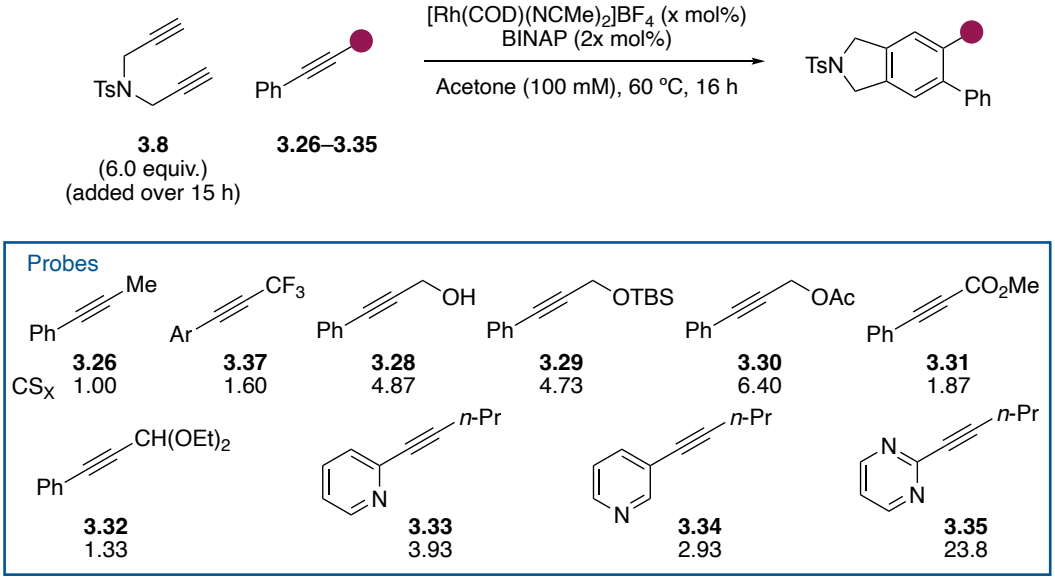
Scheme 3.7: Study of potential chelating groups in [2+2+2] cycloadditions with RTO shown. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard. Ar = 4-biphenyl.

The root of this effect is likely through chelation. All these Lewis basic groups are able to chelate the rhodium centre. This effect has been shown to be important for enforcing enantioselectivity in atroposelective [2+2+2] reactions, as well as influencing reactivity in some cycloadditions.[132, 166, 235, 255] It is clear that binding to the intermediate rhodacycle is disfavoured in most internal alkynes; however, the chelation effect of local Lewis bases allows enhanced binding to the catalyst for the subsequent step in the catalytic cycle (**Scheme 3.8**).



Scheme 3.8: Potential chelation interactions in mechanism of [2+2+2]. Charges and ligands removed for clarity.

Inspecting at **Scheme 3.6**, it can be envisaged that the gradient (m) of the lines can denote how strongly a group can enhance reactivity (assumedly through chelating effects), from which a chelation score of substituent X (CS_X) may be defined. This has been composed in the following way: $CS_X = \frac{m_{Me}}{m_X}$; where m_{Me} is the gradient of methyl substituent and m_X is the gradient of a substituent, X. This allows for the direct comparison between groups by comparing them directly to how much reactivity is enhanced relative to a methyl group. A range of these values are shown in **Scheme 3.9**.

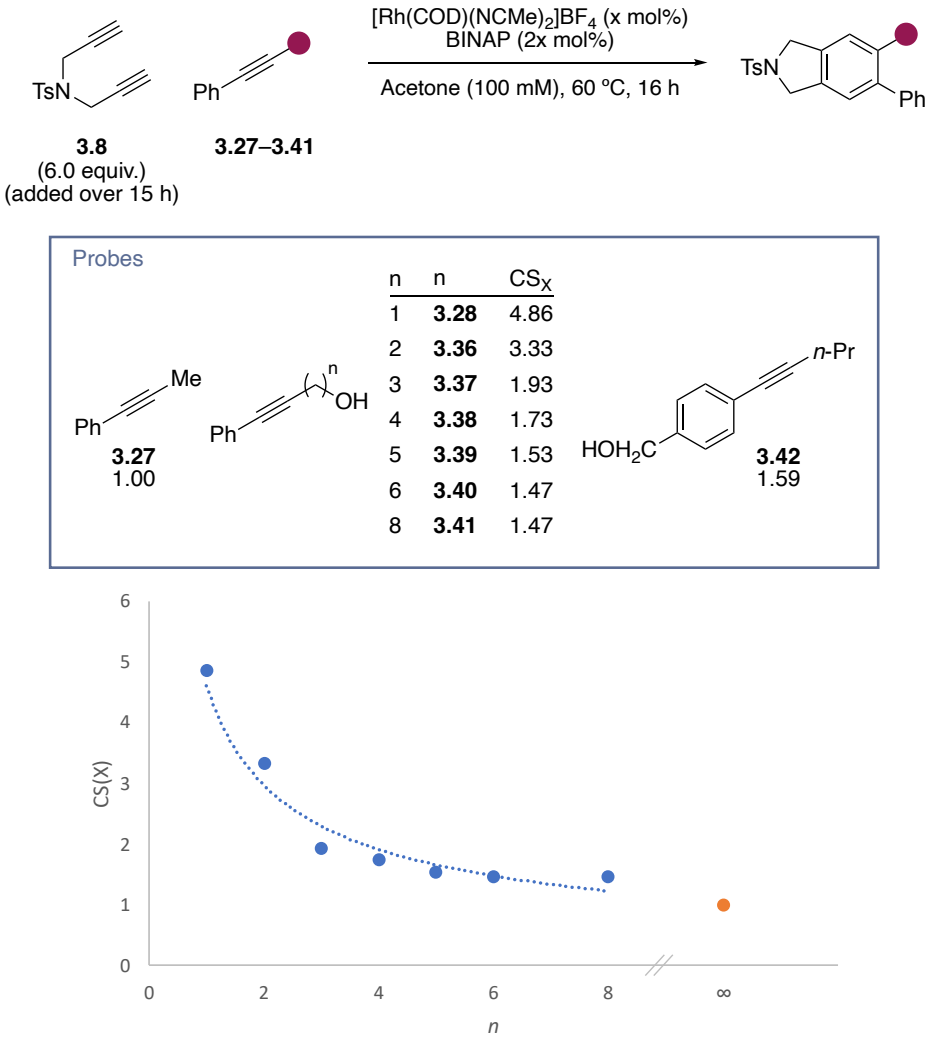


Scheme 3.9: Various substituents with CS defined. Ar = 4-biphenyl.

Of course, there are some caveats to this data. Most notably is the requirement for steric environment to be approximately equal since the reaction appears to be so sensitive to this parameter. However, this is evidently impossible, so efforts were made in order to keep the sizes of each substituent as similar as possible. As can be seen, R = Me (**3.27**) and CF_3 (**3.37**) are both poor chelators due a lack of high-lying lone pairs available for coordination. R = CH_2OH (**3.28**) and CH_2OTBS (**3.29**) are approximately equal in chelation score, implying that the TBS group has little effect on the chelation of the oxygen in spite of its large size. The degree to which R = CH_2OAc (**3.30**) coordinates is also surprising; however, the result may be rationalised by the group being able to coordinate through two heteroatoms rather than one. Conversely, the acetal (**3.32**) and ester (**3.31**) offer little in ways of CS, this is possibly a function of local sterics since they are similarly sized to an *iso*-propyl group. The pyridines (**3.34** and **3.35**) both chelate well; however, this number does not capture the fact that the 3-pyridyl (**3.35**) substrate exhibits lower reactivity than the 2-pyridyl (**3.36**) (see **Section 4.3**). This is likely due to coordination of the 3-pyridine away from the alkyne. It should be noted that the 4-pyridyl derivative exhibits near trace reactivity, even at 20 mol%, possibly providing further evidence to this observation. Lastly the 2-pyrimidinyl (**3.36**) substrate is a particularly strong chelating group offering very high reactivity even at exceptionally low loading of catalyst. We postulate that this is due to the 2-nitrogens chelating the rhodium into a position near the alkyne. Efforts were made to try and synthesise the pyrazine derivative for sake of comparison; however, all attempts towards this probe failed.

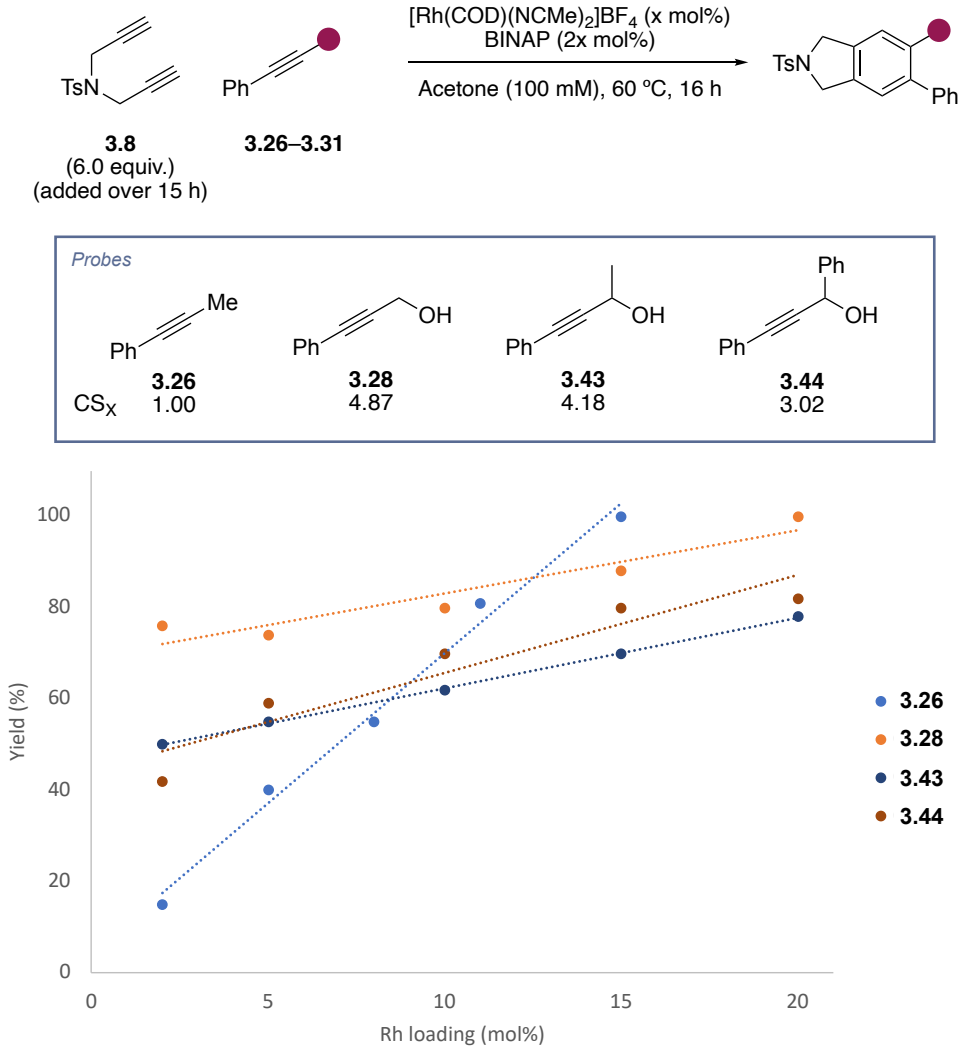
An extension to this dataset was obtained through synthesising alcohols with increasing chain lengths in order to observe how distance from the alkyne influences the reaction. A smooth decrease in chelating ability was observed as the alcohol is moved further and further away

from the alkyne. Furthermore, placing the alcohol in such a way that it is geometrically unlikely to allow coordination gives expectedly low CS (**3.42**).



Scheme 3.10: Effect of chain length of alcohol on chelation score. Orange data point represents **3.27**, with methyl group placed at infinity to represent no chelating group. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

A final observation was noted when placing substituents adjacent to an alcohol. As shown in **Scheme 3.11**, when a methyl group (**3.43**) or a phenyl group (**3.44**) was placed at the propargylic position of a propargyl alcohol derivative, the reactivity decreases as expected with the increased steric bulk. However, these molecules exhibit a similar resistance to lowering catalyst loading in terms of reactivity. The CS_X of these compounds are also shown in **Scheme 3.11** and share a similar value to the unsubstituted alcohol, albeit slightly lower. This lowering can be postulated to be due to the increased steric footprint of **3.43** and **3.44** when compared to **3.28**. This hypothesis would also account for the lower overall yield obtained in each reaction.



Scheme 3.11: Effect of propargylic substitution on chelation score. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

Using this information, we could postulate that a chelating group must involve either a Lewis-basic heterocycle or a heteroatom (or multiple heteroatoms). In the case of heterocycles, the Lewis-basic site must be directed onto the alkyne, otherwise the yield will be significantly diminished. In terms of heteroatoms, the group must be flexible enough to chelate to the metal but not too far away so that the intermediate cycle that would be formed is not too large as to be entropically disfavoured.

To conclude, a set of conditions were found to be able to accommodate generic internal alkynes into the rhodium-catalysed, semi-intramolecular [2+2+2] cycloaddition for the first time. The key contribution to increasing the yield was the application of slow addition of the dialkyne component, along with increasing the catalyst loading. These conditions were used to study the putative electronic preference revealing that the reaction is much more sensitive to sterics than electronics. However, the class of alkynes that bear electron-withdrawing groups appear to behave differently. The cause of this change in behaviour was determined to be a coordination effect. This effect was parameterised in terms of a chelation score and the anatomy of what constituted an activated alkyne was described.

4.0. Chapter 3: Substrate Scope and Applications

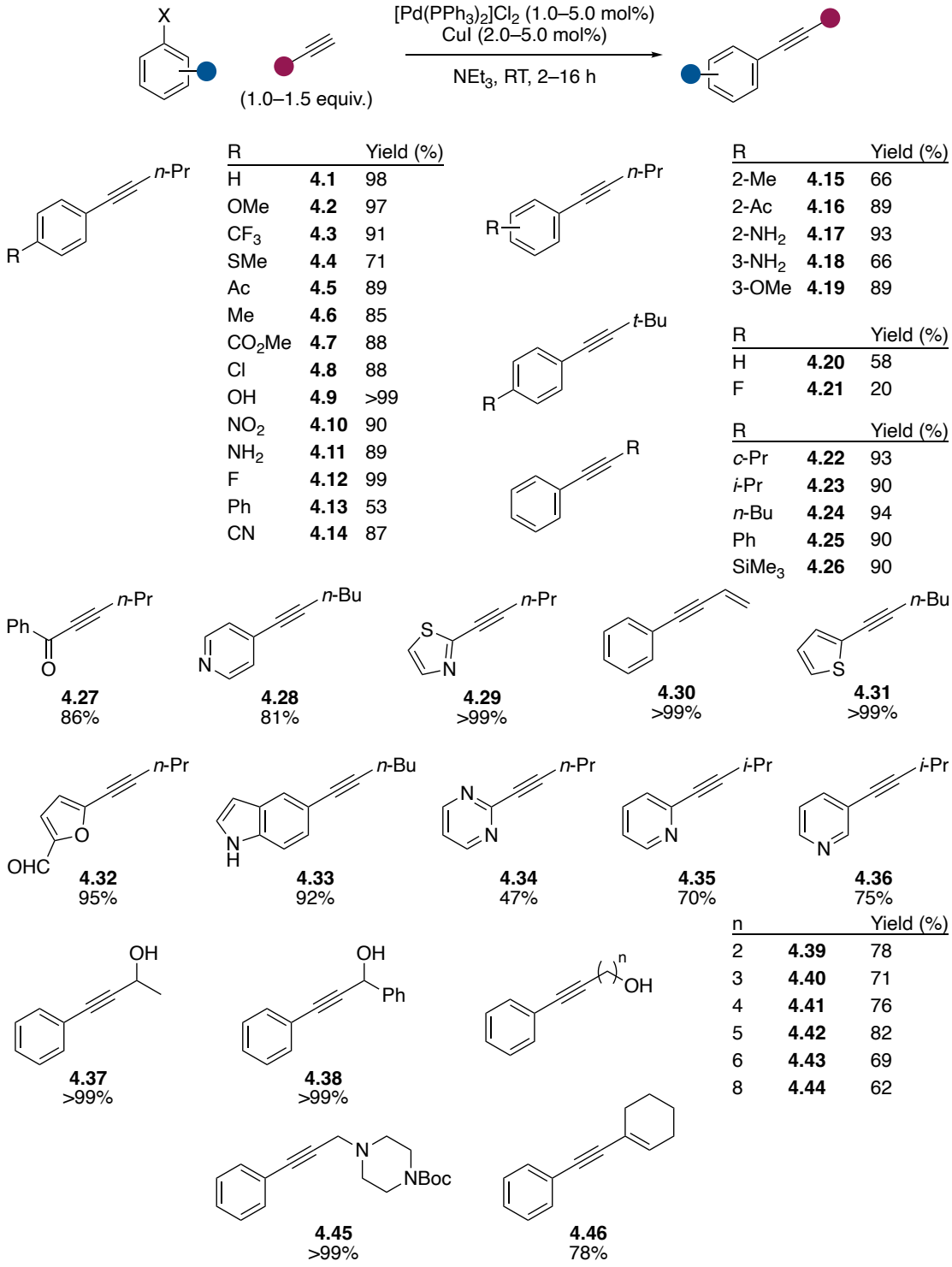
With the mechanistic insights underpinning the internal alkyne problem established, a substrate scope was investigated. The semi-intramolecular Rh-catalysed [2+2+2] cycloaddition is well known to have exceptional functional group tolerance and was alluded to in the analysis of Hammett parameters and reaction efficiency. However, the Hammett parameters of many more functional groups and heterocycles are not available. Thus, a scope would be useful to show that excessive chelation effects do not hamper the desired reactivity.

4.1. Monoalkyne Starting Material Synthesis

The synthesis of starting materials was performed using two main methods:

1) Deprotonation based strategies wherein the acidity of acetylenic protons is exploited then quenched with a suitable electrophile.
2) Sonogashira cross couplings between the parent alkyne and the relevant aryl halide.

The yields of internal alkynes synthesised through Sonogashira coupling are shown in **Scheme 4.1**. As can be seen, the Sonogashira reaction itself is highly tolerant of a variety of functional groups, and very high yields for alkynes bearing both electron withdrawing (e.g., **4.3**, **4.5**, **4.7**, **4.10**) and electron donating groups (e.g., **4.2**, **4.6**, **4.9**, **4.11**) were obtained. Furthermore, a chloride (**4.8**) and heterocycles such as thiazole (**4.29**), thiophene (**4.31**), furan (**4.32**), indole (**4.33**) and pyrimidine (**4.34**) were all tolerated in good yield. A number of alcohols with various structural features (**4.37**–**4.44**) were also well tolerated with only a few exceptions. Reactivity issues were observed with propiolate systems (**Scheme 4.2**), wherein polymeric condensation occurs through Morita-Bayliss-Hillman type reactivity.[256, 257]



R		Yield (%)
H	**4.1**	98
OMe	**4.2**	97
CF_3	**4.3**	91
SMe	**4.4**	71
Ac	**4.5**	89
Me	**4.6**	85
CO_2Me	**4.7**	88
Cl	**4.8**	88
OH	**4.9**	>99
NO_2	**4.10**	90
NH_2	**4.11**	89
F	**4.12**	99
Ph	**4.13**	53
CN	**4.14**	87

R		Yield (%)
2-Me	**4.15**	66
2-Ac	**4.16**	89
2-NH_2	**4.17**	93
3-NH_2	**4.18**	66
3-OMe	**4.19**	89

R		Yield (%)
H	**4.20**	58
F	**4.21**	20

R		Yield (%)
c-Pr	**4.22**	93
i-Pr	**4.23**	90
n-Bu	**4.24**	94
Ph	**4.25**	90
$SiMe_3$	**4.26**	90

4.27 86%

4.28 81%

4.29 >99%

4.30 >99%

4.31 >99%

4.32 95%

4.33 92%

4.34 47%

4.35 70%

4.36 75%

n		Yield (%)
2	**4.39**	78
3	**4.40**	71
4	**4.41**	76
5	**4.42**	82
6	**4.43**	69
8	**4.44**	62

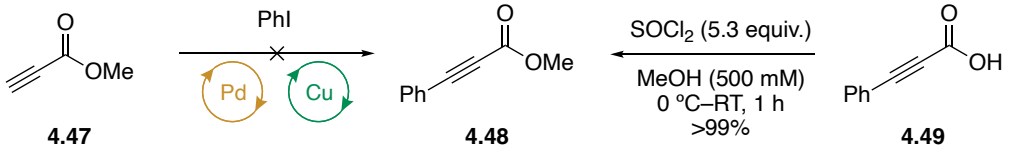
4.37 >99%

4.38 >99%

4.45 >99%

4.46 78%

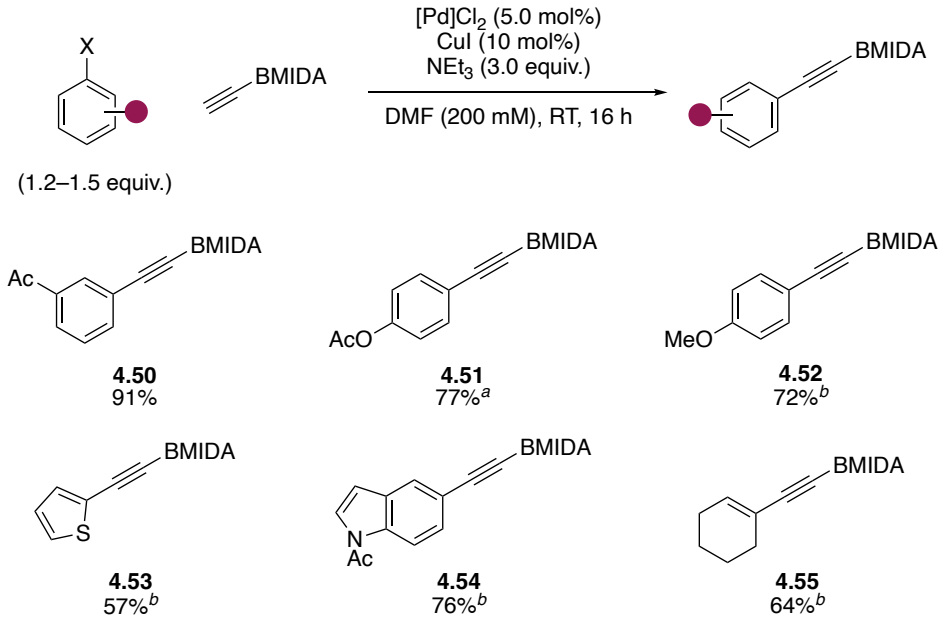
Scheme 4.1: Synthesis of internal alkynes through Sonogashira coupling.



4.47 **4.48** **4.49**

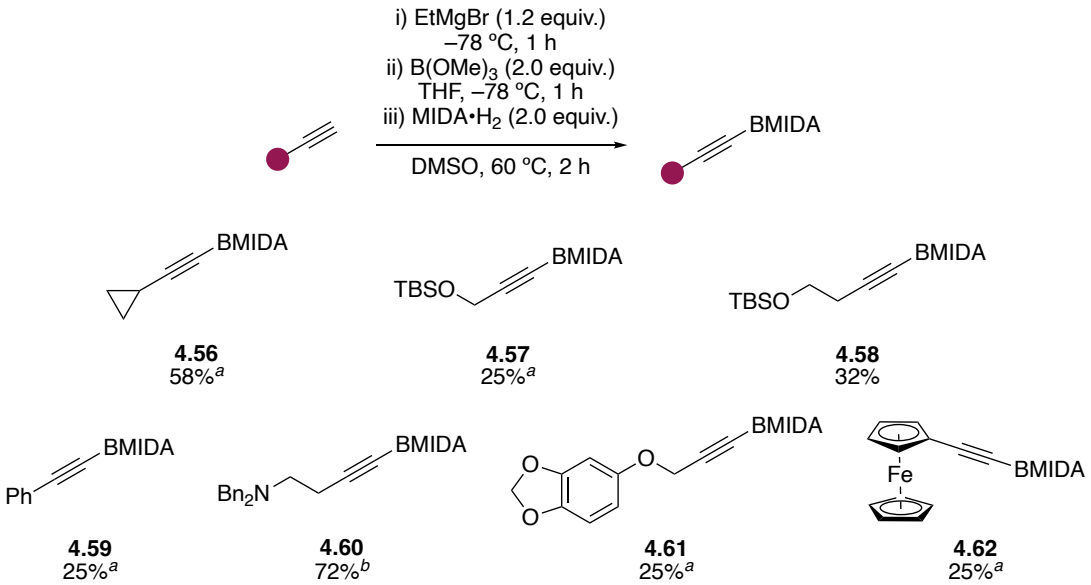
Scheme 4.2: Failure of Sonogashira reaction with methyl propiolate (**4.47**) vs successful acyl chloride formation then methanolysis.

A slightly modified Sonogashira procedure (**Scheme 4.3**) was used for alkynes bearing a BMIDA unit due to the poor solubility associated with this group.[224] The solvent was changed to DMF and the stoichiometry of the reactants was reversed due to the often-difficult chromatographic separation. As can be seen, a variety of groups can be tolerated including ketones (**4.50**), esters (**4.51**), heterocycles (**4.53** and **4.54**), and alkenes (**4.55**).



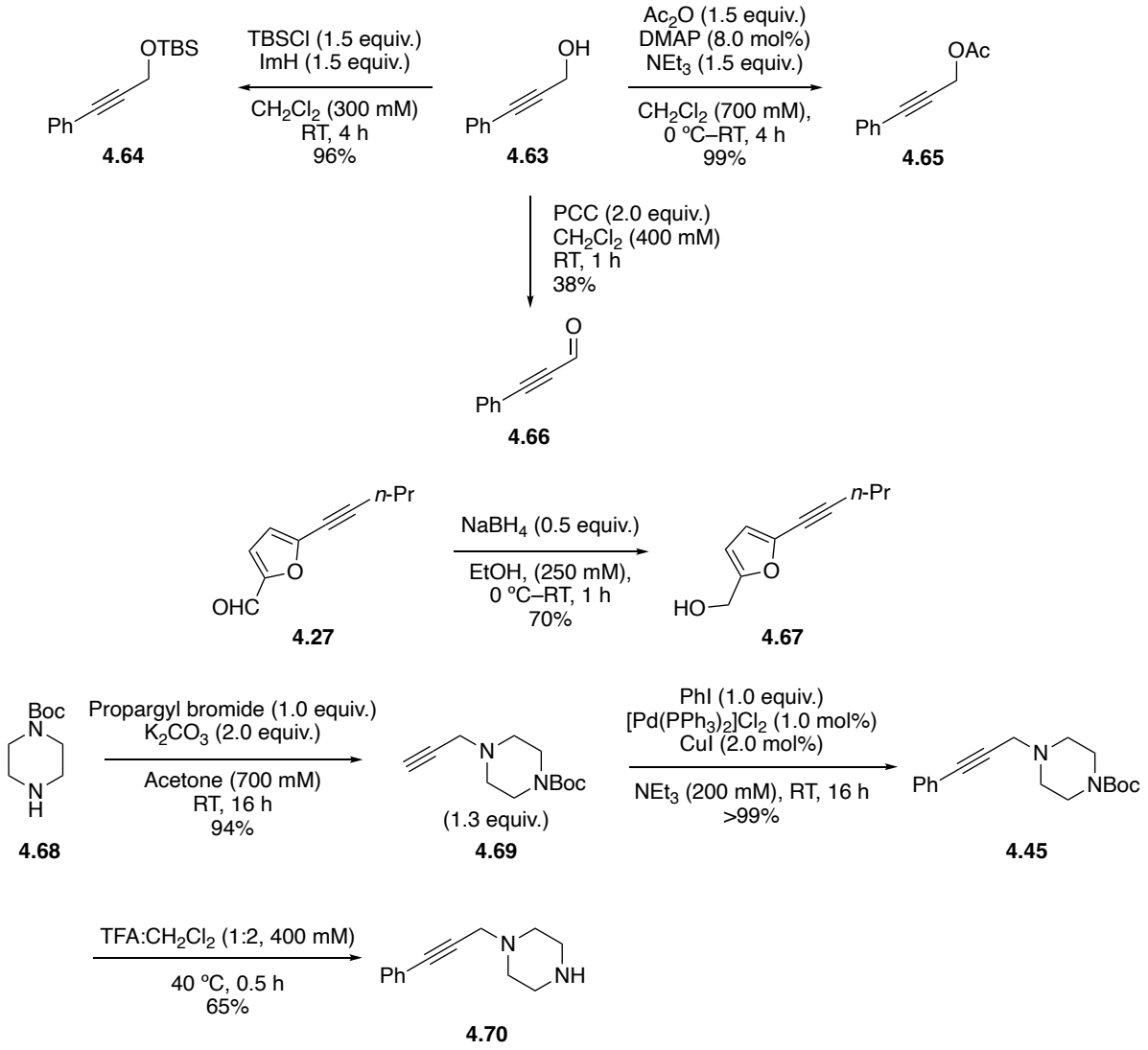
Scheme 4.3: Synthesis of alkynyl BMIDA through Sonogashira coupling. $[Pd]Cl_2$ = $Pd(PPh_3)_2Cl$ or $Pd(dppf)Cl_2$. See experimental section for further details. [a]Synthesised by Dr Jamie Fyfe. [b]Synthesised by Dr George Bell.

Further BMIDA units were synthesised through deprotonation of acetylenic protons followed by trapping with a boron source and a subsequent MIDA transligation (**Scheme 4.4**).[212] Due to the procedure requiring deprotonation, acidic protons are non-tolerated and thus had to be protected as silyl ethers in the case of alcohols, or benzylated for amines. Amines are underrepresented in the literature with respect to BMIDA syntheses. Indeed, the synthesis of **4.60** was challenging, requiring movement away from the standard MIDA procedure towards a MIDA anhydride-based route, a more recent methodology disclosed by Burke and coworkers.[258]



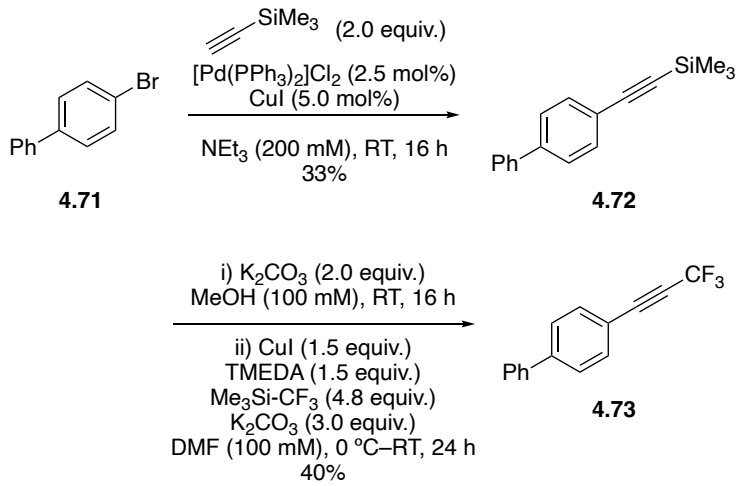
Scheme 4.4: Alkyne BMIDA synthesis through deprotonation. [a]Synthesised by Dr George Bell [b]Synthesised by Marek Varga using MIDA anhydride in place of MIDA•H_2.

Installing various protecting groups (**Scheme 4.5**, e.g. TBS: **4.64**; Ac: **4.65**) on alcohols, as well as oxidations and reductions (**4.67**) were all tolerated without any issues observed with the alkyne, except in the case of aldehyde **4.66**, which was low yielding. The reason for this was expected to be similar to the reasons why propionaldehyde is unstable, being an excellent Michael acceptor and prone to energetic polymerisation.[259] Nucleophilic substitution of propargyl bromide with a suitable amine (**4.68**) enabled a simple route to complex propargylic amines which can undergo smooth Sonogashira coupling to yield internal alkyne starting materials (**4.45**).



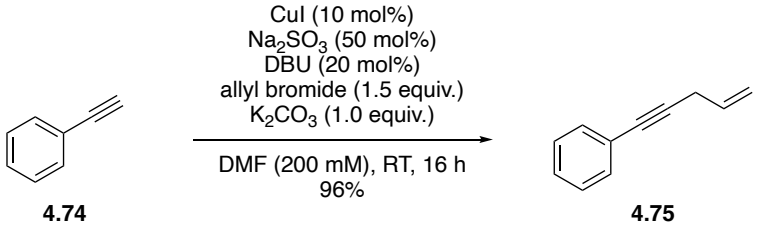
Scheme 4.5: Synthesis of various alkynes through standard manipulations.

The installation of an alkynyl CF_3 group is a generally challenging process; methods such as Pd-catalysed cross couplings exist, but often rely on the pre-existence of the F_3C acetylene.[260-262] Further methods are available that use trifluoromethyl or trifluoroacetylene based electrophiles reacting with a suitable nucleophile.[263-266] Finally, dehydrohalogenation approaches have also been disclosed; however, often these suffer from issues of functional group tolerance.[267, 268] More recent reports of the synthesis of this motif use a copper based process to oxidatively couple the acetylene with Ruppert's reagent.[269, 270] Success was found using a similar methodology published by Evano and coworkers,[271] generating the desired product (**4.73**) in acceptable yield (**Scheme 4.6**).



Scheme 4.6: Synthesis of trifluoromethyl acetylene derivative.

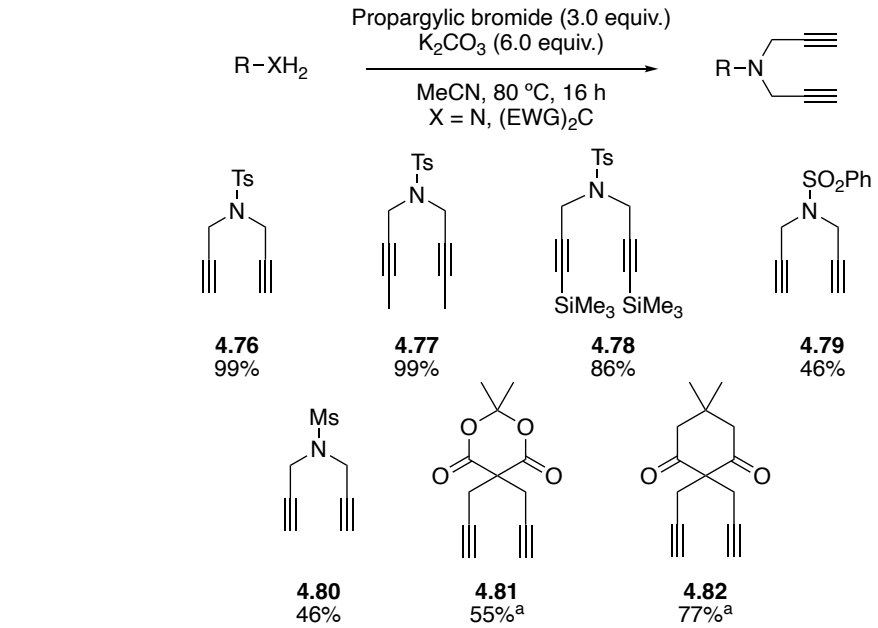
Finally, an allylic alkyne was synthesised using a copper-catalysed coupling of phenylacetylene and allyl bromide in excellent yield.[272] No migration was observed to place the allyl group in conjugation with the neighbouring π-system.



Scheme 4.7: Synthesis of allyl substituted phenyl acetylene.

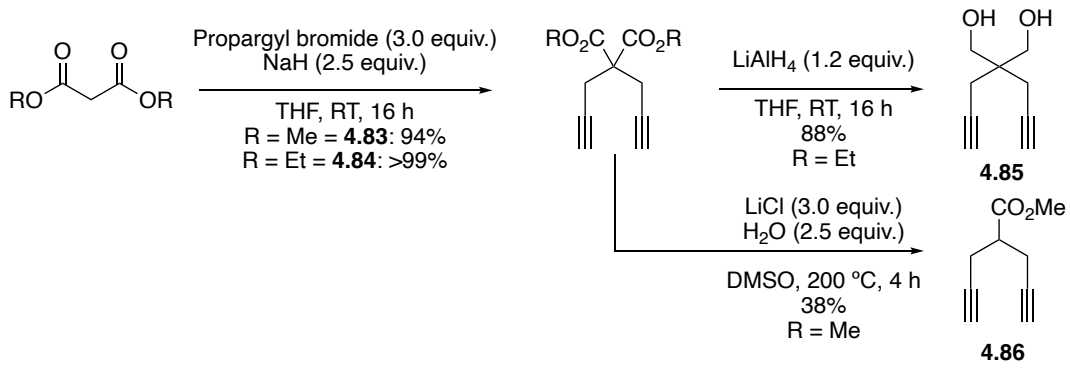
4.2. Dialkyne Starting Material Synthesis

Synthesis of symmetrical diynes was relatively facile and can be achieved by substitution reactions using the appropriate nucleophile and propargyl bromide. A variety of sulfonamide derivatives (**4.76**–**4.80**) were synthesised in this way as well as some activated diketones, such as derivatives from Meldrum's acid (**4.81**) and dimedone (**4.82**).



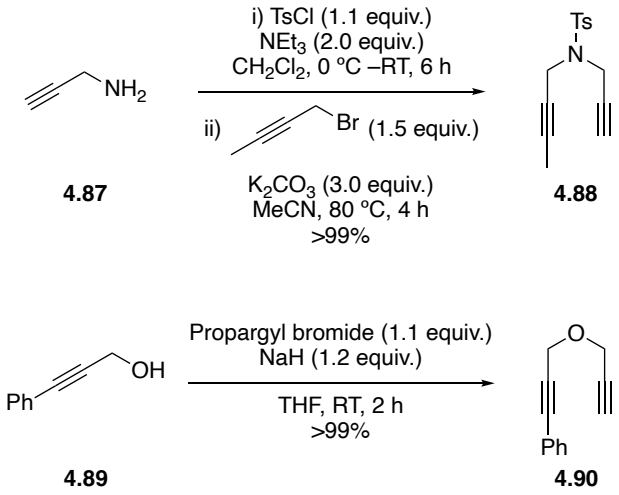
Scheme 4.8: Synthesis of diynes through base-mediated substitution. [a]Cs_2CO_3 used as base.

When a stronger base was required, for example, for malonate derivatives, sodium hydride could be used to perform the alkylation leading to the desired dialkyne (**4.83** and **4.84**), which can be further functionalised (**Scheme 4.9**). In the case of the ethyl ester, a reduction to yield the diol (**4.85**) was carried out in good yield. With the methyl ester, a Krapcho decarboxylation was performed to yield the mono ester (**4.86**), albeit in poor yield.[273-275]



Scheme 4.9: Synthesis of malonate-derived dialkynes.

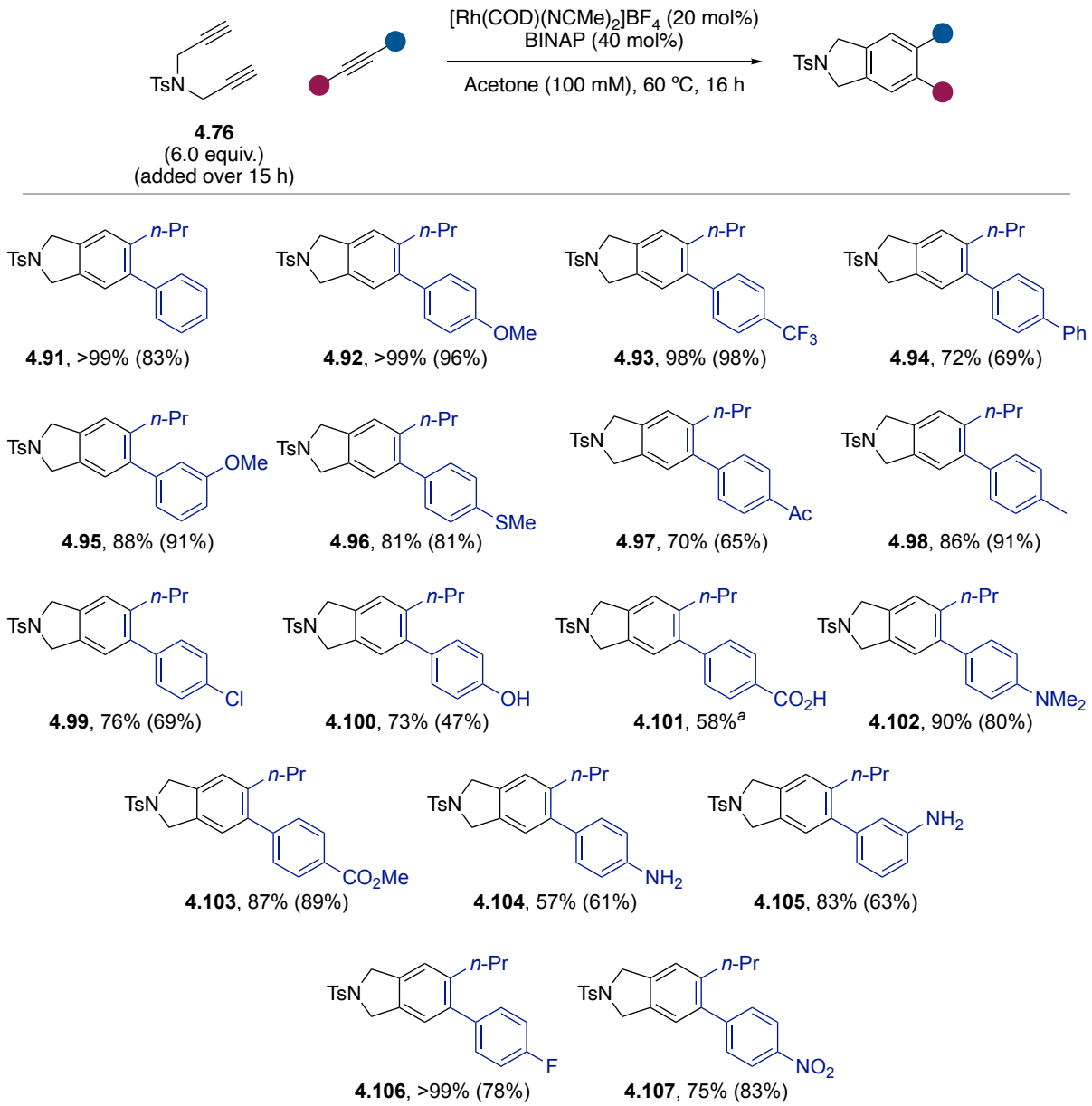
When synthesising unsymmetrical diynes, more care must be taken in order to prevent mixtures of products. Propargyl amine was tosylated and alkylated as before to yield the monomethylated dialkyne (**4.88; Scheme 4.10**). Similarly, an unsymmetrical ether was synthesised through deprotonation of the alcohol (**4.89**), followed by reaction with propargyl bromide to yield **4.90**.



Scheme 4.10: Synthesis of unsymmetrical dialkynes **4.88** and **4.90**.

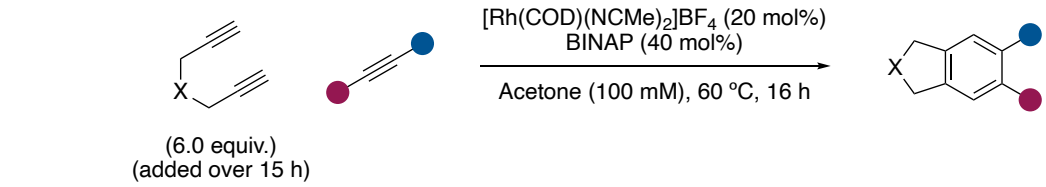
4.3. Synthesis of Complex Benzene Derivatives through Rhodium-catalysed, Semi-Intramolecular [2+2+2] Cycloaddition of Internal Alkynes

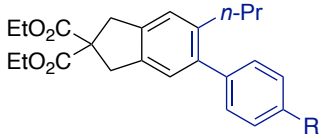
The scope of the Rh-catalysed, semi-intramolecular [2+2+2] cycloaddition of internal alkynes is wide and will thus be discussed in individual sections: (1) electronic, (2) steric (3) miscellaneous (i.e., those with no defined Hammett parameters or A-values). First, with respect to electronics, as can be seen (**Scheme 4.11**), a wide number of functional groups can be tolerated providing products in moderate to exceptional yields, with ethers (**4.92**), thioethers (**4.96**), ketones (**4.97**), phenols (**4.100**), halides (**4.93**, **4.99**, **4.106**), esters (**4.103**), anilines (**4.102**, **4.104**, **4.105**), nitro groups (**4.107**), and acids (**4.101**) all being well tolerated. There are the limitations in assessing Hammett parameters for *ortho*-substituted molecules, which are discussed in **Scheme 4.14**.[276]



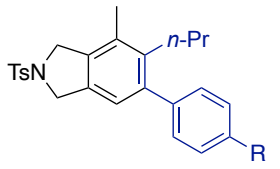
Scheme 4.11: Electronic scope of internal alkynes. Isolated yields in brackets. [a]Unisolable from reaction mixture, see experimental section for further details. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

This could be further extended to other dialkynes with similar functional group tolerance. Of note is the overall lower yield observed with 1,7 diynes (**4.130**–**4.134**). Furthermore, as substituents are added to the terminal alkyne of the dialkyne (e.g. from **4.120** to **4.129**), a drop in yield was observed, consistent with the observation that the reaction was sensitive to steric environment. An observation of note is the almost constant *rr* in compounds **4.120**–**4.124**. A report by the Anderson group suggests that the regioselectivity of a similar reaction was dependent on the electronic nature of the ring substitutents.[139] Since this was not observed here, it stands to reason that this trend is unique to ynamide based systems.

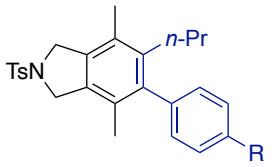




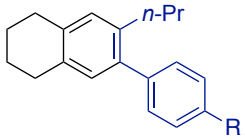
R		Yield (%)
H	**4.108**	70 (70)
F	**4.109**	71 (10)
Me	**4.110**	73 (45)
Ac	**4.111**	>99 (97)
Cl	**4.112**	67 (26)
Ph	**4.113**	70 (76)
CF_3	**4.114**	32 (30)
CO_2Me	**4.115**	61 (5)
OMe	**4.116**	33 (47)
NO_2	**4.117**	56 (41)
SMe	**4.118**	57 (56)
NH_2	**4.119**	61 (28)



R		Yield (%) [*rr*]
H	**4.120**	70 (64)[a] [1:2.9]
OMe	**4.121**	69 (11) [1:2.7]
Me	**4.122**	50 (11) [1:2.5]
CF_3	**4.123**	50 (33)[a] [1:2.7]
NO_2	**4.124**	49 (35) [1:2.9]



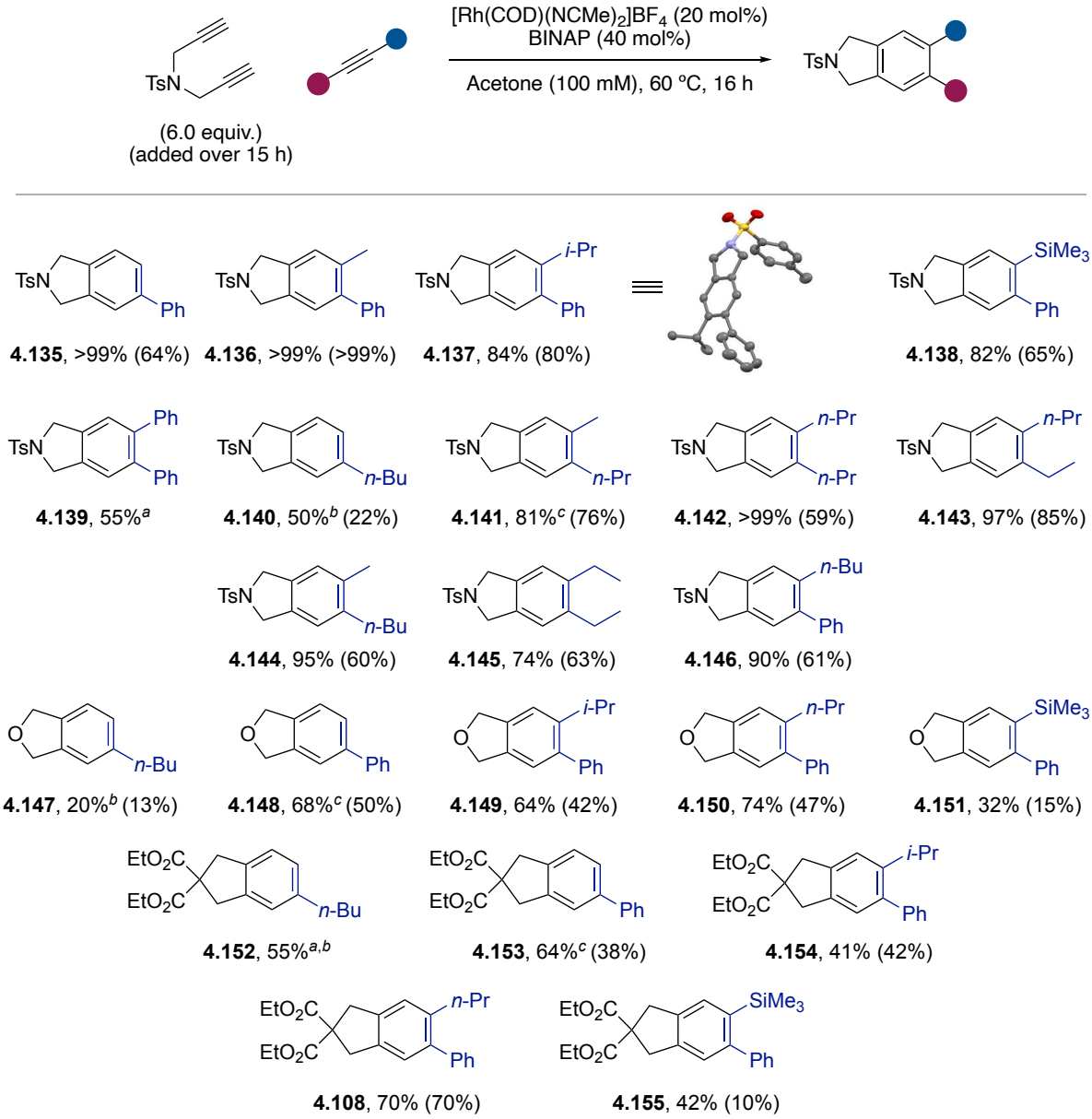
R		Yield (%)
H	**4.125**	50 (24)
OMe	**4.126**	37 (12)
Me	**4.127**	29 (17)
CF_3	**4.128**	9 (2)
NO_2	**4.129**	58 (48)



R		Yield (%)
H	**4.130**	44 (44)
OMe	**4.131**	47 (26)
Me	**4.132**	47 (23)
CF_3	**4.133**	36 (9)
NO_2	**4.134**	32 (30)

Scheme 4.12: Electronic variation with diyne scope. Isolated yields in brackets. *rr* determined through ^{1}H NMR analysis of the crude mixture then major regioisomer confirmed through ^{1}H-^{1}H NOESY analysis of purified mixture. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

Next, the ability of the reaction to tolerate sterically demanding alkynes was studied. Consistent with the aforementioned results, increasing monoalkyne size led to a lowering of the reaction efficiency (**Scheme 4.13**). Terminal alkynes can perform the reaction well, even when the catalyst loading was dropped to 5 or 10 mol% in cases such as **4.140**. Highly sterically congested alkynes, such as those with *t*-Bu substitution, exhibited no reactivity and remained intact after the end of diyne addition (*vide infra*). Two other dialkynes were employed to ascertain whether the same trend of RTO dependence could be observed with other alkynes and indeed this was the case (**Figure 4.1**). The absolute structure of **4.137** was confirmed by SCXRD, giving confidence in the structural identities of the products.



Scheme 4.13: Scope of steric environment of alkynes. Isolated yields in brackets. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard. Hydrogens removed from the SCXRD for clarity. [a]Unisolable from reaction mixture, see experimental section for further details. [b][Rh(COD)(NCMe)$_2$]BF$_4$ (5.0 mol%), BINAP (10 mol%). [c][Rh(COD)(NCMe)$_2$]BF$_4$ (10 mol%), BINAP (20 mol%).

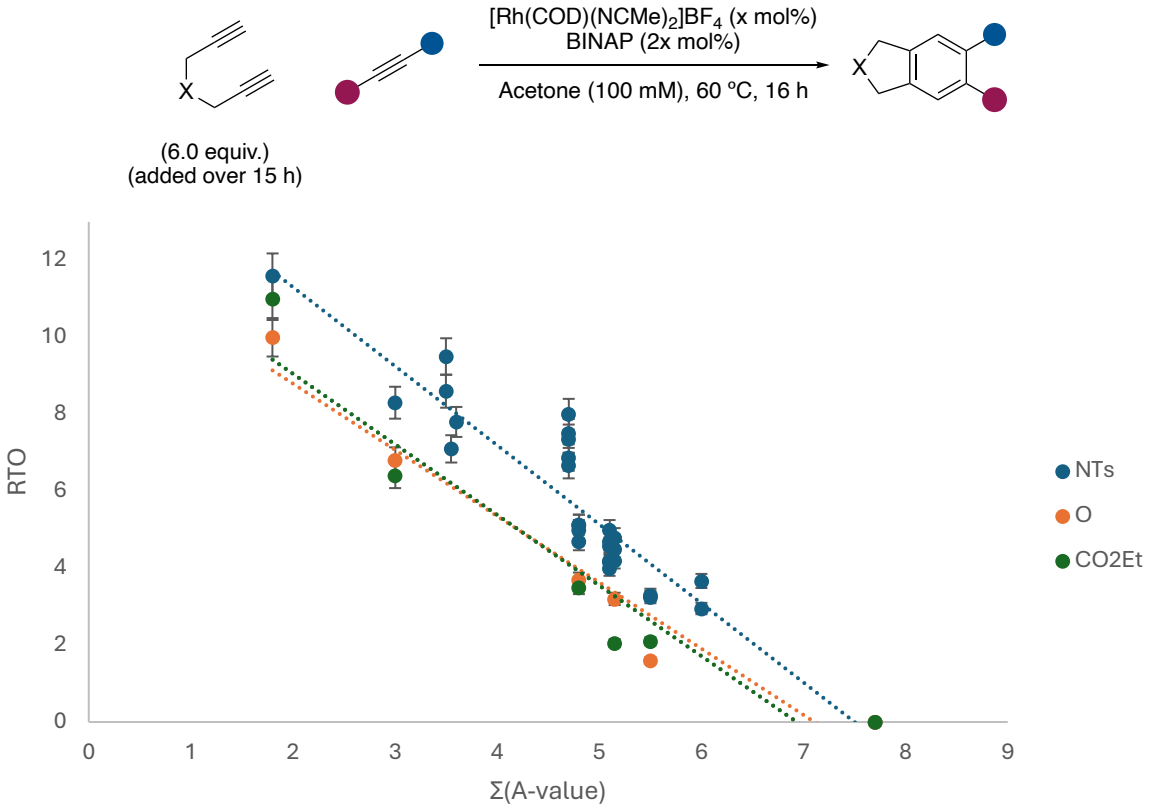
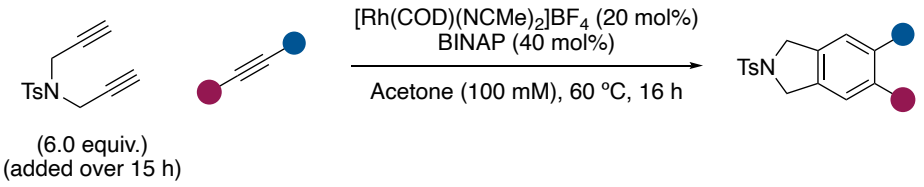
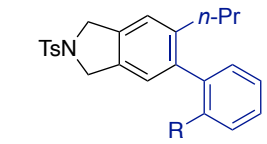


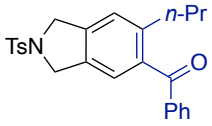
Figure 4.1: RTO vs Σ(A-value) correlation for selected dialkynes.

Finally, the miscellaneous monoalkynes are shown in **Scheme 4.14**. Numerous functional groups were tolerated such as the aforementioned anilines (**4.1458**), ketones (**4.157**, **4.159**, **4.184**), and esters (**4.180**, **4.183**). Heterocycles were also well tolerated including thiophene (**4.160**), furan (**4.161**), pyrimidine (**4.163**), pyridines (**4.164**, **4.165**), and indole (**4.181**). An acetal (**4.162**) was maintained throughout the reaction (however this moiety was hydrated into the aldehyde on purification). Several chelating groups were also accommodated with the exception of the 3-pyridyl (**4.165**), likely due to strong coordination of Rh away from the alkyne.

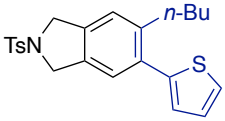




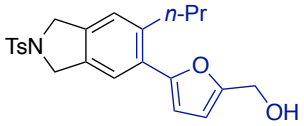
R = Me = **4.156**, 46% (20%)
R = Ac = **4.157**, 10% (3%)
R = NH_2 = **4.158,** 57% (40%)



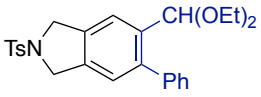
4.159, 93% (77%)



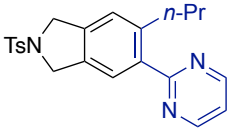
4.160, 85% (92%)



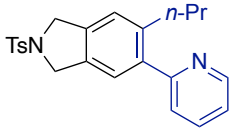
4.161, 96% (75%)



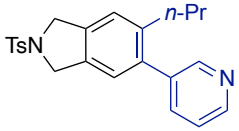
4.162, 99%[a]



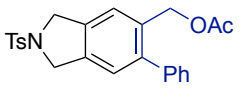
4.163, >99% (52%)



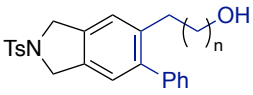
4.164, 96% (97%)



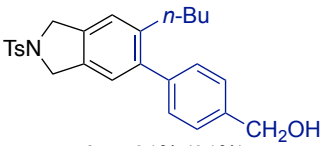
4.165, 35% (26%)



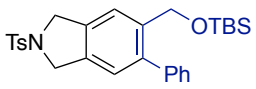
4.166, 82% (78%)



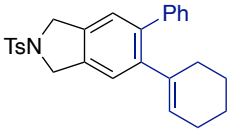
n		Yield (%)
0	**4.167**	>99 (66)
1	**4.168**	95 (85)
2	**4.169**	84 (50)
3	**4.170**	90 (79)
4	**4.171**	94 (97)
5	**4.172**	90 (87)
7	**4.173**	94 (95)



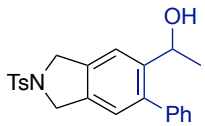
4.174, 91% (91%)



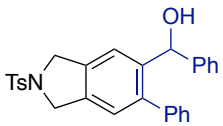
4.175, 90% (84%)



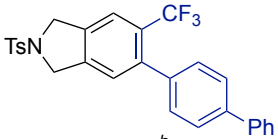
4.176, 57% (63%)



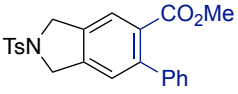
4.177, 78% (72%)



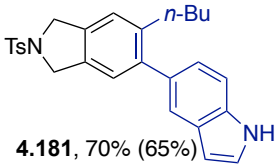
4.178 82% (37%)



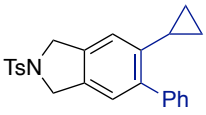
4.179, 63%[b] (51%)



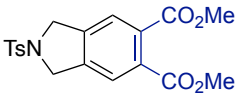
4.180, >99% (99%)



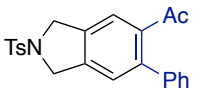
4.181, 70% (65%)



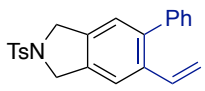
4.182, 82% (65%)



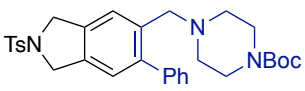
4.183, >99% (15%)



4.184, >99% (94%)



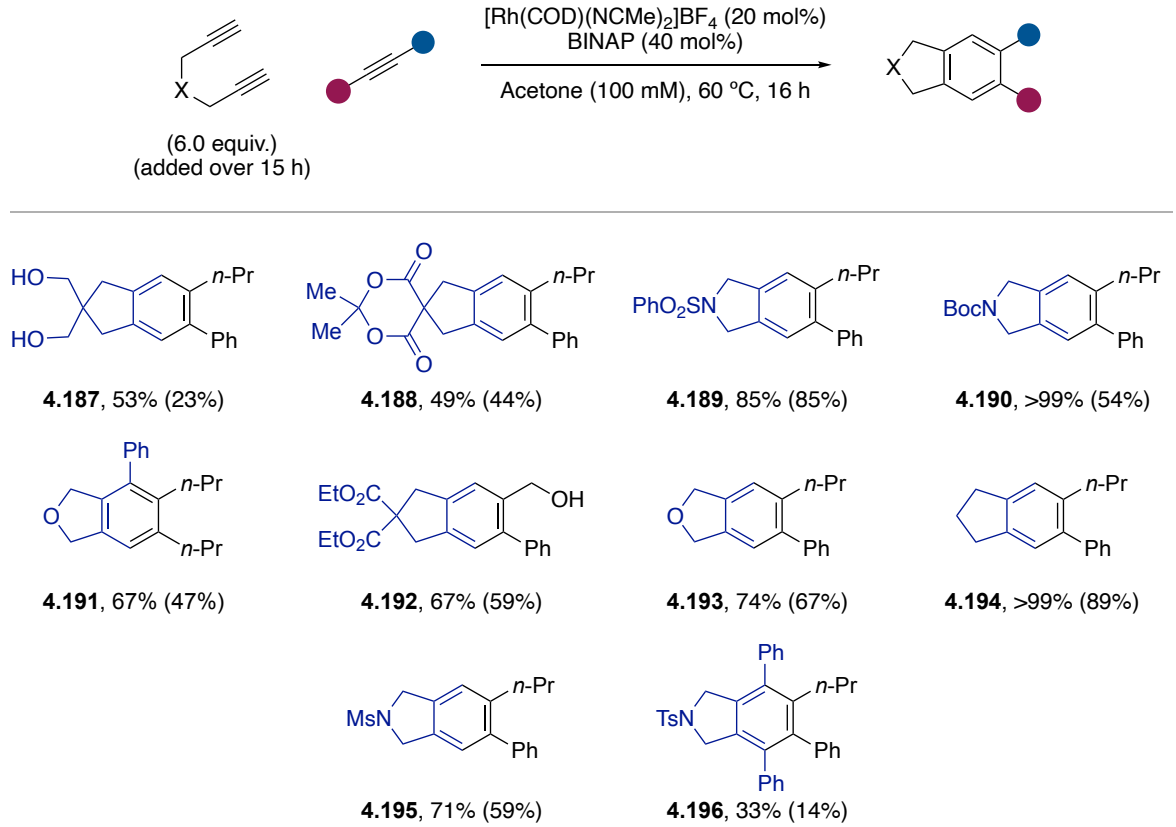
4.185, 76% (75%)



4.186, 97% (78%)

Scheme 4.14: Scope of steric environment of alkynes. Isolated yields in brackets. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard. [a]Not isolable as the acetal, purified after deprotection as the aldehyde. [b]$[Rh(COD)(NCMe)_2]BF_4$ (15 mol%), BINAP (30 mol%) used due to poor solubility of this compound at high loadings of rhodium.

A selection of diynes were also selected to explore the scope of that component of the reaction (**Scheme 4.15**). Dialkynes containing functional groups including diols (**4.187**), esters (**4.188**, **4.192**), sulfonamides (**4.189**, **4.195**, **4.196**), and carbamates (**4.190**) could be tolerated. Furthermore, an exceptionally densely functionalised benzene core (**4.196**) could be synthesised using a diphenyl substituted diyne in acceptable yield.



Scheme 4.15: Scope of steric environment of alkynes. Isolated yields in brackets. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

Finally, a selection of the limitations of the reaction are shown (**Figure 4.2**). Nitriles (**4.14**) were not tolerated as they are able to perform [2+2+2] cycloadditions to generate pyridines.[71] Whilst the vinyl substituted phenylacetylene (**4.30**) was able to perform the reaction in good aptitude (**4.185**), the allyl derivative (**4.75**) yielded a very complex reaction mixture. This is likely due to the formation of products arising from higher order cycloadditions, such as those pioneered by the Evans group.[277-284] A similarly complex reaction profiles was observed with secondary amine (**4.70**), likely due to condensation reactions occurring with acetone as the solvent. An authentic sample of the product was synthesised through deprotection of (**4.186**) which revealed that only 20% of the desired product was present in the reaction mixture. Consistent with the observations in **Chapter 2**, exceptionally bulky alkynes, such as those bearing *t*-Bu (**4.20** or **4.21**) groups were not amenable to the reaction due to poor catalytic turnover. Aldehydes (**4.32** and **4.66**) were also not tolerated as they are able to undergo well-documented Rh-catalysed decarbonylations leading to the decarbonylated product.[285-289] However, it was not clear if this process occurred before, during or after the [2+2+2] event. Finally, whilst the 2-pyridyl and the 3-pyridyl reacted successfully (**4.164** and **4.165**), the 4-pyridyl (**4.28**) was unsuccessful. This is likely due to aforementioned Rh coordination away from the monoalkyne, leading to deactivated catalytic activity.

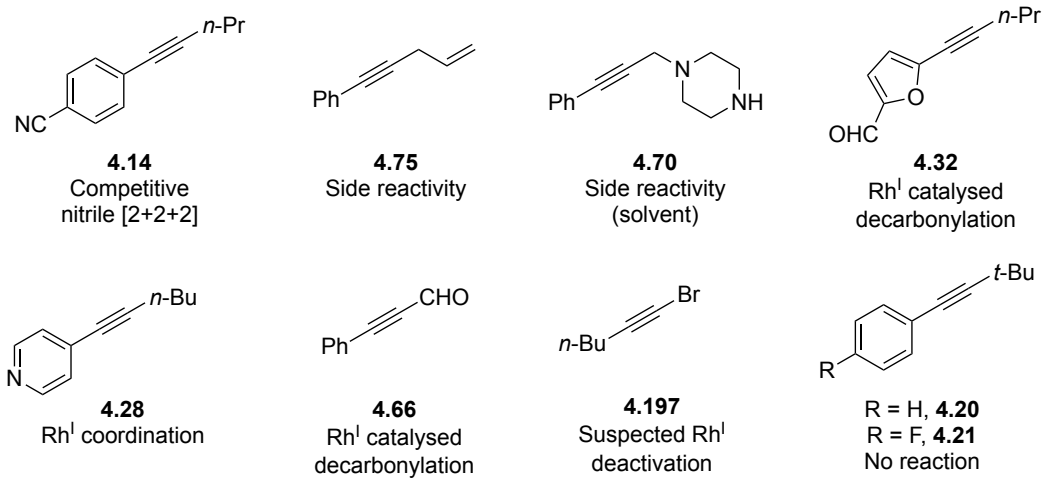
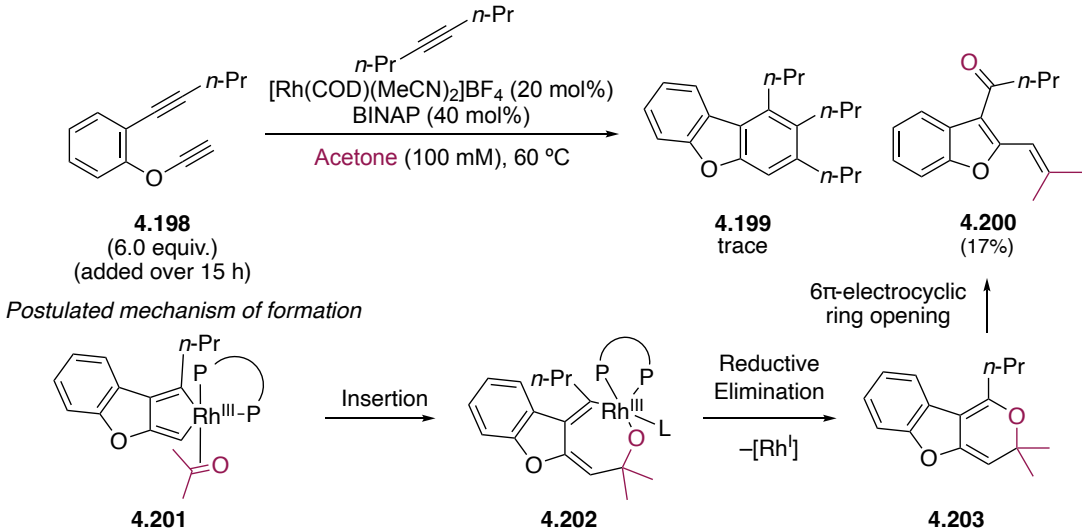


Figure 4.2: Limitations of the Rh^{I} catalysed semi-intramolecular [2+2+2] cycloaddition.

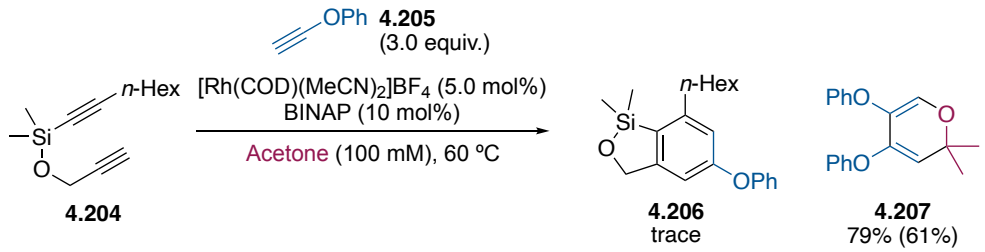
A further limitation was observed with ynol derived starting materials. Ynols and ynamides are well-studied substituents for [2+2+2] cycloadditions and are known to react rapidly due to their unusual electronic properties.[133, 139, 178, 290] Somewhat surprisingly, when such molecules (**4.198**) were screened in the [2+2+2] cycloaddition conditions presented here, the expected product (**4.199**) was only detected in trace amounts and the benzofuran (**4.200**) was the predominant product in the reaction mixture. The postulated mechanism for the formation of this product is shown. First, after oxidative cyclisation (**4.201**), the highly reactive rhodacycle inserts, in a regioselective manner, into the coordinated acetone molecule to generate the seven-membered intermediate (**4.202**). This undergoes a reductive elimination to generate the 2*H*-pyran (**4.203**) which undergoes a energetically-favourable, electrocyclic ring opening yielding the indicated benzofuran (**4.200**).



Scheme 4.16: Reactions ynol dialkyne **4.198** under the established reaction conditions yielding unexpected benzofuran (**4.200**) and the postulated mechanism of formation. Isolated yields in brackets.

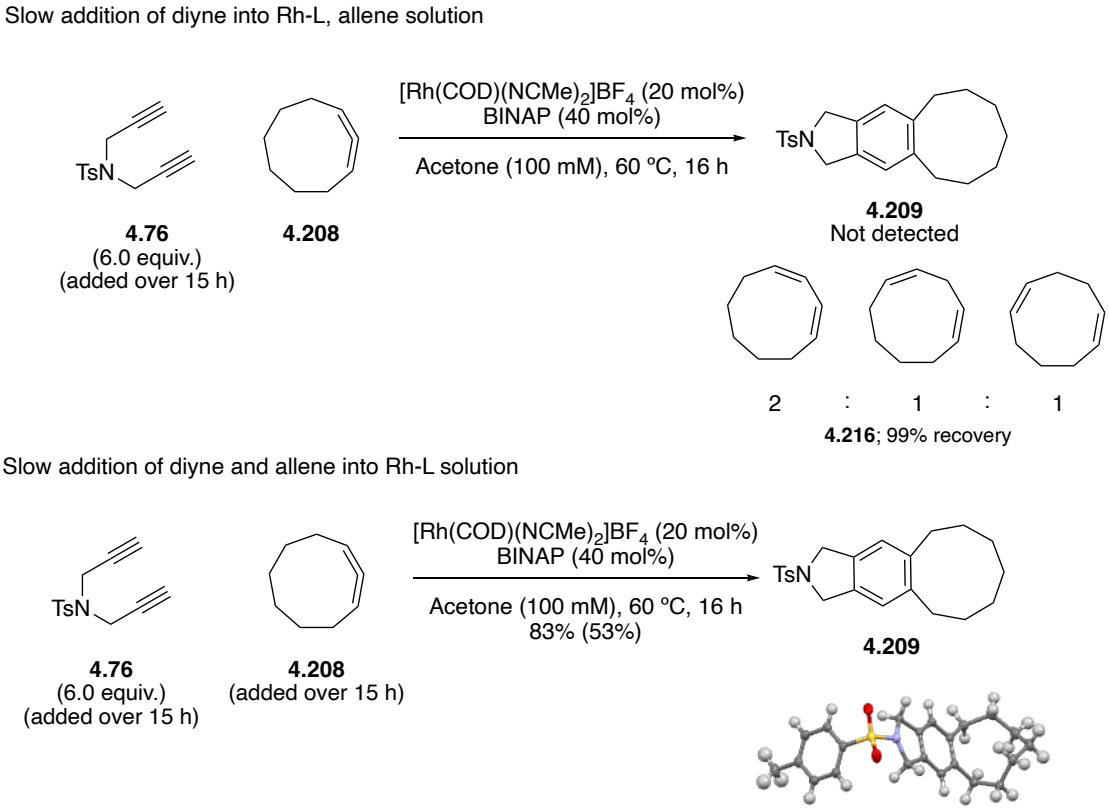
A similar reaction was noted when ynol **4.205** was subjected to the reaction. A modification of the catalytic loading and a change of stoichiometry also yielded a similar product which arises through a similar mechanism which ceases before electrocyclisation. Throughout these studies,

no intermolecular reaction of two equivalents of monoalkyne were noted until this example, indicating reactivity differences between ynols and more conventional alkynes.



Scheme 4.17: Reaction with ynol **4.205** with dialkyne **4.204** under modified conditions and the production of 1,3-diene **4.207** Isolated yields in brackets.

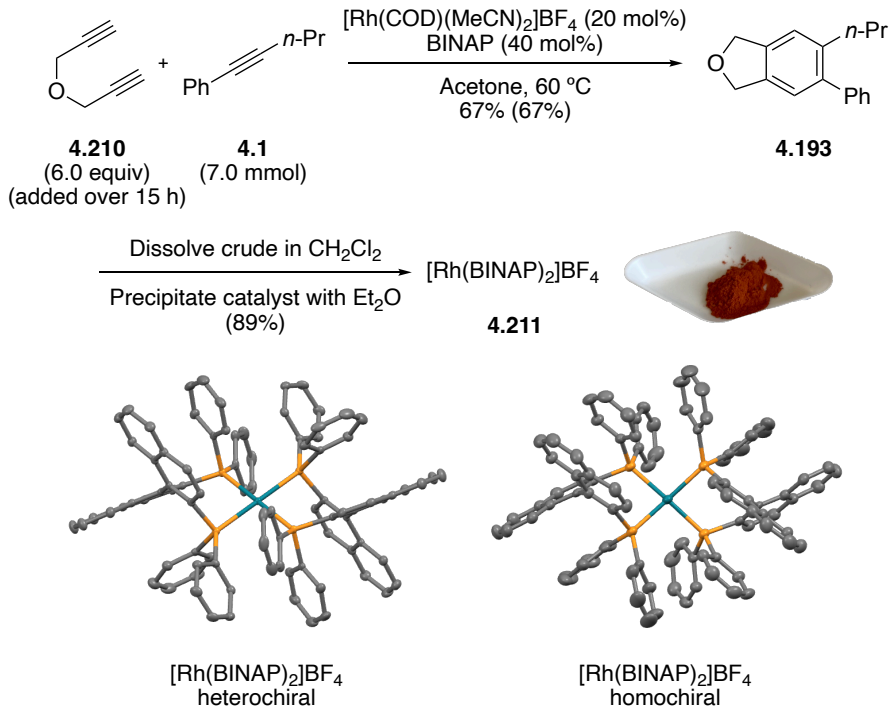
Lastly, an allene (**4.208**) was subjected to the reaction conditions (**Scheme 4.18**), however no desired reactivity was observed and, instead, isomerisation of the allene (**4.218**) accounted for the mass balance of the reaction. It was postulated that this was due to the prolonged exposure of the allene to the Rh^{I} over the course of the reaction. To prevent this, a solution of the diyne and allene were added to the Rh^{I} solution over the course of the reaction. Gratifyingly, good conversion to the desired product (**4.209**) was achieved, the structure was unambiguously confirmed by SCXRD, and is an unusual example of a 5,6,9-polycyclic molecule.



Scheme 4.18: Reaction with allene **4.208** with dialkyne **4.76** with formation of isomers of cyclononadiene and the solution by slow addition of both diyne and allene concomitantly. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard

Finally, a gram-scale reaction (**Scheme 4.19**) was also performed which yielded the desired product (**4.193**) in a similar yield to the 100 µmol test scale (74% vs 67% by ^{1}H NMR assay). Whilst the reaction overall gave products in high yield, a significant amount of rhodium and

ligand is required for this reaction. In order to alleviate these concerns, attempts were made to recover the catalyst from the reaction mixture. Gratifyingly, precipitation of the crude mixture from CH_2Cl_2 with Et_2O yielded a red solid which can be collected and recrystallised to afford the metal and ligand in high percentage recovery as $[Rh(BINAP)_2]BF_4$ (**4.211**). Unfortunately, whilst this complex was catalytically competent, it exhibits reduced activity in the [2+2+2] reaction. Whilst 2:1 stoichiometry of ligand:metal is well established, the lack of reactivity of this complex implies that this may be a resting state.[184-187] Reports exist showing that Rh-BINAP systems are excellent catalysts in [2+2+2] when COD is removed *via* hydrogenation, indicating that the **4.211** may require BINAP dissociation to re-enter catalysis.[291] Interestingly, the use of *rac*-BINAP led to two crystal systems being formed on crystallisation with a notable difference in colour (orange *vs* dark red). These are the homochiral and heterochiral complexes respectively, which appear to interconvert in solution (due to the presence of only one set of signals in NMR). The attempts were made to rescue to catalytic competence of this complex. COD, AgF, and BH_3THF all proved to be ineffective; however, the addition of further rhodium allowed for the return of catalysis. This further implies that redistribution of the BINAP from **4.211** is required for effective [2+2+2].



Scheme 4.19: Gram scale reaction and catalyst recovery SCXRD of the recovered catalyst. Yields determined by ^1H NMR assay using trichloroethylene as an internal standard. Isolated yields in brackets. Solvent molecules and counterions removed for clarity.

4.4. Synthesis of Complex Aryl Organoborons through Rhodium-Catalysed, Semi-Intramolecular [2+2+2] Cycloaddition of Internal Borylated Alkynes

The reaction scope was also extended to the examination of alkynyl boron reagents. Firstly, three organoboron reagents were tested. BMIDA and Bdan substituted alkynes performed equally well initially. On the other hand, the pinacol ester was unreactive despite similar reaction conditions being known to accommodate Bpin alkynes.[139]

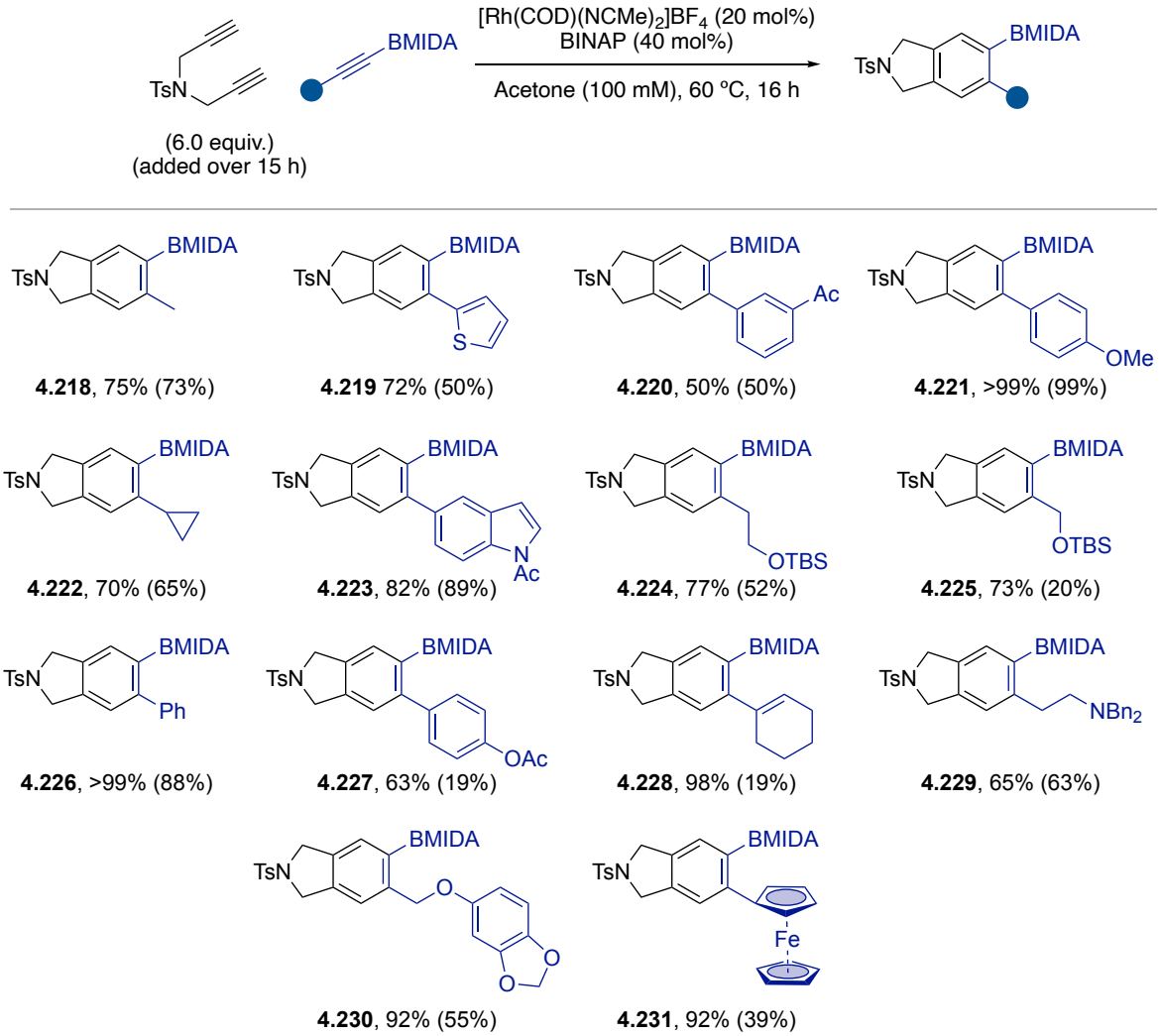
4.84
(6.0 equiv.)
(added over 15 h)

[B] = BMIDA = **4.212**
[B] = Bdan = **4.213**
[B] = Bpin = **4.214**

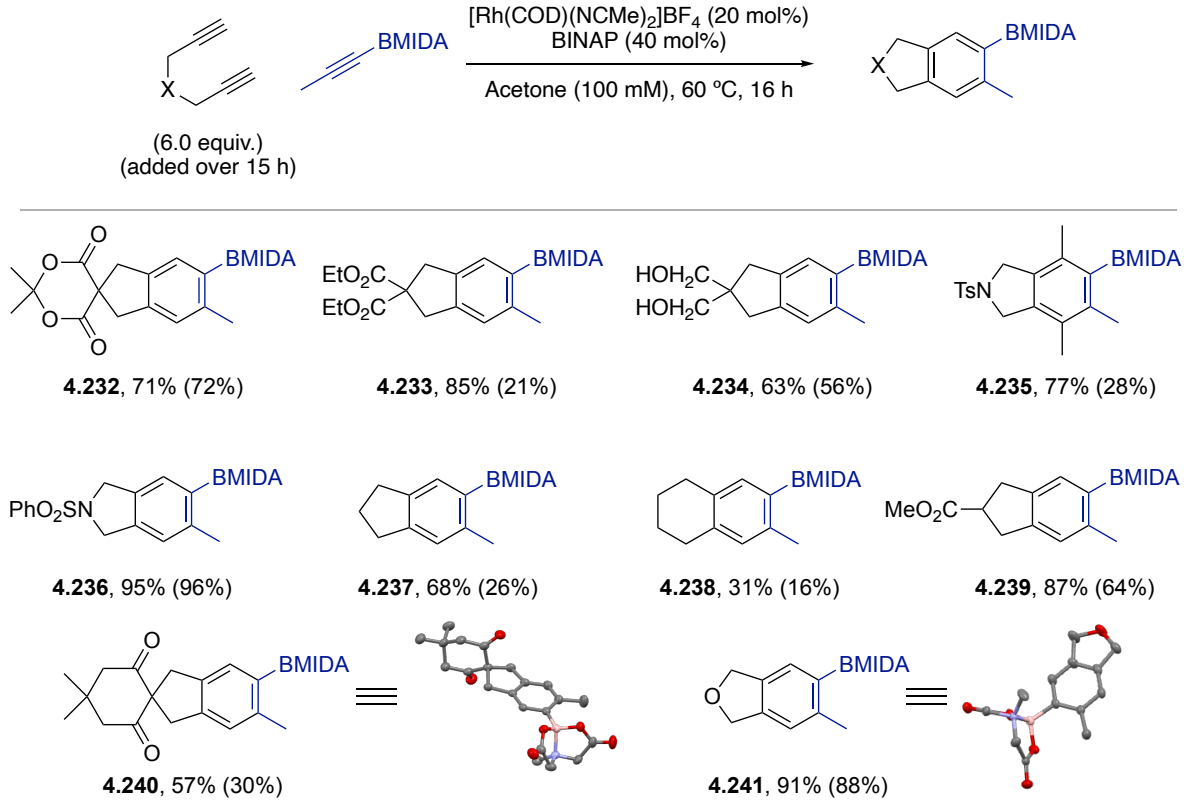
[B] = BMIDA = **4.215**; 80%
[B] = Bdan = **4.216**; 81%
[B] = Bpin = **4.217**; ND

Scheme 4.20: Initial screen of various borylated alkynes. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

With this information in hand, BMIDA alkynes were selected as the borylated alkyne system as the yields acquired were comparable. A range of BMIDA alkynes were subjected to the reaction conditions (**Scheme 4.21**). Several functional groups could be tolerated including sulfonamides (**4.218**–**4.231**), ketones (**4.220**), strained rings (**4.222**), heterocycles (**4.223**), silyl ethers (**4.224**, **4.225**), esters (**4.227**), amines (**4.229**), acetals (**4.230**), and even a ferrocene unit (**4.231**). Furthermore, several dialkynes can be employed (**Scheme 4.22**) such as those bearing, esters (**4.232**, **4.233**, **4.239**) and ketone derivatives (**4.240**), with the structures of **4.240** and **4.241** being unambiguously assigned through SCXRD. As noted above, 1,7-dialkynes (**4.245**) exhibited lower reactivity, possibly due to increased degrees of freedom. It should be noted that throughout the reaction, no concerns arose with the stability of the BMIDA unit and the mass balance is accounted for by unreacted BMIDA alkyne.

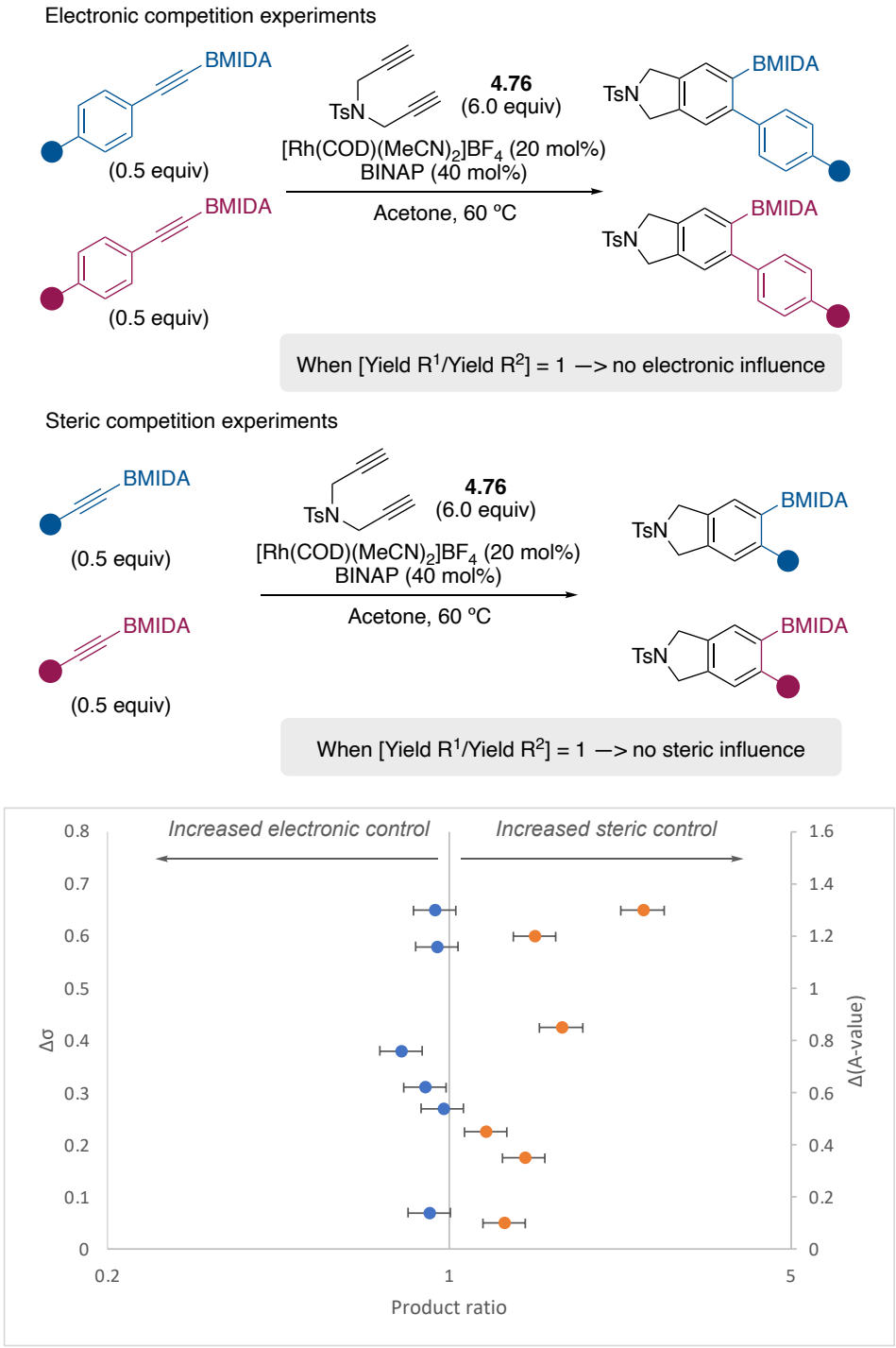


Scheme 4.21: Scope of BMIDA alkynes in Rh-catalysed semi-intramolecular [2+2+2] cycloadditions. Isolated yields in brackets. Yields determined by ^{1}H NMR assay using trichloroethylene or 1,4-dinitrobenzene as an internal standard.



Scheme 4.22: Scope of dialkynes Rh-catalysed semi-intramolecular [2+2+2] cycloadditions of BMIDA alkynes. Isolated yields in brackets. Yields determined by ^{1}H NMR assay using trichloroethylene or 1,4-dinitrobenzene as an internal standard

To further examine the electronic and steric preference of the BMIDA alkyne, a small competition study was performed. BMIDA alkynes of varying steric footprint were reacted, and the product distribution was noted. The same experiments were performed for electronics. In the graph below, a deviation further to the left would indicate an electronic control, in contrast, the further right the points move, the more likely the reaction is under steric control. As illustrated in **Scheme 4.23**, the blue (electronic) datapoints are approximately constant around 1. At high Δ(A-values), the orange (steric) datapoints show that the reaction is more likely to be under steric control.

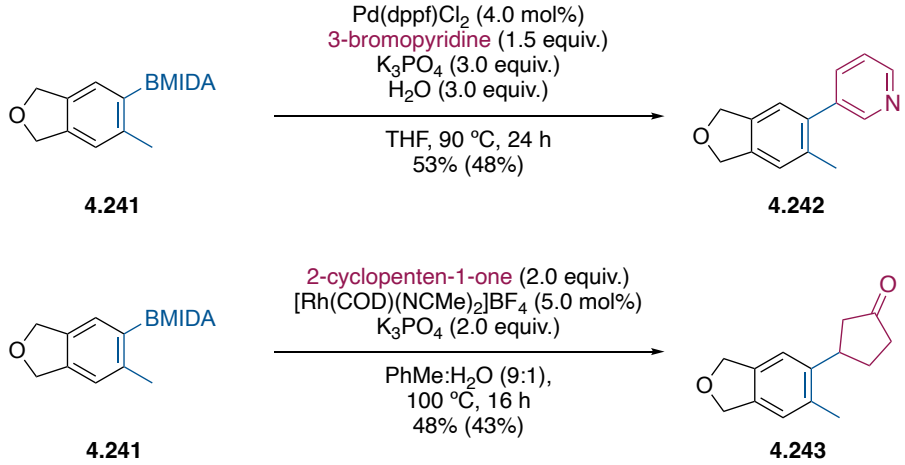


Scheme 4.23: Electronic vs steric competition studies. Yields determined by ^{1}H NMR assay using 1,4-dinitrobenzene as an internal standard.

4.5. Downstream Modification of Complex BMIDAs Synthesised Through [2+2+2] Cycloaddition

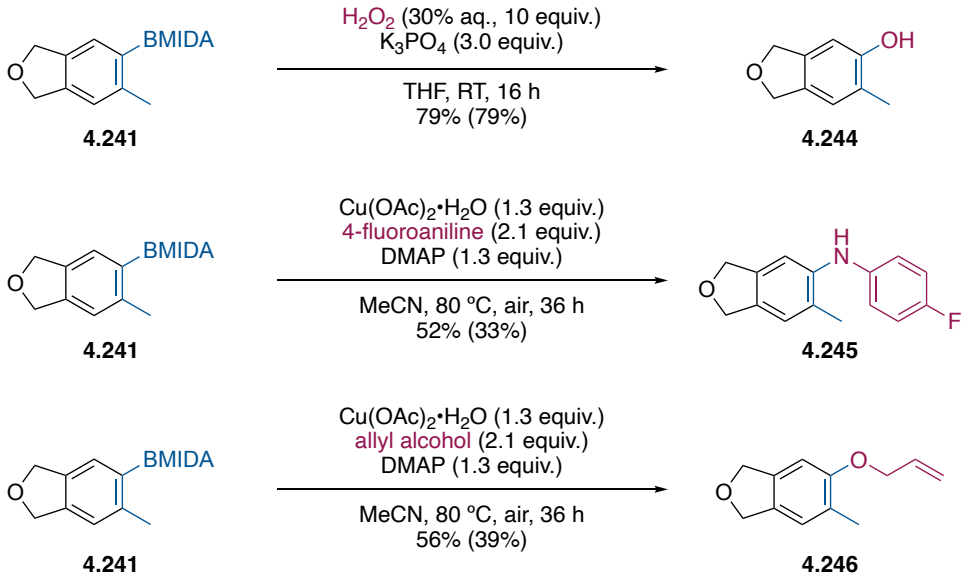
The molecules presented in **Schemes 4.21** and **4.22** were all isolated as the BMIDA ester. This allowed for the retention of the boron functional group and thus the synthetic utility of these molecules could be demonstrated.

Firstly, C–C bond formations were performed using Suzuki-Miyaura cross coupling[200, 292] conditions published by the Watson group to yield product **4.242**.[293, 294] Although the yield is moderate this could be accounted for on steric grounds. By the very nature of doing a semi-intramolecular [2+2+2] cycloaddition with internal alkyne BMIDAs, the products will contain an *ortho*-substituent which can reduce reaction efficiency. The reduced yield when steric repulsion was relevant was noted by the authors during this reaction.[293] Secondly, a Hayashi-Miyaura coupling[295, 296] was performed, which is a conjugate addition of an organoboron into an *α*,*β*-unsaturated carbonyl. These reactions are commonly performed with the corresponding boronic acids. However, publications exist using BF_3Ks,[297, 298] Bpin,[299] and BMIDAs.[299] Using conditions optimised in house from unpublished work, the desired product (**4.243**) was obtained in moderate yield.



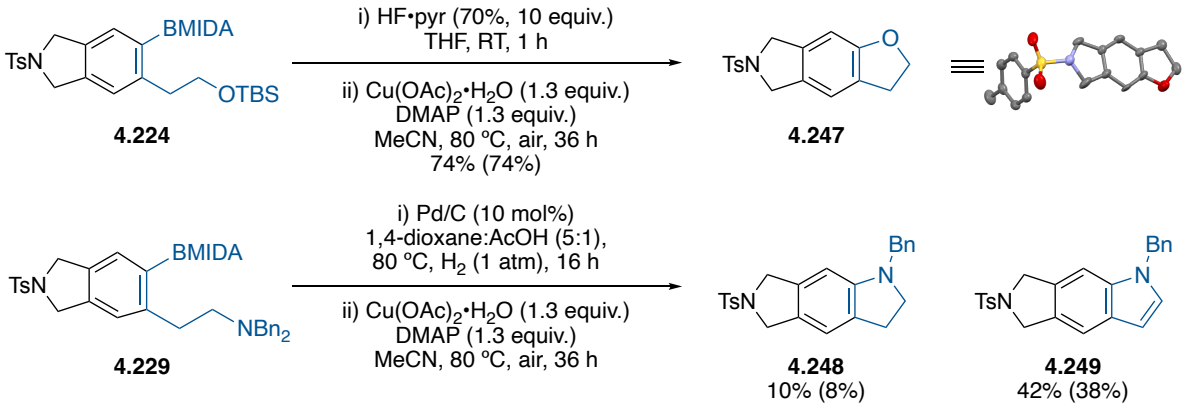
Scheme 4.24: C–B to C–C bond formations through Suzuki-Miyaura and Hayashi-Miyaura couplings. Isolated yields in brackets. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

Next, heteroatom bond formations were considered (**Scheme 4.25**). For this, a Brown oxidation[300] and Chan-Lam reactions were selected.[301, 302] With respect to the Brown oxidation, conditions reported by the Watson group were utilised to obtain the desired phenol (**4.244**) in excellent yield.[303] At the time of this project, conditions did not yet exist for the Chan-Lam reaction of BMIDAs and were thus developed.[304]As noted by numerous authors, the Chan-Lam reaction is very sensitive to steric environment and, as such, the moderate yields of **4.245** and **4.246** observed were expected.[305-309]



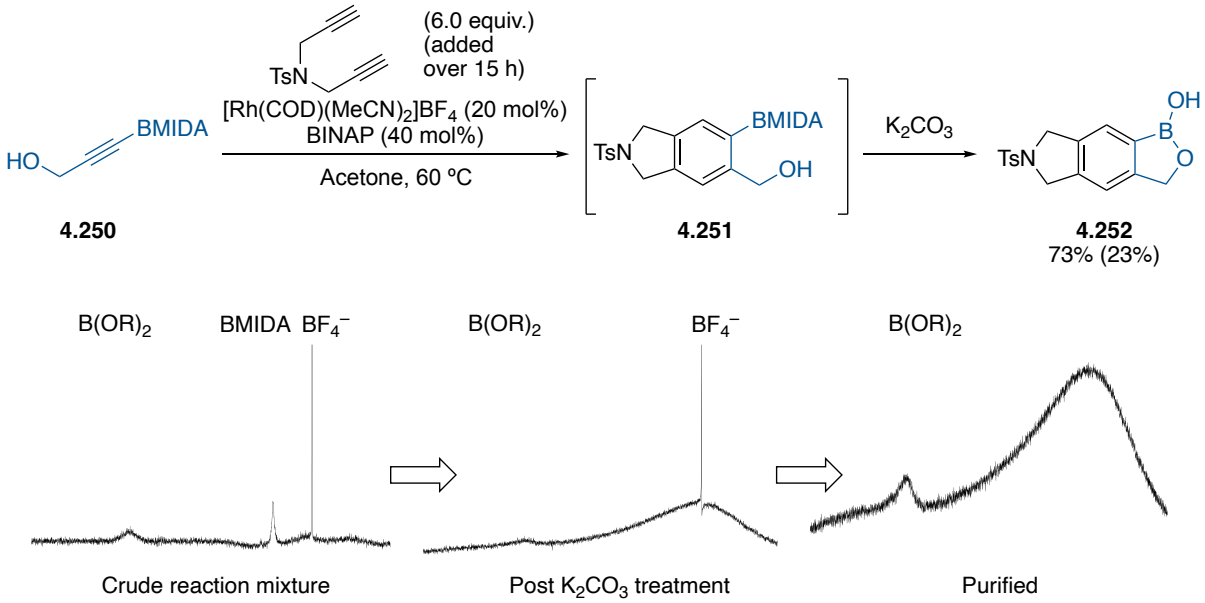
Scheme 4.25: C–B to C–X bond formations through Brown oxidation and Chan-Lam reactions. Isolated yields in brackets. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

Also, of note within the scope were some of the more complex aryl BMIDAs synthesised bearing a protected pendant nucleophile, namely **4.224** and **4.229**. These molecules could be deprotected using standard conditions to yield an intermediate which could be subjected to the aforementioned BMIDA Chan-Lam conditions to generate extended heterocycles. Firstly, the alcohol was unmasked using HF•pyr, then immediately reacted to give the tetrahydrofuroisoindole **4.247** in good yield. Secondly, the deprotection of the benzyl groups of **4.229** required more forcing conditions to remove a benzyl group. Once deprotection was verified by NMR spectroscopy, the mixture was subjected to the Chan-Lam conditions to yield a surprising mixture of hexa- and tetrahydropyrroloindole (**4.248** and **4.249**). It was assumed that the oxidation from indoline to indole is mediated by copper and atmospheric oxygen. Whilst this process is not precisely described in the literature, there is precedent that this type of process may occur.[310-312]



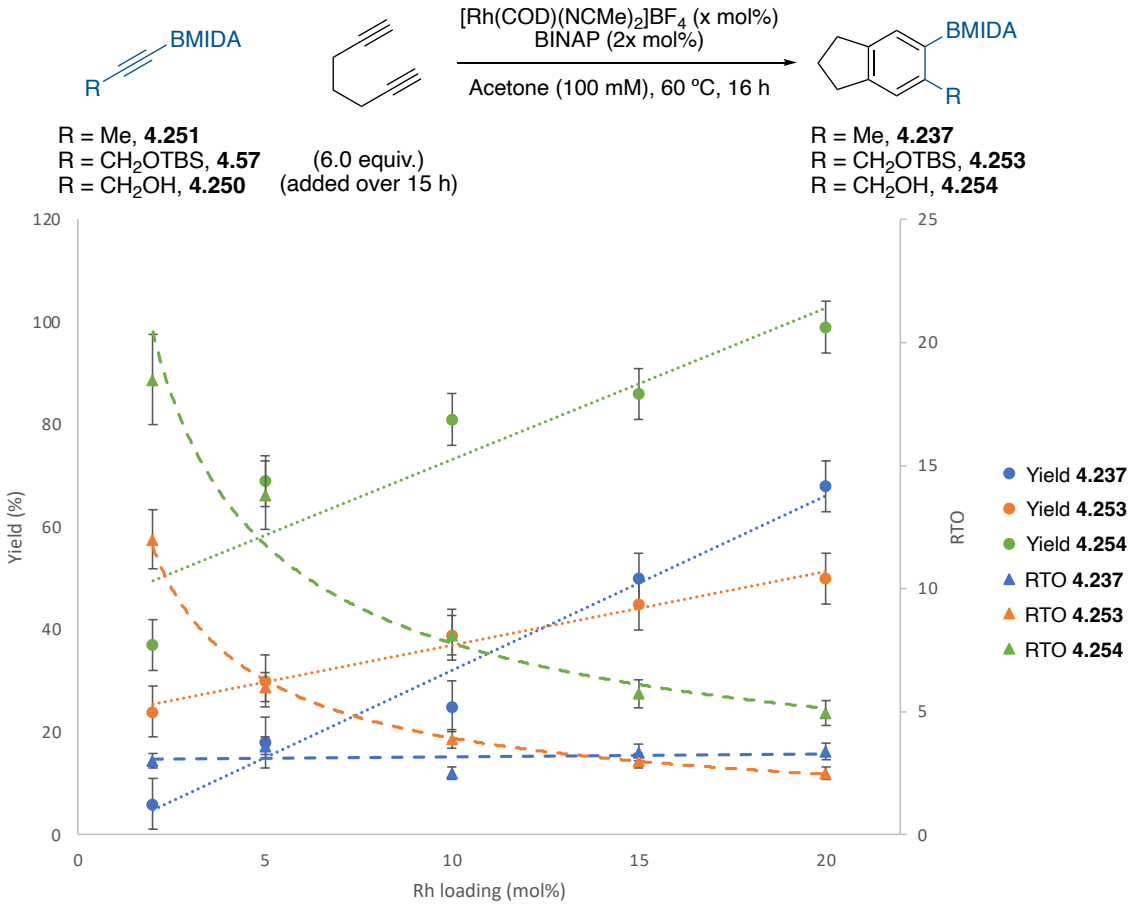
Scheme 4.26: Formation of extended heterocycles through C–B to C–X bond formations *via* deprotection-Chan-Lam reaction cascades. Isolated yields in brackets. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

As a final demonstration of the utility of this methodology, an alcohol substituted alkyne BMIDA (**4.250**) was subjected to the [2+2+2] conditions. The crude mixture showed two products present consistent with a BMIDA and a boronic acid/ester. Cleavage of the BMIDA component (**4.251**) leaves only the boronic acid/ester signal which could be isolated yielding a benzoxaborole (**4.252**) in good yield. These molecules are highly sought after units in drug discovery due to their desirable characteristics *in vivo*.[313-317] This methodology offers a new route to complex derivatives of these molecules in a modular fashion.



Scheme 4.27: Formation if a complex benzoxaborole through a [2+2+2] cycloaddition followed by BMIDA cleavage. Isolated yields in brackets. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

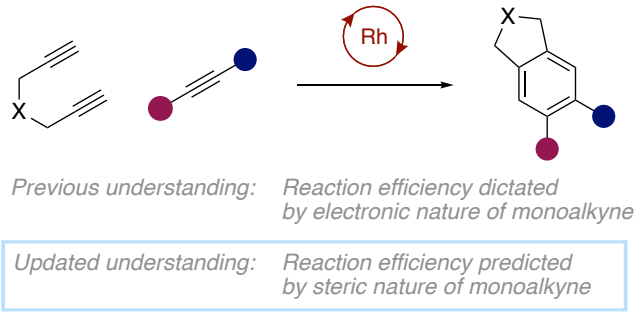
Further investigations (**Scheme 4.28**) have revealed that whilst BMIDAs are not activated (i.e. static turnover for propyne BMIDA, **4.251**), the presence of a chelating group in **4.57** and **4.250** led to a non-static turnover regime, implying these alkynes are activated. This allows for the potential use of [2+2+2] cycloadditions towards the synthesis of complex benzoxaboroles with acceptable catalyst loadings.



Scheme 4.28: Study of chelation effect of various alkyne BMIDAs. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

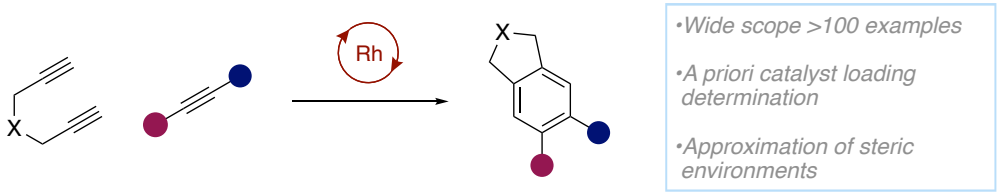
5.0. Conclusions

Conditions that allow for the general application of internal alkynes in semi-intramolecular [2+2+2] cycloadditions have been developed. This process was used to investigate several features of the reaction, including its electronic and steric biases. A number of conclusions were drawn.



Scheme 5.1: Previously understood reaction predictors and the conclusions drawn from these studies.

1) The electronic nature of the alkyne, whether it be electron rich or deficient, is not a good predictor of reaction efficiency in contrast to consensus in the literature
2) Steric descriptors (e.g., A-value, Taft-Dubois, $\Delta\Delta G_{GA}$) are much more valuable to determining whether a [2+2+2] will be successful or not. This allows for *a priori* catalyst loading determination in order to obtain the best yield for the smallest amount of catalyst. Furthermore, the opposite is true, and the yield of a reaction can be used to establish the approximate size of an unknown substituent.
3) The apparent electronic preference in fact appears to be a misattribution of the chelating nature of a number of these electron-withdrawing groups. Whilst molecules like propiolate esters do contain an electron deficient alkyne, it is not the alkyne that enhances reactivity in the [2+2+2] but, instead, it is the secondary coordination through the carbonyl that enhances reactivity. The anatomy of a chelating group was also determined, showing the distance between an coordinating group (e.g. an alcohol) and alkyne moieties must be reasonably short, such that the Rh is held close to the alkyne, and must also allow for a degree of conformational flexibility. It was also found that other directing groups (e.g., pyrimidine) are very good activating groups, although the heteroatoms must be positioned in such a way that the Rh can come into contact with the alkyne.

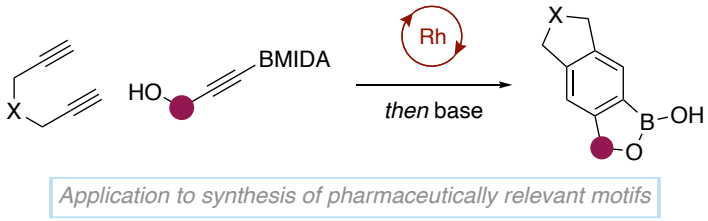


Scheme 5.2: Summary of scope and insights from these studies.

Using this information, a wide scope was performed showing the limitations of the method. The functional group tolerance is very high, with several typically sensitive functionalities proving to be amenable. This was further extended to borylated alkynes which were used to generate complex aryl organoborons. The value of these products was demonstrated by performing standard organoboron manipulations to generate a variety of C-C and C-X bonds.

The effect of various steric and electronic groups was probed using competition experiments which revealed that, as with standard unactivated alkynes, highly sterically congested alkynes lead to a lower yield.

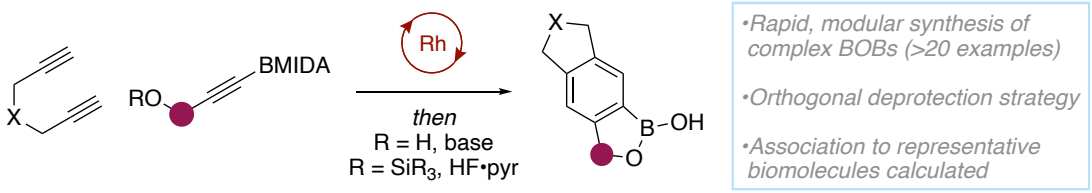
Finally, the totality of this dataset was used to demonstrate the use of chelation assisted [2+2+2] semi-intramolecular cycloadditions towards the synthesis of benzoxaboroles. These molecules are highly sought after targets in drug discovery and this methodology would allow for their modular access with high functional group tolerance.



Scheme 5.3: Applications of the developed [2+2+2] cycloadditions to the synthesis of complex benzoxaboroles.

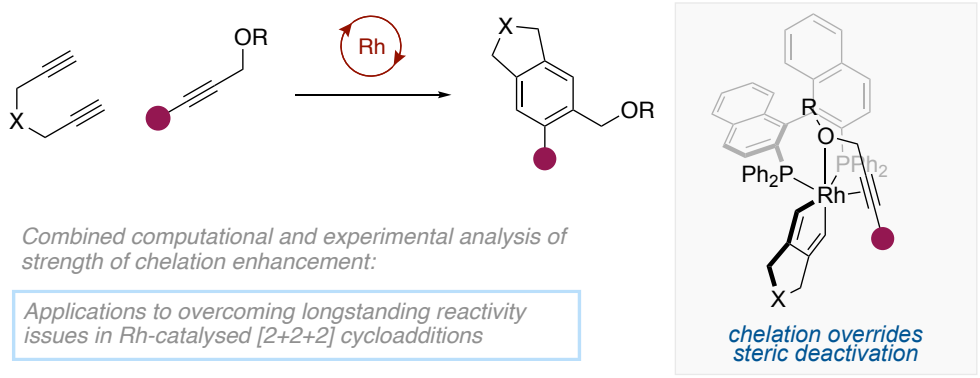
6.0. Future Work

Future work for this process involves further exploration of the formation of benzoxaborole derivatives as these structures are difficult to access but are of significant importance to the pharmaceutical sector. The [2+2+2] method allows for a mild, functional group tolerant approach towards complex derivatives of these valuable moieties with high modularity. This study has now been published.[318]



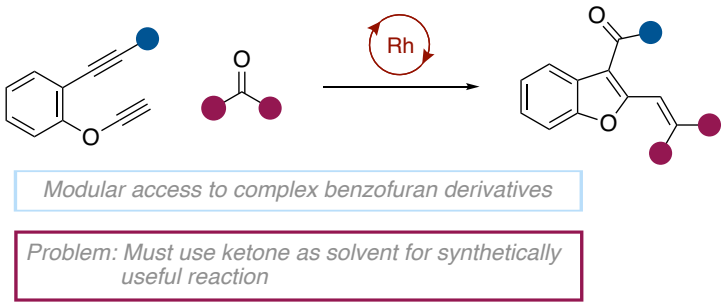
Scheme 6.1: Study on the synthesis of complex BOBs through chelation-enhanced, rhodium-catalysed [2+2+2] cycloadditions.

Computational collaboration is currently underway to add further credence to chelation assistance in [2+2+2] cycloadditions. This will be paired with future physical organic focussed investigations (e.g. kinetic isotope effects, Eyring plots and other kinetic experiments) to allow full description of this effect.



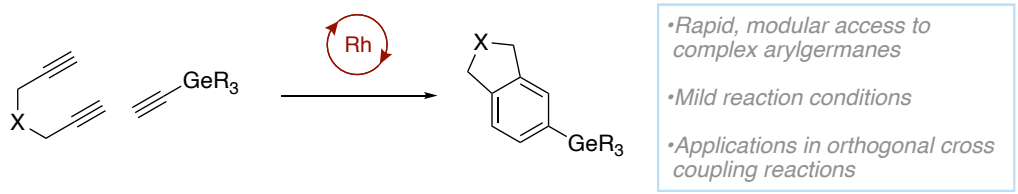
Scheme 6.2: Proposed computational and experimental study of chelation effect in [2+2+2] cycloadditions.

The interesting observation with regards to ynol reactivity with acetone is also of interest. The reactivity of these systems is very different to previously studied alkynes and may be of use for the synthesis of complex benzofurans. Efforts are underway to allow these conditions to be applied to ketones in stoichiometric amounts rather than in solvent quantities.



Scheme 6.3: Synthesis of complex benzofurans through ynol diyne-ketone [2+2+2].

Preliminary work in our laboratory has shown that alkynyl germanium compounds can successfully undergo [2+2+2] cycloaddition. This allows for a mild, modular route into complex derivatives of arylgermanes which are traditionally synthesised through use of lithiated intermediates.



Scheme 6.4: Synthesis of complex arylgermanes through [2+2+2] cycloadditions.

7.0. Experimental Section

7.1. General Experimental Information

Reagents and solvents were obtained from standard commercial sources and were not subjected to purification unless specified. Purification was performed using standard techniques where necessary.[319] Dried solvents (THF, Et_2O, CH_2Cl_2) were provided by a PureSolv SPS-400-5 solvent purification system.

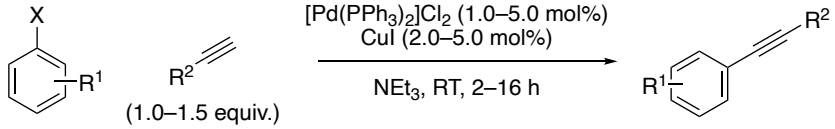
Reactions were carried out in standard borosilicate glassware or 2, 5, or 20 mL microwave vials where appropriate with septum caps. Glassware was either flame-dried under vacuum or allowed to dry in an oven set to 180 ºC for at least 24 h before use. Room temperature was approximately 18 °C. When heating was required, a DrySyn metal heating baths or a silicone oil bath was used. Reactions at 0 °C were performed using and ice/water bath, −5 °C reaction temperatures were achieved with ice/brine mixture, and −78 °C was using dry ice/acetone baths. Degassing was performed by the freeze-pump-thaw technique over three cycles. Slow addition (≥1 h addition period) were performed using a kdScientific 200 or a World Precision Instruments Aladdin-220 syringe pump.

Thin layer chromatography (TLC) was carried out using Merck aluminum-backed silica plates coated with F_{254} fluorescent indicator, visualised under UV light, and developed using basic, aqueous $KMnO_4$ or acidic, ethanolic vanillin stains. Flash column chromatography utilised silica gel (40-62 μm, Fluorochem).

^1H, ^{13}C (DEPTQ), and ^{19}F NMR (with or without ^1H decoupling) spectra were recorded by either a Bruker AVII 400 (BBFO probe) or AVIII-HD 500 (and AVIII 500 with BBFO+ and Prodigy BBFO probes, respectively) at 400-101-376 MHz or at 500-126-377 MHz, respectively. ^1H NMR Spectra recorded at 700 MHz and ^{13}C at 176 MHZ were recorded on a Bruker AVIII-HD 700 with Prodigy TCI probe. ^{11}B NMR spectra were recorded on a Bruker AV300 spectrometer at 96 MHz or a Bruker AV400 at 126 MHz. All spectra were recorded at room temperature with the deuterated solvents used as a lock for spectra and internal reference (chloroform-*d*: ^1H, 7.26 ppm; ^{13}C, 77.16 ppm; acetone-d_6: ^1H, 2.05 ppm, ^{13}C, 29.8 ppm; dimethylsulfoxide-d_6: ^1H, 2.50 ppm, ^{13}C, 39.5 ppm; acetonitrile-d_6: ^1H, 1.94 ppm, ^{13}C, 1.3 ppm). ^1H NMR shifts are relative to $SiMe_4$. ^{11}B NMR, samples were externally referenced to $F_3B{\bullet}OEt_2$ in $CDCl_3$, ^{19}F NMR externally referenced to $CFCl_3$ in $CDCl_3$, and ^{31}P to 80% D_3PO_4 in D_2O. NMR spectra are reported as follows: chemical shift/ppm (multiplicity, coupling constant(s), number of nuclei, assignment). Multiplicity given as br (broad), s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), h (hextet), hept (heptet), m (multiplet), and combinations thereof. Throughout, ^{13}C NMR signals adjacent to boron were not observed. In general, exchangeable protons (e.g. OH signals) are not observed. Overlapping signals are described as multiplets. IR spectra were recorded using a Shimadzu IT Affinity-1 Fourier transform IR spectrophotometer with a Specac Quest ATR (diamond puck). The spectra were recorded as specified in the assignment as films (using CH_2Cl_2 or acetone), as solids, or as neat liquids. Transmittance was recorded with maximal absorption wavenumbers given as cm^{-1}. High resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF benchtop ESI with either positive or negative electrospray ionisation or EI using a Thermo Mat 900XP, Double Focusing Hi-resolution mass spectrometer. The accuracy of the spectrometer determines the number of decimal places listed (*i.e.*, 4 or 5 decimal place accuracy is listed where accuracy of spectrometer allows).

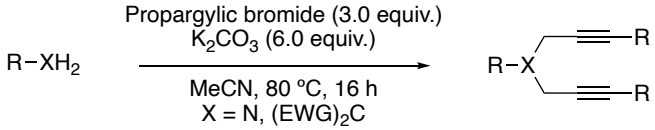
7.2. General Procedures

General Procedure A: Sonogashira Coupling.



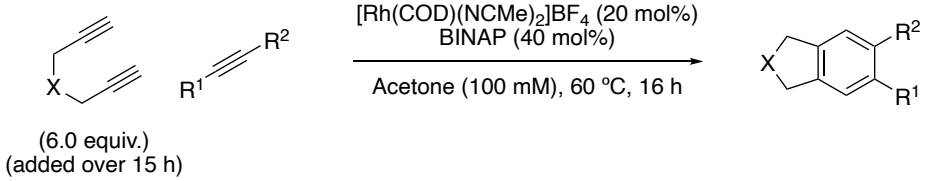
An oven-dried microwave vial was charged with the relevant (hetero)aryl halide (1.0 equiv.), $[Pd(PPh_3)_2]Cl_2$ (1.0–5.0 mol%), and CuI (2.0–5.0 mol%) before sealing, evacuating, and backfilling with N_2. NEt_3 (500 mM) was added and then the relevant alkyne (1.0–1.5 equiv.) was added. The mixture was allowed to stir at RT for 2–16 h before diluting with EtOAc, filtering through celite (washing with EtOAc as necessary), and concentrating *in vacuo* to yield the crude product, which was purified by flash column chromatography.

General Procedure B: Synthesis of dialkynes.



A flame-dried flask was charged with the relevant nucleophile (1.0 equiv.) and K_2CO_3 (6.0 equiv.) then MeCN (100 mM) was added under N_2. The desired propargylic bromide (3.0 equiv.) was added, and the mixture was heated to 80 ºC and allowed to stir at the same temperature for 16 h. The flask was allowed to cool to RT and the mixture was filtered and concentrated *in vacuo* to yield the crude product, which was purified by flash column chromatography.

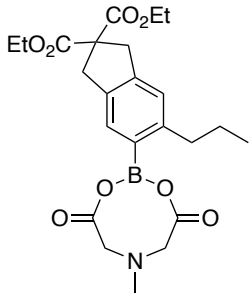
General Procedure C: [2+2+2] cycloaddition.



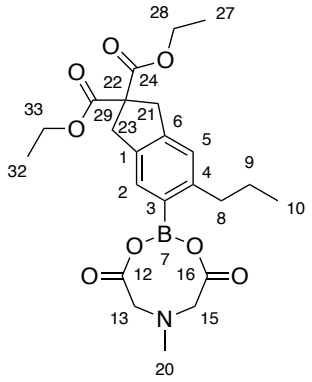
An oven-dried microwave vial was charged with the internal alkyne (1.0 equiv.), $[Rh(COD)(NCMe)_2]BF_4$ (20 mol%), and BINAP (40 mol%) before the vial was sealed, evacuated, and backfilled with N_2. Dried acetone ([100 mM]/2) was added and the mixture was heated to 60 ºC for 10 minutes. A separate vial was charged with the diyne (6.0 equiv.) and dissolved in the remaining dry acetone ([100 mM]/2). The diyne solution was added to the internal alkyne solution (stirred at 60 ºC) *via* syringe pump over 15 h. After the addition was complete, the solution was allowed to stir for a further 1 h before the mixture was allowed to cool to RT, filtered through celite (washing with acetone as necessary), and concentrated *in vacuo* to yield the crude product, which was purified by flash column chromatography.

7.3. Characterisation Data

Diethyl 5-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-6-propyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (3.6)



An oven-dried microwave vial was charged with methyl-2-(pent-1-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (19.5 mg, 100 μmol, 1.00 equiv.), $[Rh(COD)(NCMe)_2]BF_4$ (20 mol%) and *rac*-BINAP (40 mol%) before sealing, evacuating, and backfilling with N_2. Distilled acetone (500 μL) was added, and the mixture was heated to 60 ºC for 10 min. A separate dried flask was charged with diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 μmol, 6.00 equiv.). before distilled acetone (500 μL) was added. This solution was added to the microwave vial at 60 ºC over 15 h. After addition complete, the solution was allowed to stir for a further hour before filtering through celite and concentrating *in vacuo*. Using this material, the general procedure was repeated a further two times so that full conversion to the desired product had occurred. This was purified by flash column chromatography (silica, 0–10% MeCN in CH_2Cl_2) to yield the desired product as a yellow solid (34.6 mg, 75%).



^{1}H NMR (500 MHz, Acetone-d_6) δ_H 7.27 (s, 1H, 2), 7.07 (s, 1H, 5), 4.34 (d, J = 17.2 Hz, 2H, 13, 15), 4.21 – 4.13 (m, 6H, 13, 15, 28, 33), 3.57 – 3.53 (m, 2H, 21), 3.52 (s, 2H, 23), 2.74 (s, 3H, 20), 2.60 – 2.56 (m, 2H, 8), 1.65 – 1.55 (m, 2H, 9), 1.22 (t, J = 7.1 Hz, 6H, 27, 32), 0.95 (t, J = 7.3 Hz, 3H, 10).

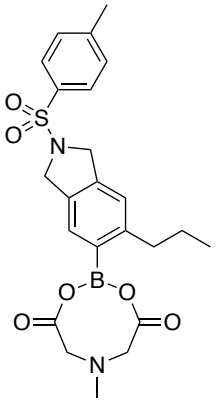
^{13}C NMR (126 MHz, Acetone-d_6) δ_C 172.2 (24, 29), 169.3 (12, 16), 147.4 (4), 142.1 (1), 137.9 (6), 130.5 (2), 126.6 (5), 63.5 (13, 15), 62.1 (28, 33), 60.7 (22), 48.4 (20), 41.1 (21), 40.9 (23), 39.2 (8), 27.3 (9), 14.7 (10), 14.3 (27, 32).

^{11}B NMR (96 MHz, Acetone-d_6) δ_B 12.1.

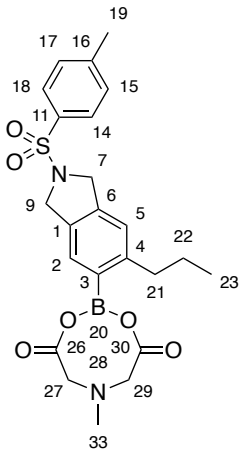
IR (ATR, film): 1728, 1238, 1159, 1094, 1067, 1028, 665, 548 cm^{-1}.

HRMS (ESI): Calculated for 482.1957 *m*/*z*, found 482.1956 *m*/*z* $[C_{23}H_{30}BNO_8+Na]^+$.

6-Methyl-2-(6-propyl-2-tosylisoindolin-5-yl)-1,3,6,2-dioxazaborocane-4,8-dione (**3.21**)



Prepared according to General Procedure C from 6-methyl-2-(prop-1-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (19.5 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% MeCN in CH_2Cl_2) to yield the desired product as a white solid (25.6 mg, 58%).



^{1}H NMR (400 MHz, Acetone-d_6) δ_H 7.82 – 7.77 (m, 2H, 14, 18), 7.45 – 7.38 (m, 2H, 15, 17), 7.30 (s, 1H, 2), 7.10 (s, 1H, 5), 4.55 (m, 4H, 7, 9), 4.34 (d, *J* = 17.2 Hz, 2H, 27, 29), 4.14 (d, *J* = 17.1 Hz, 2H, 27, 29), 2.70 (s, 3H, 33), 2.61 – 2.53 (m, 2H, 21), 2.39 (s, 3H, 19), 1.61 – 1.50 (m, 2H, 22), 0.92 (t, *J* = 7.3 Hz, 3H, 23).

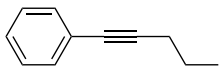
^{13}C NMR (101 MHz, Acetone-d_6) δ_C 169.2 (26, 30), 148.3 (4), 144.5 (16), 138.2 (1), 134.8 (6), 134.2 (11), 130.7 (15, 17), 129.1 (2), 128.6 (14, 18), 124.9 (5), 63.4 (27, 29), 54.4 (9), 54.3 (7), 48.4 (33), 39.1 (21), 27.2 (22), 21.4 (19), 14.5 (23).

^{11}B NMR (128 MHz, Acetone) δ 11.7.

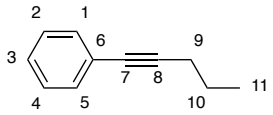
IR (ATR, film): 1763, 1331, 1304, 1161, 1096, 1026, 1009, 835, 667, 548 cm^{-1}.

HRMS (ESI): Calculated for 471.1756 *m*/*z*, found 471.1768 *m*/*z* $[C_{23}H_{27}BN_2O_6S+H]^+$.

Pent-1-yn-1-ylbenzene (4.1)



Prepared according to General Procedure A from iodobenzene (560 µL, 5.02 mmol, 1.00 equiv.) and 1-pentyne (550 µL, 5.58 mmol, 1.11 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a pale-yellow oil (708 mg, 98%).

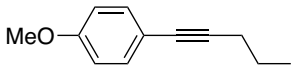


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.45 – 7.40 (m, 2H, 1, 5), 7.34 – 7.27 (m, 3H, 2, 3, 4), 2.41 (t, *J* = 7.1 Hz, 2H, 9), 1.66 (m, 2H, 10), 1.08 (t, *J* = 7.4 Hz, 3H, 11).

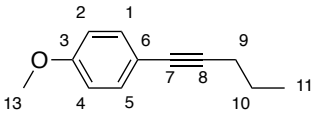
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 131.6 (1, 5), 128.2 (2, 4), 127.5 (3), 124.1 (6), 90.3 (8), 80.7 (7), 22.2 (10), 21.4 (9), 13.6 (11).

Spectral data consistent with the literature.[320]

1-Methoxy-4-(pent-1-yn-1-yl)benzene (4.2)



Prepared according to General Procedure A from 4-iodoanisole (1.17 g, 5.00 mmol) and 1-pentyne (640 µL, 6.49 mmol, 1.30 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a pale-yellow oil (843 mg, 97%).

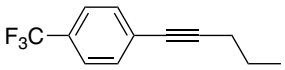


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.38 – 7.33 (m, 2H, 1, 5), 6.87 – 6.81 (m, 2H, 2, 4), 3.82 (s, 3H, 13), 2.39 (t, *J* = 7.1 Hz, 2H, 9), 1.64 (m, 2H, 10), 1.07 (t, *J* = 7.4 Hz, 3H, 11).

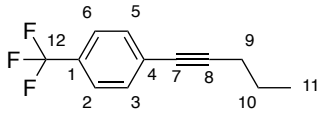
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 159.0 (3), 132.9 (1, 5), 116.3 (6), 113.8 (2, 4), 88.6 (8), 80.3 (7), 55.3 (13), 22.3 (10), 21.4, (9) 13.6 (11).

Spectral data consistent with the literature.[321]

1-(Pent-1-yn-1-yl)-4-(trifluoromethyl)benzene (4.3)



Prepared according to General Procedure A from 4-iodobenzotrifluoride (1.83 g, 6.73 mmol, 1.00 equiv.) and 1-pentyne (900 µL, 9.13 mmol, 1.36 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a yellow oil (1.29 g, 91%).



^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.54 (d, *J* = 8.8 Hz, 2H, 2, 6), 7.49 (d, *J* = 8.2 Hz, 2H, 3, 5), 2.41 (t, *J* = 7.0 Hz, 2H, 9), 1.65 (m, 2H, 10), 1.06 (t, *J* = 7.4 Hz, 3H, 11).

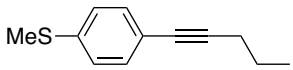
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 131.8 (3, 5), 129.3 (q, $^{2}J_{CF}$ = 32.6 Hz, 1), 128.0 (4), 125.1 (q, $^{3}J_{CF}$ = 3.7 Hz, 2, 5), 124.0 (q, $^{1}J_{CF}$ = 272.1 Hz, 12), 93.1 (8), 79.7 (7), 22.0 (10), 21.4 (9), 13.5 (11).

^{19}F{^{1}H} NMR (470 MHz, Chloroform-*d*) δ_F −62.8.

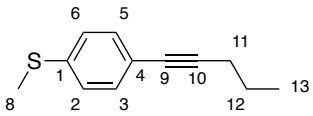
IR (ATR, neat): 1319, 1165, 1123, 1103, 1067, 1018, 839 cm^{-1}.

HRMS (EI): Calculated for 212.08074 *m*/*z*, found 212.080904 *m*/*z* $[C_{12}H_{11}F_3+H]^+$.

Methyl(4-(pent-1-yn-1-yl)phenyl)sulfane (**4.4**)



Prepared according to General Procedure A from 4-iodothioanisole (500 mg, 2.00 mmol, 1.00 equiv.) and 1-pentyne (270 µL, 2.74 mmol, 1.37 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a yellow oil (271 mg, 71%).

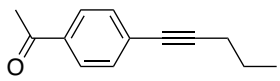


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.34 – 7.29 (m, 2H, 3, 5), 7.17 – 7.11 (m, 2H, 2, 6), 2.47 (s, 3H, 8), 2.38 (t, *J* = 7.0 Hz, 2H, 11), 1.62 (m, 2H, 12), 1.04 (t, *J* = 7.4 Hz, 3H, 13).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 138.2 (1), 132.0 (3, 5), 126.1 (2, 6), 120.7 (4), 90.5 (10), 80.5 (9), 22.4 (12), 21.6 (11), 15.7 (8), 13.7 (13).

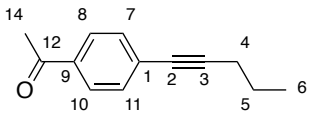
Spectral data consistent with the literature.[322]

1-(4-(Pent-1-yn-1-yl)phenyl)ethan-1-one (**4.5**)



Prepared according to General Procedure A from 4'-iodoacetophenone (150 µL, 1.05 mmol, 1.00 equiv.) and 1-pentyne (150 µL, 1.52 mmol, 1.45 equiv.). Purified by flash column

chromatography (silica, hexane) to yield the desired product as a pale-yellow oil (174 mg, 89%).

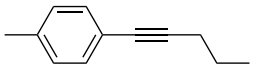


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.95 – 7.85 (m, 2H, 8, 10), 7.49 (d, *J* = 8.5 Hz, 2H, 7, 11), 2.61 (s, 3H, 14), 2.44 (t, *J* = 7.0 Hz, 2H, 4), 1.67 (m, 2H, 5), 1.08 (t, *J* = 7.4 Hz, 3H, 6).

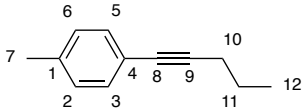
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 197.5 (12), 135.7 (9), 131.7 (7, 11), 129.9 (1), 128.2 (8, 10), 94.2 (3), 80.3 (2), 26.6 (14), 22.1 (5), 21.5 (4), 13.6 (6).

Spectral data consistent with the literature.[323]

1-Methyl-4-(pent-1-yn-1-yl)benzene (**4.6**)



Prepared according to General Procedure A from 4-iodotoluene (218 mg, 1.00 mmol, 1.00 equiv.) and 1-pentyne (150 µL, 1.52 mmol, 1.52 equiv.) and [Pd(dppf)]Cl_2 (7.02 mg, 10.0 µmol, 1.00 mol%). Purified by flash column chromatography (silica, hexane) to yield the desired product as a pale-yellow oil (134 mg, 85%).

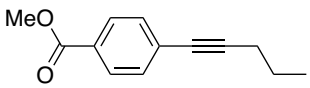


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.31 – 7.27 (m, 2H, 3, 5), 7.10 – 7.06 (m, 2H, 2, 6), 2.38 (t, *J* = 7.1 Hz, 2H, 10), 2.33 (s, 3H, 7), 1.63 (m, 2H, 11), 1.05 (t, *J* = 7.4 Hz, 3H, 12).

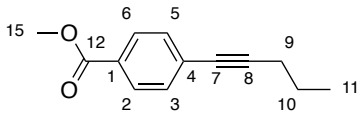
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 137.6 (1), 131.6 (3, 5), 129.1 (2, 6), 121.1 (4), 89.6 (8), 80.9 (9), 22.4 (11), 21.6 (10), 21.5 (7), 13.7 (12).

Spectral data consistent with the literature.[324]

Methyl 4-(pent-1-yn-1-yl)benzoate (**4.7**)



Prepared according to General Procedure A from methyl 4-iodobenzoate (297 mg, 1.13 mmol, 1.00 equiv.) and 1-pentyne (150 µL, 1.52 mmol, 1.35 equiv.). Purified by flash column chromatography (silica, 0–10% Et_2O in hexane) to yield the desired product as a yellow oil (203 mg, 88%).

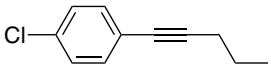


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.97 – 7.89 (m, 2H, 2, 6), 7.49 – 7.42 (m, 2H, 3, 5), 3.91 (s, 3H, 15), 2.41 (t, *J* = 7.1 Hz, 2H, 9), 1.64 (m, 2H, 10), 1.05 (t, *J* = 7.4 Hz, 3H, 11).

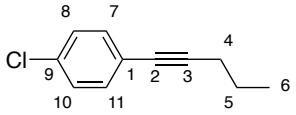
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 166.8 (12), 131.6 (3, 5), 129.5 (2, 6), 129.1 (1), 129.0 (4), 93.9 (8), 80.4 (7), 52.3 (15), 22.2 (10), 21.6 (9), 13.7 (11).

Spectral data consistent with the literature.[325]

1-Chloro-4-(pent-1-yn-1-yl)benzene (4.8)



Prepared according to General Procedure A from chloro-4-iodobenzene (394 mg, 1.65 mmol, 1.00 equiv.) and 1-pentyne (250 µL, 2.43 mmol, 1.47 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as an orange oil (259 mg, 88%).

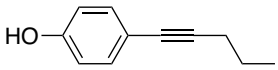


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.34 – 7.29 (m, 2H, 7, 11), 7.26 – 7.22 (m, 2H, 8, 10), 2.37 (t, *J* = 7.1 Hz, 2H, 4), 1.62 (m, 2H, 5), 1.04 (t, *J* = 7.4 Hz, 3H, 6).

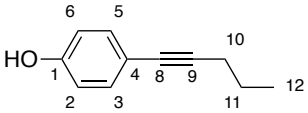
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 133.4 (9), 132.8 (7, 11), 128.5 (8, 10), 122.6 (1), 91.4 (3), 79.7 (2), 22.1 (5), 21.4 (4), 13.6 (6).

Spectral data consistent with the literature.[326]

4-(Pent-1-yn-1-yl)phenol (4.9)



Prepared according to General Procedure A from 4-iodophenol (119 mg, 541 µmol, 1.00 equiv.) and 1-pentyne (80.0 µL, 811 µmol, 1.50 equiv.) and [Pd(dppf)]Cl_2 (3.80 mg, 5.41 µmol, 1.00 mol%). Purified by flash column chromatography (silica, 0–20% Et_2O in hexane) to yield the desired product as a brown oil (86.7 mg, >99%).

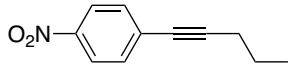


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.32 – 7.27 (m, 2H, 3, 5), 6.77 – 6.72 (m, 2H, 2, 6), 2.36 (t, *J* = 7.1 Hz, 2H, 10), 1.61 (m, 2H, 11), 1.04 (t, *J* = 7.4 Hz, 3H, 12).

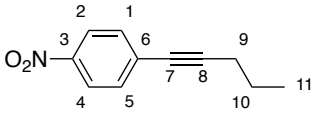
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 155.1 (1), 133.2 (3, 5), 116.6 (4), 115.4 (2, 6), 88.8 (9), 80.4 (8), 22.4 (11), 21.5 (10), 13.7 (12).

Spectral data consistent with the literature.[327]

1-Nitro-4-(pent-1-yn-1-yl)benzene (4.10)



Prepared according to General Procedure A from iodo-4-nitrobenzene (1.61 g, 6.46 mmol, 1.30 equiv.) and 1-pentyne (490 µL, 4.97 mmol, 1.00 equiv.). Purified by flash column chromatography (silica, 0–5% EtOAc in hexane) to yield the desired product as a dark orange oil (851 mg, 90%).

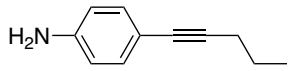


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 8.21 – 8.15 (m, 2H, 2, 4), 7.59 – 7.51 (m, 2H, 1, 5), 2.46 (t, *J* = 7.0 Hz, 2H, 9), 1.68 (m, 2H, 10), 1.09 (t, *J* = 7.4 Hz, 3H, 11).

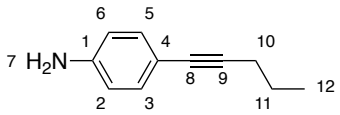
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 146.6 (3), 132.3 (1, 5), 131.3 (6), 123.5 (2, 4), 96.7 (8), 78.3 (7), 21.9 (10), 21.5 (9), 13.6 (11).

Spectral data consistent with the literature.[328]

4-(Pent-1-yn-1-yl)aniline (4.11)



Prepared according to General Procedure A from 4-iodoaniline (110 mg, 500 µmol, 1.00 equiv.) and 1-pentyne (50 µL, 507 µmol, 1.01 equiv.). Purified by flash column chromatography (silica, 0–20% EtOAc in hexane) to yield the desired product as an orange oil (70.8 mg, 89%).

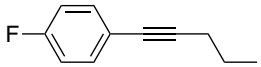


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.23 – 7.17 (m, 2H, 3, 5), 6.61 – 6.53 (m, 2H, 2, 6), 3.72 (s, 2H, 7), 2.37 (t, *J* = 7.1 Hz, 2H, 10), 1.61 (m, 2H, 11), 1.03 (t, *J* = 7.4 Hz, 3H, 12).

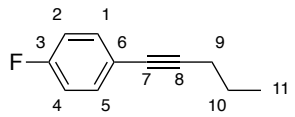
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 146.0 (1), 132.9 (3, 5), 114.9 (2, 6), 113.8 (4), 87.8 (9), 81.0 (8), 22.5 (11), 21.6 (10), 13.7 (12).

Spectral data consistent with the literature.[329]

1-Fluoro-4-(pent-1-yn-1-yl)benzene (4.12)



Prepared according to General Procedure A from 4-fluoroiodobenzene (120 µL, 1.04 mmol, 1.00 equiv.) and 1-pentyne (120 µL, 1.22 mmol, 1.17 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a pale-yellow oil (169 mg, >99 %).



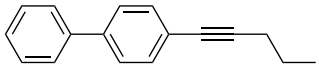
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.42 – 7.35 (m, 2H, 1, 5), 7.03 – 6.96 (m, 2H, 2, 4), 2.39 (t, *J* = 7.0 Hz, 2H, 9), 1.65 (m, 2H, 10), 1.07 (t, *J* = 7.4 Hz, 3H, 11).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 162.0 (d, $^{1}J_{CF}$ = 248.1 Hz, 3), 133.3 (d, $^{3}J_{CF}$ = 8.2 Hz, 1, 5), 120.1 (d, $^{4}J_{CF}$ = 3.4 Hz, 6), 115.4 (d, $^{2}J_{CF}$ = 21.9 Hz, 2, 4), 89.9 (8), 79.6 (7), 22.2 (10), 21.3 (9), 13.6 (11).

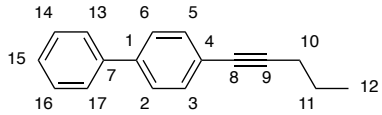
^{19}F{^{1}H} NMR (470 MHz, Chloroform-*d*) δ_F –112.5.

Spectral data consistent with the literature.[330]

4-(Pent-1-yn-1-yl)-1,1'-biphenyl (**4.13**)



Prepared according to General Procedure A from 4-iodobiphenyl (140 mg, 500 µmol, 1.00 equiv.) and 1-pentyne (50 µL, 507 µmol, 1.01 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a white solid (110 mg, 53%).

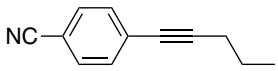


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.60 – 7.56 (m, 2H, 13, 17), 7.54 – 7.50 (m, 2H, 2, 6), 7.49 – 7.39 (m, 4H, 3, 5, 14, 16), 7.37 – 7.33 (m, 1H, 15), 2.41 (t, *J* = 7.0 Hz, 2H, 10), 1.65 (m, 2H, 11), 1.07 (t, *J* = 7.4 Hz, 3H, 12).

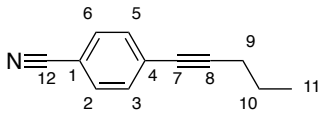
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 140.7 (7), 140.3 (4), 132.1 (14, 16), 129.0 (1, 5), 127.6 (15), 127.1 (13, 17), 127.0 (2, 6), 123.2 (1), 91.1 (8), 80.7 (9), 22.4 (11), 21.6 (10), 13.7 (12).

Spectral data consistent with the literature.[331]

4-(Pent-1-yn-1-yl)benzonitrile (**4.14**)



Prepared according to General Procedure A from 4-iodobenzonitrile (409 mg, 1.79 mmol, 1.00 equiv.) and 1-pentyne (250 µL, 2.54 mmol, 1.42 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as an orange oil (294 mg, 97%).

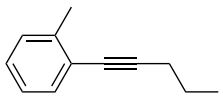


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.59 – 7.54 (m, 2H, 2, 6), 7.48 – 7.44 (m, 2H, 3, 5), 2.41 (t, *J* = 7.0 Hz, 2H, 9), 1.64 (m, 2H, 10), 1.05 (t, *J* = 7.4 Hz, 3H, 11).

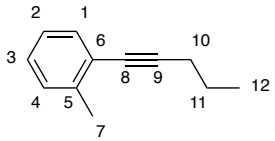
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 132.4 (3, 5), 132.1 (2, 6), 129.3 (4), 118.8 (12), 110.9 (1), 95.7 (8), 79.7 (7), 22.1 (10), 21.6 (9), 13.7 (11).

Spectral data consistent with the literature.[332]

1-Methyl-2-(pent-1-yn-1-yl)benzene (**4.15**)



Prepared according to General Procedure A from 2-iodotoluene (1.44 g, 6.59 mmol, 1.30 equiv.) and 1-pentyne (500 µL, 5.07 mmol, 1.00 equiv.). Purified by flash column chromatography (silica, 0–5% EtOAc in hexane) to yield the desired product as a colourless oil (803 mg, 66%).

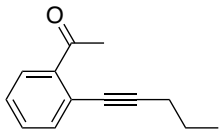


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.39 (dd, *J* = 7.3, 1.2 Hz, 1H, 1), 7.22 – 7.17 (m, 2H, 3, 4), 7.15 – 7.10 (m, 1H, 2), 2.48 – 2.43 (m, 5H, 7, 10), 1.68 (m, 2H, 11), 1.09 (t, *J* = 7.4 Hz, 3H, 12).

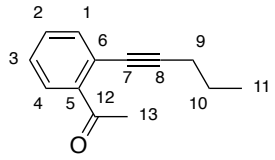
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 139.9 (5), 131.8 (1), 129.3 (4), 127.5 (3), 125.4 (2), 123.9 (6), 94.3 (9), 79.6 (8), 22.4 (11), 21.6 (10), 20.8 (7), 13.6 (12).

Spectral data consistent with the literature.[324]

1-(2-(Pent-1-yn-1-yl)phenyl)ethan-1-one (**4.16**)



Prepared according to General Procedure A from 2'-iodoacetophenone (258 mg, 1.05 mmol) and 1-pentyne (130 µL, 1.32 mmol, 1.26 equiv.). Purified by flash column chromatography (silica, 0–5% EtOAc in hexane) to yield the desired product as a pale-yellow oil (165 mg, 89%).

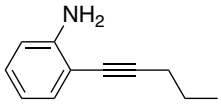


^{1}H NMR (500 MHz, Chloroform-*d*) δ_C 7.68 (dd, *J* = 7.8, 1.5 Hz, 1H, 4), 7.51 (dd, *J* = 7.7, 1.4 Hz, 1H, 1), 7.42 (td, *J* = 7.6, 1.5 Hz, 1H, 2), 7.35 (td, *J* = 7.6, 1.4 Hz, 1H, 3), 2.75 (s, 3H, 13), 2.46 (t, *J* = 7.1 Hz, 2H, 9), 1.68 (h, *J* = 7.2 Hz, 2H, 10), 1.08 (t, *J* = 7.4 Hz, 3H, 11).

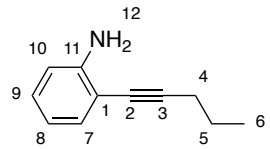
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 201.1 (12), 141.1 (5), 134.0 (1), 131.1 (2), 128.3 (4), 127.6 (3), 122.5 (6), 96.7 (8), 79.8 (7), 30.1 (13), 22.0 (10), 21.7 (9), 13.7 (10).

Spectral data consistent with the literature.[333]

2-(Pent-1-yn-1-yl)aniline (**4.17**)



Prepared according to General Procedure A from 2-iodoaniline (438 mg, 2.00 mmol, 1.00 equiv.) and 1-pentyne (300 µL, 3.04 mmol, 1.52 equiv.) using [Pd(dppf)]Cl_2 (14.6 mg, 20.0 µmol, 1.00 mol%). Purified by flash column chromatography (silica, 0–20% Et_2O in hexane) to yield the desired product as a brown oil (295 mg, 93%).

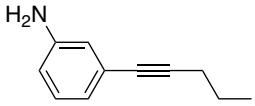


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.24 (dd, *J* = 7.8, 1.8 Hz, 1H, 7), 7.08 (ddd, *J* = 8.12, 7.3, 1.6 Hz, 1H, 9), 6.70 – 6.63 (m, 2H, 8, 10), 4.16 (brs, 2H, 12), 2.45 (t, *J* = 7.0 Hz, 2H, 4), 1.66 (m, 2H, 5), 1.06 (t, *J* = 7.4 Hz, 3H, 6).

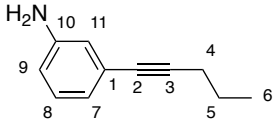
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 147.7 (1), 132.4 (7), 128.9 (9), 118.0 (10), 114.3 (8), 109.1 (10), 95.7 (3), 77.4 (2), 22.5 (5), 21.8 (4), 13.7 (6).

Spectral data consistent with the literature.[334]

3-(Pent-1-yn-1-yl)aniline (**4.18**)



Prepared according to General Procedure A from 3-iodoaniline (438 mg, 2.00 mmol, 1.00 equiv.) and 1-pentyne (300 µL, 3.04 mmol, 1.52 equiv.) using [Pd(dppf)]Cl_2 (14.6 mg, 20.0 µmol, 1.00 mol%). Purified by flash column chromatography (silica, 0–20% Et_2O in hexane) to yield the desired product as a brown oil (314 mg, 99%).



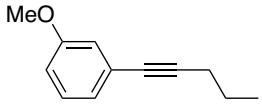
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.06 (m, 1H, 8), 6.81 (m, 1H, 7), 6.75 – 6.71 (m, 1H, 11), 6.60 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, 9), 3.62 (brs, 2H, 12), 2.36 (t, *J* = 7.1 Hz, 2H, 4), 1.63 (m, 2H, 5), 1.04 (t, *J* = 7.4 Hz, 3H, 6).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 146.3 (10), 129.3 (8), 124.9 (1), 122.2 (7), 118.1 (11), 114.7 (9), 89.8 (3), 81.0 (2), 22.4 (5), 21.5 (4), 13.7 (6).

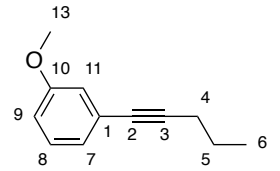
IR (ATR, neat): 1618, 1597, 1580, 779, 687, 459 cm^{-1}.

HRMS (ESI): Calculated for 160.1121 *m*/*z*, found 160.1119 *m*/*z* $[C_{11}H_{13}N+H]^+$.

1-Methoxy-3-(pent-1-yn-1-yl)benzene (4.19)



Prepared according to General Procedure A from 3-iodoanisole (468 mg, 2.00 mmol, 1.00 equiv.) and 1-pentyne (300 µL, 3.04 mmol, 1.52 equiv.) using [Pd(dppf)]Cl_2 (14.6 mg, 20.0 µmol, 1.00 mol%). Purified by flash column chromatography (silica, 0–10% Et_2O in hexane) to yield the desired product as a brown oil (350 mg, >99%).

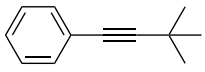


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.18 (ddd, *J* = 8.2, 7.6, 0.4 Hz, 1H, 8), 6.99 (dt, *J* = 7.6, 1.2 Hz, 1H, 7), 6.93 (dd, *J* = 2.7, 1.4 Hz, 1H, 11), 6.83 (ddd, *J* = 8.32 2.7, 1.0 Hz, 1H, 9), 3.79 (s, 3H, 13), 2.38 (t, *J* = 7.1 Hz, 2H, 4), 1.63 (m, 2H, 5), 1.05 (t, *J* = 7.4 Hz, 3H, 6).

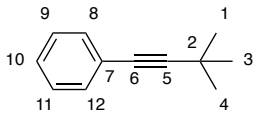
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 159.4 (10), 129.4 (1), 125.2 (1), 124.3 (7), 116.5 (11), 114.3 (9), 90.3 (3), 80.8 (2), 55.4 (13), 22.3 (5), 21.5 (4), 13.7 (6).

Spectral data consistent with the literature.[335]

(3,3-Dimethylbut-1-yn-1-yl)benzene (4.20)



Prepared according to General Procedure A from iodobenzene (220 µL, mg, 1.97 mmol, 100 equiv.) and 3,3-dimethyl-1-butyne (370 µL, 3.00 mmol, 1.52 equiv.) using [Pd(dppf)]Cl_2 (14.4 mg, 19.7 µmol, 1.00 mol%). Purified by flash column chromatography (silica, hexane) to yield the desired product as a colourless oil (181 mg, 58%).

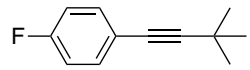


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.41 – 7.35 (m, 2H, 8, 12), 7.30 – 7.24 (m, 3H, 9–11), 1.32 (s, 9H, 1, 3, 4).

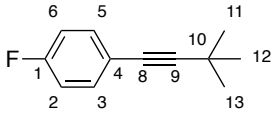
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 131.7 (8, 12), 128.3 (9, 11), 127.5 (10), 124.2 (7), 98.7 (5), 79.1 (6), 31.2 (1, 3, 4), 30.7 (2).

Spectral data consistent with the literature.[336]

1-(3,3-Dimethylbut-1-yn-1-yl)-4-fluorobenzene (4.21)



Prepared according to General Procedure A from 4-fluoroiodobezene (200 µL, 1.73 mmol, 1.00 equiv.) and 3,3-dimethyl-1-butyne (310 µL, 2.61 mmol, 1.51 equiv.). Purified by flash column chromatography (silica, 0–20% Et_2O in hexane) to yield the desired product as a pale-yellow oil (62.5 mg, 20%).



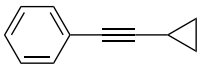
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.38 – 7.31 (m, 2H, 3, 5), 6.99 – 6.93 (m, 2H, 2, 6), 1.31 (s, 9H, 11–13).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 162.1 (d, $^1J_{CF}$ = 247.8 Hz, 1), 133.4 (d, $^3J_{CF}$ = 6.2 Hz, 3, 5), 120.2 (d, $^4J_{CF}$ = 3.5 Hz, 4), 115.4 (d, $^2J_{CF}$ = 21.9 Hz, 2, 6), 98.2 (9), 78.1 (8), 31.2 (11–13), 30.7 (10).

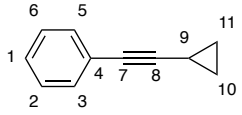
^{19}F{^{1}H} NMR (471 MHz, Chloroform-*d*) δ_F −112.7.

Spectral data consistent with the literature.[337]

(Cyclopropylethynyl)benzene (4.22)



Prepared according to General Procedure A from iodobenzene (600 µL, 5.38 mmol, 1.00 equiv.) and cyclopentylacetylene (620 µL, 7.32 mmol, 1.36 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a yellow oil (714 mg, 93%).

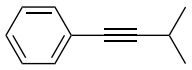


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.41 – 7.35 (m, 2H, 3, 5), 7.31 – 7.24 (m, 3H, 1, 2, 6), 1.46 (tt, *J* = 8.2, 5.1 Hz, 1H, 9), 0.90 – 0.85 (m, 2H, 10, 11), 0.81 (m, 2H, 10, 11).

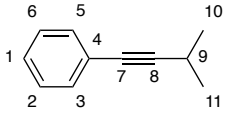
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 131.7 (3, 5), 128.3 (2, 6), 127.6 (1), 124.1 (6), 93.5 (8), 75.9 (7), 8.7 (10, 11), 0.3 (9).

Spectral data consistent with the literature.[338]

(3-Methylbut-1-yn-1-yl)benzene (**4.23**)



Prepared according to General Procedure A from iodobenzene (500 µL, 4.49 mmol, 1.00 equiv.) and 3-methylprop-1-yne (500 µL, 4.89 mmol, 1.09 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a colourless oil (581 mg, 90%).

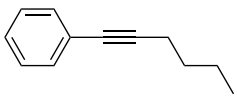


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.41 – 7.37 (m, 2H, 3, 5), 7.30 – 7.25 (m, 3H, 1, 2, 6), 2.78 (hept, *J* = 6.9 Hz, 1H, 9), 1.27 (d, *J* = 6.9 Hz, 6H, 10, 11).

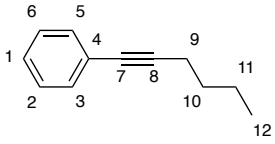
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 131.6 (3, 5), 128.3 (2, 6), 127.6 (1), 124.1 (4), 95.9 (8), 79.8 (7), 23.2 (10, 11), 21.3 (9).

Spectral data consistent with the literature.[339]

Hex-1-yn-1-ylbenzene (**4.24**)



Prepared according to General Procedure A from iodobenzene (500 µL, 4.49 mmol, 1.00 equiv.) and 1-hexyne (610 µL, 5.31 mmol, 1.18 equiv.). Purified by flash column chromatography (silica, 0–5% EtOAc in hexane) to yield the desired product as a yellow oil (668 mg, 94%).

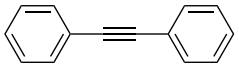


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.41 – 7.38 (m, 2H, 3, 5), 7.30 – 7.24 (m, 3H, 1, 2, 6), 2.41 (t, *J* = 7.1 Hz, 2H, 9), 1.64 – 1.56 (m, 2H, 10), 1.53 – 1.45 (m, 2H, 11), 0.95 (t, *J* = 7.3 Hz, 3H, 12).

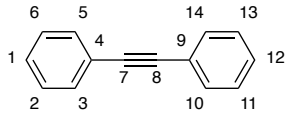
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 131.7 (3, 5), 128.3 (2, 6), 127.6 (1), 124.2 (4), 90.6 (8), 80.7 (7), 31.0 (10), 22.2 (11), 19.2 (9), 13.8 (12).

Spectral data consistent with the literature.[340]

1,2-Diphenylethyne (**4.25**)



Prepared according to General Procedure A from iodobenzene (500 µL, 4.49 mmol, 1.00 equiv.) and phenylacetylene(750 µL, 5.25 mmol, 1.17 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a white solid that turns orange on extended exposure to air (719 mg, 90%).

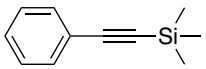


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.54 (m, 3, 5, 10, 14), 7.40 – 7.30 (m, 6H, 1, 2, 6, 11, 12, 13).

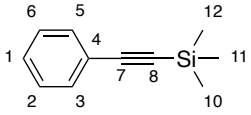
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 131.8 (3, 5, 10, 14), 128.5 (2, 6, 11, 13), 128.4 (1, 12), 123.4 (4, 9), 89.5 (7, 8).

Spectral data consistent with the literature.[339]

Trimethyl(phenylethynyl)silane (**4.26**)



Prepared according to General Procedure A from iodobenzene (500 µL, 4.49 mmol, 1.00 equiv.) and trimethylsilylacetylene (1.00 mL, 7.08 mmol, 1.58 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a yellow oil (705 mg, 90%).

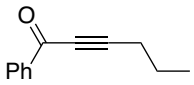


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.50 – 7.44 (m, 2H, 2, 6), 7.33 – 7.26 (m, 3H, 1, 3, 5), 0.26 (s, 9H, 10, 11, 12).

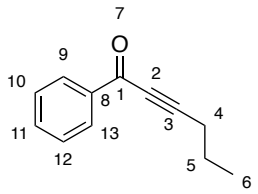
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 132.1 (2, 6), 128.6 (1), 128.3 (3, 5), 123.2 (4), 105.2 (7), 94.2 (8), 0.1 (10, 11, 12).

Spectral data consistent with the literature.[342]

1-Phenylhex-2-yn-1-one (**4.27**)



Prepared according to General Procedure A from benzoyl chloride (230 µL, 1.98 mmol, 1.00 equiv.) and 1-pentyne (300 µL, 3.05 mmol, 1.54 equiv.). Purified by flash column chromatography (silica, 0–20% Et_2O in hexane) to yield the desired product as a pale-yellow oil (293 mg, 86%).

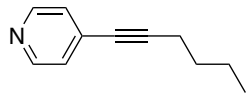


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 8.19 – 8.10 (m, 2H, 9, 13), 7.63 – 7.57 (m, 1H, 11), 7.48 (m, 2H, 10, 12), 2.49 (t, *J* = 7.0 Hz, 2H, 4), 1.72 (m, 2H, 5), 1.09 (t, *J* = 7.4 Hz, 3H, 6).

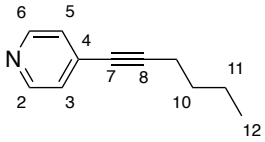
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 178.4 (1), 137.1 (8), 134.0 (11), 129.7 (9, 13), 128.6 (10, 12), 96.8 (3), 79.9 (2), 21.5 (5), 21.3 (4), 13.8 (6).

Spectral data consistent with the literature.[343]

4-(Hex-1-yn-1-yl)pyridine)benzene (**4.28**)



Prepared according to General Procedure A from 4-iodopyridine (919 mg, 4.49 mmol, 1.00 equiv.) and 1-hexyne (700 µL, 6.10 mmol, 1.36 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a dark yellow oil (580 mg, 81%).

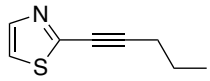


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 8.56 – 8.47 (m, 2H, 3, 5), 7.25 – 7.23 (m, 2H, 2, 6), 2.43 (t, *J* = 7.1 Hz, 2H, 9), 1.64 – 1.55 (m, 2H, 10), 1.53 – 1.42 (m, 2H, 11), 0.95 (t, *J* = 7.3 Hz, 3H, 12).

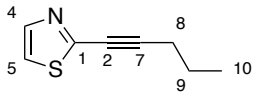
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 149.7 (3, 5), 132.5 (4), 126.0 (2, 6), 96.2 (8), 78.5 (7), 30.6 (10), 22.2 (11), 19.3 (9), 13.7 (12).

Spectral data consistent with the literature.[344]

2-(Pent-1-yn-1-yl)thiazole (**4.29**)



Prepared according to General Procedure A from 2-bromothiazole (328 mg, 2.00 mmol, 1.00 equiv.) and 1-pentyne (300 µL, 3.04 mmol, 1.52 equiv.) using [Pd(dppf)]Cl_2 (14.6 mg, 20.0 µmol, 1.00 mol%). Purified by flash column chromatography (silica, 0–20% Et_2O in hexane) to yield the desired product as a pale-yellow oil (307 mg, >99%).

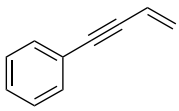


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.76 (d, *J* = 3.4 Hz, 1H, 4), 7.26 (d, *J* = 2.1 Hz, 1H, 5), 2.44 (t, *J* = 7.1 Hz, 2H, 8), 1.72 – 1.62 (m, 2H, 9), 1.05 (t, *J* = 7.4 Hz, 3H, 10).

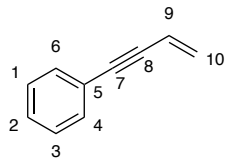
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 149.7 (1), 143.2 (4), 119.9 (5), 96.4 (7), 74.3 (2), 21.7 (9), 21.6 (8), 13.7 (10).

Spectral data consistent with the literature.[335]

But-3-en-1-yn-1-ylbenzene (**4.30**)



Prepared according to General Procedure A from phenylacetylene (550 µL, 5.00 mmol, 1.00 equiv.) and vinyl bromide solution (1.0 M in THF, 5.50 mL, 5.50 mmol, 1.10 equiv.). Purified by flash column chromatography (silica, 0–10% EtOAc in hexane) to yield the desired product as a yellow oil (652 mg, >99%).

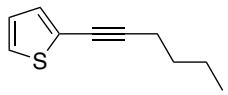


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.53 – 7.46 (m, 2H, 4, 6), 7.38 – 7.32 (m, 3H, 1–3), 6.06 (dd, *J* = 17.5, 11.1 Hz, 1H, 9), 5.77 (dd, *J* = 17.5, 2.1 Hz, 1H, 10), 5.58 (dd, *J* = 11.1, 2.1 Hz, 1H, 10).

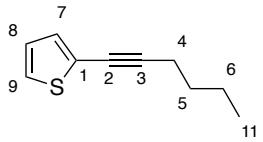
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 131.6 (4, 6), 128.3 (1, 3), 128.3 (2), 126.9 (10), 123.2 (5), 117.2 (9), 90.0 (7), 88.1 (8).

Spectral data consistent with the literature.[345]

2-(Hex-1-yn-1-yl)thiophene (**4.31**)



Prepared according to General Procedure A from 2-iodothiophene (220 µL, 1.99 mmol, 1.00 equiv.) and 1-hexyne (300 µL, 2.61 mmol, 1.31 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as an orange oil (334 mg, >99%).

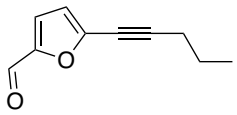


^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.16 (dd, *J* = 5.2, 1.2 Hz, 1H, 8), 7.11 (dd, *J* = 3.6, 1.2 Hz, 1H, 7), 6.93 (dd, *J* = 5.2, 3.6 Hz, 1H, 9), 2.43 (t, *J* = 7.1 Hz, 2H, 4), 1.65 – 1.53 (m, 2H, 5), 1.47 (m, 2H, 6), 0.94 (t, *J* = 7.3 Hz, 3H, 11).

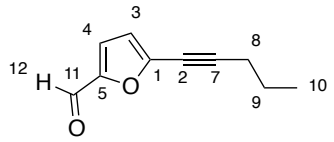
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 131.0 (7), 126.9 (9), 126.0 (8), 124.4 (1), 94.7 (3), 73.7 (2), 30.8 (5), 22.2 (6), 19.5 (4), 13.8 (11).

Spectral data consistent with the literature.[346, 347]

5-(Pent-1-yn-1-yl)furan-2-carbaldehyde (**4.32**)



Prepared according to General Procedure A from 5-bromo-2-furaldehyde (350 mg, 2.00 mmol, 1.00 equiv.) and 1-pentyne (300 µL, 3.04 mmol, 1.52 equiv.) using [Pd(dppf)]Cl_2 (14.6 mg, 20.0 µmol, 1.00 mol%). Purified by flash column chromatography (silica, 0–20% Et_2O in hexane) to yield the desired product as a red solid (350 mg, 95%).



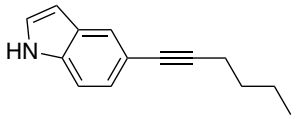
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 9.58 (s, 1H, 12), 7.19 (d, *J* = 3.7 Hz, 1H, 4), 6.59 (d, *J* = 3.6 Hz, 1H, 3), 2.44 (t, *J* = 7.0 Hz, 2H, 8), 1.65 (m, 2H, 9), 1.04 (t, *J* = 7.1 Hz, 3H, 10).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 177.3 (11), 152.0 (5), 142.7 (1), 121.6 (4), 116.0 (3), 98.9 (7), 70.6 (2), 21.7 (9), 21.6 (8), 13.7 (10).

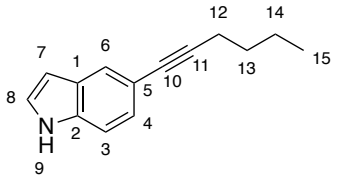
IR (ATR, film): 1659, 1503, 1387, 1275, 1028, 1011, 963, 812, 743 cm^{-1}.

HRMS (ESI): Calculated for 163.0754 *m*/*z*, found 163.0753 *m*/*z* $[C_{10}H_{10}O_2+H]^+$.

5-(Hex-1-yn-1-yl)-1*H*-indole (**4.33**)



Prepared according to General Procedure A from 5-iodoindole (486 mg, 2.00 mmol, 1.00 equiv.) and 1-hexyne (300 µL, 2.61 mmol, 1.31 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a pale-yellow oil (363 mg, 92%).



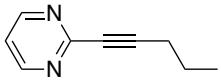
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 8.14 (s, 1H, 9), 7.72 (m, 1H, 6), 7.30 (m, 1H, 8), 7.24 (dd, *J* = 8.4, 1.5 Hz, 1H, 7), 7.20 (m, 1H, 4), 6.51 (m, 1H, 3), 2.43 (t, *J* = 7.1 Hz, 2H, 12), 1.65 – 1.58 (m, 2H, 13), 1.54 – 1.46 (m, 2H, 14), 0.96 (t, *J* = 7.3 Hz, 3H, 15).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 135.2 (1), 127.9 (2), 125.9 (4), 124.9 (7), 124.4 (6), 115.4 (5), 111.0 (8), 102.9 (3), 87.7 (11), 81.8 (10), 31.3 (13), 22.2 (14), 19.3 (12), 13.8 (15).

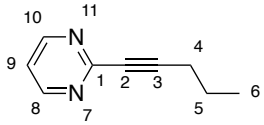
IR (ATR, neat): 3416, 1466, 1414, 1310, 882, 806, 762, 723, 602, 415 cm^{-1}.

HRMS (ESI): Calculated for 198.1277 *m*/*z*, found 198.1286 *m*/*z* $[C_{14}H_{15}N+H]^+$.

2-(Pent-1-yn-1-yl)pyrimidine (**4.34**)



Prepared according to General Procedure A from 2-bromopyrimidine (318 mg, 2.00 mmol, 1.00 equiv.) and 1-pentyne (300 µL, 3.04 mmol, 1.52 equiv.) using $[Pd(dppf)]Cl_2$ (14.6 mg, 20.0 µmol, 1.00 mol%). Purified by flash column chromatography (silica, 0–20% Et_2O in hexane) to yield the desired product as a brown solid (139 mg, 47%).

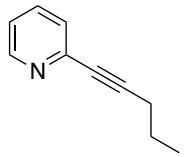


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 8.68 (d, *J* = 4.9 Hz, 2H, 8, 10), 7.19 (t, *J* = 4.9 Hz, 1H, 9), 2.44 (t, *J* = 7.1 Hz, 2H, 4), 1.68 (m, 2H, 5), 1.06 (t, *J* = 7.4 Hz, 3H, 6).

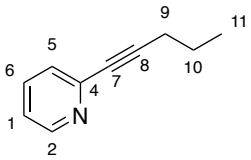
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 157.3 (8, 10), 153.5 (1), 119.6 (9), 90.8 (3), 80.2 (2), 21.7 (5), 21.4 (4), 13.8 (6).

Spectral data consistent with the literature.[348]

2-(Pent-1-yn-1-yl)pyridine (**4.35**)



Prepared according to General Procedure A from 2-bromopyridine (480 µL, 5.00 mmol, 1.00 equiv.) and 1-pentyne (640 µL, 6.49 mmol, 1.30 equiv.). Purified by flash column chromatography (silica, 0–15% EtOAc in hexane) to yield the desired product as a brown oil (505 mg, 70%).

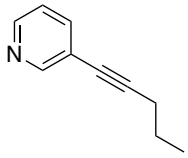


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 8.54 (m, 1H, 2), 7.61 (m, 1H, 6), 7.37 (m, 1H, 5), 7.18 (m, 1H, 1), 2.50 – 2.37 (m, 2H, 9), 1.73 – 1.61 (m, 2H, 10), 1.13 – 1.03 (m, 3H, 11).

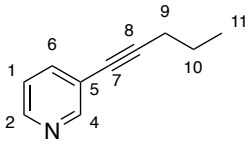
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 149.8 (2), 144.0 (4), 136.0 (6), 126.8 (5), 122.2 (1), 90.9 (8), 80.5 (7), 21.9 (10), 21.3 (9), 13.6 (11).

Spectral data consistent with the literature.[349]

3-(Pent-1-yn-1-yl)pyridine (**4.36**)



Prepared according to modified General Procedure A from 3-bromopyridine (490 µL, 5.01 mmol, 1.00 equiv.) and 1-pentyne (600 µL, 6.09 mmol, 1.21 equiv.) in diisopropylamine (6.00 mL, 800 mM) at 80 ºC. Purified by flash column chromatography (silica, 0–10% EtOAc in hexane) to yield the desired product as a brown oil (548 mg, 75%).

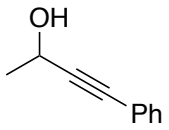


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 8.67 – 8.63 (m, 1H, 4), 8.50 (dd, J = 4.9, 1.7 Hz, 1H, 2), 7.69 (m, 1H, 6), 7.26 – 7.18 (m, 1H, 1), 2.43 (t, J = 7.0 Hz, 2H, 9), 1.67 (m, 2H, 10), 1.08 (t, J = 7.4 Hz, 3H, 11).

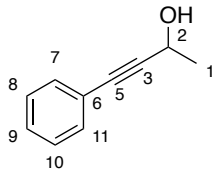
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 152.4 (4), 147.9 (2), 138.4 (6), 122.9 (5), 121.2 (1), 93.9 (8), 77.5 (7), 22.0 (10), 21.4 (9), 13.6 (11).

Spectral data consistent with the literature.[321]

4-Phenylbut-3-yn-2-ol (**4.37**)



Prepared according to General Procedure A from iodobenzene (590 µL, 4.47 mmol, 1.00 equiv.) and but-3-yn-2-ol (510 µL, 6.70 mmol, 1.50 equiv.). Purified by flash column chromatography (silica, 0–20% EtOAc in hexane) to yield the desired product as an orange oil (652 mg, >99%).

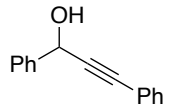


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.50 – 7.41 (m, 2H, 7, 11), 7.37 – 7.30 (m, 3H, 8–10), 4.79 (q, *J* = 6.6 Hz, 1H, 2), 1.58 (d, *J* = 6.5 Hz, 3H, 1).

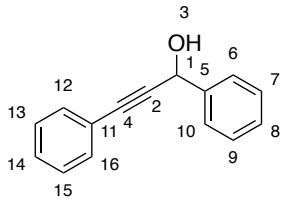
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 131.7 (7, 11), 128.4 (9), 128.3 (8, 10), 122.6 (6), 90.9 (3), 84.1 (5), 58.9 (2), 24.4 (1).

Spectral data consistent with the literature.[350]

1,3-Diphenylprop-2-yn-1-ol (**4.38**)



Prepared according to General Procedure A from iodobenzene (500 µL, 4.47 mmol, 1.00 equiv.) and 1-phenylprop-2-yn-1-ol (709 mg, 5.36 mmol, 1.20 equiv.). Purified by flash column chromatography (silica, 0–20% EtOAc in hexane) to yield the desired product as an orange oil (930 mg, >99%).

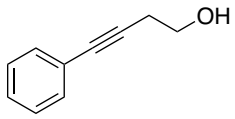


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.65 (dd, *J* = 7.4, 1.7 Hz, 2H, 6, 10), 7.55 – 7.48 (m, 2H, 12, 16), 7.44 (dd, *J* = 8.3 6.6 Hz, 2H, 7, 9), 7.41 – 7.32 (m, 4H, 8, 13–15), 5.73 (s, 1H, 1), 2.28 (s, 1H, 3).

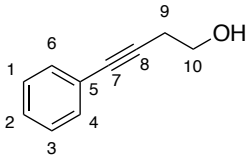
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 140.7 (5), 131.8 (12, 16), 128.7 (7, 9), 128.6 (8), 128.5 (14), 128.3 (13, 15), 126.8 (6, 10), 122.4 (11), 88.7 (2), 86.7 (4), 65.2 (1).

Spectral data consistent with the literature.[351]

4-Phenylbut-3-yn-1-ol (4.39)



Prepared according to General Procedure A from but-3-yn-1-ol (650 µg, 8.58 mmol, 1.59 equiv.) and iodobenzene (500 µL, 5.40 mmol, 1.00 equiv.). Purified by flash column chromatography (silica, 0–5% EtOAc in hexane) to yield the desired product as an orange oil (619 mg, 78%).

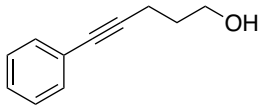


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.47 – 7.41 (m, 2H, 4, 6), 7.35 – 7.30 (m, 3H, 1, 2, 3), 3.84 (t, *J* = 6.3 Hz, 2H, 10), 2.72 (t, *J* = 6.2 Hz, 2H, 9), 1.81 (brs, 1H, OH).

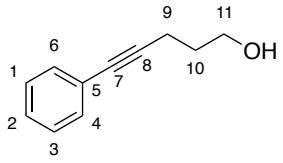
^{13}C NMR (126 MHz, Chloroform-*d*)) δ_C 131.7 (4, 6), 128.3 (1, 3), 128.0 (2), 123.3 (5), 86.3 (8), 82.5 (7), 61.2 (10), 23.9 (9).

Spectral data consistent with literature.[352]

5-Phenylpent-4-yn-1-ol (4.40)



Prepared according to General Procedure A from pent-4-yn-1-ol (750 µL, 8.04 mmol, 1.49 equiv.) and iodobenzene (500 µL, 5.40 mmol, 1.00 equiv.). Purified by flash column chromatography (silica, 0–5% EtOAc in hexane) to yield the desired product as an orange oil (615 mg, 71%).

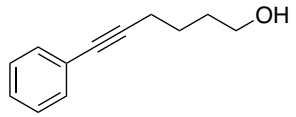


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.43 – 7.35 (m, 2H, 4, 6), 7.31 – 7.27 (m, 3H, 1, 2, 3), 3.83 (t, *J* = 6.1 Hz, 2H, 11), 2.54 (t, *J* = 6.9 Hz, 2H, 9), 1.95 – 1.79 (m, 2H, 10), 1.76 – 1.54 (brs, 1H, OH).

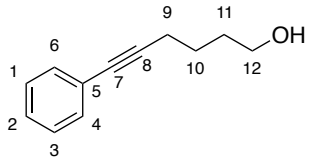
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 131.7 (4, 6), 128.4 (1, 3), 127.8 (2), 123.8 (5), 89.4 (8), 81.3 (7), 62.0 (11), 31.5 (10), 16.1 (9).

Spectral data consistent with literature.[353]

6-Phenylhex-5-yn-1-ol (4.41)



Prepared according to General Procedure A from hex-5-yn-1-ol (1.00 mL, 8.96 mmol, 1.66 equiv.) and iodobenzene (500 μL, 5.40 mmol, 1.00 equiv.). Purified by flash column chromatography (silica, 0–5% EtOAc in hexane) to yield the desired product as an orange oil (719 mg, 76%).

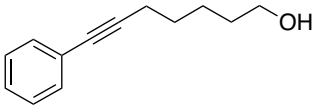


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.45 – 7.38 (m, 2H, 4, 6), 7.35 – 7.25 (m, 3H, 1, 2, 3), 3.74 (t, *J* = 6.3 Hz, 2H, 12), 2.49 (t, *J* = 6.7 Hz, 2H, 9), 1.87 – 1.68 (m, 4H, 10, 11).

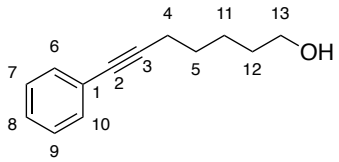
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 131.6 (4, 6), 128.2 (1, 3), 127.6 (2), 123.9 (5), 89.9 (8), 81.0 (7), 62.5 (12), 31.9 (11), 25.0 (10), 19.2 (9).

Spectral data consistent with literature.[354]

7-Phenylhept-6-yn-1-ol (4.42)



Prepared according to General Procedure A from hept-6-yn-1-ol (183 mg, 1.63 mmol, 1.00 equiv.) and iodobenzene (250 μL, 2.23 mmol, 1.37 equiv.). Purified by flash column chromatography (silica, 0–10% EtOAc in hexane) to yield desired product as an orange oil (251 mg, 82%).

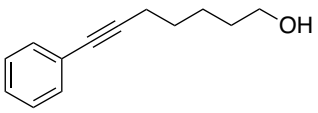


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.42 – 7.36 (m, 2H, 6, 10), 7.32 – 7.24 (m, 3H, 7–9), 3.68 (t, *J* = 6.5 Hz, 2H, 13), 2.43 (t, *J* = 7.0 Hz, 2H, 4), 1.74 – 1.58 (m, 4H, 5, 12), 1.58 – 1.47 (m, 2H, 11).

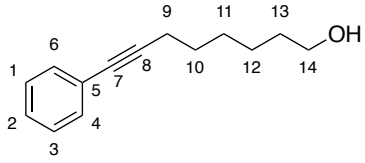
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 131.6 (6, 10), 128.2 (7, 8), 127.6 (8), 124.0 (1), 90.1 (3), 80.8 (2), 62.9 (13), 32.3 (12), 28.5 (5), 25.1 (11), 19.4 (4).

Spectral data consistent with the literature.[355]

8-Phenyloct-7-yn-1-ol (**4.43**)



Prepared according to General Procedure A from oct-7-yn-1-ol (820 mg, 6.50 mmol, 1.30 equiv.) and iodobenzene (560 µL, 5.00 mmol, 1.00 equiv.). Purified by flash column chromatography (silica, 0–20% EtOAc in hexane) to yield desired product as an orange oil (698 mg, 69%).



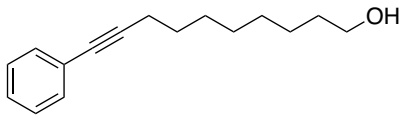
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.43 – 7.34 (m, 2H, 4, 6), 7.30 – 7.21 (m, 3H, 1–3), 3.64 (t, *J* = 6.7 Hz, 2H, 14), 2.41 (t, *J* = 7.0 Hz, 2H, 9), 1.68 – 1.53 (m, 4H, 10, 13), 1.56 – 1.33 (m, 4H, 11, 12).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 131.6 (4, 8), 128.2 (1, 3), 127.5 (2), 124.0 (5), 90.3 (8), 80.7 (7), 62.9 (14), 32.7 (13), 28.7 (10), 28.7 (11), 25.3 (12), 19.4 (9).

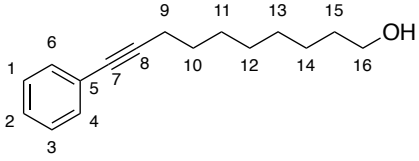
IR (ATR, film): 2932, 2857, 1489, 1441, 1071, 1055, 1028, 1003 cm^{-1}.

HRMS (ESI): Calculated for 225.1255 *m*/*z*, found 225.1251 *m*/*z* $[C_{14}H_{18}O+Na]^+$.

10-Phenyldec-9-yn-1-ol (**4.44**)



Prepared according to General Procedure A from dec-9-yn-1-ol (500 mg, 3.24 mmol, 1.00 equiv.) and iodobenzene (560 µL, 5.02 mmol, 1.55 equiv.). Purified by flash column chromatography (silica, 0–20% EtOAc in hexane) to yield desired product as an orange oil (463 mg, 62%).



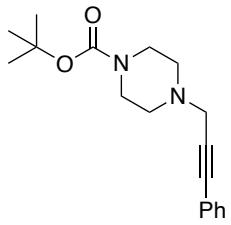
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.44 – 7.33 (m, 2H, 4, 6), 7.32 – 7.24 (m, 3H, 1–3), 3.63 (t, *J* = 6.6 Hz, 2H, 16), 2.40 (t, *J* = 7.0 Hz, 2H, 9), 1.66 – 1.51 (m, 4H, 10, 15), 1.50 – 1.26 (m, 8H, 11–14).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 131.6 (4, 6), 128.2 (1, 3), 127.5 (2), 124.1 (5), 90.4 (8), 80.6 (7), 63.0 (16), 32.8 (15), 29.3 (10), 29.1 (11), 28.9 (12), 28.7 (13), 25.7 (14), 19.4 (9).

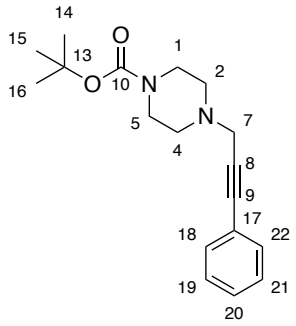
IR (ATR, film): 2928, 2855, 1489, 1441, 1069, 1028 cm^{-1}.

HRMS (ESI): Calculated for 253.1568 *m*/*z*, found 253.1565 *m*/*z* $[C_{16}H_{22}O+Na]^+$.

***tert*-Butyl 4-(3-phenylprop-2-yn-1-yl)piperazine-1-carboxylate (4.45)**



Prepared according to General Procedure A from *tert*-butyl 4-(prop-2-yn-1-yl)piperazine-1-carboxylate (159 mg, 700 µmol, 1.28 equiv.) and iodobenzene (60.0 µL, 545 µmol, 1.00 equiv.). Purified by flash column chromatography (silica, 1% NEt_3 in CH_2Cl_2) to yield the desired product as a pale-yellow oil (175.3 mg, >99%).



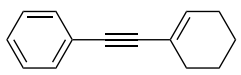
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.45 – 7.39 (m, 2H, 19, 21), 7.33 – 7.27 (m, 3H, 18, 20, 22), 3.53 (s, 2H, 7), 3.50 (m, 4H, 1, 5), 2.61 – 2.56 (m, 4H, 2, 4), 1.46 (s, 9H, 14-16).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 154.8 (10), 131.7 (19, 21), 128.3 (18, 22), 128.2 (20), 123.0 (17), 85.6 (9), 84.0 (8), 79.7 (13), 51.9 (2, 4), 47.9 (7), 46.3 (1, 5), 28.4 (14-16.

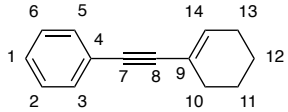
IR (ATR, film): 1695, 1420, 1366, 1246, 1171, 1123, 1107, 756 cm^{-1}.

HRMS (ESI): Calculated for 301.1911 *m*/*z*, found 301.1922 *m*/*z* $[C_{18}H_{24}N_2O_2+H]^+$.

(Cyclohex-1-en-1-ylethynyl)benzene (4.46)



Prepared according to General Procedure A from iodobenzene (500 µL, 4.49 mmol, 1.00 equiv.) and 1-ethynylcyclohexene (770 µL, 6.55 mmol, 1.46 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as an orange oil (638 mg, 78%).

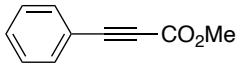


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.42 (m, 2H, 3, 5), 7.31 – 7.25 (m, 3H, 1, 2, 6), 6.22 (m, 1H, 14), 2.23 (m, 2H, 10), 2.15 (m, 2H, 13), 1.70 – 1.66 (m, 2H, 11), 1.64 – 1.61 (m, 2H, 12).

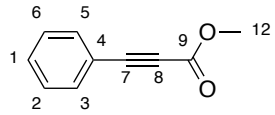
^{13}C NMR (126 MHz, Chloroform-*d*) δ_H 135.3 (14), 131.6 (3, 5), 128.4 (2, 6), 127.9 (1), 123.9 (4), 120.9 (9), 91.4 (8), 86.9 (7), 29.4 (10), 25.9 (13), 22.5 (11), 21.7 (12).

Spectral data consistent with the literature.[338]

Methyl 3-phenylpropiolate (**4.48**)



A flask was charged with phenylpropiolic acid (760 mg, 5.20 mmol, 1.00 equiv.) and methanol (10.0 mL, 520 mM). After cooling to 0 ºC, $SOCl_2$ (2.00 mL, 27.6 mmol, 5.30 equiv.) was added dropwise and the mixture was allowed to warm to RT to stir for 1 h. This solution was quenched with the addition of saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL) then the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product which was purified by flash column chromatography (silica, 0-5% EtOAc in hexane) to yield the desired product as a colourless oil (830 mg, >99%).

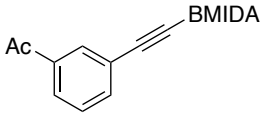


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.62 – 7.57 (m, 2H, 3, 5), 7.48 – 7.44 (m, 1H, 1), 7.41 – 7.36 (m, 2H, 2, 6), 3.84 (s, 3H, 12).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 154.6 (9), 133.2 (3, 5), 130.9 (1), 128.7 (2, 6), 119.6 (4), 86.7 (7), 80.5 (8), 53.0 (12).

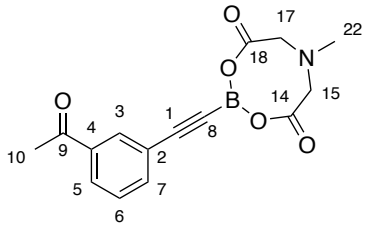
Spectral data consistent with the literature.[337, 355]

2-((3-Acetylphenyl)ethynyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4.50)



Prepared according to General Procedure A from 3-bromoacetophenone (55.0 μL, 418 μmol, 1.20 equiv.) and 2-ethynyl-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (63.0 mg, 347 mmol, 1.00 equiv.) using $Pd(dppf)Cl_2$. A modified work up procedure was used. The reaction mixture was diluted with acetone (5.0 mL), filtered through celite (washing with acetone), and concentrated *in vacuo* to yield the crude product which was purified by flash column

chromatography (silica, 0–10% MeCN in CH_2Cl_2) to yield the desired product as a white solid (95.0 mg, 91%).



^{1}H NMR (500 MHz, Acetone-*d*$_6$) δ_H 8.08 (m, 1H, 3), 8.00 (ddd, *J* = 7.8, 1.8, 1.2 Hz, 1H, 7), 7.74 (m, 1H, 5), 7.55 (m, 1H, 6), 4.37 (d, *J* = 17.0 Hz, 2H, 15, 17), 4.22 (d, *J* = 16.9 Hz, 2H, 15, 17), 3.37 (s, 3H, 22), 2.62 (s, 3H, 10).

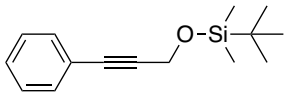
^{13}C NMR (126 MHz, Acetone-*d*$_6$) δ_C 196.5 (9), 167.7 (14, 18), 137.5 (4), 135.7 (5), 131.3 (3), 128.9 (6), 128.3 (7), 123.6 (2), 98.6 (1), 61.5 (15, 17), 47.7 (22), 25.9 (10).

^{11}B NMR (96 MHz, Acetone-*d*$_6$) δ_B 6.6.

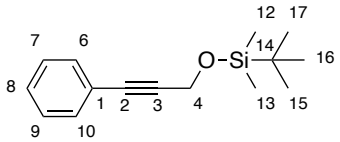
IR (ATR, solid): 1767, 1682, 1275, 1223, 1098, 1069, 1024, 1009, 993, 959 cm^{-1}.

HRMS (ESI): Calculated for 300.1038 *m*/*z*, found 300.1035 *m*/*z* $[C_{15}H_{14}BNO_5+H]^+$.

***tert*-Butyldimethyl((3-phenylprop-2-yn-1-yl)oxy)silane (4.64)**



A flask was charged with imidazole (205 mg, 3.01 mmol, 1.50 equiv.) and *tert*-butyldimethylchlorosilane (453 mg, 3.01 mmol, 1.50 equiv.). CH_2Cl_2 (10 mL) was added followed by 3-phenyl-2-propyn-1-ol (250 µL, 2.01 mmol, 1.00 equiv.). The resulting mixture was allowed to stir at RT for 4 h before quenching with H_2O (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL) then the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product which was purified by flash column chromatography (silica, CH_2Cl_2) to yield the desired product as a pale-yellow oil (476 mg, 96%).



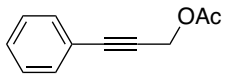
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.45 – 7.40 (m, 2H, 6, 10), 7.32 – 7.28 (m, 3H, 7–9), 4.54 (s, 2H, 4), 0.94 (s, 9H, 15, 16, 18), 0.17 (s, 6H, 12, 13).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 131.7 (6, 10), 128.4 (7, 9), 128.4 (8), 123.1 (1), 88.0 (3), 84.9 (2), 52.4 (4), 26.0 (15, 16, 18), 18.5 (14), −4.9 (12, 13).

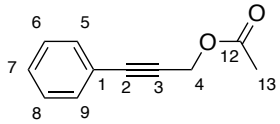
IR (ATR, neat): 1254, 1084, 833, 814, 777, 754, 689 cm^{-1}.

HRMS (ESI): Calculated for 245.1356 *m*/*z*, found 245.1354 *m*/*z* $[C_{15}H_{22}OSi–H]^+$.

3-Phenylprop-2-yn-1-yl acetate (**4.65**)



A flask was charged with DMAP (47.0 mg, 386 µmol, 8 mol%) and CH_2Cl_2 (10 mL). Acetic anhydride (700 µL, 7.42 mmol, 1.54 equiv.), NEt_3 (1.00 mL, 7.17 mmol, 1.49 equiv.), and 3-phenyl-2-propyn-1-ol (600 µL, 4.81 mmol, 1.00 equiv.) were added and the mixture was allowed to stir at RT for 4 h before quenching with dilute aqueous HCl (2.0 M, 10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product which was purified by flash column chromatography (silica, CH_2Cl_2) to yield the desired product as a yellow oil (849 mg, >99%).

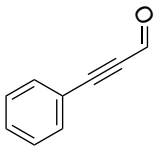


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.50 – 7.42 (m, 2H, 5, 9), 7.38 – 7.28 (m, 3H, 6–8), 4.91 (s, 2H, 4), 2.13 (s, 3H, 13).

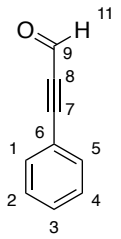
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 170.5 (12), 132.0 (5, 9), 128.9 (7), 128.4 (6, 8), 122.3 (1), 86.6 (2), 83.0 (3), 53.0 (4), 21.0 (13).

Spectral data consistent with the literature.[356]

3-Phenylpropiolaldehyde (**4.66**)



A flask was charged with 3-phenyl-2-propyn-1-ol (1.00 mL, 8.02 mmol, 1.00 equiv.), celite (~5 g) and CH_2Cl_2 (20.0 mL, 401 mM). Pyridinium chlorochromate (3.46 g, 16.0 mmol, 2.00 equiv.) was added and the mixture was allowed to stir for 1 h before filtering through celite, (washing with CH_2Cl_2) and concentrating *in vacuo* in the presence of silica. This was immediately transferred to a chromatographic column and the desired product was obtained after purification by flash column chromatography (silica, 0–20% EtOAc in hexane) to yield the desired product as a yellow oil (400 mg, 38%).

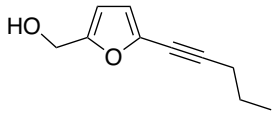


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 9.43 (s, 1H, 11), 7.63 – 7.59 (m, 2H, 1, 5), 7.52 – 7.47 (m, 1H, 3), 7.41 (dd, *J* = 8.4, 7.0 Hz, 2H, 2, 4).

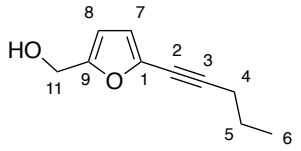
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 177.0 (9), 133.4 (1, 5), 131.5 (3), 128.9 (2, 4), 119.6 (6), 95.3 (7), 88.6 (8).

Spectral data consistent with the literature.[357]

(5-(Pent-1-yn-1-yl)furan-2-yl)methanol (**4.67**)



A flask was charged with 5-(pent-1-yn-1-yl)furan-2-carbaldehyde (174 mg, 1.07 mmol, 1.00 equiv.) and EtOH (4.0 mL). After cooling to 0 ºC, $NaBH_4$ (20.3 mg, 536 umol, 0.50 equiv.) was added and the mixture was allowed to stir for 1 h whilst coming up to RT. After this period, saturated aqueous NH_4Cl (10.0 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product. Purified by flash column chromatography (silica, 0–20% EtOAc in hexane) to yield the desired product as a pale-yellow oil (123.6 mg, 70%).



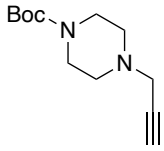
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 6.41 (d, *J* = 3.3 Hz, 1H, 7), 6.25 (d, *J* = 3.3 Hz, 1H, 8), 4.56 (s, 2H, 11), 2.41 (t, *J* = 7.1 Hz, 2H, 4), 1.82 (brs, 1H, OH), 1.62 (h, *J* = 7.3 Hz, 2H, 5), 1.03 (t, *J* = 7.4 Hz, 3H, 6).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 154.2 (9), 137.6 (1), 114.6 (7), 108.9 (8), 95.1 (3), 71.1 (2), 57.7 (11), 22.0 (5), 21.6 (4), 13.7 (6).

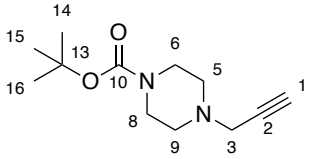
IR (ATR, film): 2963, 2934, 1190, 1011, 964, 791 cm^{-1}.

HRMS (ESI): Calculated for 165.0910 *m*/*z*, found 165.0911 *m*/*z* $[C_{10}H_{12}O_2+H]^+$.

***tert*-Butyl 4-(prop-2-yn-1-yl)piperazine-1-carboxylate** (**4.69**)



A flask was charged with K_2CO_3 (2.57 g, 18.6 mmol, 2.00 equiv.), *tert*-butyl piperazine-1-carboxylate (1.73 mg, 9.28 mmol, 1.00 equiv.), and acetone (14.0 mL, 663 mM). Propargyl bromide (80% in PhMe, 1.00 mL, 9.28 mmol, 1.00 equiv.) was added and the mixture was stirred for 16 h before filtering and concentrating *in vacuo* to yield the crude which was purified by flash column chromatography (silica, CH_2Cl_2) to yield the desired product as an orange oil (1.95 g, 94%).

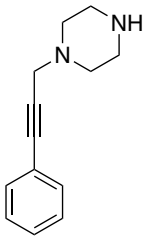


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 3.51 – 3.43 (m, 4H, 6, 8), 3.34 – 3.28 (m, 2H, 3), 2.50 (m, 4H, 5, 9), 2.25 (m, 1H, 1), 1.47 – 1.44 (m, 9H, 14–16).

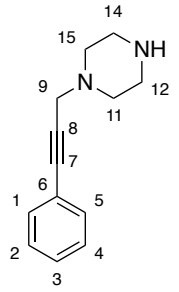
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 154.8 (10), 79.8 (13), 78.6 (2), 73.6 (1), 51.8 (5, 9), 47.1 (3), 28.6 (14–16).

Spectral data consistent with the literature.[358]

1-(3-Phenylprop-2-yn-1-yl)piperazine (**4.70**)



A flask was charged with *tert*-butyl 4-(3-phenylprop-2-yn-1-yl)piperazine-1-carboxylate (89.8 mg, 299 µmol, 1.00 equiv.) and CH_2Cl_2 (1.50 mL, 199 mM). Trifluoroacetic acid (750 µL, 9.79 mmol, 32.8 equiv.) was added and the mixture was allowed to stir for 0.5 h before concentrating *in vacuo*. Saturated aqueous $NaHCO_3$ was added until a pH of >11 was reached, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the desired product as a pale-yellow oil (38.7 mg, 65%).



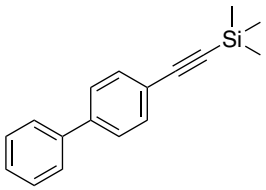
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.46 – 7.41 (m, 2H, 1, 5), 7.32 – 7.28 (m, 3H, 2–4), 3.51 (s, 2H, 9), 2.97 (brs, 4H), 2.62 (brs, 4H), 1.77 (brs, 1H, NH).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 131.9 (1, 5), 128.4 (2, 4), 128.2 (3), 123.2 (6), 85.5 (7), 84.6 (8), 53.5, 48.5 (9), 46.1.

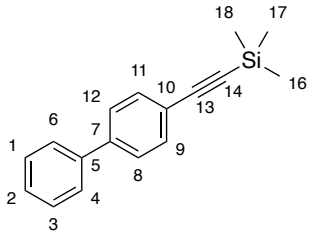
Unambiguous assignment of ^{1}H and ^{13}C NMR piperazine signals could not be performed.

Spectral data consistent with the literature.[359]

([1,1'-Biphenyl]-4-ylethynyl)trimethylsilane (4.72)



Prepared according to General Procedure A from trimethylsilylacetylene (2.7 mL, 19.2 mmol, 1.92 equiv.) and 4-bromobiphenyl (2.33 g, 10.0 mmol, 1.00 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a white solid (824 mg, 33%).

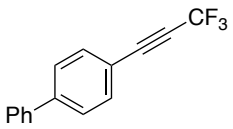


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.64 – 7.59 (m, 2H, 4, 6), 7.56 (m, 4H, 8, 9, 11, 12), 7.47 (dd, *J* = 8.5, 6.9 Hz, 2H, 1, 3), 7.41 – 7.34 (m, 1H, 2), 0.29 (s, 9H, 16–18).

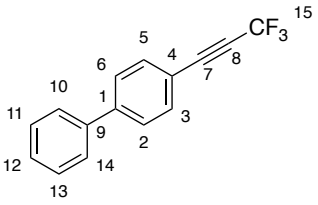
^{13}C NMR (126 MHz, Chloroform-*d*)) δ_C 141.2 (7), 140.3 (5), 132.4 (9, 11), 128.9 (1, 3), 127.7 (2), 127.0 (4, 6), 126.9 (8, 12), 122.0 (10), 105.0 (13), 94.9 (14), 0.0 (16–18).

Spectral data consistent with literature.[360]

4-(3,3,3-Trifluoroprop-1-yn-1-yl)-1,1'-biphenyl (4.73)



A flask was charged with TMEDA (940 µL, 6.25 mmol, 1.50 equiv.), K_2CO_3 (1.73 g, 12.50 mmol, 3.0 equiv.), CuI (1.19 g, 6.25 mmol, 1.50 equiv.), and DMF (40 mL) then stirred under air for 15 mins before trimethyl(trifluoromethyl)silane (1.50 mL, 10.1 mmol, 2.43 equiv.) was added. The mixture was allowed to stir for 5 mins before cooling to 0 ºC and adding a solution of 4-ethynyl-1,1'-biphenyl (743 mg, 4.17 mmol, 1.00 equiv.) and trimethyl(trifluoromethyl)silane (1.50 mL, 10.1 mmol, 2.43 equiv.) in DMF (40.0 mL). This mixture was stirred for 40 mins at 0 ºC before allowing to warm to RT and stirred for 24 h. H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 × 20 mL), and the combined organic phases were combined, washed with H_2O (10 mL), brine (10 mL), then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude product which was purified by flash column chromatography (silica, hexane) to yield the desired product as a pale-yellow solid (413 mg, 40%).



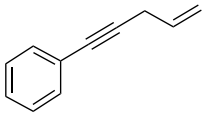
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.66 (m, 4H, 2, 3, 5, 6), 7.64 – 7.59 (m, 2H, 10, 14), 7.53 – 7.45 (m, 2H, 11, 13), 7.45 – 7.40 (m, 1H, 12).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.8 (1), 139.8 (9), 133.4 (3, 5), 129.1 (11, 13), 128.4 (12), 127.4 (10, 14), 127.3 (2, 6), 117.3 (q, $^4J_{CF}$ = 1.3 Hz, 4), 115.0 (q, $^1J_{CF}$ = 256.7 Hz, 15), 86.7 (q, $^3J_{CF}$ = 6.4 Hz, 7), 76.3 (q, $^2J_{CF}$ = 52.6 Hz, 8).

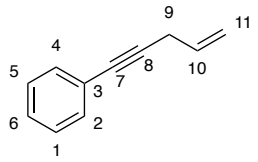
^{19}F{^{1}H} NMR (470 MHz, Chloroform-*d*) δ_F −49.7.

Spectral data consistent with literature.[361]

Pent-4-en-1-yn-1-ylbenzene (**4.75**)



A microwave vial was charged with CuI (38.1 mg, 200 µmol, 10 mol%), Na_2SO_3 (126 mg, 1.00 mmol, 50 mol%), and K_2CO_3 (276 mg, 2.00 mmol, 1.00 equiv.) then evacuated and backfilled with N_2 before DMF (10.0 mL) was added. Phenylacetylene (220 µL 2.00 mmol, 1.00 equiv.), DBU (56.0 µL, 400 µmol, 20 mol%), and allyl bromide (260 µL, 3.00 mmol, 1.50 equiv.) were added and the mixture was allowed to stir for 16 h at RT. Dilute aqueous HCl (2.0 M, 10 mL) was added and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product. Purified by flash column chromatography (silica, hexane) to yield the desired product as a colourless oil (273 mg, 96%).

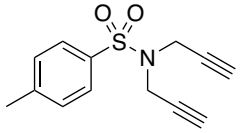


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.50 – 7.40 (m, 2H, 2, 4), 7.40 – 7.29 (m, 3H, 1, 5, 6), 5.93 (ddt, *J* = 17.0, 10.0, 5.4 Hz, 1H, 10), 5.44 (m, 1H, 11), 5.20 (m, 1H, 11), 3.23 (m, 2H, 9).

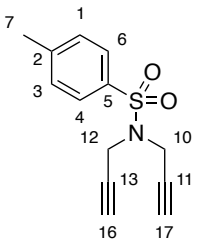
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 132.5 (10), 131.6 (2, 4), 128.2 (1, 5), 127.8 (6), 123.7 (3), 116.3 (11), 86.6 (8), 82.9 (7), 23.7 (9).

Spectral data consistent with the literature.[362]

4-Methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (4.76)



Prepared according to General Procedure B from *p*-toluenesulfonamide (5.00 g, 29.2 mmol, 1.00 equiv.) and propargyl bromide (80% in PhMe, 7.00 mL 65.0 mmol, 2.22 equiv.). Purified by flash column chromatography (silica, CH_2Cl_2) to yield the desired product as a yellow solid (7.16 g, 99%).

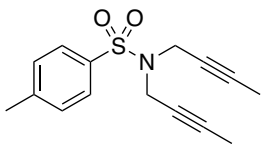


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.75 – 7.66 (m, 2H, 4, 6), 7.30 (d, *J* = 8.0 Hz, 2H, 1, 3), 4.17 (d, *J* = 2.4 Hz, 4H, 10, 12), 2.43 (s, 3H, 7), 2.15 (t, *J* = 2.4 Hz, 2H, 16, 17).

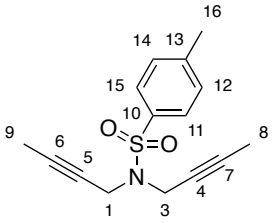
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 144.0 (2), 135.2 (5), 129.6 (1, 3), 127.9 (4, 6), 76.1 (11, 13), 74.0 (16, 17), 36.2 (10, 12), 21.6 (7).

Spectral data consistent with the literature.[363]

***N*,*N*-Di(but-2-yn-1-yl)-4-methylbenzenesulfonamide (4.77)**



Prepared according to General Procedure B from *p*-toluenesulfonamide (342 mg, 2.00 mmol, 1.00 equiv.) and 1-bromo-2-butyne (500 µL, 5.72 mmol, 2.86 equiv.). Purified by flash column chromatography (silica, CH_2Cl_2) to yield the desired product as a yellow solid (545 mg, 99%).

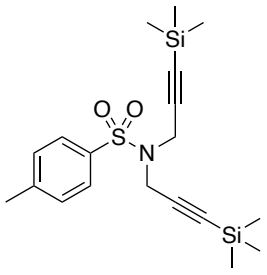


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.73 – 7.69 (m, 2H, 11, 15), 7.30 – 7.27 (m, 2H, 12, 14), 4.06 (q, *J* = 2.3 Hz, 4H, 1, 3), 2.41 (s, 3H, 16), 1.64 (t, *J* = 2.4 Hz, 6H, 8, 9).

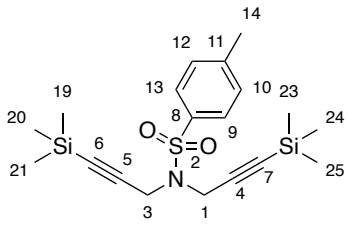
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.6 (13), 135.7 (10), 129.3 (12, 14), 128.2 (11, 15), 81.8 (6, 7), 71.8 (4, 5), 36.8 (1, 3), 21.6 (16), 3.5 (8, 9).

Spectral data consistent with the literature.[364]

4-Methyl-*N*,*N*-bis(3-(trimethylsilyl)prop-2-yn-1-yl)benzenesulfonamide (4.78)



Prepared according to General Procedure B from *p*-toluenesulfonamide (171 mg, 1.00 mmol, 1.00 equiv.) and 3-bromo-1-(trimethylsilyl)-1-propyne (500 µL, 3.06 mmol, 3.06 equiv.). Purified by flash column chromatography (silica, CH_2Cl_2) to yield the desired product as a white solid (337 mg, 86%).

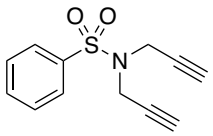


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.70 (d, *J* = 8.0 Hz, 2H, 9, 13), 7.29 (d, *J* = 8.1 Hz, 2H, 10, 12), 4.15 (s, 4H, 1, 3), 2.42 (s, 3H, 14) 0.06 (s, 18H, 19–21, 23–25).

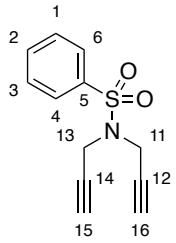
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (11), 135.4 (8), 129.6 (10, 12), 127.9 (9, 13), 97.7 (4, 5), 91.0 (6, 7), 37.2 (1, 3), 21.6 (14), –0.3 (19-21, 23-25).

Spectral data consistent with the literature.[365]

***N*,*N*-Di(prop-2-yn-1-yl)benzenesulfonamide (4.79)**



Prepared according to General Procedure B from benzenesulfonamide (786 mg, 5.00 mmol, 1.00 equiv.) and propargyl bromide (80% in toluene, 1.20 mL, 11.2 mmol, 2.24 equiv.). Purified by flash column chromatography (silica, CH_2Cl_2) to yield the desired product as a yellow solid (342 mg, 46%).

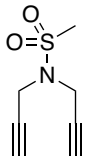


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.88 – 7.84 (m, 2H, 4, 6), 7.65 – 7.59 (m, 1H, 2), 7.56 – 7.51 (m, 2H, 1, 3), 4.21 (d, *J* = 2.4 Hz, 4H, 11, 13), 2.16 (t, *J* = 2.4 Hz, 2H, 15, 16).

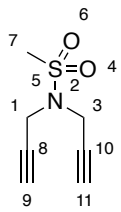
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 138.2 (5), 133.1 (2), 129.0 (1, 3), 127.8 (4, 6), 76.0 (12, 14), 74.1 (15, 16), 36.2 (11, 13).

Spectral data consistent with the literature.[366]

***N*,*N*-Di(prop-2-yn-1-yl)methanesulfonamide (4.80)**



Prepared according to General Procedure B from methanesulfonamide (190 mg, 2.00 mmol, 1.00 equiv.) and propargyl bromide (80% in PhMe, 520 µL, 6.04 mmol, 3.02 equiv.). Purified by flash column chromatography (silica, CH_2Cl_2) to yield the desired product as a yellow solid (342 mg, 46%).

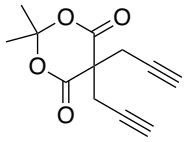


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 4.19 (d, *J* = 2.5 Hz, 4H, 1, 3), 2.98 (s, 3H, 7), 2.39 (t, *J* = 2.4 Hz, 2H, 9, 11).

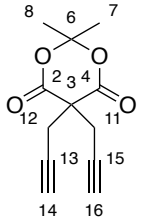
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 76.7 (8, 10), 74.7 (9, 11), 38.7 (7), 36.6 (1, 3).

Spectral data consistent with the literature.[367]

2,2-Dimethyl-5,5-di(prop-2-yn-1-yl)-1,3-dioxane-4,6-dione (4.81)



Prepared according to General Procedure B from Meldrum's acid (600 mg, 4.16 mmol, 1.00 equiv.) and propargyl bromide (80% in PhMe, 1.00 mL, 9.28 mmol, 2.23 equiv.) in acetone (20 mL). Purified by flash column chromatography (silica, CH_2Cl_2) to yield the desired product as a pale-yellow solid (509 mg, 55%).

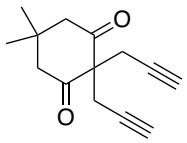


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 2.91 (d, J = 2.7 Hz, 4H, 11, 12), 2.21 (t, J = 2.6 Hz, 2H, 14, 16), 1.87 (s, 6H, 7, 8).

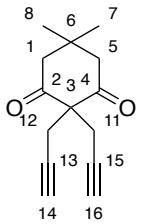
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 167.0 (2, 4), 107.0 (6), 77.3 (13, 15), 73.6 (14, 16), 53.4 (3), 30.0 (7, 8), 27.8 (11, 12).

Spectral data consistent with the literature.[368]

5,5-Dimethyl-2,2-di(prop-2-yn-1-yl)cyclohexane-1,3-dione (4.82)



Prepared according to General Procedure B from dimedone (1.00 g, 7.13 mmol, 1.00 equiv.) and propargyl bromide (80% in PhMe, 1.70 mL, 15.8 mmol, 2.21 equiv.) in acetone (35 mL). Purified by flash column chromatography (silica, CH_2Cl_2) to yield the desired product as a pale-yellow solid (1.19 g, 77%).

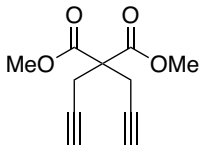


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 2.72 (s, 4H, 1, 5), 2.70 (d, J = 2.7 Hz, 4H, 11, 12), 2.10 (t, J = 2.7 Hz, 2H, 14, 16), 1.09 (s, 6H, 7, 8).

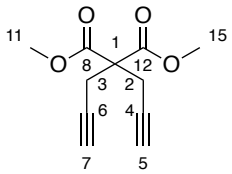
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 206.1 (2, 4), 78.9 (13, 15), 72.5 (14, 16), 65.9 (3), 52.1 (1, 5), 30.7 (6), 28.8 (7, 8), 24.2 (11, 12).

Spectral data consistent with the literature.[369]

Dimethyl 2,2-di(prop-2-yn-1-yl)malonate (4.83)



A flame-dried flask under N_2 was charged with dimethyl malonate (2.00 mL, 17.5 mmol, 1.00 equiv.), dry THF (50.0 mL), and propargyl bromide (80% in PhMe, 5.50 mL, 51.1 mmol, 2.92 equiv.) and cooled to 0 ºC. NaH (60% suspension in oil, 1.75 g, 43.7 mmol, 2.50 equiv.) was added in one portion and the reaction was allowed to stir at 0 ºC for 2 hours before coming up to RT to stir for a further 4 hours. The reaction was quenched with saturated aqueous NH_4Cl, extracted with EtOAc (5 × 20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product. Purified by flash column chromatography (silica, Et_2O) to yield the desired product as a yellow solid (3.55 g, 97%).

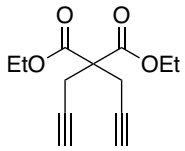


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 3.77 (s, 6H, 11, 15), 3.00 (d, J = 2.7 Hz, 4H, 2, 3), 2.03 (t, J = 2.6 Hz, 2H, 5, 7).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 169.0 (8, 12), 71.7 (4, 6), 56.5 (5, 7), 53.1 (1), 29.7 (11, 15), 22.7 (2, 3).

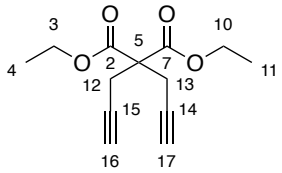
Spectral data consistent with the literature.[370]

Diethyl 2,2-di(prop-2-yn-1-yl)malonate (4.84)



A flame-dried flask was charged with diethyl malonate (3.00 mL, 19.8 mmol, 1.00 equiv.), dry THF (60.0 mL) and propargyl bromide (80% in PhMe, 6.20 mL, 57.5 mmol, 2.91 equiv.) under N_2 and cooled to 0 ºC. NaH (60% suspension in oil, 1.98 g, 49.4 mmol, 2.50 equiv.) was added in one portion and the reaction was allowed to stir at 0 ºC for 2 h before coming up to RT to stir for a further 4 h. The reaction was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (5 × 20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product. This was purified by flash column chromatography (silica, 0–5% EtOAc in hexane)

to yield the desired product as a colourless oil which solidifies on cooling into a white solid (4.67 g, 19.8 mmol, >99%).

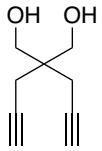


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 4.25 (q, *J* = 7.1 Hz, 4H, 3, 10), 3.01 (d, *J* = 2.7 Hz, 4H, 12, 13), 2.05 (t, *J* = 2.6 Hz, 2H, 16, 17), 1.28 (t, *J* = 7.1 Hz, 6H, 4, 11).

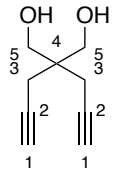
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 168.6 (2, 7), 78.5 (14, 15), 71.7 (16, 17), 62.1 (3, 10), 56.3 (5), 22.5 (12, 13), 14.0 (4, 11).

Spectral data consistent with the literature.[371]

2,2-Di(prop-2-yn-1-yl)propane-1,3-diol (**4.85**)



A flame-dried flask was charged with diethyl 2,2-di(prop-2-yn-1-yl)malonate (2.80 g, 11.9 mmol, 1.00 equiv.) and dry THF (25.0 mL) under N_2 then cooled to 0 ºC. $LiAlH_4$ (540 mg, 14.2 mmol, 1.20 equiv.) was added in one portion and the reaction was allowed to stir at 0 ºC for 16 h whilst coming up to RT. The reaction was quenched with aqueous Rochelle salt solution (10 mL), extracted with CH_2Cl_2 (5 × 20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product. This was purified by flash column chromatography (silica, 0–5% MeOH in CH_2Cl_2) to yield the desired product as a white solid (1.582 g, 88%).

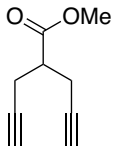


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 3.78 (d, *J* = 5.6 Hz, 4H, 5), 2.40 (d, *J* = 2.7 Hz, 4H, 3), 2.13 (brs, 2H, OH), 2.07 (t, *J* = 2.7 Hz, 2H, 1).

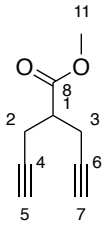
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 80.2 (2), 71.2 (1), 66.6 (5), 42.1 (4), 21.7 (3).

Spectral data consistent with the literature.[372]

Methyl 2-(prop-2-yn-1-yl)pent-4-ynoate (**4.86**)



A flask was charged with dimethyl 2,2-di(prop-2-yn-1-yl)malonate (1.61 g, 7.74 mmol, 1.00 equiv.), LiCl (984 mg, 23.2 mmol, 3.00 equiv.), H_2O (350 µmol, 19.3 mmol, 2.50 equiv.), and DMSO (17.5 mL, 445 mM). The mixture was heated to 200 ºC to stir for 1 h before allowing to cool to RT. H_2O (20 mL) was added ad the mixture was extracted with chloroform (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product which was purified by flash column chromatography (silica, 0–10% Et_2O in hexane) to yield the desired product as a yellow oil (484 mg, 38%).

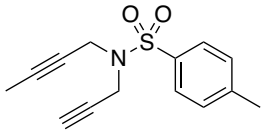


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 3.74 (s, 3H, 11), 2.78 (tt, *J* = 7.2, 6.0 Hz, 1H, 1), 2.71 – 2.58 (m, 4H, 2, 3), 2.02 (t, *J* = 2.6 Hz, 2H, 5, 7).

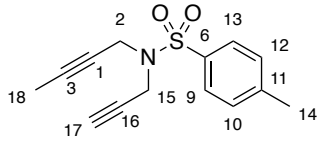
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 172.8 (8), 80.4 (4, 6), 70.5 (5, 7), 52.1 (11), 43.0 (1), 19.9 (2, 3).

Spectral data consistent with the literature.[373]

_N_-(But-2-yn-1-yl)-4-methyl-_N_-(prop-2-yn-1-yl)benzenesulfonamide (4.88)



Prepared according to General Procedure B from 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (250 mg, 1.19 mmol, 1.00 equiv.) and 1-bromobut-2-yne (160 µL, 1.83 mmol, 1.53 equiv.). Purified by flash column chromatography (silica, 0–20% EtOAc in hexane) to yield the desired product as a white solid (311 mg, >99%).

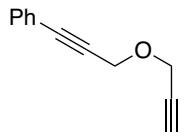


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.76 – 7.71 (m, 2H, 9, 13), 7.35 – 7.30 (m, 2H, 10, 12), 4.16 (d, *J* = 2.6, 2H, 15), 4.12 (q, *J* = 2.4, 2H, 2), 2.45 (s, 3H, 14), 2.15 (t, *J* = 2.5 Hz, 1H, 17), 1.67 (t, *J* = 2.4 Hz, 3H, 18).

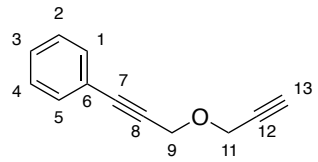
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.9 (11), 135.5 (6), 129.5 (10, 12), 128.1 (9, 13), 82.1 (3), 76.9 (16), 73.8 (17), 71.4 (1), 36.8 (2), 36.3 (15), 21.7 (14), 3.6 (18).

Spectral data consistent with literature.[374]

(3-(Prop-2-yn-1-yloxy)prop-1-yn-1-yl)benzene (**4.90**)



A flame-dried flask was charged with 3-phenyl-2-propyn-1-ol (600 µL, 4.89 mmol, 1.00 equiv.) and dried THF (25.0 mL, 196 mM) under N_2. NaH (60% suspension in oil, 235 mg, 5.87 mmol, 1.20 equiv.) was added followed by propargyl bromide (80 % in PhMe, 600 µL, 5.38 mmol, 1.10 equiv.). The resulting mixture was allowed to stir for 2 h before quenching with H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product. Purified by flash column chromatography (silica, 100% Et_2O) to yield the desired product as a yellow oil (843 mg, >99%).

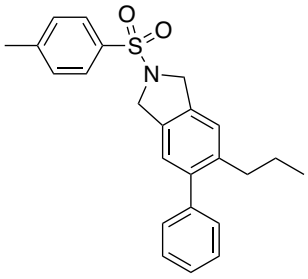


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.51 – 7.45 (m, 2H, 1, 5), 7.38 – 7.31 (m, 3H, 2–4), 4.52 (s, 2H, 9), 4.36 (d, *J* = 2.4 Hz, 2H, 11), 2.50 (t, *J* = 2.4 Hz, 1H, 13).

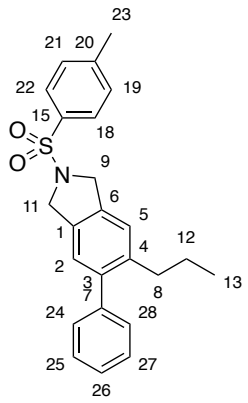
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 131.8 (2, 4), 128.6 (3), 128.3 (1, 5), 122.4 (6), 86.9 (7), 84.1 (8), 79.0 (12), 75.0 (13), 57.4 (9), 56.6 (11).

Spectral data consistent with the literature.[374]

5-Phenyl-6-propyl-2-tosylisoindoline (**4.91**)



Prepared according to General Procedure C from pent-1-yn-1-ylbenzene (14.4 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–5% Et_2O in PhMe) to yield the desired product as white solid (32.4 mg, 83%).



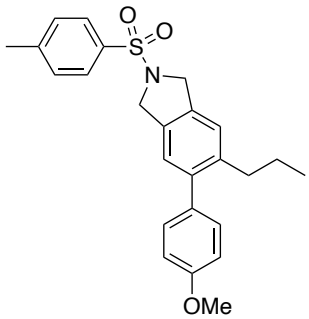
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.80 – 7.77 (m, 2H, 18, 22), 7.42 – 7.30 (m, 5H, 19, 21, 25–27), 7.23 – 7.19 (m, 2H, 24, 28), 7.09 (s, 1H, 5), 6.99 (s, 1H, 2), 4.64 (s, 2H, 11), 4.61 (m, 2H, 9), 2.52 – 2.46 (m, 2H, 8), 2.41 (s, 3H, 23), 1.46 – 1.37 (m, 2H, 12), 0.77 (t, *J* = 7.3 Hz, 3H, 13).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.8 (20), 141.9 (3), 141.6 (7), 140.3 (4), 135.4 (1), 133.9 (15), 133.6 (6), 129.9 (19, 21), 129.3 (24, 28), 128.2 (25, 27), 127.8 (18, 22), 127.1 (26), 124.2 (2), 123.3 (5), 55.8 (9), 53.8 (11), 35.2 (8), 24.6 (12), 21.7 (23), 14.1 (13).

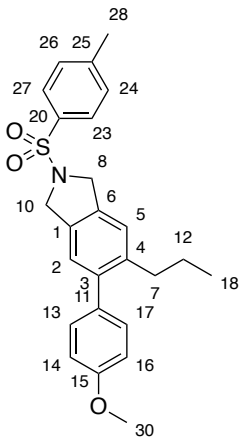
IR (ATR, film): 2957, 2926, 1344, 1161, 1098, 814, 764, 704, 665, 611, 552 cm^{-1}.

HRMS (ESI): Calculated for 392.1679 *m*/*z*, found 395.1679 *m*/*z* $[C_{24}H_{25}NO_2S+H]^+$.

5-(4-Methoxyphenyl)-6-propyl-2-tosylisoindoline (**4.92**)



Prepared according to General Procedure C from 1-methoxy-4-(pent-1-yn-1-yl)benzene (17.4 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–2% Et_2O in PhMe) to yield the desired product as white solid (40.5 mg, 96%).



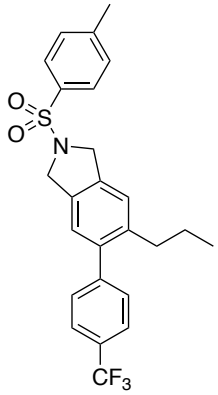
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.81 – 7.76 (m, 2H, 24, 26), 7.34 – 7.29 (m, 2H, 23, 27), 7.17 – 7.09 (m, 2H, 14, 16), 7.07 (s, 1H, 2), 6.98 (s, 1H, 5), 6.96 – 6.88 (m, 2H, 13, 17), 4.69 – 4.57 (m, 4H, 8, 10), 3.84 (s, 3H, 30), 2.55 – 2.45 (m, 2H, 7), 2.41 (s, 3H, 28), 1.54 – 1.36 (m, 2H, 12), 0.78 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 158.8 (15), 143.7 (25), 141.5 (11), 140.5 (4), 135.1 (6), 133.9 (1), 133.8 (20), 133.6 (3), 130.3 (14, 16), 129.9 (24, 26), 127.8 (23, 27), 124.3 (5), 123.2 (2), 113.6 (13, 17), 55.4 (30), 53.72 (8), 53.71 (10), 35.2 (7), 24.6 (12), 21.6 (28), 14.1 (18).

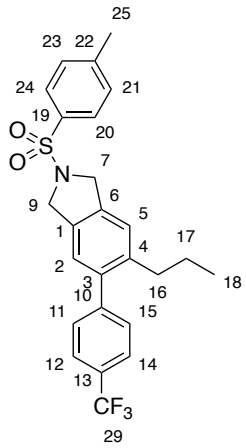
IR (ATR, film): 2957, 1607, 1344, 1294, 1246, 1163, 1099, 1061, 1034, 812, 665, 606, 550 cm^{-1}.

HRMS (ESI): Calculated for 422.1784 *m*/*z*, found 422.1775 *m*/*z* $[C_{25}H_{27}NO_3S+H]^+$.

5-Propyl-2-tosyl-6-(4-(trifluoromethyl)phenyl)isoindoline (**4.93**)



Prepared according to General Procedure C from 1-(pent-1-yn-1-yl)-4-(trifluoromethyl)benzene (21.2 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as white solid (45.0 mg, 98%).



^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.82 – 7.76 (m, 2H, 20, 24), 7.65 (d, *J* = 8.1 Hz, 2H, 12, 14), 7.33 (m, 4H, 11, 15, 21, 23), 7.11 (s, 1H, 5), 6.97 (s, 1H, 2), 4.65 (s, 2H, 7), 4.62 (s, 2H, 9), 2.49 – 2.43 (m, 2H, 16), 2.42 (s, 3H, 25), 1.47 – 1.36 (m, 2H, 17), 0.77 (t, *J* = 7.3 Hz, 3H, 18).

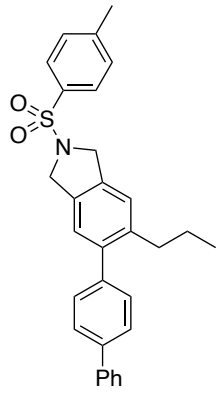
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 145.3 (10), 143.8 (22), 140.4 (4), 140.1 (19), 136.2 (1), 133.9 (6), 133.8 (3), 130.0 (11, 15), 129.7 (21, 23), 129.4 (q, $^{2}J_{CF}$ = 32.5 Hz, 13), 127.8 (20, 24), 125.2 (q,$^{3}J_{CF}$ = 3.8 Hz, 12, 14), 124.3 (q, $^{1}J_{CF}$ = 270.6 Hz, 29), 124.0 (2), 123.6 (5), 53.7 (7), 53.6 (9), 35.1 (16), 24.6 (17), 21.7 (25), 14.0 (18).

^{19}F NMR (471 MHz, Chloroform-*d*) δ −62.4.

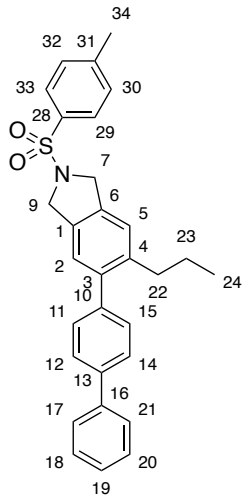
IR (ATR, film): 1346, 1323, 1161, 1123, 1105, 1065, 1018, 665, 548 cm^{-1}.

HRMS (ESI): Calculated for 460.1553 *m*/*z*, found 460.1540 *m*/*z* $[C_{25}H_{24}F_3NO_2S+H]^+$.

5-([1,1'-Biphenyl]-4-yl)-6-propyl-2-tosylisoindoline (**4.94**)



Prepared according to General Procedure C from 4-(pent-1-yn-1-yl)-1,1'-biphenyl (22.0 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as pale-blue solid (32.3 mg, 69%).



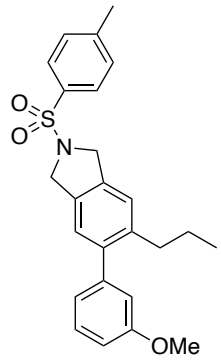
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.82 – 7.78 (m, 2H, 30, 32), 7.67 – 7.60 (m, 4H, 11, 12, 14, 15), 7.49 – 7.44 (m, 2H, 18, 20), 7.39 – 7.31 (m, 3H, 17, 19, 21), 7.31 – 7.27 (m, 2H, 29, 33), 7.11 (s, 1H, 2), 7.04 (s, 1H, 5), 4.66 (s, 2H, 9), 4.63 (s, 2H, 7), 2.59 – 2.51 (m, 2H, 22), 2.42 (s, 3H, 34), 1.52 – 1.41 (m, 2H, 23), 0.81 (t, *J* = 7.3 Hz, 3H, 24).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 143.8 (31), 141.5 (3), 140.8 (16), 140.6 (13), 140.3 (4), 139.9 (10), 135.5 (6), 133.9 (28), 133.7 (1), 130.0 (17, 21), 129.7 (29, 33), 129.0 (18, 20), 127.8 (30, 32), 127.5 (19), 127.2 (11, 15), 126.9 (12, 14), 124.2 (5), 123.4 (2), 53.8 (9), 53.7 (7), 35.2 (22), 24.7 (23), 21.7 (34), 14.1 (24).

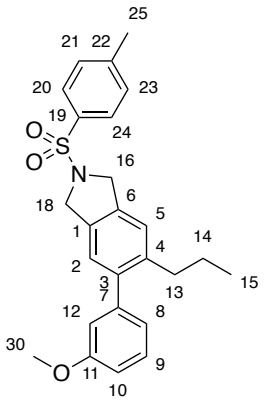
IR (ATR, film): 1344, 1161, 1096, 735, 665, 546 cm^{-1}.

HRMS (ESI): Calculated for 468.1992 *m*/*z*, found 468.1990 *m*/*z* $[C_{30}H_{29}NO_2S+H]^+$.

5-(3-Methoxyphenyl)-6-propyl-2-tosylisoindoline (**4.95**)



Prepared according to General Procedure C from 1-methoxy-3-(pent-1-yn-1-yl)benzene (17.4 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as white solid (42.2 mg, 91%).



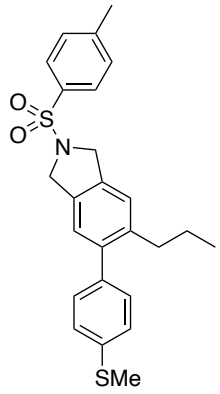
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.79 (d, *J* = 7.9 Hz, 2H, 20, 24), 7.31 (m, 3H, 9, 21, 23), 7.08 (s, 1H, 5), 6.99 (s, 1H, 2), 6.88 (dd, *J* = 8.3, 2.6 Hz, 1H, 10), 6.79 (m, 1H, 8), 6.75 (dd, *J* = 2.8, 1.5 Hz, 1H, 12), 4.64 (s, 2H, 16), 4.61 (s, 2H, 18), 3.81 (s, 3H, 30), 2.52 – 2.46 (m, 2H, 13), 2.41 (s, 3H, 25), 1.43 (m, 2H, 14), 0.82 – 0.75 (m, 3H, 15).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 159.4 (11), 143.8 (22), 143.0 (3), 141.7 (7), 140.2 (4), 135.5 (1), 133.9 (19), 133.6 (6), 129.9 (21, 23), 129.2 (9), 127.8 (20, 24), 124.0 (2), 123.3 (5), 121.7 (8), 115.0 (12), 112.6 (10), 55.4 (30), 53.8 (16), 53.7 (18), 35.2 (13), 24.7 (14), 21.6 (25), 14.1 (15).

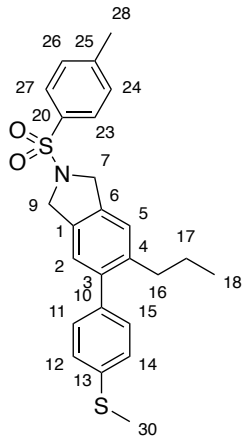
IR (ATR, film): 1344, 1161, 1096, 1047, 708, 665, 619, 548 cm^{-1}.

HRMS (ESI): Calculated for 422.1784 *m*/*z*, found 422.1784 *m*/*z* $[C_{25}H_{27}NO_3S+H]^+$.

5-(4-(Methylthio)phenyl)-6-propyl-2-tosylisoindoline (4.96)



Prepared according to General Procedure C from methyl(4-(pent-1-yn-1-yl)phenyl)sulfane (19.0 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as pale-yellow solid (35.3 mg, 81%).



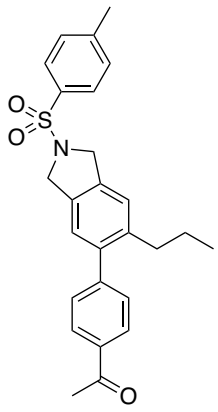
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.89 – 7.74 (m, 2H, 24, 26), 7.34 – 7.30 (m, 2H, 23, 27), 7.29 – 7.25 (m, 2H, 11, 15), 7.15 – 7.12 (m, 2H, 12, 14), 7.08 (s, 1H, 5), 6.97 (s, 1H, 2), 4.63 (s, 2H, 7), 4.60 (s, 2H, 9), 2.52 (s, 3H, 30), 2.50 – 2.44 (m, 2H, 16), 2.41 (s, 3H, 28), 1.48 – 1.36 (m, 2H, 17), 0.78 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 143.8 (25), 141.2 (3), 140.3 (4), 138.3 (10), 137.3 (13), 135.4 (6), 133.8 (20), 133.7 (1), 129.9 (23, 27), 129.7 (12, 14), 127.8 (24, 26), 126.2 (11, 15), 124.2 (2), 123.4 (5), 53.74 (7), 53.66 (9), 35.2 (16), 24.7 (17), 21.7 (30), 15.9 (28), 14.1 (18).

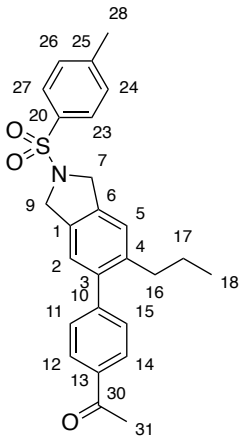
IR (ATR, film): 1346, 1163, 1096, 667, 548 cm^{-1}.

HRMS (ESI): Calculated for 438.1556 *m*/*z*, found 438.1553 *m*/*z* $[C_{25}H_{27}NO_2S_2+H]^+$.

1-(4-(6-Propyl-2-tosylisoindolin-5-yl)phenyl)ethan-1-one (**4.97**)



Prepared according to General Procedure C from 1-(4-(pent-1-yn-1-yl)phenyl)ethan-1-one (18.6 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–20% EtOAc in hexane) to yield the desired product as pale-yellow solid (28.2 mg, 65%).



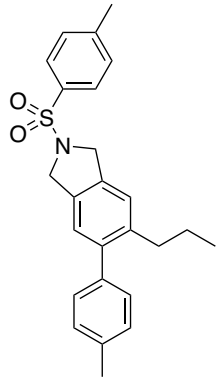
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.98 (d, *J* = 8.3 Hz, 2H, 12, 14), 7.78 (d, *J* = 8.3 Hz, 2H, 24, 26), 7.32 (m, 4H, 11, 15, 23, 27), 7.10 (s, 1H, 5), 6.97 (s, 1H, 2), 4.64 (s, 2H, 7), 4.61 (s, 2H, 9), 2.64 (s, 3H, 31), 2.49 – 2.44 (m, 2H, 16), 2.41 (s, 3H, 28), 1.46 – 1.35 (m, 2H, 17), 0.76 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 197.9 (30), 146.6 (10), 143.8 (25), 140.7 (20), 140.1 (4), 136.1 (13), 135.9 (1), 133.84 (3), 133.76 (6), 130.0 (23, 27 or 11, 15), 129.6 (23, 27 or 11, 15), 128.4 (12, 14), 127.8 (24, 26), 123.8 (2), 123.6 (5), 53.7 (7), 53.6 (9), 35.1 (16), 26.8 (31), 24.7 (17), 21.7 (28), 14.1 (18).

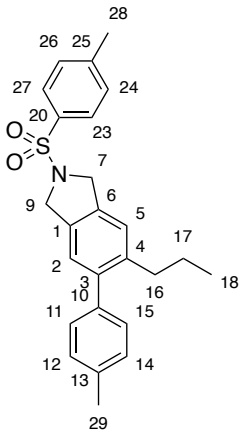
IR (ATR, film): 1680, 1344, 1267, 1161, 1096, 665, 548 cm^{-1}.

HRMS (ESI): Calculated for 434.1784 *m*/*z*, found 434.1775 *m*/*z* $[C_{26}H_{27}NO_3S+H]^+$.

5-Propyl-6-(*p*-tolyl)-2-tosylisoindoline (**4.98**)



Prepared according to General Procedure C from 1-methyl-4-(pent-1-yn-1-yl)benzene (15.8 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as pale-yellow solid (36.9 mg, 91%).



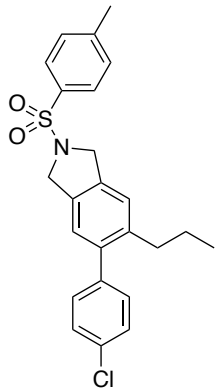
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.78 (d, *J* = 8.2 Hz, 2H, 24, 26), 7.32 (d, *J* = 8.0 Hz, 2H, 23, 27), 7.19 (d, *J* = 7.8 Hz, 2H, 11, 15), 7.12 – 7.08 (m, 2H, 12, 14), 7.08 (s, 1H, 5), 6.98 (s, 1H, 2), 4.64 (s, 2H, 7), 4.60 (s, 2H, 9), 2.51 – 2.46 (m, 2H, 16), 2.41 (s, 3H, 28), 2.39 (s, 3H, 29), 1.48 – 1.38 (m, 2H, 17), 0.78 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.8 (25), 141.8 (3), 140.3 (4), 138.6 (10), 136.8 (13), 135.2 (6), 133.8 (20), 133.6 (1), 129.9 (23, 27), 129.1 (12, 14), 128.9 (11, 15), 127.8 (24, 26), 124.2 (2), 123.2 (5), 53.8 (7), 53.7 (9), 35.2 (16), 24.7 (17), 21.7 (28), 21.3 (29), 14.1 (18).

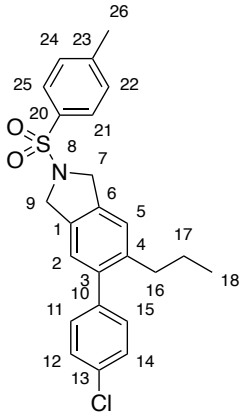
IR (ATR, film): 1344, 1161, 1096, 1059, 812, 665, 606, 548, 538 cm^{-1}.

HRMS (ESI): Calculated for 406.1835 *m*/*z*, found 406.1833 *m*/*z* $[C_{25}H_{27}NO_2S+H]^+$.

5-(4-Chlorophenyl)-6-propyl-2-tosylisoindoline (**4.99**)



Prepared according to General Procedure C from 1-chloro-4-(pent-1-yn-1-yl)benzene (17.9 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 1.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as white solid (29.2 mg, 69%).



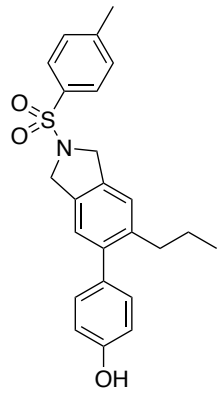
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.78 (d, *J* = 8.2 Hz, 2H, 21, 25), 7.35 (d, *J* = 8.2 Hz, 2H, 11, 15), 7.32 (d, *J* = 8.0 Hz, 2H, 22, 24), 7.16 – 7.12 (m, 2H, 12, 14), 7.08 (s, 1H, 5), 6.95 (s, 1H, 2), 4.66 – 4.62 (m, 2H, 7), 4.62 – 4.59 (m, 2H, 9), 2.49 – 2.44 (m, 2H, 16), 2.41 (s, 3H, 26), 1.46 – 1.35 (m, 2H, 17), 0.78 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.8 (23), 140.6 (13), 140.2 (4), 140.0 (3), 135.8 (1), 133.9 (20), 133.8 (6), 133.2 (10), 130.6 (12, 14), 130.0 (22, 24), 128.5 (11, 15), 127.8 (21, 25), 124.1 (2), 123.4 (5), 53.7 (7), 53.6 (9), 35.1 (16), 24.6 (17), 21.7 (26), 14.1 (18).

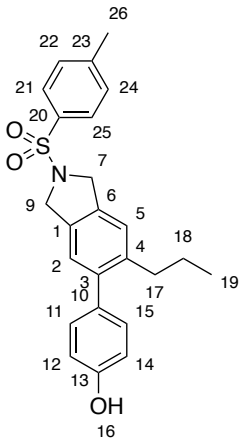
IR (ATR, film): 1344, 1161, 1092, 1061, 1015, 810, 735, 665, 546 cm^{-1}.

HRMS (ESI): Calculated for 426.1289 *m*/*z*, found 426.1283 *m*/*z* $[C_{24}H_{24}ClNO_2S+H]^+$.

4-(6-Propyl-2-tosylisoindolin-5-yl)phenol (**4.100**)



Prepared according to General Procedure C from 4-(pent-1-yn-1-yl)phenol (16.0 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–40% Et_2O in PhMe) to yield the desired product as pale-yellow solid (19.3 mg, 47%).



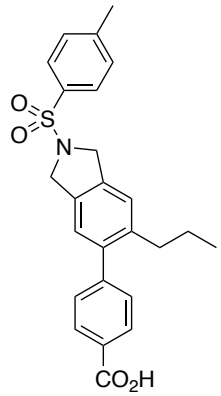
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.78 (d, *J* = 7.9 Hz, 2H, 21, 25), 7.32 (d, *J* = 7.9 Hz, 2H, 22, 24), 7.07 (m, 3H, 5, 12, 14), 6.96 (s, 1H, 2), 6.85 (d, *J* = 8.0 Hz, 2H, 11, 15), 4.99 (s, 1H, 16), 4.63 (d, *J* = 2.5 Hz, 2H, 7), 4.60 (s, 2H, 9), 2.48 (t, *J* = 7.9 Hz, 2H, 17), 2.41 (s, 3H, 26), 1.41 (m, 18), 0.78 (t, *J* = 7.3 Hz, 3H, 19).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 154.8 (13), 143.8 (23), 141.5 (10), 140.5 (4), 135.1 (3), 134.1 (20), 133.8 (6), 133.6 (1), 130.5 (12, 14), 130.0 (22, 24), 127.8 (21, 25), 124.3 (5), 123.3 (2), 115.1 (11, 15), 53.8 (7), 53.7 (9), 35.2 (17), 24.6 (18), 21.7 (26), 14.1 (19).

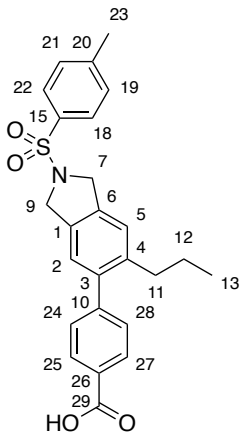
IR (ATR, film): 1339, 1265, 1159, 1096, 1061, 835, 816, 667, 608, 550 cm^{-1}.

HRMS (ESI): Calculated for 408.1628 *m*/*z*, found 408.1623 *m*/*z* $[C_{24}H_{25}NO_3S+H]^+$.

4-(6-Propyl-2-tosylisoindolin-5-yl)benzoic acid (**4.101**)



Unable to isolate from [2+2+2] reaction however compared NMR to authentic product prepared as described. A flask was charged with methyl 4-(6-propyl-2-tosylisoindolin-5-yl)benzoate (21.0 mg, 49.7 µmol) and H_2O:MeOH:THF (1:1:1, 150 µL) and the mixture was heated to 100 ºC. After stirring for 2 h, the mixture was allowed to cool to RT before concentrated hydrochloric acid was added dropwise (~0.5 mL) and the white precipitate that formed was filtered off. The residue was washed with cold H_2O and then was collected to yield the desired product as a white powder (20.0 mg, 98%).



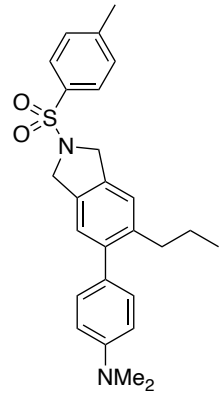
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 8.18 – 8.13 (m, 2H, 25, 27), 7.83 – 7.79 (m, 2H, 18, 22), 7.40 – 7.33 (m, 4H, 19, 21, 24, 28), 7.13 (s, 1H, 5), 7.01 (s, 1H, 2), 4.67 (s, 2H, 9), 4.64 (s, 2H, 7), 2.50 (m, 2H, 11), 2.44 (s, 3H, 23), 1.43 (m, 2H, 12), 0.79 (t, *J* = 7.3 Hz, 3H, 13).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 171.1 (29), 147.4 (26), 143.9 (20), 140.7 (15), 140.1 (4), 136.2 (1), 133.9 (6), 133.8 (3), 130.2 (25, 27), 130.0 (19, 21 or 24, 28), 129.6 (19, 21or 24, 28), 128.0 (10), 127.8 (18, 22), 123.9 (2), 123.6 (5), 53.7 (9), 53.6 (7), 35.2 (11), 24.7 (12), 21.7 (23), 14.1 (13).

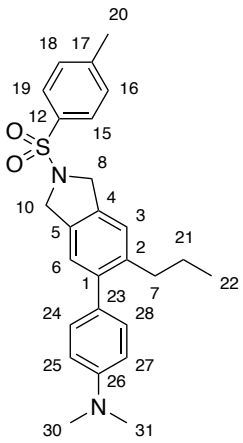
IR (ATR, film): 1688, 1346, 1161, 1098, 667, 548 cm^{-1}.

HRMS (ESI): Calculated for 436.1577 *m*/*z*, found 436.1569 *m*/*z* $[C_{25}H_{25}NO_4S+H]^+$.

5-Methyl-6-propyl-2-tosylisoindoline (**4.102**)



Prepared according to General Procedure C from *N*,*N*-dimethyl-4-(pent-1-yn-1-yl)aniline (18.7 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–1% Et_2O in PhMe) to yield the desired product as a green oil (34.7 mg, 80%).



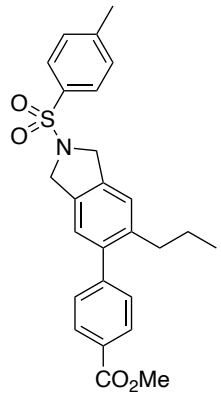
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.83 – 7.78 (m, 2H, 15, 18), 7.35 – 7.32 (m, 2H, 16, 18), 7.15 – 7.10 (m, 2H, 25, 27), 7.09 (s, 1H, 3), 7.01 (s, 1H, 6), 6.82 – 6.73 (m, 2H, 24, 28), 4.65 (s, 2H, 8), 4.62 (s, 2H, 1), 3.01 (s, 6H, 30, 31), 2.59 – 2.51 (m, 2H, 7), 2.43 (s, 3H, 20), 1.52 – 1.42 (m, 2H, 21), 0.82 (t, *J* = 7.3 Hz, 3H, 22).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 149.5 (26), 143.6 (17), 141.9 (23), 140.4 (2), 134.6 (1), 133.8 (5), 133.41 (4 or 12), 133.41 (4 or 12), 129.9 (25, 27), 129.8 (16, 18), 127.7 (15, 19), 124.3 (6), 123.1 (3), 112.1 (24, 28), 53.7 (8), 53.6 (10), 40.6 (30, 31), 35.1 (7), 24.6 (21), 21.5 (20), 14.1 (22).

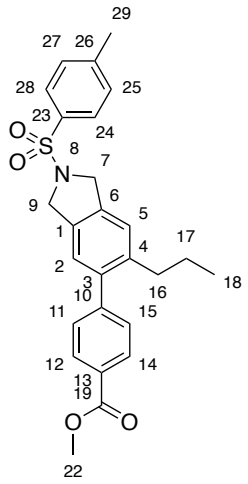
IR (ATR, film): 1611, 1526, 1487, 1344, 1161, 1096, 1059, 812, 735, 708, 665, 604, 586, 548 cm^{-1}.

HRMS (ESI): Calculated for 435.2101 *m*/*z*, found 435.2093 *m*/*z* $[C_{26}H_{30}N_2O_2S+H]^+$.

Methyl 4-(6-propyl-2-tosylisoindolin-5-yl)benzoate (**4.103**)



Prepared according to General Procedure C from methyl 4-(pent-1-yn-1-yl)benzoate (20.2 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as pale-yellow solid (40.1 mg, 89%).



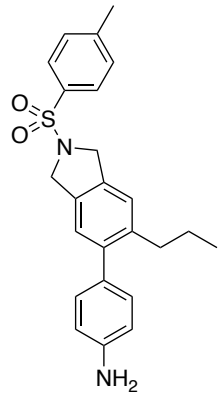
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 8.09 – 8.04 (m, 2H, 12, 14), 7.80 – 7.77 (m, 2H, 24, 28), 7.32 (d, *J* = 8.1 Hz, 2H, 25, 27), 7.30 – 7.27 (m, 2H, 11, 15), 7.10 (s, 1H, 5), 6.98 (s, 1H, 2), 4.64 (s, 2H, 7), 4.61 (s, 2H, 9), 3.94 (s, 3H, 22), 2.49 – 2.43 (m, 2H, 16), 2.41 (s, 3H, 29), 1.44 – 1.33 (m, 2H, 17), 0.75 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 167.1 (19), 146.4 (10), 143.8 (26), 140.8 (3), 140.1 (4), 136.0 (1), 133.81 (6), 133.78 (23), 130.0 (12, 14), 129.6 (11, 15), 129.4 (25, 27), 129.0 (13), 127.8 (24, 28), 123.9 (2), 123.5 (5), 53.7 (7), 53.6 (9), 52.3 (22), 35.2 (16), 24.7 (17), 21.7 (29), 14.1 (18).

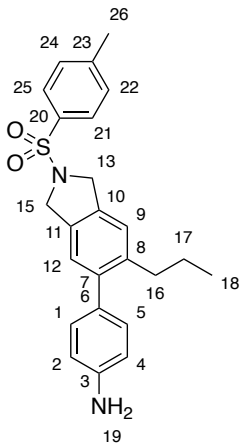
IR (ATR, film): 1719, 1344, 1275, 1161, 1098, 708, 665, 548 cm^{-1}.

HRMS (ESI): Calculated for 450.1734 *m*/*z*, found 450.1731 *m*/*z* $[C_{26}H_{27}NO_4S+H]^+$.

4-(6-Propyl-2-tosylisoindolin-5-yl)aniline (**4.104**)



Prepared according to General Procedure C from 4-(pent-1-yn-1-yl)aniline (15.9 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–2% Et_2O in PhMe) to yield the desired product as yellow solid (24.8 mg, 61%).



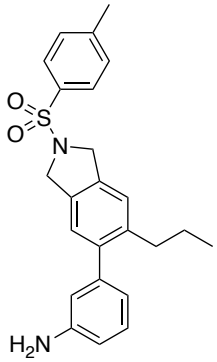
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.80 – 7.77 (m, 2H, 21, 25), 7.31 (d, *J* = 8.2 Hz, 2H, 22, 24), 7.05 (s, 1H, 9), 7.01 – 6.98 (m, 2H, 1, 5), 6.97 (s, 1H, 12), 6.72 – 6.67 (m, 2H, 2, 4), 4.62 (s, 2H, 13), 4.59 (s, 2H, 15), 3.72 (s, 2H, 19), 2.54 – 2.47 (m, 2H, 16), 2.41 (s, 3H, 26), 1.48 – 1.37 (m, 2H, 17), 0.79 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 145.4 (3), 143.7 (23), 141.9 (7), 140.5 (8), 134.8 (11), 133.8 (20), 133.5 (10), 131.8 (6), 130.1 (1, 5), 129.9 (22, 24), 127.8 (21, 25), 124.3 (12), 123.2 (9), 114.8 (2, 4), 53.8 (13), 53.7 (15), 35.3 (16), 24.7 (17), 21.6 (26), 14.2 (18).

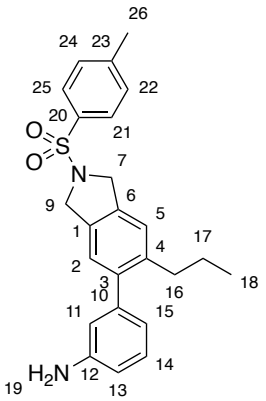
IR (ATR, film): 1341, 1159, 1094, 665, 606, 548 cm^{-1}.

HRMS (ESI): Calculated for 407.1788 *m*/*z*, found 407.1790 *m*/*z* $[C_{24}H_{26}N_2O_2S+H]^+$.

3-(6-Propyl-2-tosylisoindolin-5-yl)aniline (**4.105**)



Prepared according to General Procedure C from 3-(pent-1-yn-1-yl)aniline (15.9 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% Et_2O in PhMe) to yield the desired product as pale-yellow solid (25.8 mg, 63%).



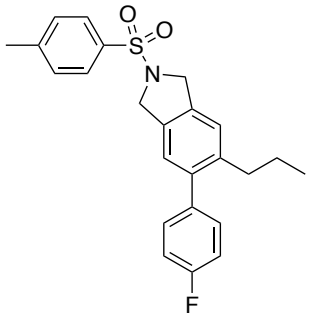
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.80 – 7.77 (m, 2H, 21, 25), 7.32 (d, *J* = 8.0 Hz, 2H, 22, 24), 7.15 (t, *J* = 7.7 Hz, 1H, 14), 7.06 (s, 1H, 5), 6.98 (s, 1H, 2), 6.68 – 6.64 (m, 1H, 13), 6.59 (m, 1H, 15), 6.52 (m, 1H, 11), 4.63 (s, 2H, 7), 4.60 (s, 2H, 9), 3.70 (s, 2H, 19), 2.53 – 2.48 (m, 2H, 16), 2.41 (s, 3H, 26), 1.47 – 1.39 (m, 2H, 17), 0.79 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 146.2 (12), 143.8 (23), 142.7 (10), 142.1 (3), 140.2 (4), 135.2 (1), 133.8 (20), 133.4 (6), 129.9 (22, 24), 129.1 (14), 127.8 (21, 25), 123.9 (2), 123.2 (5), 119.7 (15), 116.0 (11), 113.9 (13), 53.8 (7), 53.7 (9), 35.1 (16), 24.7 (17), 21.6 (26), 14.1 (18).

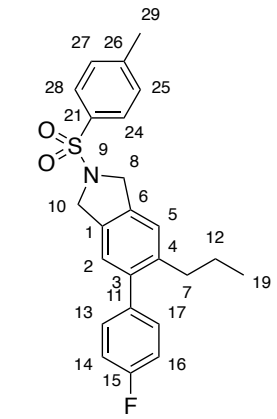
IR (ATR, film): 1341, 1159, 1096, 1059, 735, 708, 665, 619, 548 cm^{-1}.

HRMS (ESI): Calculated for 407.1788 *m*/*z*, found 407.1788 *m*/*z* $[C_{24}H_{26}N_2O_2S+H]^+$.

5-(4-Fluorophenyl)-6-propyl-2-tosylisoindoline (**4.106**)



Prepared according to General Procedure C from 1-fluoro-4-(pent-1-yn-1-yl)benzene (16.2 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–2% Et_2O in PhMe) to yield the desired product as white solid (32.0 mg, 78%).



^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.83 – 7.75 (m, 2H, 25, 27), 7.35 – 7.30 (m, 2H, 24, 28), 7.21 – 7.13 (m, 2H, 13, 17), 7.11 – 7.03 (m, 3H, 5, 14, 16), 6.96 (s, 1H, 2), 4.63 (s, 2H, 10), 4.60 (s, 2H, 8), 2.49 – 2.43 (m, 2H, 7), 2.41 (s, 3H, 29), 1.47 – 1.32 (m, 2H, 12), 0.77 (t, *J* = 7.3 Hz, 3H, 19).

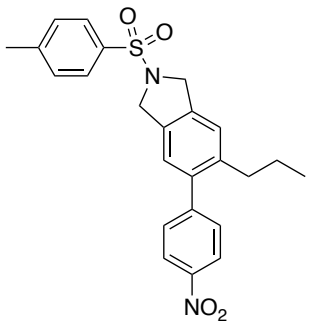
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 162.1 (d, $^{1}J_{CF}$ = 245.9 Hz, 15), 143.8 (26), 140.8 (3), 140.2 (4) 137.5 (d, $^{4}J_{CF}$ = 3.3 Hz, 11), 135.7 (1) 133.9 (21), 133.7 (6), 130.8 (d, $^{3}J_{CF}$ = 8.0 Hz, 13, 17), 130.0 (24, 28), 127.8 (25, 27), 124.2 (2), 123.4 (5), 115.2 (d, $^{2}J_{CF}$ = 21.4 Hz, 14, 16), 53.7 (10), 53.6 (8), 35.2 (7), 24.6 (12), 21.7 (29), 14.1 (19).

^{19}F{^{1}H} NMR (377 MHz, Chloroform-*d*) δ_F −115.6.

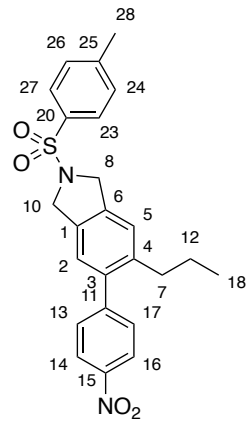
IR (ATR, film): 1344, 1221, 1161, 1098, 1059, 841, 814, 665, 606, 546 cm^{-1}.

HRMS (ESI): Calculated for 410.1585 *m*/*z*, found 410.1582 *m*/*z* $[C_{24}H_{24}FNO_2S+H]^+$.

5-(4-Nitrophenyl)-6-propyl-2-tosylisoindoline (**4.107**)



Prepared according to General Procedure C from 1-nitro-4-(pent-1-yn-1-yl)benzene (18.9 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–2% Et_2O in PhMe) to yield the desired product as white solid (36.2 mg, 83%).



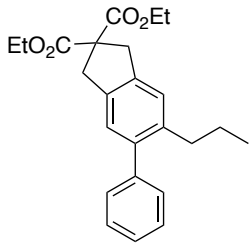
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 8.29 – 8.21 (m, 2H, 14, 16), 7.82 – 7.75 (m, 2H, 23, 27), 7.41 – 7.36 (m, 2H, 13, 17), 7.35 – 7.30 (m, 2H, 24, 26), 7.13 (s, 1H, 5), 6.97 (s, 1H, 2), 4.67 – 4.60 (m, 4H, 8, 10), 2.50 – 2.43 (m, 2H, 7), 2.41 (s, 3H, 28), 1.47 – 1.33 (m, 2H, 12), 0.77 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 148.5 (3), 147.1 (15), 143.9 (25), 140.0 (11), 139.5 (4), 136.7 (6), 134.1 (1), 133.8 (20), 130.3 (13, 17), 130.0 (24, 26), 127.8 (23, 27), 123.76 (2 or 5), 123.75 (2 or 5), 123.6 (14, 16), 53.7 (8), 53.5 (10), 35.1 (7), 24.6 (12), 21.7 (24), 14.0 (18).

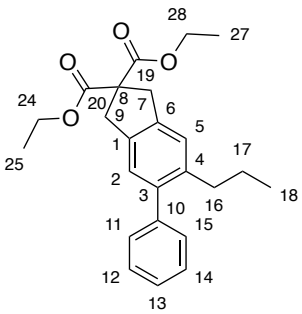
IR (ATR, film): 2957, 2928, 2864, 1597, 1516, 1462, 1400, 1344, 1307, 1161, 1099, 1061, 1018, 855, 814, 756, 704, 667, 606, 548 cm^{-1}.

HRMS (ESI): Calculated for 437.1530 *m*/*z*, found 437.1527 *m*/*z* $[C_{24}H_{24}N_2O_4S+H]^+$.

Diethyl 5-phenyl-6-propyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.108)



Prepared according to General Procedure C from pent-1-yn-1-ylbenzene (14.4 mg, 100 µmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–70% PhMe in hexane) to yield the desired product as a colourless oil (26.6 mg, 70%).



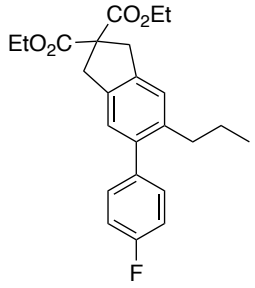
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.42 – 7.33 (m, 2H, 12, 14), 7.36 – 7.29 (m, 1H, 13), 7.28 – 7.24 (m, 2H, 11, 15), 7.11 (s, 1H, 5), 7.01 (s, 1H, 2), 4.22 (q, *J* = 7.1 Hz, 4H, 24, 28), 3.62 (s, 2H, 7), 3.59 (s, 2H, 9), 2.52 – 2.45 (m, 2H, 16), 1.50 – 1.38 (m, 2H, 17), 1.27 (t, *J* = 7.1 Hz, 6H, 25, 27), 0.79 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 172.0 (19, 20), 142.4 (3), 140.9 (10), 139.3 (4), 139.1 (6), 137.4 (1), 129.5 (11, 15), 128.1 (12, 14), 126.7 (13), 125.8 (2), 124.9 (5), 61.8 (24, 28), 60.6 (8), 40.5 (7), 40.4 (9), 35.3 (16), 24.8 (17), 14.2 (18), 14.2 (25, 27).

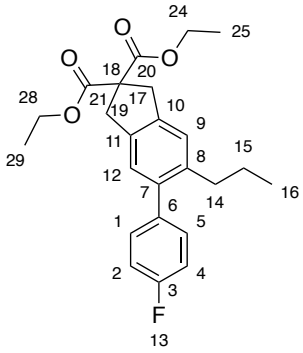
IR (ATR, film): 1730, 1275, 1240, 1186, 1153, 1067, 702 cm^{-1}.

HRMS (ESI): Calculated for 381.2060 *m*/*z*, found 381.2050 *m*/*z* $[C_{24}H_{28}O_4+H]^+$.

Diethyl 5-(4-fluorophenyl)-6-propyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.109)



Prepared according to General Procedure C from 1-fluoro-4-(pent-1-yn-1-yl)benzene (20.2 mg, 100 µmol, 1.00 equiv.), and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–75% PhMe in hexane) to yield the desired product as a colourless oil (5.2 mg, 10%).



^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.24 – 7.18 (m, 2H, 1, 5), 7.10 (s, 1H, 9), 7.09 – 7.03 (m, 2H, 2 , 4), 6.98 (s, 1H, 12), 4.22 (q, *J* = 7.1 Hz, 4H, 24, 28), 3.61 (s, 2H, 17), 3.58 (s, 2H, 19), 2.49 – 2.39 (m, 2H, 14), 1.49 – 1.36 (m, 2H, 15), 1.27 (t, *J* = 7.1 Hz, 6H, 25, 29), 0.79 (t, *J* = 7.3 Hz, 3H, 16).

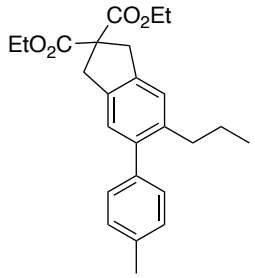
^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 171.9 (20, 21), 162.1 (d, $^{1}J_{CF}$ = 215.4 Hz, 3), 139.8 (11), 139.5 (8), 139.2 (7), 138.2 (10), 137.5 (6), 130.9 (d, $^{3}J_{CF}$ = 7.8 Hz, 1, 5), 125.9 (12), 125.0 (9), 114.8 (d, $^{2}J_{CF}$ = 21.2 Hz, 2, 4), 61.9 (24, 28), 60.6 (18), 40.5 (19), 40.3 (17), 35.3 (14), 24.7 (15), 14.22 (25, 29), 14.19 (16).

$^{19}F\{^{1}H\}$ NMR (470 MHz, Chloroform-*d*) δ_F −116.5.

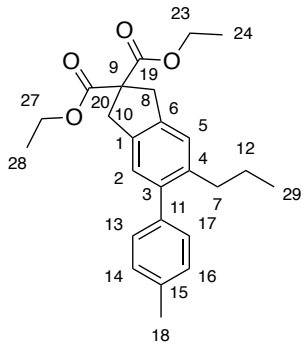
IR (ATR, film): 1732, 1244, 1229, 1188, 1157, 417 cm^{-1}.

HRMS (ESI): Calculated for 421.1787 *m*/*z*, found 421.1772 *m*/*z* $[C_{24}H_{27}FO_4+Na]^+$.

Diethyl 5-propyl-6-(*p*-tolyl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.110)



Prepared according to General Procedure C from 1-methyl-4-(pent-1-yn-1-yl)benzene (10.0 mg, 63.2 µmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (89.6 mg, 379 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% Et2O in PhMe) to yield the desired product as a white solid (11.2 mg, 45%).



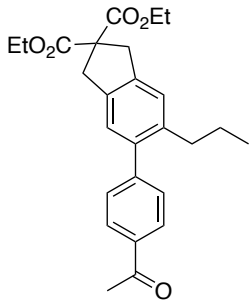
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.19 (m, 2H, 14, 16), 7.15 (d, 2H, *J* = 8.4 Hz, 13, 17), 7.10 (s, 1H, 5), 7.00 (s, 1H, 2), 4.22 (q, *J* = 7.1 Hz, 4H, 23, 27), 3.61 (s, 2H, 9), 3.58 (s, 2H, 7), 2.53 – 2.45 (m, 2H, 7), 2.39 (s, 3H, 18), 1.53 – 1.41 (m, 2H, 12), 1.26 (t, *J* = 7.1 Hz, 6H, 24, 28), 0.80 (t, *J* = 7.3 Hz, 3H, 29).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 172.0 (19, 20), 140.8 (11), 139.4 (4), 139.2 (1), 139.1 (6), 137.4 (3), 136.3 (15), 129.3 (13, 17), 128.8 (14, 16), 125.9 (2), 124.9 (5), 61.8 (23, 27), 60.6 (9), 40.5 (10), 40.4 (8), 35.3 (7), 24.8 (12), 21.3 (10), 14.24 (29), 14.19 (24, 28).

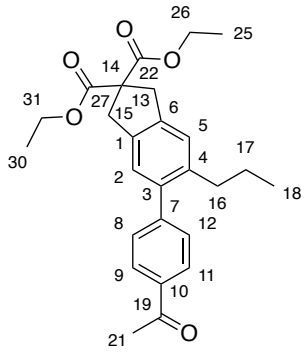
IR (ATR, film): 1734, 1246, 436 cm^{-1}.

HRMS (ESI): Calculated for 395.2217 *m*/*z*, found 395.2216 *m*/*z* $[C_{25}H_{30}O_4+H]^+$.

Diethyl 5-(4-acetylphenyl)-6-propyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.111)



Prepared according to General Procedure C from 1-(4-(pent-1-yn-1-yl)phenyl)ethan-1-one (18.6 mg, 100 μmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% Et_2O in PhMe) to yield the desired product as yellow oil (41.1 mg, 97%).



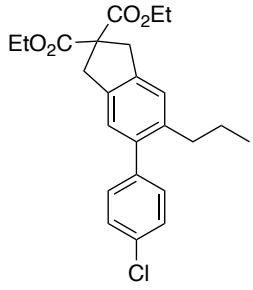
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 8.02 – 7.94 (m, 2H, 9, 11), 7.40 – 7.34 (m, 2H, 8, 12), 7.12 (s, 1H, 5), 7.00 (s, 2H, 2), 4.22 (q, *J* = 7.1 Hz, 4H, 26, 31), 3.62 (s, 2H, 13), 3.59 (s, 2H, 15), 2.64 (s, 3H, 21), 2.50 – 2.44 (m, 2H, 16), 1.49 – 1.39 (m, 2H, 17), 1.27 (t, *J* = 7.1 Hz, 6H, 25, 30), 0.78 (t, *J* = 7.3 Hz, 3H, 18).

13C NMR (101 MHz, Chloroform-*d*) δ_C 198.1 (19), 171.8 (22, 27), 147.6 (7), 140.0 (3), 139.7 (6), 138.9 (4), 137.7 (1), 135.6 (10), 129.7 (8, 12), 128.2 (9, 11), 125.5 (2), 125.2 (5), 61.9 (26, 31), 60.6 (14), 40.5 (15), 40.3 (13), 35.2 (16), 26.8 (21), 24.7 (17), 14.17 (18), 14.14 (25, 30).

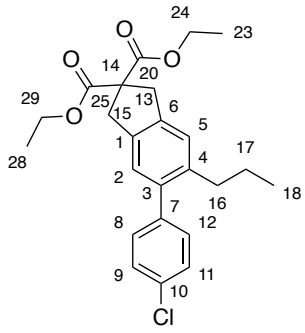
IR (ATR, film): 2969, 1732, 1684, 1603, 1445, 1364, 1246, 1184, 1063, 1015, 957, 855, 602 cm^{-1}.

HRMS (ESI): Calculated for 423.2166 *m*/*z*, found 423.2158 *m*/*z* $[C_{26}H_{30}O_5+H]^+$.

Diethyl 5-(4-chlorophenyl)-6-propyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.112)



Prepared according to General Procedure C from 1-chloro-4-(pent-1-yn-1-yl)benzene (17.9 mg, 100 µmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–2% Et_2O in PhMe) to yield the desired product as white solid (10.6 mg, 26%).



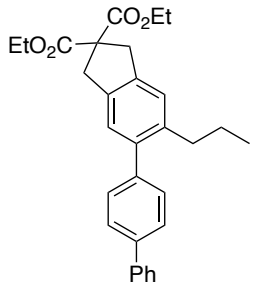
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.38 – 7.32 (m, 2H, 9, 11), 7.19 (m, 2H, 8, 12), 7.10 (s, 1H, 5), 6.97 (s, 1H, 2), 4.22 (q, *J* = 7.1 Hz, 4H, 24, 29), 3.61 (s, 2H, 15), 3.58 (s, 2H, 13), 2.52 – 2.40 (m, 2H, 16), 1.49 – 1.37 (m, 2H, 17), 1.27 (t, *J* = 7.1 Hz, 6H, 23, 28), 0.80 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 171.9 (20, 25), 140.8 (10), 139.7 (3), 139.6 (7), 139.1 (4), 137.6 (6), 132.8 (1), 130.8 (8, 12), 128.3 (9, 11), 125.7 (2), 125.1 (5), 61.9 (24, 29), 60.6 (14), 40.5 (15), 40.3 (13), 35.2 (16), 24.7 (17), 14.20 (18), 14.20 (23, 28).

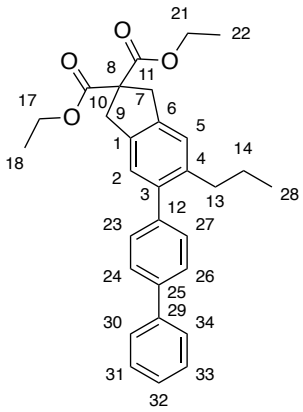
IR (ATR, film): 2928, 1732, 1244, 1182, 1063, 831 cm^{-1}.

HRMS (ESI): Calculated for 415.1671 *m*/*z*, found 415.1677 *m*/*z* $[C_{24}H_{27}ClO_4+H]^+$.

Diethyl 5-([1,1'-biphenyl]-4-yl)-6-propyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.113)



Prepared according to General Procedure C from 4-(pent-1-yn-1-yl)-1,1'-biphenyl (22.0 mg, 100 µmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–5% Et_2O in PhMe) to yield the desired product as a white solid (34.5 mg, 76%).



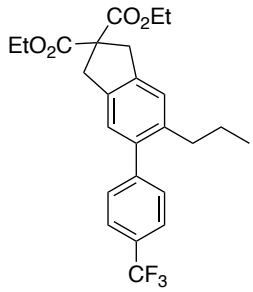
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.68 – 7.64 (m, 2H, 30, 34), 7.63 – 7.60 (m, 2H, 24, 26), 7.46 (m, 2H, 31, 33), 7.38 – 7.32 (m, 3H, 23, 27, 32), 7.13 (s, 1H, 2), 7.06 (s, 1H, 5), 4.23 (q, *J* = 7.1 Hz, 4H, 17, 21), 3.63 (s, 2H, 9), 3.60 (s, 2H, 7), 2.60 – 2.50 (m, 2H, 13), 1.53 – 1.46 (m, 2H, 14), 1.27 (t, *J* = 7.1 Hz, 6H, 18, 22), 0.82 (t, *J* = 7.3 Hz, 3H, 28).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 172.0 (10, 11), 141.4 (12), 141.0 (25), 140.5 (3), 139.5 (29), 139.4 (4), 139.2 (1/6), 137.5 (1/6), 129.9 (31, 33), 128.9 (23, 27), 127.4 (32), 127.2 (30, 34), 126.8 (24, 28), 125.8 (5), 125.0 (2), 61.9 (17, 21), 60.6 (8), 40.5 (7 or 9), 40.4 (7 or 9), 35.3 (13), 24.8 (14), 14.3 (28), 14.2 (18, 22).

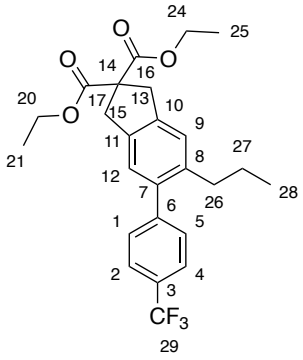
IR (ATR, film): 2924, 1730, 1242, 1061, 764, 735, 696 cm^{-1}.

HRMS (ESI): Calculated for 457.2373 *m*/*z*, found 457.2362 *m*/*z* [$C_{30}H_{32}O_4$+H]$^+$.

Diethyl 5-propyl-6-(4-(trifluoromethyl)phenyl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.114)



Prepared according to General Procedure C from 1-(pent-1-yn-1-yl)-4-(trifluoromethyl)benzene (21.2 mg, 100 µmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–2% Et_2O in PhMe) to yield the desired product as yellow oil (13.3 mg, 30%).



^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.64 (d, *J* = 8.0 Hz, 2H, 2, 4), 7.38 (d, *J* = 8.0 Hz, 2H, 1, 5), 7.13 (s, 1H, 9), 6.98 (s, 1H, 12), 4.22 (q, *J* = 7.1 Hz, 4H, 20, 24), 3.62 (s, 2H, 13 or 15), 3.59 (s, 2H, 13 or 15), 2.49 – 2.41 (m, 2H, 26), 1.50 – 1.39 (m, 3H, 27), 1.27 (t, *J* = 7.1 Hz, 6H, 21, 25), 0.80 (t, *J* = 7.3 Hz, 3H, 28).

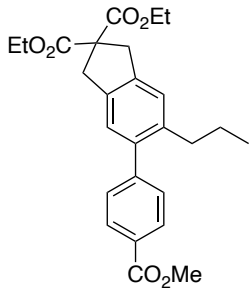
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 171.9 (16, 17), 146.1 (6), 140.1 (11), 139.4 (7), 139.0 (8), 137.7 (10), 129.8 (1, 5), 128.9 (q, $^{2}J_{CF}$ = 32.4 Hz, 3), 125.6 (12), 125.2 (9), 125.1 (q, $^{3}J_{CF}$ = 3.5 Hz, 2, 4), 124.5 (q, $^{1}J_{CF}$ = 271.5 Hz, 29), 61.9 (20, 24), 60.6 (14), 40.5 (15), 40.3 (13), 35.1 (26), 24.8 (27), 14.19 (21, 25), 14.17 (28).

^{19}F{^{1}H} NMR (471 MHz, Chloroform-*d*) δ_F −62.3.

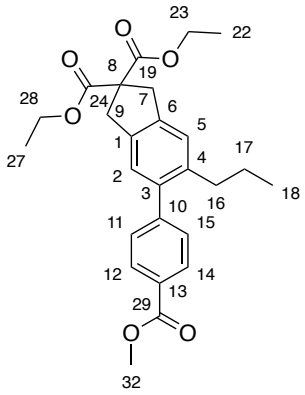
IR (ATR, film): 419, 1063, 1121, 1161, 1246, 1323, 1730 cm^{-1}.

HRMS (ESI): Calculated for 449.1934 *m*/*z*, found 449.1934 *m*/*z* [$C_{25}H_{27}F_3O_4$+H]$^{+}$.

Diethyl 5-(4-(methoxycarbonyl)phenyl)-6-propyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (**4.115**)



Prepared according to General Procedure C from methyl 4-(pent-1-yn-1-yl)benzoate (20.2 mg, 100 µmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–2% Et_2O in PhMe) to yield the desired product as white solid (2.0 mg, 5%).



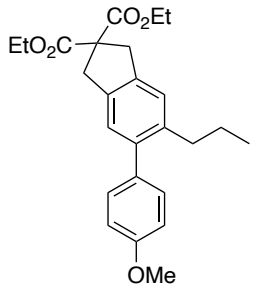
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 8.08 – 8.02 (m, 2H, 12, 14), 7.37 – 7.32 (m, 2H, 11, 15), 7.12 (s, 1H, 5), 7.00 (s, 1H, 2), 4.22 (q, *J* = 7.1 Hz, 4H, 23, 28), 3.94 (s, 3H, 32), 3.62 (s, 2H, 7), 3.59 (s, 2H, 9), 2.47 (m, 2H, 16), 1.48 – 1.38 (m, 2H, 17), 1.27 (t, *J* = 7.1 Hz, 6H, 22, 27), 0.78 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 171.9 (19, 24), 167.3 (29), 147.4 (3), 140.0 (6), 139.8 (13), 139.0 (4), 137.7 (1), 129.6 (11, 15), 129.5 (12, 14), 128.6 (10), 125.5 (2), 125.2 (5), 61.9 (23, 28), 60.6 (8), 52.3 (32), 40.5 (7), 40.3 (9), 35.2 (16), 24.8 (17), 14.19 (22, 27), 14.18 (18).

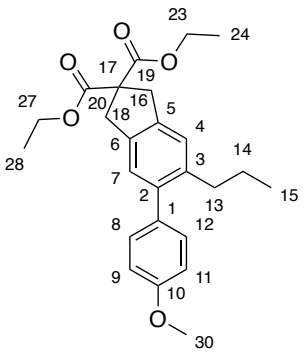
IR (ATR, film): 1722, 1275, 1244, 1099 cm^{-1}.

HRMS (ESI): Calculated for 439.2115 *m*/*z*, found 439.2121 *m*/*z* $[C_{26}H_{30}O_6+H]^+$.

Diethyl 5-(4-methoxyphenyl)-6-propyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (**4.116**)



Prepared according to General Procedure C from 1-methoxy-4-(pent-1-yn-1-yl)benzene (17.4 mg, 100 µmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–75% PhMe in hexane) to yield the desired product as a white oil (41.1 mg, 47%).



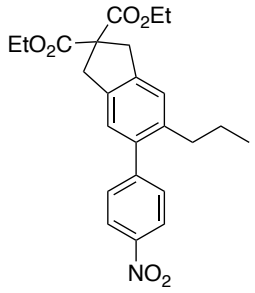
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.21 – 7.15 (m, 2H, 8, 12), 7.09 (s, 1H, 4), 6.99 (s, 1H, 7), 6.95 – 6.89 (m, 2H, 9, 11), 4.22 (q, *J* = 7.2 Hz, 4H, 23, 27), 3.85 (s, 3H, 30), 3.61 (s, 2H, 18), 3.58 (s, 2H, 16), 2.48 (m, 2H, 13), 1.51 – 1.41 (m, 2H, 14), 1.26 (t, *J* = 7.1 Hz, 6H, 24, 28), 0.80 (t, *J* = 7.3 Hz, 3H, 15).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 172.0 (19, 20), 158.5 (10), 140.5 (2), 139.3 (6), 139.0 (5), 137.4 (3), 134.8 (1), 130.6 (8, 12), 126.0 (7), 124.9 (4), 113.5 (9, 11), 61.8 (23), 60.6 (17), 55.4 (30), 40.5 (11), 40.4 (16), 35.3 (13), 24.8 (14), 14.3 (15), 14.2 (24).

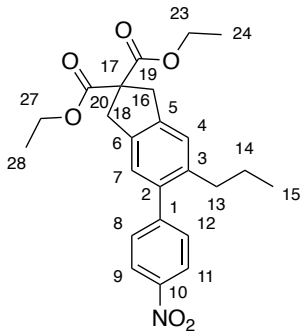
IR (ATR, film): 1730, 1275, 1242, 1155, 1067 cm^{-1}.

HRMS (ESI): Calculated for 411.2166 *m*/*z*, found 411.2155 *m*/*z* $[C_{25}H_{30}O_5+H]^+$.

Diethyl 5-(4-nitrophenyl)-6-propyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.117)



Prepared according to General Procedure C from 1-nitro-4-(pent-1-yn-1-yl)benzene (18.9 mg, 100 µmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% EtOAc in hexane) to yield the desired product as a yellow solid (17.5 mg, 41%).



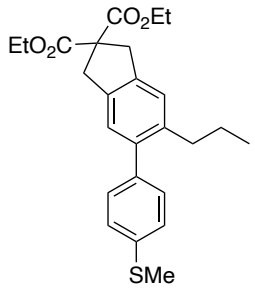
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 8.28 – 8.22 (m, 2H, 8, 12), 7.47 – 7.40 (m, 2H, 9, 11), 7.14 (s, 1H, 7), 6.99 (s, 1H, 4), 4.22 (q, *J* = 7.1 Hz, 4H, 23, 27), 3.62 (s, 2H, 16), 3.59 (s, 2H, 18), 2.52 – 2.41 (m, 2H, 13), 1.49 – 1.38 (m, 2H, 14), 1.27 (t, *J* = 7.1 Hz, 6H, 24, 28), 0.79 (t, *J* = 7.3 Hz, 3H, 15).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 171.8 (19, 20), 149.5 (2), 146.9, (10) 140.7 (6), 138.9 (3), 138.5 (1), 138.0 (5), 130.4 (9, 11), 125.39 (4 or 7), 125.36 (4 or 7), 123.5 (8, 12), 61.9 (23, 27), 60.6 (17), 40.5 (18), 40.3 (16), 35.2 (13), 24.7 (14), 14.2 (24, 28), 14.1 (15).

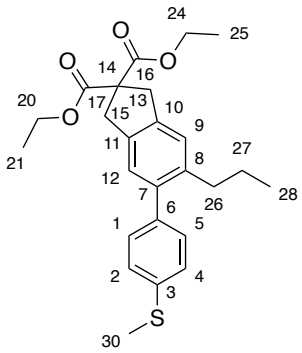
IR (ATR, film): 1730, 1595, 1517, 1365, 1366, 1244, 1188 cm^{-1}.

HRMS (ESI): Calculated for 448.1731 *m*/*z*, found 448.1723 *m*/*z* $[C_{24}H_{27}NO_6+Na]^+$.

Diethyl 5-(4-(methylthio)phenyl)-6-propyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.118)



Prepared according to General Procedure C from methyl(4-(pent-1-yn-1-yl)phenyl)sulfane (19.0 mg, 100 µmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–2% Et_2O in PhMe) to yield the desired product as yellow oil (23.7 mg, 56%).



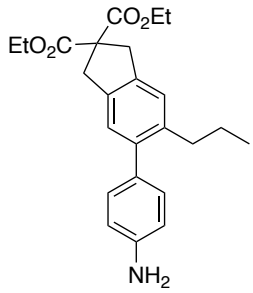
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.31 – 7.26 (m, 2H, 1, 5), 7.21 – 7.16 (m, 2H, 2, 4), 7.10 (s, 1H, 9), 6.99 (s, 1H, 12), 4.22 (q, *J* = 7.1 Hz, 4H, 20, 24), 3.61 (s, 2H, 13), 3.58 (s, 2H, 15), 2.52 (s, 3H, 30), 2.51 – 2.46 (m, 2H, 26), 1.50 – 1.41 (m, 2H, 27), 1.27 (t, *J* = 7.1 Hz, 6H, 21, 25), 0.80 (t, *J* = 7.3 Hz, 3H, 28).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 171.9 (16, 17), 140.2 (6), 139.4 (7), 139.3 (11), 139.2 (8), 137.5 (10), 136.7 (3), 129.9 (2, 4), 126.3 (1, 5), 125.8 (12), 125.0 (9), 61.8 (20, 24), 60.6 (14), 40.5 (13), 40.3 (15), 35.2 (26), 24.8 (27), 16.0 (30), 14.2 (21, 25), 14.2 (28).

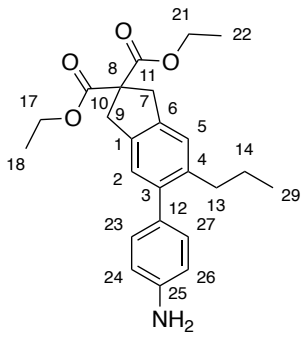
IR (ATR, film): 2961, 2866, 1730, 1439, 1368, 1242, 1184, 1157, 1061, 1011, 907, 862, 822, 642 cm^{-1}.

HRMS (ESI): Calculated for 427.1938 *m*/*z*, found 427.1937 *m*/*z* $[C_{25}H_{30}O_4S+H]^+$.

Diethyl 5-(4-aminophenyl)-6-propyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.119)



Prepared according to General Procedure C from 4-(pent-1-yn-1-yl)aniline (15.9 mg, 100 µmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% Et_2O in PhMe) to yield the desired product as an orange solid (11.0 mg, 28%).



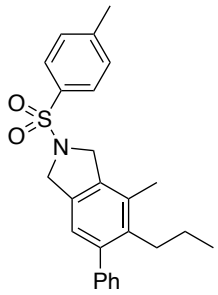
1H NMR (400 MHz, Chloroform-*d*) δ_H 7.12 – 7.06 (m, 3H, 5, 24, 26), 7.02 (s, 1H, 2), 6.73 (m, 2H, 23, 27), 4.27 – 4.20 (m, 4H, 17, 21), 3.62 (s, 2H, 7 or 9), 3.60 (s, 2H, 7 or 9), 2.55 – 2.48 (m, 2H, 13), 1.47 (m, 2H, 14), 1.28 (t, *J* = 7.1 Hz, 6H, 18, 22), 0.83 (t, J = 7.3 Hz, 3H, 29).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 171.9 (10, 11), 144.6 (25), 140.9 (3), 139.2 (4), 138.6 (6), 137.2 (1), 132.1 (12), 130.2 (24, 26), 125.9 (2), 124.7 (5), 114.7 (23, 27), 61.7 (17, 21), 60.5 (8), 40.4 (7 or 9), 40.3 (7 or 9), 35.2 (13), 24.6 (14), 14.2 (18, 22), 14.1 (29).

IR (ATR, film): 1729, 1244, 1060 cm^{-1}.

HRMS (ESI): Calculated for 396.2169 *m*/*z*, found 396.2155 *m*/*z* $[C_{24}H_{29}NO_4+H]^+$.

4-Methyl-6-phenyl-5-propyl-2-tosylisoindoline (4.120)



Prepared according to General Procedure C from pent-1-yn-1-ylbenzene (28.8 mg, 200 µmol, 1.00 equiv.) and *N*-(but-2-yn-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (314 mg, 1.20 mmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the

desired product as a yellow solid (isolated as 4:1 mixture of regioisomers, 52.1 mg, 64%).

NMR signals for major regioisomer assigned.

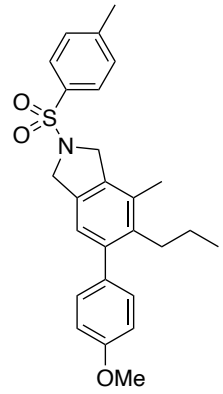
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.83 (dd, *J* = 8.3, 1.7 Hz, 2H), 7.46 – 7.40 (m, 2H), 7.38 – 7.34 (m, 4H), 7.12 – 7.05 (m, 2H), 6.97 (s, 1H), 4.78 – 4.67 (m, 2H), 4.60 (t, *J* = 1.9 Hz, 2H), 2.45 (s, 4H), 2.34 – 2.25 (m, 2H), 1.86 (s, 3H), 1.46 – 1.33 (m, 3H), 0.76 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 143.6, 141.1, 141.0, 139.9, 134.7, 133.9, 132.9, 130.9, 129.8, 129.4, 128.3, 127.7, 126.9, 120.2, 54.2, 53.5, 35.9, 24.5, 21.5, 17.2, 14.0.

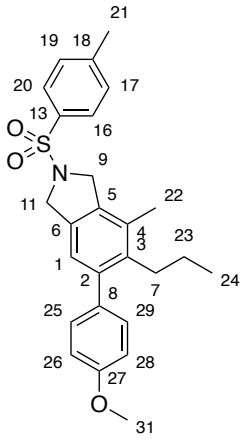
IR (ATR, film): 2959, 1344, 1163, 1098, 735, 704, 669, 586, 565, 548 cm^{-1}.

HRMS (ESI): Calculated for 406.1635 *m*/*z*, found 406.1833 *m*/*z* $[C_{25}H_{27}NO_2S+H]^+$.

6-(4-Methoxyphenyl)-4-methyl-5-propyl-2-tosylisoindoline (**4.121**)



Prepared according to General Procedure C from 1-methoxy-4-(pent-1-yn-1-ylbenzene (17.4 mg, 100 µmol, 1.00 equiv.) and *N*-(but-2-yn-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (157 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a yellow solid (4.8 mg, 11%).



^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.81 – 7.76 (m, 2H, 16, 20), 7.35 – 7.30 (m, 2H, 17, 19), 7.00 – 6.90 (m, 5H, 1, 25, 26, 28, 29), 4.68 – 4.63 (m, 2H, 11), 4.57 – 4.55 (m, 2H, 9),

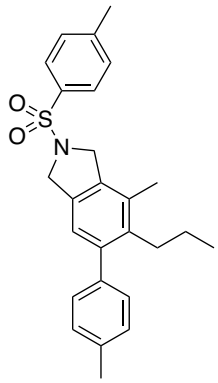
3.85 (s, 3H, 31), 2.42 (s, 3H, 21), 2.31 – 2.22 (m, 2H, 7), 1.84 (s, 3H, 22), 1.41 – 1.28 (m, 2H, 23), 0.74 (t, J = 7.3 Hz, 3H, 24).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 158.4 (27), 143.6 (18), 141.5 (8), 140.8 (3), 134.6 (6), 133.8 (5), 132.9 (2), 132.0 (4), 131.4 (13), 130.4 (25, 29), 129.8 (17, 19), 127.7 (16, 20), 120.1 (1), 113.7 (26, 28), 55.2 (31), 54.2 (11), 53.5 (9), 35.9 (7), 24.5 (23), 21.5 (21), 17.2 (22), 14.1 (24).

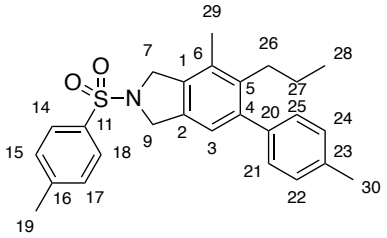
IR (ATR, film):2957, 1609, 1514, 1344, 1285, 1242, 1161, 1098, 1034, 831, 812, 667, 608, 581, 548 cm^{-1}.

HRMS (ESI): Calculated for 436.1941 *m*/*z*, found 436.1951 *m*/*z* $[C_{26}H_{29}NO_3S+H]^+$.

4-Methyl-5-propyl-6-(*p*-tolyl)-2-tosylisoindoline (4.122)



Prepared according to General Procedure C from 1-methyl-4-(pent-1-yn-1-yl)benzene (31.6 mg, 200 µmol, 1.00 equiv.) and *N*-(but-2-yn-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (314 mg, 1.20 mmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a yellow solid (9.3 mg, 11%).



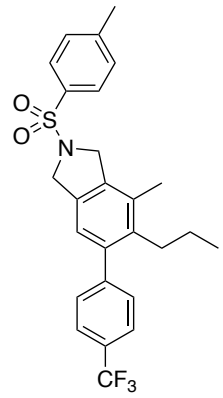
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.85 – 7.80 (m, 2H, 14, 18), 7.37 – 7.32 (m, 2H, 15, 17), 7.24 – 7.18 (m, 2H, 22, 24), 6.98 – 6.93 (m, 2H, 3, 21, 25), 4.71 – 4.67 (m, 2H, 9), 4.59 (s, 1H, 7), 2.44 (s, 3H, 19), 2.42 (s, 3H, 30), 2.35 – 2.25 (m, 2H, 26), 1.85 (s, 3H, 29), 1.46 – 1.32 (m, 2H, 27), 0.76 (t, J = 7.3 Hz, 2H, 28).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 143.6 (16), 141.2 (5), 141.1 (6), 136.8 (23), 136.4 (4), 134.5 (2), 133.9 (1), 132.9 (11), 131.1 (20), 129.8 (15, 17), 129.2 (21, 25), 129.0 (22, 24), 127.7 (14, 18), 120.1 (3), 54.2 (9), 53.5 (7), 35.9 (26), 24.5 (27), 21.5 (19), 21.2 (30), 17.2 (29), 14.0 (28).

IR (ATR, film): 2959, 1344, 1265, 1163, 1098, 814, 735, 704, 667, 548 cm^{-1}.

HRMS (ESI): Calculated for 420.1992 *m*/*z*, found 420.1991 *m*/*z* $[C_{26}H_{29}NO_2S+H]^+$.

4-Methyl-5-propyl-2-tosyl-6-(4-(trifluoromethyl)phenyl)isoindoline (**4.123**)



Prepared according to General Procedure C from 1-(pent-1-yn-1-yl)-4-(trifluoromethyl)benzene (21.2 mg, 100 µmol, 1.00 equiv.) and *N*-(but-2-yn-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (157 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a yellow solid (isolated as 3:1 ration of regioisomers, 14.9 mg, 33%).

NMR signals of major regioisomer assigned.

^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.80 (dd, *J* = 8.3, 1.5 Hz, 2H), 7.70 – 7.64 (m, 2H), 7.37 – 7.32 (m, 2H), 7.19 (dt, *J* = 7.8, 0.8 Hz, 2H), 6.95 (s, 1H), 4.71 – 4.65 (m, 2H), 4.57 (d, *J* = 2.3 Hz, 2H), 2.42 (s, 3H), 2.25 – 2.17 (m, 2H), 1.81 (s, 3H), 1.40 – 1.29 (m, 2H), 0.76 – 0.69 (m, 3H).

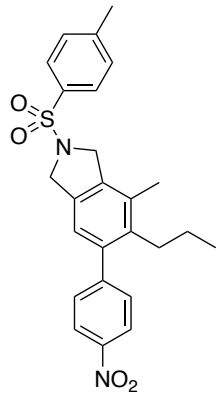
^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.9, 143.7, 140.7, 139.6, 135.4, 133.8, 133.2, 130.6, 129.9, 129.3 (q, $^2J_{CF}$ = 32.6 Hz), 127.7, 125.4 (q, $^3J_{CF}$ = 3.8 Hz), 125.3 (q, $^1J_{CF}$ = 271.7 Hz), 120.4, 54.1, 53.4, 35.7, 24.4, 21.6, 17.2, 14.0.

^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*) δ_F −62.4.

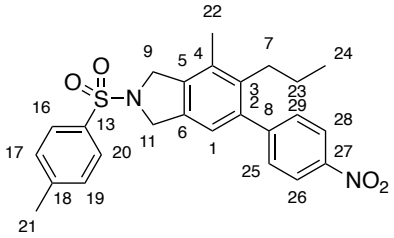
IR (ATR, film): 2928, 1323, 1163, 1123, 1105, 1067, 814, 671, 548 cm^{-1}.

HRMS (ESI): Calculated for 474.1709 *m*/*z*, found 474.1711 *m*/*z* $[C_{26}H_{27}F_3NO_2S]^+$.

4-Methyl-6-(4-nitrophenyl)-5-propyl-2-tosylisoindoline (**4.124**)



Prepared according to General Procedure C from 1-nitro-4-(pent-1-yn-1-yl)benzene (18.9 mg, 100 μmol, 1.00 equiv.) and *N*-(but-2-yn-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (157 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a yellow solid (15.8 mg, 35%).



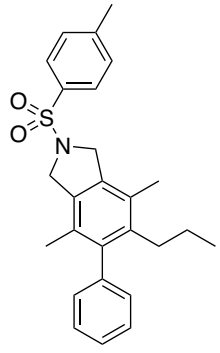
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 8.32 – 8.24 (m, 2H, 26, 28), 7.85 – 7.76 (m, 2H, 17, 19), 7.34 (m, 2H, 16, 20), 7.26 (d, *J* = 8.6 Hz, 2H, 25, 29), 6.96 (s, 1H, 1), 4.67 (s, 2H, 9), 4.57 (s, 2H, 11), 2.42 (s, 3H, 21), 2.24 – 2.16 (m, 2H, 7), 1.81 (s, 3H, 22), 1.39 – 1.29 (m, 2H, 23), 0.73 (t, *J* = 7.3 Hz, 3H, 24).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 147.4 (27), 147.1 (8), 143.7 (13), 140.4 (3), 138.7 (2), 135.9 (18), 133.8 (5), 133.4 (6), 130.6 (25, 29), 130.3 (4), 129.9 (16, 20), 127.7 (17, 19), 123.7 (26, 28), 120.6 (1), 54.1 (11), 53.3 (9), 35.8 (7), 24.4 (23), 21.6 (21), 17.2 (22), 14.0 (24).

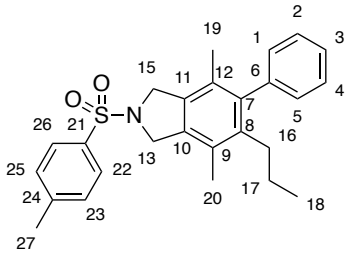
IR (ATR, film): 2957, 1597, 1518, 1344, 1161, 1098, 853, 735, 1706, 671, 604, 594, 548 cm^{-1}.

HRMS (ESI): Calculated for 451.1686 *m*/*z*, found 451.1683 *m*/*z* $[C_{25}H_{26}N_2O_4S+H]^+$.

4,7-Dimethyl-5-phenyl-6-propyl-2-tosylisoindoline (**4.125**)



Prepared according to General Procedure C from pent-1-yn-1-ylbenzene (14.4 mg, 100 µmol, 1.00 equiv.) and *N*,*N*-di(but-2-yn-1-yl)-4-methylbenzenesulfonamide (165 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (10.0 mg, 24%).



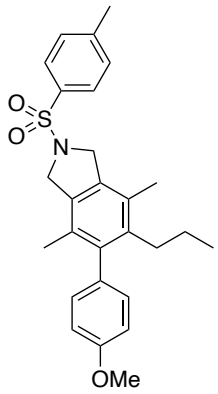
^{1}H NMR (300 MHz, Chloroform-*d*) δ_H 7.83 (d, *J* = 8.2 Hz, 2H, 22, 26), 7.47 – 7.33 (m, 5H, 2–4, 23, 25), 7.10 – 7.04 (m, 2H, 1, 5), 4.67 (s, 2H, 13 or 15), 4.62 (s, 2H, 13 or 15), 2.45 (s, 3H, 19 or 20), 2.31 – 2.23 (m, 2H, 16), 2.19 (s, 3H, 27), 1.79 (s, 3H, 19 or 20), 1.35 – 1.23 (m, 2H, 17), 0.73 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (24), 142.0 (6), 140.8 (8), 139.5, 134.6, 134.0, 132.5 (21), 130.0 (22, 26), 129.4, 128.4 (11), 128.0 (10), 127.8 (23, 25), 126.9 (6), 54.3 (15), 54.1 (13), 32.9 (16), 23.8 (17), 21.7 (27), 17.3 (19), 15.8 (20), 14.6 (18).

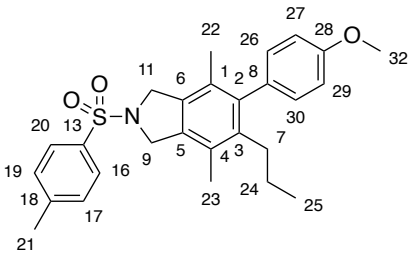
IR (ATR, film): 1348, 1165, 1098, 669, 405 cm^{-1}.

HRMS (ESI): Calculated for 420.1992 *m*/*z*, found 420.1990 *m*/*z* $[C_{26}H_{29}NO_2S+H]^+$.

5-(4-Methoxyphenyl)-4,7-dimethyl-6-propyl-2-tosylisoindoline (**4.126**)



Prepared according to General Procedure C from 1-methoxy-4-(pent-1-yn-1-yl)benzene (17.4 mg, 100 µmol, 1.00 equiv.) and *N*,*N*-di(but-2-yn-1-yl)-4-methylbenzenesulfonamide (165 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a yellow solid (5.3 mg, 12%).



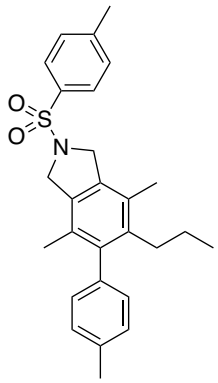
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.82 – 7.78 (m, 2H, 16, 20), 7.34 – 7.30 (m, 2H, 17, 19), 6.99 – 6.88 (m, 4H, 26, 27, 29, 30), 4.63 (m, 2H, 9), 4.59 (m, 2H, 11), 3.85 (s, 3H, 32), 2.42 (s, 3H, 21), 2.30 – 2.21 (m, 2H, 7), 2.15 (s, 3H, 23), 1.77 (s, 3H, 22), 1.29 – 1.23 (m, 2H, 24), 0.72 (t, *J* = 7.3 Hz, 3H, 25).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 158.3 (28), 143.6 (18), 141.5 (8), 139.8 (3), 134.4 (13), 132.9 (2), 132.4 (1), 130.3 (26, 30), 129.8 (17, 19), 128.7 (5), 127.8 (4), 127.6 (16, 20), 127.0 (6), 113.6 (27, 29), 55.2 (32), 54.1 (9), 54.0 (11), 32.8 (7), 23.6 (24), 21.5 (21), 17.2 (23), 15.7 (23), 14.6 (25).

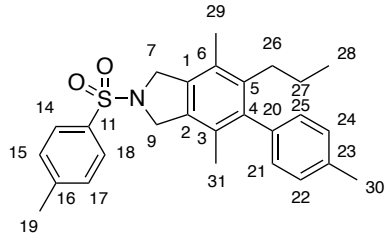
IR (ATR, film): 2957, 2361, 1609, 1514, 1346, 1244, 1163, 1103, 833, 669, 548 cm^{-1}.

HRMS (ESI): Calculated for 450.2097 *m*/*z*, found 450.2094 *m*/*z* $[C_{27}H_{23}NO_3S+H]^+$.

4,7-Dimethyl-5-propyl-6-(*p*-tolyl)-2-tosylisoindoline (**4.127**)



Prepared according to General Procedure C from 1-methyl-4-(pent-1-yn-1-yl)benzene (31.6 mg, 200 μmol, 1.00 equiv.) and *N*,*N*-di(but-2-yn-1-yl)-4-methylbenzenesulfonamide (330 mg, 1.20 mmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (15.5 mg, 17%).



^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.83 (d, *J* = 8.2 Hz, 2H, 14, 18), 7.38 – 7.33 (m, 2H, 15, 17), 7.25 – 7.19 (m, 2H, 22, 24), 6.98 – 6.92 (m, 2H, 21, 25), 4.66 (m, 2H, 7), 4.62 (m, 2H,

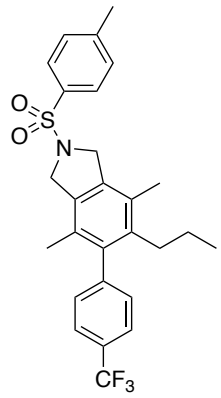
9), 2.45 (s, 3H, 19), 2.42 (s, 3H, 30), 2.32 – 2.22 (m, 2H, 26), 2.18 (s, 3H, 29), 1.79 (s, 3H, 31), 1.35 – 1.23 (m, 2H, 27), 0.74 (t, J = 7.3 Hz, 3H, 28).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 143.6 (16), 141.9 (4), 139.5 (5), 137.6 (20), 136.3 (23), 134.3 (1), 133.9 (11), 132.4 (2), 129.8 (15, 17), 129.1 (21, 25), 129.0 (22, 24), 128.4 (3), 127.8 (6), 127.6 (14, 18), 54.1 (7), 54.0 (9), 32.7 (26), 23.7 (27), 21.5 (19), 21.3 (30), 17.2 (31), 15.7 (29), 14.5 (28).

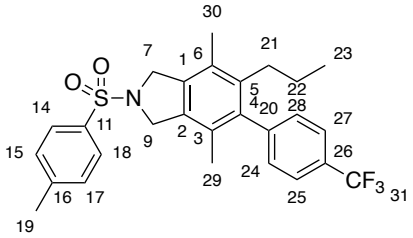
IR (ATR, film): 2957, 1449, 1344, 1161, 1098, 1065, 816, 737, 669, 606, 596, 563, 546, 525 cm^{-1}.

HRMS (ESI): Calculated for 434.2148 *m*/*z*, found 434.2145 *m*/*z* $[C_{27}H_{31}NO_2S+H]^+$.

4,7-Dimethyl-5-propyl-2-tosyl-6-(4-(trifluoromethyl)phenyl)isoindoline (4.128)



Prepared according to General Procedure C from 1-(pent-1-yn-1-yl)-4-(trifluoromethyl)benzene (42.4 mg, 200 μmol, 1.00 equiv.) and *N*,*N*-di(but-2-yn-1-yl)-4-methylbenzenesulfonamide (330 mg, 1.20 mmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (1.5 mg, 2%).



^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.81 (d, J = 8.3 Hz, 2H, 14, 18), 7.66 (d, J = 8.0 Hz, 2H, 24, 28), 7.34 (d, J = 8.0 Hz, 2H, 15, 17), 7.19 (d, J = 7.9 Hz, 2H, 25, 27), 4.64 (s, 2H, 7), 4.59 (s, 2H, 9), 2.42 (s, 3H, 19), 2.30 – 2.18 (m, 2H, 21), 2.16 (s, 3H, 30), 1.74 (s, 3H, 29), 1.27 – 1.19 (m, 2H, 22), 0.71 (t, J = 7.3 Hz, 3H, 23).

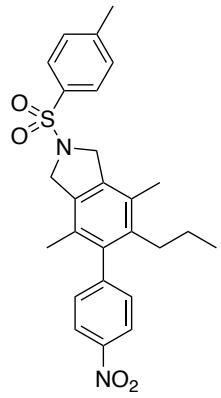
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 144.7 (20), 143.7 (16), 140.3 (5), 139.0 (4), 135.1 (2), 133.8 (11), 132.7 (1), 129.9 (15, 17), 129.8 (24, 28), 128.0 (q, $^2J_{CF}$ = 40.5 Hz, 26), 127.6 (14, 18) 127.8 (6) 125.3 (q, $^3J_{CF}$ = 3.6 Hz, 25, 27), 122.4 (3) 121.4 (q, $^1J_{CF}$ = 265.8 Hz, 31), 54.1 (9), 53.9 (7), 32.7 (21), 23.6 (22), 21.6 (19), 17.1 (29), 15.7 (30), 14.5 (23).

^{19}F{^{1}H} NMR (470 MHz, Chloroform-*d*) δ −62.4.

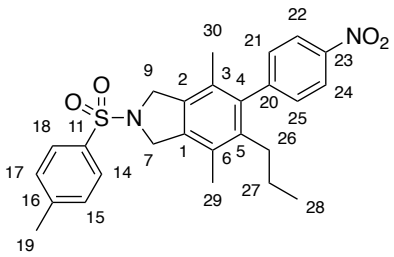
IR (ATR, film): 2959, 2359, 1325, 1163, 1125, 1067, 669, 584, 548, 413 cm^{-1}.

HRMS (ESI): Calculated for 488.1866 *m*/*z*, found 488.1860 *m*/*z* $[C_{27}H_{28}F_3NO_2S+H]^+$.

4,7-Dimethyl-5-(4-nitrophenyl)-6-propyl-2-tosylisoindoline (**4.129**)



Prepared according to General Procedure C from 1-nitro-4-(pent-1-yn-1-yl)benzene (18.9 mg, 100 μmol, 1.00 equiv.) and *N*,*N*-di(but-2-yn-1-yl)-4-methylbenzenesulfonamide (165 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–100% PhMe in hexane) to yield the desired product as a yellow solid (22.1 mg, 48%).



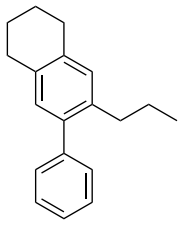
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 8.35 – 8.23 (m, 2H, 22, 24), 7.85 – 7.76 (m, 2H, 14, 18), 7.34 (d, *J* = 8.1 Hz, 2H, 15, 17), 7.29 – 7.22 (m, 2H, 21, 25), 4.64 (m, 2H, 7), 4.59 (m, 2H, 9), 2.43 (s, 3H, 19), 2.24 – 2.18 (m, 2H, 26), 2.17 (s, 3H, 29), 1.75 (s, 3H, 30), 1.31 – 1.17 (m, 2H, 27), 0.71 (t, *J* = 7.3 Hz, 3H, 28).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 148.2 (23), 147.0 (20), 143.7 (16), 139.5 (4), 138.7 (5), 135.6 (1), 133.9 (11), 132.9 (2), 130.5 (21, 25), 129.9 (15, 17), 128.4 (6), 127.6 (14, 18), 127.5 (3), 123.6 (22, 24), 54.1 (7), 53.8 (9), 32.7 (26), 23.6 (27), 21.6 (19), 17.1 (30), 15.6 (29), 14.5 (28).

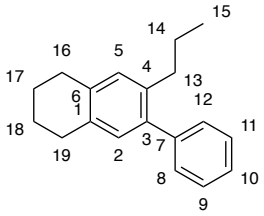
IR (ATR, film): 2957, 1597, 1518, 1346, 1163, 1101, 669, 588, 548 cm^{-1}.

HRMS (ESI): Calculated for 465.1843 *m*/*z*, found 465.1843 *m*/*z* $[C_{26}H_{29}N_2O_4S+H]^+$.

6-Phenyl-7-propyl-1,2,3,4-tetrahydronaphthalene (**4.130**)



Prepared according to General Procedure C from pent-1-yn-1-ylbenzene (14.4 mg, 100 µmol, 1.00 equiv.) and 1,7-octadiyne (63.7 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as white solid (11.0 mg, 44%).



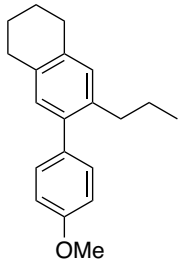
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.42 – 7.36 (m, 2H, 9, 11), 7.35 – 7.28 (m, 3H, 8, 10, 12), 7.00 (s, 1H, 5), 6.92 (s, 1H, 2), 2.86 – 2.72 (m, 4H, 16, 19), 2.54 – 2.44 (m, 2H, 13), 1.82 (m, 17, 18), 1.53 – 1.42 (m, 2H, 14), 0.81 (t, J = 7.3 Hz, 3H, 15).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 142.3 (7), 139.4 (3), 137.3 (4), 136.3 (1), 134.4 (6), 130.8 (2), 130.0 (5), 129.5 (8, 12), 128.1 (9, 11), 126.6 (10), 34.9 (13), 29.3 (19), 29.1 (16), 24.8 (14), 23.5 (18), 23.5 (17), 14.3 (15).

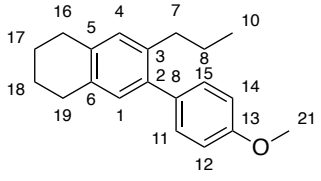
IR (ATR, film): 2926, 2857, 1483, 736, 700, 419 cm^{-1}.

HRMS (EI): Calculated for 250.17215 *m*/*z*, found 250.172210 *m*/*z* $[C_{19}H_{22}]^+$.

6-(4-Methoxyphenyl)-7-propyl-1,2,3,4-tetrahydronaphthalene (**4.131**)



Prepared according to General Procedure C from 1-methoxy-4-(pent-1-yn-1-yl)benzene (17.4 mg, 100 µmol, 1.00 equiv.) and 1,7-octadiyne (63.7 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a colourless oil (7.3 mg, 26%).



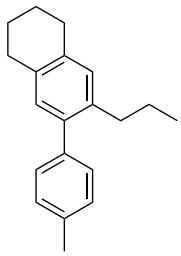
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.23 – 7.19 (m, 2H, 12, 14), 6.98 (s, 1H, 1), 6.94 – 6.91 (m, 2H, 11, 15), 6.90 (s, 1H, 4), 3.85 (s, 3H, 21), 2.86 – 2.73 (m, 4H, 16, 19), 2.54 – 2.45 (m, 2H, 7), 1.97 – 1.76 (m, 4H, 17, 18), 1.52 – 1.40 (m, 2H, 9), 0.82 (t, J = 7.4 Hz, 3H, 10).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 158.3 (13), 138.8 (2), 137.4 (3), 135.9 (5), 134.5 (6), 134.3 (8), 130.8 (4), 130.3 (12, 14), 129.8 (1), 113.3 (11, 15), 55.3 (21), 34.9 (7), 29.1 (19), 28.9 (16), 24.7 (9), 23.4 (17 or 18), 23.4 (17 or 18), 14.2 (10).

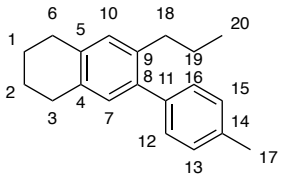
IR (ATR, film): 2924, 1609, 1491, 1242, 1175, 1040, 833 cm^{-1}.

HRMS (EI): Calculated for 280.18217 *m*/*z*, found 280.181428 *m*/*z* $[C_{20}H_{24}O]^+$.

6-Propyl-7-(*p*-tolyl)-1,2,3,4-tetrahydronaphthalene (4.132)



Prepared according to General Procedure C from 1-methyl-4-(pent-1-yn-1-yl)benzene (31.6 mg, 200 µmol, 1.00 equiv.) and 1,7-octadiyne (127 mg, 1.20 mmol, 6.00 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a yellow solid (12.2 mg, 23%).



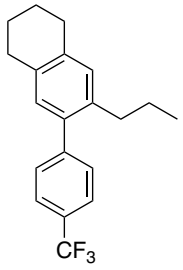
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.19 (m, 4H, 12, 13, 15, 16), 6.99 (s, 1H, 10), 6.91 (s, 1H, 7), 2.81 – 2.71 (m, 4H, 3, 6), 2.58 – 2.44 (m, 2H, 18), 2.40 (s, 3H, 17), 1.92 – 1.74 (m, 4H, 1, 2), 1.53 – 1.42 (m, 2H, 19), 0.83 (t, J = 7.3 Hz, 3H, 20).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 139.2 (4 or 8), 139.2 (4 or 8), 137.3 (9), 136.0 (14), 136.0 (11), 134.3 (5), 130.8 (7), 129.8 (10), 129.2 (12, 16), 128.7 (13, 15), 34.8 (18), 29.1 (6), 28.9 (3), 24.7 (19), 23.4 (1 or 2), 23.4 (1 or 2), 21.2 (17), 14.2 (20).

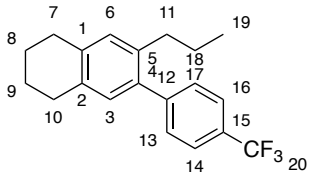
IR (ATR, film): 2924, 2859, 1491, 1344, 1163, 1098, 822, 667, 546, 403 cm^{-1}.

HRMS (EI): Calculated for 264.18725 *m*/*z*, found 264.186897 *m*/*z* $[C_{20}H_{24}]^+$.

6-Propyl-7-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydronaphthalene (4.133)



Prepared according to General Procedure C from 1-(pent-1-yn-1-yl)-4-(trifluoromethyl)benzene (21.2 mg, 100 µmol, 1.00 equiv.) and 1,7-octadiyne (63.7 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, hexane) to yield the desired product as a colourless oil (2.9 mg, 9%).



^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.64 (d, J = 8.0 Hz, 2H, 13, 17), 7.41 (d, J = 7.9 Hz, 2H, 14, 16), 7.01 (s, 1H, 6), 6.89 (s, 1H, 3), 2.90 – 2.69 (m, 4H, 7, 10), 2.50 – 2.44 (m, 2H, 11), 1.87 – 1.79 (m, 4H, 8, 9), 1.52 – 1.42 (m, 2H, 18), 0.82 (t, J = 7.3 Hz, 3H, 19).

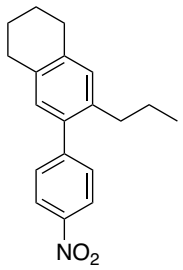
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 145.9 (4), 137.8 (12), 137.0 (2), 136.9 (5), 134.6 (1), 130.5 (3), 130.1 (6), 129.7 (13, 17), 128.7 (q, $^{2}J_{CF}$ = 32.4 Hz, 15), 124.9 (q, $^{3}J_{CF}$ = 3.5 Hz, 14, 16), 124.4 (q, $^{1}J_{CF}$ = 271.9 Hz, 20), 34.7 (11), 29.2 (7), 28.9 (10), 24.7 (18), 23.3 (9), 23.3 (8), 14.1 (19).

^{19}F{^{1}H} NMR (470 MHz, Chloroform-*d*) δ_F −62.3.

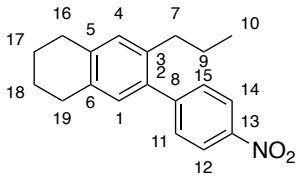
IR (ATR, film): 2930, 1618, 1321, 1163, 1123, 1105, 1067, 1020, 845 cm^{-1}.

HRMS inconclusive due to excessive fragmentation.

6-(4-Nitrophenyl)-7-propyl-1,2,3,4-tetrahydronaphthalene (4.134)



Prepared according to General Procedure C from 1-nitro-4-(pent-1-yn-1-yl)benzene (18.9 mg, 100 µmol, 1.00 equiv.) and 1,7-octadiyne (63.7 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% PhMe in hexane) to yield the desired product as a yellow solid (8.9 mg, 30%).



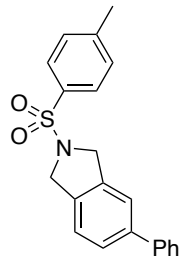
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 8.27 – 8.22 (m, 2H, 12, 14), 7.51 – 7.43 (m, 2H, 11, 15), 7.02 (s, 1H, 4), 6.89 (s, 1H, 1), 2.83 – 2.73 (m, 4H, 16, 19), 2.50 – 2.42 (m, 2H, 7), 1.87 – 1.78 (m, 4H, 17, 18), 1.50 – 1.37 (m, 2H, 9), 0.81 (t, J = 7.3 Hz, 3H, 10).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 149.3 (8), 146.2 (13), 137.6 (6), 136.9 (3), 136.8 (2), 134.8 (5), 130.3 (1), 130.2 (4), 130.2 (11, 15), 123.3 (12, 14), 34.7 (7), 29.2 (16), 28.9 (19), 24.7 (9), 23.2 (17 or 18), 23.2 (17 or 18), 14.1 (10).

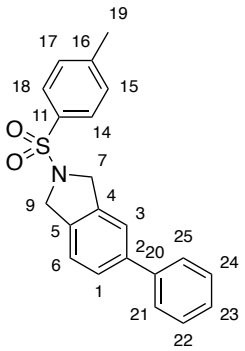
IR (ATR, film): 2934, 1595, 1518, 1344, 1179, 854 cm^{-1}.

HRMS (ESI): Calculated for 296.1645 *m*/*z*, found 296.1638 *m*/*z* $[C_{19}H_{21}NO_2+H]^+$.

5-Phenyl-2-tosylisoindoline (**4.135**)



Prepared according to General Procedure C from phenylacetylene (10.2 mg, 100 μmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% EtOAc in hexane) to yield the desired product as a white solid (22.2 mg, 64%).

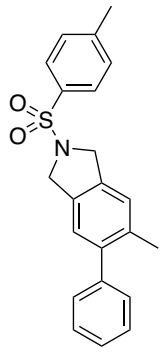


^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.82 – 7.77 (m, 2H, 14, 18), 7.53 – 7.49 (m, 2H, 21, 25), 7.47 – 7.39 (m, 3H, 6, 22, 24), 7.39 – 7.30 (m, 4H, 3, 15, 17, 23), 7.25 – 7.21 (m, 1H, 1), 4.69 – 4.64 (m, 4H, 7, 9), 2.41 (s, 3H, 19).

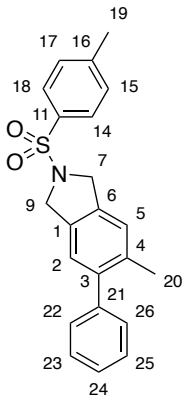
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.9 (16), 141.4 (2), 140.7 (20), 137.0 (5), 135.3 (4), 133.8 (11), 130.0 (15, 17), 129.0 (22, 24), 127.8 (14, 18), 127.7 (23), 127.3 (21, 25), 127.1 (6), 123.1 (1), 121.5 (3), 53.9 (7 or 9), 53.7 (7 or 9), 21.7 (19).

Spectral data consistent with the literature.[375]

5-Methyl-6-phenyl-2-tosylisoindoline (4.136)



Prepared according to General Procedure C from 1-phenyl-1-propyne (11.6 mg, 100 μmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 μmol). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (37.4 mg, >99%).



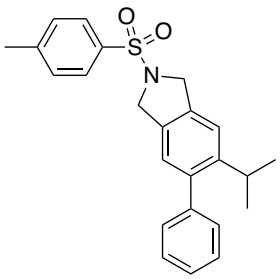
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.83 – 7.77 (m, 2H, 14, 18), 7.39 (m, 2H, 23, 25), 7.36 – 7.31 (m, 3H, 15, 17, 24), 7.25 – 7.21 (m, 2H, 22, 26), 7.08 (s, 1H, 5), 7.03 (s, 1H, 2), 4.63 (s, 2H, 7 or 9), 4.62 (s, 2H, 7 or 9), 2.41 (s, 3H, 19), 2.21 (s, 3H, 20).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.9 (16), 141.9 (4), 141.4 (3), 135.4 (21), 135.3 (1), 133.78 (6), 133.77 (11), 129.9 (15, 17), 129.2 (22, 26), 128.3 (23, 25), 127.8 (14, 18), 127.2 (24), 124.3 (5), 123.9 (2), 53.7 (9), 53.7 (7), 21.6 (19), 20.6 (20).

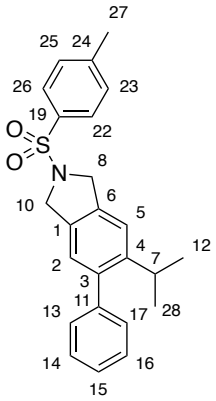
IR (ATR, film): 1339, 1265, 1161, 1096, 1017, 735, 702, 665, 606, 557, 548 cm^{-1}.

HRMS (ESI): Calculated for 364.1365 *m*/*z*, found 364.1370 *m*/*z* $[C_{22}H_{21}NO_2S+H]^+$.

5-Isopropyl-6-phenyl-2-tosylisoindoline (4.137)



Prepared according to General Procedure C from (3-methylbut-1-yn-1-yl)benzene (14.4 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as white solid (31.3 mg, 80%).



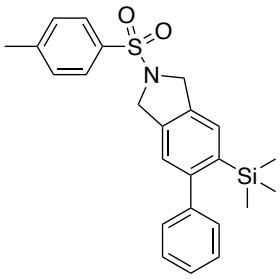
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.82 – 7.77 (m, 2H, 22, 26), 7.41 – 7.31 (m, 5H, 14–16, 23, 25), 7.22 – 7.17 (m, 3H, 5, 13, 17), 6.98 (s, 1H, 2), 4.64 (m, 4H, 8, 10), 3.00 (hept, J = 6.8 Hz, 1H, 7), 2.42 (s, 3H, 27), 1.10 (d, J = 6.9 Hz, 6H, 12, 19).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 146.7 (24), 143.8 (4), 141.6 (11), 141.1 (19), 135.8 (1), 133.9 (6), 133.3 (3), 129.9 (23, 25), 129.3 (13, 17), 128.2 (14, 16), 127.8 (22, 26) 127.1 (15), 124.1 (2), 119.8 (5), 53.9 (8), 53.7 (10), 29.6 (7), 24.4 (12, 28), 21.6 (27).

IR (ATR, film): 2961, 2924, 1344, 1163, 1099, 1061, 667, 546 cm^{-1}.

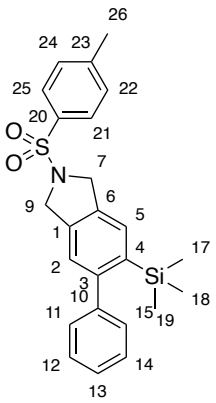
HRMS (ESI): Calculated for 392.1679 *m*/*z*, found 392.1677 *m*/*z* $[C_{24}H_{25}NO_2S+H]^+$.

5-Phenyl-2-tosyl-6-(trimethylsilyl)isoindoline (4.138)



Prepared according to General Procedure C from trimethyl(phenylethynyl)silane (17.4 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600

μmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as white solid (27.4 mg, 65%).



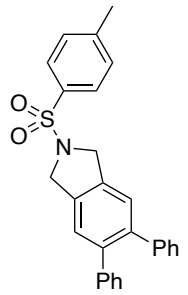
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.84 – 7.79 (m, 2H, 21, 25), 7.43 (s, 1H, 2), 7.41 – 7.36 (m, 3H, 12–14), 7.35 (d, *J* = 8.0 Hz, 2H, 22, 24), 7.25 – 7.20 (m, 2H, 11, 15), 7.06 (s, 1H, 5), 4.69 (s, 2H, 7), 4.66 (s, 2H, 9), 2.44 (s, 3H, 26), –0.02 (s, 9H, 17–19).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 149.2 (3), 143.82 (23), 143.81 (10), 138.7 (4), 136.8 (1), 134.4 (6), 133.7 (20), 130.0 (22, 24), 129.5 (11, 15), 128.8 (2), 127.9 (21, 25), 127.8 (12, 14), 127.5 (13), 123.8 (5), 53.9 (9), 53.8 (7), 21.7 (26), 0.7 (17–19).

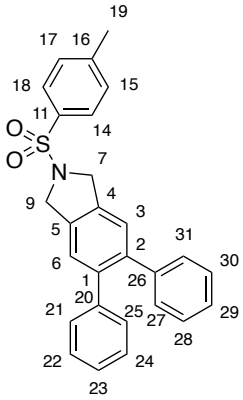
IR (ATR, film): 1346, 1165, 1098, 839, 665, 548 cm^{-1}.

HRMS (ESI): Calculated for 422.1605 *m*/*z*, found 422.1596 *m*/*z* $[C_{24}H_{27}NO_2SSi+H]^+$.

5,6-Diphenyl-2-tosylisoindoline (**4.139**)



Unable to isolate from [2+2+2] reaction however compared NMR to authentic product prepared as described. A flame-dried flask was charged with diphenylethyne (89.1 mg, 500 μmol, 1.00 equiv.), Ti(O*i*-Pr)$_4$ (330 μL, 1.09 mmol, 2.18 equiv.), and dry THF (5.00 mL, 100 mM) under N_2. After cooling to 0 ºC, *n*-butyllithium solution (2.10 M in hexane, 800 μL, 1.68 mmol, 3.36 equiv.) was added dropwise. After stirring for 0.5 h, a solution of 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (155 mg, 625 μmol, 1.25 equiv.) in dry THF (1.00 mL) was added. This mixture was stirred for 0.5 h at 0 ºC before allowing to come up to RT to stir for a further 2 h. The solution was then quenched with the addition of excess dilute aqueous HCl (10 mL), then extracted with Et_2O (3 × 10 mL). The organic extracts were combined and dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product. Purified by flash column chromatography (silica, 0–10% EtOAc in hexane) to yield the desired product as a white powder (52.9 mg, 25%).



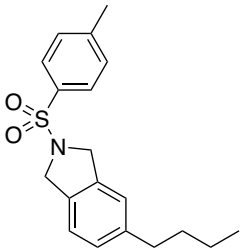
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.81 (d, *J* = 8.2 Hz, 2H, 14, 18), 7.34 (d, *J* = 8.1 Hz, 2H, 15, 17), 7.22 (s, 2H, 3, 6), 7.21 – 7.16 (m, 6H, 22–24, 28–30), 7.05 (dd, *J* = 6.6, 3.0 Hz, 4H, 21, 25, 27, 31), 4.70 (s, 4H, 7, 9), 2.42 (s, 3H, 19).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.9 (16), 141.0, 140.8, 135.6 (4, 5), 133.7 (11), 130.0 (15, 17), 129.9 (21, 25, 27, 31), 128.1 (22, 24, 28, 30), 127.8 (14, 18), 126.8 (23, 29), 124.8 (3, 6), 53.7 (7, 9), 21.7 (19).

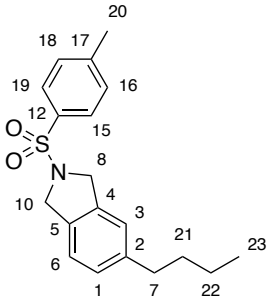
Unambiguous assignment of all ^{13}C NMR signals could not be performed.

Spectral data consistent with the literature.[376]

5-Butyl-2-tosylisoindoline (**4.140**)



Prepared according to General Procedure C from 1-hexyne (8.21 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% EtOAc in hexane) to yield the desired product as a white solid (7.2 mg, 22%).

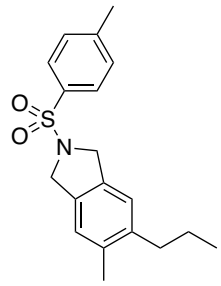


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.76 (d, *J* = 8.3 Hz, 2H, 15, 19), 7.33 – 7.29 (m, 2H, 16, 18), 7.09 – 7.01 (m, 2H, 1, 6), 6.98 (s, 1H, 3), 4.58 (m, 4H, 8, 10), 2.59 – 2.52 (m, 2H, 7), 2.40 (s, 3H, 20), 1.58 – 1.49 (m, 2H, 21), 1.32 (m, 2H, 22), 0.90 (t, *J* = 7.4 Hz, 3H, 23).

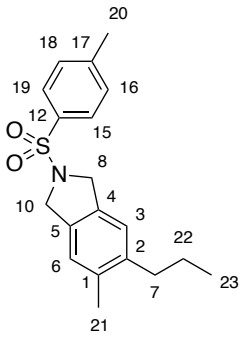
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (17), 143.0 (2), 136.3 (5), 133.9 (12), 133.5 (4), 129.9 (16, 18), 128.1 (6), 127.8 (15, 19), 122.6 (3), 122.5 (1), 53.8 (8 or 10), 53.7 (8 or 10), 35.6 (7), 33.9 (21), 22.4 (22), 21.6 (20), 14.0 (23).

Spectral data consistent with the literature.[377]

5-Methyl-6-propyl-2-tosylisoindoline (**4.141**)



Prepared according to General Procedure C from 2-hexyne (8.21 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (25.0 mg, 76%).



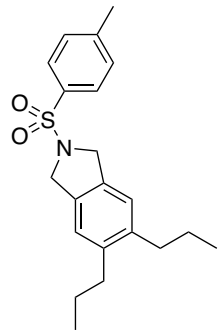
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.77 – 7.74 (m, 2H, 15, 19), 7.30 (d, *J* = 8.0 Hz, 2H, 16, 18), 6.93 (m, 2H, 3, 6), 4.58 – 4.54 (m, 4H, 8, 10), 2.54 – 2.48 (m, 2H, 7), 2.39 (s, 3H, 20), 2.25 (s, 3H, 21), 1.59 – 1.48 (m, 2H, 22), 0.95 (t, *J* = 7.3 Hz, 3H, 23).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (17), 140.9 (2), 135.8 (1), 133.9 (4 or 5 or 12), 133.8 (4 or 5 or 12), 133.7 (4 or 5 or12), 129.9 (16, 18), 127.7 (15, 19), 124.1 (3 or 6), 122.9 (3 or 6), 53.8 (8), 53.7 (10), 35.5 (7), 23.6 (22), 21.6 (20), 19.5 (21), 14.3 (23).

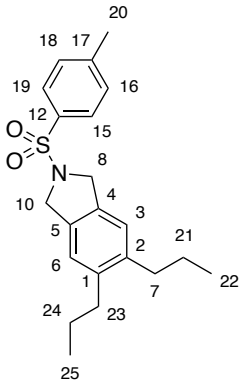
IR (ATR, film): 1343, 1163, 1098, 667, 550 cm^{-1}.

HRMS (ESI): Calculated for 330.1522 *m*/*z*, found 330.1523 *m*/*z* $[C_{19}H_{23}NO_2S+H]^+$.

5,6-Dipropyl-2-tosylisoindoline (**4.142**)



Prepared according to General Procedure C from 4-octyne (11.0 mg, 100 μmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (21.2 mg, 59%).



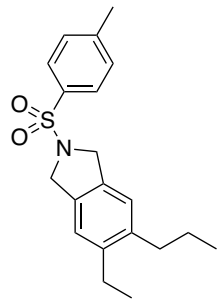
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.79 – 7.74 (m, 2H, 15, 19), 7.30 (d, *J* = 8.0 Hz, 2H, 16, 18), 6.94 (s, 2H, 3, 6), 4.56 (s, 4H, 8, 10), 2.58 – 2.51 (m, 4H, 7, 23), 2.40 (s, 3H, 20), 1.60 – 1.46 (m, 4H, 21, 24), 0.96 (t, *J* = 7.3 Hz, 6H, 22, 25).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (17), 140.4 (1, 2), 133.9 (12), 133.7 (4, 5), 129.9 (16, 18), 127.8 (15, 19), 123.2 (3, 6), 53.7 (8, 10), 34.8 (7, 23), 24.6 (21, 24), 21.6 (20), 14.3 (22, 25).

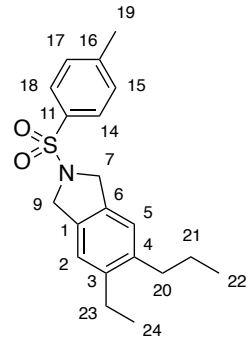
IR (ATR, film): 1344, 1163, 1098, 1061, 665, 550 cm^{-1}.

HRMS (ESI): Calculated for 358.1835 *m*/*z*, found 358.1834 *m*/*z* $[C_{21}H_{27}NO_2S+H]^+$.

5-Ethyl-6-propyl-2-tosylisoindoline (**4.143**)



Prepared according to General Procedure C from 3-heptyne (9.62 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (29.9 mg, 85%).



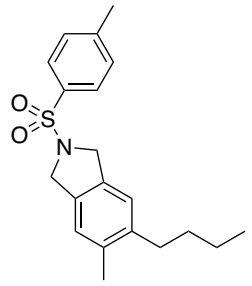
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.78 – 7.73 (m, 2H, 14, 18), 7.30 (d, *J* = 8.0 Hz, 2H, 15, 17), 6.97 (s, 1H, 2), 6.94 (s, 1H, 5), 4.57 (m, 4H, 7, 9), 2.60 (q, *J* = 7.6 Hz, 2H, 23), 2.56 – 2.51 (m, 2H, 20), 2.40 (s, 3H, 19), 1.57 – 1.49 (m, 2H, 21), 1.17 (t, *J* = 7.5 Hz, 3H, 24), 0.96 (t, *J* = 7.3 Hz, 3H, 22).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (16), 141.9 (3), 140.2 (4), 133.9 (6), 133.8 (11), 133.7 (1), 129.9 (15, 17), 127.8 (14, 18), 123.2 (5), 122.4 (2), 53.8 (9), 53.7 (7), 34.8 (20), 25.6 (23), 24.5 (21), 21.6 (19), 15.6 (24), 14.3 (22).

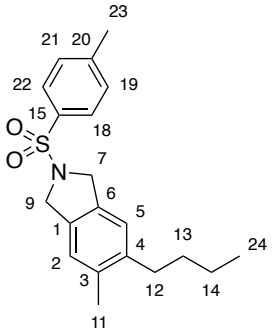
IR (ATR, film): 1344, 1161, 1096, 1061, 814, 665, 611, 550 cm^{-1}.

HRMS (ESI): Calculated for 344.1679 *m*/*z*, found 344.1679 *m*/*z* $[C_{20}H_{25}NO_4S+H]^+$.

5-Butyl-6-methyl-2-tosylisoindoline (4.144)



Prepared according to General Procedure C from 2-heptyne (9.62 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (20.6 mg, 60%).



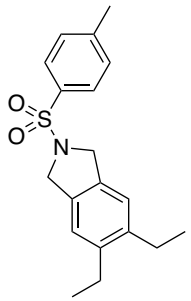
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.76 (d, *J* = 8.3 Hz, 2H, 18, 22), 7.30 (d, *J* = 8.0 Hz, 2H, 19, 21), 6.95 – 6.91 (m, 2H, 2, 5), 4.56 (m, 4H, 7, 9), 2.57 – 2.48 (m, 2H, 12), 2.39 (s, 3H, 23), 2.25 (s, 3H, 11), 1.48 (tt, *J* = 7.9, 6.1 Hz, 2H, 13), 1.37 (m, 2H, 14), 0.92 (t, *J* = 7.3 Hz, 2H, 24).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (20), 141.1 (4), 135.7 (3), 133.8 (15), 133.8 (1), 133.6 (6), 129.9 (19, 21), 127.7 (18, 22), 124.1 (2), 122.8 (5), 53.74 (7), 53.70 (9), 33.1 (12), 32.7 (13), 22.8 (14), 21.6 (23), 19.5 (11), 14.1 (24).

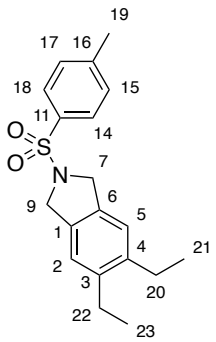
IR (ATR, film): 1344, 1161, 1096, 1061, 814, 665, 550, 534 cm^{-1}.

HRMS (ESI): Calculated for 344.1679 *m*/*z*, found 344.1670 m/*z* $[C_{25}H_{25}NO_4S+H]^+$.

5,6-Diethyl-2-tosylisoindoline (**4.145**)



Prepared according to General Procedure C from 3-hexyne (8.2 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (20.6 mg, 63%).



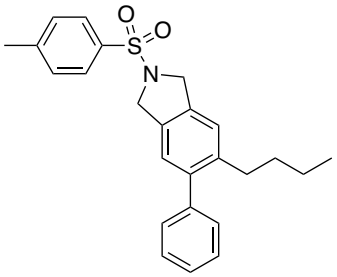
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.79 – 7.74 (m, 2H, 14, 18), 7.30 (d, *J* = 8.0 Hz, 2H, 15, 17), 6.97 (s, 2H, 2, 5), 4.57 (s, 4H, 7, 9), 2.60 (q, *J* = 7.5 Hz, 4H, 20, 22), 2.40 (s, 3H), 1.17 (t, *J* = 7.5 Hz, 6H, 21, 23).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (16), 141.7 (3, 4), 133.8 (1, 6), 133.8 (11), 129.9 (15, 17), 127.8 (14, 18), 122.4 (2, 5), 53.8 (7, 9), 25.6 (20, 22), 21.6 (19), 15.5 (21, 23).

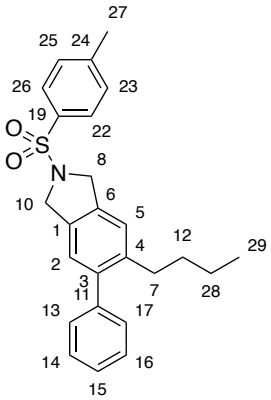
IR (ATR, film): 1343, 1163, 1096, 1055, 808, 664, 606, 548 cm^{-1}.

HRMS (ESI): Calculated for 330.1522 *m*/*z*, found 330.1522 *m*/*z* $[C_{19}H_{23}NO_2S+H]^+$.

5-Butyl-6-phenyl-2-tosylisoindoline (4.146)



Prepared according to General Procedure C from hex-1-yn-1-ylbenzenebenzene (15.8 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–2% Et_2O in PhMe) to yield the desired product as white solid (24.6 mg, 61%).



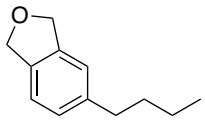
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.81 – 7.76 (m, 2H, 22, 26), 7.41 – 7.30 (m, 5H, 14–16, 23, 25), 7.22 – 7.17 (m, 2H, 13, 17), 7.09 (s, 1H, 5), 6.99 (s, 1H, 2), 4.62 (m, 4H, 8, 10), 2.53 – 2.46 (m, 2H, 7), 2.41 (s, 3H, 27), 1.42 – 1.31 (m, 2H, 12), 1.23 – 1.11 (m, 2H, 28), 0.75 (t, *J* = 7.3 Hz, 3H, 29).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 143.8 (24), 141.8 (3), 141.5 (11), 140.5 (4), 135.4 (1), 133.9 (19), 133.6 (6), 129.9 (23, 25), 129.3 (13, 17), 128.2 (14, 16), 127.8 (22, 26), 127.1 (15), 124.2 (2), 123.3 (5), 53.8 (10), 53.7 (8), 33.8 (12), 32.8 (7), 22.5 (28), 21.7 (27), 13.9 (29).

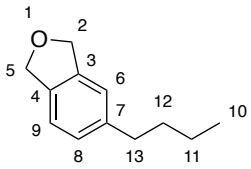
IR (ATR, film): 2955, 2926, 2860, 1346, 1163, 1099, 1061, 814, 704, 667, 611, 552 cm^{-1}.

HRMS (ESI): Calculated for 406.1835 *m*/*z*, found 406.1833 *m*/*z* $[C_{26}H_{27}NO_2S+H]^+$.

5-Butyl-1,3-dihydroisobenzofuran (**4.147**)



Prepared according to General Procedure C from 1-hexyne (9.22 mg, 100 µmol, 1.00 equiv.) and dipropargyl ether (56.5 mg, 600 µmol, 6.00 equiv.) at 2 mol% catalytic system. Purified by flash column chromatography (silica, 0–100% PhMe in hexane) to yield the desired product as a colourless oil (2.3 mg, 13%).

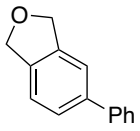


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.16 (d, *J* = 7.7 Hz, 1H, 9), 7.10 (dd, *J* = 7.6, 1.5 Hz, 1H, 8), 7.08 (d, *J* = 1.6 Hz, 1H, 6), 5.11 (m, 4H, 2, 5), 2.66 – 2.62 (m, 2H, 13), 1.65 – 1.58 (m, 2H, 12), 1.42 – 1.34 (m, 2H, 11), 0.95 (t, *J* = 6.9 Hz, 3H, 10).

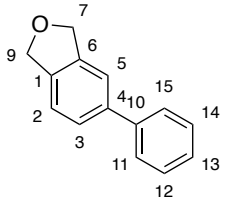
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 142.2 (7), 139.3 (3), 136.4 (4), 127.5 (6), 120.9 (8), 120.7 (9), 73.5 (2), 73.5 (5), 35.5 (13), 34.0 (12), 22.4 (11), 14.0 (10).

Spectral data consistent with the literature.[378]

5-Phenyl-1,3-dihydroisobenzofuran (**4.148**)



Prepared according to General Procedure C from phenylacetylene (10.2 mg, 100 µmol, 1.00 equiv.) and dipropargyl ether (56.5 mg, 600 µmol, 6.00 equiv.) at 10 mol% catalytic system. Purified by flash column chromatography (silica, 0–100% PhMe in hexane) to yield the desired product as a white solid (9.9 mg, 50%).

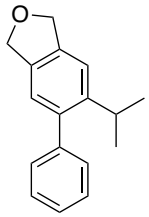


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.64 – 7.58 (m, 2H, 11, 15), 7.52 (dd, *J* = 7.8, 1.6 Hz, 1H, 3), 7.49 – 7.42 (m, 3H, 5, 12, 14), 7.40 – 7.35 (m, 1H, 13), 7.33 (d, *J* = 7.8 Hz, 1H, 2), 5.47 – 5.01 (m, 4H, 7, 9).

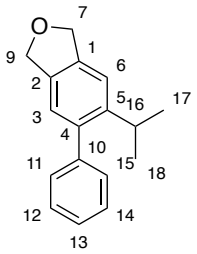
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 141.1 (10), 140.8 (4), 140.0 (1), 138.2 (6), 128.8 (12, 14), 127.4 (13), 127.2 (11, 15), 126.6 (3), 121.3 (2), 119.7 (5), 73.6 (9), 73.5 (7).

Spectral data consistent with the literature.[379]

5-Isopropyl-6-phenyl-1,3-dihydroisobenzofuran (**4.149**)



Prepared according to General Procedure C from (3-methylbut-1-yn-1-yl)benzene (14.4 mg, 100 μmol, 1.00 equiv.) and dipropargyl ether (56.5 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–100% PhMe in hexane) to yield the desired product as a white solid (10.1 mg, 42%).



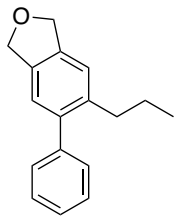
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.43 – 7.39 (m, 2H, 12, 14), 7.38 – 7.34 (m, 1H, 13), 7.30 – 7.26 (m, 3H, 6, 11, 15), 7.05 (s, 1H, 3), 5.16 (m, 2H, 7), 5.12 (m, 2H, 9), 3.06 (hept, J = 6.8 Hz, 1H, 16), 1.16 (d, J = 6.9 Hz, 6H, 17, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 146.0 (5), 142.1 (4), 140.5 (10), 138.7 (1), 136.3 (2), 129.3 (11, 15), 128.1 (12, 14), 126.8 (13), 122.4 (3), 117.9 (6), 73.6 (7), 73.5 (9), 29.4 (16), 24.4 (17, 18).

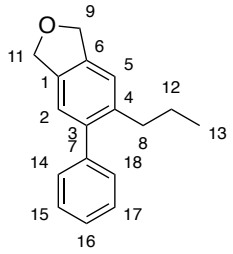
IR (ATR, film): 2961, 1765, 1341, 1045, 1007, 968, 876, 774, 735, 700 cm^{-1}.

HRMS (ESI): Calculated for 237.1274 *m*/*z*, found 237.1266 *m*/*z* [$C_{17}H_{18}O$−H]$^+$.

5-Phenyl-6-propyl-1,3-dihydroisobenzofuran (**4.150**)



Prepared according to General Procedure C from pent-1-yn-1-ylbenzene (14.4 mg, 100 µmol, 1.00 equiv.) and propargyl ether (56.5 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as white solid (11.3 mg, 47%).



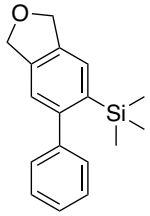
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.43 – 7.38 (m, 2H, 15, 17), 7.37 – 7.32 (m, 1H, 16), 7.30 – 7.27 (m, 2H, 14, 18), 7.17 (s, 1H, 5), 7.07 (s, 1H, 2), 5.14 (m, 2H, 11), 5.12 (m, 2H, 9), 2.58 – 2.52 (m, 2H, 8), 1.52 – 1.44 (m, 2H, 12), 0.81 (t, *J* = 7.4 Hz, 3H, 13).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 142.2 (7), 141.4 (3), 139.7 (4), 138.5 (1), 136.7 (6), 129.4 (14, 18), 128.2 (15, 17), 127.0 (16), 122.6 (2), 121.7 (5), 73.63 (9), 73.59 (11), 35.3 (8), 24.8 (12), 14.2 (13).

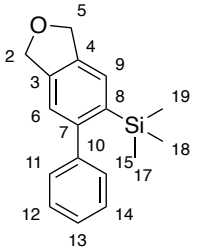
IR (ATR, film): 2957, 2859, 1472, 1364, 1258, 1072, 1044, 899, 874, 768, 704 cm^{-1}.

HRMS (ESI): Calculated for 237.1274 *m*/*z*, found 237.1272 *m*/*z* $[C_{17}H_{18}O–H]^+$.

Trimethyl(6-phenyl-1,3-dihydroisobenzofuran-5-yl)silane (4.151)



Prepared according to General Procedure C from trimethyl(phenylethynyl)silane (17.4 mg, 100 µmol, 1.00 equiv.) and propargyl ether (56.5 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–100% PhMe in hexane) to yield the desired product as white solid (3.9 mg, 15%).



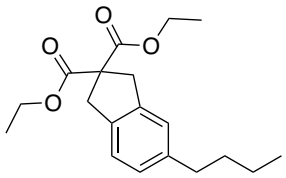
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.52 (s, 1H, 6), 7.42 – 7.37 (m, 3H, 12–14), 7.33 – 7.29 (m, 2H, 11, 15), 7.14 (s, 1H, 9), 5.20 (m, 2H, 5), 5.17 (m, 2H, 2), 0.02 (s, 9H, 17–19).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 148.7 (7), 144.2 (10), 139.9 (4), 137.8 (8), 137.3 (3), 129.5 (11, 15), 127.8 (12, 14), 127.2 (13), 126.9 (6), 122.2 (9), 73.6 (2), 73.0 (3), 0.6 (17–19).

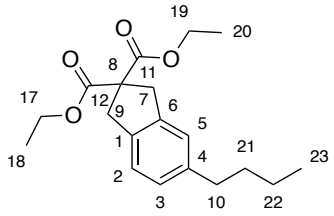
IR (ATR, film): 2951, 2359, 1248, 1072, 1049, 839, 764, 710, 700, 407 cm^{-1}.

HRMS (ESI): Calculated for 267.1120 *m*/*z*, found 267.1196 *m*/*z* [$C_{17}H_{20}OSi$–H]$^+$.

Diethyl 5-butyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (**4.152**)



Unable to isolate from [2+2+2] procedure thus prepared *via* alternative method. An oven dried microwave vial was charged with 1-hexyne (148 mg, 1.80 mmol, 6.00 equiv.), [Rh(COD)(NCMe)$_2$]BF$_4$ (5.70 mg, 15.0 µmol, 5.00 mol%), BINAP (18.7 mg, 30.0 µmol, 10.0 mol%) then sealed. Diethyl 2,2-di(prop-2-yn-1-yl)malonate (70.9 mg, 300 µmol, 1.00 equiv.) in acetone (5.00 mL) was added and the mixture was heated to 60 ºC for 16 h. The mixture was then cooled to RT, filtered through celite, and concentrated *in vacuo* to yield the crude which was purified by flash column chromatography (silica, 0–100% PhMe in hexane) to yield the desired product as a yellow oil (83.7 mg, 88%).

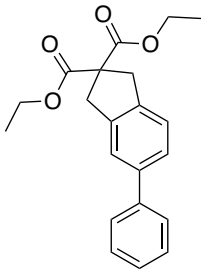


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.11 (d, *J* = 7.6 Hz, 1H, 2), 7.03 (s, 1H, 5), 7.00 (dd, *J* = 7.7, 1.7 Hz, 1H, 3), 4.22 (q, *J* = 7.1 Hz, 4H, 17, 19), 3.70 – 3.46 (m, 4H, 7, 9), 2.65 – 2.46 (m, 2H, 10), 1.64 – 1.54 (m, 2H, 21), 1.41 – 1.31 (m, 2H, 22), 1.28 (t, *J* = 7.1 Hz, 6H, 18, 20), 0.94 (t, *J* = 7.4 Hz, 3H, 23).

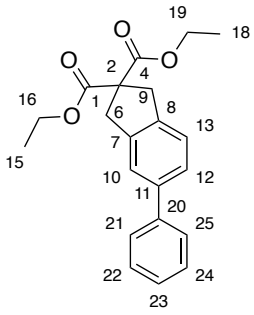
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 171.8 (11, 12), 141.8 (4), 140.1 (1), 137.2 (6), 127.2 (3), 124.2 (5), 123.9 (2), 61.7 (17, 19), 60.5 (8), 40.5 (7), 40.2 (9), 35.5 (10), 33.9 (21), 22.4 (22), 14.0 (18, 20), 14.0 (23).

Spectral data consistent with the literature.[380]

Diethyl 5-phenyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (**4.153**)



Prepared according to General Procedure C from phenylacetylene (10.2 mg, 100 μmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 μmol, 6.00 equiv.) at 10 mol% catalytic system. Purified by flash column chromatography (silica, 0–100% PhMe in hexane) to yield the desired product as a white solid (19.9 mg, 38%).

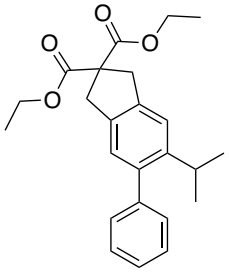


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.60 – 7.56 (m, 2H, 21, 25), 7.44 (m, 4H, 10, 12, 22, 24), 7.39 – 7.32 (m, 1H, 23), 7.32 – 7.27 (m, 1H, 13), 4.25 (q, *J* = 7.1 Hz, 4H, 16, 19), 3.68 (s, 2H, 6), 3.66 (s, 2H, 9), 1.30 (t, *J* = 7.1 Hz, 6H, 15, 18).

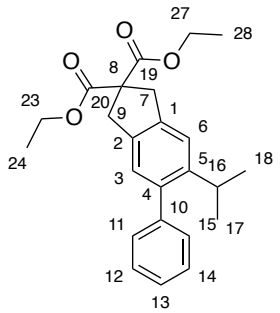
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 171.7 (1, 4), 141.3 (20), 140.7 (8), 140.3 (11), 139.2 (7), 128.7 (22, 24), 127.2 (21, 25), 127.1 (23), 126.2 (12), 124.5 (13), 123.0 (10), 61.8 (16, 19), 60.5 (2), 40.5 (9), 40.2 (6), 14.1 (15, 18).

Spectral data consistent with the literature.[380]

Diethyl 5-isopropyl-6-phenyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.154)



Prepared according to General Procedure C from (3-methylbut-1-yn-1-yl)benzene (14.4 mg, 100 μmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–70% PhMe in hexane) to yield the desired product as a white solid (10.1 mg, 42%).



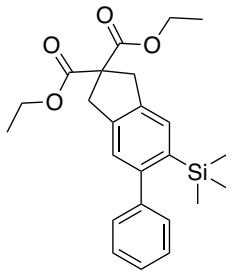
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.41 – 7.36 (m, 2H, 12, 14), 7.35 – 7.30 (m, 1H, 13), 7.29 – 7.22 (m, 2H, 11, 15), 7.20 (s, 1H, 6), 6.99 (s, 1H, 3), 4.22 (q, *J* = 7.1 Hz, 4H, 23, 27), 3.64 (s, 2H, 7), 3.59 (s, 2H, 9), 2.99 (hept, *J* = 6.9 Hz, 1H, 16), 1.27 (t, *J* = 7.1 Hz, 6H, 24, 28), 1.12 (d, *J* = 6.9 Hz, 6H, 17, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 171.9 (19, 20), 145.3 (5), 142.3 (10), 140.0 (4), 139.5 (1), 137.0 (2), 129.4 (11, 15), 127.9 (12, 14), 126.6 (13), 125.6 (3), 121.2 (6), 61.7 (23, 27), 60.4 (8), 40.5 (7), 40.2 (9), 29.3 (16), 24.4 (17, 18), 14.1 (24, 28).

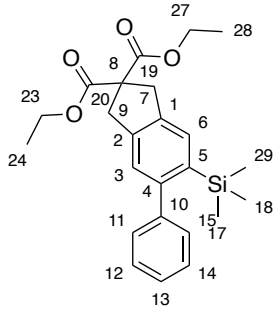
IR (ATR, film): 2961, 1730, 1481, 1445, 1366, 1258, 1238, 1206, 1182, 1155, 1096, 1067, 773, 702 cm^{-1}.

HRMS (ESI): Calculated for 403.1880 *m*/*z*, found 403.1868 *m*/*z* $[C_{24}H_{28}O_4+Na]^+$.

Diethyl 5-phenyl-6-(trimethylsilyl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.155)



Prepared according to General Procedure C from trimethyl(phenylethynyl)silane (17.4 mg, 100 µmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–100% PhMe in hexane) to yield the desired product as white solid (4.3 mg, 10%).



^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.45 – 7.40 (m, 1H, 6), 7.39 – 7.31 (m, 3H, 11, 13, 15),

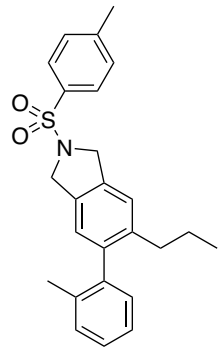
7.29 – 7.21 (m, 2H, 12, 14), 7.06 (s, 1H, 3), 4.22 (q, *J* = 7.2 Hz, 4H, 23, 27), 3.65 (s, 2H, 7), 3.61 (s, 2H, 9), 1.27 (t, *J* = 7.1 Hz, 6H, 24, 28), –0.04 (s, 9H, 17–19).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 171.8 (19, 20), 148.2 (4), 144.5 (10), 140.7 (1), 138.1 (2), 137.1 (5), 130.3 (6), 129.5 (12, 14), 127.6 (11, 15), 127.0 (13), 125.5 (3), 61.8 (23, 27), 61.4 (8), 40.5 (9), 40.4 (7), 14.1 (24, 28), 0.7 (17, 18, 29).

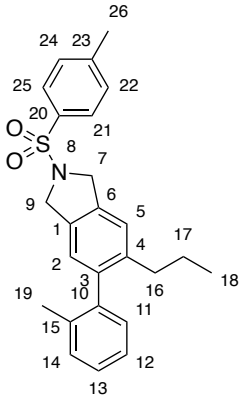
IR (ATR, film): 2926, 1732, 1258, 1244, 1186, 1151, 1067, 837 cm^{-1}.

HRMS (ESI): Calculated for 433.1806 *m*/*z*, found 433.1794 *m*/*z* $[C_{24}H_{30}O_4Si+Na]^+$.

5-Propyl-6-(*o*-tolyl)-2-tosylisoindoline (4.156)



Prepared according to General Procedure C from 1-methyl-2-(pent-1-yn-1-yl)benzene)benzene (15.8 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as white solid (8.3 mg, 20%).



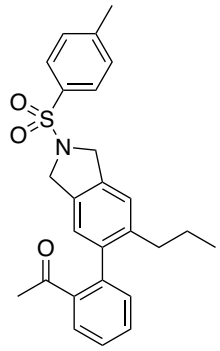
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.82 – 7.77 (m, 2H, 21, 25), 7.35 – 7.30 (m, 2H, 22, 24), 7.25 – 7.21 (m, 2H, 13, 14), 7.21 – 7.15 (m, 1H, 12), 7.08 (s, 1H, 5), 7.01 (dd, *J* = 7.1, 1.2 Hz, 1H, 11), 6.88 (s, 1H, 2), 4.70 – 4.62 (m, 2H, 9), 4.62 – 4.54 (m, 2H, 7), 2.42 (s, 3H, 26), 2.33 (dt, *J* = 13.7, 7.8 Hz, 1H, 16), 2.21 (m, 1H, 16), 1.99 (s, 3H, 19), 1.37 (m, 2H, 17), 0.73 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 143.7 (20), 141.2 (15), 140.9 (3), 140.5 (4), 135.9 (10), 135.3 (1), 134.0 (23), 133.5 (6), 130.0 (14), 129.9 (22, 24), 129.7 (11), 127.8 (21, 25), 127.5 (13), 125.6 (12), 123.7 (2), 123.0 (5), 53.8 (9), 53.7 (7), 35.1 (16), 24.0 (17), 21.7 (26), 20.2 (19), 14.1 (18).

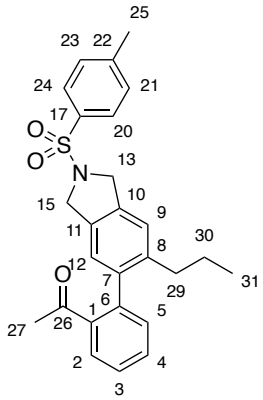
IR (ATR, film): 1344, 1161, 1096, 665, 548 cm^{-1}.

HRMS (ESI): Calculated for 406.1835 *m*/*z*, found 406.1840 *m*/*z* $[C_{25}H_{27}NO_2S+H]^+$.

1-(2-(6-Propyl-2-tosylisoindolin-5-yl)phenyl)ethan-1-one (**4.157**)



Prepared according to General Procedure C from 1-(2-(pent-1-yn-1-yl)phenyl)ethan-1-one (18.6 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–5% EtOAc in PhMe) to yield the desired product as a white solid (1.1 mg, 3%).



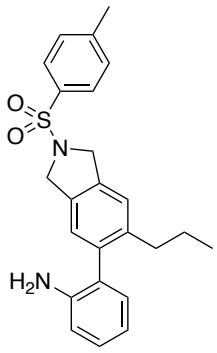
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.78 (d, *J* = 8.2 Hz, 2H, 20, 24), 7.70 (dd, *J* = 7.7, 1.5 Hz, 1H, 2), 7.49 (m, 1H, 4), 7.43 (m, 1H, 3), 7.33 (d, *J* = 7.8 Hz, 2H, 21, 23), 7.15 (dd, *J* = 7.6, 1.4 Hz, 1H, 5), 7.08 (s, 1H, 12), 6.89 (s, 1H, 9), 4.63 (m, 2H, 13), 4.58 (m, 2H, 15), 2.42 (s, 3H, 27), 2.38 – 2.31 (m, 1H, 29), 2.31 – 2.22 (m, 1H, 29), 2.08 (s, 3H, 25), 1.44 – 1.36 (m, 2H, 30), 0.75 (m, 3H, 31).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 202.1 (26), 143.8 (17), 140.7 (1), 140.2 (7), 139.5 (8), 135.9 (11), 133.9 (22), 133.6 (10), 131.3 (3), 131.1 (4), 130.0 (20, 24), 128.6 (2), 127.8 (21, 23), 127.7 (5), 126.2 (6), 123.6 (12), 123.1 (9), 53.8 (13), 53.6 (15), 35.2 (29), 29.9 (27), 23.9 (30), 21.7 (25), 14.1 (31).

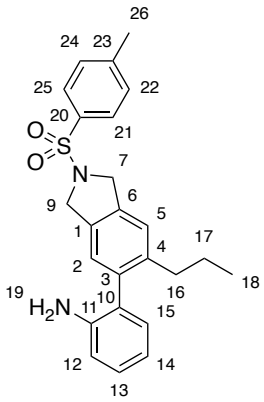
IR (ATR, film): 1686, 1346, 1163, 1096, 667, 548 cm^{-1}.

HRMS (ESI): Calculated for 434.1784 *m*/*z*, found 434.1784 *m*/*z* $[C_{26}H_{27}NO_3S+H]^+$.

2-(6-Propyl-2-tosylisoindolin-5-yl)aniline (**4.158**)



Prepared according to General Procedure C from 2-(pent-1-yn-1-yl)aniline (15.9 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% Et_2O in PhMe) to yield the desired product as pale-yellow solid (16.3 mg, 40%).



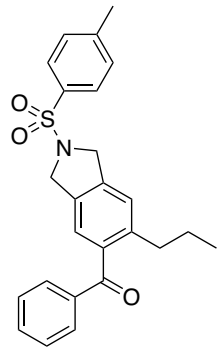
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.79 (d, *J* = 8.3 Hz, 2H, 21, 25), 7.33 (d, *J* = 8.0 Hz, 2H, 22, 24), 7.19 – 7.15 (m, 1H, 13), 7.12 (s, 1H, 5), 6.98 (s, 1H, 2), 6.91 (dd, *J* = 7.5, 1.6 Hz, 1H, 12), 6.77 (m, 1H, 14), 6.73 (dd, *J* = 7.9, 1.1 Hz, 1H, 15), 4.68 – 4.62 (m, 2H, 9), 4.62 – 4.55 (m, 2H, 7), 3.41 (s, 2H, 19), 2.46 – 2.34 (m, 5H, 16, 26), 1.45 – 1.36 (m, 2H, 17), 0.76 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.8 (23), 143.7 (11), 141.6 (4), 138.2 (3), 135.9 (6), 134.2 (1), 133.9 (20), 130.4 (12), 130.0 (22, 24), 128.7 (13), 127.8 (21, 25), 126.7 (10), 124.5 (2), 123.5 (5), 118.3 (14), 115.2 (15), 53.8 (9), 53.6 (7), 35.1 (16), 24.3 (17), 21.7 (26), 14.1 (18).

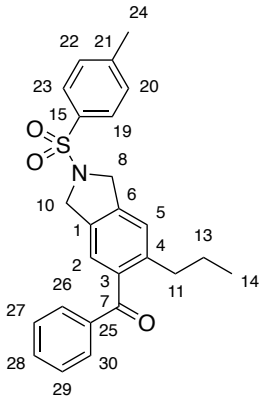
IR (ATR, film): 1343, 1161, 1096, 665, 550 cm^{-1}.

HRMS (ESI): Calculated for 407.1788 *m*/*z*, found 407.1787 *m*/*z* $[C_{24}H_{26}N_2O_2S+H]^+$.

Phenyl(6-propyl-2-tosylisoindolin-5-yl)methanone (4.159)



Prepared according to General Procedure C from 1-phenylhex-2-yn-1-one (17.2 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (32.4 mg, 77%).



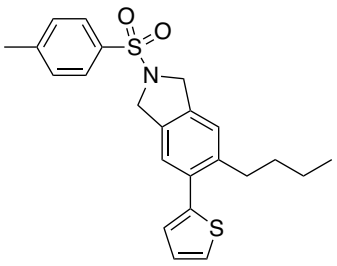
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.77 (d, *J* = 8.0 Hz, 2H, 19, 23), 7.75 – 7.72 (m, 2H, 26, 30), 7.62 – 7.56 (m, 1H, 28), 7.44 (m, 2H, 27, 29), 7.33 (d, *J* = 8.0 Hz, 2H, 20, 22), 7.12 (s, 1H, 5), 7.06 (s, 1H, 2), 4.65 (s, 2H, 8), 4.58 (s, 2H, 10), 2.60 – 2.52 (m, 2H, 11), 2.42 (s, 3H, 24), 1.48 (m, 2H, 13), 0.81 (t, *J* = 7.3 Hz, 3H, 14).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 198.3 (7), 143.9 (21), 141.7 (4), 138.7 (3), 138.4 (1), 137.7 (25), 133.8 (15), 133.6 (28), 133.4 (6), 130.2 (26, 30), 130.0 (20, 22), 128.7 (27, 29), 127.8 (19, 23), 124.3 (5), 122.5 (2), 53.8 (8), 53.5 (10), 35.4 (11), 25.0 (13), 21.7 (24), 14.0 (14).

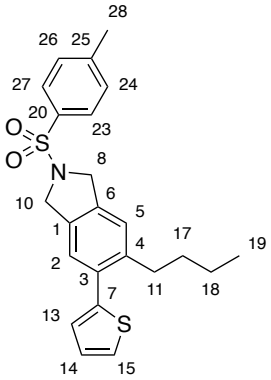
IR (ATR, film): 1662, 1344, 1161, 1096, 716, 665, 548 cm^{-1}.

HRMS (ESI): Calculated for 420.1628 *m*/*z*, found 420.1622 *m*/*z* $[C_{25}H_{25}NO_3S+H]^+$.

5-Butyl-6-(thiophen-2-yl)-2-tosylisoindoline (4.160)



Prepared according to General Procedure C from 2-(hex-1-yn-1-yl)thiophene (16.4 mg, 100 μmol) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 μmol). Purified by flash column chromatography (silica, 0–5% Et_2O in PhMe) to yield the desired product as yellow solid (37.9 mg, 92%).



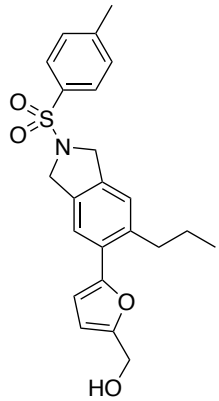
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.81 – 7.76 (m, 2H, 23, 27), 7.35 – 7.30 (m, 3H, 15, 24, 26), 7.14 (s, 1H, 2), 7.08 (s, 1H, 5), 7.06 (dd, *J* = 5.1, 3.5 Hz, 1H, 14), 6.94 (dd, *J* = 3.5, 1.2 Hz, 1H, 13), 4.62 (s, 2H, 8), 4.60 (s, 2H, 10), 2.68 – 2.60 (m, 2H, 11), 2.41 (s, 3H, 28), 1.51 – 1.38 (m, 2H, 17), 1.33 – 1.19 (m, 2H, 18), 0.83 (t, *J* = 7.3 Hz, 3H, 19).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 143.8 (20), 143.8 (25), 142.3 (7), 141.6 (4), 136.2 (1), 133.77 (3), 133.76 (6), 130.0 (24, 26), 127.8 (23, 27), 127.1 (14), 126.7 (13), 125.5 (15), 125.2 (2), 123.7 (5), 53.7 (10), 53.9 (8), 34.0 (17), 33.3 (11), 22.6 (18), 21.6 (28), 14.0 (19).

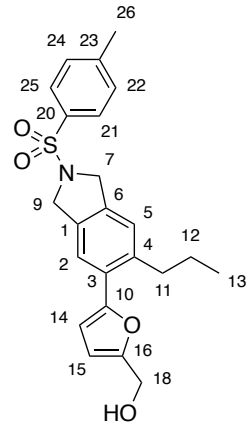
IR (ATR, film): 2924, 1344, 1161, 1098, 1061, 810, 702, 665, 615, 550 cm^{-1}.

HRMS: Calculated for 412.1400 *m*/*z*, found 412.1391 *m*/*z* $[C_{23}H_{25}NO_2S_2+H]^+$.

(5-(6-Propyl-2-tosylisoindolin-5-yl)furan-2-yl)methanol (4.161)



Prepared according to General Procedure C from (5-(pent-1-yn-1-yl)furan-2-yl)methanol (16.4 mg, 100 μmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–50% Et_2O in hexane) to yield the desired product as a white solid (30.8 mg, 75%).



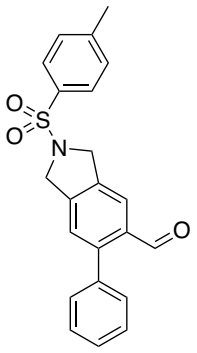
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.79 – 7.75 (m, 2H, 21, 25), 7.40 (s, 1H, 2), 7.31 (d, *J* = 8.1 Hz, 2H, 22, 24), 7.04 (s, 1H, 5), 6.38 (m, 2H, 14, 15), 4.65 (s, 2H, 18), 4.61 (m, 4H, 7, 9), 2.74 – 2.68 (m, 2H, 11), 2.40 (s, 3H, 26), 1.60 – 1.51 (m, 2H, 12), 0.94 (t, *J* = 7.4 Hz, 3H, 13).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 153.5 (16), 153.1 (10), 143.8 (23), 140.0 (4), 136.0 (1), 134.1 (6), 133.8 (20), 130.0 (22, 24), 129.7 (3), 127.7 (21, 25), 124.2 (5), 122.2 (2), 109.8 (15), 109.3 (14), 57.8 (18), 53.8 (7 or 9), 53.6 (7 or 9), 36.3 (11), 24.2 (12), 21.7 (26), 14.2 (13).

IR (ATR, film): 1343, 1161, 1096, 667, 548, 405 cm^{-1}.

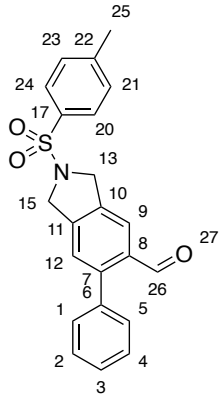
HRMS (ESI): Calculated for 412.1577 *m*/*z*, found 412.1580 *m*/*z* $[C_{23}H_{25}NO_4S+H]^+$.

6-Phenyl-2-tosylisoindoline-5-carbaldehyde (4.162)



Prepared according to General Procedure C from (3,3-diethoxyprop-1-yn-1-yl)benzene (15.9 mg, 100 μmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–2% Et_2O in PhMe) to yield the desired product as a mixture of acetal and aldehyde. This material was suspended in THF (1.00 mL), and H_2O (0.50 mL) before 2–3 drops of dilute aqueous HCl (2.0 M) was added. This mixture was concentrated *in vacuo*, loaded onto silica then the compound

was repurified by flash column chromatography (silica, 0–5% Et_2O in PhMe) to yield the desired product as a yellow solid (19.5 mg, 52%).



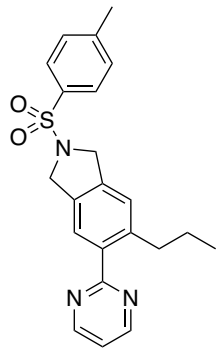
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 9.88 (s, 1H, 26), 7.83 (s, 1H, 9), 7.82 – 7.77 (m, 2H, 20, 24), 7.48 – 7.43 (m, 3H, 2–4), 7.34 (d, *J* = 8.1 Hz, 3H, 21, 23), 7.32 – 7.28 (m, 2H, 1, 5), 7.25 (s, 1H, 12), 4.71 – 4.67 (m, 4H, 13, 15), 2.41 (s, 3H, 25).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 191.7 (26), 146.3 (7), 144.1 (22), 142.2 (10), 137.3 (6), 136.3 (11), 133.8 (8), 133.5 (17), 130.1 (1, 5), 130.0 (21, 23), 128.7 (2, 4), 128.6 (3), 127.8 (20, 24), 125.1 (12), 121.9 (9), 53.8 (15), 53.5 (13), 21.7 (25).

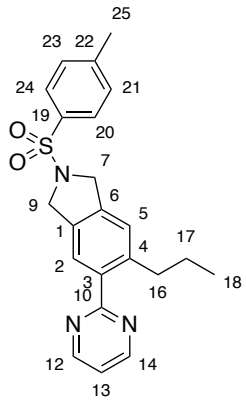
IR (ATR, film): 1686, 1344, 1161, 1096, 760, 665, 602 cm^{-1}.

HRMS (ESI): Calculated for 378.1158 *m*/*z*, found 378.1164 *m*/*z* $[C_{22}H_{19}NO_3S+H]^+$.

5-Propyl-6-(pyrimidin-2-yl)-2-tosylisoindoline (4.163)



Prepared according to General Procedure C from 2-(pent-1-yn-1-yl)pyrimidine (14.6 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–25% Et_2O in PhMe) to yield the desired product as pale-yellow solid (20.3 mg, 52%).



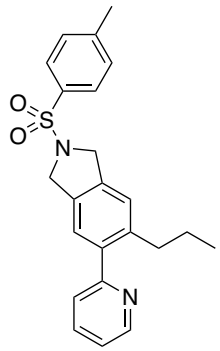
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 8.84 – 8.79 (m, 2H, 12, 14), 7.76 (d, *J* = 7.9 Hz, 2H, 20, 24), 7.52 (s, 1H, 2), 7.30 (d, *J* = 8.0 Hz, 2H, 21, 23), 7.24 – 7.20 (m, 1H, 13), 7.10 (s, 1H, 5), 4.70 – 4.62 (m, 4H, 7, 9), 2.84 (t, *J* = 7.8 Hz, 2H, 16), 2.40 (s, 3H, 25), 1.49 – 1.39 (m, 2H, 17), 0.80 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 167.5 (10), 157.0 (12, 14), 143.7 (22), 141.9 (4), 137.9 (3), 137.3 (1), 133.9 (19), 133.7 (6), 129.9 (21, 23), 127.6 (20, 24), 124.7 (2), 124.4 (5), 118.8 (13), 53.8 (7 or 9), 53.6 (7 or 9), 35.5 (16), 24.7 (17), 21.5 (25), 14.0 (18).

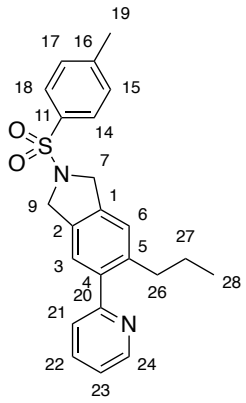
IR (ATR, film): 1402, 1343, 1161, 1096, 665, 602, 565, 546 cm^{-1}.

HRMS (ESI): Calculated for 394.1584 *m*/*z*, found 394.1584 *m*/*z* $[C_{22}H_{23}N_3O_2S+H]^+$.

5-Propyl-6-(pyridin-2-yl)-2-tosylisoindoline (**4.164**)



Prepared according to General Procedure C from 2-(pent-1-yn-1-yl)pyridine (14.5 mg, 100 μmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–20% EtOAc in hexane) to yield the desired product as a white solid (37.8 mg, 96%).



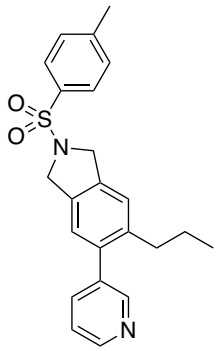
^{1}H NMR (700 MHz, Chloroform-*d*) δ_H 8.65 (m, 1H, 24), 7.81 – 7.75 (m, 2H, 14, 18), 7.72 (m, 1H, 22), 7.30 (m, 2H, 15, 17), 7.25 (ddd, *J* = 7.6, 4.9, 1.1 Hz, 1H, 23), 7.14 (s, 1H, 3), 7.09 (s, 1H, 6), 4.64 (s, 2H, 9), 4.62 (s, 2H, 7), 2.70 – 2.53 (m, 2H, 26), 2.40 (s, 3H, 19), 1.49 – 1.35 (m, 2H, 27), 0.76 (t, *J* = 7.3 Hz, 3H, 28).

^{13}C NMR (176 MHz, Chloroform-*d*) δ_C 159.6 (20), 149.3 (24), 143.7 (16), 140.5 (5), 140.3 (4), 136.2 (22), 136.1 (2), 133.7 (1 or 11), 133.7 (1 or 11), 129.9 (15, 17), 127.6 (14, 18), 124.0 (21), 123.9 (3), 123.7 (6), 121.9 (23), 53.7 (9), 53.6 (7), 35.0 (26), 24.5 (27), 21.5 (19), 14.0 (28).

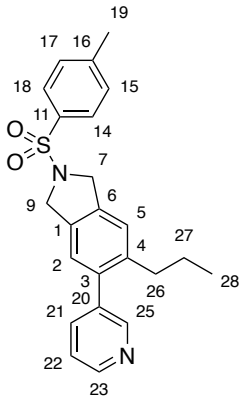
IR (ATR, film): 2961, 1586, 1468, 1343, 1159, 1094, 1059, 814, 735, 706, 665, 615, 602, 563, 546 cm^{-1}.

HRMS (ESI): Calculated for 393.1631 *m*/*z*, found 393.1629 *m*/*z* $[C_{23}H_{24}N_2O_2S+H]^+$.

5-Propyl-6-(pyridin-3-yl)-2-tosylisoindoline (**4.165**)



Prepared according to General Procedure C from 3-(pent-1-yn-1-yl)pyridine (29.0 mg, 200 µmol, 1.00 equiv.) and 4-methyl-N,N-di(prop-2-yn-1-yl)benzenesulfonamide (297 mg, 1.20 mmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–30% EtOAc in hexane) to yield the desired product as brown solid (20.1 mg, 26%).



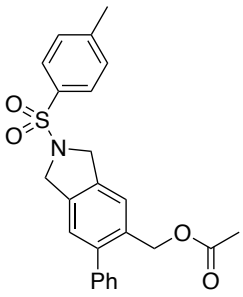
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 8.63 (brs, 1H, 25), 7.84 – 7.75 (m, 3H, 14, 18, 21), 7.59 (d, *J* = 7.7 Hz, 1H, 23), 7.36 – 7.33 (m, 3H, 15, 17, 22), 7.14 (s, 1H, 5), 7.00 (s, 1H, 2), 4.70 – 4.63 (m, 4H, 7, 9), 2.53 – 2.47 (m, 2H, 26), 2.43 (s, 3H, 19), 1.51 – 1.35 (m, 2H, 27), 0.79 (t, *J* = 7.3 Hz, 3H, 28).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 143.8 (16), 140.4 (4), 137.8 (1), 136.5 (23), 136.3 (3), 135.6 (20), 133.9 (6), 133.6 (11), 129.9 (14, 180, 128.0 (21), 127.7 (15, 17), 127.2 (22), 124.2 (2), 123.5 (5), 122.6 (25), 53.6 (7), 53.5 (9), 35.0 (26), 24.5 (27), 21.6 (19), 13.9 (28).

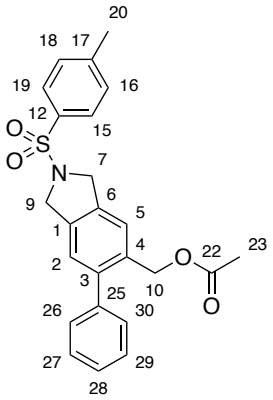
IR (ATR, film): 2963, 1343, 1306, 1265, 1159, 1092, 1028, 1017, 814, 733, 704, 665, 567, 546 cm^{-1}.

HRMS (ESI): Calculated for 393.1631 *m*/*z*, found 393.1642 *m*/*z* $[C_{23}H_{24}N_2O_2S+H]^+$.

(6-Phenyl-2-tosylisoindolin-5-yl)methyl acetate (**4.166**)



Prepared according to General Procedure C from 3-phenylprop-2-yn-1-yl acetate (17.4 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–5% Et_2O in PhMe) to yield the desired product as a white solid (32.8 mg, 78%).



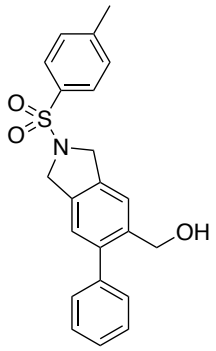
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.81 – 7.76 (m, 2H, 15, 19), 7.42 – 7.35 (m, 3H, 27–29), 7.33 (d, *J* = 8.1 Hz, 2H, 16, 18), 7.30 (s, 1H, 5), 7.25 – 7.22 (m, 2H, 26, 30), 7.10 (s, 1H, 2), 4.96 (s, 2H, 10), 4.68 – 4.66 (m, 2H, 7), 4.66 – 4.63 (m, 2H, 9), 2.42 (s, 3H, 20), 2.02 (s, 3H, 23).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 170.8 (22), 143.9 (17), 142.4 (3), 139.9 (25), 136.5 (1), 135.8 (6), 133.6 (12), 133.4 (4), 130.0 (16, 18), 129.1 (26, 30), 128.5 (27, 29), 127.8 (28), 127.8 (15, 19), 124.4 (2), 123.8 (5), 64.2 (10), 53.70 (7), 53.66 (9), 21.7 (20), 21.1 (23).

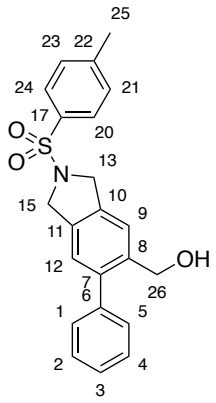
IR (ATR, film): 1736, 1344, 1227, 1161, 1096, 704, 665, 548 cm^{-1}.

HRMS (ESI): Calculated for 422.1421 *m*/*z*, found 422.1416 *m*/*z* $[C_{23}H_{24}NO_4S+H]^+$.

(6-Phenyl-2-tosylisoindolin-5-yl)methanol (**4.167**)



Prepared according to General Procedure C from 3-phenylprop-2-yn-1-ol (15.9 mg, 100 μmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–20% Et_2O in PhMe) to yield the desired product as a yellow solid (24.9 mg, 66%).



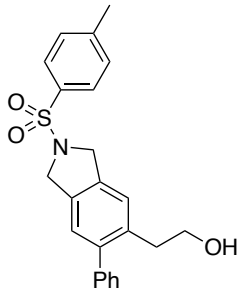
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.82 – 7.76 (m, 2H, 20, 24), 7.43 – 7.36 (m, 4H, 2–4, 9), 7.33 (d, *J* = 8.0 Hz, 2H, 21, 23), 7.28 – 7.25 (m, 2H, 1, 5), 7.07 (s, 1H, 12), 4.67 (m, 2H, 15), 4.64 (m, 2H, 13), 4.55 (s, 2H, 26), 2.41 (s, 3H, 25).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.9 (22), 141.2 (7), 140.2 (6), 138.2 (8), 135.8 (11), 135.6 (10), 133.7 (17), 130.0 (21, 23), 129.1 (1, 5), 128.5 (2, 4), 127.8 (20, 24), 127.7 (3), 124.2 (12), 122.5 (9), 63.0 (26), 53.8 (15), 53.7 (13), 21.7 (25).

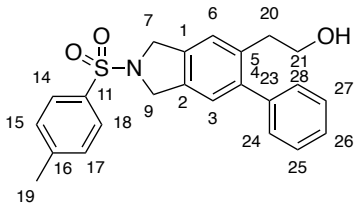
IR (ATR, film): 1341, 1159, 1096, 665, 548 cm^{-1}.

HRMS (ESI): Calculated for 380.1315 *m*/*z*, found 380.1314 *m*/*z* $[C_{22}H_{21}NO_3S+H]^+$.

2-(6-Phenyl-2-tosylisoindolin-5-yl)ethan-1-ol (**4.168**)



Prepared according to General Procedure C from 4-phenylbut-3-yn-1-ol (14.6 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–20% Et_2O in hexane) to yield desired product as a yellow solid (33.6 mg, 85%).



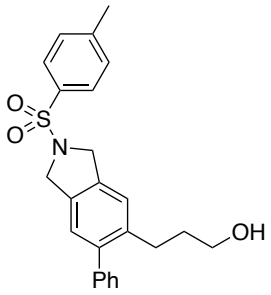
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.83 – 7.79 (m, 2H, 14, 18), 7.43 – 7.36 (m, 3H, 25–27), 7.35 (d, *J* = 8.1 Hz, 2H, 15, 17), 7.26 – 7.23 (m, 2H, 24, 28), 7.18 (s, 1H, 6), 7.05 (s, 1H, 3), 4.71 – 4.65 (m, 2H, 7), 4.65 – 4.62 (m, 2H, 9), 3.64 (t, *J* = 6.8 Hz, 2H, 21), 2.84 (t, *J* = 6.8 Hz, 2H, 20), 2.44 (s, 3H, 19).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (16), 142.3 (4), 141.0 (23), 135.8 (5), 135.5 (2), 134.3 (1), 133.6 (11), 129.9 (15, 17), 129.1 (24, 28), 128.3 (25, 27), 127.7 (14, 18), 127.3 (26), 124.4 (3), 123.9 (6), 63.1 (21), 53.6 (7), 53.6 (9), 36.1 (20), 21.6 (19).

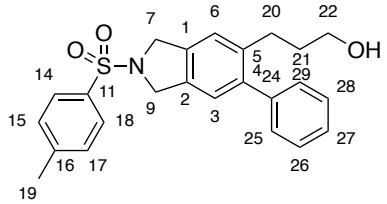
IR (ATR, film): 1343, 1159, 1096, 1044, 735, 702, 665, 561, 546 cm^{-1}.

HRMS (ESI): Calculated for 394.1471 *m*/*z*, found 394.1486 *m*/*z* $[C_{23}H_{23}NO_3S+H]^+$.

3-(6-Phenyl-2-tosylisoindolin-5-yl)propan-1-ol (**4.169**)



Prepared according to General Procedure C from 5-phenylpent-4-yn-1-ol (16.0 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–20% Et_2O in hexane) to yield desired product as an orange solid (20.4 mg, 50%).



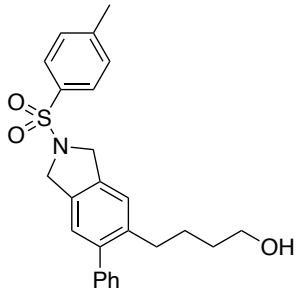
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.95 – 7.79 (m, 2H, 14, 18), 7.44 – 7.36 (m, 3H, 26–28), 7.36 – 7.34 (m, 2H, 15, 17), 7.27 – 7.21 (m, 2H, 25, 29), 7.13 (s, 1H, 6), 7.03 (s, 1H, 3), 4.69 – 4.65 (m, 2H, 7), 4.65 – 4.62 (m, 2H, 9), 3.48 (t, *J* = 6.4 Hz, 2H, 22), 2.69 – 2.61 (m, 2H, 20), 2.44 (s, 3H, 19), 1.74 – 1.60 (m, 2H, 21).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (16), 141.8 (4), 141.2 (24), 139.3 (5), 135.5 (2), 133.8 (1), 133.7 (11), 129.9 (15, 17), 129.1 (25, 29), 128.3 (26, 28), 127.7 (14 ,18), 127.2 (27), 124.2 (3), 123.3 (6), 62.1 (22), 53.6 (7), 53.5 (9), 34.2 (20), 29.1 (21), 21.6 (19).

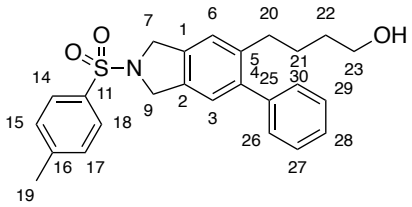
IR (ATR, film): 1343, 1161, 1096, 1059, 814, 702, 665, 546 cm^{-1}.

HRMS (ESI): Calculated for 408.1628 *m*/*z*, found 408.1628 *m*/*z* $[C_{24}H_{25}NO_3S+H]^+$.

4-(6-Phenyl-2-tosylisoindolin-5-yl)butan-1-ol (**4.170**)



Prepared according to General Procedure C from 6-phenylhex-5-yn-1-ol (17.4 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–20% Et_2O in hexane) to yield desired product as white solid (37.4 mg, 89%).



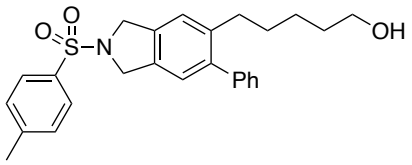
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.86 – 7.75 (m, 2H, 14, 18), 7.44 – 7.33 (m, 5H, 15, 17, 27–29), 7.25 – 7.22 (m, 2H, 26, 30), 7.12 (s, 1H, 6), 7.02 (s, 1H, 3), 4.68 – 4.65 (m, 2H, 7), 4.65 – 4.62 (m, 2H, 9), 3.49 (t, *J* = 6.2 Hz, 2H, 23), 2.63 – 2.53 (m, 2H, 20), 2.44 (s, 3H, 19), 1.53 – 1.37 (m, 4H, 21, 22).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (16), 141.7 (4), 141.3 (25), 139.8 (5), 135.4 (2), 133.7 (1 or 11), 133.7 (1 or 11), 129.9 (14, 18), 129.1 (26, 30), 128.2 (27, 29), 127.7 (15, 17), 127.1 (28), 124.1 (3), 123.2 (6), 62.5 (23), 53.6 (7), 53.6 (9), 32.6 (20), 32.2 (21), 27.4 (22), 21.6 (19).

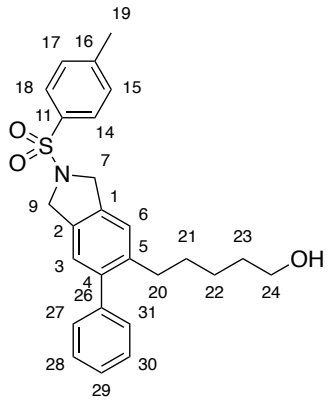
IR (ATR, film): 2924, 2855, 1736, 1343, 1167, 1096, 1069, 1009, 741, 621, 419 cm^{-1}.

HRMS (ESI): Calculated for 422.1784 *m*/*z*, found 422.1774 *m*/*z* $[C_{25}H_{27}NO_3S+H]^+$.

5-(6-Phenyl-2-tosylisoindolin-5-yl)pentan-1-ol (**4.171**)



Prepared according to General Procedure C from 7-phenylhept-6-yn-1-ol (18.8 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–15% Et_2O in PhMe) to yield the desired product as a yellow solid (42.3 mg, 97%).



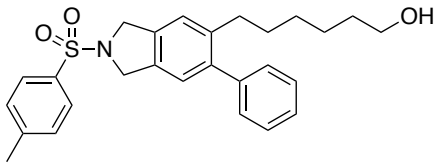
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.87 – 7.78 (m, 2H, 14, 18), 7.44 – 7.32 (m, 5H, 15, 17, 28–30), 7.24 – 7.17 (m, 2H, 27, 31), 7.10 (s, 1H, 6), 7.01 (s, 1H, 3), 4.66 (m, 2H, 7), 4.63 (m, 2H, 9), 3.53 (t, *J* = 6.6 Hz, 2H, 24), 2.62 – 2.52 (m, 2H, 20), 2.44 (s, 3H, 19), 1.43 (m, 4H, 21, 23), 1.27 – 1.19 (m, 2H, 22).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (16), 141.7 (4), 141.3 (26), 140.1 (5), 135.3 (2), 133.7 (1), 133.6 9 (11), 129.8 (15, 17), 129.1 (27, 31), 128.2 (28, 30), 127.7 (14, 18), 127.1 (29), 124.1 (3), 123.2 (6), 62.8 (24), 53.6 (7), 53.6 (9), 32.9 (20), 32.3 (21), 31.1 (23), 25.5 (22), 21.6 (19).

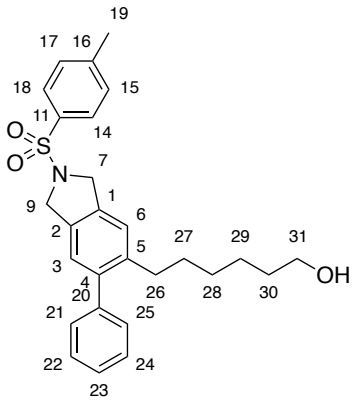
IR (ATR, film): 2926, 1460, 1344, 1163, 1096, 704, 667, 548 cm^{-1}.

HRMS (ESI): Calculated for 458.1760 *m*/*z*, found 458.1762 *m*/*z* $[C_{26}H_{29}NO_3S+Na]^+$.

6-(6-Phenyl-2-tosylisoindolin-5-yl)hexan-1-ol (**4.172**)



Prepared according to General Procedure C from 8-phenyloct-7-yn-1-ol (20.2 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–15% Et_2O in PhMe) to yield the desired product as a yellow solid (39.3 mg, 87%).



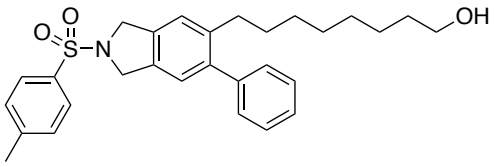
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.86 – 7.78 (m, 2H, 14, 18), 7.40 (dd, *J* = 8.1, 6.3 Hz, 2H, 22, 24), 7.38 – 7.31 (m, 3H, 15, 17, 23), 7.24 – 7.20 (m, 2H, 21, 25), 7.10 (s, 1H, 6), 7.01 (s, 1H, 3), 4.66 (m, 2H, 7), 4.63 (m, 2H, 9), 3.57 (t, *J* = 6.6 Hz, 2H, 31), 2.57 – 2.49 (m, 2H, 26), 2.44 (s, 3H, 19), 1.50 – 1.36 (m, 4H, 27, 30), 1.27 – 1.14 (m, 4H, 28, 29).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (16), 141.7 (4), 141.4 (20), 140.2 (5), 135.3 (2), 133.8 (11), 133.5 (1), 129.8 (15, 17), 129.1 (21, 25), 128.1 (22, 24), 127.7 (14, 18), 127.0 (23), 124.1 (3), 123.2 (6), 62.9 (31), 53.6 (7), 53.5 (9), 32.8 (26), 32.5 (27), 31.3 (28), 29.0 (29), 25.3 (30), 21.5 (31).

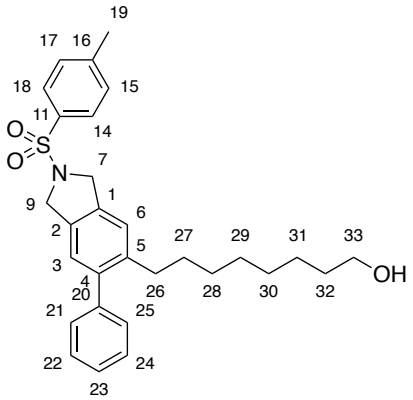
IR (ATR, film): 2928, 2857, 2361, 1343, 1161, 1096, 1057, 814, 735, 702, 665, 617, 602, 561, 546, 523 cm^{-1}.

HRMS (ESI): Calculated for 450.2094 *m*/*z*, found 450.2090 *m*/*z* $[C_{27}H_{32}NO_3S+H]^+$.

8-(6-Phenyl-2-tosylisoindolin-5-yl)octan-1-ol (**4.173**)



Prepared according to General Procedure C from 8-phenyloct-7-yn-1-ol (23.0 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–15% Et_2O in PhMe) to yield the desired product as a yellow solid (45.3 mg, 95%).



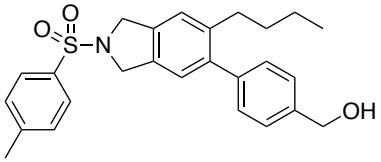
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.80 – 7.76 (m, 2H, 14, 18), 7.42 – 7.30 (m, 5H, 15, 17, 22, 23, 24), 7.23 – 7.17 (m, 2H, 21, 25), 7.08 (s, 1H, 6), 6.99 (s, 1H, 3), 4.64 (m, 2H, 7), 4.61 (m, 2H, 9), 3.60 (t, *J* = 6.7 Hz, 2H, 33), 2.53 – 2.46 (m, 2H, 26), 2.41 (s, 3H, 19), 1.50 (m, 2H, 32), 1.41 – 1.31 (m, 2H, 27), 1.29 – 1.21 (m, 2H, 31), 1.23 – 1.09 (m, 6H, 28, 29, 30).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (16), 141.7 (4), 141.4 (20), 140.4 (5), 135.3 (2), 133.7 (11), 133.5 (1), 129.8 (15, 17), 129.1 (21, 25), 128.1 (22, 24), 127.7 (14, 18), 127.0 (23), 124.0 (3), 123.2 (6), 63.0 (33), 53.6 (7), 53.6 (9), 32.9 (26), 32.7 (31), 31.4 (27), 29.2 (28), 29.2 (29), 29.2 (30), 25.7 (32), 21.5 (19).

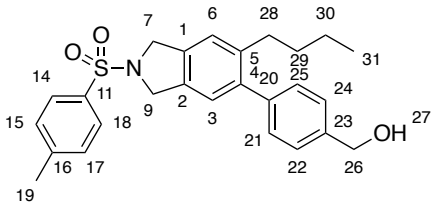
IR (ATR, film): 2926, 2855, 1343, 1161, 1096, 1059, 814, 735, 702, 665, 617, 602, 561, 520 cm^{-1}.

HRMS (ESI): Calculated for 478.2410 *m*/*z*, found 478.2392 *m*/*z* $[C_{29}H_{35}NO_3S+H]^+$.

(4-(6-Butyl-2-tosylisoindolin-5-yl)phenyl)methanol (4.174)



Prepared according to General Procedure C from (4-(hex-1-yn-1-yl)phenyl)methanol (18.8 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% EtOAc in hexane) to yield the desired product as a white solid (39.8 mg, 91%).



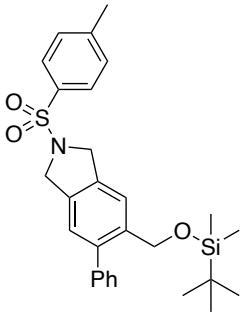
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.89 – 7.73 (m, 2H, 14, 18), 7.50 – 7.39 (m, 2H, 22, 24), 7.36 – 7.32 (m, 2H, 15, 17), 7.24 – 7.19 (m, 2H, 21, 25), 7.11 (s, 1H, 6), 7.00 (s, 1H, 3), 4.77 (d, *J* = 4.9 Hz, 2H, 26), 4.66 (m, 2H, 7), 4.63 (m, 2H, 9), 2.62 – 2.48 (m, 2H, 28), 2.44 (s, 3H, 19), 1.75 (t, *J* = 5.8 Hz, 1H, 27), 1.45 – 1.34 (m, 2H, 29), 1.19 (h, *J* = 7.4 Hz, 2H, 30), 0.79 (t, *J* = 7.4 Hz, 3H, 31).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (16), 141.3 (20), 140.8 (4), 140.4 (5), 139.6 (23), 135.4 (1), 133.7 (11), 133.5 (2), 129.8 (15, 17), 129.4 (21, 25), 127.7 (14, 18), 126.8 (22, 24), 124.0 (3), 123.2 (6), 65.2 (26), 53.6 (7), 53.6 (9), 33.7 (29), 32.6 (28), 22.4 (30), 21.6 (19), 13.8 (31).

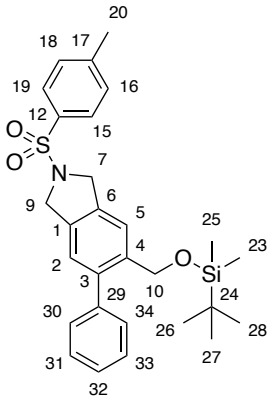
IR (ATR, film): 2926, 1458, 1344, 1161, 1096, 1057, 1017, 667, 615, 548 cm^{-1}.

HRMS (ESI): Calculated for 458.1760 *m*/*z*, found 458.1754 *m*/*z* $[C_{26}H_{29}NO_3S+Na]^+$.

5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-6-phenyl-2-tosylisoindoline (4.175)



Prepared according to General Procedure C from *tert*-butyldimethyl((3-phenylprop-2-yn-1-yl)oxy)silane (24.6 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (41.3 mg, 84%).



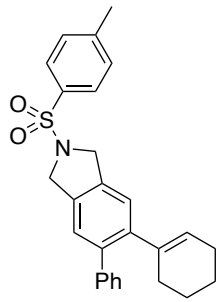
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.81 – 7.76 (m, 2H, 15, 19), 7.41 – 7.30 (m, 6H, 5, 16, 18, 31–33), 7.25 – 7.22 (m, 2H, 30, 34), 7.02 (s, 1H, 2), 4.71 – 4.65 (m, 2H, 9), 4.65 – 4.62 (m, 2H, 7), 4.51 (s, 2H, 10), 2.41 (s, 3H, 20), 0.87 (s, 9H, 26–28), –0.02 (s, 6H, 23, 25).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.8 (17), 140.6 (29), 140.3 (3), 138.7 (4), 135.5 (1), 134.9 (6), 133.8 (12), 130.0 (16, 18), 129.1 (30, 34), 128.3 (31, 33), 127.8 (15, 19), 127.5 (32), 123.9 (2), 121.9 (5), 63.0 (10), 53.9 (9), 53.8 (7), 26.0 (26–28), 21.7 (20), 18.5 (24), –5.3 (23, 25).

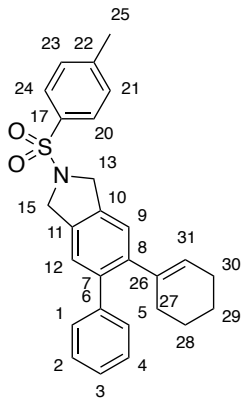
IR (ATR, film): 1346, 1163, 1061, 835, 665, 548 cm^{-1}.

HRMS (ESI): Calculated for 494.2180 *m*/*z*, found 494.2175 *m*/*z* $[C_{28}H_{35}NO_3SSi+H]^+$.

5-(Cyclohex-1-en-1-yl)-6-phenyl-2-tosylisoindoline (**4.176**)



Prepared according to General Procedure C from (cyclohex-1-en-1-ylethynyl)benzene (18.2 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a yellow solid (27.1 mg, 63%).



^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.78 (d, J = 8.2 Hz, 2H, 20, 24), 7.37 – 7.27 (m, 7H, 1–5, 21, 23), 7.08 (s, 1H, 12), 7.04 (s, 1H, 9), 5.66 – 5.54 (m, 1H, 31), 4.64 (m, 4H, 13, 15), 2.41 (s, 3H, 25), 2.05 (m, 2H, 30), 1.71 (m, 2H, 27), 1.52 – 1.36 (m, 4H, 28, 29).

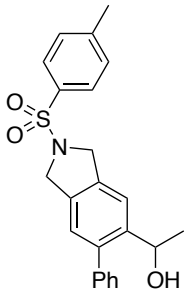
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.8 (22), 141.7 (8), 139.9, 139.1 (26), 135.2 (11), 134.8 (10), 133.8 (17), 130.0, 128.9, 128.3 (31), 128.1, 127.8 (20, 24), 127.1 (3), 124.2 (12), 123.5 (9), 53.74 (13 or 15), 53.74 (13 or 15), 29.6 (27), 25.8 (30), 23.0 (29), 22.0 (28), 21.7 (25).

IR (ATR, film): 1348, 1163, 1098, 667, 548 cm^{-1}.

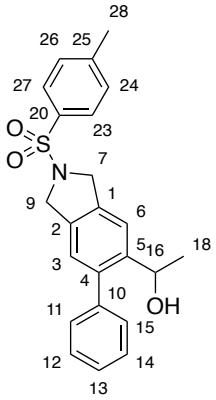
HRMS (ESI): Calculated for 430.1835 *m*/*z*, found 430.1839 *m*/*z* $[C_{27}H_{25}NO_2S+H]^+$.

Unambiguous assignment of all ^{13}C NMR signals could not be performed.

1-(6-Phenyl-2-tosylisoindolin-5-yl)ethan-1-ol (**4.177**)



Prepared according to General Procedure C from 4-phenylbut-3-yn-2-ol (16.0 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.) at 15 mol% catalytic loading. Purified by flash column chromatography (silica, 0–15% Et_2O in PhMe) to yield the desired product as a white solid (28.3 mg, 72%).



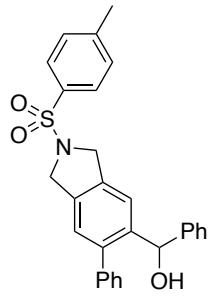
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.86 – 7.77 (m, 2H, 24, 26), 7.52 (s, 1H, 3), 7.48 – 7.37 (m, 3H, 12–14), 7.37 – 7.33 (m, 2H, 23, 27), 7.27 – 7.19 (m, 2H, 11, 15), 7.02 (s, 1H, 6), 4.95 (q, *J* = 6.4 Hz, 1H, 16), 4.73 – 4.67 (m, 2H, 9), 4.65 (m, 2H, 7), 2.44 (s, 3H, 28), 1.36 (d, *J* = 6.4 Hz, 3H, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (25), 143.3 (5), 140.4 (10), 140.2 (4), 136.0 (1), 135.1 (2), 133.7 (20), 129.9 (23, 27), 129.1 (11, 15), 128.3 (12, 14), 127.7 (24, 26), 127.4 (13), 124.0 (6), 119.7 (3), 66.3 (16), 53.7 (9), 53.6 (7), 25.2 (18), 21.5 (28).

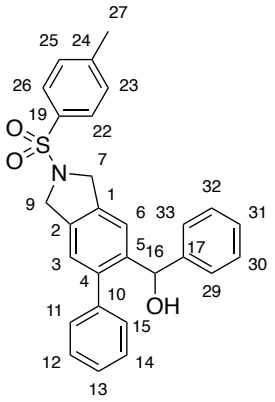
IR (ATR, film): 3501, 2363, 1333, 1155, 1096, 704, 669, 540, 449, 430, 424, 417, 403 cm^{-1}.

HRMS (ESI): Calculated for 416.1291 *m*/*z*, found 416.1297 *m*/*z* $[C_{23}H_{23}NO_3S+Na]^+$.

Phenyl(6-phenyl-2-tosylisoindolin-5-yl)methanol (**4.178**)



Prepared according to General Procedure C from 1,3-diphenylprop-2-yn-1-ol (16.0 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.) at 15 mol% catalytic loading. Purified by flash column chromatography (silica, 0–5% Et_2O in PhMe) to yield the desired product as a white solid (16.8 mg, 37%).



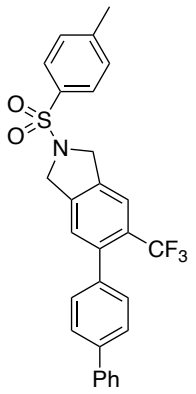
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.79 (d, *J* = 8.30 Hz, 2H, 22, 26), 7.41 (s, 1H, 6), 7.37 (m, 3H, 11, 15, 31), 7.37 – 7.31 (m, 2H, 23, 25), 7.28 – 7.21 (m, 3H 12–14), 7.19 (m, 2H, 32, 30), 7.13 – 7.08 (m, 2H, 29, 33), 7.05 (s, 1H, 3), 5.90 (s, 1H, 16), 4.68 – 4.60 (m, 4H, 7, 9), 2.44 (s, 3H, 27).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (24), 143.5 (17), 141.2 (5), 140.3 (4), 135.9 (2), 135.4 (1), 133.6 (10), 129.9 (23, 25), 129.3 (11, 15), 128.4 (30, 32), 128.3 (12, 14), 127.7 (22, 26), 127.5 (13), 127.5 (31), 126.4 (29, 33), 124.1 (3), 121.3 (6), 72.2 (16), 53.7 (7), 53.6 (9), 21.6 (27).

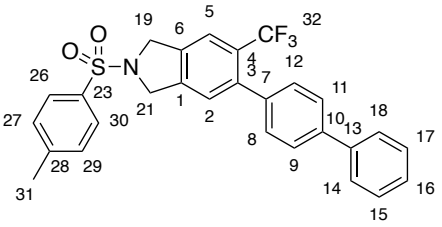
IR (ATR, film): 1344, 1163, 1098, 702, 667, 548, 403 cm^{-1}.

HRMS (ESI): Calculated for 478.1447 *m*/*z*, found 478.1434 *m*/*z* $[C_{28}H_{25}NO_3S+Na]^+$.

5-([1,1'-Biphenyl]-4-yl)-2-tosyl-6-(trifluoromethyl)isoindoline (4.179)



Prepared according to General Procedure C from 4-(3,3,3-trifluoroprop-1-yn-1-yl)-1,1'-biphenyl (22.6 mg, 200 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (25.3 mg, 51%).



^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.85 – 7.79 (m, 2H, 26, 30), 7.69 – 7.57 (m, 5H, 5, 8, 12, 14, 18), 7.52 – 7.43 (m, 2H, 15, 17), 7.44 – 7.31 (m, 5H, 9, 11, 16, 27, 29), 7.20 (s, 1H, 2), 4.74 (s, 2H, 19), 4.71 (s, 2H, 21), 2.45 (s, 3H, 31).

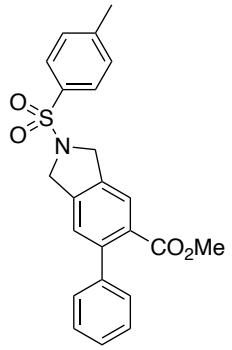
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 144.0 (28), 141.2 (23), 140.7 (10), 140.5 (13), 139.8 (1), 138.1 (7), 135.7 (6), 133.4 (q, $^{3}J_{CF}$ = 5.2 Hz, 3), 130.0 (9, 11), 129.3 (26, 30), 128.8 (15, 17), 128.5 (q, $^{2}J_{CF}$ = 30.4 Hz, 4), 127.7 (27, 29), 127.5 (16), 127.1 (14, 18), 126.6 (8, 12), 126.4 (2), 123.9 (q, $^{1}J_{CF}$ = 273.9 Hz, 32), 120.7 (q, $^{3}J_{CF}$ = 5.4 Hz, 5), 53.5 (19), 53.4 (21), 21.6 (31).

^{19}F{^{1}H} NMR (377 MHz, Chloroform-*d*) δ_F −56.6.

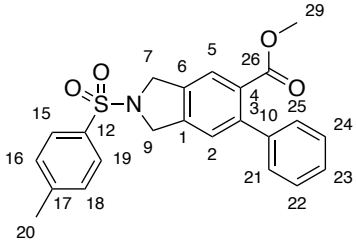
IR (ATR, film): 1350, 1312, 1163, 1125, 667, 584, 548 cm^{-1}.

HRMS (ESI): Calculated for 494.1396 *m*/*z*, found 494.1404 *m*/*z* $[C_{28}H_{22}F_3NO_2S+H]^+$.

Methyl 6-phenyl-2-tosylisoindoline-5-carboxylate (**4.180**)



Prepared according to General Procedure B from methyl 3-phenylpropiolate (16.0 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–3% Et_2O in PhMe) to yield the desired product as a white solid (41.1 mg, >99%).



^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.78 (d, *J* = 8.3 Hz, 2H, 15, 19), 7.63 (s, 1H, 5), 7.42 –

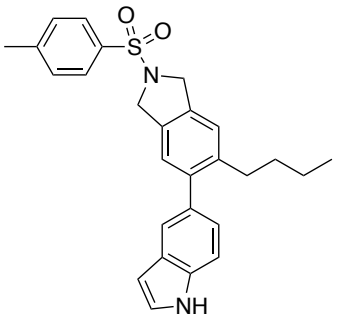
7.29 (m, 5H, 16, 18, 22, 23, 24), 7.24 – 7.21 (m, 2H, 21, 25), 7.17 (s, 1H, 2), 4.69 – 4.65 (m, 4H, 7, 9), 3.59 (s, 3H, 29), 2.41 (s, 3H, 20).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 168.7 (26), 144.1 (17), 142.7 (3), 140.8 (10), 139.7 (6), 135.4 (1), 133.6 (12), 130.9 (4), 130.1 (16, 18), 128.3 (21, 25), 128.3 (22, 24), 127.7 (15, 19), 127.6 (23), 125.0 (2), 124.2 (5), 53.7 (7 or 9), 53.5 (7 or 9), 52.2 (29), 21.7 (20).

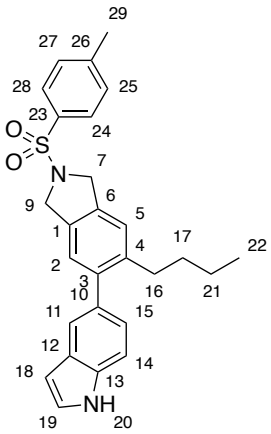
IR (ATR, film): 1721, 1346, 1302, 1256, 1161, 1096, 733, 700, 665, 584, 569, 548 cm^{-1}.

HRMS (ESI): Calculated for 408.1264 *m*/*z*, found 408.1262 *m*/*z* $[C_{23}H_{21}NO_4S+H]^+$.

5-(6-Butyl-2-tosylisoindolin-5-yl)-1*H*-indole (4.181)



Prepared according to General Procedure C from 5-(hex-1-yn-1-yl)-1*H*-indole (19.7 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–5% Et_2O in PhMe) to yield the desired product as white solid (29.1 mg, 65%).



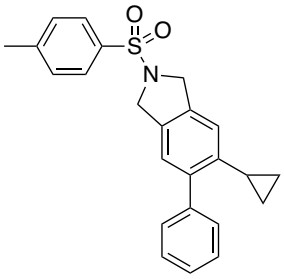
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 8.26 (s, 1H, 20), 7.82 – 7.76 (m, 2H, 25, 27), 7.47 – 7.44 (m, 1H, 11), 7.40 (m, 1H, 14), 7.33 (d, *J* = 8.0 Hz, 2H, 24, 28), 7.27 – 7.25 (m, 1H, 19), 7.10 (s, 1H, 5), 7.07 – 7.03 (m, 2H, 2, 15), 6.56 (m, 1H, 18), 4.66 (s, 2H, 7), 4.62 (s, 2H, 9), 2.59 – 2.52 (m, 2H, 16), 2.42 (s, 3H, 29), 1.45 – 1.35 (m, 2H, 17), 1.16 (m, 2H, 21), 0.75 (t, *J* = 7.4 Hz, 3H, 22).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.7 (26), 143.0 (3), 140.9 (4), 135.0 (6), 134.8 (12), 133.8 (23), 133.3 (1), 133.3 (10), 129.9 (24, 28), 127.8 (13), 127.8 (25, 27), 124.9 (19), 124.7 (2), 123.7 (15), 123.1 (5), 121.2 (11), 110.6 (14), 102.8 (18), 53.8 (7), 53.8 (9), 33.8 (17), 32.9 (16), 22.6 (21), 21.7 (29), 14.0 (22).

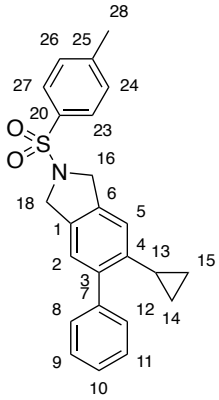
IR (ATR, film): 3404, 2955, 2924, 2860, 1597, 1464, 1418, 1341, 1159, 1098, 1061, 882, 812, 768, 733, 667, 604, 548, 424 cm^{-1}.

HRMS (ESI): Calculated for 445.1944 *m*/*z*, found 445.1946 *m*/*z* $[C_{27}H_{28}N_2O_2S+H]^+$.

5-Cyclopropyl-6-phenyl-2-tosylisoindoline (**4.182**)



Prepared according to General Procedure C from (cyclopropylethynyl)benzene (14.2 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as white solid (25.3 mg, 65%).



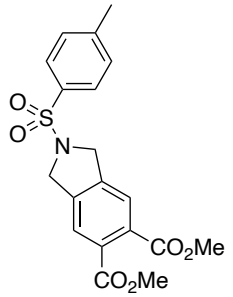
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.79 – 7.75 (m, 2H, 24, 26), 7.42 – 7.37 (m, 2H, 9, 11), 7.37 – 7.28 (m, 5H, 5, 8, 12, 23, 27), 7.02 (s, 1H, 2), 6.74 (s, 1H, 5), 4.65 – 4.58 (m, 4H, 16, 18), 2.41 (s, 3H, 28), 1.82 (tt, *J* = 8.4, 5.3 Hz, 1H, 13), 0.84 – 0.77 (m, 2H, 14, 15), 0.64 – 0.58 (m, 2H, 14, 15).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.8 (23), 142.4 (4), 141.4 (7), 141.1 (3), 135.6 (6), 133.7 (20), 133.2 (1), 129.9 (8, 12), 129.6 (23, 27), 128.2 (9, 11), 127.8 (24, 26), 127.1 (10), 123.9 (2), 118.0 (5), 53.8 (18), 53.7 (16), 21.7 (28), 13.7 (13), 9.9 (14, 15).

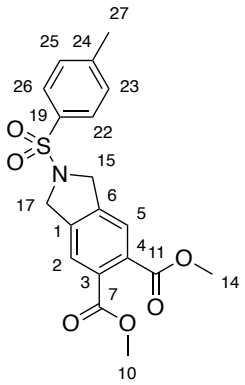
IR (ATR, film): 1343, 1300, 1159, 1098, 1059, 1022, 883, 812, 770, 735, 704, 665, 621, 598, 544 cm^{-1}.

HRMS (ESI): Calculated for 390.1522 *m*/*z*, found 390.1513 *m*/*z* $[C_{24}H_{23}NO_2S+H]^+$.

Dimethyl 2-tosylisoindoline-5,6-dicarboxylate (**4.183**)



Prepared according to General Procedure C from dimethyl acetylenedicarboxylate (28.4 mg, 200 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (297 mg, 1.20 mmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–5% Et_2O in PhMe) to yield the desired product as a white solid (11.3 mg, 15%).



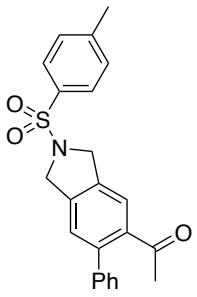
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.77 – 7.73 (m, 2H, 22, 26), 7.52 (s, 2H, 2, 5), 7.34 – 7.31 (m, 2H, 23, 25), 4.65 (s, 4H, 15, 17), 3.88 (s, 6H, 10, 14), 2.41 (s, 3H, 27).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 167.6 (7, 11), 144.3 (24), 139.7 (1, 6), 133.4 (19), 132.1 (3, 4), 130.1 (23, 25), 127.7 (22, 26), 123.5 (2, 5), 53.6 (15, 17), 53.0 (10, 14), 21.7 (27).

IR (ATR, film): 1726, 1302, 1163, 1098, 667 cm^{-1}.

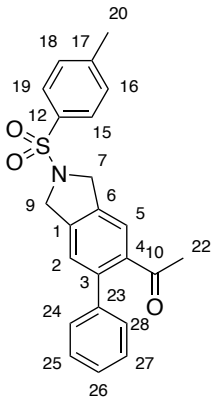
HRMS (ESI): Calculated for 390.1006 *m*/*z*, found 390.1006 *m*/*z* $[C_{19}H_{19}NO_6S+H]^+$.

1-(6-Phenyl-2-tosylisoindolin-5-yl)ethan-1-one (**4.184**)



Prepared according to General Procedure C from 4-phenylbut-3-yn-2-one (14.4 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol,

6.00 equiv.). Purified by flash column chromatography (silica, 0–10% Et_2O in PhMe) to yield the desired product as a white solid (36.8 mg, 94%).



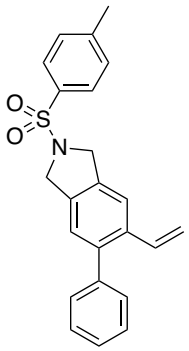
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.81 – 7.76 (m, 2H, 15, 19), 7.43 – 7.38 (m, 3H, 25–27), 7.35 – 7.31 (m, 3H, 5, 16, 18), 7.29 – 7.24 (m, 2H, 24, 28), 7.18 (s, 1H, 2), 4.70 – 4.66 (m, 4H, 7, 9), 2.41 (s, 3H, 20), 1.92 (s, 3H, 22).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 204.4 (10), 144.1 (17), 141.1 (4), 140.8 (3), 140.2 (23), 139.1 (6), 135.8 (1), 133.6 (12), 130.1 (16, 18), 129.0 (24, 28), 128.9 (25, 27), 128.4 (26), 127.7 (15, 19), 124.5 (2), 122.4 (5), 53.7 (9), 53.5 (7), 30.5 (22), 21.7 (20).

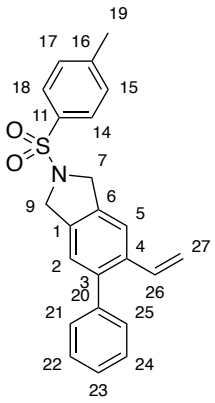
IR (ATR, film): 1680, 1346, 1161, 1096, 735, 702, 665, 544 cm^{-1}.

HRMS (ESI): Calculated for 391.1309 *m*/*z*, found 391.1309 *m*/*z* $[C_{23}H_{21}NO_3S+H]^+$.

5-Phenyl-2-tosyl-6-vinylisoindoline (**4.185**)



Prepared according to General Procedure C from but-3-en-1-yn-1-ylbenzene (12.8 mg, 100 μmol) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 μmol). Purified by flash column chromatography (silica, 0–5% Et_2O in PhMe) to yield the desired product as a white solid (30.8 mg, 75%).



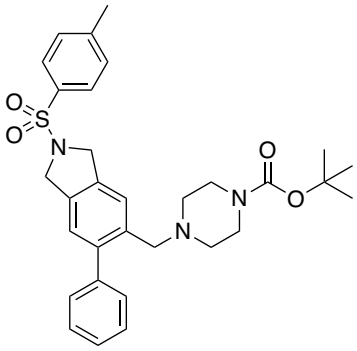
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.85 – 7.79 (m, 2H, 14, 18), 7.46 (s, 1H, 2), 7.44 – 7.33 (m, 6H, 15, 17, 21, 22, 24, 25), 7.27 (m, 1H, 23), 7.10 (s, 1H, 5), 6.64 (dd, *J* = 17.5, 11.0 Hz, 1H, 26), 5.66 (dd, *J* = 17.5, 1.2 Hz, 1H, 27), 5.19 (dd, *J* = 10.9, 1.2 Hz, 1H, 27), 4.71 – 4.68 (m, 2H, 7), 4.66 (m, 2H, 9), 2.44 (s, 3H, 19).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.8 (16), 140.9 (3), 140.3 (20), 135.8 (1), 135.6 (6), 135.6 (4), 135.4 (26), 133.6 (11), 129.9 (14, 18), 129.7 (22, 24), 128.2 (21, 25), 127.7 (15, 17), 127.3 (23), 124.1 (5), 119.7 (2), 115.0 (27), 53.6 (9), 53.6 (7), 21.6 (19).

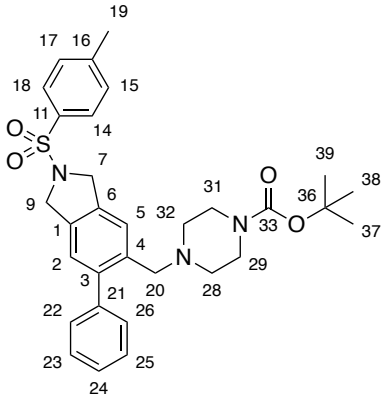
IR (ATR, film): 1344, 1163, 1096, 704, 667, 548 cm^{-1}

Calculated for 398.1185 m/z, found 398.1171 m/z $[C_{23}H_{21}NO_2S+Na]^+$

***tert*-Butyl 4-((6-phenyl-2-tosylisoindolin-5-yl)methyl)piperazine-1-carboxylate (4.186)**



Prepared according to General Procedure C from *tert*-butyl 4-(3-phenylprop-2-yn-1-yl)piperazine-1-carboxylate (30.0 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–20% EtOAc in PhMe) to yield the desired product as a yellow solid (42.6 mg, 78%).



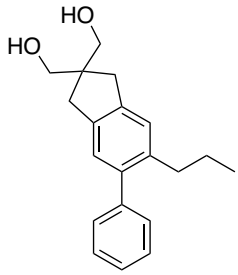
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.81 – 7.78 (m, 2H, 14, 18), 7.39 – 7.32 (m, 6H, 5, 15, 17, 23–25), 7.26 – 7.22 (m, 2H, 22, 26), 7.04 (s, 1H, 2), 4.65 (s, 2H, 7), 4.63 (s, 2H, 9), 3.32 (m, 6H, 20, 29, 31), 2.41 (s, 3H, 19), 2.22 (m, 4H, 28, 32), 1.42 (s, 9H, 37–39).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 154.9 (33), 143.8 (16), 142.6 (4), 140.9 (21), 135.7 (1), 135.4 (6), 135.0 (3), 133.8 (11), 130.0 (15, 17), 129.4 (22, 26), 128.1 (23, 25), 127.8 (14, 18), 127.3 (24), 124.3 (2), 123.9 (5), 79.7 (36), 59.7 (20), 53.7 (7 or 9), 53.7 (7 or 9), 52.7 (28, 32), 43.7 (29, 31), 28.5 (37, 38, 39), 21.7 (19).

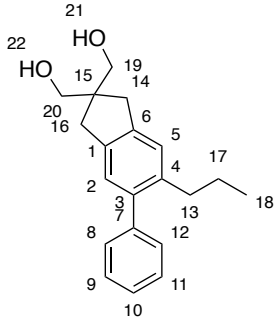
IR (ATR, film): 1686, 1344, 1161, 1096, 735, 702, 665, 546 cm^{-1}.

HRMS (ESI): Calculated for 548.2578 *m*/*z*, found 548.2595 *m*/*z* $[C_{31}H_{37}N_3O_4S+H]^+$.

(5-Phenyl-6-propyl-2,3-dihydro-1*H*-indene-2,2-diyl)dimethanol (**4.187**)



Prepared according to General Procedure C from pent-1-yn-1-ylbenzene (14.4 mg, 100 µmol, 1.00 equiv.) and 2,2-di(prop-2-yn-1-yl)propane-1,3-diol (183 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% MeOH in PhMe) to yield the desired product as a white solid (13.6 mg, 23%).



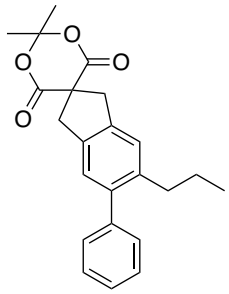
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.41 – 7.36 (m, 2H, 9, 11), 7.34 – 7.30 (m, 1H, 10), 7.28 (dd, *J* = 7.0, 1.6 Hz, 2H, 8, 12), 7.11 (s, 1H, 5), 7.01 (s, 1H, 2), 3.78 (s, 4H, 19, 20), 2.87 (s, 2H, 14), 2.83 (s, 2H, 16), 2.56 (brs, 2H, 21, 22), 2.52 – 2.47 (m, 2H, 13), 1.51 – 1.41 (m, 2H, 17), 0.80 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 142.5 (7), 140.9 (1), 140.5 (3), 139.0 (6), 138.6 (4), 129.5 (8, 12), 128.1 (9, 11), 126.7 (2), 126.6 (10), 125.8 (5), 69.9 (19, 20), 49.2 (15), 38.5 (14), 38.3 (16), 35.2 (13), 24.9 (17), 14.3 (18).

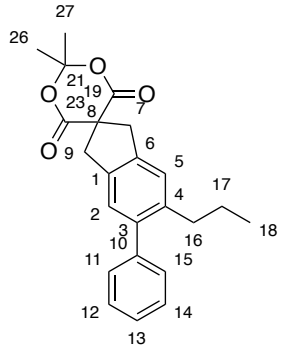
IR (ATR, film): 3366, 2924, 2864, 1437, 1078, 1026, 895, 700, 573, 532 cm^{-1}.

HRMS (ESI): Calculated for 319.1669 *m*/*z*, found 319.1683 *m*/*z* $[C_{20}H_{24}O_2+Na]^+$.

2',2'-Dimethyl-5-phenyl-6-propyl-1,3-dihydrospiro[indene-2,5'-[1,3]dioxane]-4',6'-dione (4.188)



Prepared according to General Procedure C from pent-1-yn-1-ylbenzene (14.4 mg, 100 µmol, 1.00 equiv.) and 2,2-dimethyl-5,5-di(prop-2-yn-1-yl)-1,3-dioxane-4,6-dione (132 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (11.0 mg, 44%).



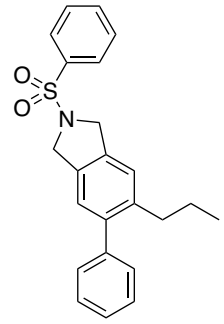
^{1}H NMR (400 MHz, Chloroform-*d*) δ_H 7.42 – 7.36 (m, 2H, 12, 14), 7.36 – 7.30 (m, 1H ,13), 7.27 (dd, *J* = 6.8, 1.8 Hz, 2H, 11, 15), 7.13 (s, 1H, 5), 7.03 (s, 1H, 2), 3.76 (s, 2H, 7 or 9), 3.72 (s, 2H, 7 or 9), 2.54 – 2.46 (m, 2H, 16), 1.85 – 1.83 (m, 6H, 26, 27), 1.52 – 1.40 (m, 2H, 17), 0.80 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (101 MHz, Chloroform-*d*) δ_C 170.9 (19, 23), 142.1 (10), 141.6 (3), 139.9 (4), 138.2 (1), 136.2 (6), 129.4 (11, 15), 128.1 (12, 14), 126.9 (13), 125.6 (2), 124.7 (5), 105.3 (21), 52.7 (8), 45.64 (7 or 9), 45.64 (7 or 9), 35.2 (16), 29.13 (26 or 27), 29.12 (26 or 27), 24.6 (17), 14.2 (18).

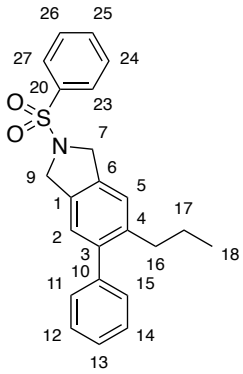
IR (ATR, film): 1736, 1290, 702 cm^{-1}.

HRMS (ESI): Calculated for 387.1567 *m*/*z*, found 387.1569 *m*/*z* $[C_{23}H_{24}O_4+Na]^+$.

5-Phenyl-2-(phenylsulfonyl)-6-propylisoindoline (**4.189**)



Prepared according to General Procedure C from pent-1-yn-1-ylbenzene (14.6 mg, 100 µmol, 1.00 equiv.) and *N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (140 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a pale-yellow solid (32.1 mg, 85%).



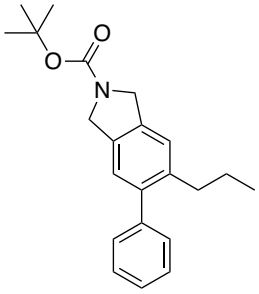
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.94 – 7.90 (m, 2H, 23, 27), 7.62 – 7.51 (m, 3H, 24–26), 7.40 – 7.31 (m, 3H, 12–14), 7.23 – 7.19 (m, 2H, 11, 15), 7.10 (s, 1H, 5), 7.00 (s, 1H, 2), 4.67 (s, 2H, 7), 4.64 (s, 2H, 9), 2.51 – 2.45 (m, 2H, 16), 1.46 – 1.38 (m, 2H, 17), 0.77 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 141.9 (3), 141.5 (10), 140.3 (4), 136.9 (20), 135.3 (6), 133.5 (1), 133.0 (25), 129.3 (24, 26), 129.2 (11, 15), 128.2 (23, 27), 127.7 (12, 14), 127.1 (13), 124.2 (2), 123.3 (5), 53.8 (7), 53.7 (9), 35.2 (16), 24.6 (17), 14.1 (18).

IR (ATR, film): 1346, 1165, 1098, 720, 691, 627, 577 cm^{-1}.

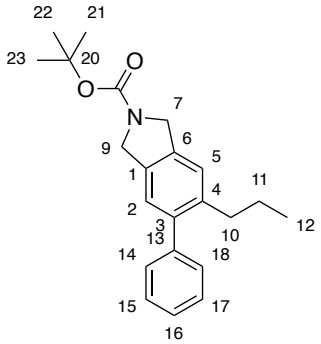
HRMS (ESI): Calculated for 378.1522 *m*/*z*, found 378.1527 *m*/*z* $[C_{23}H_{23}NO_2S+H]^+$.

***tert*-Butyl 5-phenyl-6-propylisoindoline-2-carboxylate** (**4.190**)



Prepared according to General Procedure C from pent-1-yn-1-ylbenzene (14.4 mg, 100 μmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–5% Et_2O in hexane) to yield the desired product as a white solid (18.1 mg, 54%).

1:1 ratio of rotamers observed. Equivalent rotameric ^1H signals reported as ranges. All observed ^{13}C NMR signals reported



^1H NMR (500 MHz, Chloroform-*d*) δ_H 7.43 – 7.38 (m, 2H, 15, 17), 7.37 – 7.32 (m, 1H, 16), 7.29 – 7.26 (m, 2H, 14, 18), 7.21 – 7.12 (m, 1H, 2), 7.12 – 7.03 (m, 1H, 5), 4.72 – 4.62 (m, 4H, 7, 9), 2.57 – 2.50 (m, 2H, 10), 1.53 – 1.51 (m, 9H, 21–23), 1.50 – 1.42 (m, 2H, 11), 0.83 – 0.77 (m, 3H, 12).

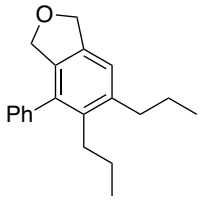
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 154.78 (24), 154.76 (24), 141.9, 141.5, 141.4, 139.8, 139.6, 136.7, 136.3, 134.9, 134.5, 129.4, 128.19, 128.18, 127.0, 124.4 (2 or 5), 124.1 (2 or 5), 123.5 (2 or 5), 123.2 (2 or 5), 79.8 (20), 79.8 (20), 52.3 (7 or 9), 52.2 (7 or 9), 52.0 (7 or 9), 52.0 (7 or 9), 35.2 (10), 35.2 (10), 28.7 (21–23), 24.7 (11), 24.7 (11), 14.1 (12), 14.1 (12).

IR (ATR, film): 1697, 1391, 1364, 1167, 1107, 878, 702 cm^{-1}.

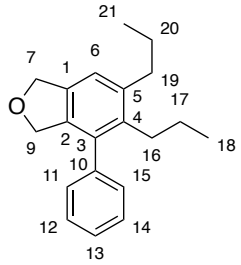
HRMS (ESI): Calculated for 338.2115 *m*/*z*, found 338.2112 *m*/*z* $[C_{22}H_{27}NO_2+H]^+$.

Unambiguous assignment of all ^{13}C NMR signals could not be performed.

4-Phenyl-5,6-dipropyl-1,3-dihydroisobenzofuran (4.191)



Prepared according to General Procedure C from 4-octyne (11.0 mg, 100 µmol, 1.00 equiv.) and (3-(prop-2-yn-1-yloxy)prop-1-yn-1-yl)benzene (102 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a pale-yellow solid (14.1 mg, 50%).



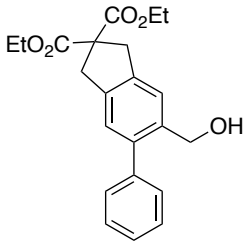
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.45 – 7.40 (m, 2H, 12, 14), 7.39 – 7.34 (m, 1H, 13), 7.25 – 7.21 (m, 2H, 11, 15), 7.09 (s, 1H, 6), 5.16 (m, 2H, 7), 4.76 (m, 2H, 9), 2.74 – 2.64 (m, 2H, 19), 2.50 – 2.40 (m, 2H, 16), 1.74 – 1.64 (m, 2H, 20), 1.43 – 1.30 (m, 2H, 17), 1.06 (t, *J* = 7.3 Hz, 3H, 21), 0.77 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 140.6 (5), 140.1 (10), 137.6 (4), 136.2 (1), 136.0 (2), 136.0 (3), 128.6 (11, 15), 128.3 (12, 14), 127.0 (13), 120.8 (6), 74.2 (7), 73.7 (9), 35.4 (19), 31.5 (16), 24.9 (20), 24.6 (17), 14.6 (18), 14.5 (21).

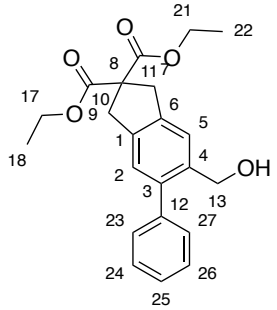
IR (ATR, film): 2959, 2780, 2359, 1748, 1042, 764, 750, 702, 424, 411, 405 cm^{-1}.

HRMS (ESI): Calculated for 279.1743 *m*/*z*, found 279.1737 *m*/*z* $[C_{20}H_{24}O-H]^+$.

Diethyl 5-(hydroxymethyl)-6-phenyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.192)



Prepared according to General Procedure C from 3-phenylprop-2-yn-1-ol (13.2 mg, 100 µmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–5% Et_2O in PhMe) to yield the desired product as a white solid (21.6 mg, 59%).



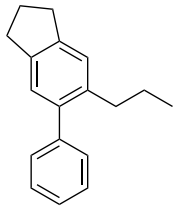
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.43 – 7.38 (m, 3H, 5, 23, 27), 7.38 – 7.31 (m, 3H, 24–26), 7.11 (s, 1H, 2), 4.58 – 4.55 (m, 2H, 13), 4.22 (q, *J* = 7.1 Hz, 4H, 17, 21), 3.64 (s, 2H, 7), 3.61 (s, 2H, 9), 1.27 (t, *J* = 7.1 Hz, 6H, 18, 22).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 171.8 (10, 11), 142.2 (4), 141.0 (12), 140.5 (3), 139.8 (1), 137.1 (6), 129.3 (24, 26), 128.4 (23, 27), 127.3 (25), 126.0 (2), 124.4 (5), 63.4 (13), 61.9 (17, 21), 60.8 (8) 40.5 (9), 40.4 (7), 14.2 (18, 22).

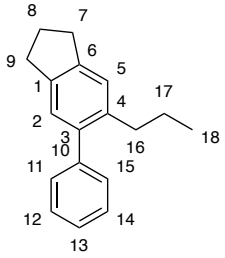
IR (ATR, film): 1726, 1244, 1186 cm^{-1}.

HRMS (ESI): Calculated for 391.1516 *m*/*z*, found 391.1504 *m*/*z* [$C_{22}H_{24}O_5$+Na]$^+$.

5-Phenyl-6-propyl-2,3-dihydro-1*H*-indene (**4.194**)



Prepared according to General Procedure C from pent-1-yn-1-ylbenzene (14.4 mg, 100 µmol, 1.00 equiv.) and 1,6-heptadiyne (55.3 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–1% PhMe in hexane) to yield the desired product as a white solid (21.0 mg, 89%).



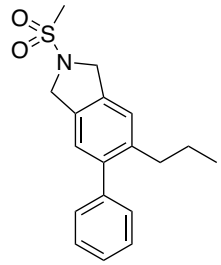
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.39 (m, 2H, 12, 14), 7.35 – 7.28 (m, 3H, 11, 13, 15), 7.17 (s, 1H, 5), 7.08 (s, 1H, 2), 2.99 – 2.88 (m, 4H, 7, 9), 2.55 – 2.49 (m, 2H, 16), 2.11 (m, 2H, 8), 1.53 – 1.42 (m, 2H, 17), 0.81 (t, *J* = 7.3 Hz, 3H, 18).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.6 (1), 142.8 (10), 141.6 (6), 140.0 (3), 138.1 (4), 129.5 (11, 15), 128.0 (12, 14), 126.6 (13), 126.0 (2), 125.2 (5), 35.3 (16), 32.8 (7), 32.6 (9), 25.7 (8), 24.9 (17), 14.3 (18).

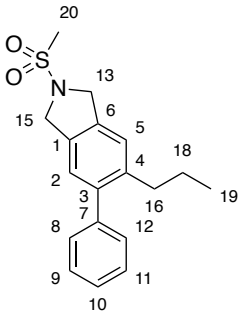
IR (ATR, film): 2955, 2928, 1479, 700 cm^{-1}.

HRMS (ESI): Calculated for 235.1481 *m*/*z*, found 235.1472 *m*/*z* $[C_{18}H_{20}–H]^+$.

2-(Methylsulfonyl)-5-phenyl-6-propylisoindoline (**4.195**)



Prepared according to General Procedure C from pent-1-yn-1-ylbenzene (14.4 mg, 100 µmol, 1.00 equiv.) and *N*,*N*-di(prop-2-yn-1-yl)methanesulfonamide (103 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (18.6 mg, 59%).



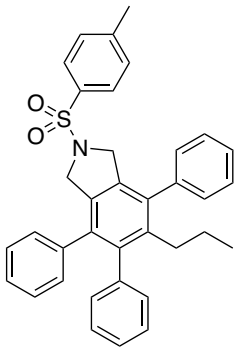
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.41 (m, 2H, 9, 11), 7.38 – 7.34 (m, 1H, 10), 7.29 – 7.24 (m, 2H, 8, 12), 7.18 (s, 1H, 5), 7.09 (s, 1H, 2), 4.76 – 4.72 (m, 2H, 13), 4.72 – 4.69 (m, 2H, 15), 2.89 (s, 3H, 20), 2.58 – 2.50 (m, 2H, 16), 1.47 (m, 2H, 18), 0.80 (t, *J* = 7.3 Hz, 3H, 19).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 142.2 (3), 141.5 (7), 140.6 (4), 135.3 (1), 133.6 (6), 129.3 (8, 12), 128.3 (9, 11), 127.2 (10), 124.3 (2), 123.4 (5), 53.9 (13), 53.8 (15), 35.2 (16), 34.9 (20), 24.7 (18), 14.1 (19).

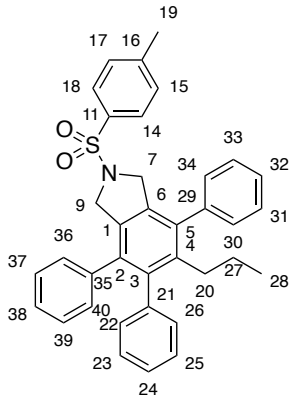
IR (ATR, film): 1323, 1146, 1088, 775, 766, 748, 704, 540, 513 cm^{-1}.

HRMS (ESI): Calculated for 316.1366 *m*/*z*, found 316.1369 *m*/*z* $[C_{18}H_{21}NO_2S+H]^+$.

4,5,7-Triphenyl-6-propyl-2-tosylisoindoline (**4.196**)



Prepared according to General Procedure C from pent-1-yn-1-ylbenzene (14.4 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-bis(3-phenylprop-2-yn-1-yl)benzenesulfonamide (240 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (7.5 mg, 14%).



^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.66 – 7.63 (m, 2H, 14, 18), 7.47 – 7.42 (m, 2H), 7.41 – 7.37 (m, 1H), 7.31 – 7.28 (m, 2H, 15, 17), 7.25 – 7.21 (m, 2H), 7.16 – 7.06 (m, 6H), 7.01 – 6.97 (m, 2H), 6.96 – 6.92 (m, 2H), 4.43 – 4.33 (m, 4H, 7, 9), 2.41 (s, 3H, 19), 2.26 – 2.20 (m, 2H, 20), 1.12 – 1.00 (m, 2H, 27), 0.36 (t, *J* = 7.3 Hz, 3H, 28).

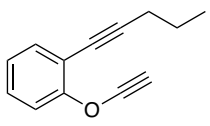
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.6 (16), 141.4, 139.6, 139.5 (4), 139.2, 139.0, 136.6, 136.4, 134.7, 133.9 (11), 132.4, 130.6, 129.9 (15, 17), 129.3, 128.8, 128.7, 127.9 (14, 18), 127.7, 127.6, 127.5, 126.8, 126.5, 54.3 (7 or 9), 54.3 (7 or 9), 32.9 (20), 24.3 (27), 21.7 (19), 14.4 (28).

IR (ATR, film): 1350, 1165, 1098, 750, 702, 669, 548 cm^{-1}.

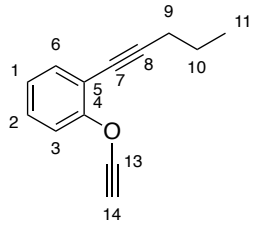
HRMS (ESI): Calculated for 544.2305 *m*/*z*, found 544.2291 *m*/*z* $[C_{36}H_{33}NO_2S+H]^+$.

Unambiguous assignment of all ^{13}C NMR signals could not be performed.

1-(Ethynyloxy)-2-(pent-1-yn-1-yl)benzene (4.198)



A flame-dried flask was charged with (*E*)-1-((1,2-dichlorovinyl)oxy)-2-(pent-1-yn-1-yl)benzene (635 mg, 2.49 mmol, 1.00 equiv.) and Et_2O (60 mL) under N_2 then –78 ºC. *n*-Butyllithium (1.095 M in hexane, 9.86 mmol, 3.96 equiv.) was added dropwise and the resulting solution was stirred for 1 h at –78 ºC and then –50 ºC for 2 h before adding MeOH (5.0 mL) to quench (at –50 ºC). The resulting mixture was washed with H_2O (20 mL) and then the organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* yielding the crude product which was purified by flash column chromatography (silica, hexane) to yield the desired product as a yellow oil (158 mg, 34%).



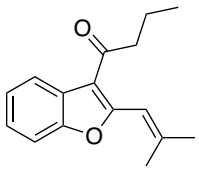
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.56 (d, *J* = 8.4 Hz, 1H, 3), 7.42 (dd, *J* = 7.6, 1.7 Hz, 1H, 6), 7.37 – 7.32 (m, 1H, 1), 7.11 (m, 1H, 2), 2.47 (t, *J* = 7.0 Hz, 2H, 9), 2.23 – 2.08 (m, 1H, 14), 1.68 (m, 2H, 10), 1.09 (t, *J* = 7.4 Hz, 3H, 11).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 155.5 (4), 133.5 (6), 128.8 (1), 124.3 (2), 113.8 (3), 113.1 (5), 96.5 (8), 84.1 (13), 74.5 (7), 34.3 (14), 22.1 (10), 21.6 (9), 13.5 (11).

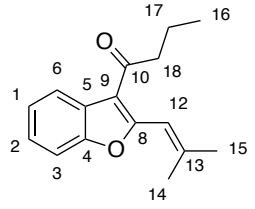
IR (ATR, film): 3316, 2963, 2162, 1589, 1487, 1449, 1225, 1200, 1155, 820, 750 cm^{-1}.

HRMS (ESI): Calculated for 185.0961 *m/z*, found 185.0955 *m/z* $[C_{13}H_{12}O+H]^+$.

1-(2-(2-Methylprop-1-en-1-yl)benzofuran-3-yl)butan-1-one (4.200)



Synthesised according to General Procedure C from 4-octyne (14.7 µL, 100 µmol, 0.17 equiv.) and 1-(ethynyloxy)-2-(pent-1-yn-1-yl)benzene (111 mg, 600 µmol, 1.00 equiv.). The octyne was not incorporated into the product and instead the diyne reacted with acetone. Purified by flash column chromatography (silica, PhMe) to yield the desired product as a yellow solid (24.5 mg, 17%).



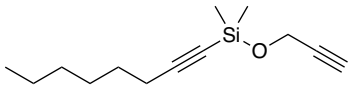
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.98 – 7.90 (m, 1H, 6), 7.54 – 7.47 (m, 1H, 3), 7.37 – 7.30 (m, 2H, 1, 2), 6.99 – 6.90 (m, 1H, 12), 2.97 (t, *J* = 7.3 Hz, 2H, 18), 2.25 (d, *J* = 1.2 Hz, 3H, 14 or 15), 2.09 (d, *J* = 1.4 Hz, 3H, 14 or 15), 1.83 (m, 2H, 17), 1.07 (t, *J* = 7.4 Hz, 3H, 16).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 197.1 (10), 160.0 (8), 153.6 (5), 147.7 (13), 125.8 (4), 124.6 (1), 123.9 (2), 121.6 (6), 116.1 (9), 114.2 (12), 111.1 (3), 45.4 (18), 28.2 (14 or 15), 21.5 (14 or 15), 17.4 (17), 14.0 (16).

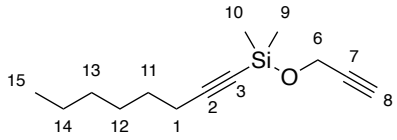
IR (ATR, film): 2957, 1659, 1640, 1520, 1454, 1379, 1215, 984, 893 cm^{-1}.

HRMS (ESI): Calculated for 243.1380 *m*/*z*, found 243.1381 *m*/*z* $[C_{16}H_{18}O_2+H]^+$.

Dimethyl(oct-1-yn-1-yl)(prop-2-yn-1-yloxy)silane (4.204)



A vial was charged with propargyl alcohol (300 µL, 5.15 mmol, 1.03 equiv.) and dimethyl(octyn-1-yl)silane (842 mg, 5.00 mmol, 1.00 equiv.). [Ru(*p*-cymene)Cl_2]$_2$ (30.6 mg, 50.0 µmol, 1.00 mol%) was added in small portions and the mixture was stirred for 1 h at RT before hexane (20 mL) was added and the mixture was filtered. After concentrating *in vacuo,* the desired product was obtained as a yellow oil (1.00 g, 90%).



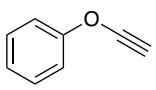
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 4.40 (d, *J* = 2.4 Hz, 2H, 6), 2.44 (t, *J* = 2.5 Hz, 1H, 8), 2.26 (t, *J* = 7.2 Hz, 2H, 1), 1.59 – 1.51 (m, 2H, 11), 1.45 – 1.38 (m, 2H, 12), 1.37 – 1.26 (m, 4H, 13, 14), 0.91 (t, *J* = 7.0 Hz, 3H, 15), 0.31 (s, 6H, 9, 10).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 109.3 (2), 81.9 (3), 81.3 (7), 73.2 (8), 51.4 (6), 31.3 (14), 28.5 (12), 28.4 (11), 22.5 (13), 19.7 (1), 14.1 (15), 0.3 (9, 10).

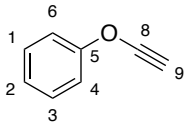
IR (ATR, film): 2930, 2174, 2154, 1088, 1049, 831, 791 cm^{-1}.

HRMS (ESI): Calculated for 245.1332 *m*/*z*, found 245.1341 *m*/*z* $[C_{13}H_{22}OSi+Na]^+$.

(Ethynyloxy)benzene (4.205)



A flame-dried flask was charged with (*E*)-((1,2-dichlorovinyl)oxy)benzene (945 mg, 5.00 mmol, 1.00 equiv.) and THF (50.0 mL) under N_2 then cooled to –78 ºC. *n*-Butyllithium solution (2.50 M in hexane, 8.00 mL, 20.0 mmol, 4.00 equiv.) was added dropwise and the solution was then stirred for a further 2 h at –78 ºC before being allowed to come up to RT to stir for 2 h. H_2O (50 mL) was added, and the solution was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product which was purified by flash column chromatography (silica, hexane) to yield the desired product as a brown oil (358 mg, 61%).

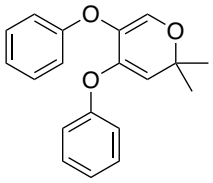


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.54 – 7.37 (m, 2H, 1, 3), 7.36 – 7.29 (m, 2H, 4, 6), 7.20 (tt, *J* = 7.3, 1.1 Hz, 1H, 2), 2.12 (s, 1H, 9).

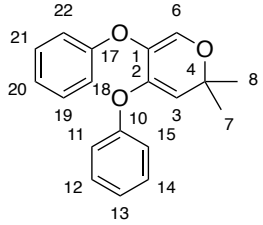
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 155.5 (5), 129.7 (1, 3), 124.6 (2), 115.0 (4, 6), 84.5 (8), 33.4 (9).

Spectral data consistent with the literature.[381]

2,2-Dimethyl-4,5-diphenoxy-2*H*-pyran (**4.207**)



Synthesised according to General Procedure C from dimethyl(oct-1-yn-1-yl)silane (50.5 mg, 100 µmol, 0.33 equiv.), propargyl alcohol (17.5 µL, 300 µmol, 0.33 equiv.) and (ethynyloxy)benzene (106 mg, 300 µmol, 1.00 equiv.). The silyl ether diyne was not incorporated into the product and instead the ynol reacted with acetone. Purified by flash column chromatography (silica, PhMe) to yield the desired product as a white solid (145 mg, 61%).



^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.48 – 7.42 (m, 2H, 12, 14), 7.37 – 7.32 (m, 2H, 19, 21), 7.30 – 7.23 (m, 1H, 13), 7.20 – 7.16 (m, 1H, 20), 7.15 – 7.09 (m, 2H, 11, 15), 7.07 – 7.03 (m, 2H, 18, 22), 6.98 (m, 1H, 3), 5.06 (s, 1H, 6), 2.11 (d, *J* = 1.3 Hz, 3H, 7 or 8), 1.97 (d, *J* = 1.3 Hz, 3H, 7 or 8).

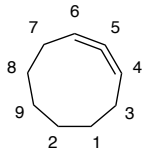
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 170.7 (4), 165.8 (1), 153.5 (10), 150.8 (17), 148.1 (2), 130.1 (12, 14), 129.3 (19, 21), 125.6 (13), 125.4 (20), 121.9 (18, 22), 121.3 (11, 15), 117.6 (3), 95.4 (6), 28.3 (7 or 8), 21.3 (7 or 8).

IR (ATR, film): 1719, 1638, 1568, 1485, 1391, 1260, 1198, 1119, 985 cm^{-1}.

HRMS (ESI): Calculated for 295.1329 *m*/*z*, found 295.1338 *m*/*z* $[C_{19}H_{18}O_3+H]^+$.

Cyclonona-1,2-diene (**4.208**)

cis-9,9-Dibromobicyclo[6.1.0]nonane (5.00 g, 16.8 mmol, 1.00 equiv.) and dry THF (35.0 mL) were added to a flask under N_2. Ethylmagnesium bromide (2.9 M in Et_2O, 10.5 mL, 30.5 mmol, 1.82 equiv.) was added dropwise and after addition complete, the reaction was stirred at RT for 1 h. The resulting mixture was quenched with the careful addition of H_2O (10 mL) followed by saturated aqueous NH_4Cl (10 mL). The mixture was extracted with Et_2O (3 × 20 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product which was purified by Kugelrohr distillation (80 ºC, 10 mbar) to yield the desired product as a colourless oil (1.12 g, 55%).

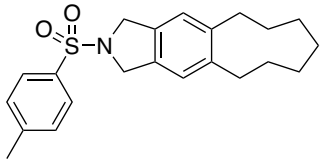


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 5.28 (m, 2H, 4, 6), 2.24 (m 2H, 3, 7), 1.85 – 1.75 (m, 2H, 3, 7), 1.73 – 1.60 (m, 4H, 1, 2, 8, 9), 1.62 – 1.51 (m, 2H, 1, 8), 1.40 (m, 2H, 2, 9).

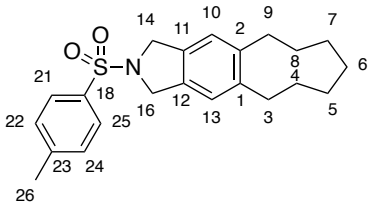
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 205.6 (5), 92.5 (4, 6), 28.0 (1, 8), 27.4 (3, 7), 25.3 (2, 9).

Spectral data consistent with the literature.[382]

2-Tosyl-1,2,3,5,6,7,8,9,10,11-decahydrocyclonona[*f*]isoindole (4.209)



Prepared according to a modified version of General Procedure C from cyclonona-1,2-diene (24.4 mg, 200 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (297 mg, 1.20 mmol, 6.00 equiv.) added slowly (over 15 h using a syringe pump) into solution of catalyst and ligand. Purified by flash column chromatography (silica, 0–10% Et_2O in hexane) to yield desired product as white solid (39.4 mg, 53%).



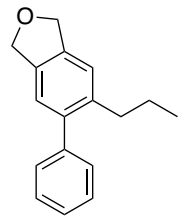
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.83 – 7.77 (m, 2H, 21, 25), 7.37 – 7.30 (m, 2H, 22, 24), 6.91 (s, 2H, 10, 13), 4.59 (s, 4H, 14, 16), 2.79 – 2.69 (m, 4H, 3, 9), 2.42 (s, 3H, 26), 1.73 – 1.64 (m, 4H, 4, 8), 1.42 (m, 2H, 6), 1.38 – 1.29 (m, 4H, 5, 7).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.5 (23), 141.7 (1, 2), 133.9 (11, 12), 133.9 (18), 129.8 (22, 24), 127.7 (21, 25), 123.4 (10, 13), 53.6 (14, 16), 33.1 (3, 9), 29.5 (4, 8), 27.9 (6), 24.4 (5, 7), 21.5 (26).

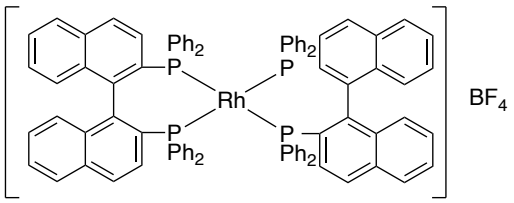
IR (ATR, film): 2829, 2857, 1456, 1341, 1155, 1101, 667, 610, 540 cm^{-1}.

HRMS (ESI): Calculated for 392.16547 *m*/*z*, found 392.16497 *m*/*z* $[C_{22}H_{27}NO_2S+Na]^+$.

Gram-scale Modification of Synthesis of 4.150 and catalyst recovery (4.211)



An oven-dried 250 mL flask was charged with pent-1-yn-1-ylbenzene (1.00 g, 6.93 mmol, 1.00 equiv.), $[Rh(COD)(NCMe)_2BF_4$ (527 mg, 1.39 mmol, 20.0 mol%) and *rac*-BINAP (1.73 g, 2.77 mmol, 40.0 mol%). The flask was sealed, evacuated and backfilled with N_2 before dry, degassed acetone (35.0 mL) was added, a N_2 balloon was attached, and the mixture was heated to 60 ºC. A separate flask was charged with acetone (35.0 mL) and propargyl ether (3.92 g, 41.6 mmol, 6.00 equiv.). This solution was added to the monoalkyne solution over 15 h. The mixture was allowed to stir for a further hour before filtering through celite and adding 1,4-dinitrobenzene (291 mg, 1.73 mmol, 0.25 equiv, internal standard). A portion of this material was taken for NMR analysis to determine yield. The crude mixture was suspended in a minimum volume of CH_2Cl_2 and excess Et_2O was added. The solution was filtered and the solid was reserved for NMR analysis. This was found to be the rhodium catalyst returned as $[Rh(BINAP)_2]BF_4$. This process was repeated until no further catalyst was obtained (1.78 g, 1.24 mmol, 89%).



^{1}H NMR (500 MHz, Dichloromethane-d_2) δ_H 7.72 (m, 8H), 7.67 (m, 4H), 7.64 (m, 4H), 7.57 – 7.51 (m, 4H), 7.37 (m, 4H), 7.14 (m, 4H), 6.99 (m, 4H), 6.89 (m, 8H), 6.80 (m, 8H), 6.56 (m, 4H), 6.49 (m, 4H), 6.21 (m, 8H).

^{13}C NMR (126 MHz, Dichloromethane-d_2) δ_C 139.0, 134.7, 134.3, 133.8, 133.4, 128.7, 128.3, 128.1, 127.9, 127.9, 127.5, 127.4, 126.4, 126.3.

^{11}B NMR (96 MHz, Dichloromethane-d_2) δ_B −1.23

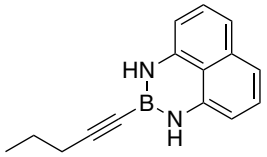
^{19}F NMR (471 MHz, Dichloromethane-d_2) δ_F −153.4, −153.5.

^{31}P NMR (202 MHz, Dichloromethane-d_2) δ_P 25.5 (d, $^1J_{PRh}$ = 138.2 Hz).

Spectral data consistent with the literature.[291]

Unambiguous assignment of ^{1}H and ^{13}C NMR signals could not be performed.

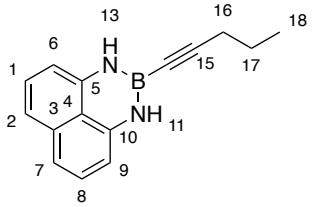
2-(Pent-1-yn-1-yl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine (**4.213**)



Prepared *via* one of two methods:

1 – Freshly sublimed HBdan (55.3 mg, 300 μmol, 1.00 equiv.) and $Zn(OTf)_2$ (5.5 mg, 15.0 μmol, 5.00 mol%) were placed in a flame-dried microwave vial. After evacuating and backfilling with N_2, EtCN (300 μL, 1.0 M) was added followed by 1-pentyne (50.0 μL, 507 μmol, 1.69 equiv.) then pyridine (5.00 μL, 61.9 μmol, 20.6 mol%). The mixture was slowly heated to 100 ºC to stir for 20 h after which time the solution was allowed to cool to RT and then quenched with the addition of saturated aqueous NH_4Cl (5 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product which was purified by flash column chromatography (silica, 0–5% EtOAc in hexane) to yield the desired product as a white solid (10.1 mg, 14%).

2 – A flame-dried flask was charged with 1-pentyne (300 μL, 3.04 mmol, 1.00 equiv.) and dry THF (10 mL, 300 mM) under N_2 then cooled to −78 ºC. *n*-Butyllithium solution (2.27 M in hexane, 1.80 mL, 4.08 mmol, 1.34 equiv.) was added dropwise and the resulting solution was allowed to stir for 1 h. After this period, $B(O\textit{i}\text{-}Pr)_3$ (700 μL, 3.04 mmol, 1.00 equiv.) was added and the solution was allowed to continue to stir at the same temperature for 2 h. At this point, HCl (2.0 M in Et_2O, 1.60 mL, 3.2 mmol, 1.05 equiv.) was added and the mixture was allowed to come up to RT to stir for 0.5 h. The mixture was concentrated *in vacuo* and the solution was suspended in *t*-BuOMe (10 mL), filtered through celite then reconcentrated *in vacuo* to yield the crude diisopropyl boronic ester which was dissolved in PhMe (15.0 mL, 200 mM) and 1,8-diaminonaphthalene (481 mg, 3.04 mmol, 1.00 equiv.) was added. The mixture was heated to 120 ºC for 1 h. then concentrated *in vacuo* to yield the crude product which was purified by flash column chromatography (silica, 0–5% EtOAc in hexane) to yield the desired product as a white solid (320.2 mg, 42%).



^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.10 (dd, J = 8.3, 7.3 Hz, 2H, 1, 8), 7.03 (dd, J = 8.3, 1.0 Hz, 2H, 2, 7), 6.30 (dd, J = 7.3, 1.0 Hz, 2H, 6, 9), 5.88 – 5.73 (brs, 2H, 11, 13), 2.30 (t, J = 7.1 Hz, 2H, 16), 1.62 (m, 2H, 17), 1.06 (t, J = 7.4 Hz, 3H, 18).

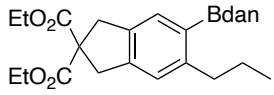
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 140.8 (4), 136.3 (3), 127.5 (1, 8), 119.8 (5, 10), 117.8 (2, 7), 105.7 (6, 9), 78.7 (15), 21.9 (16), 21.6 (17), 13.6 (18).

^{11}B NMR (96 MHz, Chloroform-*d*) δ_B 21.9.

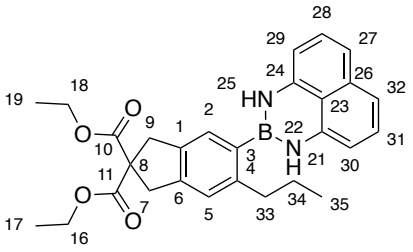
IR: (ATR, film): 3385, 2201, 1597, 1506, 1406, 1371, 1329, 1196, 1071, 820, 764, 658 cm^{-1}.

HRMS (ESI): Calculated for 235.1401, found 235.1402 $[C_{15}H_{15}BN_2+H]^+$.

Diethyl 5-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-6-propyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.213)



Prepared according to General Procedure C from 2-(pent-1-yn-1-yl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinine (25.0 mg, 100 µmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% Et_2O in hexane) to yield the desired product as a yellow solid (38.2 mg, 81%).



^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.27 (s, 1H, 2), 7.16 – 7.10 (m, 2H, 28, 31), 7.09 – 7.04 (m, 3H, 5, 27, 32), 6.34 (d, *J* = 7.2 Hz, 2H, 29, 30), 5.80 (s, 2H, 21, 25), 4.22 (q, *J* = 7.1 Hz, 4H, 16, 18), 3.60 (s, 2H, 7), 3.57 (s, 2H, 9), 2.73 – 2.65 (m, 2H, 33), 1.62 (m, 2H, 34), 1.27 (t, *J* = 7.1 Hz, 6H, 17, 19), 0.94 (t, *J* = 7.3 Hz, 3H, 35).

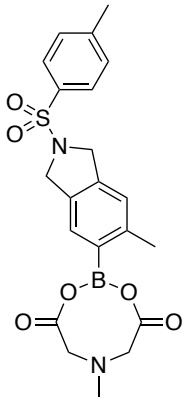
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 171.9 (10, 11), 144.7 (4), 141.5 (6), 141.3 (22, 24), 137.2 (1), 136.4 (26), 128.1 (2), 127.7 (28, 31), 124.7 (5), 119.9 (23), 117.8 (27, 32), 106.0 (29, 30), 61.9 (16, 18), 60.5 (8), 40.7 (7), 40.3 (9), 38.2 (33), 26.0 (34), 14.3 (35), 14.2 (17, 19).

^{11}B NMR (96 MHz, Chloroform-*d*) δ_B 31.6.

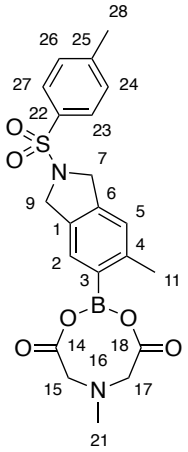
IR: (ATR, film): 3391, 2961, 1724, 1597, 1510, 1414, 1242, 1067, 822, 766 cm^{-1}.

HRMS (ESI): Calculated for 470.23714, found 430.23691 $[C_{28}H_{31}BN_2O_4]^+$.

6-Methyl-2-(6-methyl-2-tosylisoindolin-5-yl)-1,3,6,2-dioxazaborocane-4,8-dione (4.218)



Prepared according to General Procedure C from 6-methyl-2-(prop-1-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (19.5 mg, 100 μmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% MeCN in CH_2Cl_2) to yield the desired product as a white solid (25.6 mg, 58%).



^{1}H NMR (400 MHz, Acetone-d_6) δ_H 7.79 (d, J = 8.3 Hz, 2H, 23, 27), 7.43 – 7.38 (m, 2H, 24, 26), 7.33 (s, 1H, 2), 7.05 (s, 1H, 5), 4.57 – 4.53 (m, 4H, 7, 9), 4.34 (d, J = 17.2 Hz, 2H, 15, 17), 4.14 (d, J = 17.2 Hz, 2H, 15, 17), 2.72 (s, 3H, 21), 2.41 – 2.35 (m, 6H, 11, 28).

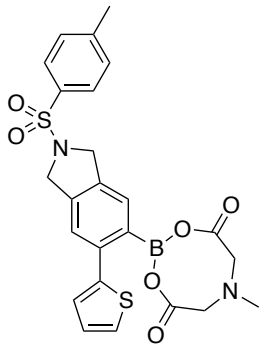
^{13}C NMR (101 MHz, Acetone-d_6) δ_C 169.3 (14, 18), 144.6 (25), 143.0 (1), 138.4 (6), 134.9 (4), 134.2, (22) 130.8 (24, 26), 129.1 (2), 128.6 (23, 27), 125.9 (5), 63.6 (15, 17), 54.5 (7), 54.4 (9), 48.3 (21), 23.1 (11), 21.4 (28).

^{11}B NMR (128 MHz, Acetone-d_6) δ_B 11.6.

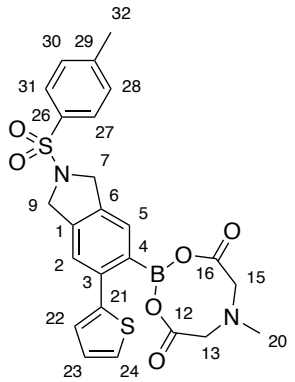
IR (ATR, film): 1161, 1098, 1034, 667, 598, 550 cm^{-1}.

HRMS (ESI): Calculated for 443.1443 m/z, found 443.1457 m/z $[C_{21}H_{24}BN_2O_6S+H]^+$.

6-Methyl-2-(6-(thiophen-2-yl)-2-tosylisoindolin-5-yl)-1,3,6,2-dioxazaborocane-4,8-dione (4.219)



Prepared according to General Procedure C from 6-methyl-2-(thiophen-2-ylethynyl)-1,3,6,2-dioxazaborocane-4,8-dione (26.3 mg, 100 μmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–15% MeCN in CH_2Cl_2) to yield the desired product as an off-white solid (25.4 mg, 50%).



^{1}H NMR (500 MHz, Acetone-d_6) δ_H 7.83 – 7.77 (m, 2H, 27, 31), 7.67 (s, 1H, 5), 7.45 – 7.40 (m, 3H, 24, 28, 30), 7.18 (s, 1H, 2), 7.01 (dd, J = 3.5, 1.2 Hz, 1H, 22), 6.96 (dd, J = 5.1, 3.5 Hz, 1H, 23), 4.68 – 4.61 (m, 4H, 7, 9), 4.10 (d, J = 17.0 Hz, 2H, 13, 15), 3.53 (d, J = 16.9 Hz, 2H, 13, 15), 2.66 (s, 3H, 20), 2.39 (s, 3H, 32).

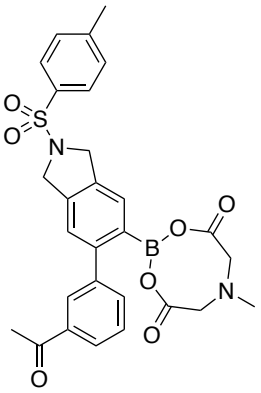
^{13}C NMR (126 MHz, Acetone-d_6) δ_C 167.7 (12, 16), 143.8 (29), 143.5 (21), 139.0 (3), 137.3 (6), 136.0 (1), 133.8 (26), 129.9 (28, 30), 128.9 (5), 128.5 (22), 127.7 (27, 31), 127.2 (23), 126.6 (2), 125.7 (24), 62.7 (13, 15), 53.6 (9), 53.5 (7), 47.6 (20), 20.5 (32).

^{11}B NMR (96 MHz, Acetone-d_6) δ_B 11.9.

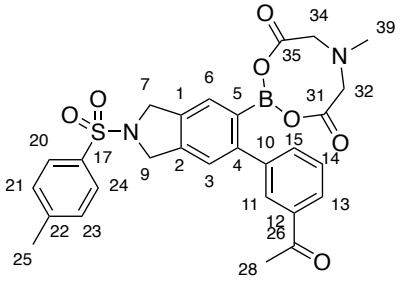
IR (ATR, film): 1769, 1705, 1339, 1161, 1096, 1030, 1005, 667, 575, 546 cm^{-1}.

HRMS (ESI): calculated for 511.1163 *m*/*z*, found 511.1186 *m*/*z* $[C_{24}H_{23}BN_2O_6S_2+H]^+$

2-(6-(3-Acetylphenyl)-2-tosylisoindolin-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (**4.220**)



Prepared according to General Procedure C from 2-((3-acetylphenyl)ethynyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (29.9 mg, 100 μmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–15% MeCN in CH_2Cl_2) to yield the desired product as an off-white solid (25.3 mg, 50%).



^{1}H NMR (500 MHz, Acetone-d_6) δ_H 7.93 – 7.86 (m, 2H, 11, 13), 7.85 – 7.80 (m, 2H, 20, 24), 7.66 (s, 1H, 6), 7.52 (m, 1H, 15), 7.50 – 7.42 (m, 3H, 14, 21, 23), 7.06 (s, 1H, 3), 4.68 (m, 2H, 9), 4.64 (m, 2H, 7), 4.04 (d, J = 16.7 Hz, 2H, 32, 34), 3.73 – 3.20 (m, 2H, 32, 34), 2.60 (s, 3H, 39), 2.59 (s, 3H, 28), 2.41 (s, 3H, 25).

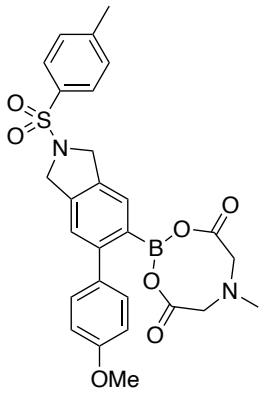
^{13}C NMR (126 MHz, Acetone-d_6) δ_C 198.0 (26), 168.4 (31, 35), 147.5 (22), 144.7 (12), 144.4 (10), 138.2 (1), 137.5 (4), 136.2 (2), 134.8 (15), 134.7 (17), 130.9 (14), 130.7 (20, 24), 129.5 (13), 129.0 (6), 128.6 (21, 23), 127.2 (11), 126.1 (3), 63.4 (32, 34), 54.5 (9), 54.4 (7), 48.5 (30), 26.8 (28), 21.4 (25).

^{11}B NMR (128 MHz, Acetone-d_6) δ_B 11.8.

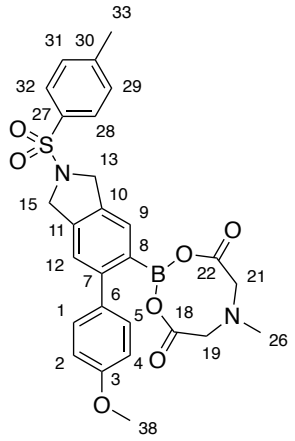
IR (ATR, film): 1763, 1682, 1339, 1289, 1250, 1161, 1121, 1096, 1055, 1030, 667, 575, 548 cm^{-1}.

HRMS (ESI): calculated for 569.1524 *m*/*z*, found 569.1507 *m*/*z* $[C_{28}H_{27}BN_2O_7S+Na]+$

2-(6-(4-Methoxyphenyl)-2-tosylisoindolin-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (**4.221**)



Prepared according to General Procedure C from 2-((4-methoxyphenyl)ethynyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (28.7 mg, 100 μmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% MeCN in CH_2Cl_2) to yield the desired product as an off-white solid (54.1 mg, >99%).



^{1}H NMR (500 MHz, Acetone-d_6) δ_H 7.84 – 7.79 (m, 2H, 28, 32), 7.64 (s, 1H, 12), 7.43 (m, 2H, 29, 31), 7.22 – 7.17 (m, 2H, 2, 4), 7.01 – 6.98 (m, 1H, 9), 6.89 – 6.84 (m, 2H, 1, 5), 4.66 – 4.63 (m, 2H, 13), 4.62 – 4.60 (m, 2H, 15), 4.00 (d, J = 16.9 Hz, 2H, 19, 21), 3.79 (s, 3H, 38), 3.39 (d, J = 16.9 Hz, 2H, 19, 21), 2.58 (s, 3H, 26), 2.40 (s, 3H, 33).

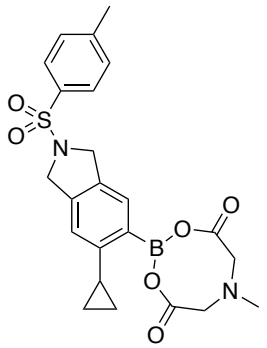
^{13}C NMR (126 MHz, Acetone-d_6) δ_C 167.6 (18, 22), 158.8 (3), 147.3 (7), 143.7 (30), 137.1 (11), 135.4 (6), 134.6 (10), 133.8 (27), 130.9 (2, 4), 129.9 (29, 31), 128.5 (12), 127.8 (28, 32), 125.4 (9), 113.4 (1, 5), 62.6 (19, 21), 54.7 (38), 53.61 (13), 53.56 (15), 47.4 (26), 20.5 (33).

^{11}B NMR (96 MHz, Acetone-d_6) δ_B 11.94.

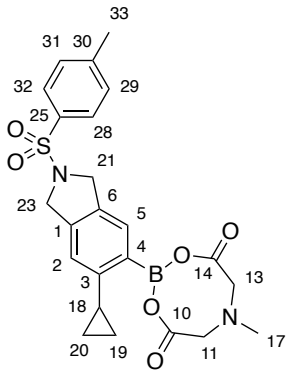
IR (ATR, film): 763, 1707, 1339, 1223, 1161, 1094, 1028, 667, 548, 530 cm^{-1}.

HRMS (ESI): calculated for 535.1705 *m*/*z*, found 535.1695 *m*/*z* [$C_{27}H_{28}BN_2O_7S$+H]+

6-Methyl-2-(6-cyclopropyl-2-tosylisoindolin-5-yl)-1,3,6,2-dioxazaborocane-4,8-dione (4.222)



Prepared according to General Procedure C from 2-(cyclopropylethynyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (22.1 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% MeCN in CH_2Cl_2) to yield the desired product as an off-white solid (32.7 mg, 70%).



^{1}H NMR (500 MHz, Acetone-d_6) δ_H 7.80 – 7.76 (m, 2H, 28, 32), 7.43 – 7.39 (m, 2H, 29, 31), 7.34 (s, 1H, 2), 6.85 (s, 1H, 5), 4.54 (m, 4H, 21, 23), 4.34 (d, J = 17.2 Hz, 2H, 11, 13), 4.13 (d, J = 17.2 Hz, 2H, 11, 13), 2.81 (s, 3H, 17), 2.38 (s, 3H, 33), 2.31 (tt, J = 8.4, 5.39 Hz, 1H, 18), 0.94 – 0.89 (m, 2H, 19, 20), 0.70 – 0.64 (m, 2H, 19, 20).

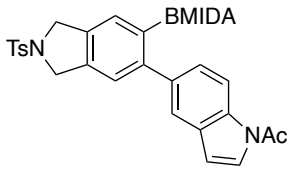
^{13}C NMR (126 MHz, Acetone-d_6) δ_C 169.3 (10, 14), 148.5 (3), 144.5 (30), 138.6 (1), 134.8 (25), 133.8 (6), 130.7 (29, 31), 129.0 (2), 128.6 (28, 32), 118.9 (5), 63.5 (11, 13), 54.6 (21), 54.3 (23), 48.4 (17), 21.4 (33), 15.4 (18), 9.9 (19, 20).

^{11}B NMR (128 MHz, Acetone-d_6) δ_B 12.5.

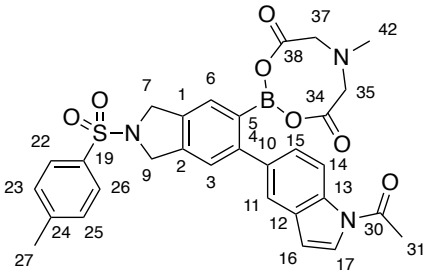
IR (ATR, film): 763, 1707, 1339, 1190, 1161, 1096, 1053, 1026, 667, 550 cm^{-1}.

HRMS (ESI): calculated for 469.1599 *m*/*z*, found 469.1618 *m*/*z* [$C_{23}H_{25}BN_2O_6S$+H]+

2-(6-(1-Acetyl-1*H*-indol-5-yl)-2-tosylisoindolin-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (**4.223**)



Prepared according to General Procedure C from 2-((1-acetyl-1*H*-indol-5-yl)ethynyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (33.8 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–15% MeCN in CH_2Cl_2) to yield the desired product as a yellow solid (52.0 mg, 89%).



^{1}H NMR (500 MHz, Acetone-d_6) δ_H 8.36 (d, J = 8.4 Hz, 1H, 14), 7.87 – 7.80 (m, 2H, 22, 26), 7.76 (d, J = 3.8 Hz, 1H, 17), 7.69 (s, 1H, 6), 7.52 (dd, J = 1.8, 0.7 Hz, 1H, 11), 7.47 – 7.40 (m, 2H, 23, 25), 7.24 (dd, J = 8.4, 1.8 Hz, 1H, 15), 7.06 (s, 1H, 3), 6.66 (dd, J = 3.7, 0.7 Hz, 1H, 16), 4.68 (s, 2H, 7), 4.65 (m, 2H, 9), 3.96 (m, 2H, 35, 37), 3.60 – 3.10 (m, 2H, 35, 37), 2.69 (s, 3H, 31), 2.63 (s, 3H, 42), 2.41 (s, 3H, 27).

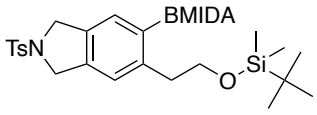
^{13}C NMR (126 MHz, Acetone-d_6) δ_C 169.0 (30), 167.6 (34, 38), 147.8 (10), 143.8 (24), 138.5 (12), 137.1 (1), 134.7 (2), 134.4 (4), 133.8 (19), 130.3 (13), 129.9 (23, 25), 128.5 (6), 127.8 (22, 26), 127.1 (17), 126.4 (15), 125.7 (3), 122.3 (11), 115.6 (14), 108.6 (16), 62.6 (35, 37), 53.6 (7), 53.6 (9), 47.5 (42), 23.1 (31), 20.6 (27).

^{11}B NMR (96 MHz, Acetone d_6) δ_B 11.7.

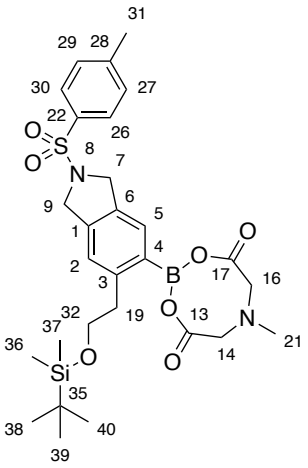
IR (ATR, film): 2363, 1767, 1706, 1331, 1161, 1026, 667 cm^{-1}.

HRMS (ESI): Calculated for 608.1633 *m*/*z*, found 608.1633 *m*/*z* $[C_{30}H_{28}BN_3O_7S+Na]^+$.

2-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-tosylisoindolin-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4.224)



Prepared according to General Procedure C from 2-(4-((*tert*-butyldimethylsilyl)oxy)but-1-yn-1-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (33.9 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–15% MeCN in CH_2Cl_2) to yield the desired product as a white solid (30.6 mg, 52%).



^{1}H NMR (500 MHz, Acetonitrile-d_3) δ_H 7.75 (d, J = 8.3 Hz, 2H, 26, 30), 7.40 – 7.35 (m, 2H, 27, 29), 7.23 (s, 1H, 5), 7.11 (s, 1H, 2), 4.58 (s, 2H, 7), 4.55 (s, 2H, 9), 4.06 (d, J = 17.2 Hz, 2H, 14, 16), 3.89 (d, J = 17.2 Hz, 2H, 14, 16), 3.78 (t, J = 6.7 Hz, 2H, 32), 2.80 (t, J = 6.6 Hz, 2H, 19), 2.47 (s, 3H, 21), 2.39 (s, 3H, 31), 0.82 (s, 9H, 38–40), –0.07 (s, 6H, 36, 37).

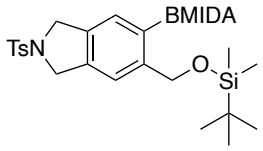
^{13}C NMR (126 MHz, Acetonitrile-d_3) δ_C 168.4 (13, 17), 144.1 (28), 143.6 (3), 137.2 (6), 133.9 (1), 133.4 (22), 129.9 (27, 29), 128.1 (5), 127.6 (26, 30), 125.6 (2), 64.4 (32), 62.3 (14, 16), 53.6 (7), 53.6 (9), 47.4 (21), 38.8 (19), 25.3 (38–40), 20.5 (31), 17.9 (35), –6.2 (36, 37).

^{11}B NMR (96 MHz, Acetonitrile-d_3) δ_B 12.1.

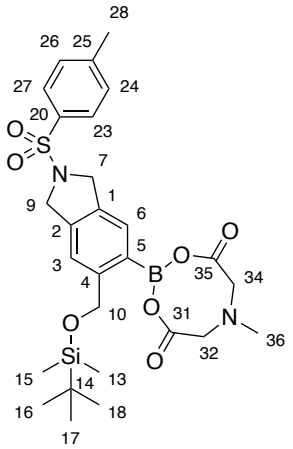
IR (ATR, film): 1763, 1709, 1163, 1034, 835, 667, 550, 530 cm^{-1}.

HRMS (ESI): Calculated for 587.2413 m/z, found 587.2418 m/z $[C_{28}H_{39}BN_2O_7SSi+H]^+$.

2-(6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-tosylisoindolin-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4.225)



Prepared according to General Procedure C from 2-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-yn-1-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (32.5 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–15% MeCN in CH_2Cl_2) to yield the desired product as a white solid (11.3 mg, 20%).



^{1}H NMR (500 MHz, Acetonitrile-d_3) δ_H 7.77 – 7.73 (m, 2H, 23, 27), 7.39 – 7.35 (m, 2H, 24, 26), 7.31 (s, 1H, 6), 7.28 (s, 1H, 3), 4.78 (s, 2H, 10), 4.61 – 4.58 (m, 4H, 7, 9), 4.08 (d, J = 17.2 Hz, 2H, 32, 34), 3.93 (d, J = 17.2 Hz, 2H, 32, 34), 2.48 (s, 3H, 36), 2.38 (s, 3H, 28), 0.92 (s, 9H, 16–18), 0.11 (s, 6H, 13, 15).

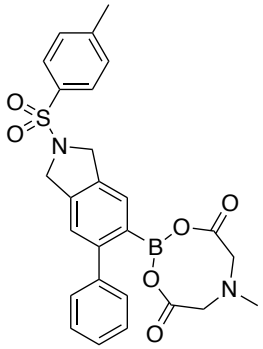
^{13}C NMR (126 MHz, Acetonitrile-d_3) δ_C 168.5 (31, 35), 144.8 (4), 144.1 (25), 137.7 (1), 135.1 (20), 133.5 (2), 129.8 (24, 26), 128.4 (6), 127.6 (23, 27), 122.9 (3), 65.2 (10), 62.8 (32, 34), 53.7 (9), 53.6 (7), 48.3 (36), 25.5 (16–18), 20.5 (28), 18.3 (14), –6.0 (13, 15).

^{11}B NMR (96 MHz, Acetonitrile-d_3) δ_B 12.1.

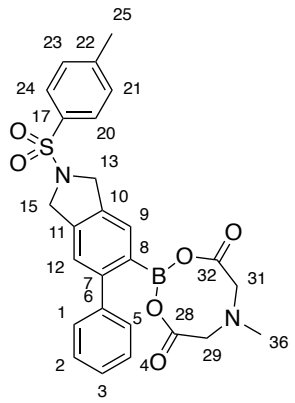
IR (ATR, film): 1767, 1341, 1163, 1098, 1045, 837, 667 cm^{-1}.

HRMS (ESI): Calculated for 573.2257 *m*/*z*, found 573.2276 *m*/*z* $[C_{27}H_{37}BN_2O_7SSi+H]^+$.

6-Methyl-2-(6-phenyl-2-tosylisoindolin-5-yl)-1,3,6,2-dioxazaborocane-4,8-dione (**4.226**)



Prepared according to General Procedure C from 6-methyl-2-(phenylethynyl)-1,3,6,2-dioxazaborocane-4,8-dione (25.7 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0-15% MeCN in CH_2Cl_2) to yield the desired product as an off-white solid (44.5 mg, 88%).



^{1}H NMR (400 MHz, Acetonitrile-d_3) δ_H 7.81 – 7.75 (m, 2H, 20, 24), 7.58 (s, 1H, 9), 7.44 – 7.38 (m, 2H, 21, 23), 7.37 – 7.30 (m, 3H, 2–4), 7.24 – 7.18 (m, 2H, 1, 5), 6.97 (m, 1H, 12), 4.66 (m, 2H, 13), 4.64 – 4.59 (m, 2H, 15), 3.75 (d, J = 17.0 Hz, 2H, 29, 31), 3.29 (d, J = 17.0 Hz, 2H, 29, 31), 2.41 (s, 3H, 36), 2.39 (s, 3H, 25).

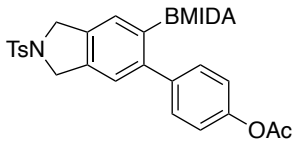
^{13}C NMR (101 MHz, Acetonitrile-d_3) δ_C 168.7 (28, 32), 148.3 (7), 145.1 (22), 144.2 (6), 138.2 (11), 135.9 (10), 134.4 (17), 130.9 (21, 22), 130.6 (1, 5), 129.4 (9), 128.9 (2, 4), 128.6 (20, 24), 127.9 (3), 126.1 (12), 63.5 (29, 31), 54.6 (13), 54.6 (15), 48.6 (36), 21.5 (25).

^{11}B NMR (128 MHz, Acetonitrile-d_3) δ_B 11.3.

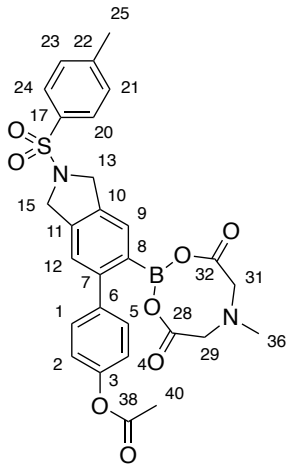
IR (ATR, film): 761, 1709, 1337, 1290, 1161, 1096, 1030, 665, 548, 530 cm^{-1}.

HRMS (ESI): calculated for 505.1599 *m*/*z*, found 505.1620 *m*/*z* $[C_{26}H_{25}BN_2O_6S+H]^+$.

4-(6-(6-Methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-2-tosylisoindolin-5-yl)phenyl acetate (4.227)



Prepared according to General Procedure C from 4-((6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)ethynyl)phenyl acetate (31.5 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–15% MeCN in CH_2Cl_2) to yield the desired product as a pale-yellow solid (10.9 mg, 19%).



^{1}H NMR (500 MHz, Acetone-d_6) δ_H 7.87 – 7.81 (m, 2H, 20, 24), 7.66 (s, 1H, 12), 7.49 – 7.43 (m, 2H, 21, 23), 7.34 – 7.28 (m, 2H, 1, 5), 7.09 – 7.03 (m, 3H, 2, 4, 9), 4.70 – 4.66 (m, 2H, 15), 4.66 – 4.63 (m, 2H, 13), 4.04 (d, J = 17.0 Hz, 2H, 29, 31), 3.46 (d, J = 16.9 Hz, 2H, 29, 31), 2.61 (s, 3H, 36), 2.42 (s, 3H, 25), 2.28 (s, 3H, 40).

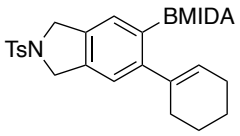
^{13}C NMR (126 MHz, Acetone-d_6) δ_C 169.6 (38), 168.4 (28, 32), 150.9 (3), 147.6 (7), 144.6 (17), 141.5 (6), 138.1 (11), 135.9 (10), 134.7 (22), 131.6 (1, 5), 130.7 (21, 23), 129.4 (12), 128.6 (20, 24), 126.1 (9), 122.1 (2, 4), 63.5 (29, 31), 54.5 (13), 54.4 (15), 48.4 (36), 21.4 (25), 21.0 (40).

^{11}B NMR (96 MHz, Acetone-d_6) δ_B 12.2.

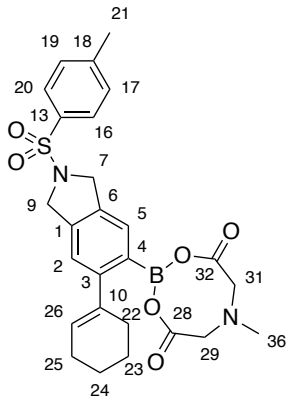
IR (ATR, film): 1749, 1707, 1339, 1221, 1194, 1161, 1096, 667, 586, 559, 542 cm^{-1}.

HRMS (ESI): Calculated for 535.14734 m/z, found 535.14532 m/z $[C_{28}H_{27}BN_2O_8S+Na]^+$.

2-(6-(Cyclohex-1-en-1-yl)-2-tosylisoindolin-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4.228)



Prepared according to General Procedure C from 2-(cyclohex-1-en-1-ylethynyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (31.5 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–15% MeCN in CH_2Cl_2) to yield the desired product as a pale-yellow solid (10.9 mg, 19%).



^{1}H NMR (500 MHz, Acetonitrile-d_3) δ_H 7.85 – 7.73 (m, 2H, 16, 20), 7.41 – 7.35 (m, 3H, 2 or 5, 17, 19), 6.86 (s, 1H, 2 or 5), 5.38 – 5.30 (m, 1H, 26), 4.62 – 4.55 (m, 4H, 7, 9), 4.01 (d, J = 17.1 Hz, 2H, 29, 31), 3.81 (m, 2H, 29, 31), 2.44 (s, 3H, 21), 2.40 (s, 3H, 36), 2.02 (m, 2H, 25), 1.79 – 1.69 (m, 2H, 23), 1.64 (m, 2H, 24).*

2H at ~2.20 ppm (corresponding to 22) overlaps with residual H_2O in NMR solvent.

^{13}C NMR (126 MHz, Acetone-d_6) δ_C 168.5 (28, 32), 150.0, 144.1, 143.3, 137.3, 134.1, 133.9, 129.9 (17, 19), 128.2, 127.6 (16, 20), 123.6 (26), 123.5, 62.8 (29, 31), 53.6 (9), 53.5 (7), 48.3 (36), 32.1 (22), 24.9 (25), 22.2 (23), 21.3 (24), 20.5 (21).

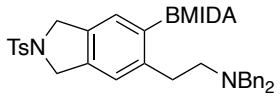
^{11}B NMR (96 MHz, Acetone-d_6) δ_B 12.1.

IR (ATR, film): 1773, 1341, 1161, 1034, 669, 411 cm^{-1}.

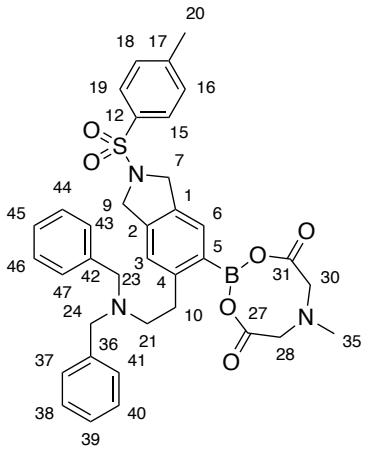
HRMS (ESI): Calculated for 531.17316 *m*/*z*, found 531.17177 *m*/*z* $[C_{26}H_{29}BN_2O_6S+Na]^+$.

Unambiguous assignment of all ^{13}C NMR signals could not be performed.

2-(6-(2-(Dibenzylamino)ethyl)-2-tosylisoindolin-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4.229)



Prepared according to General Procedure C from 2-(4-(dibenzylamino)but-1-yn-1-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (404 mg, 1.00 mmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (1.48 mg, 6.00 mmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–15% MeCN in CH_2Cl_2) to yield the desired product as a brown solid (413 mg, 63%).



^{1}H NMR (500 MHz, Acetonitrile-d_3) δ_H 7.78 – 7.74 (m, 2H, 15, 19), 7.39 – 7.35 (m, 2H, 16, 18), 7.34 – 7.31 (m, 4H, 37, 41, 43, 47), 7.29 – 7.25 (m, 4H, 38, 40, 44, 46), 7.25 – 7.20 (m, 2H, 39, 45), 7.16 (s, 1H, 6), 6.93 (s, 1H, 3), 4.56 (s, 2H, 7), 4.52 (s, 2H, 9), 4.02 (d, J = 17.2 Hz, 2H, 28, 30), 3.82 (d, J = 17.2 Hz, 2H, 28, 30), 3.64 (s, 4H, 23, 24), 2.85 (m, 2H, 10), 2.65 – 2.59 (m, 2H, 21), 2.37 (s, 3H, 20), 2.34 (s, 3H, 35).

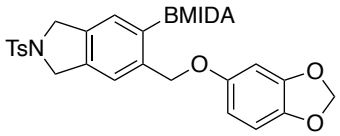
^{13}C NMR (126 MHz, Acetonitrile-d_3) δ_C 168.4 (27, 31), 145.2 (4), 144.1 (17), 139.9 (36, 42), 137.4 (1), 133.7 (2), 133.4 (12), 129.9 (16, 18), 128.7 (37, 41, 43, 47), 128.1 (38, 40, 44, 46), 128.1 (6), 127.6 (15, 19), 126.8 (39, 45), 124.8 (3), 62.2 (28, 30), 57.7 (23, 24), 56.0 (21), 53.6 (7), 53.5 (9), 47.1 (35), 32.8 (10), 20.5 (20).

^{11}B NMR (96 MHz, Acetonitrile-d_3) δ_B 12.7.

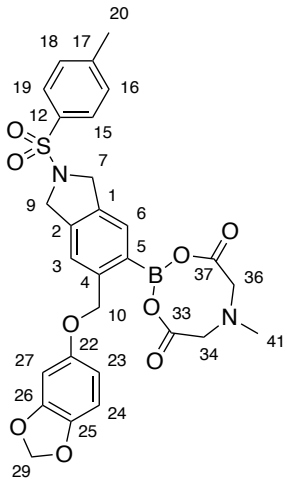
IR (ATR, film): 1763, 1618, 1341, 1161, 1096, 1028, 702, 667, 548, 409, 401 cm^{-1}.

HRMS (ESI): Calculated for 674.24666 *m*/*z*, found 674.24452 *m*/*z* $[C_{36}H_{38}BN_3O_6S+Na]^+$.

2-(6-((Benzo[*d*][1,3]dioxol-5-yloxy)methyl)-2-tosylisoindolin-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4.230)



Prepared according to General Procedure C from the 2-(3-(benzo[*d*][1,3]dioxol-5-yloxy)prop-1-yn-1-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (33.1 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% MeCN in CH_2Cl_2) to yield the desired product as an off-white solid (31.9 mg, 55%).



^{1}H NMR (500 MHz, Acetone-d_6) δ_H 7.85 – 7.79 (m, 2H, 15, 19), 7.49 (s, 1H, 6), 7.45 – 7.41 (m, 3H, 3, 16, 18), 6.74 (d, J = 8.5 Hz, 1H, 24), 6.59 (d, J = 2.6 Hz, 1H, 27), 6.44 (dd, J = 8.5, 2.6 Hz, 1H, 23), 5.95 (s, 2H, 29), 5.11 (s, 2H, 10), 4.66 – 4.65 (m, 2H, 9), 4.64 (m, 2H, 7), 4.36 (d, J = 17.2 Hz, 2H, 34, 36), 4.14 (d, J = 17.2 Hz, 2H, 34, 36), 2.83 (s, 3H, 41), 2.40 (s, 3H, 20).

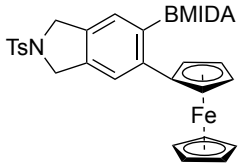
^{13}C NMR (126 MHz, Acetone-d_6) δ_C 168.1 (33, 37), 154.2 (22), 148.3 (26), 143.7 (25), 141.9 (4), 140.8 (17), 137.6 (1), 136.0 (2), 133.9 (12), 129.8 (16, 18), 128.9 (6), 127.7 (15, 19), 124.5 (3), 107.9 (24), 105.9 (23), 101.2 (29), 97.7 (27), 71.2 (10), 63.2 (34, 36), 53.6 (9), 53.5 (7), 48.7 (41), 20.5 (20).

^{11}B NMR (96 MHz, Acetone-d_6) δ_B 12.5.

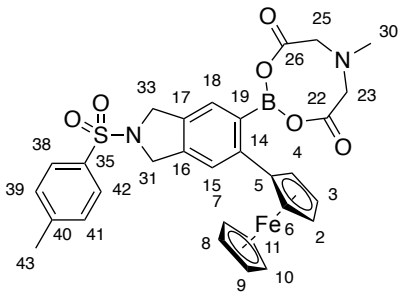
IR (ATR, film): 1763, 1487, 1341, 1184, 1161, 1096, 1034, 667, 548 cm^{-1}.

HRMS (ESI): Calculated for 493.15751 m/z, found 493.11013 m/z $[C_{23}H_{27}BN_2O_6S+Na]^+$.

6-Methyl-2-(6-ferrocenyl-2-tosylisoindolin-5-yl)-1,3,6,2-dioxazaborocane-4,8-dione (4.231)



Prepared according to General Procedure C from the 6-methyl-2-(ferrocenyl)-1,3,6,2-dioxazaborocane-4,8-dione (36.5 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–5% MeCN in CH_2Cl_2) to yield the desired product as a red-brown solid (24.0 mg, 39%).



^{1}H NMR (500 MHz, Acetone-d_6) δ_H 8.09 (s, 1H, 15), 7.87 – 7.83 (m, 2H, 38, 42), 7.52 (s, 1H, 18), 7.49 – 7.45 (m, 2H, 39, 41), 4.74 – 4.69 (m, 2H, 31), 4.65 – 4.59 (m, 2H, 33), 4.49 (t, J = 1.8 Hz, 2H, 2, 3), 4.25 – 4.18 (m, 7H, 4, 6–11), 4.01 (d, J = 16.8 Hz, 2H, 23, 25), 3.39 (d, J = 16.9 Hz, 2H, 23, 25), 2.43 (s, 3H, 30), 2.37 (s, 3H, 43).

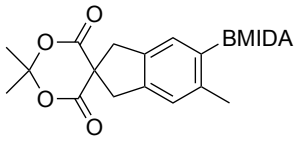
^{13}C NMR (126 MHz, Acetone-d_6) δ_C 167.8 (22, 26), 143.7 (40), 142.8 (14), 137.0 (16), 134.2 (35), 133.9 (17), 129.8 (39, 41), 128.1 (18), 127.9 (15), 127.8 (18, 42), 92.6 (5), 72.0 (2, 3), 69.5 (7–11), 67.5 (4, 6), 62.9 (23, 25), 53.7 (31), 53.6 (33), 47.1 (30), 20.5 (43).

^{11}B NMR (96 MHz, Acetone-d_6) δ_B 12.0.

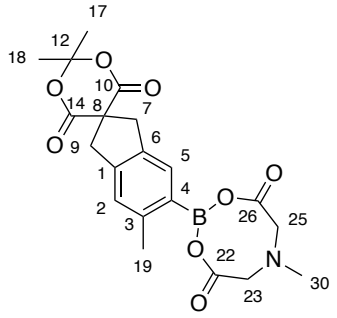
IR (ATR, film): 1763, 1339, 1292, 1277, 1161, 1098, 1055, 1028, 829, 667, 581, 548, 407 cm^{-1}.

HRMS (ESI): Calculated for 612.11833 m/z, found 612.11615 m/z $[C_{30}H_{29}BFeN_2O_6S]^+$.

2-(5-Methyl-2',2'-dimethyl-4',6'-dioxo-1,3-dihydrospiro[indene-2,5'-[1,3]dioxan]-6-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4.232)



Prepared according to General Procedure C from the 6-methyl-2-(prop-1-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (19.5 mg, 100 μmol, 1.00 equiv.) 2,2-dimethyl-5,5-di(prop-2-yn-1-yl)-1,3-dioxane-4,6-dione (132 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–15% MeCN in CH_2Cl_2) to yield the desired product as a white solid (29.9 mg, 72%).



^{1}H NMR (500 MHz, Acetonitrile-d_3) δ_H 7.29 (s, 1H, 5), 7.09 (s, 1H, 2), 4.09 (d, J = 17.2 Hz,

2H, 23, 25), 3.93 (d, *J* = 17.2 Hz, 2H, 23, 25), 3.68 (m, 4H, 7, 9), 2.57 (s, 3H, 30), 2.40 (s, 3H, 19), 1.84 – 1.79 (m, 6H, 17, 18).

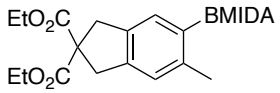
^{13}C NMR (126 MHz, Acetonitrile-d_3) δ_C 170.5 (10, 14), 168.6 (22, 26), 141.7 (3), 141.3 (6), 136.5 (1), 129.5 (5), 126.5 (2), 105.4 (12), 62.5 (23, 25), 52.3 (8), 47.4 (3), 45.2 (7), 44.9 (9), 28.1 (17 or 18), 28.1 (17 or 18), 22.0 (19).

^{11}B NMR (96 MHz, Acetonitrile-d_3) δ_B 12.6.

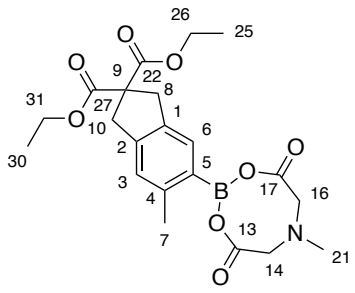
IR (ATR, film): 1763, 1736, 1300, 1299, 1098, 1036, 953, 855 cm^{-1}.

HRMS (ESI): Calculated for 438.1331 *m*/*z*, found 438.1329 *m*/*z* [$C_{20}H_{22}BNO_8$+Na]$^+$.

Diethyl 5-methyl-6-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.233)



Prepared according to General Procedure C from 6-methyl-2-(prop-1-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (19.5 mg, 100 µmol, 1.00 equiv.) and diethyl 2,2-di(prop-2-yn-1-yl)malonate (142 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–10% MeCN in CH_2Cl_2) to yield the desired product as an off-white solid (9.06 mg, 21%).



^{1}H NMR (500 MHz, Acetonitrile-d_3) δ_H 7.26 (s, 1H, 6), 7.06 (s, 1H, 3), 4.18 (q, *J* = 7.1 Hz, 4H, 26, 31), 4.08 (d, *J* = 17.2 Hz, 2H, 14, 16), 3.92 (d, *J* = 17.2 Hz, 2H, 14, 16), 3.52 (m, 4H, 8, 10), 2.54 (s, 3H, 21), 2.37 (s, 3H, 7), 1.23 (t, *J* = 7.1 Hz, 6H, 25, 30).

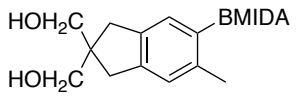
^{13}C NMR (126 MHz, Acetonitrile-d_3) δ_C 171.6 (22, 27), 168.6 (13, 17), 141.7 (1), 141.2 (2), 137.2 (4), 129.7 (6), 126.8 (3), 62.6 (14, 16), 61.6 (26, 31), 60.0 (9), 47.5 (21), 40.0 (10), 39.8 (8), 22.0 (7), 13.3 (25, 30).

^{11}B NMR (96 MHz, Acetonitrile-d_3) δ_B 12.6.

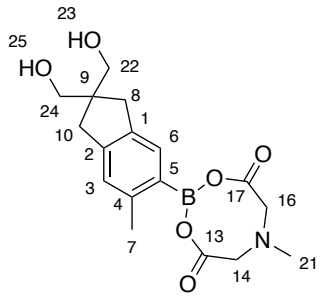
IR (ATR, film): 1724, 1275, 1233, 1179, 1069, 1051, 1028, 1011, 993, 978, 851 cm^{-1}.

HRMS (ESI): Calculated for 454.16437 *m*/*z*, found 454.16287 *m*/*z* [$C_{21}H_{26}BNO_8$+Na]$^+$.

2-(2,2-Bis(hydroxymethyl)-6-methyl-2,3-dihydro-1*H*-inden-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4.234)



Prepared according to General Procedure C from 6-methyl-2-(prop-1-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (19.5 mg, 100 µmol, 1.00 equiv.) and 2,2-di(prop-2-yn-1-yl)propane-1,3-diol (91.3 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–100% MeCN in CH_2Cl_2) to yield the desired product as an off-white solid (19.3 mg, 56%).



^{1}H NMR (500 MHz, Acetonitrile-d_3) δ_H 7.21 (s, 1H, 6), 7.02 (s, 1H, 3), 4.07 (d, J = 17.2 Hz, 2H, 14, 16), 3.91 (d, J = 17.2 Hz, 2H, 14, 16), 3.53 (d, J = 5.4 Hz, 4H, 22, 24), 2.99 (t, J = 5.4 Hz, 2H, 23, 25), 2.74 (m, 4H, 8, 10), 2.55 (s, 3H, 21), 2.36 (s, 3H, 7).

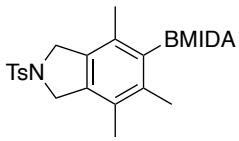
^{13}C NMR (126 MHz, Acetonitrile-d_3) δ_C 168.6 (13, 17), 144.0 (1), 140.3 (4), 139.4 (2), 130.3 (6), 127.5 (3), 66.4 (22, 24), 62.5 (14, 16), 49.4 (9), 47.4 (21), 37.7 (8 or 10), 37.4 (8 or 10), 22.0 (7).

^{11}B NMR (96 MHz, Acetonitrile-d_3) δ_B 12.3.

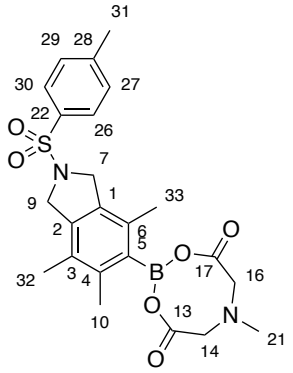
IR (ATR, film): 3404, 1763, 1744, 1703, 1026 cm^{-1}.

HRMS (ESI): Calculated for 370.14324 m/z, found 370.14223 m/z $[C_{17}H_{22}BNO_6+Na]^+$.

6-Methyl-2-(4,6,7-trimethyl-2-tosylisoindolin-5-yl)-1,3,6,2-dioxazaborocane-4,8-dione (4.235)



Prepared according to General Procedure C from the 6-methyl-2-(prop-1-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (19.5 mg, 100 µmol, 1.00 equiv.) and *N*,*N*-di(but-2-yn-1-yl)-4-methylbenzenesulfonamide (165 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–15% MeCN in CH_2Cl_2) to yield the desired product as an off-white solid (13.3 mg, 28%).



^{1}H NMR (500 MHz, Acetonitrile-d_3) δ_H 7.80 (d, J = 8.3 Hz, 2H, 26, 30), 7.44 – 7.38 (m, 2H, 27, 29), 4.64 – 4.57 (m, 4H, 7, 9), 4.12 (d, J = 17.6 Hz, 2H, 14, 16), 4.01 (d, J = 17.6 Hz, 2H, 14, 16), 2.67 (s, 3H, 21), 2.41 (s, 3H, 31), 2.17 (s, 3H, 32), 2.11 (s, 3H, 10), 2.09 (s, 3H, 33).

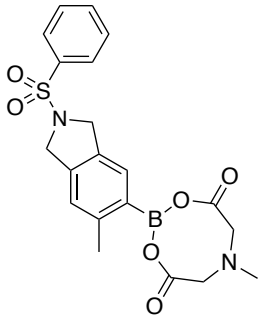
^{13}C NMR (126 MHz, Acetonitrile-d_3) δ_C 168.6 (13, 17), 144.1 (28), 142.2 (6), 136.1 (3), 135.5 (2), 133.5 (23), 133.5 (1), 129.9 (27, 29), 129.1, (4) 127.6 (26, 30), 64.3 (14, 16), 54.5 (7 or 9), 54.2 (7 or 9), 48.8 (21), 20.5 (31), 20.0 (10), 19.4 (32), 16.0 (33).

^{11}B NMR (96 MHz, Acetonitrile-d_3) δ_B 13.1.

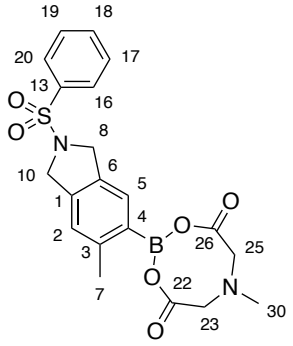
IR (ATR, film): 1763, 1705, 1335, 1161, 1098, 667, 548, 409 cm^{-1}.

HRMS (ESI): Calculated for 493.15751 m/z, found 493.15793 m/z $[C_{23}H_{27}BN_2O_6S+Na]^+$.

6-Methyl-2-(6-methyl-2-(phenylsulfonyl)isoindolin-5-yl)-1,3,6,2-dioxazaborocane-4,8-dione (**4.236**)



Prepared according to General Procedure C from 6-methyl-2-(prop-1-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (19.5 mg, 100 μmol, 1.00 equiv.) and *N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (140 mg, 600 μmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0-10% MeCN in CH_2Cl_2) to yield the desired product as a yellow solid (41.2 mg, 96%).



^{1}H NMR (500 MHz, Acetone-d_6) δ_H 7.96 – 7.90 (m, 2H, 16, 20), 7.69 – 7.60 (m, 3H, 17–19), 7.35 (s, 1H, 5), 7.07 (s, 1H, 2), 4.63 – 4.56 (m, 4H, 8, 10), 4.36 (d, J = 17.2 Hz, 2H, 23, 25), 4.15 (d, J = 17.2 Hz, 2H, 23, 25), 2.73 (s, 3H, 30), 2.40 (s, 3H, 7).

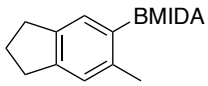
^{13}C NMR (126 MHz, Acetone-d_6) δ_C 168.4 (22, 26), 142.1 (3), 137.4 (6), 136.9 (13), 133.2 (1), 132.9 (18), 129.3 (17, 19), 128.2 (5), 127.6 (16, 20), 124.9 (2), 62.6 (23, 25), 53.6 (8 or 10), 53.5 (8 or 10), 47.4 (30), 22.2 (7).

^{11}B NMR (96 MHz, Acetone-d_6) δ_B 12.3.

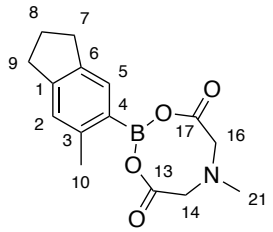
IR (ATR, film): 1736, 1339, 1296, 1165, 1098, 1032, 720, 608, 575 cm^{-1}.

HRMS (ESI): calculated for 429.1286 m/z, found 429.1295 m/z $[C_{20}H_{21}BN_2O_6S+H]^+$.

6-Methyl-2-(6-methyl-2,3-dihydro-1*H*-inden-5-yl)-1,3,6,2-dioxazaborocane-4,8-dione (4.237)



Prepared according to General Procedure C from 6-methyl-2-(prop-1-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (19.5 mg, 100 µmol, 1.00 equiv.) and 1,6-heptadiyne (55.3 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–15% MeCN in CH_2Cl_2) to yield the desired product as an off-white solid (8.4 mg, 29%).



^{1}H NMR (500 MHz, Acetonitrile-d_3) δ_H 7.27 (s, 1H, 5), 7.07 (s, 1H, 2), 4.08 (d, J = 17.1 Hz, 2H, 14, 16), 3.91 (d, J = 17.2 Hz, 2H, 14, 16), 2.92 – 2.84 (m, 4H, 7, 9), 2.55 (s, 3H, 21), 2.39 – 2.35 (m, 3H, 10), 2.10 – 2.01 (m, 2H, 8).

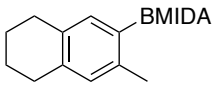
^{13}C NMR (126 MHz, Acetonitrile-d_3) δ_C 168.7 (13, 17), 145.7 (1 or 6), 141.1 (1 or 6), 140.1 (3), 129.7 (5), 127.1 (2), 62.5 (14, 16), 47.4 (21), 32.4 (7 or 9), 32.0 (7 or 9), 25.1 (8), 22.0 (10).

^{11}B NMR (96 MHz, Acetone-d_6) δ_B 12.6.

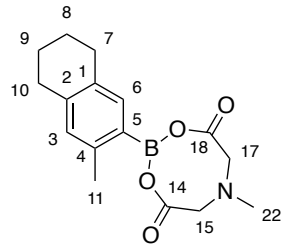
IR (ATR, film): 3348, 1751, 1086, 1044, 880 cm^{-1}.

HRMS (ESI): Calculated for 288.1402 *m*/*z*, found 288.1398 *m*/*z* $[C_{15}H_{18}BNO_4+H]^+$.

6-Methyl-2-(3-methyl-5,6,7,8-tetrahydronaphthalen-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (4.238)



Prepared according to General Procedure C from 6-methyl-2-(prop-1-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (19.5 mg, 100 µmol, 1.00 equiv.) and 1,7-octadiyne (63.7 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–5% MeCN in CH_2Cl_2) to yield the desired product as an off-white solid (6.2 mg, 21%)



^{1}H NMR (500 MHz, Acetonitrile-d_3) δ_H 7.08 (s, 1H, 6), 6.89 (s, 1H, 3), 4.07 (d, J = 17.2 Hz, 2H, 15, 17), 3.91 (d, J = 17.2 Hz, 2H, 15, 17), 2.76 – 2.71 (m, 4H, 7, 10), 2.55 (s, 3H, 22), 2.31 (s, 3H, 11), 1.81 – 1.76 (m, 4H, 8, 9).

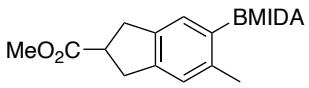
^{13}C NMR (126 MHz, Acetonitrile-d_3) δ_C 168.7 (14, 18), 139.0 (1 or 2), 138.1 (1 or 2), 135.0 (6), 133.7 (4), 131.6 (3), 62.5 (15, 17), 47.4 (22), 28.7 (7 or 10), 28.5 (7 or 10), 23.3 (8 or 9), 23.1 (8 or 9), 21.6 (11).

^{11}B NMR (96 MHz, Acetonitrile-d_3) δ_B 12.5.

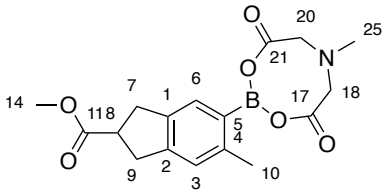
IR (ATR, film): 1763, 1298, 1238, 1105, 1032, 993, 702, 540 cm^{-1}.

HRMS (ESI): Calculated for 302.1558 *m*/*z*, found 302.1568 *m*/*z* $[C_{16}H_{20}BNO_4+H]^+$.

Methyl 5-methyl-6-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-2,3-dihydro-1H-indene-2-carboxylate (4.239)



Prepared according to General Procedure C from 6-methyl-2-(prop-1-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (19.5 mg, 100 µmol, 1.00 equiv.) and methyl 2-(prop-2-yn-1-yl)pent-4-ynoate (90.1 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–15% MeCN in CH_2Cl_2) to yield the desired product as a yellow solid (22.2 mg, 64%).



^{1}H NMR (500 MHz, Acetonitrile-d_3) δ_H 7.27 (s, 1H, 6), 7.06 (s, 1H, 3), 4.24 – 4.03 (m, 2H, 18, 20), 3.92 (m, 2H, 18, 20), 3.68 (s, 3H, 14), 3.35 (m, 1H, 8), 3.23 – 3.11 (m, 4H, 7, 9), 2.55 (s, 3H, 25), 2.37 (s, 3H, 10).

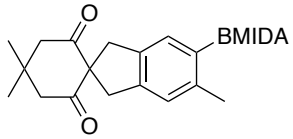
^{13}C NMR (126 MHz, Acetonitrile-d_3) δ_C 175.7 (11), 168.7 (17, 21), 168.7 (17, 21), 143.3 (4), 140.8 (1), 138.8 (2), 129.8 (6), 127.0 (3), 62.5 (18, 20), 62.5 (18, 20), 51.4 (14), 47.5 (25), 43.0 (8), 35.8 (7 or 9), 35.6 (7 or 9), 22.1 (10).

^{11}B NMR (96 MHz, Acetonitrile-d_3) δ_B 12.2.

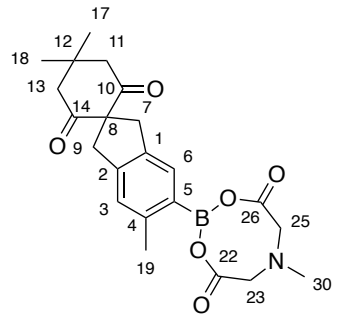
IR (ATR, film): 1765, 1452, 1339, 1296, 1209, 1028, 849, 411cm^{-1}.

HRMS (ESI): Calculated for 368.12759 *m*/*z*, found 368.12724 *m*/*z* $[C_{17}H_{20}BNO_6+Na]^+$.

6-Methyl-2-(4,4,5'-trimethyl-2,6-dioxo-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-6'-yl)-1,3,6,2-dioxazaborocane-4,8-dione (4.240)



Prepared according to General Procedure C from 6-methyl-2-(prop-1-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (19.5 mg, 100 µmol, 1.00 equiv.) and 5,5-dimethyl-2,2-di(prop-2-yn-1-yl)cyclohexane-1,3-dione (130 mg, 600 µmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–5% MeCN in CH_2Cl_2) to yield the desired product as a white solid (12.3 mg, 30%).



^{1}H NMR (500 MHz, Acetonitrile-d_3) δ_H 7.20 (s, 1H, 6), 7.03 (s, 1H, 3), 4.07 (d, J = 17.2 Hz, 2H, 23, 25), 3.89 (d, J = 17.2 Hz, 2H, 23, 25), 3.41 (m, 4H, 7, 9), 2.79 (d, J = 14.3 Hz, 2H, 11, 13), 2.68 (d, J = 14.3 Hz, 2H, 11, 13), 2.54 (s, 3H, 30), 2.36 (s, 3H, 19), 1.04 (s, 3H, 17 or 18), 0.98 (s, 3H, 17 or 18).

^{13}C NMR (126 MHz, Acetonitrile-d_3) δ_C 207.2 (10, 14), 168.6 (22, 26), 141.9 (1), 141.2 (2),

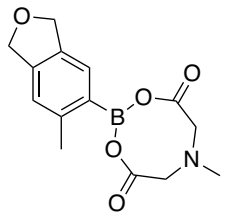
136.7 (4), 129.7 (6), 126.8 (3), 71.0 (8), 62.5 (23, 25), 50.8 (11, 13), 47.4 (30), 39.0 (7), 37.3 (9), 30.1 (12), 27.6 (17 or 18), 27.0 (17 or 18), 22.0 (19).

^{11}B NMR (96 MHz, Acetonitrile-d_3) δ_B 12.1.

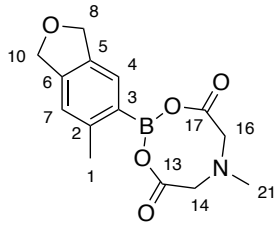
IR (ATR, film): 1763, 1692, 1030, 434, 426, 411 cm^{-1}.

HRMS (ESI): Calculated for 434.17454 *m*/*z*, found 434.17349 *m*/*z* $[C_{22}H_{26}BNO_6+Na]^+$.

6-Methyl-2-(6-methyl-1,3-dihydroisobenzofuran-5-yl)-1,3,6,2-dioxazaborocane-4,8-dione (4.241)



Prepared according to General Procedure C from 6-methyl-2-(prop-1-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (195 mg, 1.00 mmol, 1.00 equiv.) and propargyl ether (565 mg, 6.00 mmol, 6.00 equiv.). Purified by flash column chromatography (silica, 0–20% MeCN in CH_2Cl_2) followed by precipitation from CH_2Cl_2 and Et_2O to yield the desired product as an off-white solid (253 mg, 88%).



^{1}H NMR (500 MHz, Acetonitrile-d_3) δ_H 7.34 (s, 1H, 4), 7.13 (s, 1H, 7), 5.09 – 4.98 (m, 4H, 8, 10), 4.10 (d, J = 17.2 Hz, 2H, 14, 16), 3.93 (d, J = 17.2 Hz, 2H, 14, 16), 2.56 (s, 3H, 21), 2.42 (s, 3H, 1).

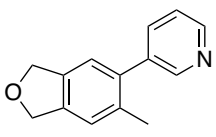
^{13}C NMR (126 MHz, Acetonitrile-d_3) δ_C 168.6 (13, 17), 141.6 (5), 141.0 (6), 136.6 (2), 132.7 (3), 126.5 (4), 123.5 (7), 72.8 (8 or 10), 72.8 (8 or 10), 62.6 (14, 16), 47.5 (21), 22.1 (1).

^{11}B NMR (96 MHz, Acetonitrile-d_3) δ_B 12.0.

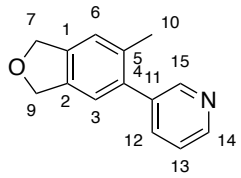
IR (ATR, film): 1753, 1300, 1099, 1084, 1030, 856 cm^{-1}.

HRMS (ESI): calculated for 290.1194 *m*/*z*, found 290.1202 *m*/*z* $[C_{14}H_{16}NBO_6+H]^+$.

3-(6-Methyl-1,3-dihydroisobenzofuran-5-yl)pyridine (4.242)



An oven dried microwave vial was charged with 6-methyl-2-(6-methyl-1,3-dihydroisobenzofuran-5-yl)-1,3,6,2-dioxazaborocane-4,8-dione (28.9 mg, 100 µmol, 1.00 equiv.), [Pd(dppf)]Cl_2 (2.9 mg, 4.00 µmol, 4.00 mol%), K_3PO_4 (63.7 mg, 300 µmol, 3.00 equiv.). The vial was capped, evacuated, and backfilled with N_2 and then 3-bromopyridine (15.0 µL, 154 µmol, 1.54 equiv.), H_2O (25.0 µL, 302 µmol, 3.02 equiv.) and THF (400 µL, 250 mM) were added. The mixture was heated to 90 ºC to stir for 24 h before cooling to RT and diluting with H_2O (10 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product which was purified by flash column chromatography (silica, 1:99 NEt_3:hexane – 1:20:79 NEt_3:EtOAc:hexane) to yield the desired product as a white solid (10.2 mg, 48%).



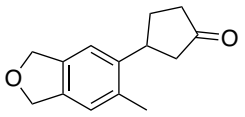
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 8.65 (m 2H, 13, 16), 7.67 (m, 1H, 14), 7.40 (m, 1H, 12), 7.21 (s, 1H, 6), 7.11 (s, 1H, 3), 5.16 (m, 4H, 7, 9), 2.29 (s, 3H, 10).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 150.0 (12 or 13), 148.2 (12 or 13), 139.3 (2), 137.6 (11), 137.4 (1), 137.2 (5), 136.5 (14), 134.9 (4), 123.2 (16), 122.9 (6), 122.3 (3), 73.4 (9), 73.4 (7), 20.5 (10).

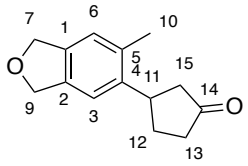
IR (ATR, film): 2922, 2853, 1765, 1472, 1454, 1404, 1364, 1049, 1011, 901, 872, 812, 718 cm^{-1}.

HRMS (ESI): Calculated for 212.10699 *m*/*z*, found 212.10626 *m*/*z* $[C_{14}H_{13}NO+H]^+$.

3-(6-Methyl-1,3-dihydroisobenzofuran-5-yl)cyclopentan-1-one (4.243)



An oven dried microwave vial was charged with 6-methyl-2-(6-methyl-1,3-dihydroisobenzofuran-5-yl)-1,3,6,2-dioxazaborocane-4,8-dione (28.9 mg, 100 µmol, 1.00 equiv.), K_3PO_4 (42.5 mg, 200 µmol, 2.00 equiv.) and [Rh(COD)$(NCMe)_2$]BF_4 (1.90 mg, 5.00 µmol, 5.00 mol%) then capped, evacuated, and backfilled with N_2. PhMe (900 µL), H_2O (150 µL) and 2-cyclopenten-1-one (17.0 µL, 203 µmol, 2.03 equiv.) were added and the mixture was heated to 100 ºC for 24 h. The reaction flask was allowed to cool to RT before adding saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product which was purified by flash column chromatography (silica, 0–20% EtOAc in hexane) to yield the product as a white solid (9.2 mg, 43%).



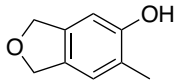
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.12 (s, 1H, 3), 7.10 (s, 1H, 6), 5.11 – 5.06 (m, 4H, 7, 9), 3.69 – 3.60 (m, 1H, 11), 2.71 – 2.65 (m, 1H, 15), 2.55 – 2.47 (m, 1H, 13), 2.45 – 2.25 (m, 6H, 10, 12, 13, 15), 2.07 – 1.98 (m, 1H, 12).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 218.5 (14), 140.3 (4), 137.5 (1 or 2), 137. 4 (1 or 2), 135.2 (5), 123.0 (6), 117.3 (3), 73.5 (7 or 9), 73.4 (7 or 9), 45.5 (15), 38.5 (13), 38.3 (11), 30.2 (12), 19.9 (10).

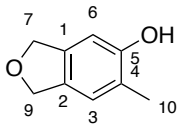
IR (ATR, film): 2853, 1736, 1153, 1040, 901, 866, 419 cm^{-1}.

HRMS (ESI): Calculated for 239.10425 *m*/*z*, found 239.10349 *m*/*z* $[C_{14}H_{16}O_2+Na]^+$.

6-Methyl-1,3-dihydroisobenzofuran-5-ol (2.444)



A flask was charged with 6-methyl-2-(6-methyl-1,3-dihydroisobenzofuran-5-yl)-1,3,6,2-dioxazaborocane-4,8-dione (28.9 mg, 100 µmol, 1.00 equiv.) and THF (400 µL, 250 mM). K_3PO_4 (63.7 mg, 300 µmol, 3.00 equiv.) and H_2O_2 (30% in H_2O, 100 µL, 980 µmol, 9.80 equiv.) was added and the mixture was allowed to stir at RT for 16 h. The mixture was then quenched by the addition of $Na_2S_2O_5$ and then suspended between H_2O (10 mL) and EtOAc (10 mL). The organic phase was collected, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product which was purified by flash column chromatography (silica, 0–100% CH_2Cl_2 in hexane) to yield the desired product as a white powder (11.8 mg, 79%).



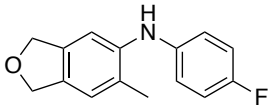
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 6.98 (s, 1H, 3), 6.65 (s, 1H, 6), 5.08 – 4.98 (m, 4H, 7, 9), 2.25 (s, 3H, 10).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 153.6 (5), 138.2 (2), 131.0 (1), 123.2 (3), 116.2 (4), 107.5 (6), 73.5 (9), 73.4 (7), 16.1 (10).

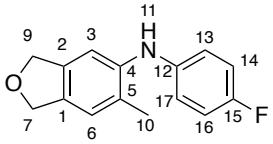
IR (ATR, film): 3318, 2922, 1302, 1260, 1225, 1030, 893, 851 cm^{-1}.

HRMS (ESI): Calculated for 173.05730 *m*/*z*, found 173.05678 *m*/*z* $[C_9H_{10}O_2+Na]^+$.

***N*-(4-Fluorophenyl)-6-methyl-1,3-dihydroisobenzofuran-5-amine (4.245)**



An oven dried microwave vial was charged with 6-methyl-2-(6-methyl-1,3-dihydroisobenzofuran-5-yl)-1,3,6,2-dioxazaborocane-4,8-dione (28.9 mg, 100 µmol, 1.00 equiv.), $Cu(OAc)_2$ (23.6 mg, 130 µmol, 1.30 equiv.) and DMAP (15.9 mg, 130 µmol, 1.30 equiv.). The vial was capped and MeCN (200 µL, 500 mM) followed by 4-fluoroaniline (20.0 µL, 208 µmol, 2.08 equiv.). The mixture was heated to 80 ºC to stir for 36 h before allowing to cool to RT, filtering through celite, and diluting with CH_2Cl_2 (10 mL) and 10% aqueous NH_3 (10 mL) The organic phase was collected and the aqueous mixture was extracted with CH_2Cl_2 (2 × 10 mL) and the organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product. This was purified by flash column chromatography (silica, 0–5% EtOAc in hexane) to yield the desired product as a yellow solid (8.0 mg, 33%).



^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.09 (s, 1H, 6), 7.04 – 6.93 (m, 5H, 3, 13, 14, 16, 17), 5.29 (br s, 1H, 11), 5.08 (m, 2H, 7), 5.05 (m, 2H, 9), 2.28 (s, 3H, 10).

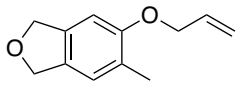
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 157.9 (d, $^1J_{CF}$ = 239.8 Hz, 15), 141.6 (5), 139.8 (d, $^4J_{CF}$ = 2.1 Hz, 12), 138.0 (1), 132.1 (2), 126.7 (4), 123.2 (6), 120.2 (d, $^3J_{CF}$ = 7.7 Hz, 13, 17), 116.0 (d, $^2J_{CF}$ = 22.4 Hz, 14, 16), 109.9 (3), 73.6 (9), 73.4 (7), 18.1 (10).

^{19}F NMR (471 MHz, Chloroform-*d*) δ_F –122.6 (m).

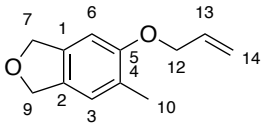
IR (ATR, film): 1505, 1362, 1310, 1211, 1042, 895, 828, 783, 503, 488, 432 cm^{-1}.

HRMS (ESI): Calculated for 244.11322 *m*/*z*, found 244.11245 *m*/*z* $[C_{15}H_{14}FNO+H]^+$.

5-(Allyloxy)-6-methyl-1,3-dihydroisobenzofuran (4.246)



An oven dried microwave vial was charged with 6-methyl-2-(6-methyl-1,3-dihydroisobenzofuran-5-yl)-1,3,6,2-dioxazaborocane-4,8-dione (28.9 mg, 100 µmol, 1.00 equiv.), $Cu(OAc)_2$ (23.6 mg, 130 µmol, 1.30 equiv.) and DMAP (15.9 mg, 130 µmol, 1.30 equiv.). The vial was capped and MeCN (200 µL, 500 mM) followed by allyl alcohol (14.0 µL, 206 µmol, 2.06 equiv.). The mixture was heated to 80 ºC to stir for 36 h before allowing to cool to RT, filtering through celite, and diluting with CH_2Cl_2 (10 mL) and 10% aqueous NH_3 (10 mL). The organic phase was collected, and the aqueous mixture was extracted with CH_2Cl_2 (2 × 10 mL) and the organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product. This was purified by flash column chromatography (silica, 0–3% EtOAc in hexane) to yield the desired product as a white solid (7.5 mg, 39%).



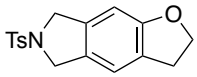
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.03 (s, 1H, 6), 6.71 (s, 1H, 3), 6.10 (ddt, *J* = 17.3, 10.3, 5.0 Hz, 1H, 13), 5.46 (app dq, *J* = 17.3, 1.7 Hz, 1H, 14), 5.35 – 5.29 (m, 1H, 14), 5.10 – 5.08 (m, 2H, 9), 5.08 – 5.06 (m, 2H, 7), 4.56 (app dt, *J* = 5.0, 1.7 Hz, 2H, 12), 2.28 (s, 3H, 10).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 156.5 (4), 137.5 (1), 133.5 (13), 130.5 (2), 126.4 (5), 122.8 (6), 117.1 (14), 104.1 (3), 73.8 (9), 73.5 (7), 69.0 (12), 16.6 (10).

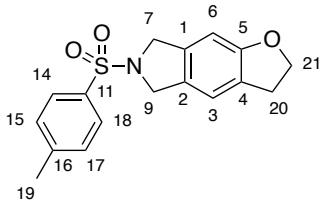
IR (ATR, film): 2924, 2853, 1497, 1281, 1206, 1049, 419 cm^{-1}.

HRMS (ESI): Calculated for 189.0910 *m*/*z*, found 189.0912 *m*/*z* $[C_{12}H_{14}O_2–H]^+$.

6-Tosyl-3,5,6,7-tetrahydro-2*H*-furo[2,3-*f*]isoindole (4.247)



A flask was charged with 2-(6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-tosylisoindolin-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (58.7 mg, 100 µmol, 1.00 equiv.) and THF (500 µL, 200 mM). Pyridine•HF (70% HF, 100 µL, 1.11 mmol, 11.1 equiv.) was added and the mixture was allowed to stir for 1 h at RT. One drop of H_2O was then added followed by the addition of excess $NaHCO_3$. Excess Na_2SO_4 was added, and the mixture was suspended in acetone then filtered. The filtrated was concentrated *in vacuo* then transferred to an oven-dried microwave vial with $Cu(OAc)_2$ (23.6 mg, 130 µmol, 1.30 equiv.) and DMAP (15.9 mg, 130 µmol, 1.30 equiv.). The vial was capped and MeCN (200 µL, 500 mM) was added then the mixture was heated to 80 ºC to stir for 24 h before allowing to cool to RT, filtering through celite, and diluting with CH_2Cl_2 (10 mL) and 10% aqueous NH_3 (10 mL). The organic phase was collected, and the aqueous mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product. This was purified by flash column chromatography (silica, 0–3% EtOAc in hexane) to yield the desired product as a white solid (23.3 mg, 74%).



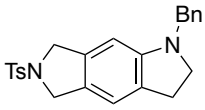
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.78 (d, *J* = 8.2 Hz, 2H, 14, 18), 7.33 (d, *J* = 8.0 Hz, 2H, 15, 17), 6.97 (s, 1H, 3), 6.57 (s, 1H, 6), 4.63 – 4.51 (m, 6H, 7, 9, 21), 3.16 (t, *J* = 8.6 Hz, 2H, 20), 2.42 (s, 3H, 19).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 160.2 (5), 143.5 (16), 135.9 (2), 134.0 (11), 129.8 (15, 17), 127.7 (1), 127.6 (14, 18), 127.3 (4), 118.9 (3), 103.5 (6), 71.7 (21), 53.7 (7 or 9), 53.3 (7 or 9), 29.5 (20), 21.5 (19).

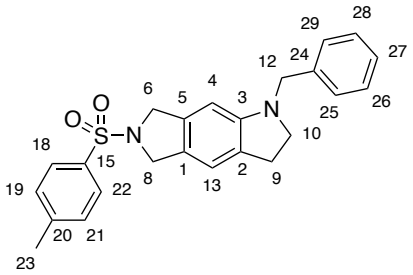
IR (ATR, film): 1339, 1161, 1096, 1059, 665, 602, 550 cm^{-1}.

HRMS (ESI): Calculated for 338.08214 *m/z*, found 338.08115 *m/z* $[C_{17}H_{17}NO_3S+Na]^+$.

1-Benzyl-6-tosyl-1,2,3,5,6,7-hexahydropyrrolo[3,4-*f*]indole (4.248)



An oven-dried microwave vial was charged with 2-(6-(2-(dibenzylamino)ethyl)-2-tosylisoindolin-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (65.2 mg, 100 µmol, 1.00 equiv.) and Pd/C (10%, 10.6 mg, 10.0 µmol, 10.0 mol%) before sealing, evacuating, and backfilling with N_2. A balloon of H_2 was then added followed by dioxane (500 µL, 200 mM) and acetic acid (120 µL, 2.09 mmol, 20.9 equiv.). The mixture was heated to 80 ºC and stirred under an atmosphere of H_2 for 16 h before allowing to cool to RT, diluting with acetone, filtering through celite, and concentrating *in vacuo* to yield the crude. This was transferred to another oven-dried microwave vial and $Cu(OAc)_2$ (26.0 mg, 130 µmol, 1.30 equiv.) and DMAP (15.9 mg, 130 µmol, 1.30 equiv.) were added. The vial was sealed and MeCN (200 µL, 500 mM) was added, and the mixture was heated to 80 ºC to stir for 24 h before allowing to cool to RT, filtering through celite, and diluting with CH_2Cl_2 (10 mL) and 10% aqueous NH_3 (10 mL). The organic phase was collected, and the aqueous mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product. This was purified by flash column chromatography (silica, 0–20% EtOAc in hexane) to yield the desired product as a pale-yellow solid (3.3 mg, 8%).



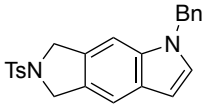
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.80 – 7.74 (m, 2H, 18, 22), 7.40 – 7.30 (m, 7H, 19, 21, 25–29), 6.87 (s, 1H, 13), 6.24 (s, 1H, 4), 4.52 (m, 4H, 6, 8), 4.21 (s, 2H, 12), 3.34 (t, *J* = 8.3 Hz, 2H, 10), 2.93 (t, *J* = 8.2 Hz, 2H, 9), 2.42 (s, 3H, 23).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 152.8 (20), 143.5 (3), 138.0 (24), 135.1 (1), 133.8 (15), 130.6 (2), 129.7 (19, 21), 128.6 (26, 28), 127.7 (25, 29), 127.6 (18, 22), 127.3 (27), 124.6 (5), 118.6 (13), 100.6 (4), 54.0 (6 or 8 or 10), 54.0 (6 or 8 or 10), 53.5 (6 or 8 or 12), 53.5 (6 or 8 or 12), 28.2 (9), 21.5 (23).

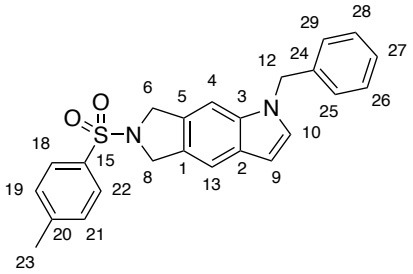
IR (ATR, film): 2922, 2361, 1344, 1161, 1096, 667, 550, 405 cm^{-1}.

HRMS (ESI): Calculated for 404.1559 *m/z*, found 404.1551 *m/z* $[C_{24}H_{24}N_2O_2S]^+$.

1-Benzyl-6-tosyl-1,5,6,7-tetrahydropyrrolo[3,4-*f*]indole (4.249)



Prepared from same procedure as 2-(6-(2-(dibenzylamino)ethyl)-2-tosylisoindolin-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione. Purified by flash column chromatography (silica, 0–20% EtOAc in hexane) to yield the desired product as a yellow solid (15.6 mg, 38%).



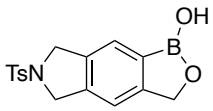
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.79 – 7.73 (m, 2H, 18, 22), 7.39 – 7.38 (m, 1H, 13), 7.32 – 7.23 (m, 5H, 19, 21, 26–28), 7.12 (d, *J* = 3.2 Hz, 1H, 10), 7.06 – 7.03 (m, 2H, 25, 29), 7.02 – 7.00 (m, 1H, 4), 6.48 (dd, *J* = 3.2, 0.8 Hz, 1H, 9), 5.29 – 5.25 (s, 2H, 12), 4.68 – 4.66 (m, 2H, 8), 4.66 – 4.63 (m, 2H, 6), 2.38 (s, 3H, 23).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 143.5 (20), 137.2 (24), 136.2 (2), 133.6 (15), 130.3 (1), 129.7 (19, 21), 129.3 (27), 128.9 (3), 128.9 (26, 28), 127.8 (5), 127.7 (18, 22), 126.6 (25, 29), 114.4 (13), 103.5 (4), 101.5 (9), 53.6 (6), 53.3 (8), 50.2 (12), 21.5 (23).

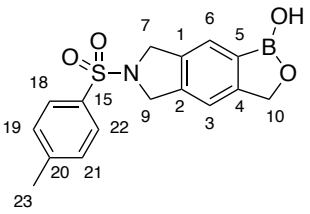
IR (ATR, film): 2922, 1716, 1341, 1161, 1096, 667 cm^{-1}.

HRMS (ESI): Calculated for 425.12942 *m*/*z*, found 425.12839 *m*/*z* $[C_{24}H_{22}N_2O_2S+Na]^+$.

6-Tosyl-3,5,6,7-tetrahydro-1H-[1,2]oxaborolo[3,4-*f*]isoindol-1-ol (4.252)



Prepared according to General Procedure C from 2-(3-hydroxyprop-1-yn-1-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (21.1 mg, 100 µmol, 1.00 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol). *i*-PrOH (1.00 mL) was then added followed by K_2CO_3 (55.3 mg, 400 µmol, 4.00 equiv.) and the resulting suspension was allowed to stir for 2 h at RT. This mixture was filtered through celite an concentrated *in vacuo* to yield the crude product which was purified by flash column chromatography (silica, 0–5% acetone in CH_2Cl_2) before precipitating from CH_2Cl_2:Et_2O to yield the desired product as a white powder (7.9 mg, 23%).



^{1}H NMR (500 MHz, Acetone-d_6) δ_H 7.85 – 7.78 (m, 2H, 18, 22), 7.59 (s, 1H, 6), 7.49 – 7.42 (m, 2H, 19, 21), 7.31 (q, J = 1.0 Hz, 1H, 3), 4.98 (s, 2H, 10), 4.63 (m, 4H, 7, 9), 2.40 (s, 3H, 23).

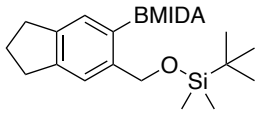
^{13}C NMR (126 MHz, Acetone-d_6) δ_C 154.2 (4), 143.8 (20), 139.5 (1), 135.4 (2), 133.8 (15), 129.8 (19, 21), 127.7 (18, 22), 124.5 (6), 115.7 (3), 70.1 (10), 53.4 (7), 53.1 (9), 20.5 (23).

^{11}B NMR (96 MHz, Acetone-d_6) δ_B 32.6.

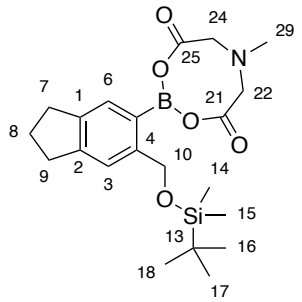
IR (ATR, film): 1163, 667, 600, 457, 419, 411, 403 cm^{-1}.

HRMS (ESI): Calculated for 352.07853 m/z, found 352.07817 m/z $[C_{16}H_{16}BNO_4S+Na]^+$.

2-(6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,3-dihydro-1*H*-inden-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (**4**.**253**)



Prepared according to General Procedure C from 2-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-yn-1-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (32.5 mg, 100 µmol, 1.00 equiv.) to yield the desired product which was further purified by precipitation of an impurity with CH_2Cl_2-hexane yielding the desired product as a pale-orange solid (25.3 mg, 61%).



^{1}H NMR (400 MHz, Chloroform-d) δ_H 7.42 (s, 1H, 6), 7.16 (s, 1H, 3), 4.82 (s, 2H, 10), 4.02 (d, J = 16.5 Hz, 2H, 22, 24), 3.89 (d, J = 16.6 Hz, 2H, 22, 24), 2.92 (m, 4H, 7, 9), 2.69 (s, 3H, 29), 2.17 – 2.00 (m, 2H, 8), 0.93 (s, 9H, 16–18), 0.14 (s, 6H, 14, 15).

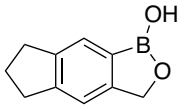
^{13}C NMR (101 MHz, Chloroform-d) δ_C 167.7 (21, 25), 146.3 (1), 143.7 (2), 142.5 (4), 130.0 (6), 127.0 (3), 66.5 (10), 63.3 (22, 24), 48.9 (29), 32.8 (9), 32.6 (7), 26.2 (16–18), 25.2 (8), 18.8 (13), –5.0 (14, 15).

^{11}B NMR (128 MHz, Chloroform-d) δ_B 12.0.

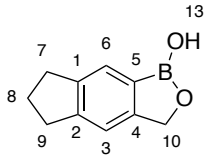
IR (ATR, film): 2928, 1759, 1462, 1337, 1296, 1250, 1180, 1028, 818 cm^{-1}.

HRMS (ESI): Calculated for 440.2035 *m/z*, found 440.2031 *m/z* $[C_{21}H_{32}BNO_5Si+Na]^+$.

3,5,6,7-Tetrahydro-1H-indeno[5,6-c][1,2]oxaborol-1-ol (4.254)



Prepared according to General Procedure C from 2-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-yn-1-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (21.1 mg, 100 µmol, 1.00 equiv.) and heptadiyne (55.3 mg, 600 µmol). *i*-PrOH (1.00 mL) was then added followed by K_2CO_3 (55.3 mg, 400 µmol, 4.00 equiv.) and the resulting suspension was allowed to stir for 2 h at RT. This mixture was filtered through celite an concentrated *in vacuo* to yield the crude which was purified by flash column chromatography (silica, 0–5% acetone in CH_2Cl_2) before precipitating from CH_2Cl_2:Et_2O to yield the desired product as a white powder (13.0 mg, 68%).



^{1}H NMR (500 MHz, Acetonitrile-d_3) δ_H 7.56 (s, 1H, 6), 7.25 (d, J = 1.5 Hz, 1H, 3), 6.54 (s, 1H, 13), 4.99 (s, 2H, 10), 2.95 (m, 4H, 7, 9), 2.14 – 2.06 (m, 2H, 8).

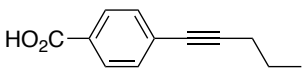
^{13}C NMR (126 MHz, Acetonitrile-d_3) δ_C 156.8 (4), 148.2 (1), 130.9 (2), 125.7 (6), 117.1 (3), 70.4 (10), 32.5 (7), 31.9 (9), 25.5 (8).

^{11}B NMR (96 MHz, Acetonitrile-d_3) δ_B 32.7.

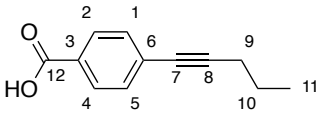
IR (ATR, film): 3310, 2361, 1410, 991 cm^{-1}.

HRMS (ESI): Calculated for 197.0744 *m/z*, found 197.0748 *m/z* $[C_{10}H_{11}BO_2+Na]^+$.

4-(Pent-1-yn-1-yl)benzoic acid (S1)



A flask was charged with methyl 4-(pent-1-yn-1-yl)benzoate (100 mg, 8496 µmol, 1.00 equiv.), NaOH (55.4 mg, 1.39 mmol, 2.80 equiv.), and H_2O:MeOH (700 µL: 770 µL). The mixture was heated to 100 ºC to stir for 5 h before cooling to RT. Concentrated aqueous hydrochloric acid was added dropwise and the resultant white precipitate was filtered and washed with H_2O. The residue was collected yielding the desired product as a white powder (58.7 mg, 63%).

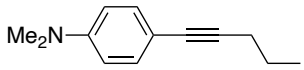


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 8.04 – 7.97 (m, 2H, 2, 4), 7.50 – 7.45 (m, 2H, 1, 5), 2.42 (t, *J* = 7.1 Hz, 2H, 9), 1.65 (h, *J* = 7.2 Hz, 2H, 10), 1.06 (t, *J* = 7.4 Hz, 3H, 11).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 171.0 (12), 131.7 (1, 5), 130.2 (2, 4), 130.0 (6), 128.0 (3), 94.6 (8), 80.4 (7), 22.2 (10), 21.6 (9), 13.7 (11).

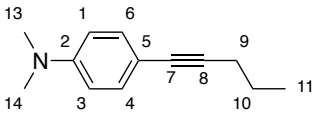
Spectral data consistent with the literature.[383]

_N_,_N_-Dimethyl-4-(pent-1-yn-1-yl)aniline (S2)



A flask was charged with H_2O (25.0 mL, 947 mM), $NaHCO_3$ (3.98 g, 47.3 mmol, 2.00 equiv.) and *N*,*N*-dimethylaniline (3.00 mL, 23.7 mmol, 1.00 equiv.). I_2 (9.01 g, 35.5 mmol, 1.50 equiv.) was added in small portions and the reaction mixture was allowed to vigorously stir for 1 h at RT. The mixture was extracted with Et_2O (4 × 50 mL) then the combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (3 × 20 mL). The organic extracts were recombined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude iodide a portion of which was used directly in the next step without further purification.

An oven-dried microwave vial was charged with 4-iodo-*N*,*N*-dimethylaniline (1.00 g, 4.05 mmol, 1.00 equiv.), CuI (77.1 mg, 405 µmol, 10.0 mol%), and $Pd(PPh_3)_2Cl_2$ (28.4 mg, 40.5 µmol, 1.00 mol%). The vial was capped, evacuated, and backfilled with N_2. NEt_3 (8.00 mL, 506 mM) was added, and the mixture was allowed to stir at RT for 16 h. The vial was decapped, and the contents were filtered through celite (washing with EtOAc) before concentrating *in vacuo* to yield the crude product which was purified by flash column chromatography (silica, 0–100% CH_2Cl_2 in hexane) to yield the desired product as an orange-brown oil (244 mg, 32%).



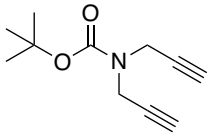
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.30 – 7.26 (m, 2H, 4, 6), 6.64 – 6.58 (m, 2H, 1, 3), 2.95 (s, 6H, 13, 14), 2.37 (t, *J* = 7.1 Hz, 2H, 9), 1.62 (h, *J* = 7.2 Hz, 2H, 10), 1.04 (t, *J* = 7.4 Hz, 3H, 11).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 149.8 (2), 132.6 (4, 6), 112.1 (1, 3), 111.4 (5), 87.7 (8), 81.3 (7), 40.5 (13, 14), 22.6 (10), 21.7 (9), 13.7 (11).

IR (ATR, neat): 1609, 1518, 1445, 1354, 1337, 1199, 1167, 814 cm^{-1}.

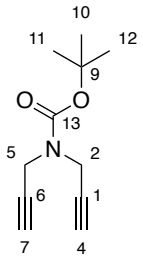
HRMS (ESI): Calculated for 188.1434 *m*/*z*, found 188.1441 *m*/*z* $[C_{13}H_{18}N+H]^+$.

***tert*-Butyl di(prop-2-yn-1-yl)carbamate (S3)**



A flame-dried flask was charged with propargyl amine (1.00 mL, 15.6 mmol, 1.00 equiv.), NEt_3 (2.20 mL, 15.8 mmol, 1.01 equiv.) and dry CH_2Cl_2 (15.0 mL, 1.04 M) under N_2. A solution of Boc_2O (3.41 g, 15.6 mmol, 1.00 equiv.) in dry CH_2Cl_2 (10 mL) was added dropwise. After complete addition, the reaction mixture was allowed to continue stirring for 1 h at RT before quenching with H_2O (20 mL) and extracting the resultant mixture was CH_2Cl_2 (3 × 20 mL). Organic extracts were combined and dried over Na_2SO_4 before filtering and concentrating *in vacuo* to yield the crude product. This material was purified by flash column chromatography (silica, 0–20% EtOAc in hexane) to yield *tert*-butyl prop-2-yn-1-ylcarbamate which was used directly in the next step without further purification.

A flame-dried flask was charged with *tert*-butyl prop-2-yn-1-ylcarbamate (663 mg, 4.27 mmol, 1.00 equiv.) and dry THF (8.50 mL, 503 mM) under N_2 then cooled to 0 ºC. NaH (60% suspension in oil, 205 mg, 5.13 mmol, 1.20 equiv.) was added followed by the dropwise addition of propargyl bromide (80% in PhMe, 600 µL, 5.38 mmol, 1.26 equiv.) then the mixture was allowed to stir for 4 h whilst coming up to RT. After the allotted period, the reaction was quenched with H_2O (20 mL) then the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo.* To yield the crude product which was purified by flash column chromatography (silica, 0–10% Et_2O in hexane) to yield the desired product as a colourless oil (516 mg, 19% over 2 steps).

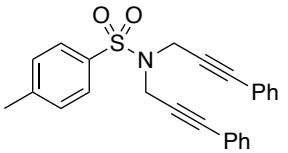


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 4.17 (m, 4H, 2, 5), 2.22 (t, J = 2.5 Hz, 2H, 4, 7), 1.48 (s, 9H, 10–12).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 154.4 (13), 81.3 (9), 78.9 (1, 6), 72.0 (4, 7), 35.3 (2, 5), 28.4 (10–12).

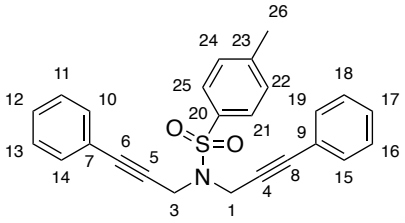
Spectral data consistent with the literature.[384]

4-Methyl-*N*,*N*-bis(3-phenylprop-2-yn-1-yl)benzenesulfonamide (S4)



Prepared according to General Procedure A from iodobenzene (420 µL, 2.50 mmol, 2.50 equiv.) and 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (247 mg, 1.00 mmol).

Purified by flash column chromatography (silica, hexane) to yield the desired product as an orange oil (282.3 mg, 71%).

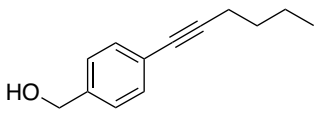


^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.84 – 7.77 (m, 2H, 21, 25), 7.34 – 7.13 (m, 12H, 10–19, 22, 24), 4.45 (s, 4H, 1, 3), 2.32 (s, 3H, 26).

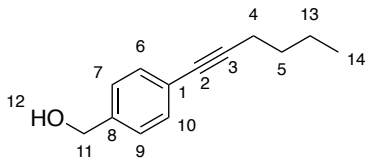
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 144.0 (23), 135.5 (20), 131.8 (10, 14, 15, 19), 129.7 (21, 25), 128.6 (12, 17), 128.3 (11, 13, 16, 18), 128.1 (22, 24), 122.3 (7, 9), 85.9 (4, 5), 81.8 (6, 8), 37.6 (1, 3), 21.5 (26).

Spectral data consistent with the literature.[385]

(4-(Hex-1-yn-1-yl)phenyl)methanol (**S5**)



A flask was charged with methyl 4-iodobenzeoate (1.31 g, 5.00 mmol, 1.00 equiv.) and THF (20.0 mL). $LiAlH_4$ (190 mg, 5.00 mmol, 1.00 equiv.) was then added portionwise and the resulting mixture was stirred at RT for 2 h before quenching with the careful addition of H_2O (10 mL). The mixture was filtered and extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to yield the crude. This material was then subjected to General Procedure A without further purification assuming 100% conversion (i.e. 5.00 mmol). The product was purified by flash column chromatography (silica, 0–15% EtOAc in hexane) to yield the desired product as a brown oil (652 mg, 75%).

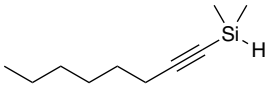


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.41 (d, *J* = 8.2 Hz, 2H, 8, 10), 7.37 – 7.21 (m, 2H, 7, 9), 4.69 (d, *J* = 5.4 Hz, 2H, 11), 2.43 (t, *J* = 7.1 Hz, 2H, 4), 1.72 (t, *J* = 5.8 Hz, 1H, 12), 1.66 – 1.58 (m, 2H, 5), 1.58 – 1.47 (m, 2H, 13), 0.98 (t, *J* = 7.3 Hz, 3H, 14).

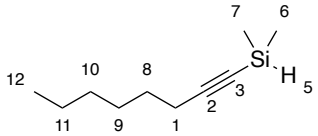
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 140.1 (4), 131.7 (6, 10), 126.8 (7, 9), 123.4 (1), 90.6 (3), 80.3 (2), 65.1 (11), 30.9 (4), 22.0 (5), 19.1 (13), 13.7 (14).

Spectral data consistent with the literature.[386]

Dimethyl(oct-1-yn-1-yl)silane (**S6**)



A flame-dried flask was charged with THF (13.5 mL) and 1-octyne (1.00 mL, 6.78 mmol, 1.00 equiv.) under N_2. After cooling to 0 ºC, *n*-butyllithium (1.10 M in hexane, 7.90 mL, 8.69 mmol, 1.28 equiv.) was added dropwise and the resulting mixture was stirred at 0 ºC for 20 mins before chlorodimethylsialne (1.13 mL, 10.2 mmol, 1.50 equiv.) was added in one portion. The mixture was stirred at 0 ºC for 1 h before being allowed to come up to RT to stir for a further 1 h. The mixture was quenched with the addition of H_2O (50 mL) and then extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product which was purified by flash column chromatography (silica, hexane) to yield the desired product as a pale-yellow oil (987 mg, 87%).



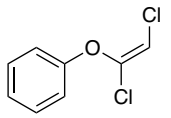
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 4.19 – 4.10 (m, 1H, 5), 2.25 (td, *J* = 7.2, 1.2 Hz, 2H, 1), 1.57 – 1.50 (m, 2H, 8), 1.46 – 1.38 (m, 2H, 9), 1.36 – 1.26 (m, 4H, 10 , 11), 0.91 (t, *J* = 7.0 Hz, 3H, 12), 0.24 (d, *J* = 3.8 Hz, 6H, 6, 7).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 109.4 (2), 81.3 (3), 31.3 (1), 28.5 (9), 28.5 (10), 22.5 (8), 19.9 (11), 14.1 (12), –2.7 (6, 7).

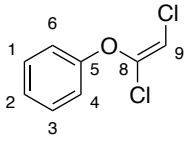
IR (ATR, film): 2957, 2926, 2857, 2137, 1250, 862, 839, 816, 770 cm^{-1}.

HRMS (ESI): Calculated for 191.1227 *m*/*z*, found 191.1222 *m*/*z* $[C_{10}H_{20}Si+Na]^+$.

(*E*)-((1,2-Dichlorovinyl)oxy)benzene (**S7**)



A flask was charged phenol (4.71 g, 50.0 mmol, 1.00 equiv.) and DMSO (25 mL). Crushed NaOH (2.13 g, 53.3 mmol, 1.07 equiv.) was added and the mixture was stirred for 1 h before trichloroethylene (7.23 g, 55.0 mmol, 1.10 equiv.) was added dropwise. The solution was allowed to stir for 18 h at RT before H_2O (50 mL) was added and the solution was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with H_2O (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude product which was purified by flash column chromatography (silica, hexane) to yield the desired product as a colourless oil (9.36 g, 99%).

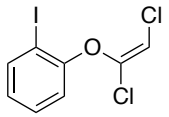


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.51 – 7.36 (m, 2H, 1, 3), 7.25 – 7.18 (m, 1H, 2), 7.17 – 7.05 (m, 2H, 4, 6), 5.99 (s, 1H, 9).

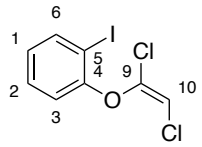
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 153.9 (5), 140.1 (8), 129.8 (1, 3), 124.5 (2), 117.1 (4, 6), 103.8 (9).

Spectral data consistent with the literature.[387]

(*E*)-1-((1,2-Dichlorovinyl)oxy)-2-iodobenzene (S8)



A flask was charged with 2-iodophenol (2.50 g, 11.4 mmol, 1.00 equiv.) and DMSO (25.0 mL). NaOH (500 mg, 12.5 mmol, 1.10 equiv.) was added and the mixture was stirred for 2 h then trichloroethylene (2.00 mL, 22.5 mmol, 1.98 equiv.) was added. This mixture was stirred for 5 h at RT before H_2O (10 mL) was added followed by CH_2Cl_2 (20 mL) The biphasic system was extracted with CH_2Cl_2, (3 × 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the crude which was purified by FCC (silica, 0–5% Et_2O in hexane) to yield the desired product as a yellow oil (2.41 g, 67%).

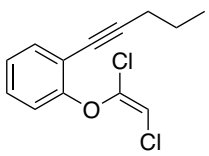


^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.86 (dd, *J* = 7.9, 1.6 Hz, 1H, 6), 7.38 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 1H, 1), 7.02 (dd, *J* = 8.2, 1.4 Hz, 1H, 3), 6.95 (ddd, *J* = 7.9, 7.4, 1.4 Hz, 1H, 2), 6.02 (s, 1H, 10).

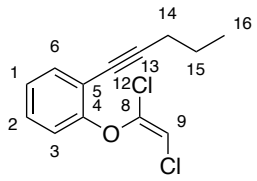
^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 153.2 (5), 140.0 (6), 139.8 (4), 129.6 (1), 126.2 (2), 116.5 (3), 104.2 (10), 86.4 (9).

Spectral data consistent with literature.[381]

(*E*)-1-((1,2-Dichlorovinyl)oxy)-2-(pent-1-yn-1-yl)benzene (S9)



Prepared according to General Procedure A from (*E*)-1-((1,2-dichlorovinyl)oxy)-2-iodobenzene (2.00 g, 6.35 mmol, 1.00 equiv.) and 1-pentyne (750 µL, 7.61 mmol, 1.20 equiv.). Purified by FCC (silica, 0–2% Et_2O in hexane) to yield the desired product as an orange oil (1.021 g, 63%).



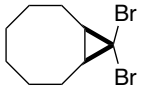
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 7.46 (dd, *J* = 7.6, 1.7 Hz, 1H, 6), 7.35 – 7.25 (m, 1H, 2), 7.13 (m, 1H, 1), 7.04 (dd, *J* = 8.3, 1.2 Hz, 1H, 3), 5.91 (s, 1H, 9), 2.46 (t, *J* = 7.0 Hz, 2H, 14), 1.67 (m, 2H, 15), 1.08 (t, *J* = 7.4 Hz, 3H, 16).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 153.9 (4), 140.2 (8), 133.8 (6), 128.6 (2), 124.6 (1), 117.2 (3), 116.0 (5), 102.2 (9), 96.2 (13), 75.1 (12), 22.1 (15), 21.7 (14), 13.5 (16).

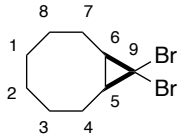
IR (ATR, film): 2962, 1630, 1487, 1445, 1265, 1252, 1192, 1113, 1059, 1038 cm^{-1}.

HRMS (ESI): Calculated for 277.0157 *m*/*z*, found 277.0152 *m*/*z* $[C_{13}H_{12}Cl_2O+Na]^+$.

cis-9,9-Dibromobicyclo[6.1.0]nonane (S10)



A flask was charged with *cis*-cyclooctene (6.50 mL, 49.9 mmol, 1.00 equiv.), bromoform (8.80 mL, 101 mmol, 2.02 equiv.), benzyltriethylammonium chloride (125 mg, 549 µmol, 11.0 mol%), CH_2Cl_2 (10 mL) and EtOH (500 µL) A solution of NaOH (20.0 g, 499 mmol, 10.0 equiv.) in H_2O (20 mL) was then added in small portions after which point a condenser was equipped and the resulting solution was stirred for 3 h at 60 ºC. The mixture was then diluted with H_2O (10 mL) and the biphasic system was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude product which was purified by Kugelrohr distillation (10 mbar, 170 ºC) to yield the desired product as a colourless oil which solidified on standing (6.67 g, 45%).



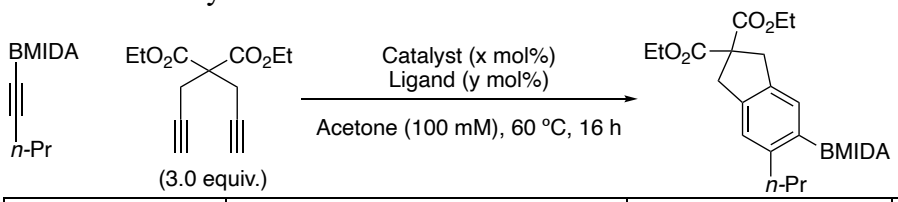
^{1}H NMR (500 MHz, Chloroform-*d*) δ_H 2.12 – 2.05 (m, 2H, 5, 6), 1.66 (m 2H, 1, 2), 1.59 – 1.53 (m, 4H, 3, 4, 7, 8), 1.52 – 1.35 (m, 4H, 1, 2), 1.18 (m, 2H, 4, 7).

^{13}C NMR (126 MHz, Chloroform-*d*) δ_C 37.2 (9), 33.3 (5, 6), 27.9 (4, 7), 26.4 (3, 8), 25.4 (1, 2).

Spectral data consistent with literature.[388]

7.4. Optimisation Data

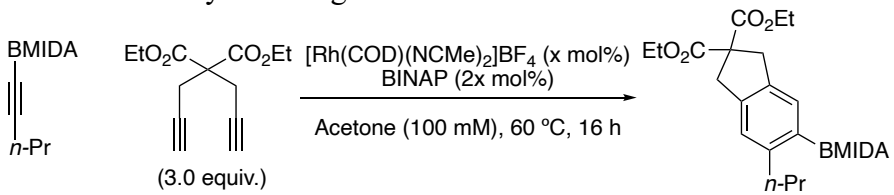
Table S1: Catalyst selection



Entry	Catalyst (x mol%)	Ligand (y mol%)	Yield (%)[a]
1	[Ru(COD)Cp*]Cl (5.0)	0	7
2	$[Ir(COD)]_2Cl_2$ (5.0)	0	<5
3	$[Rh(COD)(NCMe)_2]BF_4$ (5.0)	BINAP (10.0)	10
4	$[Rh(PPh_3)_3]Cl$ (5.0)	0	<5[b]
5	$(acac)Rh(C_2H_2)_2$ (5.0)	BINAP (10.0)	<5
6	$CoCl_2.H_2O$ (5.0)	dppe (6.0)	<5[c]

[a]Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.
[b]Performed in ethanol.
[c]Acetylene BMIDA used as substrate, Zn (0.1 equiv.), DCE (400 mM).

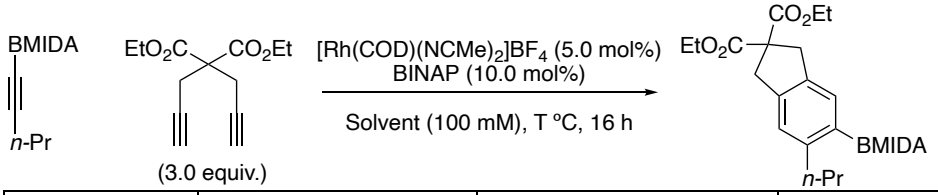
Table S2: Catalyst loading



Entry	Loading (x mol%)	Yield (%)[a]
1	5	10
2	10	14
3	15	31
4	20	43
5	30	39
6	50	27
7	50	28[b]
8	100	29[b]
9	5	21[c]
10	10	37[c]
11	15	63[c]
12	20	80[c]

[a]Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.
[b]Performed at 50 mM.
[c]6.0 equiv of diyne added over 15 h (see **Tables S4** and **S5**).

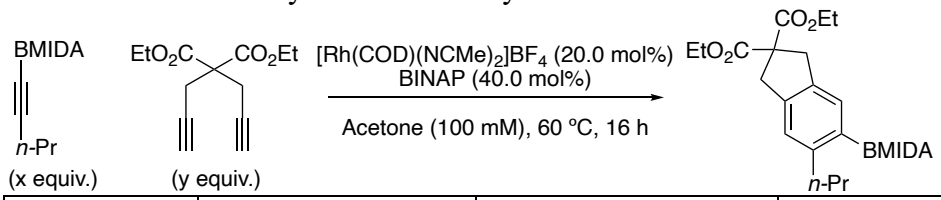
Table S3: Solvent/Temperature selection



Entry	Solvent	Temperature (°C)	Yield (%)[a]
1	Acetone	60	10
2	DCE	60	<5
3	DMSO	100	<5
4	DMSO	140	<5
5	MEK	90	30[b]
6	Acetone	RT	17[b]
7	Acetone	50	25[b]
8	Acetone	60	50[b]
9	Acetone	70	50[b]

[a]Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.
[b]Performed using 20 mol% $[Rh(COD)(NCMe)_2]BF_4$.

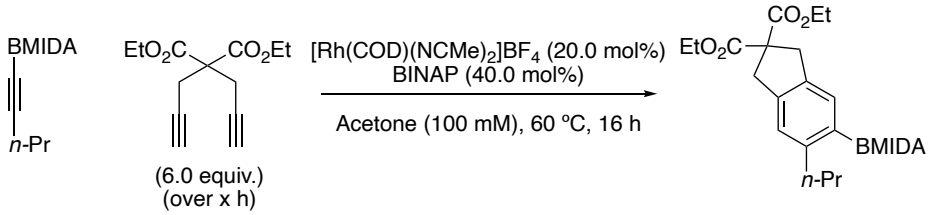
Table S4: Mono/dialkyne stoichiometry



Entry	x (equiv.)	y (equiv.)	Yield (%)
1	1	3	63
2	3	1	27[b]
3	5	1	29[b]
4	1	2	23
5	1	3	43
6	1	4	52
7	1	5	56
8	1	6	63
9	1	7	58
10	1	8	50
11	1	9	59

[a]Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.
[b]Performed using 10 mol% $[Rh(COD)(NCMe)_2]BF_4$.

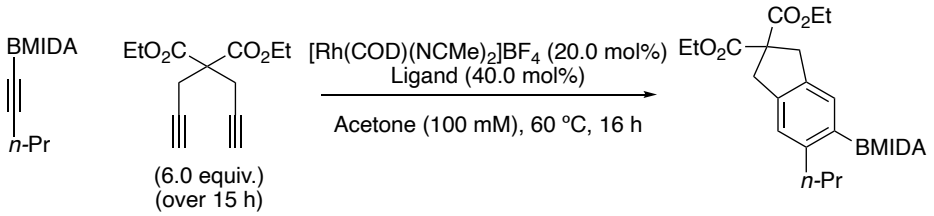
Table S5: Dialkyne addition rate



Entry	x (h)	Yield (%)[a]
1	5	54
2	10	63
3	15	80
4	20	52

[a]Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

Table S6: Ligand Selection



Entry	Ligand	Yield (%)[a]
1	DPEPhos	33
2	Xantphos	<5
3	dppp	44
4	dppe	<5
5	SEGPHOS	<5
6	dtbpf	<5
7	dppf	50
8	tBu$_3$P.HBF$_4$	NR
9	dppm	NR
10	PPh$_3$	NR
11	SPhos	NR
12	XPhos	NR
13	BINAP	80
14	dppb[b]	55
15	(*S*)-(−)-TolBINAP	61
16	(*R*)-SEGPHOS	34
17	(*R*)-DIFLUORPHOS	<5
18	-	NR
19	BINAP[c]	21

[a]Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.
[b][Rh(dppb)(COD)]BF$_4$ (20.0 mol%), dppb (20.0 mol%) as catalyst.
[c][Rh(COD)Cl]$_2$ (10.0 mol%) used as Rh source.

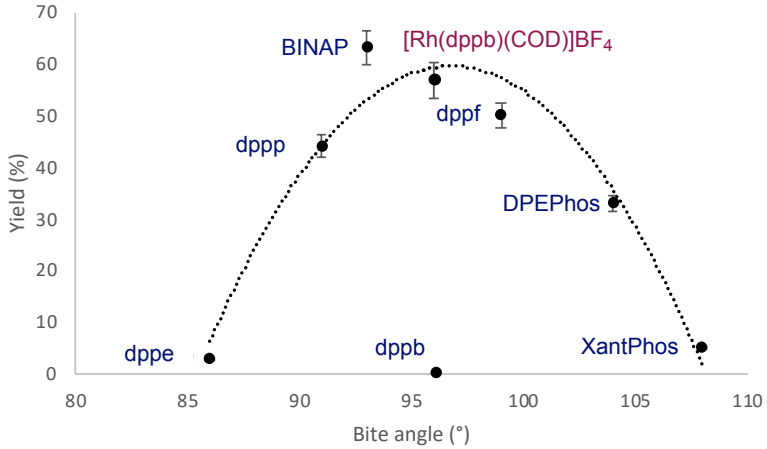
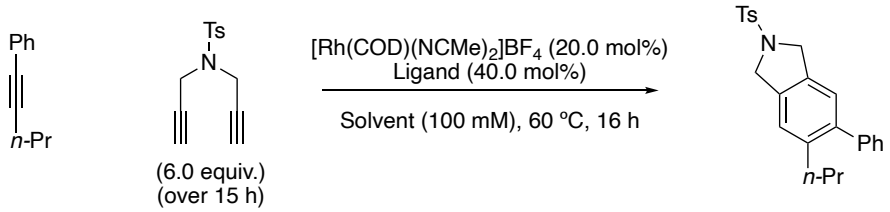


Figure S1: Apparent yield vs phosphine bite angle dependence

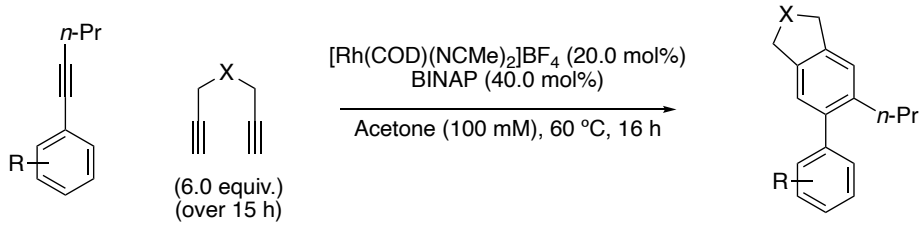
Table S7: Reaction robustness



Entry	Solvent	Degassed	Atmosphere	Yield (%)[a]
1	Acetone (dry)	Y	N_2	>99
2	Acetone (dry)	Y	Ar	>99
3	Acetone (dry)	Y	Air	89
4	Acetone (dry)	N	N_2	>99
5	Acetone (wet)	N	N_2	>99
6	DCE (dry)	N	N_2	68
7	Acetone (dry)	Y	N_2	9[b]
8	DCE (dry) + Acetone (5.0 equiv.)	N	N_2	73
9	DCE (dry) + Acetone (10.0 equiv.)	N	N_2	81

[a]Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.
[b]Phenylpropyne as monoalkyne. No ligand added.

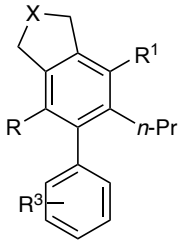
7.5. Hammett Parameter Analysis



An oven-dried microwave vial was charged with the relevant internal alkyne (100 µmol, 1.00 equiv.), $[Rh(COD)(NCMe)_2]BF_4$ (7.60 mg, 20.0 µmol, 20.0 mol%) and *rac*-BINAP (24.9 mg, 40 .0 µmol, 40.0 mol%) before sealing, evacuating, and backfilling with N_2. Distilled acetone ([100 mM]/2) was added and the mixture was heated to 60 ºC for 10 min. A separate dried flask was charged with the requisite diyne (6.00 equiv.) under N_2 before distilled acetone ([100 mM]/2) was added. This solution was added to the microwave vial at 60 ºC over 15 h.

After addition complete, the solution was allowed to stir for a further hour before filtering through celite and concentrating *in vacuo* to yield the crude product. *d*-Chloroform (~1.00 mL) was added followed by trichloroethylene (9.00 µL, 100 µmol, 1.00 equiv.). This solution was mixed until homogeneous then a small portion (~100 µL) was taken and diluted with more *d*-chloroform for analysis by quantitative ^{1}H NMR.

Table S8: Hammett Parameter Analysis



Entry	X	R^1	R^2	R^3	σ^{389}	Yield (%) (*rr*)
1	NTs	H	H	4-NH_2	–0.66	61
2	NTs	H	H	4-Ph	–0.01	72
3	NTs	H	H	4-CF_3	0.54	98
4	NTs	H	H	4-SMe	0.00	81
5	NTs	H	H	4-Ac	0.50	70
6	NTs	H	H	4-Me	–0.17	86
7	NTs	H	H	H	0.00	100
8	NTs	H	H	4-F	0.06	100
9	NTs	H	H	4-OMe	–0.27	100
10	NTs	H	H	4-NO_2	0.78	75
11	NTs	H	H	4-Cl	0.23	76
12	NTs	H	H	4-OH	–0.37	73
13	NTs	H	H	3-NH_2	–0.16	83
14	NTs	H	H	3-OMe	0.12	88
15	NTs	H	H	4-CO_2H	0.45	58
16	NTs	H	H	4-NMe_2	–0.83	90
17	$C(CO_2Et)_2$	H	H	H	0.00	70
18	$C(CO_2Et)_2$	H	H	4-F	0.06	71
19	$C(CO_2Et)_2$	H	H	4-Me	–0.17	73
20	$C(CO_2Et)_2$	H	H	4-Ac	0.50	100
21	$C(CO_2Et)_2$	H	H	4-OMe	–0.27	33
22	$C(CO_2Et)_2$	H	H	4-SMe	0.00	57
23	$C(CO_2Et)_2$	H	H	4-Cl	0.23	67
24	$C(CO_2Et)_2$	H	H	4-Ph	–0.01	70
25	$C(CO_2Et)_2$	H	H	4-CF_3	0.54	32
26	$C(CO_2Et)_2$	H	H	4-NO_2	0.78	56
27	$C(CO_2Et)_2$	H	H	4-NH_2	–0.66	61
28	NTs	H	Me	4-OMe	–0.27	69 (1:2.71)
29	NTs	H	Me	4-Me	–0.17	50 (1:2.48)
30	NTs	H	Me	H	0.00	70 (1:2.94)
31	NTs	H	Me	4-CF_3	0.54	51 (1:2.67)
32	NTs	H	Me	4-NO_2	0.78	49 (1:2.91)
33	NTs	Me	Me	4-OMe	–0.27	37

34	NTs	Me	Me	4-Me	–0.17	20
35	NTs	Me	Me	H	0.00	50
36	NTs	Me	Me	4-CF_3	0.54	9
37	NTs	Me	Me	4-NO_2	0.78	58
38	$(CH_2)_2$	H	H	4-OMe	–0.27	47
39	$(CH_2)_2$	H	H	4-Me	–0.17	48
40	$(CH_2)_2$	H	H	H	0.00	44
41	$(CH_2)_2$	H	H	4-CF_3	0.54	36
42	$(CH_2)_2$	H	H	4-NO_2	0.78	32
43	NTs	H	H	4-OMe	–0.27	34[a]
44	NTs	H	H	4-Me	–0.17	75[a]
45	NTs	H	H	H	0.00	31[a]
46	NTs	H	H	4-CF_3	0.54	62[a]
47	NTs	H	H	4-NO_2	0.78	45[a]
48	NTs	H	H	4-OMe	–0.27	19[b]
49	NTs	H	H	4-Me	–0.17	15[b]
50	NTs	H	H	H	0.00	30[b]
51	NTs	H	H	4-CF_3	0.54	12[b]
52	NTs	H	H	4-NO_2	0.78	12[b]

[a]Performed in DCE. [b]Performed in PhMe. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

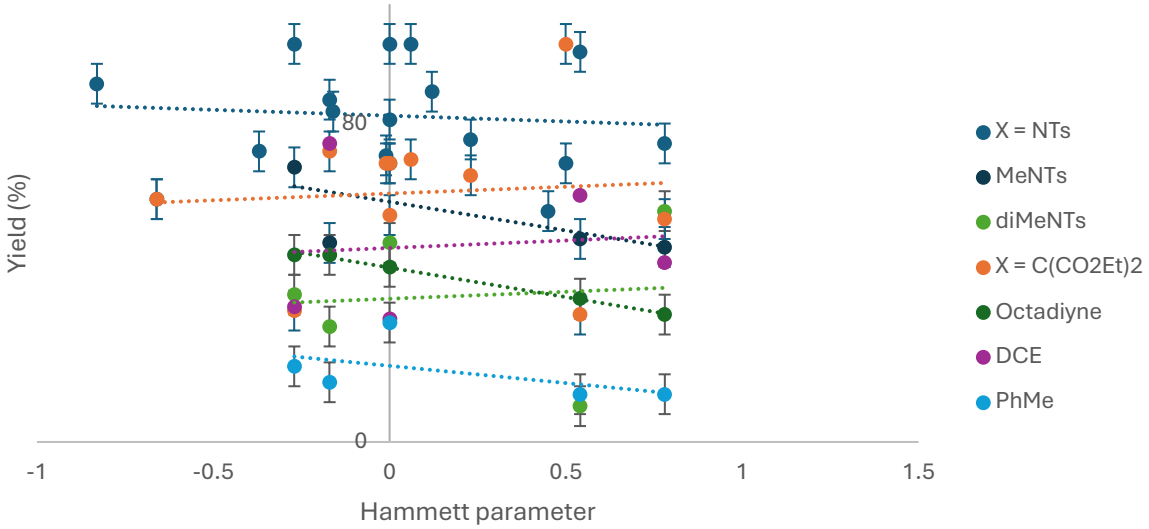
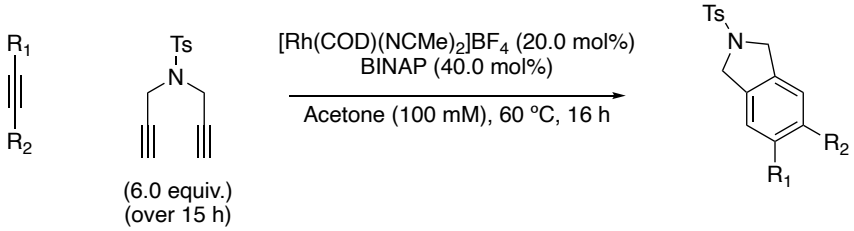


Figure S4: Hammett parameter analysis

7.6. Steric Parameterisation Data



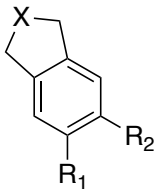
An oven-dried microwave vial was charged with the relevant internal alkyne (100 µmol, 1.00 equiv.), $[Rh(COD)(NCMe)_2]BF_4$ (7.60 mg, 20.0 µmol, 20.0 mol%) and *rac*-BINAP (24.9 mg, 40 .0 µmol, 40.0 mol%) before sealing, evacuating, and backfilling with N_2. Distilled acetone ([100 mM]/2) was added and the mixture was heated to 60 ºC for 10 min. A separate dried flask was charged with 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.) under N_2 before distilled acetone ([100 mM]/2) was added. This solution was added to the microwave vial at 60 ºC over 15 h. After addition complete, the solution was allowed to stir for a further hour before filtering through celite and concentrating *in vacuo* to yield the crude product. *d*-Chloroform (~1.00 mL) was added followed by trichloroethylene (9.00 µL, 100 µmol, 1.00 equiv.). This solution was mixed until homogeneous then a small portion (~100 µL) was taken and diluted with more *d*-chloroform for analysis by quantitative ^{1}H NMR.

Table S9: Steric screen data. TDB = Taft-Dubois

	R_1	R_2	$A(R_1)$	$A(R_2)$	Σ(Alkynes[A])	$\Delta\Delta G(R_1)$	$\Delta\Delta G(R_2)$	Σ(Alkynes[ΔΔG])	TDB (R_1)	TDB (R_2)	TDB (D_1)	TDB (D_2)	Σ(Alkynes[TDB])	Yield (%)	Rh loading (mol%)	RTO
1	Ph	*n*-Pr	3	1.8	4.8	75.5	61.9	137.4	2.31	0.31	−1.24	−1.24	0.14	100	20	5
2	Ph	*i*-Pr	3	2.15	5.15	75.5	101.6	177.1	2.31	0.48	−1.24	−1.24	0.31	84	20	4.2
3	Ph	TMS	3	2.6	5.5	75.5	80.5	156	2.31	1.79	−1.24	−1.24	1.62	65	20	3.25
4	Ph	Ph	3	3	6	75.5	75.5	151	2.31	2.31	−1.24	−1.24	2.14	59	20	2.95
5	*t*-Bu	Ph	4.7	3	7.7	142.0	75.5	217.5	2.31	1.43	−1.24	−1.24	1.26	0	20	0
6	*n*-Bu	Me	1.8	1.7	3.5	61.5	34.9	96.4	0.31	0	−1.24	−1.24	−2.17	95	10	9.5
7	Ph	Me	3	1.7	4.7	75.5	34.9	110.4	2.31	0	−1.24	−1.24	−0.17	81	11	7.36
8	Ph	H	3	0	3	75.5	0	75.5	2.31	−1.24	−1.24	−1.24	−1.41	83	10	8.3
9	Ph	*n*-Pr	3	1.8	4.8	75.5	61.9	137.4	2.31	0.31	−1.24	−1.24	0.14	77	15	5.13
10	*n*-Pr	Et	1.8	1.75	3.55	61.9	61.9	125.2	0.31	0.08	−1.24	−1.24	−2.09	71	10	7.1
11	*n*-Bu	H	1.8	0	1.8	61.5	0	51.6	0.31	−1.24	−1.24	−1.24	−3.41	58	5	11.6
12	*n*-Pr	*n*-Pr	1.8	1.8	3.6	61.9	61.9	123.8	0.31	0.31	−1.24	−1.24	−1.86	78	10	7.8
13	*n*-Pr	Me	1.8	1.7	3.5	61.9	61.9	123.8	0.31	0	−1.24	−1.24	−2.17	86	10	8.6
14	Ph	Me	3	1.7	4.7	75.5	34.9	110.4	2.31	0	−1.24	−1.24	−0.17	40	5	8
15	Ph	Me	3	1.7	4.7	75.5	34.9	110.4	2.31	0	−1.24	−1.24	−0.17	15	2	7.5
16	Ph	Me	3	1.7	4.7	75.5	34.9	110.4	2.31	0	−1.24	−1.24	−0.17	100	15	6.67
17	Ph	Me	3	1.7	4.7	75.5	34.9	110.4	2.31	0	−1.24	−1.24	−0.17	55	8	6.88
18	Ph	Ph	3	3	6	75.5	75.5	151	2.31	2.31	−1.24	−1.24	2.14	55	15	3.67
19	Ph	TMS	3	2.5	5.5	75.5	80.5	156	2.31	1.79	−1.24	−1.24	1.62	33	10	3.3
20	Ph	*n*-Pr	3	1.8	4.8	75.5	61.9	137.4	2.31	0.31	−1.24	−1.24	0.14	47	10	4.7
21	Ph	*n*-Pr	3	1.8	4.8	75.5	61.9	137.4	2.31	0.31	−1.24	−1.24	0.14	77	15	5.13
22	Ph	*i*-Pr	3	2.15	5.15	75.5	101.6	177.1	2.31	0.48	−1.24	−1.24	0.31	72	15	4.8
23	Ph	*i*-Pr	3	2.15	5.15	75.5	101.6	177.1	2.31	0.48	−1.24	−1.24	0.31	45	10	4.5
24	Ph	CF_3	3	2.1	5.1	72.1	101.6	173.7	0.78	2.31	−1.24	−1.24	0.61	63	15	4.2
25	Ph	CF_3	3	2.1	5.1	72.1	101.6	173.7	0.78	2.31	−1.24	−1.24	0.61	47	10	4.7
26	Ph	CF_3	3	2.1	5.1	72.1	101.6	173.7	0.78	2.31	−1.24	−1.24	0.61	25	5	5.0
27	Ph	CF_3	3	2.1	5.1	72.1	101.6	173.7	0.78	2.31	−1.24	−1.24	0.61	8	2	4.0
28	Ph	CF_3	3	2.1	5.1	72.1	101.6	173.7	0.78	2.31	−1.24	−1.24	0.61	32	7	4.6
29	Ph	CF_3	3	2.1	5.1	72.1	101.6	173.7	0.78	2.31	−1.24	−1.24	0.61	50	12	4.17

A-value data used may be found in following references.[390–392] Assumed A(*n*-Pr) = A(*n*-Bu) = A(Et). Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

Table S10: Alternate diyne Steric screen data



	X	R_1	R_2	$A(R_1)$	$A(R_2)$	Σ(Alkynes[A])	Yield (%)	Rh loading	RTO
1	O	*n*-Bu	H	1.8	0	1.8	20	2	10
2	O	Ph	H	3	0	3	68	10	6.8
3	O	Ph	*n*-Pr	3	1.8	4.8	74	20	3.7
4	O	Ph	*i*-Pr	3	2.15	5.15	64	20	3.2
5	O	Ph	TMS	3	2.5	5.5	32	20	1.6
6	O	*t*-Bu	Ph	4.7	3	7.7	0	20	0
7	$(CO_2Et)_2$	*n*-Bu	H	1.8	0	1.8	55	5	11
8	$(CO_2Et)_2$	Ph	H	3	0	3	64	10	6.4
9	$(CO_2Et)_2$	Ph	*n*-Pr	3	1.8	4.8	70	20	3.5
10	$(CO_2Et)_2$	Ph	*i*-Pr	3	2.15	5.15	41	20	2.05
11	$(CO_2Et)_2$	Ph	TMS	3	2.5	5.5	42	20	2.1
12	$(CO_2Et)_2$	*t*-Bu	Ph	4.7	3	7.7	0	20	0

A-value data used may be found in following references.[390–392] Assumed A(*n*-Pr) = A(*n*-Bu) = A(Et). Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

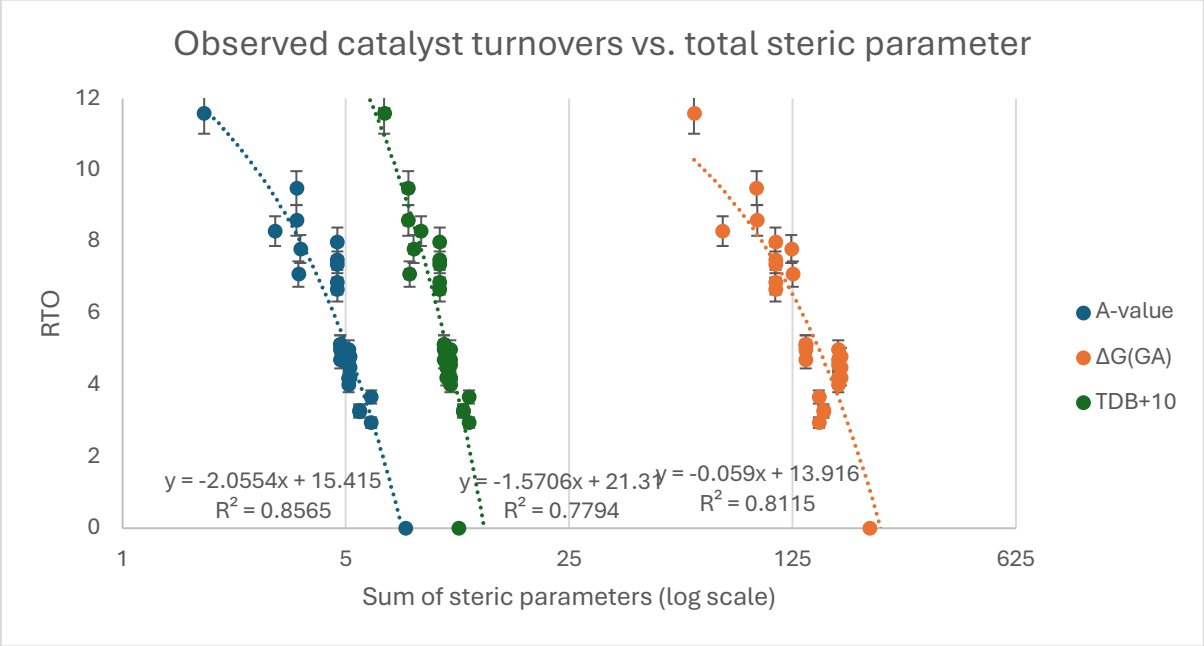


Figure S5: Correlation between RTO and A-value.

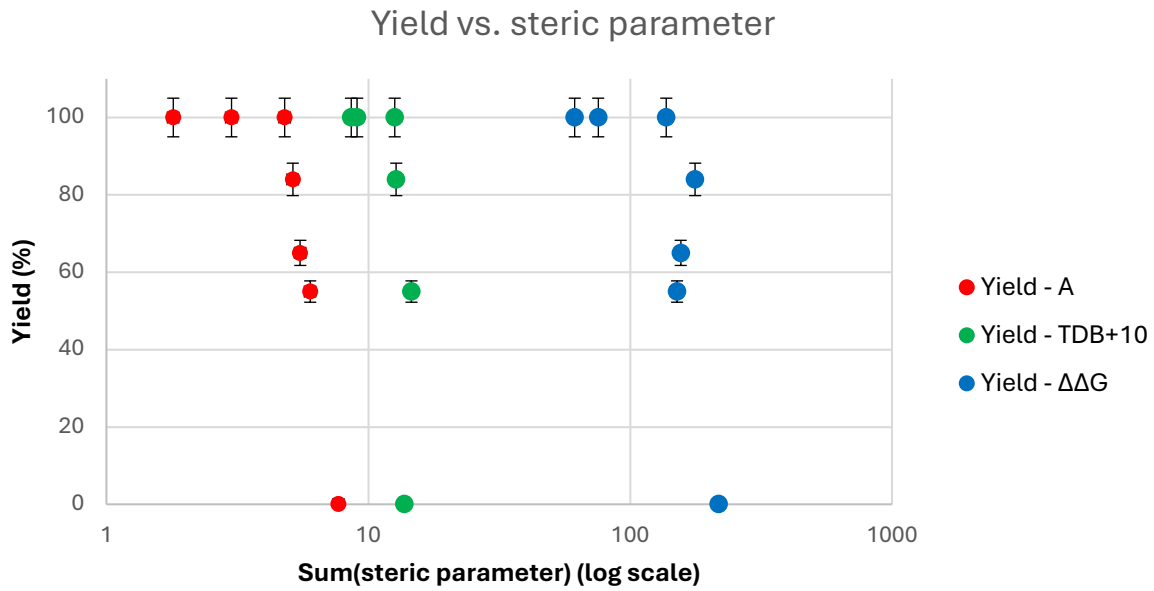


Figure S6: Correlation between yield and sum of steric parameter. Plateau occurs when too much rhodium catalyst is used.

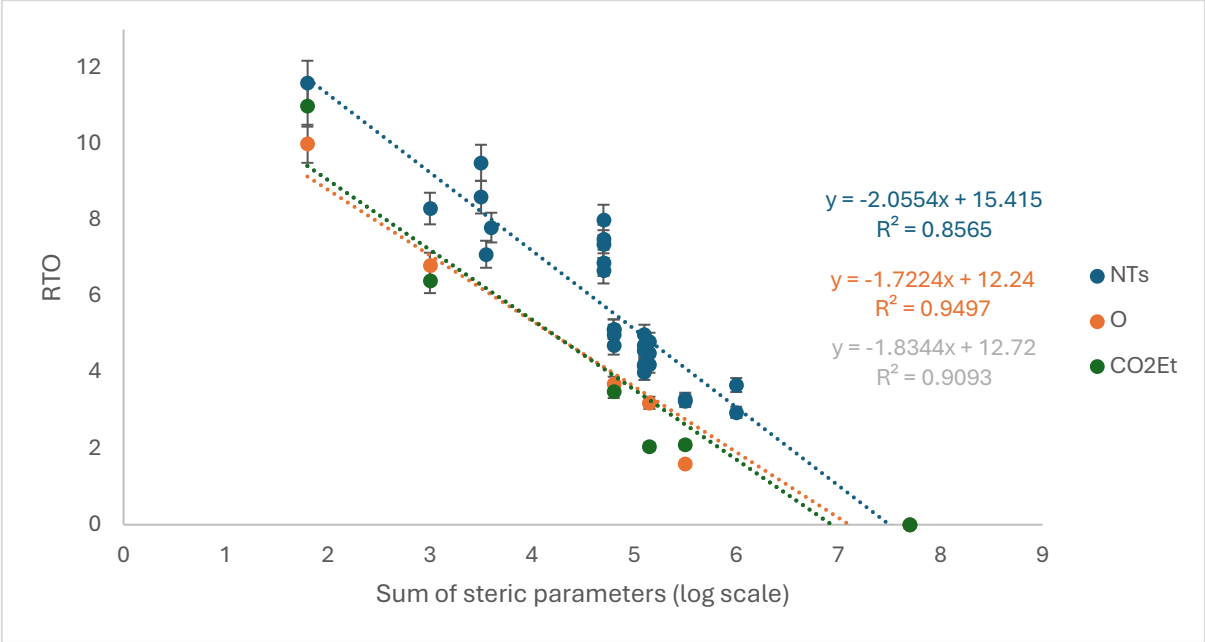
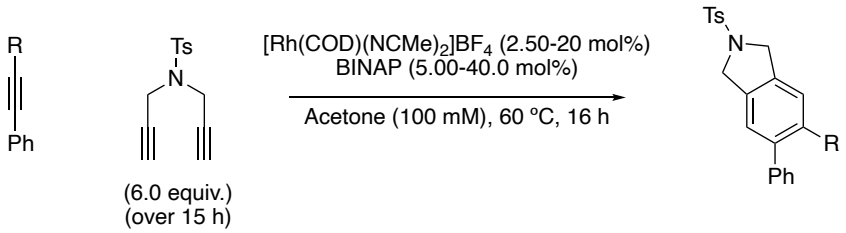


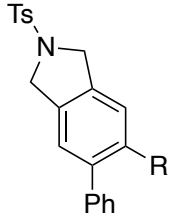
Figure S7: Correlation between RTO and A-value with other dialkynes

7.7. Chelation Paramaterisation Data



An oven-dried microwave vial was charged with the relevant internal alkyne (100 µmol, 1.00 equiv.), $[Rh(COD)(NCMe)_2]BF_4$ and *rac*-BINAP before sealing, evacuating, and backfilling with N_2. Distilled acetone ([100 mM]/2) was added and the mixture was heated to 60 ºC for 10 min. A separate dried flask was charged with 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.) under N_2 before distilled acetone ([100 mM]/2) was added. This solution was added to the microwave vial at 60 ºC over 15 h. After addition complete, the solution was allowed to stir for a further hour before filtering through celite and concentrating *in vacuo* to yield the crude product. *d*-Chloroform (~1.00 mL) was added followed by trichloroethylene (9.00 µL, 100 µmol, 1.00 equiv.). This solution was mixed until homogeneous then a small portion (~100 µL) was taken and diluted with more *d*-chloroform for analysis by quantitative ^1H NMR.

Table S11: Chelation data



Entry	R	Rh loading (mol%)	Yield	RTO
1	Me	20	100	5.00
2	Me	15	100	6.67
3	Me	11	81	7.36
4	Me	8	55	6.88
5	Me	5	40	8.00
6	Me	2	15	7.50
7	CH_2OH	20	100	5.00
8	CH_2OH	15	88	5.87
9	CH_2OH	10	80	8.00
10	CH_2OH	5	74	14.8
11	CH_2OH	2	76	38.0
22	CO_2Me	20	100	5.00
23	CO_2Me	15	100	6.67
24	CO_2Me	10	82	8.20
25	CO_2Me	8	75	8.38
26	CO_2Me	5	64	12.8
27	CO_2Me	2	55	27.5
28	CF_3[a]	15	63	4.20
29	CF_3[a]	10	47	4.70
30	CF_3[a]	5	25	5.00
31	CF_3[a]	2	8	4.00
32	CF_3[a]	7	32	4.57
33	CF_3[a]	12	50	4.17
35	CH(OH)Me	20	78	3.90
36	CH(OH)Me	15	70	3.67
37	CH(OH)Me	10	62	6.2
38	CH(OH)Me	5	55	11.0
39	CH(OH)Me	2	50	25.0
40	CH(OH)Ph	20	82	4.10
41	CH(OH)Ph	15	80	5.33
42	CH(OH)Ph	10	70	7.00
43	CH(OH)Ph	5	59	11.8
44	CH(OH)Ph	2	42	21.0
45	CH_2OTBS	20	90	4.5
46	CH_2OTBS	15	87	5.8
47	CH_2OTBS	10	85	8.5
48	CH_2OTBS	5	71	14.2
49	CH_2OTBS	2	65	32.5

50	CH_2OAc	20	82	4.1
51	CH_2OAc	15	74	4.93
52	CH_2OAc	10	69	6.85
53	CH_2OAc	5	64	12.7
54	CH_2OAc	2	64	32
55	$(CH_2)_2OH$	20	95	4.75
56	$(CH_2)_2OH$	15	84	5.6
57	$(CH_2)_2OH$	10	71	7.1
58	$(CH_2)_2OH$	5	67	13.4
59	$(CH_2)_2OH$	2	57	28.5
60	$(CH_2)_3OH$	15	84	5.6
61	$(CH_2)_3OH$	12	75	6.25
62	$(CH_2)_3OH$	10	59	5.9
63	$(CH_2)_3OH$	5	50	10
64	$(CH_2)_3OH$	2	39	19.5
65	$(CH_2)_4OH$	20	90	4.5
66	$(CH_2)_4OH$	15	74	4.93
67	$(CH_2)_4OH$	10	59	5.9
68	$(CH_2)_4OH$	5	24	7
69	$(CH_2)_4OH$	2	22	11
70	$(CH_2)_5OH$	20	100	5
71	$(CH_2)_5OH$	15	66	4.4
72	$(CH_2)_5OH$	10	61	6.1
73	$(CH_2)_5OH$	5	39	7.8
74	$(CH_2)_5OH$	2	12	6
75	$(CH_2)_6OH$	20	90	4.5
76	$(CH_2)_6OH$	10	47	4.7
77	$(CH_2)_6OH$	5	21	4.2
78	$(CH_2)_6OH$	2.5	11	4.4
79	$(CH_2)_8OH$	20	94	4.7
80	$(CH_2)_8OH$	10	48	4.8
81	$(CH_2)_8OH$	5	29	5.8
82	$(CH_2)_8OH$	2.5	12	4.8
83	$CH(OEt)_2$	20	100	5
84	$CH(OEt)_2$	15	83	5.3
85	$CH(OEt)_2$	10	63	6.3
86	$CH(OEt)_2$	8	45	5.63
87	$CH(OEt)_2$	2	10	5
88[b]	*n*-Pr	20	100	5
89[b]	*n*-Pr	15	100	6.67
90[b]	*n*-Pr	10	100	10
91[b]	*n*-Pr	5	98	19.6
92[b]	*n*-Pr	2	94	47
93[c]	*n*-Bu	20	91	4.56
94[c]	*n*-Bu	15	74	4.93
95[c]	*n*-Bu	10	45	4.5

96[c]	*n*-Bu	8	37	4.63
97[c]	*n*-Bu	5	33	6.6
98[d]	*n*-Pr	20	96	4.8
99[d]	*n*-Pr	15	93	6.2
100[d]	*n*-Pr	10	93	9.3
101[d]	*n*-Pr	5	83	16.6
102[d]	*n*-Pr	2	60	30
103[e]	*n*-Pr	20	35	1.75
104[e]	*n*-Pr	15	13	0.87
105[e]	*n*-Pr	10	5	0.5
107[e]	*n*-Pr	5	0	0

[a]4-biphenyl substitution instead of phenyl. [b]pyrimidin-2-yl instead of phenyl. [c]4-hydroxymethylphenyl instead of phenyl. [d]pyridin-2-yl instead of phenyl. [e]pyridin-3-yl instead of phenyl. Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

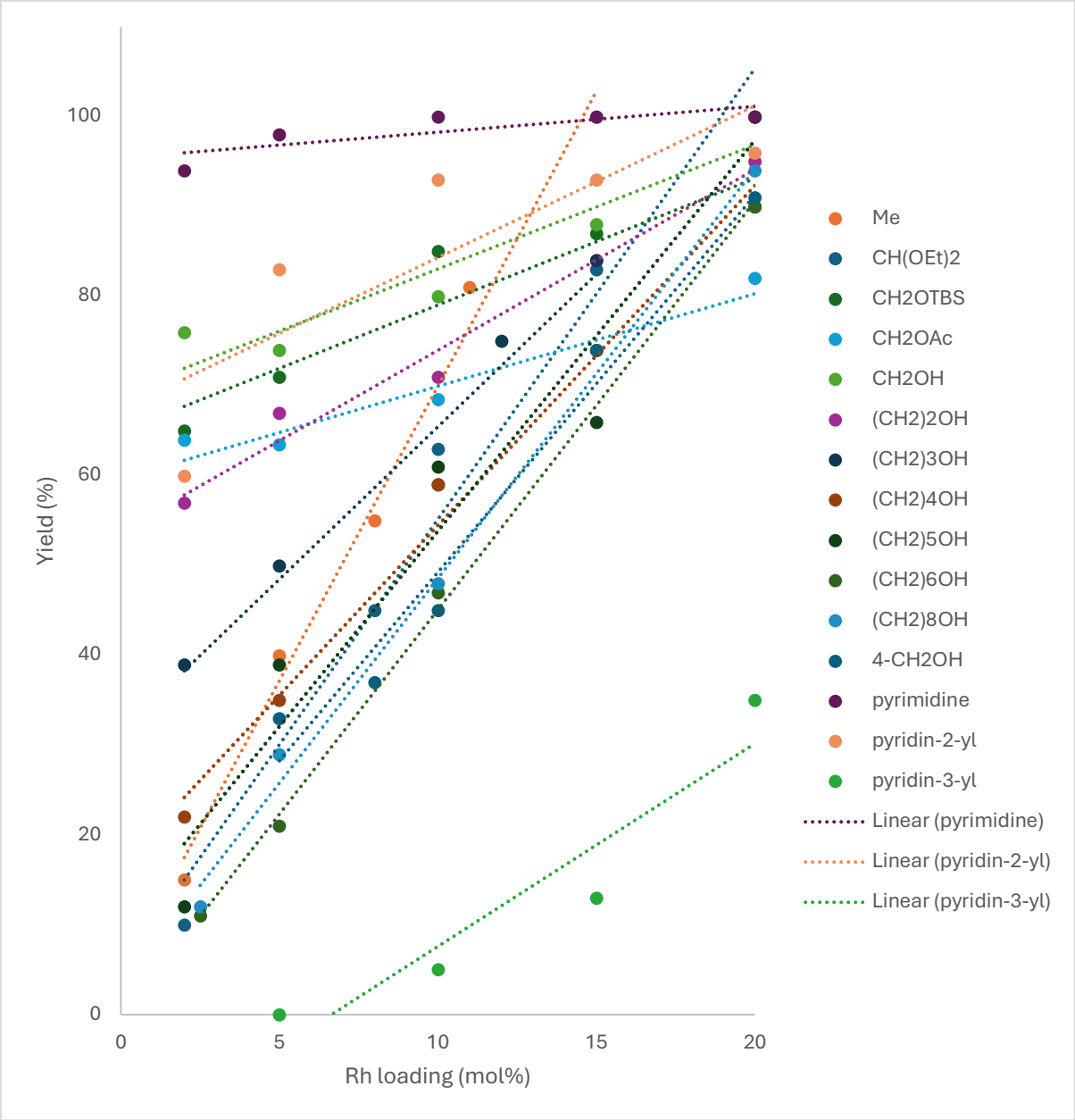
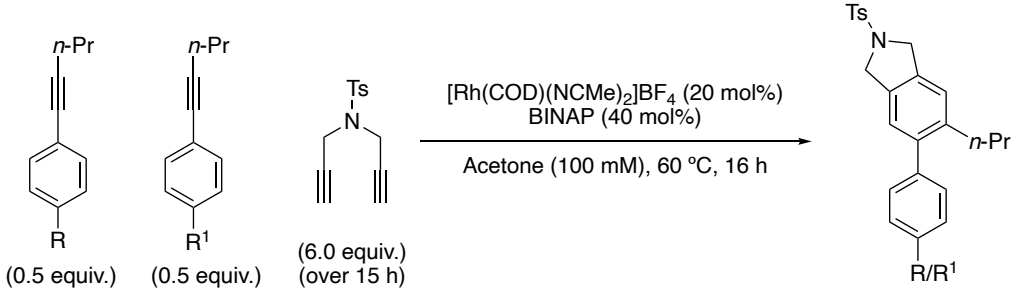


Figure S8: Chelation effect data.

7.8. Electronic Competition Experiments



An oven-dried microwave vial was charged with the one internal alkyne (50 µmol, 0.5 equiv.), the competing internal alkyne (50 µmol, 0.5 equiv.), $[Rh(COD)(NCMe)_2]BF_4$ and *rac*-BINAP before sealing, evacuating, and backfilling with N_2. Distilled acetone ([100 mM]/2) was added and the mixture was heated to 60 ºC for 10 min. A separate dried flask was charged with 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.) under N_2 before distilled acetone ([100 mM]/2) was added. This solution was added to the microwave vial at 60 ºC over 15 h. After addition complete, the solution was allowed to stir for a further hour before filtering through celite and concentrating *in vacuo* to yield the crude product. *d*-Chloroform (~1.00 mL) was added followed by trichloroethylene (9.00 µL, 100 µmol, 1.00 equiv.). This solution was mixed until homogeneous then a small portion (~100 µL) was taken and diluted with more *d*-chloroform for analysis by quantitative ^{1}H NMR.

Table S12: Competition experiments data.[389]

Entry	R	R^1	σ_p (R)	σ_p (R^1)	$\Delta\sigma_p$	Yield R (%)[a]	Yield R^1 (%)[a]	Ratio (R:R^1)
1	OMe	CF_3	−0.27	0.54	0.81	42	41	1.02
2	F	CF_3	0.06	0.54	0.48	37	34	1.09
3	H	CF_3	0	0.54	0.54	35	38	0.91
4	NMe_2	H	−0.83	0	0.83	38	31	1.22
5	OMe	H	−0.27	0	0.27	43	42	1.04
6	H	F	0	0.06	0.06	20	20	1.00
7	H	Cl	0	0.23	0.23	33	32	1.04
8	NMe_2	CF_3	−0.83	0.54	1.37	30	38	0.79

[a]Yields determined by ^{1}H NMR assay using trichloroethylene as an internal standard.

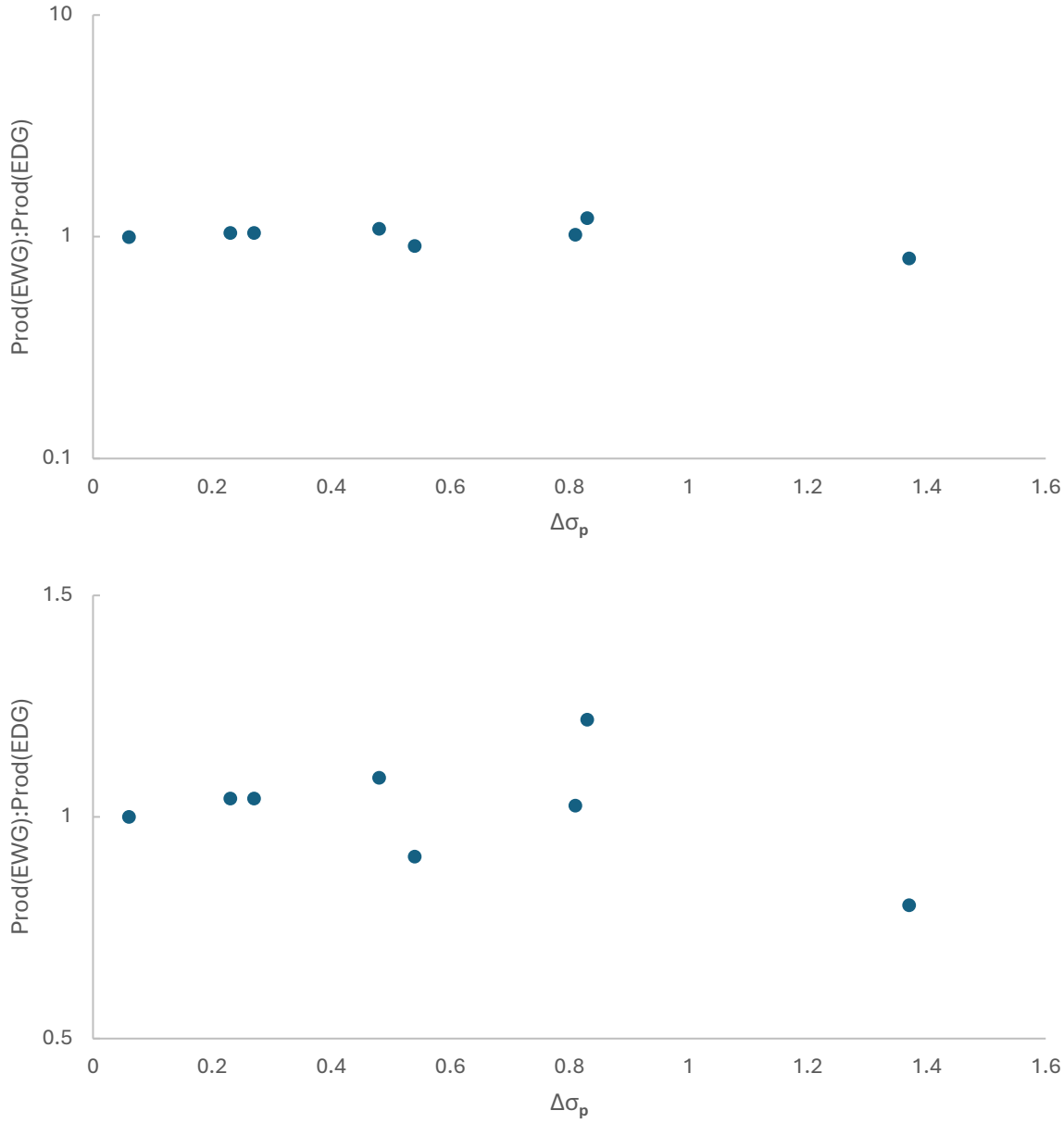
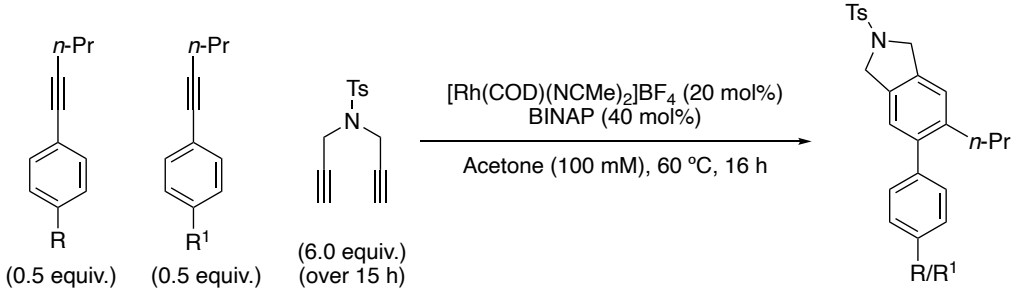


Figure S9: Competition experiments data. Above = logarithmic ordinate (base 10), below = linear ordinate.

7.9. Electronic Competition Experiments Ratio Monitoring



An oven-dried microwave vial was charged with the one internal alkyne (100 µmol, 0.50 equiv.), the competing internal alkyne (100 µmol, 0.50 equiv.), $[Rh(COD)(NCMe)_2]BF_4$ and *rac*-BINAP before sealing, evacuating, and backfilling with N_2. Distilled acetone (1.0 mL) was added, and the mixture was heated to 60 ºC for 10 min. A separate dried flask was charged with 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (6.00 equiv.) under N_2 before distilled acetone (1.0 mL) was added. This solution was added to the microwave vial at 60 ºC over 15 h. A small sample of the reaction mixture was taken (assume that this volume does not significantly change concentration) at regular intervals, concentrated *in vacuo*, and analysed by quantitative ^{1}H NMR.

Table S17: Competition product formation over time (F *vs*. CF_3)

Time (h)	Yield F (%)	Yield CF_3 (%)	Yield F/Yield CF_3
0	0	0	
0.5	5.2	3.1	1.67
1	6.6	5.0	1.32
2	10.1	5.3	1.90
3	11.5	12.0	0.96
4	17.7	11.1	1.60
5	17.9	14.5	1.24
6.167	23.9	15.1	1.58
7.25	21.0	18.4	1.14
8	23.1	16.9	1.36
16	25.6	22.7	1.13

Table S18: Competition product formation over time (OMe *vs*. CF_3)

Time (h)	Yield OMe (%)	Yield CF_3 (%)	Yield OMe/Yield CF_3
0	0	0	
0.5	6.9	5.7	1.19
1	8.4	6.6	1.27
2	13.7	9.7	1.41
3	16.9	14.0	1.21
4	20.2	15.5	1.30
5	21.7	17.3	1.25
6.167	24.2	17.5	1.38
7.25	24.2	17.7	1.37
8	23.5	19.8	1.19
16	26.1	22.2	1.2

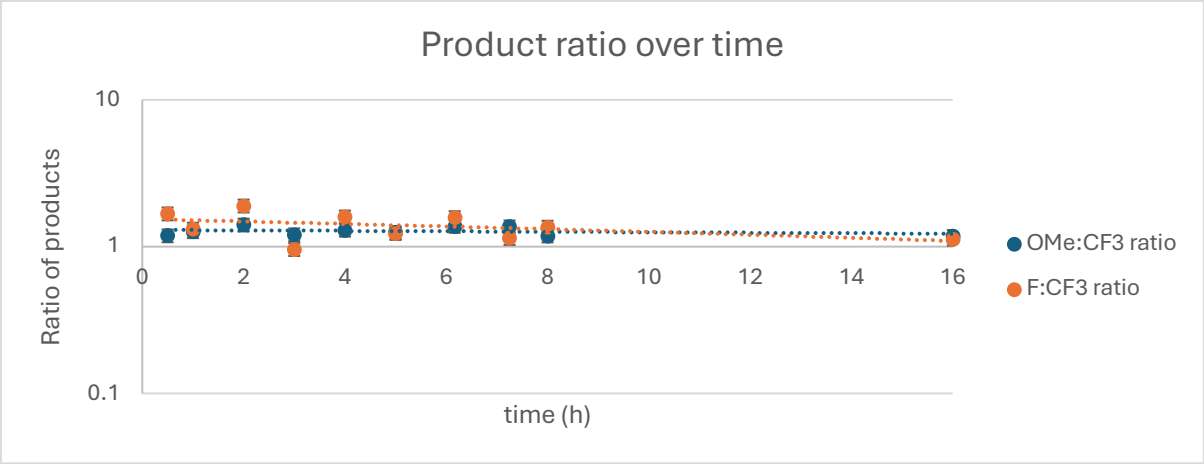
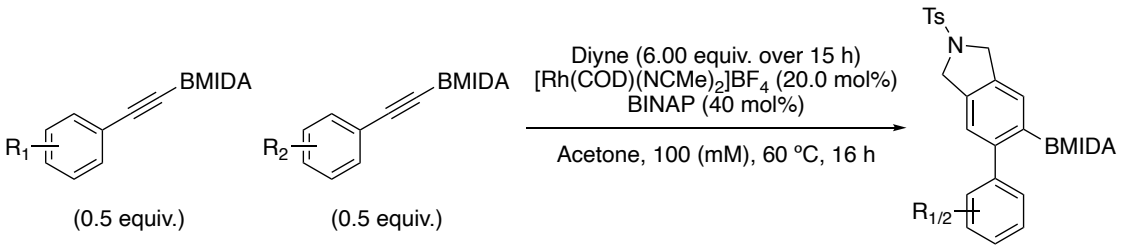


Figure S14: Product ratio over course of reaction.

7.10. General Procedure for Electronic Competition Experiments (BMIDA)



An oven-dried microwave vial was charged with the relevant BMIDA alkyne (50.0 µmol, 0.50 equiv.) and its competing partner BMIDA alkyne (50.0 µmol, 0.50 equiv.). $[Rh(COD)(NCMe)_2]BF_4$ (7.6 mg, 20.0 µmol, 20.0 mol%), and BINAP (24.9 mg, 40.0 µmol, 40.0 mol%) were added and the vial was capped, evacuated, and backfilled with N_2. Acetone (0.5 mL) was added to the vial and then heated to 60 °C. A separate flask was charged with 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.) and acetone (0.5 mL) was added. The diyne solution was added *via* syringe pump over 15 h and the final solution was stirred for 1 h before allowing to cool to RT, filtering through celite, and concentrating *in vacuo* to yield the crude mixture. 1,4-dinitrobenzene (4.8 mg, 25.0 µmol, 0.25 equiv.) added and d_6-acetone was added until the mixture was homogeneous, then a sample was taken for quantitative NMR analysis to determine the product ratio.

Table S20: Electronic competition experiments results.[389]

Entry	R_1	R_2	$\sigma(R_1)$	$\sigma(R2)$	$\Delta\sigma$	Yield (R_1)	Yield (R_2)	Ratio (R_1/R_2)
1	H	4-OMe	0	-0.27	0.27	38	39	0.9744
2	4-OAc	H	0.31	0	0.31	26	29	0.8966
3	4-OAc	4-OMe	0.31	-0.27	0.58	37	39	0.9487
4	3-Ac	H	0.38	0	0.38	12	15	0.8000
5	3-Ac	4-OMe	0.38	-0.27	0.65	15	16	0.9375
6	3-Ac	4-OAc	0.38	0.31	0.07	53	58	0.9138

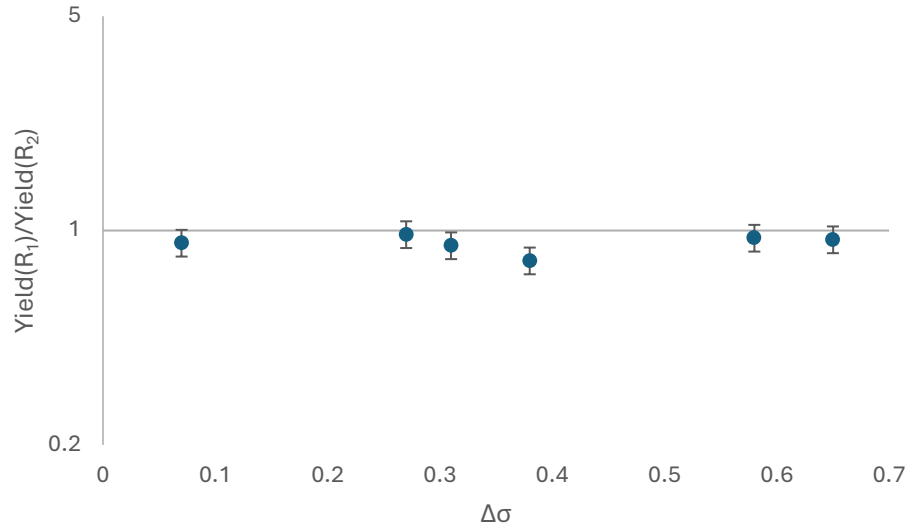
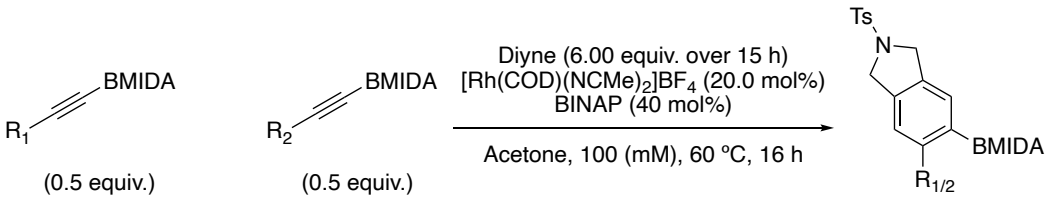


Figure S20: Electronic competition experiments results.

7.11. General Procedure for Steric Competition Experiments (BMIDA)



An oven-dried microwave vial was charged with the relevant BMIDA alkyne (50.0 µmol, 0.50 equiv.) and its competing partner BMIDA alkyne (50.0 µmol, 0.5 equiv.). $[Rh(COD)(NCMe)_2]BF_4$ (7.6 mg, 20.0 µmol, 20.0 mol%), and BINAP (24.9 mg, 40.0 µmol, 40.0 mol%) were added and the vial was capped, evacuated, and backfilled with N_2. Acetone (0.5 mL) was added to the vial and then heated to 60 ºC. A separate flask was charged with 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.00 equiv.) and acetone (0.5 mL) was added. The diyne solution was added *via* syringe pump over 15 h and the final solution was stirred for 1 h before allowing to cool to RT, filtering through celite, and concentrating *in vacuo* to yield the crude mixture. 1,4-dinitrobenzene (4.8 mg, 25.0 µmol, 0.25 equiv.) was added and d_6-acetone was added until the mixture was homogeneous, then a sample was taken for quantitative NMR analysis to determine the product ratio.

Table S21: Steric competition experiments results.[390–392]

Entry	R_1	R_2	$A(R_1)$	A(R2)	ΔA	NMR yield (R_1)	NMR yield (R_2)	Ratio (R_1/R_2)
1	Me	*c*-Pr	1.7	2.15	0.45	37	31	1.19
2	Me	Ph	1.7	3	1.3	50	20	2.50
3	*c*-Pr	Ph	2.15	3	0.85	46	27	1.70
4	Me	*n*-Pr	1.7	1.8	0.1	39	30	1.30
5	*n*-Pr	*c*-Pr	1.8	2.15	0.35	30	21	1.42
6	*n*-Pr	Ph	1.8	3	1.2	24	16	1.50

Assumed A(*c*-Pr) = A(*i*-Pr) = 2.15; A(*n*-Pr) = A(Et) = 1.8.

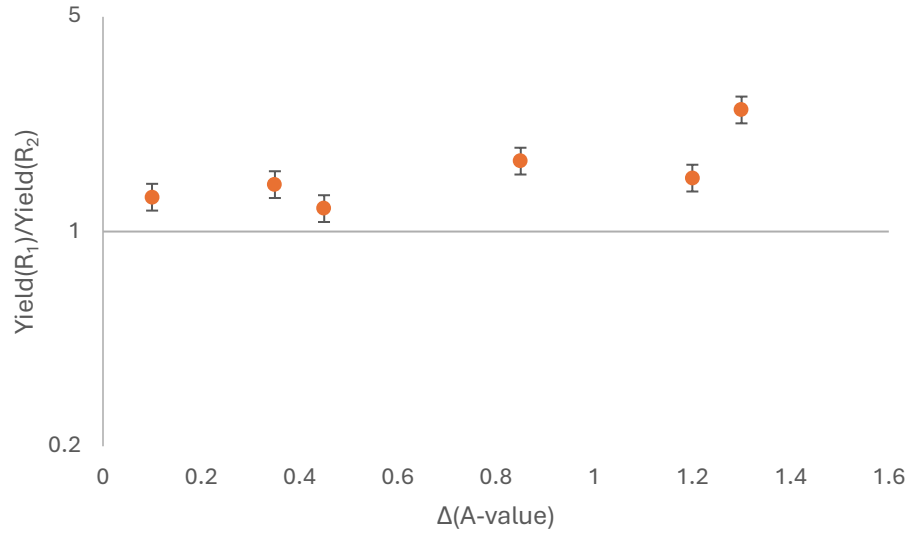


Figure S22: Steric competition experiments results.

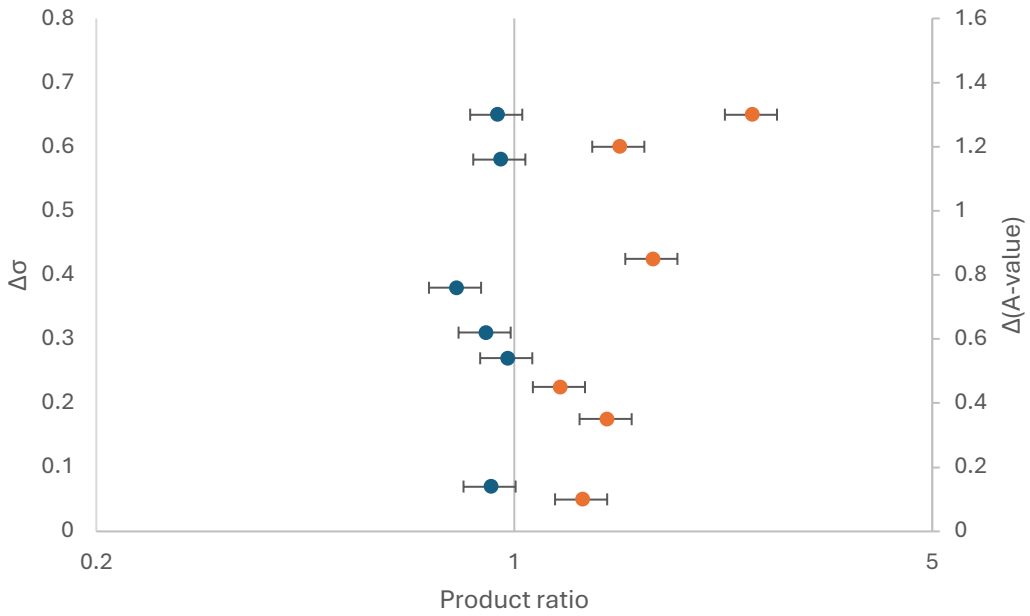
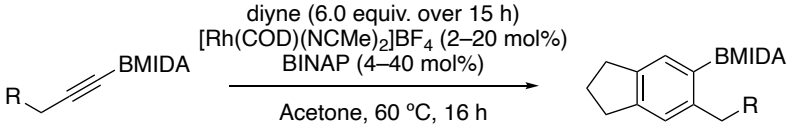


Figure S23: Combined data results from **Figures 1** and **2.**

7.12. Chelation Data (BMIDA)

Table S22: Chelation data of various alkynyl BMIDAs



Entry	R	Rh loading (mol%)	Yield (%)	RTO
1	H	20	68	3.4
2	H	15	50	3.3
3	H	10	25	2.5
4	H	5	18	3.6
5	H	2	6	3.0
6	OTBS	20	50	2.5
7	OTBS	15	45	3.0
8	OTBS	10	39	3.9
9	OTBS	5	30	6.0
10	OTBS	2	24	12.0
11	OH	20	99	4.95
12	OH	15	86	5.73
13	OH	10	81	8.1
14	OH	5	69	13.8
15	OH	2	37	18.5

[a]Yields determined by ^{1}H NMR assay using 1,4-dinitrobenzene as an internal standard.

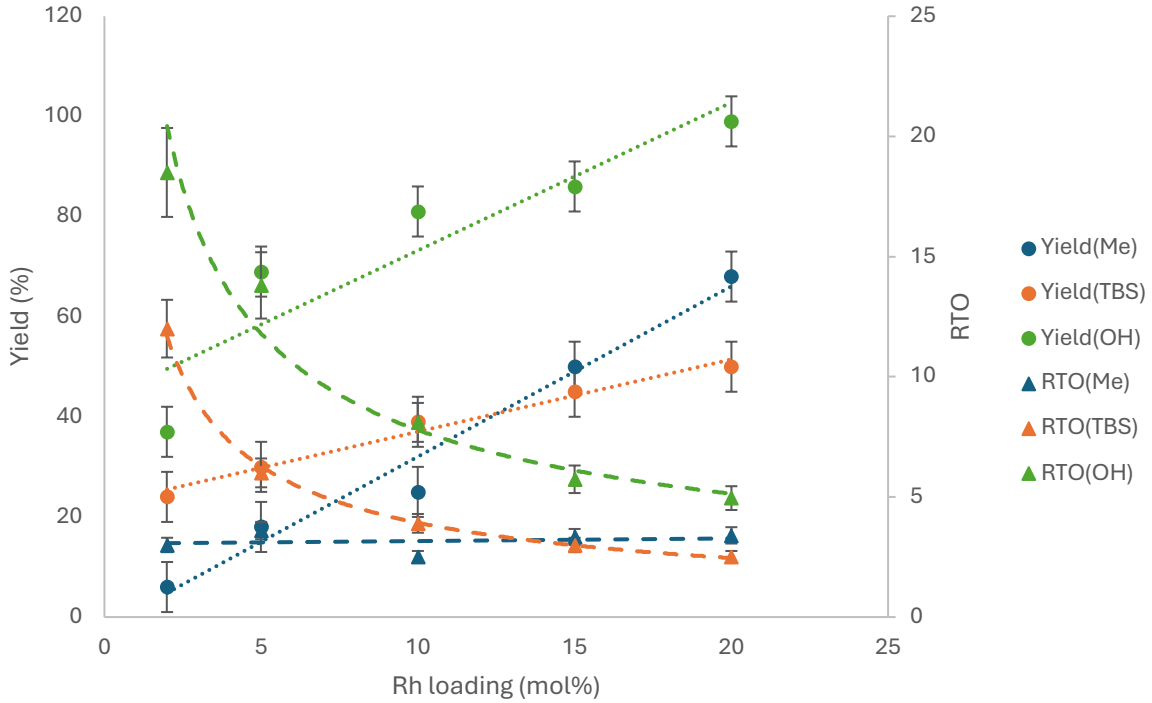


Figure S24: Graph of Yield and RTO vs Rh loading (errors bars refer to standard 5% error in NMR spectroscopy).

7.13. X-ray Diffraction Data

X-ray diffraction data for compound **4.211(he)**, and **4.211(ho)** were collected at 100 and 173 K using a Rigaku FR-X Ultrahigh Brilliance Microfocus RA generator/confocal optics with XtaLAB P200 diffractometer [Mo Kα radiation (λ = 0.71073 Å)]. Data for all compounds analysed were collected (using a calculated strategy) and processed (including correction for Lorentz, polarisation, and absorption) using CrysAlisPro.[393] Structures were solved by dual-space methods (SHELXT[394]) and refined by full-matrix least-squares against F^2 (SHELXL-2019/3[395]). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using a riding model. All calculations were performed using the Olex2[396] interface. X-ray diffraction data for compounds **4.137** and **4.240** were collected at 173 K using a Rigaku MM-007HF High Brilliance RA generator/confocal optics with XtaLAB P200 diffractometer [Cu Kα radiation (λ = 1.54187 Å)]. Data for compounds **4.209, 4.241** and **4.247** were collected at 173 K using a Rigaku FR-X Ultrahigh Brilliance Microfocus RA generator/confocal optics with XtaLAB P200 diffractometer [Mo Kα radiation (λ = 0.71075 Å)]. Intensity data for all compounds were collected using ω steps accumulating area detector images spanning at least a hemisphere of reciprocal space. Data were collected using CrystalClear[397] or CrysAlisPro[393] and processed (including correction for Lorentz, polarisation, and absorption) using CrysAlisPro. The structure was solved by direct (SIR2011[398]) or dual-space (SHELXT[394]) methods and refined by full-matrix least-squares against F^2 (SHELXL-2013[395]). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using a riding model. The structure of **4.247** showed disorder in the orientation of the tricyclic ring system which was modelled over two sites with occupancies of 0.55:0.45. Restraints to bond distances and to thermal motion were used for the disordered atoms. Selected crystallographic data are presented in **Table S25**, along with the corresponding CCDC deposition numbers. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Table S25. Selected crystallographic data.

	4.137	**4.209**	**4.211 (he)**	**4.211 (ho)**	**4.240**	**4.241**	**4.247**
formula	$C_{49}H_{52}Cl_2N_2O_4S_2$	$C_{22}H_{27}NO_2S$	$C_{91}H_{70}BCl_6F_4P_4Rh$	$C_{89}H_{66}BCl_2F_4P_4Rh$	$C_{22}H_{26}BNO_6$	$C_{17}H_{22}BNO_6$	$C_{17}H_{17}NO_3S$
fw	867.99	369.50	1689.77	1519.91	411.25	347.16	315.37
crystal description	Colourless prism	Colourless prism	Yellow prism	Red prism	Colourless plate	Colourless prism	Colourless plate
crystal size [mm^3]	0.10×0.10×0.10	0.31×0.05×0.02	0.05×0.03×0.01	0.06×0.04×0.03	0.15×0.04×0.01	0.07×0.04×0.02	0.30×0.24×0.03
space group	*P*-1	*I*2/a	$\bar{P}1$	*C*2/c	*Pc*	$P2_1/c$	$P2_1/c$
a [Å]	9.9402(5)	24.7901(11)	11.8853(3)	23.8207(10)	15.3311(2)	13.1060(4)	15.1250(4)
b [Å]	12.7171(7)	5.0588(2)	12.7651(3)	15.1455(10)	10.06926(11)	9.9589(3)	7.7985(2)
c [Å]	18.3349(10)	29.9976(11)	15.0023(4)	22.7761(8)	13.62417(19)	13.1775(5)	12.6248(3)
α [°]	87.852(4)	90	113.887(3)				
β [°]	83.866(4)	98.524(4)	91.812(2)	110.748(4)	101.3120(13)	91.771(4)	95.692(2)
γ [°]	75.096(3)	90	109.247(2)				
vol [Å]^3	2226.8(2)	3720.4(3)	1928.57(10)	7684.1(7)	2062.35(5)	1719.14(10)	1481.78(7)
Z	2	8	1	4	4	4	4
ρ (calc) [g/cm^3]	1.294	1.319	1.455	1.314	1.324	1.341	1.414
μ [mm^{-1}]	0.286	0.191	0.570	0.430	0.782	0.100	0.231
F(000)	916.0	1584.9	864.0	3120.0	872	736	664
reflections collected	38509	23510	42240	42395	29685	11853	19815
independent reflections (R_{int})	8108 (0.0222)	6645 (0.0691)	9015 (0.0472)	9053 (0.0568)	7388 (0.0267)	3951 (0.0257)	3514 (0.0405)
parameters, restraints	538, 0	236, 0	576, 80	593, 226	549, 2	230, 0	300, 380
GooF on F^2	1.029	1.024	1.021	1.096	1.061	1.034	0.1017
R_1 [$I > 2\sigma(I)$]s	0.0473	0.0619	0.0388	0.0616	0.0430	0.0402	0.0393
wR_2 (all data)	0.0534	0.1103	0.0868	0.1815	0.1224	0.1031	0.1017
largest diff. peak/hole [e/Å^3]	0.75/-0.75	0.28/-0.33	0.67/-0.45	1.17/-0.40	0.498, -0.164	0.296, -0.164	0.299, -0.339
Flack parameter					-0.04(7)		
CCDC	2164403		23332665	23332665	2181492	2181493	2181494

8.0. References

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