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Late transition metals in the synthesis of arenes and heteroarenes

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Contents

Abstract

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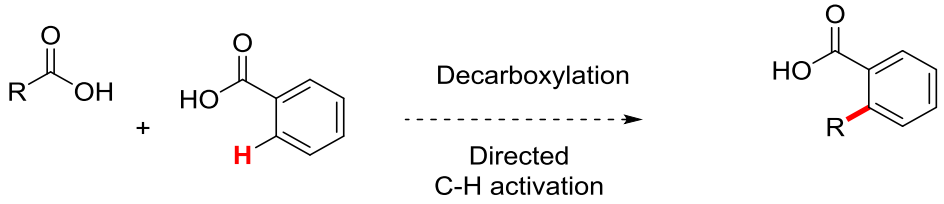
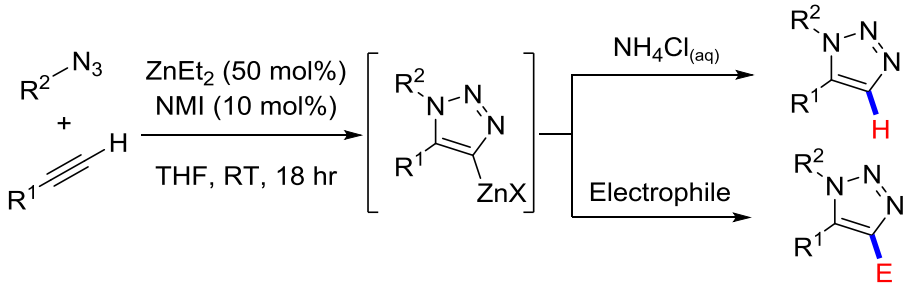
The use of transition metals in synthesis is an incredibly useful tool for organic chemists. Co-ordination of a metal can occur with most function groups in some manner resulting in dramatic changes in the reactivity.

Decarboxylative cross-couplings provide a new route to the construction of C–C bonds without the necessity of costly organometallic precursors. Similarly C–H activation provides an environmentally and economically desirable method to cross-coupling products, and this can be facilitated by the presence of *ortho*-directing groups. The decarboxylative coupling of carboxylic acids, combined with carboxylate directed C–H activation has been investigated to demonstrate *ortho*-arylation and acylation of benzoic acids. In doing so the different functionality of the carboxylate group is demonstrated in one process.



Following this, a mild $ZnEt_2$ mediated 1,5-substituted 1,2,3-triazole formation reaction has been investigated. Significantly, this method is compatible with many different substrates including halides, esters, nitriles, ketones and amides which have proven to be incompatible with analogous Mg or Li methods. The resultant heteroaryl zinc can be utilised further in cross-coupling reactions, or with other electrophiles, enabling the formation of a wide range of substituted triazoles.



Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning

Copyright Statement

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Abbreviations

Ac	-	acetyl
acac	-	acetylacetone
AcOH	-	acetic acid
Ad	-	adamantyl
Ar	-	aryl
atm	-	atmosphere
BDTBPMB	-	palladium-1,2-bis-(di-tert-butylphosphinomethyl)benzene
BINAP	-	2,2'-*bis*(diphenylphosphino)-1,1'-binapthyl
Boc	-	*tert*-butoxycarbonyl
BOX	-	bis(oxazoline)
BQ	-	benzoquinone
Brettphos	-	2-(dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
n-BuLi	-	*n*-butyl lithium
s-BuLi	-	*s*-butyl lithium
^{t}Bu	-	*tert*-butyl
^{t}BuOH	-	*tert*-butanol
^{t}BuXPhos	-	[2-(Di-*tert*-butylphosphino)-2′,4′,6′-triisopropyl-1,1′-biphenyl][2-(2-aminoethyl)phenyl)]palladium(II) chloride
Bz	-	benzoyl
cat	-	catalytic
Cp	-	cyclopentyldienyl
Cp*	-	pentamethylcyclopentadiene
cod	-	cyclooctadiene

CuAAC	-	Copper-Catalyzed Azide-Alkyne Cycloaddition
dba	-	dibenzylideneacetone
DBU	-	1,8-diazabicycloundec-7-ene
DCM	-	dichloromethane
DCPE	-	1,2-bis(dicyclohexylphosphino)ethane
DFT	-	density functional theory
DG	-	directing group
DIPEA	-	*N,N*-diisopropylethylamine
DiPhen	-	4,7-diphenyl-1,10-phenanthroline
DMA	-	*N,N*-dimethylacetamide
DMAP	-	4-dimethylaminopyridine
DME	-	dimethoxyethane
DMEDA	-	*N,N*-dimetylethane-1,2-diamine
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
dppp	-	1,3-bis(diphenylphosphino)propane
EDG	-	electron donating group
eq	-	equivalent
Et	-	ethyl
EtOAc	-	ethyl acetate
EWG	-	electron withdrawing group
Fmoc	-	fluorenylmethyloxycarbonyl

FTIR	-	fourier transform infra-red spectroscopy
het	-	heteroaryl
HMDS	-	hexamethyldisilazane
HMPA	-	hexamethylphosphoramide
hr/hrs	-	hours
KHMDS	-	potassium bis(trimethylsilyl)amide
LCMS	-	liquid chromatography mass spectrometry
LDA	-	lithium diisopropylamide
LiHMDS	-	lithium bis(trimethylsilyl)amide
M	-	molar
Me	-	methyl
MeCN	-	acetonitrile
MeOH	-	methanol
min	-	minutes
MP	-	melting point
MW/μW	-	microwave
NBS	-	*N*-bromosuccinimide
NCS	-	*N*-chlorosuccinimide
NFSI	-	*N*-fluorobenzenesulfonimide
NHC	-	*N*-heterocyclic carbene
NIS	-	*N*-iodosuccinimide
NMI	-	*N-methylimidazole*
NMP	-	*N*-methylpyrrolidone
NMR	-	nuclear magnetic resonance
OMs	-	mesylate
OTf	-	triflate

OTs	-	tosylate
PCy_3	-	tricyclohexylphosphine
PEPPSI-^{i}Pr	-	[1,3-bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
Ph	-	phenyl
Phen	-	1,10-phenanthroline
PivOH	-	pivalic acid
P(*o*-furyl)$_3$	-	tri-*ortho*-furylphosphine
P(*o*-tol)$_3$	-	tri-*ortho*-tolylphosphine
PPh_3	-	triphenylphosphine
ppm	-	parts per million
^{i}Pr	-	isopropyl
pyr	-	pyridine
RT	-	room temperature
RuAAC	-	Ruthenium-Catalyzed Azide-Alkyne Cycloaddition
SM	-	starting material
T	-	temperature
TBAF	-	tetrabutylammonium fluoride
TBS	-	tert-butyldimethylsilyl
TEA	-	triethylamine
tert	-	tertiary
TEMPO	-	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA	-	trifluoroacetic acid
THF	-	tetrahydrofuran
TLC	-	thin layer chromatography
TM	-	transition metal

TMEDA	-	tetramethylethylenediamine
TMS	-	trimethylsilane
$TMSCF_3$	-	(trifluoromethyl)trimethylsilane
TMSO	-	tetramethylene sulfoxide
tol	-	toluene
Xantphos	-	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Unit Abbreviations

µl	-	10^{-6} L
mg	-	10^{-3} g
ml	-	10^{-3} L
mmol	-	10^{-3} mol

NMR abbreviations

Singlet (s), broad singlet (br. s) doublet (d), triplet (t), quartet (q), doublet of doublets (dd), triplet of doublets (td), doublet of triplets (dt), multiplet (m)

1. Transition metals in synthesis

The use of transition metals in synthesis is an incredibly useful tool for organic chemists. Co-ordination of a metal can occur with Lewis basic functional groups in some manner resulting in dramatic changes in the reactivity.[1] This can be through;

- Increasing the reactivity of stable systems to allow reactions to take place
- Stabilising reactive systems to allow access to higher energy intermediates
- Switching between nucleophilicity and electrophilicity – inverting the reactivity of a species to dramatically alter a reaction pathway.

This widely increases the scope of available synthetic transformations by allowing access to reactive intermediates and pathways previously thought of as "impossible" under normal conditions. Further to this organometallic transformations often show high specificity, with the ability to target a specific group or section of a complex system allowing both region and chemo-specificity. This can alleviate the necessity for time-consuming protection/deprotection steps in synthetic routes.

However as with many synthetic processes this is not without limitations. The often advantageous specificity of reactions can make the development of a general synthetic procedure challenging. Slight changes in a system will often cause massive differences in the overall reaction pathway leading to unprecedented and undesirable outcomes. The complex nature of transition metal reactivity means that mechanistically transformations are often a task to predict or understand. Reasonably postulated mechanisms with significant kinetic and physical evidence exist, but these reactions are often poorly understood. This inherent lack of understanding means rationalising and predicting new transformations is a tiresome process, requiring a certain level of luck and serendipity.

The interest in the use of transition metals in synthetic protocol has dramatically increased in the last 150 years. As early as 1849 Frankland reported the first organozinc compounds.[2] This paved the way for Grignard's famous organomagnesium chemistry, which (despite magnesium not being a transition metal) remains an important tool in organic chemistry.[3] However the development of transition metal chemistry was sluggish to gain momentum. In 1890 Ludwig Mond isolated $Ni(CO)_4$ as a highly volatile liquid from the reaction of nickel metal with carbon monoxide.[4] This observation led to the development of the Mond process for purifying nickel contaminated with iron and cobalt impurities.[5] At a similar time Sabatier demonstrated the use of finely divided metals such

as nickel, palladium or platinum in the catalysed hydrogenation of alkenes.[6] This process was initially used in the manufacture of margarine. Despite these early discoveries, it wasn't until the 1950s that organometallic chemistry began to gain sufficient momentum. It is argued that the simultaneous determination of the structure of ferrocene in 1952 by Wilkinson[7] and Fischer[8] provided the catalyst for this surge of interest in the field.

In recent times huge progress has been made in organometallic chemistry, and recognition for the development of this field has been shown in the award of a number of Nobel prizes (**Table 1**). The main focus for development of organometallic chemistry has been in catalysis due to benefits associated with atom economy and environmental impact. The use of palladium (Pd), rhodium (Rh) ruthenium (Ru), platinum (Pt), silver (Ag) and gold (Au) is currently prevelant in catalytic organometallic transformations, however these metals are expensive – driving the need for catalytic approaches. Due to the expense of materials recent interest has been in cheaper first row transition metals such as nickel (Ni), copper (Cu), iron (Fe), zinc (Zn) or cobalt (Co).

Table 1: Chemistry Nobel prizes for the development of organometallic chemistry

Year	Awarded	Contribution
1912	Sabatier and Grignard	Hydrogenating organic compounds in the presence of finely disintegrated metals / Discovery of the Grignard reagent
1963	Ziegler and Natta	Development and use of the Ziegler catalyst in polymerisation and synthesis of macromolecules
1973	Wilkinson and Fischer	Organometallic sandwich compounds
2001	Sharpless, Nayori and Knowles	Catalysed chiral oxidation and hydrogenation reactions
2005	Grubbs, Schrock and Chauvin	The development of alkene metathasis
2010	Heck, Negishi and Suzuki	Palladium catalysed cross-couplings

This thesis has two main research focuses within transition metal mediated synthetic processes; the decarboxylative cross-coupling of benzoic acids and zinc mediated 1,5-triazole formation. An introduction presenting the benefits of these areas and the recent literature developments within the respective fields will be presented and discussed in each case.

2. Introduction to carboxylate directed decarboxylative *ortho*-arylation and *ortho*-acylation

2.1. Decarboxylative cross-coupling

2.1.1. Interest and early development

Cross-coupling reactions are of fundamental importance in modern chemical synthesis for the formation of C–C bonds. A large number of top selling pharmaceuticals, agrochemicals, and organic materials require (hetero)biaryl skeletons (**Figure 1**) the synthesis of which often relies on these crucial C–C bond forming reactions.[9]

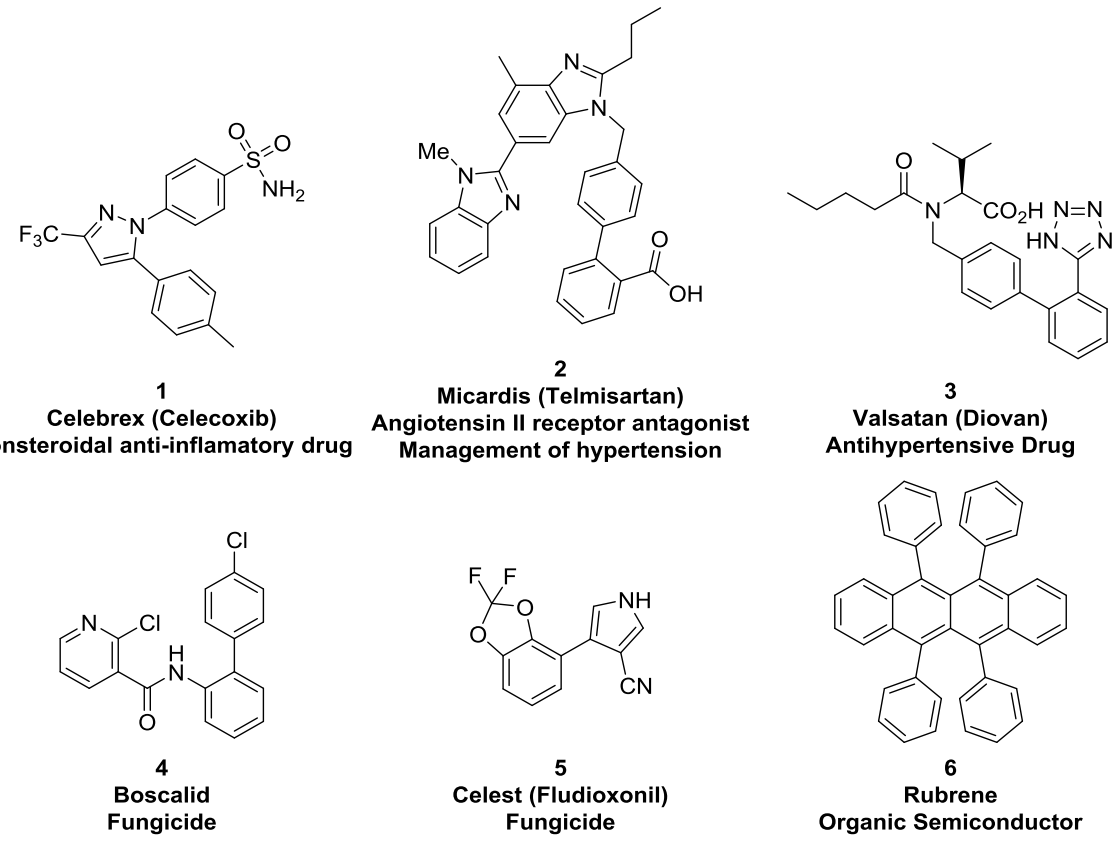
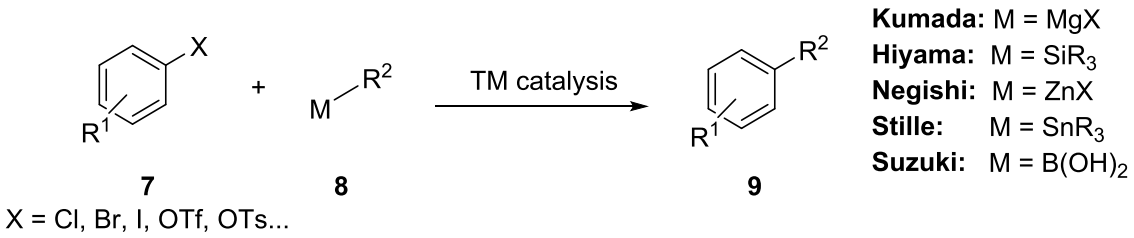


Figure 1: Important compounds containing polyaromatic skeletons

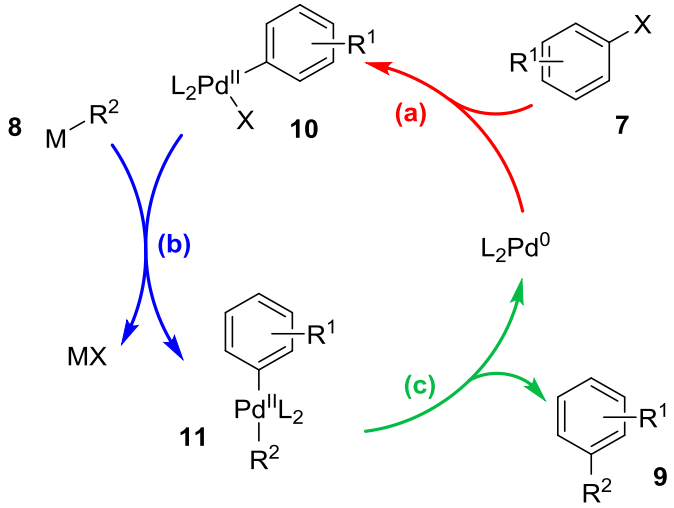
The coupling of aryl halides or pseudohalides with organometallic precursors in the formation of C–C bonds is used extensively in research and industrial processes due to the robust nature of the reactions and the ability to tune the system to gain access to a wide variety of products (**Scheme 1**). These reactions require prefunctionalisation of both the organohalide (or pseudohalide) and the organometallic – this can be time consuming and costly if the reagents are not commercially available.[10] As it stands the majority of

currently available processes for cross-coupling reactions use a stoichiometric amount of expensive organometallic reagents.[11-15] These organometallic precursors can often be unstable, highly sensitive to water or oxygen, toxic or difficult to source.



Scheme 1: Transition metal catalysed cross-coupling between aryl halides and organometallic reagents

In most cases these organometallic cross-coupling reactions work *via* a palladium or nickel catalysed process (**Scheme 2**). Oxidative addition of the aryl halide (**7**) or pseudohalide and transmetallation of the organometallic species (**8**) provide intermediate **11** which undergoes reductive elimination to form the product and regenerate the palladium catalyst. In general these processes are believed to operate *via* a Pd^0/Pd^{II} cycle.[16]



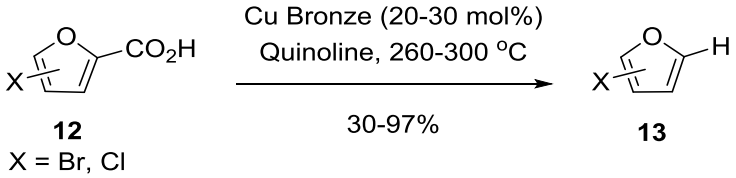
(a) oxidative addition (b) transmetallation (c) reductive elimination

Scheme 2: General mechanism of cross-coupling reactions

Alternative processes are under constant development; particularly with regard to catalytic transformations.[10] Decarboxylative cross-couplings have emerged in the past two decades as an advantageous alternative. The use of cheap, benign and readily available carboxylic acids as organometallic surrogates is favourable, alleviating the need for prefunctionalisation of potentially toxic or unstable organometallic precursors.[17]

Transition metal catalysed extrusion of CO_2 is less environmentally damaging than many of the stoichiometric heavy metal salt by-products produced in classical cross-coupling methods.[18]

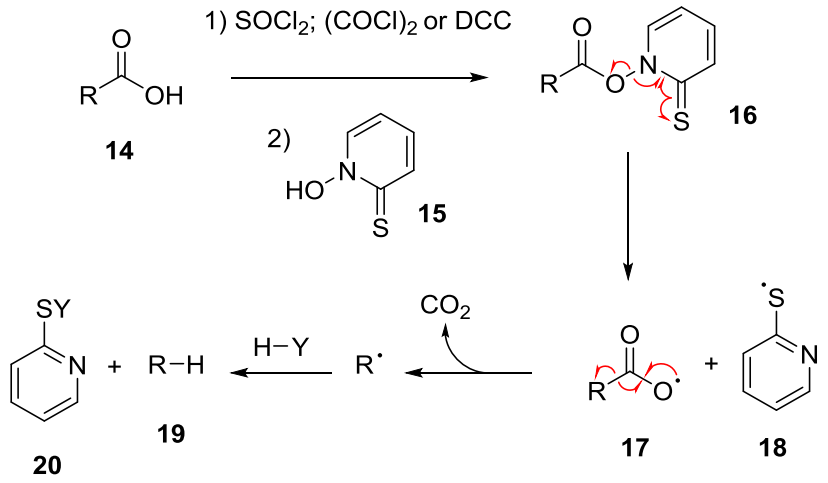
Carboxylic acids have been known for many years to undergo decarboxylation under harsh conditions, in the presence of heavy metal mediators at elevated temperatures (>250 °C) and pressures.[19] In 1930 Shepard reported the protodecarboxylation of furoic acids under copper mediated conditions. This methodology required high temperatures, however a range of halogenated furoic acids were decarboxylated to give the corresponding furan in reasonable yields (**Scheme 3**). [20]



Scheme 3: Shepard decarboxylation of furoic acids

Protodecarboxylation is not the only useful transformation that can occur under metal mediated conditions. The Hunsdiecker reaction notably replaces the carboxylate with a halide – generally this works best for aliphatic carboxylic acids however there are select examples involving aromatic substrates.[21] Originally the process required a stoichiometric amount of silver, however since 2000 research has indicated a similar catalytic process in the presence of tetrabutylammonium trifluoroacetate.[22] Most recently a catalytic silver procedure was developed.[23]

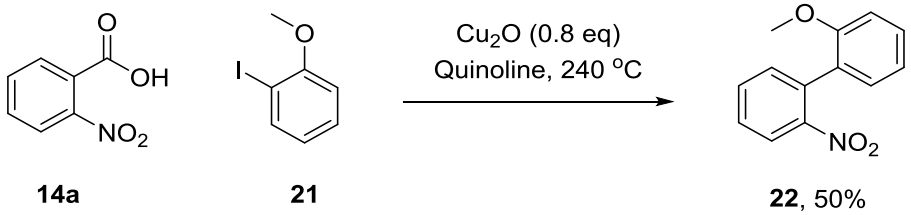
Of note is the Barton reaction, which transforms a carboxylic acid into a radical source through conversion of the acid into a thiohydroxamate **16** (or Barton ester).[24] Using a suitable radical trap (represented by H–Y), this sequence of steps has been shown to generate new bonds, including carbon-carbon, carbon-sulfur, carbon-oxygen, carbon-selenium and carbon-halogen bonds (**Scheme 4**).[25] The wide applicability of this reaction has led to its use in many synthetic strategies towards carbohydrates,[26-28] amino acids,[29-31] vitamins[32] and terpenoids.[33-35]



Scheme 4: Barton Decarboxylation *via* hemolytic cleavage of thiohydroxamate 16

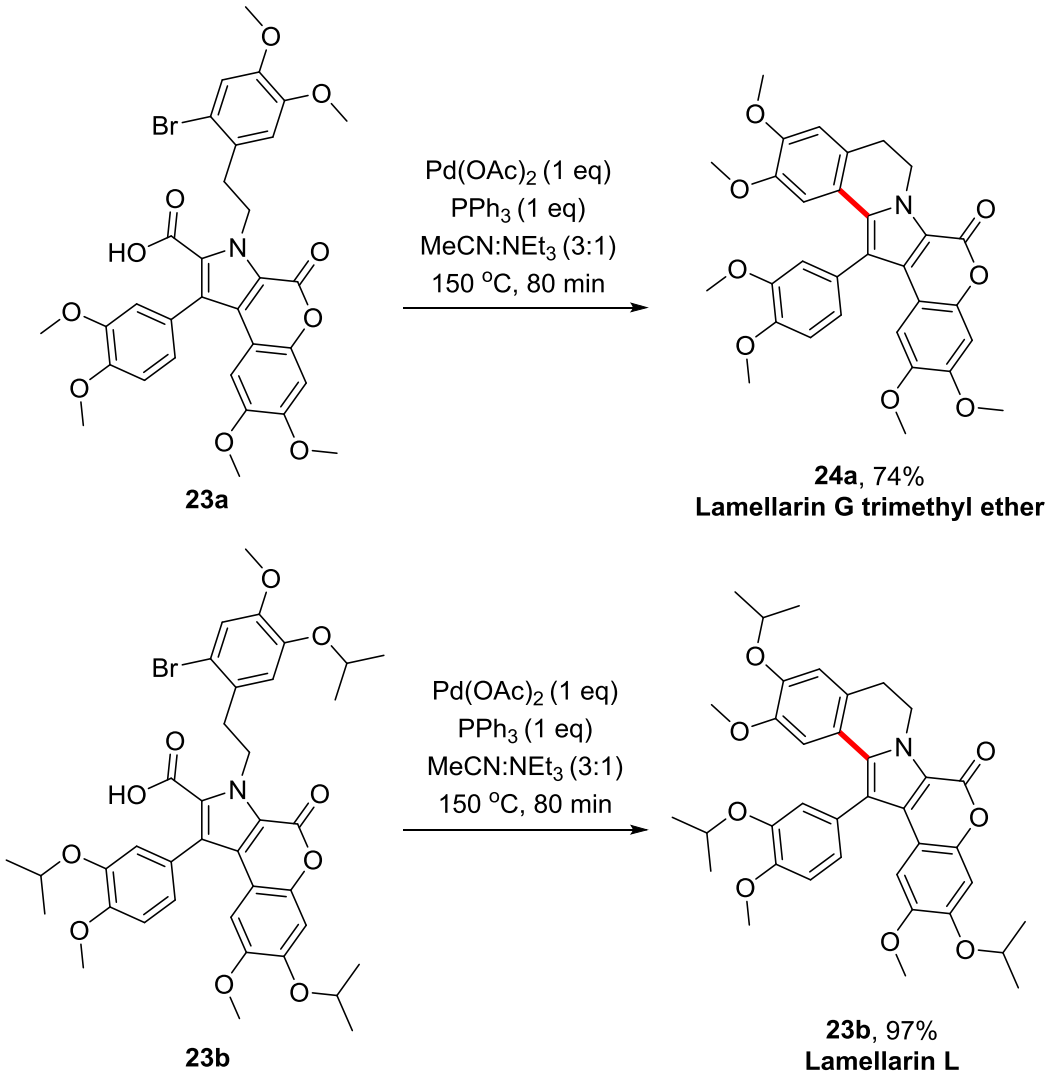
Kolbe electrolysis describes the electrochemical oxidative decarboxylation of carboxylic acids (usually as salts).[36] This generates radical species which will then dimerise. The reaction was discovered by Hermann Kolbe in 1849, when the electrolysis of potassium acetate provided carbon dioxide and ethane at the anode – however evidence of Faraday observing the same phenomenon in 1834 is in existance.[37] This environmentally friendly process is simple in application and requires no additional oxidising or reducing agents. These benefits mean that it is still occasionally used synthetically in the construction of complex molecules.[38]

Nilsson was first to determine the utility of the carboxylic acid as an organometallic precursor. His work in 1966 demonstrated how *ortho*-nitrobenzoic acids could function as an organometallic surrogate in an Ullman style coupling (**Scheme 5**).[39] It was proposed that the reactive intermediate would be analogous to the Ullman system and that "The reactive intermediate in the Ullmann reaction is likely to be an arylcopper."[40] However with high temperatures, and relatively low yields (30-50%) this discovery stayed unelaborated for more than 35 years.



Scheme 5: Nilsson decarboxylative Ullman style cross-coupling

Steglich and co-workers have demonstrated the potential applicability of this chemistry by utilising decarboxylative chemistry for the final step in the synthesis of both Lamellarin G trimethyl ether (1997)[41] and Lamellarin L (2000)[42] (**Scheme 6**). This work demonstrates that this chemistry can be used in the synthesis of complex molecules, but the necessity of a stoichiometric amount of palladium reagent is economically unfavourable. The necessity for a mild, robust, catalytic procedure to perform these transformations has therefore been of high interest since the early 2000s.

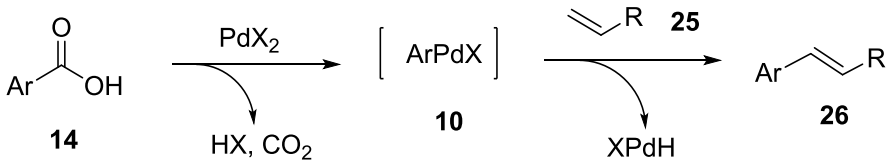


Scheme 6: Use of decarboxylative cross-coupling in the synthesis of Lamellarin G trimethyl ether and Lamellarin L

2.1.2. Transition metal catalysed decarboxylative cross-coupling

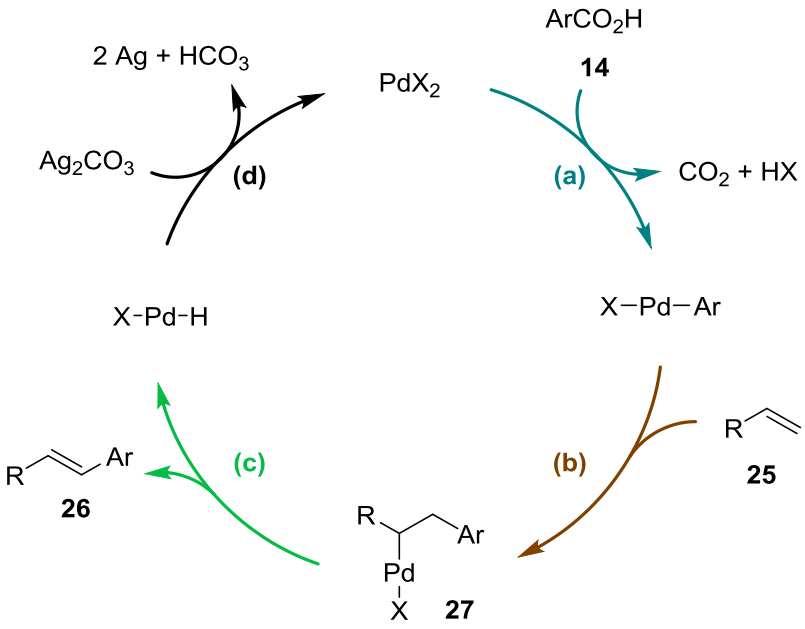
It was Myers who initially caused the resurgence in the investigation of decarboxylative cross-coupling. In 2002 pioneering work demonstrated the decarboxylative palladation of benzoic acids, and subsequent Heck type olefination (**Scheme 7**).[43] Yields were high and

a diverse substrate scope was determined. Perhaps most importantly, the temperature required for this reaction was only 120 °C. It was also noted that in order for decarboxylation to occur an *ortho*-substituent on the benzoic acid was required.



Scheme 7: Pd catalysed decarboxylative Heck-type reaction with olefins

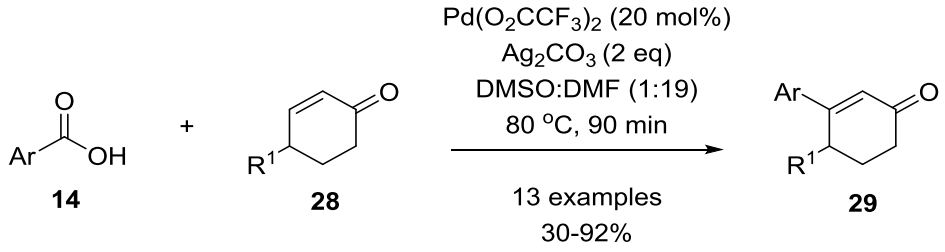
Mechanistic investigations lead to the proposition of a catalytic cycle (**Scheme 8**). Decarboxylative palladation followed by olefin insertion leads to intermediate **27** which undergoes β-hydride elimination to form the desired product. The silver carbonate is proposed to act as both a base and an oxidant to regenerate the catalyst and complete the catalytic cycle. Evidence from crystal structures and isolated intermediates published in 2005 supported this mechanism, and the rate limiting step was determined to be the palladium mediated decarboxylation of the benzoic acid.[44]



Scheme 8: Proposed mechanism for Pd catalysed decarboxylative Heck-type reaction

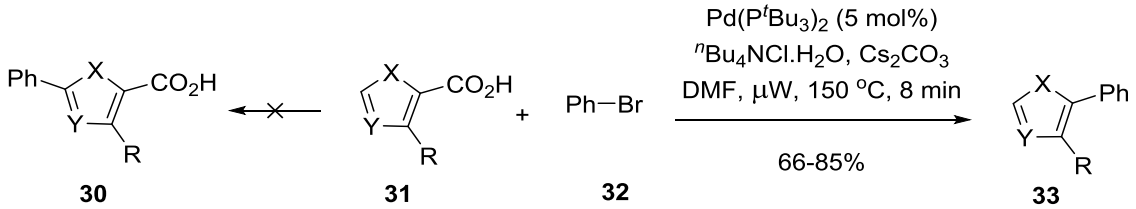
This methodology was extended in 2004 to include Heck-type arylation of 2-cycloalk-1-enes *via* decarboxylative cross-coupling, and while the temperature for these reactions was further reduced to 80 °C, yields were not as impressive as the previous study (**Scheme 9**).[45] While the literature contains numerous examples of decarboxylative

additions to alkenes or alkynes the remainder of this introduction will focus on transformations resulting in biaryl products. See publications by Larrosa or Gooβen for a review including alkene and alkyne transformations.[46,47]



Scheme 9: Myers Pd catalysed decarboxylative Heck-type reaction with enones

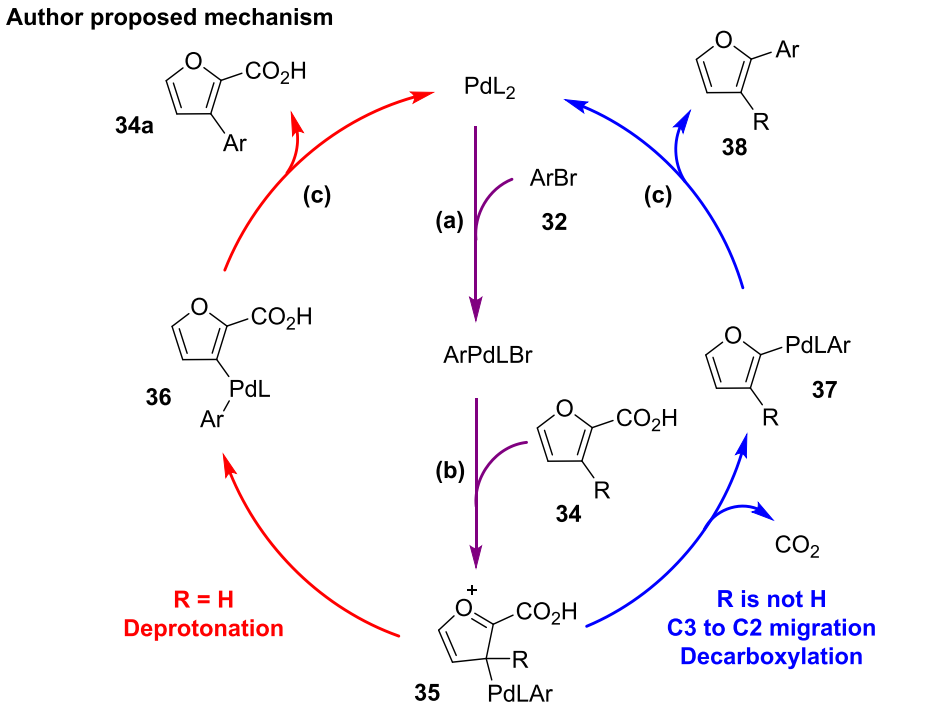
In 2006 Forgione serendipitously developed a palladium catalysed heterocyclic decarboxylative cross-coupling to bromobenzene.[48] The initial intent of this methodology was to perform a C–H activation/cross-coupling at the 2 position to give product 30. However under the reaction conditions coupling through the decarboxylation of the 5 position was observed to give product **33** (Scheme **10**). This methodology was extended to pyrroles, furans, thiazoles, thiophenes and benzofurans, with high yields obtained in most cases. Further studies also showed that this method could be extended to the coupling with aryl-chlorides.[49] Forgione observed that upon removal of the *ortho*-substituent the yields dropped significantly, this is consistent with observations by Myers.



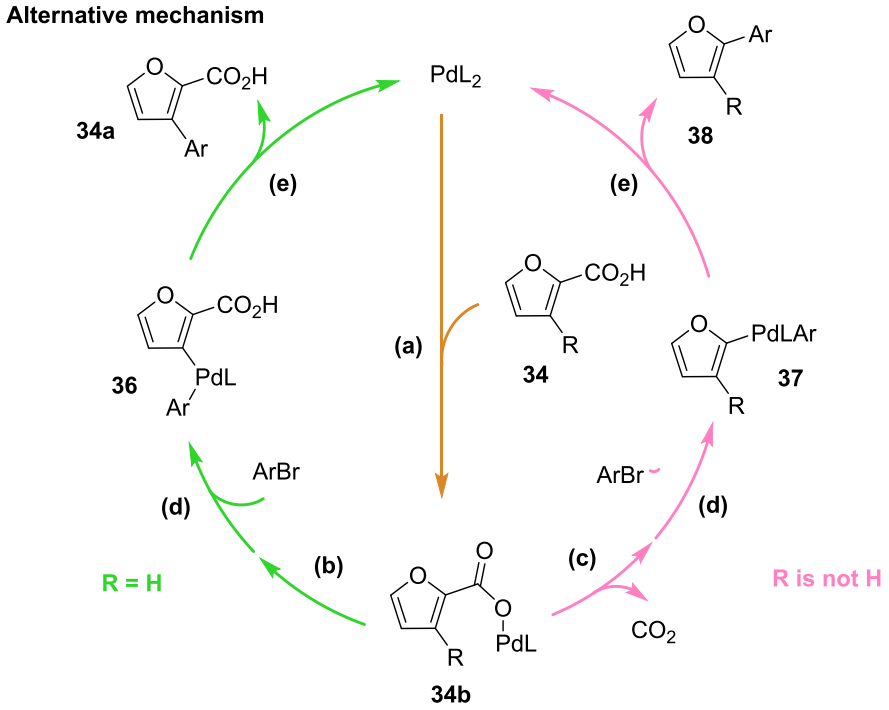
Scheme 10: Forgione Pd catalysed decarboxylative cross-coupling of heteroaromatics

When no substituent was present at the 3 position formation of 2,3-diphenylfuran was observed. This led the authors to propose the mechanism shown in **Scheme 11** (**top**). Oxidative addition of the aryl bromide to the palladium, followed by electrophilic palladation at the 3 position of the furan generates inrermediate **35**. In the case where there is a substituent at the 3 position (blue arrows) C3 to C2 migration occurs leading to **37**, and subsequent decarboxylation and reductive elimination generates the C2 arylated product. Where no substituent is present at the 3 position (red arrows) deprotonation occurs to rearomatise the furan giving intermediate **36** which undergoes reductive

elimination to form the C3 arylated species. Under the reaction conditions this can then be further converted to the 2,3-diarylated product.



(a) oxidative addition (b) electrophilic aromatic substitution (c) reductive elimination

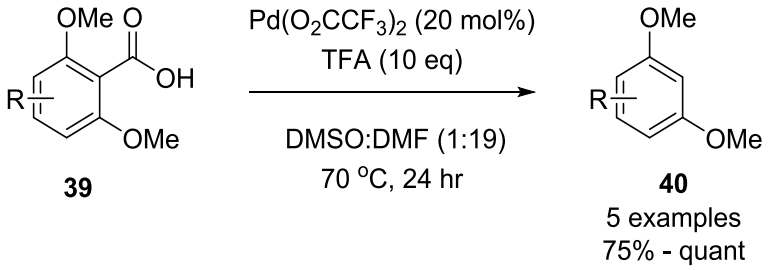


(a) ligand exchange (b) carboxylate directed C-H insertion (c) decarboxylation
(d) oxidative addition (e) reductive elimination

Scheme 11: Author proposed (top), and another alternative (bottom) mechanism for decarboxylative arylation of heteromatic acids

While this mechanism presents a reasonable account of the observed product, the inherent reactivity of the furan is at the 2 and 5 positions, so oxidative addition at the 3-position would not be favourable. Another plausible explanation would be that initially co-ordination of the palladium ocurrs at the carboxylate (**Scheme 11, bottom**). Where the C3 position is substituted palladium assisted decarboxylation occurs, leading to co-ordination of the palladium at the ipso-position (the mechanism of this is discussed further in **Section 2.1.6.**). Oxidatie addition would follow, leading to intermediate **37** which will reductively eliminate to give desired product **38**. Where the C3 position is a hydrogen co-ordination of the palladium leads to directed C-H activation (discussed further in **Section 2.2.2.**) at the 3 position, and following oxidative addition of the aryl bromide intermediate **36** is generated. Reductive elimination from this species generates **34a.**

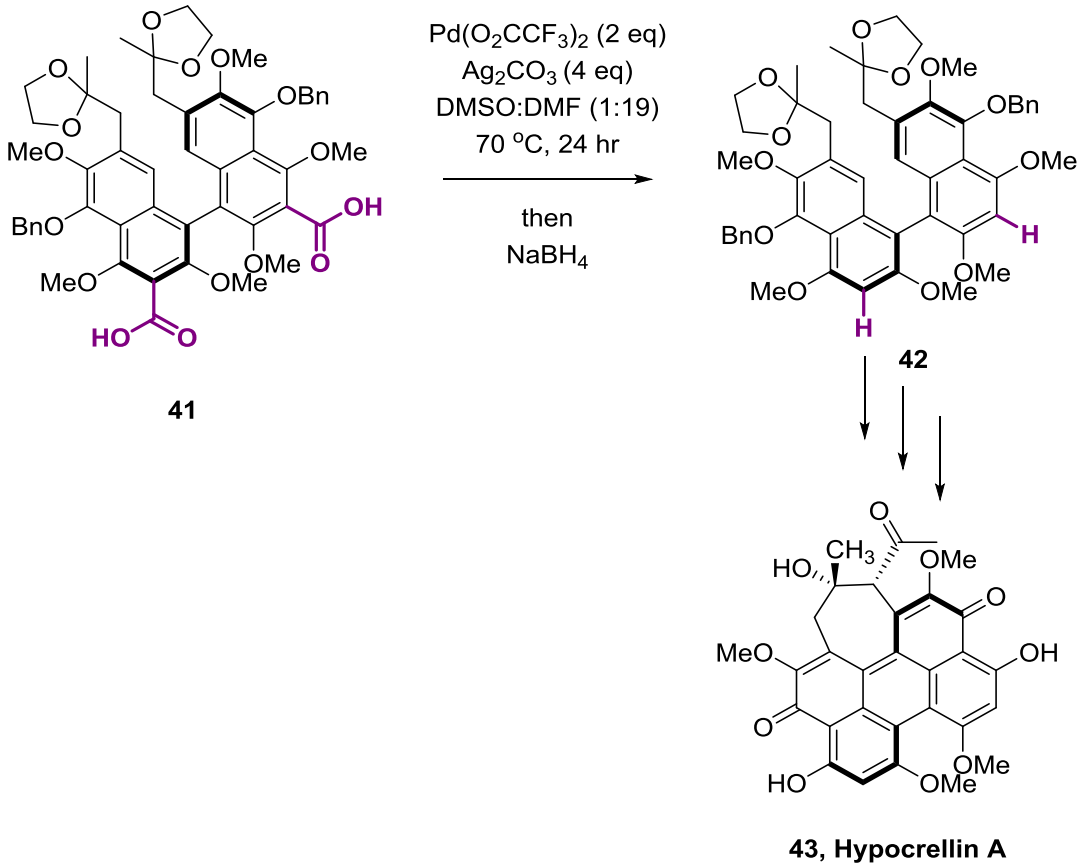
Where Palladium catalysed protodecarboxylation was investigated further by Kozlowski and co-workers in 2007.[50] The group published results indicating the protodecarboxylation of a series of benzoic acids with catalytic $Pd(O_2CCF_3)_2$ at 70 °C (**Scheme 12**). Despite the benefits of performing this reaction at significantly lower temperatures, the reaction is severely limited to acids bearing two *ortho*-substituents. In the initial methodology paper high yields were only shown for substrates bearing two *ortho*-methoxy groups. Switching to an *ortho/meta*-dimethoxy acid, or with methyl groups in place of the methoxy groups significantly decreased the yield. Kinetic studies suggested a mechanism involving electrophilic palladation of the *ipso*-position, with decarboxylation leading to a palladium-arene species. This species was stable under stoichiometric palladium conditions and required the addition of a reducing agent (in this case $NaBH_4$) to successfully remove the co-ordinated palladium. The mechanism will be discussed further in **Section 2.1.6**.



Scheme 12: Kozlowski palladium catalysed decarboxylation of *ortho*-substituted acids

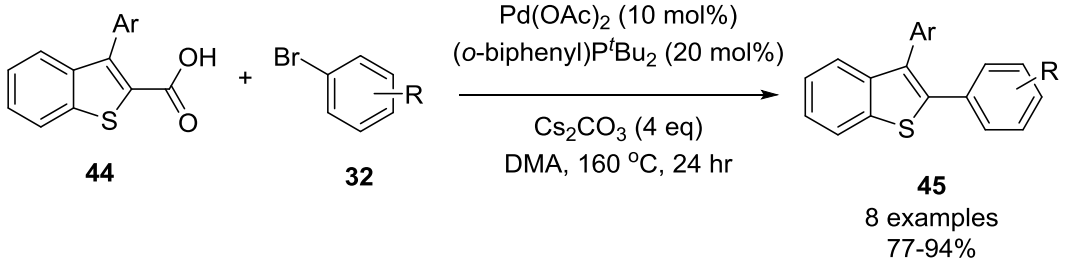
This reaction was developed for use in the total synthesis of Hypocrellin A.[51] Where conventional decarboxylation methods requiring high temperatures would cause racemisation of a late stage intermediate, this low temperature procedure allowed the

decarboxylation without loss of stereochemical information (**Scheme 13**). In the absence of the TFA this transformation did require stoichiometric palladium, and also required the addition of $NaBH_4$ to protodemetallate the desired product. However this does not diminish the significance of the development of a lower temperature decarboxylation and the successful use in synthesis.



Scheme 13: Kozlowski palladium mediated decarboxylation in the synthesis of Hypocrellin A

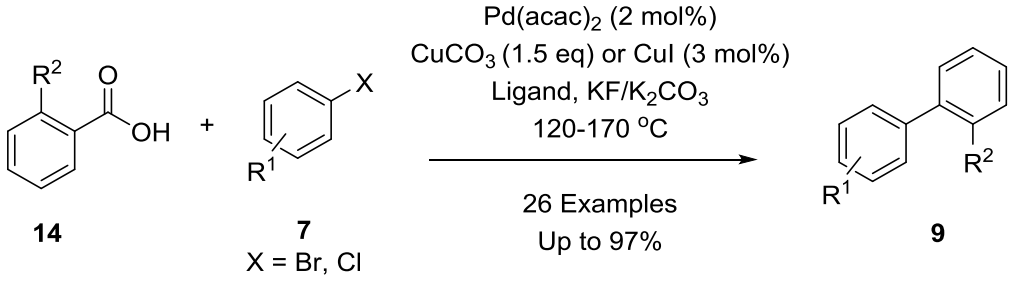
Miura and co-workers reported the decarboxylative arylation of benzothiophenes with aryl bromides in 2009 (**Scheme 14**).[52] This was following previous research in the group where desired arylation of 3-furan and 3-thiophene carboxylic acids resulted in perarylation.[53] Yields were consistently high across a modest aryl bromide substrate scope.



Scheme 14: Miura decarboxylative arylation of benzothiophenes with aryl bromides

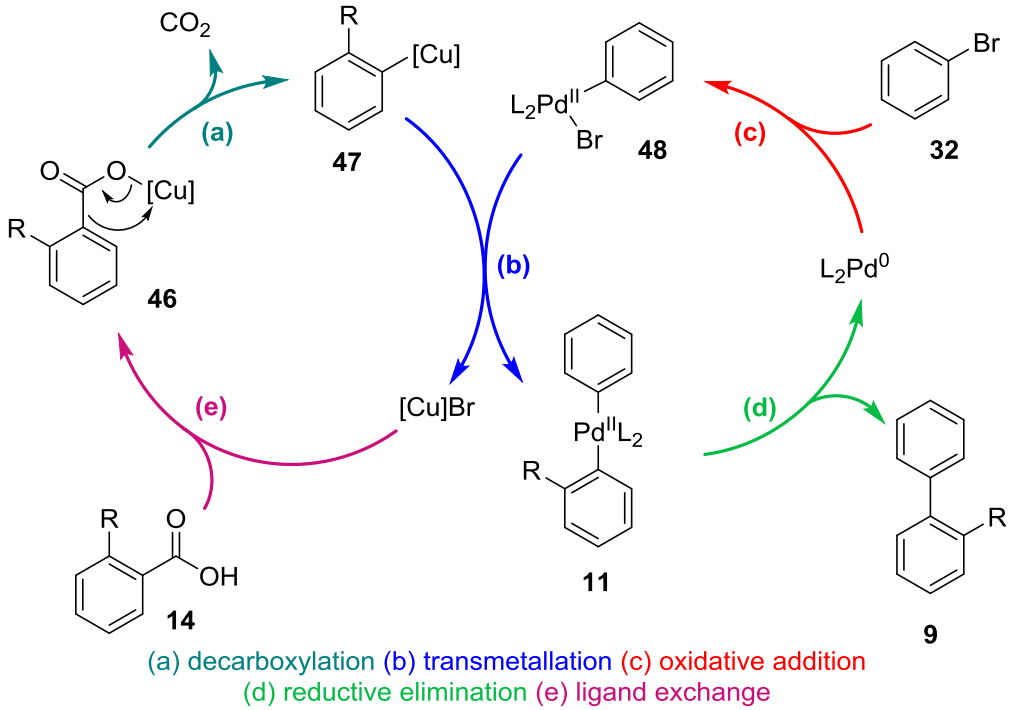
2.1.3. Development of Cu catalysed decarboxylative cross-coupling

The area of copper catalysed decarboxylation has been extensively researched by the Gooβen group. This began when Gooβen first reported the copper catalysed decarboxylative cross-coupling of aryl halides in 2006.[54] A Pd/Cu catalysed method was disclosed which facilitated the direct formation of biaryl structures from aryl halides and benzoic acids (**Scheme 15**).



Scheme 15: Decarboxylative cross-coupling with aryl bromides

The mechanism utilised the formation of a known organocopper intermediate (**47**) (demonstrated by Cohen and Nilsson)[55] as an aryl anion equivalent which is trapped by transmetallation to palladium in the intersection of two catalytic cycles. Decarboxylation occurs through co-ordination of the copper to the carboxylate oxygen, followed by a shift to the aryl π-system and insertion into the C–C bond. Release of CO_2 generates the stabilised copper intermediate **47**.[56] Simultaneously, oxidative addition of the aryl halide to a Pd^0 species occurs, generating the Pd^{II} complex **48**. Transmetallation of these two species results in palladium species **11**, which undergoes reductive elimination to give the desired product **9**, and regenerate the Pd^0 catalyst (**Scheme 16**).[54]



Scheme 16: Mechanism for Pd/Cu catalysed decarboxylative cross-coupling

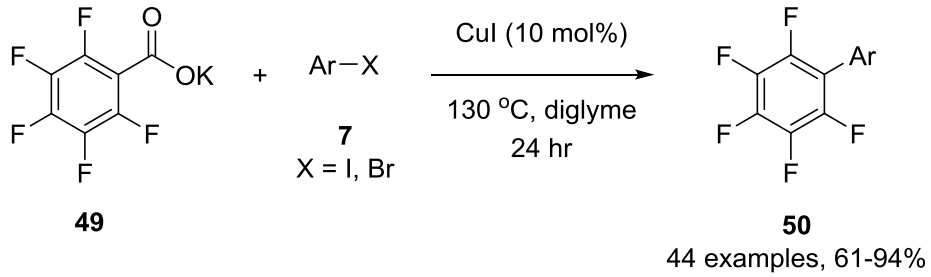
The yields for this transformation were generally high; however it is notable that in some cases stoichiometric copper was required in order to obtain this. A diverse range of substrates were applicable, both for the aryl halide and the benzoic acid with both electron rich and electron deficient systems being suitable.[57] High yields were only reported for the transformation of *ortho*-substituted benzoic acids – though these could also withstand both electron rich and electron poor groups – with *meta*- and *para*-substituted acids causing substantially depleted yields.[54]

Since the initial development in 2006, Gooβen has gradually extended the scope of copper catalysed decarboxylative cross-couplings to be compatible with aryl chlorides,[58] triflates,[59] tosylates[60] and mesylates.[61] In 2009 the group also developed a microwave assisted protocol which significantly reduced the reaction time while maintaining high yields.[62]

The group have also used computational studies to rationalise the use of the phenanthroline ligand to stabilise catalytic turnover (particularly with electron rich substituents) and to help develop lower temperature conditions involving silver catalysis. This will be discussed in later sections (**Section 2.1.4.**). Most notably however, in 2011 the Gooβen group published a practical protocol for the decarboxylative arylation of aryl triflates in flow.[63] This vastly increases the applicability of the decarboxylative carbon–

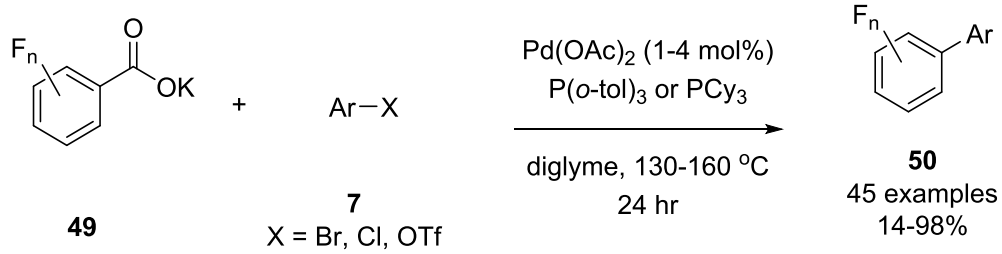
carbon bond forming process as it allows for potential implementation of such a process on an industrial scale.

In 2009 Liu disclosed the copper catalysed decarboxylative cross-coupling of perfluorobenzoates with aryl iodides and bromides (**Scheme 17**).[64] This palladium free coupling is reminiscent of Nilsson's Ullman type coupling (**Section 2.1.1.**),[39] though is achieved at substantially lower temperatures, and with only 10 mol% catalyst. The limitations of this reaction are clear with only highly electron poor perfluorobenzoates with two *ortho*-substituents suitable for achieving high yields.



Scheme 17: Copper mediated decarboxylative cross-coupling with aryl bromides/iodides

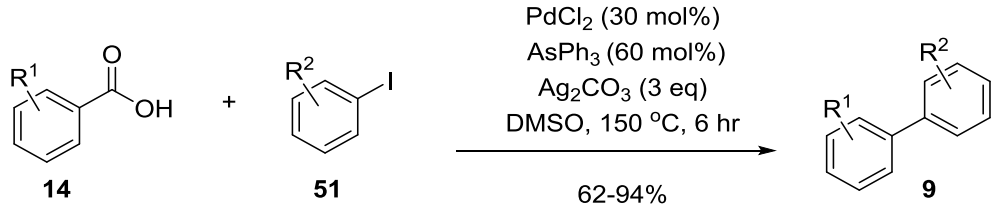
The method was improved in 2010 to allow cross-coupling of bromides chlorides and triflates – massively expanding the scope of possible coupling partners.[65] This palladium catalysed cross-coupling resulted in high yields across a wide range of biaryls (**Scheme 18**). Kinetic studies determined a mechanism consistent with that put forward by Kozlowski *et al.*[50] However the acid group remained limited to substrates bearing multiple fluorine substituents, and specifically required substitution at both *ortho*-positions



Scheme 18: Pd catalysed cross-coupling with aryl bromides, chlorides and triflates

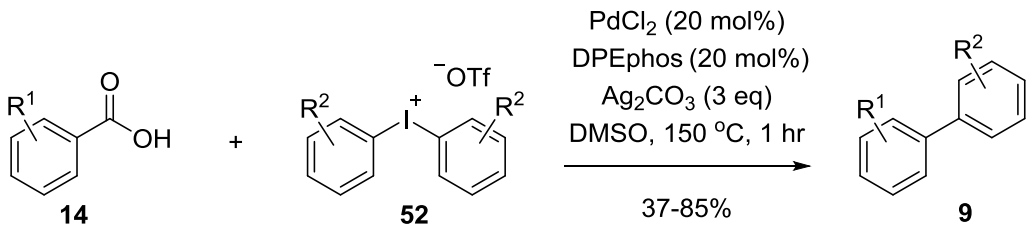
2.1.4. Development of Ag mediated decarboxylative cross-coupling

In 2007 Becht and co-workers reported the decarboxylative cross-coupling of benzoic acids with aryl iodides under palladium catalysed conditions with an arsine ligand ($AsPh_3$) (**Scheme 19**).[66] While the temperature still remained at 150 °C yields were high and particularly successful for electron rich aromatics. It was also shown to be possible to cross-couple sterically hindered doubly *ortho*-substituted benzoic acids using this methodology. However the high catalyst loading, large quantity of silver salt and toxicity of the arsine ligand limited the utility of this reaction.



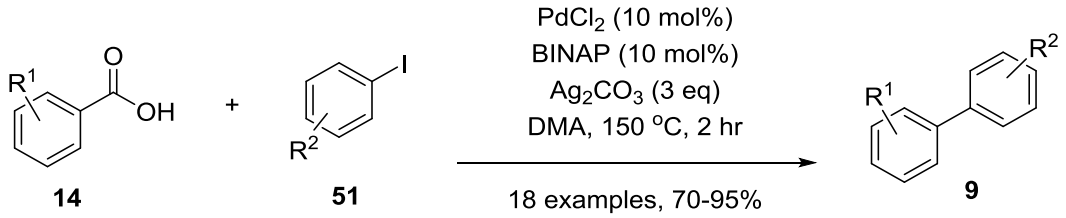
Scheme 19: Pd catalysed decarboxylative cross-coupling with aryl iodides

In 2008 this methodology was extended to the decarboxylative cross-coupling reaction of arene carboxylic acids and diaryliodonium triflates.[67] The conditions were essentially the same however the toxic arsine ligand had been replaced with DPEphos and the palladium loading was slightly lower (**Scheme 20**). While yields were reasonable the necessity to synthesise the starting materials and the high loading of both the palladium catalyst and silver species limit the versatility of this chemistry. The substrate scope was further diminished by the requirement of an *ortho*-substituent on the benzoic acid. It has been demonstrated by Fairlamb and co-workers that at high temperatures diaryliodoniums degrade to the corresponding aryl iodides, and it is probable that in Becht's case it is the aryl iodide which is cross-coupling with the benzoic acid.[68] This would account for the poor atom-economy of the reaction.



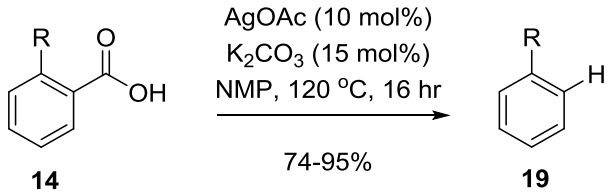
Scheme 20: Pd catalysed decarboxylative cross-coupling with diaryliodonium triflates

A complementary system for Ag/Pd decarboxylative cross-coupling with aryl iodides has also been reported by Wu in 2009.[69] The reaction still required a threefold excess of Ag_2CO_3, but the palladium catalyst loading was lowered again, as was the ligand quantity. The temperature required was still 150 °C (**Scheme 21**). Yields were consistently high and the method is applicable to a diverse substrate substrate scope – though still restricted to *ortho*-substituted acids.



Scheme 21: Silver mediated decarboxylative cross-coupling of aryl iodides

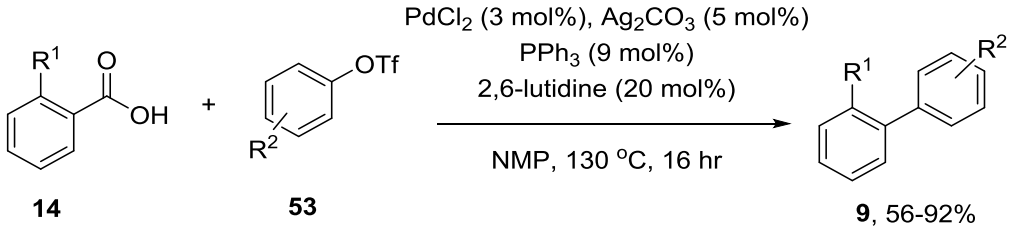
Recently it has also been discovered that silver based catalytic systems are also active towards decarboxylation, and that these systems are able to further decrease the temperature required. Gooβen reported in 2009 that silver acetate (AgOAc) or silver carbonate (Ag_2CO_3) could catalytically decarboxylate a series of benzoic acids at only 120 °C; 50 °C lower than the most successful known catalysed system at that time (**Scheme 22**).[70] This procedure was tolerant of a wide range of functional groups, however the substrate scope is limited by the requirement of an *ortho*-substituent in the benzoic acid in order for the transformation to occur.



Scheme 22: Silver catalysed protodecarboxylation of benzoic acids

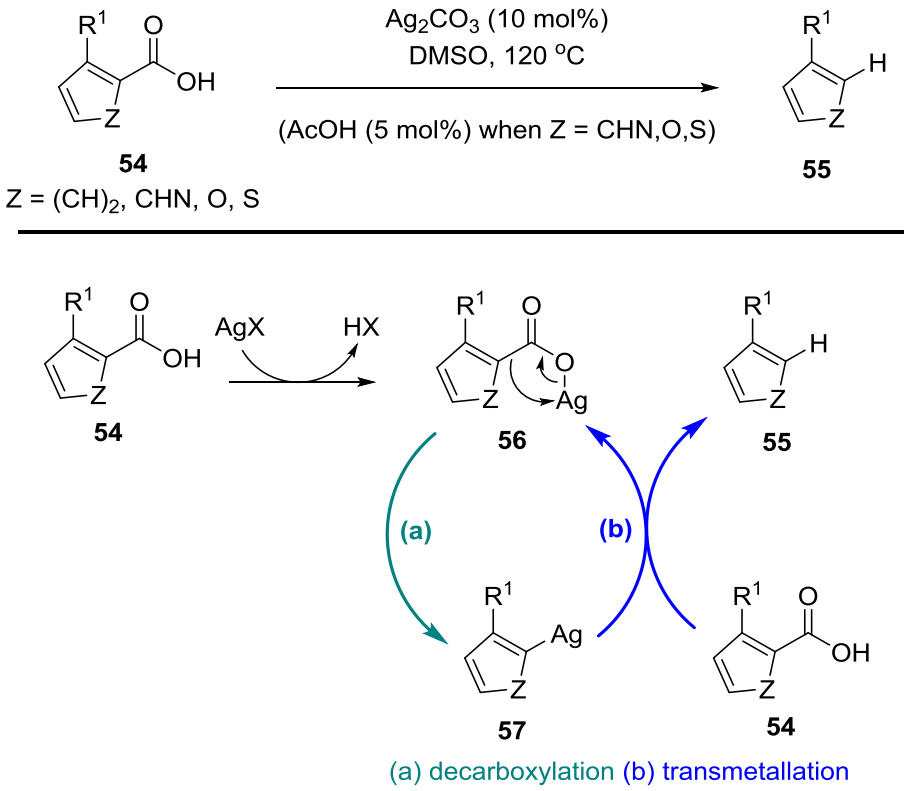
As with copper, Ag/Pd-catalysed cross-coupling was demonstrated with aryl triflates to construct biaryl structures (**Scheme 23**).[71] In the presence of 5 mol% of an Ag^I species and 3 mol% palladium chloride ($PdCl_2$) with triphenylphosphine (PPh_3) and 2,6-lutidine, cross-coupling was successful in consistently high yields at 130 °C. Exchange of the acid with the potassium carboxylate was also shown to improve the yield further. Sterically demanding triflates were suitable, as were a diverse range of functionalities – the

synthetic limit being strongly electron withdrawing substituents at the 4 position of the triflate coupling partner. The mechanism for this transformation is proposed as being mechanistically similar to that of the analogous copper process.



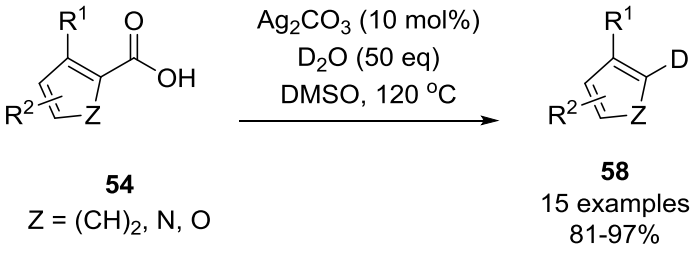
Scheme 23: Silver catalysed decarboxylative cross-coupling with triflates

Larrosa has also developed decarboxylation systems functioning through silver catalysis. Benzoic acids,[72] or heterocyclic acids,[73] could be protodecarboxylated in consistently high yields at 120 °C (**Scheme 24**). The electronics of the substrates did not seem important, with electron rich and electron deficient species being suitable. However, as with Gooβen and Becht's work, they found the reaction scope limited to substrates bearing an *ortho*-substituent, or an *ortho*-heteroatom.[70] The mechanism for protodecarboxylation *via* silver catalysis proceeds similarly to that of the analogous copper system, with the eventual formation of the silver co-ordinated aryl species **57**, which will undergo rapid demetallation to form the protodecarboxylation product. Trapping this metal species (**57**) through transmetallation to palladium can provide a handle for cross-coupling reactions, in an identical fashion to those demonstrated by the copper mediated system. Kashani later showed that a similar procedure was available for the decarboxylation of coumarin-3-carboxylic acids.[74]



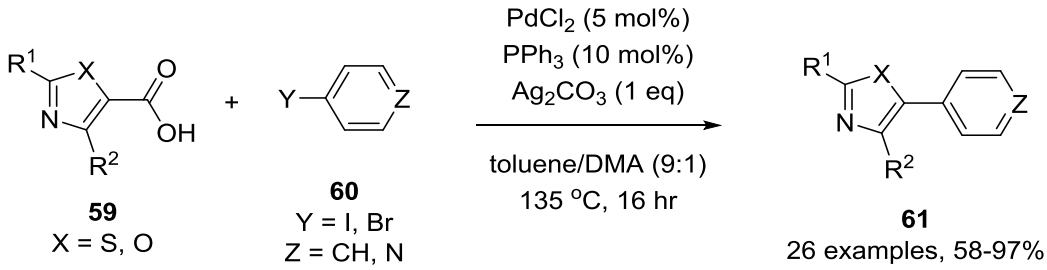
Scheme 24: Procedure and mechanism for silver catalysed protodecarboxylation of *ortho*-benzoic acids and heterocycles

The Larrosa group extended this protodecarboxylation methodology by publishing a mild decarboxylative deuteration of aromatic compounds using D_2O and silver salts (**Scheme 25**).[75] The reaction tolerates a wide substrate scope similar to the previous protodecarboxylation studies. Generation of deuterated species is particularly useful for mechanistic studies so the development of a mild route to specifically label compounds with one deuterium atom is beneficial. Mechanistically the decarboxylative procedure is the same as shown in **Scheme 24**, however trapping of the organometallic intermediate is performed by the added D_2O allowing for specific deuteration at the *ipso*-position.



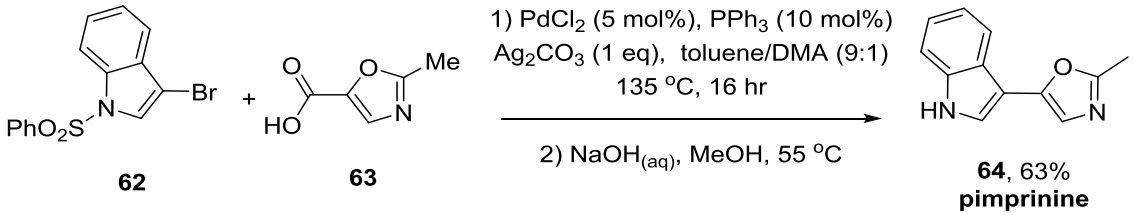
Scheme 25: Larrosa decarboxylative deuteration with catalytic silver

In 2010 the Greaney group published methodology for the decarboxylative cross-coupling of azoyl carboxylic acids with aryl halides (**Scheme 26**).[76] This study required a stoichiometric quantity of silver however the palladium catalyst loading was significantly reduced in relation to previous work. Yields were generally high and allowed the synthesis of a diverse range of novel products under relatively mild conditions.



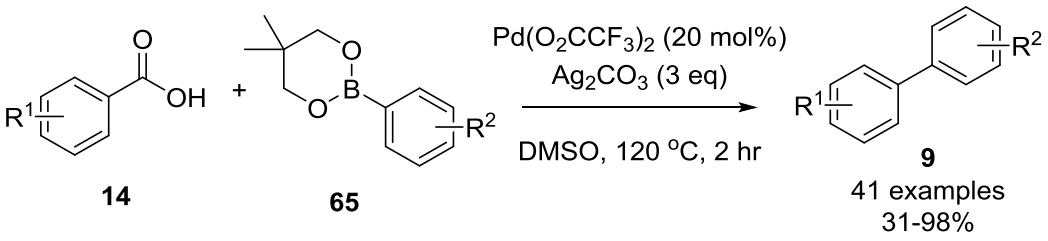
Scheme 26: Greaney decarboxylative cross-coupling of azoyl acids with aryl halides

The group were also able to demonstrate the applicability of this methodology in the synthesis of pimprinine. This indole alkaloid is produced by many species of Streptomyces, and has shown biological activity particularly for antiepileptic effects.[77] The synthesis was completed in 2 steps with an overall yield of 63%, from commercially available starting materials (**Scheme 27**)



Scheme 27: Greaney synthesis of pimprine *via* decarboxylative cross-coupling

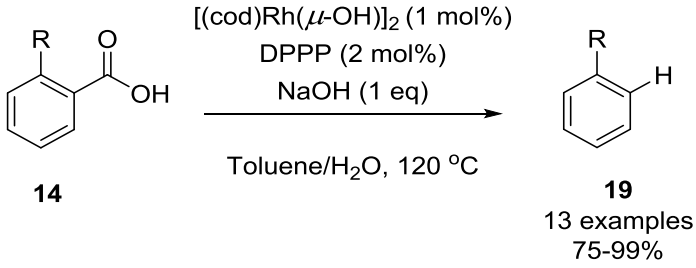
In 2011 Liu *et al.* reported the decarboxylative Suzuki type coupling of benzoic acids and boronate esters (**Scheme 28**).[78] This was again under silver and palladium mediated conditions, and gave high yields across a wide substrate scope. The common *ortho*-substituent was still necessary and the palladium loading is disagreeable, however the reaction conditions were remarkably quick with all reactions reaching completion within 2 hours. While high levels of silver were necessary, it is notable that one equivalent is required to reoxidise the palladium catalyst as there is no oxidative addition step.



Scheme 28: Liu decarboxylative Suzuki type coupling of benzoic acids with boronate esters

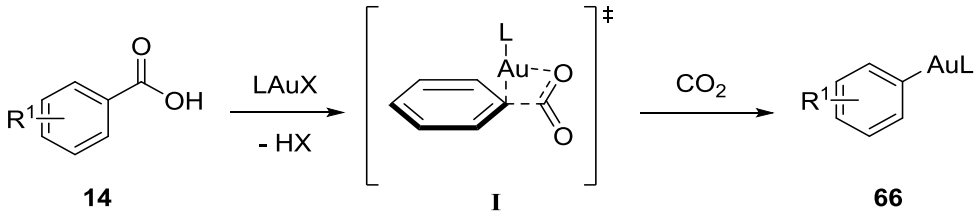
2.1.5. The use of other transition metals in decarboxylative cross-couplings

In 2010 Zhao disclosed the protodecarboxylation of benzoic acids under rhodium catalysed conditions (**Scheme 29**).[79] Specific ligand selection was crucial in mediating this transformation. Yields were high however the substrate scope remained limited to acids bearing a heteroatomic *ortho*-substituent. This procedure was developed further to allow Heck-Mizoroki type cross-coupling of α,β-unsaturated carbonyl compounds.



Scheme 29: Zhao protodecarboxylation under rhodium catalysed conditions

Gold(I) has the same electronic configuration as silver(I), copper(I) and palladium(0) so it is unsurprising that this metal has also been used successfully in the decarboxylation of benzoic acids (**Scheme 30**). The groups of both Nolan and Larrosa consecutively developed decarboxylation procedures in the presence of gold(I) in 2011.[80,81]

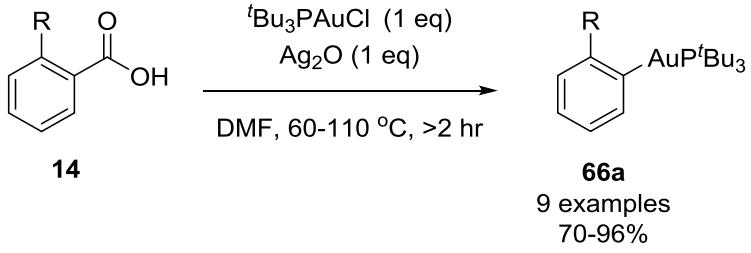


Scheme 30: Proposed gold mediated decarboxylation of benzoic acids

This decarboxylation reaction results in the formation of a stoichiometric gold species which is stable to silica column chromatography. The benefits of forming this species

were that it could work as stable intermediate to reduce protodemetallated by-products in cross-coupling reactions. However to date this has not been fully realised.

Larrosa and co-workers showed that the use of the commercially available [Au[P^{t}Bu$_2$biphen](MeCN)]SbF$_6$ salt could facilitate decarboxylation of benzoic acids in high yield, and in the presence of Ag$_2$O, [P^{t}Bu$_2$biphen]AuCl gave similar results.[80] Use of the gold species was found to vastly reduce the required temperature for decarboxylation, with temperatures as low as 50 °C achieved. A general method using (the slightly less expensive) ^{t}Bu$_3$PAuCl and Ag$_2$O was used to explore the substrate scope (**Scheme 31**). Temperatures of 110 °C gave the aurated products in as little as 2 hours, but lower temperatures were able to generate similar yields at much longer reaction times. Yields of the aurated product were high however still required a heteroatomic *ortho*-substituent on the acid. This methodology was also used in a one-pot decarboxylation, halogenation method reminiscent of the Hunsdieker reaction. The use of stoichiometric gold(I) and silver(I) in the reaction is not economically favourable. The stability of the aurated products mean that in order to further develop this reaction transmetallation to palladium/ruthenium/rhodium would be required – adding further quantities of expensive transition metal reagents. Industrially using a high quantity of expensive materials would be undesirable, and a catalytic protocol would need to be establish before the full utility of this chemistry can be realised.



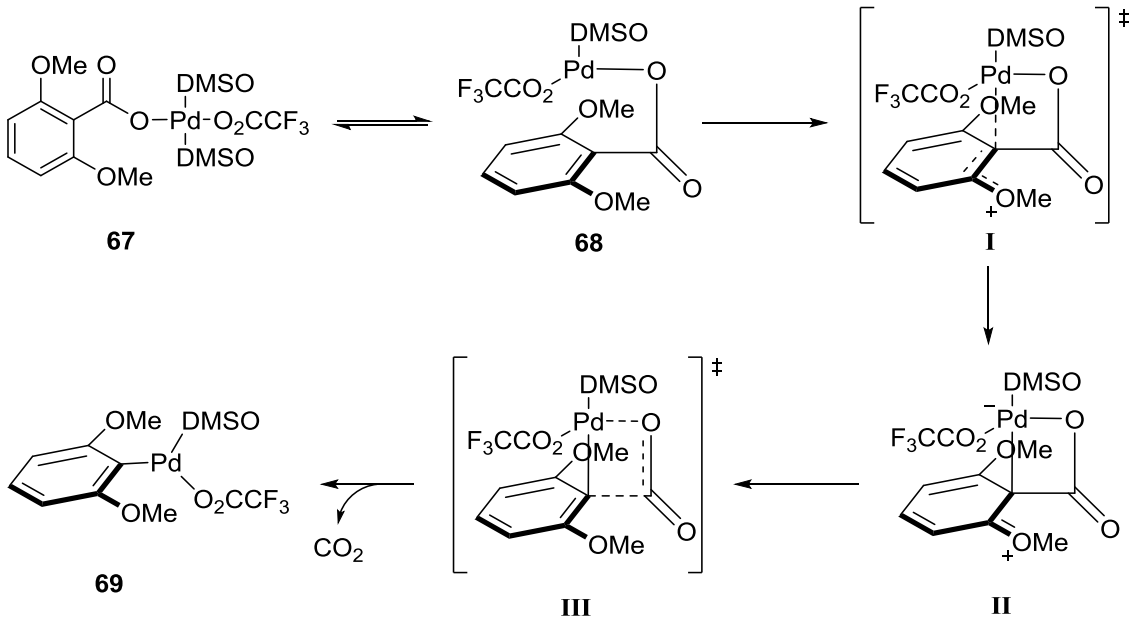
Scheme 31: Larrosa decarboxylative auration of *ortho*-substituted benzoic acids

Work by Nolan and Cazin displayed similar effects, with *N*-heterocyclic carbene (NHC) ligands used to stabilise the desired aurated species.[81] Successful decarboxylative auration of *ortho*-substituted acids, or *ortho*-heteroaromatic acids was demonstrated in 20 hours. Notably the decarboxylative auration of *para*-methoxy benzoic acid was also possible in 70 hours; however this remains the only example of non-*ortho*-substituted species being decarboxylated in the presence of gold.

2.1.6. The *ortho*-effect

Throughout the field of decarboxylative cross-coupling one limitation is constant. In order for decarboxylation of the benzoic acid to occur, there needs to be an *ortho*-substituent, and generally that substituent needs to be either strongly electron donating or electron withdrawing. In the case of heteroaromatics, this is also displayed in the necessity for the carboxylate group to be *ortho*- to the heteroatom.

Kozlowski has examined the kinetics of the palladium mediated decarboxylative process.[82] This generally requires bis-*ortho*-substitution of the benzoic acid, however does occur at temperatures as low as 70 °C. These mechanistic studies support the hypothesis that the generation of palladated species **69** occurs through intramolecular electrophilic palladation at the *ipso*-position, followed by decarboxylation (**Scheme 32**) and this transition state is supported in studies by Liu and co-workers.[65] With the palladation happening intramolecularly it is required that the carbonyl become almost perpendicular to the arene – this is facilitated by the steric impact of the *ortho*-substituents. This is potentially why these acids can undergo decarboxylation at such low temperatures. With electron rich systems it is suggested that the electrophilic palladation is the rate determining step, however depending on the electronics of the substrate this will shift between the palladation and the decarboxylation.

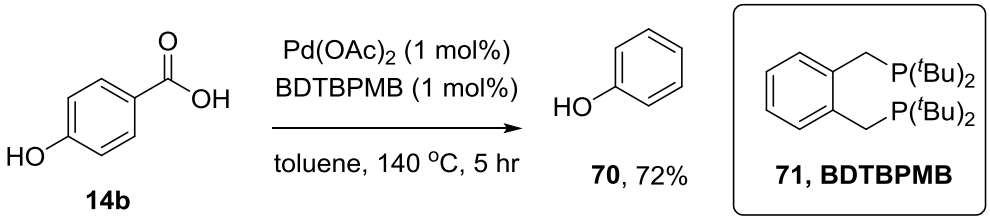


Scheme 32: Kozlowski proposed mechanism for decarboxylative palladation

DFT calculations have been used by Su and Lin to rationalise the mechanism for copper and silver mediated carboxylation and to gain an understanding for the requirement of an

ortho-substituent or heteroatom.[83] It is suggested that when an *ortho*-substituent is present the steric impacts destabilise the starting state of the acid as the acid group is forced out of the plane of the ring - similar to that with the palladation mechanism.[82] This raises the energy of the acid with respect to a planar acid without an *ortho*-substituent. Consequently the energy barrier is smaller for acids bearing an *ortho*-substituent, which is a plausible explanation as to why the reaction is only observed to proceed for these substrates under the assessed conditions.

In general the reaction can sometimes be forced using higher temperatures or by carefully controlling the ligand environment. Cole-Hamilton has demonstrated the successful decarboxylation of 4-hydroxybenzoic acid in the presence of 1 mol% palladium acetate using bidentate ligand 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (BDTBPMB) at 140 °C (**Scheme 33**).[84] The bite angle of the diphosphine ligand was found to be important, with ligands such as dppe, dppf and dppb all showing reduced yields. Highly electron rich P^tBu_3 also demonstrated high yield, with other electron rich phosphines only being slightly lower, demonstrating that highly electron rich ligand environments can help support this transformation.



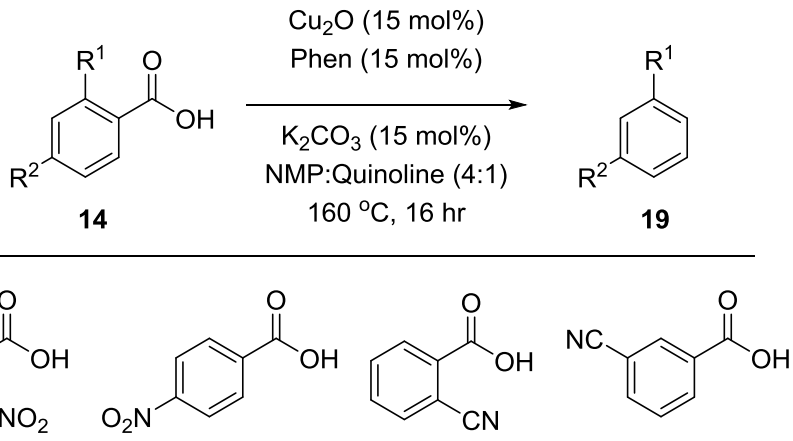
Scheme 33: Cole-Hamilton decarboxylation of 4-hydroxybenzoic acid

Gooβen has demonstrated the decarboxylation of *meta*- and *para*- substituted benzoic acids under copper catalysed conditions at 170 °C in the presence of 1,4-biphenyl-1,10-phenanthroline (Diphen).[56] Through these studies, the Gooβen group also shed some insight on the *ortho*-substitution effect. In their research it was noted that the addition of halide anions (i.e. through addition of LiBr) severely impacted the overall conversion of the protodecarboxylation reaction when non-*ortho* substituted acids were used – and this was not the case for *ortho*-substituted acids (**Table 2**).[54]

It was suggested that the release of halides from the aryl halide species is generating copper halide salts which are inactive in the reaction. Formation of these salts is in competition with co-ordination of the copper complex to the carboxylate to propagate the decarboxylation process. It is hypothesised that co-ordination of the *ortho*-substituent

would enhance the copper-carboxylate ligation and therefore outcompete generation of the copper halide salts – allowing for the reaction to be catalytic in copper. This is demonstrated in that reactions where non-*ortho*-substituted acids require superstoichiometric quantities of copper (as well as harsher conditions) to allow full conversion, whereas the process is catalytic for *ortho*-substituted acids.

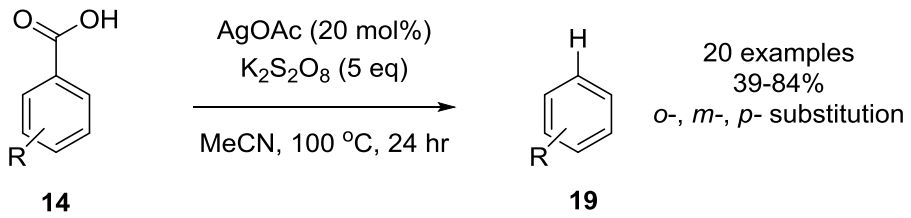
Table 2: Change in yield of protodecarboxylation for *ortho*- and *para*- substituted acids in the presence of LiBr



	14a	**14c**	**14d**	**14e**
Cu	59%	49%	40%	72%
Cu + LiBr (15 mol%)	63%	6%	25%	24%

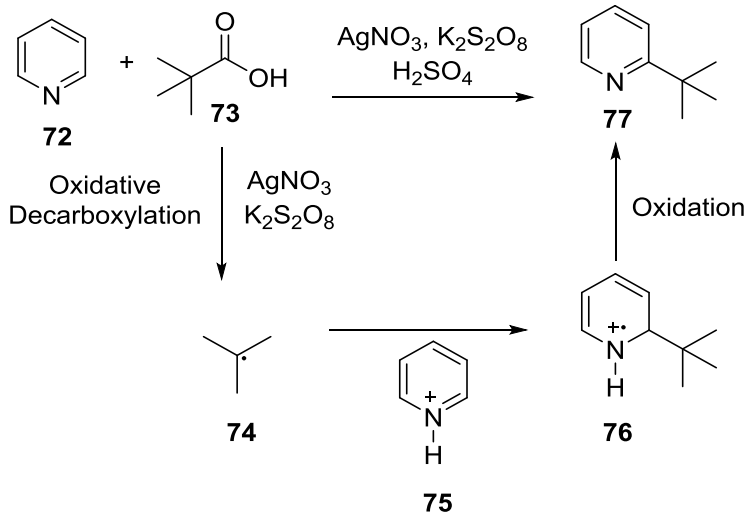
This co-ordination effect would also provide an explanation as to why the substituent generally needs to be some sort of heteroatom. In later work the group have succeeded in coupling benzoic acids with triflates, tosylates and mesylates.[59-61] The absence of the aryl halide in this case prevents the generation of inactive copper halide salts from sequestering the copper away from the decarboxylative process. This allows the reaction to function well for *ortho- meta-* and *para-* substituted acids. While the high temperatures required for these transformations are not ideal this evidence does support the considered co-ordination effect of the *ortho*-substituent.

Despite the success of the Gooβen group in facilitating the decarboxylation of *meta-* and *para-* substituted benzoic acids, the reliance on such harsh conditions is not ideal. Work within the Greaney group has demonstrated that under radical conditions generated from the combination of Ag^{I} and potassium persulfate ($K_2S_2O_8$) protodecarboxylation of *meta-* and *para-* substituted acids can be achieved at 100 °C (**Scheme 34**).[85]



Scheme 34: Greaney decarboxylation of benzoic acids under radical conditions

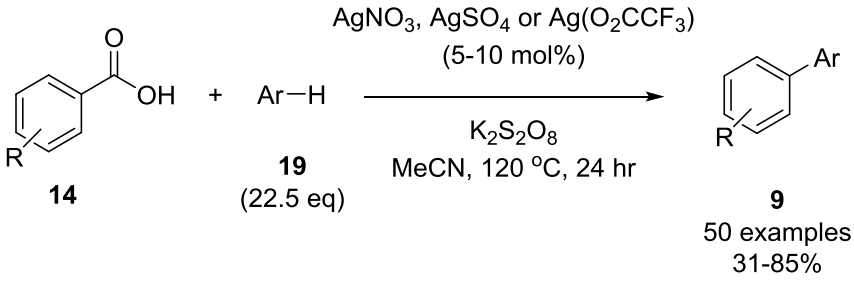
These conditions are reminiscent of the Minisci reaction chemistry which uses silver and persulfate anions to generate alkyl radicals from alkyl carboxylates, with subsequent addition to protonated heteroaromatic bases (**Scheme 35**).[86,87] Oxidative decarboxylation generates alkyl radical **74** which adds to the protonated heteroaromatic. Subsequent oxidation of the intermediate leads to the alkylated product.



Scheme 35: The Minisci reaction

While attempts were made within the Greaney group to generate a method for the decarboxylative cross-coupling of arenes using the radical oxidative methodology, the group were unsuccessful in doing this. This has since been realised by Su and co-workers who were able to develop conditions for the decarboxylative cross-coupling of arenes and heteroarenes (**Scheme 36**).[88] This method employs C–H activation in the cross-coupling, a method which will be further discussed in **Section 2.1.8**. The silver species was altered depending on the specific substrates, so one general method resulting in high yields across a broad substrate range was not found. In systems with simple unsubstituted arenes one product was synthesised, however use of arene and heteroarene coupling partners bearing substituents lead to a mixture of inseparable regioisomers. The development of

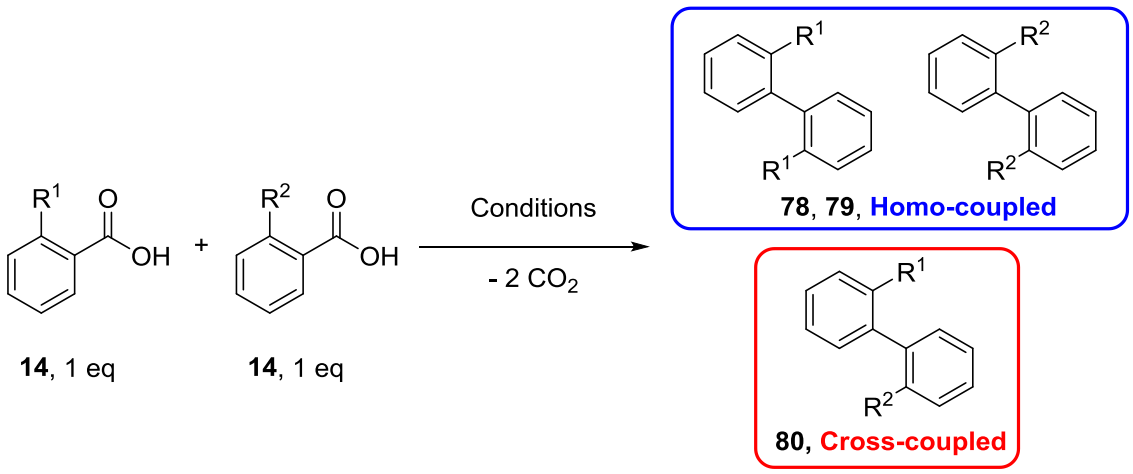
conditions which lead to the regiospecific coupling of non-*ortho*-substituted benzoic acids with arene partners remains unrealised.



Scheme 36: Decarboxylative arylation of arenes/heteroarenes under radical conditions

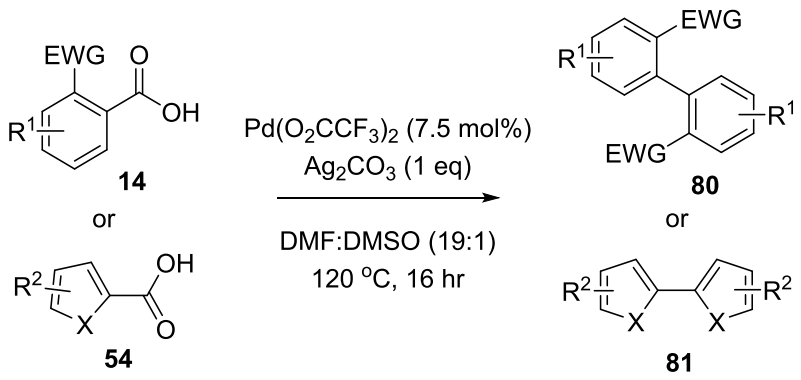
2.1.7. Decarboxylative cross-coupling of two acids

The decarboxylative cross-coupling of two acids is a challenge as this can result in either the symmetrical homo-coupled products, or the unsymmetrical product (**Scheme 37**). In most cases a mixture of all of the products would be expected, and specific attention would need to be paid to the electronics of the substrates and the transition states in order to bias the generation of one product.



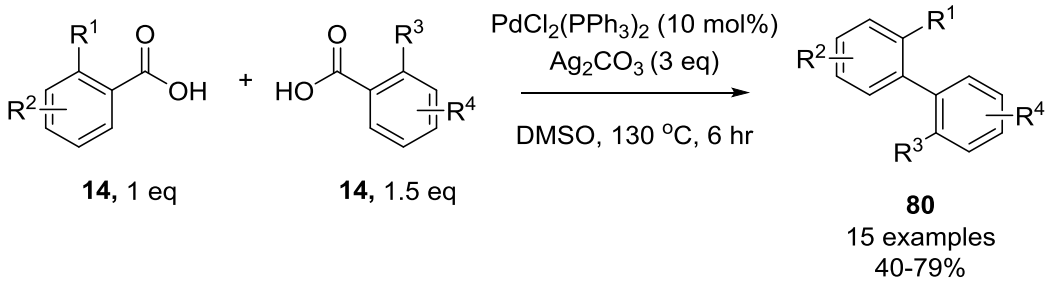
Scheme 37: Products from the decarboxylative cross-coupling of two benzoic acids

Larrosa disclosed the first example of homo-coupling of arenes and heteroarenes in 2010.[89] Reaction conditions required catalytic palladium and stoichiometric silver and allowed the synthesis of symmetrical biaryls in reasonable yields (**Scheme 38**). The main limitation of this protocol is the necessity of an electron withdrawing group at the *ortho*-position of the acid or, in the case of heteroaromatic acids, that the heteroatom is *ortho*- to the carboxylate group.



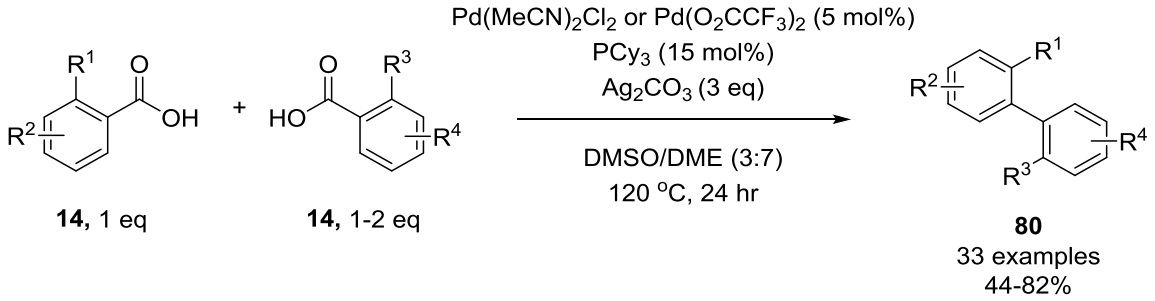
Scheme 38: Larrosa decarboxylative homo-coupling of benzoic acids

In 2011 a methodology from Tan and Deng realised the unsymmetrical cross-coupling of two benzoic acids (**Scheme 39**).[90] Initial examples showed that using two electronically different benzoic acids could generate the desired unsymmetrical product with only trace amounts of each respective homo-coupled product. The complex nature of this reaction is clear from the published results as many examples result in mixtures of the 3 possible products. However, in general the major product was the desired unsymmetrical biaryl and this was shown to still be the case when moving to more electronically similar acids.



Scheme 39: Tan and Deng decarboxylative cross-coupling in the formation of unsymmetrical biaryls

In complementary methodology published in 2012, Su and co-workers also demonstrated the successful decarboxylative cross-coupling of two benzoic acids to form unsymmetrical biaryls (**Scheme 40**).[91] Inclusion of tricyclohexylphosphine allowed for the palladium catalyst loading to be reduced by half, and the substrate scope was extended to demonstrate a wide range of suitable functionalities. The group found that both electronically different and electronically similar benzoic acids could be unsymmetrically coupled together in high yields, and that the choice of solvent and ligand was crucial in facilitating this transformation.

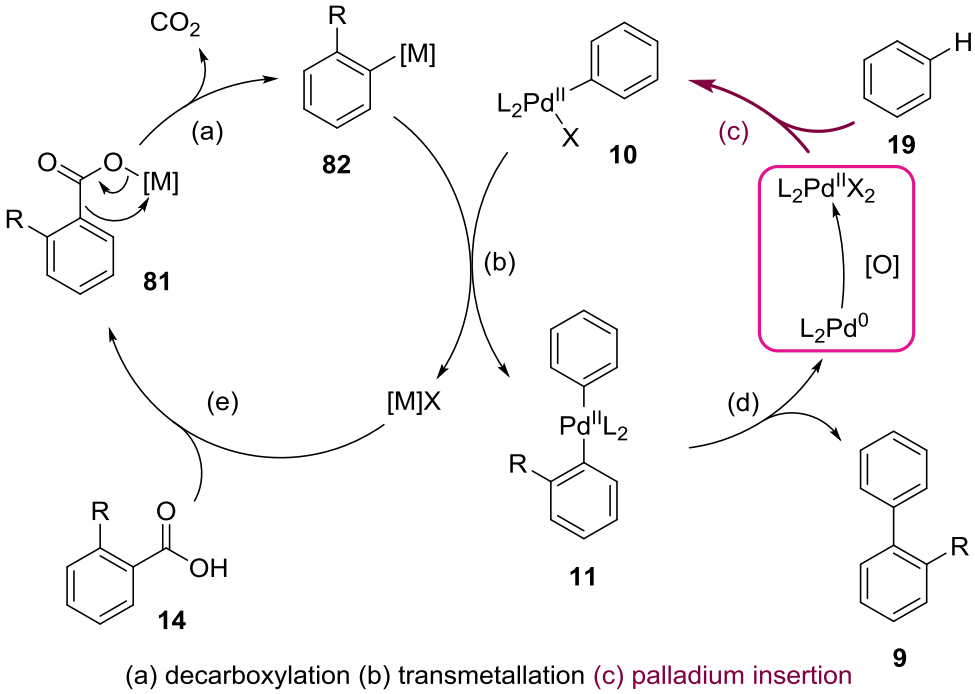


Scheme 40: Su decarboxylative cross-coupling in the formation of unsymmetrical biaryls

2.1.8. Decarboxylative cross-coupling in conjunction with C–H activation

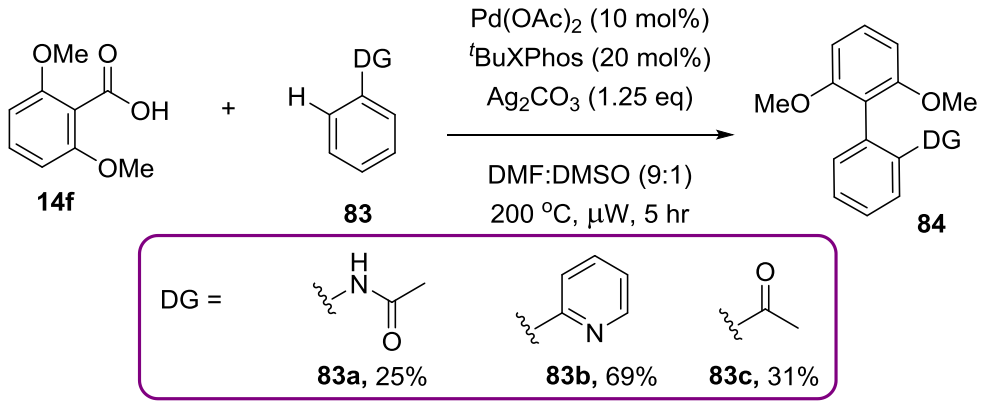
While the scope of decarboxylative transformations has grown substantially in the past 5 years, there are limited cases where tandem decarboxylation and C–H activation have been used in the construction of biaryls. The example shown in **Scheme 36 (Section 2.1.6.**) is one of the most recent examples of this chemistry. While the coupling with aryl halides is generally a less challenging approach, the impact of a method allowing the direct coupling with a C–H bond improves the environmental impact and the industrial appeal of the reaction by removing the need for pre-functionalisation of the arene coupling partner. There can be regioselectivity issues if multiple C–H bonds are present, therefore some way of distinguishing which C–H bond reacts is necessary. This is achieved either through electronically tuning the species, using sterics to hinder selected C–H bonds, or through the use of directing groups (**See section 2.2.**).[92-95]

Mechanistically the main difference between cross-coupling with C–H bonds and coupling with aryl halides is that this transformation will require oxidative conditions. Palladium insertion into a C–H bond is often a redox neutral process, therefore reductive elimination of the resultant biaryl would lead to a reduced catalyst. It is necessary to have a stoichiometric oxidant to regenerate the palladium catalyst to complete the catalytic cycle (**Scheme 41**).



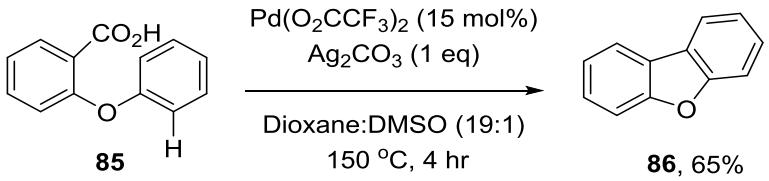
Scheme 41: General mechanism for the non-oxidative decarboxylative cross-coupling of arenes

One of the first examples of decarboxylative arylation using C–H activation was published in 2008 by Crabtree and co-workers. The group used directing groups to specifically activate a C–H bond for decarboxylative arylation (directing groups will be discussed more in **Section 2.2.**) (**Scheme 42**).[96] Unfortunately yields were poor over a limited substrate scope, with the main issue being generation of large quantities of the protodecarboxylation product. The Crabtree notes the necessity for the removal of water, as water content increases the quantity of the undesired protodecarboxylation product. It is notable that both *para*-tolyl benzoic acid and *para*-fluoro benzoic acid were successfully cross-coupled under the reaction conditions. While the novelty of a reaction combining two relatively "green" chemical processes was clearly demonstrated, there was still significant room for improvement.



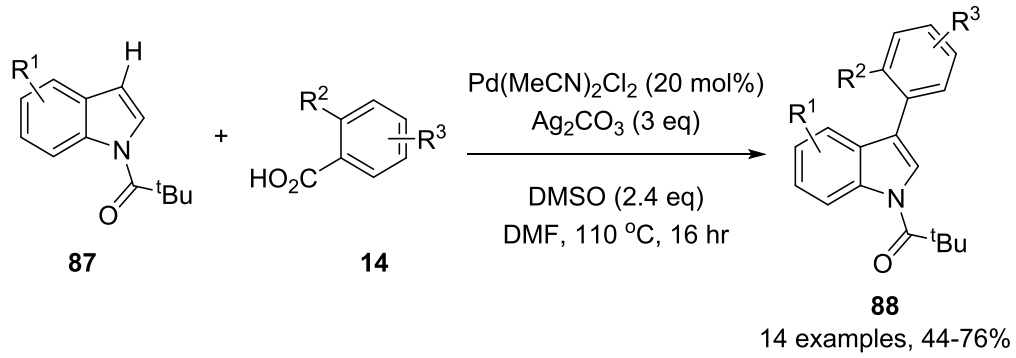
Scheme 42: Crabtree directing group assisted decarboxylative C–H arylation

Glorius has demonstrated a tandem decarboxylation/C–H activation procedure in an intramolecular fashion (**Scheme 43**).[97] High conversion to dibenzofuran compounds was possible, though in some cases significant protodecarboxylation was also observed. Extending the scope of this transformation to be performed in intermolecular systems would be highly desirable.



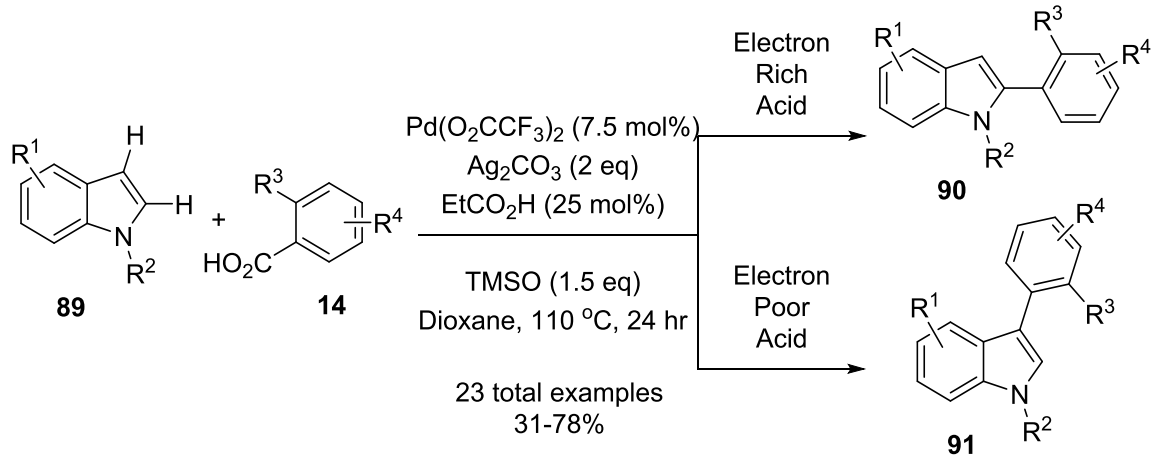
Scheme 43: Glorius intramolecular decarboxylation/C–H activation

In 2009 Larrosa developed the decarboxylative C–H arylation of indoles under palladium catalysed conditions (**Scheme 44**).[98] Diverse functionality was tolerated under these conditions, however the scope for the acid was limited to those bearing an electron withdrawing group (EWG) as an *ortho*-substituent (such as NO_2, Cl or F). While *meta*- or *para*- substitution with electon donating groups (EDG) was tolerated in conjunction with an *ortho*-EWG, having only EDG's in the *ortho*-positions was not tolerated.



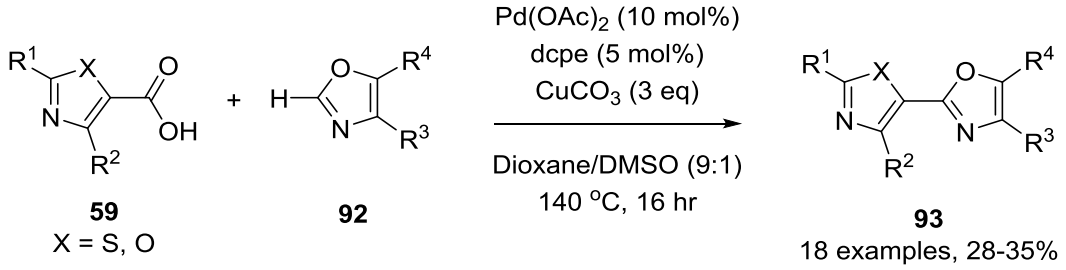
Scheme 44: Larrosa decarboxylative C–H arylation of indoles

Su and co-workers also developed a complementary method for the direct arylation of indoles under decarboxylative conditions.[99] In this full study the electronics of the benzoic acid were observed to alter the resultant substitution of the indole. While there was often trace formation of the opposing substituted product, generally this was in a >95:5 ratio. Electron rich acids were shown to favour arylation at the 2 position, and electron poor acids favoured arylation at the 3 position (**Scheme 45**).



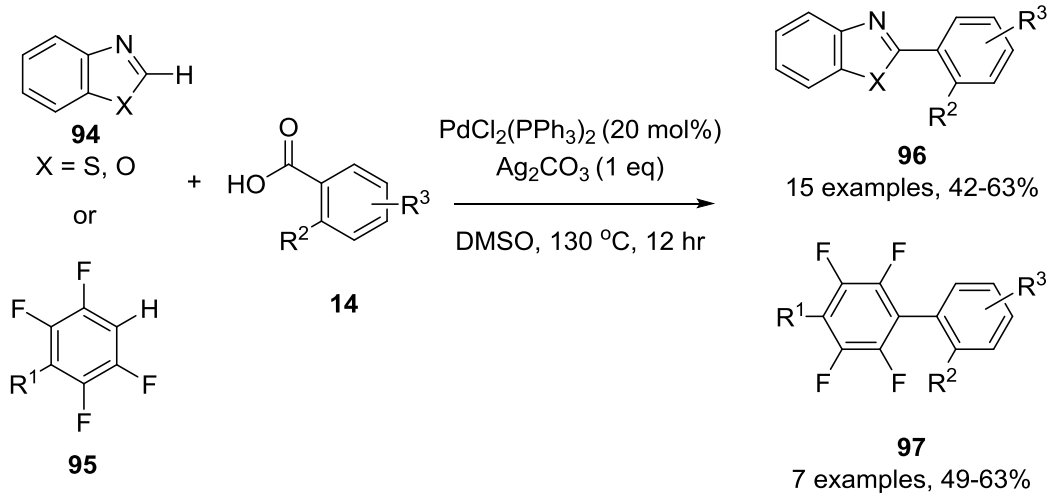
Scheme 45: Su decarboxylative direct arylation of indoles

Work in the Greaney group in 2010 has demonstrated the application of decarboxylative cross-coupling *via* C–H activation in the construction of bis-azoles (**Scheme 46**).[100] Similarly, Tan has reported the cross-coupling of benzoic acids with thiazoles and benzoxazole *via* C–H activation (**Scheme 47**).[101]



Scheme 46: Greaney decarboxylative cross-coupling in the formation of bis-oxazoles

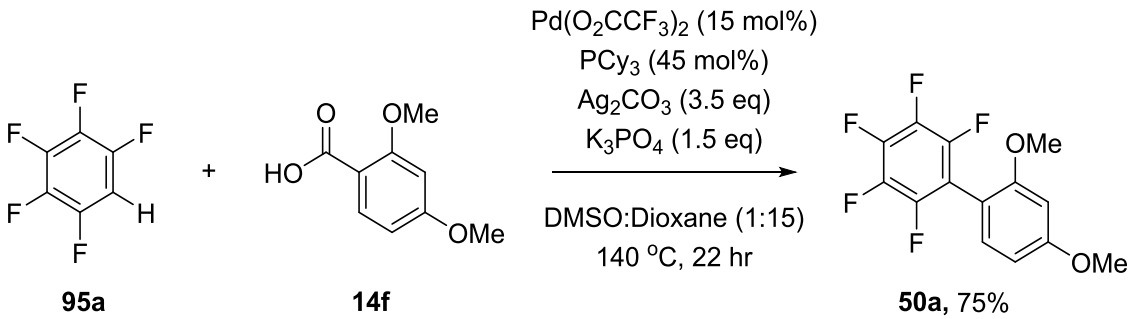
The method by Tan and co-workers was also demonstrated to work for polyfluorobenzenes – the similarity of these species being that the C–H bond is more electronically accessible for C–H activation. These methods use a silver or copper oxidant allowing the species to mediate the decarboxylation process as well as closing the palladium catalysed cycle.



Scheme 47: Tan decarboxylative arylation with thiazoles, benzoxazoles and fluorobenzenes

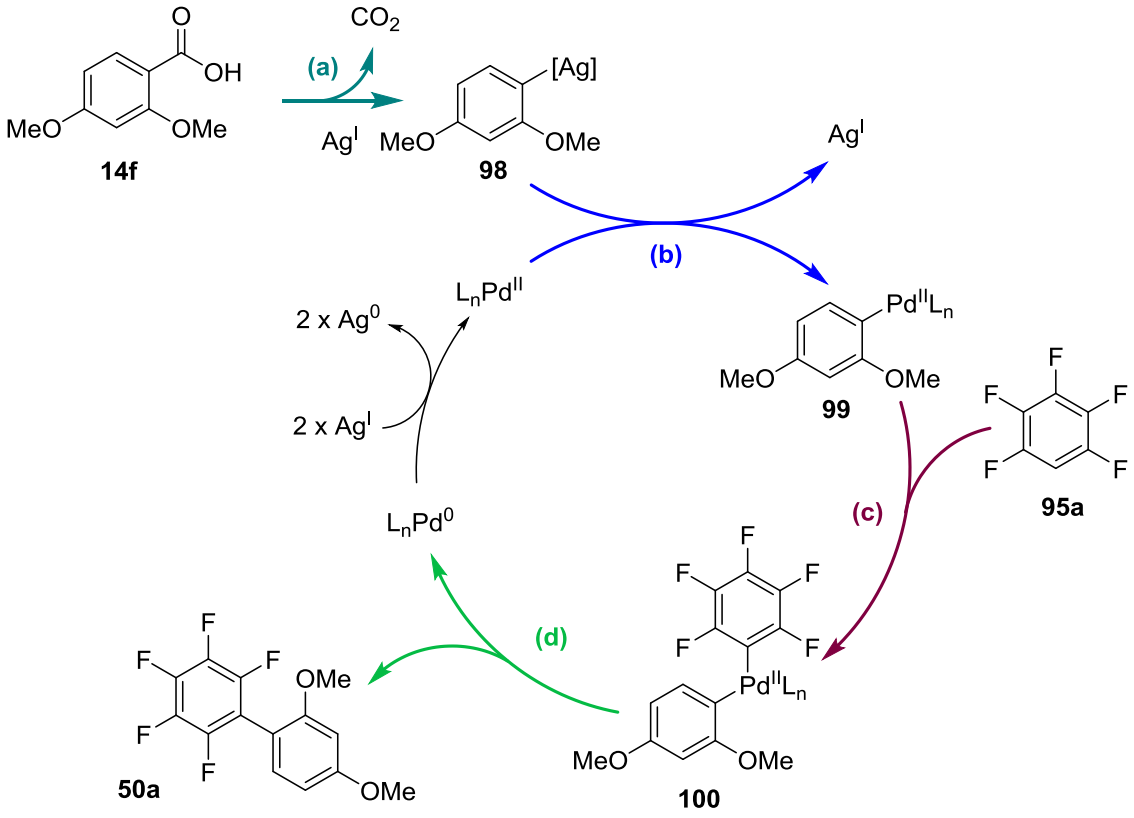
Further work by Su in 2010 showed another variety of intermolecular decarboxylative arylation.[102] Employing pentafluorobenzene (**95a**) they demonstrated the cross-coupling with 2,4-dimethoxybenzoic acid (**14f**) in 75% yield, with catalytic palladium and excess silver (**Scheme 48**). 30 other examples were demonstrated, varying both the benzoic acid and the fluoroarene coupling partner, giving consistently moderate to high yields. A number of aromatic heterocyclic carboxylic acids were successfully coupled; however, as with most decarboxylation reactions reported the acid substrate was limited to those bearing *ortho*-substituents or *ortho*-heteroatoms. The arene partner was restricted to highly electron poor aromatics bearing multiple electronegative fluorine groups. While

arenes with 4 or 3 fluorines were tolerated, yields started to decrease and substrates bearing only 2 fluorine atoms resulted in low yields.



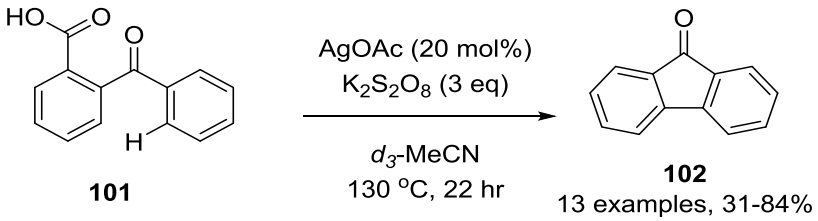
Scheme 48: Decarboxylative cross-coupling through C–H activation

The mechanism is proposed via a Pd^0/Pd^{II} catalytic cycle (**Scheme 49**). Decarboxylation of the benzoic acid in the presence of Ag^I forms the silver coordinated aryl complex **98**, which transmetallates to Pd^{II} forming **99**. Insertion of the Pd^{II} into the C–H bond occurs, forming complex **100**, and reductive elimination yields the desired biaryl product **50a** and Pd^0. The presence of an excess of silver is necessary to reoxidise the Pd^0 to Pd^{II} to complete the catalytic cycle.



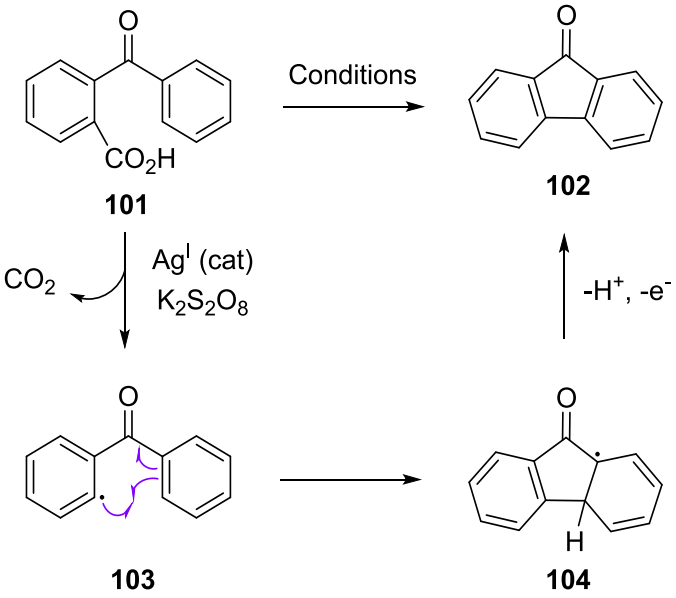
Scheme 49: Proposed Pd^0/Pd^{II} mechanism for decarboxylative arylation

More recently the Greaney group has disclosed methodology for the synthesis of fluorenones through an intramolecular decarboxylative arylation/cyclisation (**Scheme 50**).[103] The silver/persulfate combination is evocative of the Minisci type conditions,[86] therefore a radical based mechanism was anticipated. Yields were moderate to high, and a range of functionality was tolerated on the aromatic rings in either the *ortho*- or *para*- positions.



Scheme 50: Greaney decarboxylative C–H arylation in the synthesis of fluorenones

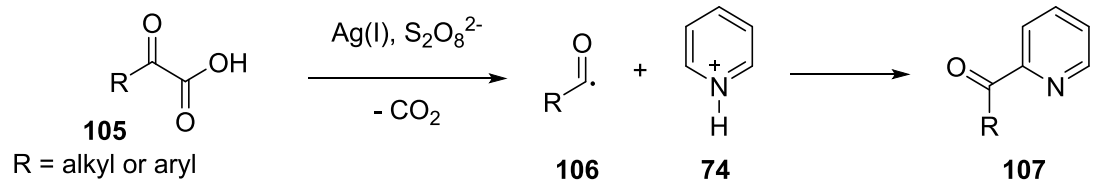
Conversion to the protodecarboxylated product was competitive with product formation when standard acetonitrile was used. Change of the solvent to deuterated acetonitrile prevented this – presumably as it is abstraction of a proton from the solvent which generates the protodecarboxylated species. The expense of this solvent and necessity of its use to maintain high yields significantly impacts the utility of the reaction. Mechanistically it was reported that oxidative decarboxylation under silver/persulfate conditions would generate radical **103**. Cyclisation of this species occurs, before single electron oxidation and proton loss generated the final product (**Scheme 51**).



Scheme 51: Proposed radical mechanism for the synthesis of fluorenones

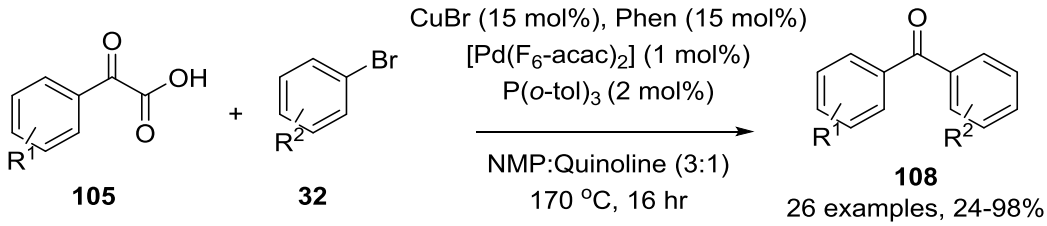
2.1.9. Extension to α-oxocarboxylic acids

Minisci's work with silver and persulfate in the production and use of alkyl radicals has been extended to use α-oxocarboxylic acids to generate carbonyl radicals. This process is accessible at room temperature in the presence of catalytic silver and stoichiometric persulfate.[104] The use of these species in a decarboxylative manner has increased interest in the compound set as a potential acylation precursor (**Scheme 52**). It has been known since the early 2000s that α-oxocarboxylic acids (also known as α-ketoacids) will undergo decarboxylative arylation in a Friedel Crafts type manner in acidic media. Low yields of the acylated product and mixtures with by-products resulting from decarbonylation and decarboxylation however limited the applicability of such a reaction.[105]



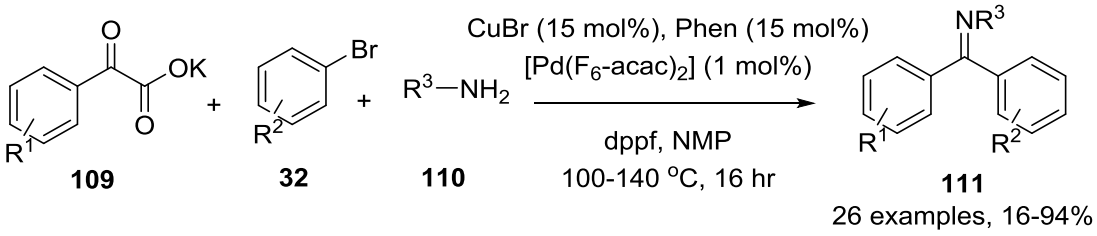
Scheme 52: Minisci reaction using α-oxocarboxylic acids to generate carbonyl radicals

Recently the inclusion of α-oxocarboxylic acids into decarboxylative cross-coupling processes has been explored in the formation of biaryl ketones. Studies by Gooβen have demonstrated applicability of phenylglyoxylic acid (**105**) in Cu/Pd catalysed cross-coupling with aryl bromides in a similar manner to the decarboxylative process used for benzoic acids.[106] Yields were temperamental; however ketone products were isolable in high yield for certain substrates (**Scheme 53**). Later the process was extended to allow the coupling with aryl chlorides[58] and aryl triflates.[59]



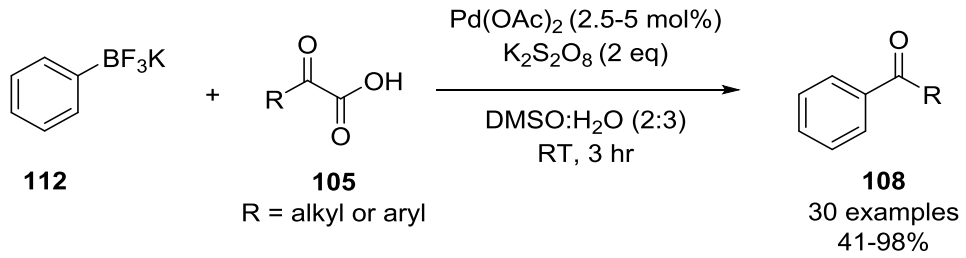
Scheme 53: Gooβen decarboxylative couplings of α-oxocarboxylic acids

Gooβen has also developed a multi-component reaction utilising the decarboxylation of α-oxocarboxylic acid salts in the synthesis of azomethines.[107] A one pot reaction with **109**, an amine and an aryl bromide, in the presence of CuBr, phenanthroline, $Pd(F_6\text{-acac})_2$ and 1,1'-bis(diphenylphosphanyl)ferrocene (dppf) gave the desired azomethine products (**111**) in high yields (**Scheme 54**).



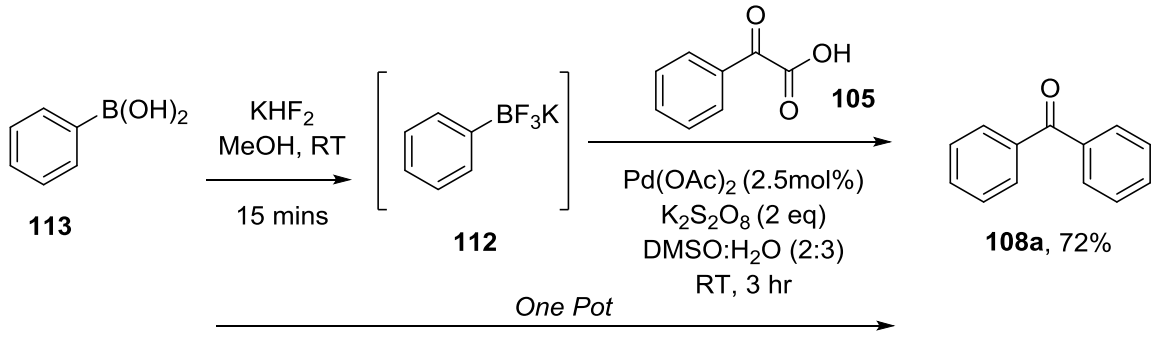
Scheme 54: Gooβen decarboxylative couplings of α-oxocarboxylic acids

In 2011 Ge and co-workers published the decarboxylative cross-coupling of *α*-oxocarboxylic acids with potassium trifluoroborates. The reaction was possible at room temperature with palladium and potassium persulfate (**Scheme 55**).[108] The main limitation of this methodology however is the necessity for prior formation of the potassium trifluoroborates which have restricted commercial availability.



Scheme 55: Ge decarboxylative coupling of *α*-ketoacids with potassium trifluoroborates

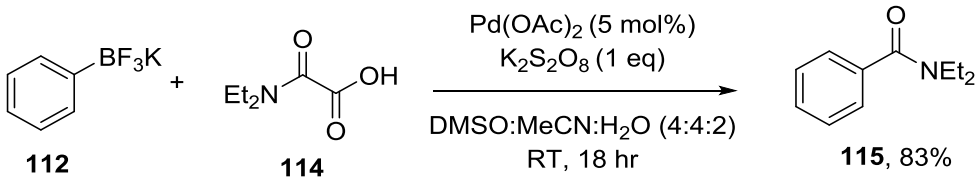
This limitation was realised by the group and they successfully demonstrated that a one-pot procedure for the coupling can be performed from phenylboronic acid. Generation of the potassium trifluoroborate with KHF_2 was complete in 15 minutes, and tandem addition of the reagents for the desired ketone formation gave benzophenone in an overall yield of 72% (**Scheme 56**).



Scheme 56: One pot procedure for the acylation of phenylboronic acid *via* initial generation of the potassium trifluoroborates

In a slightly different approach from Ge and co-workers, oxamic acids have also been shown to effectively undergo decarboxylative cross-coupling with potassium

phenyltrifluoroborates to generate benzamides.[109] This reaction also occurs at room temperature, with catalytic palladium, and yields are consistently high (**Scheme 57**).



Scheme 57: Cross-coupling of oxamic acids with potassium phenyltrifluoroborates

There are also numerous examples of the decarboxylative cross-coupling of α-oxocarboxylic acids with C–H bonds, using Lewis basic directing groups to convey regioselectivity. This will be discussed further in **Section 2.2.1**.

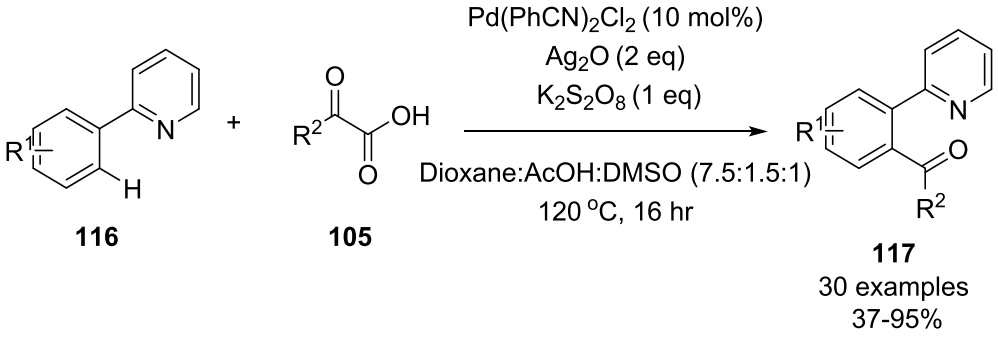
2.2. *Ortho*-directed arylation *via* C–H activation of benzoic acids

2.2.1. The use of directing groups in decarboxylative chemistry

C–H activation provides an environmentally and economically desirable method to cross-coupling products, favourable to that of classical methods involving pre-functionalised substrates. While C–H activation of inactive arene species is notably challenging, one of the main methods for facilitating this transformation is the installation of Lewis basic *ortho*-directing groups. This involves the presence of an *ortho*-substituent, which often co-ordinates the metal species to generate a stable chelating metallocycle. This directs the C–H activation and lowers the energy required for C–H bond insertion. The past decade has seen significant development in the availability of directing groups, and recent studies have shown that, amoung others, amides,[110] anilides,[111,112] esters,[113] sulfonamides[114] and carboxylate groups all contribute to *ortho*-activation. *Meta*-selectivity has also been indicated with α-aryl carbonyl compounds in the presence of catalytic copper.[115]

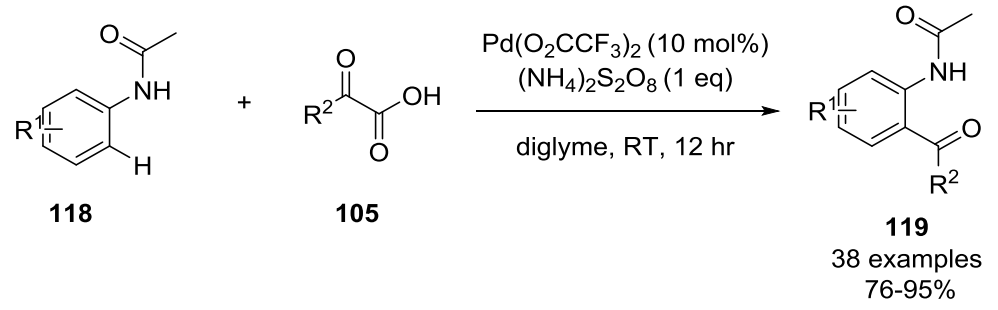
The use of directing groups in conjunction with decarboxylative chemistry has already been mentioned through work by Crabtree (**Scheme 42, Section 2.1.8.**). Despite this the use of directing groups in conjunction with the decarboxylation of benzoic acids remains largely unexplored. In comparison, the use of directing groups to impart selectivity in the decarboxylative cross-coupling of α-oxocarboxylic acids is far more defined. Ge was one of the first to published in the area of decarboxylative α-oxocarboxylic acid cross-coupling and a self-penned review of this work was published in 2014.[116] In 2010 methodology was developed for the decarboxylative acylation of arenes, *via* palladium

catalysed tandem decarboxylation of phenylglyoxylic acids and C–H activation of phenylpyridines (**Scheme 58**).[117] This was extended to room temperature catalysed decarboxylative *ortho*-arylation of acetanilides later the same year (**Scheme 59**).[118]



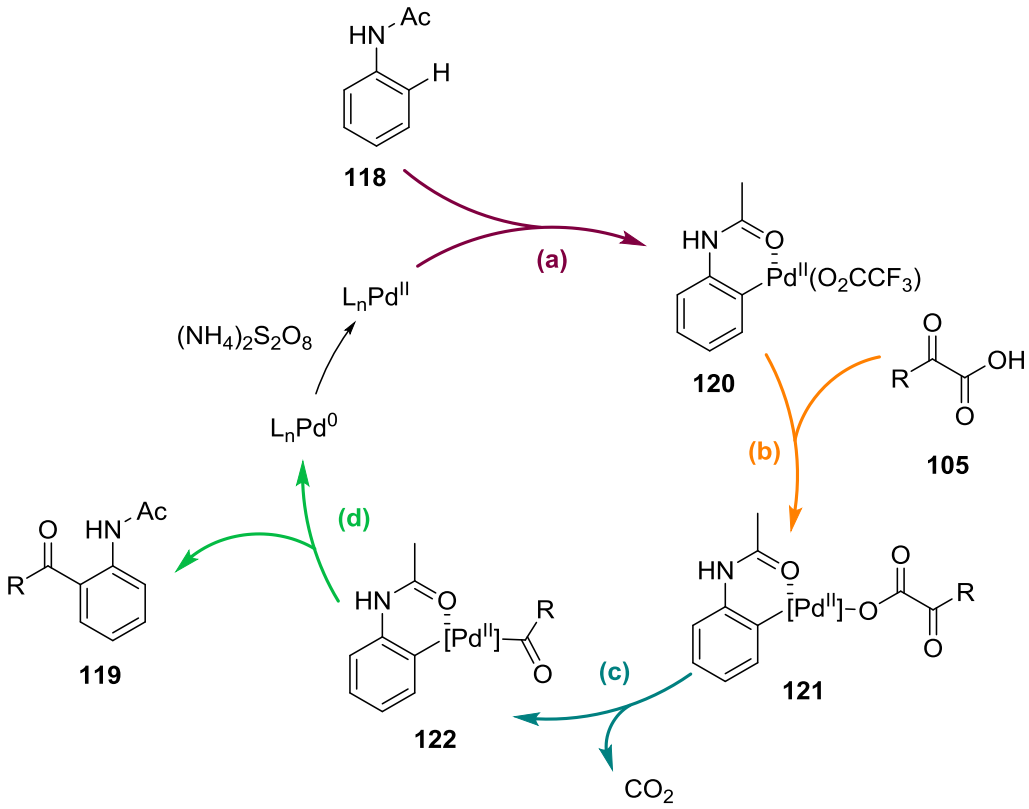
Scheme 58: Ge decarboxylative *α*-oxocarboxylic acid cross-coupling

The significant difference in the temperatures of these two reactions was noted by the group. Distinguishing between a radical type mechanism as evidenced by Minisci and co-workers, or a mechanism involving metallated species as proposed by Gooβen could help to rationalise the difference in temperatures. However the ability for the second reaction to be performed at room temperature implies that a different mechanism is involved. This became particularly clear when it was shown that the room temperature decarboxylative arylation of acetanilides was accomplished in the absence of the persulfate species, under O_2 or air, in lower yields. This would imply that a Minisci type oxidative decarboxylation to form the acyl radical was not occurring.



Scheme 59: Ge decarboxylative *α*-oxocarboxylic acid cross-coupling

The proposed mechanism is therefore based on a palladium mediated decarboxylation, involving ligand exchange (**Scheme 60**) however further mechanistic evidence would be required to determine whether this was the case.

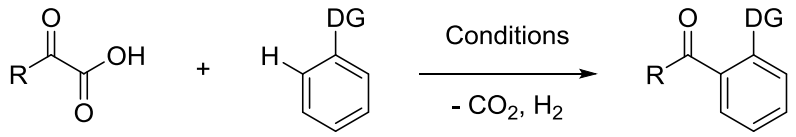


(a) C-H insertion (b) ligand exchange (c) decarboxylation (d) reductive elimination

Scheme 60: Proposed mechanism for the room temperature decarboxylative acylation of acetanilides

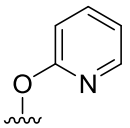
In the years following these initial publications there has been a surge of literature demonstrating the use of a wide range of directing groups in regioselective, decarboxylative C–H acylation reactions (**Table 3**). Zhang accomplished this with alkoxypyridines,[119] Kim with phenylacetamides,[120] *O*-methyl ketoximes[121] and *O*-phenyl carbamates,[122] Tan with *O*-methyl oximes,[123] Wang with azobenzenes[124] and azoxybenzenes,[125] and Kuang with thioesters.[126] Cyclic enamides and pyridine *N*-oxides have also been demonstrated to undergo selected C–H acylation under similar conditions.[127,128] Generally this is accomplished through a combination of palladium and silver, with some groups opting for the use of persulfate however a number of reactions work successfully without this. Temperatures are significantly lower than for the decarboxylation of benzoic acids. Most of these reactions are run at temperatures below 100 °C and a number proceed at room temperature.

Table 3: Range of directing groups for regeioselective decarboxylative C–H acylation

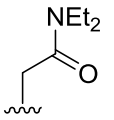


105 **83** **123**

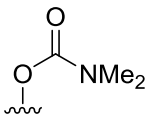
Directing groups



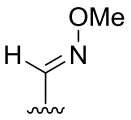
123a
alkoxypyridines
Zhang, 2013



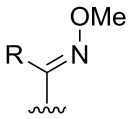
123b
phenylacetamides
Kim, 2013



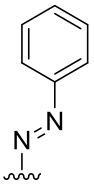
123c
***O*-phenylcarbamates**
Kim, 2013



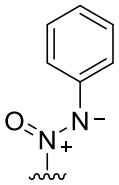
123d
***O*-methyl ketoximes**
Kim, 2013



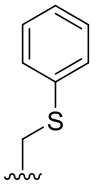
123e
***O*-methyl oximes**
Tan, 2013



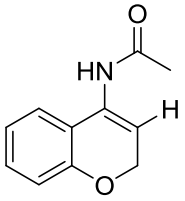
123f
azobenzenes
Wang, 2013



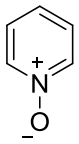
123g
azoxybenzenes
Wang, 2013



123h
thioethers
Kuang, 2014



124
cyclic enamides
Duan, 2012



125
pyridine *N*-oxides
Muthusubramanian, 2014

2.2.2. The use of carboxylic acids as directing groups

Carboxylic acids have been known to display regioselective lithiation *ortho* to the carboxylate with *s*-BuLi, *s*-BuLi/TMEDA and *n*-BuLi.[129] This regioselectivity has been shown by Mortier to be tuneable in the presence of potassium *tert*-butoxide (KO^tBu) to selectively activate *ortho*- to the methoxy group rather than the carboxylic acid in *o*- and *m*-anisic acid. (**Figure 2**).[130]

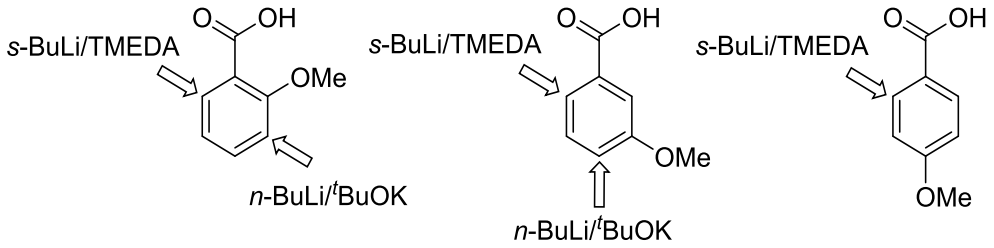
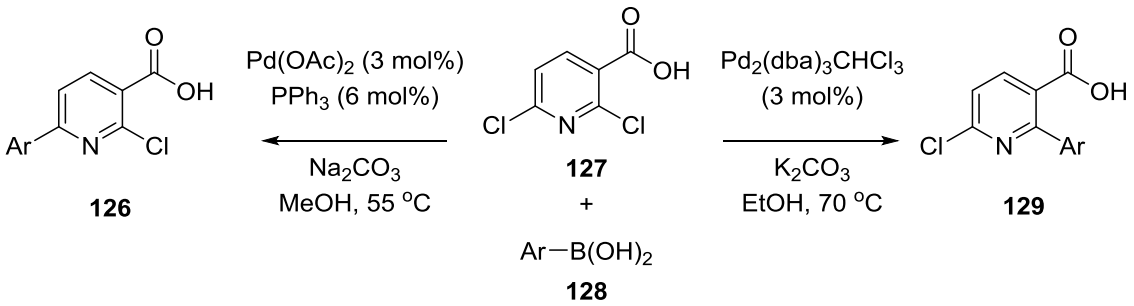


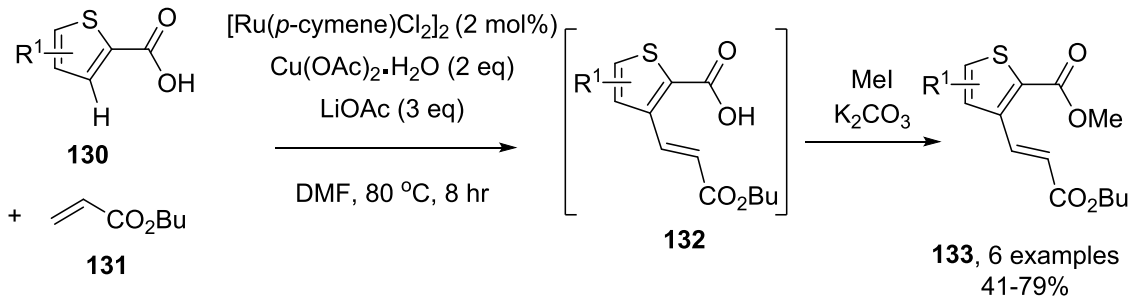
Figure 2: Regioselective lithiation of *o*- *m*- and *p*-anisic acid

However despite knowledge of carboxylate directing groups, relatively few successful methods for *ortho*-arylation of benzoic acids exist, and these methods often only produce moderate yields. The process is complicated by the potential for the arylated products (or the starting materials) to decarboxylate, especially at elevated reaction temperatures. Houpis has demonstrated the use of carboxylate directing groups in the regioselective Suzuki style coupling of dihalo-heterocycles (**Scheme 61**).[131] Here, switching between a palladium(II) and a palladium(0) species is shown to have significant impact on the regioselectivity of the reaction.



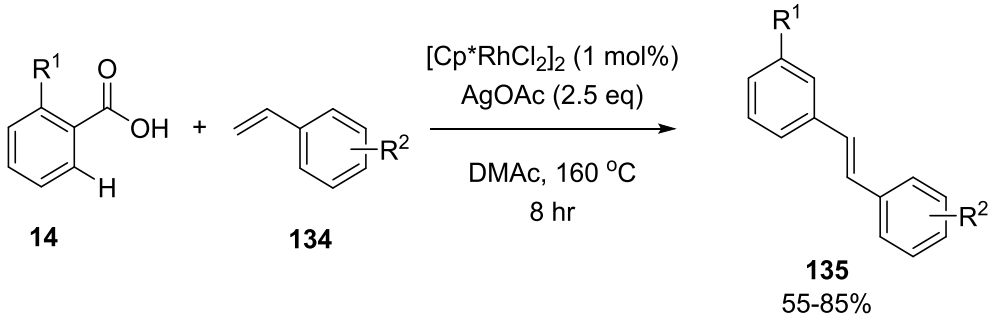
Scheme 61: Houpis use of carboxylate as a tunable directing group for Suzuki coupling of dichloro-heteroarenes

Similarly, Miura demonstrated the use of carboxylate directing groups in the regioselective alkylation of heteroarenes, with the carboxylate specifically directing C–H activation at the 3-position.[132] With the 2 position of the heteroarene generally being most active towards substitution; the effect of the carboxylate clearly directs the alkylation to the less commonly substituted position (**Scheme 62**).



Scheme 62: Carboxylate directed *ortho*-activation in Suzuki coupling (Houpis) and alkylation of heteroarenes (Satoh/Miura)

Miura has also demonstrated the rhodium catalysed alkenylation and subsequent decarboxylation of benzoic acids in the formation of stilbene related structures (**Scheme 63**). This silver mediated reaction can be performed as a one pot transformation at 160 °C.[133] The group also showed that splitting the procedure into a tandem process where olefination was performed at 120 °C after which addition of K_2CO_3 and increasing the temperature to 160 °C for the decarboxylation resulted in increased overall yields.

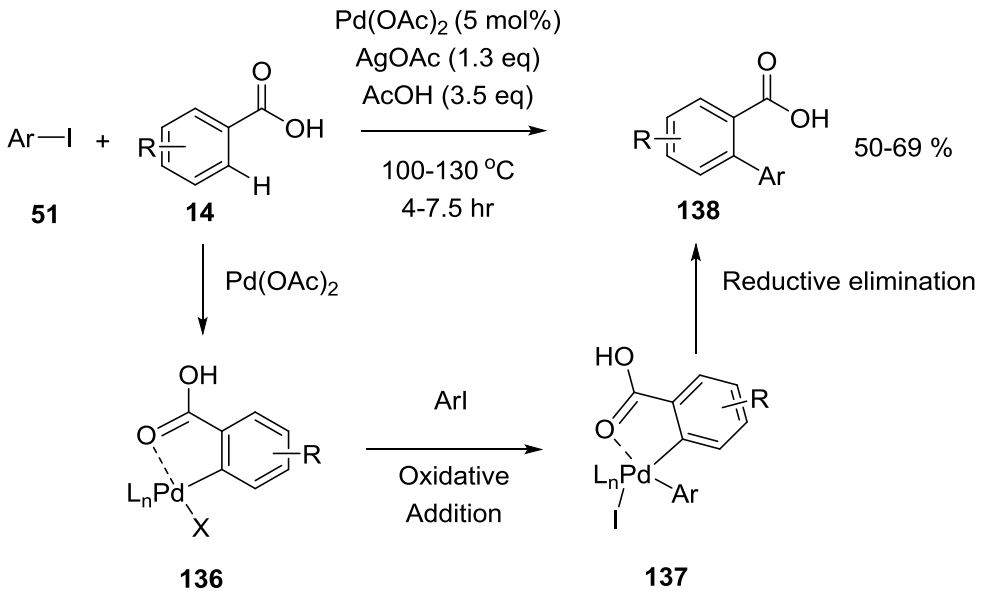


Scheme 63: Miura synthesis of stilbenes through rhodium catalysed carboxylate directed C–H activation and subsequent decarboxylation

2.2.3. Use of *ortho*-directed palladation of benzoic acids in cross-coupling

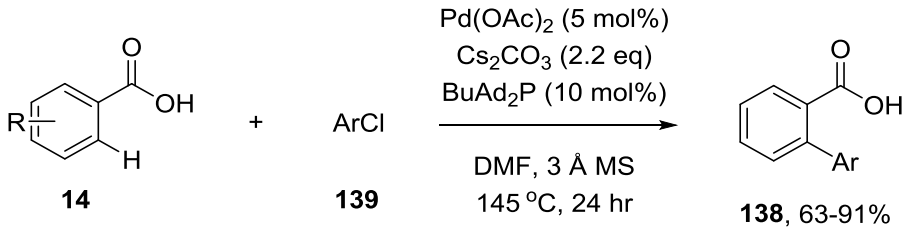
In 2007 Daugulis demonstrated two complementary methods for the direct *ortho*-arylation of benzoic acids.[134] The first method employed aryl iodides and proceeded in the presence of catalytic $Pd(OAc)_2$ and stoichiometric AgOAc. The optimal solvent for this method was acetic acid (AcOH) however yields were not impressively high. This was due to competing solvent arylation. Electron rich benzoic acids were most productive, with moderately electron deficient species also possible, with the coupling partner available as both electron rich and electron poor aryl iodides. The mechanism is proposed as a Pd^{II}/Pd^{IV} catalytic cycle, however this is disputed as evidence leading to this postulation was limited and a Pd^{0}/Pd^{II} cycle would be more common under these

conditions. Cyclometallation of the benzoic acid **14** followed by oxidative addition of the aryl iodide would give the Pd^{IV} species **137**, and this high energy complex would readily undergo reductive elimination to give the arylated product **138**. While a Pd^0/Pd^{II} could also be proposed, the absence of arylation when a Pd^0 species was used as the catalyst was seen as sufficient evidence to support the Pd^{II}/Pd^{IV} cycle (**Scheme 64**).



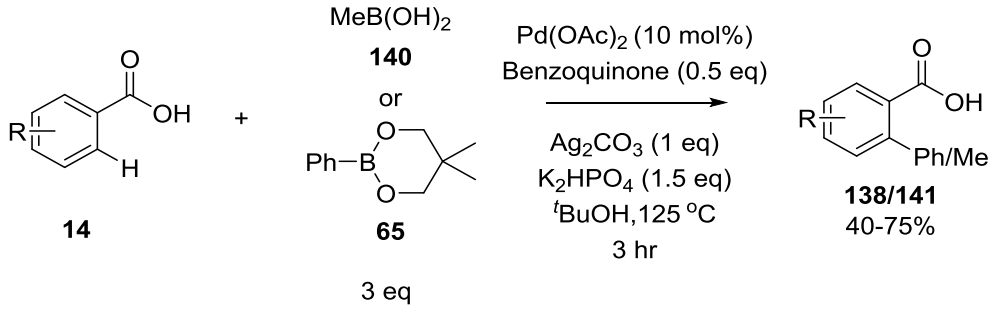
Scheme 64: Procedure and proposed mechanism for the *ortho*-arylation of benzoic acids with aryl iodides

The second method reported by Daugulis was employing aryl chlorides.[134] Successful arylation was achieved in the presence of catalytic $Pd(OAc)_2$, a bulky phosphine ligand, and cesium carbonate (Cs_2CO_3) (**Scheme 65**). Arylation with aryl chlorides generally proceeds *via* a Pd^0/Pd^{II} catalytic cycle, and cheap aryl chlorides are more economically viable than expensive aryl iodides. The use of the electron rich, bulky *n*-butyl-di-1-adamantylphosphine ($BuAd_2P$) ligand helps promote the Pd^0/Pd^{II} cycle. Yields were higher than the corresponding aryl iodide method, and the substrate scope was much broader. However other halide substituents were not viable, and when electron rich benzoic acids were combined with electron rich aryl chlorides decarboxylation of the corresponding product was often observed.



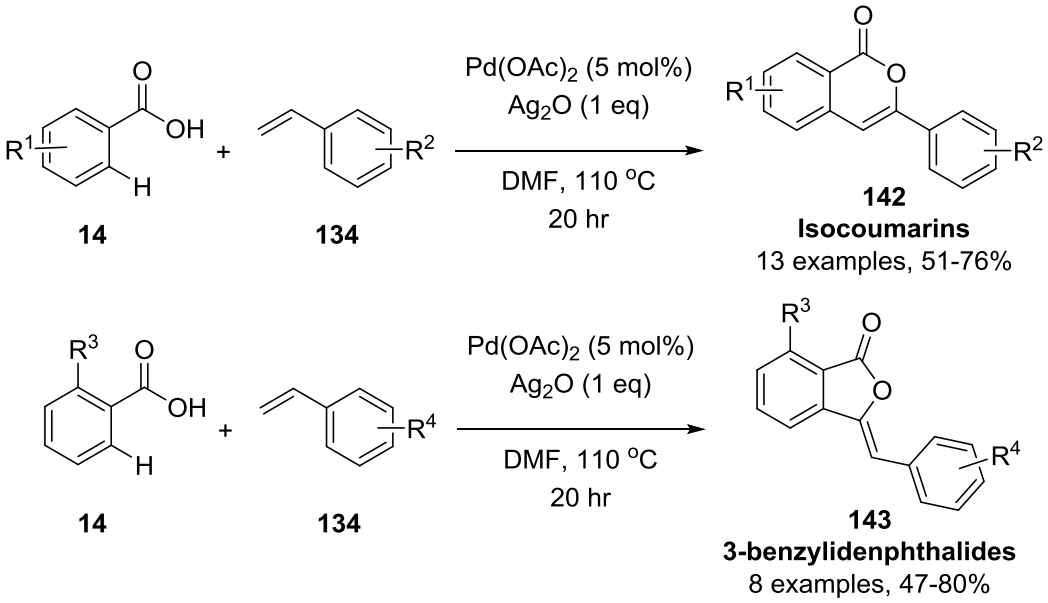
Scheme 65: *Ortho*-arylation of benzoic acids with aryl chlorides

Yu has also proposed a method for the *ortho*-arylation of benzoic acids.[135] Methyl boronic acid, or phenyl boronic ester **65** was coupled with a selection of methyl/methoxy substituted benzoic acids, and the yields were moderate to good (**Scheme 66**). Arylation generally occurred in lower yield than methylation, and the substrate scope was limited with electron deficient arenes giving poor yields. Dipotassium phosphate (K_2HPO_4) was necessary for *in situ* formation of the potassium carboxylate, as the free acid showed no transformation under the proposed reaction conditions. A Pd^0/Pd^{II} process seems most likely in this case, with 1 equivalent Ag^I necessary for reoxidation of the palladium species to complete the catalytic cycle. The same procedure also allowed *β*-arylation of aliphatic acids. Yu has also published an account into the development of the use of the carboxylate group in the functionalization of C–H bonds. This account discusses the modes of co-ordination of the palladium complex and this will be shown later to be relevant in this research.[136]



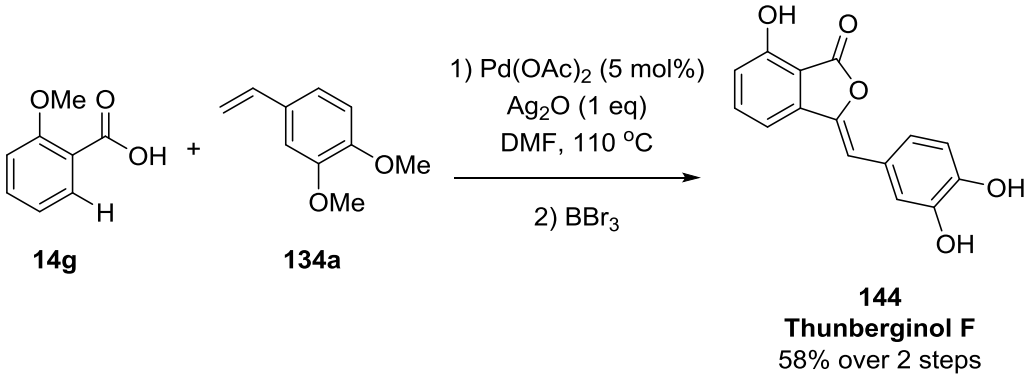
Scheme 66: *Ortho*-arylation of benzoic acids with boronic acids/esters

In 2013 Lee and co-workers developed a carboxylate directed synthetic approach to isocoumarins and 3-benzylidenphthalides (**Scheme 67**).[137] C–H olefination directed by the *ortho*-benzoic acid and subsequent palladium catalysed ring closure gave isocoumarin structures in moderate to high yields. Where an *ortho*-substituent was present on the acid the reactivity was moderated to cause the 5-membered-ring closure to give the corresponding 3-benzylidenphthalides.



Scheme 67: Lee synthesis of isocoumarins and 3-benzylidenephthalides

The novelty of this reaction is exemplified in the use of the directing group as part of the final product, alleviating the need for removal of the group at a later stage. The group displayed the applicability of this methodology in the synthesis of Thunberginol F with a yield of 58% in two steps from commercially available substrates (**Scheme 68**).



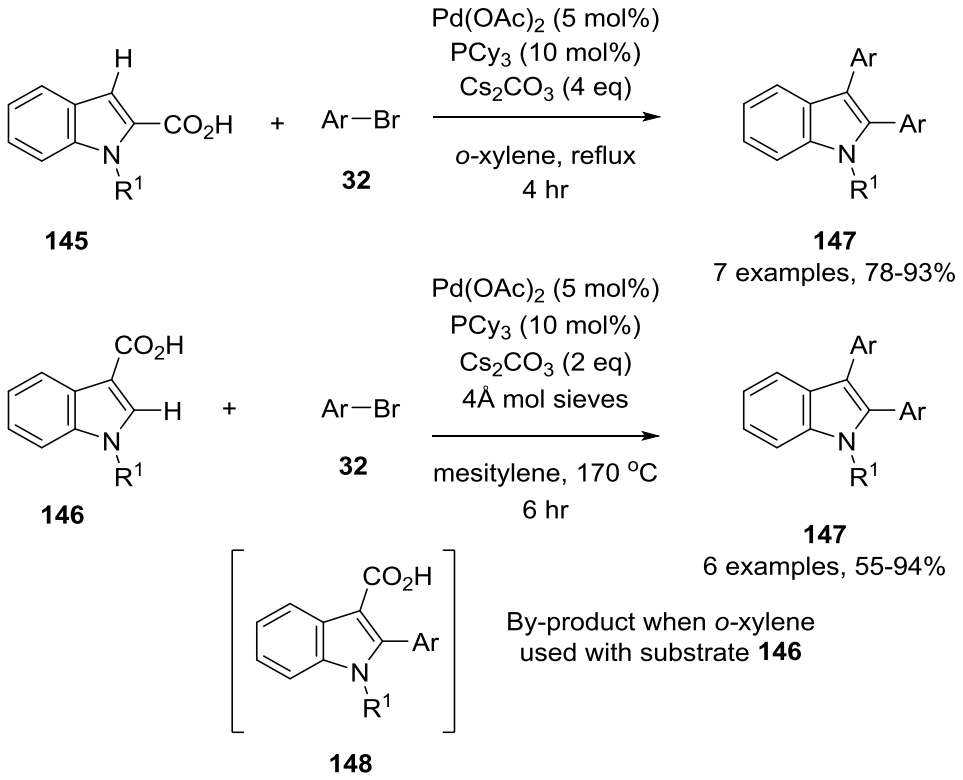
Scheme 68: Application of Lee procedure to the synthesis of Thunberginol F

2.2.4. Combining *ortho*-directed C–H activation of benzoic acids with decarboxylation

One of the main issues with using a directed C–H arylation approach is the necessity to install and then remove the directing group from the final product. This increases the number of synthetic steps required in a transformation and can cause issues where installation/removal requires conditions not tolerated by wide ranges of functionality. The ability to manipulate a directing group to either be removed, or exhibit further

functionality in the reaction, within a one-pot system is therefore a synthetically useful tool. While selected examples previously discussed in this introduction demonstrate this kind of reactivity, only a number of publications validate the process in the construction of biaryl structures.

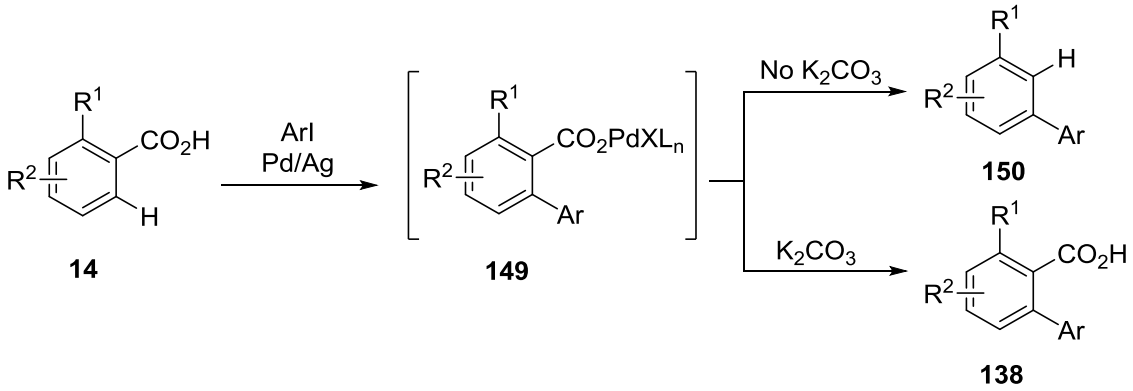
Miura reported in 2009 the synthesis of di-arylated indoles starting from 2 or 3 substituted indolecarboxylic acids (**Scheme 69**).[138] This work was an extension of syntheses previously discussed in **Section 2.1.8.** on the arylation of benzothiophenes. Wanting to generate fluorescent molecules, the group turned attention to arylating indoles. Results showed that under the reaction conditions both region-isomers of the starting acid could be successfully di-arylated in high yields. Isolation of **148** as an intermediate was possible when the reaction failed to go to completion. This revealed a plausible mechanism whereby carboxylate directed C–H arylation occurs initially, followed by decarboxylative cross-coupling at the *ipso*-position



Scheme 69: Miura work from 2009 demonstrating C–H arylation and decarboxylative cross-coupling in one pot

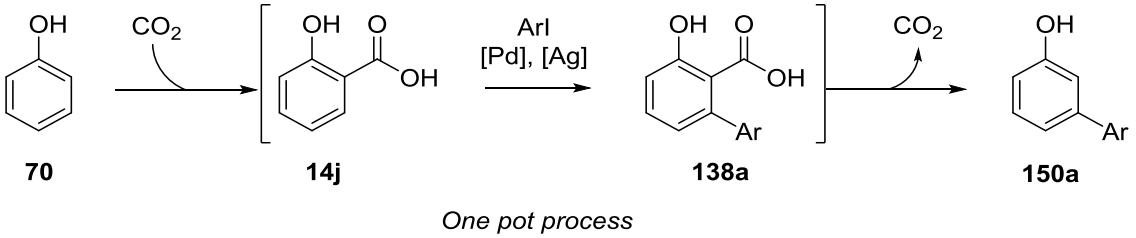
Larrosa and co-workers have published extensively on the reactivity of arylated benzoic acids. Initial results disclosed a method for the carboxylic acid directed arylation and subsequent decarboxylation to form biaryl species under palladium catalysed conditions

(**Scheme 70**).[139] Yields were high and a diverse set of biaryls were readily synthesised, giving effectively *meta*-substituted products. Further results showed that on inclusion of K_2CO_3 the benzoic acid could be retained, providing the 2-carboxylic acid substituted biaryl.[140] Again, this was demonstrated across a wide range of functionalities, with minimal decarboxylation observed in the final products.



Scheme 70: Larrosa work detailing one-pot carboxylate directed arylation and subsequent decarboxylation – or retaining the acid using K_2CO_3

This was taken further in 2013 with the publication of the *meta*-arylation of phenols *via* a "traceless" carboxylate directing group.[141] Installation and removal of the carboxylic acid was performed without purification between the steps, allowing a one-pot conversion to *meta*-substituted phenols (**Scheme 71**). Yields were high considering the complex nature of the transformation, and a widely varied substrate was shown for both the phenol and the aryl iodide coupling partner – with complete *meta*-selectivity shown in all cases.



Scheme 71: Larrosa one-pot installation and removal of carboxylic acid directing group in the effective meta-arylation of phenols

2.3. Summary

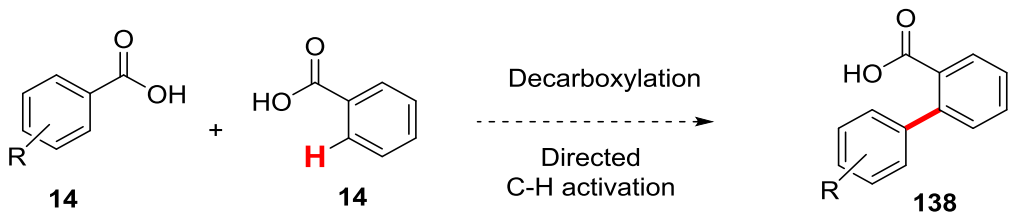
Studies involving decarboxylation have shown significant development in the past 10-15 years, with an astounding number of reports depicting a wide range of transformations. Since the initial development, decarboxylative reaction conditions have shown vast improvement, with temperatures, catalyst loading and substrate scope being continuously improved. Despite this conditions still remain relatively harsh with high temperatures and quantities of metal additives still essential.

The necessity for a general procedure that performs at low temperatures remains unrealised as methods are often unreliable and specific to a particular substrate scope. This would be required to envisage industrial application of the process, or indeed simply to tolerate sensitive functional groups. The necessity for *ortho*-substituents bearing either strongly electron rich or electron withdrawing character is also prevalent in this field, and this remains a problem that has still not been entirely overcome.

This research will consider decarboxylative processes in combination with directed C–H activation. It is hoped that the combination of these two methods will result in greener, more industrially viable processes.

2.4. Aims for carboxylate directed decarboxylative *ortho*-arylation

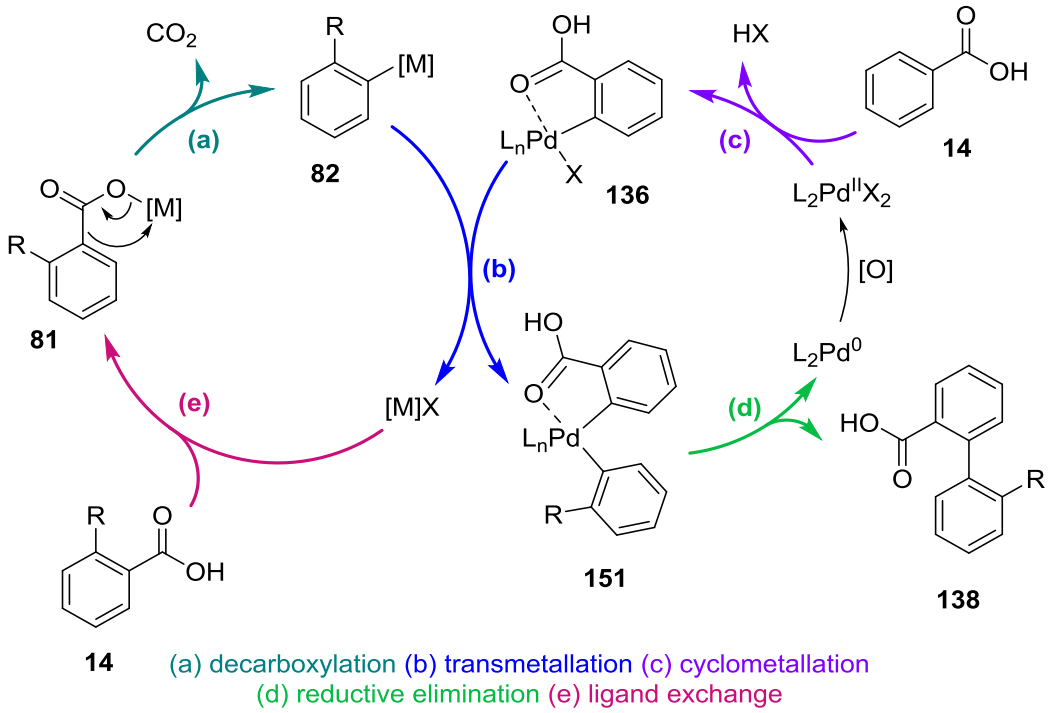
The aim of this project is to demonstrate the two different functionalities of the carboxylic acid group in the same reaction. Using one acid which decarboxylates relatively easily and coupling that with a second acid, which will not decarboxylate, *via* directed C–H activation (**Scheme 72**).



Scheme 72: Proposed methodology

The proposed mechanism for this transformation is shown (**Scheme 73**), drawing inspiration from the work of both Gooßen[54] and Yu.[135] In order for the reaction to proceed two cycles must interact, with palladium insertion into the C–H bond **(c)** to give the

palladacycle **136**, and decarboxylation of the carboxylic acid to give **82** happening simultaneously. Transmetallation of **82** to the palladium and reductive elimination will lead to the desired biaryl product **138,** with a stoichiometric oxidant required to regenerate the Pd catalyst.



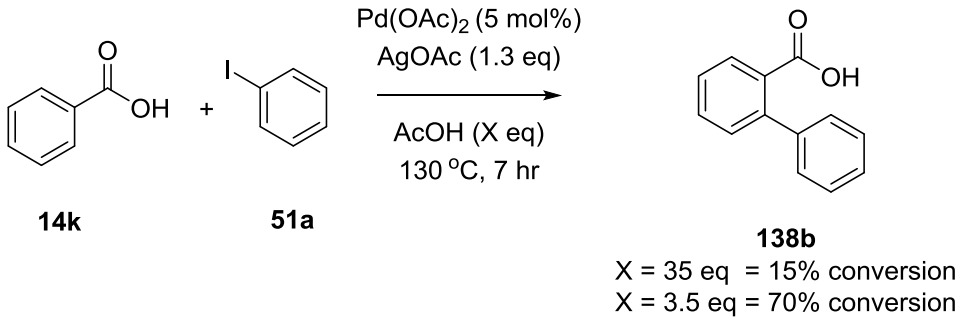
Scheme 73: Proposed mechanism for the ortho-directed arylation of benzoic acids via decarboxylative cross-coupling

This challenging concept relies on these two processes occurring on a similar time scale in order for successful interaction of the two cycles. If these cycles are out of sync with one another, protodecarboxylation or homo-dimerization could be an issue. If successful, this reaction would utilise the orthogonal behaviour of the carboxylic acid, by showing the strength as both a directing group and as a leaving group. Also, by installing an *ortho*-substituent on the benzoic acid it can be envisaged that further synthesis would be possible from the products formed through a second decarboxylative coupling.

3. Results and Discussion

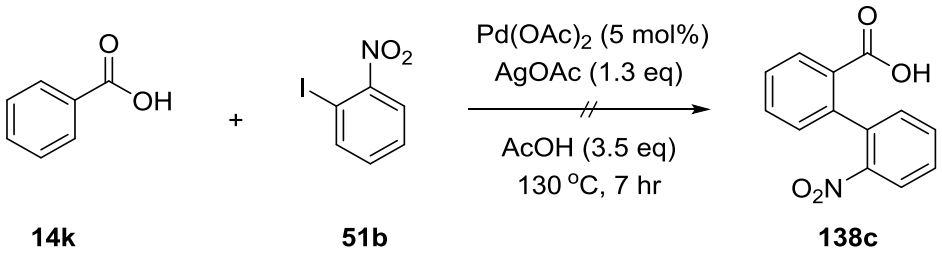
3.1.1. *Ortho*-palladation and arylation of benzoic acids

Initial studies focussed on assessing the accessibility of the C–H activation step. Three main methods for this process were considered, two from Daugulis and one from Yu.[134,135] Considering a simple system of benzoic acid (**14k**) and iodobenzene (**51a**), application of Daugulis conditions was relatively low yielding (**Scheme 74**). Despite the LCMS analysis indicating significant product formation, 85% pure starting material was recovered, and 5% of the desired biphenyl was isolated. Repeating the reaction in a more concentrated system indicated 70% conversion by crude NMR, however separation of this product from remaining starting material proved problematic, with only 11% pure product isolated – the remainder being contaminated with ~20% benzoic acid. Full conversion of the acid would be necessary to achieve high purity.



Scheme 74: Carboxylate directed *ortho*-activation under Yu's conditions

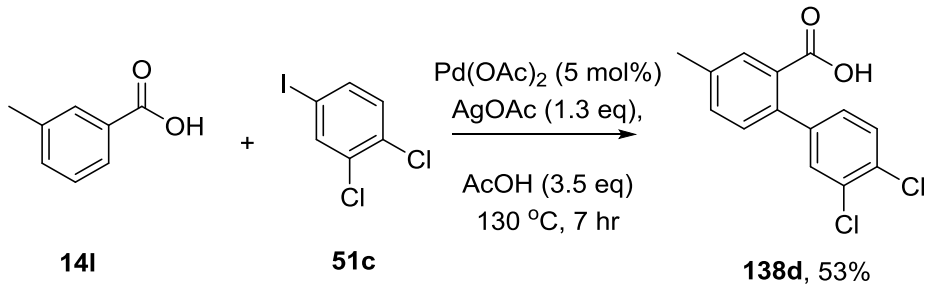
Daugulis conditions were also attempted to couple benzoic acid with 2-nitroiodobenzene. However while LCMS indicated trace amounts of the desired biaryl **138c**, 87% recovery of starting material was achieved on isolation (Scheme **75**).



Scheme 75: Failed coupling of nitroiodobenzene with benzoic acid

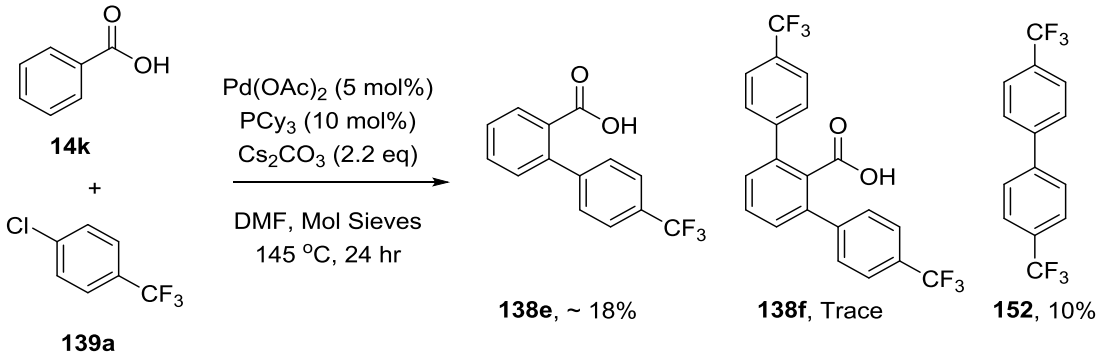
Using *meta*-toluic acid (**14l**) and 1,2-dichloro-4-iodobenzene (**51c**) (as an example directly from Daugulis' work) 53% yield of the desired biaryl was isolated (**Scheme 76**).

While this appears low it should be noted that these yields are comparable with yields from the paper, demonstrating that while the procedure itself is not a problem, the substrate scope is limited.



Scheme 76: Daugulis coupling of dichloroiodobenzene with meta-toluic acid

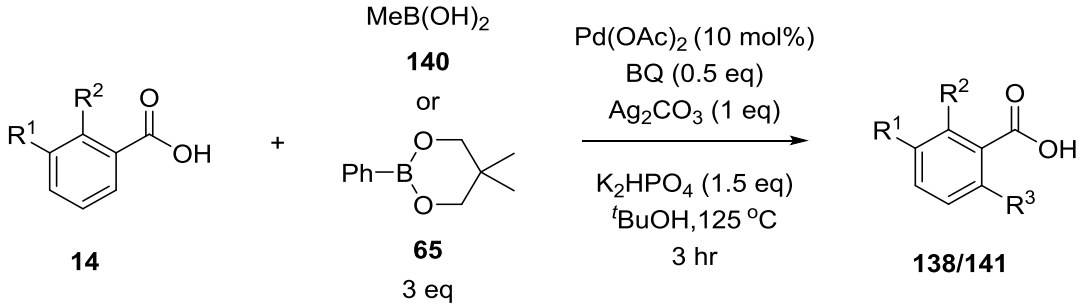
The second method proposed by Daugulis using aryl chlorides has a larger substrate scope, however conditions required the use of a glove box. Without access to these facilities, it remained unlikely that these conditions would be reproducible. Indeed, coupling of 1-chloro-4-(trifluoromethyl)benzene (**139a**) with benzoic acid resulted in an inseparable mixture of (**138e**) and (**138f**) with approximately 18% of mono-arylated (**138e**) (determined by ^{1}H NMR), and 59% recovered **14k** (**Scheme 77**). Homo-coupling of the chloride was also observed in 10% yield. This method was not considered further.



Scheme 77: Coupling of chloro-trifluoromethylbenzene with benzoic acid under Daugulis' reported conditions

Methods proposed by Yu and co-workers were then considered.[135] Arylations of benzoic acids were attempted with methyl boronic acid **140** and phenyl boronic ester **65**, and proceeded with limited success. Purification of the crude material generally led to a mixture of starting material and product – the ratio of which were determined by ^{1}H NMR (**Table 4**). Coupling of *m*-toluic acid with phenylboronic ester **128** afforded a 16% yield of pure isolated **138** despite ~60% conversion by crude NMR.

Table 4: Attempted Yu conditions for *ortho*-arylation

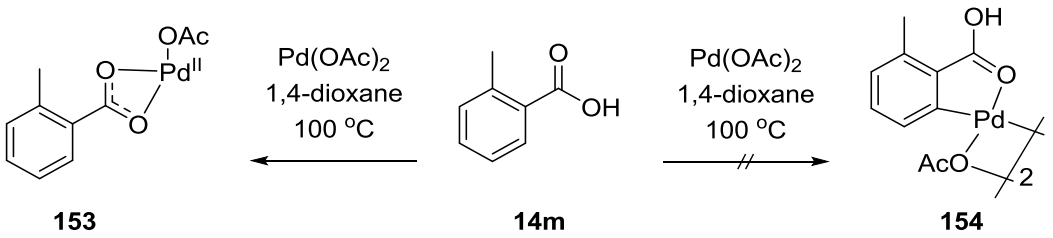


#	R^1	R^2	Boron species	R^3	Outcome	
					Conversion	Isolated pure
1	H	H	**65**	Ph	55%	-[a]
2	Me	H	**65**	Ph	60%	16%
3	H	Me	**140**	Me	60%	-[a]
4	Me	H	**140**	Me	40%	-[a]

[a]Pure material could not be isolated separately from starting material

3.1.2. Formation of stoichiometric palladacycles

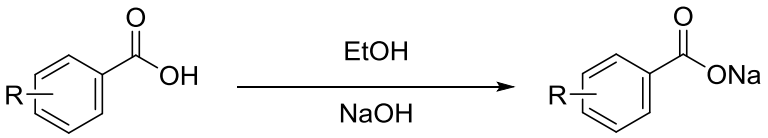
To this point experiments had demonstrated that carboxylate directed C–H activation was possible, however yields were modest, and inconsistent. In order to gain a further understanding of this process stoichiometric conversion of the benzoic acid to the desired palladacycle was attempted. Work by Yu demonstrated that formation of this complex was not possible directly from the acid – in this situation the palladium co-ordinates to the acid moiety (**153**) and does not interact with the C–H bond (**Scheme 78**).[136]



Scheme 78: Yu demonstration of co-ordination of Pd to benzoic acids

In order for the desired C–H insertion to occur this co-ordination site needs to be blocked by the presence of a counterion (such as Na or K). Potassium and sodium carboxylates of a series of simple benzoic acids were therefore prepared (**Table 5** and **Table 6**). These salts are utilised further in **Sections 3.1.4.** and **3.2.4**.

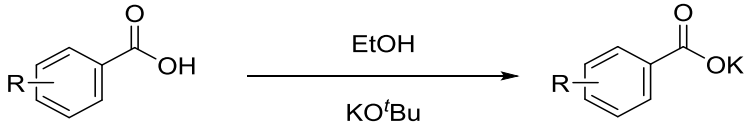
Table 5:Yields of sodium carboxylates prepared *via* known procedure[142]



14 **155a-c**

R	Yield	R	Yield
2-methyl, **155a**	68%	2-nitro, 1**55c**	97%
3-methoxy, **155b**	50%		

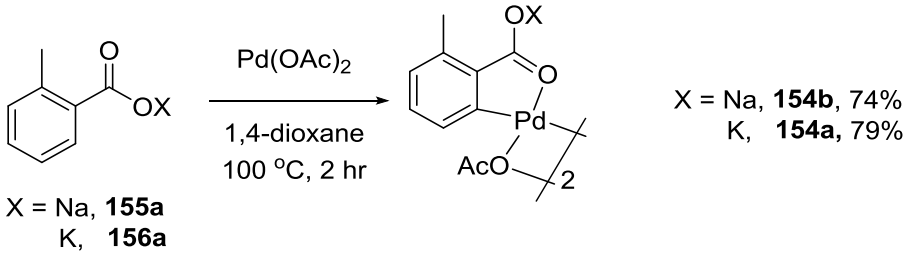
Table 6: Yields of potassium carboxylates prepared *via* known procedure[62]



14 **156a-p**

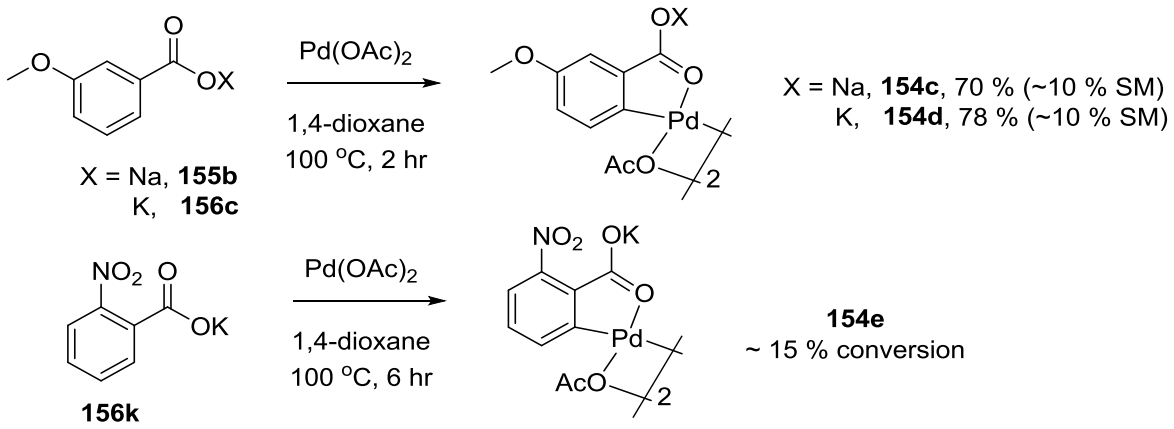
R	Yield	R	Yield
2-methyl, **156a**	95%	4-methyl, **156i**	94%
3-methyl, **156b**	78%	2,4-dimethoxy, **156j**	85%
2-methoxy, **156c**	97%	2-nitro, **156k**	93%
3-methoxy, **156d**	82%	3-nitro, **156l**	67%
1-naphthoate, **156e**	86%	3,4-dimethyl, **156m**	67%
2-naphthoate, **156f**	71%	4-chloro, **156n**	79%
4(*tert*-butyl) , **156g**	93%	3-(trifluoromethyl) , **156n**	92%
4-methoxy, **156h**	86%	Phenylglyoxylic acid**, 109a**	71%

Indeed it was found that the desired palladacycle could be formed from both the sodium or potassium carboxylate in high yield through heating the species at 100 °C (**Scheme 79**).[142] This was initially performed in dioxane, however reproducible results were seen when various other high boiling solvents were used (DMF, DMSO, NMP, DMA, DME). FTIR (Fourier Transform Infrared) spectroscopy studies performed at a concentration of 0.1 M indicated that the species doesn't form rapidly until the reaction temperature reaches 100 °C at which point gradual conversion to the product over ~1 hr is observed. There is no change in the reaction mixture after this time (including when cooled). The process is also concentration dependent; at lower concentrations conversion is slower.



Scheme 79: Synthesis of palladacycles

Palladacycle formation has been demonstrated for other benzoates to see how the electronics of the aromatic group has an effect. (**Scheme 80**). Electron rich benzoates show high conversion to the desired palladacycle, however electron poor substrates were remarkably less reactive with very slow conversion observed, and the reaction stalling at ~15%.

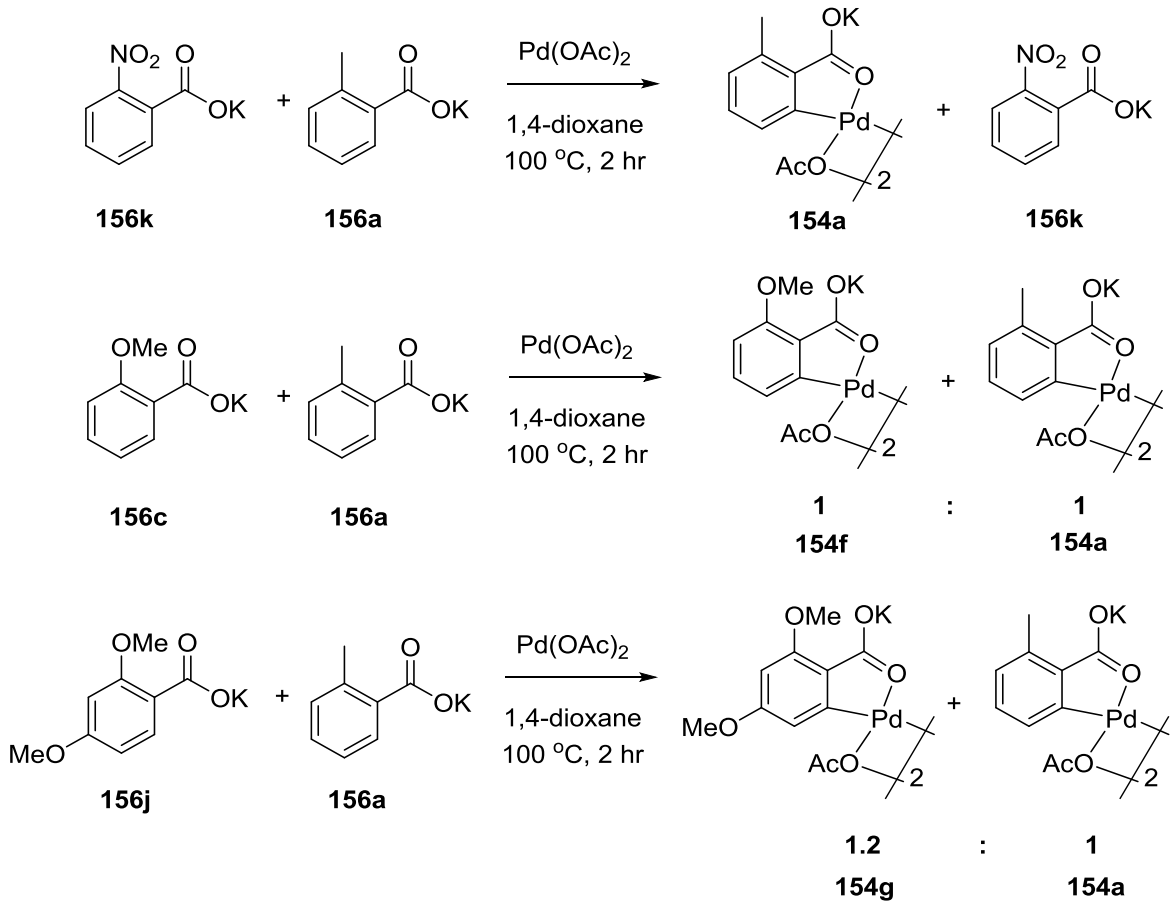


Scheme 80: Synthesis of electron rich and electron poor palladacycles

These results indicate that the C–H activation for the substrates selected should occur so long as the temperature is above 100 °C. This is compatible with decarboxylation methodology as it has been shown that this also requires high temperatures. However there are two disparate carboxylate species in the reaction and it needs to be established whether the C–H activation would occur on the desired acid. C–H insertion into the decarboxylative counterpart could inhibit decarboxylation and prevent the reaction from occurring. This could also lead to a complex mixture of products were the reaction to proceed. Competition reactions were performed, using solvent suppression NMR to monitor the reactions (**Scheme 81**).

Unsurprisingly the combination of nitrobenzoate **156k** with toluate **156a** leads to complete selectivity for the insertion happening on the toluate species. However, as the electronics of the counterpart are tuned to become more electron rich this distinction is

lost and complex mixtures are formed, with the eventual favouring of strongly electron rich species (**154g**). While this electronic differentiation could potentially allow tuning of specific conditions to allow the coupling of electronically diverse acids it does provide a limitation to the potential substrate scope.



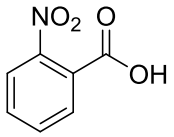
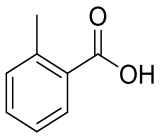
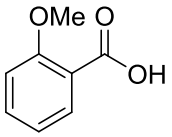
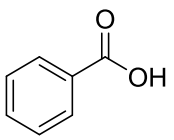
Scheme 81: Competition experiments for palladium insertion

Despite these potential limitations, the potential for developing a system for the decarboxylative arylation of benzoic acids is still an attractive consideration. Knowing that the selectivity of the desired C–H bond activation can be tuned through the electronics of the C–H component gives us a starting point as to how to approach this reaction using two electronically different species.

The necessity for a the counter-ion to facilitate the C–H bond activation is an important consideration when realising that two disparate carboxylic acids will be involved in the reaction. The pK_a of these species fluctuates slightly dependent on the aromatic substitution (**Table 7**) of the carboxylic acid. When two acids are used in one reaction the equilibrium of the two salts will lie closer to the more acidic species. This is an issue

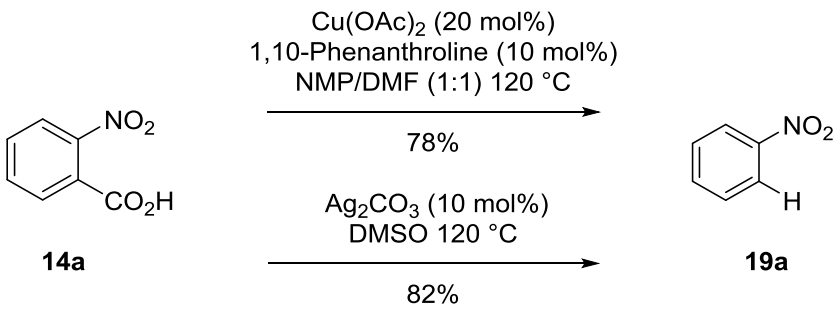
which will need to be kept in mind. Experimental proceedures for decarboxylation and C–H activation often require superstoichiometric quantities of metallic salts, generally copper or silver. It was hoped in the case of this project formation of the copper/silver salt within the reaction would be sufficient to facilitate the desired C–H activation and result in decarboxylative cross-coupling.

Table 7: pK_a data for substituted benzoic acids[143]

Acid				
	14a	**14m**	**14g**	**14k**
pK_a	2.16	3.91	4.09	4.19

3.1.3. Decarboxylation and screening with *ortho*-nitrobenzoic acid

Having studied the C–H activation step at length, attention was turned to the desired decarboxylation, with the aim of developing a cross-coupling process. *Ortho*-nitrobenzoic acid **14a** was used as the initial substrate for development of reaction conditions. The strong electron-withdrawing character of the nitro substituent means that decarboxylation readily occurs under standard conditions. Knowledge of the relative ease with which this substrate decarboxylates and successful usage as a screening substrate in Gooßen's work, were seen as legitimate reasons for using this substrate as a starting point, despite the unsuccessful coupling of 2-iodonitrobenzene shown in **Scheme 75**. Protodecarboxylation of the benzoic acid to form nitrobenzene was demonstrated to proceed in the presence of catalytic copper[59] and catalytic silver[72] in 82% and 78% yield respectively (**Scheme 82**). Temperatures above 120 °C were required, with substantial decrease in yield and rate of decarboxylation at lower temperatures.

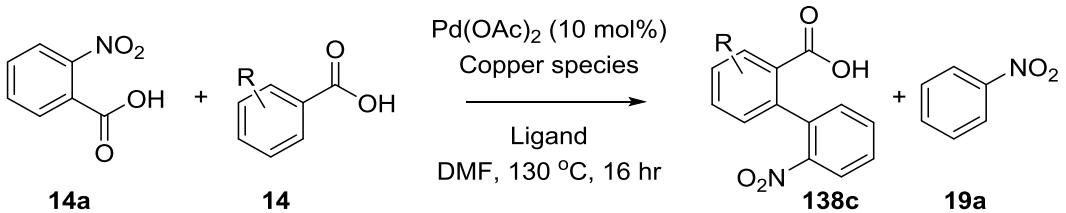


Scheme 82: Protodecarboxylation of *ortho*-nitrobenzoic acid

With assurance that decarboxylation was possible, initial reaction conditions were designed for the proposed acid directed cross-coupling. Attempts were made to couple with benzoic acids which will not readily decarboxylate unless subjected to extreme temperatures and pressures. This reaction was attempted in DMF under a series of copper conditions in the presence of catalytic palladium with various ligands (**Table 8**). These types of conditions have been used throughout the work of Gooßen therefore it was seen as a suitable foundation for reaction discovery.

Reactions were monitored by LCMS and TLC however despite successful decarboxylation of the nitrobenzoic acid no cross-coupling occurred. On work up of reactions under specific conditions (**Table 8**, **Entry 1**) a reasonable yield of nitrobenzene was isolated, with quantitative recovery of benzoic acid possible. Similar conditions were screened using 3-methylbenzoic acid and 3-methoxybenzoic acid as the C–H component (**Table 8, Entries 14-17**). Decarboxylation of these acids is inhibited due to the absence of an *ortho*-substituent, and the species have been shown to undergo C–H insertion in **Section 3.1.2**. In all cases the only observed products were nitrobenzene and the recovered benzoic acid, with no evidence of desired biphenyl product.

Table 8: Copper mediated attempted *ortho*-directed decarboxylative arylation



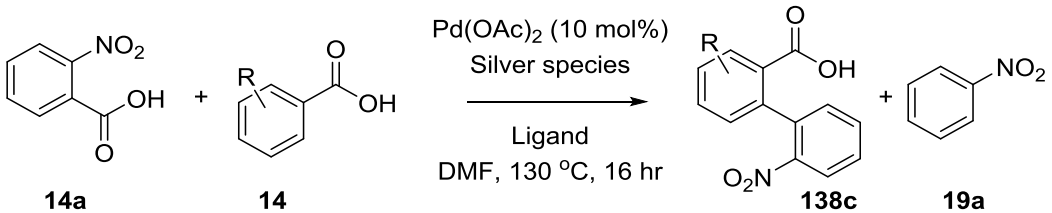
14a **14** **138c** **19a**

#	R	Cu Salt (eq)	Ligand (20 mol%)	Conversion		Yield
				138c	19a	19a
1	H	CuBr (1 eq)	-	0%	100%	68%
2	H	CuI (1 eq)	-	0%	100%	-[a]
3	H	$Cu(OAc)_2$ (1 eq)	-	0%	100%	-[a]
4	H	$Cu(OAc)_2$ (20 mol%)	-	0%	100%	-[a]
5	H	CuBr (1 eq)	Phen	0%	100%	-[a]
6	H	CuI (1 eq)	Phen	0%	100%	-[a]
7	H	$CuCO_3$ (1 eq)	Phen	0%	100%	-[a]
8	H	$CuCl_2$ (1 eq)	Phen	0%	100%	-[a]
9	H	$Cu(OAc)_2$ (1 eq)	Phen	0%	100%	-[a]
10	H	$Cu(OAc)_2$ (1 eq)	Phen, PPh_3	0%	100%	-[a]
11	H	$Cu(OAc)_2$ (1 eq)	Phen, DCPE	0%	100%	-[a]
12	H	$Cu(OAc)_2$ (20 mol%)	Phen, PPh_3	0%	100%	-[a]
13	H	$Cu(OAc)_2$ (20 mol%)	Phen, DCPE	0%	100%	-[a]
14	*m*-OMe	$Cu(OAc)_2$ (1 eq)	Phen	0%	100%	-[a]
15	*m*-OMe	CuI (1 eq)	Phen	0%	100%	-[a]
16	*m*-Me	$Cu(OAc)_2$ (1 eq)	Phen	0%	100%	-[a]
17	*m*-Me	CuI (1 eq)	Phen	0%	100%	-[a]

[a]Not isolated. Phen = 1,10-phenanthroline. DCPE = 1,2-Bis(dicyclohexylphosphino)ethane

Work by Larrosa[89] and Su[102] has often focussed on a silver mediated process, and previous experience in the group has shown the propensity of silver to facilitate decarboxylation. Therefore conditions for this reaction were also screened using the same substrates under silver mediated conditions (**Table 9**). Again successful decarboxylation of the nitrobenzoic acid was observed in all cases, with a 63% yield isolated under certain conditions, however no interaction between the two species was observed.

Table 9: Silver mediated attempted *ortho*-directed decarboxylative arylation



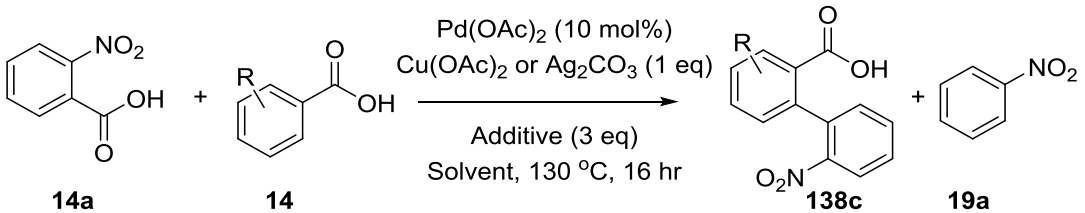
14a **14** **138c** **19a**

#	R	Ag Salt (1 eq)	Ligand (20 mol%)	Conversion		Yield
				138c	19a	19a
1	H	Ag_2CO_3	-	0%	100%	63%
2	H	$AgNO_3$	-	0%	100%	-[a]
3	H	AgOAc	-	0%	100%	-[a]
4	H	AgI	-	0%	100%	-[a]
5	H	AgF	-	0%	100%	-[a]
6	H	Ag_2CO_3	PPh_3	0%	100%	-[a]
7	H	Ag_2CO_3	Phen	0%	100%	-[a]
8	H	Ag_2CO_3	DCPE	0%	100%	-[a]
9	H	Ag_2CO_3	DCPE, PPh_3	0%	100%	-[a]
10	H	AgOAc	DCPE, PPh_3	0%	100%	-[a]
11	H	AgI	DCPE, PPh_3	0%	100%	-[a]
12	H	Ag_2CO_3	PCy_3, PPh_3	0%	100%	-[a]
13	*m*-OMe	Ag_2CO_3	-	0%	100%	-[a]
14	*m*-OMe	Ag_2CO_3	PPh_3	0%	100%	-[a]
15	*m*-Me	Ag_2CO_3	-	0%	100%	-[a]
16	*m*-Me	Ag_2CO_3	PPh_3	0%	100%	-[a]

[a]Not isolated. Phen = 1,10-phenanthroline. DCPE = 1,2-bis(dicyclohexylphosphino)ethane

Assuming that high temperatures would be required for both cycles, a series of high boiling solvents were screened under similar copper or silver mediated reaction conditions (**Table 10, Entries 1-3**). A series of acidic/basic and oxidising additives were also added to the reaction (**Table 10 Entries 14-24**), but the outcome remained unchanged.

Table 10: Solvent and additive screening conditions



14a **14** **138c** **19a**

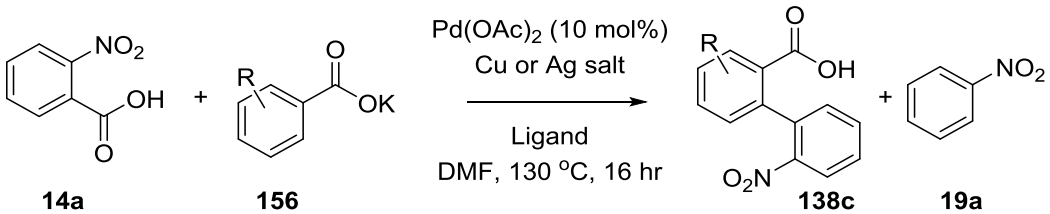
#	R	Solvent	Additive (3 eq)	Conversion		Yield
				138c	19a	19a
1	H	DMF	-	0%	100%	-[a]
2	H	DMA	-	0%	100%	-[a]
3	H	DMSO	-	0%	100%	-[a]
4	H	Toluene	-	0%	100%	-[a]
5	H	^{t}BuOH	-	0%	100%	-[a]
6	H	NMP	-	0%	100%	-[a]
7	H	1,4,-Dioxane	-	0%	100%	-[a]
8	*m*-OMe	DMF	-	0%	100%	-[a]
9	*m*-OMe	DMA	-	0%	100%	-[a]
10	*m*-OMe	DMSO	-	0%	100%	-[a]
11	*m*-Me	DMF	-	0%	100%	-[a]
12	*m*-Me	DMA	-	0%	100%	-[a]
13	*m*-Me	NMP	-	0%	100%	-[a]
14	H	DMF	AcOH	0%	100%	-[a]
15	H	DMF	$K_2S_2O_8$	0%	100%	-[a]
16	H	DMF	K_2CO_3	0%	100%	-[a]
17	H	DMF	KPF_6	0%	100%	-[a]
18	H	DMF	K_2HPO_4	0%	100%	-[a]
19	H	DMF	K_3PO_4	0%	100%	-[a]
20	H	DMF	KOAc	0%	100%	-[a]
21	H	DMF	NaOAc	0%	100%	-[a]
22	H	DMF	LiOH	0%	100%	-[a]
23	H	DMF	NaOH	0%	100%	-[a]
24	H	DMF	3Å mol sieves	0%	100%	-[a]

[a]Not isolated

It has been previously demonstrated that in order for the C–H activation to occur the presence of a counter-ion is required. Yu's methodology for the *ortho*-arylation of benzoic acids produces the carboxylate *in situ*.[135] However, basic additives did not facilitate our reaction.

Potassium carboxylates were subjected to a series of both copper and silver mediated conditions (**Table 11**). The presence of the carboxylate did not impede the decarboxylation process, with full conversion to nitrobenzene observed by crude ^{1}H NMR, however the outcome remained unchanged, with no interaction observed with the C–H component.

Table 11: *Ortho*-directed decarboxylative arylation with potassium carboxylates

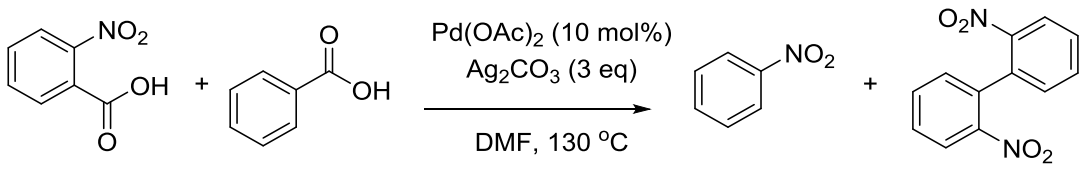


14a **156** **138c** **19a**

#	R	Ag Salt (1 eq)	Cu Salt (1 eq)	Ligand (20 mol%)	Conversion		Yield
					138c	19a	19a
1	H	Ag_2CO_3	-	-	0%	100%	-[a]
2	*m*-OMe	Ag_2CO_3	-	-	0%	100%	-[a]
3	*m*-Me	Ag_2CO_3	-	-	0%	100%	-[a]
4	H	-	$Cu(OAc)_2$	Phen	0%	100%	-[a]
5	H	-	CuI	Phen	0%	100%	-[a]
6	*m*-OMe	-	$Cu(OAc)_2$	Phen	0%	100%	-[a]
7	*m*-OMe	-	CuI	Phen	0%	100%	-[a]
8	*m*-Me	-	$Cu(OAc)_2$	Phen	0%	100%	-[a]
9	*m*-Me	-	CuI	Phen	0%	100%	-[a]

[a]Not isolated

It was noted that when a high excess of silver was used a further product was observed. This was isolated and identified to be 2,2'-dinitro-1,1'-biphenyl (**80a**) resulting from the decarboxylative homo-coupling of the nitrobenzoic acid (**Scheme 83**).

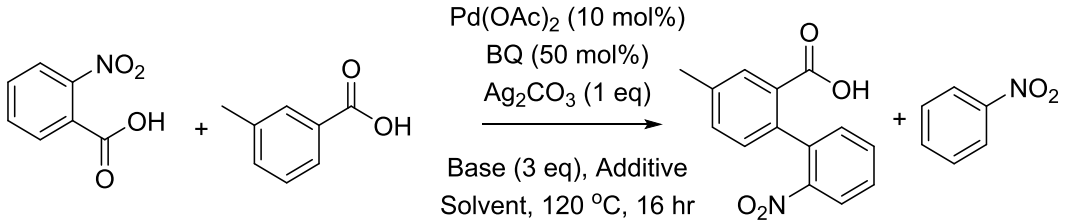


14a **14k** **19a**, 31% **80a**, 28%

Scheme 83: Decarboxylative homocoupling of 2-nitrobenzoic acid

Further consideration of conditions from Yu was also tested. Inclusion of benzoquinone (BQ) in ^{t}BuOH or DMF with other additives was attempted (**Table 12**). However this did not change the outcome.

Table 12: Decarboxylative arylation of 2-nitrobenzoic acid



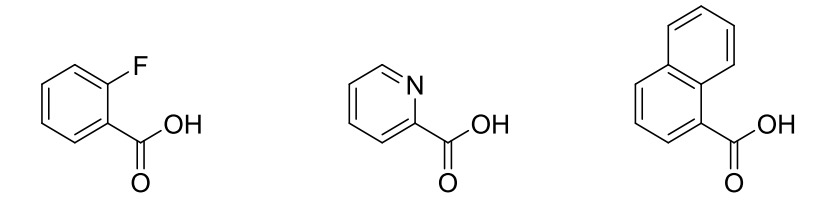
14a **14m** **138g** **19a**

#	Solvent	Base (3 eq)	Additive	Conversion		Yield
				138g	19a	19a
1	^{t}BuOH	K_2HPO_4	3Å mol sieves	0%	100%	-[a]
2	^{t}BuOH	K_2CO_3	3Å mol sieves	0%	100%	-[a]
3	DMF	K_2HPO_4	3Å mol sieves	0%	100%	-[a]
4	DMF	K_2CO_3	3Å mol sieves	0%	100%	-[a]
5	^{t}BuOH	K_2HPO_4	PCy_3 (20 mol%)	0%	100%	-[a]
6	^{t}BuOH	K_2CO_3	PCy_3 (20 mol%)	0%	100%	-[a]
7	DMF	K_2HPO_4	PCy_3 (20 mol%)	0%	100%	-[a]
8	DMF	K_2CO_3	PCy_3 (20 mol%)	0%	100%	-[a]

[a]Not isolated. BQ = Benzoquinone

3.1.4. Variation of the substrate

Proposing that the issue was the selection of decarboxylative partner, a number of other acids were subjected to the reaction conditions. These acids were substrates that have shown high yields in previously reported decarboxylative cross-coupling reactions. *o*-Fluorobenzoic acid, picolinic acid, and 1-naphthoic acid (**Figure 3**) were selected as examples of acids known to decarboxylate. Decarboxylation of the acids was observed by LCMS and crude ^{1}H NMR, however there was still no cross-coupling observed with the C–H component (**Table 13**).

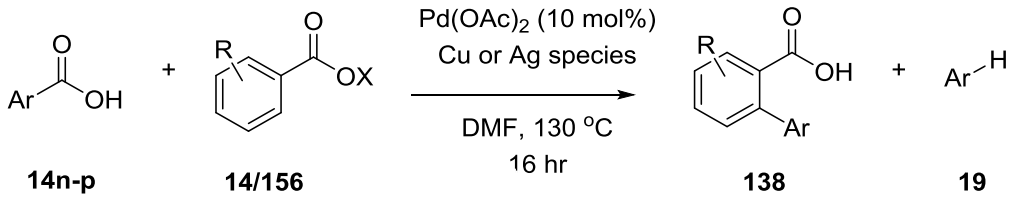


14n *o*-fluorobenzoic acid | **14o** picolinic acid | **14p** 1-naphthoic acid

Figure 3: Selected acids for decarboxylative partner

2,4-dimethoxybenzoic acid **14f** has been shown by Myers to successfully participate in decarboxylative Heck type reactions[45] and was also one of the main substrates used by Su to optimise their perfluoroarylation reaction conditions.[102] However upon subjecting this acid to silver mediated conditions similar to those previously discussed decarboxylation was not observed to full conversion (**Scheme 84**). LCMS indicated only trace amounts of decarboxylation, and almost quantitative yield of both starting materials were recovered. Furthermore it was established that under standard Larrosa conditions the decarboxylation was not occurring (**Scheme 85**).[72]

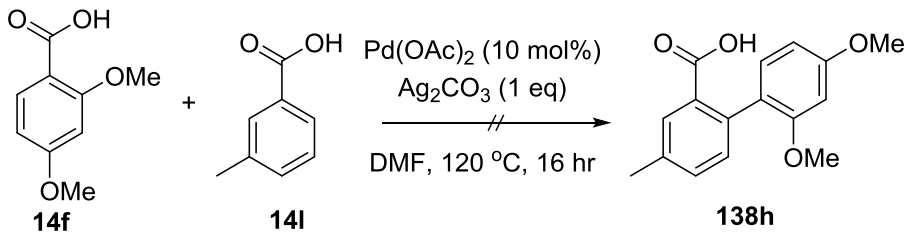
Table 13: *Ortho*-directed decarboxylative arylation with a series of different carboxylic acids and potassium carboxylates



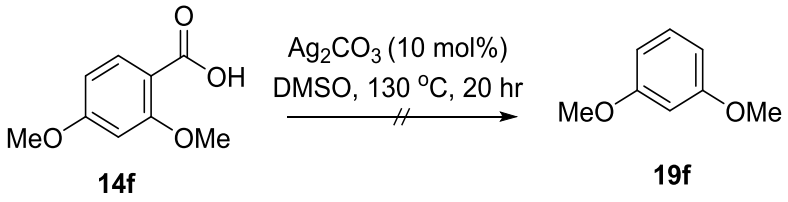
14n-p **14/156** **138** **19**

#	Ar	R	X	Ag (1 eq)	Cu (1 eq)	Conversion		Yield
						138	19	19
1	2-Fluoro	H	H	Ag_2CO_3	-	0%	100%	-[a]
2	2-Fluoro	H	K	Ag_2CO_3	-	0%	100%	-[a]
3	2-Fluoro	*m*-OMe	H	Ag_2CO_3	-	0%	100%	-[a]
4	2-Fluoro	*m*-OMe	K	Ag_2CO_3	-	0%	100%	-[a]
5	2-Fluoro	H	H	-	$Cu(OAc)_2$	0%	100%	-[a]
6	2-Fluoro	H	K	-	$Cu(OAc)_2$	0%	100%	-[a]
7	2-Fluoro	*m*-OMe	H	-	$Cu(OAc)_2$	0%	100%	-[a]
8	2-Fluoro	*m*-OMe	K	-	$Cu(OAc)_2$	0%	100%	-[a]
9	Picolinic	H	H	Ag_2CO_3	-	0%	100%	-[a]
10	Picolinic	H	K	Ag_2CO_3	-	0%	100%	-[a]
11	Picolinic	*m*-OMe	H	Ag_2CO_3	-	0%	100%	-[a]
12	Picolinic	*m*-OMe	K	Ag_2CO_3	-	0%	100%	-[a]
13	Picolinic	H	H	-	$Cu(OAc)_2$	0%	100%	-[a]
14	Picolinic	H	K	-	$Cu(OAc)_2$	0%	100%	-[a]
15	Picolinic	*m*-OMe	H	-	$Cu(OAc)_2$	0%	100%	-[a]
16	Picolinic	*m*-OMe	K	-	$Cu(OAc)_2$	0%	100%	-[a]
17	1-Naphthoic	H	H	Ag_2CO_3	-	0%	100%	-[a]
18	1-Naphthoic	H	K	Ag_2CO_3	-	0%	100%	-[a]
19	1-Naphthoic	*m*-OMe	H	Ag_2CO_3	-	0%	100%	-[a]
20	1-Naphthoic	*m*-OMe	K	Ag_2CO_3	-	0%	100%	-[a]
21	1-Naphthoic	H	H	-	$Cu(OAc)_2$	0%	100%	-[a]
22	1-Naphthoic	H	K	-	$Cu(OAc)_2$	0%	100%	-[a]
23	1-Naphthoic	*m*-OMe	H	-	$Cu(OAc)_2$	0%	100%	-[a]
24	1-Naphthoic	*m*-OMe	K	-	$Cu(OAc)_2$	0%	100%	-[a]

[a]Not isolated

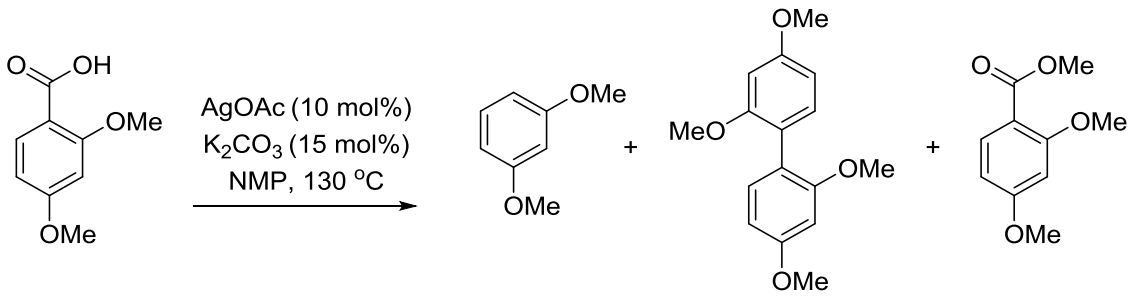


Scheme 84: Attempted decarboxylative *ortho*-arylation with dimethoxybenzoic acid



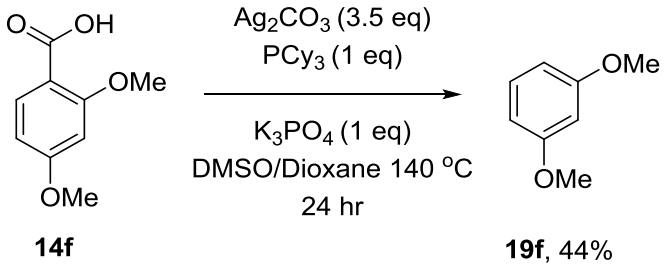
Scheme 85: Unsuccessful protodecarboxylation of 4 under Larrosa conditions

Work by Su[102] has discussed the importance of the tricyclohexylphosphine (PCy_3) ligand in facilitating decarboxylation of this substrate in the presence of 3.5 equivalents of silver carbonate, while Gooβen's 2009 paper implied the addition of potassium carbonate would also aid the decarboxylation.[70] Under Gooβen conditions the protodecarboxylation was achieved in 56% yield, however other by-products were observed, with methyl ester **157** isolated in 7% yield, and the dimerised product, 2,2',4,4'-tetramethoxybiphenyl **80b** observed in 12% yield (**Scheme 86**). Full conversion was still not achieved, with 15% recovered starting material isolated.



Scheme 86: Products formed under silver catalysed decarboxylation of 14f

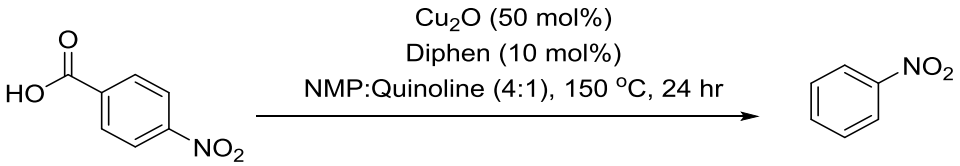
Su's conditions also led to increased decarboxylation, and while the observation of unfavourable by-products was lower, LCMS indicated a large presence of retained starting material, even at extended reaction time. As a consequence the maximum yield achieved for reaction was 44% (**Scheme 87**), which is poor, however is should be noted that Su only report a 55 % yield for this reaction.



14f **19f**, 44%

Scheme 87: Decarboxylation of 4 under Su conditions

It was considered that steric issues caused by the *ortho*-substitution of the benzoic acid could be hindering the reaction, as the formation of a doubly *ortho*-substituted biphenyl product can be challenging. An *ortho*-substituent is a common requirement for decarboxylation, however limited reports of non *ortho*-substituted acids undergoing decarboxylative cross-coupling reactions under more forcing conditions. *Para*-nitrobenzoic acid was used as a substrate. This acid was successfully decarboxylated under harsher conditions[47] than those used for *ortho*-substituted acids (**Scheme 88**).

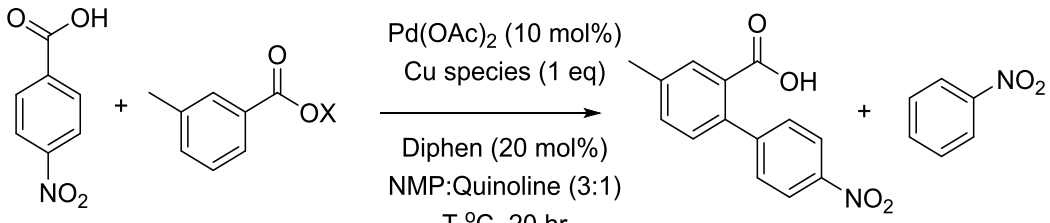


14c **19a**, 58%

Scheme 88: Protodecarboxylation of *para*-nitrobenzoic acid

Attempts to combine this process with the C–H activation were unsuccessful. Similar copper mediated conditions to those screened for *ortho*-benzoic acid were screened, though at elevated temperature and with the inclusion of the specific phenanthroline ligand (**Table 14**). Unfortunately no substantial change in the outcome was observed, with nitrobenzene being the only detected product in all cases, and protodecarboxylation being significantly reduced, with less than 50% conversion to nitrobenzene.

Table 14: *Ortho*-directed decarboxylative arylation with a series of different carboxylic acids and potassium carboxylates



14c **14l** **138h** **19a**

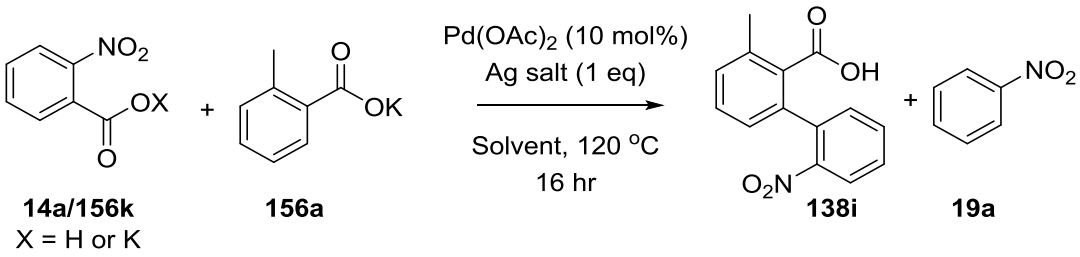
#	R	Cu Salt (1 eq)	Temp (°C)	Conversion		Yield
				138h	19a	19a
1	H	$Cu(OAc)_2$	130	0%	0%	-[a]
2	H	CuI	130	0%	0%	-[a]
3	K	$Cu(OAc)_2$	130	0%	0%	-[a]
4	K	CuI	130	0%	0%	-[a]
5	H	$Cu(OAc)_2$	150	0%	<30%	-[a]
6	H	CuI	150	0%	<30%	-[a]
7	K	$Cu(OAc)_2$	150	0%	<30%	-[a]
8	K	CuI	150	0%	<30%	-[a]
9	H	$Cu(OAc)_2$	180	0%	<50%	-[a]
10	H	CuI	180	0%	<50%	-[a]
11	K	$Cu(OAc)_2$	180	0%	<50%	-[a]
12	K	CuI	180	0%	<50%	-[a]

[a]Not isolated. Diphen = 4,7-diphenyl-1,10-phenanthroline

3.1.5. Further screening attempts

In an attempt to force the reaction it was considered that the carboxylate salt of both species should be used. Under the reaction conditions it was probable that salt exchange to the more acidic species would occur and this was considered to be inhibiting the C–H activation step. Reactions were therefore prepared to test the feasibility of using the carboxylate of both acids. Knowing from previous results (**Section 3.1.2.**) that the desired C–H bond activation would occur selectively on the *ortho*-toluate in the presence of the *ortho*-nitro species a series of conditions were screened using this combination of substrates (**Table 15**). It was noted that under identical conditions, where full decarboxylation of the nitrobenzoic acid was observed (**Table 15, Entries 1-6**) inclusion of potassium nitrobenzoate severely inhibited decarboxylation resulting in only the recovery of starting materials (**Table 15, Entries 7-12**).

Table 15: Further screening *for ortho*-directed decarboxylative arylation



14a/156k
X = H or K

156a

138i

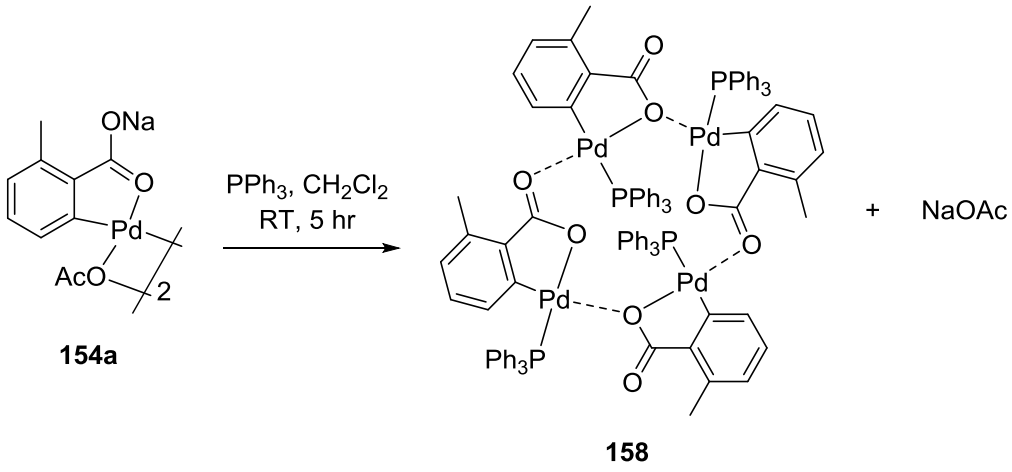
19a

#	R	Ag Salt (1 eq)	Temp (°C)	Conversion		Yield
				138i	19a	19a
1	H	Ag_2CO_3	Dioxane	0%	100%	-[a]
2	H	Ag_2CO_3	DMSO	0%	100%	-[a]
3	H	Ag_2CO_3	DMF	0%	100%	-[a]
4	H	AgOAc	Dioxane	0%	100%	-[a]
5	H	AgOAc	DMSO	0%	100%	-[a]
6	H	AgOAc	DMF	0%	100%	-[a]
7	K	Ag_2CO_3	Dioxane	0%	0%	-[a]
8	K	Ag_2CO_3	DMSO	0%	0%	-[a]
9	K	Ag_2CO_3	DMF	0%	0%	-[a]
10	K	AgOAc	Dioxane	0%	0%	-[a]
11	K	AgOAc	DMSO	0%	0%	-[a]
12	K	AgOAc	DMF	0%	0%	-[a]

[a]Not isolated.

Further to this, the use of previously synthesised palladacycle **154a** as a stoichiometric precursor of the C–H counterpart was also seen to inhibit decarboxylation (**Table 16**) with no conversion to nitrobenzene observed under and of the attempted conditions.

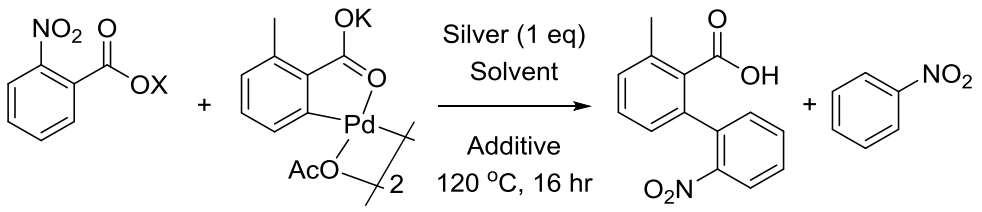
Yu and co-workers have also demonstrated the activation of palladacycle **154a** through formation of tetrameric species **158**.[142] Inclusion of ligands had not previously been successful in driving this reaction, but nevertheless the tetrameric species was synthesised for use as a stoichiometric precursor of the C–H counterpart (**Scheme 89**).



Scheme 89: Synthesis of tetrameric species 158 as a stoichiometric C–H counterpart precursor

Unfortunately the use of this species in reactions as with those described in **Table 16** did not result in the desired product. Under these reaction conditions the use of the stoichiometric palladacycle was found to inhibit decarboxylation of the nitrobenzoic acid, and conversion remained low at extended reaction times. Where potassium nitrobenzoate was used decarboxylation was not observed under the reaction conditions.

Table 16: Further screening *for ortho*-directed decarboxylative arylation using stoichiometric palladacycle 154a



14a/156k X = H or K **154a** **138i** **19a**

#	R	Ag Salt (1 eq)	Temp (°C)	Conversion		Yield
				138i	19a	19a
1	H	Ag_2CO_3	Dioxane	0%	~20%	-[a]
2	H	Ag_2CO_3	DMSO	0%	~20%	-[a]
3	H	Ag_2CO_3	DMF	0%	~20%	-[a]
4	H	Ag_2CO_3	DMA	0%	~20%	-[a]
5	H	AgOAc	Dioxane	0%	~20%	-[a]
6	H	AgOAc	DMSO	0%	~20%	-[a]
7	H	AgOAc	DMF	0%	~20%	-[a]
8	H	AgOAc	DMA	0%	~20%	-[a]
9	H	Ag_2O	Dioxane	0%	~20%	-[a]
10	H	Ag_2O	DMSO	0%	~20%	-[a]
11	H	Ag_2O	DMF	0%	~20%	-[a]
12	H	Ag_2O	DMA	0%	~20%	-[a]
13	K	Ag_2CO_3	Dioxane	0%	0%	-[a]
14	K	Ag_2CO_3	DMSO	0%	0%	-[a]
15	K	Ag_2CO_3	DMF	0%	0%	-[a]
16	K	Ag_2CO_3	DMA	0%	0%	-[a]
17	K	AgOAc	Dioxane	0%	0%	-[a]
18	K	AgOAc	DMSO	0%	0%	-[a]
19	K	AgOAc	DMF	0%	0%	-[a]
20	K	AgOAc	DMA	0%	0%	-[a]
21	K	Ag_2O	Dioxane	0%	0%	-[a]
22	K	Ag_2O	DMSO	0%	0%	-[a]
23	K	Ag_2O	DMA	0%	0%	-[a]

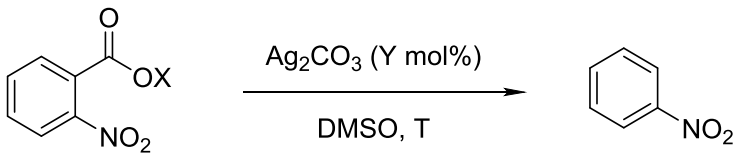
[a]Not isolated. Additives were AcOH (2 eq), $K_2S_2O_8$ (1 eq) or KOAc (2 eq) however their inclusion did not promote the reaction.

3.1.6. Decarboxylation Study

A closer look at the decarboxylation step was therefore required. Under standard conditions the acid decarboxylates readily, with an increase in temperature or catalyst loading serving to increase the rate significantly (**Table 17**, **Entries 1-3**). However under the same conditions the potassium carboxylate failed to decarboxylate (**Entry 4**), with only trace decarboxylation observed at extended reaction times. This was not shown to improve significantly with increased temperature (**Entry 5**), and while some increase in rate was observed with higher catalyst loading (**Entry 6**) the reaction stalled at 33% conversion.

It is noted that work by Gooβen often used the carboxylate salt in decarboxylative cross-couplings, however this is often at much higher temperatures which are incompatible with our research.[58,60] Larrosa and co-workers have encountered the same phenomenon with the presence of K_2CO_3 preventing decarboxylation of di-substituted carboxylate species synthesised from carboxylate directed arylation. In the absence of K_2CO_3 these species readily undergo palladium assisted decarboxylation.[140]

Table 17: Decarboxylation study



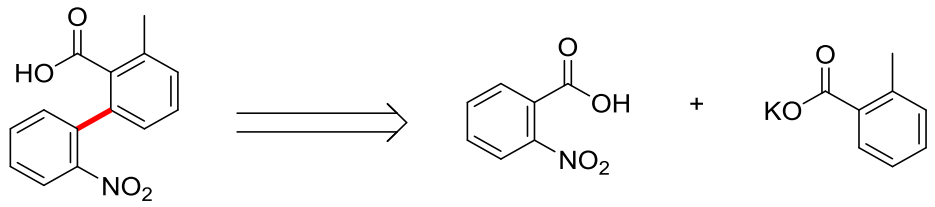
14a or **156k** **19a**

#	X	Silver Loading (mol%)	Temp (°C)	Outcome[a]
1	H	10	100	**Full conversion in 24 hr**
2	H	10	120	**Full conversion in 4 hr**
3	H	50	100	**Full conversion in 4 hr**
4	K	10	100	**7% conversion in 29 hr**
5	K	10	120	**7% conversion in 29 hr**
6	K	50	100	**33% conversion in 29 hr**

[a]Conversions calculated by NMR

3.1.7. Summary

This marrying of these disparate processes shows many indications of being incompatible under the proposed palladium catalysed reaction conditions. While both the decarboxylation and the C–H insertion require high temperatures, and seem to utilise a similar selection of reagents, the combination of the two reactions has not been possible. Retrosynthetically, in order to form the desired C–C bond would require the salt of the C–H activation component and the acid of the decarboxylating component (**Scheme 90**).

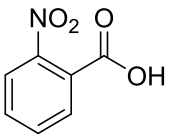
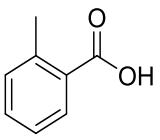
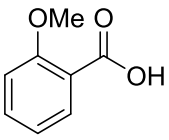
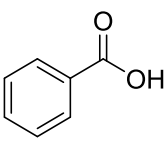


138i **19a** **156a**

Scheme 90: Retrosynthetic analysis of desired diphenyl product

However, pK_a data for these substrates has serious implications (**Table 18**), as in solution the carboxylate will not exist purely on one acid. It would be unfeasible to use 2-nitrobenzoic acid with potassium *ortho*-toluate as the equilibrium established would favour the nitrobenzoate as that proton is more acidic. However decarboxylation of this species is severely inhibited. Considering the data collected, it would be highly unlikely to find conditions where this process is facilitated. For this reason the project was not pursued any further.

Table 18: pK_a data for substituted benzoic acids[143]

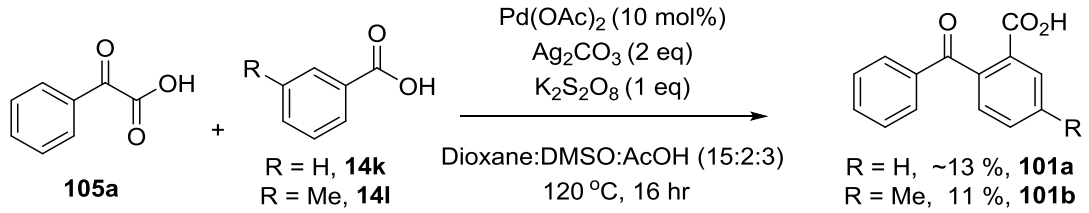
Acid				
	14a	**14m**	**14g**	**14k**
pK_a	2.16	3.91	4.09	4.19

3.2. Carboxylate directed decarboxylative *ortho*-acylation of benzoic acids

3.2.1. Concept analysis and initial results

Recent work by both Gooßen[58,106,107] and Ge[117,118] has shown the potential for oxycarboxylic acids (keto-acids) to undergo decarboxylative cross-coupling reactions. These substrates are known to decarboxylate readily under standard conditions without the need for *ortho*-substituents. It was considered that oxycarboxylic acids could be used in a similar process to that attempted previously (**Section 3.1.**) in order to effectively benzoylate the *ortho*-position of a benzoic acid.

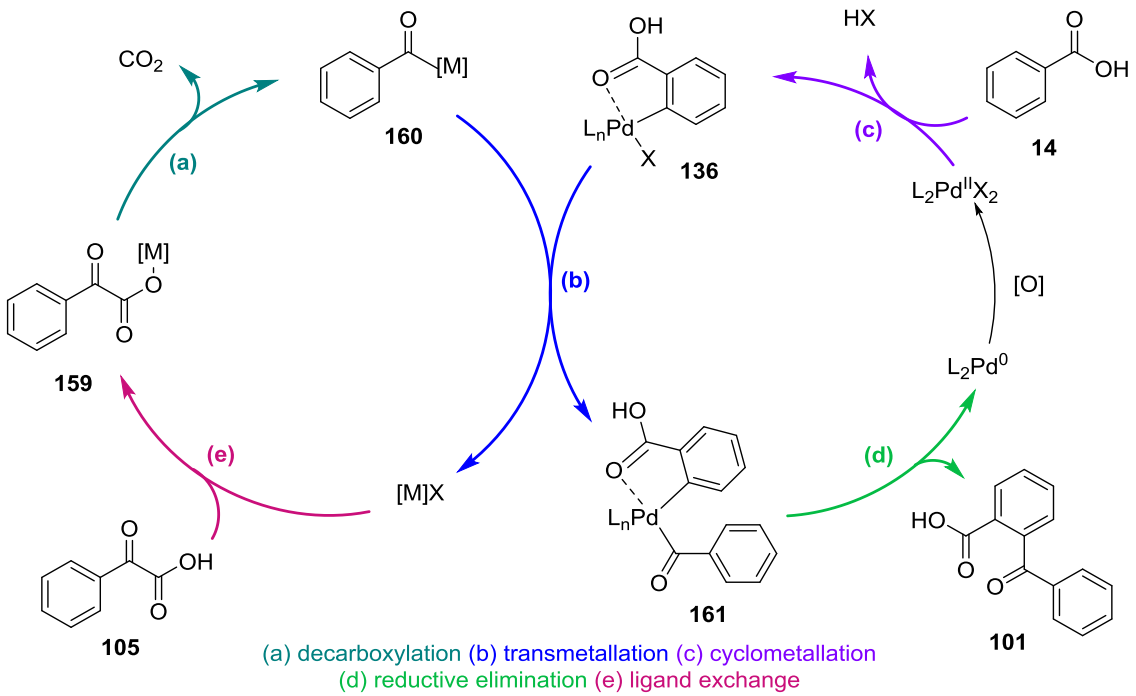
With inspiration from Ge's work using acetanilides,[117] the cross-coupling of oxycarboxylic acid **105** with benzoic acid **14k** was attempted in the presence of $Pd(OAc)_2$, Ag_2CO_3, and potassium persulfate ($K_2S_2O_8$) (**Scheme 91**). Ketone **101a** was isolated in approximately 13% yield (90% pure by ^1H NMR). Attempting the reaction with *meta*-toluic acid **14l** yielded ketone **101b** isolated in 11% yield.



Scheme 91: Decarboxylative cross-coupling of phenylglyoxylic acid and benzoic acids

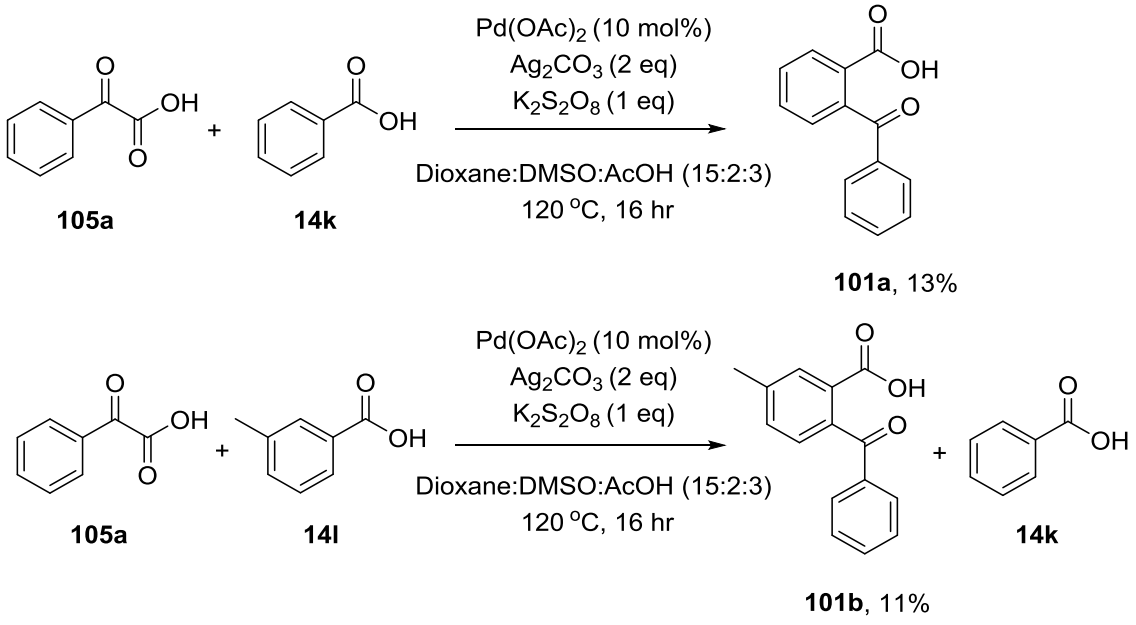
Mechanistically this would still involve the interaction of two catalytic cycles - C–H palladation and decarboxylation - in a similar way to that shown before (**Section 3.1.**). While the mechanism for keto-acid decarboxylation has been less widely studied, the implication is that transition metal mediated decarboxylation leads to the metal co-ordinated acyl intermediate **160**. This transmetallates to the preformed Pd-insertion product and reductive elimination from the palladium centre gives the product **101**. The presence of super stoichiometric levels of oxidant oxidises the palladium catalyst and completes the catalytic cycle (**Scheme 92**).

Due to the absence of an *ortho*-substituent to drive the decarboxylation of the keto-acid, steric impacts may not have such a significant effect. Whilst mechanistically this reaction could still present the problems discussed previously, having an initial hit from the reaction was determined to be a suitable basis for optimisation.



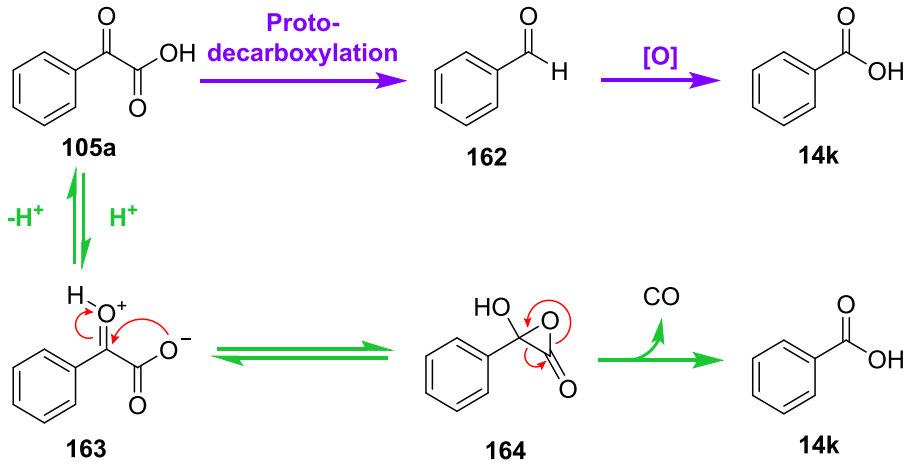
Scheme 92: Proposed mechanism for the *ortho*-directed benzoylation of benzoic acids *via* decarboxylative cross-coupling

The by-products of the reaction were identified and characterised. Despite a 13% yield of ketone product **101a**, benzoic acid **14k** was isolable from the reaction in quantitative yield (**Scheme 93**). However when *meta*-toluic acid **14l** was used the products were desired ketone **101b** and benzoic acid **14k,** with *m*-toluic acid **14l** recovered from the reaction



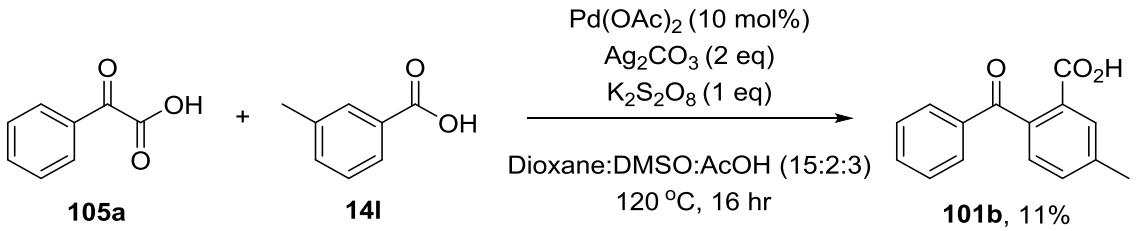
Scheme 93: Isolated products under the standard reaction conditions

It is proposed that under the reaction conditions, benzoic acid is formed by protodecarboxylation and subsequent oxidation of the keto-acid (**Scheme 94, Purple arrows**). Alternatively, decarbonylation of keto-acids upon heating is known in the literature. While the mechanism for this transformation has not been elucidated it is suggested to be caused *via* a rearrangement of the keto-acid to the epoxide, resulting in expulsion of C=O (**Scheme 94, Green arrows**). This is generally only observed in low yield alongside decarboxylation to the aldehyde, however acidic conditions have been demonstrated to increase production of this by-product.[144-146]



Scheme 94: Two possible routes to benzoic acid by-product from keto acid 105a

3.2.2. Attempted optimisation of initial result

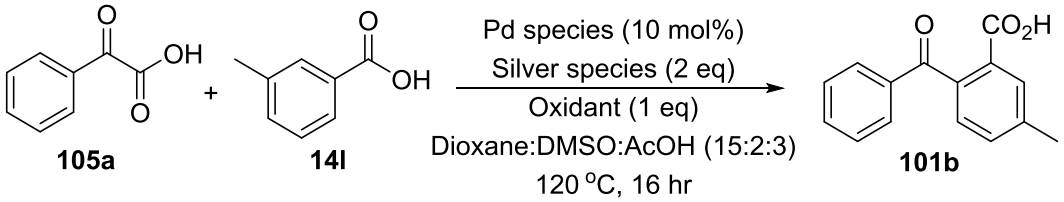


Scheme 95: Starting point for optimisation

With these results in hand (**Scheme 95**) various conditions were screened in an attempt to improve the yield of the reaction (**Table 19**). Modification of the silver species had little effect; however the use of more hygroscopic silver species was shown to inhibit the reaction, as did exclusion of the silver (**Table 19**, **Entries 1-9**). Similarly alteration of the palladium catalyst used had little impact with the yield remaining consistently at ~10% - however palladium was also shown to be necessary for product formation (**Table 19**, **Entries 10-14**). The use of potassium peroxidisulfate was determined to be critical to the reaction, as the use of other oxidants was detrimental to the yield, and without the oxidant the reaction failed (**Table 19**, **Entries 15-20**).

The solvent system was considered and the reaction was attempted using various high boiling solvents known to facilitate decarboxylative transformations (**Table 20**). However the main impact of this was to stall the reaction, and only reactions where one solvent from the ternary solvent system was omitted showed any trace product formation (**Table 20**, **Entries 4 and 5**). Changing the acid was detrimental to the yield and inclusion of molecular sieves and extensively dry conditions also showed little improvement (**Table 20**, **Entries 11-13**). It was also considered that the issue could be with catalytic turnover, however repeating the reaction with 50 mol% or 1 eq $Pd(OAc)_2$ did not dramatically improve results (**Table 20**, **Entries 17 and 18**).

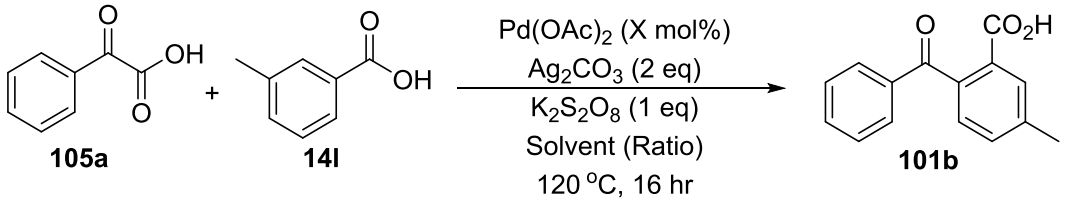
Table 19: Initial screening attempts.



#	Pd Species	Ag Species	Oxidant (1 eq)	Yield
1	$Pd(OAc)_2$	AgOAc	$K_2S_2O_8$	10%
2	$Pd(OAc)_2$	Ag_2CO_3	$K_2S_2O_8$	11%[a]
3	$Pd(OAc)_2$	Ag_2O	$K_2S_2O_8$	8%
4	$Pd(OAc)_2$	AgI	$K_2S_2O_8$	10%
5	$Pd(OAc)_2$	$Ag(O_2CCF_3)$	$K_2S_2O_8$	7%
6	$Pd(OAc)_2$	AgF	$K_2S_2O_8$	-[b]
7	$Pd(OAc)_2$	AgCl	$K_2S_2O_8$	-[b]
8	$Pd(OAc)_2$	$AgSO_4$	$K_2S_2O_8$	-[b]
9	$Pd(OAc)_2$	-	$K_2S_2O_8$	-[b]
10	$Pd(dba)_2$	Ag_2CO_3	$K_2S_2O_8$	7%
11	$Pd(O_2CCF_3)_2$	Ag_2CO_3	$K_2S_2O_8$	9%
12	$PdCl_2$	Ag_2CO_3	$K_2S_2O_8$	10%
13	$Pd(acac)_2$	Ag_2CO_3	$K_2S_2O_8$	8%
14	-	Ag_2CO_3	$K_2S_2O_8$	-[b]
15	$Pd(OAc)_2$	Ag_2CO_3	$(NH_4)_2S_2O_8$	< 5 %[c]
16	$Pd(OAc)_2$	Ag_2CO_3	$Na_2S_2O_8$	< 5 %[c]
17	$Pd(OAc)_2$	Ag_2CO_3	$PhI(OAc)_2$	< 5 %[c]
18	$Pd(OAc)_2$	Ag_2CO_3	BQ	-[b]
19	$Pd(OAc)_2$	Ag_2CO_3	$Ce(SO_4)_2$	-[b]
20	$Pd(OAc)_2$	Ag_2CO_3	-	-[b]

[a]Average isolated yield from reactions performed. [b]No product detected by LCMS. [c]Required product detected by LCMS in trace amounts.

Table 20: Initial screening attempts

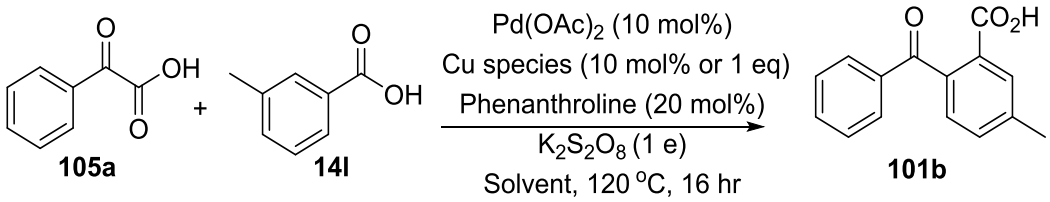


#	$Pd(OAc)_2$ (mol%)	Solvent	Ratio (X:X)	Yield
1	10	Dioxane	1:2	- [a]
2	10	DMSO	1:2	- [a]
3	10	AcOH	1:2	- [a]
4	10	Dioxane/AcOH (15:1)	1:2	< 5 % [b]
5	10	Dioxane/DMSO (15:2)	1:2	< 5 % [b]
6	10	Diglyme	1:2	- [a]
7	10	DMA	1:2	- [a]
8	10	DMF	1:2	- [a]
9	10	DME	1:2	- [a]
10	10	NMP/Quinoline (3:1)	1:2	- [a]
11	10	Dioxane/DMSO/PivOH (15:2:3)	1:2	< 5 % [b]
12	10	Dioxane/DMSO/TFA (15:2:3)	1:2	< 5 % [b]
13[c]	10	Dioxane/DMSO/AcOH (15:2:3)	1:2	12%
14	10	Dioxane/DMSO/AcOH (15:2:3)	1:1	< 5 % [b]
15	10	Dioxane/DMSO/AcOH (15:2:3)	2:1	< 5 % [b]
16	10	Dioxane/DMSO/AcOH (15:2:3)	1:3	< 5 % [b]
17	50	Dioxane/DMSO/AcOH (15:2:3)	1:2	14%
18	100	Dioxane/DMSO/AcOH (15:2:3)	1:2	17%

[a] No product detected by LCMS. [b] Required product detected by LCMS in trace amounts.
[c] Inclusion of 4 Å mol sieves.

Work by Gooßen[106,107] involving α-ketoacids was promoted *via* a copper catalysed system, so with inspiration from this an alternative system was assessed. Initial reactions involved the replacement of the silver species with a copper species in either catalytic or stoichiometric amounts. 1,10-phenanthroline was also added as a ligand. A variety of copper species were tested, and when this showed no productivity alteration of the acid or co-oxidant was attempted (**Table 21**).

Table 21: Gooßen inspired copper mediated screening attempts

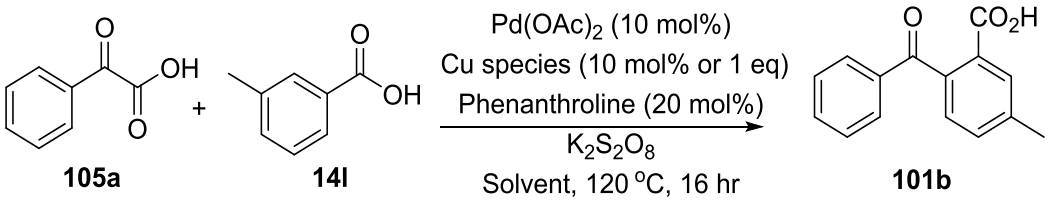


Entry	Cu Species	Eq. Cu species	Solvent (Ratio)	Yield
1	$Cu(OAc)_2$	10 mol%	Dioxane/DMSO/AcOH (15:2:3)	-[a]
2	Cu_2O	10 mol%	Dioxane/DMSO/AcOH (15:2:3)	-[a]
3	CuBr	10 mol%	Dioxane/DMSO/AcOH (15:2:3)	-[a]
4	CuI	10 mol%	Dioxane/DMSO/AcOH (15:2:3)	-[a]
5	$Cu(OAc)_2$	1 eq	Dioxane/DMSO/AcOH (15:2:3)	-[a]
6	Cu_2O	1 eq	Dioxane/DMSO/AcOH (15:2:3)	-[a]
7	CuBr	1 eq	Dioxane/DMSO/AcOH (15:2:3)	-[a]
8	CuI	1 eq	Dioxane/DMSO/AcOH (15:2:3)	-[a]
9	CuI	10 mol%	Dioxane/DMSO/PivOH (15:2:3)	-[a]
10	CuI	10 mol%	Dioxane/DMSO/TFA (15:2:3)	-[a]
11	CuI	1 eq	Dioxane/DMSO/PivOH (15:2:3)	-[a]
12	CuI	1 eq	Dioxane/DMSO/TFA (15:2:3)	-[a]
13[b]	CuI	10 mol%	Dioxane/DMSO/AcOH (15:2:3)	-[a]
14[b]	CuI	1eq	Dioxane/DMSO/AcOH (15:2:3)	-[a]

[a]None of required product isolated on purification, isolated products were benzoic acid and recovered *m*-toluic acid. [b]Reaction performed in the absence of $K_2S_2O_8$

Under these attempted conditions the desired product was not observed. Decarboxylation of the keto-acid was observed; however the isolated products were benzoic acid and recovered *m*-toluic acid (as a mixture by NMR). Gooßen's work has been indicated to be particularly solvent dependent. A wide range of high boiling solvents were also tested under the reaction conditions, in the presence of both catalytic and stoichiometric copper iodide and copper acetate (**Table 22**). However this still failed to generate the desired product.

Table 22: Gooβen inspired copper mediated screening attempts



105a **14l** **101b**

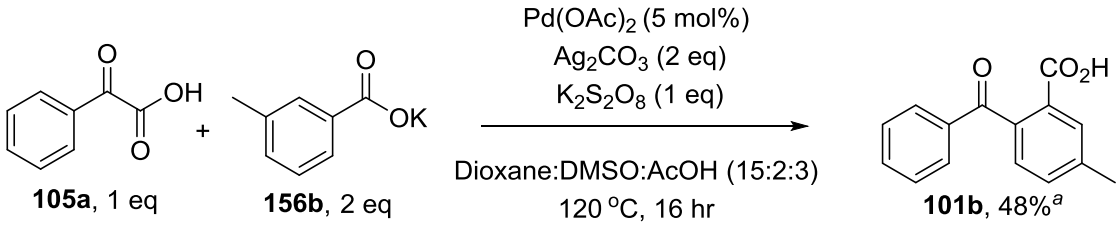
Entry	Cu Species	Eq. Cu species	Solvent (Ratio)	Yield
1	CuI	10 mol%	DMF	- [a]
2	CuI	10 mol%	DMF/NMP (1:1)	- [a]
3	CuI	10 mol%	NMP/Quinoline (3:1)	- [a]
4	CuI	10 mol%	NMP	- [a]
5	CuI	10 mol%	DME	- [a]
6	CuI	10 mol%	Digyme	- [a]
7	CuI	1eq	DMF	- [a]
8	CuI	1eq	DMF/NMP (1:1)	- [a]
9	CuI	1eq	NMP/Quinoline (3:1)	- [a]
10	CuI	1eq	NMP	- [a]
11	CuI	1eq	DME	- [a]
12	CuI	1eq	Digyme	- [a]
13[b]	$Cu(OAc)_2$	10 mol%	DMF	- [a]
14[b]	$Cu(OAc)_2$	10 mol%	DMF/NMP (1:1)	- [a]
15	$Cu(OAc)_2$	10 mol%	NMP/Quinoline (3:1)	- [a]
16	$Cu(OAc)_2$	10 mol%	NMP	- [a]
17	$Cu(OAc)_2$	10 mol%	DME	- [a]
18	$Cu(OAc)_2$	10 mol%	Digyme	- [a]
19	$Cu(OAc)_2$	1eq	DMF	- [a]
20	$Cu(OAc)_2$	1eq	DMF/NMP (1:1)	- [a]
21	$Cu(OAc)_2$	1eq	NMP/Quinoline (3:1)	- [a]
22	$Cu(OAc)_2$	1eq	NMP	- [a]
23	$Cu(OAc)_2$	1eq	DME	- [a]
24	$Cu(OAc)_2$	1eq	Digyme	- [a]

[a]None of required product isolated on purification, isolated products were benzoic acid and recovered *m*-toluic acid

3.2.3. Use of potassium carboxylates in the C–H activation

Work by Yu demonstrates that the presence of K_2HPO_4 is necessary in the *ortho*-activation of benzoic acids, in order to form the potassium salt of the acid *in situ*. They found that without the presence of the K^+ or Na^+ counterion no reaction was observed, and through use of the potassium carboxylate rather than the acid they retained reasonable yields.[135]

Attempting the reaction with the potassium carboxylate demonstrated a dramatic improvement in the yield (**Scheme 95**) with 48% isolated in high purity (by ^{1}H NMR and LCMS), while also allowing for reduction in the palladium loading. Attempts to form the potassium salt *in situ* through the inclusion of K^+ bases (K_2CO_3, K_2HPO_4, KO^{t}Bu) was less successful however yields did show some improvement (~20% at best).

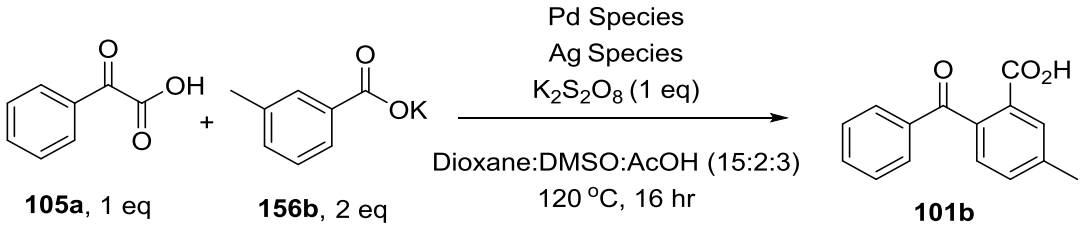


Scheme 95: Reaction between 23a and potassium 55b. [a] Isolated yield averaged over 4 repeats

Screening of conditions was therefore repeated using this improved protocol, however similar trends were observed. Results are summarised in **Tables 23**, **24** and **25**. Isolated yields are quoted. Where poor conversion was shown by LCMS reactions were discarded.

Results indicated that alteration of the palladium species, silver species, or oxidant proved to either have little impact on the yield of the reaction, or to hinder formation of the product – and removal of any of these species caused the reaction to fail (**Table 23**). Reduction in the equivalents of silver, while having a slight impact on the yield, did not significantly impact it, however use of catalytic silver was seen to be detrimental (**Table 23**, **Entry 3** and **Entry 17**). Increasing the amount of oxidant did not allow for reduction of the silver species to a catalytic amount (**Table 23**, **Entries 17** and **18**). Inclusion of the potassium salt of the keto-acid was not productive (**Table 24**, **Entry 1**), while addition of phosphine ligands also showed no improvement with the reaction stalling in many cases.

Table 23: Screening conditions for reaction between 105a and 156b

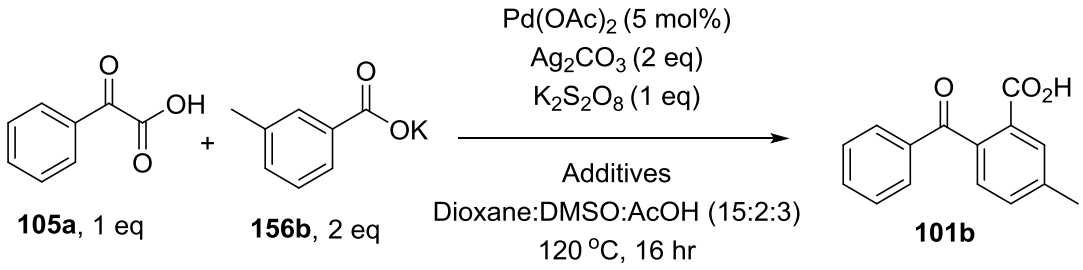


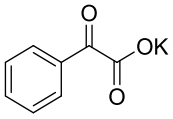
105a, 1 eq **156b**, 2 eq **101b**

#	Pd Species (eq)	Ag Species (eq)	Oxidant (eq)	Yield
1	$Pd(OAc)_2$ (5 mol%)	Ag_2CO_3 (2 eq)	$K_2S_2O_8$ (1 eq)	48% [a]
2	$Pd(OAc)_2$ (10 mol%)	Ag_2CO_3 (2 eq)	$K_2S_2O_8$ (1 eq)	47%
3	$Pd(OAc)_2$ (5 mol%)	Ag_2CO_3 (1 eq)	$K_2S_2O_8$ (1 eq)	42% [b]
4	$Pd(O_2CCF_3)$ (5 mol%)	Ag_2CO_3 (1 eq)	$K_2S_2O_8$ (1 eq)	38% [b]
5	$Pd(PhCN)_2Cl_2$ (5 mol%)	Ag_2CO_3 (1 eq)	$K_2S_2O_8$ (1 eq)	34%
6	$PdCl_2$ (5 mol%)	Ag_2CO_3 (1 eq)	$K_2S_2O_8$ (1 eq)	40%
7	$Pd(dba)_2$ (5 mol%)	Ag_2CO_3 (1 eq)	$K_2S_2O_8$ (1 eq)	27%
8	-	Ag_2CO_3 (1 eq)	$K_2S_2O_8$ (1 eq)	- - [d]
9	$Pd(OAc)_2$ (5 mol%)	AgOAc (1 eq)	$K_2S_2O_8$ (1 eq)	39%
10	$Pd(OAc)_2$ (5 mol%)	AgI (1 eq)	$K_2S_2O_8$ (1 eq)	37%
11	$Pd(OAc)_2$ (5 mol%)	$AgNO_3$ (1 eq)	$K_2S_2O_8$ (1 eq)	41%
12	$Pd(OAc)_2$ (5 mol%)	Ag_2O (1 eq)	$K_2S_2O_8$ (1 eq)	37%
13	$Pd(OAc)_2$ (5 mol%)	$AgBF_4$ (1 eq)	$K_2S_2O_8$ (1 eq)	23%
14	$Pd(OAc)_2$ (5 mol%)	AgF (1 eq)	$K_2S_2O_8$ (1 eq)	< 5% [c]
15	$Pd(OAc)_2$ (5 mol%)	Ag_2CO_3 (2 eq)	$K_2S_2O_8$ (50 mol%)	< 5% [c]
16	$Pd(OAc)_2$ (5 mol%)	Ag_2CO_3 (2 eq)	-	- - [d]
17	$Pd(OAc)_2$ (5 mol%)	Ag_2CO_3 (10 mol%)	$K_2S_2O_8$ (1 eq)	< 5% [c]
18	$Pd(OAc)_2$ (5 mol%)	Ag_2CO_3 (10 mol%)	$K_2S_2O_8$ (2 eq)	< 5% [c]
19	$Pd(OAc)_2$ (5 mol%)	Ag_2CO_3 (2 eq)	$Na_2S_2O_8$ (1 eq)	< 5% [c]
20	$Pd(OAc)_2$ (5 mol%)	Ag_2CO_3 (2 eq)	$(NH_4)_2S_2O_8$ (1 eq)	< 5% [c]
21	$Pd(OAc)_2$ (5 mol%)	Ag_2CO_3 (2 eq)	$PhI(OAc)_2$ (1 eq)	< 5% [c]
22	$Pd(OAc)_2$ (5 mol%)	Ag_2CO_3 (2 eq)	BQ (1 eq)	< 5% [c]
23	$Pd(OAc)_2$ (5 mol%)	-	$K_2S_2O_8$ (1 eq)	- - [d]

[a] Isolated yield averaged over 4 repeats. [b] Isolated yield averaged over 3 repeats. [c] Product detected by LCMS in trace amounts. [d] No product detected

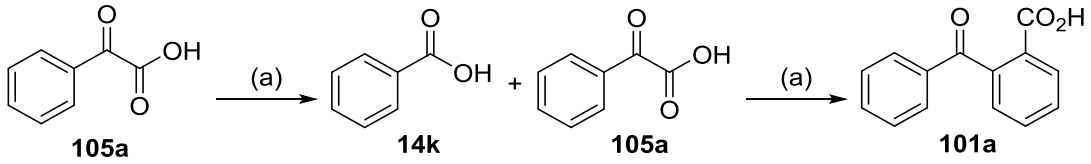
Table 24: Further screening conditions for reaction between 105a and 156b



#	Ligand	Additive	Quantity	Yield
1	-	 **109a**	1 eq (replace **105a**)	20%
2	PPh_3		10 mol%	43%
3	P(*o*-tol)$_3$		15 mol%	< 5% [a]
4	P(*o*-furyl)$_3$		15 mol%	< 5% [a]
5	BrettPhos		10 mol%	< 5% [a]
6	PCy_3		15 mol%	< 5% [a]

[a] Product detected by LCMS in trace amounts

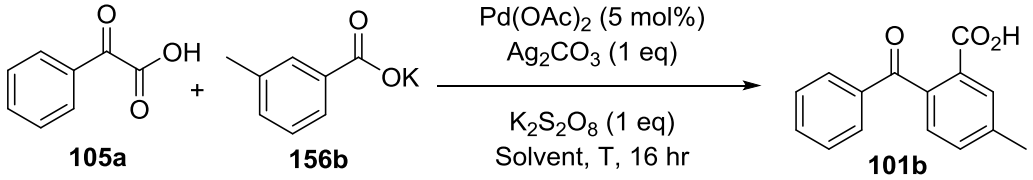
The exclusion of either DMSO or AcOH in the reaction solvent still gave reasonable conversion to the product, however neat dioxane showed poor conversion, potentially due to the low solubility of **156b** in dioxane (**Table 25**, **Entries 1-3**). Changing the ratio of the starting materials indicated the necessity for an excess of the C–H component. Where less than 1.5 equivalents of **156b** was used additional by-product 2-benzoylbenzoic acid (**101a**) was observed, presumably from the cross-coupling of the decarboxylated keto-acid (**Scheme 96**) with the unwanted benzoic acid by-product.



(a) $Pd(OAc)_2$ (5 mol%), Ag_2CO_3 (1 eq), $K_2S_2O_8$ (1 eq), Dioxane:DMSO:AcOH (15:2:3), 120 °C, 16 hr

Scheme 96: Proposed cross-coupling of keto-acid 105a with 14k to form by-product 101a

Table 25: Further screening of reaction between 105a and 156b



#	Temp	Solvent (Ratio)	Ratio (23a : 55b)	Yield
1	120 °C	Dioxane/DMSO (15:2)	1:2	38%
2	120 °C	Dioxane/HOAc (5:1)	1:2	44%
3	120 °C	Dioxane	1:2	17%
4	120 °C	Dioxane/DMSO/AcOH (15:2:3)	1:1.5	12%
5	120 °C	Dioxane/DMSO/AcOH (15:2:3)	1:1	< 5% [a]
6	120 °C	Dioxane/DMSO/AcOH (15:2:3)	1:1	< 5% [a, b]
7	120 °C	Dioxane/DMSO/AcOH (15:2:3)	2:1	< 5% [a, b]
8	120 °C	Dioxane/DMSO/AcOH (15:2:3)	3:1	< 5% [a, b]
9	120 °C	DMSO/AcOH	2:1	< 5% [a, b]
10	120 °C	DMSO	2:1	< 5% [a, b]
11	120 °C	AcOH	2:1	< 5% [a, b]
12	140 °C	Dioxane/DMSO/AcOH (15:2:3)	1:2	43%
13	90 °C	Dioxane/DMSO/AcOH (15:2:3)	1:2	< 5% [b]
14	60 °C	Dioxane/DMSO/AcOH (15:2:3)	1:2	- [c]
15 [d]	120 °C	Dioxane/DMSO/AcOH (15:2:3)	1:2	- [c]
16 [e]	120 °C	Dioxane/DMSO/AcOH (15:2:3)	1:2	- [c]

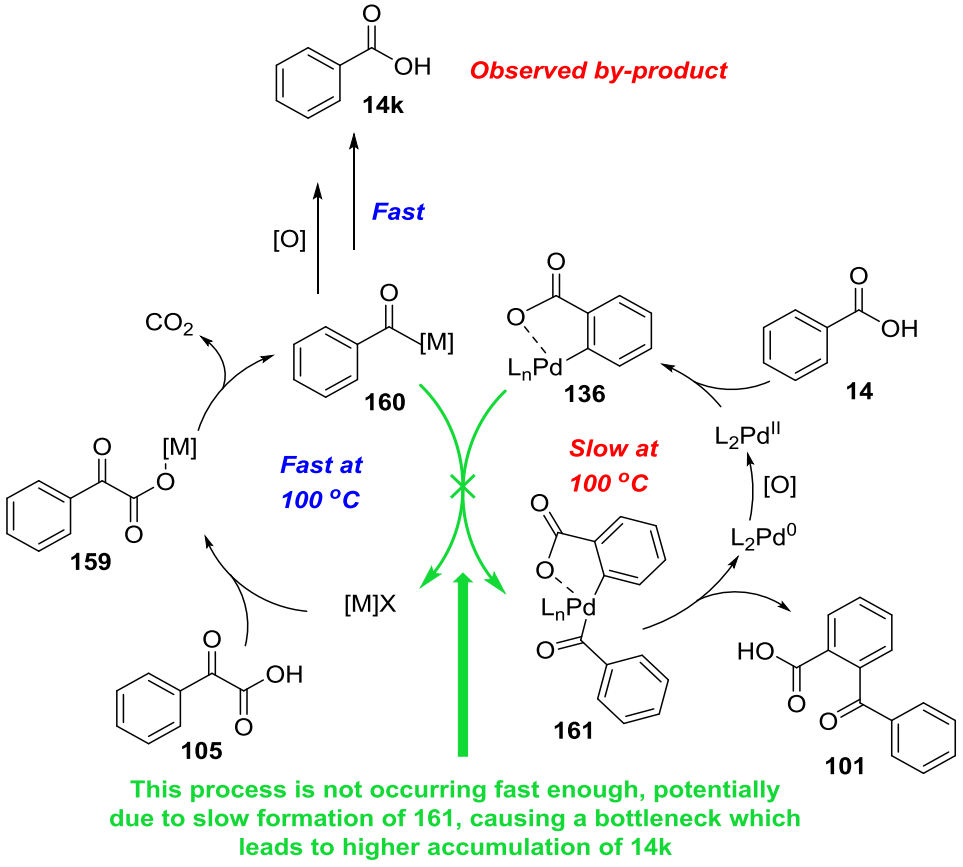
[a] Product detected by LCMS in trace amounts [b] LCMS showed production of **101a** in addition to required product. [c] Reaction conditions included 10 eq H_2O. [d] Non-anhydrous solvents.

Increasing the reaction temperature did not improve the yield and attempts to perform the reaction at lower temperatures were unsuccessful (**Table 25**, **Entries 12–14**). The inclusion of 10 equivalents of H_2O to the reaction halted product formation (**Table 25**, **Entry 15**). It is also notable that the use of non-anhydrous solvents was detrimental (**Table 25**, **Entry 16**).

The cause of the low yield of this reaction could potentially lie with the concept of two interacting catalytic cycles. Previous studies (**Section 3.1.2.**) have demonstrated that the desired C–H insertion does not occur below 100 °C, At this temperature the C–H insertion process is still relatively slow. As decarboxylation of the α-keto-acid occurs at

temperatures as low as 50 °C and the rate of the reaction is dependent on temperature, it is clear that at temperatures above 100 °C decarboxylation will be occurring readily. It would appear that we have one cycle progressing quickly, and the other struggling to keep up. The possibility that the decarboxylation is occurring too quickly to fully interact with the C–H insertion process would therefore be a reasonable assumption (**Scheme 97**).

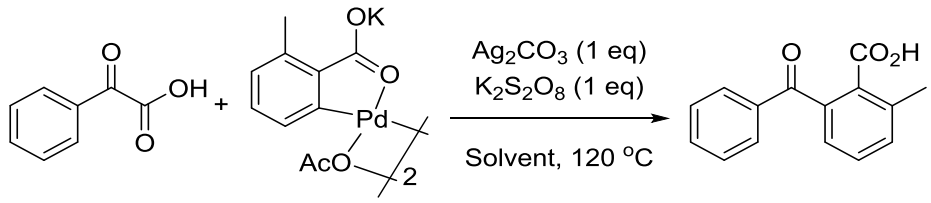
The hypothesis here is that formation of palladacycle **136** is not occurring quickly enough to support rapid generation of intermediate **161**. This causes a bottleneck of **160** to build up in the reaction mixture as transmetallation cannot occur if there is not sufficient palladacycle to react with. As this intermediate is not particularly stable under the reaction conditions it oxidises to become benzoic acid (**14k**) which is usually the only observed by-product.



Scheme 97: Hypothesis for the low yields generated from this reaction

Having previously synthesised palladacycle **154a** (**Scheme 79**, **Section 3.1.2**) this species was added to the reaction in an attempt to overcome this bottleneck effect. The reaction was repeated in various solvents at 120 °C. However presence of the palladacycle was found to stall decarboxylation of the keto-acid and yields remained low (**Table 26**).

Table 26: Addition of palladacycle 154a to keto acid 105a



105a **154a** **101c**

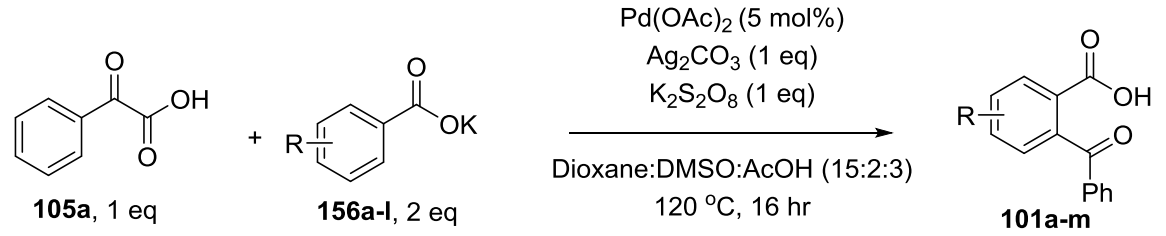
#	Solvent	Outcome
1	Dioxane/DMSO (15:2)	- [a]
2	Dioxane/HOAc (5:1)	- [a]
3	Dioxane/DMSO/AcOH (15:2:3)	- [a]
4	Dioxane/DMSO (15:2)	- [a]
5	DMF	- [a]
6	DMF/NMP (1:1)	- [a]
7	NMP/Quinoline (3:1)	- [a]
8	NMP	- [a]

[a] No product detected

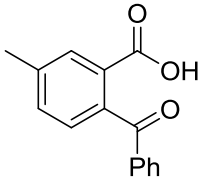
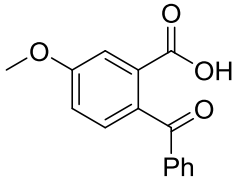
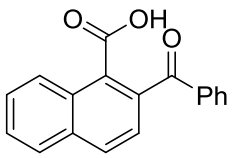
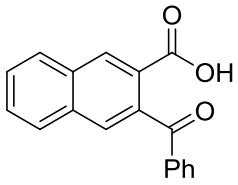
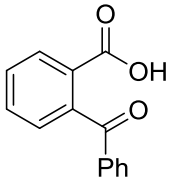
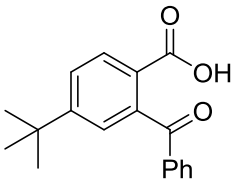
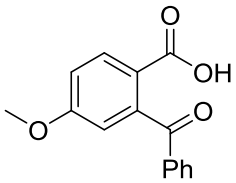
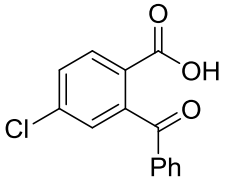
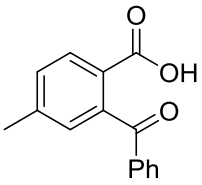
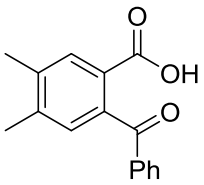
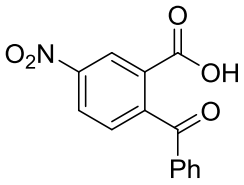
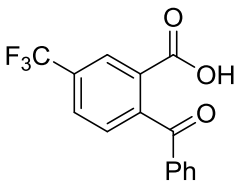
3.2.4. Exploration of reaction scope

At this point the scope of the reaction with was explored relation to the C–H component. A series of potassium salts (previously synthesised in **Section 3.1.2.**) were subjected to the developed reaction conditions (**Table 27**). Reasonable yields were isolated for specific examples (**101a-g**), consistent with the yield for the optimised *m*-toluic acid example, and slight reduction in yield for **101h** and **101i**. However in other cases (**101j-m**) yields were negligible. Despite detection of the required products by LCMS this was in poor conversion and full recovery of the C–H component was possible. Full decarboxylation of the keto-acid was observed, however the only isolated by-product of these transformations was benzoic acid (often as a mixture with the C–H component).

Table 27: Reaction scope concerning the C–H component

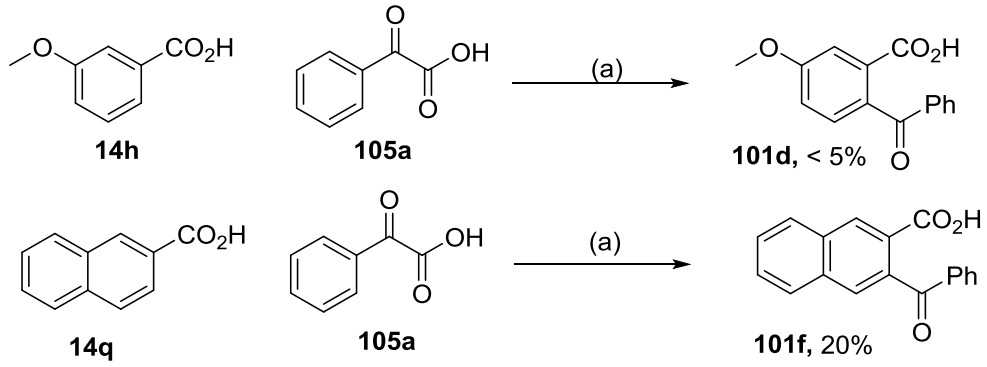


105a, 1 eq + **156a-l**, 2 eq → **101a-m**

 **101b**, 42%[a]	 **101d**, 51%	 **101e**, 33%	 **101f**, 50%
 **101a**, 34%	 **101g**, 24%	 **101h**, 12%	 **101i**, 16%
 **101j**, < 5% [b]	 **101k** < 5% [b]	 **101l,** < 5% [b]	 **101m,** < 5% [b]

[a] Yield based on average of 4 repeats. [b] Trace product detected by LCMS

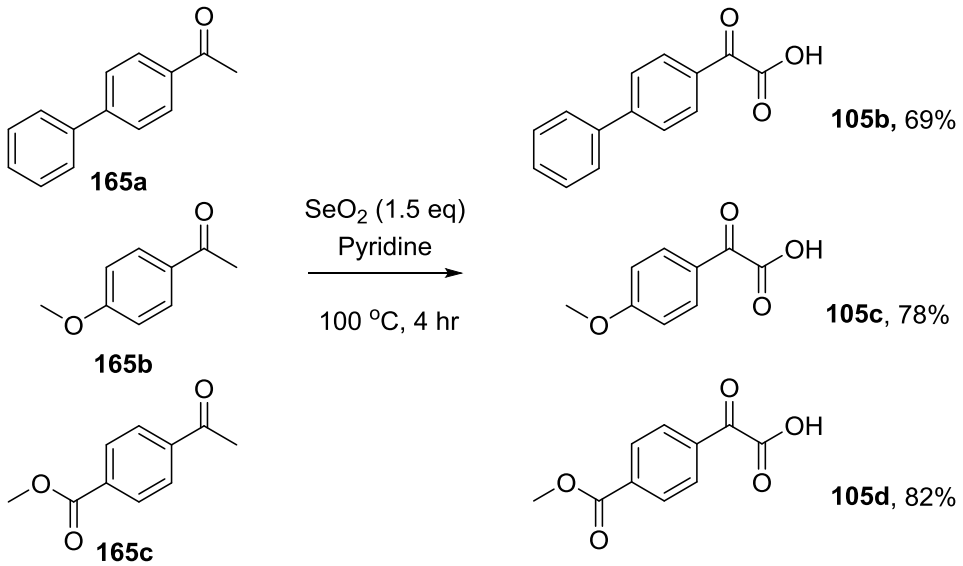
Concerning compounds **101d** and **101f** corresponding reactions were also performed with the acid C–H component rather than the potassium salt, to reinforce the positive effect that the counter ion was having on the yield (**Scheme 98**). Yields were considerably lower in both cases, with only trace amounts of **101d**, detected by LCMS, and 20% isolated yield of **101f**.



(a) $Pd(OAc)_2$ (5 mol%), Ag_2CO_3 (1 eq), $K_2S_2O_8$ (1 eq), Dioxane/DMSO/AcOH, 120 ^oC

Scheme 98: Corresponding reactions between acid C–H component

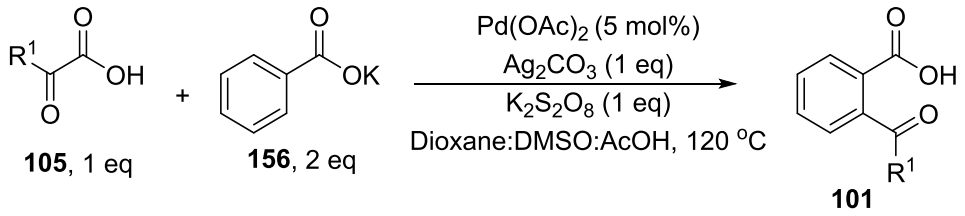
The scope of the decarboxylative component was also investigated. While some *α*-keto acids were commercially available, other derivatives were either incredibly costly, or not obtainable. Synthesis of *α*-keto acids is performed by oxidation of the relevant acetophenone using selenium dioxide in pyridine.[147] *Para*-phenyl, *para*-methoxy, and *para*-ester derivatives **105b, 105c** and **105d** were prepared using this method to demonstrate electron-neutral, electron-rich and electron-poor species respectively (**Scheme 99**).



Scheme 99: Synthesis and availability of *α*-keto acids

Under the established reaction conditions acids **105b** and **105c** were successfully cross-coupled with benzoic acid in moderate yields. However the remaining keto-acid species did not exhibit any decarboxylation under the standard conditions, and species **101p**, **101q** and **101r** were not accessible (**Table 28**).

Table 28: Attempts to extend the reaction scope for the decarboxylative component using a series of *α*-keto-acids



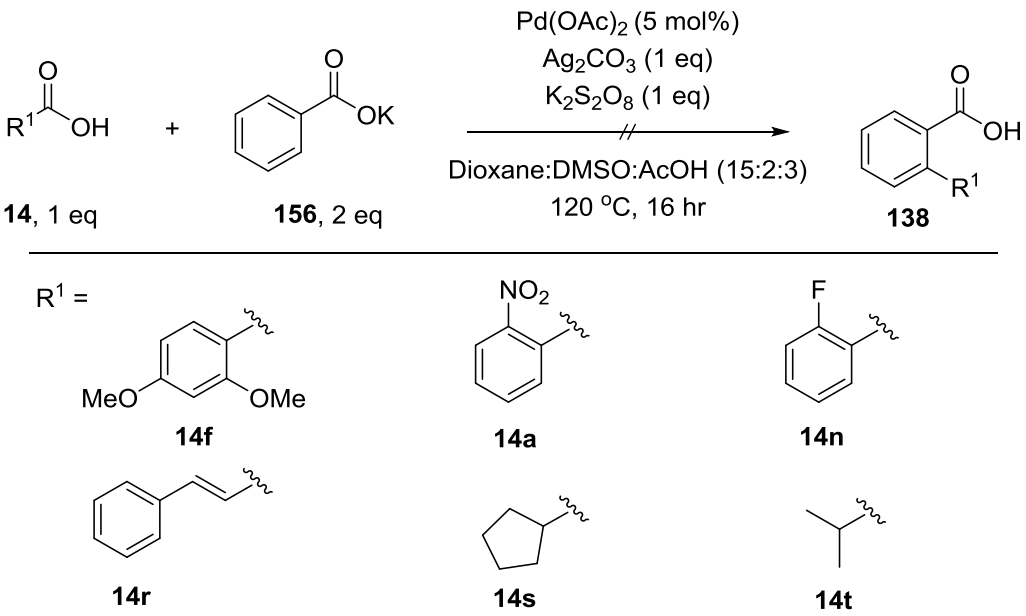
R^1 =					
	101n, 31%	**101o**, 28%	**101p**, - [a]	**101q**, - [a]	**101r**, - [a]

[a]Decarboxylation of SM not observed.

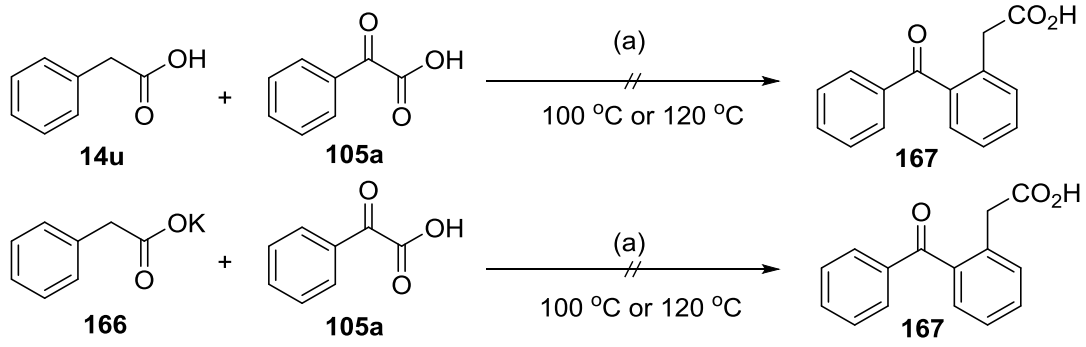
In an attempt to extend the scope of this reaction, other types of acids were exposed to the same reaction conditions (**Table 29**). Unsurprisingly benzoic acids **14f**, **14a** and **14n** did not undergo cross-coupling under the developed conditions. Trans-cinnamic acid has been demonstrated as a decarboxylative cross-coupling partner in work by Wu[148] and Mao,[149] however when subjected to the standard conditions no cross-coupling was evident. Minisci type conditions for decarboxylative cross-coupling of alkyl carboxylic acids with protonated heterocycles include the use of silver and peroxidisulfate.[87] Alkyl acids **14s** and **14t** were also tested under the standard conditions to see whether Minisci type cross-coupling could be observed. Unfortunately this proved unsuccessful and no evidence of decarboxylation of the starting materials was apparent.

Table 29: Attempts to extend the reaction scope for the decarboxylative component –

Change in the type of acid. Unsuccessful coupling in all cases



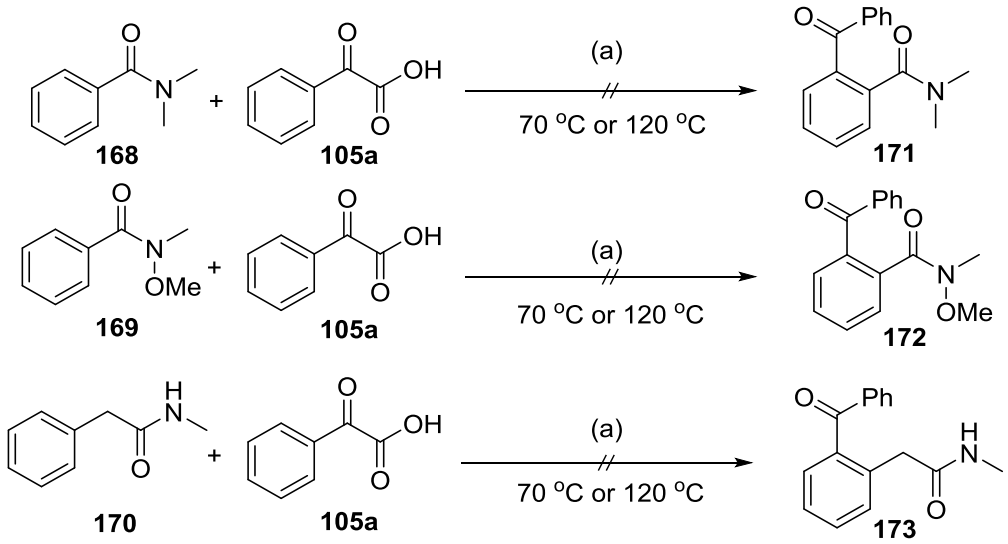
Yu has indicated that phenylacetic acids could also be used to direct C–H activation, through a 6-membered palladacycle rather than the 5-membered cycle.[150] The coupling was attempted between phenylacetic acid **14u** and phenylglyoxylic acid using the developed reaction conditions at both 100 and 120 °C. The corresponding potassium salt **166** was subjected to the same conditions (**Scheme 100**). Both systems indicated some product formation by LCMS, however this was more substantial for the potassium salt. Despite this, on work up crude ^{1}H NMR indicated that product formation was only in trace amounts (<5%), with the majority of the material identified as unreacted phenylacetic acid **14u** and benzoic acid **14k**.



Conditions (a) $Pd(OAc)_2$ (5 mol%), Ag_2CO_3 (1 eq), $K_2S_2O_8$ (1 eq)
Dioxane:DMSO:AcOH (15:2:3), 16 hr

Scheme 100: Attempted coupling between phenylacetic acid and phenylglyoxylic acid

Attention was also turned to other directing groups. Benzamide **168**, Weinreb amide **169** and phenylacetamide **170** were all subjected to the developed coupling conditions with phenylglyoxylic acid. Reactions were tried both at 120 °C and 70 °C (**Scheme 101**). While decarboxylation of the phenylglyoxylic acid was observed none of the required product was observed. While further screening or optimisation could have led to more productive results in these cases, a series of literature publications at the time demonstrated the cross-coupling of keto acids with acetanilides, alkoxypyridines, phenylacetamides and others similar species discussed in the introduction. These publications reduced the impact research into amide directing groups would present, and therefore these reactions were not pursued beyond this point.

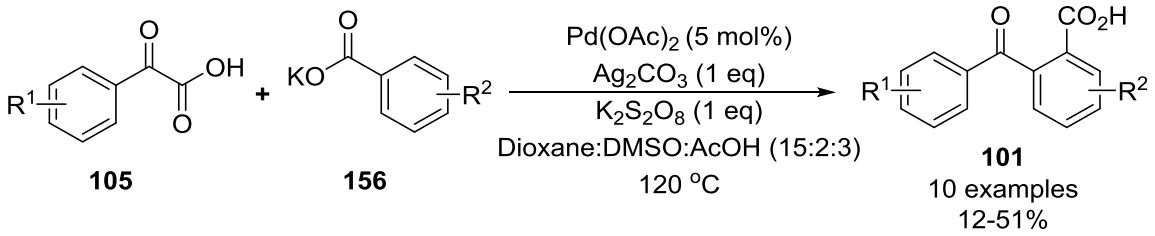


Conditions (a) $Pd(OAc)_2$ (5 mol%), Ag_2CO_3 (1 eq), $K_2S_2O_8$ (1 eq), Dioxane:DMSO:AcOH (15:2:3)

Scheme 101: Attempted reactions with alternative directing groups

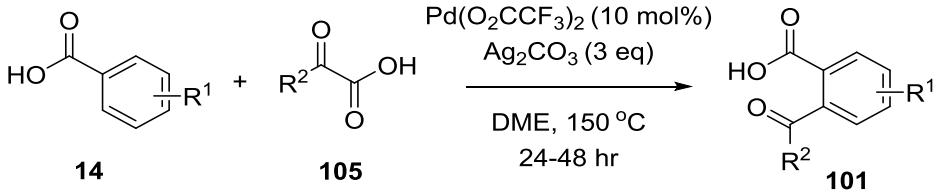
3.2.5. Summary and conclusions

Palladium catalysed conditions have been developed for the successful decarboxylative *ortho*-benzoylation of benzoic acids, leading to the synthesis of ten substituted benzophenones in moderate yield (**Scheme 102**). The process of this research has generated an understanding of the complex nature of decarboxylative cross-coupling, and justification of some of the limitations of this chemistry has been achieved.



Scheme 102: Palladium catalysed decarboxylative *ortho*-acylation of benzoic acids

In unison with our studies Ge published a method for palladium catalysed decarboxylative *ortho*-acylation of benzoic acids (**Scheme 103**).[151] Reactions were performed at a minimum temperature of 150 °C (with many examples requiring up to 170 °C), in DME (bp = 85 °C[152]). Therefore reactions are performed under significant pressure in sealed vessels, for up to 48 hours. The method uses 3 equivalents of Ag_2CO_3 (a 6 fold excess of Ag^I) and 10 mol% of $Pd(O_2CCF_3)_2$. This is a high metal loading of an expensive catalyst. Industrial applicability of this method is therefore unlikely, as the economic feasibility, and practicalities of large scale production would be an issue.



Scheme 103: Work published by Ge and co-workers detailing the successful decarboxylative *ortho*-acylation of benzoic acids

The mechanism is postulated to be *via* a similar process to that detailed in **Section 3.2.1**. The high equivalents of Ag_2CO_3 are justified by claiming that the silver salt of benzoic acid is formed initially, allowing for the palladium insertion to occur. This demonstrates a similar counter ion effect to that which has been observed throughout this research.

The publication of this work exemplifies the harsh conditions required in order to facilitate this transformation. The research presented in this thesis demonstrates a milder

method to enable the same transformation. However a re-evaluation of the impact of this research was necessary with regards to the recent literature. While further effort could be spent optimising the conditions to improve yields, it was decided that the benefits of the scientific impact were this to be successful, would not equate to the time spent on the research. Therefore until further inspiration could be gained, this research was halted.

The benefits of this successful transformation show the ability to chemically manipulate one functional group in two distinct ways within the confines of one reaction. The complex nature of this process relies on two interacting catalytic cycles and the ability to manipulate these to generate the desired product is an impressive feat.

4. Introduction to zinc mediated 1,5- and 1,4,5-substituted 1,2,3-triazole synthesis

4.1. Significance of 1,2,3-triazoles

1,2,3-Triazoles have been of synthetic interest for a number of years. The structure of these units can mimic the atom placement and electronic properties of a peptide bond, with the rigidity and chemical stability of the triazole moiety making it more biologically robust (**Figure 5**).[153-156] Direct analogies can be drawn between the E configured amide and the 1,4-isomer, and similarly the Z amide and the 1,5-isomer. There is a far stronger dipole moment in the triazole structure than in an amide bond,[157] which increases the hydrogen bond donor and acceptor capacities of the triazole. Both the N(2) and the N(3) atoms can act as a hydrogen bond acceptor. Additionally the strong dipole moment can polarise the C–H bond of each isomer and this can allow this proton to act as a hydrogen bond donor, similar to the NH in the peptide.[158] In the 1,4-isomer, differences in atom displacement in the backbone mean slight changes in the configuration of the structure. Conversely, the atom displacement in the 1,5-isomer is the same, allowing the moiety to be a closer structural bioisostere of the Z amide.[159]

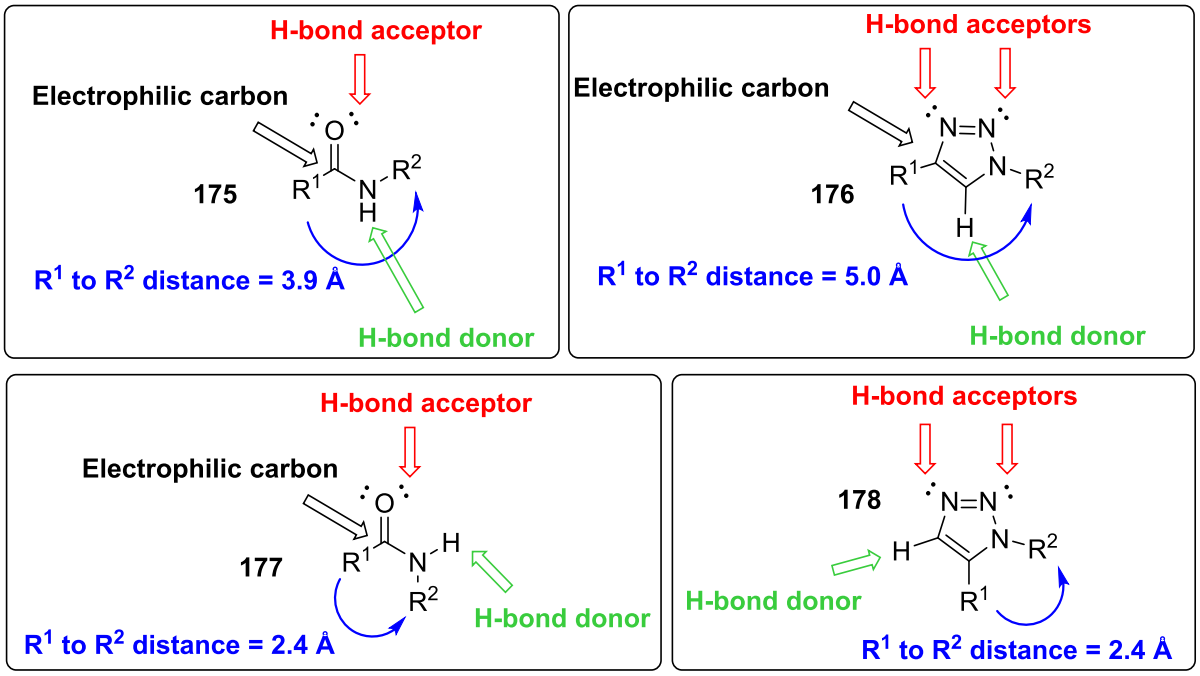


Figure 5: Similarities between peptide motif's and 1,2,3-triazoles

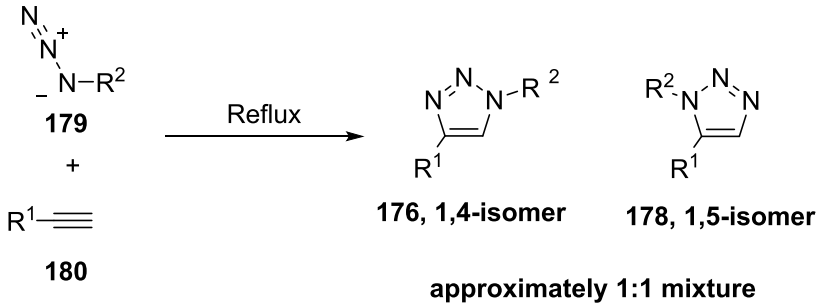
This bioisosterism with peptide bonds have led to significant interest in the biological activity of these species. Evidence has shown that triazoles possess anti-HIV

activity,[160,161] anti-microbial activity against gram positive bacteria,[162] anti-fungal activity,[163] acetylcholinesterase inhibition,[164] selective β_3 agrenergic inhibition[165,166] and potent anti-histamine activity.[167] In addition to this there is interest in the industrial uses of these structures, with applications ranging from dyes,[168] anti-corrosion agents,[169] and photographic materials.[170] Utility has also been displayed in agrochemicals with 1,2,3-triazoles demonstrating pesticidal, fungicidal, insecticidal and acaricidal activity.[171,172]

4.2. Synthesis of 1,2,3-triazoles

4.2.1. Early methods

Traditionally the synthesis of 1,2,3-triazoles has been through the Huisgen 1,3-dipolar cycloaddition of an azide and an alkyne (**Scheme 104**).[173-175] Cycloadditions of this type usually occur between two unsaturated reagents and are notable for their incredible atom economy and efficiency.



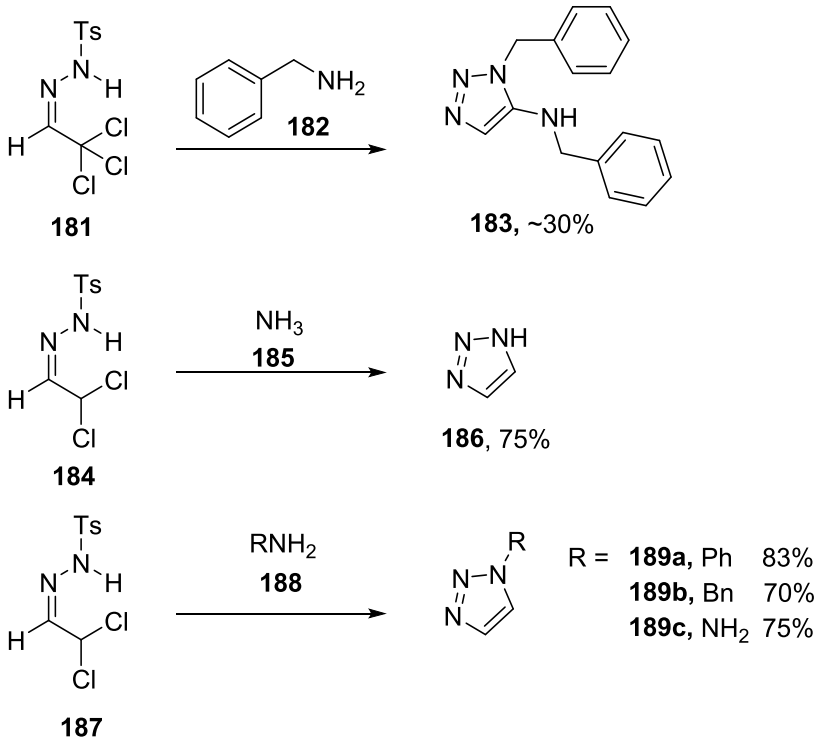
Scheme 104: Traditional method for synthesising 1,2,3-triazoles through thermal Huisgen cycloaddition giving a mixture of isomers

The ease of synthesis of both the alkyne and the azide counterpart and physical stability of these functional groups make the reaction ideal for synthetic applications. Both these functional groups are essentially inert to most biological and organic conditions – this is particularly surprising for the azide, as the high nitrogen content of this group leads to concerns over stability. Saxon and Kiick have demonstrated the stability of azides in complex biomolecules.[176] Despite the absence of azides from natural products, it is clear that there are a limited number of actual reaction partners for this species. Furthermore, the stability of these reagents to highly functionalised biomolecules, molecular oxygen, water and common synthetic organic conditions make the pairing ideal for bioconjugation.

The Huisgen cyclisation is not without significant drawbacks. The reaction typically requires temperatures >100 °C and long reaction times to achieve high conversion. Such high temperatures impact the range of functionality tolerated by the reaction. The main issue with the reaction however, is selectivity. In most cases a mixture of the two available regioisomers are produced (1,4- and 1,5-isomers, **Scheme 104**). Separation of these isomers can be difficult and when only one specific isomer was required the yield was greatly impacted.[177] While highly electron deficient terminal alkynes could sometimes impart some selectivity,[178] the lack of discrimination remained a barrier to the synthetic utility of the reaction.

The use of sodium or lithium acetylide salts has allowed employment of lower temperatures, but this was often with limited success.[179,180] In 1984 L'Abbé reported the unexpected formation of a triazole product in low yield from the *in situ* azide generation by displacement of a sulfonate with lithium azide (LiN_3) and copper(I) chloride (CuCl).[181] This is the first evidence of the copper catalysed [3+2] cycloaddition, now most commonly referred to as the click reaction (**Section 4.2.2.**). Despite the implications of this, the reaction was not investigated further. Sharpless later attributed this lack of attention to the concerns over the safety of working with azides as 1,3-dipoles, due to their toxic and potentially explosive nature. This was despite knowledge that azides had been proven suitable for late-stage cyclisations as they could be carried through a number of synthetic steps without decomposition.[182]

Alternatively, it has been demonstrated that cyclisation of α,α,α-trichloroketone tosylhydrazone (**181**) will result in the formation of 1,5-triazoles in low yield (~30%).[183] Similarly the cyclisation of dichloroacetaldehyde tosylhydrazone with ammonia or amine derivatives leads to the unsubstituted 1,2,3-triazole or the 1-substituted 1,2,3-triazole respectively (**Scheme 105**).[184] This is also true for the corresponding mesitylhydrazones.



Scheme 105: Alternative triazole synthesis by cyclisation of hydrazones

4.2.2. Development of the click reaction

While synthetic interest in triazole moieties was present prior to 2000, the methods available for construction of these units were lacklustre, suffering from poor yields, poor functional group tolerance, long reaction times or poor selectivity. Realisation of the full potential utility of these interesting molecules would not be facilitated until alternative synthetic methods were developed to overcome such problems. In 2001, Sharpless and co-workers presented a review describing a desirable new strategy for organic chemistry, aimed at widening the applications of synthesis to meet modern day demands – particularly in drug discovery.[185] The review describes a new area of click chemistry whereby the construction of carbon–heteroatom bonds could be achieved using high energy "spring-loaded" reagents. In nature carbon–heteroatom bonds are as ubiquitous as C–C bonds, and most biomolecules – polysaccharides, proteins, nucleic acids – are formed by connection of small subunits by carbon–heteroatom bonds (**Figure 6**). The overall goal of the click chemistry approach was to generate a large selection of reactions which are reliable, predictable, can be performed under mild conditions from readily available materials, and give the desired products in a pure and selective manner. The reactions were required to be wide in scope giving only high yields, without undesirable by-products. Purification was to be through non-chromatographic methods. An important

feature of this click chemistry was the Husigen cycloaddition, however it wasn't until the following year that the copper(I) catalysed Huisgen 1,3-dipolar cycloaddition was presented for the formation of 1,4-substituted 1,2,3-triazoles. This powerful reaction is viewed as the gold standard of "Click Chemistry" and as such is often mistakenly called the Click Reaction but was actually renamed by the authors as Copper-catalysed Azide-Alkyne Cycloaddition, or "CuAAC".

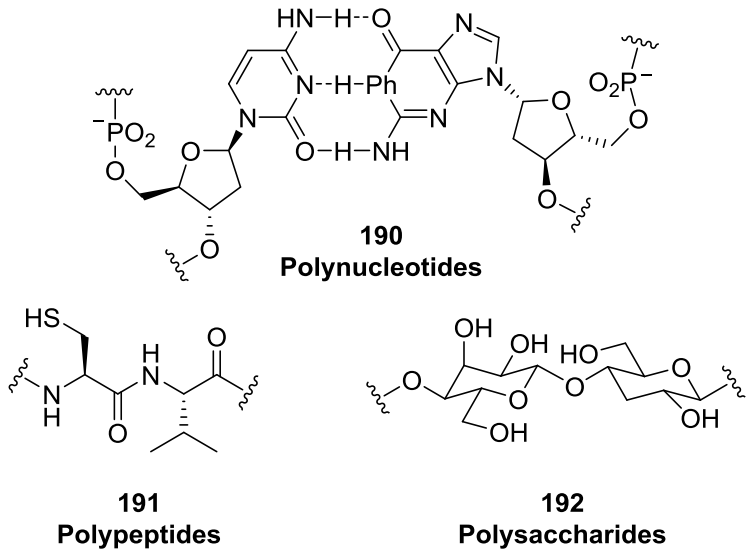
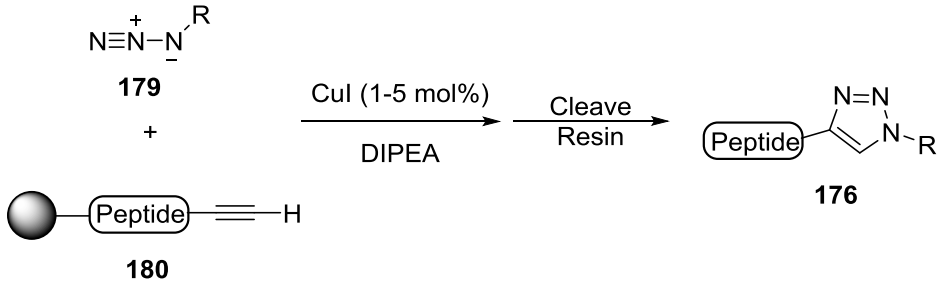


Figure 6: Biomolecules containing carbon–heteroatom bonds

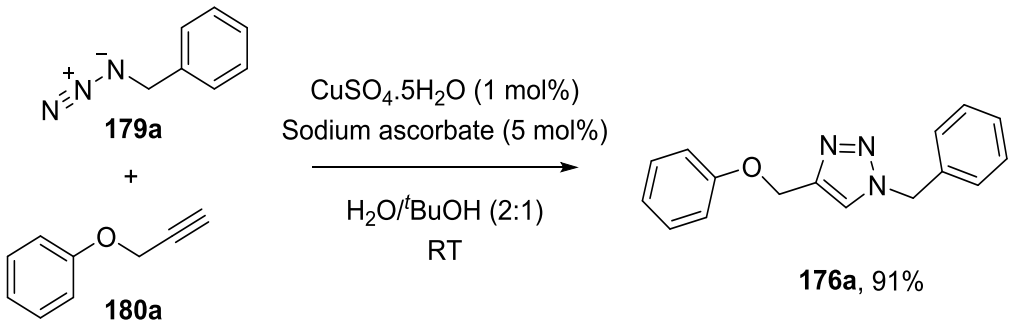
CuAAC was developed simultaneously by the groups of Sharpless and Meldal in 2002.[182,186] The benefits of this development were not only the incredible selectivity towards the 1,4-isomer, but also the vast increase in the rate of the reaction with reaction proceeding up to 10^7 times faster. Meldel's publication came first, demonstrating the use of solid-supported peptide in a regiospecific method for the formation of exclusively 1,4-peptidotriazole (**Scheme 106**). This ground-breaking work demonstrated not only the impact of this new ligation, but also the potential for application in bioconjugation due to the included peptide supports.[186] These solid-supports were necessary for the reaction in order to prevent Glaser-type coupling (homo-coupling of terminal alkynes in the presence of copper)[187] which was overwhelming the reaction and required explicit removal of O_2 from the system. The reaction united resin-bound copper acetylides with primary, secondary, tertiary or aryl azides, as well as sugars bearing azides. Some steric effects were observed with trimethylsilylazide (TMS-Azide) and 2-azide-2,2-diphenyl acetic acid both failing to generate the desired products, however other than this the substrate scope was broad. In general, electron deficient alkynes were more reactive to the ligation, proceeding in high yields and short reaction times.



Scheme 106: Meldel solid supported formation of 1,4-peptidotriazoles through CuAAC

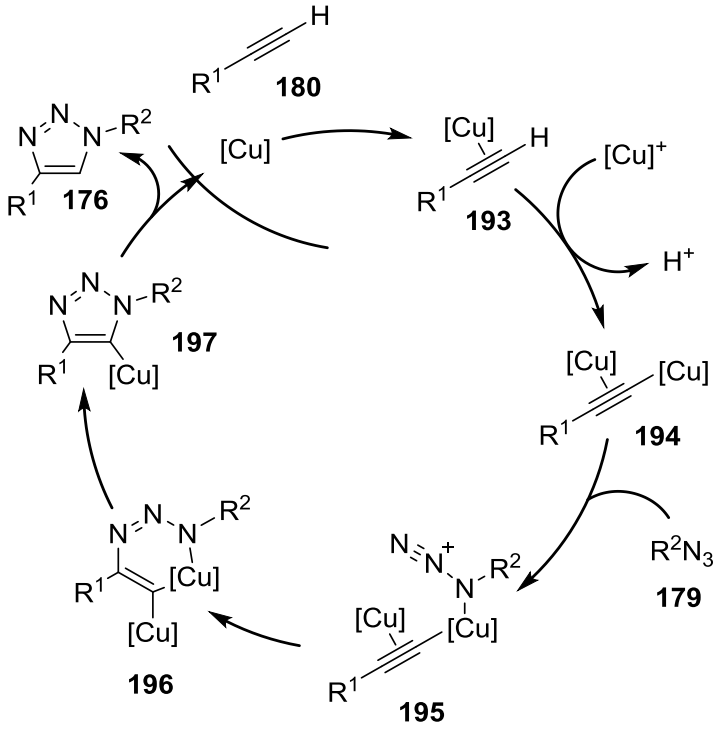
The mild conditions allowed the reaction to proceed at room temperature (25 °C) with only 1 mol% copper iodide (or another copper(I) source) without dependence on solvent choice. DCM, MeCN, THF, toluene, DMF and neat DIPEA were all demonstrated as suitable solvents for the reaction. Notably sensitive Fmoc and Boc groups were all tolerated under these mild conditions. Quantitative yields were available in high purity (75-95%) without column chromatography. The mechanism is alluded as being a stepwise procedure rather than a concerted mechanism. Initial insertion of the copper into the terminal alkyne in the presence of an amine base is known from Sonogashira couplings[188] and this copper acetylide is sufficiently polarised to participate readily in the cycloaddition.

At the same time Sharpless and co-workers disclosed their incredibly robust procedure for the regiospecific ligation of azides and alkynes in the formation of 1,4-triazoles (**Scheme 107**).[182] While Cu^{I} salts were demonstrated to work well as a catalyst for this transformation, the preferred method for the group was to generate the Cu^{I} species *in situ* by the reduction of Cu^{II} with sodium ascorbate. Cu^{II} salts are commercially more robust, and less costly than Cu^{I} salts. By removing the base (TEA) and using water with low quantities of *in situ* generated Cu^{I} unproductive Glaser coupling (which proved such an issue in Meldel's work) was prevented. Similar to Meldel's procedure, the reaction had an exceptionally broad substrate scope at room temperature, with no special precautions required to remove oxygen or water from the reactions. The solvents used in the procedure ranged from the common organic solvents, to tolerating alcohols, and even water, without an organic co-solvent. The catalyst loading was only 0.25-2 mol%, with 5 mol% sodium ascorbate to reduce the Cu^{II} catalyst. The reaction could be performed across a range of pH values, and showed a complete lack of functional group interference.



Scheme 107: Sharpless development of Cu^{I} catalysed click reaction[REF]

Mechanistically, DFT calculations implied that a concerted cycloaddition was strongly disfavoured, and that the procedure was likely to be stepwise. Initial insertion of the copper into the terminal alkyne was suggested, as with Meldel. Sharpless proposed a 6 membered copper intermediate, formed from the ligation of the copper acetylide and the azide. The mechanism has since been fully explored by others, and whilst evidence supports a step-wise mechanism[153] studies have shown that the reaction is second order in copper and there are numerous reports suggesting a bi-nuclear or polynuclear pathway rather than the 6 membered transition state.[189] The most widely accepted mechanism was proposed in 2007 (**Scheme 108**).[190] Staub and co-workers succeeded in isolating copper(I) triazolide species **197** in 2007, demonstrating further insight to the reaction mechanism.[191]



Scheme 108: Sharpless proposed mechanism for the Cu^{I} catalysed click reaction

Since the initial discovery, CuAAC has been of constant synthetic use, with studies constantly demonstrating the robust predictability of the reaction. It is notorious as the most reliable of the click chemistry reactions. The use of microwave radiation to reduce the reaction time has been successfully demonstrated.[192] The use of solid-phase synthesis with the click reaction is also now well established.[193-195] Flow conditions have also been successfully developed allowing large scale synthesis of these molecules, with the potential for industrial use.[196]

The high efficiency of this protocol under physiological conditions has resulted in the reaction being routinely used in bioconjugation experiments. These systems often call for a stabilising ligand to protect the complex biomolecules from other copper mediated processes. The reaction has been used to decorate modified DNA strands,[197] peptides and peptoid structures,[198] and oligomers.[199] The utility of this has been demonstrated in the conjugation of fluorescent tags or dye molecules to viruses to serve as tracers in biological systems.[200] Similarly studies have shown incorporation of azides and alkynes into enzymes which can then be "clicked" with reporter tags to determine targets of enzyme inhibitors.[201,202] There are also reports of usage in materials science as a useful tool for generating nanomaterials such as dendritic polymers, organogels and functionalised carbon nanotubes.[203-207] The Leigh group have utilised this chemistry in the synthesis of supramolecular structures such as catenanes and rotaxannes.[208] Reviews on the wide ranging applications of this reaction are available.[209-211] Despite this versatility, however, the CuAAC cannot be used in cells as the copper generates radicals that kill the cell. This has led to the investigation into other bioconjugational strategies including work from Bertozzi and co-workers on the copper free cycloaddition reaction between cyclooctynes and azides.[212]

4.3. Methods for synthesising 1,5-substituted 1,2,3-triazoles

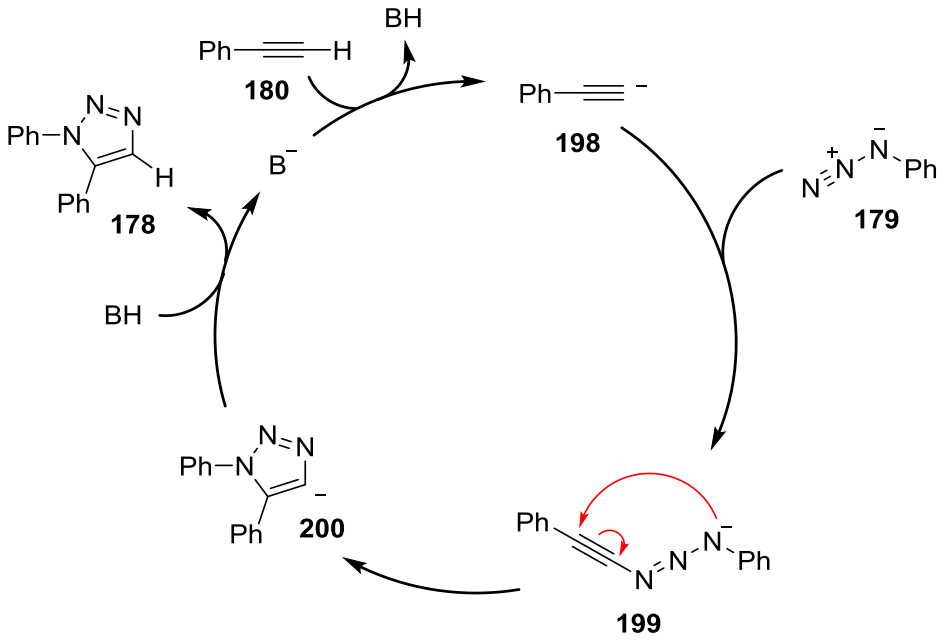
4.3.1. Synthesis in the presence of strong bases

Methods for generating the 1,4-isomer of 1,2,3-triazoles are now sophisticated and exceptionally well developed since the discovery of the reliable CuAAC reaction. In contrast, reactions to generate the 1,5-isomer are far less dependable. Previously mentioned attempts involved lithium, sodium, or magnesium acetylides, where the stoichiometric generation of the acetylides, low overall yields and limited functional group tolerance hindered these methods within the scientific community.[179,213,214]

In 2010, Fokin and co-workers demonstrated the successful generation of the 1,5-isomer using alkoxides.[215] This work was built on the observation by Ishikawa that acetylide intermediates could be easily formed by hydroxide or alkoxide bases in DMSO.[216] Fokin hypothesised that the generation of these acetylide intermediates would allow nucleophilic attack on the electrophilic terminal nitrogen of the azide, to then form the 1,5-isomer. It was found that 10 mol% of sodium, potassium, caesium or tetramethyl ammonium hydroxides could catalyse the reaction efficiently in less than 10 minutes (**Scheme 109**). The substrate scope was limited to aryl azides and aryl alkynes, and the strongly basic conditions limited the functional group tolerance available for the reaction. Highly electron deficient alkynes were shown to exhibit lower yields than electron rich species.

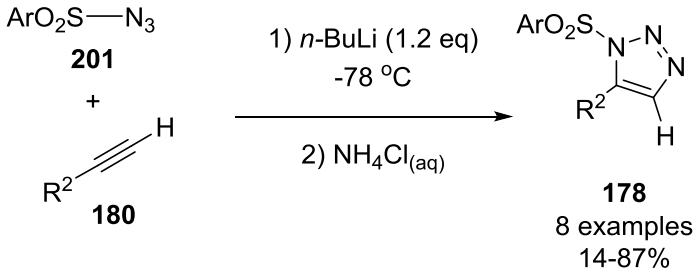
Scheme 109: Fokin synthesis of 1,5-triazoles under strongly basic conditions

The mechanism was proposed to proceed through the formation of the acetylide as expected, followed by nucleophilic attack on the azide to form intermediate **199**. Formation of the triazole ring through either a 6π-electrocyclization or 5-*endo*-dig cyclisation forms the deprotonated intermediate **200** which is quenched by the protonated base, to regenerate the catalyst and complete the catalytic cycle (**Scheme 110**). Evidence of the deuterated product was observed when the reaction was performed in deuterated DMSO, implying that a potential mode for quenching the 1,2,3-triazolyl anion is deprotonation of the solvent.



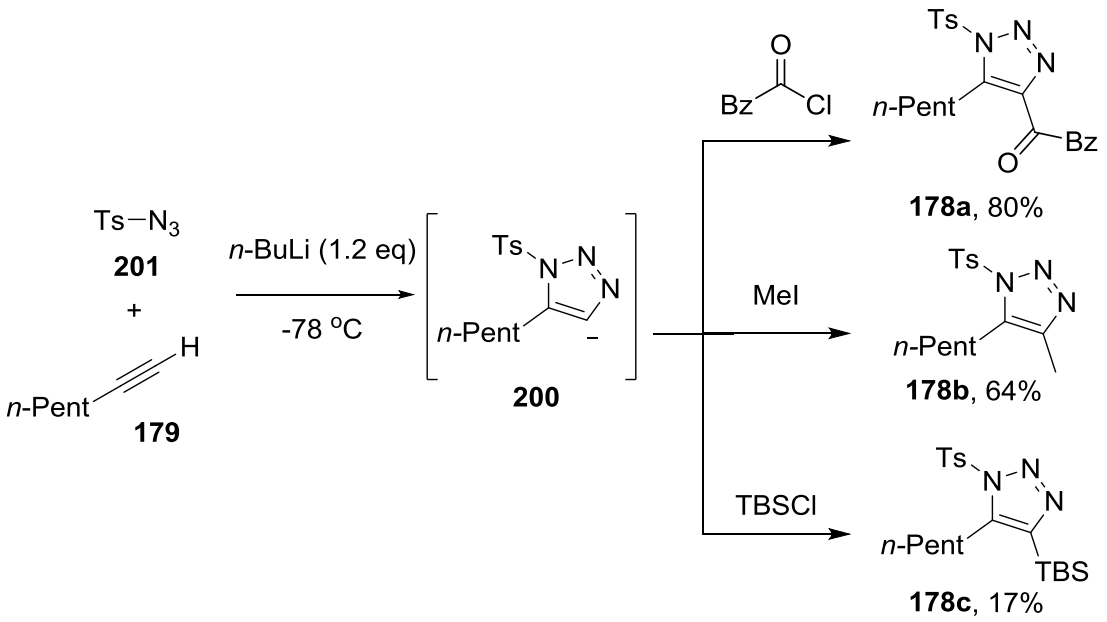
Scheme 110: Proposed mechanism for the formation of 1,5-triazoles under strong basic conditions

Other work by Croatt and co-workers also demonstrated the base catalysed formation of 1,5-triazoles.[217] In this study *n*-BuLi was used at −78 °C to prepare 1,5-substituted sulfonyl triazoles from acetylides and sulfonyl azides (**Scheme 111**). After quenching with $NH_4Cl_{(aq)}$ and isolation only the 1,5-isomer was determined to be present. The reaction requires the step-wise deprotonation of the alkyne with *n*-BuLi before addition of the azide. Where Fokin's work could only tolerate aryl alkynes and azides, this work was shown to tolerate aliphatic and TMS protected alkynes in reasonable yields. However, in general, yields were moderate with only a few examples showing high conversion. In similarity to Fokin's study, electron deficient alkynes were either unsuccessful or resulted in depleted yields. The mechanism is postulated as the same as the previous study, with quenching of the resultant heterocyclic anion by the $NH_4Cl_{(aq)}$.



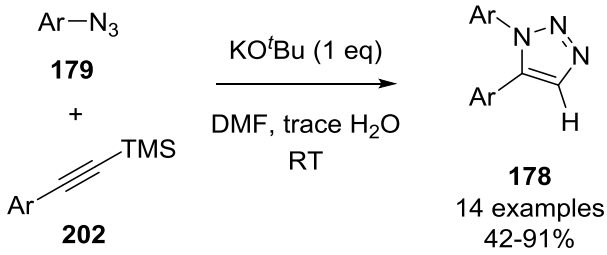
Scheme 111: Croatt synthesis of 1,5-triazoles under strongly basic conditions

This study also demonstrated the quenching of the 1,2,3-triazolyl anion with a series of electrophiles to form 1,4,5-substituted triazole products. Acid chlorides, TBS chloride and methyl iodide were all used successfully and generated the desired products in poor to good yields (**Scheme 112**).



Scheme 112: Quenching the 1,2,3-triazolyl anion with electrophiles

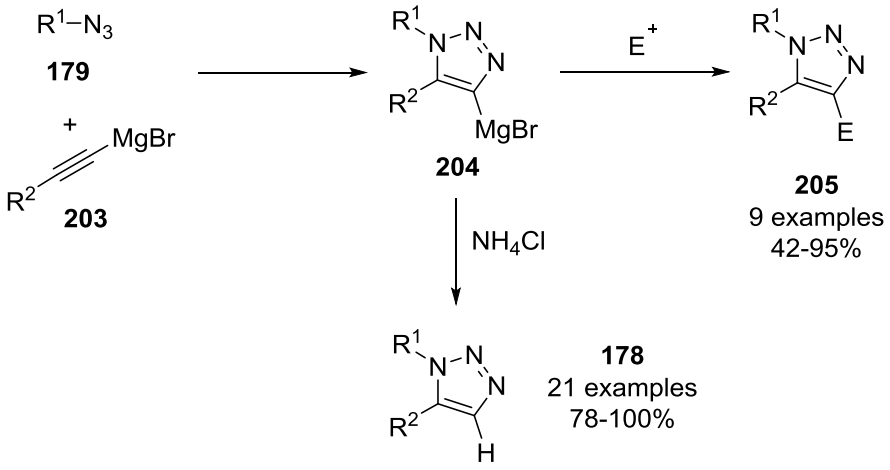
A further example was disclosed by Wu in 2012.[218] The group used TMS protected alkynes, and performed an *in situ* deprotection to form the acetylide anion allowing cyclisation with the azide (**Scheme 113**). As with Fokin's examples only aromatic azides and alkynes were tolerated, and electron deficient substrates showed lower yields. Despite the novelty of synthesising exclusively the 1,5-isomer of the triazole, the necessity for strongly basic conditions limits the functional group tolerance of these reactions.



Scheme 113: Wu formation of 1,5-triazoles through *in situ* deprotection of TMS alkynes

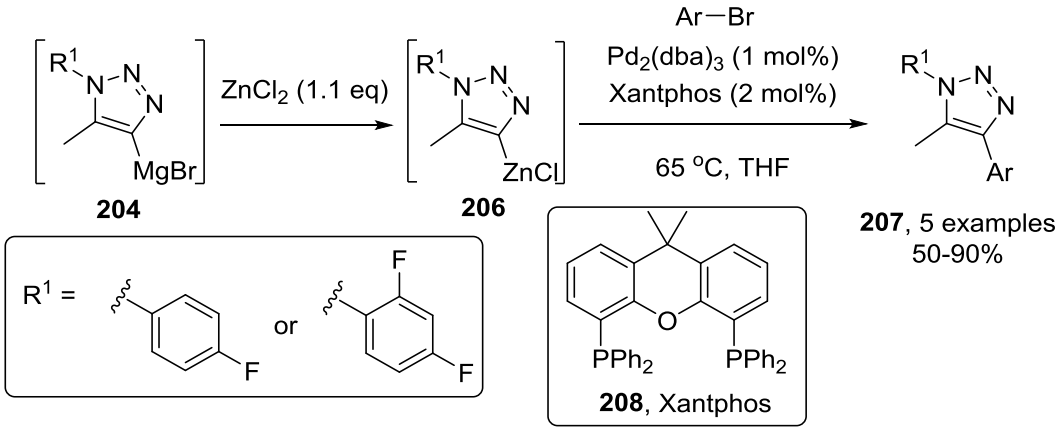
4.3.2. Synthesis with magnesium acetylides

While early examples employing magnesium acetylides had limited impact, featuring low yields and poor distribution of products,[213,214] a study revisiting this method in 2004 by Fokin and Sharpless had more success.[219] This resulted in the addition of magnesium bromide acetylides to azides, and the subsequent quenching of the generated magnesium species with a range of electrophiles (**Scheme 114**). Aliphatic alkynes were slower to react than aryl species, but were tolerated under the reaction conditions. As with previous studies, the yields were lower for electron deficient alkynes. Interestingly, electron deficient azides were shown to react faster than electron rich azides, presumably due to the increased electrophilicity of the terminal nitrogen of the azide. Many yields of the protonated species were quantitative, requiring no further purification. Other electrophiles were used to quench the 4-halomagnesiotriazole intermediate **204** giving moderate to high yields. D_2O, iodine, carbon dioxide, acid chlorides esters, aldehydes and isocyanates were all demonstrated to react with the organometallic intermediate.



Scheme 114: Fokin 1,5- and 1,4,5-triazole synthesis with magnesium acetylides

In 2007 this work was furthered by Akao and co-workers.[220] The group established that the generated 4-halomagnesium triazole could undergo transmetallation to zinc, using zinc chloride, and this would provide suitable substrates for palladium catalysed Negishi cross-coupling reactions (**Scheme 115**). By using palladium(0) and the bidentate Xantphos ligand the group were able to demonstrate 5 cross-coupling examples with aryl bromides in moderate to good yields. Further studies into the scope of this reaction are required before the utility of the process is fully realised.

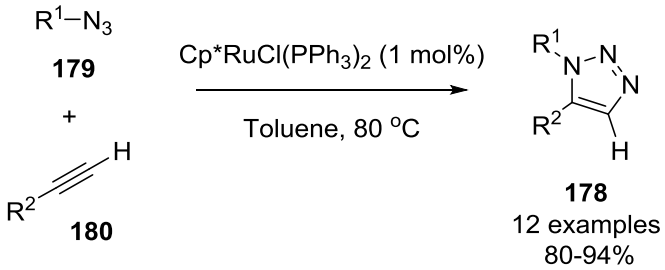


Scheme 115: Akao synthesis of 1,4,5-substituted triazoles through Negishi cross-coupling of *in situ* formed triazolyl-zinc reagents

Despite the significant improvements of the magnesium acetylide method for the synthesis of 1,5-triazoles, the substrate scope remains limited due to the highly reactive nature of the magnesium species. Ketones, esters, amides, nitriles, nitros and halides are all unable to withstand the reaction conditions presented – severely limiting the chemical space that can be investigated *via* this method

4.3.3. Synthesis with ruthenium

One of the most successful methods to date for the generation of 1,5-triazoles has been ruthenium-catalysed azide-alkyne cyclisation (RuAAC). First disclosed by Jia, Fokin *et al*. in 2005, this methodology uses 1 mol% [Cp*RuCl(PPh_3)$_2$] in dioxane or toluene at 80 °C to catalyse the formation of the 1,5-isomer (**Scheme 116**).[221] The use of [Ru(Cp)Cl] only demonstrated modest reactivity and gave a mixture of the two isomers, and the use of the pentamethylcyclopentadienyl (Cp*) ligand was found to be beneficial on both of these counts. The reaction was also feasible using microwave heating in DMF with [Cp*RuCl]$_4$, which allowed completion of the reaction in only 20 minutes.[222]

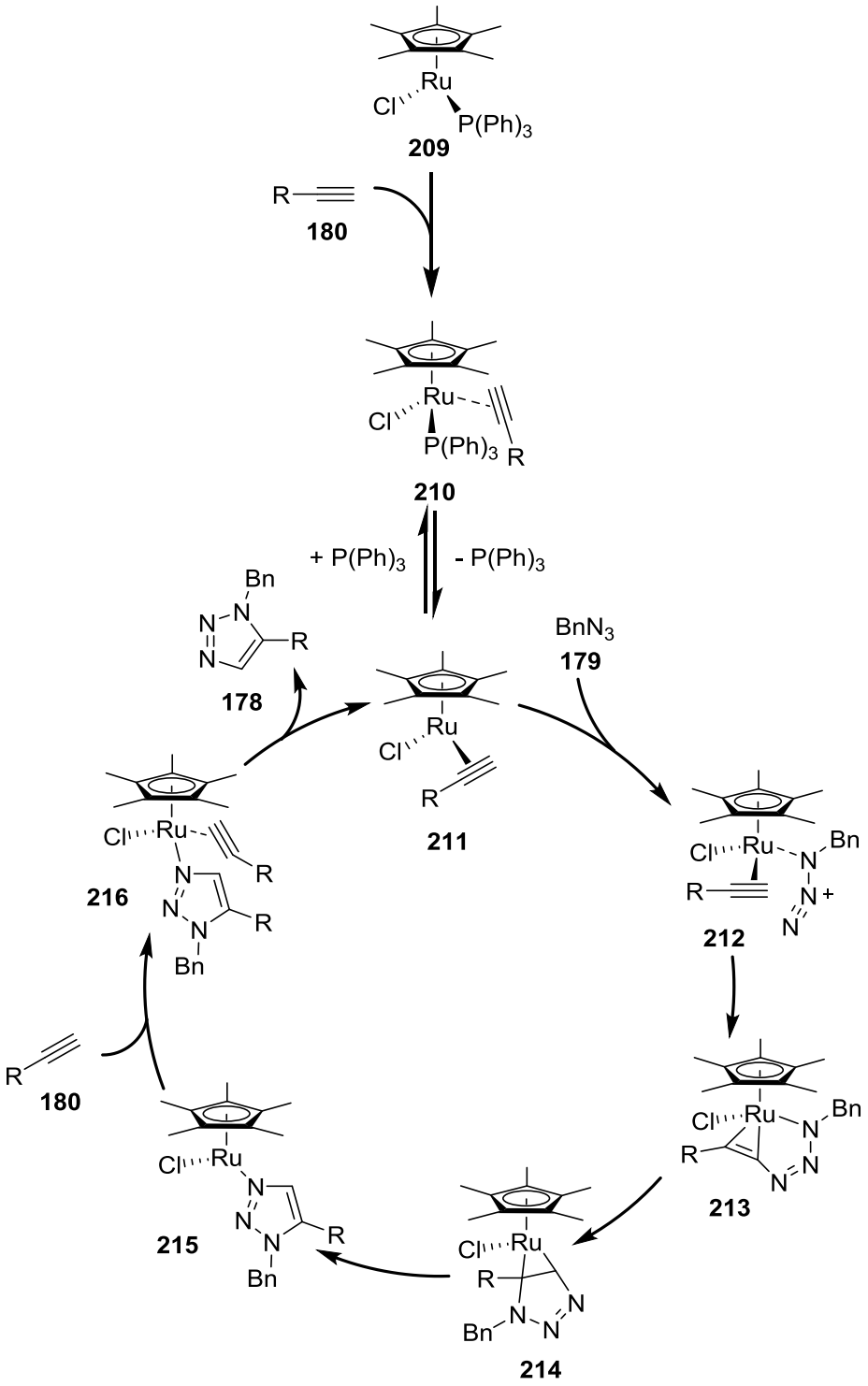


Scheme 116: Fokin and Jia Ruthenium-catalysed azide-alkyne cyclisation (RuAAC)

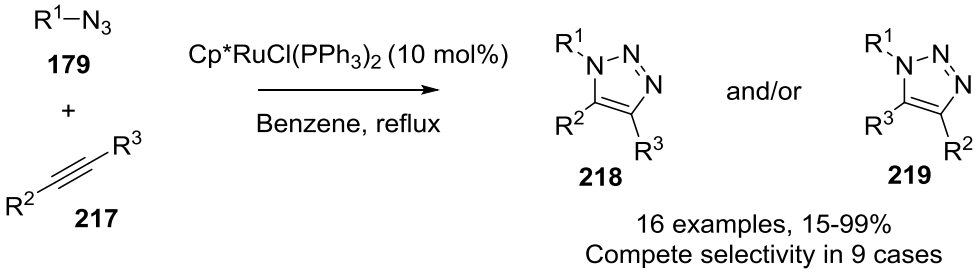
The mechanism for this transformation has been proposed by Fokin and Jia,[223] and later elaborated by Nolan *et al.* supported by full mechanistic studies (**Scheme 117**).[224] Ligand substitution of the phosphine generates the catalytically active species **211** which has a *p*-coordinated alkyne. The azide is co-ordinated through the proximal nitrogen to form intermediate **212** and a subsequent oxidative coupling takes place to form **213**. Computational calculations indicated that this metalo-cyclopropene species is in equilibrium with a vinyl complex, which is slightly more stable due to reduced strain. However this vinyl species is not prone to the required reductive elimination and is therefore a "resting state" for the cycle. The reductive elimination to generate intermediate **215** was calculated as the rate-limiting step, and the triazole remains co-ordinated to the ruthenium(II) at this stage. The complex isomerises to the *N*-bound complex and liberation of the triazole occurs with co-ordination of a new alkyne. In general, the regioselectivity of the reaction is reasoned by spatial arguments in the bond forming step. With terminal alkynes the bulky group will preferentially point away from the bulky Cp* plane, which leads to incorporation at the 5 position.

While the CuAAC method is generally only applicable to terminal alkynes, by tuning the catalyst RuAAC was established as a method for the use of both terminal and internal alkynes.[223] Fokin and Jia initially demonstrated one example of this using the symmetrical diphenylacetylene.[221] This was extended to exemplify a number of unsymmetrical alkynes, and complete regioselectivity was observed in most cases.[223] Weinreb *et al*. later performed extensive studies on the regioselectivity of this reaction (**Scheme 118**).[225,226] These studies demonstrated that the selectivity of the RuAAC reaction is complex and incredibly substrate dependent.

In the presence of benzyl azide, alkynes produce a mixture of regioisomers, generally with a bias to placing the more bulky substituent at the 5 position. This is consistent with the steric argument presented in accordance with the proposed mechanism. Propargyl alcohols and propargyl amines convey selectivity on the system and give a single isomer. Addition of a bulky group (such as an adamantly group) to the azide promotes formation of a single isomer, with the less bulky alkyne substituent in the 5-position due to steric effects.

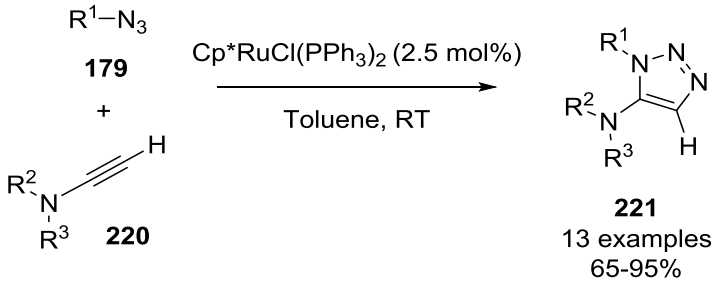


Scheme 117: Proposed method for the RuAAC reaction



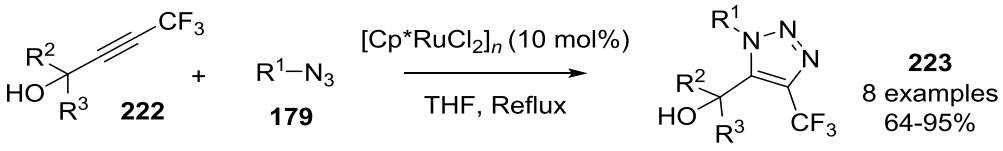
Scheme 118: Weinreb study on the regioselectivity of the RuAAC reaction

Cintrat *et al*. disclosed the ruthenium catalysed cyclisation of azides and ynamides in the synthesis of 5-amido 1,2,3-triazoles (**Scheme 119**).[227] The reaction generated single isomers with the nitrogen exclusively at the 5-position and exhibited a wide functional group tolerance. Most examples utilised terminal alkynes however internal alkynes were also presented and the desired 5-amido regioselectivity was retained.



Scheme 119: Cintrat ruthenium-catalysed cyclisation of azides and ynamides

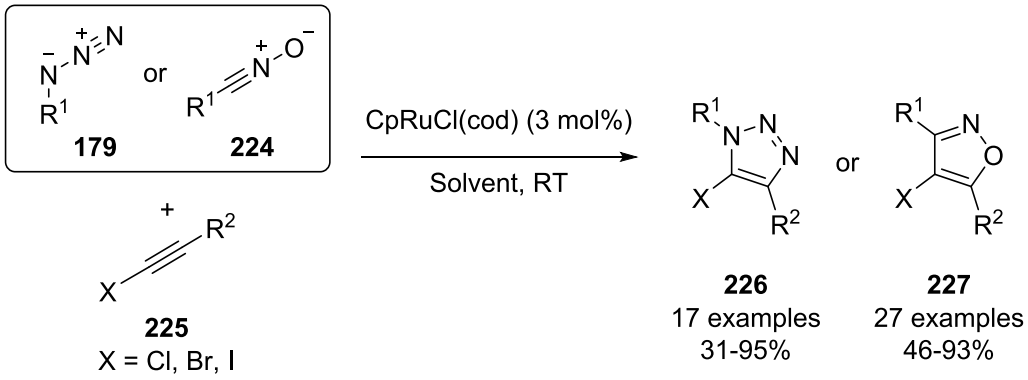
Qing has also demonstrated the use of propargyl alcohols with ruthenium catalysis to give regioselectivity in trifluoromethylated alkynes (**Scheme 120**).[228] These non-terminal alkynes exhibited complete selectivity to the 4-trifluoromethyl 5-alcohol isomer under $[Cp^*RuCl_2]_n$ conditions in refluxing THF. A range of aliphatic and aryl azides substituents were demonstrated and yields were generally high.



Scheme 120: Qing ruthenium-catalysed triazole formation

In 2014 Fokin *et al.* demonstrated the use of ruthenium in the cyclisation of azides with internal haloalkynes.[229] This gave exclusively the isomer with the halide at the 5-position (**Scheme 121**). The reaction was also demonstrated with nitrile oxides to generate the analogous isoxazoles. Yields were moderate to high and a diverse substrate scope was

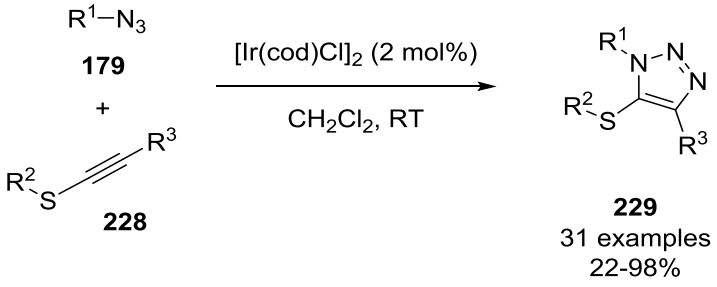
developed showing excellent functional group tolerance. Products were also further derivatised through cross-coupling of the halide.



Scheme 121: Fokin ruthenium catalysed cyclisation of azides with internal haloalkynes

4.3.4. Synthesis with other metals

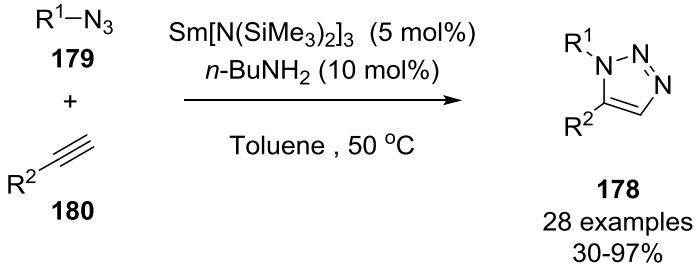
Iridium catalysed methods have been demonstrated in the cyclisation of azides with internal thioalkynes.[230] Reaction conditions were developed to selectively form the 5-thiolated product (**Scheme 122**). The reaction was typically performed in CH_2Cl_2, however results showed high yields could be achieved in water. The explored substrate was broad and generated the desired products in moderate to high yields. Changing the internal alkyne under the same conditions had limited results; dialkylated alkynes failed, as did diarylated alkynes and ynamides used in previous ruthenium methods. Selenyl alkynes or aryloxy alkynes gave modest yields at best. The use of an internal sulfonyl alkyne reversed the selectivity and resulted in a high yield of the 1,4-isomer.



Scheme 122: Jia and Sun iridium catalysed cyclisation of azides with internal thioalkynes

In 2013 Zhou and co-workers presented a samarium catalysed method for the formation of 1,5-triazoles.[231] The mild procedure, requiring 5 mol% $Sm[N(SiMe_3)_2]_3$, 10 mol% of an amine base and toluene at 50 °C, showed a broad substrate scope and consistently high yields (**Scheme 123**). The authors hypothesised a samarium co-ordinated intermediate which was successfully reacted further with methyliodide to generate the 4-methyl 1,5-

triazole, albeit in low yield (23%). Yttrium acetylides also performed regioselective cyclisation in moderate yields under the same conditions.

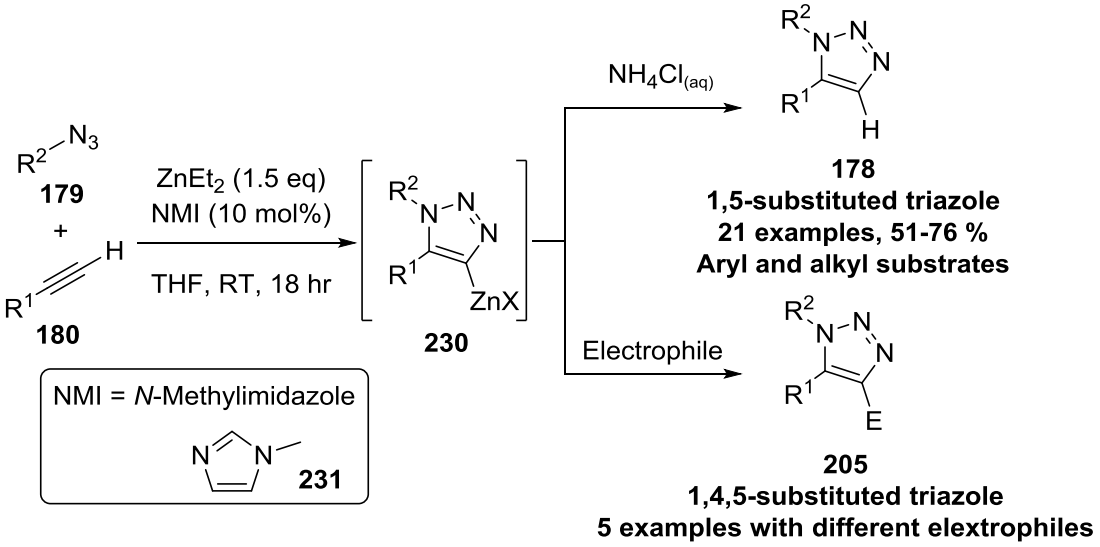


Scheme 123: Zhou samarium catalysed 1,5-triazole formation

While these studies all demonstrate significant advances in the metal catalysed regioselective generation of 1,5-triazoles, the high cost of noble metals cannot be overlooked. This remains a significant drawback of most commonly used methods.

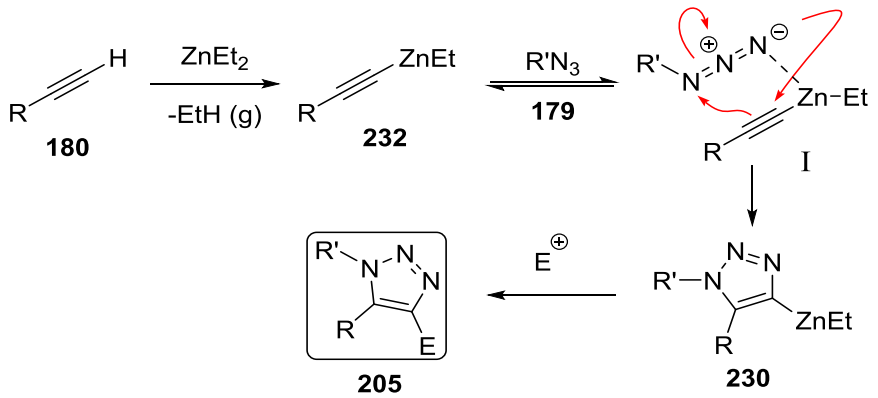
4.4. Previous work within the Greaney group

Studies within the group towards new molecules to combat the 'orphan disease' Sleeping Sickness (*African Trypanosomiasis*) have required the synthesis of a number of 1,4- and 1,5-substituted 1,2,3-triazoles.[232,233] Due to the significant drawbacks of current methods for the regioselective synthesis of the 1,5-substituted isomers we developped a new economically sound, general method for the generation of a series of these compounds. Work by Carreira, Bolm, Trost and others has established the significant advances of zinc-acetylide chemistry in particular in the addition to carbonyl compounds.[234-240] With inspiration from these studies, a zinc mediated method for the formation of 1,5-triazoles was developed (**Scheme 124**).[241] Zinc acetylides were successfully generated at room temperature in THF and the subsequent addition to the azide gave zincated species **230**. This species could either be directly quenched to form the 1,5-substituted triazole, or further functionalised with an electrophile to generate 1,4,5-substituted triazoles. The zincated species was determined to be less nucleophilic than the analogous magnesium reagents generated in Fokin's studies, which enabled a wider scope for functionalization.[219]



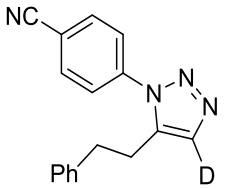
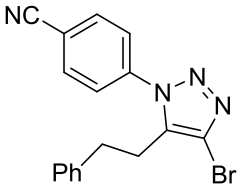
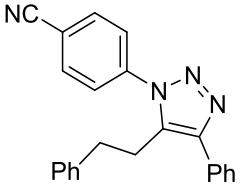
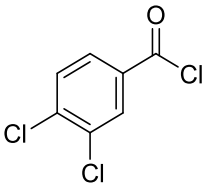
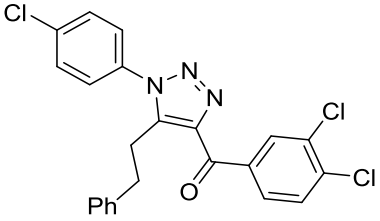
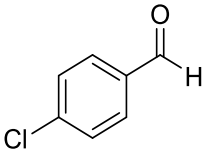
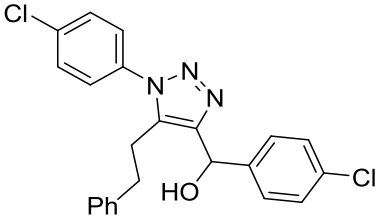
Scheme 124: Previous work within the Greaney group on the zinc mediated synthesis of 1,5- and 1,4,5-substituted 1,2,3-triazoles

Moderate to high yields were obtained across a broad substrate scope. Notably the inclusion of ketones, esters, amides, nitrogroups and halides were all tolerated under the reaction conditions, and the reaction tolerates heterocyclic substrates. These types of substrate are all examples generally found challenging with both the base catalysed and magnesium acetylide methods. The mild conditions, ease of operation, and exceptional substrate scope make this procedure beneficial over many of the existing methods presented for the synthesis of these compounds. While the mechanism has not been fully studied, previous literature has implied that the stepwise addition of the zinc acetylide to the azide, and subsequent cyclisation to give the zincated intermediate **230** (**Scheme 125**). This intermediate is stable until quenched by an electrophile or a proton. The range of possible electrophilic quenches is indicated in **Table 30**.



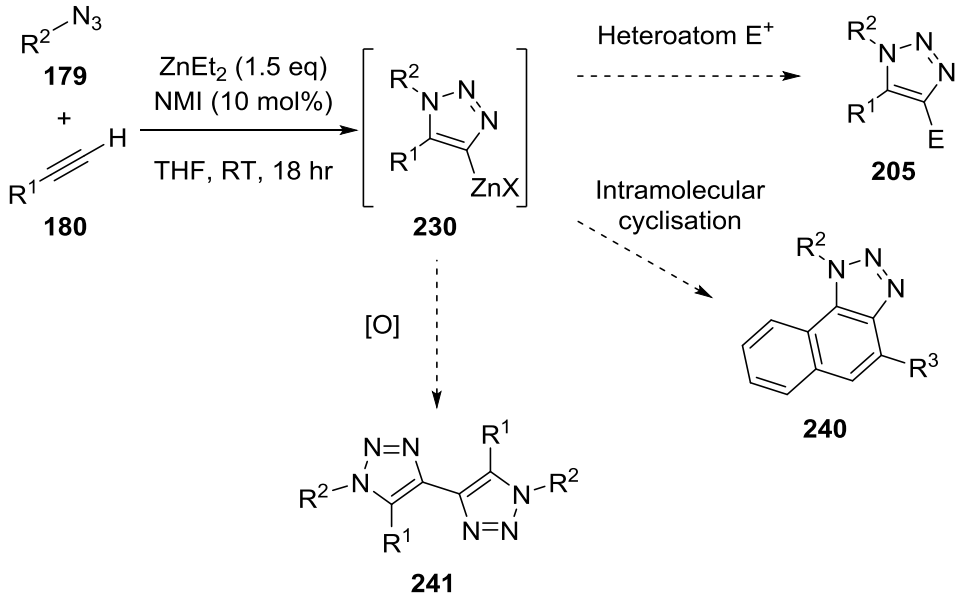
Scheme 125: Proposed mechanism for the zinc mediated triazole formation

Table 30: Range of electrophilic quenches demonstrated for the 1,2,3-triazolyl-zinc species

Quench	Product	Yield
D_2O (1 ml) D_3CCO_2D (1 ml)	 **233** 89% deuterium incorporation	71%
Br_2 (2 eq)	 **234**	76%
$Pd(PPh_3)_4$ (2 mol%) PhI (2 eq)	 **235**	68%
$Ni(acac)_2$ (5 mol%)  **236,** (2 eq)	 **237**	66%
$MgBr_2$ (2 eq)  **238,** (2 eq)	 **239**	52%

4.5. Aims of the project

The research presented in this thesis aims to extend on the research previously performed in the group. While the initial publication demonstrated the various utility of this reaction it was considered that the full potential of the triazolyl-zinc species as a nucleophile had not been reached. The aim was to extend the possible reactivity profile to include other hetero-atoms, intramolecular cyclisations and to develop oxidative conditions to lead to dimerization of the zinc species (**Scheme 126**). It was also decided to examine the reaction conditions for generating the initial zinc species, with the aim of generating a process catalytic in diethyl zinc ($ZnEt_2$).



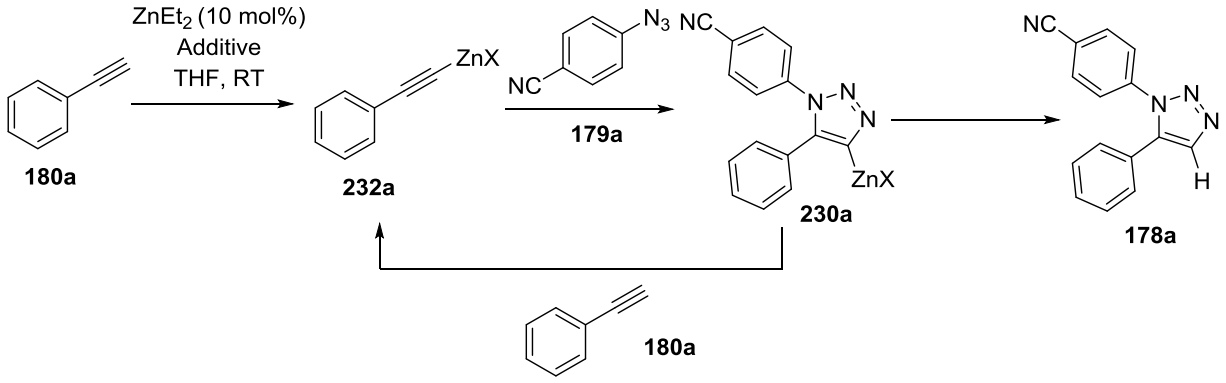
Scheme 126: Proposed aims for this research

5. Results and Discussion

5.1. Expanding the reaction scope for the diethyl zinc mediated formation of 1,5 and 1,4,5-triazoles

5.1.1. Assessment of $ZnEt_2$ stoichiometry

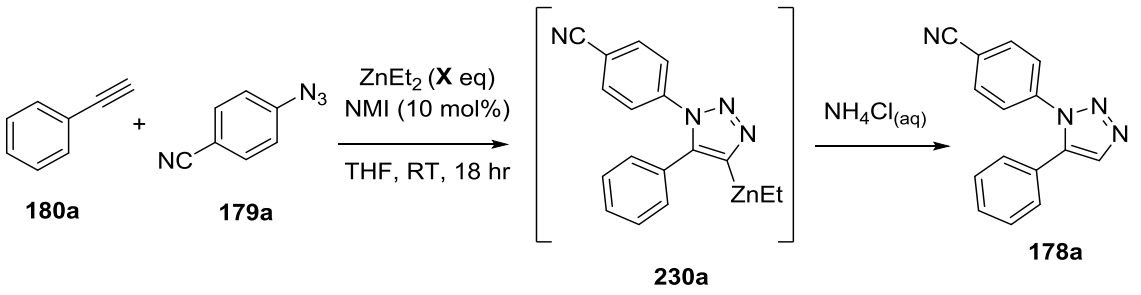
Although the reaction had previously been optimised within the group,[241] the stoichiometry of the $ZnEt_2$ still had to be addressed. The initially published conditions required 1.5 equivalents of $ZnEt_2$ and the aim was to reduce this, with the intention of developing a catalytic process due to its cost and pyrophoric nature. It is hypothesised that the alkyne starting material could transfer a proton to the heteroaromatic zinc species **230a**. In doing so the final 1,5-triazole will be formed and the zinc acetylide **232a** will be regenerated, thus leading to a catalytic process (**Scheme 127**).



Scheme 127: Potential mechanism for a reaction catalytic in $ZnEt_2$

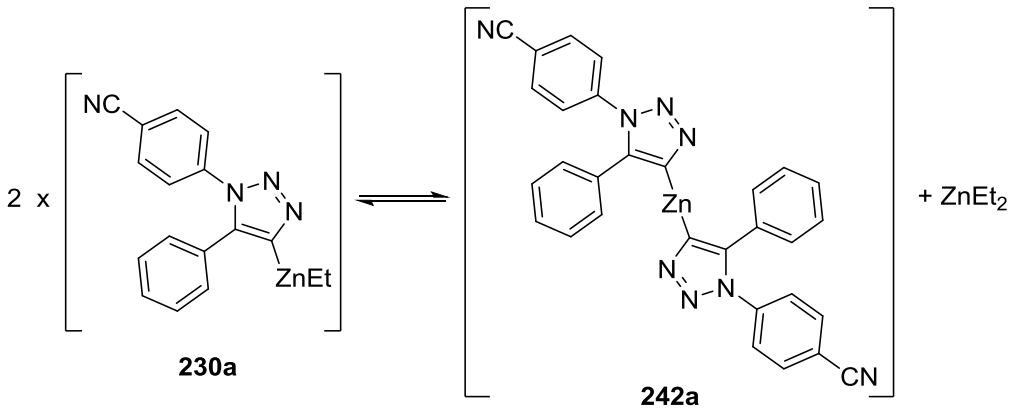
For this to occur, a significant difference in pK_a between the starting material and the triazole product is required. Without such a strong energetic driving force, such an interaction would be unfeasible. While the pK_a for the triazole proton has not been experimentally determined, values for similar systems imply a value of approximately 30.[242,243] The pK_a of terminal alkynes are known to be ~25.[244] The alkyne therefore does have the more acidic proton, however the question posed is whether there is significant enough of a difference to develop a catalytic system. Initial reactions with reduced stoichiometry of diethyl zinc showed promising results (**Table 31**). The yield remained consistently high when 1.5 equivalents, 1.0 equivalents and 50 mol% $ZnEt_2$ were employed. However, use of 10 mol% $ZnEt_2$ resulted in a significantly lowered 19% yield of the desired triazole.

Table 31: Reducing the quantity of $ZnEt_2$



Equivalents $ZnEt_2$	Yield of Triazole 178a
1.5	86%
1.0	83%
0.5	81%
0.1	19%

These results further gave some insight into the mechanism of the reaction. Previous work has assumed an intermediate **230**, with a heteroleptic zinc species with ethyl and triazole substituents (**Scheme 128**). The difference in yield between reactions performed with 10 mol% and 50 mol% $ZnEt_2$ implies that a dimeric species, such as **242**, must be formed through the utilisation of both ethyl groups. Disubstituted zinc reagents are known to undergo equilibrium exchange and it is likely that in solution an equilibrium of the two species **230** and **242** will exist. Whilst this remains a non-catalytic process, reducing the stoichiometry of $ZnEt_2$ represents an important improvement in the methodology. The next conceptual step would be to develop a truly catalytic system.



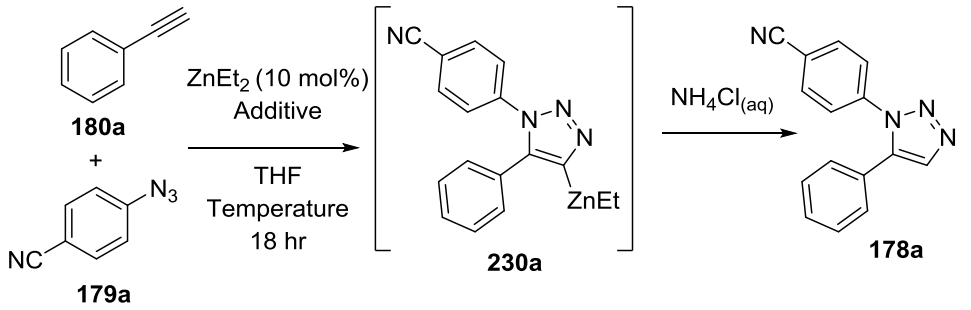
Scheme 128: Possible zincate intermediates for the triazole formation

The initial attempts to develop a reaction catalytic in $ZnEt_2$ utilised a series of amine bases. These may either ligate the zinc in order to facilitate the exchange of zinc from the triazole species to the acetylene, or interact with the acetylene to act as a proton shuttle between the triazole and the acetylene under general base mechanism. Reactions were performed with the addition of either 10 mol% or 1 eq of the amine base in combination with 10 mol% $ZnEt_2$ (**Table 32**). After work up, the reactions were analysed by LCMS and NMR to determine conversion to the product. In all instances only trace product was observed, with many cases resulting purely in isolation of starting material. Reduction of the azide to the aniline was also often observed.

A recent paper utilised $Sm(HMDS)_3$ at high temperatures and high loadings to successfully form the desired 1,5-disubstituted triazoles in combination with *n*-$BuNH_2$.[231] To this end the formation of zinc-hexamethyldisilazane complex was hoped to facilitate this transformation. Experiments were carried out with the initial addition of $ZnEt_2$ to either KHMDS, LiHMDS or HMDS, before addition of this mixture to a solution of the substrates (**Table 32, Entries 14-17**). This was performed both with 10 mol% or 1 equivalent of the HMDS additive. Where 1 equivalent of LiHMDS was used in conjunction with 10 mol% $ZnEt_2$ roughly 30% conversion to the desired triazole was observed – indicating some extent of catalytic turnover. However, this was a complex mixture with a number of unidentifiable by-products and could not be isolated as pure material.

The cost of $ZnEt_2$ as a solution in hexane is ca. £400 mol^{-1} and the cost of LiHMDS only slightly lower at ca. £360 mol^{-1} (figures from Sigma Aldrich March 2014). It was decided that the cost of adding one equivalent of LiHMDS in order to reduce the amount of $ZnEt_2$ from 50 mol% to 10 mol% was not economically viable.

Table 32: Attempts to optimise a reaction catalytic in $ZnEt_2$

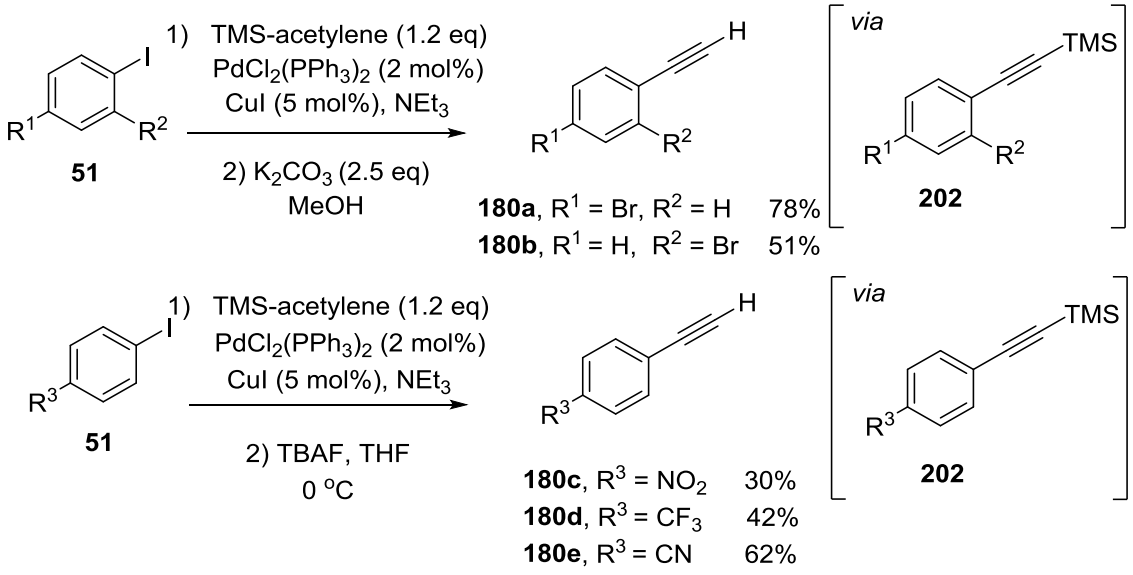


#	Additive	Additive quantity	Temp (°C)	Yield
1	*n*-$BuNH_2$	10 mol% or 1 eq	RT	< 10% [a]
2	Aniline	10 mol% or 1 eq	RT	< 10% [a]
3	Triethylamine	10 mol% or 1 eq	RT	- [b]
4	KHMDS	10 mol% or 1 eq	RT	< 10% [a]
5	LiHMDS	10 mol% or 1 eq	RT	< 10% [a]
6	LDA	10 mol% or 1 eq	RT	< 10% [a]
7	Pyridine	10 mol% or 1 eq	RT	- [b]
8	DBU	10 mol% or 1 eq	RT	- [b]
9	TMEDA	10 mol% or 1 eq	RT	- [b]
10	TMP	10 mol% or 1 eq	RT	- [b]
11	DMAP	10 mol% or 1 eq	RT	- [b]
12	DIPEA	10 mol% or 1 eq	RT	- [b]
13	NMI	10 mol% or 1 eq	RT	< 10% [a]
14	KHMDS[c]	10 mol%	RT	< 10% [a]
15	LiHMDS[c]	10 mol%	RT	< 10% [a]
16	KHMDS[d]	1 eq	RT	< 10% [a]
17	LiHMDS[d]	1 eq	RT	30%[e]
18	KHMDS	10 mol% or 1 eq	40	< 10% [a]
19	LiHMDS	10 mol% or 1 eq	40	< 10% [a]
20	NMI	10 mol% or 1 eq	40	< 10% [a]
21	KHMDS	10 mol% or 1 eq	110[f]	< 10% [a]
22	LiHMDS	10 mol% or 1 eq	110[f]	< 10% [a]
23	NMI	10 mol% or 1 eq	110[f]	< 10% [a]

[a] Low conversion observed by LCMS/NMR. [b] No product formation observed. [c] 1:1 solution (in 1 ml THF) of $ZnEt_2$ with additive prepared and 10 mol% added to solution of substrates [d] 10 mol% $ZnEt_2$ added to solution of 1 equivalent additive, solution then added to substrates [e] Reaction resulted in complex mixture approximation of yield by crude NMR. [f] Reaction performed in toluene.

5.1.2. Substrate scope of the developed conditions

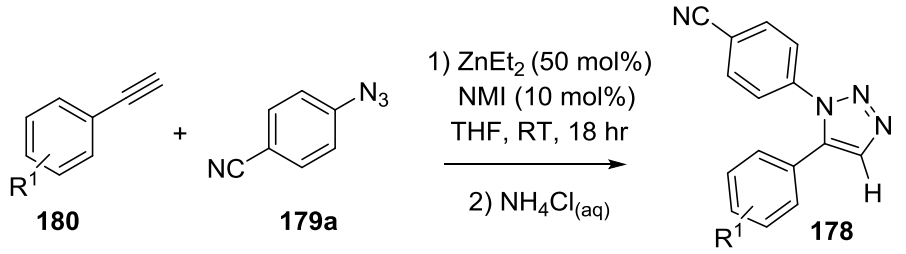
With the newly developed conditions substoichiometric with respect to $ZnEt_2$ in hand, a substrate scope was developed. Initially, a series of aromatic alkynes were reacted with 4-azidobenzonitrile under the standard conditions. Where necessary terminal alkynes were synthesised *via* a two-step process from the aryl iodide. Palladium-catalysed Sonogashira coupling with TMS-acetylene, followed by deprotection either with TBAF or K_2CO_3 gave the required alkynes in moderate to good yield (**Scheme 129**).



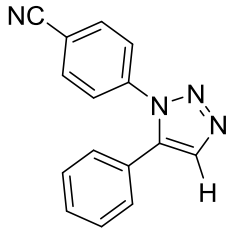
Scheme 129: Synthesis of aromatic alkyne substrates

Using these alkynes the zinc-mediated triazole synthesis substrate scope was investigated under the newly determined conditions (**Table 33**). As expected, aromatic halides can be retained. These are not tolerated by the Grignard methods and provide further scope for functionalization. Alkynes containing electron withdrawing groups exhibit lower yields consistent with previous studies.[219] The *para*-trifluoromethylphenyl alkyne substrate **178k** and *para*-esterphenyl **178m** resulted in poor conversions. The latter required a further 50 mol% $ZnEt_2$ addition before substantial conversion was observed. The strongly withdrawing nitrile **178n** and nitro **178o** functionality failed to generate the desired products. Adding further quantities of $ZnEt_2$ or using microwave heating (100 °C for 2 hours) still gave only minimal conversion, and the desired products were not isolated. Steric hindrance *ortho* to the alkyne could be tolerated as with methoxy substrate **178f**. However often this caused a slight depletion in yield. Having a large group *ortho*- to the alkyne was found to inhibit the reaction, as demonstrated with aldehyde substrate **178q** and bromide substrate **178p**.

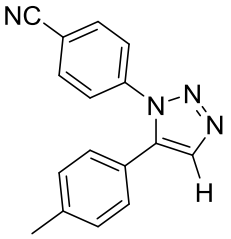
Table 33: Substrate scope with aromatic alkynes



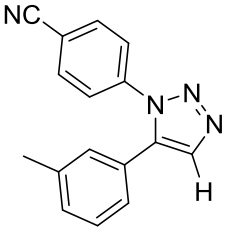
180 + **179a** → **178**



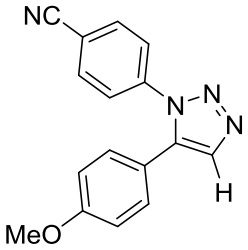
178a, 83%



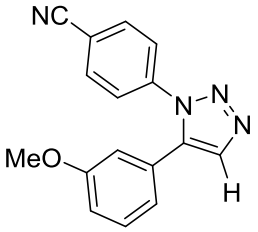
178b, 82%



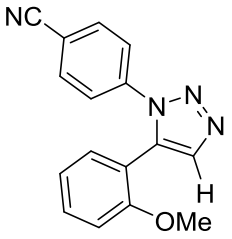
178c, 74%



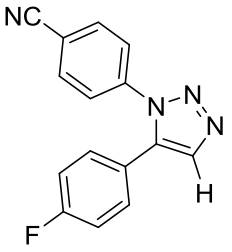
178d, 94%



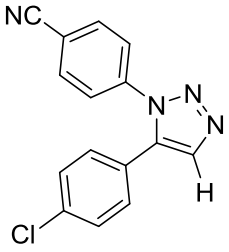
178e, 76%



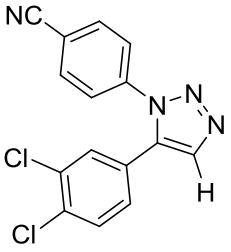
178f, 63%



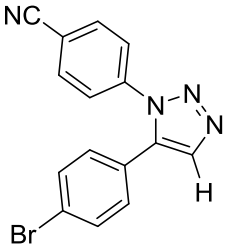
178g, 78%



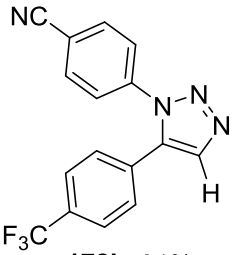
178h, 82%



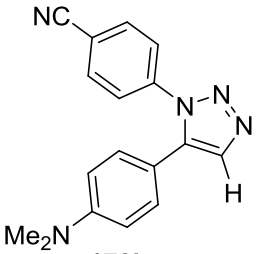
178i, 82%



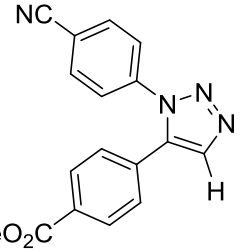
178j, 79%



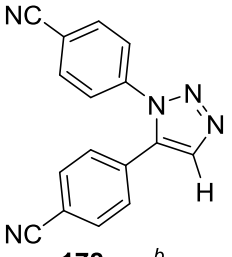
178k, 31%



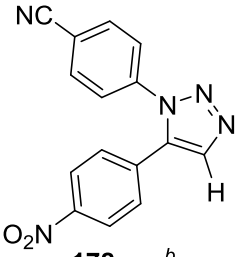
178l, 78%



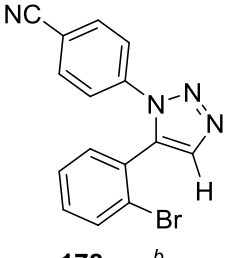
178m, 42%[a]



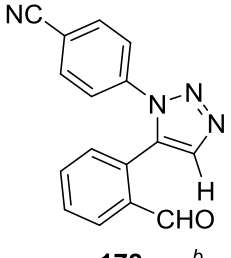
178n, --[b]



178o, --[b]



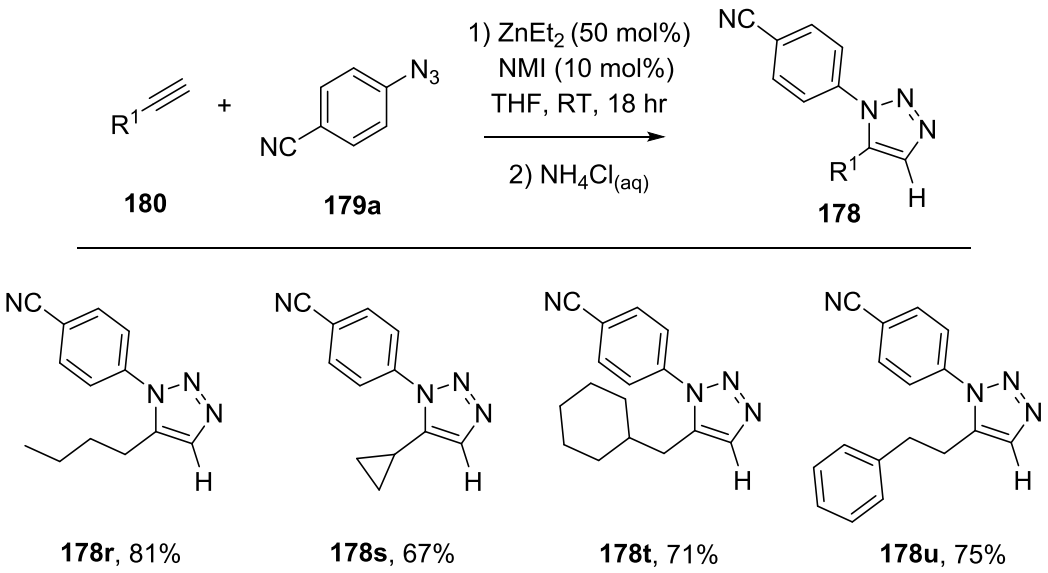
178p, --[b]



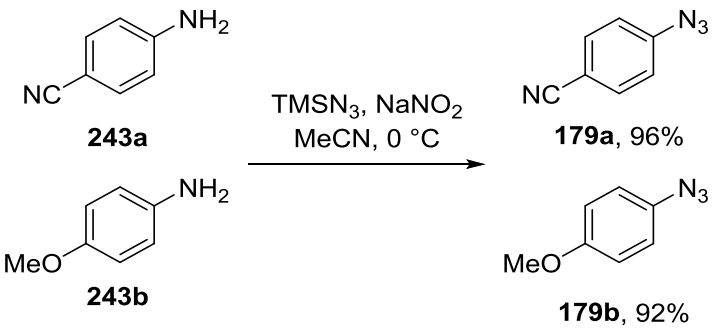
178q, --[b]

[a]Reaction conditions required addition of further 50 mol% $ZnEt_2$ at 18 hours [b]No product observed

Table 34: Substrate scope with aliphatic alkynes



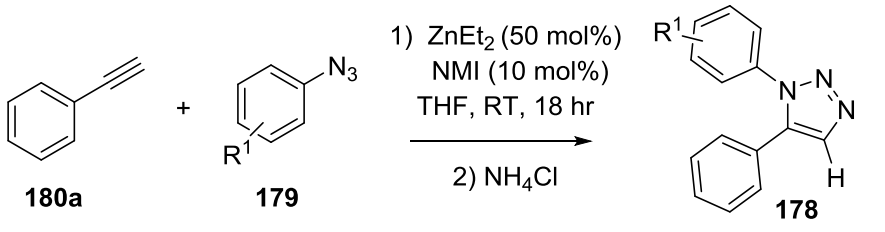
Aliphatic alkynes were also suitable for the reaction and the desired products were isolated in high yields (**Table 34**). The azide component was then considered. Limited commercial availability meant that all azides used had been synthesised. This was completed *via* a known diazatization procedure from the corresponding aniline which resulted in good yields (**Scheme 130**). [245] Most of the azides used had been synthesised for previous work in the group by Dr Chris Smith, and these azides were used without further purification (Details in experimental).



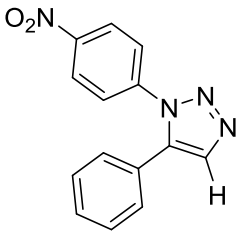
Scheme 130: Synthesis of aromatic azides

The substrate scope for the azide was less general with yields generally slightly lower than the benzonitrile azide (**Table 35**). Electron-withdrawing substrates worked particularly well, and halide functionality was still tolerated as before. Ketone containing substrates and heterocyclic substrates were also tolerated – another improvement on previous synthetic methods. However sterics were more of an issue. *Ortho*-substituted azides were often slow to react, and while a few substrates could be pushed to react through addition of a further 50 mol% of $ZnEt_2$ (such as 2,6-dichloro substituted **178ac**, and 2-bromo,4-fluoro substituted **178ad**) many would not react at all (**178ah** or **178ai**). Microwave heating at 100 °C was used to improve the yield of ester substrate **178ae**; however this did not improve reactivity of other *ortho*-substituted substrates. Electron-rich substrates proved problematic, and no product was obtained for either methoxy substituted **178af** or **178ag**. Benzylic azides did not reach completion in 18 hours – an unsurprising result as previous work showed that even with 1.5 equivalents of $ZnEt_2$ the reaction required 72 hours to reach completion.[241]

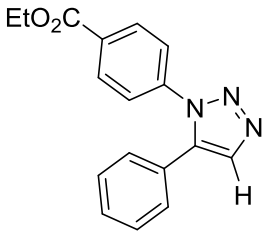
Table 35: Substrate scope with aromatic azides



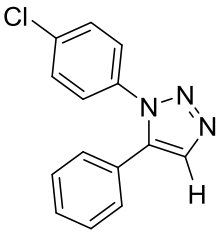
180a + **179** → **178**



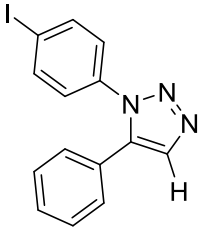
178v, 61%



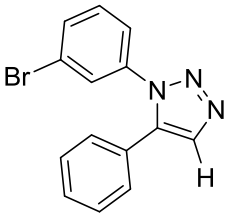
178w, 78%



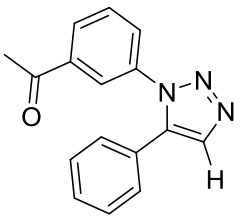
178x, 54%



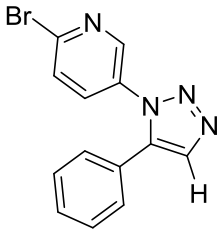
178y, 56%



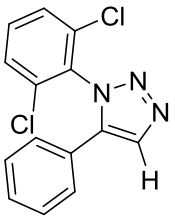
178z, 58%



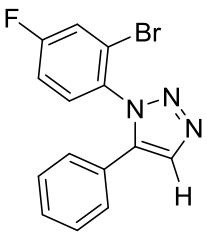
178aa, 54%



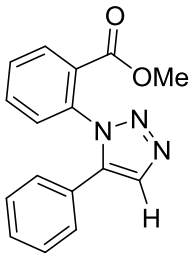
178ab, 71%



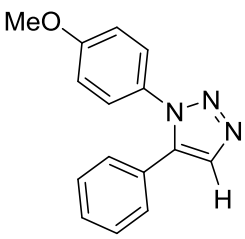
178ac, 78%[a]



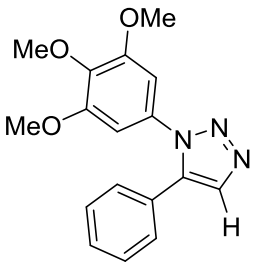
178ad, 81%[a]



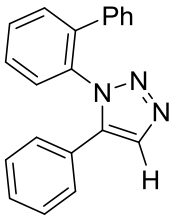
178ae, 65%[b]



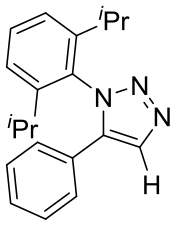
178af, --[c]



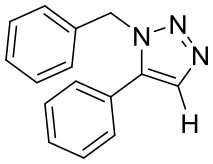
178ag, --[c]



178ah, --[c]



178ai, --[c]



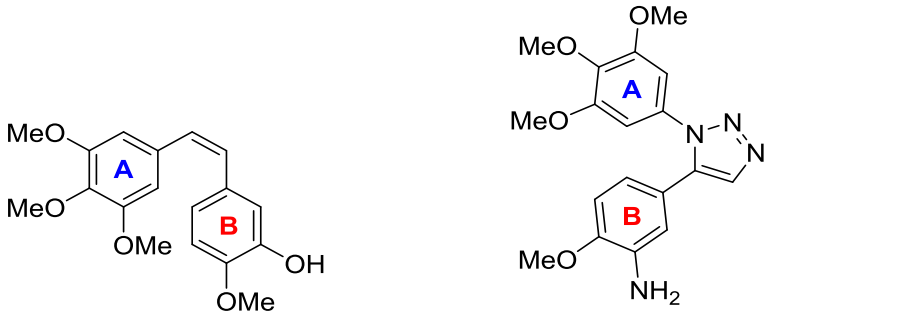
178aj, --[c]

[a]Reacions required the addition of a further 50 mol% $ZnEt_2$ at 16 hours [b]Reaction conditions required microwave heating at 100 °C for 2 hours before quenching [c]No product observed

5.1.3. Synthesis of triazolyl Combretestatin A-4 analogue

Having successfully demonstrated the wide substrate scope applicable to these reaction conditions, attention was drawn to whether the methodology could be used to generate industrially applicable targets. Combretestatin A-4 (**Figure 7**) is a natural product isolated in 1989 from tree bark in South Africa.[246] It has been demonstrated to be highly cytotoxic against a variety of human cancer cell lines, including those that have shown resistance to other drugs. This structurally simple molecule binds to the colchicine binding site of tubulin and inhibits tubulin polymerisation (causing apoptosis), and also disrupts the cell signalling pathways and causes selective shutdown of blood flow to tumours. The large capacity of biological effects combined with the simple structure of combretestatin mean is has been an attractive lead compound for anticancer agents for a number of years.[247,248]

The cytotoxic activity is attributed to the combination of the 3,4,5,-trimethoxysubstituted A ring,the 4-methoxysubstituted B ring, separated by a double bond bridge – and that the *cis*-configuration of this double bond is essential (**Figure 7**). The main disadvantages of the natural product as a drug candidate are largely related to the facile isomerisation of the *cis*-form to the far less active *trans*-form, as well as the low water solubility of the compound, and bio-availability.



244
Combretestatin A-4

178aj
Combretestatin analogue
2-methoxy-5-(1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazol-5-yl)aniline

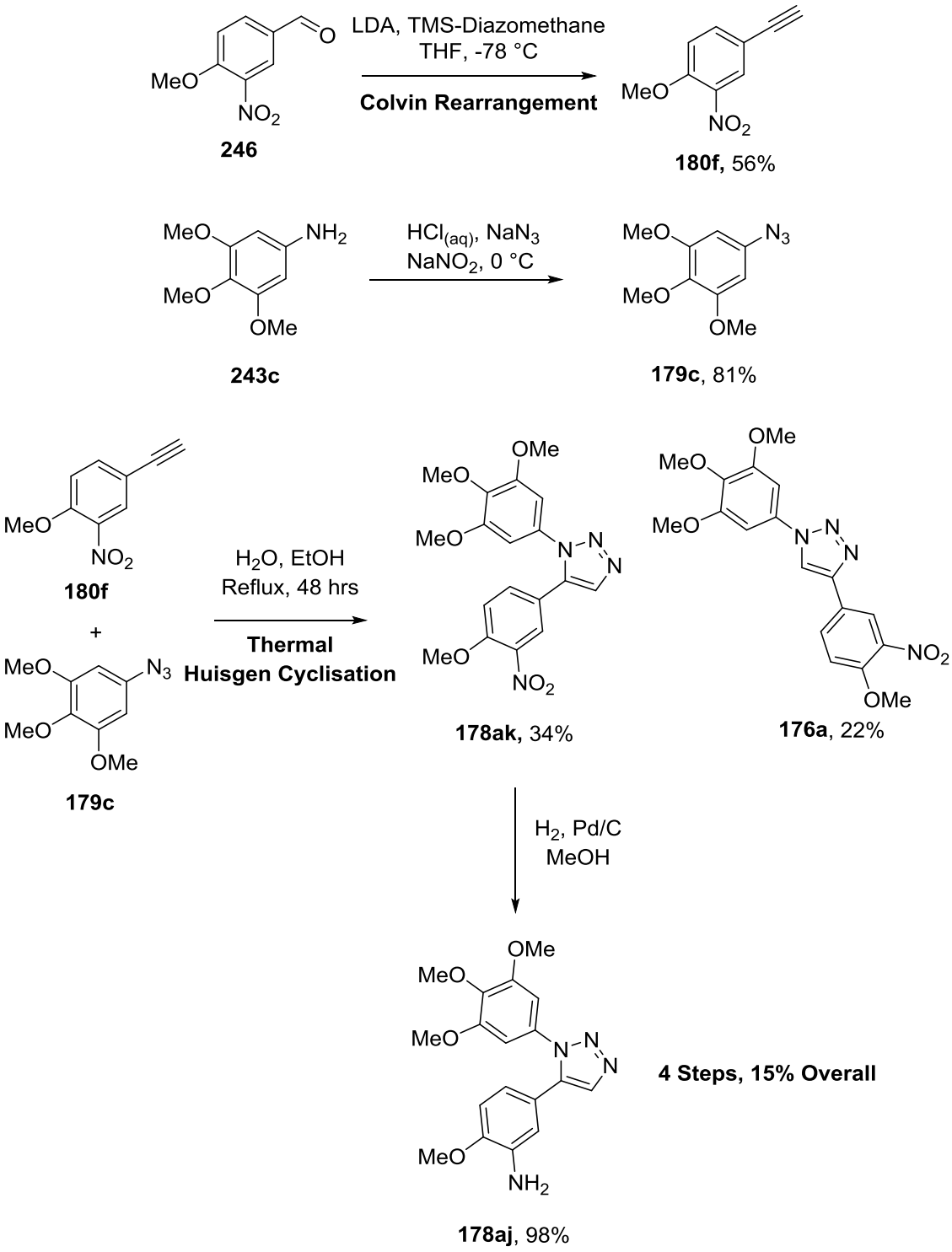
Figure 7: Natural product combretestatin A-4 and triazole analogue 178aj

Studies have therefore focused on generating a library of molecules with the *cis*-relationship locked in place to restrict isomerisation to the *trans*-form. Introduction of a triazole moiety between the A and B ring was developed in 2008, and studies showed that the most active compound was 2-methoxy-5-(1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazol-5-yl)aniline (**178aj**).[249 250] This molecule displayed a 1,5-relationship of the A and

B rings, with the A ring coming from the azide starting material, and the B ring from the alkyne. This compound showed *in vitro* cytotoxic activity against several cancer cell lines, and moderate inhibition of tubulin polymerisation. Molecular modelling studies were also performed for this compound with the colchicine binding site and this revealed hydrogen bonding interactions with several amino acids within the binding site.

The described literature synthesis of this molecule is low yielding (15% over 4 steps). Triazole formation was approached *via* the alkyne and the azide. Alkyne **180f** was formed through Colvin rearrangement of **246** with LDA and TMS-diazomethane in a 56% yield. Azide **179c** was obtained from aniline **243c** in 81% yield employing standard diazotization conditions (**Scheme 131**).

Other analogues in this study were synthesised with magnesium methods to generate the 1,5-triazole relationship, as demonstrated by Fokin and Sharpless.[219] However, the nitro-group proved problematic and the magnesium acetylide was not successfully generated for this compound. The triazole was therefore formed through thermally induced Huisgen cycloaddition, giving a mixture of the 1,4- and 1,5- regioisomers, with the 1,5- isomer being the major product. The isomers were separable by column chromatography to give the desired 1,5- compound in 34% yield. This then underwent palladium on charcoal reduction to give the aniline, with the desired product isolated in 15% total yield across the 4 steps (**Scheme 131**).



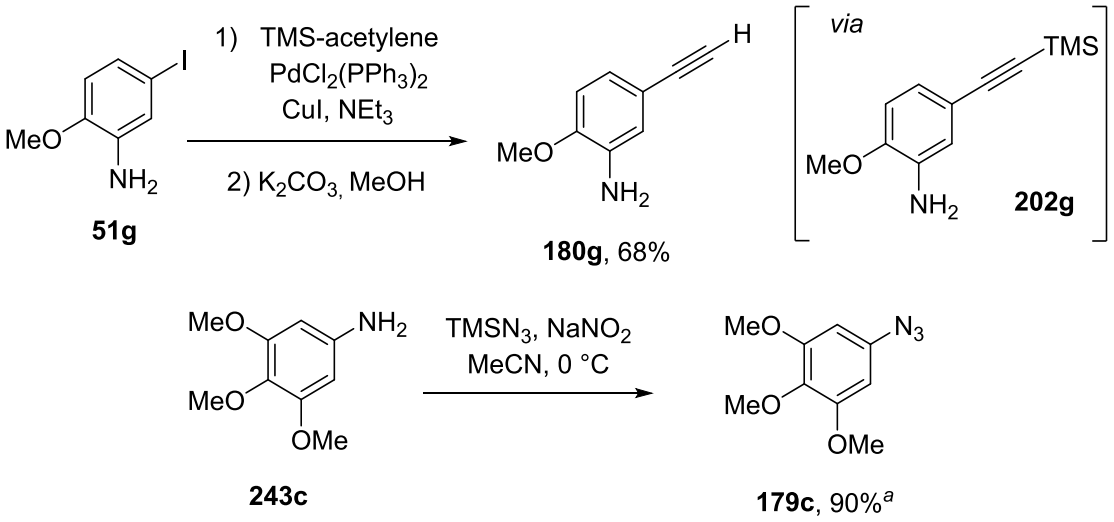
Scheme 131: Literature route to 178aj

Similar studies in 2012 from Ley and Myers in 2012 reinforced the importance of the A and B ring relationship, and showed that replacing the 2- and 4-methoxy substituents on the azide with halides improved the biological activity of the species.[251] In this series aniline was replaced with a hydroxyl group. This required protection throughout the synthesis, adding an extra step for deprotection. The group used Fokin's Grignard method

for the synthesis of the triazole, with variable results (16-77%) depending on the substitution pattern.

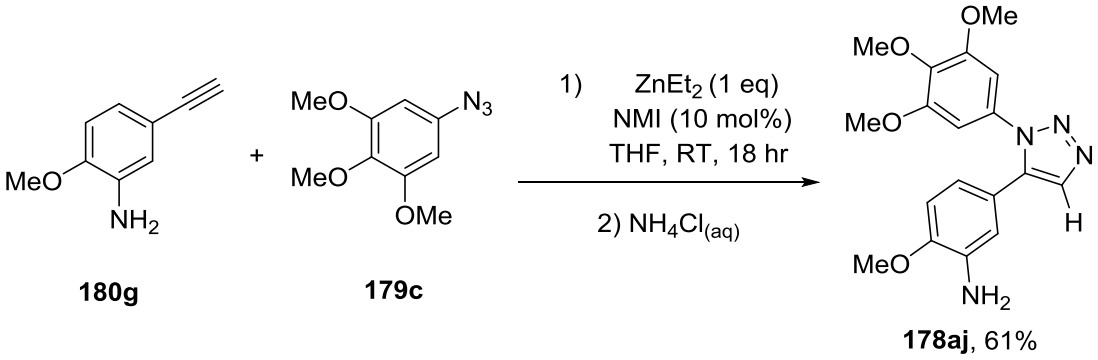
The low yield is largely caused by the key triazole forming step. Since the zinc methodology has already been shown to be applicable to a wider range of functional groups than the magnesium mediated chemistry, it was proposed that this may be a more efficient route. It was also considered that the triazole could be directly generated from aniline alkyne **180g** removing the necessity for the final reduction step.

Synthesis of the azide and alkyne were performed in high yield. The azide was synthesised from the aniline *via* the previously used diazotisation method. The alkyne was formed under the one-pot, two-step Sonogashira/deprotection protocol (**Scheme 132**).



Scheme 132: Synthesis of substrates for the formation of 178aj [a]Synthesis performed by Dr. Chris Smith

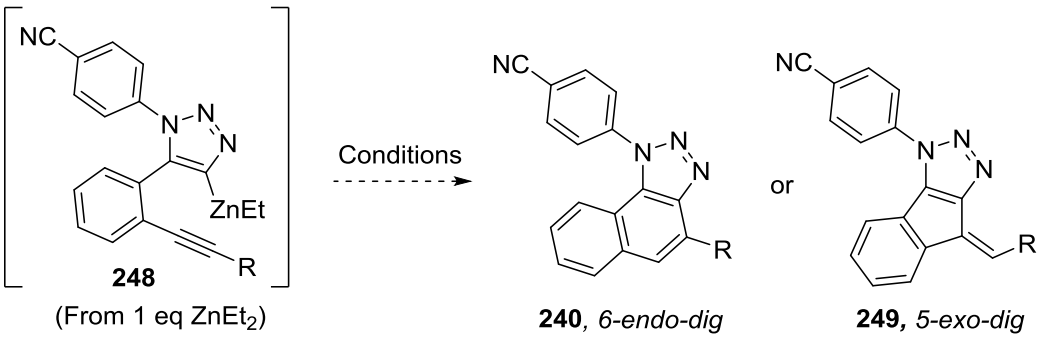
These substrates were then subjected to the developed reaction conditions. Pleasingly the desired 1,5-triazole product could be generated directly. However, with 50% $ZnEt_2$ the yield was low (32%). Increasing the amount of $ZnEt_2$ to 1 equivalent gave the desired product in a good yield of 61% as a single isomer. This results in a 37% yield overall, representing double that of the literature yield.



Scheme 132: Synthesis of 178aj through zinc mediated triazole formation

5.1.4. Attempted formation of bicyclic species using bis-alkyne substrates

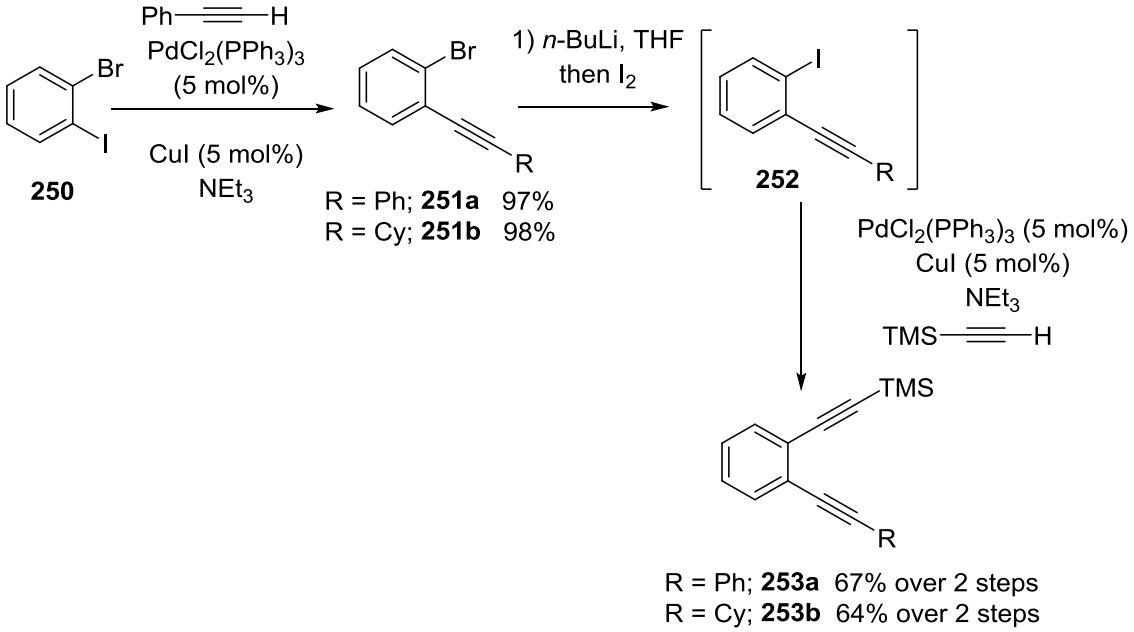
It has already been established that the zinc ligation process was only possible using a terminal alkyne, as the mechanism proceeds *via* the initial formation of the zinc acetylide. It was proposed that by using a bis-alkyne substrate, where the second alkyne was not a terminal alkyne (**247**), intermediate **248** would be generated. Under certain conditions this could undergo a second cyclisation to form a polycyclic molecule (**240** or **249** in **Scheme 133**). The addition of alkyl or aryl zinc reagents across alkyne double bonds is well established in the literature by Knochel, Cann and Oshima where transition metal catalysis is used to promote the reaction.[252-254] Work by Hayashi and co-workers has also demonstrated the addition of aryl magnesium reagents across triple bonds using iron and copper catalysis.[255] The desired cyclisation process could either be through a *5-exo-dig* transformation to form **249**, or a *6-endo-dig* transformation to form **240**, both of which are allowed in accordance with Baldwin's Rules.[256]



Scheme 133: Proposed formation of polycyclic structures 240 and 249

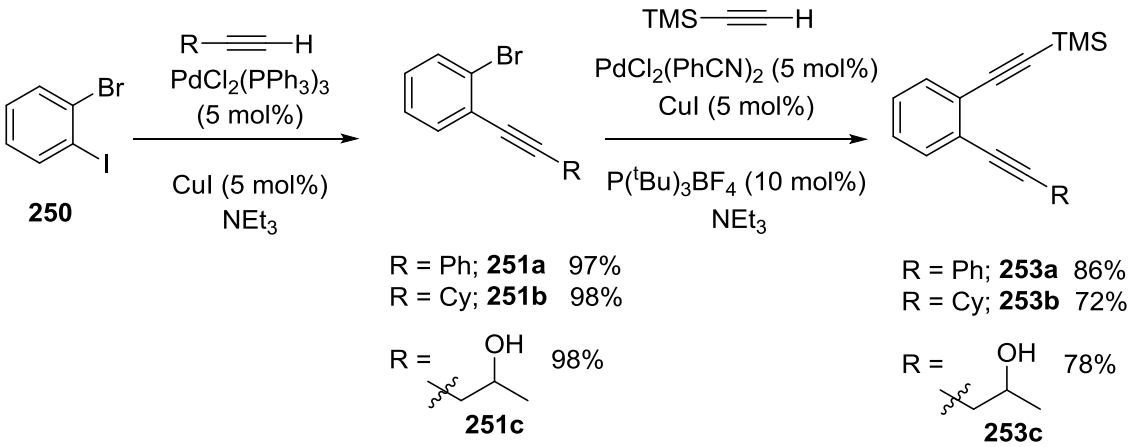
Synthesis of di-alkyne substrates was attempted using literature conditions starting from 2-bromoiodobenzene.[257] The first alkyne was installed by Sonogashira cross-coupling in quantitative yield. Lithium halogen exchange of bromide **251** furnished iodide **252**.

Without extensive purification, a second Sonogashira reaction with the protected TMS-acetylene resulted in the desired di-alkyne substrates in moderate yields (**Scheme 134**).



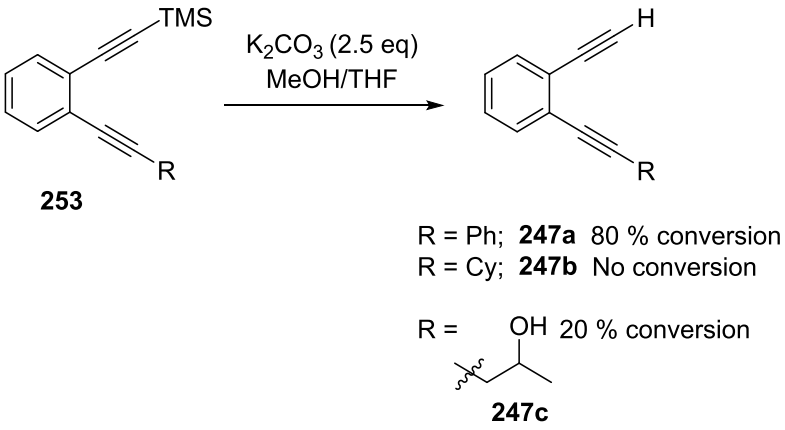
Scheme 134: Synthesis of dialkyne substrates *via* lithium halogen exchange

Performing the second Sonogashira reaction directly with bromide **251** was also attempted as a more direct and economic methodology.[258] This resulted in improved overall yields, and removed a step from the synthetic pathway. (**Scheme 135**). This process was also effective for the synthesis of species **253c** which was not successful through the lithium-halogen exchange method.

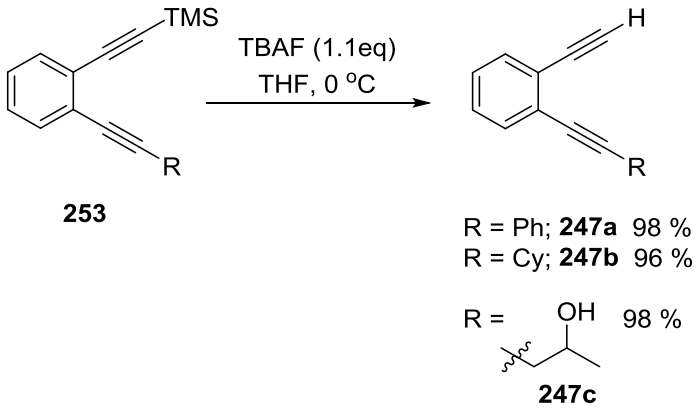


Scheme 135: Synthesis of dialkyne substrates in two steps

Deprotection of the bis-alkynes *via* the procedure of Alabugin *et al.* using an excess of potassium carbonate in methanol.[258] Although a maximum of 80% conversion could be observed with substrate **247a** at extended reaction times, the separation of the protected and deprotected forms proved challenging (**Scheme 136**). For other substrates the conversion was either low or not observed. The deprotection of these substrates was eventually performed successfully using TBAF and gave quantitative yields of the desired dialkyne products (**Scheme 137**).[259]



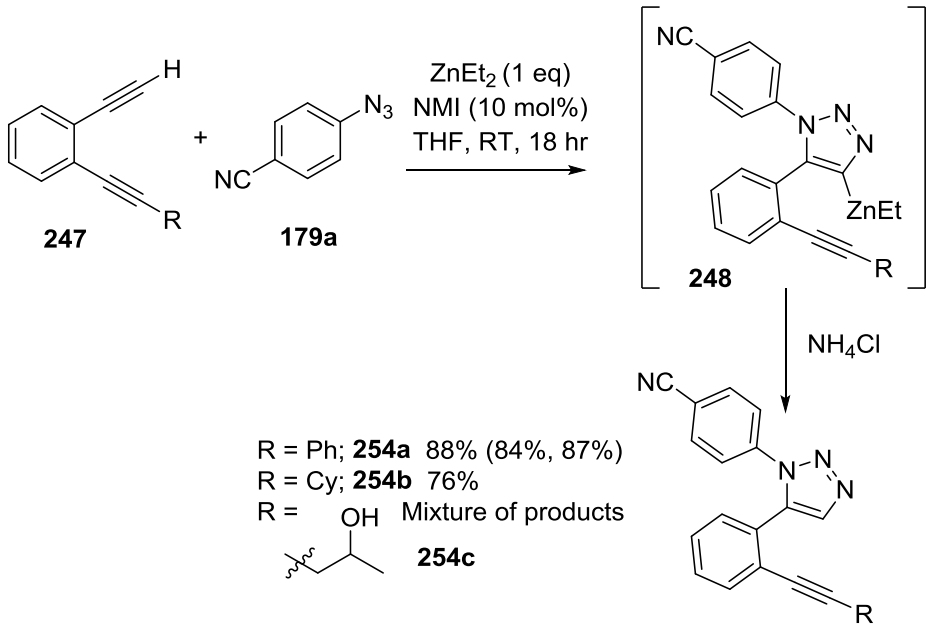
Scheme 136: Deprotection of di-alkyne substrates 247a, 247b and 247c with K_2CO_3



Scheme 137: Successful of di-alkyne substrates 247a, 247b and 247c with TBAF

To be sure that the desired zinc intermediate (**248**) would be formed under the reaction conditions, the isolated di-alkyne products were subjected to the standard conditions for formation of the protonated triazoles (**Scheme 138**). For aryl and alkyl substrates **247a** and **247b** high yields of the desired 1,5-triazole products were obtained, and this result was demonstrated to be reproducible. Unfortunately **247c**, which includes an alcohol side chain, resulted in a complex mixture of compounds which could not be cleanly isolated or

characterised. It was believed that the $ZnEt_2$ was initially deprotonating the alcohol, and this could be inhibiting generation of the desired product. The reaction was repeated with 1.0, 1.5 and 2.0 equivalents of $ZnEt_2$ to try and drive the reaction towards the desired triazole product; however, the outcome remained the same.

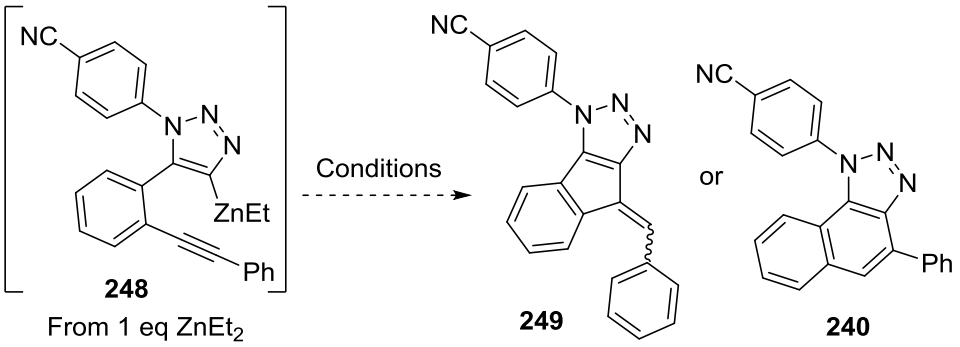


Scheme 138: Reaction of alkyne species 247a, 247b and 247c under standard conditions

Using substrate **247a**, conditions were explored to generate the desired tricyclic product from the zinc triazole intermediate (**Table 36**). No reaction was observed without addition of extra reagents even at raised temperature. A series of transition metal additives were considered. Addition of zinc(I) chloride or zinc(I) bromide did not change the outcome (**Table 36**, **Entries 3-4**). Copper additives also failed to improve the result (**Table 36**, **Entries 5-10**) Addition of silver species has been shown to promote alkyne cyclisation.[260,261] Again, none of the desired tricyclic products were observed on addition of a range of silver salts (**Table 36**, **Entries 11-16**). Inspired by Knochel, Cann and Oshima, cobalt and nickel catalysis were also attempted (**Table 36**, **Entries 17-20**).[252-254]Palladium mediated conditions were also tried without success (**Table 36**, **Entries 21-22**).[262] In all cases only the protonated triazole was observed by LCMS and crude NMR.

It was proposed that initial formation of the iodide, followed by oxidative addition of the iodide to palladium and subsequent cyclisation could be possible. Quenching the reaction with I_2 followed by reaction with a series of palladium catalysts (palladium(0) or (II)) (**Table 37**). Unfortunately none of the desired tricyclic products were observed.

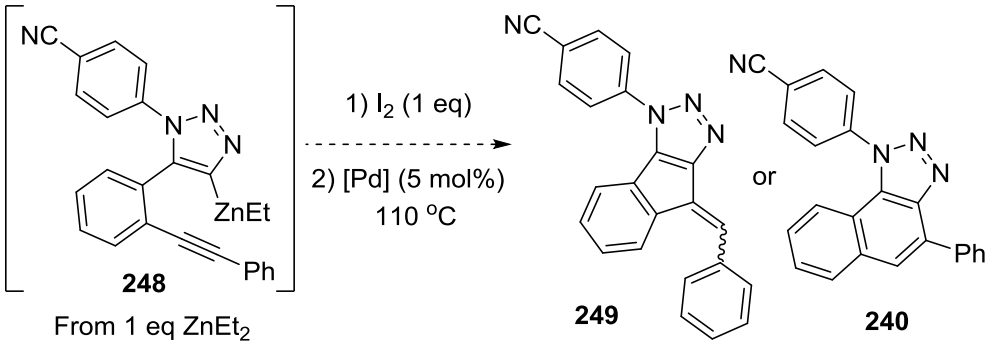
Table 36: Screening conditions for attempted formation of a polycyclic structure



#	Additive	Additive quantity	Temp (°C)	Outcome
1	-	-	RT	-[a]
2	-	-	70	-[a]
3	$ZnBr_2$	1 eq	70	-[a]
4	$ZnCl_2$	1 eq	70	-[a]
5	$CuCl_2$	20 mol%	RT	-[a]
6	CuI	20 mol%	RT	-[a]
7	CuCN.2LiCl	20 mol%	RT	-[a]
8	$CuCl_2$	20 mol%	70	-[a]
9	CuI	20 mol%	70	-[a]
10	CuCN.2LiCl	20 mol%	70	-[a]
11	AgI	20 mol%	RT	-[a]
12	AgOAc	20 mol%	RT	-[a]
13	$AgBF_4$	20 mol%	RT	-[a]
14	AgI	20 mol%	70	-[a]
15	AgOAc	20 mol%	70	-[a]
16	$AgBF_4$	20 mol%	70	-[a]
17	$CoBr_2$	20 mol%	RT	-[a]
18	$CoBr_2$	20 mol%	70	-[a]
19[b]	$Ni(acac)_2$	25 mol%	RT	-[a]
20[b]	$Ni(acac)_2$	25 mol%	70	-[a]
21	$Pd(OAc)_2$ / $Cu(OAc)_2$	5 mol% / 1 eq	70	-[a]
22	$Pd(OAc)_2$ / $K_2S_2O_8$	5 mol% / 1 eq	70	-[a]

[a]No evidence of desired product by LCMS/Crude NMR – protonated triazole only observed product [b]Reaction conditions included 1 ml NMP as co-solvent

Table 37: Attempted formation of a polycyclic structure *via* initial formation of the iodide and subsequent palladium catalysis



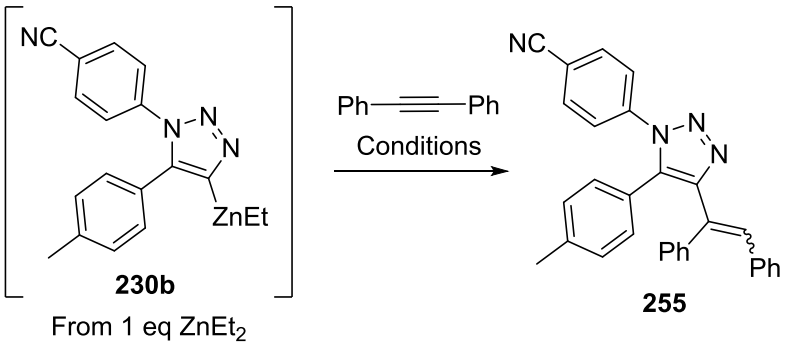
#	[Pd]	Outcome
1	$Pd(OAc)_2$	- [a]
2	$PdCl_2$	- [a]
3	Pd-PEPPSI-^{I}Pr	- [a]
4	$Pd_2(dba)_3$	- [a]
5	$Pd(PPh_3)_4$	- [a]

[a]No evidence of desired product by LCMS/Crude NMR – iodotriazole only observed product

The intermolecular carbometallation of the triazolyl-zinc was investigated with a newly added symmetrical alkyne. Diphenylacetylene and a wide range of metal catalysed conditions were screened, focussing on methods described for successful transition metal-mediated carbometallation of alkynes (**Table 38**).[263,264] Unfortunately, none of the attempted conditions led to formation of the desired product. Only the protonated triazole was observed in the reactions.

Focussing on the work by Knochel and co-workers whereby a nickel catalyst was used to perform the carbometallation of alkyne zinc reagents, a series of conditions were screened.[253] Attention was focussed on changing the stoichiometry of the initial zinc reaction, changing the electronics of the alkyne, the temperature of the reaction, and the absence/presence of the NMP co-solvent (shown to be necessary in Knochel's chemistry) (**Table 39**). In all cases only the protonated triazole was observed.

Table 38: Attempted intermolecular carbometallation with an alkyne



230b

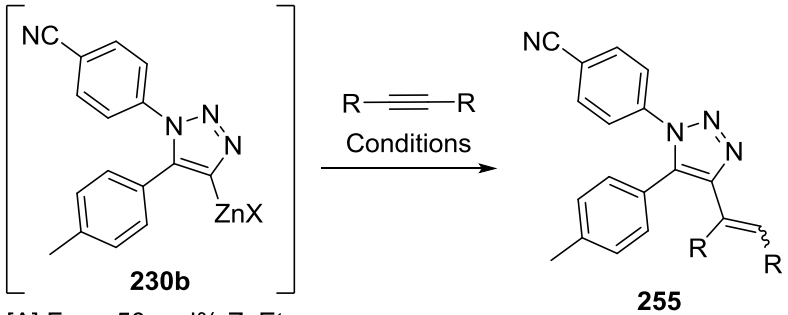
From 1 eq $ZnEt_2$

255

#	Additive	Additive quantity	Temp (°C)	Outcome
1	$ZnBr_2$	1 eq	RT	- [a]
2	$ZnCl_2$	1 eq	RT	- [a]
3	$MgBr_2$	1 eq	RT	- [a]
4	$Rh_2(OAc)_4$	5 mol%	RT	- [a]
5	$RhCl(PPh_3)_3$	5 mol%	RT	- [a]
6	CuI	1 eq	RT	- [a]
7	$CuBr_2$	1 eq	RT	- [a]
8	$Cu(OAc)_2$	1 eq	RT	- [a]
9	$Cu(OAc)_2$ / Phen	1 eq / 10 mol%	RT	- [a]
10	$CuBr_2$ / $FeCl_3$	20 mol% / 10 mol%	RT	- [a]
11	AuCl	1 eq	RT	- [a]
12	AgOAc	10 mol%	RT	- [a]
13	Ag_2CO_3	10 mol%	RT	- [a]
14	$Pd(OAc)_2$ / $Cu(OAc)_2$	5 mol% / 10 mol%	70	- [a]
15	$Pd(OAc)_2$ / $Cu(OAc)_2$	5 mol% / 1 eq	70	- [a]
16	$Pd(OAc)_2$ / $Cu(OAc)_2$	5 mol% / 10 mol%	100	- [a]
17	$Pd(OAc)_2$ / $Cu(OAc)_2$	5 mol% / 1 eq	100	- [a]

[a]No evidence of desired product by LCMS/Crude NMR – protonated triazole only observed product

Table 39: Attempted intermolecular carbometallation with an alkyne – Use of Knochel's conditions[253]



230b **255**

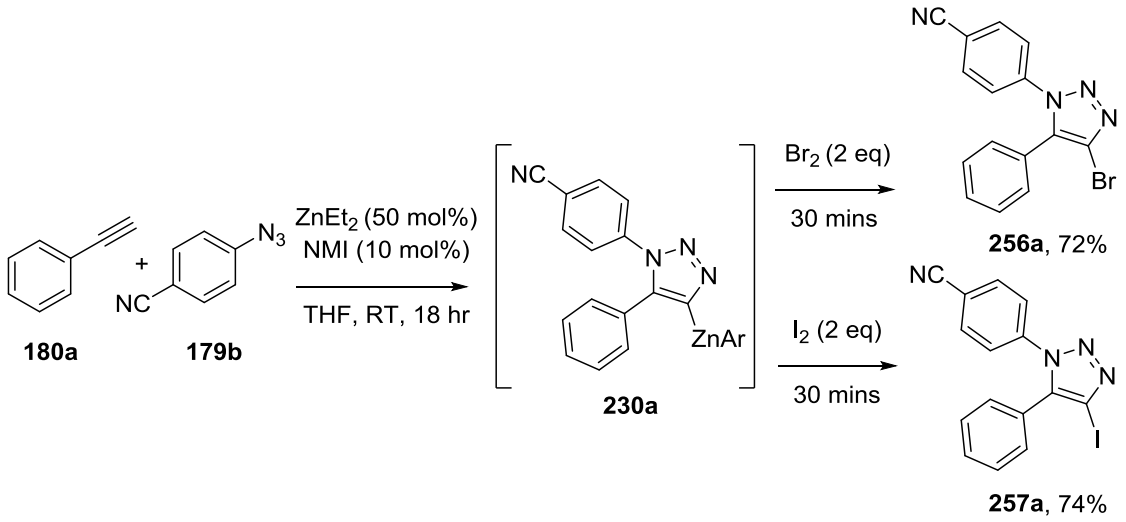
[A] From 50 mol% $ZnEt_2$
[B] From 1 eq $ZnEt_2$

#	Intermediate	R	Conditions	Temp (°C)	Outcome
1	[A]	Ph	$Ni(acac)_2$ (25 mol%)	RT	-[a]
2	[A]	Ph	$Ni(acac)_2$ (25 mol%), NMP[b]	RT	-[a]
3	[A]	CO_2Me	$Ni(acac)_2$ (25 mol%)	RT	-[a]
4	[A]	CO_2Me	$Ni(acac)_2$ (25 mol%), NMP[b]	RT	-[a]
5	[B]	Ph	$Ni(acac)_2$ (25 mol%)	RT	-[a]
6	[B]	Ph	$Ni(acac)_2$ (25 mol%), NMP[b]	RT	-[a]
7	[B]	CO_2Me	$Ni(acac)_2$ (25 mol%)	RT	-[a]
8	[B]	CO_2Me	$Ni(acac)_2$ (25 mol%), NMP[b]	RT	-[a]
9	[A]	Ph	$Ni(acac)_2$ (25 mol%)	0	-[a]
10	[A]	Ph	$Ni(acac)_2$ (25 mol%), NMP[b]	0	-[a]
11	[A]	CO_2Me	$Ni(acac)_2$ (25 mol%)	0	-[a]
12	[A]	CO_2Me	$Ni(acac)_2$ (25 mol%), NMP[b]	0	-[a]
13	[B]	Ph	$Ni(acac)_2$ (25 mol%)	0	-[a]
14	[B]	Ph	$Ni(acac)_2$ (25 mol%), NMP[b]	0	-[a]
15	[B]	CO_2Me	$Ni(acac)_2$ (25 mol%)	0	-[a]
16	[B]	CO_2Me	$Ni(acac)_2$ (25 mol%), NMP[b]	0	-[a]
17	[A]	Ph	$Ni(acac)_2$ (25 mol%), NMP[b]	-78	-[a]
18	[A]	CO_2Me	$Ni(acac)_2$ (25 mol%), NMP[b]	-78	-[a]
19	[B]	Ph	$Ni(acac)_2$ (25 mol%), NMP[b]	-78	-[a]
20	[B]	CO_2Me	$Ni(acac)_2$ (25 mol%), NMP[b]	-78	-[a]

[a]No evidence of desired product by LCMS/Crude NMR – protonated triazole only observed product [b] NMP added to reaction in 3:1 ratio THF:NMP

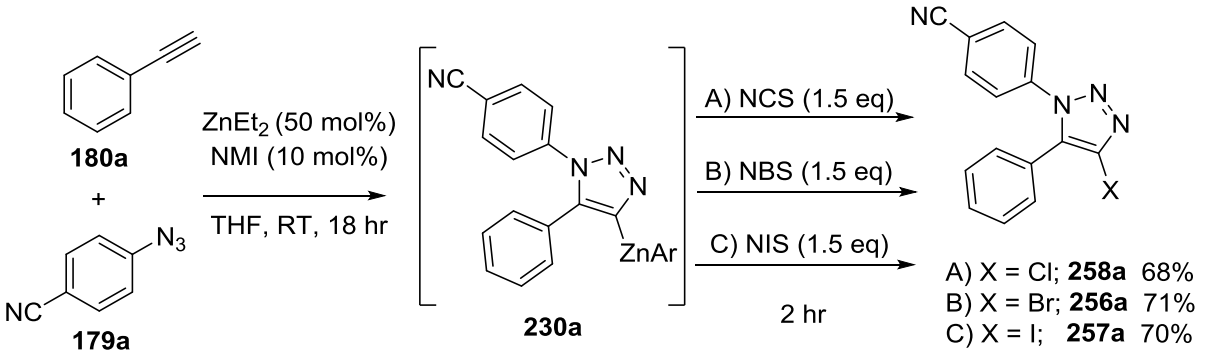
5.1.5. Formation of 4-halo 1,5-triazoles

Published work has shown the ability to quench the generated zinc species with electrophiles in order to gain access to a wide range of products.[241] This was demonstrated to be possible using elemental bromine to form the 4-bromotriazole in high yield. Iodination was also possible through addition of elemental iodine (**Scheme 139**). Other methods to generate halo-triazoles have used the RuAAC method with 1-iodo-alkynes and resulted in the 1,4,5-substituted triazole with the halide at the 5-position.[229] This method directly generates the 1,4,5-substituted triazole with the halide at the 4 position.



Scheme 139: Halogenation with bromine and iodine – Ar denotes a symmetrical homoleptic zinc species with 2 triazole substituents

The use of *N*-halosuccinimide species as milder and more easily handled halide sources was also possible (**Scheme 140**). This allowed access to the 4-chlorotriazole species **258a** in good yield.



Scheme 140: Halogenation with *N*-halosuccinimides

Under these conditions a series of chlorides (**Table 40**), bromides (**Table 41**) and iodides (**Table 42**) were synthesised. The trends were similar to those found for the protonated triazoles. Yields for the chlorides were generally lower than the iodides or bromides, and the substrate scope was also far more restricted. Aliphatic alkynes generally failed to generate the chloride species and electron withdrawing or strongly hindered alkynes also failed. Electron-rich azides and hindered azides were also unsuitable. NMR data confirm the specificity towards the 4-halo-substituted 1,5-isomer of the triazole, and this was further confirmed through X-ray crystallography of species **256a** and **257a** (**Figure 8**). Only one isomer was isolated in all cases.

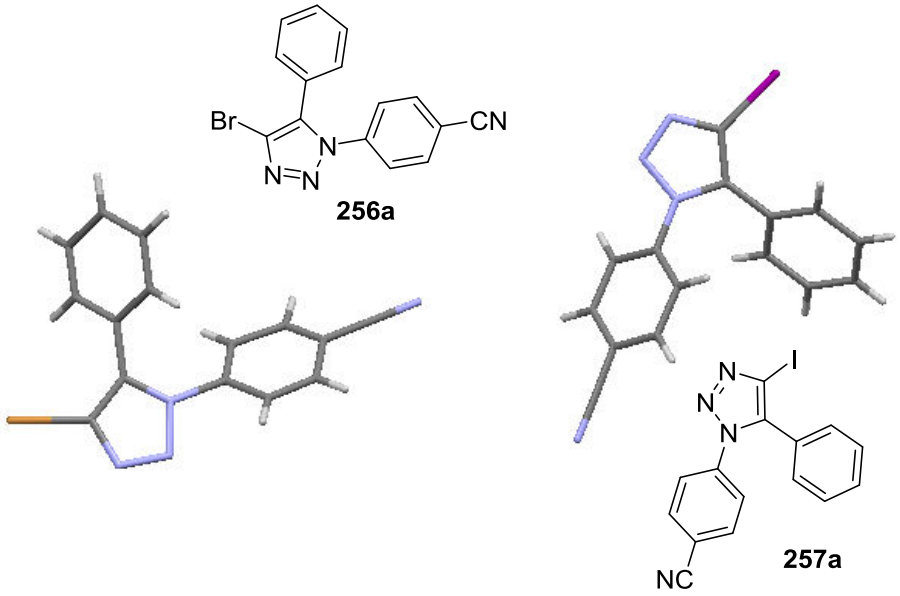
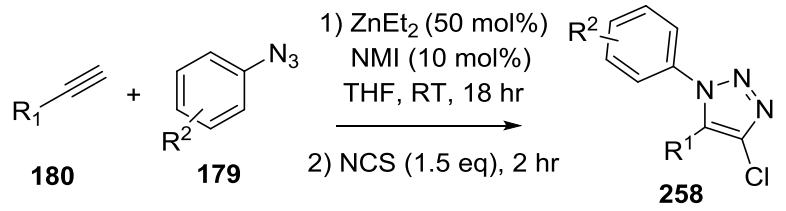
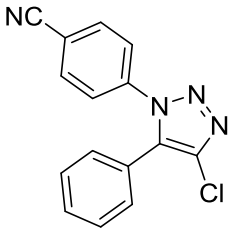


Figure 8: X-ray crystallographic analysis of 256a and 257a

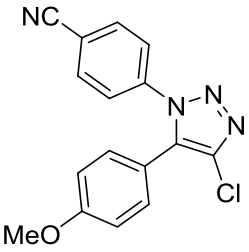
Table 40: Substrate scope for 4-chlorotriazole species



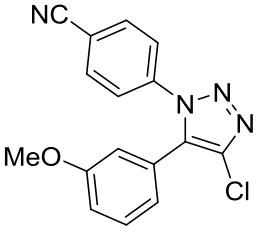
180 **179** **258**



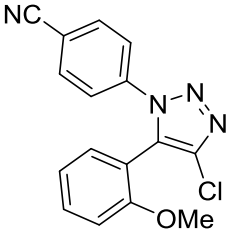
258a, 68%



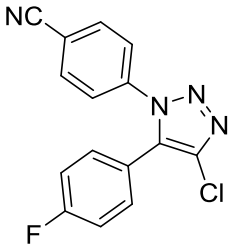
258b, 84%



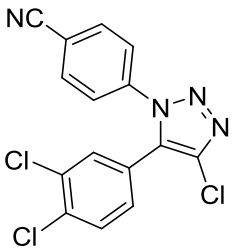
258c, 57%



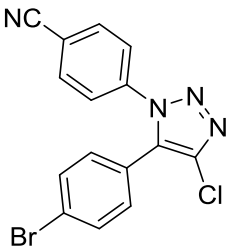
258d, 39%



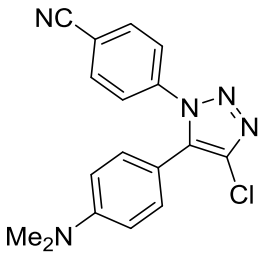
258e, 57%



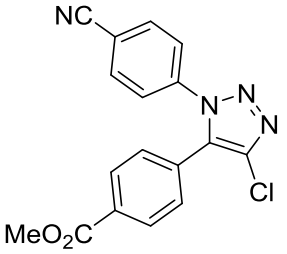
258f, 61%



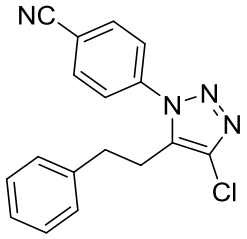
258g, 48%



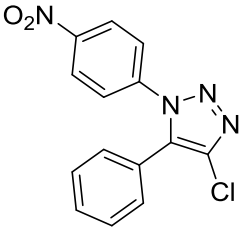
258h, 55%



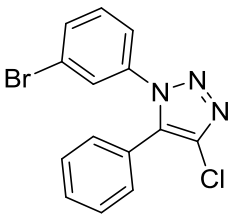
258i, 18%



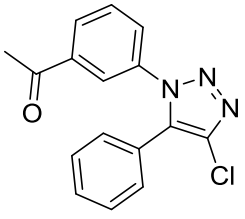
258j, 66%



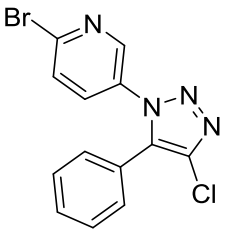
258k, 47%



258l, 49%

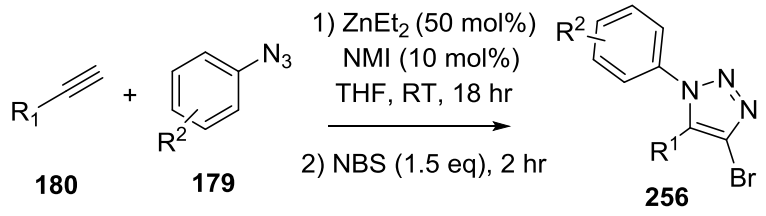


258m, 44%

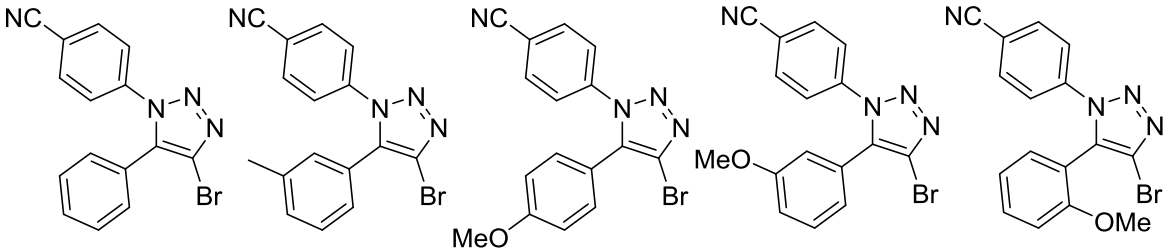


258n, 63%

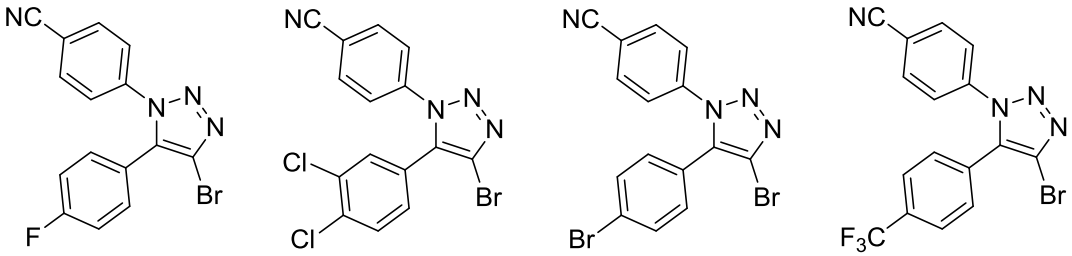
Table 41: Substrate scope for 4-bromotriazole species



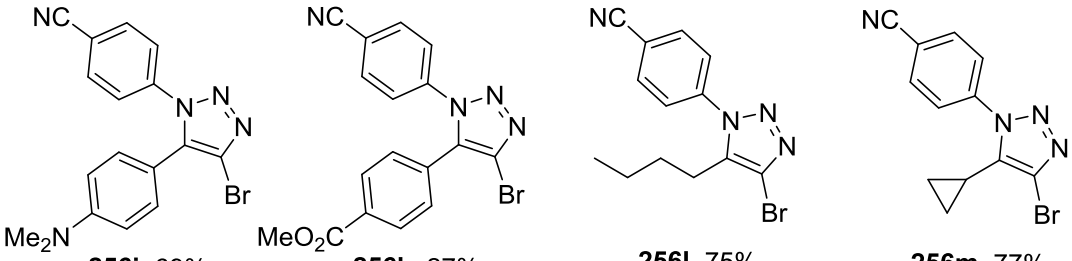
180 **179** **256**



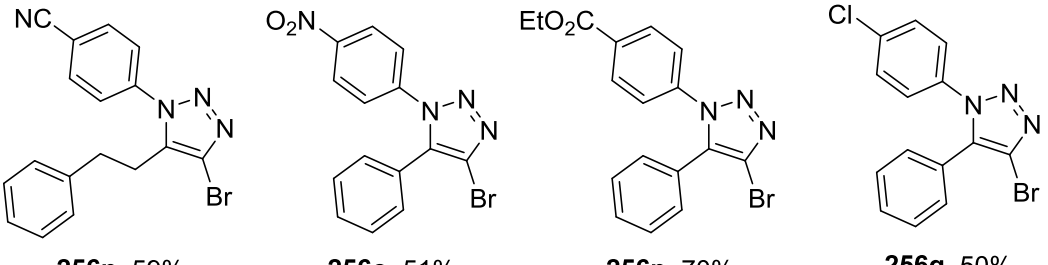
256a, 71% **256b**, 68% **256c**, 78% **256d**, 70% **256e**, 51%



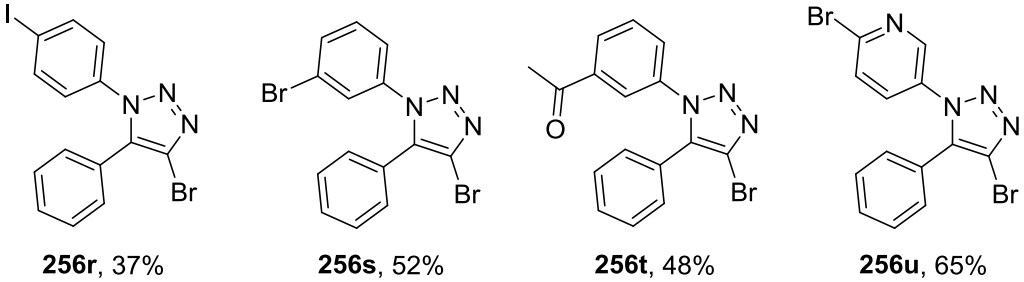
256f, 64% **256g**, 62% **256h**, 61% **256i**, 8%



256j, 69% **256k**, 27% **256l**, 75% **256m**, 77%

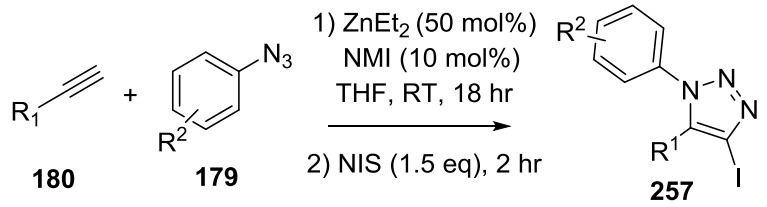


256n, 59% **256o**, 51% **256p**, 70% **256q**, 50%

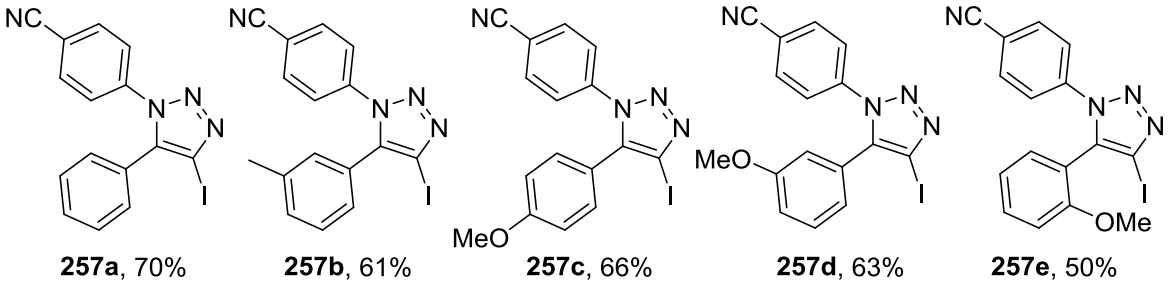


256r, 37% **256s**, 52% **256t**, 48% **256u**, 65%

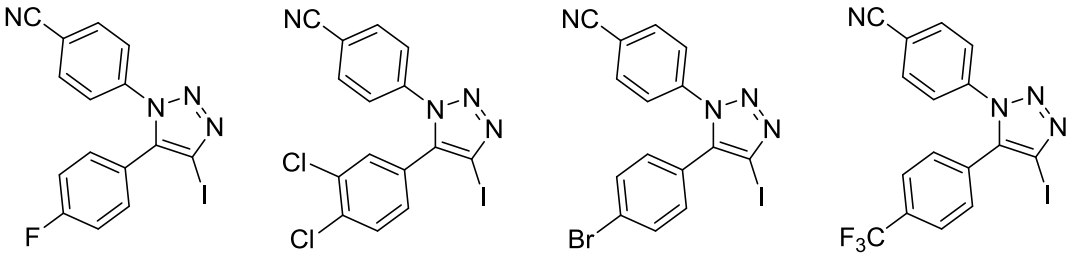
Table 42: Substrate scope for 4-iodotriazole species



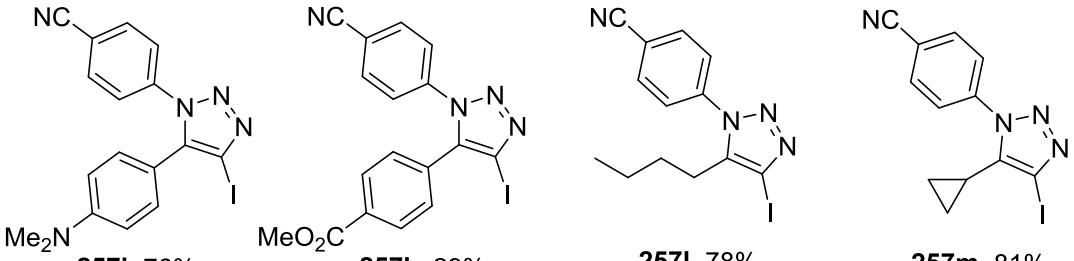
180 **179** **257**



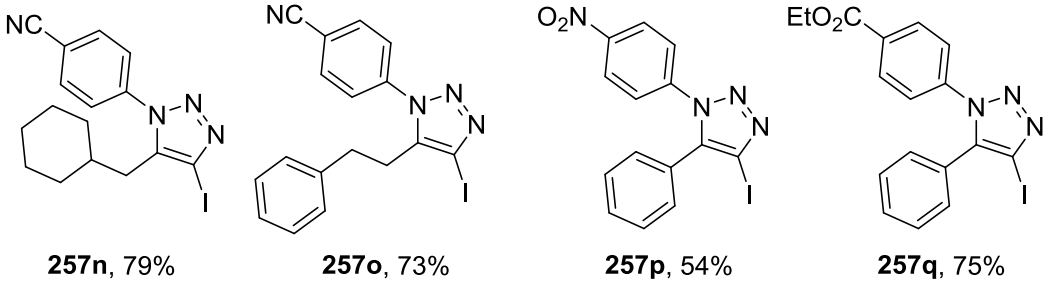
257a, 70% **257b**, 61% **257c**, 66% **257d**, 63% **257e**, 50%



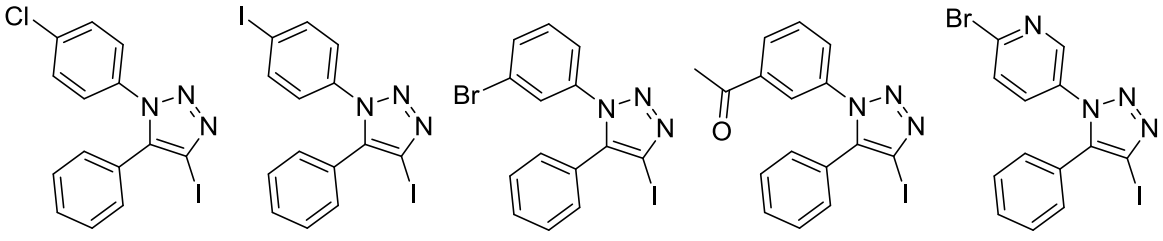
257f, 72% **257g**, 61% **257h**, 67% **257i**, 17%



257j, 76% **257k**, 29% **257l**, 78% **257m**, 81%



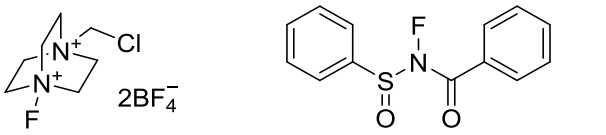
257n, 79% **257o**, 73% **257p**, 54% **257q**, 75%



257r, 51% **257s**, 44% **257t**, 47% **257u**, 49% **257v**, 64%

5.1.6. Fluorination and trifluoromethylation

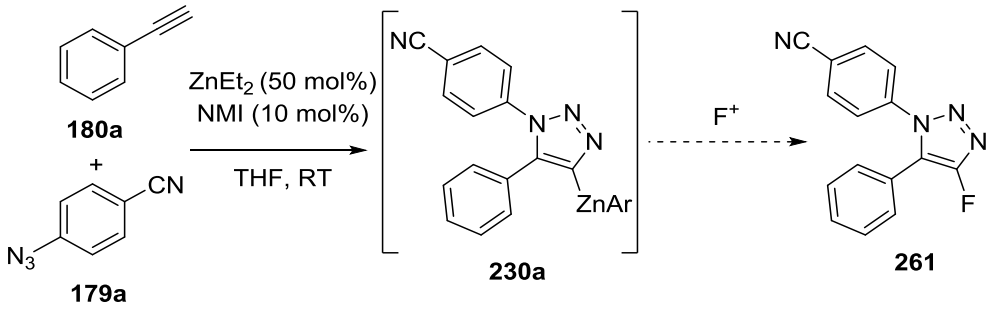
Having successfully synthesised a series of halogenated triazoles it was decided that the next target would be the 4-fluorotriazole. It was proposed that quenching the reaction with an electrophilic source of fluorine such as Selectfluor® or NFSI (**Figure 9**) could lead to the desired fluorinated compound (**Scheme 140**).[265,266]



259
Selectfluor®

260
N-Fluorobenzenesulfonimide
NFSI

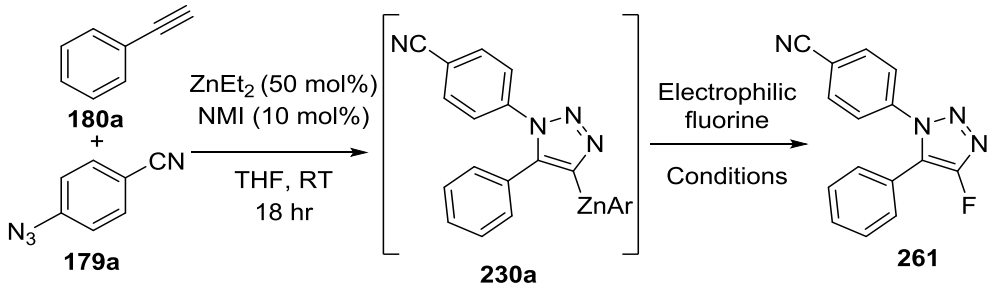
Figure 9: Electrophilic fluorinating agents



Scheme 140: Proposed fluorination using electrophilic sources of fluorine

Conditions were screened with both of the available electrophilic fluorine sources (**Table 43**). Conditions described by Li and co-workers in 2012 report the combination of Selectfluor with $AgNO_3$ in acetonitrile in the successful decarboxylative fluorination of aliphatic carboxylic acids.[267] These conditions did not prove successful with our zinc species. Reactions were attempted at a range of temperatures, however the outcome remained negative. LCMS and crude NMR indicated that the only observed product was the protonated triazole.

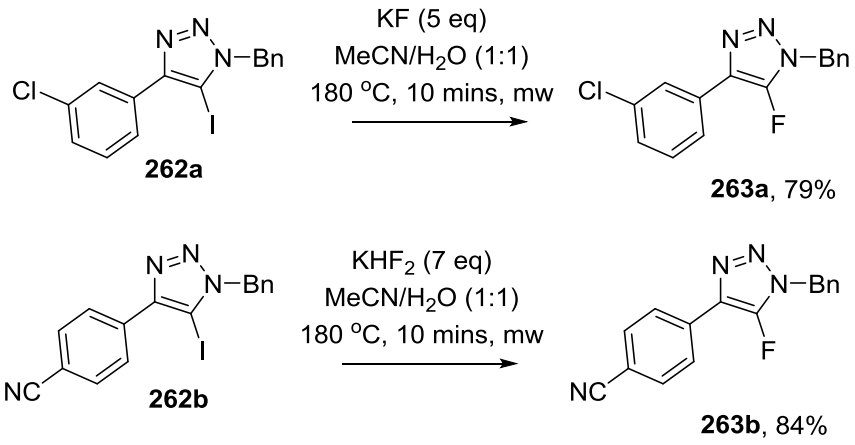
Table 43: Attempted formation of 4-fluoro 1,5-triazoles using electrophilic fluorine sources



#	F^+ Source (eq)	Additives / Co-Solvent	Temp (°C)	Outcome
1	Selectfluor (1.2 eq)	-	RT	- [a]
2	Selectfluor (2.0 eq)	-	RT	- [a]
3	Selectfluor (2.0 eq)	-	110	- [a]
4	Selectfluor (2.0 eq)	-	0	- [a]
5	Selectfluor (2.0 eq)	-	-30	- [a]
6	Selectfluor (2.0 eq)	MeCN (1 ml)	RT	- [a]
7	Selectfluor (2.0 eq)	$AgNO_3$ (50 mol%) / MeCN (1 ml)	RT	- [a]
8	NFSI (1.2 eq)	-	RT	- [a]
9	NFSI (2.0 eq)	-	RT	- [a]
10	NFSI (2.0 eq)	-	110	- [a]
11	NFSI (2.0 eq)	-	0	- [a]
12	NFSI (2.0 eq)	-	-30	- [a]

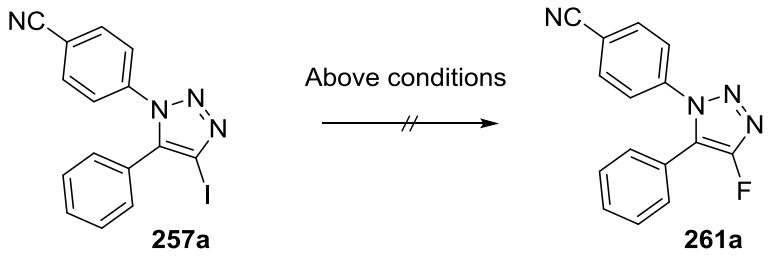
[a]No evidence of desired product by LCMS/Crude NMR – protonated triazole only observed product

Limited success with direct fluorination of the zinc species led to the proposal that access to the 4-fluoro 1,5-triazole could be possible through formation of the iodide, followed by halogen exchange to the fluorine. Literature from Fokin in 2012 demonstrates two methods for the successful halogen exchange at the 5 position of 1,4-triazoles with consistently high yields (**Scheme 141**).[268] The two sets of complimentary conditions use either the basic KF of the acidic KHF_2 to access a wide substrate scope.



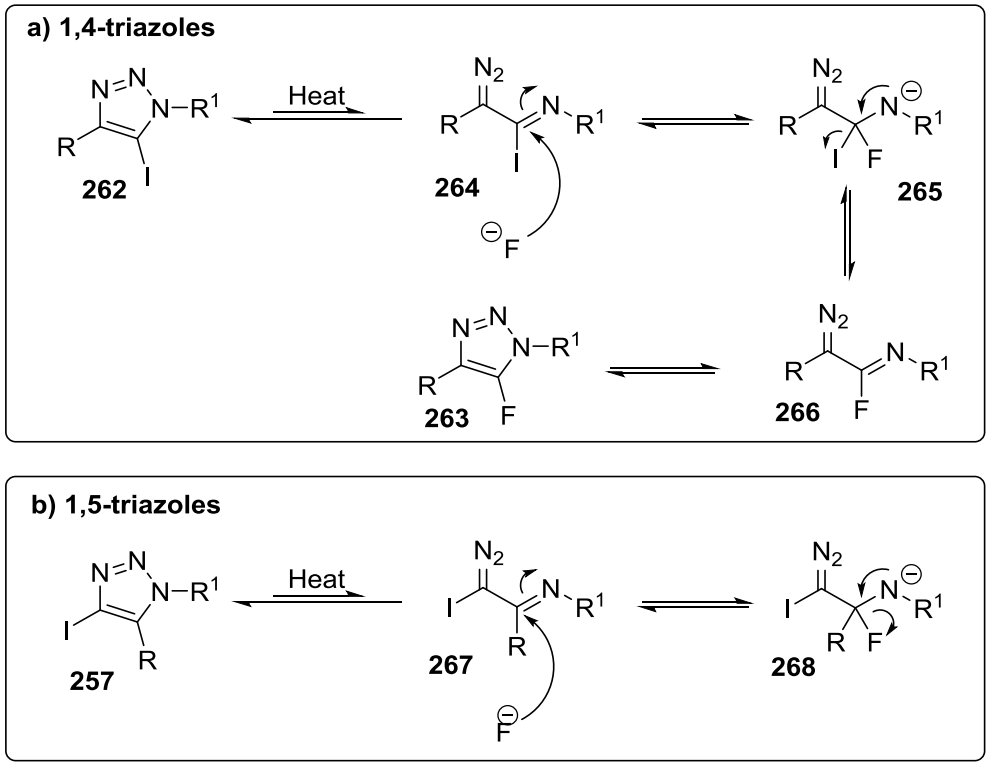
Scheme 141: Literature conditions for the fluorination of 5-iodo 1,4-triazoles

Application of these conditions to the 1,5-isomer of the iodide was unsuccessful (**Scheme 142**). This result was unchanged when performing the reaction in the absence of water. Fokin also noted that the fluorination of the 1,5-triazole was unsuccessful.



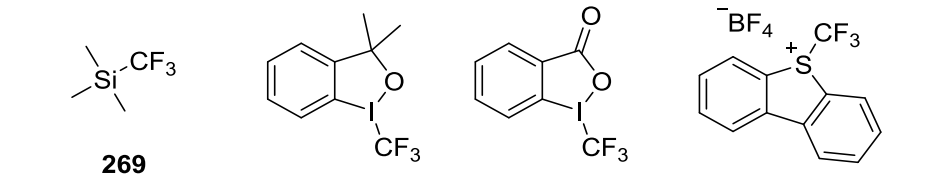
Scheme 142: Failed application of literature conditions to 4-iodo 1,5-triazoles

Fokin provided a mechanistic explanation for the failure of the reaction with the 1,5-isomer (**Scheme 143**). The reaction is performed at high temperature, and it is known that triazoles will undergo ring chain isomerisation when heated. Imidoyl halide **264** is required to react with fluoride in a successful halogen exchange reaction, leading to the desired fluorinated product (**Scheme 143 (a)**). However ring chain isomerism of the 1,5 triazole would not lead to an imidoyl halide, therefore the halogen exchange process cannot take place(**Scheme 143 (b)**). While this provides an explanation why the halogen exchange with a nucleophilic fluoride source is not possible, it does not indicate a reason for the unsuccessful fluorination of the zinc species with an electrophilic source of F^+.



Scheme 143: Plausible mechanistic explanation for the failure of fluorination of the 4 position, as proposed by Fokin *et al.*

Attention was then focussed on trifluoromethylation. Reagents developed by Ruppert, Togni and Umemoto have shown applicability numerous times as sources of CF_3, and commercial availability of these reagents has greatly increased the use of them in synthetic studies (**Figure 9**).[269-271]



269
Ruppert's Reagent
TMS-CF_3

270 and **271**
Togni's Reagents 1 and 2

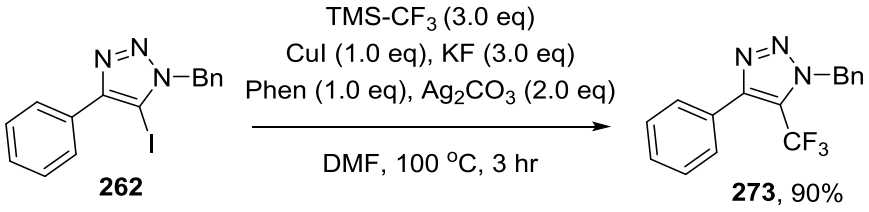
272
Umemoto's Reagent

Figure 9: Sources of reactive [CF_3]

A series of conditions were screened at ambient temperature (**Table 43**). Literature often describes the preformation of either "Cu-CF_3" or "Ag-CF_3" species prior to successful trifluoromethylation. Work within the group has successfully trifluoromethylated arenes *via* a similar process.[272] Mixing of Ruppert's reagent with Cu or Ag additives was therefore attempted prior to addition of the zinc species (**Table 43**, **Entries 3-8**). Use of both Togni reagents, and Umemoto's reagent was also attempted, with various alterations

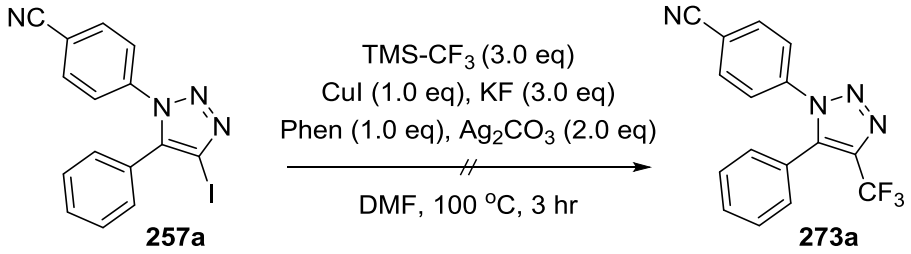
of the addition of reagents. Literature from 1993 described the use of Umemoto's reagent at low temperature; therefore these reactions were repeated at -20 °C.[273] Generally under the attempted conditions none of the desired product was observed, with LCMS and crude NMR indicating only formation of the protonated triazole. In the case where 2 eq of Togni II was used, trace amounts of the desired product were detected (**Table 43, Entry 12**). Mass spec and NMR spectroscopy indicated the successful formation of the trifluoromethylated product. However isolation led to only trace amounts (ca 4%) and this could not be fully characterised due to limited material. This is an area which could potentially be further developed in future.

In a similar manner to that attempted with the fluorination procedure, it was considered that rather than directly trifluoromethylating the zinc species, sequential iodination and trifluoromethylation might give more favourable results. Precedent exists for the successful trifluoromethylation of the 1,4-isomer in this way (**Scheme 144**), however trifluoromethylation of the 4-position remains unexplored.[274]



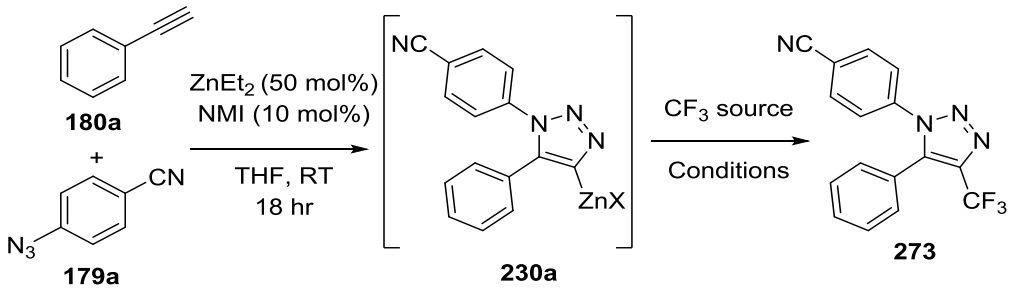
Scheme 144: Literature procedure for trifluoromethylation of 5-iodo,1,4-triazoles

Conditions adapted from the publication did not lead to the desired trifluoromethylated product, with full recovery of the iodide possible at extended reaction times and higher temperatures (**Scheme 145**).



Scheme 145: Attempted trifluoromethylation of the 1,5-isomer adapted from literature conditions

Table 43: Attempted formation of 4-trifluoromethyl 1,5-triazoles using a series of CF_3 sources



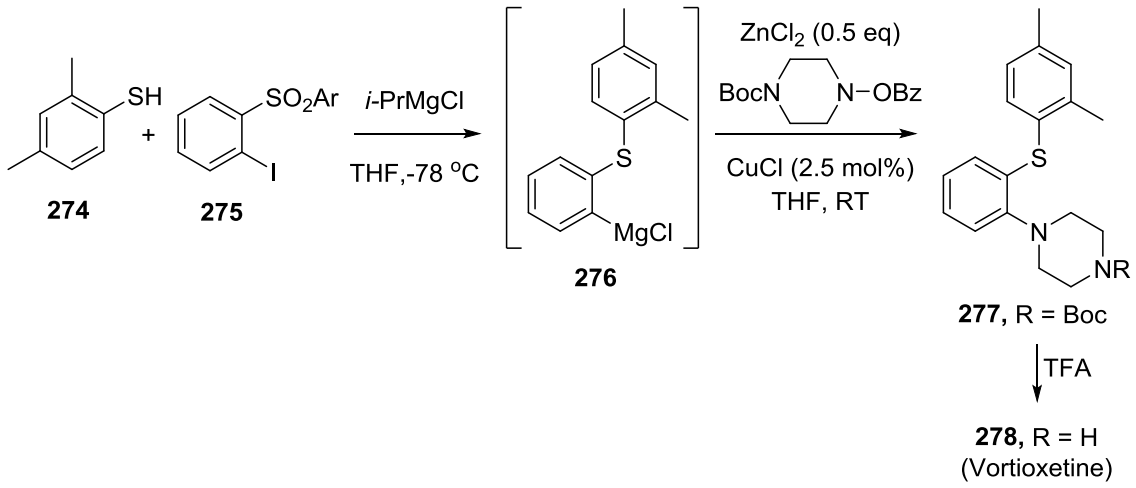
#	CF_3 Source (eq)	Additives / Co-Solvent	Temp (°C)	Outcome
1	Ruppert (1.5 eq)	-	RT	- [a]
2	Ruppert (2.0 eq)	-	RT	- [a]
3	Ruppert (2.0 eq) [b]	CuI (10 mol%)	RT	- [a]
4	Ruppert (2.0 eq) [b]	CuI (1 eq)	RT	- [a]
5	Ruppert (2.0 eq) [b]	AgF (20 mol%)	RT	- [a]
6	Ruppert (2.0 eq) [b]	AgF (20 mol%) / MeCN (1 ml)	RT	- [a]
7	Ruppert (2.0 eq) [b]	AgF (1 eq)	RT	- [a]
8	Ruppert (2.0 eq) [b]	AgF (1 eq) / MeCN (1 ml)	RT	- [a]
9	Togni 1 (1.0 eq)	-	RT	- [a]
10	Togni 1 (2.0 eq)	-	RT	- [a]
11	Togni 2 (1.0 eq)	-	RT	- [a]
12	Togni 2 (2.0 eq)	-	RT	~ 4% [c]
13	Togni 1 (2.0 eq) [d]	$Cu(OAc)_2$ (20 mol%)	RT	- [a]
14	Togni 2 (2.0 eq) [d]	$Cu(OAc)_2$ (20 mol%)	RT	- [a]
15	Umemoto (1.5 eq)	-	RT	- [a]
16	Umemoto (1.5 eq) [d]	$Cu(OAc)_2$ (20 mol%)	RT	- [a]
17	Umemoto (1.5 eq) [d]	$Cu(OAc)_2$ (1 eq)	RT	- [a]
18	Umemoto (1.5 eq)	-	-20	- [a]
19	Umemoto (1.5 eq) [d]	$Cu(OAc)_2$ (20 mol%)	-20	- [a]
20	Umemoto (1.5 eq) [d]	$Cu(OAc)_2$ (1 eq)	-20	- [a]

[a] No evidence of desired product by LCMS/Crude NMR – protonated triazole only observed product. [b] Rupperts reagent stirred in THF (or MeCN where stated) solution with Cu or Ag catalyst before slow addition of the zinc reagent. [c] Trace product isolated – approximately 4% - however full characterisation could not be carried out [d] $Cu(OAc)_2$ combined with CF_3 reagent in THF (1 ml) prior to addition of zinc reagent.

5.1.7. Amination, thiolation and alkoxylation

The addition of other hetero-atoms at the 4-position of the triazole was studied. Current research within the group has developed a procedure for the sequential addition of a magnesiated sulfur species to benzyne (*via* the 2-iodophenyl aryl-sulfonate benzyne precursor) and subsequent trapping of the formed Grignard with electrophilic nitrogen reagents to generate the aminated product.[275] This method was used in the formation of vortioxetine (**Scheme 146**). The addition of zinc chloride was necessary for high yields of the desired aminated product, and it is postulated that this was due to transmetallation to form the zinc chloride species from the Grignard.

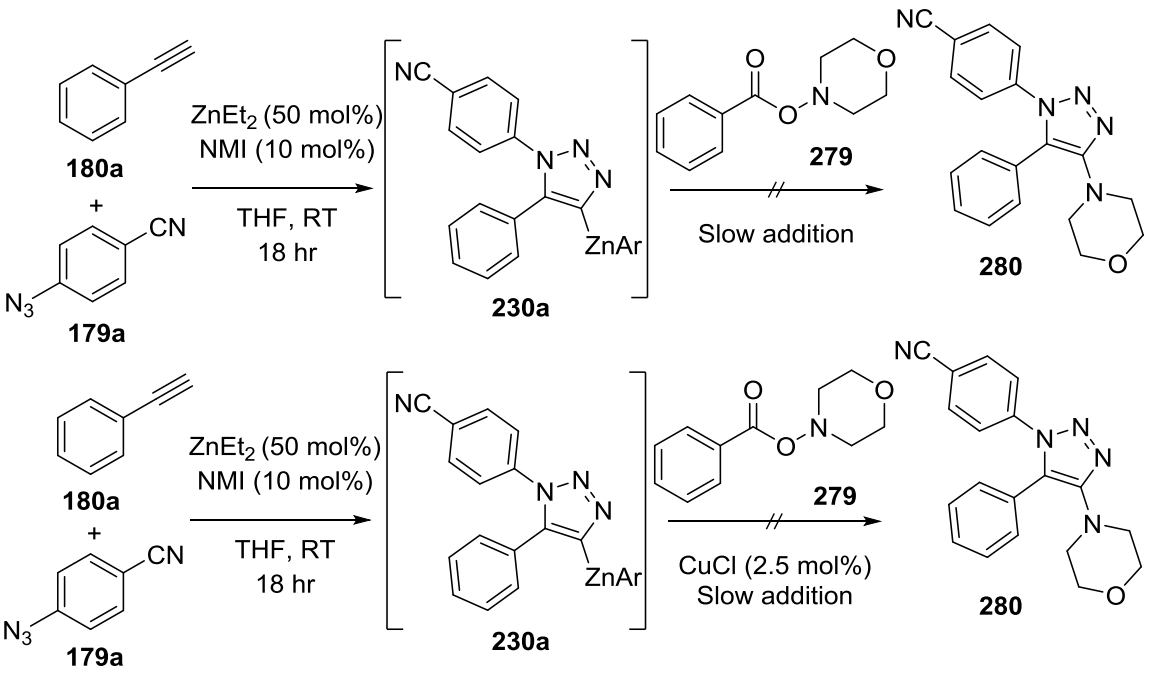
As this reaction proceeds through the formation of a zincate intermediate and subsequent quenching of this intermediate with an amine electrophile, it seemed reasonable that this process could be adapted for the amination of 1,5-triazoles at the 4-position with *N*-(benzoyloxy)morpholine **279**.



274 + **275** → **276** → **277**, R = Boc → **278**, R = H (Vortioxetine)

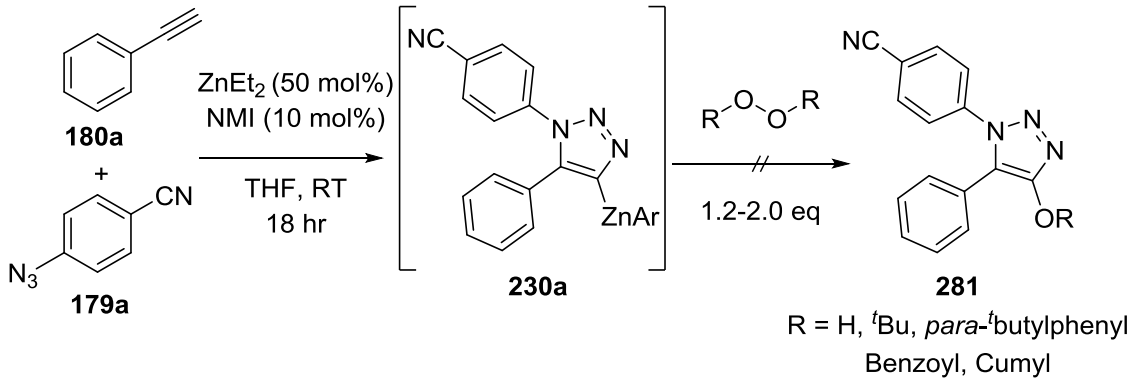
Scheme 146: Previous work in the Greaney group on the 3 component thiolation/amination of benzyne in the synthesis of Vortioxetine

The published reaction conditions require a copper co-catalyst; therefore triazole amination was attempted both in the absence and presence of 2.5 mol% CuCl. The procedure required slow addition of the generated zinc reagent to a stirred solution of *N*-(benzoyloxy)morpholine and the copper catalyst. Under the standard conditions none of the desired amination product was observed, with full conversion to the protonated form of the triazole observed by LCMS and crude NMR (**Scheme 147**).



Scheme 146: Attempted amination of zinc species 230a adapted from current work within the Greaney group

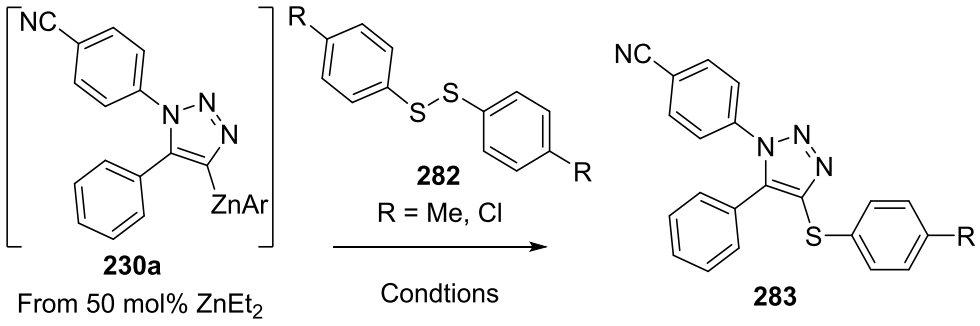
The next reaction studied was alkoxylation. Quenching of the zinc species was attempted with a series of peroxides at ambient temperature (**Scheme 147**). A similar reaction procedure was followed to that of the attempted amination, with the zinc species being added slowly to a stirred solution of the peroxide. However under these conditions none of the possible alkoxy triazoles were formed. Increasing the quantity of peroxide did not change the outcome of this reaction.



Scheme 147: Attempted alkoxylation of zinc species 230a with a series of peroxides

Thiolation was also considered while scoping the potential for interaction with heteroaromatic electrophiles. Attempts to quench the triazolyl-zinc reagent with disulfides proved to be unsuccessful even at high temperatures (**Table 44, Entries 1-3**). Literature has demonstrated the addition of copper and silver additives to thiolation reactions.[276-280] With this in mind further screening with silver and copper was attempted. None of the desired products were apparent on work up.

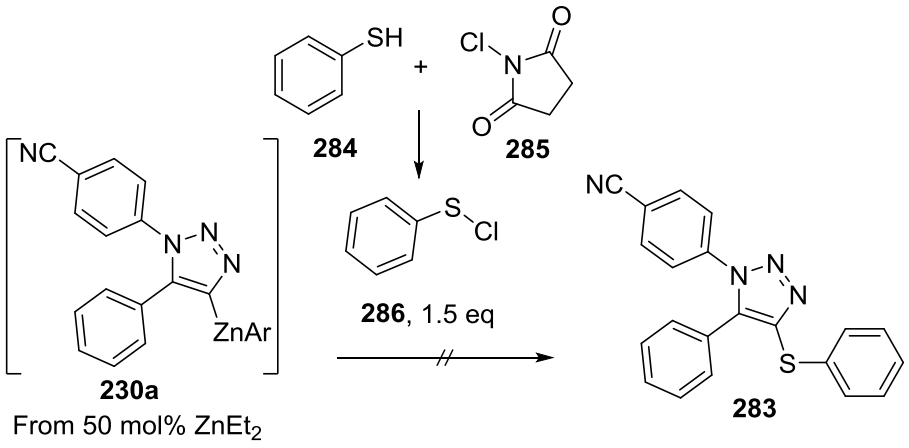
Table 44: Screening attempted for thiolation



#	Additive	Co-solvent[a]	Temp (°C)	Outcome[b]
1	-	-	RT	-[c]
2	-	-	60	-[c]
3	-	-	120	-[c]
4	$Cu(OAc)_2$ (20 mol%), AgOAc (5 mol%)	-	RT	-[c]
5	$Cu(OAc)_2$ (20 mol%), AgOAc (5 mol%)	Xylene	RT	-[c]
6	$Cu(OAc)_2$ (20 mol%), AgOAc (5 mol%)	Toluene	RT	-[c]
7	$Cu(OAc)_2$ (20 mol%), AgOAc (5 mol%)	NMP	RT	-[c]
8	$Cu(OAc)_2$ (20 mol%), AgOAc (5 mol%)	-	60	-[c]
9	$Cu(OAc)_2$ (20 mol%), AgOAc (5 mol%)	Xylene	60	-[c]
10	$Cu(OAc)_2$ (20 mol%), AgOAc (5 mol%)	Toluene	60	-[c]
11	$Cu(OAc)_2$ (20 mol%), AgOAc (5 mol%)	NMP	60	-[c]
12	CuI (20 mol%)	-	RT	-[c]
13	CuI (20 mol%)	-	60	-[c]
14	AgOAc (20 mol%)	-	RT	-[c]
15	AgOAc (20 mol%)	-	60	-[c]
16	Ag_2CO_3 (20 mol%)	-	RT	-[c]
17	Ag_2CO_3 (20 mol%)	-	60	-[c]

[a] Co-solvent added to reaction in 2:1 ratio THF:Co-solvent. [b] Reactions performed on both *para*-methyl and *para*-chloro phenyldisulfide but outcome remained same in both cases. [c] No evidence of desired product by LCMS/Crude NMR – protonated triazole only observed product.

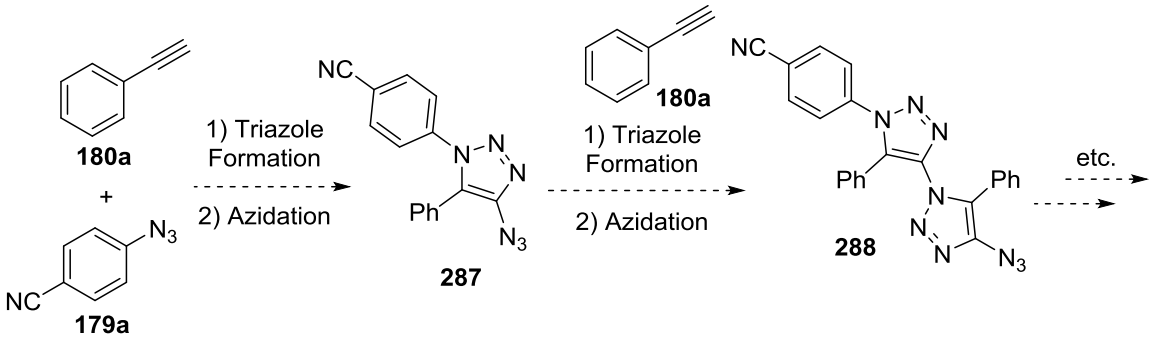
An alternative thiolation procedure was detailed by Adimurthy and co-workers in their 2014 publication. Prior combination of NCS with thiophenol results in chlorinated reagent **286** which could potentially add to the zinc species to give the desired thiolated product (**Scheme 148**).[281] This also proved to be ineffective.



Scheme 148: Attempted thiolation through the method described by Adimurthy and co-workers.

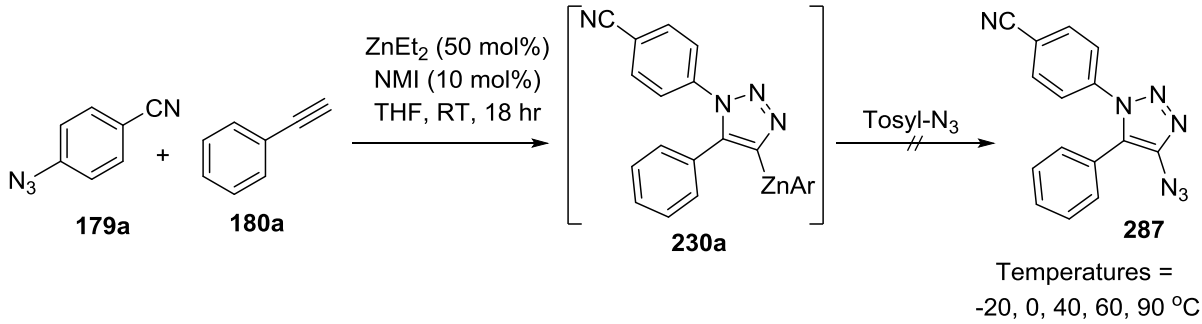
5.1.8. Azidation

The next series of reactions focussed on addition of an azide group. If successful, this could lead to a method to create chains of polycyclic structures *via* sequential triazole formation and azidation (**Scheme 149**). In terms of bioconjugation this could be seen as a way to successfully develop peptide mimics.



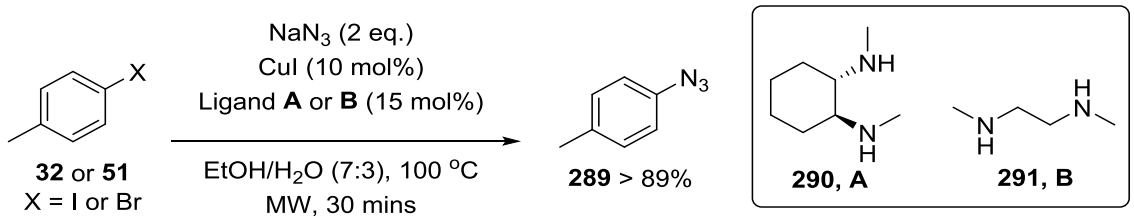
Scheme 149: Potential sequential formation of poly-cyclic structures through azidation

Attempted azidation of the triazolyl-species used tosyl-azide and was performed at a number of temperatures (**Scheme 150**). Slow addition of the zinc reagent to a solution of the tosyl-azide was also assessed. None of the desired azide product could be observed by LCMS or crude NMR.



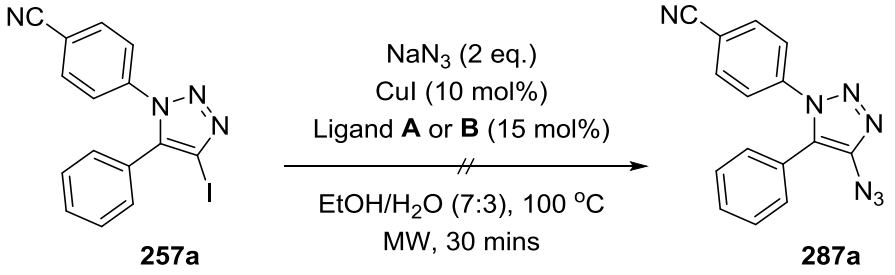
Scheme 150: Details of the attempted azidation conditions attempted with tosyl-azide

As with the fluorination/trifluoromethylation it was supposed that transformation of the 4-iodotriazole could be possible where direct azidation of the zinc species was not. No procedures are present in the literature for the conversion of a halotriazole to an azidotriazole. However conditions do exist for the conversion of aromatic halides to aromatic azides (**Scheme 151**) using sodium azide and copper catalysis.[282]



Scheme 151: Literature conditions for the conversion of aromatic halides to aromatic azides

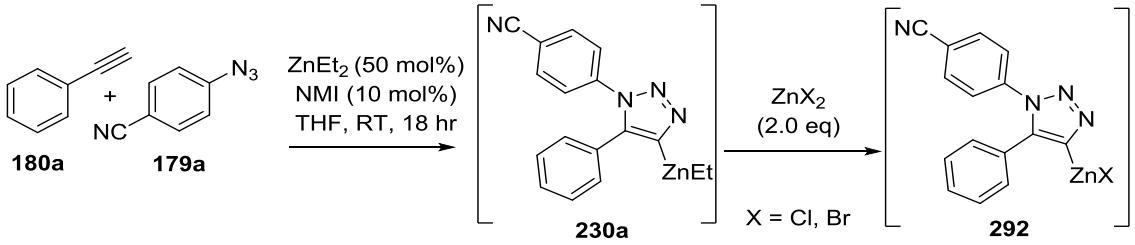
While these conditions represent the closest literature example to the proposed triazole azidation, simple haloarenes are electronically disparate from the halotriazoles used in this transformation. Consequentially attempts to adapt these conditions to the azidation of the 4-iodotriazole species failed (**Scheme 152**).



Scheme 152: Failed azidation of 4-(4-iodo-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile

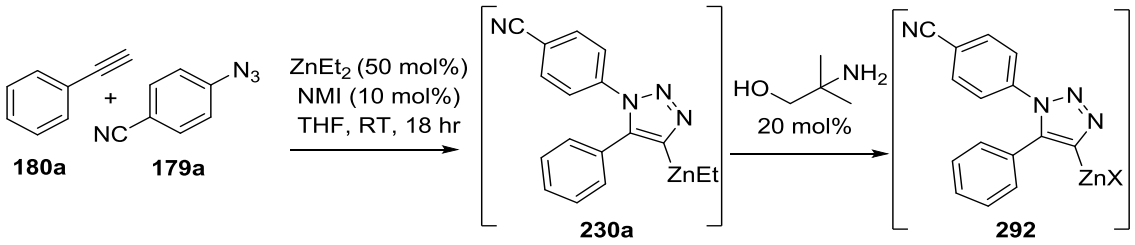
5.1.9. Activation of the zincate species

It was proposed that the issues of reactivity were the result of low nucleophilicity of the zinc species. Attempts were therefore made to activate the zinc species. Addition of zinc chloride or zinc bromide were added to the formed trizolyl-zinc species. This was in an attempt to generate the triazolyl-zinc chloride or bromide intermediate (**292**), which was envisaged as being a more nucleophilic species (**Scheme 153**).[283,284] Using this species in a number of previously failed experimental protocols (fluorination, trifluoromethylation, thiolation, amination) remained unsuccessful (**Scheme 155**).

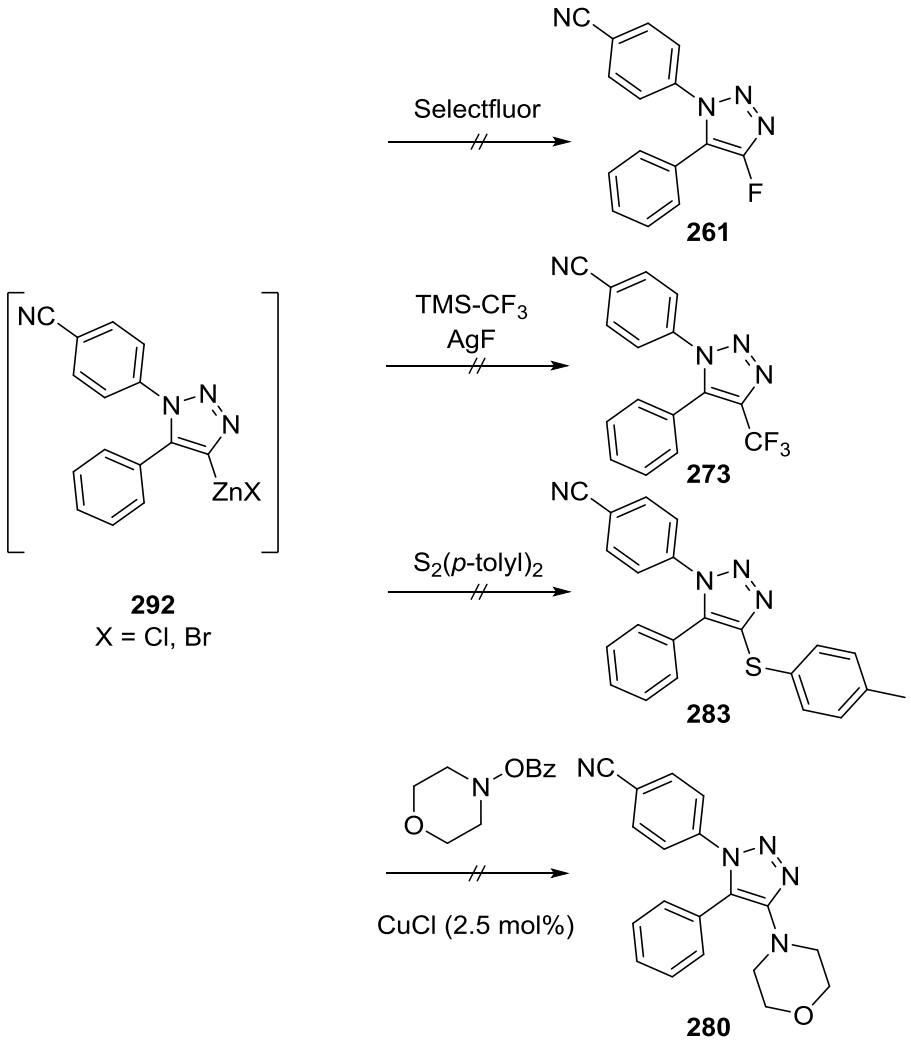


Scheme 153: Formation of triazolyl-zinc chlorides and bromides

It was also considered that using an amino-alcohol to ligate the zinc species could be possible, and could increase the nucleophilicity. 20 mol% 2-amino-2-methylpropan-1-ol was added to the triazolyl-zinc species (**Scheme 154**), and the resulting mixture was used in reactions identical to those shown in **Scheme 155**. Only the protonated triazole was observed in all of the reactions.

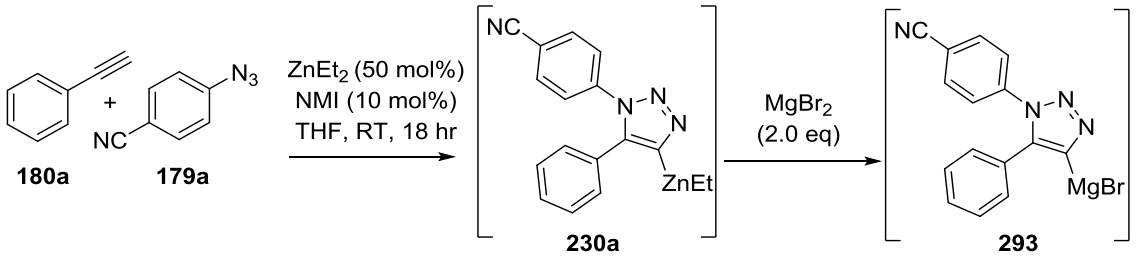


Scheme 154: Attempted ligation of the zinc reagent with 2-amino-2-methylpropan-1-ol



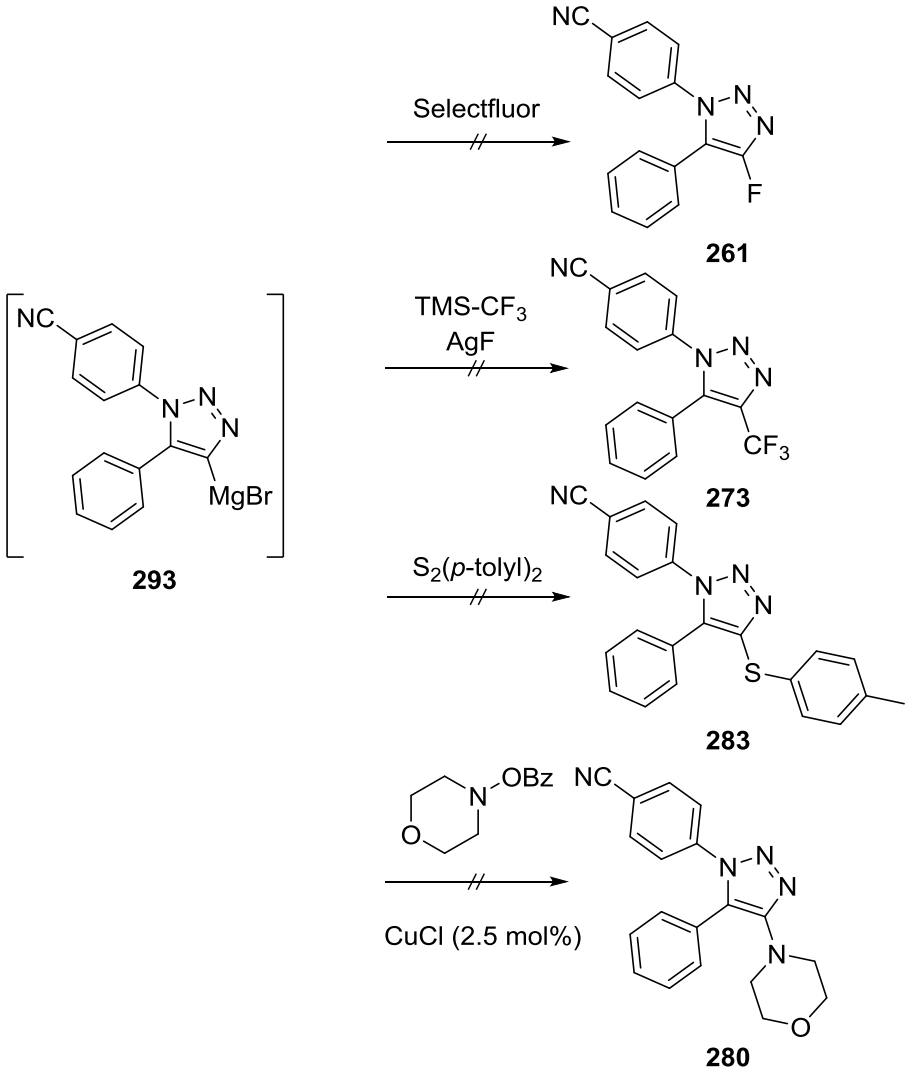
Scheme 155: Attempted usage of triazolyl-zinc chlorides and bromides in synthesis

As a final attempt to activate the nuclophilicity of the zinc species, freshly prepared magnesium bromide (from magnesium turnings and bromine) was added. This was with the aim of transmetallating the zinc species to form the magnesium species observed by Fokin and co-workers (**Scheme 156**).[219] Successful quenching of the magnesium species has been previously demonstrated, and it was hoped that this could extend the reactivity of the triazolylzinc species. While this method could potentially extend the scope of subsequent reactivity, it was considered that this could affect the substrate scope of the triazole formation. Interaction with existing unstable functional groups (carbonyls, halides etc.) which are tolerant of the zinc method could be problematic once magnesium was introduced.



Scheme 156: Attempted transmetallation of the zincated triazole to magnesium bromide

Transmetallation of the species was attempted, and the resulting reaction mixture combined with conditions for fluorination, trifluoromethylation, thiolation and amination. None of the desired products were observed, and only the protonated species was observed on work-up (**Scheme 157**).

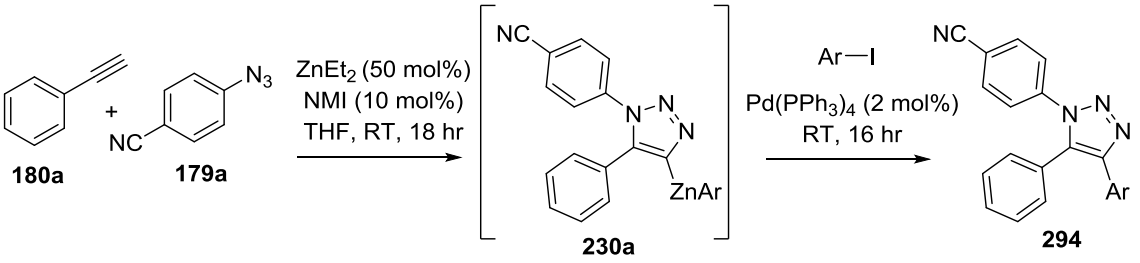


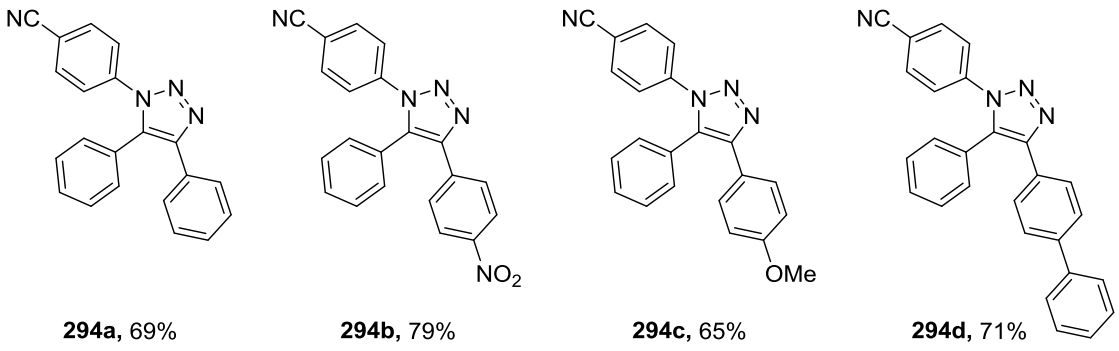
Scheme 157: Attempts to extend the reactivity of the magnesiated species

5.1.10. Negishi type cross-coupling

With the original paper detailing the successful Negishi-type cross-coupling of the triazolyl-zinc reagent with iodobenzene it was decided to explore the scope of this reaction in the synthesis of 1,4,5-substituted triazole products.[241] In the presence of 2 mol% [$Pd(PPh_3)_4$] a series of aryl iodides were successfully cross-coupled with the preformed zinc reagent at room temperature (**Table 45**). Electron-rich, electron-deficient and heterocyclic arenes were all suitable partners for the cross-coupling, representing a vast and diverse substrate scope.

Table 45: Synthesis of 1,4,5-substituted triazoles *via* Negishi-type cross-coupling with iodoarenes.





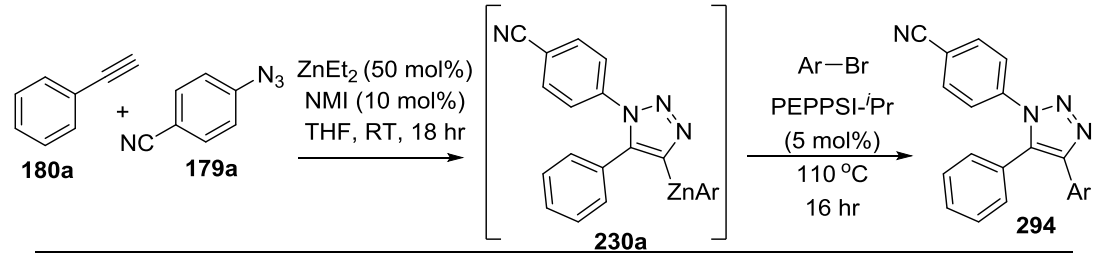
294a, 69% **294b,** 79% **294c,** 65% **294d,** 71%

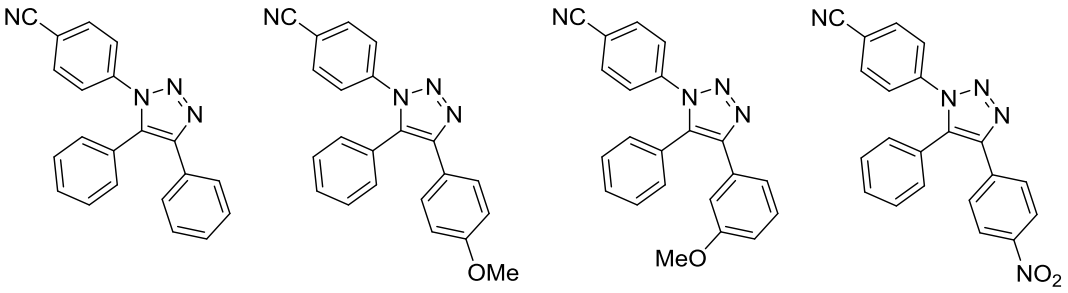
294e, 65% **294f,** 65% **294g,** 67% **294h,** 53%

Successful cross-coupling of aryl iodides led us to consider the cross-coupling of aryl bromides. This was found to require slightly more forcing conditions, with the specifically ligated PEPPSI-^{i}Pr catalyst proving most successful.[285] Temperatures of over 100 °C were required, as lower temperatures led to incomplete conversion with mixtures

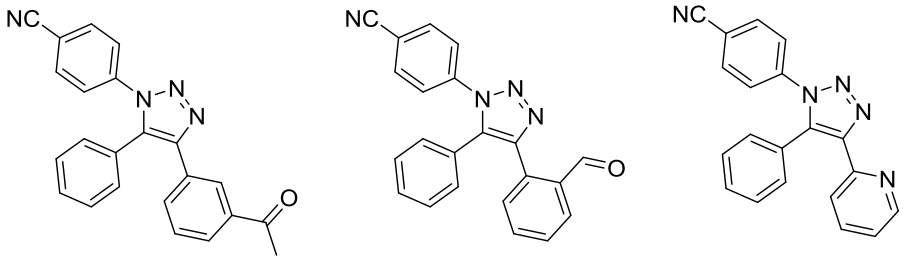
of the protonated species and the arylated species detected. As with the aryl iodides, electron-rich, electron-poor, and heterocyclic aryl bromides were all tolerated under the reaction conditions. Yields in this system remained moderate to high, and these were directly comparable with the aryl iodide analogues (e.g. the *p*-OMe example **294c**). *Ortho*-substituted species were also able to give the desired products, although yields were slightly depleted (**Table 46**).

Table 46: Synthesis of 1,4,5-substituted triazoles *via* Negishi-type cross-coupling with bromoarenes.

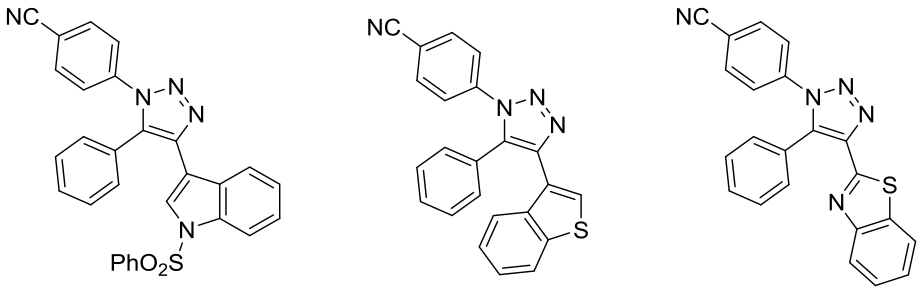




294a, 57% **294c**, 62% **294i**, 81% **294b**, 75%



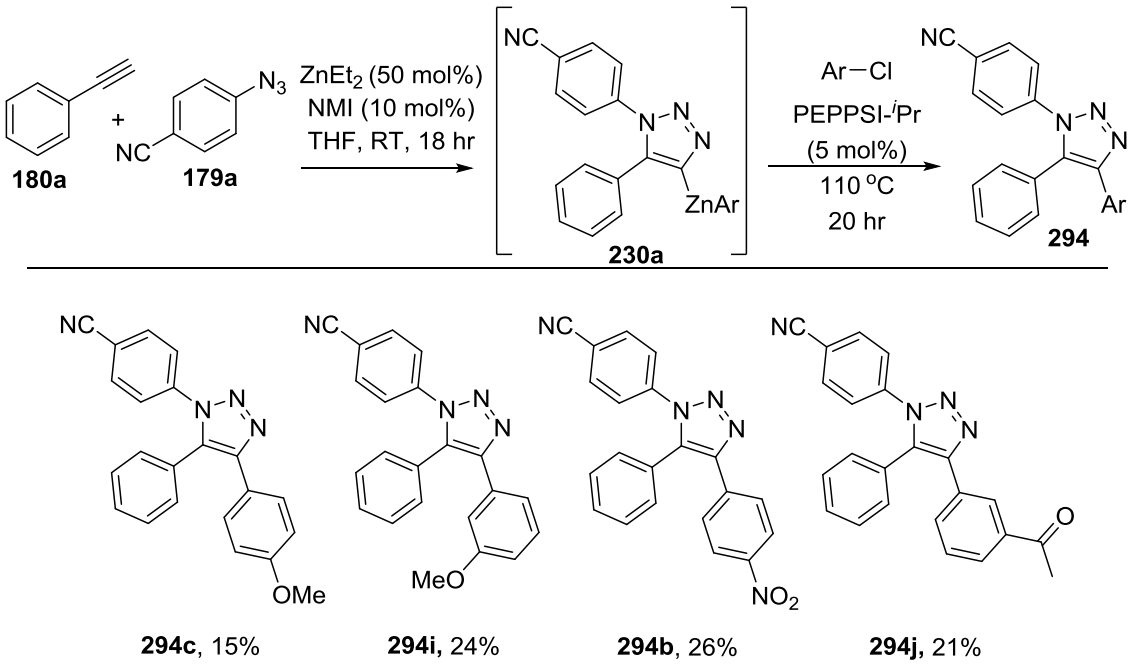
294j, 77% **294k**, 32% **294l**, 45%



294m, 67% **294n**, 72% **294o**, 77%

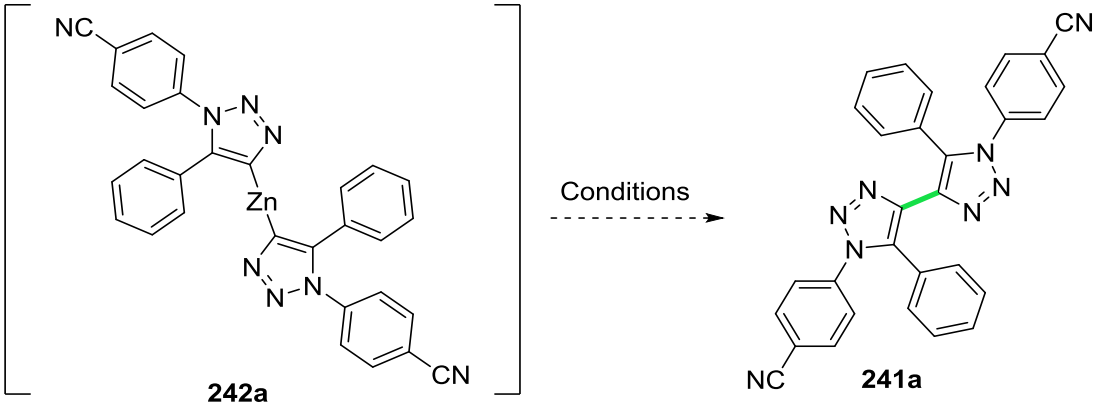
Attention was also turned to the cross-coupling of aryl-chlorides. The substrate tolerance for this was significantly lower, with arenes containing complex functional groups, or heterocyclic species failing under the reaction conditions. Yields were poor, and increasing the catalyst loading or reaction temperature resulted in no improvement (**Table 47**).

Table 47: Synthesis of 1,4,5-substituted triazoles *via* Negishi-type cross-coupling with chloroarenes.



5.1.11. Homo-dimerisation

As previously discussed results indicate that a dimeric zinc species (**242a**) is generated and then quenched to give the triazole product. It was proposed that oxidative conditions could be developed to promote reductive elimination of this species, and in doing so form the dimerised product **241a** (**Scheme 157**). Formation of this species could have potential use in transition metal chemistry as a ligand, similar to the structure of the BOX or PyBox ligands (**Figure 10**).



Scheme 157: Proposed dimerization of the intermediate zinc species

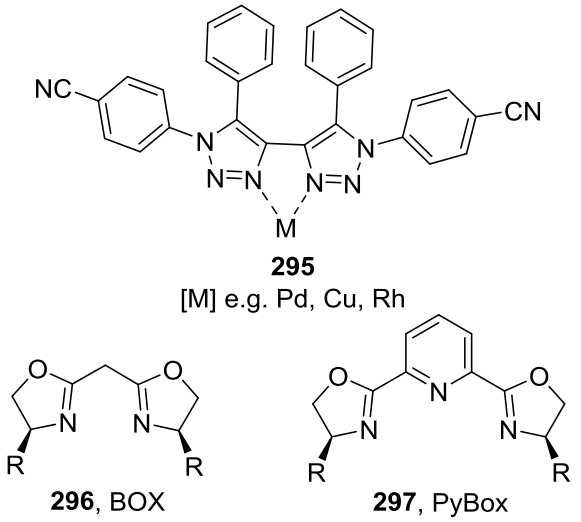
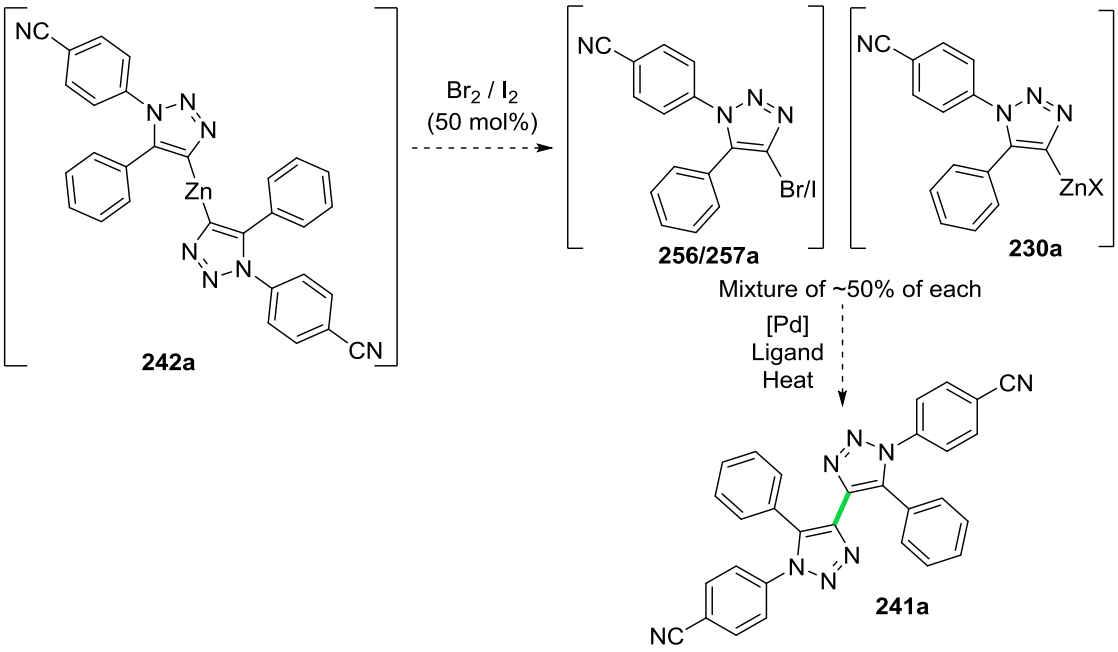


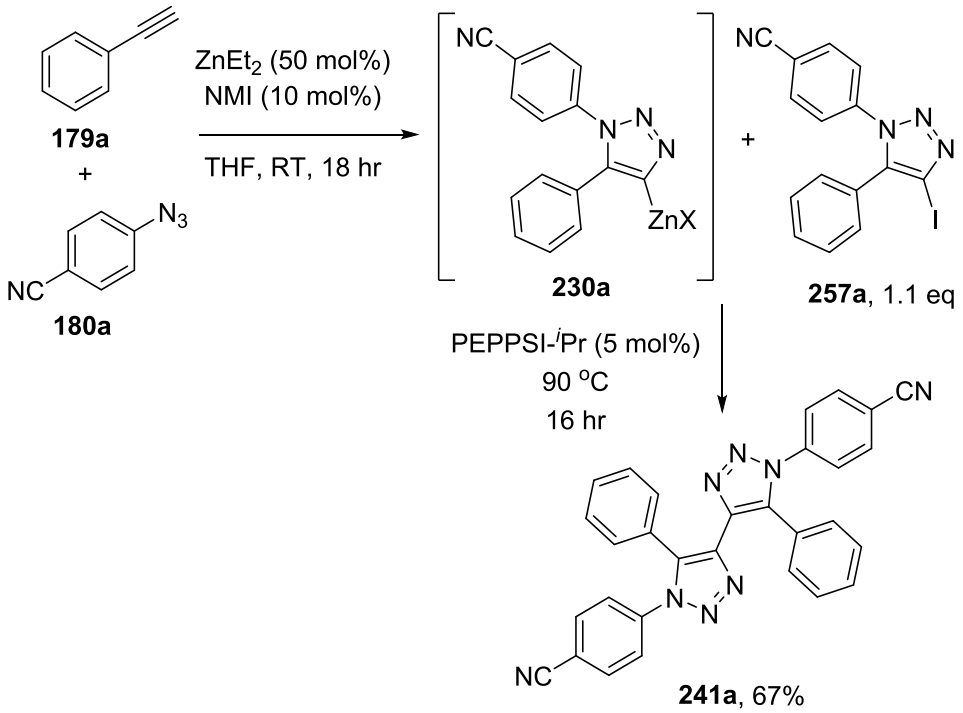
Figure 10: Dimerised triazole product similarities to the BOX or PyBox ligands

Initial reaction screening focussed on the addition of 50 mol% Br_2 or I_2 to generate half an equivalent of the bromide or iodide species *in situ*. Subsequent addition of a palladium catalyst to promote Negishi-type cross-coupling between the remaining zinc species and the iodide/bromide was hypothesised as a route to the dimerization product (**Scheme 158**).

The feasibility of this reaction was tested through the addition of an equivalent of the previously synthesised iodotriazole **257a** to the zinc reagent under palladium catalysed cross-coupling conditions. This resulted in a 67% yield of the dimerization product (**Scheme 159**).



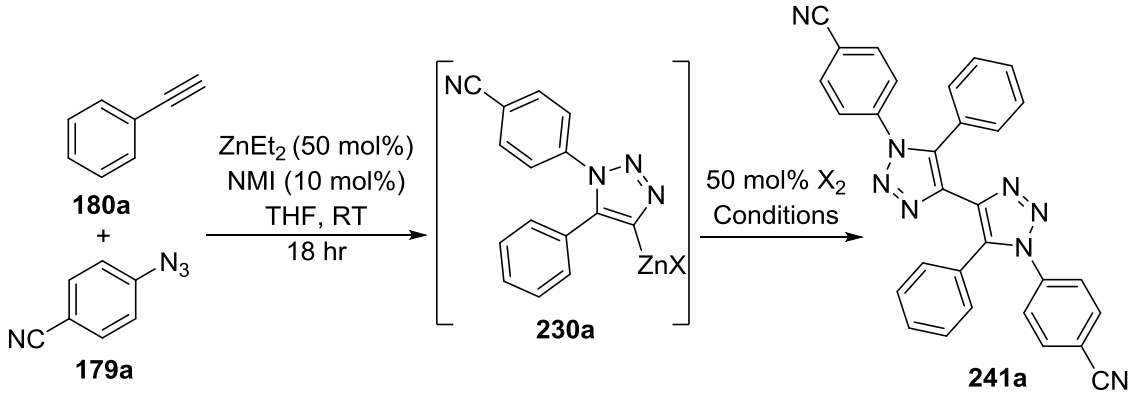
Scheme 158: First proposed route to dimerization product 241a



Scheme 159: Successful synthesis of the homocoupled product through stepwise Negishi type cross-coupling

The next step was to develop a one-pot procedure. After formation of the zinc reagent, 50 mol% iodine or bromine was added, and the resulting mixtures subjected to a series of conditions (**Table 48**). Palladium(0) and palladium(II) catalysts were used at high temperatures in the presence of ligands or oxidant additives. While trace amounts of the desired product were detected under certain conditions, only a maximum of 7% was isolated (**Table 48, Entry 9**). The iodide was more successful as an intermediate.

Table 48: Attempted dimerization of triazolyl-zinc species through one-pot Negishi cross-coupling

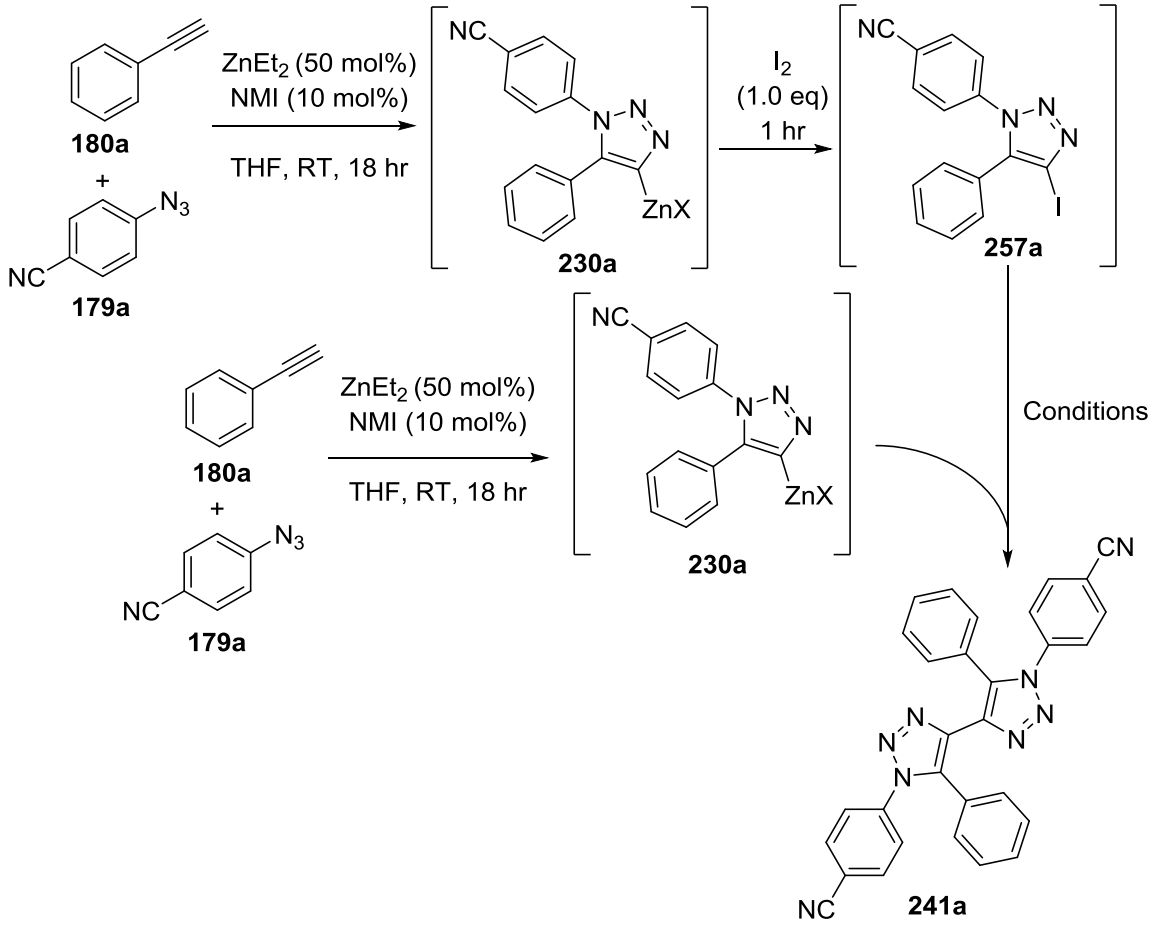


#	X_2	Pd Source (5 mol%)	Ligand (10 mol%)	Additive (1 eq)	Temp (°C)	Outcome
1	Br_2	$Pd(OAc)_2$	-	-	70/90/110	-[a]
2	Br_2	$Pd_2(dba)_3$	-	-	110	-[a]
3	Br_2	PEPPSI-^{i}Pr	-	-	110	Trace
4	Br_2	$Pd(OAc)_2$ $PdCl_2$	Cy-RuPhos XantPhos DPPF	-	110	-[a]
5	Br_2	$Pd_2(dba)_3$	Cy-RuPhos XantPhos DPPF	$Cu(OAc)_2$ $K_2S_2O_8$	110	-[a]
6	Br_2	PEPPSI-^{i}Pr	-	$Cu(OAc)_2$ $K_2S_2O_8$	90/110	-[a]
7	I_2	$Pd(OAc)_2$ $PdCl_2$	-	-	70/90/110	-[a]
8	I_2	$Pd_2(dba)_3$	-	-	110	Trace
9	I_2	PEPPSI-^{i}Pr	-	-	110	13%
10	I_2	$Pd(OAc)_2$ $PdCl_2$	Cy-RuPhos XantPhos DPPF	-	110	-[a]
11	I_2	$Pd_2(dba)_3$	Cy-RuPhos XantPhos DPPF	$Cu(OAc)_2$ $K_2S_2O_8$	110	Trace
12	I_2	PEPPSI-^{i}Pr		$Cu(OAc)_2$ $K_2S_2O_8$	110	Trace

[a]No evidence of desired product by LCMS/Crude NMR

It was proposed that slow addition of the zinc reagent to the unpurified iodide could also demonstrate a "one-pot" reaction by only requiring one purification of the final product (**Table 49**). Generation of the iodotriazole *in situ*, and slow addition of a second amount of the zinc reagent did improve the yield to 21% (**Table 49, Entry 3**).

Table 49: Conditions for the attempted dimerization of 1,5-substituted triazoles through *in situ* formation of the triozyl-iodide



#	Conditions	Temp (°C)	Outcome
1	$Pd(OAc)_2$ (5 mol%)	110	Trace
2	$Pd_2(dba)_3$ (5 mol%)	110	- [a]
3	PEPPSI-^{i}Pr (5 mol%)	110	21%
4	PEPPSI-^{i}Pr (5 mol%)	90	Trace
5	$Pd(OAc)_2$ (5 mol%), Cy-RuPhos (10 mol%)	110	- [a]
6	$Pd(OAc)_2$ (5 mol%), Xantphos (10 mol%)	110	Trace
7	$Pd(OAc)_2$ (5 mol%), DPPF (10 mol%)	110	Trace

Literature from Studer and co-workers demonstrated the oxidative homo-dimerization of magnesium reagents under oxidative conditions with TEMPO or copper salts.[286] Oxidative conditions were applied to our reaction system, and while there was no desired dimerization observed with TEMPO, in the presence of copper(II) a moderate yield of the dimerized product was formed (**Table 50**). Further screening demonstrated that copper(I) salts were not suitable, and that the nature of the copper(II) species did have some effect. $CuCl_2$ gave the highest yield (**Table 50, Entry 2**). Reducing the stoichiometry of the copper species caused a reduction of yield, however this effect was overcome with an increase in temperature. With 70 mol% $CuCl_2$ the yield was improved to 48% in 10 hours. Heating slightly to 40 °C not only enhanced the yield to 72%, it also reduced the reaction time to 4 hours (**Table 50, Entry 10**). Further increase in temperature was detrimental, as was a further increase in the stoichiometry of the copper(II) species. This is potentially caused by increased coordination of the dimerized species to the copper (in a similar manner to that shown in **Figure 10**) causing precipitation of this complex and preventing full isolation.

The optimized conditions for this reaction represent a mild and operationally simple method of generating a complex molecule in high yield (72%). The geometry of the isolated product has been confirmed by X-ray crystallography (**Figure 11**), clearly showing the bond between the 4 positions of the 2 triazoles, resulting in a symmetrical molecule with both triazoles retaining the initial 1,5-substitution pattern. The molecule appears to crystalise as a trimer. Development of the scope of this reaction would be necessary prior to publication and this is currently being undertaken.

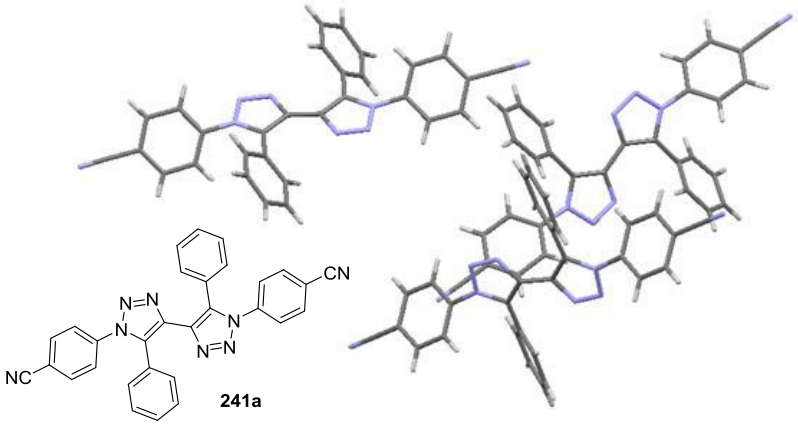
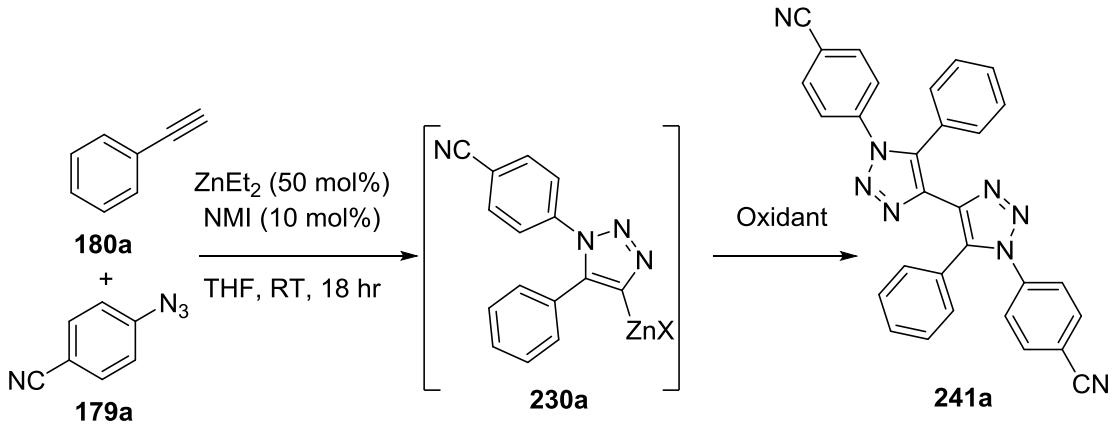


Figure 11: Crystallographic analysis of 241a

Table 50: Conditions for the attempted dimerization of 1,5-substituted triazoles under oxidative conditions



#	Oxidant (eq)	Temp (°C)	Outcome
1	TEMPO (1 eq)	RT	- [a]
2	$CuCl_2$ (50 mol%)	RT	41%
3	$CuBr_2$ (50 mol%)	RT	11%
4	$Cu(OAc)_2$ (50 mol%)	RT	38%
5	CuI (50 mol%)	RT	- [a]
6	CuBr (50 mol%)	RT	- [a]
7	$CuCl_2$ (20 mol%)	RT	37%
8	$CuCl_2$ (20 mol%)	70	49%
9	$CuCl_2$ (70 mol%)	RT	48%
10	$CuCl_2$ (70 mol%)	40	72%
11	$CuCl_2$ (70 mol%)	70	68%
12	$CuCl_2$ (70 mol%)	110	64%
13	$CuCl_2$ (1.0 eq)	40	57%
14	$CuCl_2$ (1.0 eq)	70	52%
15	$CuCl_2$ (1.2 eq)	70	20%

[a]No evidence of desired product by LCMS/Crude NMR

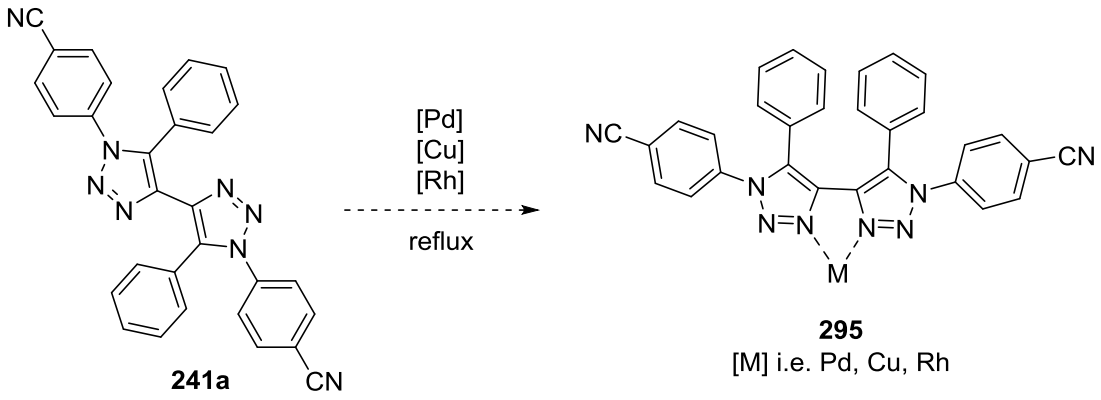
5.2. Summary

A significant addition to the regioselective formation of 1,5-substituted 1,2,3-triazoles has been presented. This method has proved successful across a wide range of azido/alkynyl substrates. Additionally, the 4-position can be further functionalised through the intermediate aryl-zinc to accommodate a diverse three-component coupling strategy, allowing for the synthesis of a diverse set of novel compounds. The scope of halides accessible through this methodology has been significantly developed. While the addition of other heteroatoms remains elusive at this point, there is potential for further development in this area. Negishi type cross-coupling reactions have proven vastly successful with the ability to generate a varied selection of 4-aryl substituted 1,5-triazoles. Successful dimerization of the triazole moiety has been optimised to high yields, allowing for future development of the scope of this reaction to be considered.

The inherently benign nature and efficient construction of these triazoles makes this protocol ideal for both library synthesis and the late stage functionalisation of complex molecules. Equally, the procedure is operationally straightforward, cost effective and eminently scalable. For these reasons it is expected to be of interest across the chemical community.

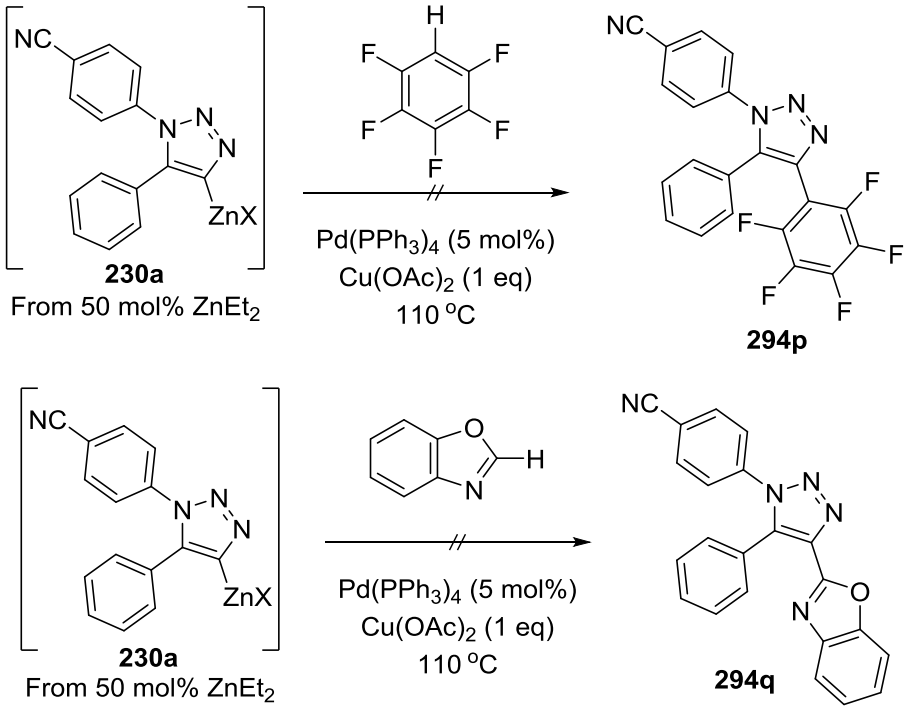
5.3. Potential further development

It has already been noted that further advances are currently being made in the scope of the homo-dimerisation of the heteroaromatic zinc reagent. Of particular interest here would be to synthesise stoichiometric metal complexes of the dimerised product in order to demonstrate the species as a potential ligand in organometallic chemistry. Refluxing the species with a stoichiometric equivalent of copper or palladium (or another metal) could lead to co-ordination with the metal centre. Precipitation and characterisation of the resulting complex could provide evidence for the utility of this species as a ligand (**Scheme 160**).



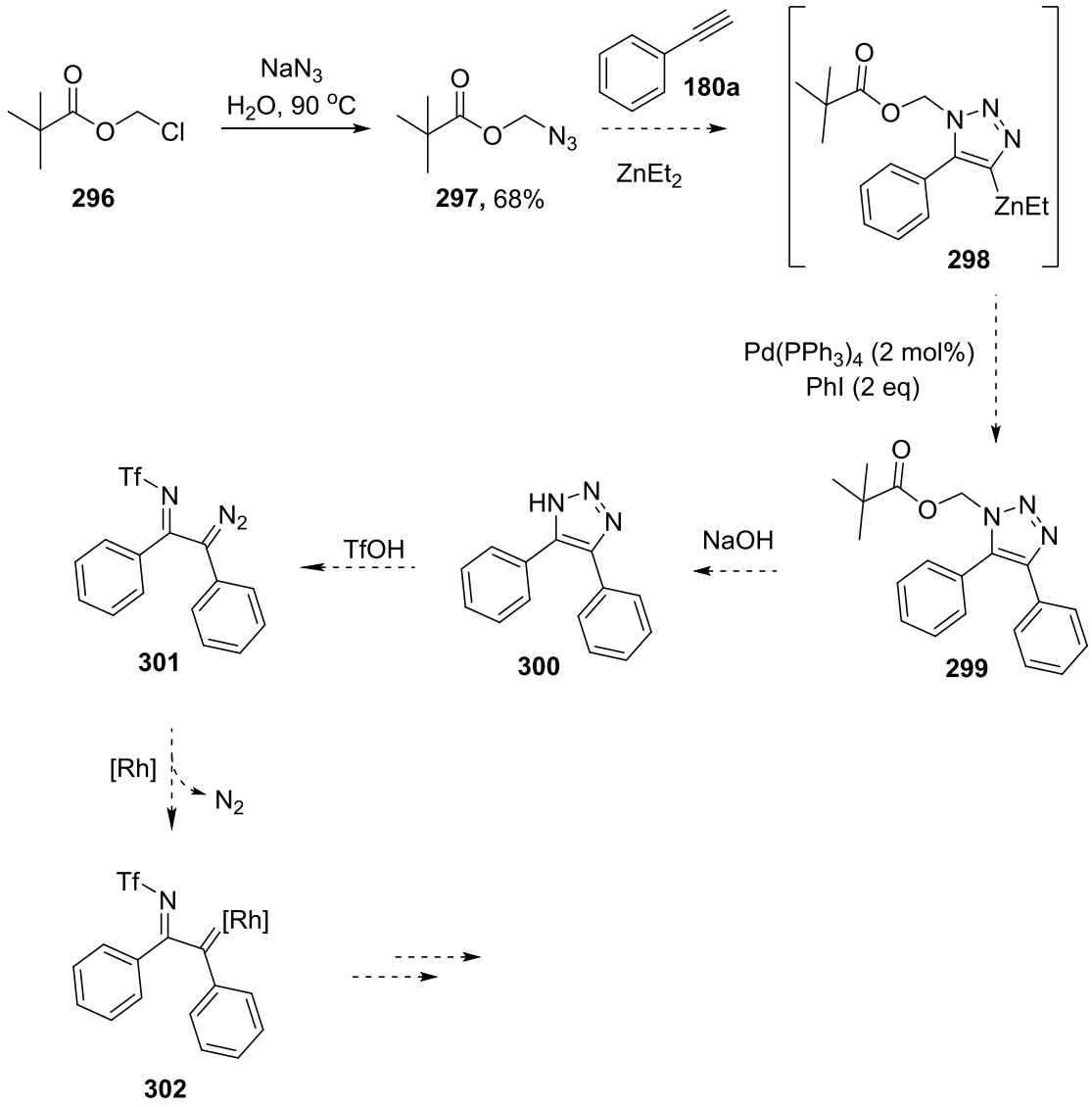
Scheme 160: Potential co-ordinaction of species 241a to metal centres

With the successful Negishi-type cross-coupling fully developed, there is potential to turn attention to combining C–H activation with the zinc-species in the synthesis of 1,4,5-substituted products. Test reactions using perfluorobenzene and benzoxazole have been tried, however this was without success. Palladium catalysed cross-coupling conditions with a stoichiometric oxidant and the pre-formed zinc species were used, however there would be substantial room for optimisation around this method (**Scheme 161**).



Scheme 161: Synthesis of 1,4,5-substituted triazoles using C–H activation

Another potential direction for this research would be in the synthesis of 4,5-substituted 1,2,3-triazoles. This could be performed through the generation of an azide component with a removable protecting group. This idea was briefly considered using pivaloylazide **297**, which is synthesised directly from the commercially available pivaloylchloride **296**. It was proposed that synthesis of the 1,5-triazole from this azide, and subsequent Negishi-type coupling would lead to intermediate **299** which could undergo base mediated deprotection to give the 4,5-substituted triazole **300**. This would then lead to interesting possibilities using Boyer's rearrangement chemistry with rhodium (**Scheme 162**).[287,288] Unfortunately the initial triazole synthesis was not productive on the first attempt, however there is potential for further investigation of this reaction. Another potential protecting group for the azide which could be removed after triazole formation would be *para*-methoxybenzene. However again, initial triazole generation with this azide has shown to be an issue and this would require further development.



Scheme 162: Potential further work to the synthesis and use of 1,4-substituted triazoles

There are many other envisaged opportunities for development of this methodology. Addition to a wide range of electrophilic species has not yet been considered - i.e. diazoniums, isocyanates, isothiocyanates and phosphines. Similarly the scope of the reactivity with acid chlorides and aldehydes (which was demonstrated in the initial publication) has not been fully developed. This methodology is proving to be beneficial for developing a large synthetic library of novel compounds.

6. Experimental

6.1. General procedures

All reactions were carried out under a nitrogen atmosphere unless otherwise stated. Glassware for inert atmosphere reactions was oven-dried and cooled under a flow of nitrogen. Tetrahydrofuran (THF) was distilled over sodium wire and benzophenone . CH_2Cl_2, toluene, di-*iso*-propylamine (DIPA) and triethylamine were distilled over calcium hydride, and dimethyl formamide (DMF) was dried over activated molecular sieves. Benzoquinone was recrystallised from toluene prior to use. All other solvents and reagents were purchased from commercial sources and used as supplied, including anhydrous solvents in sure seal bottles. Compositions of solvent mixtures are quoted as ratios of volume. 'Ether' refers to diethyl ether. 'Petrol' refers to a fraction of light petroleum, b.p. 60–80 ˚C, unless indicated otherwise.

^{1}H NMR spectra were recorded on a 300, 400, or 500 MHz spectrometer; ^{13}C NMR spectra were recorded at 75, 101 or 126 MHz; ^{19}F NMR spectra were recorded at 376 or 471 MHz. Chemical shift values are reported in parts per million (ppm) relative to the solvent signal and were determined in $CDCl_3$ unless otherwise specified, with coupling constant (*J*) values reported in Hz. The ^{1}H data is presented as follows: chemical shift (in ppm on the δ scale), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), the coupling constant (*J*, in Hertz Hz), integration and assignment. The ^{13}C data is recorded as the ppm on the δ scale. ^{19}F data is presented as follows: chemical shift (in ppm on the δ scale), multiplicity/coupling constant (where appropriate) and assignment. For multiplets and overlapping signals a range of shifts is reported. NMR spectra were assigned with the aid of 2-D correlation and DEPT-135 spectra where appropriate. Low resolution and high resolution mass spectra were obtained using either positive and/or negative electrospray ionisation (ES), electron impact ionisation (EI) or chemical ionisation (CI) techniques. Melting points were measured on a variable heater apparatus and are uncorrected. IR spectra were recorded on an ATR FTIR spectrometer as evaporated films (from $CHCl_3$) or neat. For compounds **101a** to **101i** signals are reported for the C=O stretches in the 1600-2000 cm^{-1} region. For other spectra where IR data were appropriate all notable signals are reported.

Reactions were monitored by LCMS on an Agilent 1200 series fitted with a 3.0 x 20 mm, C18, 3.0 µm column, and mass analysis performed by a single quadrupole Agilent 6100,

with ESI ionisation. Standard run conditions were a 4 minute gradient cycle with two solvents, H_2O with 0.2% formic Acid, and 9:1 Methanol:IPA with 0.2% formic acid. TLC analysis was carried out on aluminium sheets coated with silica gel 60 Å F254, 0.2 mm thickness. Plates were viewed using 254 nm ultraviolet light and/or dipped in aqueous potassium permanganate , *p*-anisaldehyde or phosphomolybdic acid . The compounds were purified by flash chromatography using Merck Kieselgel 60 (mesh size 220 – 240) silica under positive pressure.

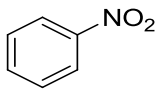
6.2. Chapter 1: Carboxylate directed decarboxylative *ortho*-arylation

6.2.1. General procedures for the protodecarboxylation of benzoic acids

Copper catalysed method[57] A solution of benzoic acid (0.50 mmol), $Cu(OAc)_2$ (18.0 mg, 0.10 mmol), and 1,10-phenanthroline (9 mg, 0.05 mmol) in DMF (1 ml) and NMP (1 ml) was stirred in a sealed tube under nitrogen for 16 hrs at 120 °C. Reaction completion was monitored by TLC (10 : 1, Hex : EtOAc). The reaction mixture was diluted with EtOAc (10 ml), washed with H_2O (3 x 10 ml) and brine (2 x 10 ml), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by silica gel chromatography (10 : 1, Hex : EtOAc) yielded the product.

Silver catalysed method[72] A solution of benzoic acid (0.50 mmol) and Ag_2CO_3 (14.0 mg, 0.05 mmol) in anhydrous DMSO (2.5 ml) was stirred in a sealed tube for 16 hrs at 120 °C. Reaction completion was monitored by TLC (10 : 1, Hex : EtOAc). The reaction mixture was partitioned with diethyl ether (10 ml) and aq. $NaHCO_3$ (10 ml) and the organic layer washed sequentially with aq. $NaHCO_3$ (2 x 10 ml) and brine (2 x 10 ml). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by silica gel chromatography (10 : 1 Hex : EtOAc) yielded the product.

General procedure for attempted decarboxylative ortho-arylation of benzoic acids (equivalents / additives / temperature specific to tables in R&D) A microwave tube charged with decarboxylating benzoic acid (1 eq, 0.40 mmol), C–H acid/carboxylate (1.5 eq, 0.60 mmol) palladium species, copper/silver species, and any additives was sealed, evacuated and filled with nitrogen (x 3). Solvent was added (total volume 3 ml) *via* syringe and the reaction stirred in a preheated oil bath for 16 hours. Reactions were monitored by TLC and LCMS. Where work up was necessary, reactions were diluted with EtOAc (10 ml) and washed with H_2O (3 x 10 ml) and brine (2 x 10 ml), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification was performed by silica gel chromatography (20 : 1 to 10 : 1 Hex : EtOAc).



Nitrobenzene (19a) was prepared in accordance with the general procedure from decarboxylation of 2-nitrobenzoic acid (84 mg, 0.50 mmol) and isolated as a yellow oil from the copper (47 mg, 0.38 mmol, 78%) and silver (50 mg, 0.41 mmol, 82%) methods.

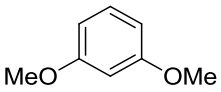
19a was also prepared in accordance with the general procedure for the attempted decaboxylative arylation of nitrobenzoic acid (67 mg, 0.40 mmol) with benzoic acid (73 mg, 0.60 mmol). With the inclusion of $Pd(OAc)_2$ (9 mg, 0.04 mmol) and CuBr (57 mg, 0.40 mmol) in DMF (3 ml) at 130 °C. the product was isolated as a yellow oil (34 mg, 0.27 mmol, 68%).

19a was also prepared in accordance with the general procedure for the attempted decaboxylative arylation of nitrobenzoic acid (67 mg, 0.40 mmol) with benzoic acid (73 mg, 0.60 mmol). With the inclusion of $Pd(OAc)_2$ (9 mg, 0.04 mmol) and Ag_2CO_3 (110 mg, 0.40 mmol) in DMF (3 ml) at 130 °C, the product was isolated as a yellow oil (31 mg, 0.25 mmol, 63%).

19a was also prepared in accordance with the general procedure for the attempted decaboxylative arylation of nitrobenzoic acid (67 mg, 0.40 mmol) with benzoic acid (73 mg, 0.60 mmol). With the inclusion of $Pd(OAc)_2$ (9 mg, 0.04 mmol) and Ag_2CO_3 (330 mg, 1.20 mmol) in DMF (3 ml) at 130 °C, the product was isolated as a yellow oil (15.5 mg, 0.12 mmol, 31%).

19a was also prepared in accordance with the general procedure for the copper catalysed decaboxylation of 4-nitrobenzoic acid (84 mg, 0.50 mmol). Inclusion of 4,7-diphenyl-1,10-phenanthroline (17 mg, 0.05 mmol) and $Cu(OAc)_2$ (27 mg, 0.15 mmol) in NMP (1.5 ml) and quinoline (0.5 ml) at 170 °C gave the product as a yellow oil (15.5 mg, 0.12 mmol, 31%).

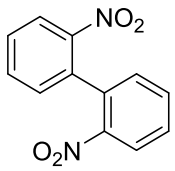
^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = δ 8.21 (d, J = 8.2 Hz, 2H, Ar-H), 7.69 (t, J = 7.4 Hz, 1H, Ar-H), 7.53 (t, J = 8.0 Hz, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm = 148.4 (qC), 134.7 (CH), 129.4 (2 x CH), 123.6 (2 x CH); Consistent with literature.[72]



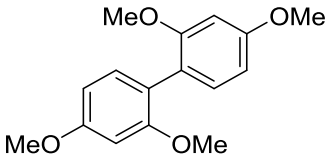
1,3-Dimethoxybenzene (**19f**) was prepared in accordance with the general procedure for the decarboxylation of 2,4-dimethoxybenzoic acid (91.0 mg, 0.50 mmol) under silver catalysed conditions with AgOAc (8.5 mg, 0.05 mmol) and K_2CO_3 (2.9 mg, 0.15 mmol) in NMP (2.0 ml) and isolated as a clear liquid (38.0 mg, 0.28 mmol, 56%).

19f was also prepared in accordance with the general procedure for the decarboxylation of 2,4-dimethoxybenzoic acid (91.0 mg, 0.50 mmol) under silver catalysed conditions with Ag_2CO_3 (481 mg, 1.75 mmol), PCy_3 (140 mg, 0.50 mmol) and K_3PO_4 (106 mg, 0.50 mmol) in DMSO/1,4-dioxane (1:4 ratio by volume, 2 ml) at 140 °C. The product was isolated as a clear liquid (30.0 mg, 0.22 mmol, 44%).

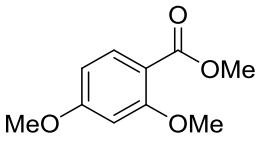
^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.19 (t, *J* = 8.2 Hz, 1H, Ar-H), 6.52 (dd, *J* = 8.2, 2.4 Hz, 2H, Ar-H), 6.48 (t, *J* = 2.4 Hz, 1H, Ar-H), 3.80 (s, 6H, 2 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 160.9 (2 x qC), 129.8 (CH), 106.1 (2 x CH), 100.4 (CH), 55.0 (2 x OCH_3); Consistent with literature.[72]



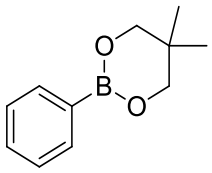
2,2'-Dinitro-1,1'-biphenyl (**80a**) was isolated, as by-product from the attempted decaboxylative arylation of nitrobenzoic acid (67 mg, 0.40 mmol) with benzoic acid (73 mg, 0.60 mmol) with the inclusion of $Pd(OAc)_2$ (9 mg, 0.04 mmol) and Ag_2CO_3 (330 mg, 1.20 mmol) in DMF (3 ml) at 130 °C. The dimer was isolated as an orange oil (19 mg, 0.07 mmol, 28%); ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm = 8.23 (dd, *J* = 8.2, 1.2 Hz, 2H, Ar-H), 7.69 (td, *J* = 7.6, 1.2 Hz, 2H, Ar-H), 7.60 (ddd, *J* = 8.2, 7.6, 1.4 Hz, 2H, Ar-H), 7.30 (dd, *J* = 7.6, 1.4 Hz, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm = 147.2 (2 x qC), 134.2 (2 x qC), 133.4 (2 x CH), 130.9 (2 x CH), 129.2 (2 x CH), 124.8 (2 x CH); Consistent with literature.[89]



2,2',4,4'-Tetramethoxy-1,1'-biphenyl (80b) was synthesised as by-product from the decarboxylation of 2,4-dimethoxybenzoic acid (91.0 mg, 0.50 mmol) *via* the general silver catalysed procedure, with inclusion of AgOAc (8.5 mg, 0.50 mmol) and K_2CO_3 (2.9 mg, 0.15 mmol) in NMP (2.0 ml), and was isolated as a clear liquid (16.2 mg, 0.06 mmol, 12%); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.74 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.47 – 6.42 (m, 4H, Ar-H), 3.91 (s, 6H, 2 x OCH_3), 3.82 (s, 6H, 2 x OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 163.9 (2 x qC), 161.0 (2 x qC), 131.3 (2 x CH), 107.6 (2 x CH), 105.5 (2 x qC), 100.7 (2 x CH), 55.5 (2 x CH_3), 55.3 (2 x CH_3); Consistent with literature.[289]



Methyl 2,4-dimethoxybenzoate (157) was synthesised as by-product from the decarboxylation of 2,4-dimethoxybenzoic acid (91.0 mg, 0.50 mmol) *via* the general silver catalysed procedure, with inclusion of AgOAc (8.5 mg, 0.05 mmol) and K_2CO_3 (2.9 mg, 0.15 mmol) in NMP (2 ml), and was isolated as a clear liquid (7.0 mg, 0.036 mmol, 7%); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.84 (dd, *J* = 7.7, 1.4 Hz, 1H, Ar-H), 6.51 – 6.44 (m, 2H, Ar-H), 3.88 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 166.2 (qC), 164.4 (qC), 161.4 (qC), 134.0 (CH), 112.4 (qC), 104.6 (CH), 99.1 (CH), 56.1 (CH_3), 55.6 (CH_3), 51.8 (CH_3); Consistent with literature.[290]



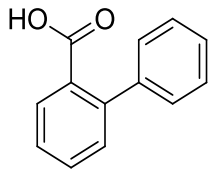
5,5-Dimethyl-2-phenyl-1,3,2-dioxaborinane (65) was prepared in accordance with literature.[291] A solution of phenyl boronic acid (310 mg, 5.00 mmol) and 2,2-dimethyl-1,3-propanediol (312 mg, 6.00 mmol) in Et_2O (7 ml), was stirred at room temperature for 6 hrs. The reaction mixture was washed with H_2O (2 x 5 ml) dried, filtered, and the solvent removed under reduced pressure. No further purification was undertaken. **65** was isolated as a white solid (684 mg, 3.6 mmol, 72%); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.88 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.48 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.41 (t, *J* = 7.4 Hz, 2H, Ar-H), 3.82 (s, 4H, 2 x CH_2), 1.07 (s, 6H, 2 x CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm = 134.0 (2 x CH), 130.8 (CH), 127.7 (2 x CH), 72.4 (2 x CH_2), 32.0 (qC), 22.0 (2 x CH_3) (C-B Not observed); Consistent with literature.[291]

6.2.2. General procedures for *ortho*-activation of benzoic acids

Daugulis procedure 1[134] An oven dried vessel charged with benzoic acid (49 mg, 0.40 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol) and AgOAc (85 mg, 0.52 mmol) was sealed and flushed with nitrogen. To this was added an aryl iodide (0.80 mmol, 2 eq) in AcOH (200 μL). The vessel was placed in a preheated oil bath at 130 °C and stirred for 7 hours. The mixture was diluted with CH_2Cl_2 (10 ml), filtered through celite, and the solvent removed under reduced pressure. The residue was suspended in $KOH_{(aq)}$ (2 M, 5 ml) and washed with CH_2Cl_2 (2 x 5 ml). The aqueous layer was acidified with $HCl_{(aq)}$ (2 M, to ph 2) and back extracted with CH_2Cl_2 (3 x 5 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification was performed by silica gel chromatography (93:5:2, Hex:EtOAc:AcOH, to 83:15:2, Hex:EtOAc:AcOH).

Daugulis procedure 2[134] An oven dried vessel charged with benzoic acid (61 mg, 0.50 mmol), $Pd(OAc)_2$ (6.0 mg, 0.025 mmol), PCy_3 (14 mg, 0.05 mmol), Cs_2CO_3 (357 mg, 1.10 mmol) and 4 Å molecular sieves (100 mg) was sealed, evacuated and backfilled with nitrogen (x 3). To this was added an aryl chloride (2.00 mmol, 4 eq) in anhydrous DMF (2.5 ml). The reaction was stirred for 2 hours at room temperature, then placed in a preheated oil bath at 145 ^{O}C and stirred for 16 hours. The mixture was diluted with CH_2Cl_2 (10 ml), filtered through celite, and the solvent removed under reduced pressure. The residue was suspended in $NaOH_{(aq)}$ (2 M, 5 ml) and washed with Et_2O (3 x 5 ml). The aqueous layer was acidified with $HCl_{(aq)}$ (2 M, to ph 2) and back extracted with EtOAc (3 x 5 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by silica gel chromatography (92:6:2, Hex:EtOAc:AcOH, to 83:15:2, Hex:EtOAc:AcOH).

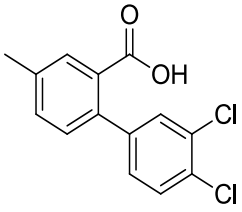
Yu Proceedure[135] A large oven dried microwave tube was charged with benzoic acid (37 mg, 0.30 mmol), *ortho*-toluic acid (41 mg, 0.30 mmol) or *meta*-toluic acid (41 mg, 0.30 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), benzoquinone (16 mg, 0.15 mmol), Ag_2CO_3 (82 mg, 0.30 mmol), K_2HPO_4 (78 mg, 0.45 mmol) and either methyl boronic acid (54.0 mg, 0.90 mmol), phenyl boronic acid (36 mg, 0.30 mmol) or boronate ester (85 mg, 0.45 mmol), sealed, evacuated and back filled with nitrogen (x 3). ^{t}BuOH (1.5 ml) was added by syringe, and the reaction placed in a preheated oil bath at 120 ^{o}C and stirred for 16 hours. The reaction mixture was basified with $NaOH_{(aq)}$ (2 M) and ^{t}BuOH was removed under reduced pressure. The aqueous solution was washed with Et_2O (3 x 5 ml), acidified with $HCl_{(aq)}$ (1 M) and back extracted with EtOAc (3 x 7 ml). The combined organic layers were washed with brine (2 x 5 ml), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Purification performed by silica gel chromatography (92:6:2, Hex:EtOAc:AcOH, to 83:15:2, Hex:EtOAc:AcOH).



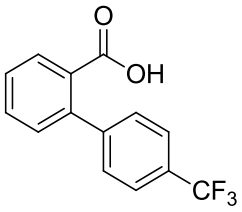
1,1'-Biphenyl-2-carboxylic acid (138b) was prepared according to Daugulis procedure 1 with iodobenzene (90 μL, 0.80 mmol) to afford **138b** as a white solid (9 mg, 0.045 mmol, 11%).

138b was also prepared in accordance with general Yu conditions from benzoic acid (37 mg, 0.30 mmol) and boronate ester **65** (85 mg, 0.45 mmol). Isolation from starting material was not possible; 55% conversion determined by ^{1}H NMR.

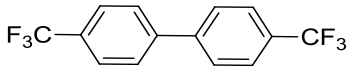
^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.95 (dd, *J* = 7.8, 1.2 Hz, 1H, Ar-H), 7.56 (td, *J* = 7.6, 1.4 Hz, 1H, Ar-H), 7.46 -7.31 (m, 7H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 173.0 (CO_2H), 143.4 (qC), 141.0 (qC), 132.1 (CH), 131.2 (CH), 130.7 (CH), 129.3 (qC), 128.5 (2 x CH), 128.1 (2 x CH), 127.4 (CH), 127.2 (CH); Consistent with literature.[134]



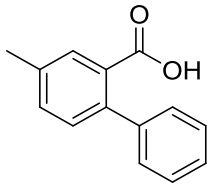
3',4'-Dichloro-4-methyl-[1,1'-biphenyl]-2-carboxylic acid (138d) was prepared according to Daugulis procedure 1 with *meta*-toluic acid (68 mg, 0.50 mmol) and 1,2-dichloro-4-iodobenzene (270 mg, 1.00 mmol) to afford **138d** as a white solid (74 mg, 0.27 mmol, 53%); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.87 (d, *J* = 0.7 Hz, 1H, Ar-H), 7.46 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.43 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.42 (dd, *J* = 7.8, 1.1 Hz, 1H, Ar-H), 7.23 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.16 (dd, *J* = 8.2, 2.1 Hz, 1H, Ar-H), 2.47 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm = 173.2 (CO_2H), 141.3 (qC), 138.6 (qC), 138.1 (qC), 133.4 (CH), 132.1 (qC), 131.8 (CH), 131.5 (qC), 131.2 (CH), 130.5 (CH), 130.0 (CH), 128.6 (qC), 128.3 (CH), 21.1 (CH_3); Consistent with literature.[134]



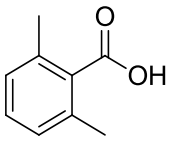
4'-(Trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid (138e) was prepared in accordance with Daugulis procedure 2, with 1-chloro-4-(trifluoromethyl)benzene (360 mg, 2.00 mmol) and was isolated as a white solid (23 mg, 0.36 mmol, 18%); ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm = 8.02 (dd, *J* = 7.8, 1.1 Hz, 1H, Ar-H), 7.63 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.59 (dd, *J* = 7.6, 1.3 Hz, 1H, Ar-H), 7.48 (td, *J* = 7.7, 1.1 Hz, 1H, Ar-H), 7.42 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.33 (dd, *J* = 7.6, 1.0 Hz, 1H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm = 172.5 (qC), 145.0 (qC), 142.4 (qC), 132.6 (CH), 131.3 (qC), 131.3 (CH), 129.7 (CH), 129.6 (q, *J* = 32.5 Hz, qC), 129.0 (2 x CH), 128.1 (CH), 125.1 (q, *J* = 3.8 Hz, 2 x CH), 124.4 (q, *J* = 272.0 Hz, CF_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ ppm = -62.4; Consistent with literature.[292]



4,4'-*bis*(Trifluoromethyl)-1,1'-biphenyl (152) was prepared in accordance with general Daugulis procedure 2, with 1-chloro-4-(trifluoromethyl)benzene (360 mg, 2.00 mmol), as an isolated by-product as a white solid (28 mg, 0.10 mmol, 10%); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.74 (d, *J* = 8.5 Hz, 4H, Ar-H), 7.70 (d, *J* = 8.5 Hz, 4H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 130.45 (d, *J* = 32.6 Hz), 126.11 (q, *J* = 3.7 Hz), 124.25 (d, *J* = 272.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ ppm = -62.6; Consistent with literature.[293]

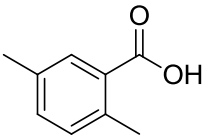


4-Methyl-[1,1'-biphenyl]-2-carboxylic acid (138g) was prepared in accordance with general Yu conditions from *meta*-toluic acid (41 mg, 0.30 mmol) and boronate ester **65** (85 mg, 0.45 mmol) and isolated as an off white solid (10 mg, 0.05 mmol, 16%); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.75 (s, 1H, Ar-H), 7.39 – 7.30 (m, 6H, Ar-H), 7.26 (d, *J* = 7.8 Hz, 1H, Ar-H), 2.43 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 173.0 (qC), 141.1 (qC), 140.7 (qC), 137.2 (qC), 133.0 (CH), 131.3 (2 x CH), 129.2 (qC), 128.7 (2 x CH), 128.2 (2 x CH), 127.3 (CH), 21.0 (CH_3); Consistent with literature.[142]



2,6-Dimethylbenzoic acid (141a) was prepared in accordance with general Yu conditions from *ortho*-toluic acid (41 mg, 0.30 mmol) and methyl boronic acid (54 mg, 0.90 mmol). Isolation from starting material not possible; 60% conversion determined by ^{1}H NMR; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.23 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.08 (d, *J* = 7.7 Hz, 2H, Ar-H), 2.45 (s, 6H, 2 x CH_3). ^{13}C not performed as pure product not isolated. Consistent with literature.[135]

[*Ortho*-toluic acid: ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.09 (dd, *J* = 8.3, 1.4 Hz, 1H, Ar-H), 7.46 (td, *J* = 7.5, 1.4 Hz, 1H, Ar-H), 7.29 (t, *J* = 7.2 Hz, 2H, Ar-H), 2.68 (s, 3H, CH_3)].

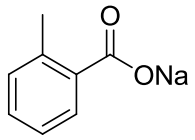


2,5-Dimethylbenzoic acid (141b) was prepared under general Yu conditions from *meta*-toluic acid (41 mg, 0.30 mmol) and methyl boronic acid (54 mg, 0.90 mmol). Isolation from starting material not possible; 40% conversion determined by ^{1}H NMR; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.90 (d, *J* = 1.3 Hz, 1H, Ar-H), 7.29 (dd, *J* = 7.7, 1.6 Hz, 1H, Ar-H), 7.19 (d, *J* = 7.8 Hz, 1H, Ar-H), 2.64 (s, 3H, CH_3), 2.39 (s, 3H, CH_3). ^{13}C not performed as pure product not isolated. Consistent with literature.[291]

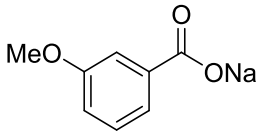
[*Meta*-toluic acid: ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.96 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.46 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.40 (t, *J* = 7.7 Hz, 1H, Ar-H), 2.46 (s, 3H, CH_3).

6.2.3. General procedure for preparation of sodium benzoates. [142]

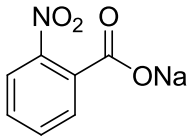
1 M ethanolic NaOH was added dropwise over 1 hour to a stirred solution of benzoic acid (1 eq) in ethanol (1 M solution) and the resulting suspension stirred for 2 hours at room temperature. The suspension was filtered and the solid washed with ethanol and ice-cold ether and dried under high vacuum. Where necessary, if precipitation did not occur, the ethanol was removed *in vacuo* and the white solid suspended in ether before filtration. No further purification of the product was required. Data for products is consistent with known literature.



Sodium 2-methylbenzoate 155a was prepared from 2-methylbenzoic acid (4.09 g, 30.00 mmol) and NaOH (1.20 g, 30.00 mmol) in accordance with the general procedure to give a white solid (3.21 g, 20.00 mmol, 68%); ^{1}H NMR (500 MHz, CD_3OD): δ ppm = 7.44 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.09 - 7.20 (m, 3H, Ar-H), 2.46 (s, 3H, CH_3); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 178.9 (CO_2Na), 142.0 (qC), 136.1 (qC), 131.3 (CH), 129.2 (CH), 128.3 (CH), 126.3 (CH), 20.7 (CH_3).



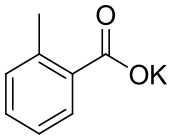
Sodium 3-methoxybenzoate 155b was prepared from 3-methoxybenzoic acid (4.56 g, 30.00 mmol) and NaOH (1.20 g, 30.00 mmol) in accordance with the general procedure to give a white solid (2.59 g, 15.00 mmol, 50%); ^{1}H NMR (500 MHz, CD_3OD): δ ppm = 7.49 - 7.56 (m, 2H, Ar-H), 7.25 (t, *J* = 8.0 Hz, 1H, Ar-H), 6.96 (dd, *J* = 8.0, 1.7 Hz, 1H, Ar-H), 3.81 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 175.5 (CO_2Na), 160.9 (qC), 140.7 (qC), 129.8 (CH), 122.8 (CH), 117.5 (CH), 115.3 CH), 55.8 (CH_3).



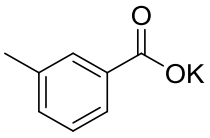
Sodium 2-nitrobenzoate 155c was prepared from 2-nitrobenzoic acid (5.01 g, 30.00 mmol) and NaOH (1.20 g, 30.00 mmol) in accordance with the general procedure to give an off white solid (5.54 g , 29.00 mmol, 97%); ^{1}H NMR (500 MHz, CD_3OD): δ ppm = 7.81 (dd, *J* = 8.2, 1.0 Hz, 1H, Ar-H), 7.55 (td, *J* = 7.5, 1.2 Hz, 1H, Ar-H), 7.48 (dd, *J* = 7.5, 1.4 Hz, 1H, Ar-H), 7.38 ppm (ddd, *J* = 8.2, 7.5, 1.4 Hz, 1H, Ar-H); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 174.1 (CO_2Na), 148.0 (qC), 138.6 (qC), 134.4 (CH), 129.7 (CH), 129.6 (CH), 124.6 (CH).

6.2.4. General procedure for the preparation of potassium benzoates[62]

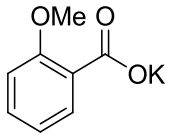
A solution of KO^{t}Bu (1 eq) in ethanol (1 M solution) was added dropwise over 1 hour to a stirred solution of benzoic acid (1 eq) in ethanol (1 M solution) and the resulting suspension stirred for 2 hours at room temperature. The suspension was filtered and the solid washed with ethanol and ice cold ether and dried under high vacuum. No further purification of the product was required. Data for products is consistent with known literature.[62]



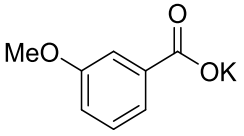
Potassium 2-methylbenzoate 156a was prepared from 2-methylbenzoic acid (10.23 g, 75.00 mmol) and KO^{t}Bu (8.42 g, 75.00 mmol) in accordance with the general procedure to give a white solid (12.38 g, 71.00 mmol, 95%); ^{1}H NMR (500 MHz, CD_3OD): δ ppm = 7.42 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.08 - 7.20 (m, 3H, Ar-H), 2.45 (s, 3H, CH_3); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 179.0 (CO_2K), 142.4 (qC), 135.9 (qC), 131.3 (CH), 129.1 (CH), 128.2 (CH), 126.3 (CH), 20.7 (CH_3).



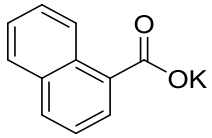
Potassium 3-methylbenzoate 156b was prepared from 3-methoxybenzoic acid (2.00 g, 14.00 mmol) and KO^{t}Bu (1.57 g, 14.00 mmol) in accordance with the general procedure as a white solid (2.29 g, 12.00 mmol, 78 %); ^{1}H NMR (400 MHz, CD_3OD): δ ppm = 7.79 (s, 1H, Ar-H), 7.75 (d, *J* = 6.3 Hz, 1H, Ar-H), 7.19 - 7.27 (m, 2H, Ar-H), 2.35 (s, 3H CH_3); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 176.0 (CO_2K), 139.2 (qC), 138.5 (CH), 132.0 (CH), 131.0 (CH), 128.8 (qC), 127.5 (CH), 21.6 (CH_3).



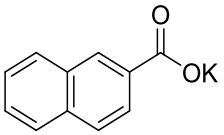
Potassium 2-methoxybenzoate 156c was prepared from 2-methoxybenzoic acid (2.13 g, 14.00 mmol) and KO^{t}Bu (1.57 g, 14.00 mmol) in accordance with the general procedure to give a white solid (2.58 g, 13.58 mmol, 97%); ^{1}H NMR (500 MHz, CD_3OD): δ ppm = 7.40 (dd, *J* = 7.4, 1.6 Hz, 1H, Ar-H), 7.26 (ddd, *J* = 8.3, 7.4, 1.6 Hz, 1H, Ar-H), 6.97 (d, *J* = 8.3 Hz, 1H, Ar-H), 6.89 (t, *J* = 7.4 Hz, 1H, Ar-H), 3.82 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 176.8 (CO_2K), 157.8 (qC), 132.0 (qC), 130.5 (CH), 129.5 (CH), 121.2 (CH), 112.6 (CH), 56.1 (OCH_3).



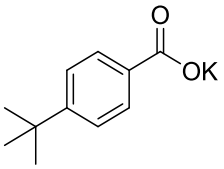
Potassium 3-methoxybenzoate 156d was prepared from 3-methoxybenzoic acid (2.13 g, 14.00 mmol) and KO^{t}Bu (1.57 g, 14.00 mmol) in accordance with the general procedure as a white solid (2.18 g, 11.50 mmol, 82%); ^{1}H NMR (400 MHz, CD_3OD): δ□ppm = 7.54 (d, *J* = 5.3 Hz, 2H , Ar-H), 7.27 (t, *J* = 7.8 Hz, 1H, Ar-H), 6.98 (d, *J* = 8.1 Hz, 1H, Ar-H), 3.83 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 175.4 (CO_2K), 160.8 (qC), 140.7 (qC), 129.8 (CH), 122.7 (CH), 117.3 (CH), 115.3 (CH), 55.8 (OCH_3).



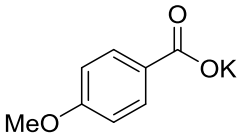
Potassium 1-naphthoate 156e was prepared from 1-naphthoic acid (1.72 g, 10.00 mmol) and KO^{t}Bu (1.21 g, 10.00 mmol) in accordance with the general procedure as a white solid (1.81 g, 8.60 mmol, 86%); ^{1}H NMR (400 MHz, CD_3OD): δ ppm = 8.47 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.83 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.67 (dd, *J* = 7.1, 1.0 Hz, 1H, Ar-H), 7.41 - 7.51 (m, 3H, Ar-H); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 178.1 (CO_2K), 140.4 (qC), 135.3 (qC), 131.8 (CH), 129.7 (CH), 129.2 (CH), 127.9 (CH), 127.0 (CH), 126.8 (CH), 126.2 (CH), 126.0 (qC).



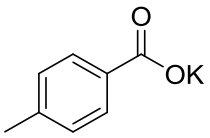
Potassium 2-naphthoate 156f was prepared from 2 naphthoic acid (1.72 g, 10.00 mmol) and KO^{t}Bu (1.21 g, 10.00 mmol) in accordance with the general procedure as a white solid (1.49 g, 7.10 mmol, 71%); ^{1}H NMR (400 MHz, CD_3OD): δ ppm = 8.47 (s, 1H, Ar-H), 8.04 (dd, *J* = 8.6, 1.5 Hz, 1H, Ar-H), 7.93 (d, *J* = 7.1 Hz, 1H, Ar-H), 7.80 - 7.89 (m, 2H, Ar-H), 7.44 - 7.54 (m, 2H, Ar-H); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 175.5 (CO_2K), 136.5 (qC), 136.0 (CH), 134.4 (CH), 130.3 (CH), 130.0 (CH), 128.6 (qC), 128.2 (CH), 127.9 (qC), 127.5 (CH), 127.0 (CH).



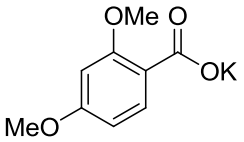
Potassium 4-(*tert*-butyl)benzoate 156g was prepared from 4-(*tert*-butyl)benzoic acid (2.51 g, 14.00 mmol) and KO^{t}Bu (1.57 g, 14.00 mmol) in accordance with the general procedure as a white solid (2.82 g, 13.00 mmol, 93%); ^{1}H NMR (400 MHz, CD_3OD): δ ppm = 7.89 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.42 (d, *J* = 8.6 Hz, 2H, Ar-H), 1.35 (s, 9H, 3 x CH_3); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 175.6 (CO_2K), 154.9 (qC), 136.0 (qC), 130.3 (2 x CH), 125.8 (2 x CH), 35.7 (qC), 31.9 (3 x CH_3).



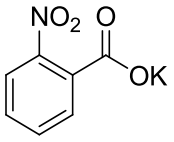
Potassium 4-methoxybenzoate 156h was prepared from 4-methoxybenzoic acid (2.19 g, 14.00 mmol) and KO^{t}Bu (1.57 g, 14.00 mmol) in accordance with the general procedure as a white solid (2.29 g, 12.00 mmol, 86%); ^{1}H NMR (400 MHz, CD_3OD): δ ppm = 7.92 (d, *J* = 9.1 Hz, 2H, Ar-H), 6.89 (d, *J* = 9.1 Hz, 2H, Ar-H), 3.83 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 175.5 (CO_2K), 163.0 (qC), 132.2 (2 x CH), 131.4 (qC), 113.9 (2 x CH), 55.8 (OCH_3).



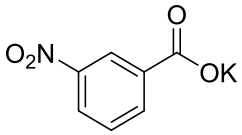
Potassium 4-methylbenzoate 156i was prepared from 4-methylbenzoic acid (1.90 g, 14.00 mmol) and KO^{t}Bu (1.57 g, 14.00 mmol) in accordance with the general procedure as a white solid (2.30 g, 13.20 mmol, 94%); ^{1}H NMR (400 MHz, CD_3OD): δ ppm = 7.84 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.16 (d, *J* = 8.1 Hz, 2H, Ar-H), 2.35 (s, 3H, CH_3); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 175.9 (CO_2K), 141.6 (qC), 136.5 (qC), 130.5 (2 x CH), 129.5 (2 x CH), 21.5 (CH_3).



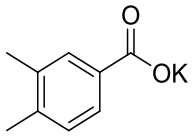
Potassium, 2,4-dimethoxybenzoate 156j was prepared from 2,4-dimethoxybenzoic acid (2.54 g, 14.00 mmol) and KO^{t}Bu (1.57 g, 14.0.0 mmol) in accordance with the general procedure to give a white solid (2.62 g, 11.90 mmol, 85%); ^{1}H NMR (500 MHz, CD_3OD): δ ppm = 7.48 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.51 (d, *J* = 2.2 Hz, 1H, Ar-H), 6.46 (dd, *J* = 8.4, 2.3 Hz, 1H, Ar-H), 3.81 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 176.3 (CO_2K), 163.0 (qC), 160.0 (qC), 131.9 (CH), 123.7 (qC), 105.3 (CH), 99.7 (CH), 56.0 (OCH_3), 55.9 (OCH_3).



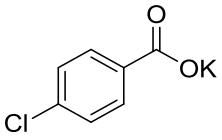
Potassium 2-nitrobenzoate 156k was prepared from 2-nitrobenzoic acid (5.01 g, 30.00 mmol) and KO^{t}Bu (3.36 g, 30.00 mmol) in accordance with the general procedure to give a white solid (5.73 g, 28.00 mmol, 93%); ^{1}H NMR (500 MHz, CD_3OD): δ ppm = 7.91 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.64 (td, *J* = 7.5, 1.0 Hz, 1H, Ar-H), 7.58 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar-H), 7.48 (ddd, *J* = 8.2, 7.5, 1.0 Hz, 1H, Ar-H); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 174.1 (CO_2K), 148.0 (qC), 138.6 (qC), 134.4 (CH), 129.7 (CH), 129.6 (CH), 124.6 (CH).



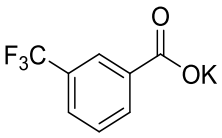
Potassium 3-nitrobenzoate 156l was prepared from 3-nitrobenzoic acid (1.17 g, 7.00 mmol) and KO^{t}Bu (0.79 g, 7.00 mmol) in accordance with the general procedure as a white solid (0.96 g, 4.70 mmol, 67%); ^{1}H NMR (400 MHz, CD_3OD): δ ppm = 8.77 (t, *J* = 2.3 Hz, 1H, Ar-H), 8.31 (dt, *J* = 8.1, 1.3 Hz, 1H, Ar-H), 8.27 (ddd, *J* = 8.1, 2.3, 1.3 Hz, 1H, Ar-H), 7.61 (t, *J* = 8.1 Hz, 1H, Ar-H); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 172.2 (CO_2K), 149.4 (qC), 141.4 (qC), 136.2 (CH), 130.1 (CH), 125.7 (CH), 124.9 (CH).



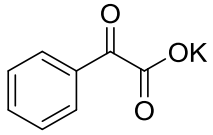
Potassium 3,4-dimethylbenzoate 156m was prepared from 3,4-dimethylbenzoic acid (375 mg, 2.50 mmol) and KO^{t}Bu (0.30 g, 2.50 mmol) in accordance with the general procedure as a white solid (414 mg, 2.20 mmol, 67%); ^{1}H NMR (400 MHz, CD_3OD): δ ppm = 7.78 (s, 1H, Ar-H), 7.73 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.21 (d, *J* = 7.9 Hz, 1H, Ar-H), 2.32 (s, 3H, CH_3), 2.31 (s, 3H, CH_3); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 175.6 (CO_2K), 140.5 (qC), 137.0 (CH), 136.2 (qC), 131.7 (CH), 130.2 (CH), 128.1 (qC), 20.0 (CH_3), 19.9 (CH_3).



Potassium 4-chlorobenzoate 156n was prepared from 4-chlorobenzoic acid (0.41 g, 2.60 mmol) and KO^{t}Bu (0.31 g, 2.60 mmol) in accordance with the general procedure as a white solid (403 mg, 2.10 mmol, 79%); ^{1}H NMR (400 MHz, CD_3OD): δ ppm = 7.91 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.34 (d, *J* = 8.6 Hz, 2H, Ar-H); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 174.1 (CO_2K), 137.8 (qC), 137.3 (qC), 131.9 (2 x CH), 128.9 (2 x CH).



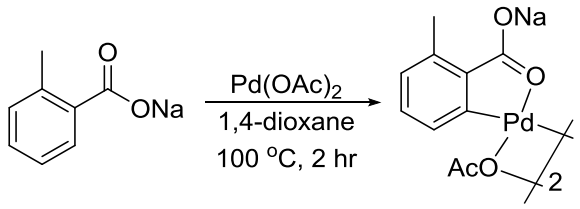
Potassium 3-(trifluoromethyl)benzoate 156o was prepared from 3-(trifluoromethyl)benzoic acid (0.95 g, 5.00 mmol) and KO^{t}Bu (0.60 g, 5.00 mmol) in accordance with the general procedure as a white solid (1.06 g, 4.60 mmol, 92%); ^{1}H NMR (400 MHz, CD_3OD): δ ppm = 8.15 (s, 1H, Ar-H), 8.08 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.59 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.45 (t, *J* = 7.8 Hz, 1H, Ar-H); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 173.29 (CO_2K), 140.19 (qC), 133.81 (CH), 131.20 (q, *J* = 31.4 Hz, qC), 129.70 (CH), 127.74 (q, *J* = 3.7 Hz, CH), 127.01 (q, *J* = 4.6 Hz, CH).



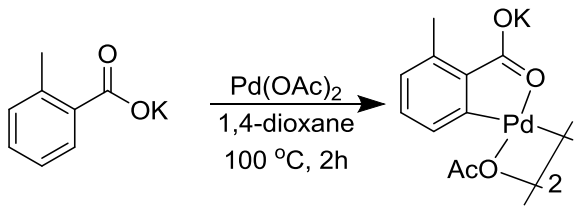
Potassium 2-oxo-2-phenylacetate 109a was prepared from phenylglyoxylic acid (1.05 g, 7.00 mmol) and KO^{t}Bu (0.79 g, 7.00 mmol) in accordance with the general procedure as a white solid (938 mg, 5.00 mmol, 71%); ^{1}H NMR (400 MHz, CD_3OD): δ ppm = 7.99 (dd, *J* = 8.6, 1.4 Hz, 2H, Ar-H), 7.62 (tt, *J* = 7.6, 1.4 Hz, 1H, Ar-H), 7.51 (t, *J* = 7.6 Hz, 2H, Ar-H); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 199.7 (C=O), 176.3 (CO_2K), 137.5 (qC), 137.4 (CH) 133.2 (2 x CH), 132.3 (2 x CH).

6.2.5. Procedure for synthesis of stoichiometric palladium complexes

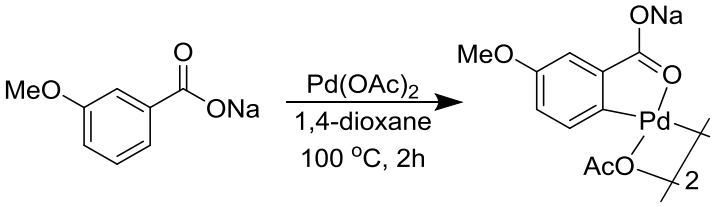
Procedure is from literature.[142] Palladium acetate (112.0 mg, 0.50 mmol) was added to a suspension of the relevant benzoate (0.50 mmol) in 1,4-dioxane (5 mL) and heated to 100 °C for 2 h. The reaction mixture was filtered, the dark residue was washed with CH_2Cl_2 (3 × 5 mL) and dried under vacuum to yield the palladacycle.



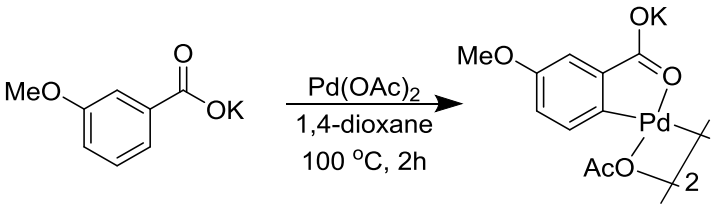
Palladacycle 154b was prepared in accordance with the general procedure from sodium *ortho*-toluate (79 mg, 0.50 mmol, to give the desired product as a dark brown solid (238 g, 0.37 mmol, 74%); ν_{max} / cm^{-1} 3424w (br), 1609s, 1547s, 1415s, 1304s, 1117m, 872w, 842w, 760m, 690m, 670m; ^1H NMR (500 MHz, $(CD_3)_2SO$): δ ppm = 7.50 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.86 (t, *J* = 7.6 Hz, 1H, Ar-H), 6.78 (d, *J* = 7.3 Hz, 1H, Ar-H), 2.43 (s, 3H, CH_3), 1.75 (s, 3H, Ac); ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ ppm = 178.3 (COMe), 175.3 (CO_2Na), 145.4 (qC), 139.1 (qC), 138.4 (qC), 129.2 (CH), 127.8 (CH), 127.8 (CH), 24.9 (Ac), 19.0 (CH_3). Data is consistent with literature. [142]



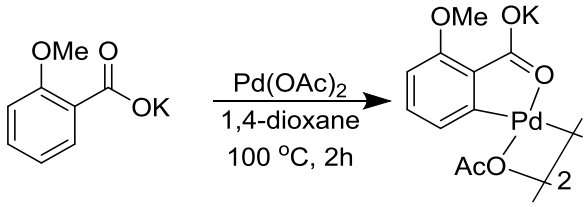
Palladacycle 154a was prepared in accordance with the general procedure from potassium *ortho*-toluate (87 mg, 0.50 mmol) to give the desired product as a dark brown solid (267 mg, mmol, 79%); ν_{max} / cm^{-1} 3388w (br), 1610s, 1597s, 1556s, 1520s, 1406s, 1386s, 1350s, 1309s, 1116w, 1073w, 862m, 829m, 747m, 698m, 689m; ^1H NMR (500 MHz, $(CD_3)_2SO$): δ ppm = 7.48 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.88 (t, J=7.5 Hz, 1H, Ar-H), 6.81 (d, J=7.4 Hz, 1H, Ar-H), 2.42 (s, 3H, CH_3), 1.76 (s, 3H, Ac); ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ ppm = 178.3 (COMe), 175.3 (CO_2K) 145.4 (qC), 139.0 (qC), 138.4 (qC), 129.2 (CH), 127.8 (2 x CH), 24.9 (Ac), 19.0 (CH_3).



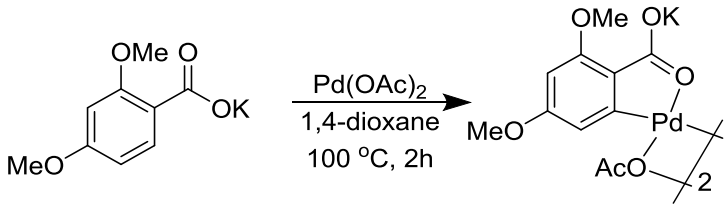
Palladacycle 154c was prepared in accordance with the general procedure from sodium *meta*-methoxybenzoate (87 mg, 0.50 mmol) to give the desired product as a dark brown solid (237 g, 0.35 mmol, 70%); ν_{max} / cm^{-1} 3390w (br), 1546s, 1408s, 1323s, 1255s, 1213s, 1115w, 1019m, 870w, 797w, 672m; ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ ppm = 7.49 (d, *J* = 8.2 Hz, 1H, Ar-H), 6.72 (d, *J* = 3.2 Hz, 1H, Ar-H), 6.68 (dd, *J* = 8.2, 3.2 Hz, 1H, Ar-H), 3.69 (s, 3H, OCH_3), 1.78 (s, 3H, Ac); ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ ppm = 184.0 (COMe), 177.8 (CO_2Na), 173.6 (qC), 157.3 (qC), 143.6 (qC), 132.2 (CH), 116.7 (CH), 113.3 (CH), 55.4 (OCH_3), 25.1 (Ac).



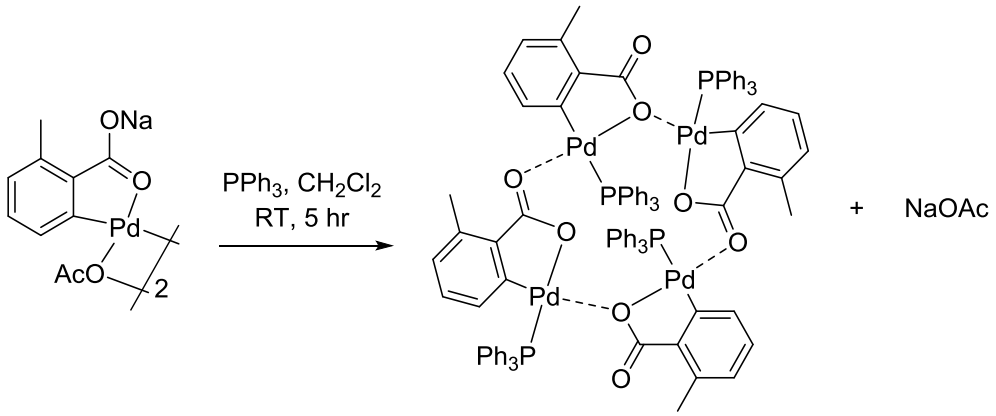
Palladacycle 154e was prepared in accordance with the general procedure from potassium *meta*-methoxybenzoate (95 mg, 0.50 mmol) to give the desired product as a dark brown solid (276 mg, 0.39 mmol, 78%); ν_{max} / cm^{-1} 3374w (br), 1538s, 1411s, 1318s, 1214s, 1107w, 1017m, 792m, 690m; ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ ppm = 7.49 (d, *J* = 8.2 Hz, 1H, Ar-H), 6.72 (d, *J* = 3.2 Hz, 1H, Ar-H), 6.68 (dd, *J* = 8.2, 3.2 Hz, 1H, Ar-H), 3.69 (s, 3H, OCH_3), 1.78 (s, 3H, Ac); ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ ppm = 185.2 (COMe), 177.7 (CO_2K), 173.5 (qC), 156.6 (qC), 143.4 (qC), 131.9 (CH), 116.0 (CH), 112.7 (CH), 54.8 (OCH_3), 22.7 (Ac).



Palladacycle 154f was prepared in accordance with the general procedure from potassium *ortho*-methoxybenzoate (95 mg, 0.50 mmol) to give the desired product as a dark brown solid (251 mg, 0.35 mmol, 71%). ν_{max} / cm^{-1} 3404w (br), 1559s, 1382s, 1320s, 1254s, 1116m, 1022s, 816m, 761w, 690m, 670m; ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ ppm = 7.27 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.95 (t, *J* = 8.0 Hz, 1H, Ar-H), 6.63 (d, *J* = 8.0 Hz, 1H, Ar-H), 3.66 (s, 3H, OCH_3), 1.75 (s, 3H, Ac); ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ ppm = 184.8 (COMe), 177.1 (CO_2K), 157.7 (qC), 146.5 (qC), 129.4 (CH), 128.9 (qC), 124.5 (CH), 109.5 (CH), 55.7 (OCH_3), 23.2 (Ac).



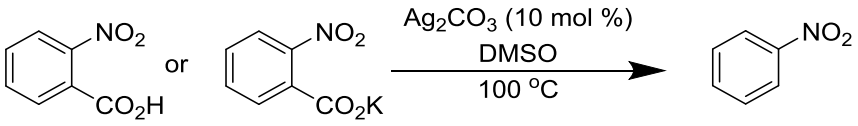
Palladacycle 154g was prepared under the general conditions from potassium 2,4-dimethoxybenzoate (110 mg, 0.50 mmol) to give the desired product as a dark brown solid (288 g, 0.37 mmol, 74%); ν_{max} / cm^{-1} 3388w (br), 1548s, 1407s, 1265s, 1211m, 1156m, 1115s, 1027m, 871w, 814w, 672m; ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ ppm = 6.96 (d, *J* = 2.2 Hz, 1H, Ar-H), 6.18 (d, *J* = 2.2 Hz, 1H, Ar-H), 3.69 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 1.75 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ ppm = 183.35 (COMe), 176.0 (CO_2K), 159.1 (qC), 158.3 (qC), 147.3 (qC), 121.2 (qC), 108.7 (CH), 95.8 (CH), 55.2 (OCH_3), 54.8 (OCH_3), 22.7 (Ac).



Palladacycle 158 was synthesised from a known literature procedure.[142] **Palladacycle 154b** (332.0 mg, 0.50 mmol) was suspended in CH_2Cl_2 (10 ml) in a screw cap vial. Triphenylphosphine (262.0 mg, 1.00 mmol) was added to the suspension and the vial was flushed with nitrogen and sealed. After stirring at room temperature for 5 hours, the reaction mixture was filtered and the solvent concentrated by half. Complex **158** was precipitated from the CH_2Cl_2 through slow addition of hexane. The precipitate was filtered and dried under high vacuum to give the desired palladacycle as a pale brown powder (364.0 mg, 0.37 mmol, 74%); ν_{max} / cm^{-1} 3045w, 1650m, 1531s, 1479w, 1434m, 1370w, 1286m, 1268m, 1184w, 1095m, 836w, 741m, 698s; ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm = 7.83 - 7.90 (m, 24H, 24 x Ar-H), 7.14 - 7.18 (m, 12H, 12 x Ar-H), 7.08 (br. s., 24H, 24 x Ar-H), 6.38 (d, *J* = 7.6 Hz, 4H, 4 x Ar-H), 6.21 (t, *J* = 7.6 Hz, 4H, 4 x Ar-H), 5.92 (t, *J* = 7.6 Hz, 4H, 4 x Ar-H), 1.87 (s, 12H, 4 x CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm = 179.1 (C=O), 146.0 (qC), 140.0 (CH), 138.4 (CH), 135.7 (d, *J* = 12.7 Hz, CH), 135.4 (d, *J* = 13.6 Hz, CH), 131.1 (d, *J* = 47.2 Hz, qC), 129.8 (CH), 127.7 (d, *J* = 10.9 Hz, CH), 127.2 (d, *J* = 6.4 Hz, CH), 126.6 (CH), 20.6 (CH_3). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ ppm = 46.6; Data consistent with literature.[142]

6.2.6. Decarboxylation Tests

Procedure - An oven dried flask was charged with *nitro*-benzoic acid (167 mg, 1.0 mmol) or potassium nitrobenzoate, (205 mg, 1.0 mmol) and Ag_2CO_3 (27.6 mg, 0.1 mmol) under an atmosphere of N_2. DMSO (5 ml) was added by syringe, and the reaction placed in a preheated oil bath at 100 ^oC and stirred for 16 hours. At regular intervals samples of 1 ml were removed and tested by LCMS and NMR for product formation.



Under standard conditions

From 2-nitrobenzoic acid; Reaction proceeded gradually once at 100 degrees. At 225 mins 18% conversion was indicated by NMR. At 7.5 hours 33% conversion was observed. At 23 hours 100% conversion to nitrobenzene was observed with no by-products.

From potassium 2 nitrobenzoate; At 23 hours was only 6 % conversion was indicated by NMR, and at 29hours this remained at 6-7 % conversion at which point the reaction was stopped.

Nitrobenzene ^1H NMR (400 MHz, $CDCl_3$): δ ppm = 8.21 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.69 (t, *J* = 7.4 Hz, 1H Ar-H), 7.53 (t, *J* = 8.0 Hz, 2H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm = 148.4 (qC), 134.7 (CH), 129.4 (2 x CH), 123.6 (2 x CH).

Repeating at 120 ^oC

From 2-nitrobenzoic acid; Reaction proceeded gradually and complete conversion was observed by NMR in 4 hours.

From potassium 2 nitrobenzoate; At 23 hours only 5% conversion was observed, and at 29 hours remained at 6% conversion at which point the reaction was stopped.

At 100 ^oC with 50 mol% Ag_2CO_3 (0.5 mmol, 137.9 mg)

From 2-nitrobenzoic acid; Reaction proceeded gradually and complete conversion was observed in 4 hours.

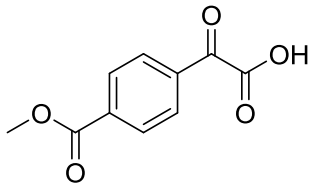
From potassium 2 nitrobenzoate; Reaction rate appears to improve slightly, but still only 33% conversion at 23 hours.

6.3. Chapter 2: Carboxylate directed decarboxylative *ortho*-acylation

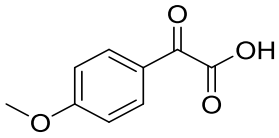
α-Oxo-carboxylic acids - Phenylglyoxylic acid, mesitylglyoxylic acid and 2-thiopheneglyoxylic acid were purchased from either Sigma Aldrich of Alfa Aesar and used without further purification.

6.3.1. General procedure for preparation of α-oxocarboxylic acids[147]

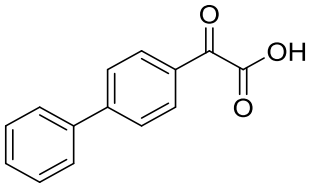
An oven dried flask was charged with required acetophenone (7.00 mmol), SeO_2 (1.10g, 10.00 mmol) and anhydrous pyridine (50 ml) under a N_2 atmosphere. The mixture was refluxed for 2 hours, cooled to room temperature and filtered. The filtrate was concentrated *in vacuo*. Aqueous $NaOH_{(aq)}$(2 M, 15 ml) was added to the residue, and extracted with ethyl acetate (2 x 10 ml). The organic layer was discarded, and the aqueous phase was acidified with $HCl_{(aq)}$ (6M) to pH 1-2 and extracted with ethyl acetate (2 x 10 ml). The organic layers were combined, dried over Mg_2SO_4 and the solvent removed *in vacuo*. Recrystallisation from benzene gave the desired product. Data were consistent with existing literature.[147]



2-(4-(Methoxycarbonyl)phenyl)-2-oxoacetic acid 105d was prepared from methyl 4-acetylbenzoate (1.25 g, 7.00 mmol) in accordance with the general procedure and the product isolated as a white solid (1.19 g, 5.70 mmol 82%); MP = 100 - 101 °C; LRMS [M + H] m/z = 209.0; ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ ppm = 7.91 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.13 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.87 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ ppm = 187.1 (C=O), 166.5 (CO_2H), 164.7 (CO_2Me), 132.0 (2 x CH), 124.7 (2 x qC), 114.7 (2 x CH), 55.8 (CH_3).



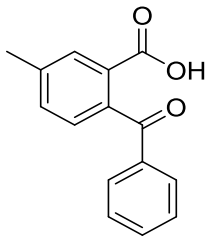
2-(4-Methoxyphenyl)-2-oxoacetic acid 105c was prepared from 1-(4-methoxyphenyl)ethan-1-one (1.05 g, 7.00 mmol) in accordance with the general procedure and the product isolated as a white solid (983 mg, 5.46 mmol, 78%); MP = 58 - 59 °C; LRMS [M + H] m/z = 181.0; ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm = 9.84 (br. s, 1H, CO_2H), 8.26 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.98 (d, *J* = 8.4 Hz, 2H, Ar-H), 3.90 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm = 183.2 (C=O), 165.5 (CO_2H), 163.9 (qC), 133.7 (qC), 124.6 (2 x CH), 114.3 (2 x CH), 55.6 (OCH_3).



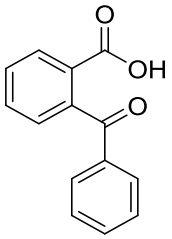
2-(Biphenyl-4-yl)-2-oxoacetic acid 105b was prepared from 1-([1,1'-biphenyl]-4-yl)ethan-1-one (1.37 g, 7.00 mmol) in accordance with the general procedure and the product was isolated as a white solid (1.09 g, 4.83 mmol, 69%); MP = 79 - 81 °C; LRMS [M + H] m/z = 185.0; ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm = 8.40 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.74 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.65 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.43-7.51 (m, 3H, Ar-H), 7.08 (br. s, 1H, CO_2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm = 189.8 (C=O), 161.6 (CO_2H), 148.1 (qC), 139.4 (qC), 131.9 (qC), 130.5 (2 x CH) 128.8 (2 x CH) 128.4 (CH) 127.5 (2 x CH) 127.4 (2 x CH).

6.3.2. General procedure for formation of benzoylbenzoic acids

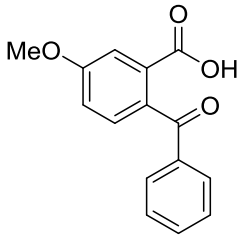
An oven dried vessel was charged with phenylglyoxylic acid (1 eq), $Pd(OAc)_2$ (0.05 eq), Ag_2CO_3 (1 eq) $K_2S_2O_8$ (1 eq) and potassium benzoate (**55a-l**, 2 eq.). The vessel was sealed with a Teflon cap, evacuated and back filled with nitrogen (x 3). Dioxane, AcOH and DMSO were added in a ratio of 15 : 3 : 2 respectively (0.2 M based on phenylglyoxylic acid in total volume of solvent) and the reaction was stirred in a preheated oil bath at 120 ^oC for 16 hours. The solution was diluted in EtOAc (10 ml), filtered through a pad of celite, rinsing with EtOAc (2 x 10 ml), and the filtrate concentrated *in vacuo*. Purification performed by silica gel chromatography (92:5:2, Hex:EtOAc:AcOH, to 72:25:3, Hex:EtOAc:AcOH).



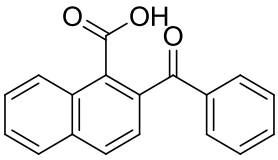
2-Benzoyl-5-methylbenzoic acid 101b was prepared using the general procedure from phenylglyoxylic acid (75 mg, 0.50 mmol) and potassium 3-methylbenzoate (174 mg, 1.00 mmol) and isolated as a yellow solid (77 mg, 0.32 mmol, 64%); MP = 143 - 146 °C; LRMS [M + H] m/z = 241.1; ν_{max} / cm^{-1} 2922s, 1683s, 1669s; ^1H NMR (500 MHz, $CDCl_3$): δ ppm = 7.87 (s, 1H, Ar-H), 7.71 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.52 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.46 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.40 (t, *J* = 7.4 Hz, 2H, Ar-H), 7.28 (d, *J* = 7.7 Hz, 1H, Ar-H), 2.46 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm = 199.8 (C=O), 170.6 (CO_2H), 140.0 (qC), 137.3 (qC), 133.7 (CH), 133.0 (CH), 131.2 (CH), 129.4 (2 x CH), 128.4 (2 x CH), 128.1 (CH), 127.8 (CH), 21.2 (CH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_{13}O_3$ calculated 241.0859 found 241.0866; Consistent with literature.[294]



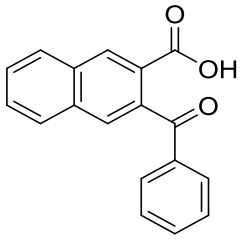
2-Benzoylbenzoic acid 101a was prepared using the general procedure from phenylglyoxylic acid (75 mg, 0.50 mmol) and potassium benzoate (166 mg, 1.00 mmol) and isolated as an off white solid (38 mg, 0.17 mmol, 34%); MP = 131 - 132 °C; LRMS [M + H] m/z = 227.2; ν_{max} / cm^{-1} 2855s, 1675s, 1653s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.12 (d, *J* = 7.2 Hz, 1H), 7.75 (dd, *J* = 8.4, 1.3 Hz, 2H, Ar-H), 7.70 (td, *J* = 7.5, 1.2 Hz, 1H, Ar-H), 7.61 (td, *J* = 7.7, 1.2 Hz, 1H, Ar-H), 7.57 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.44 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.42 (dd, *J* = 7.3, 1.0 Hz, 1H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 197.1 (C=O), 170.9 (CO_2H), 142.6 (qC), 137.0 (qC), 133.3 (CH), 133.2 (CH), 130.9 (CH), 129.6 (2 x CH), 129.4 (CH), 128.5 (2 x CH), 127.9 (qC), 127.7 (CH); HRMS ($[M + H]^+$, +ESI) m/z $C_{14}H_{11}O_3$ calculated 227.0703 found 227.0713; Consistent with literature. [294]



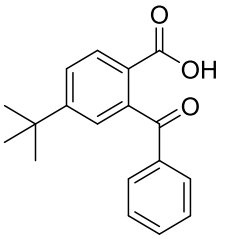
2-Benzoyl-5-methoxybenzoic acid 101d was prepared using the general procedure from phenylglyoxylic acid (45 mg, 0.30 mmol) and potassium 3-methoxybenzoate (114 mg, 0.60 mmol) and isolated as a white solid (39 mg, 0.15 mmol, 51%); MP = 149 - 151 °C; LRMS [M + H] m/z = 257.2; ν_{max} / cm^{-1} 2923s, 1671s, 1596s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.72 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.54 (m, 2H, Ar-H), 7.41 (t, *J* = 8.3 Hz, 2H, Ar-H), 7.36 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.15 (dd, *J* = 8.6, 2.5 Hz, 1H, Ar-H), 3.91 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 199.5 (C=O), 169.2 (CO_2H), 162.4 (qC), 139.3 (qC), 134.2 (CH), 131.0 (qC), 130.6 (2 x CH), 129.6 (2 x CH), 129.4 (qC), 128.9 (CH), 118.5 (CH), 116.4 (CH), 56.4 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_{13}O_4$ calculated 257.0808 found 257.0809.



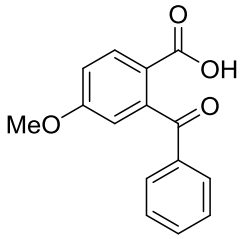
2-Benzoyl-1-naphthoic acid 101e was prepared using the general procedure from phenylglyoxylic acid (90 mg, 0.60 mmol) and potassium 1-naphthoate (252 mg, 1.20 mmol) and isolated as an off white solid (54 mg, 0.20 mmol, 33%); MP = 141 - 142 °C; LRMS [M + H] m/z = 277.1; ν_{max} / cm^{-1} 2963s, 1678s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.79 (d, *J* = 8.1 Hz, 1H, Ar-H), 8.03 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.87 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.61 (m, 4H, Ar-H), 7.47 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.36 (m, 3H, Ar-H); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 152.9 (CO_2H), 140.4, 137.6, 135.6, 130.4, 130.3, 130.2, 130.0, 129.7, 129.4, 128.9, 127.1, 124.7, 120.7, 107.2 (15 of 16, C=O not observed, signals could not be fully assigned); HRMS ($[M + H]^+$, +ESI) m/z $C_{18}H_{13}O_3$ calculated 277.0859 found 277.0856.



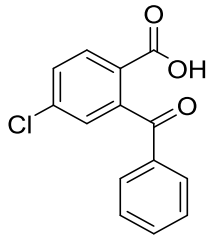
3-Benzoyl-2-naphthoic acid 101f was prepared using the general procedure from phenylglyoxylic acid (90 mg, 0.60 mmol) and potassium 2-naphthoate (252 mg, 1.20 mmol) and isolated as an off white solid (83 mg, 0.30 mmol, 50 %); MP = 209 - 210 °C; LRMS [M + H] m/z = 277.1; ν_{max} / cm^{-1} 2924s, 1675s; ^{1}H NMR (400 MHz, CD_3OD): δ ppm = 8.64 (s, 1H, Ar-H), 8.09 (d, *J* = 9.3 Hz, 1H, Ar-H), 7.99 (d, *J* = 9.3 Hz, 1H, Ar-H), 7.90 (s, 1H, Ar-H), 7.75 (d, *J* = 7.1 Hz, 1H, Ar-H), 7.67 - 7.71 (m, 3H, Ar-H), 7.58 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.45 (t, *J* = 7.4 Hz, 2H, Ar-H); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 199.7 (C=O), 169.5 (CO_2H), 139.5, 139.3, 135.9, 134.5, 134.4, 133.0, 130.8, 130.6, 130.5, 130.0, 129.8, 129.7, 129.5, 129.3 (Signals could not be fully assigned); HRMS ($[M + H]^+$, +ESI) m/z $C_{18}H_{13}O_3$ calculated 277.0859 found 277.0857; Consistent with literature.[295]



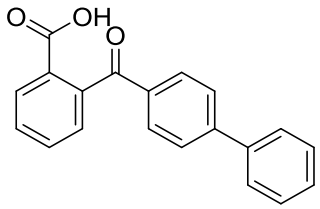
2-Benzoyl-4-(*tert*-butyl)benzoic acid 101g was prepared using the general procedure from phenylglyoxylic acid (90 mg, 0.60 mmol) and potassium 4-(*tert*-butyl)benzoate (259 mg, 1.20 mmol) and isolated as an orange solid (40 mg, 0.14 mmol, 24%); MP = 163 - 164 °C; LRMS [M + H] m/z = 284.2; ν_{max} / cm^{-1} 2963s, 1667s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.01 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.72 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.57 (dd, *J* = 8.3, 1.9 Hz, 1H, Ar-H), 7.51 - 7.60 (m, 2H, Ar-H), 7.42 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.36 (d, *J* = 1.9 Hz, 1H, Ar-H), 1.34 (s, 9H, Ar-H, 3 x CH_3); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 200.0 (C=O), 168.7 (CO_2H), 157.7 (qC), 155.8 (qC), 145.1 (qC), 143.4 (qC), 138.8 (CH), 134.3 (2 x CH), 129.6 (CH), 128.8 (2 x CH), 127.9 (CH), 125.6 (CH), 35.9 (qC), 31.6 (3 x CH_3); HRMS ($[M + Na]^+$, +ESI) m/z $C_{18}H_{18}O_3Na$ calculated 305.1154, found 305.1151.



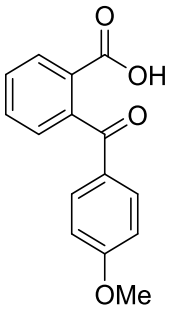
2-Benzoyl-4-methoxybenzoic acid 101h was prepared using the general procedure from phenylglyoxylic acid (90 mg, 0.60 mmol) and potassium 4-methoxybenzoate (228 mg, 1.20 mmol) and isolated as an off white solid (18 mg, 0.07 mmol, 12%); MP = 178 - 180 °C; LRMS [M + H] m/z = 257.2; ν_{max} / cm^{-1} 2924s, 1670s; ^{1}H NMR (500 MHz, CD_3OD): δ ppm = 8.05 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.70 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.56 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.44 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.14 (dd, *J* = 8.7, 2.5 Hz, 1H, Ar-H), 6.86 (d, *J* = 2.5 Hz, 1H, Ar-H), 3.88 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 197.2 (C=O), 171.1 (CO_2H), 164.5 (qC), 146.2 (qC), 138.7 (qC), 134.3 (CH), 130.5 (2 x CH), 129.8 (2 x CH), 129.7 (qC), 116.2 (CH), 115.8 (CH), 114.0 (CH), 56.5 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_{13}O_4$ calculated 257.0808 found 257.0809.



2-Benzoyl-4-chlorobenzoic acid 101i was prepared using the general procedure from phenylglyoxylic acid (90 mg, 0.60 mmol) and potassium 4-chlorobenzoate (233 mg, 1.20 mmol) and isolated as a white solid (25 mg, 0.10 mmol, 16%); MP = 176 - 178 °C; LRMS [M + H] m/z = 261.1 and 263.1 [Cl]; ν_{max} / cm^{-1} 2928s, 1687s; ^{1}H NMR (500 MHz, CD_3OD): δ ppm = 8.05 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.68 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.60 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.53 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.42 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.30 (s, 1H, Ar-H); ^{13}C NMR (126 MHz, CD_3OD): δ ppm = 195.3 (C=O), 169.7 (CO_2H), 144.1 (qC), 140.1 (qC), 136.4 (qC), 133.5 (CH), 132.4 (qC), 129.7 (2 x CH), 129.4 (2 x CH), 128.6 (CH), 127.9 (CH), 126.1 (CH); HRMS ($[M + H]^+$, +ESI) m/z $C_{14}H_9ClO_3$ calculated 260.0240, found 260.0247.



2-(4-Phenylbenzoyl)benzoic Acid 101n was prepared from 2-(biphenyl-4-yl)-2-oxoacetic acid (119 mg, 0.60 mmol) and potassium benzoate (192 mg, 1.20 mmol) in accordance with the general procedure and isolated as a white solid (56 mg, 0.19 mmol, 31%);MP = 230 °C; LRMS [M + H] m/z = 303.1; ν_{max} / cm^{-1} 2824s, 1681s. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ ppm = 8.03 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.79 (d, *J* = 8.3, 1.2 Hz, 2H, Ar-H), 7.75 – 7.64 (m, 6H, Ar-H), 7.49 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.46 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.43 (t, *J* = 7.3 Hz, 1H, Ar-H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ ppm = 196.0 (C=O), 166.9 (CO_2H), 144.5 (qC), 141.4 (qC), 138.9 (qC), 135.7 (qC), 132.5 (CH), 129.9 (qC), 129.8 (CH), 129.7 (CH), 129.6 (2 x CH), 129.1 (2 x CH), 128.4 (CH), 127.4 (CH), 127.0 (2 x CH), 126.9 (2 x CH); HRMS ($[M + H]^+$, +ESI) m/z $C_{20}H_{13}O_3$ calculated 303.1016, found 303.1020.



2-(4-Methoxybenzoyl)benzoic acid 101o was prepared from 2-(4-methoxyphenyl)-2-oxoacetic acid (108 mg, 0.60 mmol) and potassium benzoate (192 mg, 1.20 mmol) in accordance with the general procedure and isolated as a white solid (43 mg, 0.17 mmol, 28%); MP = 154 - 155 °C; LRMS [M + H] m/z = 257.2; ν_{max} / cm^{-1} 2935s, 1669s; ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ ppm = 13.11 (br. s, 1H, CO_2H), 7.98 (dd, *J* = 7.8, 0.8 Hz, 1H, Ar-H), 7.70 (td, *J* = 7.5, 1.3 Hz, 1H, Ar-H), 7.63 (td, *J* = 7.8, 1.3 Hz, 1H, Ar-H), 7.59 (d, J = 8.8 Hz, 2H, Ar-H), 7.37 (dd, *J* = 7.5, 0.9 Hz, 1H, Ar-H), 7.02 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.82 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ ppm = 195.0 (C=O), 166.9 (CO_2H), 163.1 (qC), 141.7 (qC), 132.3 (CH), 131.2 (2 x CH), 129.9 (qC), 129.8 (qC), 129.7 (CH), 129.4 (CH), 127.3 (CH), 113.8 (2 x CH), 55.5 (CH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_{13}O_4$ calculated 257.0808 found 257.0801.

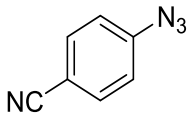
6.4. Chapter 3: Zinc mediated 1,5- and 1,4,5-triazole synthesis

CAUTION: Azides are both shock sensitive and toxic. The use of acids in the presence of the azide ion is advised against due to the possible release of hydrazoic acid gas, a known poison. Furthermore, the use of CH_2Cl_2 in the presence of the azide ion may lead to the formation of diazidomethane $N_3CH_2N_3$ which is known to self-detonate. No incidents occurred during the synthesis or use of azides but for these reasons the reactions were not performed on scales greater than 5 g.

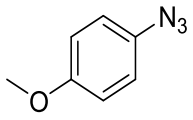
6.4.1. General procedure for the synthesis of aromatic azides from their corresponding anilines[245]

A solution of the aniline (10.00 mmol) was dissolved in MeCN (40 mL), then azidotrimethylsilane (12.00 mmol) was added before cooling to 0 °C. *tert*-Butyl nitrite (11.00 mmol) was added portion wise over 15 minutes to the solution. The reaction was allowed to warm to ambient temperature and stirred until complete by HPLC, typically 2 hours. The solvent was removed *in vacuo* and the crude material was purified by passing through a plug of silica and eluting with CH_2Cl_2.

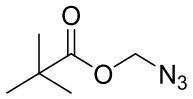
The following known azides were synthesised by Dr Chris Smith using the general procedure; 2-azido-1,3-dichlorobenzene, 1-azido-3-bromobenzene, 1-azido-4-chlorobenzene, 1-azido-4- nitrobenzene, ethyl 4-azidobenzoate, 1-azido-4-iodobenzene, 5-azido-1,2,3-trimethoxybenzene, 1-azido-2-bromo-4-fluorobenzene, 5-azido-2-bromopyridine and 1-(3-azidophenyl)ethanone.[245]



4-azidobenzonitrile 179a was prepared from 4-aminobenzonitrile (1.18 g, 10.00 mmol) in accordance with the general procedure and isolated as an orange solid (1.38 g, 9.60 mmol, 96%); MP = 61 - 62 °C; ν_{max} / cm^{-1} 2220m, 2152m, 2108s, 1597m, 1503m, 1416m, 1308m, 1279m, 1175m, 1125m, 833s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.66 (d, J = 8.8 Hz, 2H, Ar-H), 7.12 (d, J = 8.8 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 144.90 (qC), 133.81 (2 x CH), 119.71 (2 x CH), 118.36 (CN), 108.30 (qC); Consistent with literature.[245]



4-Azidoanisole 179b was prepared from 4-aminoanisole (1.23 g, 10.00 mmol) in accordance with the general procedure and isolated as a brown oil (1.37g, 9.20 mmol, 92%); ν_{max} / cm^{-1} 2836w, 2099s, 1608m, 1585m, 1517s, 1464m, 1441m, 1284m, 1250s, 1180m, 1108m, 1032m, 822s, 754m, 641m, 624m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 6.97 (d, *J* = 9.2 Hz, 2H, Ar-H), 6.90 (d, *J* = 9.2 Hz, 2H, Ar-H), 3.80 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm= 156.9 (qC), 132.3 (qC), 119.9 (2 x CH), 115.1 (2 x CH), 55.5 (OCH_3); Consistent with literature.[245]



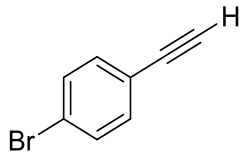
Azidomethyl pivalate 297 was prepared in accordance with known literature.[296] Chloromethyl pivalate (5.00 g, 30.00 mmol) was suspended in H_2O (20 ml) and sodium azide (2.6 g, 40 mmol) was added and the reaction heated to 90 ^{o}C under a nitrogen atmosphere for 16 hours. The mixture was diluted further with H_2O (20 ml) and extracted with diethyl ether (3 x 10 ml). The organic extract was dried over $MgSO_4$ and the solvent removed *in vacuo* to give the desired azidomethyl pivalate as a clear yellow oil (3.53 g, 19.50 mmol, 68%); ν_{max} / cm^{-1} 2972w, 2227m, 2103s, 1737s, 1605m, 1509m, 1482m, 1277m, 1238m, 1112s, 1032m, 970m, 854m, 789m, 693m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 5.14 (s, 2H, CH_2), 1.26 (s, 9H, 3 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 178.0 (C=O), 74.4 (CH_2), 38.9 (qC), 27.0 (3 x CH_3); Consistent with literature.[296]

Phenylacetylene, 4-ethynyltoluene, 3-ethynyltoluene, 4-ethynylanisole, 3-ethynylanisole, 2-ethynylanisole, 1-ethynyl-4-fluorobenzene, 3,4-dichlorophenylacetylene, 1-hexyne, 4-ethynyl-N,N-dimethylaniline, methyl 4-ethynylbenzoate, 3-cyclohexyl-1-propyne, 4-phenyl-1-butyne, pent-4-yn-2-ol, cyclohexylacetylene, cyclopentylacetylene and cyclopropylacetylene (as a 70% by wt solution in toluene) were purchased from Aldrich and used without further purification

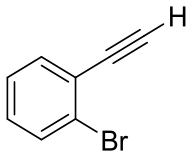
6.4.2. General procedure for synthesis of terminal alkynes

A suspension of substituted iodobenzene (8.00 mmol), $PdCl_2(PPh_3)_2$ (180 mg, 0.40 mmol) and CuI (76 mg, 0.40 mmol) in NEt_3 (50 ml) was prepared under a N_2 atmosphere. Ethynyltrimethylsilane (710 mg, 9.60 mmol) was added *via* syringe and the mixture stirred at ambient temperature for 12 hours, monitoring by TLC (1% EtOAc in Hexane). After complete consumption of the aryl iodide, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and filtered through celite. The filtrate washed with saturated $NH_4Cl_{(aq)}$ solution (2 × 30 mL), H_2O (2 × 30 mL), dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. The crude residue was dissolved in dry THF (30 ml) under a nitrogen atmosphere, and cooled to 0 ^oC. TBAF (8 ml, 1M solution in THF, 8.00 mmol), was added over 5 minutes. The reaction was stirred at 0 ^oC for 10 minutes and then warmed to room temperature. The reaction mixture was poured into saturated $NH_4Cl_{(aq)}$ solution (30 ml) and extracted with EtOAc (2 x 20 ml). The organic layers were combined, washed with H_2O (30 ml) and brine (2 x 20 ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by flash chromatography on silica gel, (eluent: 99:1, hexane:EtOAc).

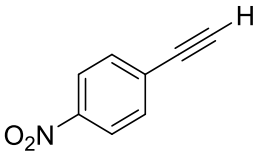
1-Chloro-4-ethynylbenzene was synthesised by Miss Sinead Balgobin in accordance with the general procedure. **4-Ethynylbenzaldehyde** was synthesised by Dr Meliha Cetin in accordance with the general procedure.



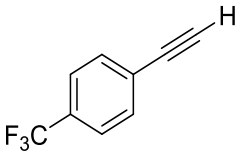
1-Bromo-4-ethynylbenzene 180a was synthesised from 1,bromo-4-iodobenzene (2.25 g, 8.00 mmol) in accordance with the general procedure, however deprotection of the TMS group was performed by stirring the crude material in a methanol solution with K_2CO_3 (2.76 g, 20.00 mmol). The product was isolated as an off white solid (1.12 g, 6.24 mmol, 78% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.52 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.41 (d, *J* = 8.4 Hz, 2H, Ar-H), 3.15 (s, 1H, Alkyne CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 133.5 (2 x CH), 131.6 (2 x CH), 123.1 (qC), 121.0 (qC), 82.6 (Alkyne qC), 78.3 (Alkyne CH); Consistent with literature.[297]



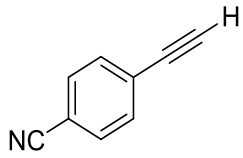
1-Bromo-2-ethynylbenzene 180b was synthesised from 1-bromo-2,iodobenzene (2.25 g, 8.00 mmol) in accordance with the general procedure, however deprotection of the TMS group was performed by stirring the crude material in a methanol solution with K_2CO_3 (2.76 g, 20.00 mmol). The product was isolated as an off white solid (732 mg, 4.07 mmol, 51% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.60 (dd, *J* = 7.6, 1.2 Hz, 1H, Ar-H), 7.54 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar-H), 7.28 (td, *J* = 7.6, 1.2 Hz, 1H, Ar-H), 7.21 (td, *J* = 7.8, 1.7 Hz, 1H, Ar-H), 3.39 (s, 1H, Alkyne-CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 134.1 (CH), 132.5 (CH), 130.0 (CH), 127.0 (CH), 125.6 (qC), 124.3 (qC), 81.9 (Alkyne qC), 81.8 (Alkyne CH); Consistent with literature.[298]



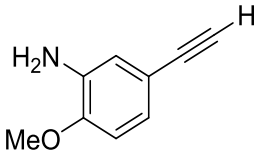
1-Ethynyl-4-nitrobenzene 180c was synthesised from 1-iodo-4-nitrobenzene (1.99 g, 8.00 mmol) in accordance with the general procedure. The product was isolated as a yellow solid (431 mg, 2.39 mmol, 30% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.21 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.65 (d, *J* = 9.0 Hz, 2H, Ar-H), 3.37 (s, 1H, Alkyne CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 147.5 (qC), 132.9 (2 x CH), 128.9 (qC), 123.5 (2 x CH), 82.3 (Alkyne qC), 81.6 (Alkyne CH); Consistent with literature.[299]



1-Ethynyl-4-(trifluoromethyl)benzene 180d was synthesised from 1-iodo-4-(trifluoromethyl)benzene (2.18 g, 8.00 mmol) in accordance with the general procedure. The product was isolated as a yellow solid (568 mg, 3.34 mmol, 42% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.60 (s, 4H, Ar-H), 3.21 (s, 1H, Alkyne-CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 132.4 (2 x CH), 130.6 (d, *J* = 33.2 Hz qC), 125.9 (q, *J* = 1.5 Hz, qC), 125.3 (q, *J* = 4.2 Hz, 2 x CH), 123.8 (q, *J* = 272.0 Hz, CF_3), 82.2 (alkyne qC), 79.6 (alkyne CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm = -62.95 (s); Consistent with literature.[300]



4-Ethynylbenzonitrile 180e was synthesised from 4-iodobenzonitrile (1.83 g, 8.00 mmol) in accordance with the general procedure and the product isolated as a yellow solid (630 mg, 4.96 mmol, 62% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.63 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.58 (d, *J* = 8.3 Hz, 2H, Ar-H), 3.31 (s, 1H, Alkyne-CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 132.7 (2 x CH), 132.0 (2 x CH), 127.0 (qC), 118.3 (CN), 112.4 (qC), 81.9 (alkyne qC), 81.5 (alkyne CH); Consistent with literature.[301]



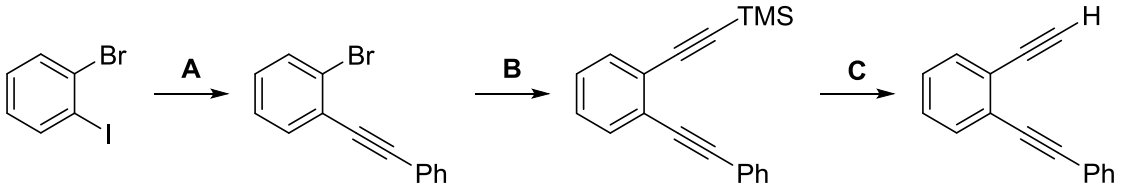
5-Ethynyl-2-methoxyaniline 180g was synthesised from 5-iodo-2-methoxyaniline (1.99 g, 8.00 mmol) in accordance with the general procedure, however deprotection of the TMS group was performed by stirring the crude material in a methanol solution with K_2CO_3 (2.76 g, 20.00 mmol). The product was isolated as a brown crystalline solid (800 mg, 5.4 mmol, 68% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 6.92 (dd, *J* = 8.2, 1.9 Hz, 1H, Ar-H), 6.86 (d, *J* = 1.9 Hz, 1H, Ar-H), 6.72 (d, *J* = 8.3 Hz, 1H, Ar-H), 3.87 (s, 3H, OCH_3), 3.70-4.00 (br. s, 2H, NH_2), 2.95 (s, 1H, Alkyne CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 148.0 (qC), 135.7 (qC), 123.2 (CH), 118.2 (qC), 114.3 (CH), 110.0 (CH), 84.1 (Alkyne qC), 75.1 (Alkyne CH), 55.5 (OCH_3);:Consistent with literature.[302]

6.4.3. Preparation of dialkyne substrates

A: General procedure for the preparation of 2,bromophenyl substituted alkynes (251a, 251b and **251c)** A suspension of 2-bromoiodobenzene (1.13 g, 4.00 mmol), $PdCl_2(PPh_3)_2$ (140 mg, 0.20 mmol) and CuI (38 mg, 0.20 mmol) in NEt_3 (20 ml) was prepared under a N_2 atmosphere. Alkyne (4.40 mmol, 1.1 eq) was added *via* syringe and the mixture stirred at ambient temperature for 12 hours, monitoring by TLC (1% EtOAc in Hexane). After complete consumption of the aryl iodide, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and filtered through celite. The filtrate was washed with saturated $NH_4Cl_{(aq)}$ solution (2 × 30 mL), H_2O (2 × 30 mL), dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. The reaction mixture was purified by flash chromatography on silica gel (eluent; 99:1, hexane:EtOAc).

B: General procedure for the preparation of trimethylsilyl protected dialkynes (253a, 253b and **253c)** A suspension of aryl bromide (3.00 mmol), $PdCl_2(PhCN)_2$ (39 mg, 0.15 mmol), CuI (29 mg, 0.15 mmol), and $P(^tBu)_3HBF_4$ (87 mg, 0.30 mmol) in NEt_3 (20 ml) was prepared under a N_2 atmosphere. Ethynyltrimethylsilane (354 mg, 3.60 mmol) was added *via* syringe and the mixture stirred for 5 hours at ambient temperature, monitoring by TLC (1% EtOAc in Hexane). After complete consumption of the aryl bromide, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and filtered through celite. The filtrate was washed with saturated $NH_4Cl_{(aq)}$ solution (2 × 30 mL), H_2O (2 × 30 mL), dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. The reaction mixture was purified by flash chromatography on silica gel (eluent; 99:1, hexane:EtOAc).

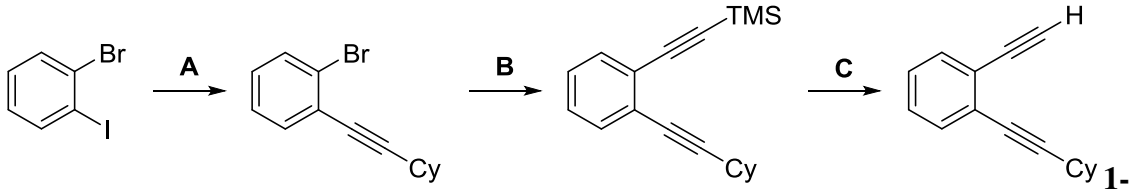
C: General procedure for the formation of terminal alkynes (247a, 247b and **247c)** An oven dried flask was charged with the TMS protected alkyne (2.00 mmol) in dry THF (15 ml) under a nitrogen atmosphere. The solution was cooled to 0 ^oC, and TBAF (2.00 ml, 2.00 mmol, 1M solution in THF), was added over 5 minutes. The reaction was stirred at 0 ^oC for 10 minutes and then allowed to return to ambient temperature. The reaction mixture was poured into saturated $NH_4Cl_{(aq)}$ solution (15 ml) and extracted with EtOAc (2 x 10 ml). The organic portions were combined, washed with H_2O (2 x 15 ml) and brine (2 x 10 ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent; 99:1, hexane:EtOAc).



1-Bromo-2-(phenylethynyl)benzene 251a was prepared in accordance with general procedure A with phenylacetylene (450 mg, 4.40 mmol) and the product isolated as a clear oil (993 mg, 3.88 mmol, 97%); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.55 - 7.65 (m, 4H), 7.36 - 7.40 (m, 3H), 7.31 (td, J = 7.5, 1.3 Hz, 1H), 7.19 (td, J = 7.8, 1.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 133.2 (CH), 132.4 (CH), 131.7 (CH), 129.4 (CH), 128.6 (CH), 128.4 (2 x CH), 127.0 (2 x CH), 125.6 (qC), 125.3 (qC), 122.8 (qC), 93.8 (qC), 88.0 (qC); Consistent with literature.[303]

1-(Trimethylsilylethynyl)-2-(ethynylphenyl)benzene 253a was prepared in accordance with general procedure B from **251a** (784 mg, 3.00 mmol) and isolated as an orange oil (707 mg, 2.58 mmol, 86%); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.47 - 7.50 (m, 2H, Ar-H), 7.43 (ddd, *J*=6.9, 5.2, 1.7 Hz, 2H, Ar-H), 7.26 - 7.29 (m, 3H, Ar-H), 7.17 - 7.22 (m, 2H, Ar-H), 0.19 (s, 9H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 132.2 (CH), 131.7 (2 x CH), 131.7 (CH), 128.4 (CH), 128.3 (2 x CH), 128.2 (CH), 127.8 (CH), 126.0 (qC), 125.5 (qC), 123.2 (qC), 103.4 (qC), 98.6 (qC), 93.4 (qC), 88.1 (qC), 0.0 (TMS); Consistent with literature.[304]

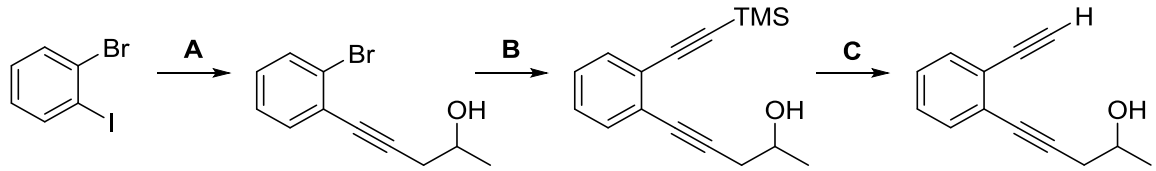
1-Ethynyl-2-(phenylethynyl)benzene 247a was prepared in accordance with general procedure C from **253a** (548 mg, 2.00 mmol) and isolated as a colourless oil (396 mg, 1.96 mmol, 98%); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.61 - 7.55 (m, 4H, Ar-H), 7.37 - 7.26 (m, 5H, Ar-H), 3.38 (s, 1H, Alkyne CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 132.5 (CH), 131.7 (CH), 128.6 (2 x CH), 128.5 (2 x CH),128.3 (CH), 127.9 (2 x CH), 126.2 (qC), 124.5 (qC), 123.1 (qC), 93.5 (Alkyne qC) , 87.8 (Alkyne qC), 82.3 (Alkyne qC), 81.1 (Alkyne CH).Consistent with literature.[258]



1-Bromo-2-(cyclohexylethynyl)benzene 251b was prepared in accordance with general procedure A with cyclohexylacetylene (476 mg, 4.40 mmol) and the product isolated as a clear oil (1.02 g, 3.92 mmol, 98%); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.56 (dd, *J* = 7.9, 0.9 Hz, 1H, Ar-H), 7.44 (dd, *J* = 7.6, 1.5 Hz, 1 H, Ar-H), 7.23 (td, *J* = 7.6, 1.2 Hz, 1H, Ar-H), 7.11 (td, *J* = 7.8, 1.7 Hz, 1H, Ar-H), 2.70 (br. s., 1H, CH), 1.76 - 1.97 (m, 4H, 2 x CH_2), 1.33 - 1.65 (m, 6H, 3 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 133.1 (CH), 132.2 (CH), 128.5 (CH), 126.8 (CH), 126.0 (qC), 125.6 (qC), 99.5 (qC), 79.4 (qC), 32.3 (2 x CH_2), 29.7 (CH), 25.9 (2 x CH_2), 24.6 (CH_2).Consistent with literature.[305]

((2-(Cyclohexylethynyl)phenyl)ethynyl)trimethylsilane 253b was prepared in accordance with general procedure B from **251b** (786 mg, 3.00 mmol) and isolated as an orange oil (605 mg, 2.16 mmol, 72%); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.46 (dd, *J* = 7.3, 1.1 Hz, 1H, Ar-H), 7.39 (dd, *J* = 7.3, 1.1 Hz, 1H, Ar-H), 7.21 (m, 2H, Ar-H), 2.62 - 2.71 (m, 1H, CH), 1.77 - 1.94 (m, 4H, CH_2), 1.51 - 1.65 (m, 3H, Alkyl CH), 1.35 - 1.41 (m, 3H, Alkyl CH), 0.27 (s, 9H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 132.2 (CH), 131.7 (CH), 128.1 (CH), 127.0 (CH), 126.7 (qC), 125.3 (qC), 103.7 (Alkyne qC), 98.8 (Alkyne qC), 97.6 (Alkyne qC), 79.2 (Alkyne qC), 32.6 (2 x CH_2), 29.8 (CH), 25.9 (2 x CH_2), 24.8 (CH_2), 0.0 (TMS).

1-(Cyclohexylethynyl)-2-ethynylbenzene 247b was prepared in accordance with general procedure C from **253b** (560 mg, 2.00 mmol) and isolated as an orange oil (400 mg, 1.92 mmol, 96%); ^{1}H NMR (400 MHz, CDCl3): δ ppm = 7.72 (dd, *J* = 7.6, 1.3 Hz, 1H, Ar-H), 7.65 (dd, *J* = 7.6, 1.6 Hz, 1H, Ar-H), 7.50 (td, J = 7.6, 1.6 Hz, 1H, Ar-H), 7.45 (td, *J* = 7.6, 1.3 Hz, 1H, Ar-H), 3.51 (s, 1H, Alkyne CH), 2.88 - 2.96 (m, 1H, CH_2), 2.01 - 2.16 (m, 4H, CH_2), 1.80 - 1.88 (m, 3H, Alkyl CH), 1.59 - 1.65 (m, 3H, Alkyl-CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 132.4 (CH), 131.7 (CH), 128.4 (CH), 127.2 (qC), 127.1 (CH), 124.4 (qC), 99.0 (Alkyne qC), 82.4 (Alkyne qC), 80.5 (Alkyne CH), 79.0 (Alkyne qC), 32.4 (2 x CH_2), 29.6 (CH), 25.9 (2 x CH_2), 24.6 (CH_2); HRMS ($[M + H]^+$, +ESI) $C_{16}H_{15}$ calculated 207.1168, found 207.1174. Consistent with literature.[306]



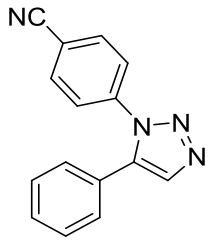
5-(2-Bromophenyl)pent-4-yn-2-ol 251c was synthesised in accordance with general procedure A with pent-4-yn-2-ol (370 mg, 4.4 mmol) and the product isolated as a clear oil (933 mg, 3.92 mmol, 98%); LRMS [M + H] m/z = 239.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.58 (dd, *J* = 7.9, 0.9 Hz, 1H, Ar-H), 7.45 (dd, *J* = 7.6, 1.5 Hz, 1H, Ar-H), 7.26 (td, *J*=7.5, 0.9 Hz, 1H, Ar-H), 7.16 (td, *J* = 7.9, 1.5 Hz, 1H, Ar-H), 4.06 - 4.16 (m, 1H, CH), 2.70 (dd, *J* = 16.9, 4.9 Hz, 1H, CH_2^a), 2.60 (dd, *J* = 16.6, 6.6 Hz, 1H, CH_2^b), 2.18 (br. s., 1H, OH), 1.37 (d, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 132.8 (CH), 131.9 (CH), 128.8 (CH), 126.7 (CH), 125.3 (qC), 124.9 (qC), 91.0 (qC), 81.6 (qC), 66.1 (CH), 29.8 (CH_2), 22.0 (CH_3).

5-(2-((Trimethylsilyl)ethynyl)phenyl)pent-4-yn-2-ol 253c was prepared in accordance with general procedure B from **251c** (714 mg, 3.00 mmol) and isolated as an orange oil (599 mg, 2.34 mmol, 78%); LRMS [M + H] m/z = 257.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.46 - 7.49 (m, 1H, Ar-H), 7.39 - 7.42 (m, 1H, Ar-H), 7.23 - 7.26 (m, 2H, Ar-H), 4.07 (quin, *J* = 6.0 Hz, 1H, CH), 2.70 (dd, *J* = 16.6, 4.8 Hz, 1H, CH_{2a}), 2.58 (dd, *J* = 16.6, 6.5 Hz, 1H, CH_{2b}), 2.28 (d, *J* = 5.0 Hz, 1H, OH), 1.35 (d, *J* = 6.3 Hz, 3H, CH_3), 0.28 (s, 9H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 132.4 (CH), 131.6 (CH), 128.2 (CH), 127.6 (CH), 125.9 (qC), 125.6 (qC), 103.9 (Alkyne qC), 98.2 (Alkyne qC), 90.5 (Alkyne qC), 82.0 (Alkyne qC), 66.4 (CH), 30.3 (CH_2), 22.4 (CH_3), 0.1 (TMS).

5-(2-Ethynylphenyl)pent-4-yn-2-ol 247c was prepared in accordance with general procedure C from **253c** (512 mg, 2.00 mmol) and isolated as a brown oil (361 mg, 1.96 mmol, 98%); LRMS [M + H] m/z = 185.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.50 (dd, *J* = 7.5, 1.3 Hz, 1H, Ar-H), 7.43 (dd, *J* = 7.1, 1.5 Hz, 1H, Ar-H), 7.26 - 7.33 (m, 2H, Ar-H), 4.03 - 4.12 (m, 1H, CH), 3.34 (s, 1H, Alkyne CH), 2.70 (dd, *J* = 16.9, 4.4 Hz, 1H, CH_2^a), 2.58 (dd, *J* = 16.9, 7.1 Hz, 1H, CH_2^b), 2.45 (br. s., 1H, OH), 1.35 (d, *J* = 6.1 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 132.6 (CH), 131.6 (CH), 128.7 (CH), 127.7 (CH), 126.3 (qC), 124.6 (qC), 90.8 (Alkyne qC), 82.8 (Alkyne qC), 81.9 (Alkyne qC), 80.7 (Alkyne CH), 66.4 (CH), 30.3 (CH_2), 22.3 (CH_3); HRMS ($[M + Na]^+$, +ESI) m/z $C_{13}H_{12}NaO$ calculated 207.0780, found 207.0788.

6.4.4. General procedure for the synthesis of 1,5-substituted 1,2,3-triazoles.

The azide (0.30 mmol), alkyne (0.36 mmol) and *N*-methylimidazole (0.03 mmol, 2.5 mg) were added to a glass vial or round bottomed flask. The vessel was purged with N_2 and sealed. Dry THF (4 mL) was added and stirred for 5 minutes before $ZnEt_2$ (0.15 mL, 0.15 mmol, 1 M in hexanes) was added. The reaction was stirred at ambient temperature overnight (approximately 18 hours) before quenching with sat. NH_4Cl (aq) (5 mL). The mixture was partitioned between H_2O (5 mL) and EtOAc (10 mL) and the organic layer was washed with brine (7 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc : hexane, 1 : 20 to 1 : 5) to afford the pure material.

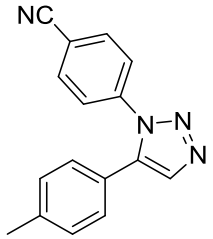


4-(5-Phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 178a was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the product as an orange solid (61 mg, 0.25 mmol 83%);

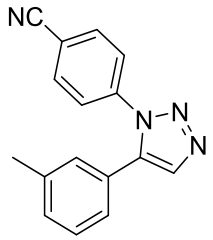
178a was also prepared on a 1.00 mmol scale with 4-azidobenzonitrile (144 mg, 1.00 mmol), phenylacetylene (122.5 mg, 130 μL, 1.2 mmol) and NMI (8.2 mg, 0.1 mmol) under the following conditions:

Entry	Diethyl Zinc (1M solution in hexanes)	**178a** Isolated	Yield
1	1.5 eq, 1.5 ml, 1.5 mmol	213 mg, 0.87 mmol	87%
2	0.5 eq, 0.5 ml, 0.5 mmol	206 mg, 0.84 mmol	84%
3	0.1 eq, 0.1 ml, 0.1 mmol	50 mg, 0.20 mmol	20%

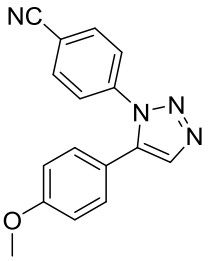
MP = 116 °C; LRMS [M + H] m/z = 247.2; ν_{max} / cm^{-1} 3057w, 2234m, 1607m, 1511s, 1478m, 1452m, 1416m, 1285m, 1230m, 1137m, 1121m, 1051m, 989s, 968m, 959m, 850m, 832s, 764s, 696s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.88 (s, 1H, Ar-H), 7.74 (d, J = 8.8 Hz, 2H, Ar-H), 7.53 (d, J = 8.8 Hz, 2H, Ar-H), 7.40 – 7.48 (m, 3H, Ar-H), 7.24 (dd, J = 7.8, 1.4 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz; $CDCl_3$)): δ ppm = 139.9 (qC), 137.9 (qC), 134.1 (CH), 133.4 (2 x CH), 129.9 (CH), 129.3 (2 x CH), 128.7 (2 x CH), 126.2 (qC), 125.3 (2 x CH), 117.7 (qC), 113.0 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_{11}N_4$ calculated 247.0978, found 247.0972.



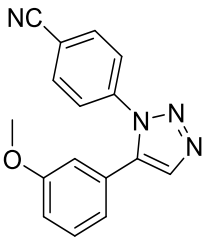
4-(5-(*p*-Tolyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 178b was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 4-ethynyltoluene (42 mg, 46 µL, 0.36 mmol) and gave the product as an orange solid (64 mg, 0.25 mmol, 82%); MP = 115 °C; LRMS [M + H] m/z = 261.0; ν_{max} / cm^{-1} 225m, 1605m, 1507m, 1410w, 1285w, 1233m, 1131m, 1048m, 989s, 969m, 839s, 816s, 763w, 698s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.84 (s, 1H, Ar-H), 7.74 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.53 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.21 (d, *J* =7.9 Hz, 2H, Ar-H), 7.12 (d, *J* = 7.9 Hz, 2H, Ar-H), 2.40 (s, 3 H);^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 139.9 (qC), 139.8 (qC), 137.8 (qC), 133.7 (CH), 133.2 (2 x CH), 129.8 (2 x CH), 128.4 (2 x CH), 125.2 (2 x CH), 122.9 (qC), 117.6 (qC), 112.6 (qC), 21.2 (CH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{13}N_4$ calculated 261.1140, found 261.1128.



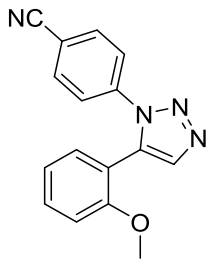
4-(5-(*m*-Tolyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 178c was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 3-ethynyltoluene (42 mg, 46 µL, 0.36 mmol) and gave the product as an off white solid (58 mg, 0.22 mmol, 74%); MP = 157 °C; LRMS [M + H] m/z = 261.2; νmax / cm^{-1} 3098w, 2226m, 1603s, 1506s, 1415w, 1284w, 1266w, 1238m, 1172w, 1125m, 1051m, 969m, 850s, 834s, 795s, 697s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm =7.86 (s, 1H, Ar-H), 7.74 (d, J=8.8 Hz, 2H, Ar-H), 7.54 (d, J = 8.8 Hz, 2H Ar-H), 7.23 - 7.32 (m, 2H, Ar-H), 7.10 (s, 1H, Ar-H), 6.97 (d, J = 6.8 Hz, 1H Ar-H), 2.36 (s, 3H, CH_3);^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 139.8 (qC), 139.1 (qC), 137.9 (qC),134.0 (CH), 133.2 (2 x CH), 130.6 (CH), 129.2 (CH), 129.0 (CH), 125.9 (qC), 125.7 (CH), 125.2 (2 x CH), 117.6 (qC), 112.8 (qC), 21.3 (CH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{13}N_4$ calculated 261.1140, found 261.1133.



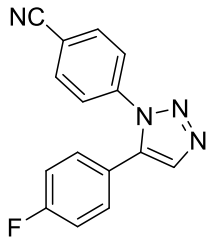
4-(5-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 178d was prepared *via* the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 4-ethynylanisole (48 mg, 47 μL, 0.36 mmol) and the product isolated as an orange solid (78 mg, 0.28 mmol, 94%); MP = 147 - 148 °C; LRMS [M + H] m/z = 277.2; ν_{max} / cm^{-1} 2930w, 2231m, 1604s, 1509m, 1496s, 1460m, 1311w, 1252s, 1187m, 1134w, 1105w, 1018m, 988m, 966w, 833s, 814s, 631m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm =7.82 (s, 1H, Ar-H), 7.74 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.54 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.15 (d, *J* = 8.9 Hz, 2H, Ar-H), 6.93 (d, *J* = 8.9 Hz, 2H, Ar-H), 3.85 (s, 3H, OCH_3); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 160.7 (qC), 140.0 (qC), 137.7 (qC), 133.7 (CH), 133.3 (2 x CH), 130.1 (2 x CH), 125.3 (2 x CH), 118.1 (qC), 117.7 (qC), 114.7 (2 x CH), 112.8 (qC), 55.4 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{13}N_4O$ calculated 277.1089, found 277.1084.



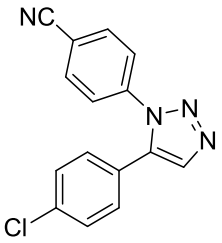
4-(5-(3-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 178e was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 3-ethynylanisole (48 mg, 46 μL, 0.36 mmol) and the product isolated as a yellow solid (63 mg, 0.23 mmol, 76%); MP = 124 °C; LRMS [M + H] m/z = 277.2; ν_{max} / cm^{-1} 2227m, 1719m, 1604m, 1583w, 1509s, 1485m, 1437m, 1278s, 1222m, 1128m, 1108m, 1046m, 990m, 968m, 840s, 788m, 769m, 693s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.87 (s, 1H, Ar-H), 7.75 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.55 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.32 (t, *J* = 8.3 Hz, 1H, Ar-H), 6.98 (ddd, J = 8.3, 2.4, 1.2 Hz, 1H, Ar-H), 6.76 - 6.80 (m, 2H, Ar-H), 3.77 (s, 3H, OCH_3); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 159.9 (qC), 139.8 (qC), 137.7 (qC), 134.1 (CH), 133.3 (2 x CH), 130.4 (CH), 127.3 (qC), 125.3 (2 x CH), 121.0 (CH), 117.7 (qC), 115.1 (CH), 114.5 (CH), 112.9 (qC), 55.3 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{13}N_4O$ calculated 277.1089, found 277.1099.



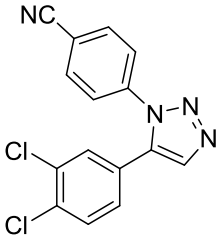
4-(5-(2-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 178f was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 2-ethynylanisole (48 mg, 47 μL, 0.36 mmol) and the product isolated as a yellow solid (52 mg, 0.19 mmol, 63%); MP = 142 - 142 °C; LRMS [M + H] m/z = 277.2; ν_{max} / cm^{-1} 2228m, 1604s, 1511s, 1478m, 1453m, 1417w, 1265m, 1251m, 1232m, 1100m, 1018m, 987m, 838s, 768s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.82 (s, 1H, Ar-H), 7.68 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.50 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.45 (dd, *J* = 8.3, 7.5 Hz, 1H, Ar-H), 7.30 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.06 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.87 (d, *J* = 8.3 Hz, 1H, Ar-H), 3.41 (s, 3H, OCH_3); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 156.1 (qC), 141.1 (qC), 134.9 (qC), 134.9 (CH), 133.0 (2 x CH), 131.9 (CH), 130.9 (CH), 123.7 (2 x CH), 121.2 (CH), 117.8 (qC), 115.4 (qC), 112.2 (qC), 111.4 (CH), 54.9 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{13}N_4O$ calculated 277.1089, found 277.1079.



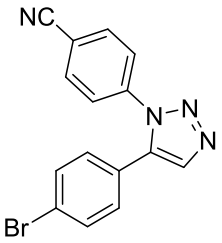
4-(5-(4-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 178g was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-ethynyl-4-fluorobenzene (43 mg, 41 μL, 0.36 mmol) and the product isolated as an orange solid (62 mg, 0.23 mmol, 78%); MP = 151 - 152 °C; LRMS [M + H] m/z = 265.1; ν_{max} / cm^{-1} 3129w, 3056w, 2923w, 2227m, 1607m, 1509m, 1489s, 1439m, 1287w, 1231s, 1199m, 1158m, 1128m, 1109m, 1078m, 1046m, 989s, 966s, 847s, 832s, 785s, 756s, 687m, 611m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.86 (s, 1H, Ar-H), 7.76 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.52 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.23 (dd, *J* = 8.7, 5.0 Hz, 2H, Ar-H), 7.12 (t, *J* = 8.7 Hz, 2H, Ar-H); ^{19}F NMR (471 MHz, $CDCl_3$): δ ppm = -109.7 (s); ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm = 163.4 (d, *J* = 250.7 Hz, qC), 139.6 (qC), 136.9 (qC), 134.0 (CH), 133.4 (2 x CH), 130.7 (d, *J* = 9.1 Hz, 2 x CH), 125.3 (2 x CH), 122.1 (d, *J* = 3.6 Hz, qC), 117.5 (qC), 116.6 (d, *J* = 22.7 Hz, 2 x CH), 114.4 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{15}H_9N_4NaF$ calculated 287.0709, found 287.0703.



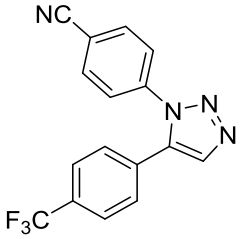
4-(5-(4-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 178h was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-ethynyl-4-chlorobenzene (49 mg, 0.36 mmol) and the product isolated as an orange solid (69 mg, 0.25 mmol, 82%); MP = 117 - 118 °C; LRMS [M + H] m/z = 281.0 and 283.0 [Cl]; ν_{max} / cm^{-1} 2922m, 2852w, 2228w, 1606m, 1510m, 1482m, 1430w, 1283w, 1234m, 1128m, 1089m, 1044w, 1016m, 988s, 966m, 835s, 821s, 737m, 695w, 567m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.88 (s, 1H, Ar-H), 7.77 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.52 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.40 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.18 (d, *J* = 8.5 Hz, 2H, Ar-H); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 139.6 (qC), 136.3 (CH), 134.2 (qC), 133.5 (2 x CH), 129.9 (2 x CH), 129.7 (2 x CH), 129.3 (qC), 125.4 (2 x CH), 120.9 (qC), 117.5 (qC), 113.3 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_{10}N_4Cl$ calculated 281.0594, found 281.0595.



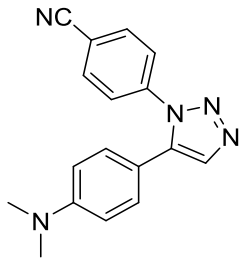
4-(5-(3,4-Dichlorophenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 178i was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1,2-dichloro-4-ethynylbenzene (61 mg, 0.36 mmol) and the product isolated as a yellow solid (77 mg, 0.24 mmol, 82%); MP = 140 °C; LRMS [M + H] m/z = 315.0 and 317,0; ν_{max} / cm^{-1} 3131w, 3060w, 2226m, 1605s, 1509s, 1460s, 1427m, 1412m, 1373m, 1281m, 1232m, 1145m, 1123s, 1058m, 1030s, 1004m, 974s, 893m, 845s, 821s, 799s, 698m, 670m, 607m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm =7.90 (s, 1H, Ar-H), 7.79 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.53 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.49 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.41 (d, *J* = 2.2 Hz, 1H, Ar-H), 7.01 (dd, *J* = 8.3, 2.3 Hz, 1H, Ar-H); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 139.3 (qC), 135.6 (qC), 134.5 (qC), 134.4 (CH), 133.8 (qC), 133.6 (2 x CH), 131.3 (CH), 130.3 (CH), 127.7 (CH), 125.9 (qC), 125.3 (2 x CH), 117.4 (qC), 113.5 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_9N_4Cl_2$ calculated 315.0204, found 315.0198.



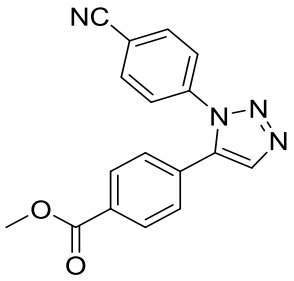
4-(5-(4-Bromophenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 178j was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-ethynyl-4-bromobenzene (65 mg, 0.36 mmol) and the product isolated as an orange solid (77 mg, 0.24 mmol, 79%); MP = 123-124 °C; LRMS [M + H] m/z = 325.0 and 326.0 [Br]; ν_{max} / cm^{-1} 3136w, 2922w, 2227m, 1604m, 1548w, 1510s, 1477m, 1401m, 1233m, 1123m, 1094m, 1070s, 1040s, 990m, 967m, 837s, 819s, 809s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.88 (s, 1H, Ar-H), 7.77 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.56 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.52 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.11 (d, *J* = 8.4 Hz, 2H, Ar-H); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 139.6 (CH), 136.9 (qC), 134.2 (qC), 133.6 (2 x CH), 132.6 (2 x CH), 130.2 (2 x CH), 125.4 (2 x CH), 125.0 (qC), 124.5 (qC), 117.6 (qC), 113.3 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_{10}N_4Br$ calculated 325.0089, found 325.0203.



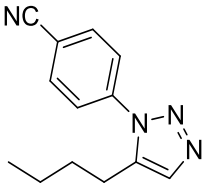
4-(5-(4-(Trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 178k was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (61 mg, 59 μL, 0.36 mmol) and gave the product as a yellow solid (29 mg, 0.09 mmol, 31%); MP = 122 - 123 °C; LRMS [M + H] m/z = 314.1; ν_{max} / cm^{-1} 2230w, 1604m, 1508m, 1324s, 1240w, 1168m, 1108s, 1066s, 990m, 846s, 829s, 697w; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.95 (s, 1H, Ar-H), 7.78 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.69 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.52 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.38 (d, *J* = 8.1 Hz, 2H, Ar-H); ^{19}F NMR (471 MHz, $CDCl_3$): δ ppm = -62.96 (s); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 139.4 (qC), 136.4 (qC), 134.5 (CH), 133.6 (2 x CH), 131.9 (q, *J* = 33.0 Hz, qC), 129.7 (qC), 129.0 (2 x CH), 126.3 (q, *J* = 3.7 Hz, 2 x CH), 125.4 (2 x CH), 123.5 (q, *J* = 270.7 Hz, CF_3), 117.4 (qC), 113.5 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{10}N_4F_3$ calculated 315.0858, found 315.0844.



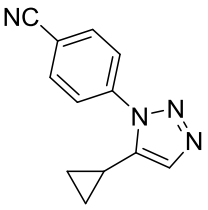
4-(5-(4-(Dimethylamino)phenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 178l was prepared *via* the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 4-ethynyl-*N,N*-dimethylaniline (52 mg, 0.36 mmol) and the product isolated as an orange solid (68 mg, 0.24 mmol, 78%); MP = 141 - 142 °C; LRMS [M + H] m/z = 290.2; ν_{max} / cm^{-1} 3058w, 2927w, 2231m, 1601m, 1506m, 1490m, 1443m, 1416m, 1285m, 1249m, 1229m, 1139m, 1110m, 1091m, 1053m, 989m, 968m, 848s, 774s, 753s, 689s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.77 (s, 1H, Ar-H), 7.74 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.57 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.06 (d, *J*=8.8 Hz, 2H, Ar-H), 6.66 (d, *J*=8.8 Hz, 2H, Ar-H), 3.01 (s, 6H, 2 x NCH_3); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 150.9 (qC), 140.4 (CH), 138.5 (qC), 133.3 (2 x CH), 133.1 (qC), 129.6 (2 x CH), 125.4 (2 x CH), 117.9 (qC), 112.6 (qC), 112.5 (qC), 112.1 (2 x CH), 40.1 (2 x CH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{17}H_{16}N_5$ calculated 290.1406, found 290.1404.



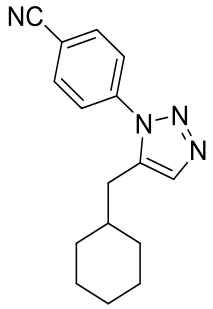
Methyl 4-(1-(4-cyanophenyl)-1*H*-1,2,3-triazol-5-yl)benzoate 178m was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and methyl 4-ethynylbenzoate (58 mg, 0.36 mmol) After 18 hours a further 0.5 eq $ZnEt_2$ (0.15 ml, 0.15 mmol, 1 M in hexanes) was added before quenching with aqueous NH_4Cl. Work up and isolation gave the product as a yellow oil (38 mg, 0.13 mmol, 42%); LRMS [M + H] m/z = 305.1; ν_{max} / cm^{-1} 2230m, 1718m, 1605m, 1508s, 1434m, 1276s, 1103s, 989s, 845s, 768m, 695m; ^1H NMR (400 MHz, $CDCl_3$): δ ppm = 8.08 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.76 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.95 (s, 1H, Ar-H), 7.52 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.32 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.95 (s, 3H, OCH_3); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 166.0 (C=O), 139.6 (qC), 136.9 (qC), 134.4 (CH), 133.5 (2 x CH), 131.4 (qC), 130.4 (qC), 130.4 (2 x CH), 128.6 (2 x CH), 125.4 (2 x CH), 117.5 (qC), 113.3 (qC), 52.5 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{17}H_{13}N_4O_2$ calculated 305.1039, found 305.1029.



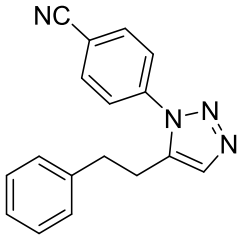
4-(5-Butyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 178r was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-hexyne (30 mg, 41 μL, 0.36 mmol) and the product isolated as a yellow oil (55 mg, 0.24 mmol, 81%); Product isolated with ~15% contamination of 4-aminobenzonitrile (calculated from ^{1}H NMR); LRMS [M + H] m/z = 227.2; ν_{max} / cm^{-1} 2962w, 2925w, 2859w, 2227m, 1604m, 1503s, 1462m, 1406m, 1271m, 1255m, 1179w, 1125m, 1051m, 1013m, 969m, 855s, 821s, 743m, 639m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.87 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.65 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.62 (s, 1H, Ar-H), 2.71 (t, *J* = 7.8 Hz, 2H, Ar-H), 1.62 (dt, *J* = 15.0, 7.8 Hz, 2H, CH_2), 1.36 (dq, *J* = 15.0, 7.3 Hz, 2H, CH_2), 0.90 (t, *J* = 7.3 Hz, 3H, CH_3); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 139.9 (qC), 138.2 (qC), 133.5 (2 x CH), 133.0 (CH), 125.4 (2 x CH), 117.6 (qC), 113.3 (qC), 30.2 (CH_2), 23.6 (CH_2), 22.1 (CH_2), 13.6 (CH_3); HRMS ([M + H]$^{+}$, +ESI) m/z $C_{13}H_{15}N_4$ calculated 227.1297, found 227.1294.



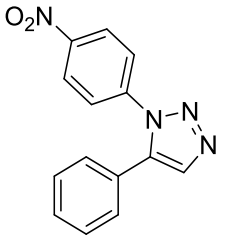
4-(5-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 178s was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and ethynylcyclopropane (1M solution in toluene, 0.36 ml, 0.36 mmol) and the product isolated as an orange solid (42 mg, 0.20 mmol, 67%); MP = 147 °C; LRMS [M + H] m/z = 211.1; ν_{max} / cm^{-1} 2921w, 2229m, 1605m, 1509m, 1252m, 1066m, 975m, 837s, 822s, 698m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.81 (d, *J* = 1.9 Hz, 4H, Ar-H), 7.34 (s, 1H, Ar-H), 1.70 - 1.77 (m, 1H, CH), 1.04 - 1.10 (m, 2H, CH), 0.77 - 0.81 (m, 2H, CH); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 140.3 (qC), 140.1 (CH), 133.4 (2 x CH), 131.4 (qC), 124.6 (2 x CH), 117.7 (qC), 112.8 (qC), 8.6 (2 x CH_2), 5.3 (CH); HRMS ([M + H]$^{+}$, +ESI) m/z $C_{12}H_{11}N_4$ calculated 211.0984, found 211.0981.



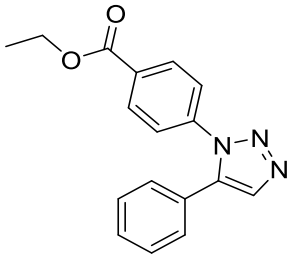
4-(5-(Cyclohexylmethyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 178t was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 3-cyclohexyl-1-propyne (44 mg, 52 μL, 0.36 mmol) and the product isolated as an orange solid (57 mg, 0.21 mmol, 71%); MP = 118 - 119 °C; LRMS [M + H] m/z = 267.2; ν_{max} / cm^{-1} 2920s, 2849m, 2230m, 1606m, 1513s, 1445m, 1258m, 1090m, 978m, 854s, 681w; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.87 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.62 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.60 (s, 1H, Ar-H), 2.59 (d, *J* = 7.1 Hz, 2H, CH_2), 1.60 - 1.71 (m, 5H, Alk-CH), 1.49 (ddd, *J* = 11.0, 7.4, 3.8 Hz, 1H, Alk-CH), 1.09 - 1.21 (m, 3H, Alk-CH), 0.79 - 0.93 (m, 2H, Alk-CH); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 139.9 (qC), 136.9 (qC), 133.6 (CH), 133.5 (2 x CH), 125.8 (2 x CH), 117.5 (qC), 113.2 (qC), 37.5 (CH), 32.8 (2 x CH_2), 31.1 (CH_2), 25.9 (CH_2), 25.7 (2 x CH_2); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{19}N_4$ calculated 267.1610, found 267.1599.



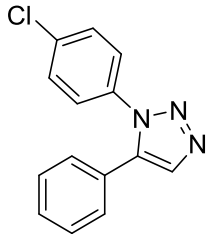
4-(5-Phenethyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 178u was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 4-phenyl-1-butyne (47 mg, 50 µL, 0.36 mmol) and gave the desired product as a yellow solid (62 mg, 0.23 mmol, 75%); MP = 126 - 127 °C; LRMS [M + H] m/z = 275.1; ν_{max} / cm^{-1} 2919w, 2227m, 1601m, 1506m, 1418w, 1252w, 1081m, 978m, 853s, 826s, 751m, 698s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.82 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.67 (s, 1H, Ar-H), 7.47 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.23 - 7.30 (m, 3 H, Ar-H), 7.05 (dd, *J* = 7.6, 1.5 Hz, 2H, Ar-H), 3.06 (t, *J* = 7.1 Hz, 2H, CH_2), 2.96 (t, *J* = 7.1 Hz, 2H, CH_2); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 139.6 (qC), 139.1 (qC), 137.3 (qC), 133.4 (2 x CH), 133.2 (CH), 128.7 (2 x CH), 128.2 (2 x CH), 126.8 (CH), 125.6 (2 x CH), 117.6 (qC), 113.3 (qC), 34.7 (CH_2), 25.7 (CH_2); HRMS ($[M + H]^+$, +ESI) m/z $C_{17}H_{15}N_4$ calculated 275.1290, found 275.1292;



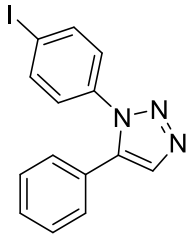
1-(4-Nitrophenyl)-5-phenyl-1*H*-1,2,3-triazole triazole benzonitrile 178v was prepared in accordance with the general procedure from 1-azido-4-nitrobenzene (49 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 µL, 0.36 mmol) and gave the desired product as an orange solid (49 mg, 0.18 mmol, 61%); MP = 161 - 162 °C; LRMS [M + H] m/z = 267.2; ν_{max} / cm^{-1} 3082w, 1594m, 1520s, 1497m, 1480m, 1453w, 1342s, 1311s, 1237m, 1173w, 1109m, 1045m, 988m, 964m, 853s, 762s, 750s, 697s, 687s; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 8.30 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.89 (s, 1H, Ar-H), 7.59 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.50-7.39 (m, 3H, Ar-H), 7.24 (dd, *J* = 8.0, 2.0 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 147.5 (qC), 141.3 (qC), 138.0 (qC), 134.2 (CH), 129.9 (CH), 129.3 (2 x CH), 128.7 (2 x CH), 126.1 (qC), 125.3 (2 x CH), 124.9 (2 x CH); HRMS ($[M + H]^+$, +ESI) m/z $C_{14}H_{11}N_4O_2$ calculated 267.0882, found 267.0888.



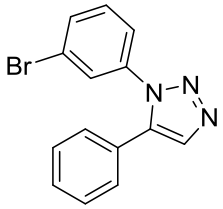
Ethyl 4-(5-phenyl-1H-1,2,3-triazol-1-yl)benzoate 178w was prepared in accordance with the general procedure from ethyl 4-azidobenzoate (57 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as a yellow solid (69 mg, 0.23 mmol, 78%); MP = 142 - 143 °C; LRMS [M + H] m/z = 294.4; ν_{max} / cm^{-1} 2970w, 1717s, 1605m, 1509m, 1479m, 1452w, 1409m, 1367w, 1272s, 1173m, 1129s, 1112s, 1101s, 1048m, 1016m, 988m, 951m, 859m, 841m, 768s, 699s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.11 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.87 (s, 1H, Ar-H), 7.45 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.34 - 7.42 (m, 3H, Ar-H), 7.23 (dd, *J* = 8.1, 1.5 Hz, 2H, Ar-H),4.40 (q, *J* = 7.1 Hz, 2H, CH_2), 1.40 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 165.4 (C=O), 139.8 (qC), 137.8 (qC), 133.8 (CH), 131.0 (qC), 130.7 (2 x CH), 129.5 (CH), 129.0 (2 x CH), 128.6 (2 x CH), 126.4 (qC), 124.7 (2 x CH), 61.4 (CH_2), 14.2 (CH_3); HRMS ($[M + Na]^+$, +ESI) m/z $C_{17}H_{15}N_3O_2Na$ calculated 316.1062, found 316.1063.



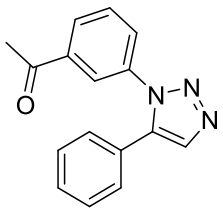
1-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,3-triazole 178x was prepared in accordance with the general procedure from 1-azido-4-chlorobenzene (46 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as a yellow solid (41 mg, 0.16 mmol, 54%); MP = 87 - 88 °C; LRMS [M + H] m/z = 256.2 and 258.2 [Cl]; ν_{max} / cm^{-1} 3076w, 2105w, 1600w, 1494s, 1440m, 1405w, 1285m, 1231m, 1177w, 1127m, 1092s, 1043m, 988s, 966m, 916w, 830s, 762s, 746m, 694s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.87 (s, 1H, Ar-H), 7.37 - 7.44 (m, 5H, Ar-H), 7.32 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.24 (dd, *J* = 7.9, 1.6 Hz, 2H, Ar-H); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 137.7 (qC), 135.1 (qC), 135.0 (qC), 133.5 (CH), 129.6 (2 x CH), 129.4 (CH), 129.0 (2 x CH), 128.6 (2 x CH), 126.4 (qC), 126.3 (2 x CH); HRMS ($[M + H]^+$, +ESI) m/z $C_{14}H_{11}N_3Cl$ calculated 256.0636, found 256.0629.



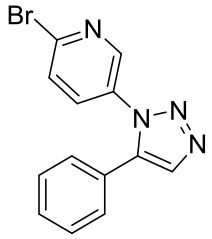
1-(4-Iodophenyl)-5-phenyl-1*H*-1,2,3-triazole 178y was prepared in accordance with the general procedure from 1-azido-4-iodobenzene (73 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as an orange solid (58 mg, 0.17 mmol, 56%); MP = 116 - 117 °C; LRMS [M + H] m/z = 348.3; ν_{max} / cm^{-1} 2922w, 2852w, 1602w, 1486s, 1414w, 1267m, 1234m 1130m, 1118m, 1043m, 987s, 922m, 835s, 819s, 760s, 696s; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 7.86 (s, 1H, Ar-H), 7.77 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.36 - 7.43 (m, 3H, Ar-H), 7.24 (dd, *J* = 7.8, 1.7 Hz, 2H, Ar-H), 7.12 (d, *J* = 8.8 Hz, 2H, Ar-H); ^{13}C NMR (101 MHZ, $CDCl_3$) δ ppm = 138.5 (CH), 137.9 (qC), 137.6 (qC), 136.2 (qC), 133.6 (2 x CH), 129.5 (2 x CH), 129.0 (2 x CH), 128.6 (CH), 126.6 (2 x CH), 126.4 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{14}H_{10}N_3NaI$ calculated 369.9817, found 369.9808.



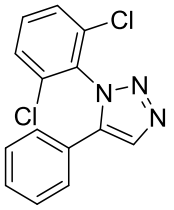
1-(3-Bromophenyl)-5-phenyl-1*H*-1,2,3-triazole 178z was prepared in accordance with the general procedure from 1-azido-3-bromobenzene (59 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as an orange solid (52 mg, 0.17 mmol, 58%); MP = 105 °C; LRMS [M + H] m/z = 300.3 and 302.3 [Br]; ν_{max} / cm^{-1} 3070w, 2922w, 1580m, 1471s, 1433m, 1263w, 1231m, 1127m, 1051m, 1004w, 991w, 966m, 882m, 830s, 786s, 762s, 750s, 694s, 677s; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 7.86 (s, 1H, Ar-H), 7.64 (t, *J* = 1.7 Hz, 1H, Ar-H), 7.59 (dq, *J* = 7.7, 1.0 Hz, 1H, Ar-H), 7.36 - 7.43 (m, 3H, Ar-H), 7.29 (t, *J* = 8.1 Hz, 1H, Ar-H), 7.22 - 7.26 (m, 3H, Ar-H); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 137.8 (qC), 137.5 (CH), 133.5 (qC), 132.3 (CH), 130.5 (CH), 129.5 (CH), 129.0 (2 x CH), 128.6 (2 x CH), 128.2 (CH), 126.3 (qC), 123.6 (CH), 122.8 (qC); HRMS ([M + Na]$^+$, +ESI) m/z $C_{14}H_{10}N_3NaBr$ calculated 321.9956, found 321.9964



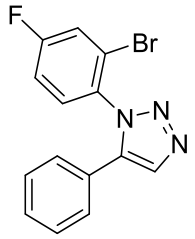
1-(3-(5-Phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)ethan-1-one 178aa was prepared in accordance with the general procedure from 1-(3-azidophenyl)ethan-1-one (48 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as an orange amorphous solid (43 mg, 0.16 mmol, 54%); LRMS [M + H] m/z = 264.3; ν_{max} / cm^{-1} 2978w, 2924w, 2110w, 1683s, 1587m, 1476m, 1457m, 1359m, 1308m, 1280m, 1248s, 1210w, 1067m, 1010m, 898m, 790m, 764s, 699s, 679s; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 7.98 (s, 1H, Ar-H), 7.90 (s, 1H, Ar-H), 7.54 - 7.57 (m, 2H, Ar-H), 7.36 - 7.43 (m, 4H, Ar-H), 7.25 (dd, *J*=7.9, 1.6 Hz, 2H, Ar-H), 2.54 (s, 3H, CH_3); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 196.4 (C=O), 138.2 (qC), 137.8 (CH), 136.9 (qC), 133.6 (qC), 129.9 (qC), 129.7 (2 x CH), 129.5 (CH), 129.2 (CH), 129.0 (CH), 128.7 (2 x CH), 128.6 (CH), 124.9 (CH), 26.6 (CH_3); HRMS ([M + Na]$^+$, +ESI) m/z $C_{16}H_{13}N_3ONa$ calculated 286.0956, found 286.0953.



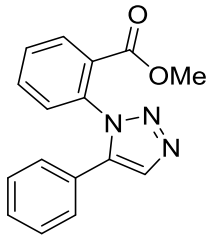
2-Bromo-5-(5-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine 178ab was prepared in accordance with the general procedure from 5-azido-2-bromopyridine (59 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as an orange amorphous solid (64 mg, 0.21 mmol, 71%); LRMS [M + H] m/z = 301.3 and 303.3 [Br]; ν_{max} / cm^{-1} 3040w, 1570w, 1538w, 1470s, 1379m, 1307m, 1271m, 1223m, 1154w, 1072s, 1017w, 983s, 919m, 833s, 771s, 754s, 725m, 695s; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 8.41 (d, *J* = 2.2 Hz, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.57 - 7.65 (m, 2H, Ar-H), 7.40 - 7.47 (m, 3H, Ar-H), 7.22 - 7.28 (m, 2H, Ar-H); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 146.7 (qC), 145.7 (CH), 142.1 (qC), 138.1 (qC), 134.4 (CH), 134.0 (CH), 130.0 (CH), 129.4 (2 x CH), 128.7 (2 x CH), 128.7 (CH), 125.8 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{13}H_9N_4NaBr$ calculated 322.9908, found 322.9922.



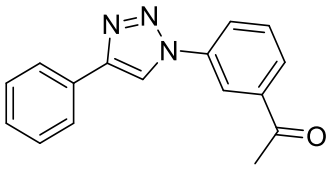
1-(2,6-Dichlorophenyl)-5-phenyl-1*H*-1,2,3-triazole 178ac was prepared in accordance with the general procedure from 2-azido-1,3-dichlorobenzene (56 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol). At 18 hours a further 0.5 eq. of $ZnEt_2$ was added (0.15 ml, 0.15 mmol, 1 M in hexanes). Work up and isolation gave the desired product as a pale yellow solid (68 mg, 0.24 mmol, 78%); MP = 125 °C; LRMS [M + H] m/z = 290.2 and 292.2 [Cl]; ν_{max} / cm^{-1} 3129w, 3077w, 1570m, 1482s, 1440s, 1284w, 1266w, 1230m, 1199m, 1144m, 1077m, 1042w, 989m, 966m, 913w, 856m, 784s, 755s, 732s, 686s; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 7.95 (s, 1H, Ar-H), 7.31 - 7.48 (m, 6H, Ar-H), 7.26 (d, *J* = 6.6 Hz, 1H, Ar-H); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 139.6 (2 x qC), 134.5 (CH), 132.7 (qC), 132.2 (CH), 131.8 (qC), 129.5 (2 x CH), 128.9 (2 x CH), 128.8 (2 x CH), 127.6 (CH), 126.0 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{14}H_9N_3NaCl_2$ calculated 312.0071, found 312.0069.



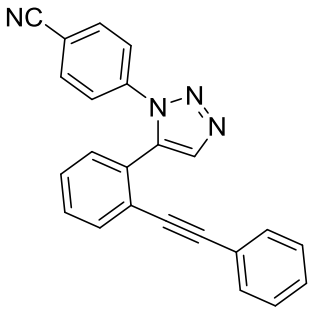
1-(2-Bromo-4-fluorophenyl)-5-phenyl-1*H*-1,2,3-triazole 178ad was prepared in accordance with the general procedure from 1-azido-2-bromo-4-fluorobenzene (65 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol). At 18 hours a further 0.5 eq. of $ZnEt_2$ was added (0.15 ml, 0.15 mmol, 1 M in hexanes). Work up and isolation gave the desired product as a pale yellow solid (77 mg, 0.24 mmol, 81%); MP = 111 - 112 °C; LRMS [M + H] m/z = 318.3 and 320.3 [Br]; ν_{max} / cm^{-1} 3051w, 1594m, 1496s, 1481s, 1416w, 1263m, 1235m, 1204s, 1135m, 1066w, 10362, 1025m, 986m, 965m, 875m, 861s, 843m, 830s, 762s, 691s, 629m; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 7.92 (s, 1H, Ar-H), 7.42 - 7.47 (m, 2H, Ar-H), 7.30 - 7.38 (m, 3H, Ar-H), 7.15 - 7.24 (m, 3H, Ar-H); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 162.8 (d, *J* = 256.0 Hz, CF), 139.3 (CH), 132.6 (d, *J* = 3.7 Hz, qC), 132.3 (CH), 130.6 (d, *J* = 9.5 Hz, CH), 129.4 (qC), 128.9 (2 x CH), 127.8 (2 x CH), 126.1 (qC), 122.6 (d, *J* = 10.3 Hz, qC), 121.1 (d, *J* = 25.7 Hz, CH), 115.7 (d, *J* = 22.0 Hz, CH); HRMS ([M + Na]$^+$, +ESI) m/z $C_{14}H_9N_3NaBrF$ calculated 339.9862, found 339.9865.



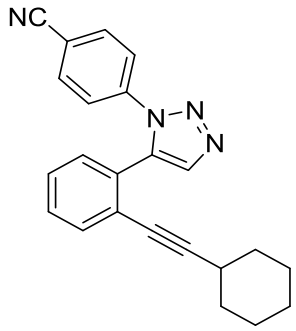
Methyl 2-(5-phenyl-1*H*-1,2,3-triazol-1-yl)benzoate 178ae was prepared in accordance with the general procedure from methyl 2-azidobenzoate (53 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol). On addition of the $ZnEt_2$ the reaction was stirred under microwave heating (100 ^oC) for 2 hours before quenching. Work up and isolation gave the desired product as an orange solid (54 mg, 0.19 mmol, 65%); MP = 123 - 124 °C; LRMS [M + H] m/z = 280.1; ν_{max} / cm^{-1} 2951w, 2925w, 1726s, 1687m, 1671m, 1601m, 1580m, 1499m, 1480m, 1447m, 1432m, 1262s, 1187w, 1162w, 1120m, 1090m, 1052m, 990m, 965m, 853m, 825w, 764s, 691s; ^1H NMR (400 MHz, $CDCl_3$) δ ppm = 8.00 (dd, *J* = 7.5, 1.6 Hz, 1H, Ar-H), 7.88 (s, 1H, Ar-H), 7.54 - 7.65 (m, 2H, Ar-H), 7.35 (dd, *J* = 7.5, 1.1 Hz, 1H, Ar-H), 7.25 - 7.33 (m, 3H, Ar-H), 7.18 (dd, *J* = 7.8, 1.2 Hz, 2H, Ar-H), 3.60 (s, 3H, OCH_3); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 165.0 (C=O), 139.0 (qC), 135.7 (qC), 132.8 (CH), 132.2 (CH), 131.3 (CH), 130.0 (CH), 129.1 (CH), 128.7 (2 x CH), 128.5 (qC), 128.4 (CH), 128.1 (2 x CH), 126.3 (qC), 52.4 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{14}N_3O_2$ calculated 280.1086, found 280.1086.



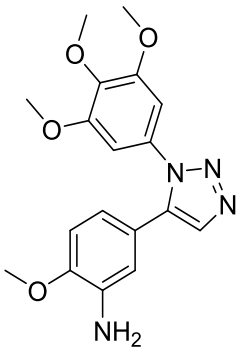
1-(3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)ethan-1-one was prepared in accordance with the general procedure from 1-(3-azidophenyl)ethan-1-one (48 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol). On addition of the $ZnEt_2$ the reaction was stirred at ambient temperature for 16 hours. At this point a suspension of $CuCl_2$ (30 mg, 0.225 mmol) in anhydrous THF (2 ml) was added to the reaction and the mixture stirred at 45 °C for 4 hours. Work up and isolation (as in the general procedure) gave the 1,4-triazole product as a white solid (26 mg, 0.10 mmol, 33%); MP = 141-142 °C; LRMS [M + H] m/z = 264.4; ν_{max} / cm^{-1} 3143w, 1676s, 1591m, 1493m, 1477s, 1450m, 1402w, 1358s, 1312w, 1268s, 1231s, 1177m, 1073m, 1042s, 1010m, 960w, 905m, 817m, 791s, 770s, 699s, 681s, 622w; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 8.35 (dd, *J* = 2.2, 1.2 Hz, 1H, Ar-H), 8.30 (s, 1H, Ar-H), 8.11 (ddd, *J* = 8.1, 2.2, 1.2 Hz, 1H, Ar-H), 8.04 (dt, *J* = 7.8, 1.2 Hz, 1H, Ar-H), 7.93 (dd, *J* = 8.3, 1.2 Hz, 1H, Ar-H), 7.69 (dd, *J* = 8.1, 7.8 Hz, 2H, Ar-H), 7.49 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.38 - 7.43 (m, 1H, Ar-H), 2.71 (s, 3H, CH_3); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 196.8 (C=O), 148.8 (qC), 138.5 (CH), 137.5 (qC), 130.3 (CH), 130.0 (qC), 129.0 (2 x CH), 128.7 (CH), 128.5 (CH), 125.9 (2 x CH), 124.8 (qC), 119.6 (CH), 117.5 (CH), 26.8 (CH_3); HRMS ($[M + Na]^+$, +ESI) m/z $C_{16}H_{13}N_3ONa$ calculated 286.0956, found 286.0964.



4-(5-(2-(Phenylethynyl)phenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 254a was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-ethynyl-2-(phenylethynyl)benzene (73 mg, 0.36 mmol) and gave the product as a yellow solid (91 mg, 0.26 mmol, 88%); MP = 141 - 142 °C; LRMS [M + H] m/z = 347.2; ν_{max} / cm^{-1} 2292w, 2230m, 1601m, 1506m, 1490m, 1443m, 1228m, 1139m, 1110m, 1090m, 989m, 967m, 848s, 774s, 753s, 689s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.00 (s, 1H, Ar-H), 7.61 (d, *J* = 8.8 Hz, 3H, Ar-H), 7.46 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.40 - 7.51 (m, 2H, Ar-H), 7.29 - 7.36 (m, 4H, Ar-H), 7.21 (dd, *J*=7.7, 1.3 Hz, 2H); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 140.0 (CH), 136.3 (qC), 135.3 (qC), 133.1 (2 x CH), 132.9 (CH), 131.3 (2 x CH), 130.0 (CH), 130.0 (2 x CH), 128.9 (CH), 128.7 (CH), 128.4 (qC), 128.4 (2 x CH), 124.1 (CH), 123.6 (qC), 121.9 (qC), 117.7 (qC), 112.4 (qC), 94.5 (alkyne qC), 86.4 (Alkyne qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{23}H_{15}N_4$ calculated 347.1291, found 347.1288.



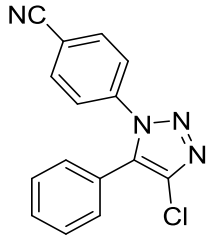
4-(5-(2-(Cyclohexylethynyl)phenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 254b was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-(cyclohexylethynyl)-2-ethynylbenzene (75 mg, 0.36 mmol) and gave the product as a yellow solid (80 mg, 0.23 mmol, 76%); MP = 122-123 °C; LRMS [M + H] m/z = 353.2; ν_{max} / cm^{-1} 2922m, 2851m, 2228m, 1604m, 1509m, 1470w, 1443m, 1146m, 992m, 851m, 830m, 765s, 567m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.91 (s, 1H, Ar-H), 7.68 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.51 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.50 (td, *J* = 6.8, 1.2 Hz, 1H, Ar-H), 7.41 (td, *J* = 7.6, 1.4 Hz, 1H, Ar-H), 7.33 (td, *J* = 7.6, 1.3 Hz, 1H, Ar-H), 7.19 (dd, *J* = 7.6, 1.0 Hz, 1H, Ar-H), 2.30 - 2.41 (m, 1H, Alkyl CH), 1.44 - 1.70 (m, 5H, Alkyl CH), 1.22 - 1.30 (m, 5H, Alkyl CH); ^{13}C NMR (101 MHZ, $CDCl_3$): δ ppm = 140.2 (qC), 136.5 (qC), 135.2 (CH), 133.2 (2 x CH), 133.0 (CH), 129.9 (CH), 129.9 (CH), 128.5 (qC), 127.9 (CH), 124.8 (qC), 124.0 (2 x CH), 117.8 (qC), 112.4 (qC), 32.2 (2 x CH_2), 29.5 (CH), 25.7 (2 x CH_2), 24.7 (CH_2); HRMS ($[M + H]^+$, +ESI) m/z $C_{23}H_{21}N_4$ calculated 353.1761, found 353.1759.



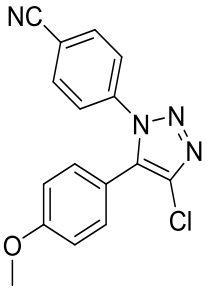
2-Methoxy-5-(1-(3,4,5-trimethoxyphenyl)-1H-1,2,3-triazol-5-yl)aniline 178aj was prepared under the standard conditions from 5-azido-1,2,3-trimethoxybenzene (63 mg 0.3 mmol) and 5-ethynyl-2-methoxyaniline (53 mg, 0.36 mmol) with 1.1 eq $ZnEt_2$ (0.33 ml, 0.33 mmol, 1 M solution in hexanes) and the product was isolated as an off white solid (65 mg, 0.18 mmol, 61%); MP = 163 - 164 °C; LRMS [M + H] m/z = 357.2; ν_{max} / cm^{-1} 3465w, 3358m, 2938w, 1599m, 1553w, 1503s, 1451m, 1418m, 1319w, 1274w, 1227s, 1180w, 1118s, 1039w, 993m, 854w, 830w, 801m, 773w, 760w, 736w, 618w; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ ppm = 7.90 (s, 1H, Ar-H), 6.81 (d, *J* = 8.3 Hz, 1H, Ar-H), 6.72 (s, 2H, Ar-H), 6.62 (d, *J* = 2.2 Hz, 1H, Ar-H), 6.46 (dd, *J* = 8.3, 2.2 Hz, 1H, Ar-H), 4.89 (br. s., 2H, NH_2), 3.76 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.68 (s, 6H, 2 x OCH_3); ^{13}C NMR (101 MHZ, $(CD_3)_2SO$): δ ppm =153.0 (2 x qC), 147.0 (qC), 138.3 (CH), 137.9 (qC), 137.8 (qC), 132.2 (qC), 132.2 (qC), 118.7 (qC), 116.5 (CH), 113.3 (CH), 110.4 (CH), 103.4 (2 x CH), 60.2 (OCH_3), 56.1 (2 x OCH_3), 55.3 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{18}H_{21}N_4O_4$ calculated 357.1562, found 357.1568.

6.4.5. General procedure for the synthesis of 4-chloro, 1,5-substituted 1,2,3-triazoles.

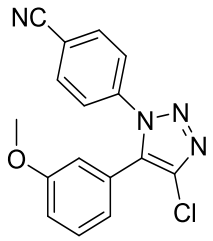
The azide (0.3 mmol), alkyne (0.36 mmol) and *N*-methylimidazole (2.5 mg, 0.03 mmol) were added to a glass vial or round bottomed flask. The vessel was purged with N_2 and sealed. Dry THF (4 mL) was added and stirred for 5 minutes before $ZnEt_2$ (0.15 mL, 0.15 mmol, 1 M in hexanes) was added. The reaction was stirred at ambient temperature overnight (approximately 18 hours). The reaction mixture was transferred by syringe to a nitrogen flushed vial containing *N*-chlorosuccinimide (60 mg, 0.45 mmol) and stirred at ambient temperature for 1 hour. The mixture was partitioned between saturated $NH_4Cl_{(aq)}$ (5 mL) and EtOAc (10 mL) and the organic layer was washed with brine (7 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc : hexane, 1 : 20 to 1 : 5) to afford the pure material.



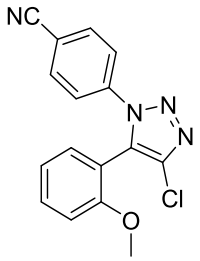
4-(4-Chloro-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 258a was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the product as a yellow solid (57 mg, 0.20 mmol, 68%); MP = 109 - 110 °C; LRMS [M + H] m/z = 281.0 and 283.0 [Cl]; ν_{max} / cm^{-1} 3021w, 2229m, 1604m, 1510m, 1494m, 1476m, 1461m, 1419m, 1241m, 1024s, 984s, 833s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.73 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.41 - 7.54 (m, 5H, Ar-H), 7.28 (dd, *J*=7.8, 1.5 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.5 (qC), 135.2 (qC), 133.4 (2 x CH), 133.1 (qC), 130.3 (CH), 129.4 (2 x CH), 129.2 (2 x CH), 124.9 (2 x CH), 124.3 (qC), 117.4 (qC), 113.3 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_{10}N_4Cl$ calculated 281.0594, found 281.0591.



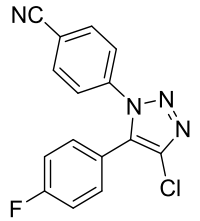
4-(4-Chloro-5-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 258b was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 4-ethynylanisole (48 mg, 47 μL, 0.36 mmol) and the product isolated as an orange solid (78 mg, 0.25 mmol, 84%); MP = 131 °C; LRMS [M + H] m/z = 311.1 and 313.1 [Cl]; ν_{max} / cm^{-1} 2964w, 2232m, 1616m, 1606m, 1562w, 1510m, 1497m, 1454m, 1415w, 1297m, 1258s, 1212,m 1178m, 1114w, 1082m, 1029m, 1018m, 989m, 836s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.73 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.50 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.20 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.96 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.86 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 161.0 (qC), 139.7 (qC), 134.9 (qC), 133.4 (2 x CH), 133.0 (qC), 130.8 (2 x CH), 124.9 (2 x CH), 117.5 (qC), 116.2 (qC), 114.8 (2 x CH), 113.2 (qC), 55.4 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{11}ClN_4O$ calculated 311.0700, found 311.0691.



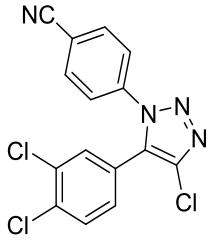
4-(4-Chloro-5-(3-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 258c was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 3-ethynylanisole (48 mg, 46 μL, 0.36 mmol) and the product isolated as a yellow solid (53 mg, 0.17 mmol, 57%); MP = 140 °C; LRMS [M + H] m/z = 311.2 and 313.2 [Cl]; ν_{max} / cm^{-1} 3070w, 2923w, 2852w, 2229m, 1606m, 1590m, 1546w, 1512m, 1480m, 1465m, 1418m, 1310m, 1282m, 1269m, 1236s, 1217m, 1180m, 1159m, 1099m, 1039m, 1014m, 995s, 867m, 846s, 834s, 789s, 696m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.73 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.50 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.35 (t, *J* = 8.2 Hz, 1H, Ar-H), 7.01 (dd, *J* = 8.2, 2.3 Hz, 1H, Ar-H), 6.84 (t, *J* = 2.2 Hz, 1H, Ar-H), 6.79 (d, *J* = 8.2 Hz, 1H, Ar-H), 3.79 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 160.0 (qC), 139.6 (qC), 135.3 (qC), 133.4 (2 x CH), 133.0 (qC), 130.5 (CH), 125.5 (qC), 124.9 (2 x CH), 121.7 (CH), 117.5 (qC), 115.7 (CH), 115.2 (CH), 113.4 (qC), 55.4 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{12}ClN_4O$ calculated 311.0700, found 311.0709.



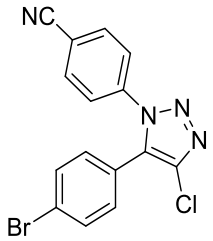
4-(4-Chloro-5-(2-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 258d was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 2-ethynylanisole (48 mg, 47 μL, 0.36 mmol) and the product isolated as a yellow solid (36 mg, 0.12 mmol, 39%); MP = 147 °C; LRMS [M + H] m/z = 311.1 and 313.1 [Cl]; ν_{max} / cm^{-1} 2964w, 2930w, 2232m, 1716m, 1606m, 1510m, 1497m, 1478m, 1463m, 1416m, 1297m, 1258s, 1212m, 1177m, 1114m, 1082m, 1027s, 990s, 836s, 797m, 753m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.69 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.50 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.48 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.39 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.13 (t, *J* = 7.6 Hz, 1H, Ar-H), 6.89 (d, *J* = 8.4 Hz, 1H, Ar-H), 3.42 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 156.3 (qC), 140.8 (qC), 135.8 (qC), 133.1 (2 x CH), 132.5 (CH), 131.2 (CH), 130.7 (qC), 123.4 (2 x CH), 121.3 (CH), 117.6 (qC), 113.4 (qC), 112.7 (qC), 111.5 (CH), 54.9 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{12}ClN_4O$ calculated 311.0700, found 311.0701;



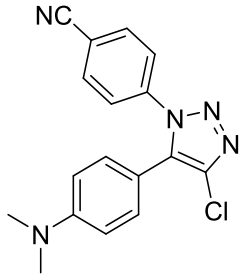
4-(4-Chloro-5-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 258e was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-ethynyl-4-fluorobenzene (43 mg, 41 μL, 0.36 mmol) and the product isolated as an pale yellow solid (56 mg, 0.17 mmol, 57%); MP = 149 - 150 °C; LRMS [M + H] m/z = 299.1 and 301.1 [Cl];]; ν_{max} / cm^{-1} 2231m, 1605m, 1509m, 1494s, 1413w, 1309w, 1216w, 1159w, 1089m, 990m, 845s, 615m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.72 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.45 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.24 (dd, *J* = 8.7, 5.2 Hz, 2H, Ar-H), 7.12 (t, *J* = 8.3 Hz, 2H, Ar-H); ^{19}F NMR (471 MHz, $CDCl_3$): δ ppm = -108.6 (s); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 164.9 (d, *J* = 252.4 Hz, qC), 139.3 (qC), 134.7 (qC), 133.5 (2 x CH), 131.7 (d, *J* = 8.8 Hz, 2 x CH), 125.0 (2 x CH), 122.2 (qC), 120.8 (d, *J* = 3.7 Hz, qC), 117.3 (qC), 116.7 (d, *J* = 22.0 Hz, 2 x CH), 113.5 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_9ClFN_4$ calculated 299.0500, found 299.0490.



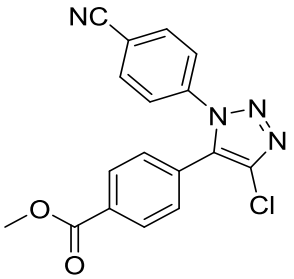
4-(4-Chloro-5-(3,4-dichlorophenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 258f was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1,2-dichloro-4-ethynylbenzene (61 mg, 0.36 mmol) and the product isolated as a yellow solid (57 mg, 0.18 mmol, 61%); MP = 175 - 176 °C; LRMS [M + H] m/z = 348.8 and 350.8 [Cl]; ν_{max} / cm^{-1} 2230m, 1604s, 1507m, 1458m, 1404w, 1280m, 1141m, 1033m, 986m, 844s, 820s, 797m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.79 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.53 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.50 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.45 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.06 (dd, *J* = 8.3, 2.0 Hz, 1H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.0 (qC), 135.7 (qC), 135.2 (qC), 134.0 (qC), 133.7 (2 x CH), 131.4 (CH), 131.0 (CH), 130.9 (qC), 128.4 (CH), 125.0 (2 x CH), 124.2 (qC), 117.2 (qC), 113.9 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_8Cl_3N_4$ calculated 348.9815, found 348.9818.



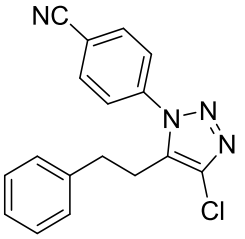
4-(5-(4-Bromophenyl)-4-chloro-1*H*-1,2,3-triazol-1-yl)benzonitrile 258g was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-ethynyl-4-bromobenzene (65 mg, 0.36 mmol) and the product isolated as a pale yellow solid (52 mg, 0.14 mmol, 48%); MP = 173-175 °C; LRMS [M + H] m/z = 359.0 and 361.0 [Cl]; ν_{max} / cm^{-1} 2924w, 2237m, 1600m, 1544w, 1507m, 1475m, 1409w, 1313m, 1261m, 1213m, 1150w, 1107w, 1072s, 1012m, 989s, 846s, 832s, 721w, 654w, 634w; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.76 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.61 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.49 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.16 (d, *J* = 8.3 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.3 (qC), 135.4 (qC), 133.6 (2 x CH), 132.7 (2 x CH), 132.1 (qC), 130.8 (2 x CH), 125.1 (qC), 125.0 (2 x CH), 123.3 (qC), 117.4 (qC), 113.7 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_9BrClN_4$ calculated 358.9699, found 358.9692.



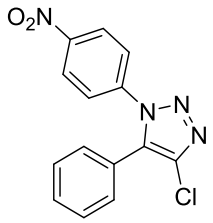
4-(4-Chloro-5-(4-(dimethylamino)phenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 258h was prepared *via* the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 4-ethynyl-N,N-dimethylaniline (52 mg, 0.36 mmol) and the product isolated as an orange solid (53 mg, 0.16 mmol, 55%); MP = 161 - 162°C; LRMS [M + H] m/z = 324.1 and 326.1 [Cl]; ν_{max} / cm^{-1} 2230m, 1605s, 1502s, 1484s, 1328m, 1290m, 1197w, 1174w, 1136m, 1094m, 985s, 945m, 935s, 824s, 803m, 720w; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.72 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.53 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.10 (d, *J* = 9.1 Hz, 2H, Ar-H), 6.69 (d, *J* = 9.1 Hz, 2H, Ar-H), 3.02 (s, 6H, 2 x NMe); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 151.0 (qC), 140.1 (qC), 134.2 (qC), 133.7 (qC), 133.3 (2 x CH), 130.2 (2 x CH), 124.9 (2 x CH), 117.6 (qC), 112.9 (qC), 111.9 (2 x CH), 110.4 (qC), 40.0 (2 x NMe); HRMS ($[M + H]^+$, +ESI) m/z $C_{17}H_{15}ClN_5$ calculated 324.1015, found 324.1004.



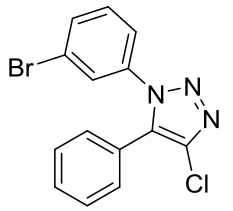
Methyl 4-(4-chloro-1-(4-cyanophenyl)-1*H*-1,2,3-triazol-5-yl)benzoate 258i was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and methyl 4-ethynylbenzoate (58 mg, 0.36 mmol). After 18 hours a further 0.5 eq $ZnEt_2$ (0.15 ml, 0.15 mmol, 1 M in hexanes) was added before quenching with NCS. Work up and isolation gave the product as a yellow sticky solid (18 mg, 0.05 mmol, 18%); LRMS [M + H] m/z = 339.1 and 341.1 [Cl]; ν_{max} / cm^{-1} 2234w, 1716s, 1605m, 1474m, 1410w, 1343w, 1311m, 1275s, 1174w, 1152w, 1124m, 1110m, 1094m, 1070m, 1019w, 991m, 923w, 859m, 770s, 697s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.12 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.75 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.47 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.37 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.96 (s, 3H, OCH_3); ^{13}C NMR could not be analysed due to weak sample. HRMS ($[M + H]^+$, +ESI) m/z $C_{17}H_{12}ClN_4O_2$ calculated 339.0649, found 339.0638.



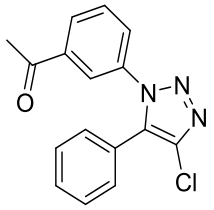
4-(4-Chloro-5-phenethyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 258j was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 4-phenyl-1-butyne (47 mg, 50 μL, 0.36 mmol) and gave the desired product as a white solid (61 mg, 0.20 mmol 66%); MP = 134 - 135 °C; LRMS [M + H] m/z = 309.1 and 310.1 [Cl]; ν_{max} / cm^{-1} 2952w, 2227m, 1718m, 1583s, 1508s, 1435m, 1276s, 1102m, 990m, 967m, 850s, 828s, 762m, 737m, 702s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.73 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.17 - 7.22 (m, 3H, Ar-H), 7.15 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.81 - 6.91 (m, 2H, Ar-H), 3.06 (t, *J* = 7.1 Hz, 2H, CH_2), 2.89 (t, *J* = 7.1 Hz, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.2 (qC), 138.7 (qC), 134.9 (qC), 133.4 (2 x CH), 132.9 (qC), 128.8 (2 x CH), 128.4 (2 x CH), 126.9 (CH), 125.8 (2 x CH), 117.4 (qC), 113.8 (qC), 33.4 (CH_2), 24.7 (CH_2); HRMS ($[M + H]^+$, +ESI) m/z $C_{17}H_{14}ClN_4$ calculated 309.0907, found 309.0897.



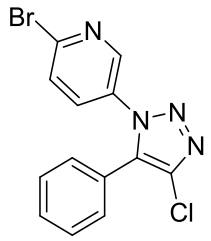
4-Chloro-1-(4-nitrophenyl)-5-phenyl-1*H*-1,2,3-triazole 258k was prepared in accordance with the general procedure from 1-azido-4-nitrobenzene (49 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as a brown solid (42 mg, 0.14 mmol, 47%); MP = 147 °C; LRMS [M + H] m/z = 301.1 and 303.1 [Cl]; ν_{max} / cm^{-1} 3082w, 2918w, 2850w, 1706w, 1594m, 1519s, 1496m, 1480m, 1453m, 1421w, 1403w, 1342s, 1312m, 1269m, 1237m, 1173w, 1111m, 1045m, 988m, 964m, 925w, 853s, 762s, 749s, 697s, 687s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.28 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.53 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.44 - 7.51 (m, 3H, Ar-H), 7.30 (dd, *J* = 8.0, 1.4 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 147.7 (qC), 140.9 (qC), 135.7 (qC), 130.5 (2 x CH), 129.6 (CH), 129.4 (2 x CH), 125.1 (2 x CH), 125.0 (2 x CH), 124.8 (qC), 122.3 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{14}H_{10}ClN_4O_2$ calculated 301.0492, found 301.0491.



1-(3-Bromophenyl)-4-chloro-5-phenyl-1*H*-1,2,3-triazole 258l was prepared in accordance with the general procedure from 1-azido-3-bromobenzene (59 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as an orange solid (49 mg, 0.15 mmol, 49%); MP = 123 - 125 °C; LRMS [M + H] m/z = 334.2 and 336.2 [Br,Cl]; ν_{max} / cm^{-1} 3068w, 2927w, 2108w, 1683w, 1580s, 1547m, 1479s, 1452m, 1428m, 1408w, 1303m, 1258m, 1213m, 1092m, 1069m, 1006m, 997m, 879m, 773s, 696s, 679s, 612m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.56 - 7.62 (m, 2H, Ar-H), 7.40 - 7.47 (m, 3H, Ar-H), 7.24 - 7.32 (m, 3H, Ar-H), 7.15 - 7.21 (m, 1H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 137.4 (qC), 134.7 (qC), 133.1 (qC), 132.7 (CH), 130.6 (CH), 130.1 (CH), 129.4 (2 x CH), 129.1 (2 x CH), 127.9 (CH), 124.6 (qC), 123.3 (CH), 122.9 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{14}H_9BrClN_3Na$ calculated 355.9566, found 355.9580.



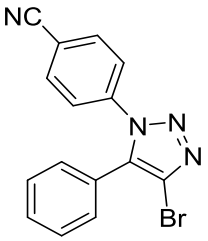
1-(3-(4-Chloro-5-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)ethan-1-one 258m was prepared in accordance with the general procedure from 1-(3-azidophenyl)ethan-1-one (48 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as an orange amorphous solid (39 mg, 0.13 mmol, 44%); LRMS [M + H] m/z = 298.3 and 300.3 [Cl]; ν_{max} / cm^{-1} 2970w, 2925w, 2110w, 1684s, 1555w, 1479m, 1458m, 1357m, 1310m, 1283w, 1250s, 1213w, 1098m, 1068m, 1036m, 1007m, 898m, 807w, 790m, 765s, 698s, 679s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.00 - 8.06 (m, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 7.53 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.42 - 7.47 (m, 3H, Ar-H), 7.29 (dd, *J* = 7.5, 1.5 Hz, 2H, Ar-H), 2.52 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 196.2 (C=O), 138.2 (qC), 136.8 (qC), 134.7 (qC), 133.1 (qC), 130.0 (qC), 129.8 (2 x CH), 129.4 (CH), 129.1 (CH), 128.9 (CH), 128.7 (2 x CH), 124.7 (CH), 124.5 (CH), 26.6 (CH_3); HRMS ($[M + Na]^+$, +ESI) m/z $C_{16}H_{12}ClN_3NaO$ calculated 320.0567, found 320.0576.



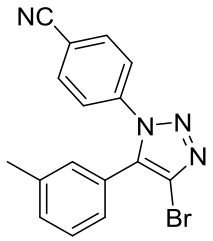
2-Bromo-5-(4-chloro-5-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine 258n was prepared in accordance with the general procedure from 5-azido-2-bromopyridine (59 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as an orange solid (63 mg, 0.19 mmol, 63%); MP = 130 °C; LRMS [M + H] m/z = 335.3 and 337.3 [Cl]; ν_{max} / cm^{-1} 3042w, 1573w, 1551w, 1520w, 1471s, 1409w, 1383m, 1310m, 1277m, 1220m, 1151w, 1080m, 1065m, 1018w, 983s, 918m, 853w, 834s, 775w, 755s, 726m, 695s, 623m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.36 (s, 1H, Ar-H), 7.58 (d, *J* = 1.6 Hz, 2H, Ar-H), 7.44 - 7.51 (m, 3H, Ar-H), 7.28 (dd, *J* = 7.8, 1.7 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 145.3 (CH), 142.5 (qC), 135.2 (qC), 133.9 (CH), 133.3 (qC), 132.6 (qC), 130.4 (CH), 129.4 (2 x CH), 129.4 (2 x CH), 128.7 (CH), 124.0 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{13}H_{12}BrClN_4Na$ calculated 356.9519, found 356.9524.

6.4.6. General procedure for the synthesis of 4-bromo, 1,5-substituted 1,2,3-triazoles

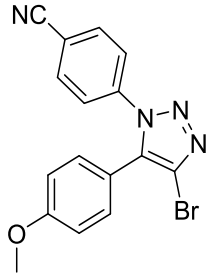
The azide (0.3 mmol), alkyne (0.36 mmol) and *N*-methylimidazole (2.5 mg, 0.03 mmol) were added to a glass vial or round bottomed flask. The vessel was purged with N_2 and sealed. Dry THF (4 mL) was added and stirred for 5 minutes before $ZnEt_2$ (0.15 mL, 0.15 mmol, 1 M in hexanes) was added. The reaction was stirred at ambient temperature overnight (approximately 18 hours). The reaction mixture was transferred by syringe to a nitrogen flushed vial containing *N*-bromosuccinimide (80 mg, 0.45 mmol) and stirred at ambient temperature for 1 hour. The mixture was partitioned between saturated $NH_4Cl_{(aq)}$ (5 mL) and EtOAc (10 mL) and the organic layer was washed with brine (7 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc : hexane, 1 : 20 to 1 : 5) to afford the pure material.



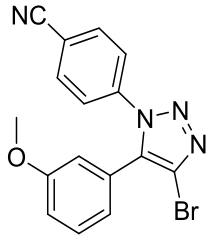
4-(4-Bromo-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 256a was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the product as an orange solid (69 mg, 0.21 mmol, 71%). **256a** was also synthesised in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol). After stirring with $ZnEt_2$ for 18 hours, a solution of Br_2 (58 mg, 18 μL, 0.36 mmol) in THF (1 ml) was added and the reaction mixture stirred vigorously for 30 minutes. Work up and isolation carried out as in the general procedure gave the product as an orange solid (70 mg, 0.22 mmol, 72%). MP = 137 - 138 °C; LRMS [M + H] m/z = 325.0 and 326.0 [Br]; ν_{max} / cm^{-1} 5052w, 2940w, 2859w, 2231m, 1604m, 1552w, 1507m, 1477m, 1447m, 1418m, 1402m, 1293m, 1261m, 1213m, 1111m, 1087s, 990s, 849s, 787m, 765s, 700s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.72 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.43 - 7.51 (m, 5H, Ar-H), 7.28 (dd, *J* = 8.1, 1.7 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.5 (qC), 135.5 (qC), 133.4 (2 x CH), 130.4 (CH), 129.5 (2 x CH), 129.3 (2 x CH), 124.9 (2 x CH), 124.8 (s), 122.1 (qC), 117.4 (qC), 113.3 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_{10}BrN_4$ calculated 325.0089, found 325.0100.



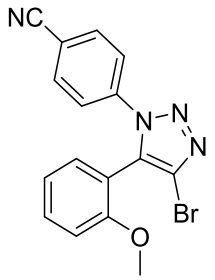
4-(4-Bromo-5-(*m*-tolyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 256b was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 3-ethynyltoluene (42 mg, 46 μL, 0.36 mmol) and gave the product as an orange solid (69 mg, 0.20 mmol, 68%); MP = 142 °C: LRMS [M + H] m/z = 339.1 and 341.1 [Br]; ν_{max} / cm^{-1} 2924w, 2227m, 2103s, 1600s, 1502s, 1415m, 1281s, 1176m, 1073m, 989s, 831s, 771m, 697s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.72 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.48 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.28 - 7.36 (m, 2H, Ar-H), 7.12 (s, 1H, Ar-H), 7.02 (d, *J* = 7.1 Hz, 1H, Ar-H), 2.37 (s, 3H, CH_3); ^{13}C NMR not performed for this sample; HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{12}BrN_4$ calculated 339.0245, found 339.0255.



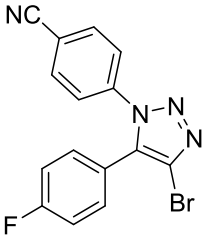
4-(4-Bromo-5-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 256c was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 4-ethynylanisole (48 mg, 47 μL, 0.36 mmol) and the product isolated as an orange solid (83 mg, 0.23 mmol, 78%); MP = 167 - 168 °C; LRMS [M + H] m/z = 355.1 and 357.1 [Br]; ν_{max} / cm^{-1} 3018w, 2963w, 2937w, 2232m, 1606m, 1576w, 1558w, 1510m, 1494m, 1454m, 1414m, 1288m, 1254s, 1204m, 1179m, 1113m, 1078m, 1026m, 987s, 835s, 616m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.72 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.48 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.20 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.95 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.85 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 160.9 (qC), 139.6 (qC), 135.4 (qC), 133.3 (2 x CH), 130.9 (2 x CH), 124.9 (2 x CH), 121.7 (qC), 117.4 (qC), 116.5 (qC), 114.7 (2 x CH), 113.1 (qC), 55.3 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{12}BrN_4$ calculated 355.0194, found 355.0198.



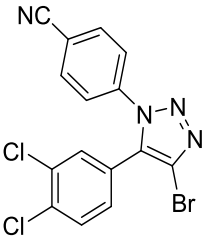
4-(4-Bromo-5-(3-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 256d was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 3-ethynylanisole (48 mg, 46 μL, 0.36 mmol) and the product isolated as a yellow solid (74 mg, 0.21 mmol, 70%); MP = 113 - 114 °C: LRMS [M + H] m/z = 355.1 and 357.1 [Br]; ν_{max} / cm^{-1} 2962w, 2836w, 2231m, 1744m, 1606m, 1582m, 1507m, 1477m, 1414m, 1291m, 1265m, 1235m, 1204m, 1181w, 1137m, 1075m, 1045m, 1009m, 989s, 901w, 843s, 790s, 731m, 695s, 648w, 566m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.72 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.49 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.35 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.01 (dd, *J* = 8.0, 2.5 Hz, 1H, Ar-H), 6.84 (t, *J* = 1.8 Hz, 1H, Ar-H), 6.79 (d, *J* = 8.0 Hz, 1H, Ar-H), 3.79 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 159.9 (qC), 139.4 (qC), 135.4 (qC), 133.3 (2 x CH), 130.4 (CH), 125.9 (CH), 124.9 (2 x CH), 122.1 (qC), 121.7 (CH), 117.4 (qC), 115.7 (CH), 115.2 (qC), 113.3 (qC), 55.4 (s); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{12}BrN_4O$ calculated 355.0194, found 355.0189.



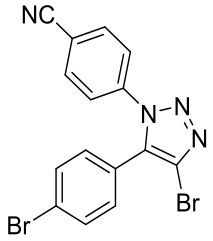
4-(4-Bromo-5-(2-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 256e was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 2-ethynylanisole (48 mg, 47 μL, 0.36 mmol) and the product isolated as a yellow solid (54 mg, 0.15mmol, 51%); MP = 179 - 180 °C: LRMS [M + H] m/z = 355.1 and 357.1 [Br]; ν_{max} / cm^{-1} 2926w, 2839w, 2230m, 1737w, 1604m, 1550w, 1506m, 1477m, 1467m, 1419m, 1302m, 1272m, 1259m, 1241m, 1205m, 1188m, 1149m, 1117m, 1089m 1024m, 989s, 845s, 753s, 670m, 565m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.68 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.47 - 7.52 (m, 1H, Ar-H), 7.46 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.39 (dd, *J* = 7.6, 1.6 Hz, 1H, Ar-H), 7.12 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.88 (d, *J* = 8.4 Hz, 1H, Ar-H), 3.41 (s, 3H OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 156.2 (qC), 140.6 (qC), 133.2 (qC), 133.1 (2 x CH), 132.5 (CH), 131.3 (CH), 123.4 (2 x CH), 122.7 (qC), 121.2 (CH), 117.6 (qC), 113.8 (qC), 112.7 (CH), 111.5 (qC), 54.9 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{12}BrN_4O$ calculated 355.0194, found 355.0184.



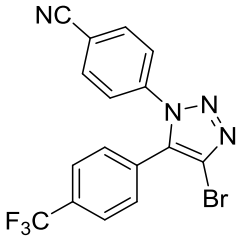
4-(4-Bromo-5-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 256f was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-ethynyl-4-fluorobenzene (43 mg, 41 μL, 0.36 mmol) and the product isolated as a pale yellow solid (65 mg, 0.19 mmol, 64%); MP = 154 - 155 °C; LRMS [M + H] m/z = 343.0 and 345.0 [Br]; ν_{max} / cm^{-1} 2230m, 1604m, 1507m, 1491s, 1412w, 1293m, 1224w, 1160w, 1083m, 990m, 845s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.74 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.47 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.27 - 7.31 (m, 2H, Ar-H), 7.17 (t, *J* = 8.8 Hz, 2H, Ar-H); ^{19}F NMR (471 MHz, $CDCl_3$): δ ppm = -108.4 (s); ^{13}C NMR (126 MHz, $CDCl_3$): δ ppm = 163.6 (d, *J* = 258.9 Hz, qC), 139.3 (qC), 134.7 (qC), 133.5 (2 x CH), 131.7 (d, *J* = 9.1 Hz, 2 x CH), 125.0 (2 x CH), 122.2 (qC), 120.8 (d, *J* = 3.6 Hz, qC), 117.3 (qC), 116.7 (d, *J* = 21.8 Hz, 2 x CH), 113.6 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_9BrFN_4$ calculated 342.9995, found 342.9989.



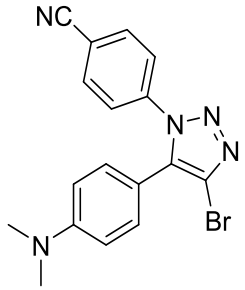
4-(4-Bromo-5-(3,4-dichlorophenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 256g was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1,2-dichloro-4-ethynylbenzene (61 mg, 0.36 mmol) and the product isolated as a yellow solid (73 mg, 0.19 mmol, 62%); MP =192 – 193 °C; LRMS [M + H] m/z = 392.9 and 394.9 [Br]; ν_{max} / cm^{-1} 3057w, 2226m, 1605m, 1508m, 1459m, 1414w, 1372w, 1282w, 1231w, 1131m, 1030m, 974m, 844s, 820s, 799m, 709m, 670m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.80 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.55 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.50 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.47 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.08 (dd, *J* = 8.3, 2.0 Hz, 1H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.0 (qC), 135.3 (qC), 134.0 (qC), 133.7 (2 x CH), 133.4 (qC) 131.4 (CH), 131.2 (CH), 128.6 (CH), 125.0 (2 x CH), 124.7 (qC), 122.6 (qC), 117.3 (qC), 113.9 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_8Cl_2BrFN_4$ calculated 392.9309, found 392.9293.



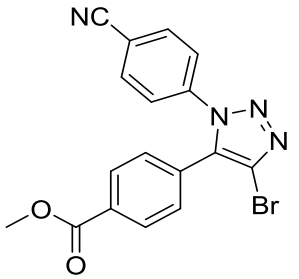
4-(4-Bromo-5-(4-bromophenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 256h was prepared *via* the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-ethynyl-4-bromobenzene (65 mg, 0.36 mmol) and the product isolated as a yellow solid (74 mg, 18 mmol, 61%); MP = 161 - 162 °C; LRMS [M + H] m/z = 403.1 and 405.1 [Br];]; ν_{max} / cm^{-1} 3069w, 2920w, 2229m, 1602m, 1508m, 1472m, 1404m, 1289m, 1264m, 1215m, 1138w, 1068s, 1014m, 988s, 849s, 830s, 754w, 719w, 617w; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.76 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.61 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.47 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.16 (d, *J* = 8.6 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.2 (qC), 134.5 (qC), 133.6 (2 x CH), 132.7 (2 x CH), 131.0 (2 x CH), 125.1 (qC), 125.0 (2 x CH), 123.6 (qC), 122.2 (qC), 117.3 (qC), 113.6 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{15}H_8Cl_2Br_2N_4Na$ calculated 424.9013, found 424.9016.



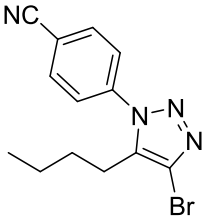
4-(4-Bromo-5-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 256i was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (61 mg, 59 μL, 0.36 mmol) and gave the product as a colourless oil (9.4 mg, 0.024 mmol 8%); LRMS [M + H] m/z = 393.0, 395.0 [Br]; IR not analysed for this sample; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.69 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.66 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.39 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.36 (d, *J* = 8.3 Hz, 2H, Ar-H); ^{19}F NMR (471 MHz, $CDCl_3$): δ ppm = -63.04 (s); ^{13}C Not analysed due to weak signals; HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_9BrF_3N_4$ calculated 392.9963, found 392.9967.



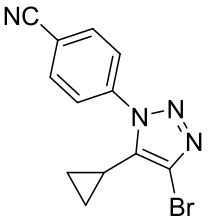
4-(4-Bromo-5-(4-(dimethylamino)phenyl)-1*H*-1,2,3-triazol-1-yl) 256j was prepared *via* the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 4-ethynyl-*N,N*-dimethylaniline (52 mg, 0.36 mmol) and the product isolated as a yellow solid (76 mg, 0.21 mmol, 69%); MP = 183 - 184 °C; LRMS [M + H] m/z = 368.1 and 370.1 [Br]; ν_{max} / cm^{-1} 2837w, 2231m, 1604s, 1504s, 1484s, 1435w, 1372m, 1285m, 1211w, 1194w, 1168w, 1137m, 1068m, 985s, 944m, 939s, 821s, 805m, 739w, 686w, 670w; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.72 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.51 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.11 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.70 (d, *J* = 8.1 Hz, 2H, Ar-H), 3.03 (s, 6H, 2 x NMe); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.9 (qC), 139.4 (qC), 134.9 (qC), 133.5 (2 x CH), 133.3 (2 x CH), 130.4 (2 x CH), 129.2 (qC), 125.0 (qC), 124.9 (2 x CH), 117.6 (qC), 112.8 (qC), 43.6 (2 x NMe); HRMS ($[M + H]^+$, +ESI) m/z $C_{17}H_{15}BrN_5$ calculated 368.0511, found 368.0490.



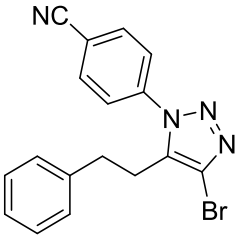
Methyl 4-(4-bromo-1-(4-cyanophenyl)-1*H*-1,2,3-triazol-5-yl)benzoate 256k was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and methyl 4-ethynylbenzoate (58 mg, 0.36 mmol). After 18 hours a further 0.5 eq $ZnEt_2$ (0.15 ml, 0.15 mmol, 1 M in hexanes) was added before quenching with NBS. Work up and isolation gave the product as a yellow solid (31 mg, 0.08 mmol, 27%); MP = 151 – 152 °C; LRMS [M + H] m/z = 382.0 and 384.0 [Br]; ν_{max} / cm^{-1} 2228m, 1707s, 1603m, 1506m, 1431m, 1411m, 1284s, 1214w, 1107m, 1074m, 988s, 843s, 769m, 699m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.12 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.74 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.46 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.38 (d, *J* = 8.3 Hz, 2H, Ar-H), 3.96 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 165.9 (C=O), 139.2 (qC), 134.6 (qC), 133.5 (2 x CH), 131.9 (qC), 130.3 (2 x CH), 129.6 (2 x CH), 129.1 (qC), 125.0 (2 x CH), 122.5 (qC), 117.3 (qC), 113.7 (qC), 52.5 (CH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{17}H_{12}BrN_5O_2$ calculated 383.0144, found 383.0141.



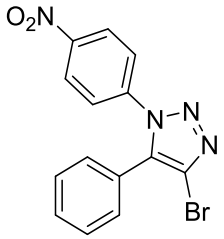
4-(4-Bromo-5-butyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 256l was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-hexyne (30 mg, 41 μL, 0.36 mmol) and the product isolated as a yellow amorphous solid (68 mg, 0.23 mmol, 75%); LRMS [M + H] m/z = 305.1 and 307.1 [Br]; IR analysis not performed; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.90 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.63 (d, *J* = 8.8 Hz, 2H, Ar-H), 2.76 (t, *J* = 7.8 Hz, 2H, CH_2), 1.48 (quin, *J* = 7.6 Hz, 2H, CH_2), 1.28 (sxt, *J*=7.4 Hz, 2H, CH_2), 0.86 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.6 (qC), 136.4 (qC), 133.7 (2 x CH), 125.6 (2 x CH), 121.6 (qC), 117.4 (qC), 114.1 (qC), 29.9 (CH_2), 22.8 (CH_2), 22.1 (CH_2), 13.4 (CH_3); HRMS ($[M + Na]^+$, +ESI) m/z $C_{13}H_{13}BrN_4Na$ calculated 327.0221, found 327.0226.



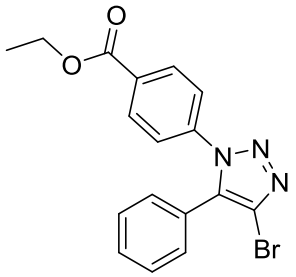
4-(4-Bromo-5-cyclopropyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 256m was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and ethynylcyclopropane (1M solution in toluene, 0.36 ml, 0.36 mmol) and the product isolated as a white solid (66 mg, 0.23 mmol, 77%); MP = 149 - 150 °C; LRMS [M + H] m/z = 289.0 and 291.0 [Br]; ν_{max} / cm^{-1} 2225m, 1604s, 1546m, 1506s, 1420m, 1403m, 1274m, 1252s, 1206w, 1123m, 1087m, 1030m, 990s, 838s, 691w; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.88 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.81 (d, *J* = 8.8 Hz, 2H, Ar-H), 1.79 (tt, *J* = 8.4, 5.3 Hz, 1H, CH), 1.04 - 1.09 (m, 2H, CH), 0.83 - 0.87 (m, 2H, CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.5 (qC), 135.7 (qC), 133.4 (2 x CH), 125.0 (2 x CH), 121.7 (qC), 117.5 (qC), 113.5 (qC), 7.1 (2 x CH_2), 4.6 (CH); HRMS ($[M + H]^+$, +ESI) m/z $C_{12}H_{10}BrN_4$ calculated 289.0088, found 289.0093.



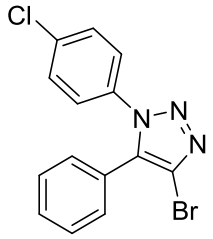
4-(4-Bromo-5-phenethyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 256n was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 4-phenyl-1-butyne (47 mg, 50 μL, 0.36 mmol) and gave the desired product as a white solid (62 mg, 0.18 mmol 59%); MP = 128 °C; LRMS [M + H] m/z = 353.2 and 355.2 [Br]; ν_{max} / cm^{-1} 2922m, 2851w, 2226m, 1602s, 1506s, 1449m, 1407w, 1287w, 1240w, 1159w, 1093w, 1062m, 995m, 970m, 853s, 758m, 737m, 701s ; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.73 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.16 - 7.22 (m, 3H, Ar-H), 7.14 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.87 (dd, *J* = 7.0, 2.1 Hz, 2H, Ar-H), 3.05 (t, *J* = 7.1 Hz, 2H, CH_2), 2.89 (t, *J* = 7.1 Hz, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.2 (qC), 138.7 (qC), 135.3 (qC), 133.3 (2 x CH), 128.8 (2 x CH), 128.4 (2 x CH), 126.9 (CH), 125.9 (2 x CH), 121.6 (qC), 117.4 (qC), 113.8 (qC), 33.6 (CH_2), 25.1 (CH_2); HRMS ($[M + H]^+$, +ESI) m/z $C_{17}H_{14}N_4Br$ calculated 353.0396, found 353.0395.



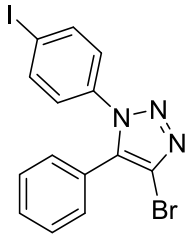
4-Bromo-1-(4-nitrophenyl)-5-phenyl-1*H*-1,2,3-triazole 256o was prepared in accordance with the general procedure from 1-azido-4-nitrobenzene (49 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as a brown solid (53 mg, 0.15 mmol, 51%); MP = 153 - 154 °C; LRMS [M + H] m/z = 345.0 and 347.0 [Br]; ν_{max} / cm^{-1} 3113w, 2923w, 1677w, 1610m, 1593s, 1519s, 11495s, 1480s, 1452m, 1421w, 1403w, 1342s, 1312s, 1269m, 1236m 1174w, 1113s, 1078m, 1044m, 988m, 964m, 923w, 853s, 762s, 749s, 697s, 687s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.27 (d, *J* = 9.1 Hz, 1 H), 7.51 (d, *J* = 9.1 Hz, 2 H), 7.45 - 7.50 (m, 3 H), 7.29 (dd, *J* = 8.4, 1.4 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 147.6 (qC), 140.8 (qC), 139.7 (qC), 130.4 (CH), 129.8 (2 x CH), 129.3 (2 x CH), 125.6 (qC), 124.9 (2 x CH), 124.8 (2 x CH), 92.0 (qC); HRMS could not be analysed.



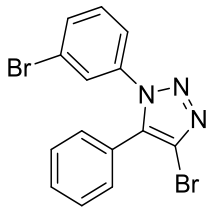
Ethyl 4-(4-bromo-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzoate 256p was prepared in accordance with the general procedure from ethyl 4-azidobenzoate (57 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as a white solid (78 mg, 0.21 mmol, 70%); MP = 118 - 119 °C; LRMS [M + H] m/z = 372.1 and 374.1 [Br]; ν_{max} / cm^{-1} 2978w, 1714s, 1605m, 1511w, 1475m, 1451m, 1406m, 1368w, 1297w, 1274s, 1214m, 1174w, 1124m, 1109m, 1089m, 1071m, 1020w, 990s, 877m, 769s, 697s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.09 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.43 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.39 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.28 (d, *J* = 7.3 Hz, 2H, Ar-H), 4.39 (q, *J* = 7.1 Hz, 2H, CH_2), 1.40 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 165.2 (C=O), 139.5 (qC), 135.5 (qC), 131.3 (qC), 130.7 (2 x CH), 130.0 (CH), 129.6 (2 x CH), 129.0 (2 x CH), 125.1 (qC), 124.4 (2 x CH), 121.7 (qC), 61.5 (CH_2), 14.2 (CH_3); HRMS ($[M + Na]^+$, +ESI) m/z $C_{17}H_{14}BrN_3NaO_2$ calculated 394.1067, found 394.1076.



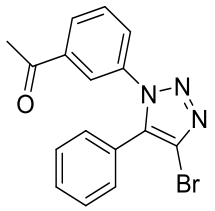
4-Bromo-1-(4-chlorophenyl)-5-phenyl-1*H*-1,2,3-triazole 256q was prepared in accordance with the general procedure from 1-azido-4-chlorobenzene (46 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as a yellow solid (50 mg, 0.15 mmol, 50%); MP = 107 °C; LRMS [M + H] m/z = 334.2 and 336.2 [Br]; ν_{max} / cm^{-1} 3060w, 1494s, 1476m, 1450m, 1405m, 1293m 1280m, 1251m, 1203m, 1149w, 1129w, 1084s, 1061m, 1032w, 1020w, 986s, 829s, 770s, 748s, 695s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.42 - 7.47 (m, 3H, Ar-H), 7.39 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.23 - 7.31 (m, 4H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 135.5 (qC), 135.4 (qC), 134.8 (qC), 130.0 (CH), 129.6 (2 x CH), 129.6 (2 x CH), 129.0 (2 x CH), 125.9 (2 x CH), 125.1 (qC), 121.4 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{14}H_9BrClN_3Na$ calculated 355.9566, found 355.9560.



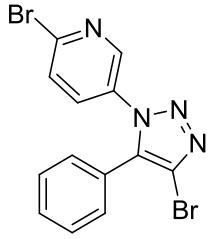
4-Bromo-1-(4-iodophenyl)-5-phenyl-1*H*-1,2,3-triazole 256r was prepared in accordance with the general procedure from 1-azido-4-iodobenzene (73 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as an orange oil (47 mg, 0.11 mmol, 37%); LRMS [M + H] m/z = 425.9 and 427.9 [Br]; IR not analysed for this sample; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.76 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.42 - 7.47 (m, 3H, Ar-H), 7.28 (dd, *J* = 7.6, 1.3 Hz, 2H, Ar-H), 7.08 (d, *J* = 8.7 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 138.6 (2 x CH), 136.1 (qC), 132.9 (qC), 130.0 (CH), 129.6 (qC), 129.4 (2 x CH), 129.1 (2 x CH), 128.1 (qC), 126.2 (2 x CH), 124.7 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{14}H_{10}BrN_3I$ calculated 425.9103, found 425.9082.



4-Bromo-1-(3-bromophenyl)-5-phenyl-1*H*-1,2,3-triazole 256s was prepared in accordance with the general procedure from 1-azido-3-bromobenzene (59 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as an orange solid (59 mg, 0.16 mmol, 52%); MP = 158-159 °C; LRMS [M + H] m/z = 378.2 and 380.2 [Br]; ν_{max} / cm^{-1} 3068w, 1684w, 1582m, 1476m, 1450m, 1431m, 1293m, 1271m, 1254m, 1206m, 1092m, 1073m, 1005m, 921w, 902w, 878m, 772s, 695s, 678s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.61 (t, *J* = 2.0 Hz, 1H, Ar-H), 7.59 (dt, *J* = 8.9, 1.0 Hz, 1H, Ar-H), 7.42 - 7.49 (m, 3H, Ar-H), 7.30 (dd, *J* = 8.1, 1.8 Hz, 2H, Ar-H), 7.27 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.18 (dt, *J* = 8.1, 1.0 Hz, 1H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 137.3 (qC), 135.5 (qC), 132.6 (CH), 130.5 (CH), 130.0 (CH), 129.5 (2 x CH), 129.0 (2 x CH), 127.8 (CH), 124.9 (qC), 123.2 (CH), 122.8 (qC), 121.4 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{14}H_9Br_2N_3Na$ calculated 399.9061, found 399.9053.



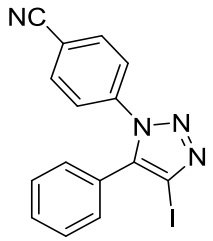
1-(3-(4-Bromo-5-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)ethan-1-one 256t was prepared in accordance with the general procedure from 1-(3-azidophenyl)ethan-1-one (48 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as a yellow solid (49 mg, 0.14 mmol, 48%); MP = 147 °C; LRMS [M + H] m/z = 342.3 and 344.3 [Br]; ν_{max} / cm^{-1} 3079w, 2923w, 2110w, 1683s, 1589m, 1479s, 1456m, 1417w, 1357m, 1300m, 1281m, 1246s, 1208m, 1136w, 1067m, 1002m, 989m, 898m, 861w, 804w, 790m, 764s, 700s, 679s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.02 (dt, *J* = 6.8, 1.7 Hz, 1H, Ar-H), 7.91 (s, 1H, Ar-H), 7.52 (d, *J* = 7.1 Hz, 2H, Ar-H), 7.40 - 7.47 (m, 3H, Ar-H), 7.29 (dd, *J* = 7.8, 1.5 Hz, 2H, Ar-H), 2.51 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 196.2 (C=O), 138.1 (qC), 136.7 (qC), 135.6 (qC), 130.1 (CH), 129.8 (CH), 129.6 (2 x CH), 129.1 (2 x CH), 128.9 (CH), 128.7 (CH), 125.1 (qC), 124.5 (CH), 121.6 (qC), 26.6 (CH_3); HRMS ([M + H]$^+$, +ESI) m/z $C_{16}H_{13}BrN_3O$ calculated 342.0242, found 342.0248.



2-Bromo-5-(4-bromo-5-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine 256u was prepared in accordance with the general procedure from 5-azido-2-bromopyridine (59 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as an orange solid (74 mg, 0.20 mmol, 65%); MP = 132 °C; LRMS [M + H] m/z = 379.2 and 381.2 [Br]; ν_{max} / cm^{-1} 3040w, 1607w, 1572w, 1544w, 1467s, 1445m, 1406w, 1382m, 1298m, 1274m, 1214m, 1178w, 1147w, 1102w, 1076m, 1056m, 1017m, 981s, 917m, 833s, 773m, 754s, 725m, 695s, 681s, 626m, 607m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.34 (t, *J* = 1.7 Hz, 1H, Ar-H), 7.57 (d, *J* = 1.5 Hz, 2H, Ar-H), 7.44 - 7.50 (m, 3H, Ar-H), 7.29 (dd, *J* = 7.8, 1.7 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 145.3 (CH), 142.5 (qC), 135.7 (qC), 133.9 (CH), 132.5 (qC), 130.5 (CH), 129.5 (2 x CH), 129.4 (2 x CH), 128.7 (CH), 124.4 (qC), 122.0 (qC); HRMS ([M + Na]$^+$, +ESI) m/z $C_{13}H_8Br_2N_4Na$ calculated 400.9013, found 400.9020.

6.4.7. General procedure for the synthesis of 4-iodo, 1,5-substituted 1,2,3-triazoles.

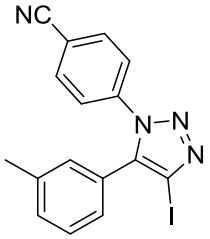
The azide (0.30 mmol), alkyne (0.36 mmol) and *N*-methylimidazole (2.5 mg, 0.03 mmol) were added to a glass vial or round bottomed flask. The vessel was purged with N_2 and sealed. Dry THF (4 mL) was added and stirred for 5 minutes before $ZnEt_2$ (0.15 mL, 0.15 mmol, 1 M in hexanes) was added. The reaction was stirred at ambient temperature overnight (approximately 18 hours). The reaction mixture was transferred by syringe to a nitrogen flushed vial containing *N*-iodosuccinimide (101 mg, 0.45 mmol) and stirred at ambient temperature for 1 hour. The mixture was partitioned between saturated $NH_4Cl_{(aq)}$ (5 mL) and EtOAc (10 mL) and the organic layer was washed with brine (7 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc : hexane, 1 : 20 to 1 : 5) to afford the pure material.



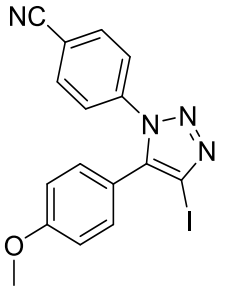
4-(4-Iodo-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 257a was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the product as an orange solid (78 mg, 0.21 mmol 70%).

257a was also synthesised in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol). After stirring with for 18 hours, the reaction mixture was transferred to a nitrogen flushed vial charged with I_2 (91 mg, 0.36 mmol) and stirred vigorously for 30 minutes. Work up and isolation as in the general procedure gave the product as an orange solid (83 mg, 0.22 mmol, 74%).

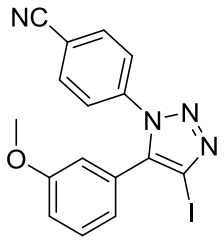
MP = 167 - 168 °C; LRMS [M + H] m/z = 373.0; ν_{max} / cm^{-1} 2923w, 2224m, 1721w, 1596m, 1500m, 1254m, 1060m, 985m, 847s, 763s, 698s ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.70 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.42 - 7.51 (m, 5H, Ar-H), 7.27 (dd, *J* = 8.1, 1.5 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.5 (qC) 139.3 (qC) 133.3 (2 x CH) 130.3 (CH) 129.7 (2 x CH) 129.2 (2 x CH) 125.6 (qC) 124.9 (2 x CH) 117.5 (qC) 113.2 (qC) 91.9 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{15}H_9IN_4Na$ calculated 394.9770, found 394.9773.



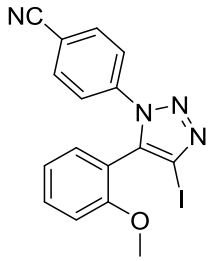
4-(4-Iodo-5-(*m*-tolyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 257b was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 3-ethynyltoluene (42 mg, 46 μL, 0.36 mmol) and gave the product as an orange solid (71 mg, 0.18 mmol, 61%); MP = 139 - 140 °C; LRMS [M + H] m/z = 387.3; ν_{max} / cm^{-1} 2229m, 1599m, 1525w, 1502m, 1477w, 1401w, 1291m, 1213w, 1062w, 988m, 849s, 797m, 698m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.70 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.45 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.28 - 7.36 (m, 2H, Ar-H), 7.10 (s, 1H, Ar-H), 7.02 (d, *J* = 7.1 Hz, 1H, Ar-H), 2.37 (s, 3H, CH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{12}IN_4$ calculated 387.0107, found 387.0094.



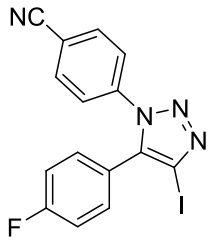
4-(4-Iodo-5-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 257c was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 4-ethynylanisole (48 mg, 47 μL, 0.36 mmol) and the product isolated as an orange solid (80 mg, 0.20 mmol, 66%); MP = 208 - 209 °C; LRMS [M + H] m/z = 403.1; ν_{max} / cm^{-1} 3009w, 2936w, 2232m, 1606m, 1552w, 1510m, 1490m, 1454w, 1413w, 1280m, 1257s, 1179m, 1111w, 1072m, 1025s, 982s, 836s, 614m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.71 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.46 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.19 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.96 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.86 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 160.9 (qC), 139.5 (qC), 139.4 (qC), 133.3 (2 x CH), 131.2 (2 x CH), 124.9 (2 x CH), 117.5 (qC), 117.3 (qC), 114.7 (2 x CH), 113.1 (qC), 91.8 (qC), 55.4 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{12}IN_4O$ Calculated 403.0056, found 403.0058.



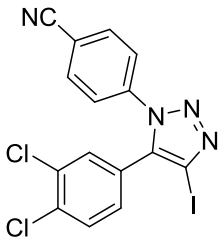
4-(4-Iodo-5-(3-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 257d was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 3-ethynylanisole (48 mg, 46 μL, 0.36 mmol) and the product isolated as a yellow solid (76 mg, 0.19 mmol, 63%); MP = 142 - 143 °C; LRMS [M + H] m/z = 403.0; ν_{max} / cm^{-1} 2967w, 2929w, 2232m, 1606m, 1580m, 1505m, 1475m, 1432m, 1417m, 1280s, 1258m, 1230s, 1198m, 1176m, 1133m, 1075m, 1046s, 986s, 952m, 891s, 838s, 788s, 701s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.71 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.47 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.35 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.02 (ddd, *J* = 8.4, 2.3, 0.9 Hz, 1H, Ar-H), 6.83 (t, *J* = 2.3 Hz, 1H, Ar-H), 6.78 (dd, *J* = 7.6, 0.9 Hz, 1H, Ar-H), 3.80 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 159.7 (qC), 139.3 (qC), 139.2 (qC), 133.3 (2 x CH), 130.4 (CH), 126.6 (qC), 124.8 (2 x CH), 121.9 (CH), 117.5 (qC), 115.6 (CH), 115.3 (CH), 113.1 (qC), 91.9 (qC), 55.4 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{12}IN_4O$ Calculated 403.0056, found 403.0061.



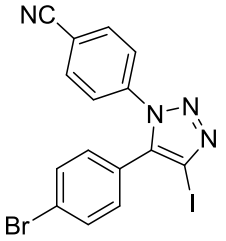
4-(4-Iodo-5-(2-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 257e was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 2-ethynylanisole (48 mg, 47 μL, 0.36 mmol) and the product isolated as an orange solid (60 mg, 0.15 mmol, 50%); MP = 204 - 205 °C; LRMS [M + H] m/z = 403.0; ν_{max} / cm^{-1} 2923w, 2839w, 2229m, 1726w, 1604m, 1507m, 1475m, 1297w, 1267m, 1253m, 1246m, 1116m, 1082m, 1022m, 983m, 837s, 754s, 671m, 563s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.67 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.47 - 7.52 (m, 1H, Ar-H), 7.45 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.36 (dd, *J* = 7.6, 1.6 Hz, 1H, Ar-H), 7.12 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.89 (d, *J* = 8.4 Hz, 1H, Ar-H), 3.44 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 156.3 (qC), 140.5 (qC), 137.3 (qC), 133.0 (2 x CH), 132.5 (CH), 131.6 (CH), 123.6 (2 x CH), 121.2 (CH), 117.6 (qC), 114.6 (qC), 112.7 (qC), 111.6 (CH), 92.8 (qC), 55.0 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{12}IN_4O$ Calculated 403.0056, found 403.0067.



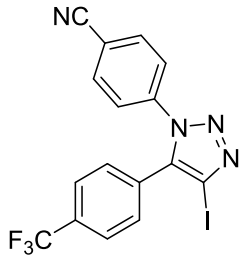
4-(5-(4-Fluorophenyl)-4-iodo-1*H*-1,2,3-triazol-1-yl)benzonitrile 257f was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-ethynyl-4-fluorobenzene (43 mg, 41 μL, 0.36 mmol) and the product isolated as an orange solid (84 mg, 0.21 mmol, 72%); MP = 189 - 190 °C; LRMS [M + H] m/z = 391.1; ν_{max} / cm^{-1} 2229m, 1604m, 1542w, 1503m, 1483s, 1400w, 1285w, 1273w, 1226w, 1190w, 1163m, 1137w, 1098w, 985m, 840s, 818m, 741w, 614m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.73 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.44 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.27 (dd, *J* = 8.6, 5.4 Hz, 2H, Ar-H), 7.17 (t, *J* = 8.6 Hz, 2H, Ar-H); ^{19}F NMR (471 MHz, $CDCl_3$): δ ppm = -108.5 (s); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 163.6 (d, *J* = 250.9 Hz, qC), 139.2 (qC), 138.7 (qC), 133.4 (2 x CH), 131.9 (d, *J* = 8.8 Hz, 2 x CH), 124.9 (2 x CH), 121.6 (d, *J* = 3.7 Hz, qC), 117.4 (qC), 116.7 (d, *J* = 22.0 Hz, 2 x CH), 113.4 (qC), 92.0 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_9FIN_4$ Calculated 390.9856, found 390.9844.



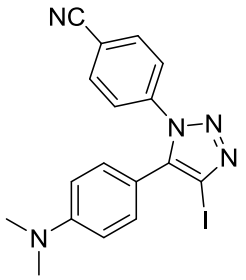
4-(5-(3,4-Dichlorophenyl)-4-iodo-1*H*-1,2,3-triazol-1-yl)benzonitrile 257g was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1,2-dichloro-4-ethynylbenzene (61 mg, 0.36 mmol) and the product isolated as a yellow amorphous solid (81 mg, 0.18 mmol, 61%); MP = 204 - 205 °C; LRMS [M + H] m/z = 440.9 and 442.9 [Cl]; ν_{max} / cm^{-1} 2227m, 1605s, 1506m, 1458m, 1402w, 1286w, 1135m, 1031m, 986m, 843s, 821s, 800m, 671m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.77 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.54 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.46 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.44 (d, *J* = 1.7 Hz, 1H, Ar-H), 7.07 (dd, *J* = 8.2, 2.1 Hz, 1H, Ar-H); ^{13}C NMR analysis not performed for this sample; HRMS ($[M + H]^+$, +ESI) m/z $C_{15}H_8Cl_2IN_4$ Calculated 440.9171, found 440.9177.



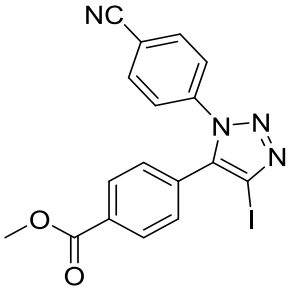
4-(5-(4-Bromophenyl)-4-iodo-1*H*-1,2,3-triazol-1-yl)benzonitrile 257h was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-ethynyl-4-bromobenzene (65 mg, 0.36 mmol) and the product isolated as an orange solid (90 mg, 20 mmol, 67%); MP = 194 °C; LRMS [M + H] m/z = 451.3 and 453.3 [Br]; ν_{max} / cm^{-1} 3050w, 2230m, 1602m, 1506s, 1470m, 1401m, 1280m, 1256m, 1200m, 1137w, 1070s, 1014m, 986s, 835s, 823s, 721w, 612w; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.74 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.61 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.45 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.15 (d, *J* = 8.6 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.1 (qC), 138.5 (qC), 133.5 (2 x CH), 132.7 (2 x CH), 131.2 (2 x CH), 125.1 (qC), 124.9 (2 x CH), 124.5 (qC), 117.3 (qC), 113.5 (qC), 92.0 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{15}H_8BrIN_4Na$ Calculated 472.8875, found 472.8865.



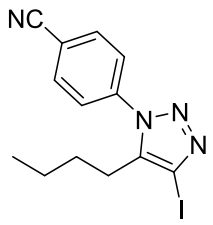
4-(4-Iodo-5-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 257i was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (61 mg, 59 μL, 0.36 mmol) and gave the product as a yellow solid (22 mg, 0.05 mmol, 17%); MP = 142 - 143 °C; LRMS [M + H] m/z = 441.0; IR analysis not performed; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 7.75 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.74 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.44 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.43 (d, *J* = 8.1 Hz, 2H, Ar-H); ^{19}F NMR (471 MHz, $CDCl_3$): δ ppm = -63.01 (s); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.0 (qC), 138.1 (qC), 133.8 (qC), 133.6 (2 x CH), 131.3 (q, *J* = 31.5 Hz, qC), 130.2 (2 x CH), 129.3 (qC), 126.3 (q, *J*=4.2 Hz, 2 x CH), 125.0 (2 x CH), 121.6 (q, *J*=275.1 Hz, CF_3), 117.3 (qC), 113.7 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_9F_3IN_4$ Calculated 440.9824, found 440.9827.



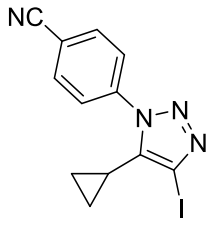
4-(5-(4-(Dimethylamino)phenyl)-4-iodo-1*H*-1,2,3-triazol-1-yl)benzonitrile 257j was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 4-ethynyl-*N*,*N*-dimethylaniline (52 mg, 0.36 mmol) and the product isolated as an orange solid (95 mg, 0.23 mmol, 76%); MP = 201 °C; LRMS [M + H] m/z = 416.2; IR analysis not performed; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7 .70 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.48 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.09 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.69 (d, *J* = 9.0 Hz, 2H, Ar-H), 3.03 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 151.0 (qC), 140.0 (qC), 139.8 (qC), 133.2 (2 x CH), 130.6 (2 x CH), 124.9 (2 x CH), 117.7 (qC), 112.7 (qC), 111.8 (2 x CH), 111.4 (qC), 91.3 (qC), 40.0 (2 x NCH_3); HRMS ($[M + Na]^+$, +ESI) m/z $C_{17}H_{14}IN_5Na$ Calculated 438.0192, found 438.0199.



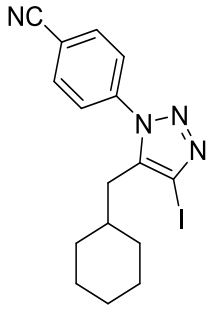
Methyl 4-(1-(4-cyanophenyl)-4-iodo-1*H*-1,2,3-triazol-5-yl)benzoate 257k was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and methyl 4-ethynylbenzoate (58 mg, 0.36 mmol) After 18 hours a further 0.5 eq $ZnEt_2$ (0.15 ml, 0.15 mmol, 1 M in hexanes) was added before quenching with NIS. Work up and isolation gave the product as a yellow amorphous solid (37 mg, 0.09 mmol, 29%); LRMS [M + H] m/z = 431.1; ν_{max} / cm^{-1} 2231m, 1711s, 1603m, 1507s, 1437m, 1408w, 1278s, 1104m, 1071m, 990s, 845s, 769m, 698m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.13 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.72 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.43 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.37 (d, *J* = 8.5 Hz, 2H, Ar-H), 3.96 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 166.0 (C=O), 138.6 (qC), 133.5 (2 x CH), 131.9 (qC), 130.4 (2 x CH), 130.0 (qC), 130.0 (qC), 129.9 (2 x CH), 125.0 (2 x CH), 123.1 (qC), 117.6 (qC), 113.6 (qC), 52.6 (OCH_3); HRMS ($[M + Na]^+$, +ESI) m/z $C_{17}H_{11}IN_4O_2Na$ Calculated 452.9824, found 452.9819.



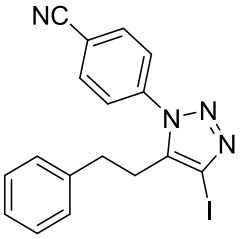
4-(5-Butyl-4-iodo-1*H*-1,2,3-triazol-1-yl)benzonitrile 257l was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 1-hexyne (30 mg, 41 μL, 0.36 mmol) and the product isolated as an orange amorphous solid (82 mg, 0.23 mmol, 78%); LRMS [M + H] m/z = 353.1; ν_{max} / cm^{-1} 2951w, 2923w, 2229m, 1607m, 1503s, 1467m, 1410m, 1267m, 1258m, 1130m, 1050m, 1013m, 970m, 850s, 820s, 658m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.89 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.62 (d, *J* = 8.8 Hz, 2H, Ar-H), 2.74 (t, *J* = 7.7 Hz, 2H, CH_2), 1.45 (quin, *J* = 7.5 Hz, 2H, CH_2), 1.27 (sxt, *J* = 7.5 Hz, 2H, CH_2), 0.85 (t, *J* = 7.5 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 140.3 (qC), 139.5 (qC), 133.7 (2 x CH), 125.6 (2 x CH), 117.4 (qC), 114.0 (qC), 90.9 (qC), 30.3 (CH_2), 23.5 (CH_2), 22.1 (CH_2), 13.4 (CH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{13}H_{14}IN_4$ Calculated 353.0263, found 353.0263.



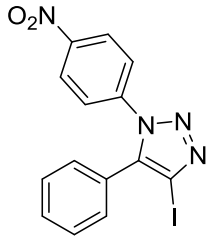
4-(4-Iodo-5-cyclopropyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 257m was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and ethynylcyclopropane (0.36 ml, 0.36 mmol, 1M solution in toluene) and the product isolated as an orange solid (82 mg, 0.24 mmol, 81%); MP = 165 °C; LRMS [M + H] m/z = 337.0; ν_{max} / cm^{-1} 2230m, 1600s, 1504s, 1415m, 1387m, 1351m, 1311m, 1248s, 1100m, 1066m, 1032m, 987s, 843s, 834s, 749m, 698m, 617m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.88 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.79 (d, *J* = 8.8 Hz, 2H, Ar-H), 1.81 (tt, *J* = 8.4, 5.4 Hz, 1H, Alk-CH), 1.04 - 1.10 (m, 2H, Alk-CH), 0.71 - 0.76 (m, 2H, Alk-CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.3 (qC), 139.1 (qC), 133.3 (2 x CH), 125.0 (2 x CH), 117.5 (qC), 113.4 (qC), 91.4 (qC), 7.7 (2 x CH_2), 5.0 (CH); HRMS ($[M + H]^+$, +ESI) m/z $C_{12}H_{10}IN_4$ Calculated 336.9950, found 336.9959.



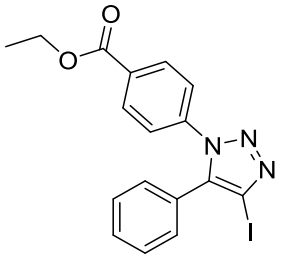
4-(4-Iodo-5-(cyclohexylmethyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 257n was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 3-cyclohexyl-1-propyne (44 mg, 52 µL, 0.36 mmol) and the product isolated as an orange solid (93 mg, 0.24 mmol, 79%); MP = 132-133 °C; LRMS [M + H] m/z = 393.2; ν_{max} / cm^{-1} 2914s, 2851m, 2234m, 1612m, 1518s, 1447m, 1258m, 1088m, 979m, 855s, 681w; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.89 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.60 (d, *J* = 8.8 Hz, 2H, Ar-H), 2.66 (d, *J* = 7.1 Hz, 2H. CH_2), 1.55 - 1.68 (m, 3H, Alk-CH), 1.38 - 1.50 (m, 3H, Alk-CH), 0.98 - 1.16 (m, 3H, Alk-CH), 0.73 - 0.89 (m, 2H, Alk-CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.8 (qC), 139.4 (qC), 133.6 (2 x CH), 126.0 (2 x CH), 117.4 (qC), 114.0 (qC), 91.8 (qC), 37.5 (CH), 32.8 (2 x CH_2), 31.1 (CH_2), 25.8 (CH_2), 25.7 (2 x CH_2); HRMS ($[M + H]^+$, +ESI) m/z $C_{16}H_{18}IN_4$ Calculated 393.0576, found 393.0579.



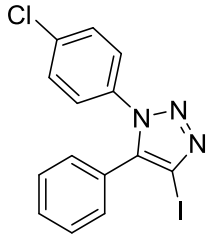
4-(4-Iodo-5-phenethyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 257o was prepared in accordance with the general procedure from 4-azidobenzonitrile (43 mg, 0.30 mmol) and 4-phenyl-1-butyne (47 mg, 50 μL 0.36 mmol) and gave the desired product as an orange solid (88 mg, 0.22 mmol, 73%); MP = 148-149 °C; LRMS [M + H] m/z = 401.0; ν_{max} / cm^{-1} 2924w, 2230m, 1604m, 1504m, 1428m, 1278m, 1238m, 1213m, 1152w, 1096m, 999m, 984m, 844s, 749s, 697s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.73 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.16 - 7.23 (m, 3H, Ar-H), 7.15 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.85 (dd, *J* = 7.2, 1.8 Hz, 2H, Ar-H), 3.04 (t, *J* = 6.8 Hz, 2H, CH_2), 2.87 (t, *J*=7.1 Hz, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.1 (qC), 139.0 (qC), 138.6 (qC), 133.3 (2 x CH), 128.7 (2 x CH), 128.4 (2 x CH), 126.8 (CH), 125.9 (2 x CH), 117.4 (qC), 113.7 (qC), 90.8 (qC), 34.0 (CH_2), 25.7 (CH_2); HRMS ($[M + H]^+$, +ESI) m/z $C_{17}H_{14}IN_4$ Calculated 401.0263, found 401.0252.



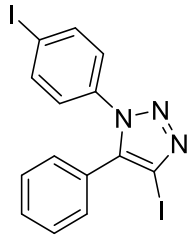
4-Iodo-1-(4-nitrophenyl)-5-phenyl-1*H*-1,2,3-triazole 257p was prepared in accordance with the general procedure from 1-azido-4-nitrobenzene (49 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as a brown solid (64 mg, 0.16 mmol, 54%); MP = 162 - 163 °C; LRMS [M + H] m/z = 393.1; ν_{max} / cm^{-1} 1598m, 1524m, 1499m, 1478m, 1400w, 1337m, 1255w, 1194w, 1109w, 1067m, 988m, 848s, 750m, 693m, 679m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.27 (d, *J* = 9.2 Hz, 2H, Ar-H), 7.51 (d, *J* = 9.2 Hz, 2H, Ar-H), 7.44 - 7.51 (m, 3H, Ar-H), 7.29 (dd, *J* = 8.2, 1.6 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 147.6 (qC), 140.7 (qC), 139.7 (qC), 130.4 (CH), 129.8 (2 x CH), 129.3 (2 x CH), 125.5 (qC), 124.9 (2 x CH), 124.8 (2 x CH), 92.0 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{14}H_{10}IN_4O_2$ Calculated 392.9849, found 392.9840.



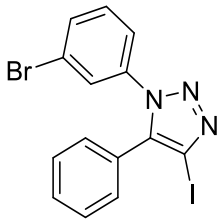
Ethyl 4-(4-iodo-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzoate 257q was prepared in accordance with the general procedure from ethyl 4-azidobenzoate (57 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as a yellow solid (94 mg, 0.23 mmol, 75%); MP = 135 - 136 °C; LRMS [M + H] m/z = 420.3; ν_{max} / cm^{-1} 2978w, 1712s, 1609m, 1514m, 1447w, 1420w, 1367w, 1308w, 1272s, 1170w, 1095m, 1070m, 988s, 928w, 852m, 766s, 696s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.06 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.39 - 7.46 (m, 3H, Ar-H), 7.36 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.26 (dd, *J* = 6.4, 1.8 Hz, 2H, Ar-H), 4.38 (q, *J* = 7.2 Hz, 2H, CH_2), 1.39 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 165.3 (C=O), 139.5 (qC), 139.5 (qC), 131.2 (qC), 130.7 (2 x CH), 130.0 (CH), 129.8 (2 x CH), 129.0 (2 x CH), 125.9 (qC), 124.3 (2 x CH), 91.4 (qC), 61.5 (CH_2), 14.2 (CH_3); HRMS ($[M + Na]^+$, +ESI) m/z $C_{17}H_{14}IN_3NaO_2$ Calculated 442.0028, found 442.0026.



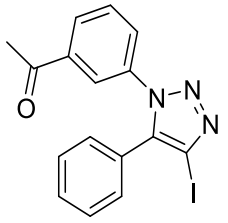
1-(4-Chlorophenyl)-4-iodo-5-phenyl-1*H*-1,2,3-triazole 257r was prepared in accordance with the general procedure from 1-azido-4-chlorobenzene (46 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as a yellow solid (58 mg, 0.15 mmol, 51%); MP = 127 °C; LRMS [M + H] m/z = 382.2 and 384.2 [Cl]; ν_{max} / cm^{-1} 2980w, 1496s, 1472m, 1448m, 1413m, 1276m, 1244m, 1194m, 1143w, 1092m, 1072s, 1019w, 983s, 826s, 771s, 746s, 696s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.43 - 7.49 (m, 3H, Ar-H), 7.40 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.29 (dd, *J* = 5.9, 2.0 Hz, 2H, Ar-H), 7.26 (d, *J* = 8.8 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.4 (qC), 135.4 (2 x qC), 134.7 (qC), 130.0 (CH), 129.8 (2 x CH), 129.6 (2 x CH), 129.0 (2 x CH), 125.9 (2 x CH), 91.1 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{14}H_9ClIN_3Na$ Calculated 403.9427, found 403.9439.



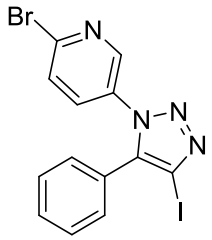
4-Iodo-1-(4-iodophenyl)-5-phenyl-1*H*-1,2,3-triazole 257s was prepared in accordance with the general procedure from 1-azido-4-iodobenzene (73 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as an orange solid (62 mg, 0.13 mmol, 44%); MP = 128 - 129 °C; LRMS [M + H] m/z = 474.1; ν_{max} / cm^{-1} 2923w, 2852w, 1488s, 1474m, 1444m, 1396m, 1276m, 1242m, 1191m, 1141m, 1073m, 1056m, 1030m, 1013m, 982s, 820s, 770s, 724m, 695s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.73 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.41 - 7.47 (m, 3H, Ar-H), 7.27 (dd, *J* = 7.9, 1.6 Hz, 2H, Ar-H), 7.04 (d, *J* = 8.8 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.4 (qC), 138.5 (2 x CH), 136.0 (qC), 130.0 (CH), 129.8 (2 x CH), 129.0 (2 x CH), 126.2 (2 x CH), 125.9 (qC), 95.0 (qC), 91.2 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{14}H_9I_2N_3Na$ Calculated 495.8784, found 495.8792.



1-(3-Bromophenyl)-4-iodo-5-phenyl-1*H*-1,2,3-triazole 257t was prepared in accordance with the general procedure from 1-azido-3-bromobenzene (59 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as an orange solid (60 mg, 0.14 mmol, 47%); MP = 142 - 143 °C; LRMS [M + H] m/z = 426.2 and 428.2 [Br]; ν_{max} / cm^{-1} 3097w, 2919w, 2106w, 1684w, 1582m, 1473m, 1449m, 1433m, 1291m, 1280m, 1268m, 1248m, 1200m, 1140w, 1100m, 1061m, 981m, 878m, 786m, 772s, 749s, 694s, 677s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.53 - 7.58 (m, 2H, Ar-H), 7.41 - 7.48 (m, 3H, Ar-H), 7.28 (dd, *J* = 7.7, 1.5 Hz, 2H, Ar-H), 7.24 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.14 (dt, *J* = 8.1, 0.9 Hz, 1H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 139.5 (qC), 137.2 (qC), 132.5 (CH), 130.4 (2 x CH), 130.1 (CH), 129.8 (CH), 129.0 (2 x CH), 127.8 (CH), 125.7 (qC), 123.2 (CH), 122.7 (qC), 91.1 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{14}H_9BrIN_3Na$ Calculated 447.8922, found 447.8934.



1-(3-(4-Iodo-5-phenyl-1H-1,2,3-triazol-1-yl)phenyl)ethan-1-one 257u was prepared in accordance with the general procedure from 1-(3-azidophenyl)ethan-1-one (48 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as an orange amorphous solid (57 mg, 0.15 mmol, 49%); LRMS [M + H] m/z = 390.2; ν_{max} / cm^{-1} 2970w, 2926w, 2108m, 1682s, 1585m, 1475m, 1454m, 1356m, 1277m, 1240s, 1199w, 1067m, 1000m, 898m, 790s, 765s, 700s, 679s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.00 (dt, *J* = 6.7, 1.8 Hz, 1H, Ar-H), 7.87 (s, 1H, Ar-H), 7.51 (d, *J* = 7.1 Hz, 2H, Ar-H), 7.40 - 7.47 (m, 3H, Ar-H), 7.28 (dd, *J* = 7.8, 1.5 Hz, 2H, Ar-H), 2.50 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 196.2 (C=O), 139.6 (qC), 138.1 (qC), 136.6 (qC), 130.1 (CH), 129.8 (2 x CH), 129.7 (CH), 129.0 (2 x CH), 128.8 (CH), 128.7 (CH), 125.9 (qC), 124.5 (CH), 91.2 (qC), 26.6 (CH_3); HRMS ($[M + Na]^+$, +ESI) m/z $C_{16}H_{12}IN_3NaO$ Calculated 411.9923, found 411.9938.



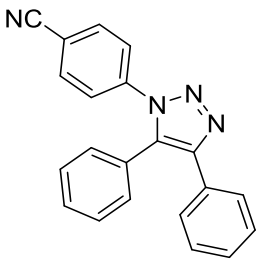
2-Bromo-5-(4-iodo-5-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine 257v was prepared in accordance with the general procedure from 5-azido-2-bromopyridine (59 mg, 0.30 mmol) and phenylacetylene (37 mg, 40 μL, 0.36 mmol) and gave the desired product as an orange solid (82 mg, 0.19 mmol, 64%); MP = 155 - 156 °C; LRMS [M + H] m/z = 427.2 and 429.2; ν_{max} / cm^{-1} 1720w, 1571w, 1468s, 1374m, 1250m, 1234m, 1192m, 1067s, 982s, 826m, 775s, 726m, 696s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.32 (t, *J* = 1.7 Hz, 1H, Ar-H), 7.55 (d, *J* = 1.2 Hz, 2H, Ar-H), 7.44 - 7.51 (m, 3H, Ar-H), 7.28 (dd, *J* = 8.1, 1.5 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 145.2 (CH), 142.4 (qC), 139.8 (qC), 133.9 (CH), 132.4 (qC), 130.5 (CH), 129.7 (2 x CH), 129.4 (2 x CH), 128.6 (CH), 125.2 (qC), 91.6 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{13}H_8BrIN_4Na$ Calculated 448.8875, found 448.8870.

6.4.8. General procedure for the synthesis of 1,4,5-substituted 1,2,3-triazoles with aryl iodides

4-azidobenzonitrile (57 mg, 0.40 mmol), phenylacetylene (49 mg, 53 μL, 0.48 mmol) and *N*-methylimidazole (0.04 mmol, 3.3 mg) were added to a glass vial or round bottomed flask. The vessel was purged with N_2 and sealed. Dry THF (5 mL) was added and stirred for 5 minutes before $ZnEt_2$ (0.2 ml, 0.20 mmol, 1 M in hexanes) was added. The reaction was stirred at ambient temperature overnight (approximately 18 hours). A vial charged with the aryl iodide (0.48 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) was prepared and sealed under nitrogen. The aryl zinc reaction mixture was added to the aryl iodide and the resulting mixture stirred for 16 hours at ambient temperature. The reaction mixture was partitioned between saturated $NH_4Cl_{(aq)}$ (5 mL) and EtOAc (10 mL) and the organic layer was washed with brine (7 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc : hexane, 1 : 20 to 1 : 5) to afford the pure material.

6.4.9. General procedure for the synthesis of 1,4,5-substituted 1,2,3-triazoles with aryl bromides or aryl chlorides

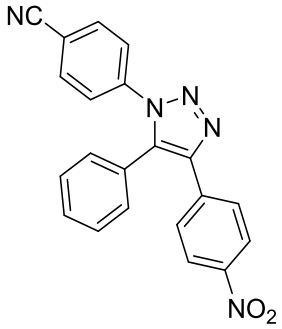
4-azidobenzonitrile (57 mg, 0.40 mmol), phenylacetylene (49 mg, 53 μL, 0.48 mmol) and *N*-methylimidazole (0.04 mmol, 3.3 mg) were added to a glass vial or round bottomed flask. The vessel was purged with N_2 and sealed. Dry THF (5 mL) was added and stirred for 5 minutes before $ZnEt_2$ (0.2 ml, 0.20 mmol, 1 M in hexanes) was added. The reaction was stirred at ambient temperature overnight (approximately 18 hours). A vial charged with the aryl bromide or aryl chloride (0.48 mmol) and PEPPSI-^{i}Pr (16 mg, 0.02 mmol) was prepared and sealed under nitrogen. The aryl zinc reaction mixture was added to the aryl bromide and the resulting mixture stirred for 16 hours (bromides) or 20 hours (chlorides) at 110 °C. The reaction mixture was partitioned between saturated $NH_4Cl_{(aq)}$ (5 mL) and EtOAc (10 mL) and the organic layer was washed with brine (7 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc : hexane, 1 : 20 to 1 : 5) to afford the pure material.



4-(4,5-Diphenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 294a was prepared in accordance with the general procedure with iodobenzene (98 mg, 0.48 mmol) and the product was isolated as a white solid (89 mg, 0.28 mmol, 69%).

294a was also prepared in accordance with the general procedure from bromobenzene (75 mg, 0.48 mmol) and the product was isolated as a white solid (74 mg, 0.23 mmol, 57%).

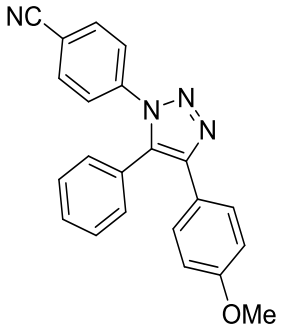
MP = 212 - 213 °C; LRMS [M + H] m/z = 323.4; ν_{max} / cm^{-1} 3062w, 2228m, 1604m, 1509s, 1443w, 1406w, 1369m, 1298w, 1272m, 1214w, 1174w, 1126m, 1102w, 1074w, 1055w, 1024w, 994m, 927w, 843s, 779m, 762s, 727m, 696s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.68 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.55 - 7.63 (m, 2H, Ar-H), 7.47 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.40 - 7.51 (m, 3H, Ar-H), 7.29 - 7.37 (m, 3H, Ar-H), 7.24 (d, *J* = 7.3 Hz, 2H , Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 145.5 (qC), 139.9 (qC), 133.5 (qC), 133.2 (2 x CH), 130.2 (qC), 130.1 (2 x CH), 130.0 (qC), 129.5 (2 x CH), 128.6 (2 x CH), 128.3 (CH), 127.3 (2 x CH), 127.1 (CH), 125.2 (2 x CH), 117.7 (qC), 112.7 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{21}H_{15}N_4$ Calculated 323.1297, found 323.1285.



4-(4-(4-Nitrophenyl)-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 294b was prepared in accordance with the general procedure with 1-iodo-4-nitrobenzene (120 mg, 0.48 mmol) and the product was isolated as a white solid (116 mg, 0.32 mmol, 79%).

294b was also prepared in accordance with the general procedure from 1-bromo-4-nitrobenzene (96 mg, 0.48 mmol) and the product was isolated as a white solid (110 mg, 0.30 mmol, 75%).

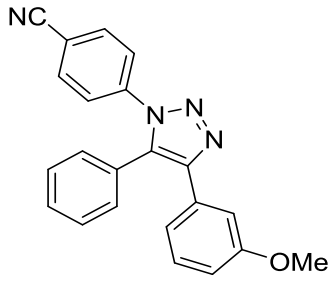
MP = 104 °C; LRMS [M + H] m/z = 368.0; ν_{max} / cm^{-1} 2922w, 2850w, 2232m, 1711w, 1598s, 1505s, 1400w, 1336s, 1274m, 1107m, 1047m, 994s, 853s, 844s, 762m, 731m, 700s, 566m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.19 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.78 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.71 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.46 - 7.62 (m, 3H, Ar-H), 7.47 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.25 (d, *J* = 7.3 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 147.4 (qC), 143.3 (qC), 139.4 (qC), 136.6 (qC), 135.0 (qC), 133.3 (2 x CH), 130.8 (CH), 130.0 (2 x CH), 129.9 (2 x CH), 127.6 (2 x CH), 126.3 (qC), 125.2 (2 x CH), 124.0 (2 x CH), 117.5 (qC), 113.2 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{21}H_{14}N_5O_2$ Calculated 368.1142, found 368.1140.



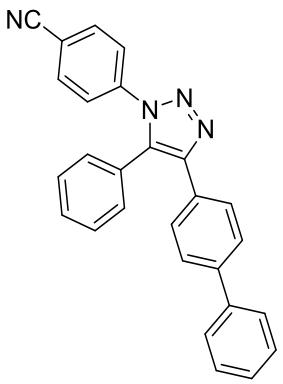
4-(4-(4-Methoxyphenyl)-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile **294c** was prepared in accordance with the general procedure with 1-iodo-4-methoxybenzene (112 mg, 0.48 mmol) and the product was isolated as a white solid (92 mg, 0.26 mmol, 65%);

294c was also prepared in accordance with the general procedure from 1-bromo-4-methoxybenzene (89 mg, 0.48 mmol) and the product was isolated as a white solid (87 mg, 0.25 mmol, 62%).

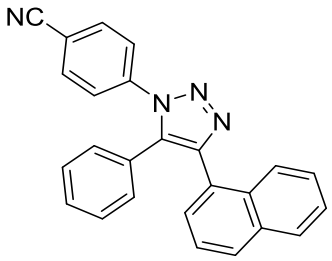
MP = 205 - 206 °C; LRMS [M + H] m/z = 353.2; ν_{max} / cm^{-1} 3056w, 2228m, 1605m, 1516s, 1483m, 1366m, 1300m, 1271m, 1249s, 1176s, 1123m, 1027m, 994m, 841s, 831s, 765m, 701m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.67 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.52 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.46 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.41 - 7.49 (m, 3H, Ar-H) 7.23 (dd, *J* = 8.2, 1.3 Hz, 2H), 6.87 (d, *J* = 9.1 Hz, 2 H), 3.82 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 159.6 (qC), 145.3 (qC), 139.9 (qC), 133.1 (2 x CH), 132.6 (qC), 130.1 (2 x CH), 129.9 (CH), 129.5 (2 x CH), 128.6 (2 x CH), 127.3 (qC), 125.1 (2 x CH), 122.6 (qC), 117.7 (qC), 114.1 (2 x CH), 112.6 (qC), 55.2 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{22}H_{16}N_4NaO$ Calculated 375.1222, found 375.1237.



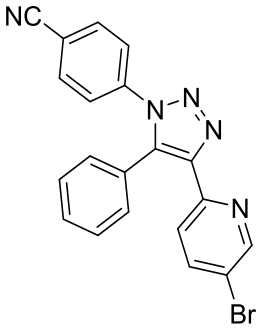
4-(4-(3-Methoxyphenyl)-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 294i was prepared in accordance with the general procedure with 1-bromo-3-methoxybenzene (89 mg, 0.48 mmol) and the product was isolated as a yellow amorphous solid (114 mg, 0.32 mmol, 81%); LRMS [M + H] m/z = 353.0; ν_{max} / cm^{-1} 2228m, 1602m, 1589m, 1510m, 1465m, 1420m, 1408m, 1271m, 1246s, 1125m, 1026m, 992w, 844s, 803s, 765m, 696s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.68 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.42 - 7.51 (m, 5H, Ar-H), 7.25 (d, *J* = 6.8 Hz, 2H, Ar-H), 7.18 - 7.23 (m, 2H, Ar-H), 7.14 (d, *J* = 7.7 Hz, 1H, Ar-H), 6.87 (dd, *J* = 8.2, 1.6 Hz, 1H, Ar-H), 3.72 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 159.6 (qC), 145.3 (qC), 139.8 (qC), 133.5 (qC), 133.2 (2 x CH), 131.3 (qC), 130.1 (2 x CH), 130.0 (CH), 129.6 (CH), 129.5 (2 x CH), 127.1 (qC), 125.1 (2 x CH), 119.6 (CH), 117.7 (qC), 114.6 (CH), 112.7 (qC), 112.1 (CH), 55.1 (OCH_3); HRMS ($[M + H]^+$, +ESI) m/z $C_{22}H_{16}N_4NaO$ Calculated 375.1222, found 375.1228.



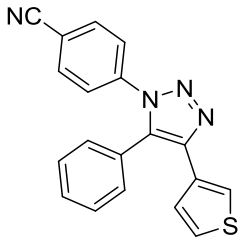
4-(4-([1,1'-Biphenyl]-4-yl)-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 294d was prepared in accordance with the general procedure with 4-iodobiphenyl (134 mg, 0.48 mmol) and the product was isolated as a white solid (113 mg, 0.28 mmol, 71%); MP = 207 - 209 °C; LRMS [M + H] m/z = 399.0; ν_{max} / cm^{-1} 2923w, 2853w, 2210m, 1605m, 1508m, 1436w, 1171m, 1107m, 996m, 847s, 759s, 732s, 718s, 694s, 539s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.65 - 7.72 (m, 4H, Ar-H), 7.55 - 7.62 (m, 4H, Ar-H), 7.42 - 7.53 (m, 7H, Ar-H), 7.36 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.26 - 7.30 (m, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 145.1 (qC), 140.9 (2 x qC), 140.4 (qC), 139.8 (qC), 133.4 (qC), 133.2 (2 x CH), 130.1 (2 x CH), 129.6 (2 x CH), 129.0 (CH), 128.8 (2 x CH), 127.6 (2 x CH), 127.5 (CH), 127.3 (2 x CH), 127.1 (qC), 126.9 (2 x CH), 125.1 (2 x CH), 117.7 (qC), 112.7 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{27}H_{19}N_4$ Calculated 399.1604, found 399.1608.



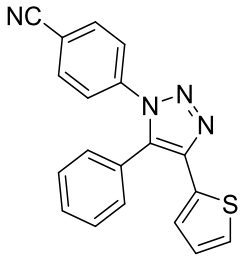
4-(4-(Naphthalen-1-yl)-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 294e was prepared in accordance with the general procedure with 4-iodonaphthalene (122 mg, 0.48 mmol) and the product was isolated as a white solid (97 mg, 0.26 mmol, 65%); MP = 234 °C; LRMS [M + H] m/z = 373.2; ν_{max} / cm^{-1} 3050w, 2919w, 2227m, 1605s, 1508s, 1294m, 1122w, 1100w, 996m, 849s, 822s, 757s, 697s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.12 (d, *J* = 0.6 Hz, 1H, Ar-H), 7.82 (dd, *J* = 6.9, 2.2 Hz, 1H, Ar-H), 7.79 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.74 (dd, *J* = 6.6, 2.5 Hz, 1H, Ar-H), 7.69 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.66 (dd, *J* = 8.5, 1.6 Hz, 1H, Ar-H), 7.50 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.43 - 7.53 (m, 5H, Ar-H), 7.26 - 7.29 (m, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 145.4 (qC), 139.8 (qC), 133.7 (qC), 133.3 (qC), 133.2 (2 x CH), 133.0 (qC), 130.1 (2 x CH), 130.1 (CH), 129.5 (2 x CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.5 (qC), 127.1 (qC), 126.6 (CH), 126.4 (CH), 126.3 (CH), 125.1 (2 x CH), 124.9 (CH), 117.7 (qC), 112.7 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{25}H_{16}N_4Na$ Calculated 395.1273, found 395.1266.



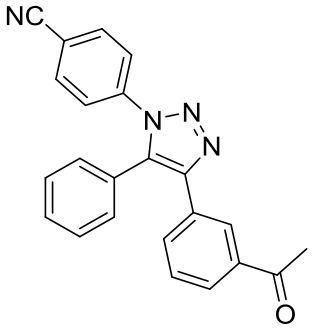
4-(4-(5-Bromopyridin-2-yl)-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 294f was prepared in accordance with the general procedure with 5-bromo-2-iodopyridine (136 mg, 0.48 mmol) and the product was isolated as a white solid 105 mg, 0.26 mmol, 65%); MP = 247 - 249 °C; LRMS [M + H] m/z = 402.4 and 404.3 [Br]; ν_{max} / cm^{-1} 2923w, 2852w, 2230m, 2210m, 1604s, 1499s, 1361m, 1286m, 1273m, 1235m, 1118m, 995s, 835s, 761s, 720s, 694s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.55 (s, 1H, Ar-H), 7.83 - 7.91 (m, 2H, Ar-H), 7.69 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.37 - 7.48 (m, 5H, Ar-H), 7.30 (d, *J* = 7.1 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 150.6 (CH), 148.6 (qC), 144.1 (qC), 139.7 (qC), 139.2 (CH), 135.7 (qC), 133.3 (2 x CH), 130.5 (2 x CH), 129.9 (CH), 128.8 (2 x CH), 126.6 (qC), 125.4 (2 x CH), 123.4 (CH), 120.1 (qC), 117.7 (qC), 112.9 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{20}H_{12}N_5NaBr$ Calculated 424.0174, found 424.0168.



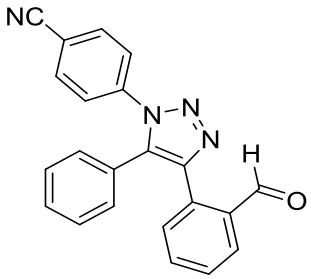
4-(5-Phenyl-4-(thiophen-3-yl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 294g was prepared in accordance with the general procedure with 3-iodothiophene (101 mg, 0.48 mmol) and the product was isolated as a brown solid (70 mg, 0.21 mmol, 53%); MP = 218 - 219 °C; LRMS [M + H] m/z = 329.2; ν_{max} / cm^{-1} 3051w, 2227m, 1603m, 1506m, 1415w, 1269w, 1232m, 993m, 943m, 845s, 830m, 766m, 697s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.75 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.67 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.44 - 7.53 (m, 4H, Ar-H), 7.30 - 7.37 (m, 2H, Ar-H), 7.28 (dd, *J* = 5.1, 0.9 Hz, 1H, Ar-H), 7.15 (dd, *J* = 3.7, 1.0 Hz, 1H, Ar-H), 6.98 (dd, *J* = 5.0, 3.8 Hz, 1H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 141.5 (qC), 139.6 (qC), 133.5 (qC), 133.3 (2 x CH), 131.7 (qC), 130.2 (2 x CH), 129.6 (2 x CH), 129.2 (CH), 128.5 (CH), 127.5 (qC), 125.9 (CH), 125.2 (CH), 124.8 (2 x CH), 117.7 (qC), 112.7 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{19}H_{12}N_4NaS$ Calculated 351.0680, found 351.0665.



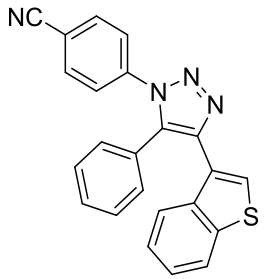
4-(5-Phenyl-4-(thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)benzonitrile 294h was prepared in accordance with the general procedure with 2-iodothiophene (101 mg, 0.48 mmol) and the product was isolated as a brown solid (88 mg, 0.27 mmol, 67%); MP = 226 - 227 °C; LRMS [M + H] m/z = 329.2; ν_{max} / cm^{-1} 3045w, 2229m, 1604m, 1508m, 1453m, 1371m, 1285m, 1231m, 1123m, 1089m, 1053m, 990s, 833s, 765s, 696s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.67 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.41 - 7.54 (m, 6H, Ar-H), 7.27 - 7.33 (m, 4H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 142.2 (qC), 139.7 (qC), 133.2 (2 x CH), 132.7 (qC) 131.0 (qC), 130.2 (CH), 130.1 (2 x CH), 129.6 (2 x CH), 127.1 (qC), 126.3 (CH), 125.9 (CH,) 124.8 (2 x CH), 122.4 (CH), 117.7 (qC), 112.6 (qC); HRMS ($[M + Na]^+$, +ESI) m/z $C_{19}H_{12}N_4NaS$ Calculated 351.0680, found 351.0678.



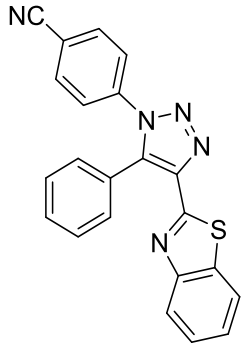
4-(4-(3-Acetylphenyl)-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 294j was prepared in accordance with the general procedure with 3-bromoacetophenone (95 mg, 0.48 mmol) and the product was isolated as a white solid (112 mg, 0.31 mmol, 77%); MP = 195 - 197 °C; LRMS [M + H] m/z = 365.2; ν_{max} / cm^{-1} 3062w, 2923w, 2235m, 1686s, 1603s, 1508s, 1362m, 1260s, 1126m, 1057m, 999m, 847s, 810s, 798s, 770s, 703s, 692s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.15 (t, *J* = 1.4 Hz, 1H, Ar-H), 7.92 (dt, *J* = 7.8, 1.4 Hz, 1H, Ar-H), 7.83 (dt, *J* = 7.8, 1.4 Hz, 1H, Ar-H), 7.70 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.49 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.42 - 7.56 (m, 4H, Ar-H), 7.26 (dd, *J* = 6.8, 1.5 Hz, 2H, Ar-H), 2.47 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 197.6 (C=O), 144.6 (qC), 139.6 (qC), 137.4 (qC), 133.9 (qC), 133.2 (2 x CH), 131.6 (CH), 130.6 (qC), 130.3 (CH), 130.0 (2 x CH), 129.7 (2 x CH), 129.0 (CH), 127.7 (CH), 127.4 (CH), 126.8 (qC), 125.1 (2 x CH), 117.6 (qC), 112.9 (qC), 26.5 (CH_3); HRMS ($[M + Na]^+$, +ESI) m/z $C_{23}H_{16}N_4ONa$ Calculated 387.1222, found 387.1208.



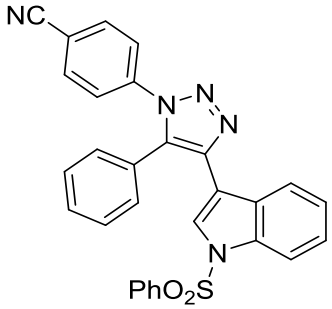
4-(4-(2-Formylphenyl)-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 294k was prepared in accordance with the general procedure with 2-bromobenzaldehyde (88 mg, 0.48 mmol) and the product was isolated as an orange solid (45 mg, 0.13 mmol, 32%); MP = 192 - 193 °C; LRMS [M + H] m/z = 351.3; ν_{max} / cm^{-1} 3044w, 2924w, 2229w, 1607m, 1576m, 1508w, 1464m, 1445m, 1365w, 1306w, 1267w, 1236m, 1154w, 1104w, 1064w, 1000m, 983m, 851m, 833m, 750s, 695s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 10.79 (s, 1H, CHO), 7.70 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.47 - 7.57 (m, 3H, Ar-H), 7.45 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.30 (d, *J* = 6.8 Hz, 2H, Ar-H), 7.21 (t, *J* = 8.1 Hz, 1H, Ar-H), 7.09 (d, *J* = 8.1 Hz, 1H, Ar-H), 6.97 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.63 (t, *J* = 7.6 Hz, 1H, Ar-H); ^{13}C NMR was not analysed for this sample; HRMS ($[M + H]^+$, +ESI) m/z $C_{22}H_{15}N_4O$ Calculated 351.1240, found 351.1234.



4-(4-(Benzothiophen-3-yl)-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 294n was prepared in accordance with the general procedure with 3-bromobenzothiophene (102 mg, 0.48 mmol) and the product was isolated as a white amorphous solid (109 mg, 0.29 mmol, 72%); LRMS [M + H] m/z = 379.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.34 - 8.40 (m, 1H, Ar-H), 7.85 - 7.91 (m, 1H, Ar-H), 7.70 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.52 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.45 (d, *J* = 7.3 Hz, 1H, Ar-H), 7.37 - 7.43 (m, 4H, Ar-H), 7.22 (dd, *J* = 8.1, 1.2 Hz, 2H, Ar-H), 7.20 (s, 1H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 141.8 (qC), 139.8 (CH), 139.7 (qC), 137.6 (qC), 134.5 (qC), 133.2 (2 x CH), 130.0 (CH), 129.8 (2 x CH), 129.5 (2 x CH), 126.7 (qC), 125.7 (qC), 125.4 (qC), 125.1 (2 x CH), 124.7 (CH), 124.6 (CH), 124.4 (CH), 122.4 (CH), 117.6 (qC), 112.7 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{23}H_{15}N_5S$ calculated 379.1017, found 379.1009.



4-(4-(Benzothiazol-2-yl)-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile 294o was prepared in accordance with the general procedure with 2-bromobenzothiazole (102 mg, 0.48 mmol) and the product was isolated as a white solid (124 mg, 0.31 mmol, 77%); MP = 205 °C; LRMS [M + H] m/z = 402.1; ν_{max} / cm^{-1} 2922w, 2226w, 1662s, 1602m, 1504w, 1464m, 1214m, 993m, 948s, 837m, 767s, 738s, 695s, 642m; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 7.97 (dq, *J* = 7.8, 0.5 Hz, 1H, Ar-H), 7.91 (dq, *J* = 8.1, 0.8 Hz, 1H, Ar-H), 7.72 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.51 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.47 - 7.49 (m, 2H, Ar-H), 7.38 - 7.43 (m, 2H, Ar-H), 7.28 (td, *J* = 7.8, 1.3 Hz, 1H, Ar-H), 7.12 - 7.18 (m, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 158.0 (qC), 153.6 (qC), 140.6 (qC), 139.3 (qC), 135.9 (qC), 134.9 (qC), 133.3 (2 x CH), 130.6 (2 x CH), 130.5 (CH), 128.9 (2 x CH), 126.1 (CH), 125.5 (CH), 125.3 (2 x CH), 125.1 (qC), 123.6 (CH), 121.5 (CH), 117.5 (qC), 113.1 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{22}H_{13}N_5S$ calculated 402.0789, found 402.0779.



4-(5-Phenyl-4-(1-(phenylsulfonyl)-1*H*-indol-3-yl)-1*H*-1,2,3-triazol-1-yl)benzonitrile

294m was prepared in accordance with the general procedure with 3-bromo-1-(phenylsulfonyl)-1*H*-indole (161 mg, 0.48 mmol) and the product was isolated as a white solid (134 mg, 0.27 mmol, 67%); MP = 200 - 202 °C; LRMS [M + H] m/z = 502.2; ν_{max} / cm^{-1} 3471w, 3368w, 3227w, 2924w, 2212m, 1627m, 1603s, 1509s, 1446m, 1368m, 1313m, 1262m, 1171s, 1133s, 1085m, 996m, 926w, 847s, 830s, 762s, 747s, 728s, 698s, 682s, 584s, 567s, 547s; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.09 (d, *J* = 7.9 Hz, 1H, Ar-H), 8.02 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.77 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.71 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.51 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.47 - 7.58 (m, 4H, Ar-H), 7.43 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.38 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.34 (s, 1H, Ar-H), 7.29 (t, *J* = 8.2 Hz, 1H, Ar-H), 7.26 (d, *J* = 8.4 Hz, 2H, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm = 140.0 (qC), 139.6 (qC), 137.8 (qC), 134.9 (qC), 134.0 (CH), 133.9 (qC), 133.3 (2 x CH), 130.4 (CH), 129.8 (2 x CH), 129.7 (2 x CH), 129.3 (2 x CH), 129.0 (qC), 126.8 (2 x CH), 126.6 (qC), 125.3 (CH), 124.9 (2 x CH), 123.9 (CH), 123.7 (CH), 122.3 (CH), 117.6 (qC), 113.4 (CH), 112.8 (qC), 112.8 (qC); HRMS ($[M + H]^+$, +ESI) m/z $C_{29}H_{19}N_5O_2S$ calculated 502.1338, found 502.1334.

6.4.10. General procedure for the preparation of dimerised 1,5-substituted, 1,2,3-triazoles

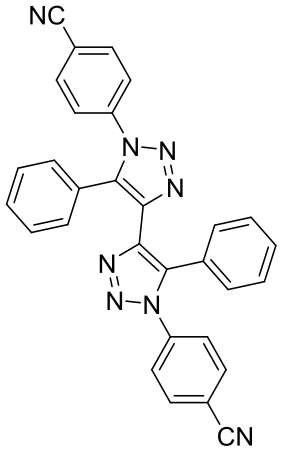
4-azidobenzonitrile (43 mg, 0.30 mmol), phenylacetylene (37 mg, 40 μL, 0.36 mmol) and *N*-methylimidazole (0.03 mmol, 2.5 mg) were added to a glass vial or round bottomed flask. The vessel was purged with N_2 and sealed. Dry THF (4 mL) was added and stirred for 5 minutes before $ZnEt_2$ (0.15 mL, 0.15 mmol, 1 M in hexanes) was added. The reaction was stirred at ambient temperature overnight (approximately 18 hours). At this point either procedure 1, 2, or 3 were followed.

Procedure 1 - To the resulting mixture was added a solution of 4-(4-iodo-5-phenyl-1*H*-1,2,3-triazol-1-yl)benzonitrile (123 mg, 0.33 mmol) in THF (2 ml). The solution was transferred by cannula to a nitrogen flushed vial containing the PEPPSI-^{i}Pr catalyst (12 mg, 0.015 mmol). The reaction was stirred in a preheated oil bath at 90 °C for 16 hours at which point the work up was performed.

Procedure 2 – To the resulting mixture was added a solution of iodine (38 mg, 0.15 mmol) in THF (2 ml). The solution was transferred by canula to a nitrogen flushed vial containing the PEPPSI-^{i}Pr catalyst (12 mg, 0.015 mmol). The reaction was stirred in a preheated oil bath at 110 °C for 16 hours at which point the work up was performed.

Procedure 3 - The reaction mixture was transferred by syringe to a nitrogen flushed vial containing a copper species (amounts specified in R&D) and stirred for 4 hours at a specified temperature at which point the work up was performed.

Work up -The mixture was partitioned between saturated $NH_4Cl_{(aq)}$ (5 mL) and EtOAc (10 mL) and the organic layer was washed with brine (7 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc : hexane, 1 : 20 to 1 : 5) to afford the pure material.



4,4'-(5,5'-Diphenyl-1*H*,1'*H*-[4,4'-bi(1,2,3-triazole)]-1,1'-diyl)dibenzonitrile 241a was prepared in accordance with general procedure 1 and isolated as a white solid (98 mg, 0.20 mmol, 67%).

241a was also prepared in accordance with general procedure 2 and isolated as a white solid (19 mg, 0.04 mmol, 13%).

241a was also prepared in accordance with general procedure 3 using $Cu(OAc)_2$ (54 mg, 0.30 mmol) at ambient temperature, and isolated as a white solid (16 mg, 0.03 mmol, 11%).

241a was also prepared in accordance with general procedure 3 using $CuCl_2$ (30 mg, 0.23 mmol) at 45 °C, and isolated as a white solid (106 mg, 0.22 mmol, 72%).

MP = 263 - 264 °C; LRMS [M + H] m/z = 491.1; ν_{max} / cm^{-1} 3076w, 2921m, 2852m, 2231m, 1604m, 1508s, 1463m, 1447m, 1403m, 1276m, 1176w, 1135w, 1109w, 1067m, 1000s, 967m, 917w, 854s, 825s, 761s, 693s; ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm = 7.68 (d, *J* = 8.8 Hz, 4H, Ar-H), 7.47 (d, *J* = 8.8 Hz, 4H, Ar-H), 7.39 (tt, *J* = 7.3, 1.4 Hz, 2H, Ar-H), 7.32 (dd, *J* = 8.4, 7.3 Hz, 4H, Ar-H), 7.22 (dd, *J* = 8.4, 1.4 Hz, 4H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm = 139.6 (2 x qC), 137.1 (2 x qC), 136.7 (2 x qC), 133.2 (4 x CH), 130.1 (4 x CH), 129.9 (2 x CH), 128.9 (4 x CH), 125.7 (2 x qC), 125.1 (4 x CH), 117.6 (2 x qC), 112.9 (2 x qC); HRMS ([M + H]$^+$, +ESI) m/z $C_{30}H_{18}N_8$ calculated 491.1773, found 491.1715.

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