Transition Metal-Free Arylation and Heterocycle Synthesis

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by

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List of Abbreviations

$(DHQD)_2PHAL$	-	hydroquinidine 1,4-phthalazinediyl diether
18-c-6	-	1,4,7,10,13,16-hexaoxacyclooctadecane
18-crown-6	-	1,4,7,10,13,16-hexaoxacyclooctadecane
Å	-	angstroms
A	-	amperes
Ac	-	acetyl
AIBN	-	2,2'-azobisisobutyronitrile
app.	-	apparent
Ar	-	aryl
atm	-	atmospheres
ATR FTIR	-	Attenuated total reflection Fourier transform infrared spectroscopy
BDD	-	boron-doped diamond
BIMP	-	bifunctional iminophosphorane
Bn	-	benzyl
Boc	-	*tert*-butyloxycarbonyl
br	-	broad
Bu	-	butyl
°C	-	degrees Celsius
CAN	-	ceric ammonium nitrate
cat	-	catalytic, catalyst
Cbz	-	carboxylbenzyl
CI	-	chemical ionisation
cm	-	centimeters
cm^{-1}	-	wavenumbers
cod	-	1,5-cyclooctadiene
$Cp^{*t\text{-Bu}}$	-	*tert*-butyl-tetra-methyl-cyclopentadienyl
DABCO	-	1,4-diazabicyclo[2.2.2]octane
DABSO	-	1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct
dba	-	dibenzylideneacetone

DBU	-	1,8-diazabicyclo(5.4.0)undec-7-ene
DCE	-	1,2-dichloroethene
DDQ	-	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPA	-	diisopropylamine
DIPEA	-	*N*,*N*-diisopropylethylamine
DMA	-	dimethylacetamide
DMAP	-	4-(dimethylamino)pyridine
DME	-	dimethoxyethane
DMEDA	-	*N*,*N*′-dimethylethylenediamine
DMF	-	dimethyl formamide
DMII	-	1,3-dimethyl-1*H*-imidazol-3-ium iodide
DMP	-	1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one
DMPU	-	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	-	dimethyl sulfoxide
DNB	-	dinitrobenzene
dppb	-	1,4-bis(diphenylphosphino)butane
dppm	-	1,1-bis(diphenylphosphino)methane
dr	-	diastereomeric ratio
dtpy	-	2,6-di-tert-butylpyridine
EI	-	electron impact
El	-	electrophile
er	-	enantiomeric ratio
EDG	-	electron-donating group
ee	-	enantiomeric excess
EPR	-	electron paramagnetic resonance
eq.	-	equivalents
ES	-	electrospray
Et	-	ethyl
Et_2O	-	diethyl ether
Et_3N	-	triethyl amine
EWG	-	electron-withdrawing group
F	-	Faraday

GC	-	gas chromatography
h	-	hour
HDDA	-	hexadehydro-Diels-Alder
Het	-	heteroaromatic
HFIPA	-	1,1,1,3,3,3-hexafluoro-2-propanol
HMDS	-	hexamethyldisilazane
HOMO	-	highest occupied molecular orbital
HPLC	-	high-performance liquid chromatography
hν	-	light
Hz	-	Hertz
IMes	-	1,3-bis(2,4,6-trimethylphenyl)-imidazolium
i-Pr	-	isopropyl
IR	-	infrared
ISC	-	intersystem crossing
J	-	coupling constant
kg	-	kilogram
KIE	-	kinetic isotope effect
LCMS	-	liquid chromatography mass spectrometry
LDA	-	lithium diisopropylamine
LED	-	light-emitting diode
LG	-	leaving group
LUMO	-	lowest unoccupied molecular orbital
m	-	*meta*
M	-	molar
max	-	maximum
MCR	-	multicomponent reaction
Me	-	methyl
MeCN	-	acetonitrile
Mes	-	mesitylene
min	-	minutes
MOF	-	molecular organic framework
mol	-	mole
MOM	-	methoxymethyl

MS	-	mass spectrometry
MTBE	-	methyl *tert*-butyl ether
MW	-	microwave heating
m/z	-	mass-to-charge ratio
n-Bu	-	normal-butyl
NFBS	-	*N*-fluorobenzenesulfonimide
NHC	-	*N*-heterocyclic carbene
nm	-	nanometers
NMM	-	*N*-methylmorpholine
NMR	-	nuclear magnetic resonance
Ns, nosyl	-	nitrobenzene sulfonyl
Nu	-	nucleophile
o	-	*ortho*
OAc	-	acetate
OLED	-	organic light-emitting diode
o-tol	-	*ortho*-tolyl
p	-	*para*
Ph	-	phenyl
phen	-	phenanthroline
PhMe	-	toluene
PIFA	-	[bis(trifluoroacetoxy)iodo]benzene
pK_a	-	logarithmic acid dissociation constant
pK_{BH+}	-	logarithmic conjugate-acid dissociation constant
PMB	-	4-methoxybenzyl
ppm	-	parts per million
ppb	-	parts per billion
py	-	pyridine
R	-	generic carbon functional group
r.t.	-	ambient temperature
S_EAr	-	electrophilic aromatic substitution
SET	-	single-electron transfer
S_N1	-	unimolecular substitution
S_NAr	-	nucleophilic aromatic substitution

SOMO	-	singly occupied molecular orbital
$S_{RN}1$	-	radical unimolecular substitution
TASF	-	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBACl	-	tetrabutylammonium chloride
TBAF	-	tetrabutylammonium fluoride
TBAI	-	tetrabutylammonium iodide
TBAT	-	tetrabutylammonium difluorotriphenylsilicate
TBHP	-	*tert*-butyl hydroperoxide
TBS	-	*tert*-butyldimethylsilyl
t-Bu	-	*tert*-butyl
temp	-	temperature
TEMPO	-	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
TES	-	triethylsilyl
Tf, triflyl	-	triflyl, trifluoromethyl sulfonyl
TFA	-	trifluroacetic acid
TFAA	-	trifluoroacetic anhydride
TFE	-	2,2,2-trifluoroethanol
THF	-	tetrahydrofuran
THP	-	tetrahydropyran
TLC	-	thin-layer chromatography
TMG	-	1,1,3,3-tetramethylguanidine
TMP	-	2,2,6,6-tetramethylpiperidine
TMS	-	trimethylsilyl
t-Oct	-	*tert*-octyl
t_R	-	retention time
Ts, tosyl	-	*p*-toluenesulfonyl
Tr	-	triphenylmethyl
TsO	-	*p*-toluenesulfonic anhydride
UVA	-	ultraviolet-A
Vis	-	visible
VNS	-	vicarious nucleophilic substitution
W	-	Watt
X	-	generic functional group

XRD	-	x-ray diffraction
w/w	-	weight per unit weight

Abstract

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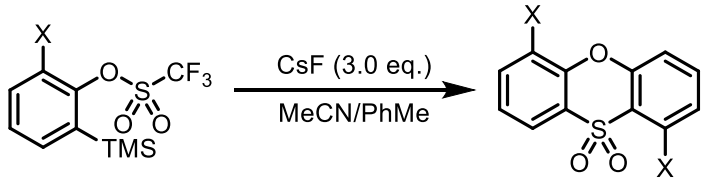
School of Chemistry — Doctor of Philosophy

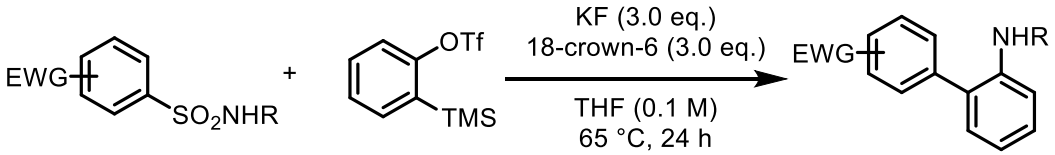
Transition Metal-Free Arylation and Heterocycle Synthesis

Arenes are ubiquitous motifs in both naturally occurring and synthetic functional organic molecules. The investigation of metal-free methodology for the installation of these motifs is important for sustainable development and the discovery of new modes of reactivity.

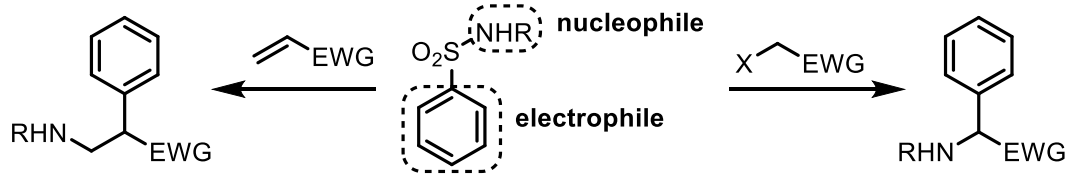
Chapter 1. The preparation of halogenated phenoxathin-10,10-dioxides was ascertained to proceed through fluoride-induced decomposition and subsequent recombination of two molecules of the *o*-trimethylsilyl(aryl) triflate aryne precursors.



Chapter 2. A new mild and metal-free methodology for the transition metal-free preparation of 2-amino biaryls using the benzyne intermediate was established. This proceeds *via* a desulfonative Truce-Smiles rearrangement of an aryl anion in the key bond-forming step.



Chapter 3. The electron-poor *S*-aryl sulfonamides developed in chapter 2 were explored as reagents for metal-free 1,1- and 1,2-carbonamination. Asymmetric catalysis was also investigated for the preparation of enantioenriched α,α-disubstituted aryl glycine derivatives.



Chapter 4. Some organocatalytic methods for the vicarious nucleophilic substitution of hydrogen were investigated to expand the remit of this classical arylation mechanism.

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.

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Introduction

1. Background

Transition metal catalysed reactions represent some of the greatest advances in organic chemistry during the past century, and cross-coupling has become one of the most widely used strategies for the formation of carbon-carbon bonds. The success of this field was highlighted through the award of a Nobel Prize in Chemistry in 2011. However, the continually rising levels of global consumption exceed the Earth's capacity for production, and whilst changing patterns of usage and waste will be critical for sustainable living, the discovery of new technologies which support this future are also required. Researchers have begun to develop metal-free conditions which complement the widely-used transition metal catalysed cross-coupling reactions to support these sustainability goals.

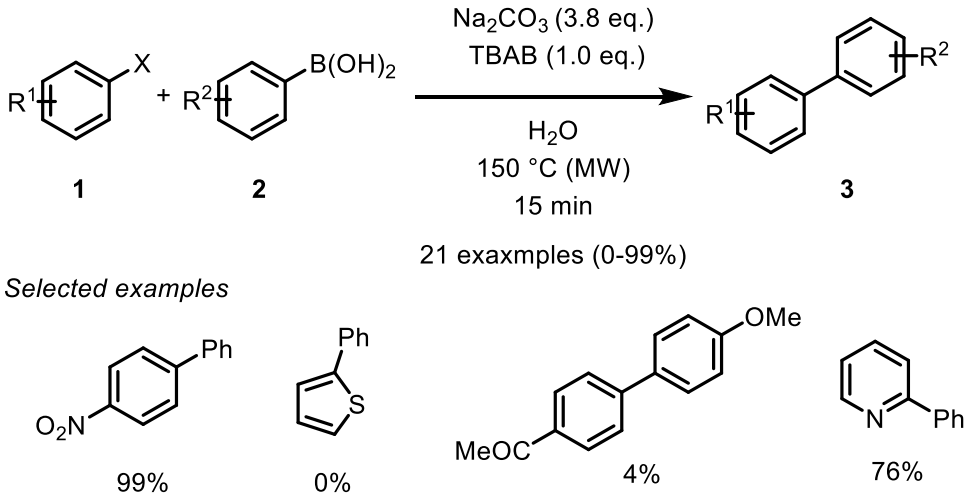
The importance of discovering new metal-free methodologies for the synthesis of organic compounds is threefold. Firstly, in the environmental benefits both through reducing toxic waste streams and improving the sustainability of chemical processes.[1] There are strict exposure limits placed upon residual metals in pharmaceutical products,[2] and there is a growing concern over the long-term implications to the environment due to the slow accumulation of heavy metals – of which the platinum group elements are an emerging group.[3] Secondly, in the provision of lower-cost routes to fine chemicals, which do not use expensive metal catalysts, specialist equipment for air-sensitive chemistry, or necessitate removal of residual metal impurities.[4] Thirdly, in the preparation of new molecular structures through the alternative modes of reactivity used by metal-free synthesis.

Aromatic compounds have unique reactivity and stability compared to their non-aromatic counterparts, and are found within naturally-occurring and synthetic organic molecules which have applications from medicine to materials science.[5] Whilst some argue that focus of research should move to sp^3-rich chemical space,[6] the discovery of new chemical methods for synthesis, functionalisation, and installation of these (hetero)arenes remains a focus of research.

There is a broad body of literature concerning transition metal-free cross-coupling which has been reviewed recently.[7] A brief introduction to the arylation of arenes and alpha to carbonyls with aryl cations and aryl radicals will be presented. The arylation with arynes will be reviewed in greater detail due to the focus on this intermediate in the ensuing research. Finally, as intramolecular aryl transfer is a key mechanism it will also be discussed.

2. A Cautionary Tale

The first transition metal-free cross-coupling reaction of two distinct arenes to be reported was a Suzuki-type cross-coupling of aryl boronic acids **2** with aryl halides (typically bromides) **1** (Scheme 1).[8] These reagents, in the presence of sodium carbonate, a phase-transfer catalyst, in water, and under microwave heating gave the biaryl cross-coupling products **3**, apparently in the absence of any transition metal catalyst.



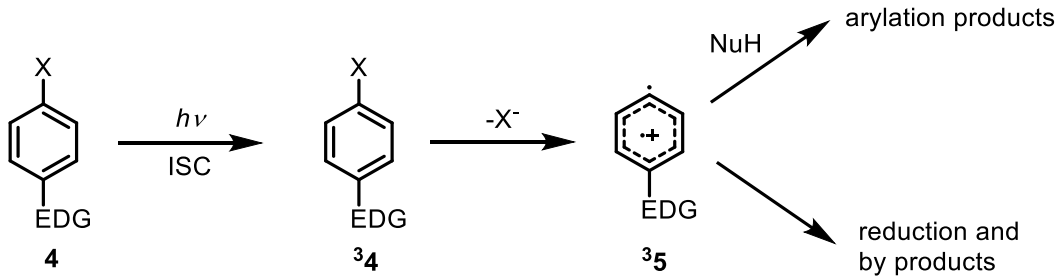
Scheme 1 "Metal-free" Suzuki cross coupling

Analysis of the reaction mixtures by inductively coupled plasma atomic emission spectroscopy purportedly confirmed that the reaction mixtures were indeed transition-metal free within the detection limits of the experiment. However, reports of C–C cross-coupling reactions catalysed by extremely low loadings of catalyst prompted a more rigorous analysis of the reaction conditions. This revealed palladium contaminants, within the sodium carbonate base, at a level of 50 ppb.[9]

3. Aryl Cations

Albini and Fagnoni pioneered the development of "green" metal-free arylation chemistry, using the S_N1 photoarylation of carbon nucleophiles.[10-11] This methodology uses aryl cations as highly electrophilic arene sources for the selective arylation of carbon nucleophiles. Aryl cations exist in two spin states; the positive charge of the singlet aryl cation is localised in a *p*-orbital and this species reacts unselectively. Whereas, the charge of the triplet aryl cation is delocalised over the ring giving carbene character to the divalent carbon, and this species reacts selectively with π-nucleophiles over *n*-nucleophiles. The ground state of phenyl cations is the singlet (lying 22 kcal/mol below the triplet state). However, electron-donating groups lower the energy of the triplet state, and so the ground state of the 4-amino, 4-thiomethoxy and 4-methoxy phenyl cations is the triplet.[12]

Irradiation (λ_{max} = 310 nm) populates the triplet state of electron-rich aryl(pseudo)halides (Scheme 2). The Ar–X **4** undergoes heterolytic cleavage, with conserved multiplicity, to form a triplet aryl cation **5**. This reaction occurs smoothly in the case of electron-rich arenes which can stabilise the positive charge, and represents Umpolung reactivity of the electron-rich. The aryl cation is a short-lived species which reacts with either suitable carbon nucleophiles or undergoes concurrent side reactions such as hydrogen abstraction or dimerisation resulting in by products. Consequently, an excess (around 10:1) of the carbon nucleophile is frequently used.

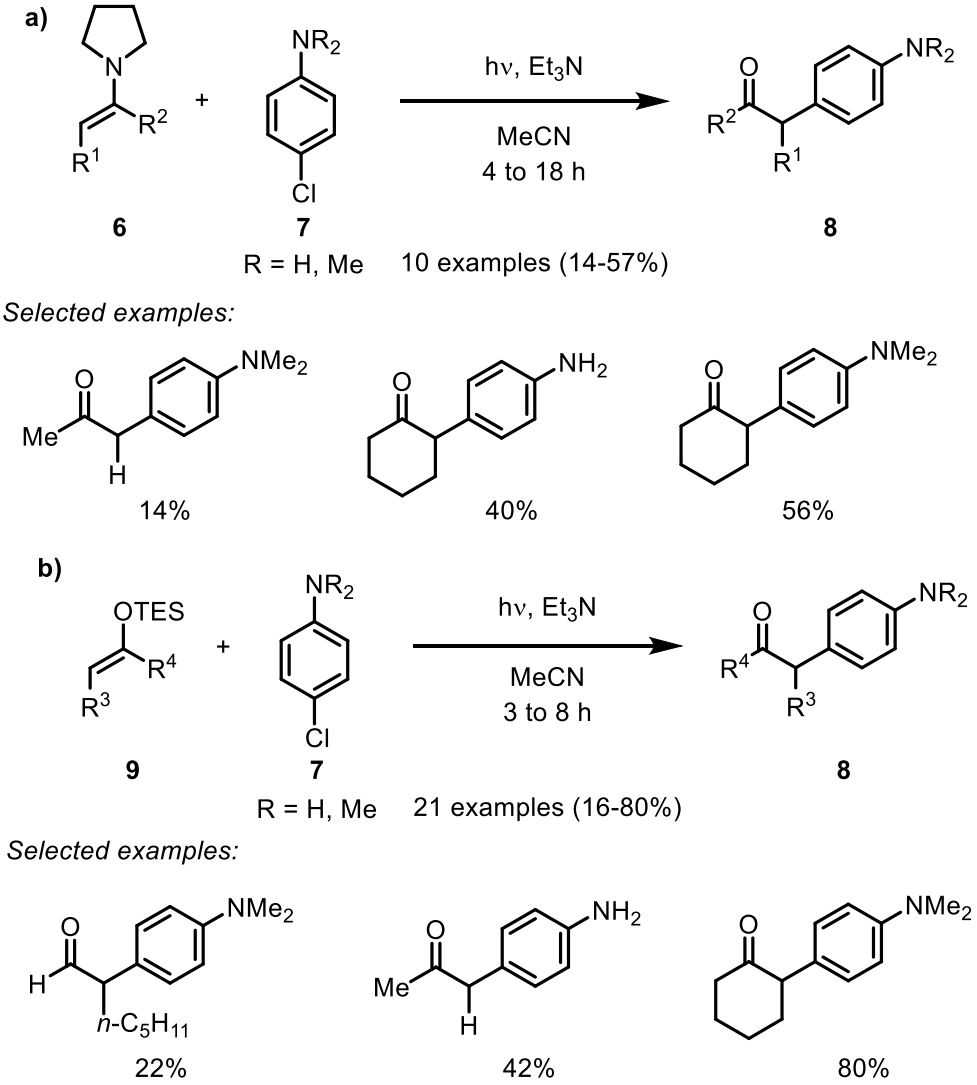


Scheme 2 The mechanism of photochemically induced aryl cation formation and arylation

Many aryl halides and esters have been demonstrated as precursors to the aryl cation, with the caveat that an electron-rich substituent is present to stabilise the triplet aryl cation intermediate. Aryl diazoniums can also be used if an electron-withdrawing group (COMe or NO_2) is present, by triplet sensitization with xanthone.[13-14]

3.1. Alpha-arylation of carbonyls

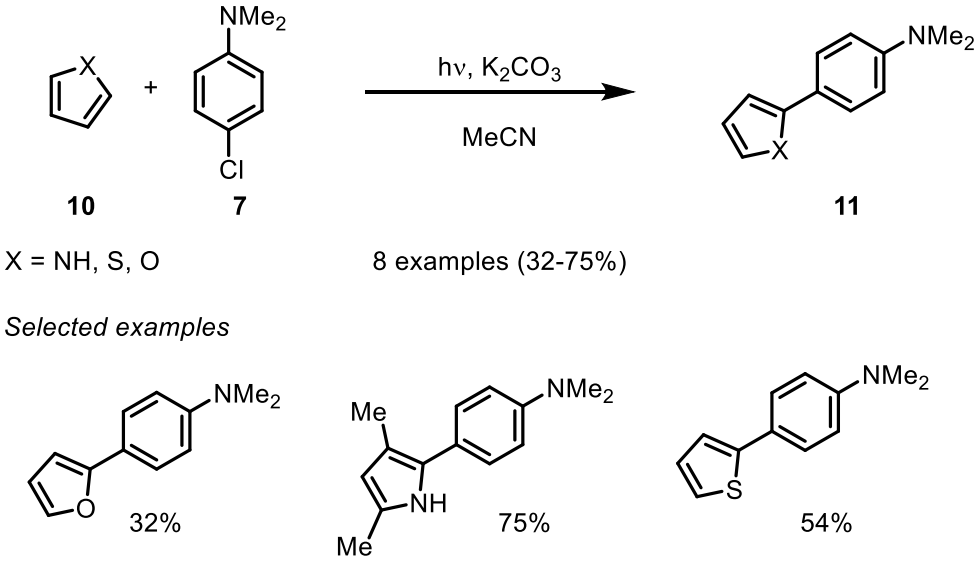
Enamines **6** silyl enol ethers **9** are suitable nucleophiles for achieving α-arylation of ketones **8** (Scheme 3).[15] Ketene silyl acetal was also demonstrated as a masked ester enolate for synthesis α-arylated esters. The advantages of this method include the use of stoichiometric triethylamine as a buffer, as opposed to a strong base, and inexpensive aryl chlorides in the place of bromides, iodides, diazonium ions or fluorides. However, a large excess of the enol-equivalent is required to favour the desired arylation.



Scheme 3 Aryl cations in α-arylation of carbonyl equivalents

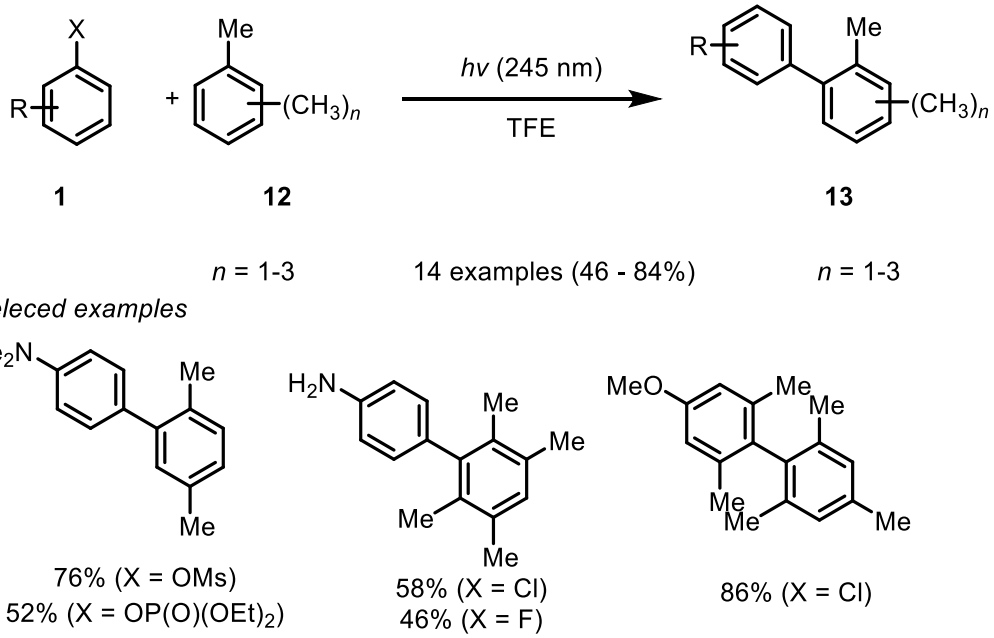
3.2. Arene Arylation

Some biphenyl dimerization products had been observed when aryl cations were generated in the absence of a π-nucleophile.[16-17] The formation of aryl cations, from *p*-chloroanilines **7**, in the presence of π-rich five-membered heterocycles **10**, such as pyrrole, furan or thiophene, resulted in virtual exclusive arylation of the 2-position **11** (Scheme 4).[18] The exceptions were in the case of 2-substituted pyrroles, where the 3-substituted product was isolated, and furans where the major product resulted from 2,5-addition.



Scheme 4 The arylation of π-excessive heterocycles with photochemically generated aryl cations

The formation of biaryls using the aryl cation intermediate was next explored with respect to *p*-xylene, mesitylene and 1,2,4,5-tetremethyl benzene **12** (durene).[19] The reaction was typically performed in TFE, and acetonitrile was reported as a convenient alternative in some cases. An equivalent of acid generated throughout the course of the reaction and so Et_3N is added as a buffer. Again, a large excess of the methyl benzene **12** (10 eq.) was required to achieve high yields of the biaryl product **13**. A variety of halides and pseudo-halide esters **1** were demonstrated under the reaction conditions, including chloride, fluoride, mesylates, phosphonates and triflates (Scheme 5). Various electron-donating functional groups could tolerate the reaction conditions: silyl protected phenol, ether, thio ether, free aniline, and free phenol, mostly in the *ortho* or *para* position. Highly sterically hindered tetra-ortho substituted biaryl products could be formed in high yields (84 and 77%). Variations on this protocol have been developed, including the use of flow technology,[20] and the use of aryl imidazylates as aryl cation precursors.[21]



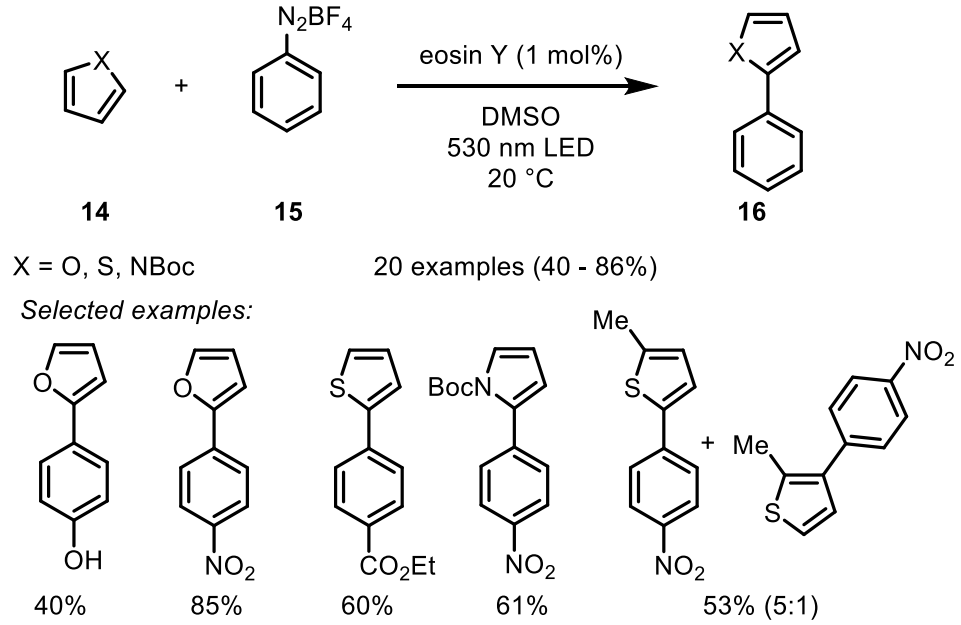
Scheme 5 The aryl cation mediated direct arylation of alkyl benzenes

4. Aryl Radicals

4.1. Arene Arylation

4.1.1. Aryl radical addition

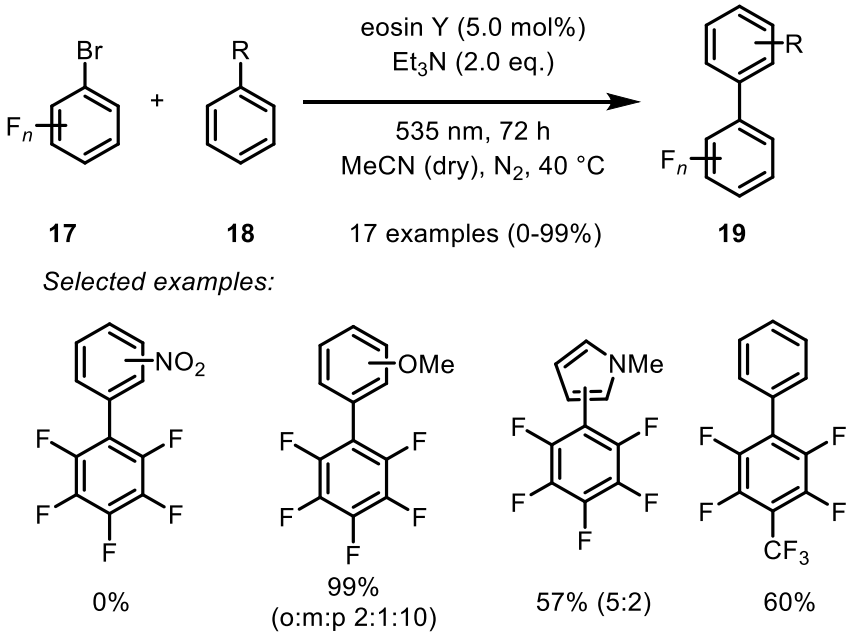
Arene diazoniums **15** are frequently used as a source of aryl radicals, through reduction and loss of di-nitrogen, due to their relatively high reduction potentials.[22] König reported the photoredox-catalysed transition metal-free arylation of heteroarenes **14** (analogous to the Gomberg-Bachmann reaction).[23] This SET-mediated direct arylation of heteroarenes **14** uses the organic dye eosin-Y and light from green LEDs (Scheme 6). Only π-rich five-membered heterocycles, such as furan, thiophene and *N*-Boc-pyrrole, were arylated and the reaction was regioselective for the C-2 position **16**. Electron-poor diazoniums generally gave better yields than electron-rich substrates. These results verify an SOMO-HOMO interaction controlled reaction, as the electron-poor aryl radicals have a lower SOMO, and therefore a more effective interaction with the HOMO of the heterocycle. Furthermore, TEMPO trapping experiments confirmed the presence of radical intermediates. It was proposed that the reaction is initiated by SET from the excited eosin Y to the diazonium salt, and then propagated through electron transfer from a radical biaryl intermediate.



Scheme 6 An organic photoredox-catalysed direct arylation of heteroarenes with diazonium salts

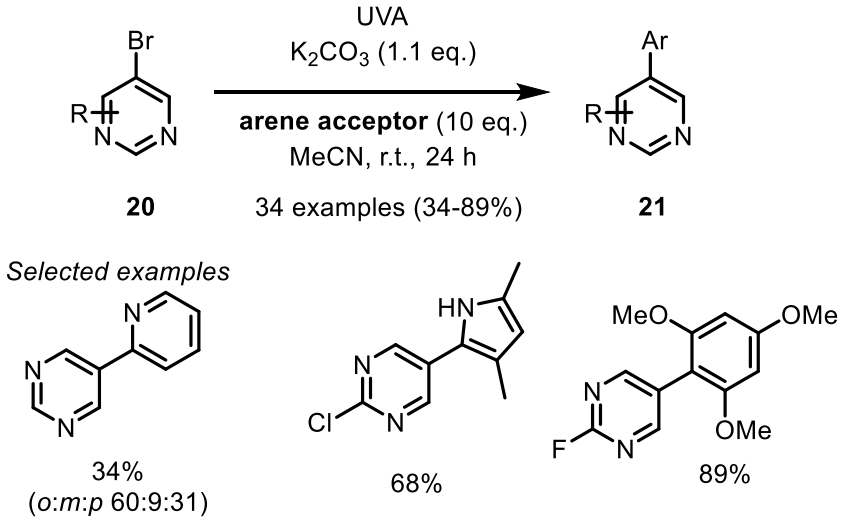
Advances in this methodology include the *in-situ* preparation of (hetero)aryl diazoniums from (hetero)aryl anilines and reaction with π-rich heterocycle to form heteroaromatic biaryls was then developed by Kundu and Ranu,[24] and the use of ascorbic acid[25] or hydrazines[26] as catalysts for the formation of aryl radicals from diazonium salts.

König has also demonstrated photoredox-catalysed direct perfluoroarylation of simple arenes **18** using an eosin Y catalyst (Scheme 7).[27] Photophysical experiments revealed that the triplet state of the eosin Y catalyst is reductively quenched by Et_3N, then the radical anion of eosin Y transfers an electron to bromopentafluorobenzene **17**. This is followed by homolytic cleavage of the C–Br bond, which reacts to form the arylated product **19**. A range of arenes could be perfluoroarylated, except very electron-poor arenes such as nitrobenzene.



Scheme 7 Visible light mediated arylation with aryl bromides

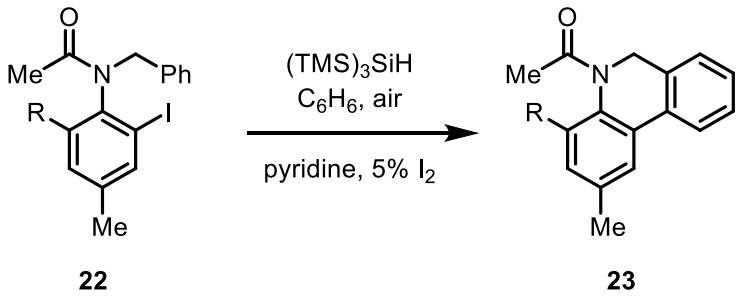
The generation of pyrimidine and pyrazine radicals from the respective bromides **20** with UVA light, and trapping with various arenes to form bi(hetero)aryls **21** was disclosed by Goddard.[28] The arene acceptor was used in a ten-fold excess, and a mild base (K_2CO_3) is present as a buffer for the equivalent of hydrogen bromine which is generated (Scheme 8). The reaction does not proceed in the absence of light, and thus an S_NAr mechanism was excluded. In the presence of TEMPO, direct and tandem radical trapping products were isolated from the reaction, confirming the radical nature of the reaction mechanism.



Scheme 8 Photochemical arylation of pyrimidines

4.1.2. Hydrogen Atom Substitution

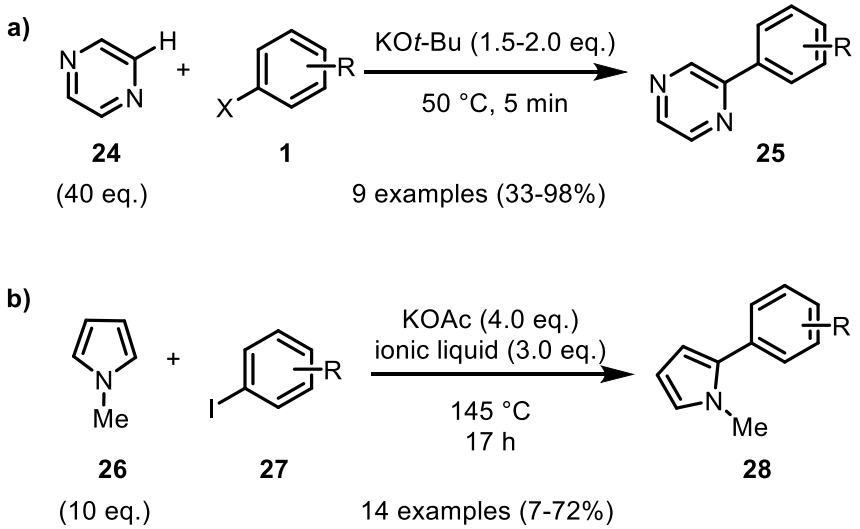
In 2006, Curran and Keller demonstrated that homolytic aromatic substitution (HAS) of benzene with aryl iodides was possible using $(TMS)_3SiH$ as a radical initiator.[29] This intramolecular reaction represents the first transition metal-free aryl cross-coupling *via* a hydrogen atom substitution mechanism.



Scheme 9 Intramolecular HAS biaryl synthesis

The intermolecular cross-coupling of aryl halides **1** with heteroarenes, mediated by potassium *tert*-butoxide was first reported by Itami and Li (Scheme 10, a).[30] Only KO*t*-Bu and NaO*t*-Bu were suitable bases, and other alkoxide bases were not effective at promoting the cross-coupling between haloarenes and pyrazines **24**. Only electron-neutral and electron-rich iodoarenes (including thiophene) underwent the coupling reactions in good yields. Iodostyrene also gave the cross-coupled product, but in a low yield (33%), and there was poor regioselectivity in the case of

unsymmetrical heteroarenes. Following this report, Gryko demonstrated the highly regioselective cross-coupling of *N*-methyl pyrroles **26** with iodoarenes **27** (Scheme 10, b).[31-32] This method used an ionic liquid in place of a volatile, organic solvent. Electron-rich aryl iodides (4-OMe, 7%) gave poor yields, whilst electron-poor aryl iodides gave the best yields (4-CN, 70%).

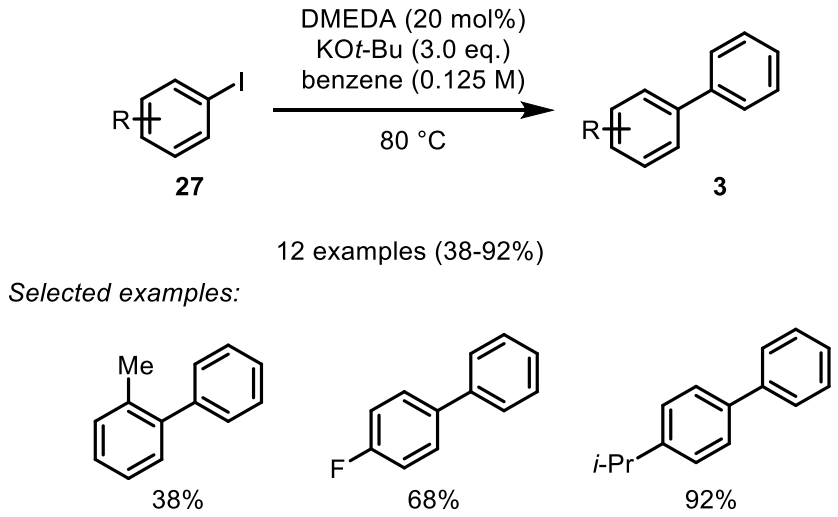


Scheme 10 The first examples of transition metal-free direct intermolecular arylation with aryl iodides

The potential role of trace transition metals has been excluded though establishing the levels of trace metals in KO*t*-Bu with inductively coupled plasma-atomic emission spectrometry.[30] Detailed analysis of the ionic liquid was also conducted, with levels of most transition metals at less than 5.0 ppm and nickel at less than 2.0 ppm.[31] Radical scavengers have been found to completely inhibit the reaction and, in the presence of cyclohexane, the cyclohexyl radical appears to be formed and then trapped by pyrazine. Finally, the benzyne pathway has been ruled out due to the high regioselectivity of product formation. Consequently, a radical pathway, either HAS or SR_N1, is thought to be involved.[33]

In 2010, Lei extended this chemistry to include the arylation of unactivated benzene through the inclusion of a sub-stoichiometric quantity of DMEDA.[34] Various amine

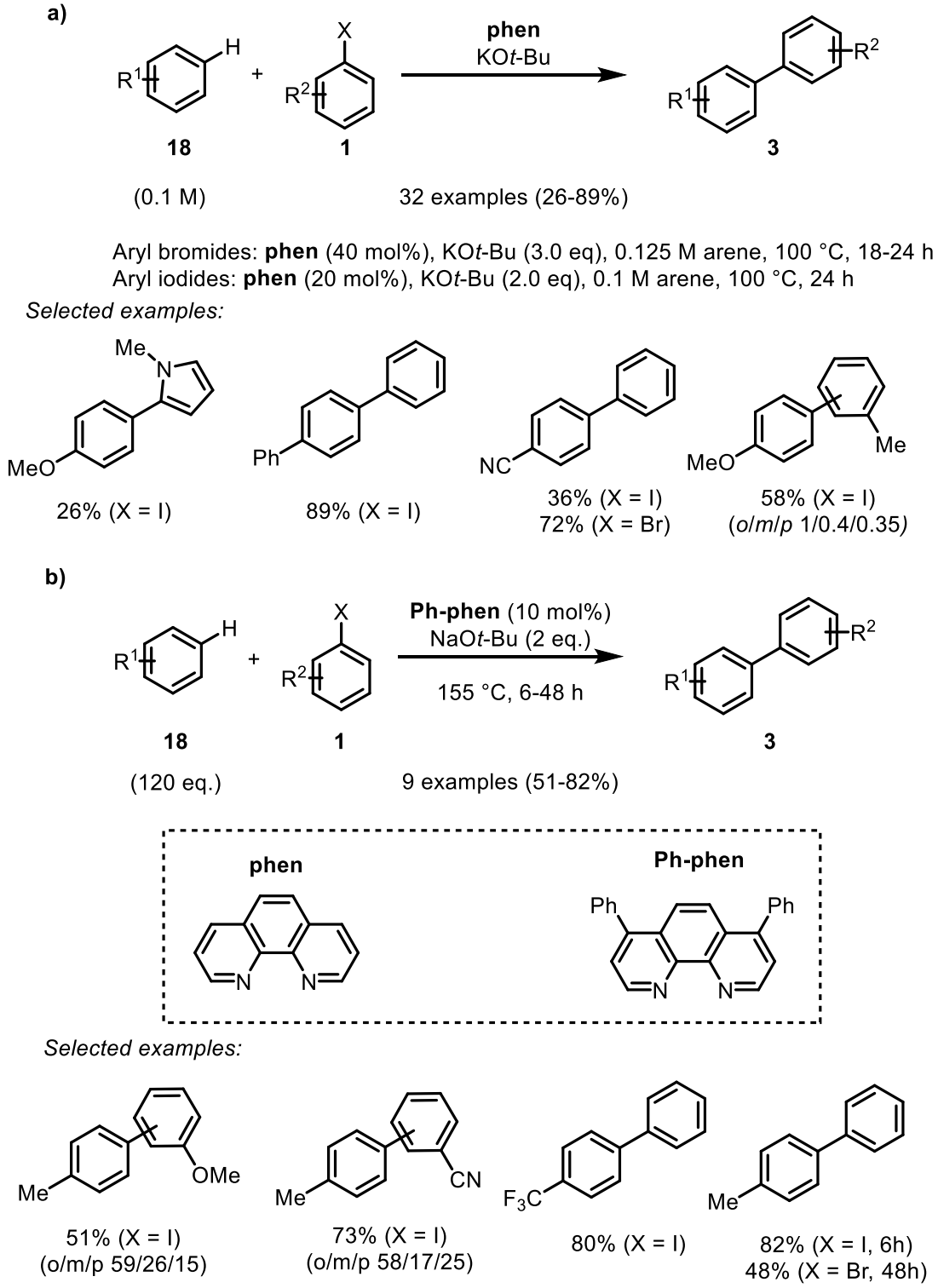
and alcohol based catalysts can facilitate the reaction. Both electron-rich and electron-poor aryl iodides were effective substrates, but substitution of the benzene was not investigated. In addition, aryl bromides or chlorides could be used, but gave progressively lower yields.



Scheme 11 Lei's direct arylation of benzene with aryl iodides

In the same year, two other reports of transition metal-free base-mediated direct arylation of unactivated arenes with aryl iodides were made independently by Shi,[35] and by Shirakawa and Hayashi.[36] Shi was investigating a cobalt catalysed direct arylation of unactivated arenes **18** with aryl halides **1**, and discovered that the transition metal catalyst was unnecessary (Scheme 12, a). Only the KO*t*-Bu and phenanthroline ligand were required to cross-couple a variety of electronically differentiated aryl iodides and bromides. However, aryl chlorides and fluorides were inactive under the reaction conditions and the regioselectivity with unsymmetrical arenes was poor. Similarly, Shirakawa unexpectedly discovered the transformation when they realised that an iron catalyst was not necessary for the direct arylation of arenes with aryl halides **1** (Scheme 12, b). The combination of NaO*t*-Bu and Ph-phen was identified as the most efficient at promoting the cross-coupling. Aryl bromides generally required longer reaction times than aryl iodides, and both electron-rich and

electron-poor arenes (benzonitrile or anisole) required higher temperatures (182 °C or 178 °C respectively).



Scheme 12 The direct arylation of arenes with aryl halides

The exploration of various ligands or reaction promoters has been the focus of investigation for these transformations, with examples ranging from reusable

heterogenous MOFs to porphyrins, and NHCs to simple amino acid additives. Although these organic additives are distinct from conventional radical initiators, they efficiently initiate the radical chain process required for cross-coupling. Two roles have been proposed for these additives. Firstly, the coordination to the metal countercation of the alkoxide base, resulting in the formation of a "super electron donor" which has an increased reducing power compared to the alkoxide base alone.[37] Alternatively, diamine additives such as DEMDA has been implicated as both "radical amplifier" and "radical regulator". That is, initiation of the radical chain process and control of reactive radical species concentration.[38] More recently, it has been found that additives are not necessary if the bonding equilibrium between the metal cation and alkoxide counterion lies sufficiently close to dissociation.[39] For example, a mixture of KOMe and KO*t*-Bu was found to be sufficient to affect the cross-coupling of aryl iodides with arenes at 80 °C.[40]

The mechanism of direct C–H arylation is proposed to consist of SET to the aryl halide **1** (Figure 1), then homolysis to afford an aryl radical **30**. The radical attacks the arene to form a cyclohexadienyl radical **31** which is deprotonated to give a biaryl radical anion **32**. The radical anion **32** propagates the cycle through reduction of **18** to re-form the aryl iodide radical anion **29**. This mechanism is based upon several mechanistic observations. Firstly, the KIE of the reaction with respect to the arene is between 1.05 for benzene and 1.22 for pyridine, which suggests cleavage of the arene C–H bond is not the rate-determining step.[41] Radical trap experiments with TEMPO partly inhibit the reaction indicating a radical mechanism,[41] and it is established that KO*t*-Bu can act as a single electron donor.[42] Finally, spectroscopic evidence of radical intermediates has been obtained through EPR analysis of the reaction mixture.[41]

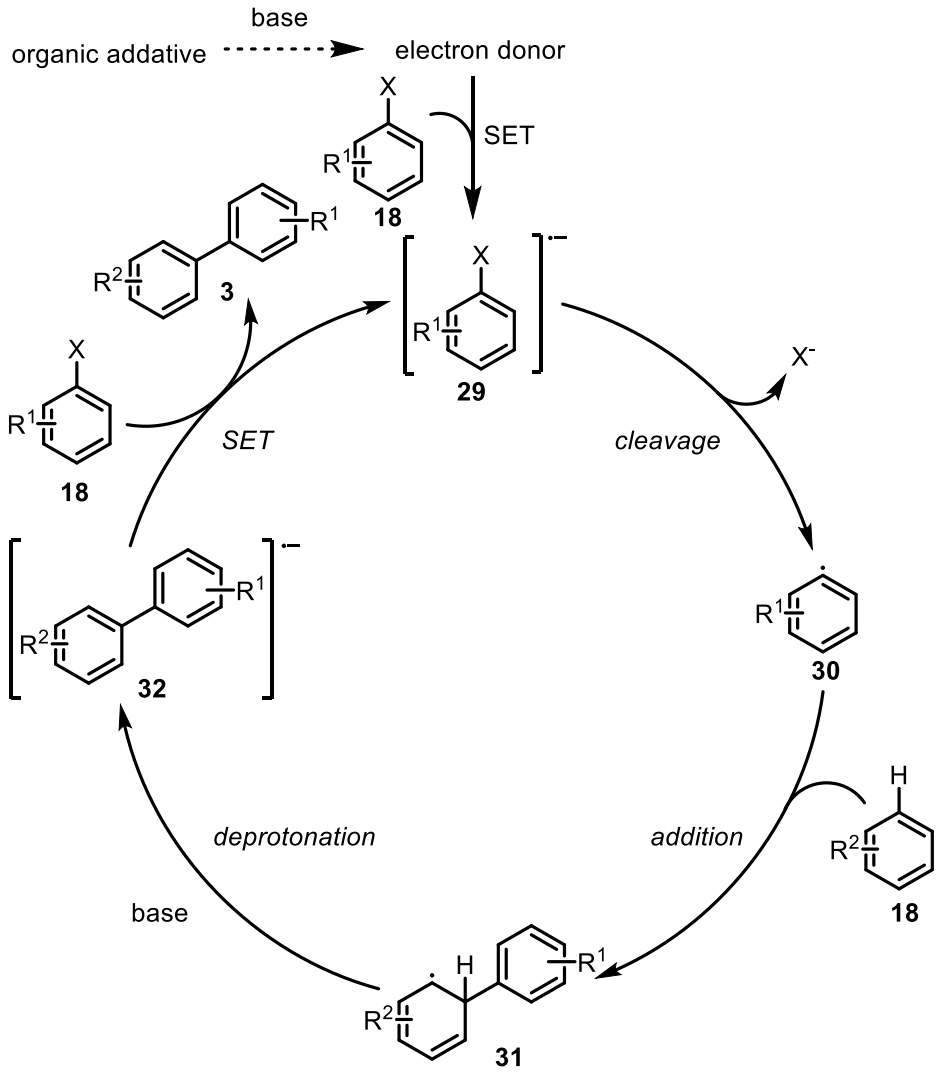
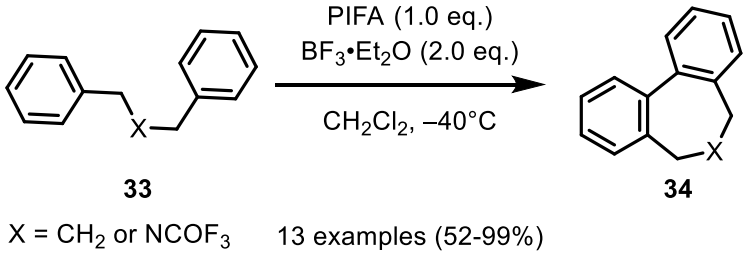


Figure 1 Proposed HAS mechanism for the direct arylation of arenes with aryl halides

4.1.3. Dehydrogenative Cross-Coupling

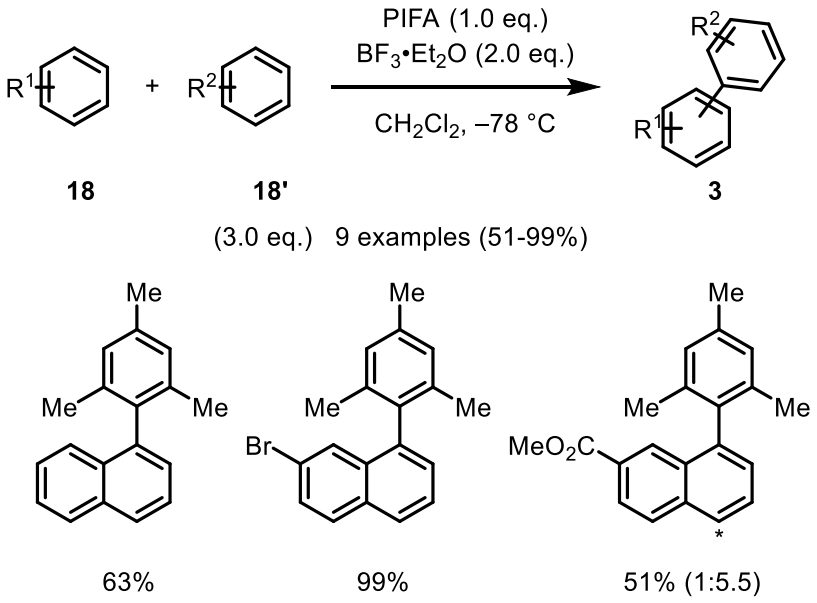
The cross-coupling of two arenes without pre-functionalisation hold significant value in synthetic organic chemistry. This can be achieved through direct oxidative C–H/C–H cross-coupling, also known as dehydrogenative cross-coupling. The first observation of a metal-free biaryl synthesis *via* dehydrogenative cross-coupling was as a side product of a phenolic oxidation and cyclisation,[43] and was developed into non-phenolic intramolecular dehydrogenative cross-coupling of electron-rich arenes **33** (Scheme 13).[44] These reactions use hypervalent iodine reagents to affect selective oxidation of the arene, followed by dimerization. Sun has also reported the use of

DDQ as an oxidant at ambient temperature, affording seven- and eight-membered biaryl containing heterocyclic products in up to 95% yields.[45]



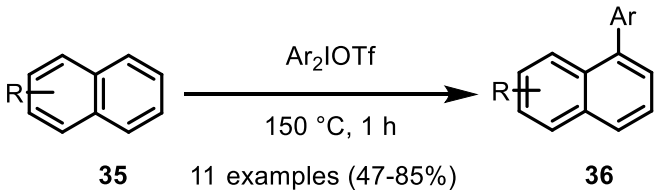
Scheme 13 The intramolecular oxidative direct cross-coupling of electron-rich arenes

The first intermolecular example was disclosed by Kita, again using hypervalent iodine oxidants (Scheme 14).[46] The mechanism of oxidation is proposed to proceed *via* the formation of a charge-transfer complex between the electron-rich aromatic **18** and the hypervalent iodine, this is followed by a single electron transfer to form the intermediate radical cation. The radical cation reacts with various nucleophiles including azide, acetate, and 1,3-dicarbonyl compounds, but has primarily been used in the synthesis of biaryl compounds **3**. The biaryl synthesis relies upon selective oxidation of one coupling partner **18** (naphthalene) over the other **18'** (mesitylene), and sufficient difference in nucleophilicity to avoid dimerisation.



Scheme 14 PIFA mediated direct intermolecular cross-coupling of arenes. *Position of arylation in major regioisomer.

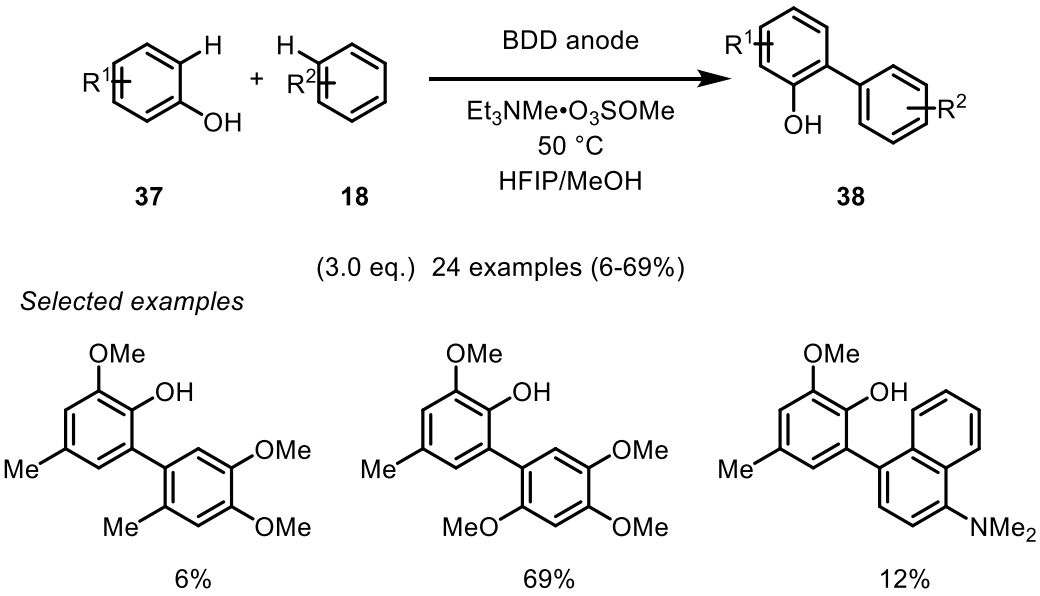
Vincente, Fananas and Rodriguez reported the direct arylation of "unbiased" arenes, such as naphthalene and phenanthrene **35**, under microwave heating to 150 °C (Scheme 15).[47] They proposed that the mechanism proceeds *via* homolysis of the carbon-iodine bond and addition to the extended π system, followed by oxidation with a second equivalent of the iodonium reagent.



Scheme 15 Direct arylation of extended π-systems with diaryl iodoniums

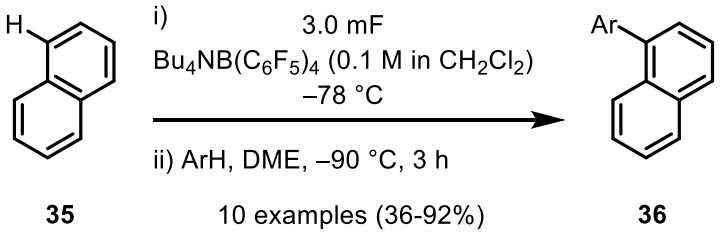
Electrochemical oxidation is an alternative approach to oxidative cross-coupling, which does not use metal catalysts or chemical oxidants. The aniodic cross-coupling of phenols **37** and arenes **18** to afford unsymmetrical biaryl products **38** was first reported by Waldvogel.[48] This method uses a boron-doped diamond (BDD) anodes and a fluorinated solvent to help prevent mineralisation of the substrates (Scheme 16). There is no pre-functionalisation of the starting materials, and therefore no waste by products formed from the reaction. The phenols could be coupled with

several electron-rich arene partners; however, the yields are low to moderate and regioselectivity dependent upon both substrates. The same group also reported the selective, dehydrogenative cross-coupling of two electronically differentiated phenols by a similar method.[49] These methods can only be applied to aromatic compounds that have a hydroxy group, because the phenoxyl radical intermediate plays a crucial role in the reaction mechanism.



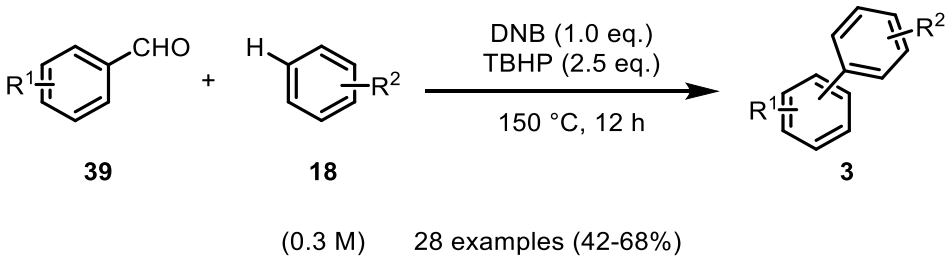
Scheme 16 The electrochemical coupling of phenols with electron-rich arenes

Yoshida utilised the radical cation pool method to overcome the lack of selectivity in dehydrogenative cross-coupling of two electron-rich arenes (Scheme 17).[50] The choice of test substrates **35**, naphthalene and mesitylene, mirrors the logic in Kita's iodonium(III) mediated methodology (*vide infra*). The substrate scope was significantly more broad, and includes a benzothiophenes, *N*-protected indoles and halogenated arenes. The elegance of the transformation is somewhat offset by the complex reaction protocol, which requires specialised equipment (divided cell), platinum plated cathode, and cryogenic temperatures.



Scheme 17 The cation-pool method of oxidative arene cross-coupling

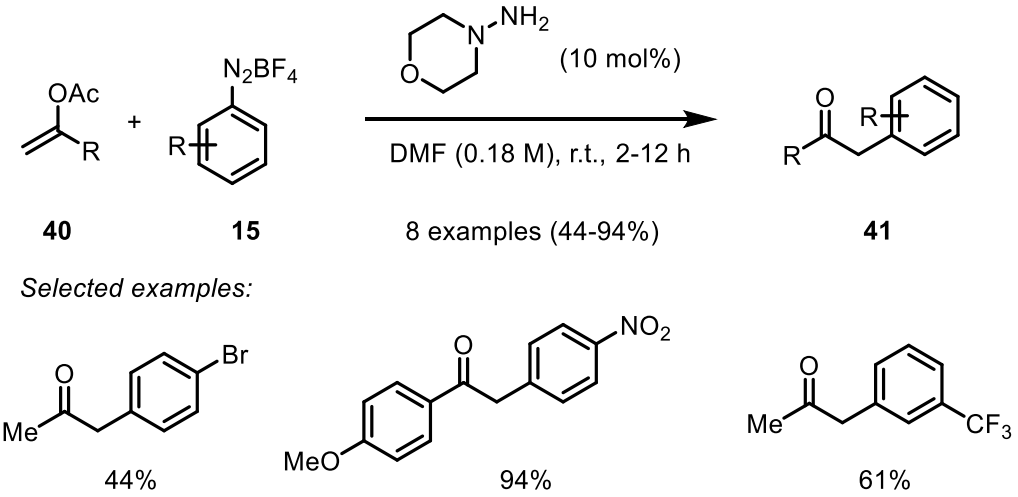
The oxidative decarbonylation of benzaldehydes **29** results in the formation of an aryl radical. The aryl radical has been shown to couple with arenes **18** and, following single electron transfer (with DNB) and deprotonation, the biaryl product **3** is formed in moderate yields affording the products of C–H arylation.[51] The yields are moderate, and poor regioselectivity is observed when unsymmetrical products can arise. Similarly, the oxidation of styrene or benzyl alcohols with TBHP produces aldehydes, and these products can then be oxidatively decarbonylated to give aryl radicals.[52]



Scheme 18 The biaryl synthesis through decarbonylative coupling of benzaldehydes with arenes

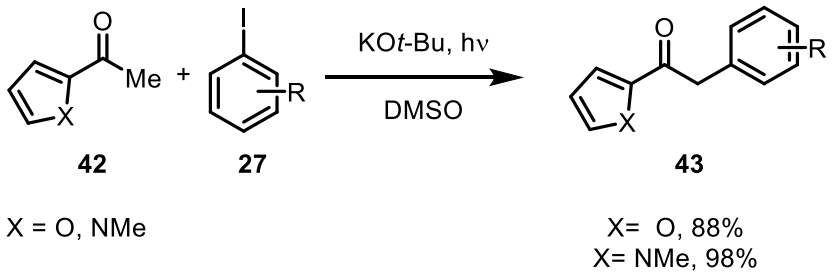
4.2. Alpha-Arylation of Carbonyls

Meerwien-type arylation can be used for transition metal-free α-arylation of carbonyls **41**.[53] Recently, Maulide demonstrated hydrazine-catalysed reductions of arene diazonium salts **15** to form aryl radicals which can be captured by enol acetates **40** (Scheme 19).[26]



Scheme 19 Meerwein arylation of enol acetates catalysed by 4-aminomorpholine

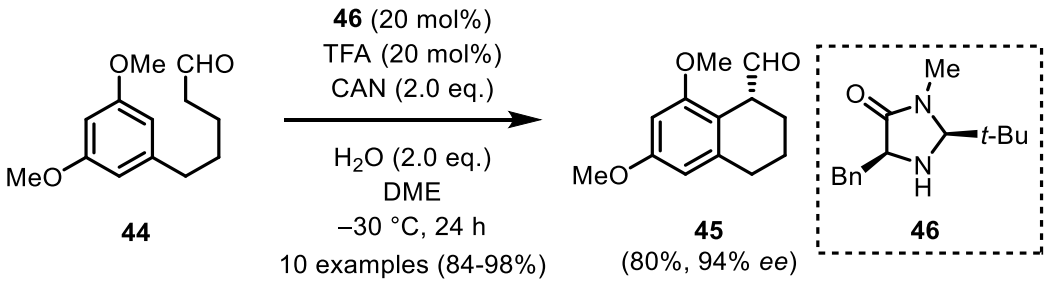
In addition to aryl cation formation through heterolysis, photochemical methods can be used to generate aryl radicals through homolysis of an Ar–X bond and form Ar–C bonds.[54] The photoinduced electron transfer between Ar–X and a neutral nucleophile gives rise to a radical anion of the aromatic and a radical cation of the nucleophile. The chemistry of this pair depends on the relative stability and reactivity of each components. An aryl radical is formed through fragmentation of the Ar–X bond, which can react with the nucleophile resulting in a chain process. However, if the aryl radical anion is stable (e.g. aryl nitriles) then the radical cation may fragment to form the neutral radical, which then couples with the aryl radical anion through substitution of the cyanide anion. Aryl radicals can also react with carbon based nucleophiles through an $S_{RN}1$ mechanism (Scheme 20).[55-56]



Scheme 20 Photochemical aryl radical α-arylation of heteroaryl acetophenones

In 2009, Nicolaou reported the enantioselective intramolecular α-arylation of aldehydes was achieved through formation of an enamine intermediate and single

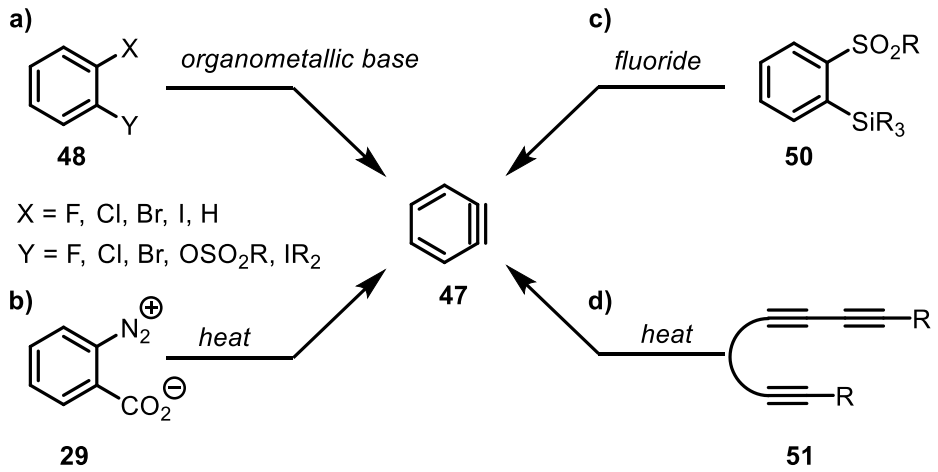
electron oxidation with CAN (Scheme 21).[57] This radical anion intermediate then undergoes cyclisation with various electron-rich arenes to give the enantioenriched multicyclic products **45**. The methodology was applied in the synthesis of demethylcalamene.



Scheme 21 SOMO activation for intramolecular α-arylation of aldehydes

5. Arynes

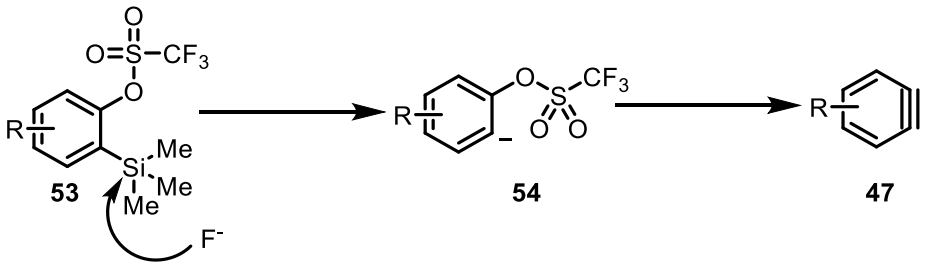
Arynes **47** are highly reactive intermediates which have been widely used in the synthesis of 1,2-disubtituted benzenes and benzannulated aromatics.[58] *o*-Arynes were traditionally prepared through the *ortho*-deprotonation of halobenzene **48**, which typically requires strong lithium and magnesium bases (Scheme 22, a).[59] Benzene diazonium 2-carboxylates **29**, which readily decompose with loss of nitrogen and carbon dioxide to form benzyne, were also used (Scheme 22, b), however, the explosive nature of diazoniums presents a serious limitation. The discovery that fluoride induces the decomposition of *o*-trimethylsilyl(aryl) triflates **50** to generate arynes has led to a resurgence in the use of arynes in organic synthesis (Scheme 22, c). Finally, the hexadehydro-Diels-Alder (HDDA) **51** reaction of triynes is a metal- and reagent-free approach to highly substituted arynes, which can be reacted inter- or intramolecularly to form complex benzo-fused products (Scheme 22, d).[60]



Scheme 22 Methods for the generation of arynes

Arynes can be generated from *o*-trimethylsilyl(aryl) triflates **53** under simple operating conditions (Scheme 23), with a variety of fluoride sources typically in THF, MeCN or toluene. In fact, the generation of benzyne can be controlled through careful selection of reaction conditions, and finely tuned by using mixtures of

solvents. This precursor can also be used over a wide range of temperatures, and thus is compatible with a diverse range of reactions.

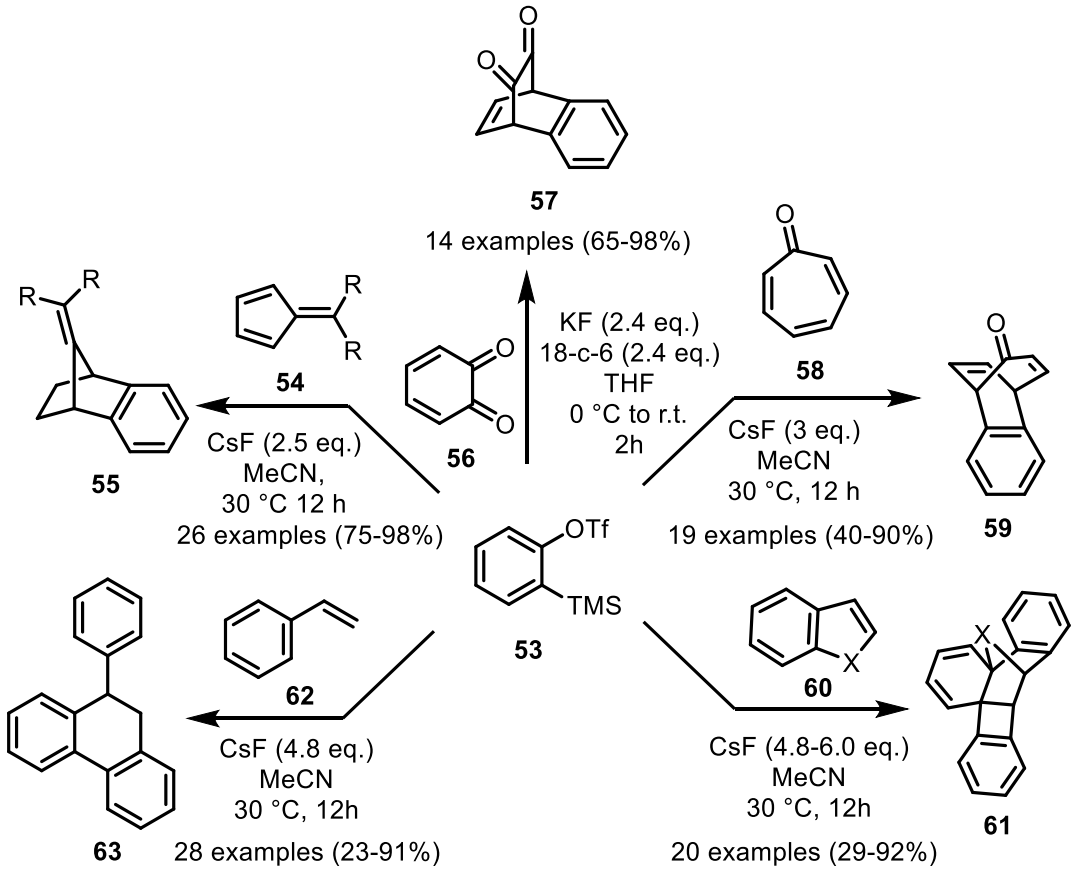


Scheme 23 The mechanism of benzyne generation from *o*-trimethylsilyl(phenyl) triflate

The unhybridized *p* orbitals of arynes do not lie parallel and have reduced overlap compared to other alkynes and which results in a low lying LUMO.[61] Arynes react as dienophiles in pericyclic reactions, or as electrophiles with a wide variety of nucleophilic species. The powerful reactivity of arynes make them very effective at performing metal-free arylations of suitably nucleophilic coupling partners; in addition, they can participate in MCRs.[62]

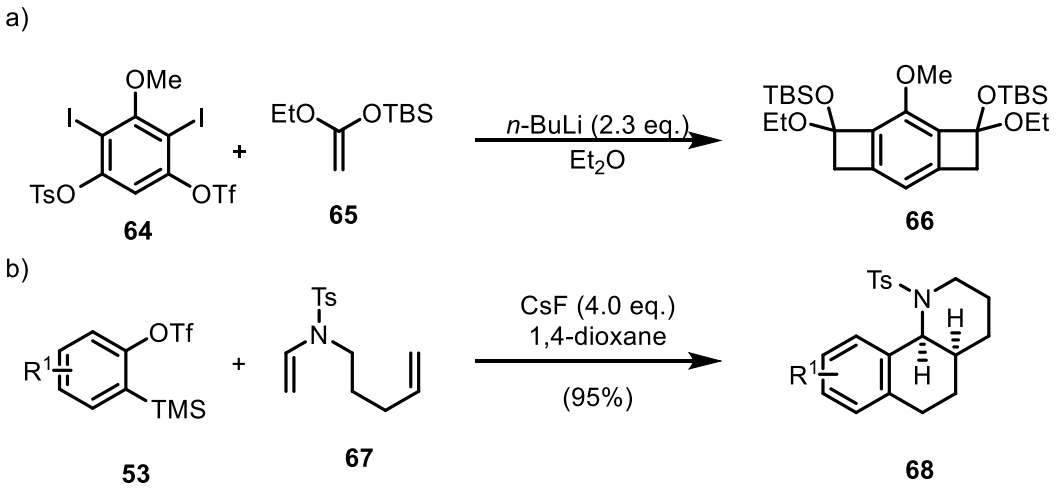
5.1. Pericyclic

The Diels-Alder reaction of benzyne with furan was first reported in 1956,[63] and has been consistently used in the subsequent years as both a method of detecting benzyne and synthetic tool. Some recent, interesting examples of aryne [4+2] reactions come from Biju and co-workers (Scheme 24), who have reported the selective [4+2] reactions between arynes **47** and pentafulvenes **54**, 1,2-benzoquinones **56**, tropones **58**, indenes and benzofurans **60**, or styrenes **62** to give complex products.[64-68] These reactions were all previously known but suffered from low yields and side reactions. Through employing *o*-trimethylsilyl(aryl) triflates **53** as benzyne precursors, conditions were tuned to attain good yields of the multi-cyclic products.



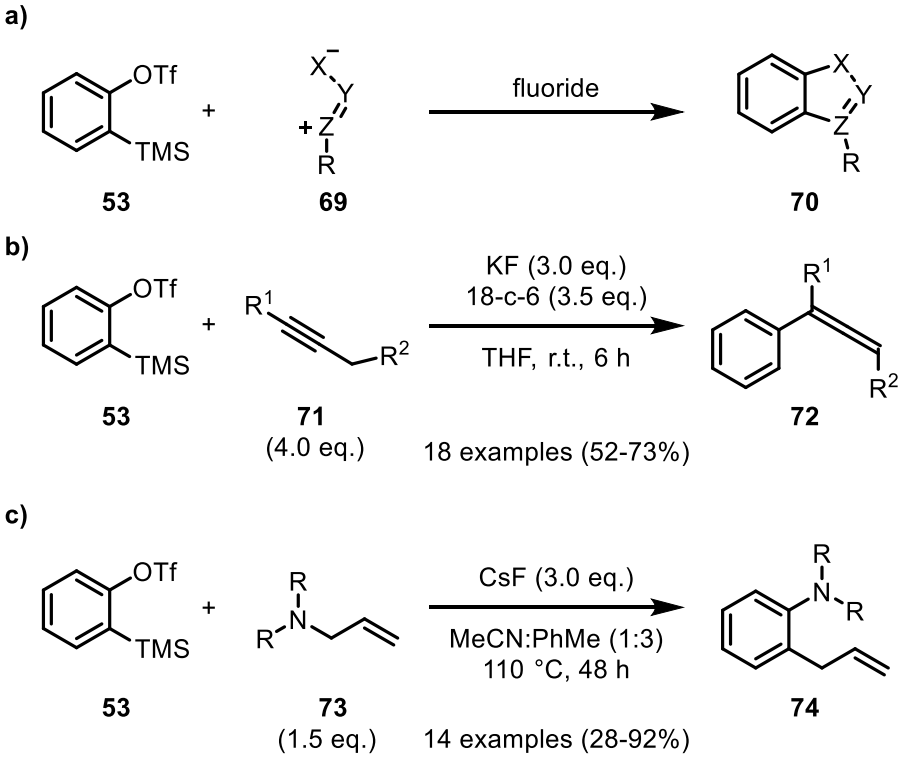
Scheme 24 Aryne [4+2] reactions with interesting dienes

Arynes will react with olefins *via* [2+2] cycloadditions to form benzocyclobutane derivatives with electron-donating substituents enhancing reactivity. Suzuki and co-workers have reported the reaction of arynes with ketene silyl acetal **65** for the preparation of poly-oxygenated tricyclobutabenzenes **66** (Scheme 25, a).[69-70] Hsung has reported that enamides **67** also participate in the [2+2] cycloaddition with arynes, and in conjunction with a retro-[2+2] then a [4+2] reaction, nitrogen heterocycles **68** were assembled (Scheme 25, b).[71]



Scheme 25 The aryne [2+2] cycloadditions with a) a ketene silyl acetal and b) an enamide

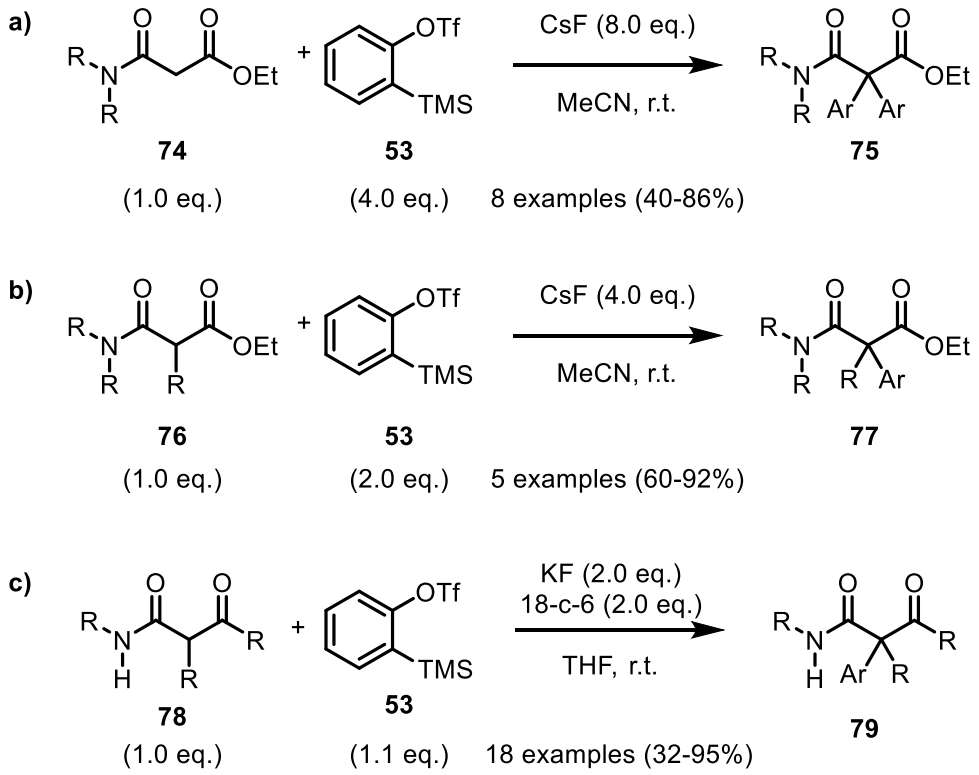
The [1,3]-dipolar cycloaddition between arynes and 1,3-dipoles **69** efficiently affords a variety of benzofused heterocycles **70** (Scheme 26, a).[72] Larock reported an interesting reaction in which pyridine *N*-oxides; these react in a [3+2] manner with arynes and then collapse to form 3-arylated pyridines (*vide infra*, pg. 68).[73] Arynes are also able to participate in ene-reactions, with alkynes **71** (Scheme 26, b), tethered olefins, and for the preparation of biaryls (*vide infra*, pg. 66).[74-75] Greaney has reported the [3,3]-sigmatropic reaction following the addition of tertiary allylamines **73** to arynes, resulting in the synthesis of *o*-allylated anilines **74** (Scheme 26, c).[76]



Scheme 26 a) A general aryne [1,3]-dipolar reaction b) aryne-alkyne ene reaction c) aryne aza-Claisen reaction

5.2. Addition

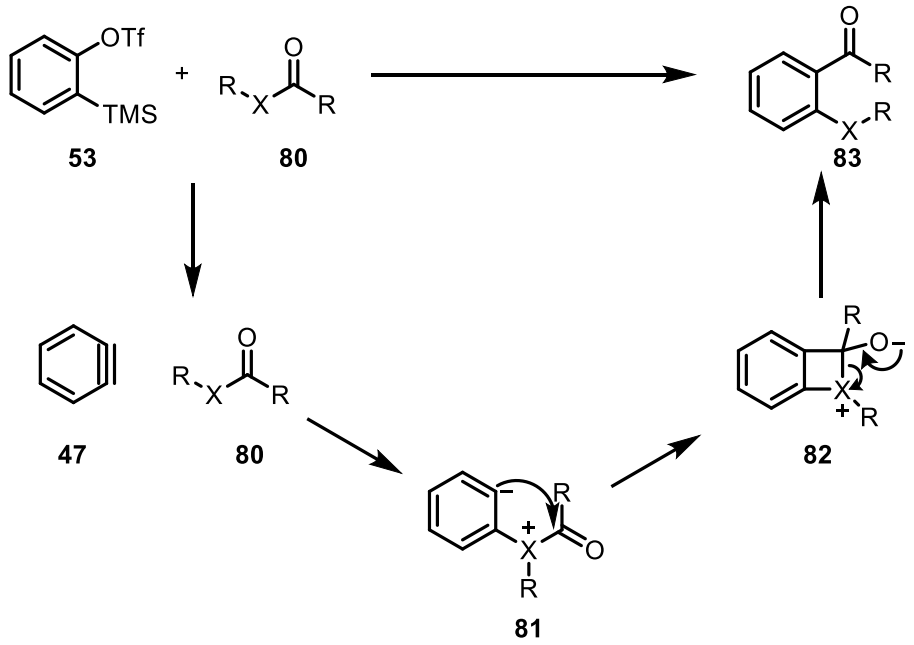
The strained triple bond renders arynes highly electrophilic, and even neutral nucleophiles which are typically unreactive towards alkynes can react efficiently. Larock reported a general methodology for *O*-arylation of phenols, and carboxylic acids, and the *N*-arylation of amines and (sulfon)amides.[77] The selective mono- or diarylation of amines could be controlled through control of the reactant ratio. Buji developed an *o*-arylation of aliphatic alcohols, a low temperature is key in this transformation.[78] However, when arynes react with active methylene compounds (those which deprotonate readily), the products are typically those of σ-insertion. Seminal examples of aryne α-arylation include the selective mono- or diarylation of malonamide esters **74** and **76** (Scheme 27, a and b),[79] and reaction of β-enamino esters **78** and ketones with arynes (Scheme 27, c).[80]



Scheme 27 The α-arylation of active 1,3-dicarbonyls with arynes

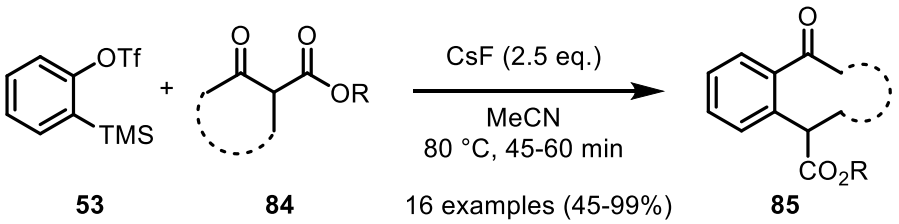
5.3. Insertion

The addition of a nucleophile to aryne forms an aryl anion which can be trapped by internal or external electrophiles to achieve annulation, an insertion, or a multicomponent reaction. When a single σ-bond joins the nucleophilic and electrophilic components **80**, a zwitterionic intermediates **81** then **82** form which then promotes the cleavage of the σ-bond (Scheme 28). Insertion of arynes into carbon-carbon and carbon-heteroatom σ-bonds provides efficient methods for the synthesis of *ortho*-substituted arenes.[81-82] A large number of aryne σ-insertions for the heterofunctionalization of arenes have been developed since the seminal report of insertion addition of ureas to arynes to from benzodiazepines and 2-aminobenzamides.[83]



Scheme 28 The general mechanism of aryne sigma-insertion

Focusing on carbon-carbon bond formation, the acyl-alkylation of arynes through insertion into β-dicarbonyls **84** was first reported by Tambar and Stoltz (Scheme 29).[84] The ring expansion of cyclic ketoester to medium sized rings **85** was applied in the synthesis of (+)-amurensinine and (-)-curvularin natural products.[85-86] Insertion into α-cyanocarbonyls, α-tosylnitriles, malononitriles and other similar C–C bonds has since been developed by Yoshida and co-workers.[87-90] The insertion into β-keto-phosphonates was reported by Liang, Li and co-workers,[91] and Hunag developed insertion into the C–C bond of α-sulfonyl cyclic ketones.[92]



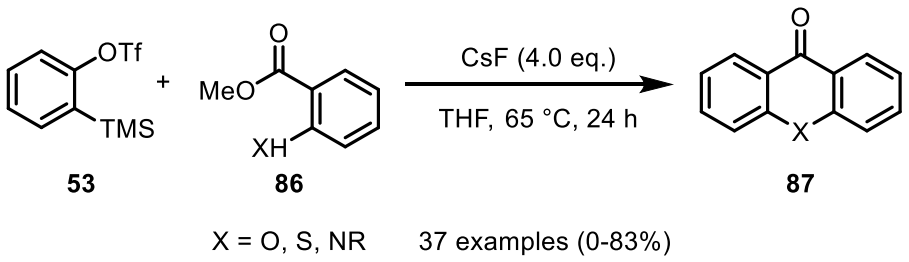
Scheme 29 The insertion of aryls into a C–C sigma bond to achieve alkyl-acylation

The insertion into the C–N bond of amides was first described for trifluoro-acetanilides, with the trifluoromethyl group key due to increasing the acidity of the amide.[93] This methodology was extended to include unactivated amides by using

TBAT in toluene at elevated temperatures,[94] and has subsequently been developed for other substrates. Carbo-phosphinylation and carbo-halogenation have also been achieved.[95-96]

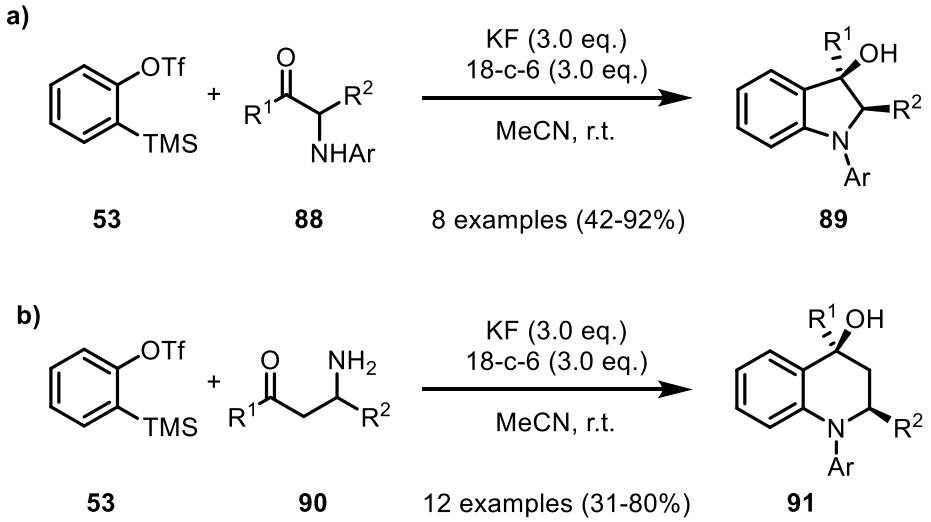
5.4. Annulation

Nucleophiles which also contains a suitably placed electrophilic site can undergo cyclisation with the aryl anion to afford a benzannulated product. Early examples consisted of addition to a carbonyl group to form structures such as xanthones, and acridones **87** through the coupling of arynes and benzoates **86** (Scheme 30).[97] There are many palladium catalysed methods for the preparation of phenanthridones and similar structures (*vide infra* pg. 62).



Scheme 30 Annulative coupling of arynes and benzoates

More recently, He and Dai reported the preparation of tetrahydroindoles **89** and tetrahydroquiolines **91** through annulative coupling of arynes with α- or β-amino ketones **88** or **90** (Scheme 31), the products were all isolate in with excellent diastereomeric ratios.[98]

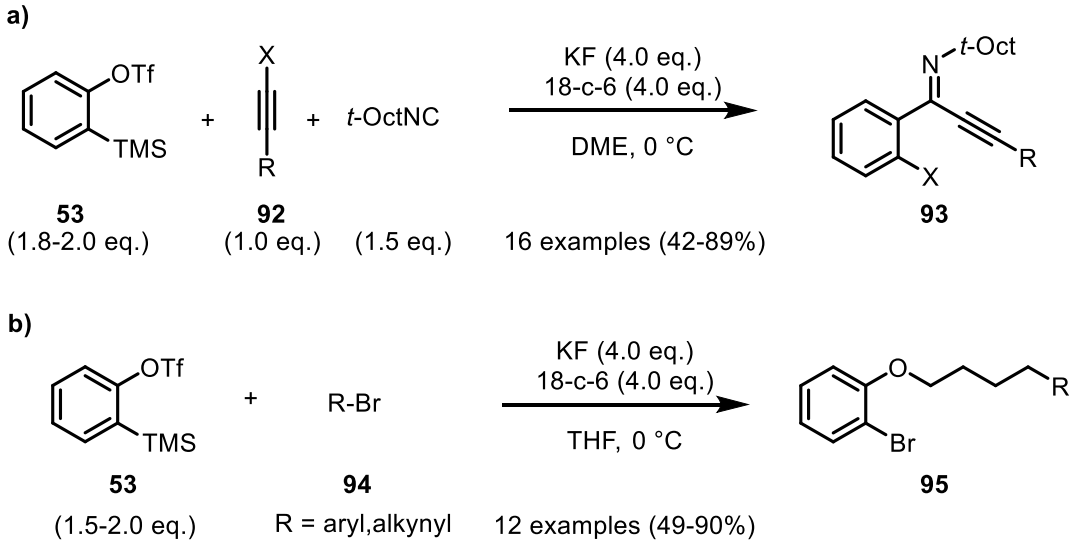


Scheme 31 The annulative coupling of arynes with α- or β-amino ketones

5.5. Multicomponent reaction

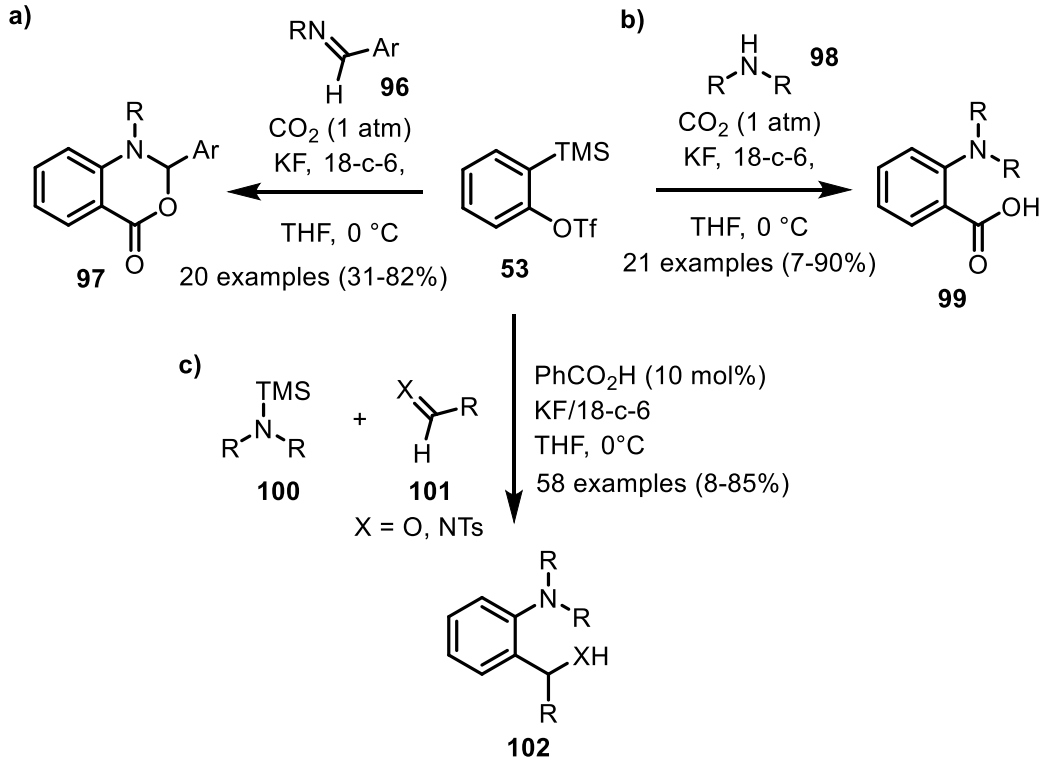
Multicomponent reactions are also possible for arynes, if the electrophilic and nucleophilic components are separate molecules. Again, this enables the preparation of highly functionalised arenes without recourse to transition metal catalysis. Aryne MCRs have been extensively investigated and these reactions have been well reviewed.[62, 99]

As with many other MCRs, isocyanide can be used to trigger MCRs with arynes. This approach has been used to construct many benzofused carbo- and heterocycles, with various electrophilic components, such as solvents, aldehydes or imines or CO_2. Notably, the Yoshida group reported the incorporation of alkynyl **92** or (polyfluorinated aryl) bromides into aryne isocyanide MCRs.[100] The isocyanide adds to the aryne forming a 1,3-zwitterionic intermediate which then de-brominates the alkyne, to form an alkynyl carbanion. The carbanion then attacks the isocyanide leading to an *ortho*-functionalised aryl bromide **93** (Scheme 32, a). THF can also act as a trigger in this type of reaction, creating a 1,4-dipole which is intercepted with either polyfluoroaryl or alkynyl bromides **94** (Scheme 32, b).



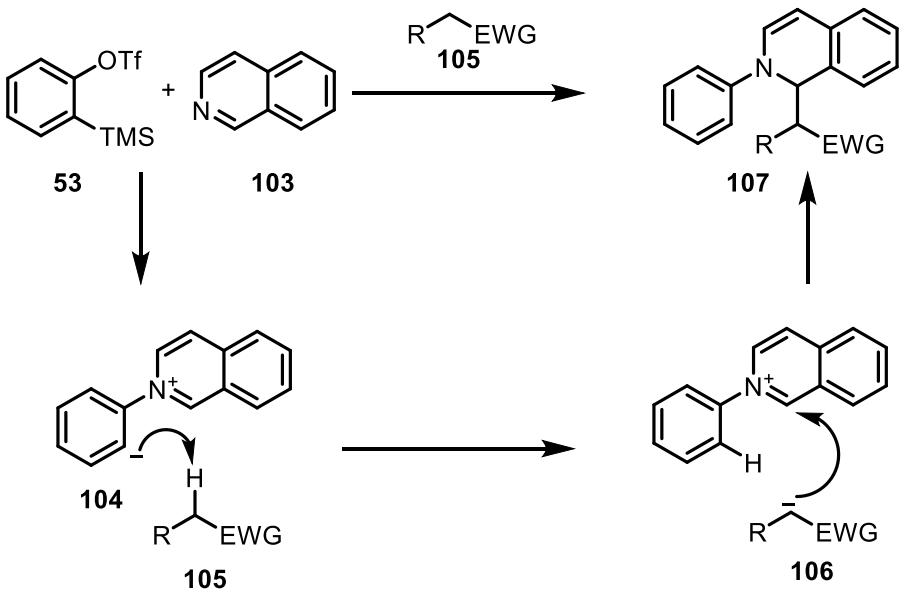
Scheme 32 Three-component coupling of arynes and organic bromides

Nitrogen nucleophiles such as imines and amines can also be used to initiate aryne MCRs. Benzoxazinone **97** and anthranilic acid **99** products can be formed by using CO_2 as the third component (Scheme 33, a and b).[101-102] Initiation of the MCR with aminosilanes **100** enables the use of aldehydes 1**01** as a third component (Scheme 33, c), a catalytic amount of benzoic acid is used to remove the TMS *in situ*.[103] If an activated imine is used in place of an aldehyde, the final product have an amine and an amino-methyl group incorporated in contiguous positions on the arene **102**.[104]



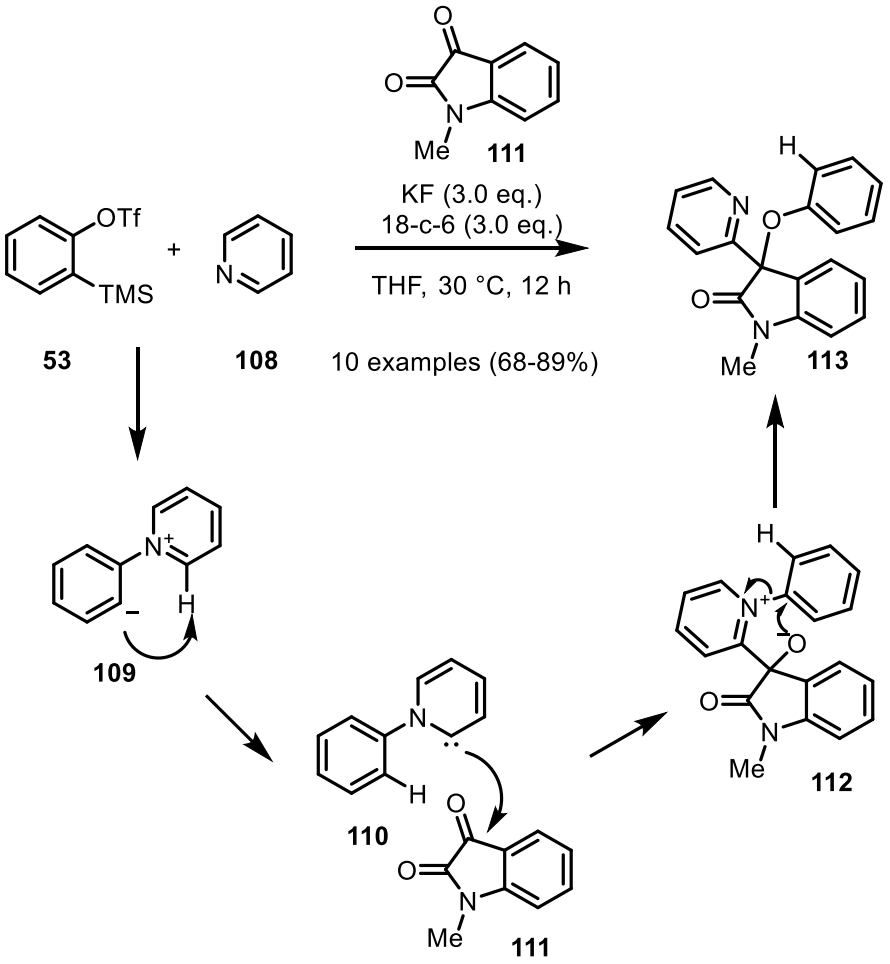
Scheme 33 Multicomponent reactions of arynes triggered by nitrogen

Nitrogen heterocycles, such as (iso)quinoline **103** can also be used to trigger aryne MCRs with the aryl anion intermediate **104** acting as a base, to deprotonate substrates **105** such as nitriles, alkynes, methyl ketones, or isatins. These deprotonated substrates **106** then add into the *N*-aryl iminium ion to form the dearomatised *N*-heterocycle product **107**. Biju has also used aldehydes as the third component in this reaction. In this case, the aryl anion adds to the aldehyde, generating an oxy-anion which cyclises onto the *N*-aryl iminium (Scheme 34).[105]



Scheme 34 The mechanism of isoquinoline initiated aryne MCRs with acidic methylene compounds

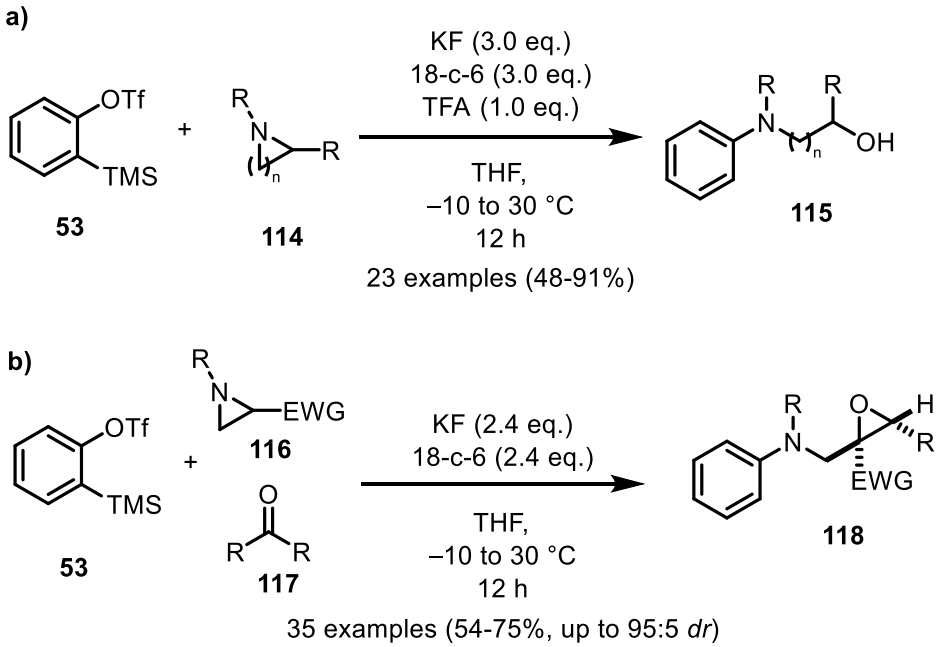
Addition of a pyridines **108** to aryne results in a different mechanistic pathway which results in both *O*-arylation and *C*-pyridylation of the isatin **113** (Scheme 35).[106] Mechanistic experiments elucidate a pyridylidene intermediate **110**, which inserts into the carbonyl of the isatin **111** to afford intermediate **112**. This undergoes an intramolecular S_NAr (Smiles rearrangement) to form the final *O*-arylated product **113**.



Scheme 35 The proposed mechanism of pyridine triggered aryne MCR

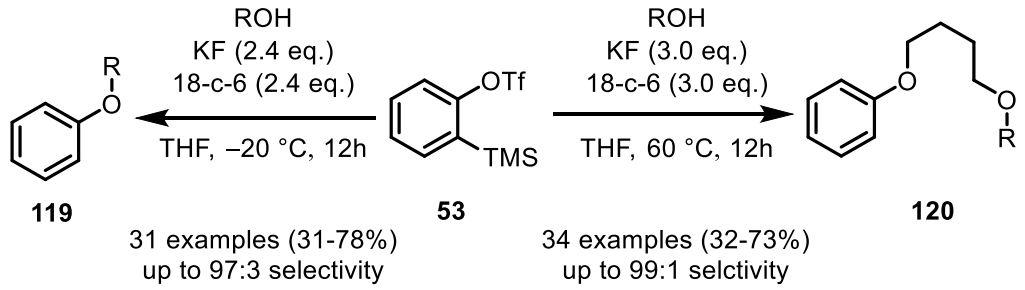
Another interesting example, is the use of aziridines **114** to trigger an aryne MCR. Like the reactions with (iso)quinolines, the aziridines form a zwitterionic intermediate which can then deprotonate acidic protons on the third component. The nucleophilic anion formed through this deprotonation then ring-opens the aziridine. The first example, from Larionov, was with acetonitrile which afforded *N*-aryl-γ-aminobutyronitles.[107] Furthermore, the interception of the aziridine-aryne zwitterion with oxygen-based nucleophiles affords 1,2-amino alcohol derivatives.[108] Water (with TFA) can be used afford *N*-aryl-β/γ-amino alcohols **115** under mild conditions, with a broad substrate scope (Scheme 36, a).[109] The key to this chemistry is initiation of the reaction at −10 °C, and then warming to ambient temperature/30 °C for 12 hours. Reactions triggered by aziridines with an electron-withdrawing substituent

116, and aldehydes **117** as the third component, result in the formation of *N*-aryl-α-amino epoxides **118** in moderate to good yields and diastereoselectivity (Scheme 36, b).[110] These products are used as building blocks in the synthesis of amino sugars and poly-oxygenated α-amino acids.



Scheme 36 The aziridine initiated aryne MCR with a) water and b) carbonyls

Most aryne MCRs are initiated with amine nucleophiles, one interesting example of oxygen nucleophiles was reported by Biju et al.[78] A temperature dependant reactivity of arynes was observed when developing a method for *O*-arylation of aliphatic alcohols **119** (Scheme 37). Under identical reactions conditions, at −20 °C, the aryne smoothly inserts in to the O–H bond of the alcohol to afford alkyl aryl ethers **119**. However, at 60 °C, the THF solvents adds to the aryne forming a zwitterionic intermediate. This intermediate deprotonates the aliphatic alcohol, which then acts as a nucleophile to ring-open the THF adduct, forming (4-(alkoxy)butoxy)arenes **120** in moderate to good yields and high selectivity.



Scheme 37 Temperature-dependent reaction of arynes with aliphatic alcohols

5.6. Metal-Mediate Benzyne Biaryl Synthesis

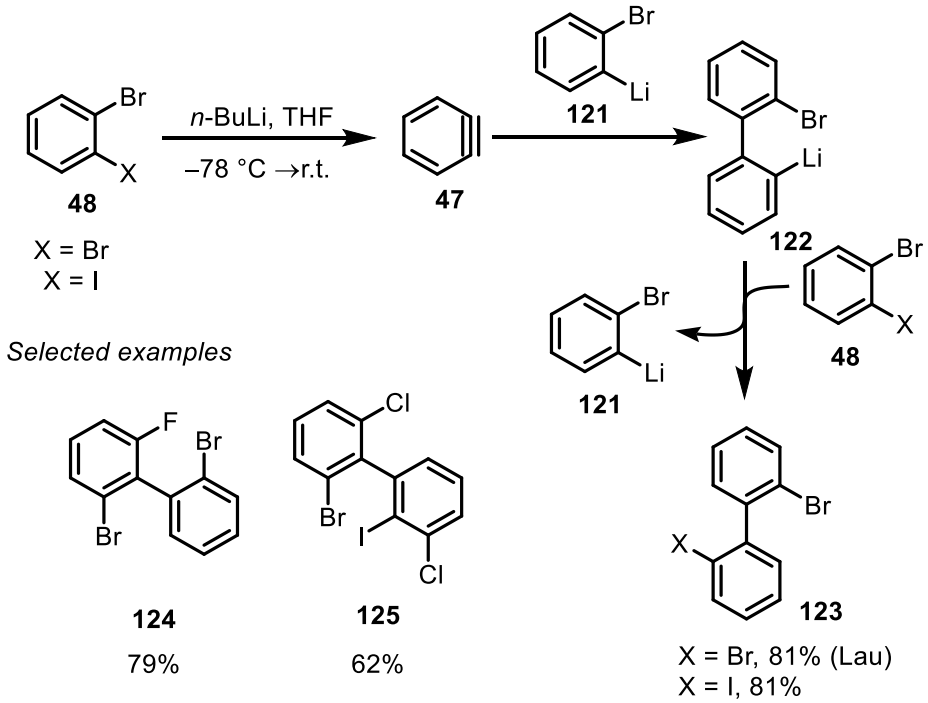
This thesis has a significant emphasis on the benzyne mediate metal-free biaryl synthesis (Chapter 3). The role of benzyne in the synthesis of biaryls has recently been reviewed.[111]

5.6.1. Organometallic

In 1940, Wittig first observed the formation of biphenyl from the reaction of phenyl lithium with fluorobenzene.[112] Phenyl lithium has a double role in this reaction, acting as base deprotonating fluorobenzene, and as nucleophile in the addition to benzyne. The biphenyl anion product was quenched with water or could be trapped using benzophenone. This represents one of the first examples of three-component couplings of arynes, which has continued to be a major area of investigation (*vide infra*, pg. 48). Roberts proved the symmetrical triple bond nature of benzyne, and that benzyne was an intermediate in the biphenyl synthesis, through radiolabelling experiments.[113]

Gilman and co-workers observed the formation of 2,2'-dibromobiphenyl derivatives when investigating the reactions of *n*-BuLi with 2-halobromophenyls **48**.[114] A noticeable solvent effect from THF was observed, which favoured the formation of 2,2'-dibromobiphenyl **123**.[113] Although, the possibility of a benzyne intermediate **47** was raised, a simple aromatic substitution mechanism was proposed due to the lack

of isomeric products from the reactions with 4-chloro-bromobenzne with 1,4-dibromobenzene. Schlosser and Leroux subsequently confirmed the presence of an aryne intermediate by demonstrating the presence of isomeric products through careful GCMS analysis.[115] The different rates of lithium-halogen exchange were exploited to achieve the synthesis non-symmetrical biaryls **124** and **125** (Scheme 38).[116]

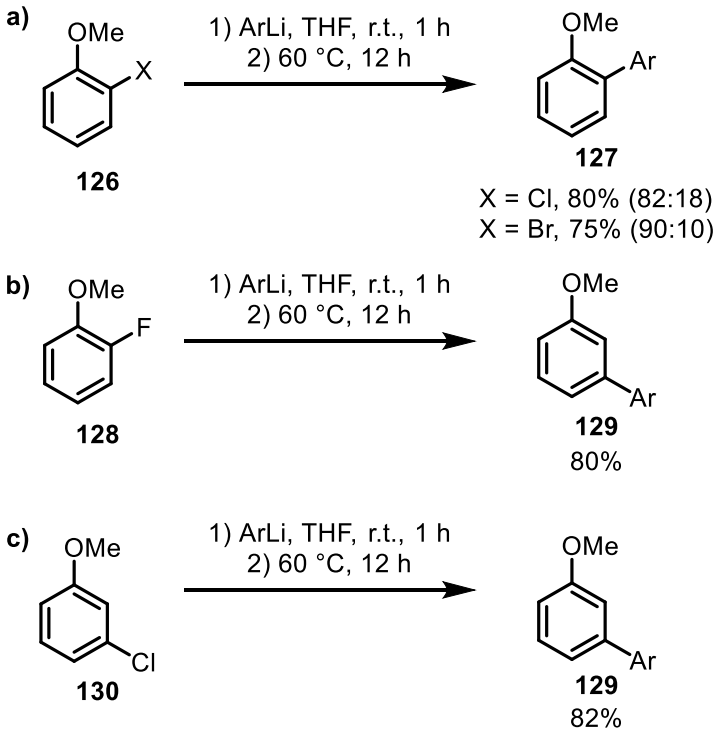


Scheme 38 Lithium mediated synthesis of halo-biaryls *via* an aryne

The nucleophilic component can also be generated through direct lithiation of a suitable arene.[117] The lithiated biaryl products are then quenched with various electrophiles, such as chlorophosphines to prepare biaryl phosphines,[118] or arylsulfinates were used in an atropselective synthesis of biaryls.[119]

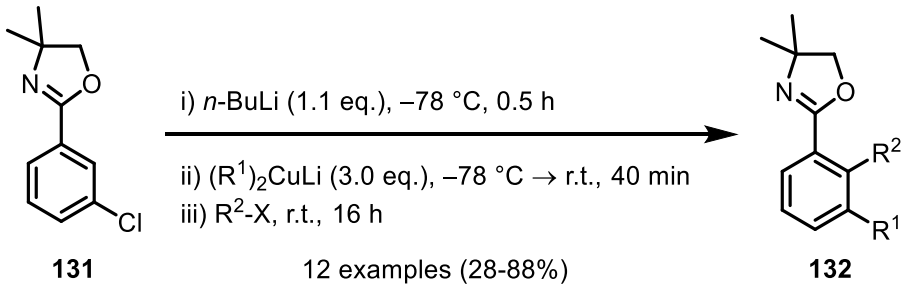
Alternatively, the aryne can be generated through direct metalation of a halo-arene (Scheme 39). Wagner and Misokowski investigate the regioselectivity of the reaction of lithiated arenes with chloro-, bromo-, and fluoroanisoles.[120] The 2-chloro and 2-bromoanisole **126** gave a mixture of *ortho* and *meta* products **127** (Scheme 39, a),

whilst the 2-fluoro anisole tetrahydro128 gave solely the *meta*-substituted product **129** (Scheme 39, b). Whereas 3-chloroanisole **130**, which should give the same aryne intermediate, afforded solely the expected *meta*-substituted product **129** (Scheme 39, c). The authors argued that this implied a direct *ipso*-substitution mechanism was occurring, in addition an aryne mechanism with 2-chloro and bromoanisole, and provided evidence in the form of deuterium labelling studies.



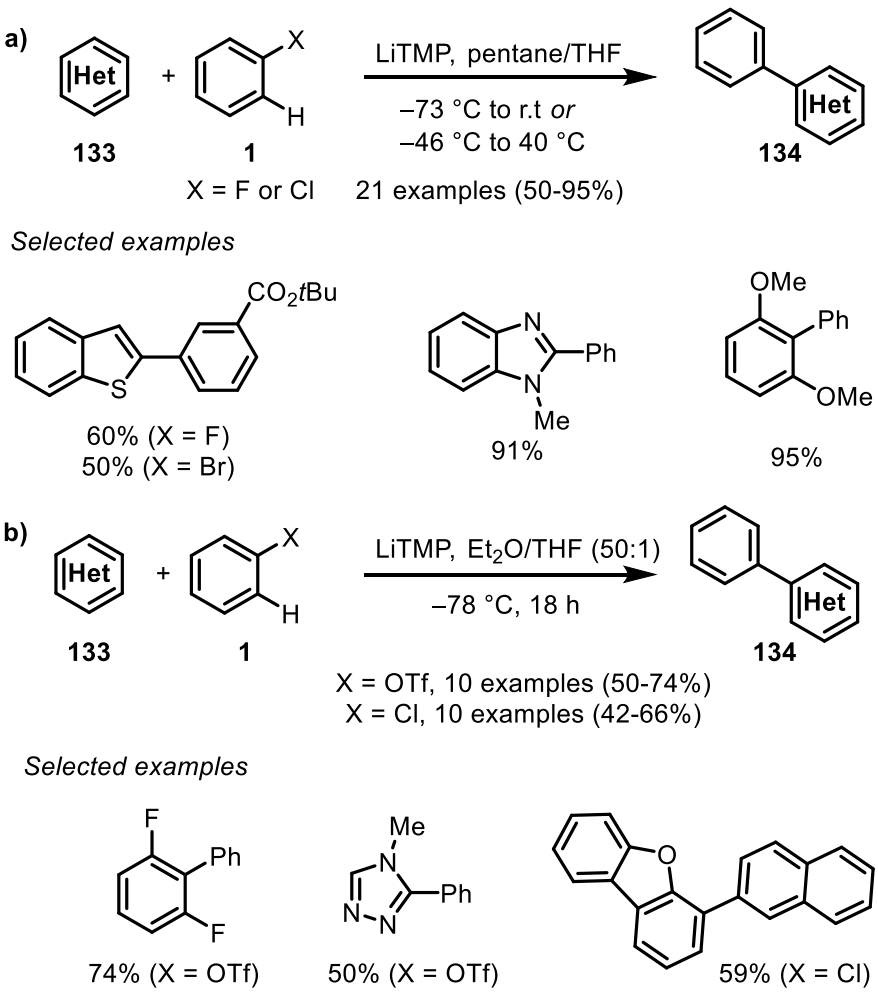
Scheme 39 The reactivity of halo-anisoles with aryl lithium reagents

Meyers used an oxazoline directing group **131** for *ortho*-metalation, elimination and addition of phenyl lithium effectively afforded biaryls (Scheme 40).[121] The group expanded the work to include the addition of alkyl cuprates, This afforded biphenyl cuprates, which could be quenched with various electrophiles to afford products in which two new carbon-carbon bonds had been formed **132**.[122]



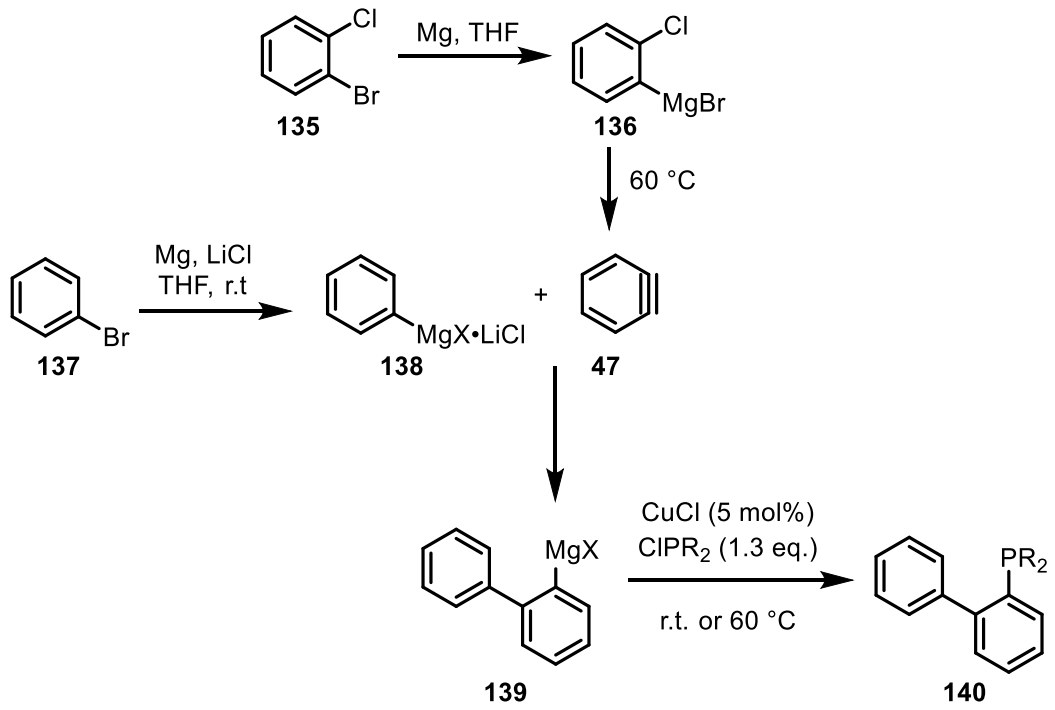
Scheme 40 Oxazoline directed lithiation for aryne formation

A more recent development is from Daugulis, who has reported the arylation of (hetero)arenes **133** with arynes generated from chloro- and fluoroarenes **1** (Scheme 41).[123] LiTMP deprotonates both the (hetero)arene and the *ortho* position of the halobenzene **1**. A rise in temperature induces aryne-forming elimination of LiX, which is then preferentially trapped by the lithiated arene whilst the hindered base retards nucleophilic addition. The exact conditions for each substrate were finely tuned to afford optimal yields. However, identification of a THF/Et_2O solvent mixture provided the key to more general conditions and aryl triflates could then also be used as aryne precursors.[124] This method was then applied in MCR reactions with various electrophilic reagents.



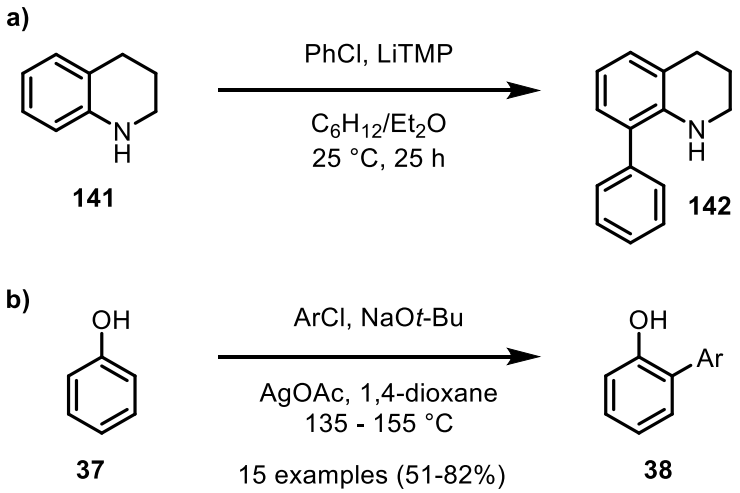
Scheme 41 LiTMP mediated aryne formation and (hetero)biaryl synthesis

Grignard reagents can also be used, both to form arynes and as the nucleophilic component. The most notable application of this method is in the synthesis of biaryl phosphine ligands **140**, using the method optimised by Buchwald.[125] Aryl Grignard reagents **136** and **138** are formed separately and react to generate an *ortho*-biphenyl Grignard **139** (Scheme 42). This is followed by a copper-catalysed trapping of **139** with P–Cl reagents to afford the biaryl-phosphine products.



Scheme 42 Grignard reagents and arynes in the preparation of biaryl phosphines

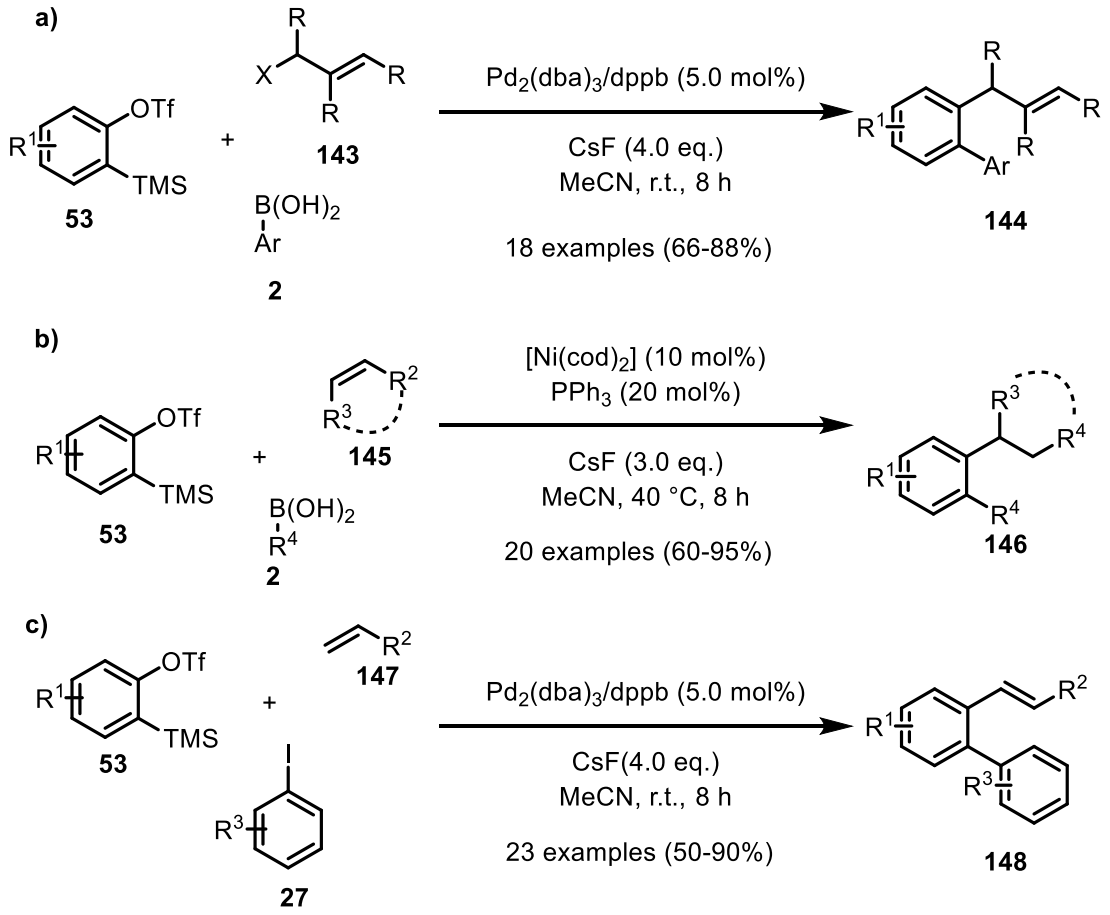
These direct arylation of phenol with arynes was first reported as an intramolecular reaction. Daugulis expanded upon older methodology using aryl *C*-nucleophiles tethered to benzyne to form biaryl bonds.[126] Daugulis and Truong then reported the *ortho*-arylation of unprotected primary and secondary anilines **141**, having noted that minor amounts of *C*-arylation had been observed in earlier *N*-arylation studies. They developed a selective process with chlorobenzenes and the strong base LiTMP, switching from THF or ether to a hydrocarbon/ether solvent mixture significantly improved the selectivity of the reaction for *C*-arylation (Scheme 43, a).[127] This was then extended for phenols **37** though the use of NaO*t*-Bu as a base, a higher temperature and silver salts (Scheme 43, b).[128]



Scheme 43 The direct arylation of a) 1,2,3,4-tetrahydroisoquinoline and b) phenol with aryne

5.6.2. Catalytic metals

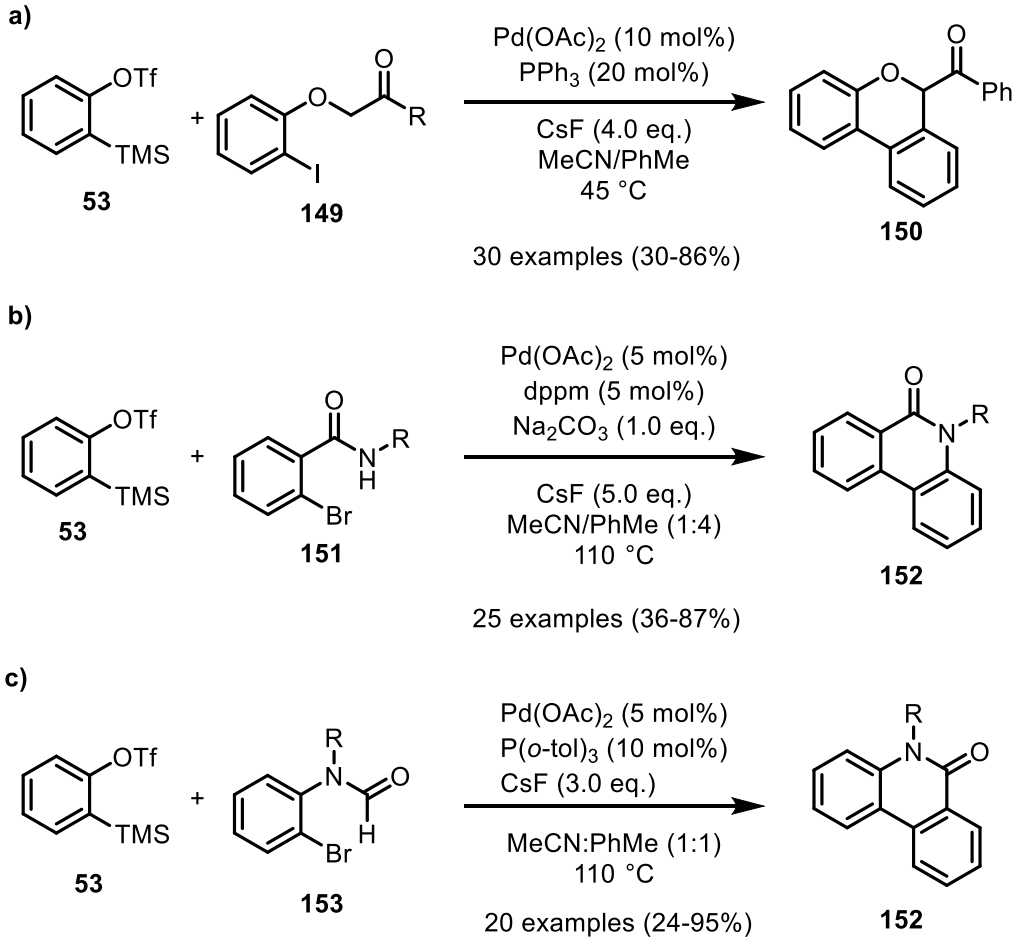
Pseudo-MCRs, in which two benzyne units are incorporated into an extended biaryl structure, has been developed using low-valent metal catalysis including palladium,[129-132] gold,[133] copper,[134-135] and nickel.[136-137] The palladium catalysed cross-coupling of arynes with allyl chloride and boronic acids to give *ortho*-allyl biaryls, reported by Chang, brought together aryne chemistry with the versatile Suzuki-Miyaura cross-coupling reaction (Scheme 44, a).[138] The group then developed a nickel catalysed coupling of arynes with Michael acceptors **145** and boronic acids **2** (including aryl boronic acids) (Scheme 44, b).[139] Greaney described the palladium-catalysed synthesis of 2-alkenyl biaryls **148** through the three-component coupling of arynes, acrylate **147** and aryl iodides **27** (Scheme 44, c).[140]



Scheme 44 Transition-metal catalysed aryne MCRs for biaryl synthesis

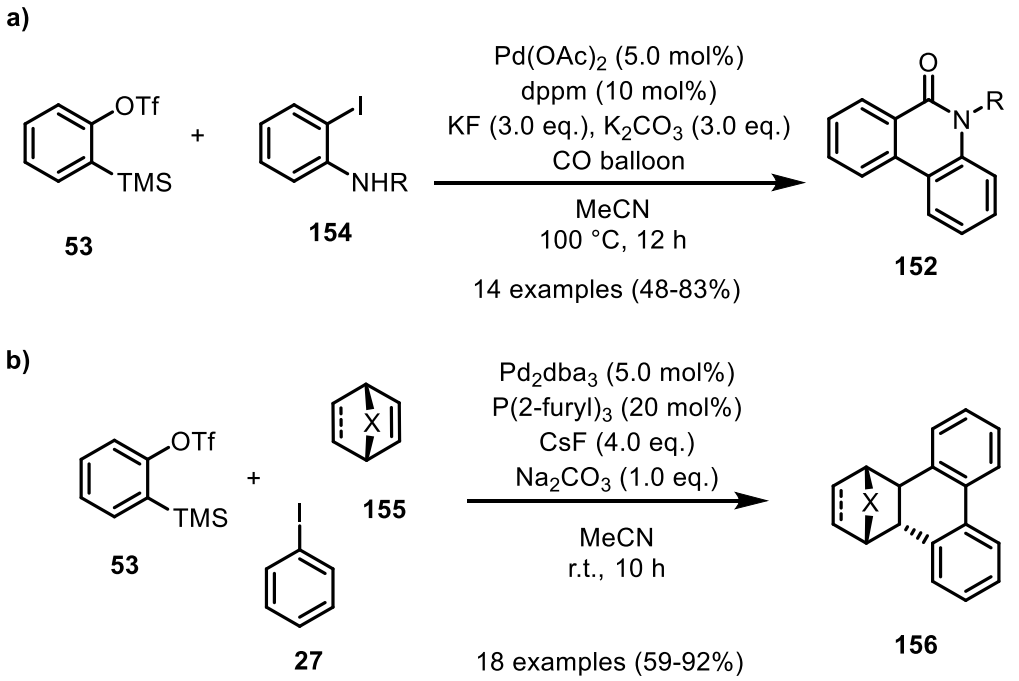
Several groups have developed annulative biaryl syntheses *via* carbopalladation of *ortho*-substituted haloarenes, followed by insertion of aryne in the Pd–C bond to form the biaryl and cyclisation. Li and co-workers developed a reaction of 2-(2-iodophenoxy)-1-arylethanones **149** which gave 6-benzo[*c*]chromenes **150** (Scheme 45, a).[141] Larock demonstrated the synthesis of phenanthridinones **152** from *N*-monosubstituted *o*-halobenzamides **151**, through sequential C–C and C–N bond formation (Scheme 45, b).[142] Ling also developed a carbocylisation of arynes which led to phenanthridinones **152**.[143] Here the starting materials were tertiary *N*-(2-halophenyl)formamides **153**, and two new C–C bonds were formed (Scheme 44, c). Although the lowest yield is only 24%, most lie in the region of 80 – 95%. The Xu[144] and Jgenmohan[145] groups independently reported another approach to

phenanthridones which uses palladium catalysed direct C–H arylation of *N*-arylated Wienreb-amides.



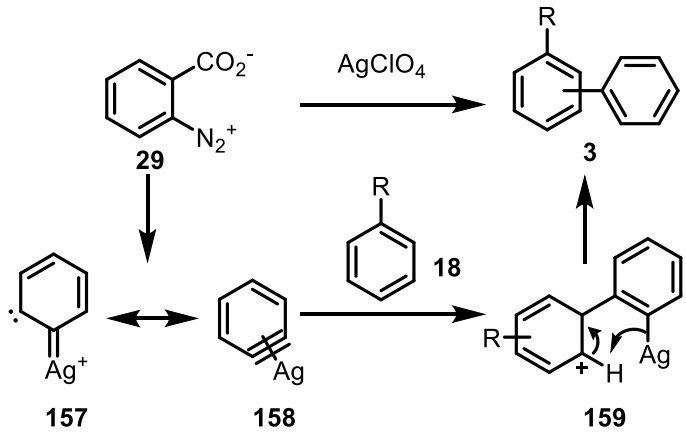
Scheme 45 Annulative synthesis of biaryl containing multicyclic heterocycles

Jiang reported a regiodivergent MCR of aryne, CO, and 2-iodoaniline **154** which formed either phenanthidinones **152** or acridones depending upon the reaction conditions (Scheme 46, a).[146] Another aryne MCR coupled aryl iodides **27**, bicyclic alkenes **155** and arynes to a multicyclic with a biaryl core **156** (Scheme 46, b).[147] Aryl generation from *ortho*-iodosulfonates can be used to form *ortho*-substituted Grignard reagents. These can be transmetallated with zinc, and then cross coupled with aryl iodides in a Negishi-coupling to prepare *ortho*-substituted biaryls.[148]



Scheme 46 Aryl iodides as coupling partners in aryne biaryl synthesis

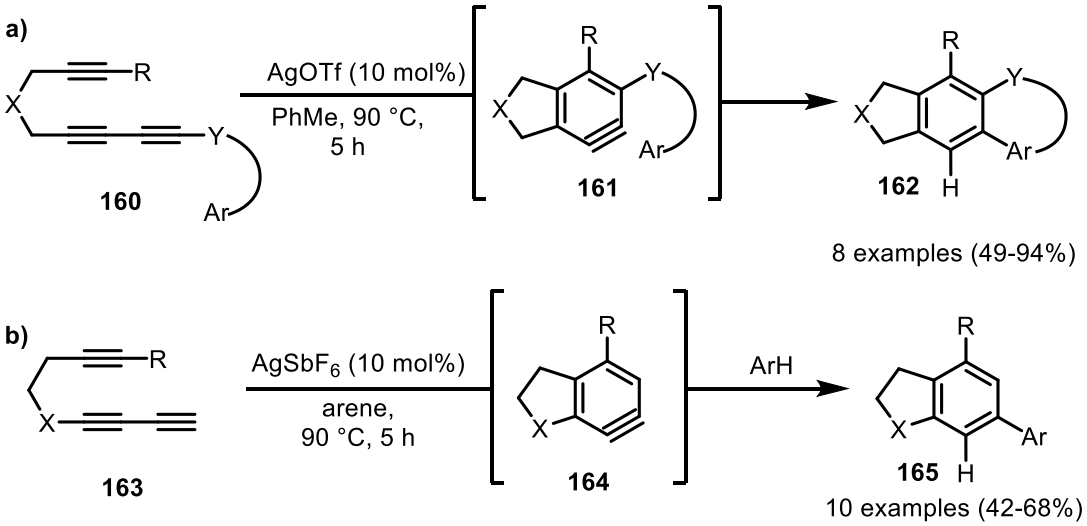
The C–H arylation with arynes, through a S_EAr mechanism, has been observed as a low yielding side reaction in several instances. This process was reported first by Friedman, and then Oda to be promoted by silver salts, potentially *via* the formation of a benzyne-Ag complex **157** and **158**, which enhances electrophilicity (Scheme 47).[149-150]



Scheme 47 Silver mediated synthesis of biaryls through a S_EAr mechanism

Lee and Xia reported the intramolecular nucleophilic trapping of tethered arenes **160** by arynes prepared though the HDDA method in the presence of silver salts (Scheme

48, a).[151] This was extended to the silver mediated intermolecular trapping of benzene, xylene or mesitylene by arynes (Scheme 48, b).



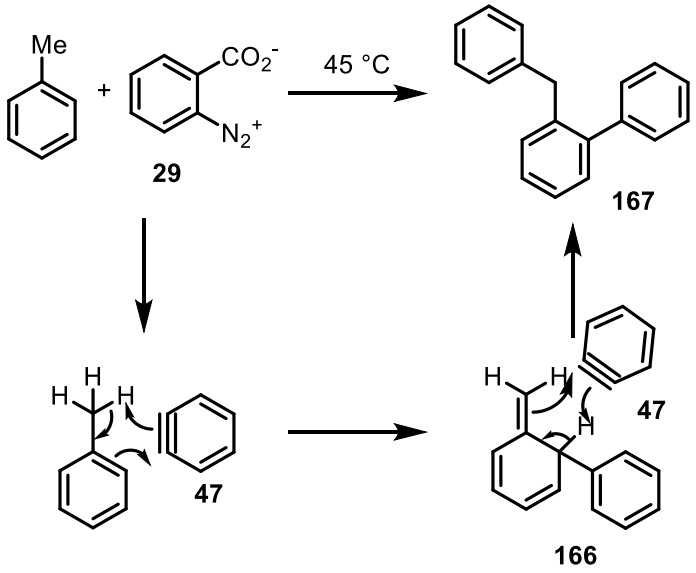
Scheme 48 Silver salts and the HDDA reaction for the preparation of biaryls

5.7. Metal-Free Benzyne Biaryl Synthesis

Despite the development of mild, metal-free methods for the generation of benzyne, there are few aryne based biaryl syntheses which are metal-free.

5.7.1. Pericyclic

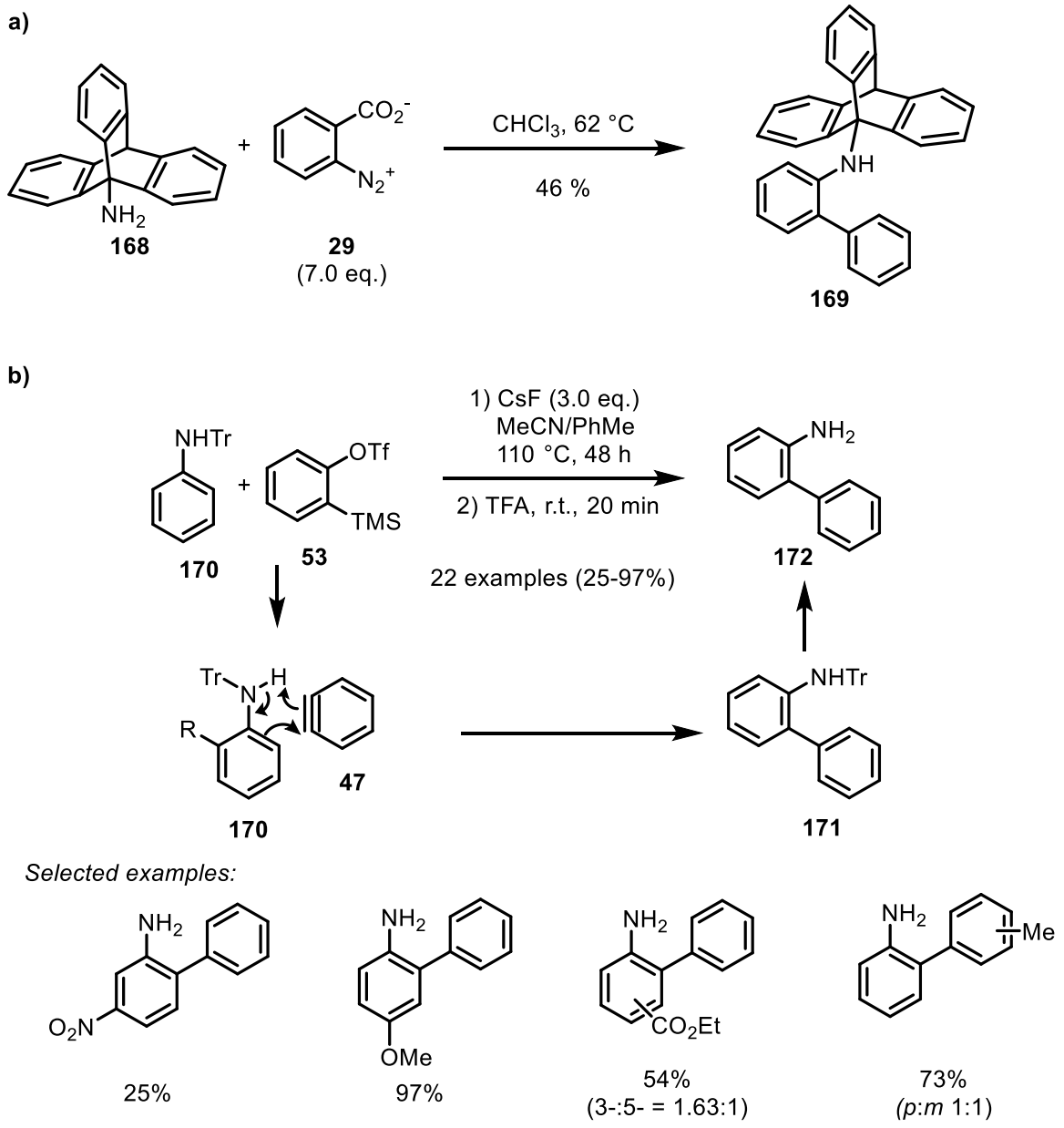
Benzyne participates in many pericyclic reactions (*vide supra*, pg. 41) and this mode of reactivity can be harnessed for the synthesis of biaryls through ene and cycloaddition reactions. This was first demonstrated by Friedman, and then Oda, to afford low yields of the *ortho*-benzyl biphenyl **167** as mixtures with other products (Scheme 49).[152-153]



Scheme 49 Silver mediate synthesis of biaryls from arynes *via* an ene reaction

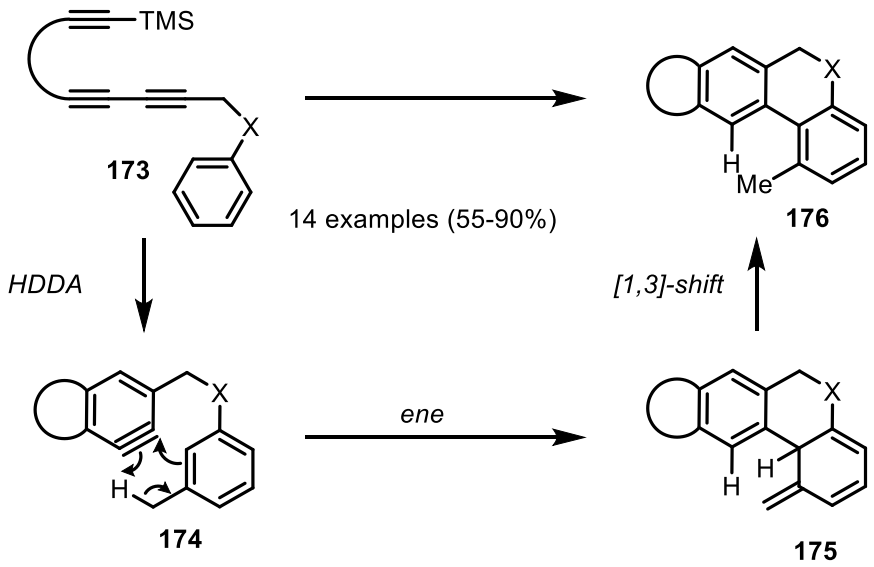
The early reports of an ene reaction between arynes and styrene to afford the biaryl containing 9-aryldihydrophenanthrenes,[154-155] was built upon by Biju who optimised the reaction to respectable yields using the 2-trimethylsilyl(aryl) triflate aryne precursors (*vide supra*, pg. 41).[68]

A successful approach for the synthesis of non-cyclic biaryls has been through the hetero-ene reaction (Scheme 50). Yamamoto reported the formation of biphenyl amines **169** from the reaction of primary triptycene amines **168** with a large excess of the diazonium-carboxylate benzyne precursor **29** (Scheme 50, a).[156] The steric bulk of the triptycene prevents a second *N*-arylation and instead promotes a hetero-ene reaction to form the biaryl bond. Greaney then developed a more practical method with the less bulky *N*-trityl anilines **170** and *ortho*-trimethylsilyl(aryl) triflate benzyne precursors **53** (Scheme 50, b).[157] Furthermore, the primary amines could be revealed with a TFA workup, and so this method gives access a range of primary *o*-amino biaryls **172**.



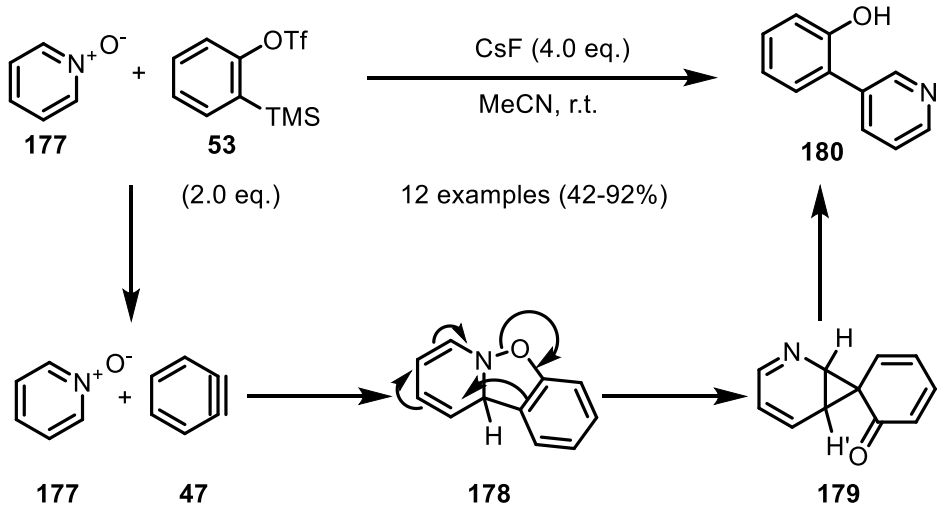
Scheme 50 The hetero-ene reaction for metal-free aryne biaryl synthesis

Hoye demonstrated intramolecular trapping of phenols derivatives linked to the triyne precursor by a flexible methylene linker 1**73**.[158] The aryl ether undergoes an ene reaction, followed by a [1,3]-hydride shift to restore aromaticity (Scheme 51). Alternatively, restoration of aromaticity was demonstrated with an intermolecular Alder-ene reaction, to afford complex multicyclic products in one step from the tri-yne starting materials.



Scheme 51 The HDDA / ene reaction for the syntheis of biaryls

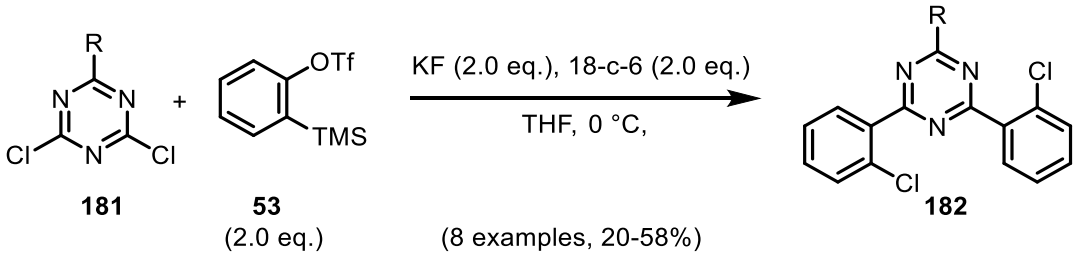
Aryne dipolar cycloaddition is widely used for heterocycle synthesis and encompasses a wide range of 1,3-dipoles (*vide supra*, pg. 41). Larock reported an example in which 3-(2-hydroxyaryl)pyridines as synthesised regioselectively from pyridine-*N*-oxides **177** and arynes.[73] The aryne undergoes a [2+3]-cycloaddition with the pyridine-*N*-oxide to form intermediate **178** (Scheme 52). This intermediate then rearranges to form intermediate **179**, which is then deprotonated at H' to from the biaryl product **180** through rearomatisation. This has also been demonstrated with aza-heteroaromatic ylides resulting in biaryl anilines.[159-160] Alternatively, the regioselectivity can be switched through employing a different solvent and fluoride combination, as reported by Lui.[161]



Scheme 52 Aryne arylation of pyridine-*N*-oxide through [3+2]-cycloaddition

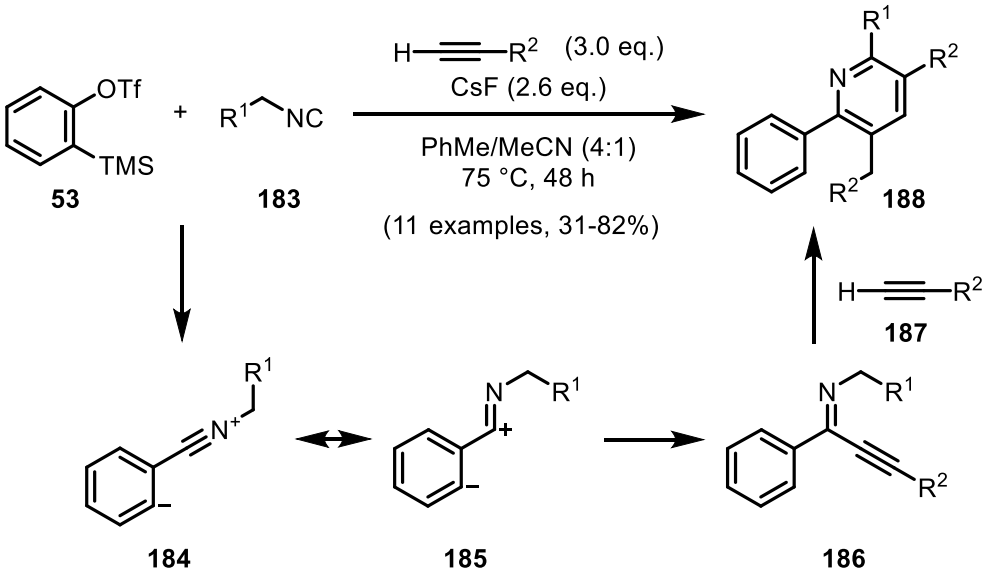
5.7.2. Non-Pericyclic

Yoshida reported the insertion of arynes into the C–Cl bond of chlorotriazines **181** (Scheme 53).[162] This was proposed to proceed through the nucleophilic displacement of chloride with fluoride, followed by an attack of benzyne by the resulting chloride anion, and an S_NAr reaction between the resultant aryl anion and the fluorotriazine. Reactions with tri- and dichloropyrazines were successful, but monochloro pyrazine was insufficiently active.



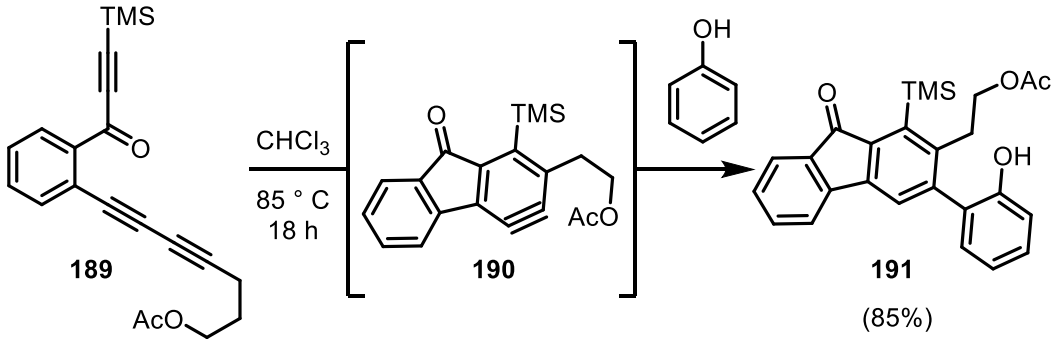
Scheme 53 The arylation of chloro-triazines throuch nucleophilic subsitution

The products of pyridine arylation were prepared by Huang and co-workers through a *de novo* construction of the heteroarene through a multicomponent reaction of arynes, isocyanides **183** and terminal alkynes **187** (Scheme 54).[163] An excess of the alkyne affords arylated pyridines are the final products **188**, whereas arylated quinolones are produced with one equivalent of the alkyne and an excess of aryne.



Scheme 54 *De novo* synthesis of arylated pyridines with an isocyanide initiated aryne MCR

The Hoye group has demonstrated that phenols can trap arynes, generated by the HDDA method, through an S_EAr mechanism (Scheme 55).[158]



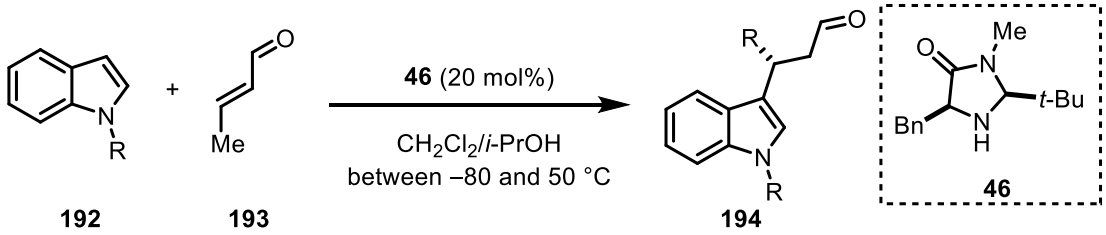
Scheme 55 S_EAr addition of phenol to an HDDA generated aryne

In conclusion, whilst the aryne mediate synthesis of biaryls is well studied, there are a limited number of methods which can be classified as a metal-free coupling of two arenes to form a discreet biaryl unit.

6. Nucleophilic Arenes

Electron rich arenes and heteroarenes can act as nucleophiles and can form carbon-carbon bonds through Friedel-Crafts alkylation. More recent examples this chemistry have used organocatalysis to activate α,β-unsaturated carbonyls and other Michael acceptors.

The enantioselective Friedel–Crafts alkylation of pyrroles was first reported by Macmillan in 2001.[164] Conensation of α,β-unsaturated aldehydes **193** with a secondary amine catalyst **46** formed the highly electrophilic iminium species which was then extended to include indoles **192**, and then anilines (Scheme 56).[165] More recently, the group have demonstrated that π-rich heteroaryl tetrafluoroboratesalts can perform this reaction, this pre-functionalisation overcomes the intrinsic nucleophilicity of the heteroaromatic.[166]



Scheme 56 The secondary amine catalysed alkylation of indole

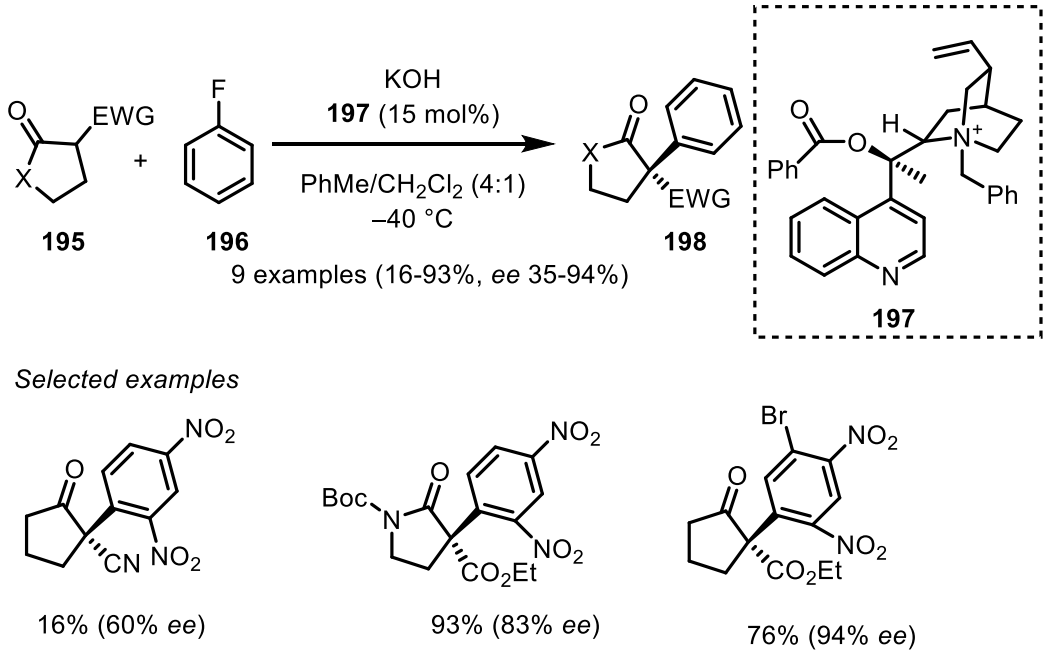
Ricci developed a thiourea-catalysed Friedel-Crafts alkylation of electron-rich arenes and heteroarene with nitro-styrene.[167] An enantioselective version was then developed using a chiral thiourea, the best catalyst also had an alcohol motif and so a bifunctional mode of action was proposed.[168] Several other groups have subsequently developed other catalytic systems for this type of transformation.[169-172]

7. Electrophilic Arenes

Electron-poor arenes, such as aryl fluorides, react through an S_NAr mechanism with highly nucleophilic carbons. Similarly, diaryl-iodoniums have been demonstrated as effecting reagents for the arylation of carbanion nucleophiles. Alternatively, *para*-quinones have been demonstrated as arene-precursors and participated in conjugate addition reactions.

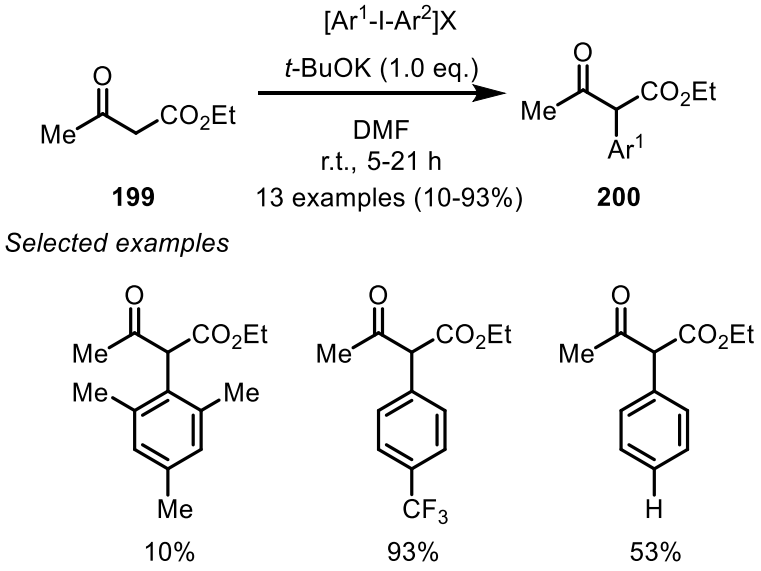
7.1. Alpha-arylation of carbonyls

Whilst substitution of alkyl halides is a facile approach to alkylation, the equivalent reaction with aryl halides is inhibited due poor orbital overlap. The majority of examples of aromatic nucleophilic substitution to form Ar–C bonds consist of highly electron-poor aryl halides and 1,3-dicarbonyl anions.[173-175] Heteroaryl halides can be used for the α-arylation of esters, amides and nitriles through α-deprotonation with sodium or potassium HMDS.[176-177] In some cases, a catalytic quantity of the phosphazene superbase have been shown to be sufficient to promote S_NAr.[178] Phase-transfer catalysis has been demonstrated for coupling of 1,3-bicarbonyls **195** and with aryl fluorides **196**.[179-180] These conditions can also be rendered enantioselective through use of a cinchona alkaloid derived catalyst (Scheme 57).



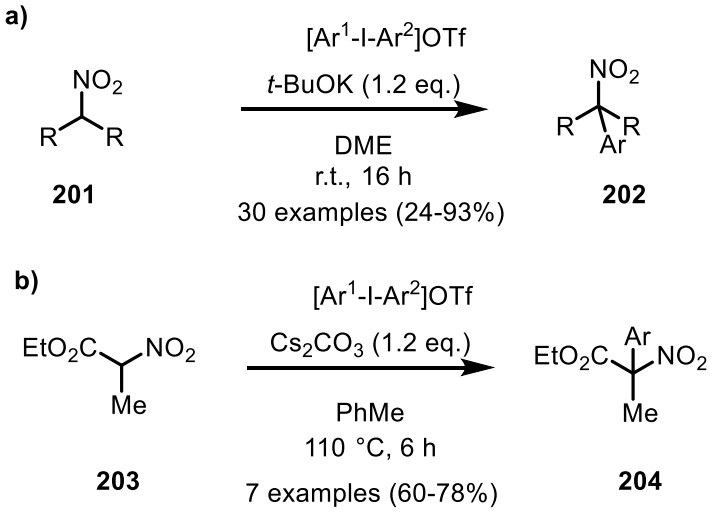
Scheme 57 The enantioselective α-arylation of dicarbonyls using phase-transfer catalysis

The ability of diaryl iodoniums to perform α-arylation was established by Beringer in the 1960's.[181] These arylations suffered from poor selectivity and were typically limited to cyclic substrates. The selective *C*-arylation of malonates or cyclic ketones was achieved by Jung,[182] and Ochiai reported the use of diaryliodonium salts to perform the asymmetric phenylation of the β-keto esters using a chiral auxiliary approach.[183] Reasonable yields were achieved, but only low to moderate enantioselectivity was observed. More recently, the α-arylation of ethyl acetoacetate **199** has been reported (Scheme 58).[184] Electron-rich arenes (i.e. *p*-methoxyphenyl) do not perform the arylation.



Scheme 58 The α-arylation of ethyl acetoacetate with diaryliodonium salts

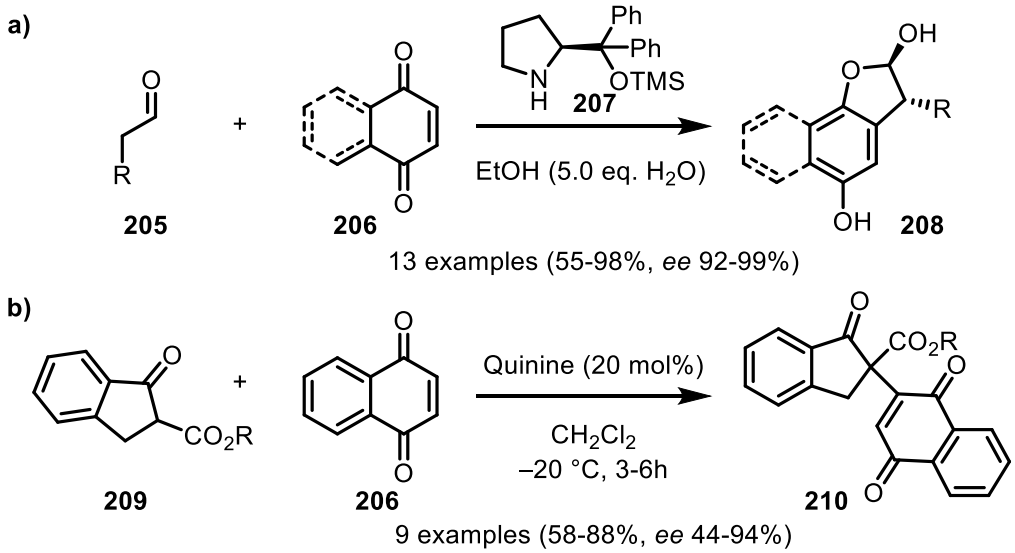
Ollofson recently reported the metal-free *C*-arylation of nitro compounds with diaryl iodonium salts.[185] Cyclic and acyclic nitro-alkanes **201** could be α-arylated (Scheme 59, a) with electronically and sterically varied arenes. The arylation of nitroesters **203** was also demonstrated (Scheme 59, b), required more forcing conditions. In the case of unsymmetrical diaryl iodonium reagents, electron-poor arenes transferred preferentially.



Scheme 59 Metal-free arylation of nitro compounds with diaryl-iodonium salts

In 2007, Jørgensen reported the α-arylation of β-ketoesters and aldehydes.[186-187] These methods both used organocatalytic strategies and *para*-quinone **206** as the arene, but the type of catalyst differed. For the α-arylation of aldehydes **205**, a

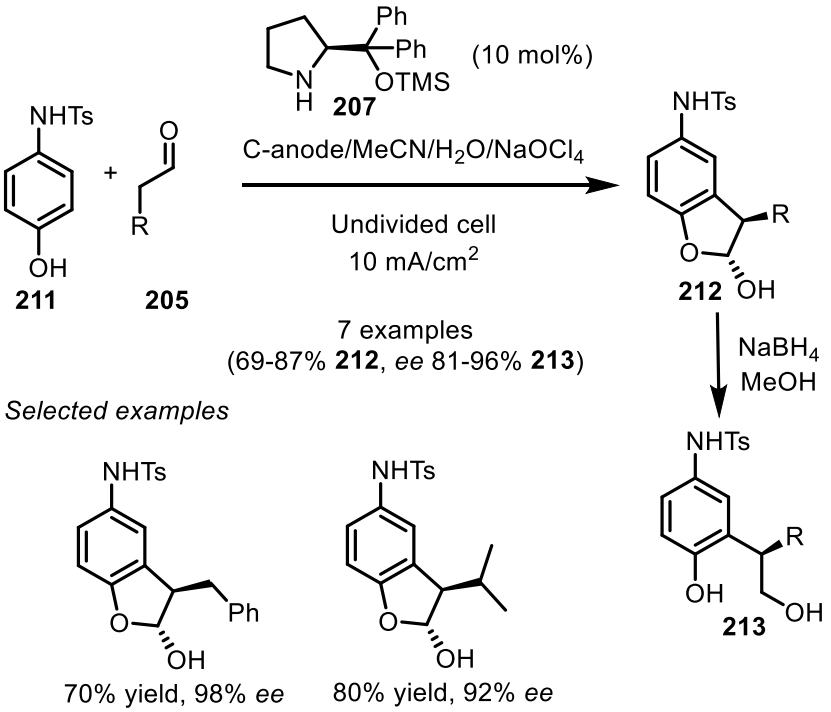
pyrrolidine-derived catalyst **207** was used to affect the enantioselective arylation. The final product of this transformation was a hemiacetal **208**, which was isolated as a diastereomerically pure compound (Scheme 60, a). Various *para*-quinone and alkyl aldehydes could be employed, and the final product could be reduced or acetylated. For β-ketoesters **209**, the cinchona alkaloid Quinine was used as the chiral catalyst (Scheme 60, b), again affording aromatised hemiketal products in some cases. Several different naphthoquinones and chloroquinones were suitable arene sources and various cyclic β-ketoesters were reactive. Jørgensen also reported the enantioselective vinylogous addition of dicyanoalkylidenes to quinone, also using the chiral base $(DHQD)_2PHAL$.[188] The products of addition could then be aromatized under acid catalysis.



Scheme 60 The organocatalyzed α-arylation with *para*-quinone

Jørgensen then reported the use of aniodic oxidation in the α-arylation of aldehydes **205** from the *meta* position of anilines **211** *via* the formation of iminoquinones.[189] This combined the electrochemical oxidation of tosyl-anilines **211** to 1,2-iminoquinones with secondary-amine catalysed aldehyde activation (Scheme 61). The enamine intermediate undergoes conjugate addition with the iminoquinone, followed by hydrolysis of the organocatalyst, then re-aromatisation and cyclisation

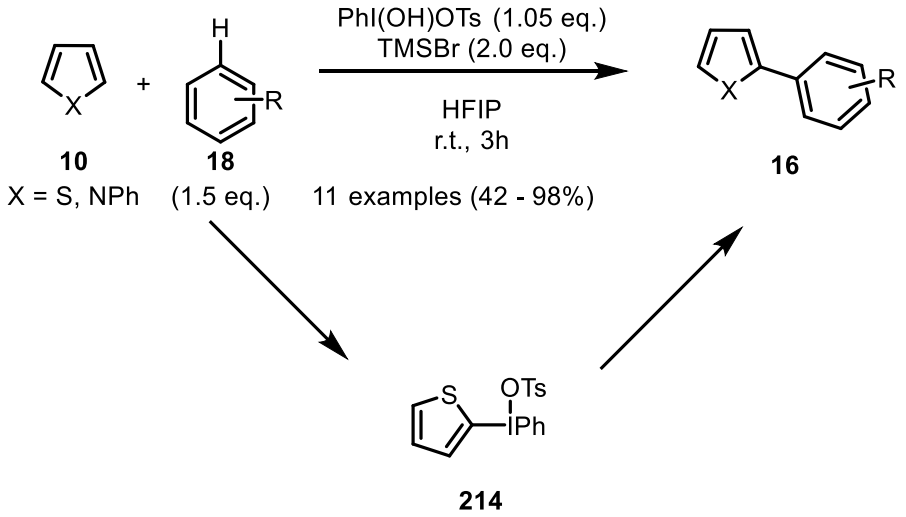
to form the final hemiketal product **212**. Chemical oxidation with PIDA could also be performed; here the aniline partner could be extended to naphthalene, or replaced with a *para*-quinone.



Scheme 61 Oxidation of tosyl-anilines for α-arylation of aldehydes

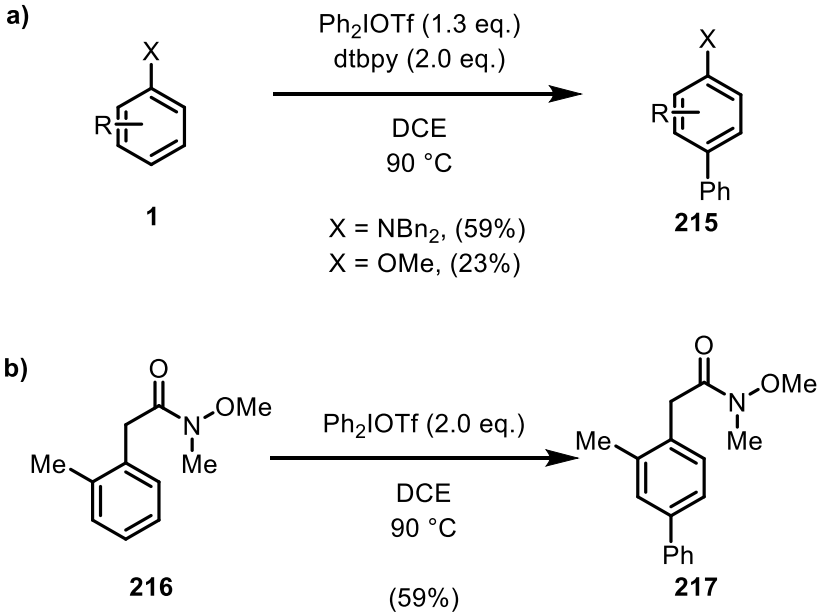
7.2. Arene Arylation

The *in-situ* formation of highly electrophilic heteroaryl iodonium reagents **214** and reaction with nucleophilic electron-rich (hetero)arenes **18** can be achieved with an iodine (III) oxidant in fluoroalcohol (Scheme 62).[190-191]



Scheme 62 The *in-situ* formation of heteroaryl iodonium(III) salts and biaryl formation

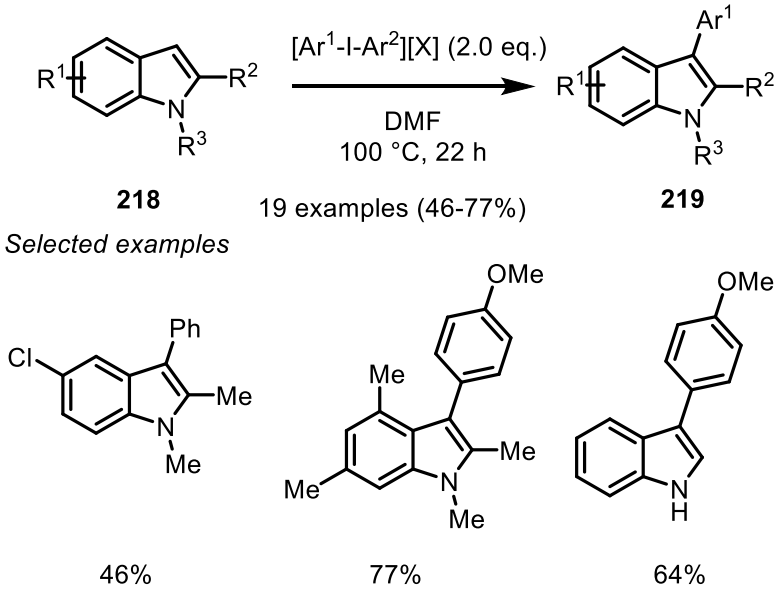
Gaunt discovered that the copper catalysed *para* arylation of aniline and anisoles **1** (Scheme 63, a), and *meta* arylation of α-aryl ketones **216** (Scheme 63, b) could also proceed without a catalyst at elevated temperatures.[192-193] A substrate scope was not established for the non-catalysed variant of these reactions.



Scheme 63 Direct arylation with diaryliodoniums in the absence of a copper catalyst

Ackermann developed a metal-free direct arylation of indoles **218** with diaryl iodoniums (Scheme 64).[194] The C-3 position was preferentially arylated **219**, but to ensure complete regioselectivity, the C-2 position was blocked in most cases. The

more nucleophilic indoles are preferentially arylated and less electron-rich arenes are preferentially transferred from the iodonium.



Scheme 64 Direct arylation of indole with diaryl iodonium salts

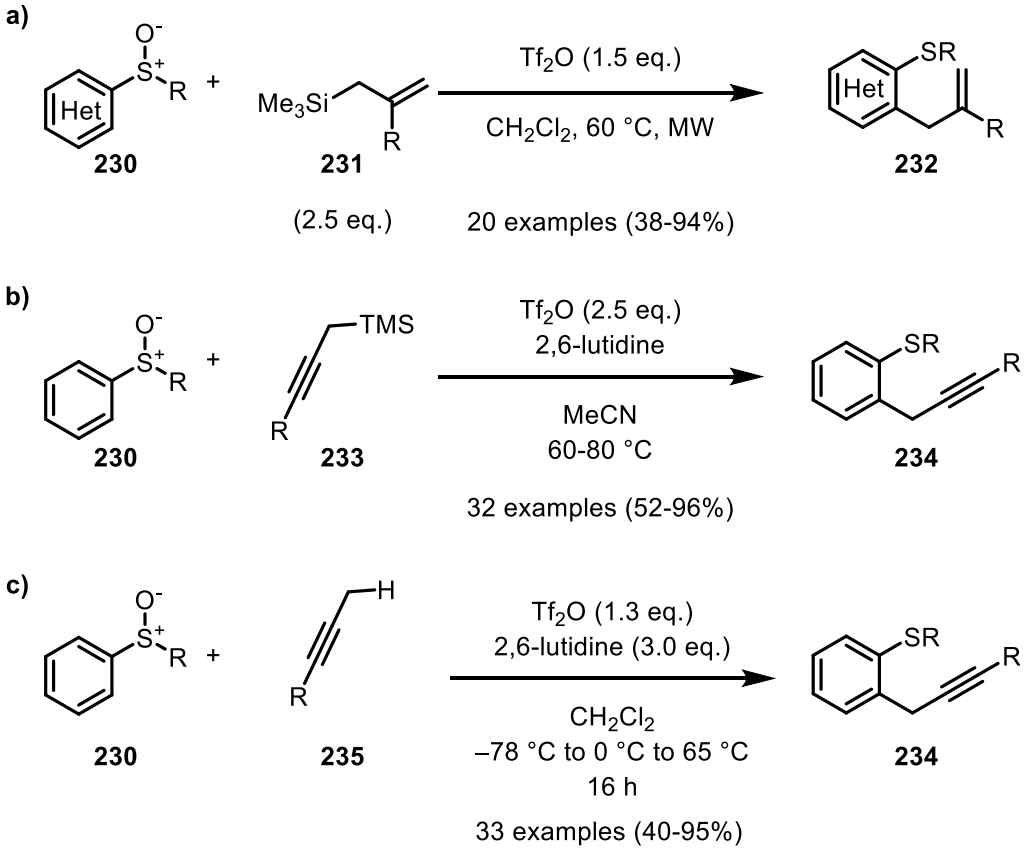
8. Rearrangements

8.1. [3,3]-Sigmatropic Rearrangements

Aryl sulfonium salts and aryl iodane reagents can rearrange to afford *C*–arylated products. The bond-forming event typically takes place adjacent to the sulfur or iodine with these functional handles remaining intact following the rearrangement. The methodologies were developed separately, but Shafir has drawn the two approaches together in a review because of similarities between the mechanisms and substrates.[195]

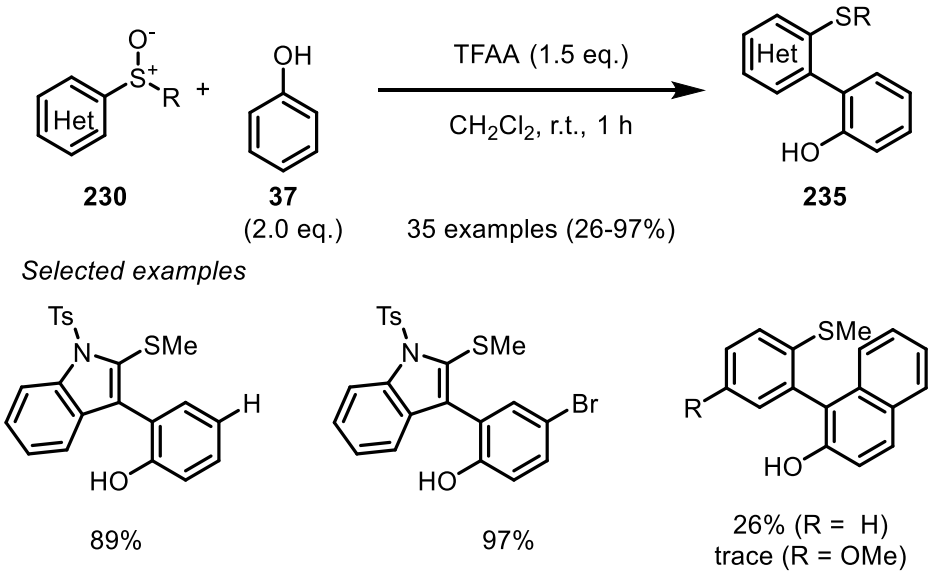
8.1.1. Sulfoxides

Kita and Padwa independently reported interrupted Pummerer reaction, followed by a sigmatropic rearrangement, with heteroaryl sulfoxides and sulfimines respectively.[196-198] Subsequently, Procter has developed *o*-allylation (Scheme 65, a), and propargylation using silane reagents (Scheme 65, b).[199-203] Furthermore, the dehydrogenative cross-coupling with alkynes **235** was achieved through careful temperature control (Scheme 65, c).[204]



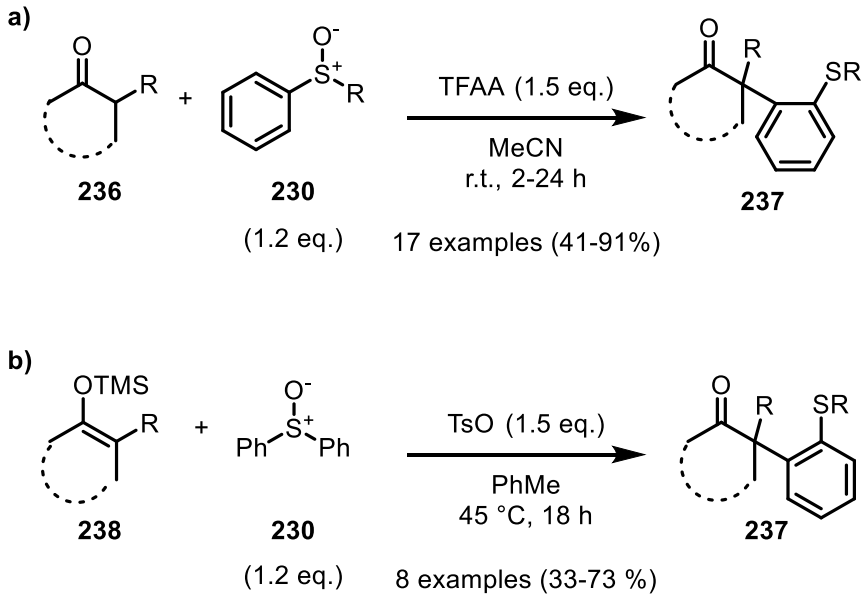
Scheme 65 Sulfoxide directed a) allylation b) propargylation with silanes and c) dehydrogenative propargylation

Recently, Yorimitsu reported a biaryl synthesis using aryl-sulfoxides **230** and phenols **37** (Scheme 66).[205] A broad substrate scope was demonstrated, including heteroaryl sulfoxides, but one limitation is in *para*-substituted sulfoxides, with both *p*-trifluoromethylphenyl and *p*-methoxylphenyl affording only trace quantities of the biaryl product.



Scheme 66 Metal-free biaryl synthesis through a [3,3]-sigmatropic rearrangement

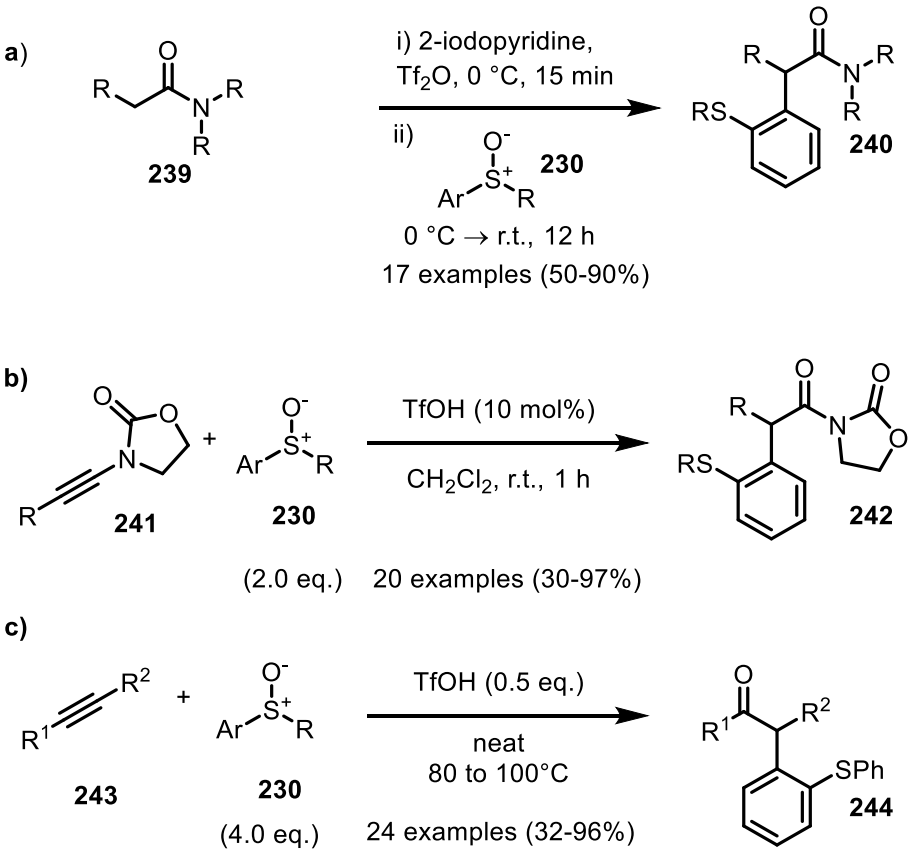
Maulide has reported the α-arylation of 1,3-dicarbonyls **236** (Scheme 67, a), and silyl enol ethers **238** to achieve the formal α-arylation of aldehydes and ketones **237** (Scheme 67, b), however, the arylation of the enol ether of acetophenone was unsucessful.[206-207]



Scheme 67 The sulfoxide mediated α-arylation of carbonyl compounds

The α-arylation of amides **239** was achieved through the formation of an activated amide with 2-iodopyridine and triflic anhydride (Scheme 68, a).[208] This method was chemoselective for the α-arylation of the amide in the presence of enolisable esters

and alkyl ketones. Alternatively, ynamides **241** have been demonstrated as a dehydrated amide synthon.[209] This chemistry requires a neat reaction mixture to be successful (Scheme 68, b) and a catalytic quantity of HOTf was sufficient to promote the reaction. Recently, Maulide has reported a hydrative arylation of alkynes **234** to afford α-arylation ketones **244** (Scheme 68, c).[210] The key to this transformation was to use an excess of the sulfoxide as the reaction medium, at high temperature.

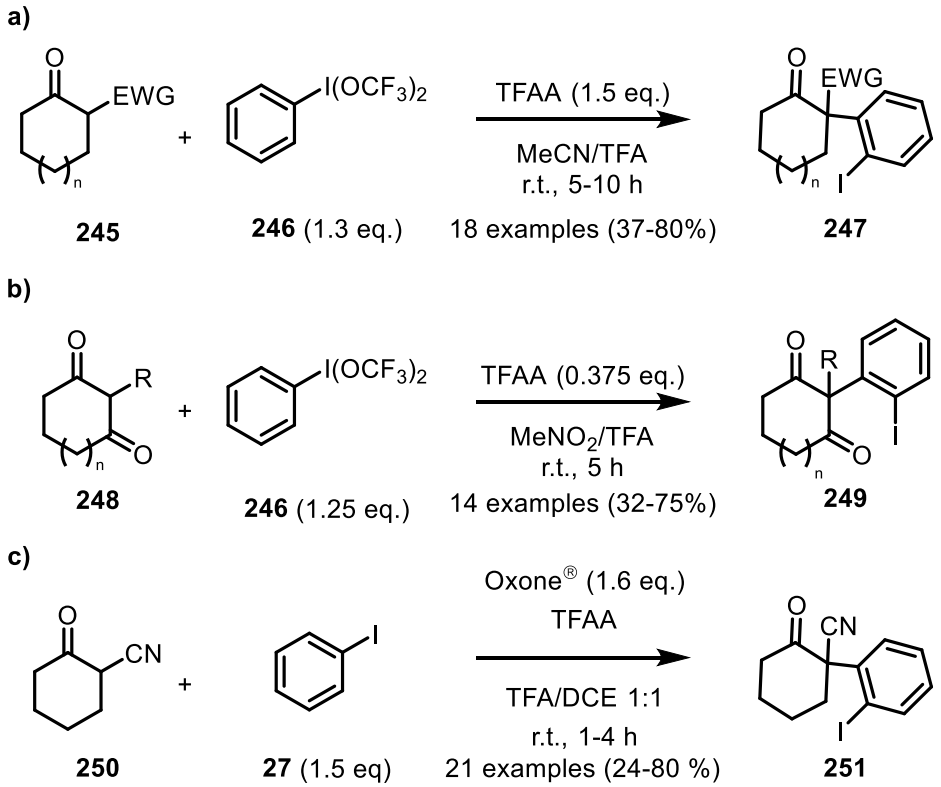


Scheme 68 Sulfoxide mediated a) α-arylation of amides b) hydrative arylation of ynamides c) hydrative arylation of alkynes

8.1.2. λ³-Iodanes

Diaryl iodoniums have been used as powerful electrophiles for metal-free arylation chemistry with carbanion nucleophiles. The [3,3]-sigmatropic rearrangement (iodo-Claisen) of hypervalent aryl-iodides is another mode of reactivity that can be exploited for arylation and was first reported by Zhu for the allylation of arenes and π-rich heteroarenes, but required electron-rich arenes.[211-212]

Shafir developed the arylation of activated cyclic ketones **245**, moderate yields were demonstrated with β-dicarbonyls, but a cyanoketones were more efficient (Scheme 69, a) and an electron-rich arene was not required.[213] The arylation of cyclic ketones **248** was also reported (Scheme 69, b), and iodoarenes **27** could be employed directly through *in situ* formation of the iodane with Oxone® (Scheme 69, c).[214]



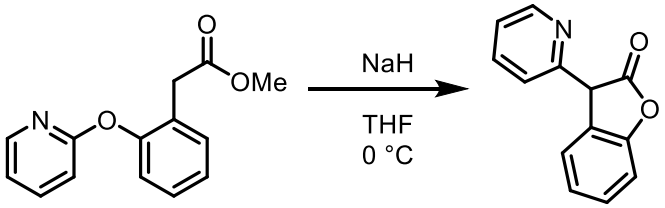
Scheme 69 The arylation of carbonyl compounds with hypervalent iodine reagents *via* [3,3]-sigmatropic rearrangement

8.2. Truce-Smiles Rearrangement

The first carbanion Smiles rearrangement was reported by Truce which involved rearrangement of an organolithium species.[215-216] Unlike later example, these rearrangements did not require the presence of a strongly activating group on the migrating arene. Early examples of the Truce-Smiles rearrangement have been documented in a review,[217] and subsequent reports will be discussed here.[218]

8.2.1. Alpha-arylation of carbonyls

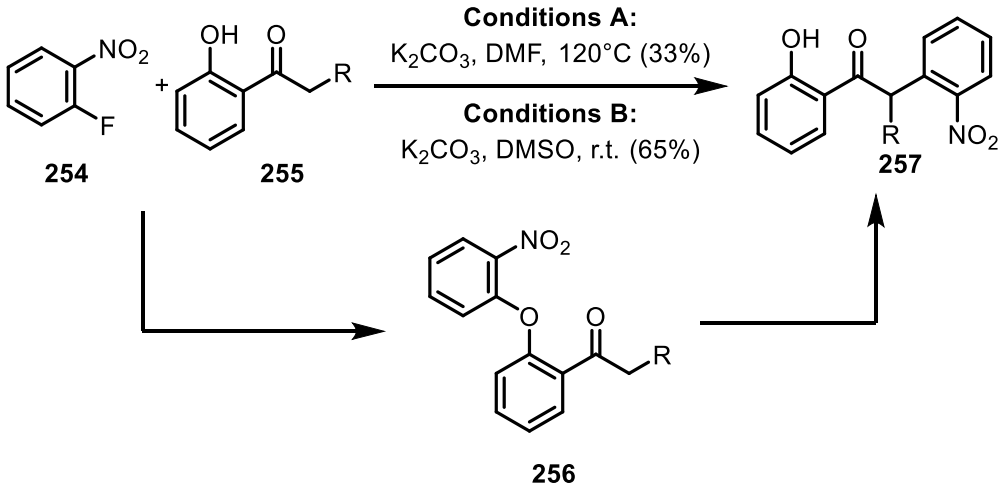
Erickson *et al.* reported an unexpected phenyl migration upon deprotonation of 2-(2-pyridloxy)phenylacetic acid esters **252** which resulted in the formation of 3-pyridyl-2-benzofuranones **253** (Scheme 70).[219] This rearrangement proceeded *via* a 5-membered transition state, whilst other Truce-Smiles rearrangements predominantly proceed through 6-membered transition states (*vide infra).*



252 **253**

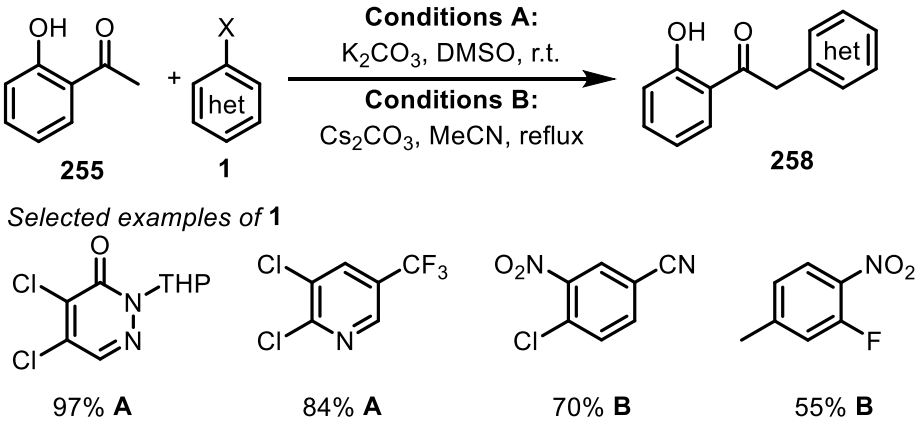
Scheme 70 First reported Truce-Smiles rearrangement of a phenyl ether

The reaction of electron-poor aryl fluorides **254** with *o*-hydroxy acetophenone **255** was observed to give *C*-arylated products **257** rather than the expected *O*-arylated products by Mitchell (Scheme 71, Conditions A).[220] The transformation was then shown to proceed at ambient temperatures in DMSO and was more fully explored with respect to compatible functionality by Snape (Scheme 71, Conditions B).[221] The process was shown to be a two-step reaction through an S_NAr *O*-arylation of the acetal-protected ketone **256**. The *O*-arylated ketone **257** was revealed under acidic conditions and then subjected to base-mediated rearrangement to give the *C*-arylated product. This methodology was used as a key step in the preparation of the core of a 2,3,6-trisubstituted indole at large (>50 kg) scale by a process chemistry group led by Alorati and Gibb at MSD.[222]



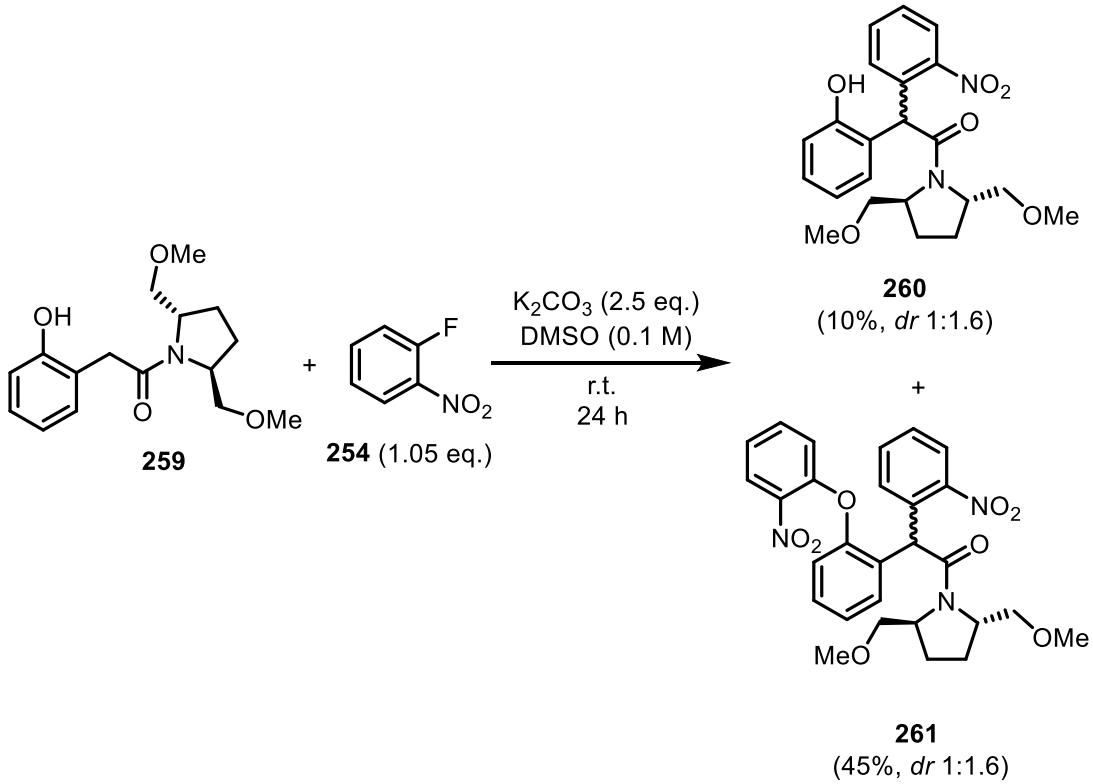
Scheme 71 α-Arylation of aryl ketones *via* an enolate Truce-Smiles rearrangement

The range of activating groups was expanded upon by Ma and Ma to include heteroarenes, nitriles trifluoromethyl and halogen functionality **1**, under similarly mild conditions (Scheme 72).[223]



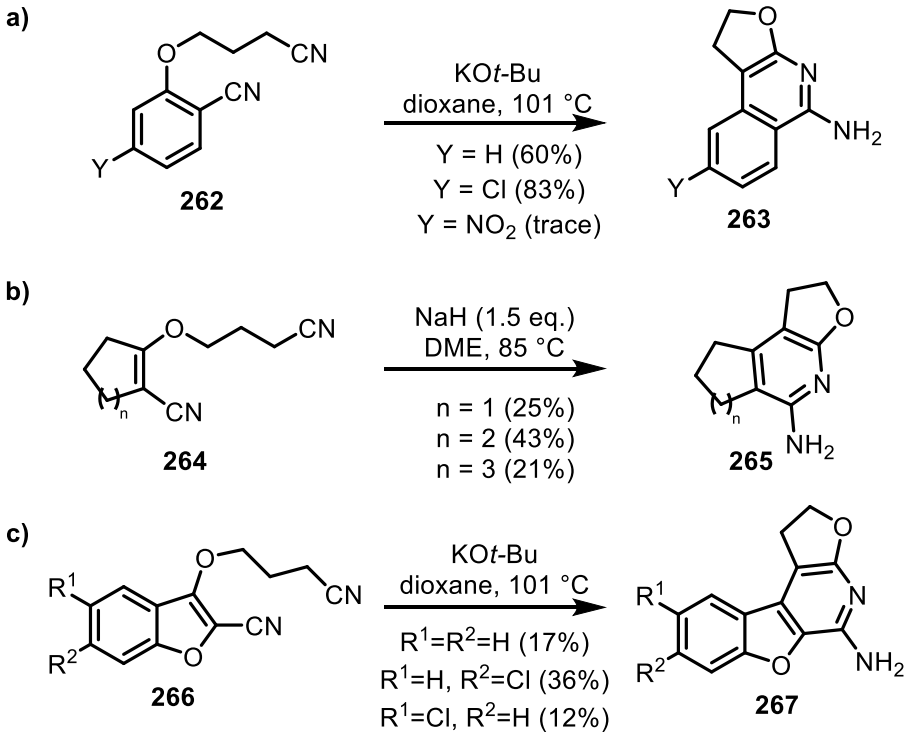
Scheme 72 Cascade S_NAr / Truce-Smiles rearrangement to prepare α-arylated acetophenones

Snape reported preliminary results concerning the development of an asymmetric *α*-arylation, using an amide chiral auxiliary **259**, in which only low levels of diastereoselectivity **260** and **261** (1:1.6) were obtained (Scheme 73).[221] The propensity for racemisation at the chiral centre in question under the reaction conditions indicated that this may be a consequence of thermodynamic equilibration in the product.



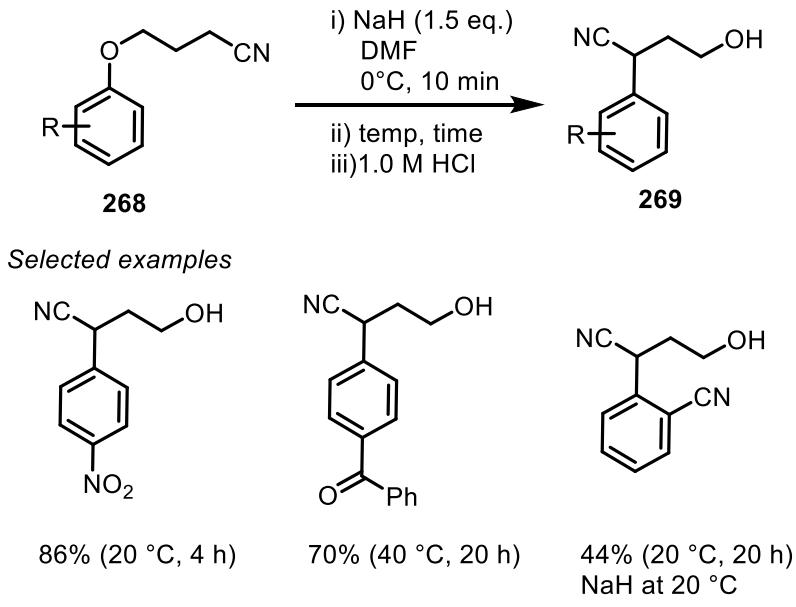
Scheme 73 Diastereoselective Truce-Smiles rearrangement

A series of reports describing the Smiles rearrangement of phenyl ethers, promoted by deprotonation of an alkyl nitrile substrate **262, 264, 266** (Scheme 74) were made by Okuda and Sasaki.[224-227] These reactions culminate in cyclization and aromatization to afford polycyclic heteroaromatic products **263, 265, 267**. The migration of non-aromatic systems (activated alkenes) can be achieved with NaH/DME, albeit in moderate yields.[225]



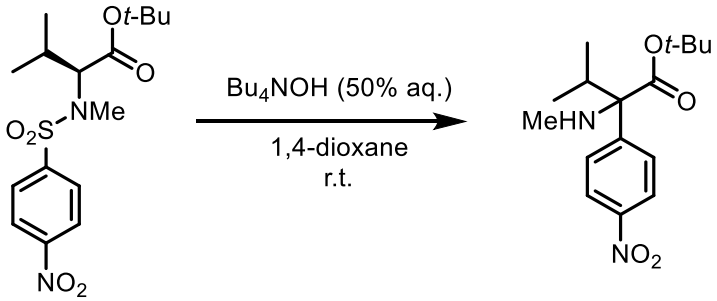
Scheme 74 Deprotonation/rearrangement/condensation cascade of nitrile phenyl ethers

The rearrangement of phenyl ethers initiated by α-nitrile deprotonation of **268** was expanded through the development of milder reaction conditions (Scheme 75) by Wood.[228] The rearrangement could be conducted at lower temperatures (up to 60 °C) using various electron-withdrawing groups on the aryl ring (nitroso, nitrile, ketone, halogens).



Scheme 75 Phenyl ether to α-nitrile aryl migration

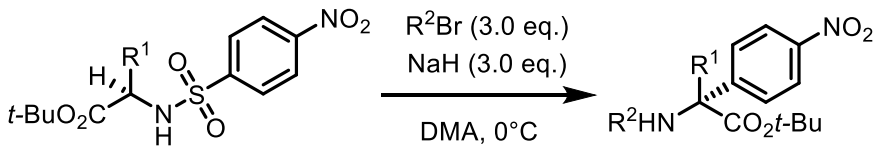
The rearrangement of nosyl protected amino acids **270** was observed in 1999 by Wilson and co-workers (Scheme 76).[229] The rearrangement proceeded rapidly at ambient temperature with 50% Bu_4NOH in dioxane. Several non-polar amino acids were shown to be susceptible to rearrangement to afford the α-arylated amino acid esters **271**. The *p*-nitrobenzene sulfonamides were more reactive than the corresponding *o*-nitrobenzene sulfonamides.



270 **271** (69%)

Scheme 76 The first sulfonamide enolate aryl migration

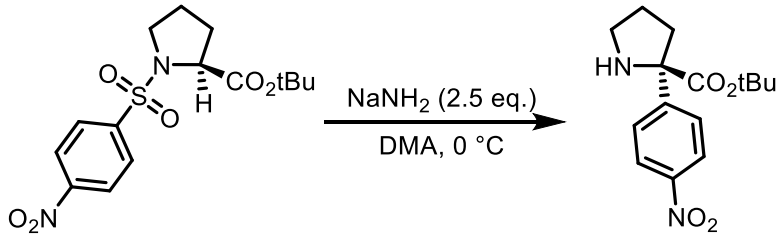
This transformation was expanded upon by Penso and Lupi through *in situ* alkylation and deprotonation of nosylated amino acids **272** which lead to desulfonative rearrangement to afford α-quaternary amino acid derivatives (Scheme 77).[230] Enantiomerically-pure starting materials were converted to products **273** a in moderate to good enantiomeric excess. The mechanism for this retention of configuration was proposed to be through "memory of chirality". A non-alkylated enantio-enriched sulfonamide additive enhanced the retention of chirality, with this ester being recovered with 100% *ee*. Phenyl glycine was recovered with particularly poor *ee*, due to the faster rate of racemisation of these substrates.[231]



272 (single enantiomer) **273** (58-98% *ee*)

Scheme 77 *N*-alkylation/aryl migration to afford α-aryl amino acids

This work was extended to the enantioselective rearrangement of sulfonamide-derived prolines **274** (Scheme 78), affording highly enantioenriched *α*-arylated rearrangement products **275**.[232] A memory of chirality mechanism was also invoked here, with the high enantioselectivity compared to the non-cyclic enolates which can be rationalised by the greater rigidity of the system. The optimal conditions used NaH with ammonia; ammonia was proposed to abstract the sodium ion from the intermediate enolate enabling the formation of a loose ion pair which is more reactive than the unsolvated sodium enolate tight ion pair. Strongly electron-withdrawing functional groups were required (nitro or nitrile), although 2,4-dinitrobenzene gave only a mixture of by-products. In addition, sterically hindered substrates were not viable under the reaction conditions.

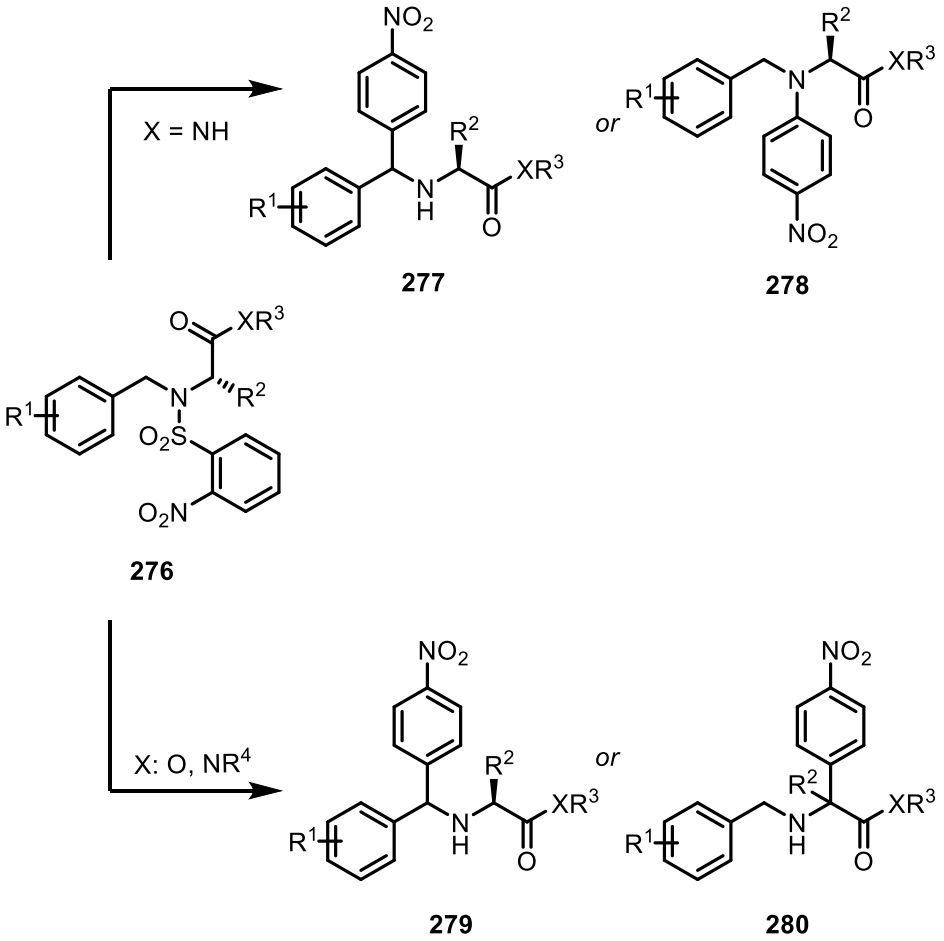


274 (single enantiomer) **275** (91-96% *ee*)

Scheme 78 Enantioselective arylation of prolines *via* a Truce-Smiles rearrangement

A desulfonative intramolecular arylation of amino acid derivatives **276** was developed for the synthesis of a library of advanced intermediates for heterocycles by Krchňák (Scheme 79).[233-234] The regioselectivity of aryl ring migration depended upon both the substitution pattern and the amino acid carboxyl-terminal functionality. A free N–H (X = NH) resulted in the dual Smiles rearrangement to afford *N*-arylated products **278**. Arylation occurred at either the benzylic **279** or α-carbonyl carbon **280** for substrates with no free N–H (X = O, NR^4), with regioselectivity dependent upon the electronics of the *N*-benzyl group (R^1). The reactions were conducted on a solid support resin in the presence of DBU in DMF at

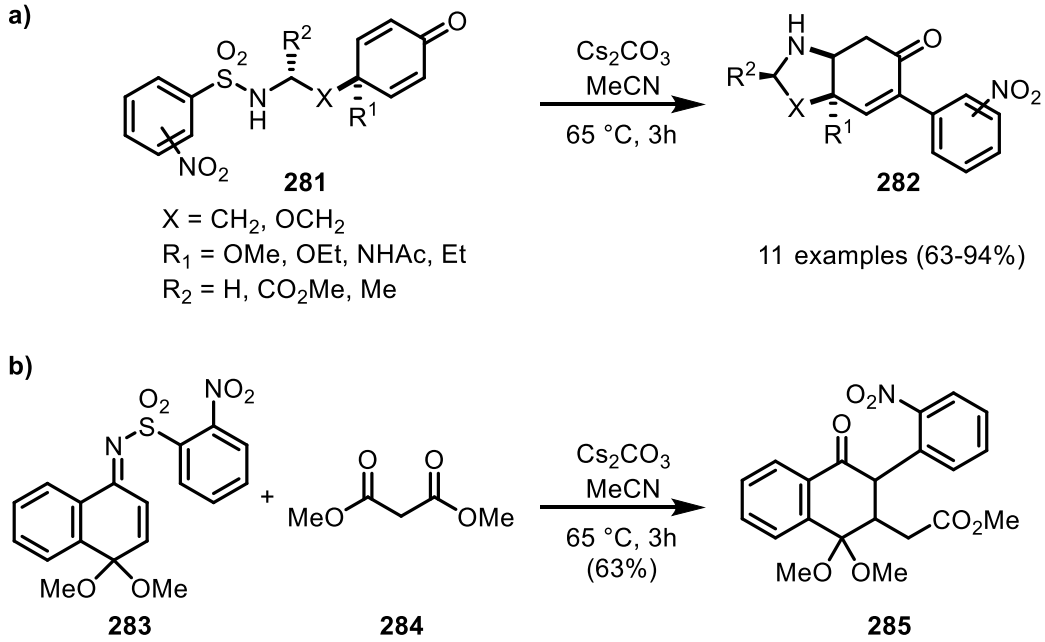
ambient temperature for 16 hours. The α-arylation of amino acid derivatives from alcohols and nitrobenzene sulfonyl chlorides was then described for a large library of compounds.[233] The reactions were all observed to proceed with epimerization of the chiral centre.



Scheme 79 Desulfonative aryl migration of amino-acid derivatives for the combinatorial preparation of heterocycles.

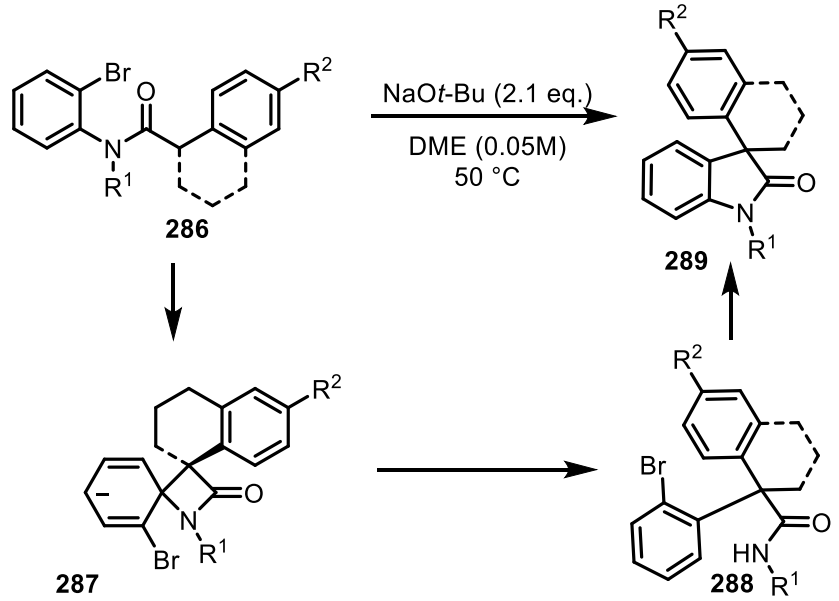
Canesi demonstrated the use of nosyl groups in an intramolecular Michael addition / Truce-Smiles rearrangement reaction.[235] The intramolecular addition of a nosyl-amine to an enone **281** led to Truce-Smiles rearrangement, however, the final product **282** was a result of a retro-Michael and second 1,4-addition of the amine (Scheme 80, a). This concept was also demonstrated with the addition of sulfones to enones and dienamines under the same reaction conditions. Finally, if the sulfonyl

moiety was incorporated into the dienamine **283**, the Truce-Smiles could be triggered by Michael addition of dimethylmalonate (Scheme 80, b).



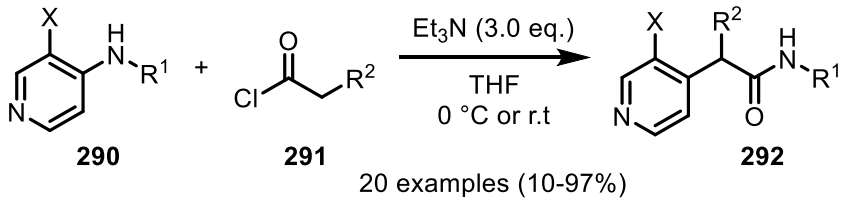
Scheme 80 Tandem Michael addition / Truce-Smiles reactions.

Kündig observed an unexpected rearrangement of aryl amides **286** *via* a 4-membered spirocycle **287**, during the investigation of parallel transition-metal catalysed processes (Scheme 81).[236] The reaction gave good to excellent yields for halogenated aza-heterocycles **289**. A pyridyne intermediate, *via* an elimination pathway, was ruled out through deuterium labelling experiments.



Scheme 81 A Truce-Smiles rearrangement via a four membered spirocycle, followed by cyclization

Al-awar reported another amide enolate Truce-Smiles rearrangement also *via* a four membered transition state, but under mildly basic conditions (Scheme 82).[237] Only 3-substituted pyridines **290** were viable substrates, substitution at the 2-position lead solely to the *N*-acylated products, and the rearrangement of a nitro-phenyl analogue did not occur under these reaction conditions. Therefore, it was proposed that activation of the pyridine occurred through acylation or protonation of the pyridine nitrogen.

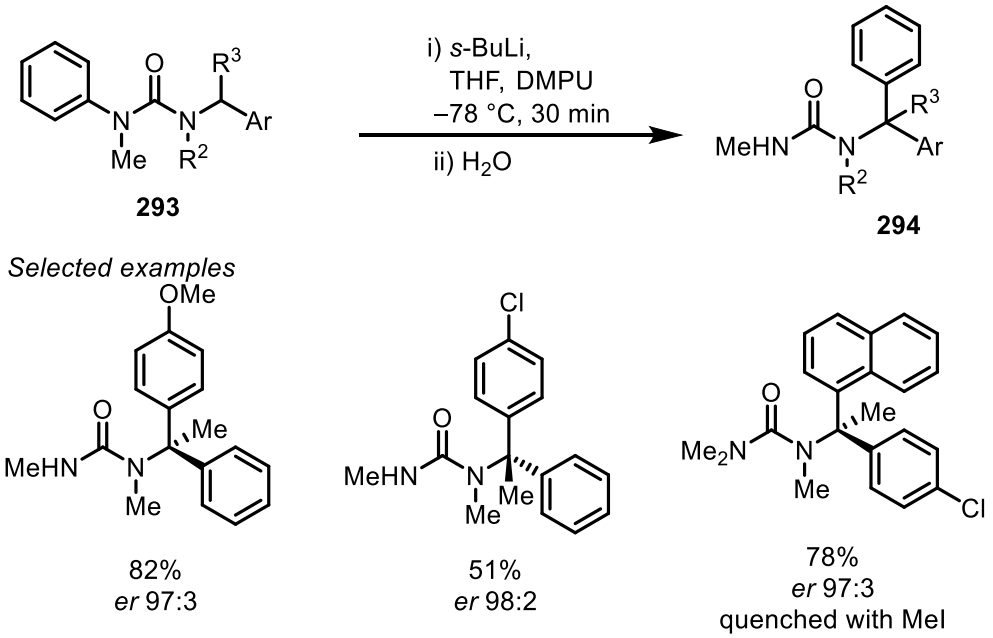


Scheme 82 An electrophile activation promoted Truce-Smiles rearrangement

8.2.2. Clayden Rearrangement

Clayden and co-workers discovered an unprecedented intramolecular aryl migration whilst investigating the lithiation of *N*-benzyl ureas. This has subsequently been developed for lithiated ureas, carbamates and thiocarbamates.[238]

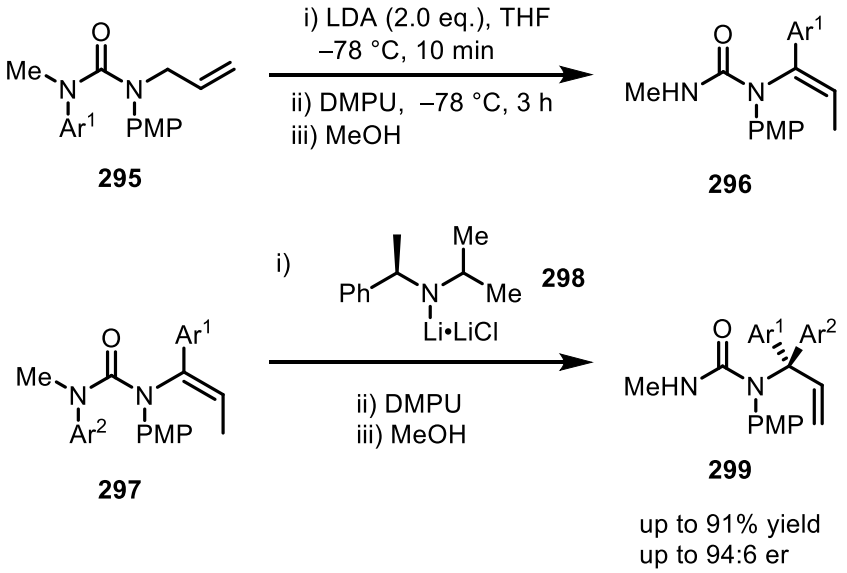
The nitrogen to carbon aryl migration was first observed during the investigation of regiospecific lithiation of ureas **293 (**Scheme 83).[239] Both lithiated benzyl and alkenyl ureas underwent rearrangement to give aminodiaryl-methanes and aminoarylalkyl-methane products **294**. The migration was shown to be stereospecific, and proceed with retention at the carbon centre. However, re-protonation of the carbolithiation intermediate was unselective and overall stereoselectivity depended upon the reaction solvent. Subsequently, α-pyridylation of chiral amines was reported, and the reaction was also applied to cyclic amines.[240-241] Secondary amines (tetrahydroisoquinoline) readily underwent aryl migration under standard conditions whereas addition of DMPU was required to affect benzylic lithiation for the more hindered tertiary amines.



Scheme 83 Benzylic lithiation induced [1,5]-aryl migration of *N*-aryl ureas

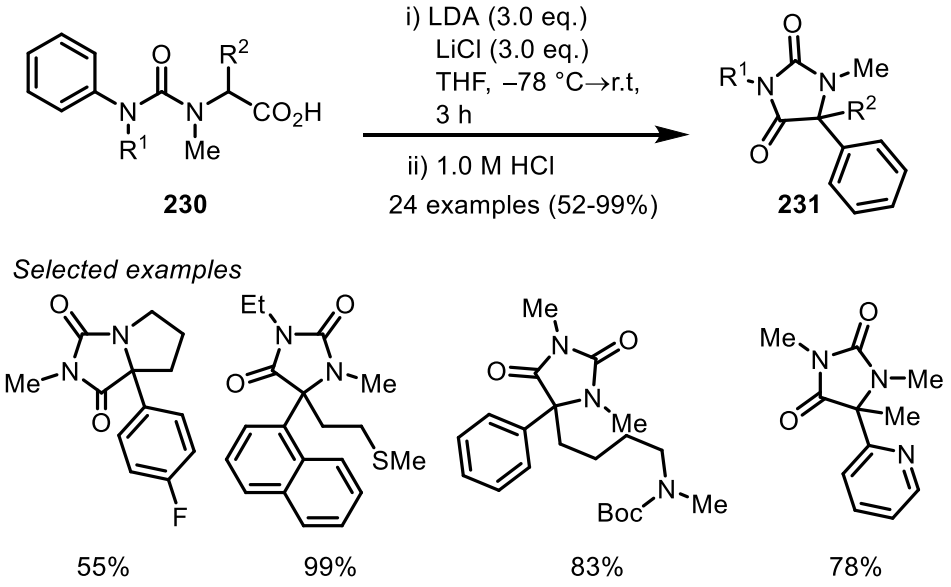
A deprotonation, rearrangement cascade sequence was demonstrated with *N*-allyl ureas **295**, with the double bond moving into conjugated following the rearrangement (Scheme 84).[242] Urea **297** was then formed through palladium catalysed *N*-arylation from which a configurationally-stable, planar, chiral allyl lithium was formed, which underwent aryl migration to give diaryl allyl amines **299**

with excellent *ee*. The rearrangement of *N*-allyl ureas was also reported for the multigram synthesis of 1-arylcycloalkenamines.[243] The direct lithiation Clayden rearrangement has also been applied to proline derivatives,[244] piperidines,[245] and pyrrolines.[245]



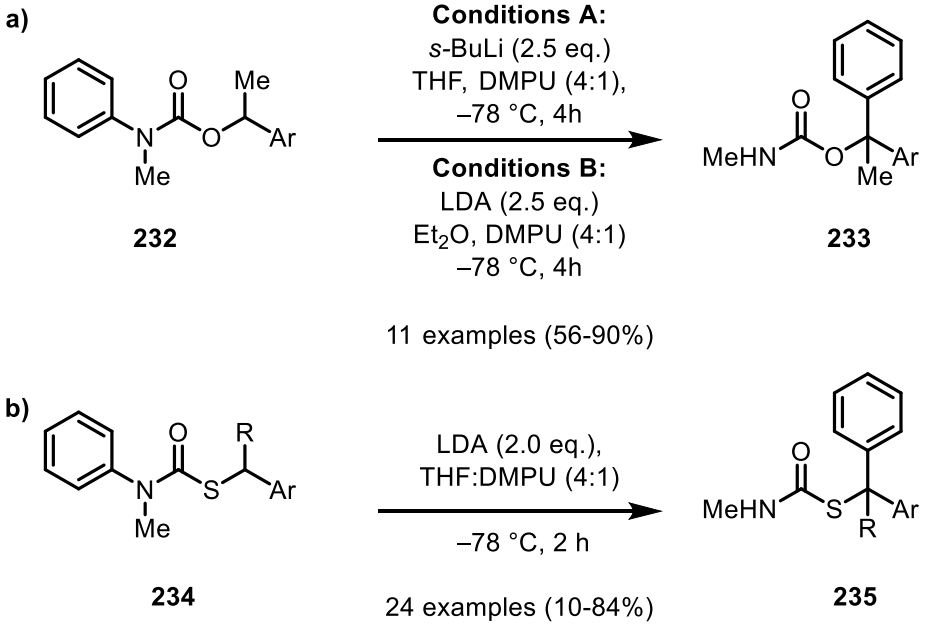
Scheme 84 Allylic lithiation of *N*-aryl ureas and [1,5]-aryl migration

The Clayden rearrangement of urea derivatives of amino acids **230** afforded hydantoin products **231** (Scheme 85). Oxidation of the *N*-PMB protecting group and hydrolysis afforded the desired amino acid derivatives. An asymmetric variant of this methodology, using a chiral auxiliary, was subsequently developed.[246] In addition, Kawabata reported the use of memory of chirality to render the aryl transfer asymmetric.[247]



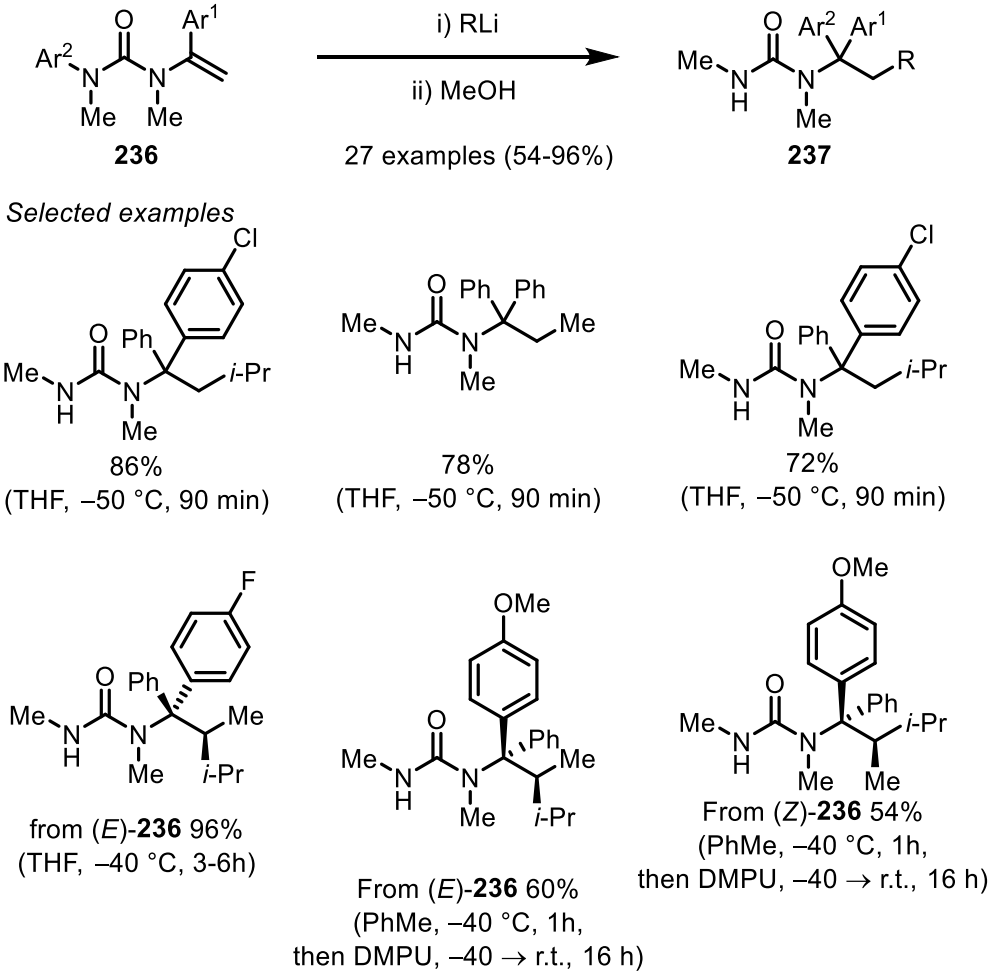
Scheme 85 Lithiation and [1,5]-aryl migration of urea-derived amino-acids

Benzylic lithiation of *N*-aryl carbamates **232** (Scheme 86, a) and thiocarbamates **234** (Scheme 86, b) with a lithium base has also been shown to induce [1,5]-aryl migration.[248-250] With enantioenriched substrates, inversion of configuration was observed for carbamates and retentive migration was observed for thiocarbamates. The transformation has also been extended to *S*-allylic thiocarbamates with similar results.[251]



Scheme 86 [1,5]-aryl migration of *N*-aryl a) carbamates and b) thiocarbamates

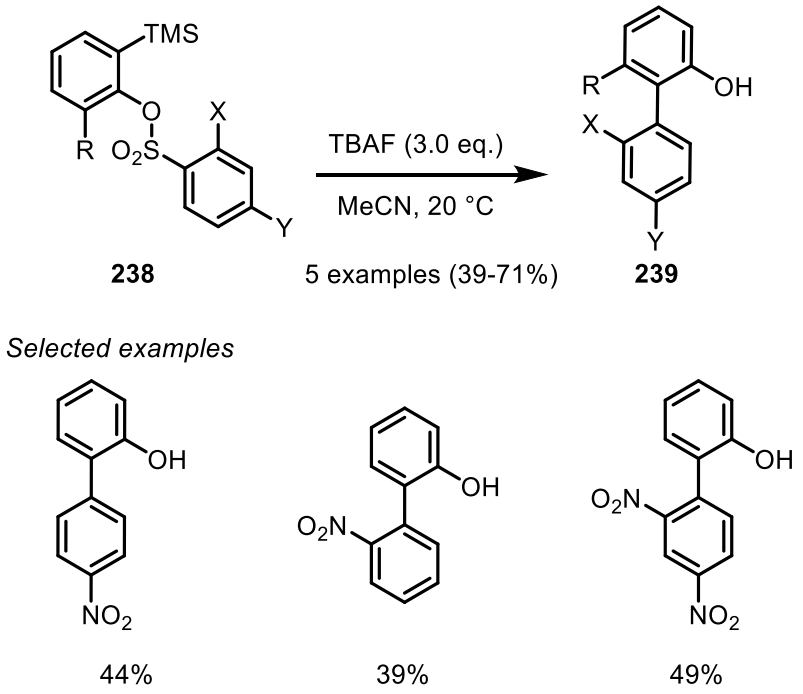
The nucleophilic addition of an organolithium also promotes nitrogen to carbon aryl migration. The tandem *β*-alkylation–*α*-arylation of vinyl ureas **236** was the first example of the formation of two carbon-carbon bonds using the aryl migration of ureas (Scheme 87).[252] Carbolithiation with various alkyl-, alkenyl and aryl-lithiums afforded rearrangement to give product **237**, with an overall *syn* addition to (*Z*)- and (*E*)-alkenes. An enantioselective carbolithiation / aryl migration was developed using (−)sparteine or a (+)sparteine surrogates to prepare enatiomerically-enriched benzyl lithium species.[253] The reaction was successfully extended to carbamates and thiocarbamates, although enantioselective rearrangement was more challenging for these substrates.[254,255,256]



Scheme 87 Tandem alkylation / nitrogen to carbon aryl migration with vinyl ureas

8.2.3. Biaryl Synthesis

The first example of a Truce-Smiles biaryl synthesis was discovered unexpectedly by Weaver.[257] Subsequently, Quayle reported a similarly unanticipated Truce-Smiles rearrangement during their preparation of potential benzyne precursors **238**.[258] The TBAF mediated de-silylation of nitrobenzene sulfonate esters resulted in a desulfonative rearrangement of the aryl anion to afford biaryl phenols **239** (Scheme 88).



Scheme 88 A desulfonative biaryl nitro-phenol synthesis

9. Project Aims

This thesis seeks to explore novel approaches to metal-free arylation and heterocycle synthesis, which are complementary to existing methodology, using the arynes intermediate, the Truce-Smiles rearrangement, and the vicarious nucleophilic substitution of hydrogen.

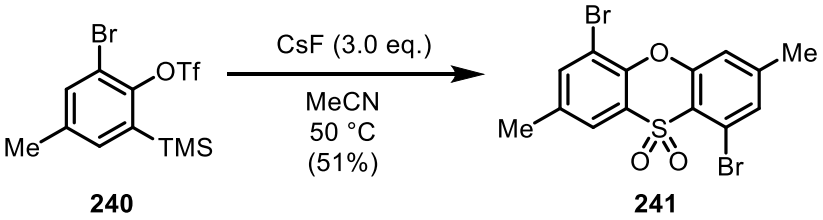
Chapter 1. The synthesis of halogenated phenoxathiin-10,10-dioxides through the tandem reaction of o-trimethylsilyl(aryl) triflates

The following results have been reported in the peer-reviewed journal Chemical Communications.[259]

1. Background

The generation of arynes *via* the fluoride induced decomposition of *o*-trimethylsilyl(phenyl) triflates **53** was first reported by Kobayashi,[260] and has been used extensively for the formation of arynes and strained alkynes under mild and metal free conditions (*vide supra*, pg. 40).

An unexpected product was isolated from the treatment of **240** with fluoride during the development of a palladium catalysed three component coupling of benzyne (Scheme 89).[261] The phenoxathiin-10,10-dioxide **241** was isolated as a single regioisomer and characterised using single crystal X-ray diffraction.[262] Two mechanisms, which both proceed *via* the formation of benzyne, were proposed for the formation of the **241** from *o*-trimethylsilyl(phenyl) triflates **53**.

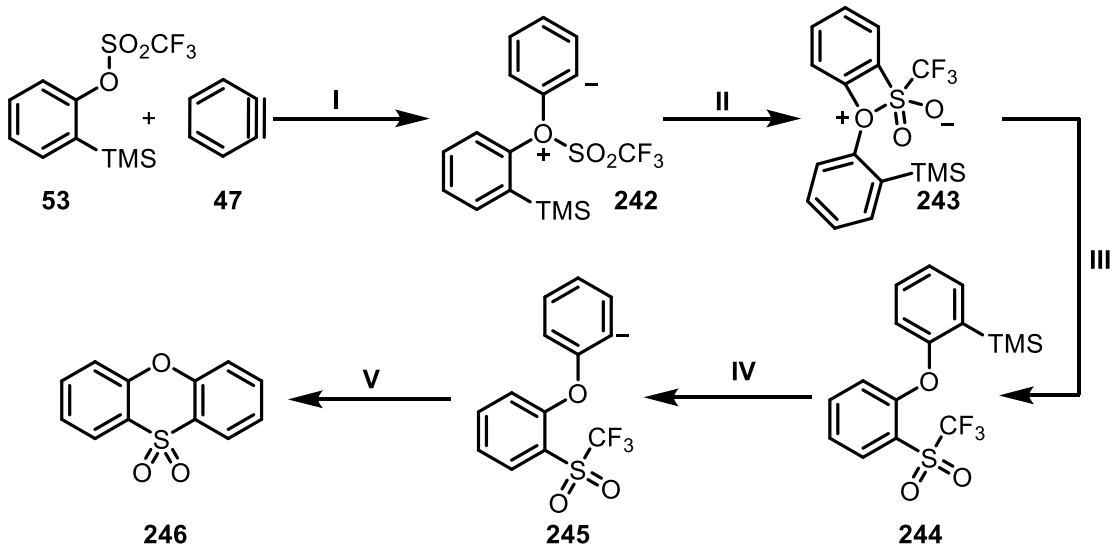


240 **241**

Scheme 89 Initial discovery of phenoxathiin-dioxide formation

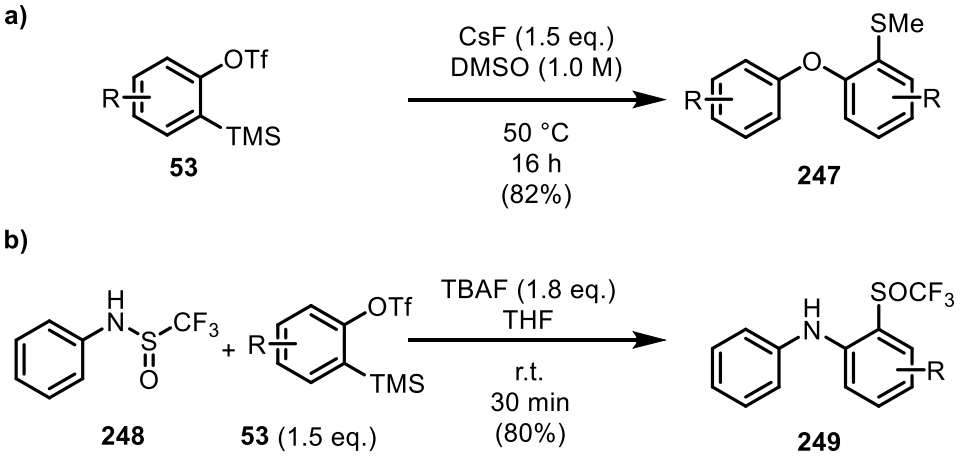
The insertion of benzyne into σ-bonds is well-documented (*vide supra*, pg. 45), and so one potential mechanism involves the insertion of benzyne into the S–O σ-bond of the triflate (Scheme 90). This proceeds *via* nucleophilic attack of **53** onto the

benzyne intermediate **47** (**I**), the formation of a cyclic zwitterion **243** (**II**), and then collapse to afford the 1,2-difunctionalised product **244** (**III**). In this case, the product of σ-insertion could then undergo fluoride-induced desilylation to form an aryl anion **245** (**IV**), which would be followed by cyclisation, with the loss of a trifluoromethyl anion, to afford the final **246** (**V**).



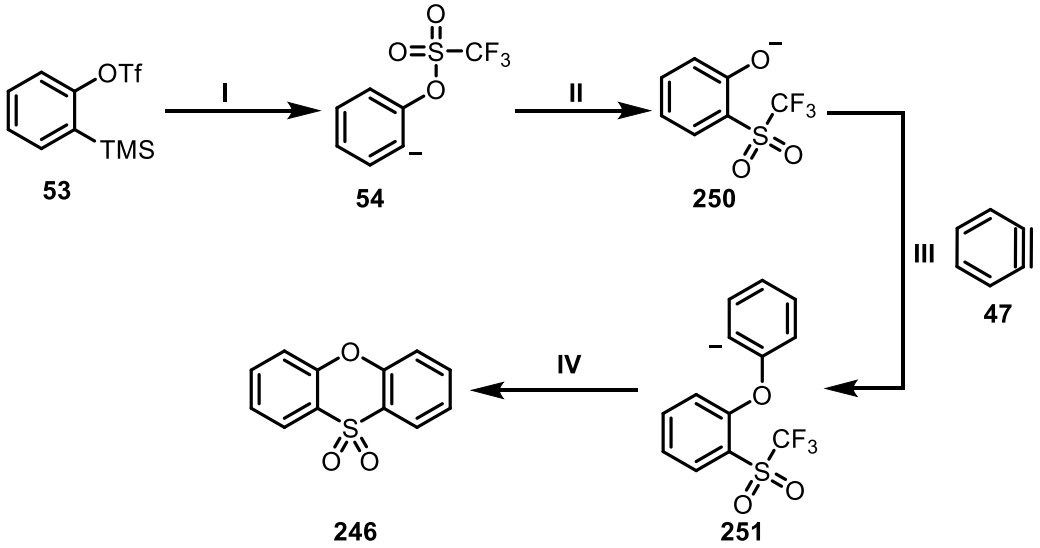
Scheme 90 Phenoxathiin-10,10-dioxide synthesis *via* σ-insertion

The insertion of benzyne into sulfur σ-bonds has been reported for sulfoxides (Scheme 91, a),[263] and sulfonimines (Scheme 91, b).[93] Whilst the oxidation state, and therefore characteristics, of the sulfur atom in **x** is different to that of a sulfonate ester, these examples represent the closest precedent for the σ-insertion mechanism.



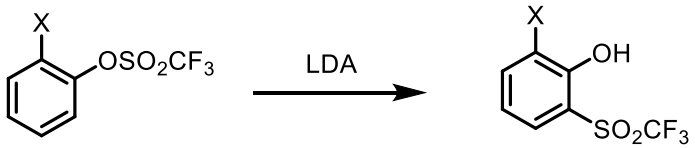
Scheme 91 The σ-insertion of benzyne into the S–X bond of a) sulfoxides and b) sulfonimines

Another possible mechanism arises through a bifurcation in the fluoride induced decomposition pathway of **53** (Scheme 92). The desilylated aryl anion **54** can either undergo an anionic thia-Fries rearrangement (**II**) to form phenoxide **250**, or elimination to form benzyne **47**. These two products then recombine (**III**) which results in the formation of the aryl anion **251** and then cyclise (**IV**), to afford **246** with concomitant loss of the trifluoromethyl anion. The annulative reactions of arynes are well established (*vide supra*, pg. 47).



Scheme 92 Phenoxathiin-dioxide synthesis *via* a thia-Fries rearrangement

The anionic thia-Fries rearrangement was first reported by Lloyd-Jones,[264] although it is possible that the rearrangement has been over-looked in the past.[265-266] It was concluded that the degree of metalation of the haloaryl trifluoromethylsulfonate **252** dictated whether rearrangement to afford phenol **253** (Scheme 93) or aryne-forming elimination occur.[267] The reaction mechanism was also elucidated through a series of labelling studies and determined to proceed *via* an intramolecular oxygen to carbon transfer of the trifluoromethylsulfonate group.



252 **253**

Scheme 93 Lloyd-Jones anionic thia-Fries rearrangement

The absence of any reports of this unusual transformation, despite the large body of literature available pertaining to the generation of benzyne from *o*-trimethylsilyl(aryl) triflates, prompted us to investigate the reaction further.

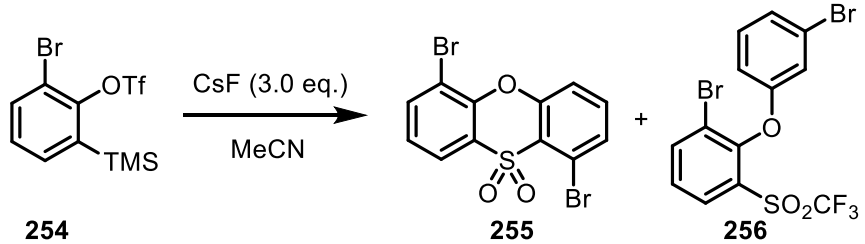
2. Results & Discussion

Conditions for the reaction were optimised and the scope of the reaction was established. Then experiments to probe the mechanism of the reaction were performed.

1.1. Optimisation

Investigation of the conditions for a simplified model substrate **254** (Table 2) revealed that longer reaction times or elevated temperatures were required for complete consumption of the *o*-trimethylsilyl(phenyl) triflate. However, at higher temperatures (Table 2, entries 5) phenoxathiin-dioxide **255** was recovered as an unseparated mixture with triflone **256**.

Table 1 The screening of reaction conditions for the synthesis of 255



254 **255** **256**

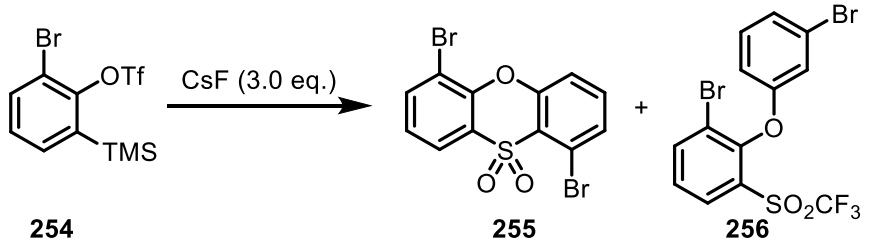
Entry[a]	Time / h	Temp / °C	255 / %[b]
1	4	r.t.	21
2	4	r.t.	20 (43[c])
3	16	r.t.	14
4	24	r.t.	43
5	4	60	47[d]

[a]Conditions: **254** (0.5 mmol), cesium fluoride (1.5 mmol), acetonitrile (2.0 mL); [b]Isolated yield; [c]recovered **254**; [d]Isolated with uncyclised product **256**

Performing the reaction in toluene gave no product (Table 2, entry 10), but by using mixtures of acetonitrile and toluene the yield was improved (Table 2, entry 4). The addition of toluene to the reaction reduces the solubility of cesium fluoride in solution, which can be used to modulate the generation of benzyne.[146] The best

conditions were found to be a 3:1 ratio of acetonitrile:toluene, and using an extended reaction time of 24 hours (Table 2, entry 6).

Table 2 Screening solvent mixtures for the synthesis of 255



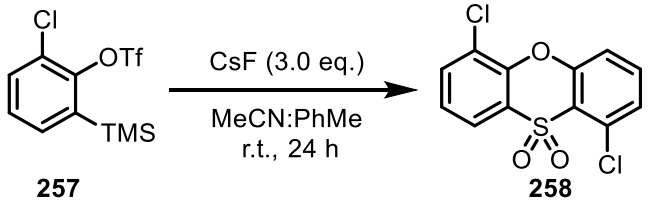
254 **255** **256**

Entry[a]	MeCN:PhMe	Time / h	Temp / °C	255 / %[b]
1	0:1	4	r.t.	0 (60[c])
2	1:1	4	r.t.	9 (27[c])
3	1:1	16	r.t.	25
4	3:1	24	r.t.	60
5	1:1	24	r.t.	51
6	1:3	24	r.t.	40
7	1:1	4	60	48[d]

[a]Conditions: **252** (0.5 mmol), cesium fluoride (1.5 mmol); [b]Isolated yield; [c]recovered starting material; [d]Isolated with uncyclized product **256**

Solvent mixtures were also explored for 2-chloro-6-(trimethylsilyl)phenyl trifluoromethanesulfonate **257** (Table 3). Optimal conditions were identified with a 3:1 mixture of acetonitrile:toluene (Table 3, entry 2).

Table 3 Investigation of solvent effects for the synthesis of 258



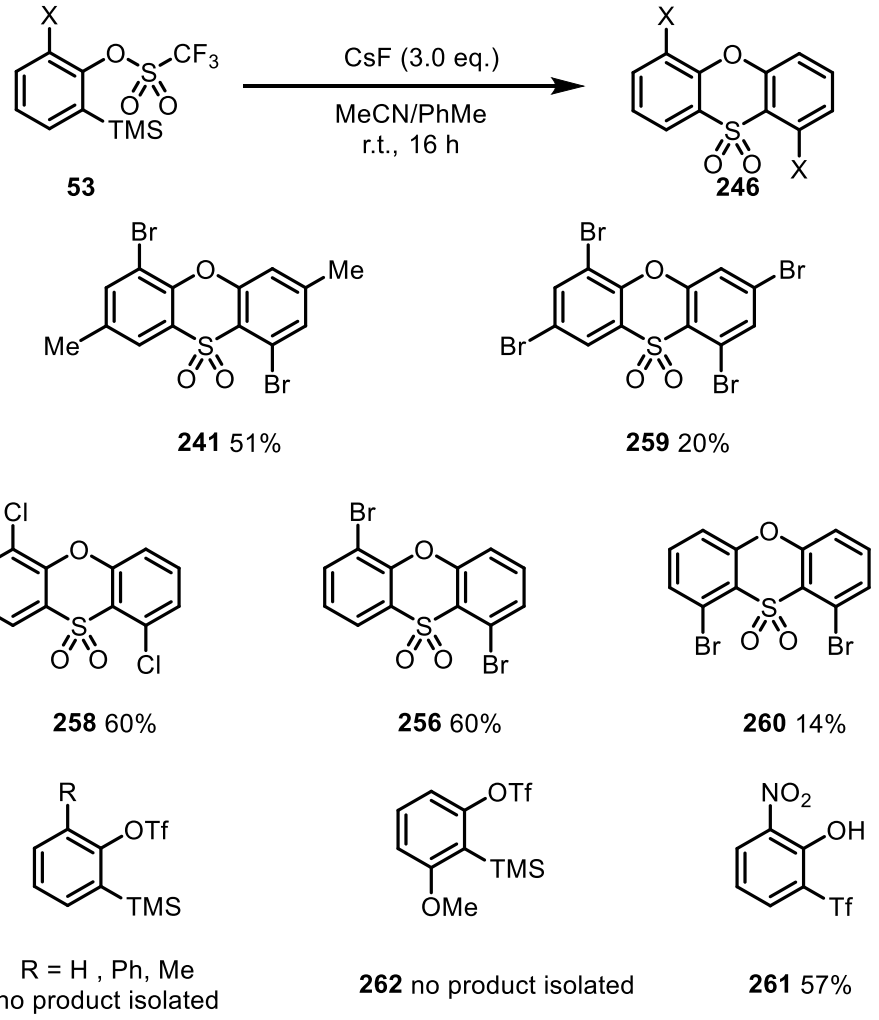
257 **258**

Entry[a]	MeCN:PhMe	258 / %[b]
1	1:0	46
2	3:1	60
3	1:1	55
4	1:3	0
5	0:1	0

[a]Conditions: **257** (0.5 mmol), cesium fluoride (1.5 mmol), r.t., 24 h; [b]Isolated yield

1.2. Substrate Scope

The scope of the reaction was then examined (Scheme 94). The additional bromine atoms in **259** reduced the reaction efficiency and when the halogen was *meta* to the triflate (as opposed to *ortho*), only a trace amount of the symmetrical phenoxathiin-dixoide **260** was observed. The product was not detected for substrates which lacked an *ortho*-halogen. Simple hydrogen substitution afforded an intractable reaction mixture, from which no phenoxathiin-10,10-dioxide could be isolated. Finally, the *ortho* nitro substituent lead to the formation of phenol **261**.



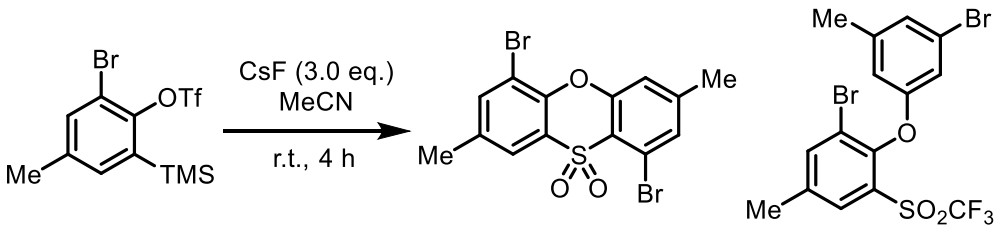
Scheme 94 The scope of the phenoxathiin-dioxide synthesis

These results indicate than an electron withdrawing effect within the σ-framework is responsible for causing the unusual reactivity of *o*-trimethylsilyl(phenyl) triflates. The lack of reactivity for substrate **262** was a result of ineffective de-silylation, and the starting material was recovered cleanly.[268]

1.3. Mechanistic considerations

When the reaction was performed for a shorter reaction time at ambient temperature, **241** was isolated in a lower yield (44%) along with triflone **263** (8%) (Scheme 95). The uncyclized triflone is formed through protonation of an aryl anion intermediate, which can be formed through either of the proposed mechanisms (*vide infra*). The

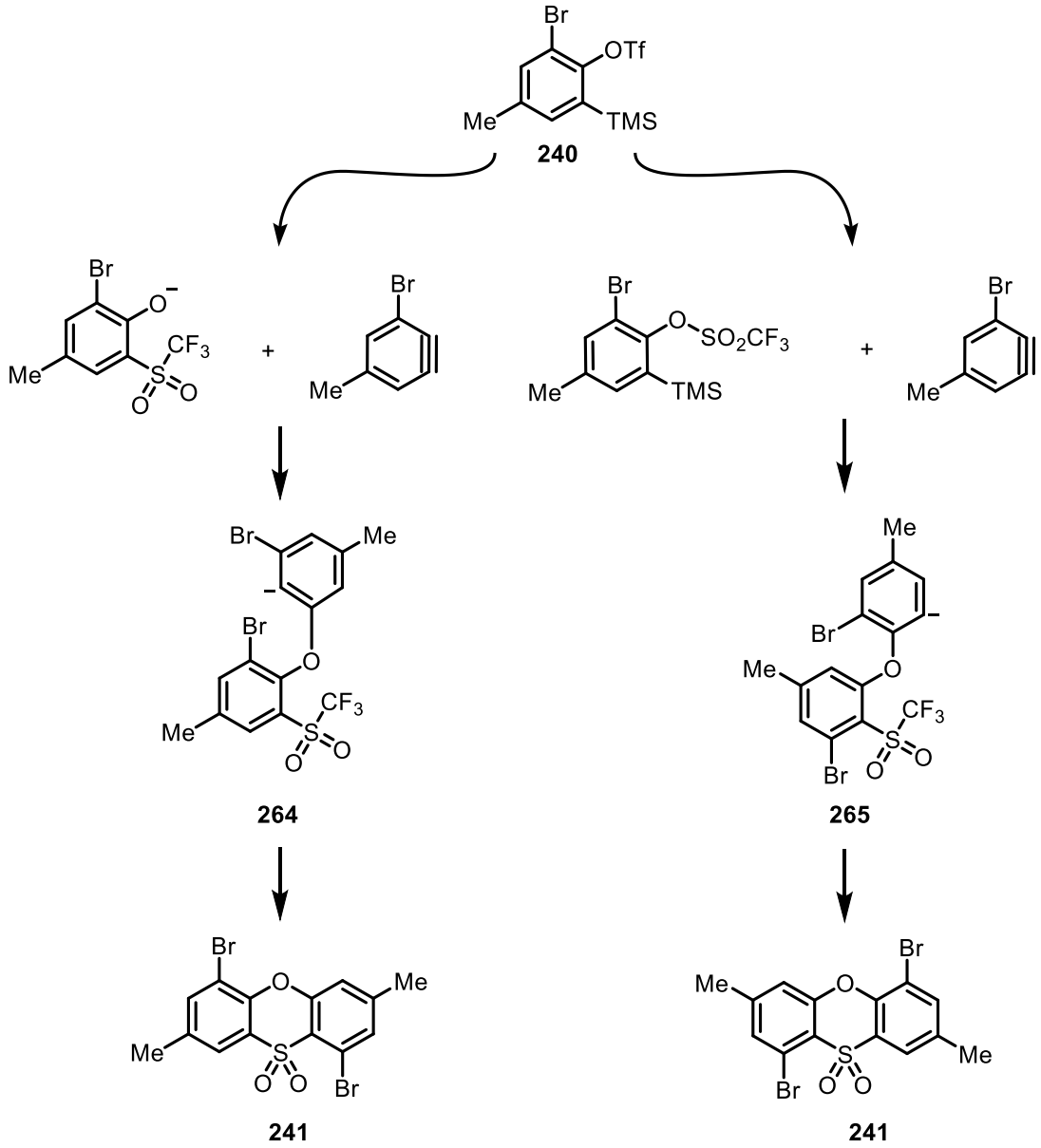
substitution pattern of **263** was established through careful analysis of NMR spectra of the isolated material.



240 **241** (44%) **263** (8%)

Scheme 95 The isolation of an uncyclized product

The consideration of the two proposed mechanisms and comparison to the isolated uncyclized triflone **263** provides further evidence for the reaction pathway (Scheme 96). Triflone **263** is derived from the protonation of intermediate **264** on the pathway **241**. Whereas the intermediate **265** is formed *via* the σ-insertion reaction and would afford a regiosomeric triflone.

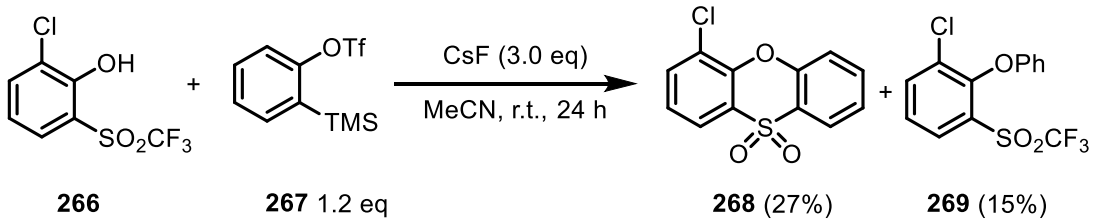


Scheme 96 The proposed mechanism of the phenoxathiin-dioxide synthesis with intermediates

Isolation of phenol **261** verifies that an anionic thia-Fries rearrangement is possible for these substrates. The electron-withdrawing capacity of the nitro-substituent decreases the nucleophilicity of the phenol **261** such that no attack of the benzyne intermediate occurs, and so none of the phenoxathiine-10,10-dioxide is formed.

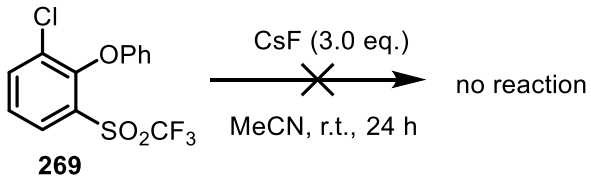
The phenol **266**, an intermediate on the proposed thia-Fries rearrangement pathway, was synthesised in order that further mechanistic investigation could be performed. Under the standard reaction conditions, this phenol was demonstrated as capable of

nucleophilic attack onto benzyne giving both **268** and the uncyclised triflone **269** (Scheme 97).



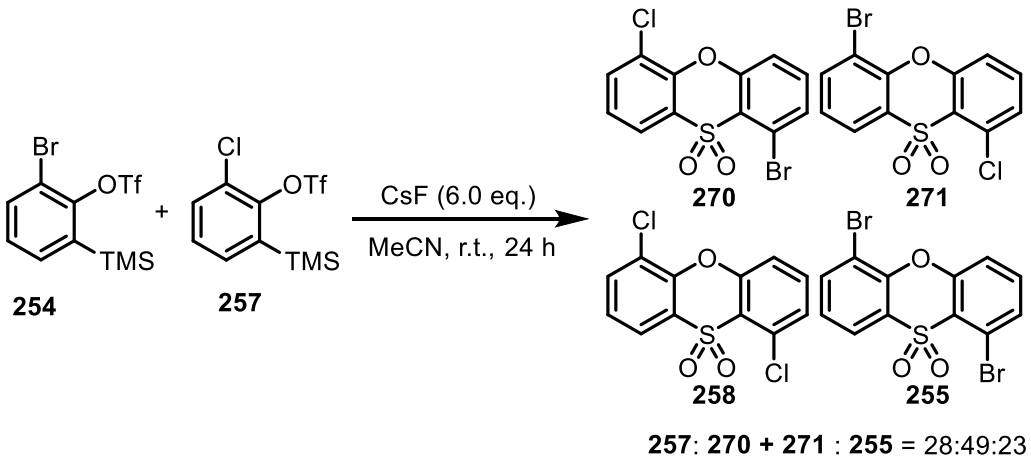
Scheme 97 Reaction of a proposed intermediate with benzyne

Exposing the uncyclised product **269** to fluoride gave no reaction, indicating that the protonated product is insufficiently nucleophilic to promote the displacement of the trifluoromethyl group (Scheme 98).



Scheme 98 The reactivity of the uncyclised product under the reaction conditions

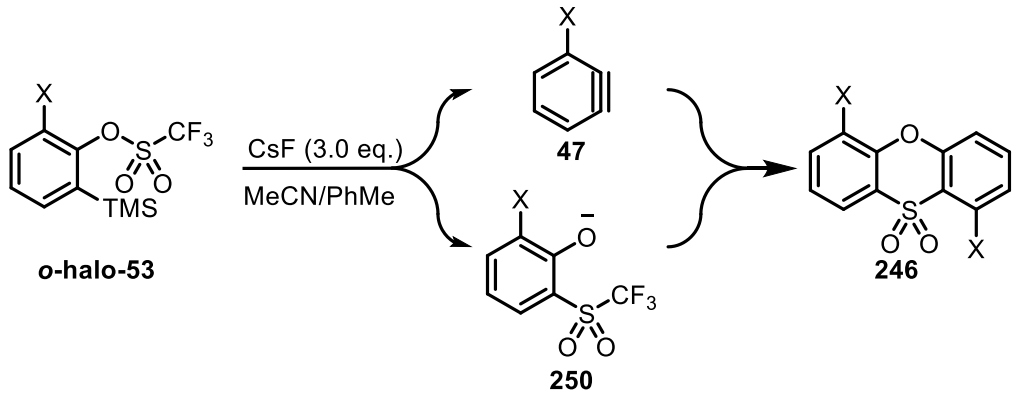
A cross-reaction with two different aryne precursors **254** and **257** in one pot was carried out. Analysis of the products by GCMS confirmed a statistical mixture of products supporting the proposed dual mode of reactivity of the starting *o*-trimethylsilyl(aryl) triflates (Scheme 99).



Scheme 99 The cross-reaction of two *o*-halo(trimethylsilyl)aryl triflates

3. Conclusion

The mechanism of this unusual reaction of the *o*-trimethylsilyl(aryl) triflates consists of a bifurcation in the fluoride-induced decomposition of the starting material along two pathways: aryne formation and thia-Fries rearrangement. The two products then recombine to afford the final phenoxathiin-10,10-dioxide product (Scheme 100).



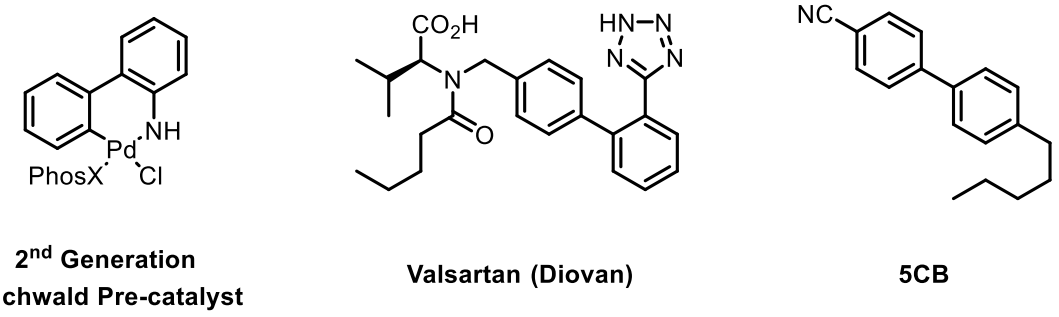
Scheme 100 Bifurcation in decomposition of *o*-haloaryne precursors leads to phenoxathiin-dioxide formation

Chapter 2. A Truce-Smiles Benzyne Biaryl Synthesis

The following results were obtained with assistance of S. M. A. Sohel and have been reported in within the peer-reviewed journal Angewandte Chemie.[269]

1. Background and Aims

The biaryl structural motif is a ubiquitous structure in applied organic chemistry, present in catalysts systems, bioactive compounds, and organic materials (Figure 2). These structures are typically formed using a variation on the transition metal cross-coupling methodology which was awarded a Nobel Prize in 2010. Whilst this methodology is widely employed, the requirement for more sustainable practices in synthetic organic chemistry has driven investigation into "metal-free" methodology.



2nd Generation Buchwald Pre-catalyst | **Valsartan (Diovan)** | **5CB**

Figure 2 Functional organic molecules containing the biaryl structural motif

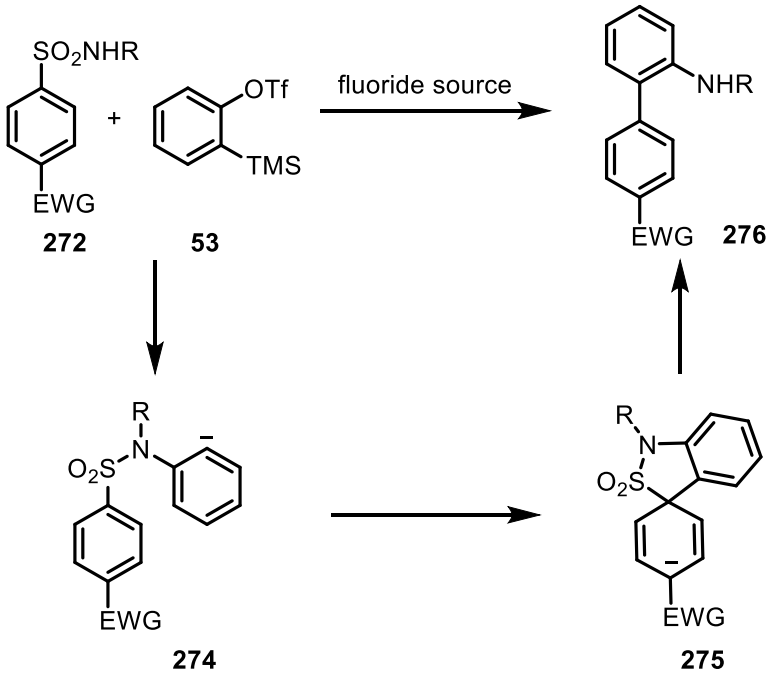
In recent years, a focus of synthetic organic research has been on methodologies for the formation of biaryls which mimic the cross-coupling disconnection without recourse to transition metals (*vide supra*, pg. 17). Many of these approaches rely on an excess of one reagent,[19, 35] or have a substrate scope limited to electron-rich arenes.[19, 23, 46] We were interested in developing a new metal-free biaryl synthesis which complements established work.

In the absence of a transition metal catalyst, the generation of a reactive aryl intermediate (e.g. aryl radical, aryl cation, aryl anion, dearomatisation) facilitates the

formation of the requisite Csp^2–Csp^2 bond. The benzyne reactive intermediate was of interest, as it provides access to two highly reactive species (benzyne and an aryl anion) under mild reaction conditions.

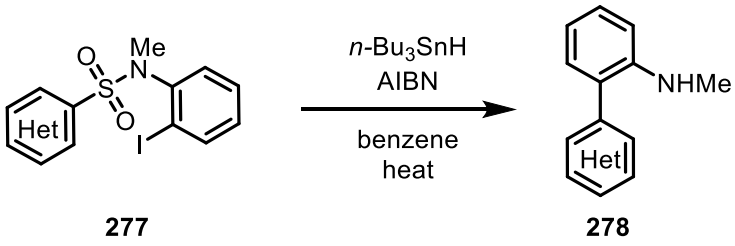
The formation of biphenyl was one of the first reported reactions of the benzyne intermediate, and many methodologies which use this reactive intermediate to make biaryls have since been developed (*vide supra*, pg. 54). The preparation of biaryls with benzyne generally requires organometallic reagents or metal catalysts to form a nucleophilic arene which can add to the electrophilic aryne. Despite the widespread use of mild, metal-free methods of generating arynes (*vide supra*, pg. 64), few metal-free methods have been disclosed for the benzyne-meditated preparation of biaryls that are not contained within an extended ring system.

An alternative approach is to capture the aryl anion, formed through the addition of a nucleophile to an aryne, with an electrophilic arene.[162] We proposed that the addition of an electron-poor *S*-aryl sulfonamide **272** to benzyne would form an intermediate aryl anion **274** which could undergo a desulfonative Truce-Smiles rearrangement (*vide supra*, pg. 82), at the *ipso*-position of the sulfonamide arene **275**, to form the biaryl axis **276** (Scheme 101).



Scheme 101 The proposed benzyne Truce-Smiles biaryl synthesis

Inspiration has been derived from Motherwell's radical mediated desulfonative intramolecular synthesis of biaryls **278** from sulfonamides **277** (Scheme 102);[270-271] a radical form of the Truce-Smiles rearrangement. An intramolecular biaryl synthesis from sulfonate esters was reported by Quayle during the course of this work (*vide supra*, pg. 96).[258]

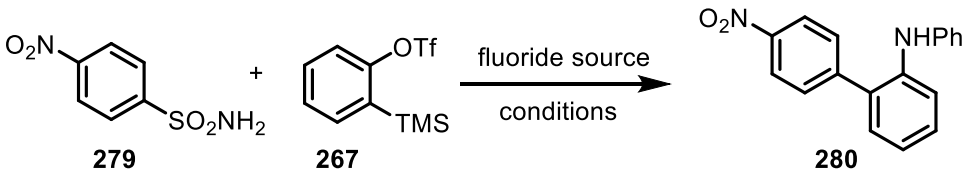


Scheme 102 Inspiration for a Truce-Smiles biaryl synthesis

2. Identification and optimisation of reaction conditions

Initial reaction conditions were based upon the sulfonamide *N*-arylation method developed by Larock.[77] Various sources of fluoride, commonly used for the generation of benzyne from *o*-trimethylsilyl(phenyl) triflates, were screened for the reaction of **279** and **267** in THF, MeCN and DME (Table 4). Solutions of TBAF invariably contains traces of water which could quench the requisite aryl anion,[272] and reduce the efficiency of the reactions, therefore, CsF and KF were used as sources of fluoride. The preliminarily tested reaction conditions revealed that the proposed transformation was feasible, and the biaryl amine **280** product was isolated and characterised. The product was not a primary 2-amino biphenyl, but rather *N*-phenyl-2-amino biphenyl resulting from reaction with a second equivalent of benzyne. KF, with 18-crown-6, was selected as a source of fluoride (Table 4, entry 4).

Table 4 Preliminary screening of reaction conditions with 279 and 267



279 **267** **280**

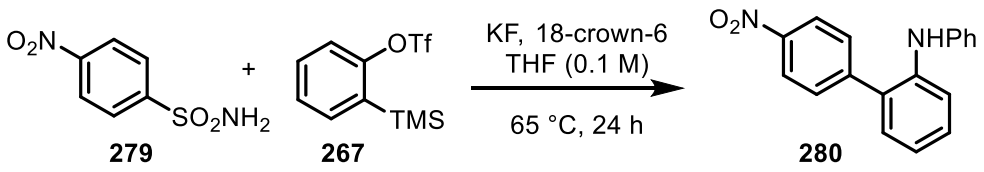
Entry[a]	Fluoride	Fluoride eq.	Solvent	280 / %[b]
1	CsF	2	MeCN	16
2	CsF	2	DME	0
3	KF, 18-c-6	4	THF	31
4	KF, 18-c-6	4	DME	34

[a]Conditions, 4-nitrobenzene sulfonamide (0.2 mmol), *o*-trimethylsilyl(phenyl) triflate (0.1 mmol), solvent (0.1 M), 16 hours, r.t., [b]Isolated yields

Increasing the amount of fluoride, at an elevated temperature, corresponded to an improved yield (Table 5, entries 1 to 4). There are two possible roles for the fluoride anion: as a nucleophile to activate the benzyne precursor and as a mild base. Four

equivalents (with respect to the sulfonamide) gave a respectable 70% yield (Table 5, entry 3), but further increasing this to 6 equivalents (Table 5, entry 4) did not improve the yield. The optimisation was therefore continued with 4 equivalents of KF and 18-crown-6.

Table 5 Equivalents of fluoride



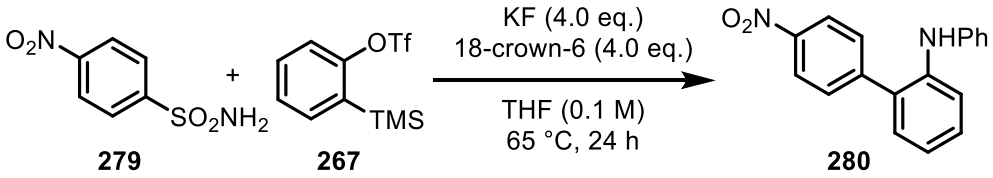
279 **267** **280**

Entry[a]	Fluoride eq.	280 / %[b]
1	2	44
2	3	62
3	4	70
4	6	70

[a]Conditions: 4-nitrobenzene sulfonamide (0.1 mmol), *o*-trimethylsilyl(phenyl) triflate (0.2 mmol), KF, 18-crown-6, THF (0.1 M), 65 °C, 24 h; [b]Isolated yield

The yield of the reaction was not significantly improved by using either reactant in excess (Table 6), therefore optimisation was continued with stoichiometric reactants. This is notable in comparison to the frequent requirement for an excess of one reagent which is required in the current metal-free arylation literature.

Table 6 Reactant equivalents



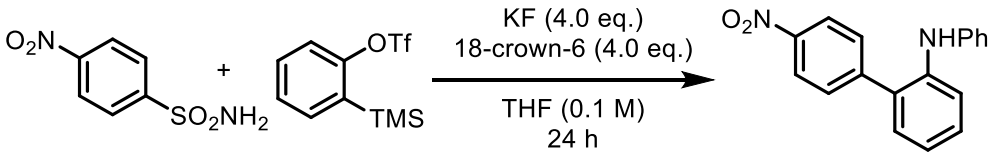
279 267 280

Entry[a]	267 eq.	280 / %[b]
1	1.3	61
2	1.6	60
3	2	70
4	3	72
5	5	71

[a]Conditions: 4-nitrobenzene sulfonamide (0.1 mmol), *o*-trimethylsilyl(phenyl) triflate, KF (4.0 eq.), 18-crown-6 (4.0 eq.), THF (0.1 M), 65 °C, 24 h; [b]Isolated yield, with respect to limiting reagent.

A comparison of the product yields at various temperatures revealed that increasing the temperature to just below the boiling point of THF (65 °C, b.p. 66 °C) was optimal (Table 7, entry 3).

Table 7 Effect of temperature on product yield.



279 267 280

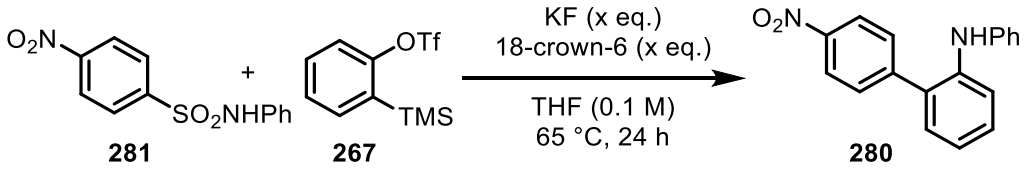
Entry[a]	Temperature / °C	280 / %[b]
1	20	31
2	50	63
3	65	70
4	70	62
5	110	51

[a]4-nitrobenzene sulfonamide (0.1 mmol), *o*-trimethylsilyl(phenyl) triflate (0.2 mmol), KF (4.0 eq.), 18-crown-6 (4.0 eq.), THF (0.1 M), 24 h [b]Isolated yield

The product of this reaction is a secondary amine, with two equivalents of aryne having been consumed. The starting sulfonamide was changed to *N*-phenyl-4-nitrobenzenesulfonamide **281** to improve the efficiency and scope of the reaction,

and a rapid screen of reaction conditions (Table 8) was conducted. An excess of *o*-trimethylsilyl(phenyl) triflate afforded the highest yields (Table 8, entries 1 and 2), however using a 1:1 ratio with 3 equivalents of KF and 18-crown-6 afforded a similar yield of 63% (Table 8, entry 6). With these optimal reaction conditions in hand, we set out to establish the scope of the transformation.

Table 8 Optimisation of reaction with *N*-phenyl-4-nitrobenzenesulfonamide

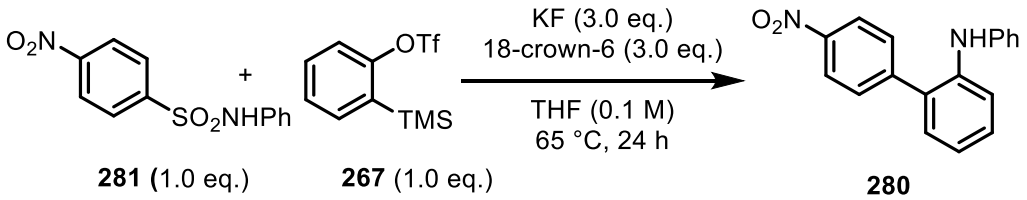


Entry[a]	281:267	KF eq.	280 / %[b]
1	1:2	2	66
2	5:4	2	65
3	1:1	2	54
4	6:5	2	51
5	2:1	2	31
6	1:1	3	63
7	1:1	4	59

[a]4-nitrobenzene sulfonamide (0.1 mmol), *o*-trimethylsilyl(phenyl) triflate (0.2 mmol), KF, 18-crown-6, THF (0.1 M), 65 °C, 24 h [b]Isolated yield with respect to the limiting reagent

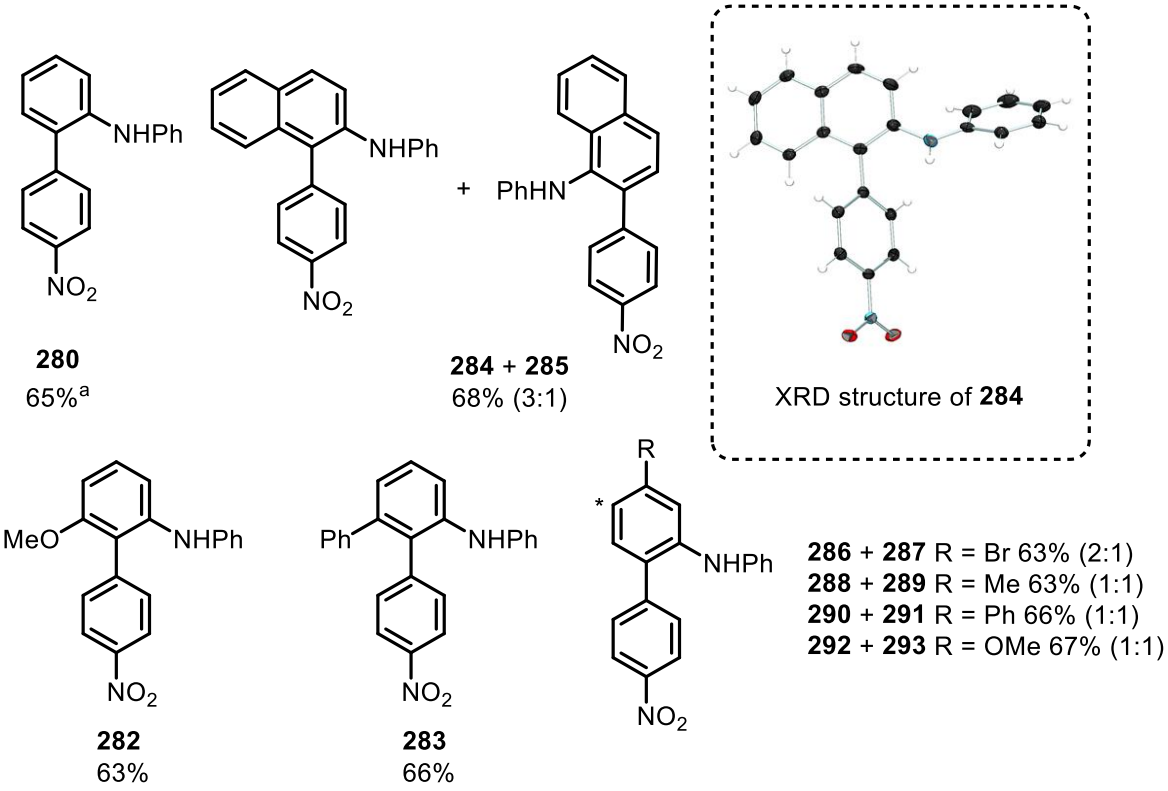
2. Substrate scope

The optimised reaction conditions were then tested with a range of *o*-trimethylsilyl(aryl) triflates (Scheme 103), and it was found that the yields of these reactions were distributed over a narrow range (Scheme 104, 63–68%). This indicates that the substitution on the aryne has little influence on the rate determining step of the reaction.[273]



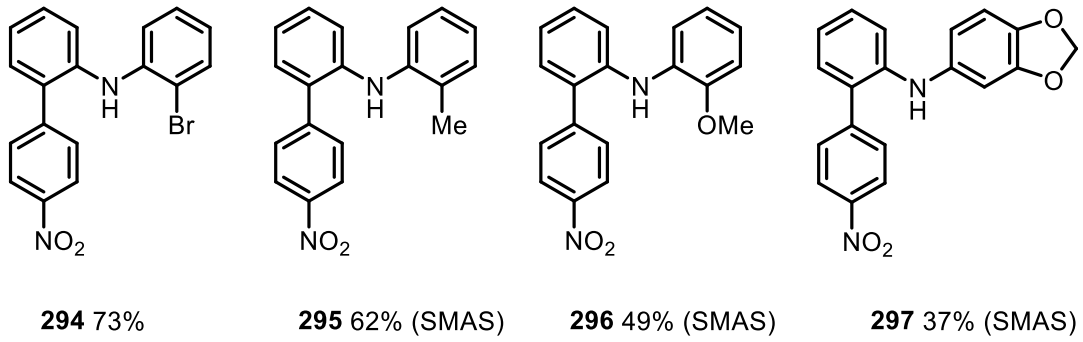
Scheme 103 The optimised reaction conditions for the benzyne Truce-Smiles biaryl synthesis

Arynes which are unsymmetrically substituted lead to a mixture of regiosomeric products, in the absence of a distortion effect.[274] The 2-methoxy aryne afforded the expected single regioisomer of **282** and 2-phenyl aryne afforded a single regioisomer of **283**. 1,2-Napthyne gave a 3:1 mixture of **284** and **285**, and the 3-bromo aryne a 2:1 mixture of **286** and **287**. The regioselectivity of 2-methoxy aryne and 1,2-napthyne are well documented, but not the 3-bromo or 2-phenyl arynes. A survey of the literature indicated 3-halo aryne regioselectivity lies in the region of 1:1.3 to 1:1.6, with an outlier of 1:5 for 3-chloro aryne reported by Werz.[275] In the case of 2-phenyl arynes, selectivity for a single regioisomer was observed in two cases,[276-277] but an 84:16 mixture for the synthesis of aryl stannanes is reported by Kazmaier.[278] Regioisomers were isolated unseparated, except in the case of the naphthalene products **284** and **285**. An XRD structure of **284** was obtained to verify the identity of the major product.[279]



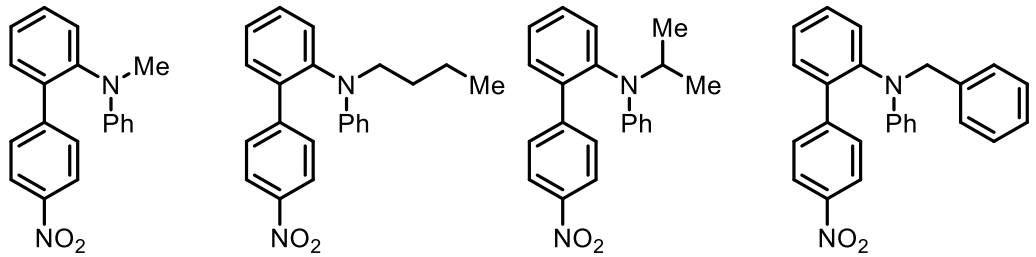
Scheme 104 Scope of biaryl synthesis with respect to arynes, *location of substitution in regioisomer

Our attention then turned to the sulfonamide substitution, on both the *S*-arene and the nitrogen (Scheme 105).[280] The *o*-bromo *N*-aryl substituent **294** was more efficient than *o*-methyl **295** or *o*-methoxy **296**, this could feasibly be a consequence of electronic or steric factors. However, the low isolated yield of substrate **297** indicates that electron-donating substituents do inhibit the reaction. This is a consequence of either stabilisation of the initial sulfonamido-anion nucleophile or improved stabilisation of the amido-anion following the Truce-Smiles rearrangement.



Scheme 105 Scope of the reaction with respect to *N*-aryl substituents. Initials indicate specific synthetic contributions by S. M. A. Sohel

The *N*-alkyl sulfonamides gave a different reaction product, in which the secondary biaryl amine product was *N*-arylated by a second equivalent of aryne. Two equivalents of *o*-trimethylsilyl(phenyl) triflate were used in the reaction to compensate for the decreased yields. Increasing the substituent size from methyl **298** to *n*-butyl **299** to *i*-propyl **300** further decreased the yield. The *N*-benzyl group also afforded a modest yield of the tertiary amine product **301**.

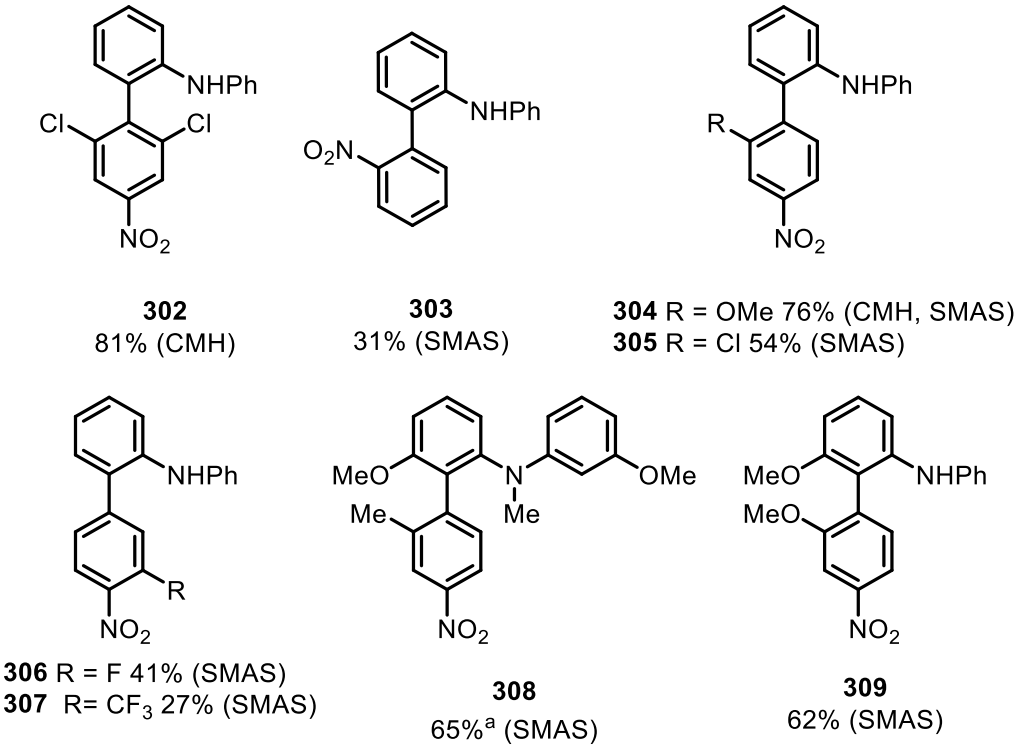


298 58% **299** 42% **300** 31% **301** 45%

Scheme 106 Scope of the reactions with respect to *N*-alkyl substituents

Substitution of the *S*-arene was then investigated for nitrobenzene sulfonamides (Scheme 107). The 2,6-dichloro-4-nitrobenzene substrate gave an excellent 88% yield of **302**, potentially due to better stabilisation of the negative charge of the Meisenheimer intermediate. However, the 2-chloro-4-nitrobenzene sulfonamide gave a lower yield of **305** that the unchlorinated substrate and 2-methoxy-4-nitrobenzene sulfonamide a greater yield of **304**, indicating that steric acceleration may also contribute to the improved yield – a consequence of steric crowding about the spirocyclic Meisenheimer intermediate. The 2-nitrobenzene substrates gave poorer yields of **303** than the 4-nitrobenzene substrate.[281] A bulky CF_3 group in **307**, *ortho* the activating nitro group, significantly hindered the reaction. This result is attributed to interruption of the coplanar arrangement formed between the nitro group and the aromatic ring. One notable facet of this transformation is the efficient formation of highly hindered and unsymmetrical biaryls. The two examples with 2,2',6-

substitution **308** and **309** were determined to be axially chiral, through separation of the two isomers by chiral stationary phase HPLC.[282]



302
81% (CMH)

303
31% (SMAS)

304 R = OMe 76% (CMH, SMAS)
305 R = Cl 54% (SMAS)

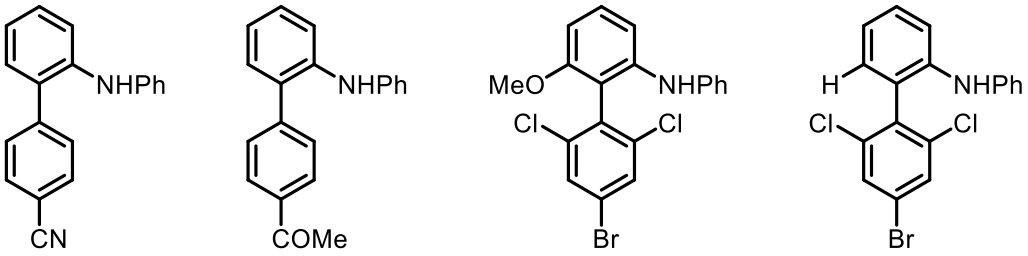
306 R = F 41% (SMAS)
307 R= CF_3 27% (SMAS)

308
65%[a] (SMAS)

309
62% (SMAS)

Scheme 107 Scope of the biaryl synthesis with respect to nitrobenzene sulfonamides

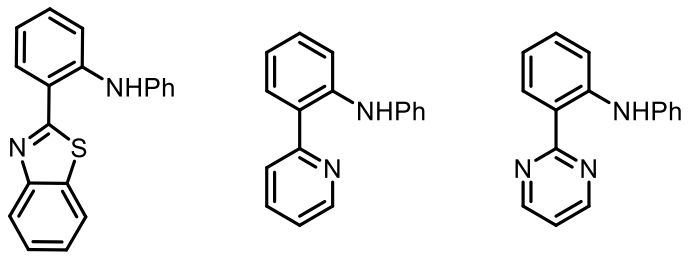
At this stage, a limitation of the method was the requirement for a nitro-substituted sulfonamide. To expand the scope of the reaction beyond nitrobenzene sulfonamides, we began to explore alternative anion-stabilising substituents (Scheme 108). The *p*-nitrile and *p*-keto substituted sulfonamides were viable substrates, albeit with a decrease in yield in the case of the *p*-nitrile **310**. Substitution with three halogens was sufficient to activate the sulfonamide to rearrangement to afford **312** or **313**, but 4,5-dichlorobenzene gave a poor yield (<20%), and the *p*-chloride or *p*-bromide afforded only *N*-arylated sulfonamide products.



310 50% (CMH) **311** 69% (CMH) **312** 74% (SMAS) **313** 88% (SMAS)

Scheme 108 Scope of the biaryl synthesis with respect to differentially substituted sulfonamides

Then the substrate scope was expanded to include *S*-heteroaryl sulfonamides due to inspiration from the classical Julia-Kocienski olefination, which proceeds *via* a Smiles (*S* to *O* aryl transfer) rearrangement.[283-284] Stabilisation of the intermediate anion could feasibly be achieved by several π-deficient heterocycles. Two synthetic approaches were used: Willis' DABSO method from metallated heteroarenes,[285] and oxidation of the commercially available mercaptan. However, only three sulfonamides (benzothiazole, pyridine and pyrimidine) were successfully synthesised. The *S*-heteroaryl sulfonamides were subjected to the standard reaction conditions, affording the corresponding hetero-biaryl amines **314**, **315**, and **316** in moderate to good yields (Scheme 109).

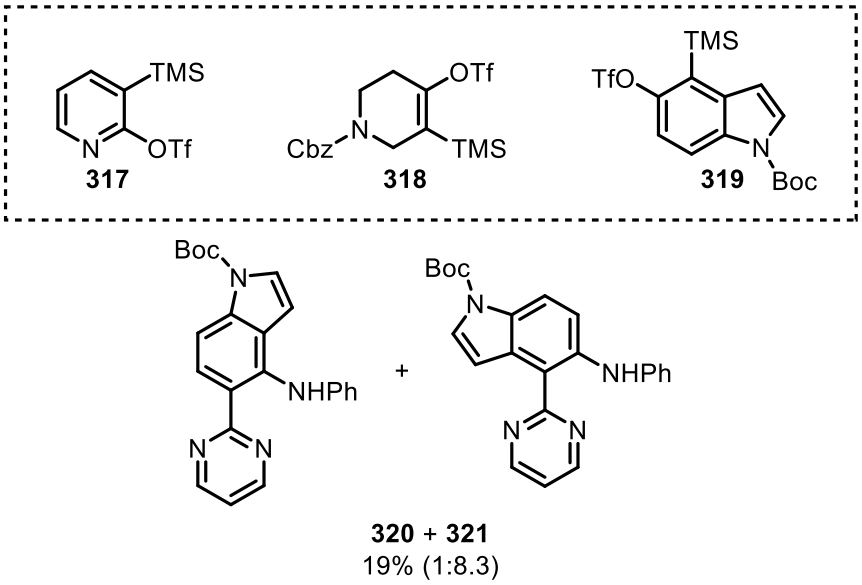


314 73% **315** 43% **316** 56%

Scheme 109 Scope of the biaryl synthesis with respect to heteroaromatic sulfonamides

Highly strained triple bonds have also been generated on heteroarenes and non-aromatic substrates.[286-288] The *o*-trimethylsilyl(aryl) triflate precursors were prepared for 2,3-pyridyne, 3,4-pipyridyne and 4,5-indolyne, and these substrates were subjected to the standard reaction conditions. Unfortunately, neither **317** nor **318**

afforded the desired biaryl product, and the reaction of **319** resulted in poor yields of **320** and **321** (Scheme 110).

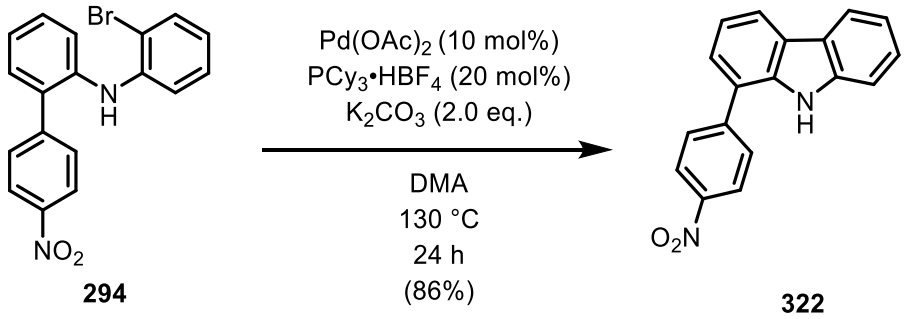


Scheme 110 The use of heteroarynes and strained alkynes

3. Product manipulation

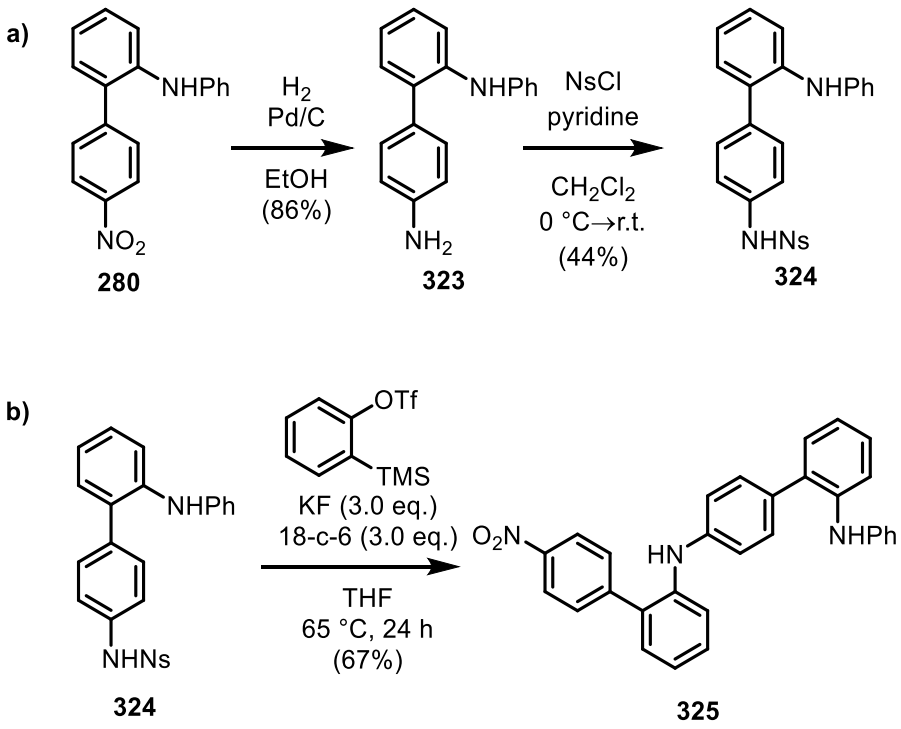
Further functionalisation was explored to demonstrate the utility of the biaryl products. This included transition metal catalysed annulation, reduction of the nitro group, and C–N bond cleavage to reveal a primary biaryl amine.

Carbazole formation was achieved through intramolecular C–H arylation using the conditions reported by Fagnou (Scheme 111).[289]



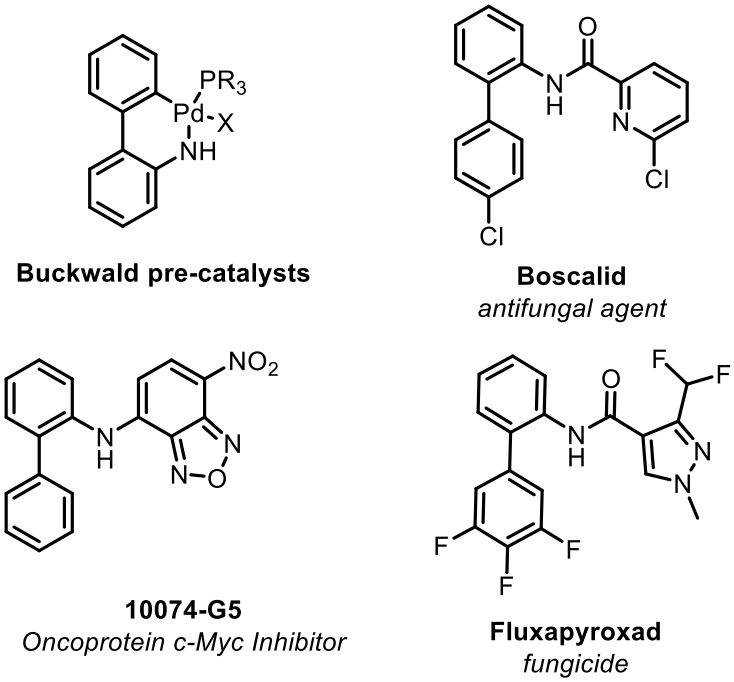
Scheme 111 The synthesis of a carbazole using Fagnou's direct C-H arylation

The aryl nitro group of **280** was reduced to the aniline **323** using Pd/C catalysed hydrogenation in flow using an H-cube™ (Scheme 112, a). This demonstrates that whilst an electron-withdrawing group is required for the biaryl formation to proceed, it can subsequently be used as a synthetic handle. This product was then converted into a sulfonamide **324**, and subjected to the benzyne-biaryl formation a second time (Scheme 112, b). The extended biaryl system **325** was isolated in a comparable yield.



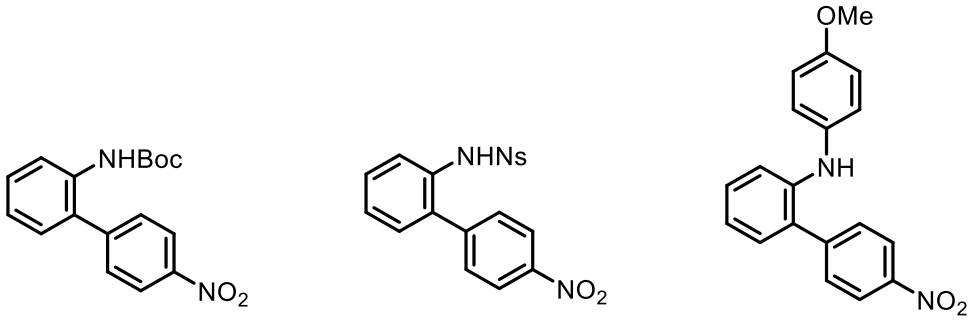
Scheme 112 The Pd/C catalysed reduction of the aryl-nitro group and iterative biaryl synthesis

The 2-amino biaryl motif can be found in chemical structures relevant to agrochemicals, pharmaceuticals, and catalysis (Scheme 113). The products of the developed methodology primarily consist of an *N*,*N*-diaryl motif, which does not readily transform into the structures of interest. Therefore, we next explored protecting group strategies which could expand the application of our methodology.



Scheme 113 Some examples of functional molecules containing a biaryl amine motif

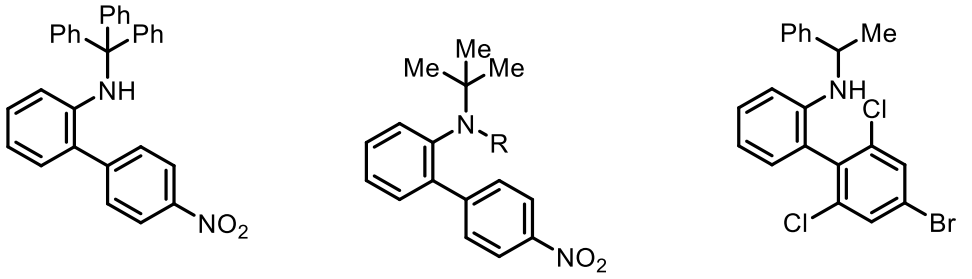
Various sulfonamides with potential protecting groups were prepared and subjected to the standard reaction conditions (Scheme 114). Protection with electron-withdrawing protecting groups rendered the sulfonamide in sufficiently nucleophilic to react with benzyne (**326** and **327**). The trityl group was too bulky to give a good yield of the biaryl product **329**and the *tert*-butyl group gave a mixture of the N–H and N–Ph biaryl products **330** and **331**. However, biaryls **328** and **332** were isolated as single products and in a reasonable yield.



326
0%

327
0%

328
42%



329
trace

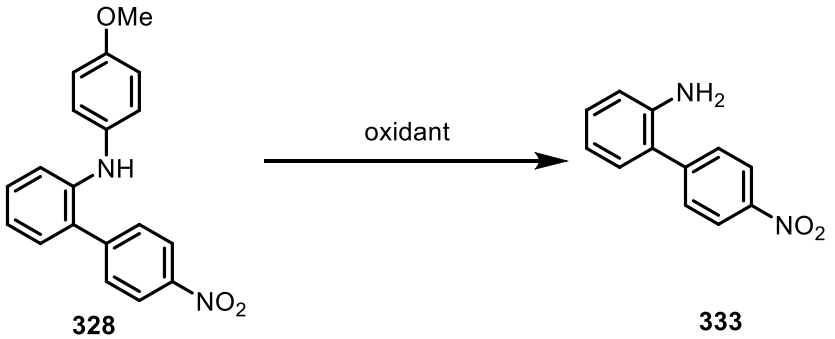
330 : 331
R = H : R = Ph
1 : 1.8

332
57%

Scheme 114 Preparation of biaryls with protecting groups.

Oxidative cleavage of the *p*-methoxyphenyl group of **328** was investigated with single-electron oxidants, DMP and CAN (Table 9).[290] Whilst some of the *para*-quinone was formed with DMP,[291-292] this could not be hydrolysed (conc. HCl, heating) to afford the primary aniline. This approach to designing a protecting group was not pursued further due to the lack of precedent.

Table 9 Oxidative cleavage of the *p*-methoxy phenyl form 328

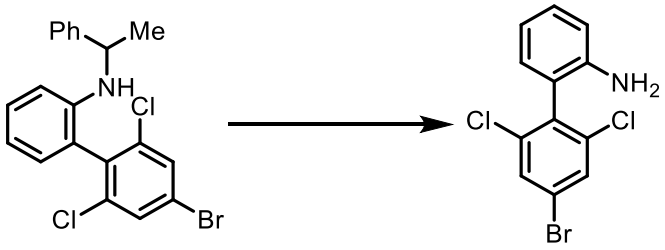


328 **333**

Entry	Oxidant	Results
1	DMP	*Para*-quinone formed
2	CAN	Nitration products formed

There is little precedent for the use of α-methyl benzyls as protecting groups for aryl amines. Hydrogenation lead to carbon-halogen bond reduction (Table 10, entry 2). A Lewis acid based de-alkylation has been reported for biarylamines by Johnston,[293] but was unsuccessful in this case (Table 10, entry 3). Acidic conditions successfully removed the α-methyl benzyl group (Table 10, entries 1, 4 to 6), with a good yield obtained through heating in concentrated HCl for 24 hours (Table 10, 6).

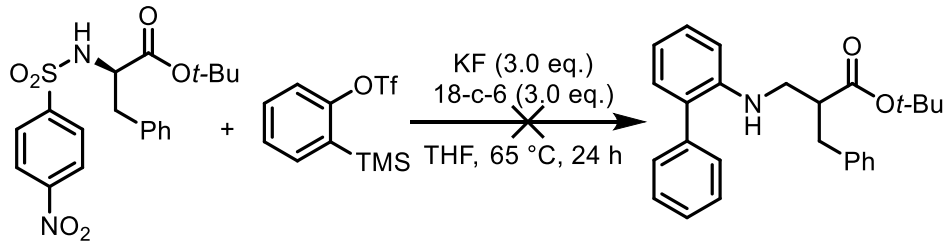
Table 10 Deprotection of 332



332 **334**

Entry	Conditions	334 / %
1	Polyphosphoric acid, 60 °C, 2 h	14
2	H_2, Pd/C, MeOH, 60 °C	0
3	$AlBr_3$, EtSH, CH_2Cl_2, 0 °C to r.t.	0
4	PPA, 60 °C, 18 h,	10
5	Conc. HCl, 100 °C, 2 h	42
6	Conc. HCl, 100 °C, 24 h	65

Extension of this strategy to other α-methylbenzyl sulfonamides was unsuccessful because of the initial biaryl formation, with less hindered substrates, lead to a mixture of the N–H and N–Ph biaryl products. The nosylated amino-acid **335** was also treated with benzyne (Scheme 115) to establish whether amino-acid derived biaryl amines **336** might be prepared directly and whether amino-acids might be used as chiral auxiliaries (*vide infra*, pg. 129). A complex reaction mixture was afforded, potentially due to a competing deprotonation and rearrangement at the α-position (*vide supra*, pg. 87).



335 **267** **336**

Scheme 115 A nosyl-protected amino-acid in the benzyne Truce-Smiles reactions

4. Atropisomerism

One feature of this transformation is the ability to efficiently form highly hindered and unsymmetrical biaryls. An asymmetric biaryl synthesis could be developed through influencing the Truce-Smiles rearrangement aryl transfer (Figure 3). A chiral auxiliary approach (Section 4.1) and the use of quaternary ammonium salts were investigated (Section 4.2).

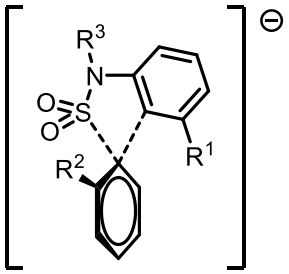
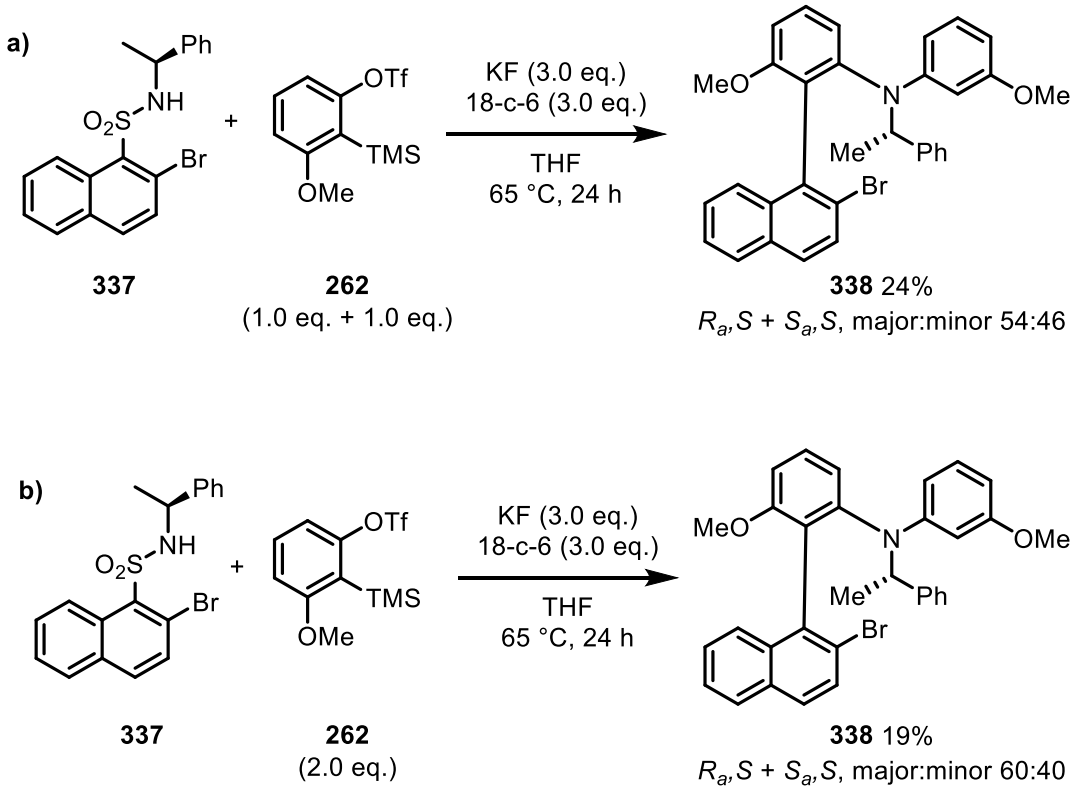


Figure 3 The representation biaryl formation which highlights asymmetry

4.1. Chiral Auxiliary

A sulfonamide containing a chiral auxiliary was prepared to investigate the potential of an asymmetric reaction. The subjection of this substrate to the standard reaction conditions gave incomplete conversion after 24 hours, and so a second equivalent of the aryne precursor was added and the reaction was heated for a further 24 hours. The diastereotopic *N*-arylated amino biaryl **338** was isolated in a modest 24% yield with a *dr* of 54:46 (Scheme 116 a). The *N*-arylated biaryl was isolated in a 19% yield, when the reaction was started with 2 equivalents of the aryne precursor, in addition to the *N*–H biaryl product in a 15% yield (Scheme 116, b). Both products had a *dr* of 60:40 which indicates that the chiral axis is set prior to *N*-arylation. Each diasereoisomer was stable on the NMR timescale (with heating to 120 °C). Unfortunately, the presence of an unidentified impurity hindered continued investigation in this direction.[294]



Scheme 116 The use of a chiral auxiliary to influence atropselectivity of the biaryl synthesis

4.2. Phase-Transfer Catalysis

Asymmetric induction could be achieved with a chiral counter-cation strategy due to the anionic pathway of the Truce-Smiles rearrangement. The *o*-trimethylsilyl(phenyl) triflate benzyne precursor can be decomposed to form benzyne with either fluoride or a hydroxide base. Some of the reagents used to promote decomposition are poorly soluble in the non-polar solvents used for benzyne reactions, therefore incorporation of chiral quaternary ammonium salts was first investigated.

Varying fluoride source, solvents at ambient temperature (Table 11, entries 2 and 3) resulted in the formation of a red solid, which is only partially soluble in the selected solvents at ambient temperature, and no biaryl product.[295] Similarly, the addition of a phase-transfer catalyst did not assist transformation to the biaryl product and in many cases, the *o*-trimethylsilyl(phenyl) triflate **267** also remained unconsumed (Table 11,

entries 1, 2, 5, 6, 8). The only exception to this was in THF (Table 11, entry 7), where **297** was consumed, but none of the biaryl product was identified. Mixing the sulfonamide **281** with the fluoride source in THF-*d8* causes the N–H proton shift to disappear in the ^{1}H NMR, indicating the formation of a sulfonamido-anion under these conditions. It is probable that the red precipitate which is formed are salts of the sulfonamido-anion.[296]

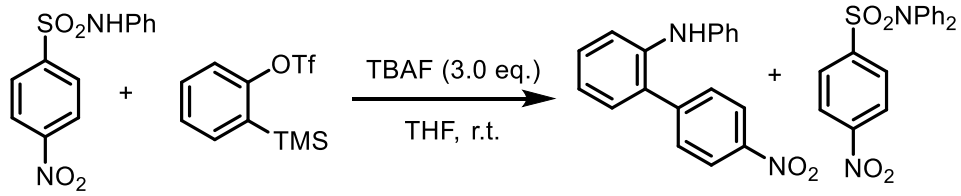
Table 11 Screening of phase-transfer conditions for a benzyne Truce-Smiles reaction

Entry[a]	Fluoride	Solvent	281 / %
1	CsF	PhMe	0
2	KF	PhMe	0
3[b]	CsF	PhMe	0
4[b]	KF	PhMe	0
5	KF	CH_2Cl_2	0
6	KF	$CHCl_3$	0
7	KF	THF	0
8	KF	PhMe	0

[a]Conditions: **281** (0.1 mmol), **267** (0.1 mmol), fluoride (0.2 mmol), solvent (0.1 M), Et_3BnNCl (10 mol%), r.t., 24 h; [b]No Et_3BnNCl

The use of TBAF was investigated for development of an entirely metal-free protocol (Table 12). A low yield was obtained using the same stoichiometry as the previously developed conditions (Table 12, entry1). The transformation takes place rapidly upon the addition of fluoride indicated by no change in the reaction composition after 15 mins. Dropwise addition of TBAF to the reaction mixture resulted in a slight increase in yield, for a 1:1:3 stoichiometry from 17% to 30% (Table 12, entry 2). An excess of sulfonamide gave a reduced yield 6% (Table 12, entry 3) whereas an excess of benzyne precursor gave an increased yield 52% (Table 12, entry 5). Premixing of the sulfonamide with the fluoride source (to achieve deprotonation) resulted in a moderate 30% yield (Table 12, entry 6).

Table 12 Screening conditions for an organic counter-cation



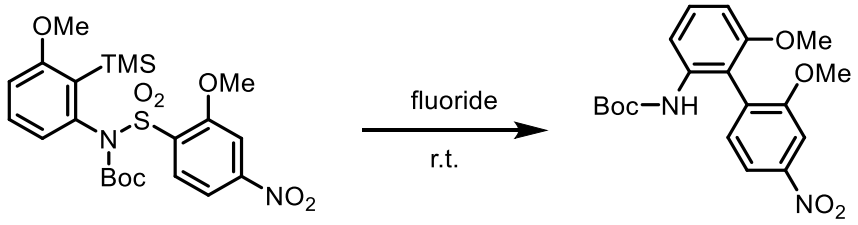
281 267 280 339

Entry[a]	281:267:F	280[b]	339[b]	281[b]
1	1:1:3	17	9	46
2[c]	1:1:3	30	30	28
3[c]	2:1:3	6	20	66
4[c]	1:1:2	22	29	45
5[c]	1:2:3	52	-	-
6[d]	1:1:2	30	34	29

[a]Conditions: *N*-phenyl-4-nitrobenzene sulfonamide, *o*-trimethylsilyl(phenyl)triflate, TBAF, THF (0.1 M), r.t., 15 minutes, 0.1 mmol scale; [b]Isolated yields; [c] Dropwise addition TBAF; [d] premix sulfonamide and TBAF

A silylated analogue of the intermediate **340** was prepared to investigate the possibility of performing the rearrangement independently of the aryne addition. Upon treatment with fluoride, the Boc-protected substrate **340** did not afford the desired biaryl product **341** (Table 13).

Table 13 Reactions for an intramolecular 2-amino biaryl synthesis

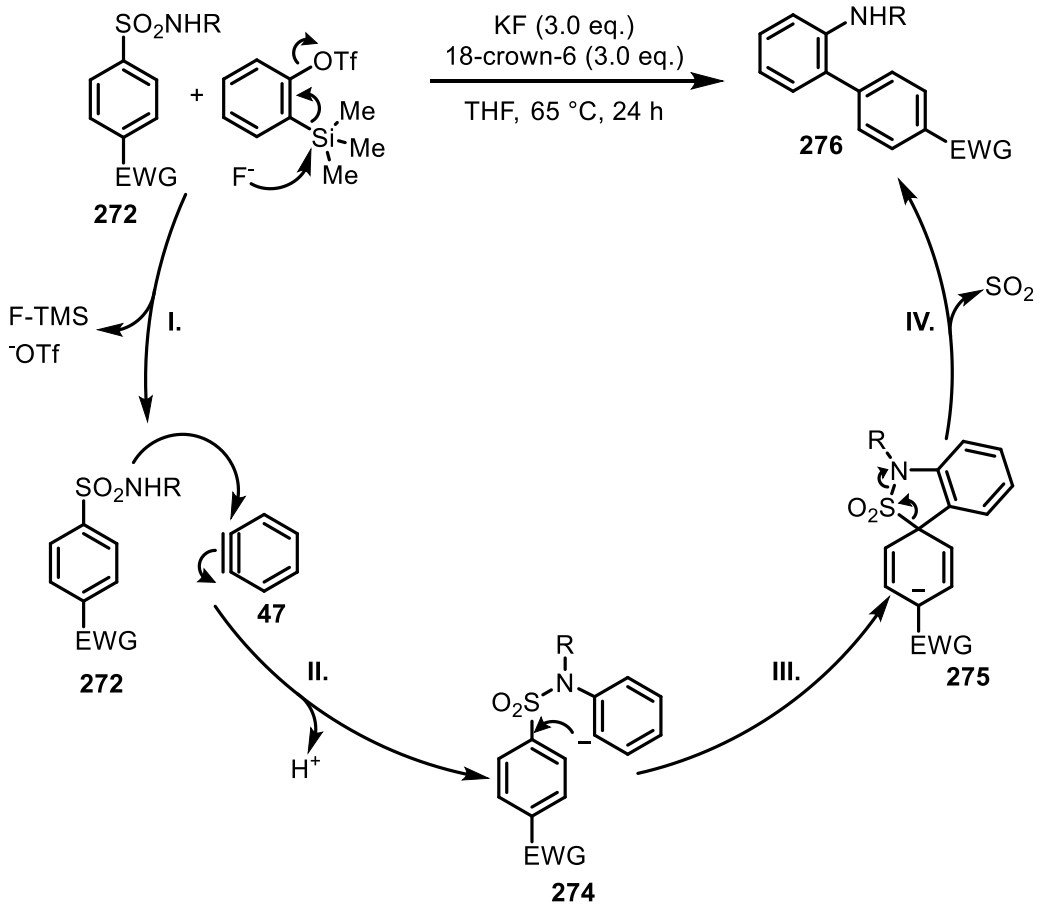


340 341

Entry	Fluoride	Solvent	Time	Result
1	TBAF (3.0 eq.)	MeCN	4 h	Complex mixture
2	CsF (10 eq.), Et_3BnNCl (10 %)	PhMe	22 h	No reaction

5. Mechanism

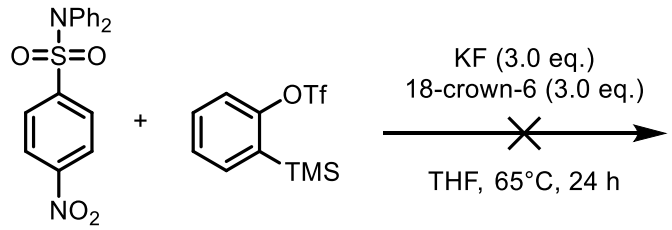
The mechanism of this transformation is proposed to proceed *via* fluoride induced decomposition of **53** (Scheme 117, **I**), then nucleophilic attack of the sulfonamide **272** to form the aryl anion intermediate **274** (Scheme 117, **II**). This anion can then either be protonated to give the *N*-arylated sulfonamide, or perform the desired intramolecular nucleophilic aromatic attack to form the Meisenheimer intermediate **275** (Scheme 117, **III**). This intermediate can then collapse, with concomitant loss of SO_2, to afford the biaryl amine product **276** (Scheme 117, **IV**).



Scheme 117 Proposed reaction mechanism of the benzyne Truce-Smiles biaryl synthesis

In the absence of an electron-withdrawing group, the product of the reaction is the *N*-arylated sulfonamide **339**. This confirms the existence of the proposed aryl anion intermediate (Scheme 117, **III** and **IV**), as opposed to a radical pathway. The

subjection of the *N*-aryl sulfonamide **339** to the reactions conditions gives no transformation to the product, excluding an electrophilic aromatic substitution mechanism (Scheme 118). Reactions with unsymmetrical arynes give regiosomeric products confirming the presence of an aryne intermediate (*vide supra*, pg. 118).

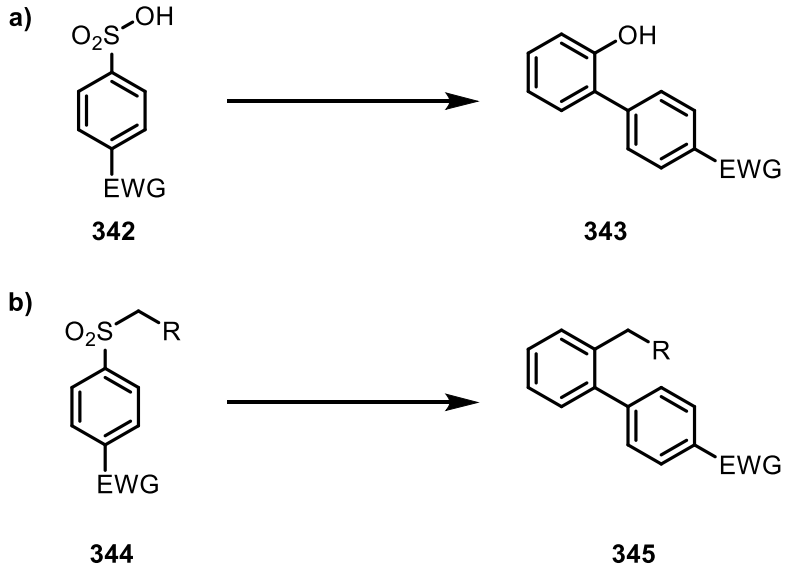


339 **267**

Scheme 118 Subjection of 339 to the reaction conditions.

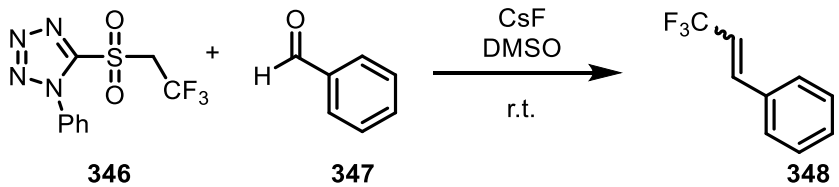
6. Sulfones and sulfoxides

Given the success of the reaction with sulfonamides, we turned our attention to expanding the scope of the reaction to alternative nucleophiles, such as sulfones **344** and sulfoxides **342** (Scheme 119).



Scheme 119 The proposed aryne Truce-Smiles reaction of a) sulfoxides and b) sulfones

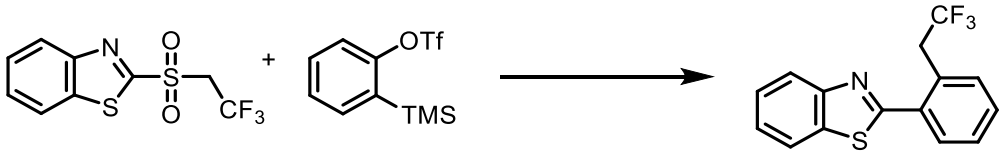
The *S*-aryl sulfones have a wide range of pK_a values, which depend upon the nature of R (Scheme 119, b). In one report into the synthesis of trifluoromethylated olefins **348**, fluoride was used to deprotonate the α-position of the sulfone **346** (Scheme 120).[297] Aldehydes **347** with electron-rich arenes, or those with extended π-systems, gave poorer yields than electron-poor benzaldehydes. The authors also observed that the trifluoromethyl sulfone had a propensity to hydrolyse, affording undesired 1-substituted alkenes.



Scheme 120 The fluoride mediated Julia-Kocienskii synthesis of triflurormethyl-olefins

Encouraged by this precedent, the related *S*-benzothiazole sulfone **349** was prepared and subjected to the reaction conditions developed for sulfonamides (Table 14). Screening a few different fluoride sources in THF quickly revealed that these conditions lead to decomposition of the starting sulfone though elimination and hydrolysis (Table 14). Trace amounts of the desired product and *C*−arylated sulfone were detected by mass spectrometry (Table 14, entries 3, 4, 5), but no substantial quantities of either substance were isolated.

Table 14 Screening conditions with a sulfone



349 **267** **350**

Entry	Fluoride	Solvent	Time	Temp	Results
1	KF/18-c-6	THF	24 h	65 °C	No product
2	CsF	THF	24 h	65 °C	Complex mixture
3	TBAF	THF	24 h	65 °C	Complex mixture
4	TBAF[b]	THF	3 days	r.t.	Complex mixture
5	TBAF[c]	THF	18 h	−78 °C to r.t.	Arylated sulfone

[a]Conditions: sulfone (0.25 mmol), *o*-trimethylsilyl(phenyl)triflate (0.25 mmol), fluoride (0.75 mmol), THF (0.1 M); [b]Dropwise addition; [c]10 equivalents

The 4-nitrobenzene sulfoxide was also tested and gave a small amount of the biaryl product (<10%), confirmed by mass spectrometry and ^{1}H NMR. This avenue of investigation was not continued due to the low intrinsic nucleophilicity of the sulfoxide substrate.

7. Conclusion

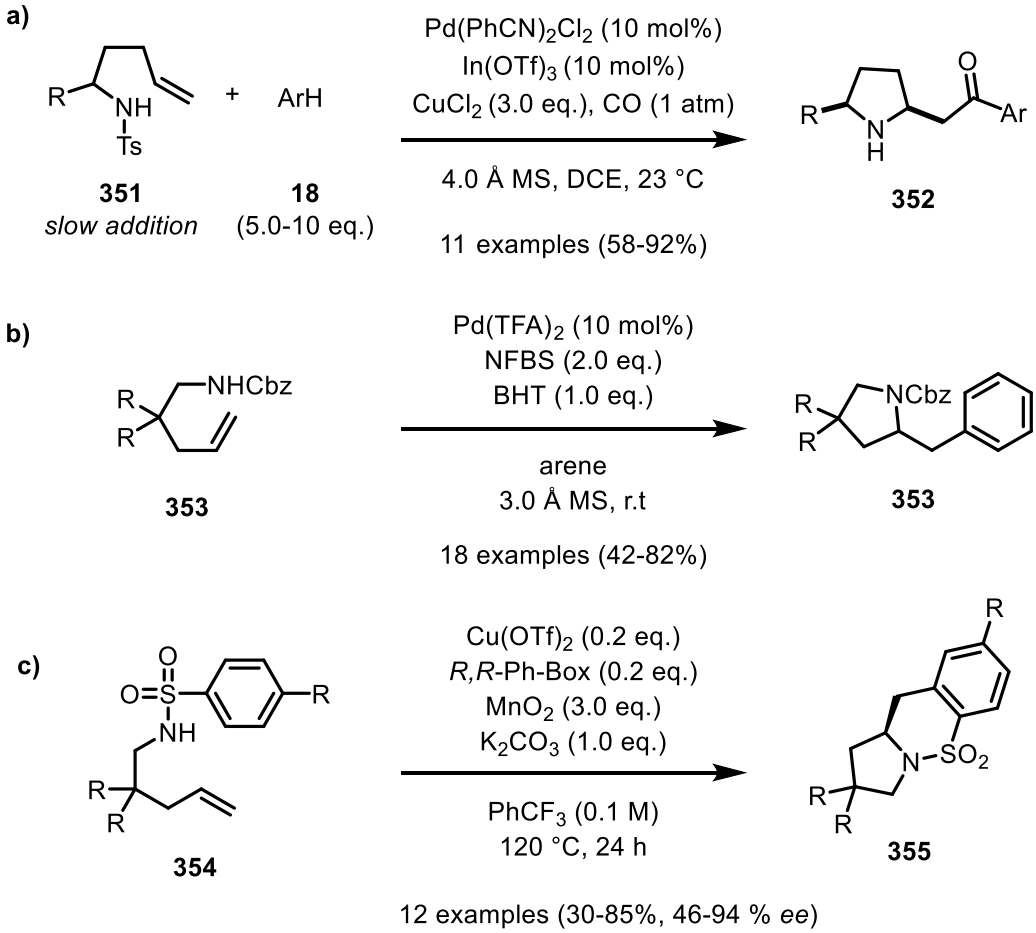
A novel approach to the transition metal-free synthesis of biaryls which utilises the aryne intermediate and a Truce-Smiles rearrangement has been developed. This reaction has a good tolerance of functional groups on each of the coupling partners, and the synthesis of highly hindered (including atropisomeric) biaryls is particularly of note. The primary limitations of this method are the requirement for an electron-poor *S*-arene, that if unsymmetrical arynes are generated a mixture of regioisomers formed, and that only sulfonamides can be used therefore only 2-amino biaryls can be prepared. Future investigations could include the exploration of the atropselective synthesis of biaryls using either chiral auxiliaries or chiral catalysis, and developing this methodology for sulfones.

Chapter 3. Carboamination using the Truce-Smiles Rearrangement

1. Introduction

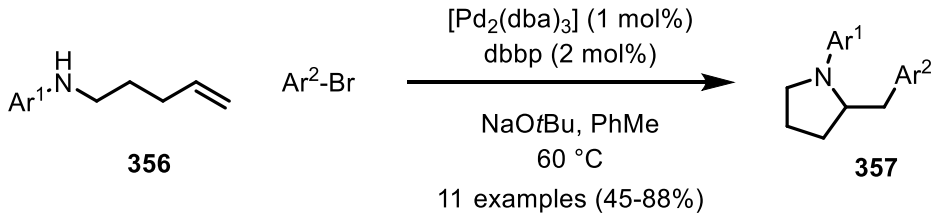
Prior art devoted to carboamination is principally related the 1,2-carboamination of alkenes. Many cases describe intramolecular C–N bond formation coupled with an intermolecular C–C bond formation, resulting in the preparation of 5-membered-ring *N*-heterocycles (e.g. pyrrolidines). These examples can be subdivided into two main categories.

The Hegedus, Tamaru and Yoshida groups pioneered oxidative carboamination.[298-301] In this approach, the Pd(II) triggered aminopalladation generates an alkyl-palladium intermediate which can then be trapped with a nucleophile. Recently, Lambert has demonstrated a tandem aminopalladation / carbonylation / Friedel-Crafts relay to afford α-pyrrolidinyl ketones **352** (Scheme 121, a),[302] and Michael has reported the NFBS promoted aminopalladation of alkenes followed by C−H activation of arenes to afford amino-arylated olefins **353** (Scheme 121, b).[303-304] In addition to palladium catalysis, Chemler has developed the copper catalysed intramolecular carboamination of alkenes, in which *syn* aminocupration occurs, followed by homolysis of the C–Cu bond to afford an alkyl radical which cyclises to form sultam products **355**.[305]



Scheme 121 a) Tandem aminochlorocarbonylation / Friedel-Crafts acylation b) Carboamination via direct C–H alkylation

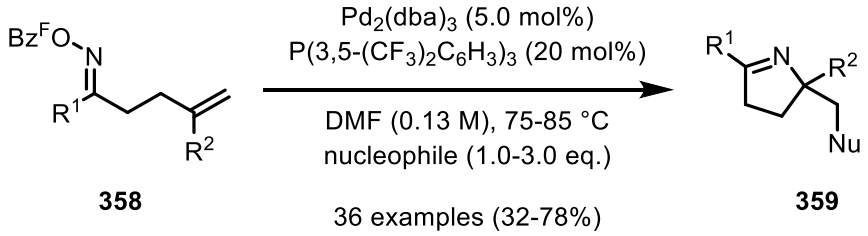
Alternatively, Wolfe developed a Pd(0) catalysed methodology which is compatible with electrophilic cross-coupling partners (Scheme 122) and has been developed for 1,2-amino-arylation, -vinylation and -alkynylation.[306-314] In addition, this mechanism has been adapted for external nitrogen nucleophiles with olefin-tethered aryl (pseudo)halides.[315]



Scheme 122 Wolfe's aminoarylation of tethered olefins.

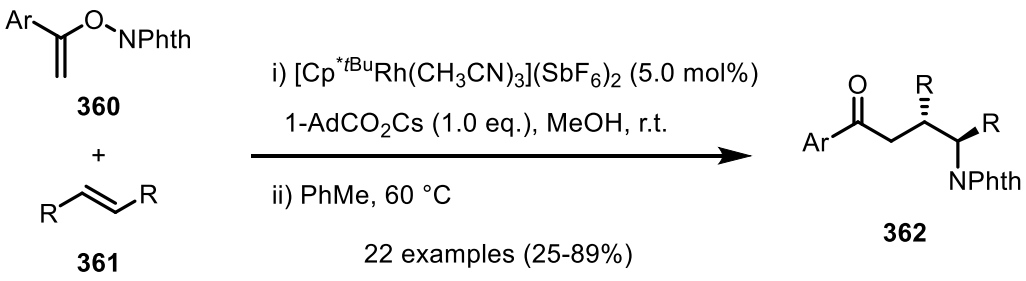
In order to expand carboamination to organometallic nucleophiles, Bower initiated the 1,2-carboamination through the oxidative addition into the N–O bond of an

oximine **358** (Scheme 123).[316] The alkene coordinates intramolecularly to the imino-Pd(II) intermediate, followed by an iminopalladation. The alkyl-Pd(II) species can then be intercepted by the organometallic nucleophiles in the final C–C bond formation step to afford **359**.



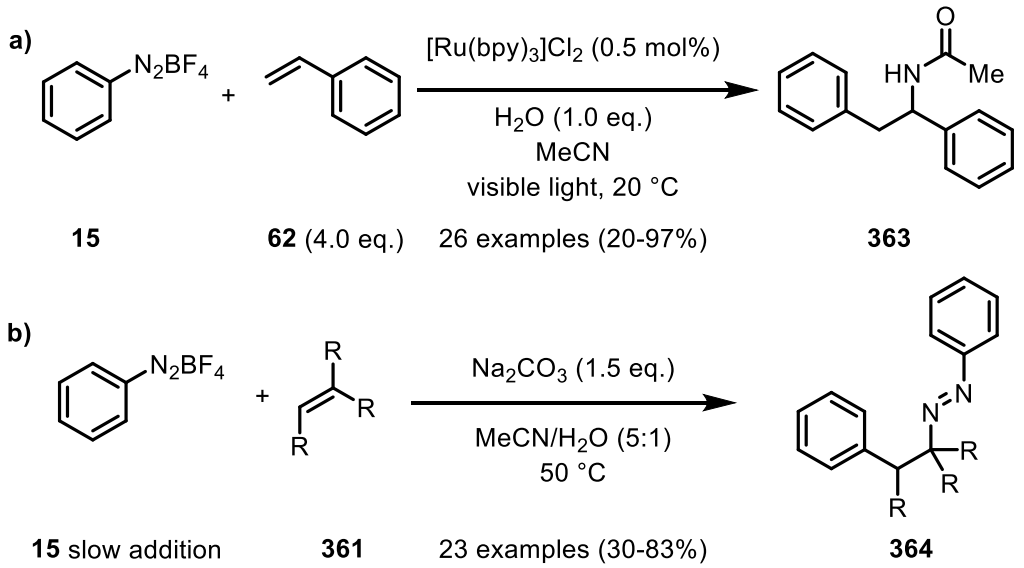
Scheme 123 Umpolung 1,2-carboamination of tethered olefins

Rovis developed a methodology for the intermolecular addition of both the nitrogen and carbon functionalities **360**, with *syn* stereoselectivity across the alkene **361** (Scheme 124).[317] This approach uses a rhodium based catalyst, with a bulky Cp$^{*t\text{-Bu}}$ ligand. The ligand provides a saturated coordination sphere to the catalyst and promotes C–N bond formation over the expected C–C bond formation.[318] Additionally, a directing group is formed *in situ* through the addition of an exogenous nucleophile to the enoxyphthalimide substrates **360**. This provides a bidentate directing group for the Rh(III) catalysed alkene insertion, to form the C–C bond. The bulky Cp$^{*t\text{-Bu}}$ ligand then promotes the C–N forming reductive elimination. Glorius has subsequently described a conceptually similar approach, which is catalysed by coordinatively-unsaturated Co(III).[319]



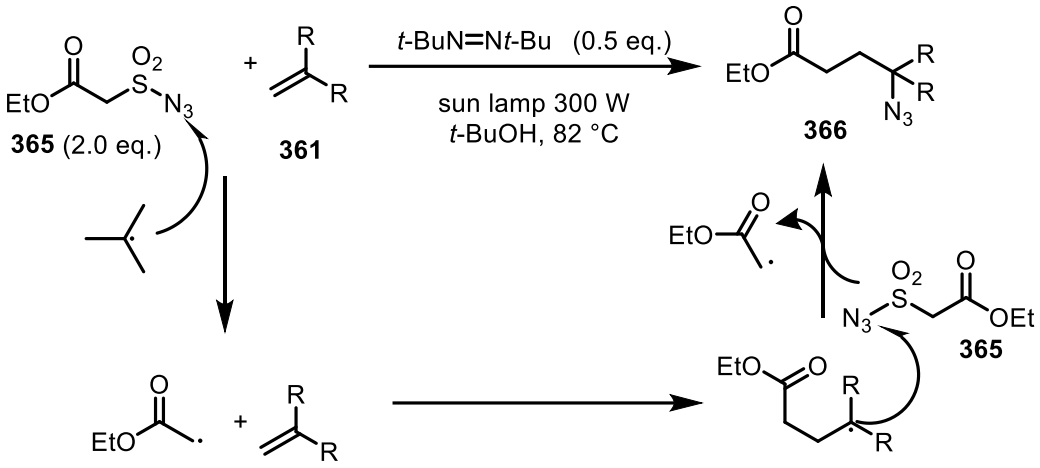
Scheme 124 Rhodium catalysed *syn* carboamination of olefins via a transient directing group

Several radical mediated carboaminations have also been described. König has reported a photoredox-catalysed Meerwein type arylation of styrene, in which the benzylic cation is quenched with acetonitrile (Scheme 125, a).[320] Heinrich has demonstrated a base induced carboamination of olefins (Scheme 125, b).[321] This use of aryldiazonium ions both as a source of the carbon and nitrogen fragment is an environmentally-friendly adaptation of their earlier work.



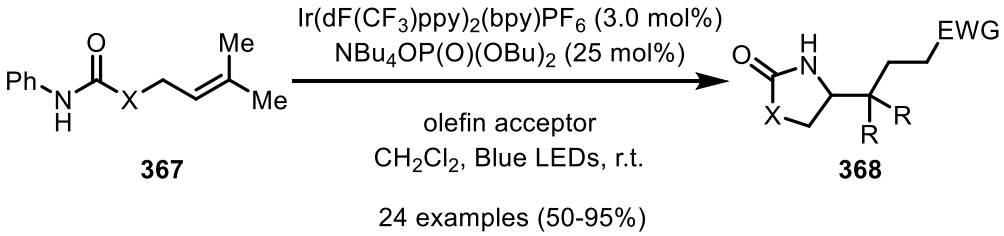
Scheme 125 Arene diazonium salts in [1,2]-carboamination of olefins

Renaud has described the desulfonative azidoalkylation of olefins.[322] In this method the electrophilic carbon radical source and the azide have been incorporated into one reagent **365** (Scheme 126). The mechanism is proposed to be a chain-propagation process, which is initiated by formation of *tert*-butyl radicals derived from di-*tert*-butyldiazene under irradiation (sun lamp, 300 W).



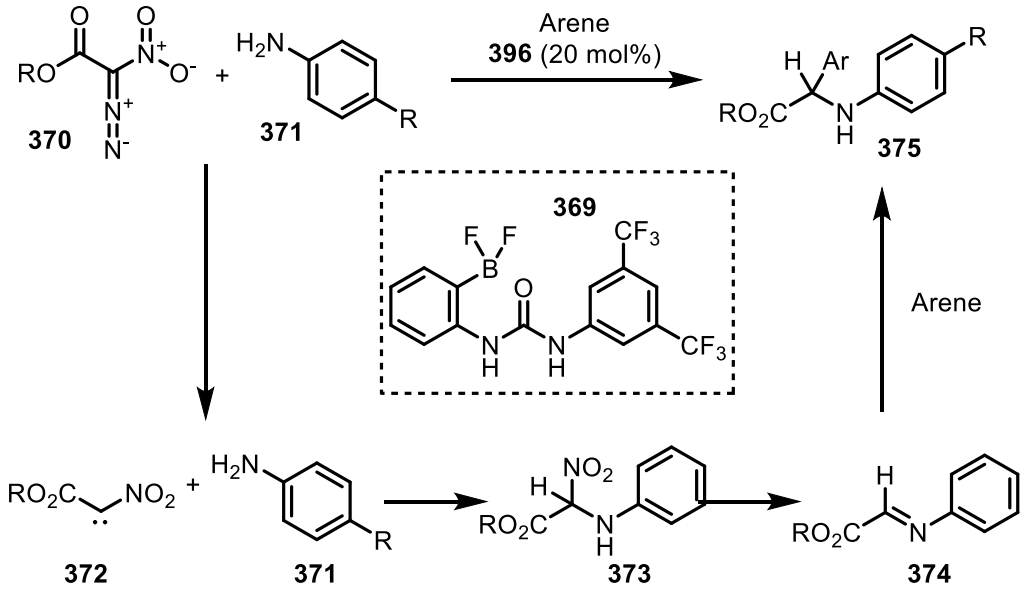
Scheme 126 Photochemically induced desulfonative azidoalkylation of olefins

Knowles has developed a photoredox catalysed method which uses proton-coupled electron-transfer to generate amidyl radicals from **367** (Scheme 127).[323] The amidyl radical is trapped by a tethered olefin of **367** to form the more stable tertiary carbon centred radical, and then undergoes intermolecular addition to methyl acrylate to form the new C–C bond in **368**.



Scheme 127 [1,2]-carboamination of tethered olefins with amidyl radicals

An example of 1,1-carboamination was reported by Mattson demonstrated that a boronate-urea catalyst **369** could be used to activate α-nitro diazoesters **370** toward N–H insertion of anilines **371**, and subsequent arylation with nucleophilic aromatics such as anilines or indoles (Scheme 128).[324] The organocatalyst activates the α-nitro diazoesters resulting in the formation of a carbene **372** which is subsequently trapped by the aniline. Intermediate **373** then forms an iminoglyoxylate species **374**, upon liberation of nitrous acid, which reacts with the arene nucleophile for the amino-arylated product **375**.[325]



Scheme 128 The boronate-urea catalysed amino-arylation of α-nitrodiazoesters

The methods for 1,2-carboamination principally afford pyrrolidine type structures and involve the functionalisation of styrenes. Furthermore, very few of the previously reported methods can be performed in the absence of metals. Therefore, we proposed to develop a new strategy for transition metal-free carboamination.

2. Proposal

Whilst developing a metal-free biaryl synthesis (Section X), we used electron-poor *S*-aryl sulfonamides as reagents for the tandem amino-arylation of arynes (Figure 4, a). These reagents consisted of a nucleophilic amine and electrophilic arene joined by a traceless linker (Figure 4, b). This type of reagent could potentially be used for the difunctionalisation of unsaturated or amphoteric molecules (Figure 4, c). Development of a general strategy for the tandem installation of an amine and an arene would streamline the synthesis of these motifs (Figure 4, d).

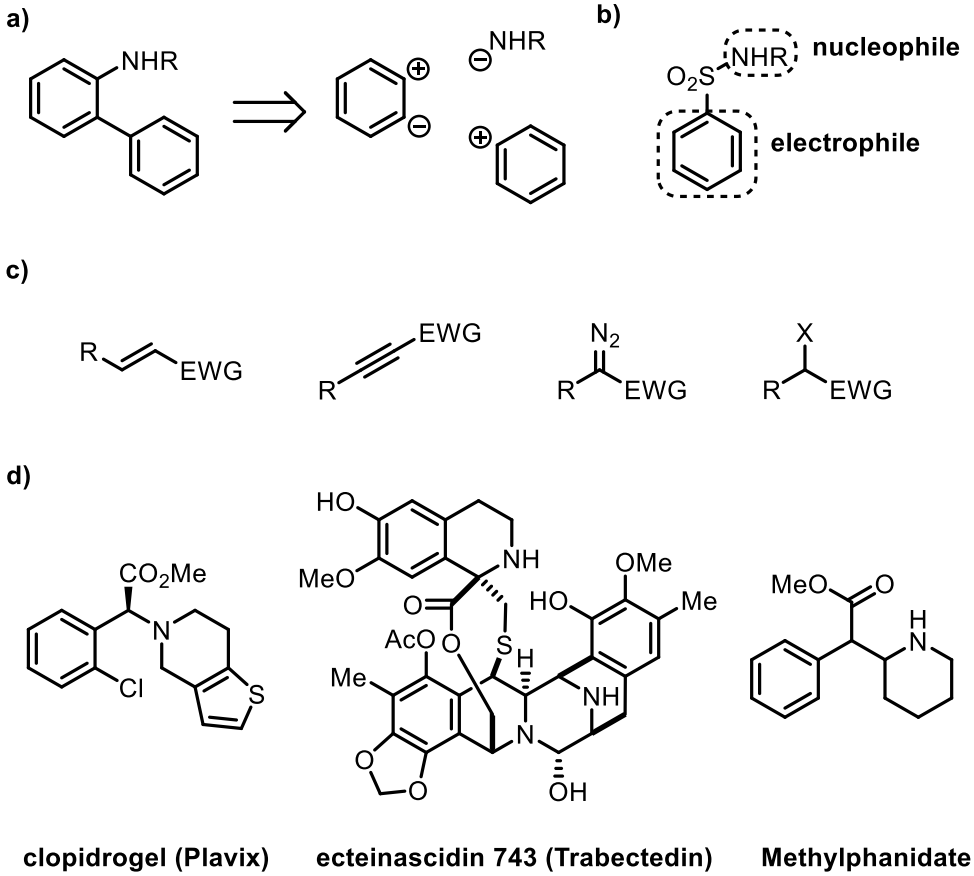
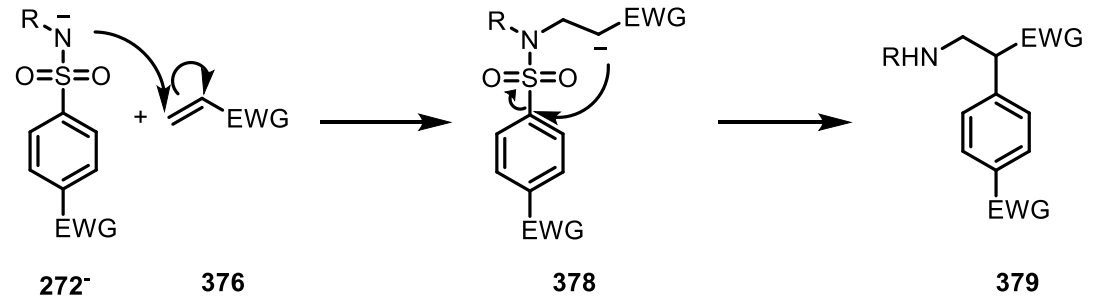


Figure 4 a) Disconnection of the amino biaryl products b) Sulfonamides as bifunctional reagents c) Potential reaction partners d) Biologically active molecules containing amine and aryl functional groups

3. 1,2-Carboamination

The carboamination of activated olefins **376** was first considered, due to the potential value of the α-aryl-β-amino-ester products **379** derived from the reaction of sulfonamides **272** with acrylates (Scheme 129). Anionic Truce-Smiles rearrangements are primarily initiated through deprotonation, rather than comparatively rare conjugate addition (*vide supra*, pg. 90). However, several examples of radical mediated rearrangements, initiated by addition to alkenes and alkynes have now been reported (*vide infra*).



Scheme 129 The proposed conjugate addition / Truce-Smiles rearrangement reaction

Radical mediated conjugate addition initiated Truce-Smiles rearrangements have been pioneered by Nevado. A highly versatile aryl migration/desulfonation cascade based upon initial copper catalysed 1,4-addition of a trifluoromethyl radical to an *α,β*-unsaturated amide **380** was first reported.[326] The resultant radical **381** can then undergo a Truce-Smiles rearrangement, with the fate of the product amidyl radical **382** dependent on the substitution pattern (aryl, alkyl), with either hydrogen abstraction or cyclization reactions possible (Figure 5). This cascade can be triggered by numerous radical sources, and the amidyl radical can be trapped by various intra- and intermolecular electrophiles resulting in a variety of multicyclic molecular scaffolds (Figure 5).[327-329] Allart-Simon et al. have reviewed these reactions and the subsequent developments.[330]

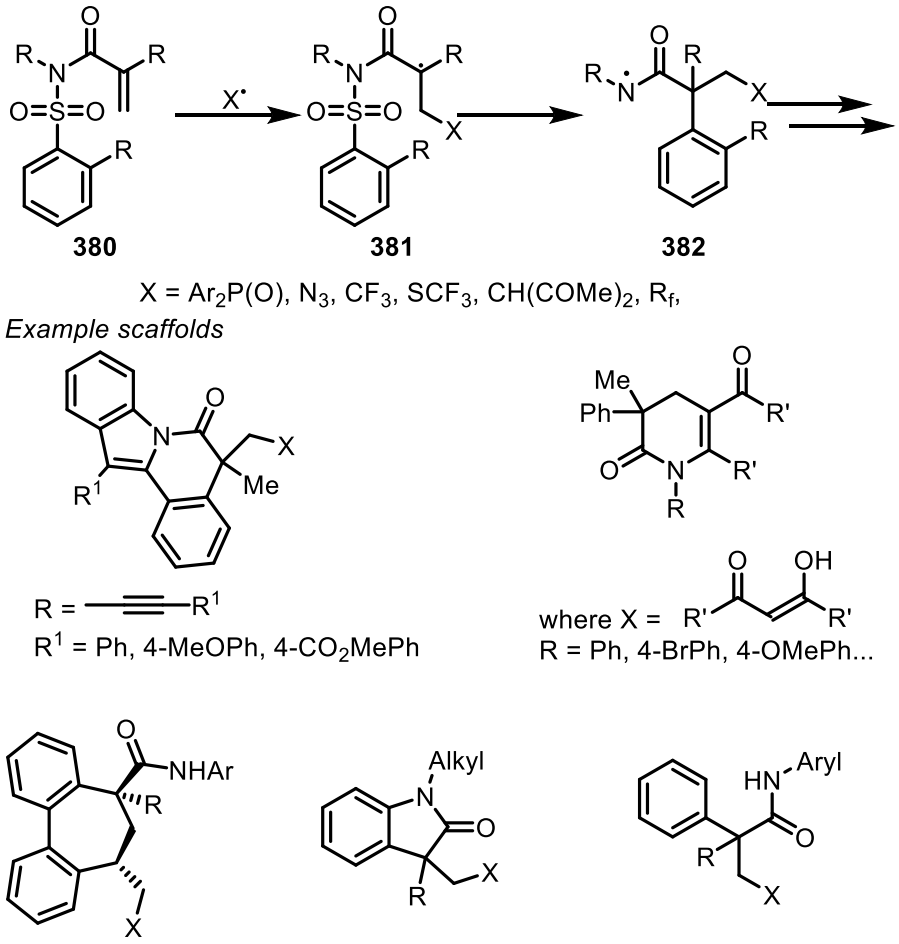


Figure 5 Amidyl radicals generated though a Smiles rearrangement

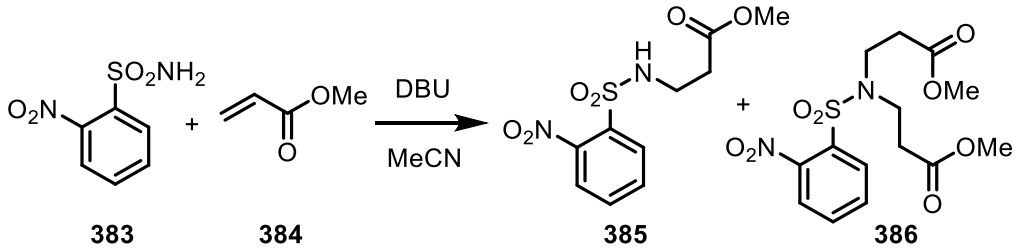
Aza-Michael reactions and asymmetric conjugate additions are well described in the literature, but there are limited reports of domino or cascade processes which use the enolate formed upon conjugate addition of an amide nucleophile.[331-336] These procedures are typically acid catalysed, with the second step comprising of an aldol reaction, due to the reversible conjugate addition of a poor nucleophile under basic conditions. Nevertheless, the intramolecular nature of the Truce-Smiles rearrangement may facilitate trapping of the intermediate enolate anion, prior to an elimination reaction reversing the reaction.

3.1. Reaction discovery

Electron-poor sulfonamides are not particularly nucleophilic, therefore initial reaction discovery first focused on identifying conditions for the conjugate addition

of *S*-aryl sulfonamides. Initial reaction conditions were based upon literature precedent for the conjugate addition of sulfonamides facilitated by DBU (Table 15).[337] The crude reactions were analysed by ^{1}H NMR spectroscopy and LCMS, and the ability of **383** to perform 1,4-addition to **384** was confirmed.

Table 15 DBU promoted conjugate addition of 2-nitrobenzene sulfonamide to methyl acrylate



383 **384** **385** **386**

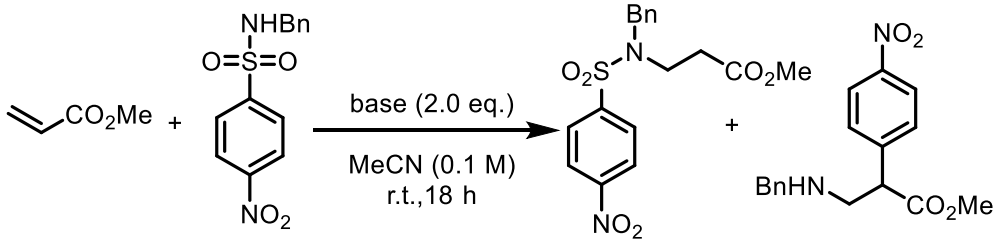
Entry[a]	384	M	Base eq.	Temp	Result[b]
1	1.5	2.0	0.5	r.t.	**385** + **386**
2	1.1	0.1	1.1	85 °C	**385** + **386**
3	1.1	2.0	1.1	85 °C	**385** + **386**

[a]Conditions: 2-nitrobenzene sulfonamide (1 mmol), methyl acrylate, DBU, MeCN, 20 h; [b]Product unseparated, confirmed by LCMS

The ability of nitrobenzene sulfonamide **383** to perform conjugate addition with **384** had been verified and so a secondary sulfonamide **387** was prepared to investigate the tandem amino-arylation of α,β-unsaturated esters.

A screen of bases, a with a range of pK_{BH+} values, was first conducted for the reaction of *N*-benzyl 4-nitrobenzenesulfonamide **387** with methyl acrylate (Table 16). This revealed that K_2CO_3, KO*t*-Bu and DBU were effective bases for the initial conjugate addition reactions (Table 16, entries 2, 4 and 7). However, there was no indication of the desired Truce-Smiles rearrangement. It was also noted that the starting sulfonamide and the aza-Michael addition product had extremely similar polarity by TLC, and the two materials were unseparated.

Table 16 Identification of a base for the reaction of 384 and 387



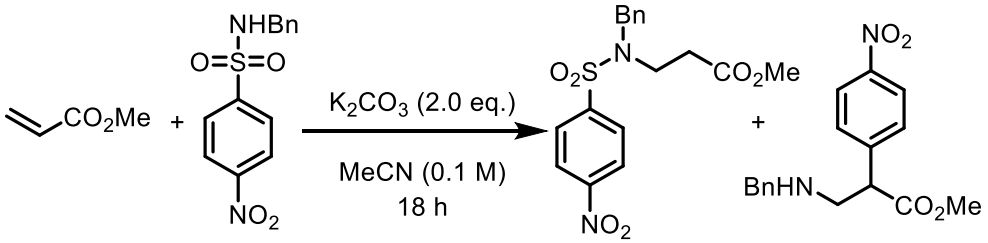
384 **387** **388** **389**

Entry[a]	Base	Result
1	NaOAc	**387**
2	K_2CO_3	**388**:**387** 26:1
3	DIPA	**387**
4	KO*t*-Bu	Decomposition
5	Et_3N	**387**
6	2,6-Lutidine	**387**
7	DBU	**388**:**387** 1:1

[a]Conditions: *N*-benzyl-4-nitrobenzenesulfonamide (0.1 mmol), methyl acrylate (0.1 mmol), base (0.2 mmol), MeCN (0.1 M), r.t., 18 hours.

A temperature screen was then conducted to induce rearrangement to **389** and improve conversion (Table 17). The best conversion to **388** was obtained at an ambient temperature (Table 17, entry 1). Although improved conversion from the sulfonamide was obtained at elevated temperatures, this was a result of decomposition.

Table 17 Determining the effect of temperature on the reaction of 384 and 387



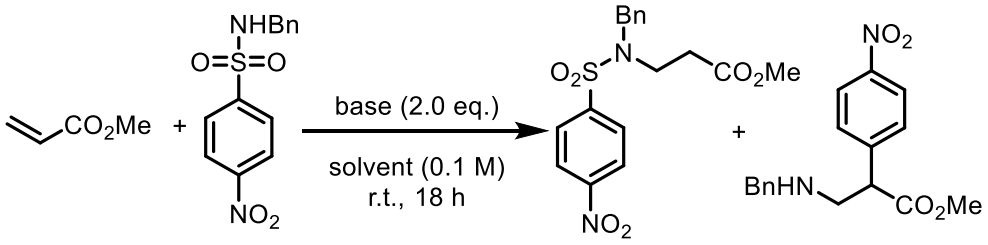
384 **387** **388** **389**

Entry[a]	Temp	388[b]
1	r.t	72%
2	40 °C	69%
3	60 °C	19%
4	80 °C	9%

[a]Conditions: *N*-benzyl-4-nitrobenzenesulfonamide (0.1 mmol), methyl acrylate (0.1 mmol) K_2CO_3 (0.2 mmol), MeCN (0.1 M), 18 hours; [b]Conversion determined by ^{1}H NMR using 1,3,5-trimethoxybenzne as an internal standard.

Solvents with a range of polarities were then screened (Table 18). More polar solvents were expected to assist the Truce-Smiles rearrangement, as many literature examples employ DMF and DMSO (*vide supra*, pg. 82). However, very polar solvents such as DMF and DMSO decreased the yield of **388** (Table 18, entries 1 and 6), and led to decomposition of the starting material. Acetonitrile gave the best conversion to the conjugate addition product **388** (Table 18, entry 2). An excess of methyl acrylate led to an increase in yield of 72% to 83% (Table 18, entry 2), and an extended reaction time also improved the yield 72% to 85% (Table 18, entry 8). A moderate conversion was observed in toluene with tetra-butyl ammonium chloride as a phase-transfer catalyst (Table 18, entry 4). No material corresponding to the Truce-Smiles product **389** was identified or isolated.

Table 18 Determining the effect of solvent on the reaction of x and x



384 **387** **388** **389**

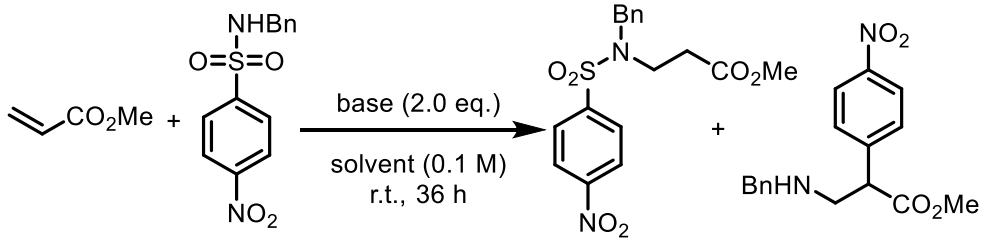
Entry[a]	Solvent	388[b]
1[c]	DMF	41%
2	MeCN	83%
3	DCE	0%
4[d]	PhMe	53%
5	HIPFA	1%
6	DMSO	21%
7	Dioxane	11%
8[e]	MeCN	85%

[a]Conditions: *N*-benzyl-4-nitrobenzenesulfonamide (0.1 mmol), methyl acrylate (0.15 mmol), K_2CO_3 (0.2 mmol), MeCN (0.1 M), r.t., 18 hours; [b]Conversion determined by ^{1}H NMR using 1,3,5-trimethoxybenzne as an internal standard; [c]methyl acrylate (1.0 mmol); [d]with tetrabutylammonium chloride (0.01); [e]72 hours

The conversion to the intermediate **388** had improved, and so the effect of the base was explored again (Table 19). K_2CO_3 again gave the best conversion to the intermediate product (Table 19, entry 1). DBU also gave a good yield of this product (Table 19, entry 4), whilst K_3PO_4 caused some decomposition (Table 19, entry 2). DABCO gave a poor yield (Table 19, entry 3) and TMG gave only a moderate yield, but with little decomposition (Table 19, entry 5). Notably, the use of 1 equivalent of sodium hydride in THF only afforded low conversion to **388** (Table 19, entry 6). This is due to the formation of a tight ion pair between the sulfonamide anion and the sodium cation in THF, which suppresses nucleophilicity. An excess of methyl acrylate with DBU over a longer time-period improved the yield of the addition

product (Table 19, entry 7), whereas decomposition occurred if the reagents were mixed with DABCO for an extended time (Table 19, entry 8).

Table 19 Determining the effect of different bases on the reaction of 384 and 387 under optimised conditions



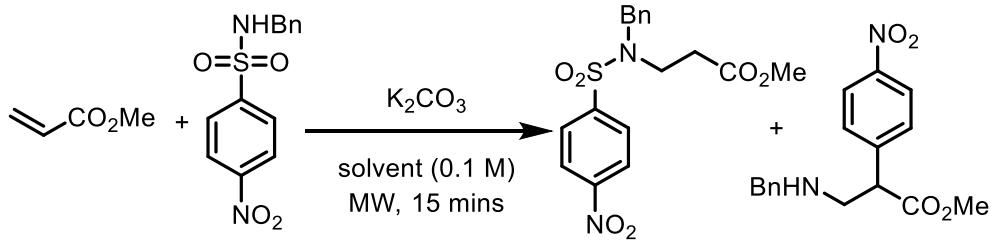
384 **387** **388** **389**

Entry[a]	Base	388[b]
1	K_2CO_3	81%
2	K_3PO_4	32%
3	DABCO	13%
4	DBU	78%
5	TMG	45%
6[c]	NaH	13%
7[d]	DBU	80%
8[d]	DABCO	9%

[a]Conditions: *N*-benzyl-4-nitrobenzenesulfonamide (0.1 mmol), methyl acrylate (0.15 mmol), base (0.2 mmol), MeCN (0.1 M), r.t., 36 hours; [b]Conversion determined by ^{1}H NMR using 1,3,5-trimethoxybenzne as an internal standard; [c]NaH (0.1 mmol), THF (0.1 M), 0 °C to RT, 18 h; [d]60 hours

Microwave heating to high temperatures was investigated to force the Truce-Smiles rearrangement (Table 20). Complete decomposition of the materials was observed upon heating the reagents to 120 °C in DMF for 15 minutes (Table 20, entry 1). Heating with an excess of methyl acrylate in toluene and with tetrabutylammonium iodide resulted in a 37% conversion to the addition product, but again no rearrangement product **389** was observed (Table 20, entry 2).

Table 20 Exploring the effect of microwave heating upon the reaction of 384 and 387



384 **387** **388** **389**

Entry[a]	Solvent	Eq. base	Temp	388
1	DMF	5	120 °C	0%
2[b]	PhMe	2	100 °C	37%

[a]Conditions: *N*-benzyl-4-nitrobenzenesulfonamide (0.1 mmol), methyl acrylate (0.15 mmol), K_2CO_3, solvent (0.1. M), 15 mins; [b]tetrabutylammonium iodide (0.115 mmol)

3.2. Alternative activated-olefins

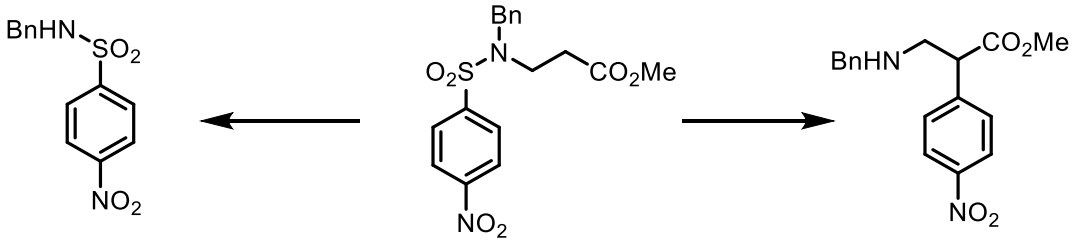
Alternative acceptor substrates were then investigated. Approximately 95% conversion to the aza-Michael addition product was observed by ^{1}H NMR with methyl vinyl ketone under phase transfer conditions. Repeating the experiment for a longer time (6 hours) gave the same conversion and an isolated yield of 87%, but none of the rearrangement product. Heating the sulfonamide with 2-vinylpyridine gave the addition product, with no rearrangement detected. Similarly, the reaction of the sulfonamide with phenyl vinyl sulfone produced the addition product and no rearrangement. To established whether a Thorpe-Ingold effect might promote the desired rearrangement, methyl-3-methyl-2-butenoate was tested at both ambient temperature overnight, and with microwave heating at 85 °C, but no reaction was observed is either case.

3.3. Elimination hypothesis

The intermediate **388** was synthesised separately, to investigate a potential Truce-Smiles rearrangement versus the elimination (Table 21). The intermediate **388** was

then subjected to a set of basic conditions. Freshly prepared LDA returned only intermediate **388** (Table 21, entry 1). Similarly, phase-transfer catalysed conditions, modelled on the work of Jøregensen,[179-180] returned the intermediate **388** (Table 21, entry 2). However, the use of NaH or KHMDS afforded the product of elimination, *N*-benzyl 4-nitrobenzene sulfonamide **387** (Table 21, entry 3 and 4). Finally, heating **388** with K_2CO_3 resulted in decomposition (Table 21, entry 6). In no case was the Truce-Smiles rearranged product **389** detected.

Table 21 Investigating the reactivity of the AM intermediate under various basic conditions



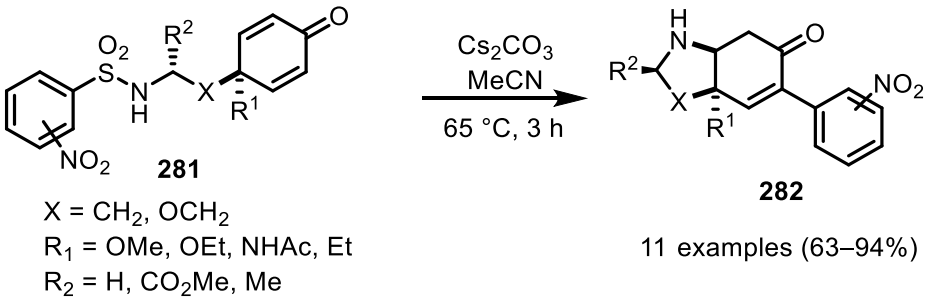
387 **388** **389**

Entry	Conditions	Result
1	LDA, THF, −78 °C to r.t.	**388**
3	$CsOH{\cdot}H_2O$, TBAI (15 mol%), PhMe, 2 h, r.t.	**388** 96%
4	NaH (1.0 eq.), THF, 0 °C to r.t., 18 h	**387** 78%
5	KHMDS (2.0 eq.), THF, −78 °C, 1 h	**387** 88%
6	K_2CO_3 (5.0 eq.), DMF, 120 °C, MW, 15 mins	Decomposition

3.4. Conclusion

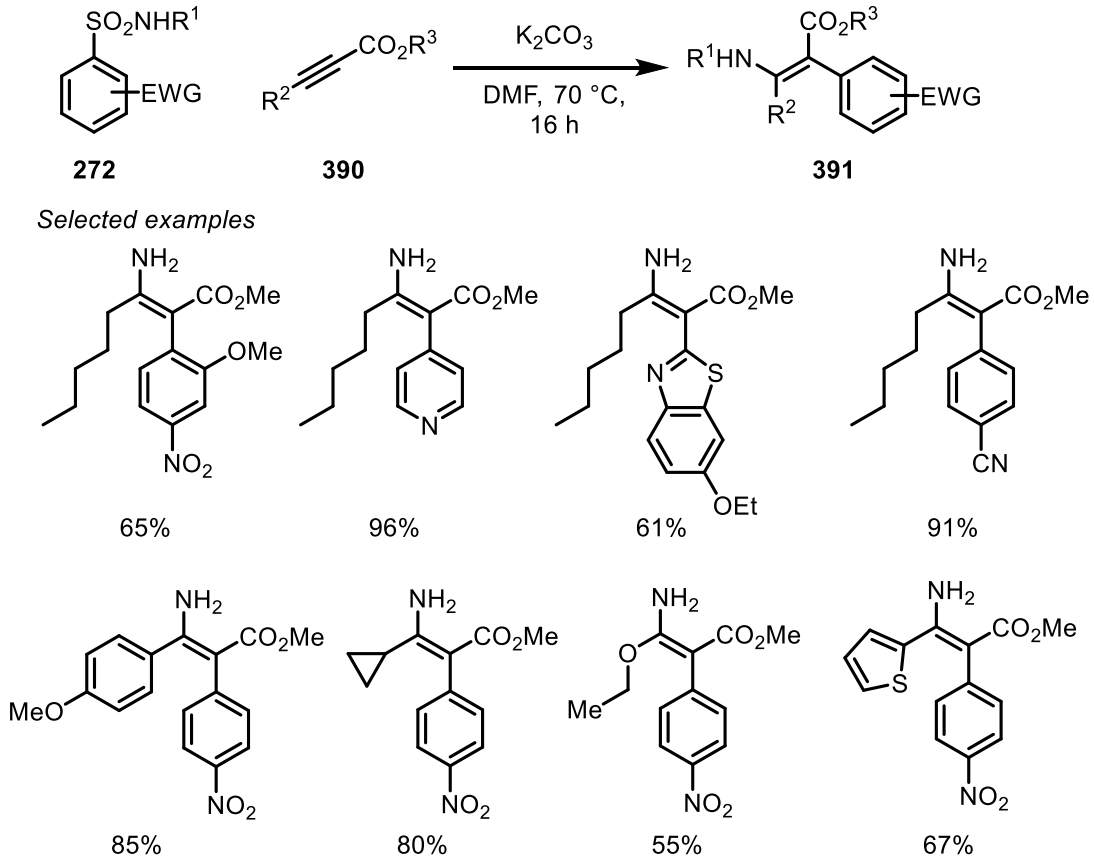
The proposed project was unsuccessful due to the nucleofugality of the electron-poor *S*-aryl sulfonamide reagent, coupled with decomposition under the reaction conditions which should promote a Truce-Smiles rearrangement. It is established that nitrobenzene sulfonamides undergo intramolecular, desulfonative rearrangements to form nitroaniline, upon deprotonation and heating.[338]

Following this investigation, an intramolecular version of this conjugate addition / rearrangement was reported (*vide infra*, pg. 90). Elimination of the desulfonylated amine formed following rearrangement was observed (Scheme 130).



Scheme 130 A conjugated addition / rearrangement / elimination / addition cascade with nitrobenzene sulfonamides

The conjugate addition / Truce-Smiles rearrangement reaction with electron-poor *S*-aryl sulfonamides and activated alkynes has also been investigated within the group by Pauline Rabat.[339] Optimal conditions for the reaction were found to be with K_2CO_3, in DMF at elevated temperatures (either 70 °C or 100 °C) over 16 hours. An extensive substrate scope was demonstrated for this transformation (Scheme 131), with the requirement that R^2 is not hydrogen. The 1,2-carbonamination of alkynes was potentially successful, where the reaction with activated alkenes was not, due to the formation of a more reactive carbanion upon conjugate addition.



Scheme 131 The conjugate addition / Truce-Smile rearrangement for the carboamination of activated alkynes.

4. 1,1-Carboamination

4.1. Background and Proposal

Amino acids are some of the most well-known chiral molecules due to their central role in nature. The preparation and modification of enantioenriched amino acids is a key target for medicinal chemistry and chemical biology.[340] Arylglycines are important non-proteogenic amino acids; some examples include β-lactam antibiotic Amoxicillin, the cardiovascular agent Plavix and the natural product anti-tumour drug Trabectedin (Figure 6).[341]

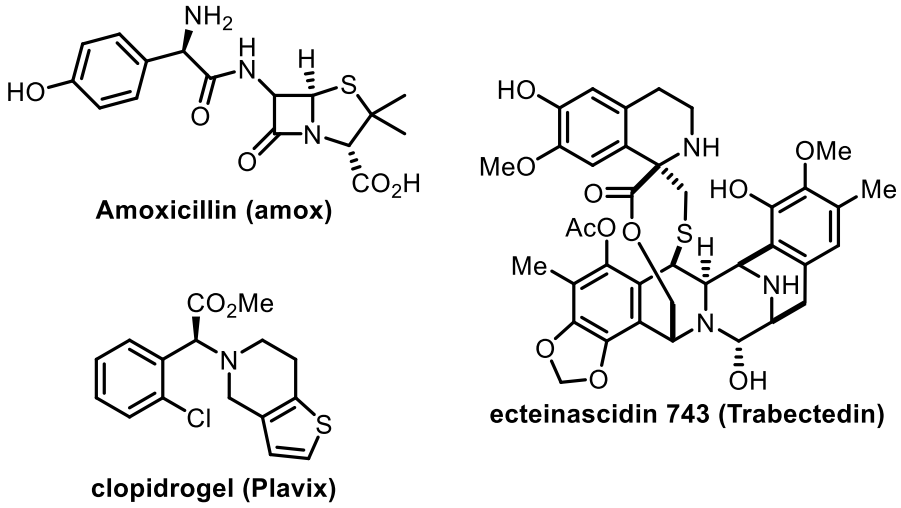


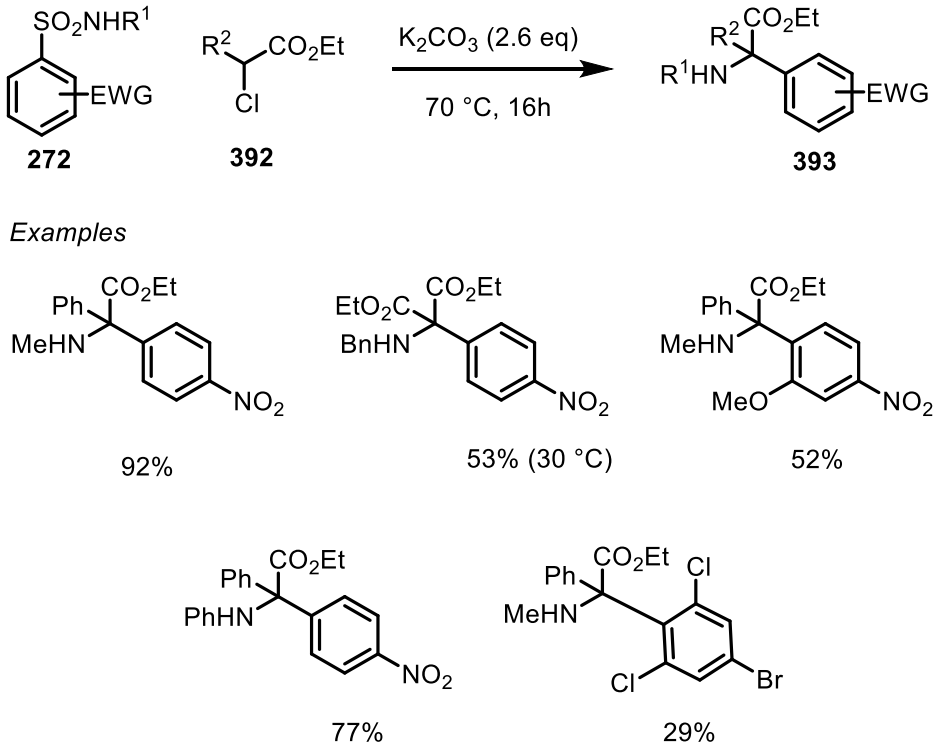
Figure 6 Biologically active molecules containing the α-aryl glycine motif

There is an ongoing interest in α,α-disubstituted α-amino acid residues within biochemical research due to their interesting physiochemical properties.[342] However, asymmetric catalytic methods for the preparation of this motif from simple building blocks are limited, particularly for those molecules containing an α,α-disubstituted aryl glycine.[343-346]

Methods for carboamination focus on the functionalisation of olefins to afford β-amino products. Mattson has reported an organocatalyzed [1,1]-amino arylation of α-nitrodizaoesters with anilines and electron-rich arenes (*vide supra*, pg. 143).[324-325]

However, the use of α-nitrodiazoesters somewhat limits the scope of this transformation, particularly with respect to the preparation of tertiary amines and the reaction conditions had to be highly optimised for each substrate. Furthermore, this transformation is not enantioselective.

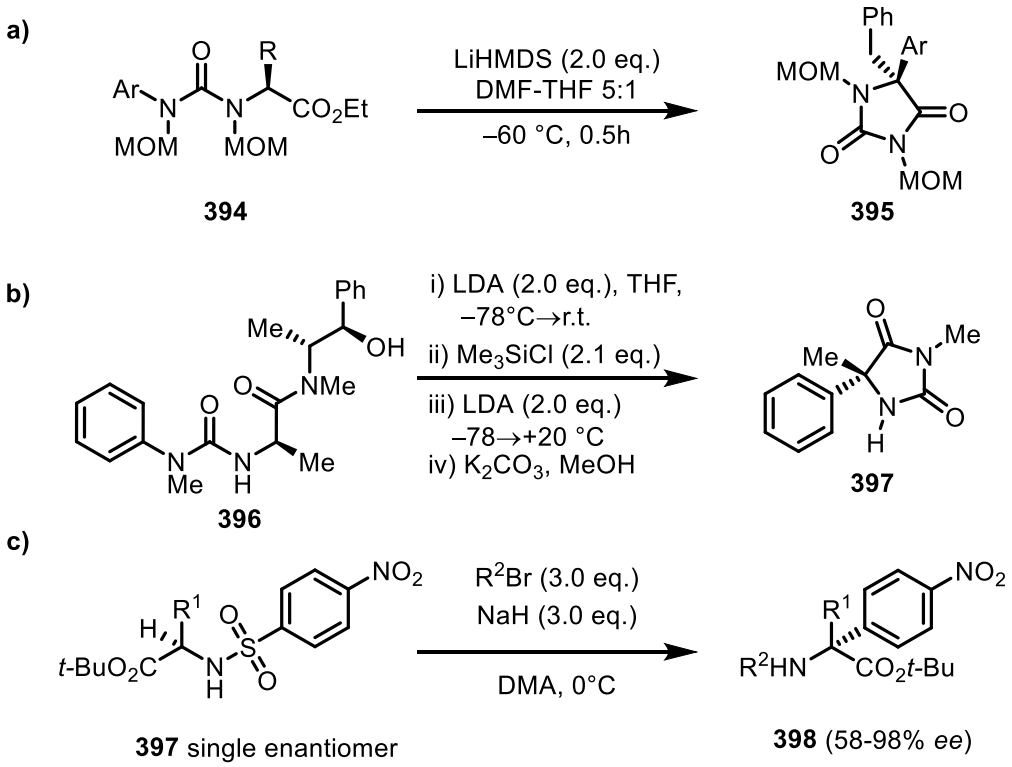
The Greaney group has established that the amination-arylation of α-halo esters with sulfonamides is possible using simple reaction conditions: K_2CO_3, DMF, and heat (Scheme 132).[347] Although the substrate scope is still under development, this presented an interesting opportunity to develop an asymmetric Smiles reaction.



Scheme 132 The carboamination of α-haloesters with electron-poor *S*-aryl sulfonamides

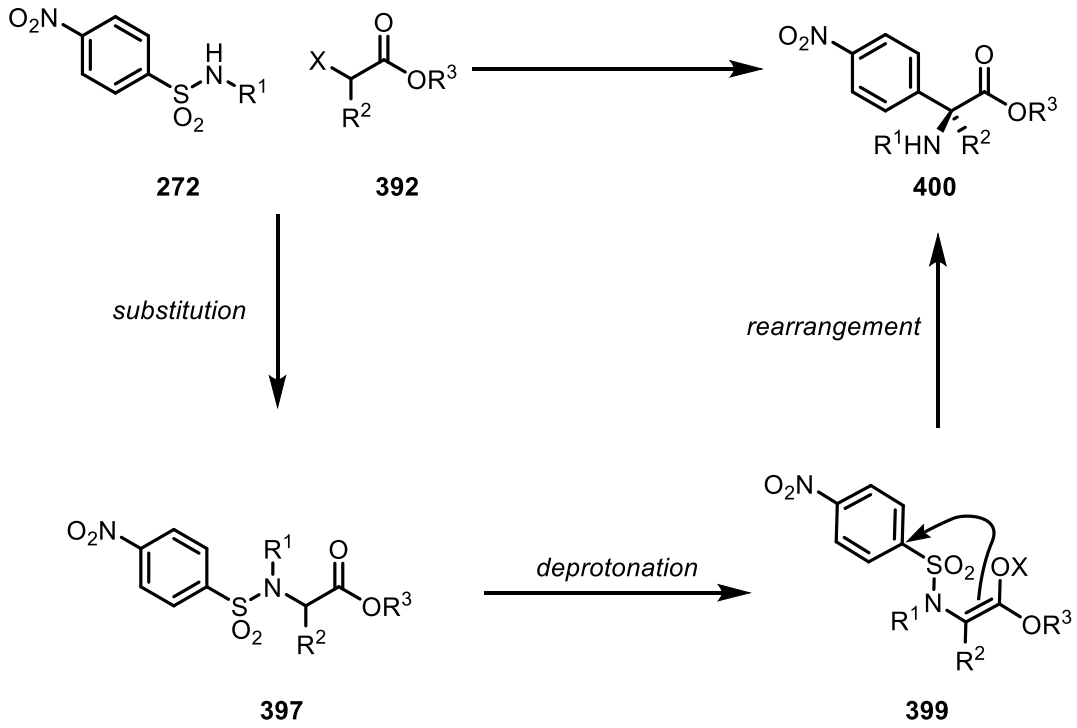
Kawabata reported the use of deprotonation-induced intramolecular nitrogen to carbon aryl transfer of ureas **394** for the for the enantioselective α-arylation of amino acids derivatives **395** which used a *memory of chirality* mechanism (Scheme 133, a).[247] Clayden has independently reported the use of a pseudoephedrine chiral auxiliary to affect a similar transformation of ureas **396** to hydantoins **397** (Scheme 133, b).[348] Furthermore, Penso has developed the memory of chirality nitrogen to

carbon aryl transfer for nosyl derived amino-acids **397** to products **398** albeit with highly variable enantioselectivity (*vide supra*, pg. 88).[230]



Scheme 133 Enantioselective nitrogen to carbon aryl transfer for enantioselective preparation of α,α-disubstituted aryl glycine derivatives

We proposed a catalytic asymmetric 1,1-carboamination of simple α-haloacetates **372** with electron-poor *S*-aryl sulfonamides **267**. The facial selectivity of the rearrangement could be influenced to afford enantioenriched products, if the racemised enolate **399** had a chiral counterion associated with it, either due to deprotonation with a chiral base or through association of a chiral quaternary ammonium cation (Scheme 134).



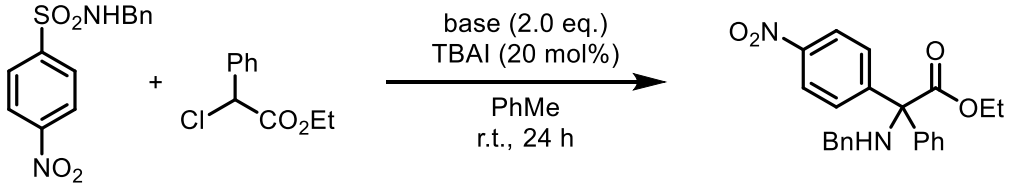
Scheme 134 Proposed enantioselective carboamination of the synthesis of α-arylglycines

4.2. Phase-Transfer Catalysis

Initially, phase-transfer catalysis was investigated, and first it had to be established whether the amination-arylation could be conducted under conditions amenable to non-covalent asymmetric organocatalysis (ambient temperature, non-polar solvents).

First, different bases were screened with *N*-benzyl-4-nitrobenzene sulfonamide **387** and ethyl α-chlorophenylacetate **401** (Table 22). These were selected from literature precedent for liquid-liquid and solid-liquid phase-transfer catalysis. Tetrabutylammonium iodide (TBAI) was selected as a readily-available, non-hygroscopic phase-transfer catalyst. Aqueous hydroxide bases such as KOH and NaOH were unsuccessful, as was $CsOH{\cdot}H_2O$ (Table 22, entry 4 – 6). K_2CO_3 was also ineffective (Table 22, entry 1), but Cs_2CO_3 performed the desired transformation with a moderate yield of **402** (Table 22, entry 2). In the absence of TBAI, no conversion was observed (Table 22, entry 6), confirming that this reagent was necessary.

Table 22 Screening bases for the racemic α-carboamination



387 **401** **402**

Entry[a]	Base	402 / %[b]
1	K_2CO_3	0
2	Cs_2CO_3	28
3	Cs_2CO_3[b]	0
4	$CsOH{\cdot}H_2O$	0
5	KOH (50%)	3
6	NaOH (50%)	0

[a]Conditions: *N*-benzyl-4-nitrobenzenesulfonamide (0.25 mmol), ethyl α-chlorophenylacetate (0.25 mmol), base (2.0 eq.), TBAI (20 mol%), PhMe (0.1M); [b]Isolated yield

The effects of reagent stoichiometry were next investigated (Table 23). When a large excess of **387** was used, without changing the number of equivalents of base, no conversion to the product occurred (Table 23, entry 1). This indicates that **387** is readily deprotonated under the reaction conditions, but this sulfonamido anion does not act as a base itself. Alternatively, when a large excess of the **401** was used (Table 23, entry 2), the yield of the reaction approximately doubled. Increasing the number of equivalents of base sequentially from 2 to 5 moderately improved the conversion to **402** (Table 23, entries 3 – 5).

Table 23 Screening stoichiometry of reagents for the racemic α-carboamination

Entry[a]	387	401	Base eq.	402 / % [b]
1	5	1	2	0
2	1	5	2	56
3	1	1	3	10
4	1	1	4	13
5	1	1	5	21

[a]Conditions: *N*-benzyl-4-nitrobenzenesulfonamide, ethyl α-chlorophenylacetate, Cs_2CO_3, TBAI (20 mol%), PhMe (0.1 M), [b]Conversion to **402** was determined by ^{1}H NMR spectroscopy, using TMB as an internal standard.

Following the conversion of the reaction over time (Figure 7) revealed that after 6 hours, conversion to **402** appeared to have stopped. However, if another equivalent of **401** was then added, conversion to **402** immediately improved. This is a single data point experiment and must be repeated in future work. This result, in combination with the effect of using a large excess of **401**, indicates that low conversions may be partly due to decomposition of this reagent **401** under the reaction conditions.

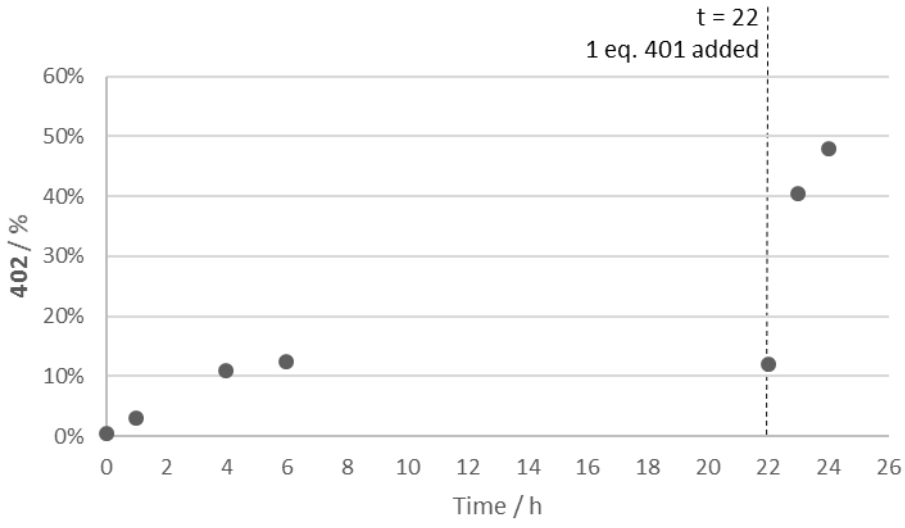


Figure 7 Conversion-time graph for the racemic α-carboamination. Single data point experiment.

Next, a variety of solvents were examined with Cs_2CO_3 as the base and TBAI as the phase-transfer catalyst (Table 24). These were selected from literature precedent for

phase-transfer catalysed transformations, and the knowledge that polar solvents can interrupt tight-ion paring required for asymmetric induction. Toluene gave a reasonable conversion to the product (Table 24, entry 1 and 2). Solvents such as $CHCl_3$, CH_2Cl_2, DCE and 2-MeTHF (a commonly used eco-friendly substitution for CH_2Cl_2) were all effective (Table 24, 3 – 8 and 13 – 14). Dichlorobenzene also afforded a comparable yield (Table 24, entry 10), but due to the impracticality of working with this solvent, this avenue was not perused. Ethreal solvents, diethyl ether and MTBE, were ineffective and gave low conversion to the product (Table 24, entry 11 and 12).

Repetition of some experiments gave inconsistent conversions (albeit within 10%). The use of round-bottom microwave vials, as opposed to flat-bottom vials, was therefore tested. However, these experiments all gave lower conversions than the equivalent experiment with flat-bottom vials (Table 24, entries 2, 7 and 14). These inconsistencies are potentially a consequence of the heterogeneous reaction mixture.

Table 24 Screening solvents for the racemic α-carboamination reaction

Entry[a]	Solvent / 0.1 M	402 / %[b]	Isolated yield /%
1	PhMe	21	18
2[c]	PhMe	14	-
3	$CHCl_3$	29	-
4	$CHCl_3$	19	-
5	CH_2Cl_2	25	21
6	CH_2Cl_2	31	-
7[c]	CH_2Cl_2	13	-
8	DCE	23	31
9	1,2-dichlorobenzene	n/a[d]	21
10	hexachloro-2-propanone	n/a[d]	0
11	Et_2O	0	0
12	MTBE	9	11
13	2-MeTHF	31	26
14[c]	2-MeTHF	27	-

[a]Conditions: *N*-benzyl-4-nitrobenzenesulfonamide (2.0 eq.), ethyl α-chlorophenylacetate (1.0 eq.), Cs_2CO_3 (2.0 eq.), TBAI (20 mol %), [b]Conversion to product was determined by ^{1}H NMR spectroscopy, using TMB as an internal standard; [c]Reaction performed in microwave vials, [d]Non-volatile.

The effect of concentration was then investigated (Table 25). A lower concentration decreased the yield (Table 25, entry 4), whilst increasing the concentration to 0.2 M improved the yield (Table 25, entry 2). A further increase to 0.25 M lead to a decrease back to around 30% (Table 25, entry 1).

Table 25 The effect of concentration on the racemic α-carboamination reaction

Entry[a]	Concentration	402 / %[b]
1	0.25	28
2	0.2	42
3	0.1	31
4	0.05	21

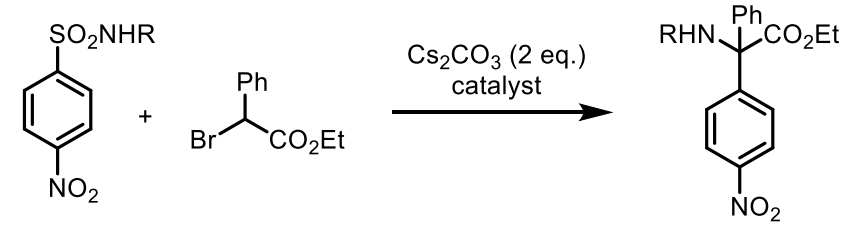
[a]Conditions: *N*-benzyl-4-nitrobenzenesulfonamide (2.0 eq.), ethyl α-chlorophenylacetate (1.0 eq.), Cs_2CO_3 (2.0 eq.), TBAI (20 mol%), 2-MeTHF, [b]Conversion to **402** was determined by ^{1}H NMR spectroscopy, using TMB as an internal standard.

The reaction between ethyl α-bromophenylacetate **403** and *N*-benzyl-4-nitrobenzene sulfonamide **387** in CH_2Cl_2 gave a better yield than the reactions with α-chlorophenylacetate **401** (Table 26, entry 1), therefore asymmetric catalysis was explored with this substrate. Conditions for the separation of the two enantiomers of **402** by chiral stationary phase HPLC were found using the Amylose-1® column.

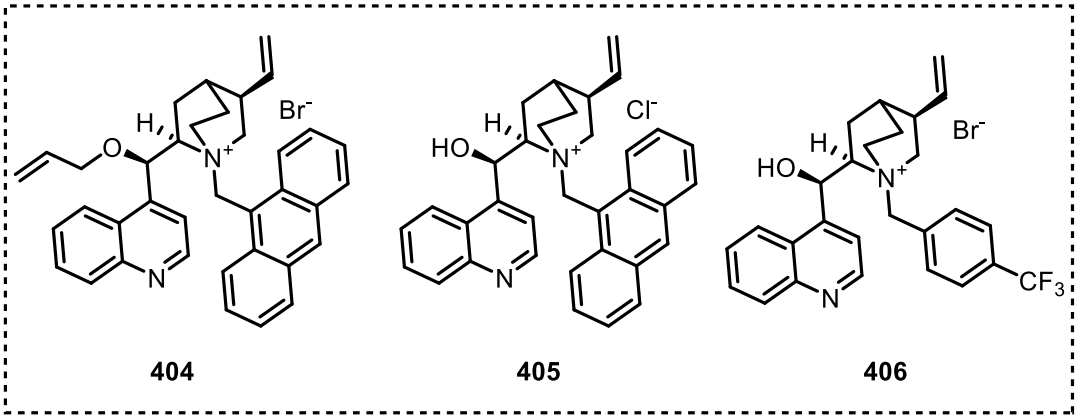
Initially, conditions were tested using *N*-benzyl-4-nitrobenzene sulfonamide **367** as the substrate. Solvents with a range of polarities were tested with **404** (Table 26, entries 3 – 5). This catalyst was initially selected to avoid potential protonation of the substitution intermediate. However, no enantioselectivity was observed regardless of the solvent.

Three quinine based catalysts **404**-**406**, which were readily available, were then tested for the reaction between *N*-methyl-4-nitrobenzene sulfonamide **407** and 2-bromophenyl ethyl acetate **403**. The sulfonamide substrate was changed for two reasons. Firstly, this was a more effective substrate in the racemic reactions with K_2CO_3 in DMF. Secondly, a larger difference between the size of the substituents (aryl vs benzyl and aryl vs methyl) may increase energy differences between enantiodetermining configurations. Unfortunately, no enantioselectivity was observed in any of these catalysts (Table 26, entries 6 – 8).

Table 26 Investigation of chiral phase-transfer catalysts for enantioselective α-carboamination



387 *or* **407** **403** **402** *or* **408**



404 **405** **406**

Entry[a]	R	Catalyst	Time	Solvent	Yield / %[b]	*ee* / %[c]
1	Bn	TBAI	19	CH_2CH_2	50	-
2	Bn	**404**	19	PhMe	33	0%
3	Bn	**404**	19	CH_2Cl_2	41	0%
4	Bn	**404**	19	2-MeTHF	26	0%
5	Me	TBAI	22	CH_2Cl_2	2	-
6	Me	**404**	22	CH_2Cl_2	10	0%
7	Me	**405**	22	CH_2Cl_2	6	0%
8	Me	**406**	22	CH_2Cl_2	20	0%

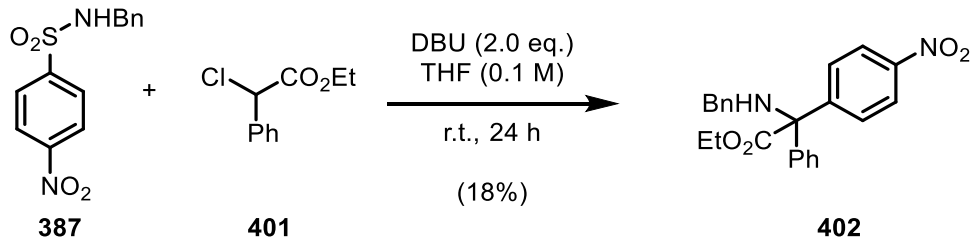
[a]Conditions: 4-nitrobenzynesulfonamide (0.1 mmol), α-bromophenylethyl acetate (0.1 mmol), Cs_2CO_3 (0.2 mmol), catalyst (0.02 mmol), solvent (0.2 mL), r.t., [b]Conversion determined by ^1H NMR spectroscopy, using TMB as an internal standard, [c]Determined from the isolated material using chiral stationary-phase HPLC.

Several observations had indicated that whilst the selected conditions can perform the 1,1-carboamination, they may not be operating as intended. No reaction occurs in the absence of a phase-transfer catalyst, indicating that the quaternary ammonium salt is acting to assist the reaction. However, it is possible that the phase-transfer catalyst is solubilising the deprotonated sulfonamide for rate-determining substitution.

A colour change, from pale yellow to deep red, is observed upon mixing the sulfonamide with even a mild base in solution. In non-polar solvents, such as toluene, the sulfonamide remains as a red solid, whilst in more polar solvents some yellow colouration of the solution is also observed. This colour change is associated with the deprotonation of nitrobenzene-sulfonamides,[296] but the nature of colouration has yet to be established.

4.3. Brønsted Base Catalysis

Achiral non-nucleophilic bases were investigated to establish whether Brønsted base catalysis might be suitable for the asymmetric amination-arylation reaction. An initial reaction between *N*-benzyl-4-nitro-benzene sulfonamide and 2-chlorophenyl-ethyl acetate afforded an 18% isolated yield of the amination-arylation product (Scheme 135).

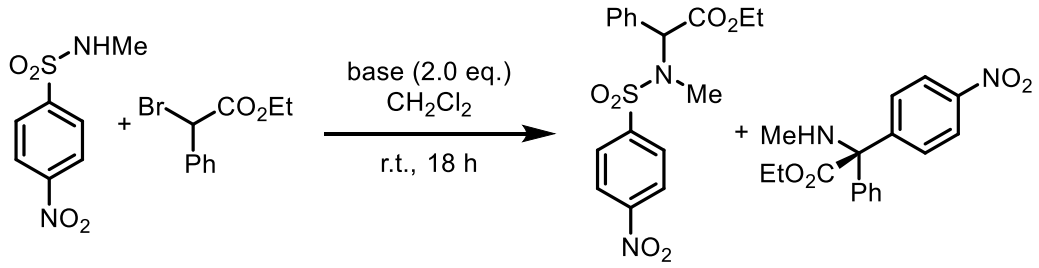


387 **401** **402**

Scheme 135 DBU catalysed α-carboamination

Organic bases with a range of pK_{BH+} values were then investigated for the reaction between **407** and **403** in CH_2Cl_2 (Table 27). Relatively weak bases, such as triethylamine and DIPA were not effective at performing the desired transformation (Table 27, 1 and 3). Stronger bases such as DBU and TMG in CH_2Cl_2 appeared to cause some decomposition of the starting materials (Table 27, 6 and 7). Notably, triethylamine in the presence of DMAP as a nucleophilic catalyst resulted in a 15% isolated yield of the substitution product (Table 27, entry 2).

Table 27 Screening bases for the Brønstead base catalysed racemic α-carboamination

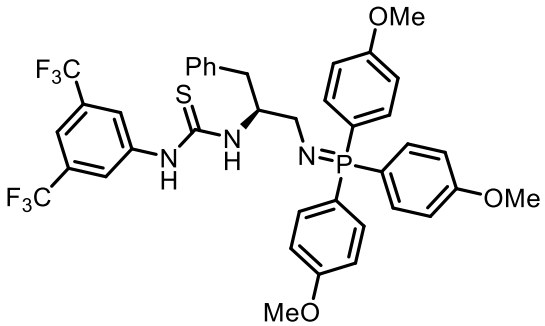


407 **403** **409** **408**

Entry[a]	Base	Additive	Result
1	Et_3N	-	0%
2	Et_3N	DMAP (10 mol%)	15% **409**
3	DIPEA	-	0%
4	DABCO	-	0%
5	NMM	-	0%
6	TMG	-	0%
7	DBU	-	0%

[a]Condtions: sulfonamide (0.1 mmol), halo acetate (0.1 mmol), base (0.2 mmol), CH_2Cl_2 (0.5 mL), r.t., 18 h

There are many asymmetric Brønsted base catalysts, with various pK_{BH+} values and functional groups which exert stereocontrol. A bifunctional iminophosphorane catalyst **410** (Figure 8), developed by the group of Dixon, was selected due to the strong basicity of the iminophosphorane.[349]



410

Figure 8 The bifunctional iminophosphorane catalyst designed by Dixon

No reaction occurred with a substoichiometric quantity of **410** (Table 28, entry 2), and in the presence of a NaOAc buffer some starting materials were consumed, but no product was isolated (Table 28, entry 2). These results may be a consequence of

the reaction solvent, diethyl ether, which was selected because this is the medium in which the catalyst is prepared in but may not be an optimal solvent for the transformation. Alternatively, it may be that **410** is not sufficiently basic to effect deprotonation of the sulfonamide,[350] or NaOAc is not effective as a terminal base.

Table 28 Screening conditions for the enantioselective α-carboamination catalysed by BIMP x

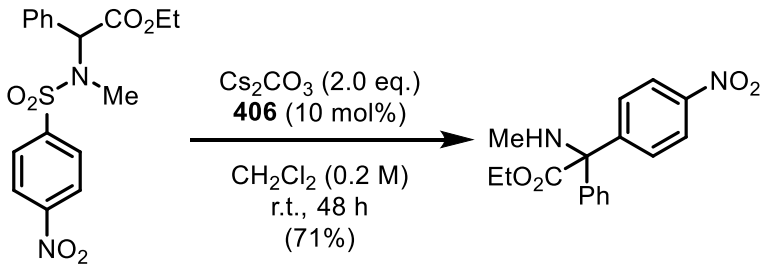
Entry[a]	Additive	408 / %
1	N/A	0
2	NaOAc (1.0 eq.)	0

[a]Conditions: *N*-methyl-4-nitrobenzynesulfonamide (0.1 mmol), α-bromophenylethyl acetate (0.1 mmol), catalyst (0.02 mmol), Et_2O (0.1 M), r.t., 18 h

4.4. Asymmetric Truce-Smiles

It had become apparent that both the sulfonamide and the halo-acetate were unsuited to phase-transfer catalysis from the initial investigations into this transformation. Before proceeding further with the tandem substitution and rearrangement, we decided to investigate the Truce-Smiles rearrangement as in individual step. The proposed substitution intermediate was prepared independently and then examined with two sets of asymmetric conditions.

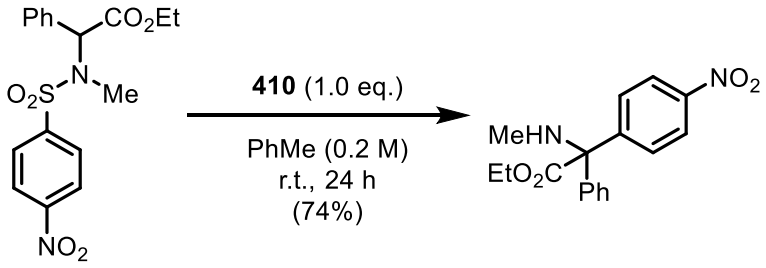
Firstly, the intermediate was examined with the quinidine derived quaternary ammonium salt catalyst which had given the best conversion in the previous section, **406 (**Scheme 136). A 71% isolated yield was achieved under similar conditions to those previously used; however, the reaction was not enantioselective.



409 **408**

Scheme 136 The reaction of 409 under phase-transfer catalysis

Secondly, one equivalent of the BIMP was tested in toluene at ambient temperature for 24 hours (Scheme 137). The reactions catalysed by BIMP catalysts are typically performed with catalytic quantities of the base for reaction times extending up to 3 days. In this case, with a stochiometric amount of base, a 74% yield was obtained, but again the reaction was not enantioselective.



409 **408**

Scheme 137 The reaction of 409 with the catalyst 410

4.5. Conclusion and Future Work

Reaction conditions for the 1,1-carboamination of α-halo esters which are amenable to non-covalent asymmetric organocatalysis have been identified, although the yields of the tandem reaction remain low (up to 50%). Asymmetric induction through a quaternary ammonium counterion appears to be unfeasible, due to the incompatibility of the sulfonamide (insolubility of the anion), and the α-halo acetate (decomposition) with the reaction conditions. The Truce-Smiles rearrangement alone was performed under phase-transfer conditions in a 71% yield, but no

enantioselectivity was achieved. Tandem 1,1-carboamination was also unsuccessful with simple Brønstead catalysis. This is due to the ineffective installation of the *S*-aryl sulfonamide, potentially due to decomposition with strong organic bases (*vide supra*, pg. 153). The Truce-Smiles rearrangement itself could be performed with the iminophosphorane base in a 74% yield. Asymmetric induction has not yet been achieved in the small number of experiments which have been conducted.

The installation of the electron-poor *S*-aryl sulfonamide and development asymmetric induction could be investigated further, and studies are on-going within the group. More specifically, some suggestions include Jørgensen phase-transfer conditions for S_NAr arylation with intermediate **409** and extensive investigation of reaction conditions;[179-180] exploring DMAP and nucleophilic catalysts; use of oxidative C–H amination to first install the sulfonamide followed by base-mediated asymmetric aryl transfer.

Chapter 4. Organocatalysis and the Vicarious Nucleophilic Substitution of Hydrogen

1. Introduction

1.1. Mechanism

The vicarious nucleophilic substitution of hydrogen (VNS) in electron-deficient arenes is a classical reaction which has primarily found use within the process chemical industry for the installation of methyl groups onto nitroarenes. [351] The mechanism of VNS (Figure 9) involves the addition of a carbanion nucleophile **413** to an electron-deficient arene **412** which results in the formation of a short lived σ^H-adduct **414**. Base induced elimination of H–X follows this to form intermediate **415**, which is protonated upon acidic work up to afford benzyl products **416**. Alternatively, oxidation of the σ^H-adduct can be performed to afford similar products, in oxidative nucleophilic aromatic substitution. Other electrophiles have been demonstrated to be effective in the quenching of the elimination intermediate **416**.

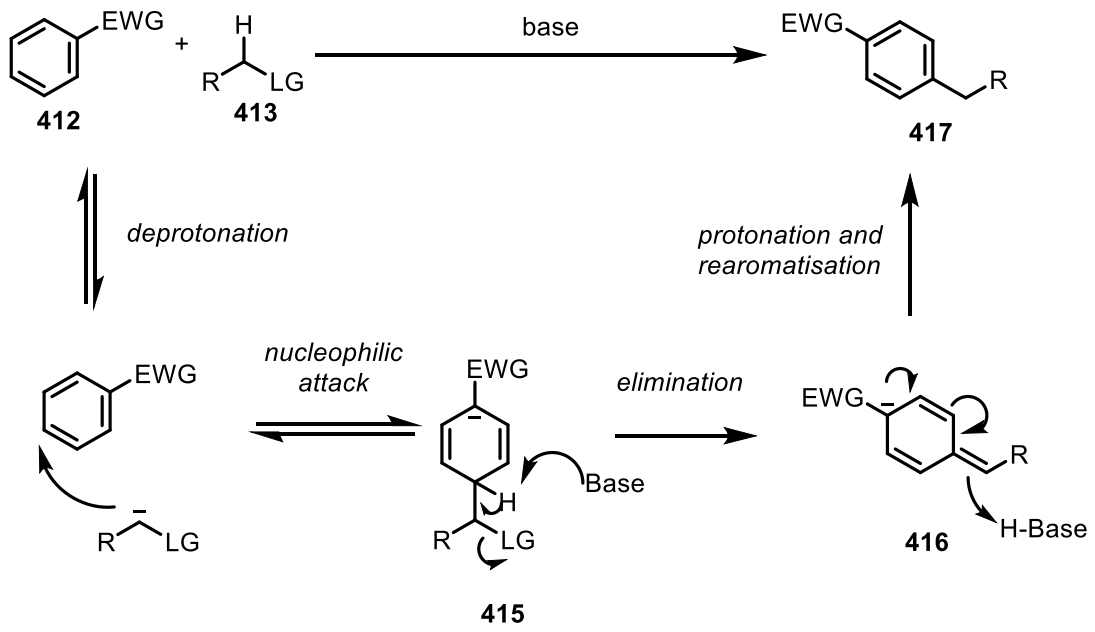


Figure 9 The mechanism of VNS

The mechanism of this reaction has been well investigated to clarify an anionic or radical pathway.[352-353] As nitroarenes are active electron acceptors and carbanions are good electron donors, it is possible that these two substrates could enter a radical pathway through single electron transfer to give a nitrobenzene radical anion and an electrophilic carbon radical. These species could then combine to form a σ^H-adduct. However, several pieces of evidence support the anionic substitution mechanism: firstly, a notable selectivity for *ortho*-addition in nitrobenzene; secondly, a well resolved and characterised ^{1}H NMR spectra of the σ^H-adduct;[354] thirdly, a cyclopropyl radical clock does not ring-open under standard reaction conditions.[355]

The transformation of σ^H-adducts **416** into the products of VNS **417** has also been studied.[356] The comparison of VNS with competing S_NAr reactions of nitrophenyl fluorides revealed that the rate of VNS is dependent on base concentration. At low base concentration, the collapse of the σ^H-adduct is faster than β-elimination, and β-elimination becomes the rate-limiting step through equilibration. Whereas, at high base concentrations β-elimination is fast, and so nucleophilic addition becomes rate-

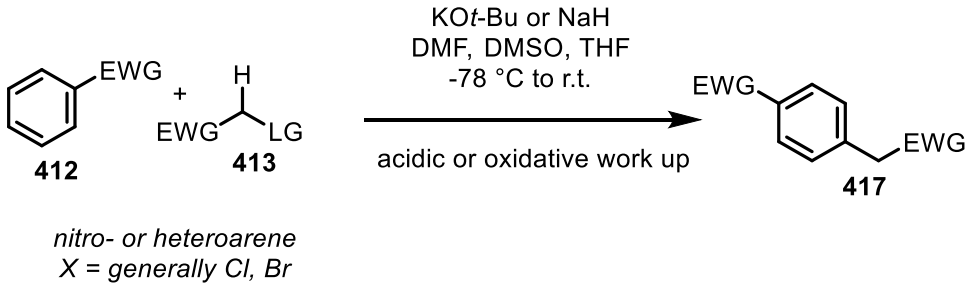
limiting. The formation and reaction of the σ^H-adduct has also been monitored by UV-vis spectroscopy.[354]

VNS and S_NAr have the same requirement of an electron deficient arene to facilitate the nucleophilic attack. Whilst these two reactions have many similarities, the mechanisms fundamentally differ at the rate determining step. As such, with the same reactants, either reaction can be achieved depending upon whether the conditions favour a thermodynamic or kinetic pathway. Under the appropriate conditions, the carbanion can react with *para*- and *ortho*-nitrobenzene *via* the VNS pathway, in preference to the substitution of the halogen. However, with conditions which disfavour the substitution of hydrogen, such as without strong base or at higher temperatures, the halogen is preferentially displaced.

1.2. Scope

The arene coupling partner must be sufficiently electrophilic to be reactive toward the initial addition reaction, and the alkyl coupling partner must have a nucleofugal group in the alpha position to a basic proton (Scheme 138). The requirements for this reaction include a strong base and polar medium. Typically, chloromethyl phenylsulfone is used is chosen as a nucleophile for these transformations, particularly in the mechanistic work which has been conducted.[354] Substituted α-chloroalkanenitriles, alkyl α-chloroalkanoates, chloroalkyl oxazolines, and chloroform, etc., are also effective nucleophiles. The nucleofugal group is usually a halogen, but alkyoxy, aryloxy, alkylthio and arylthio groups have also been demonstrated.[351] Besides carbanions, heteroanions with nucleofugal groups can also participate in VNS reactions. Many electron deficient arenes are suitable for VNS reactions, including both carbo- and heteroaromatics which are activated by a nitro-

group,[357] and arenes which are electrophilic due to the electronic configuration.[358-359] Pyridines, although moderately electron deficient, require activation either with nitro groups,[360] or through the formation of the pyridinium salts.[361]



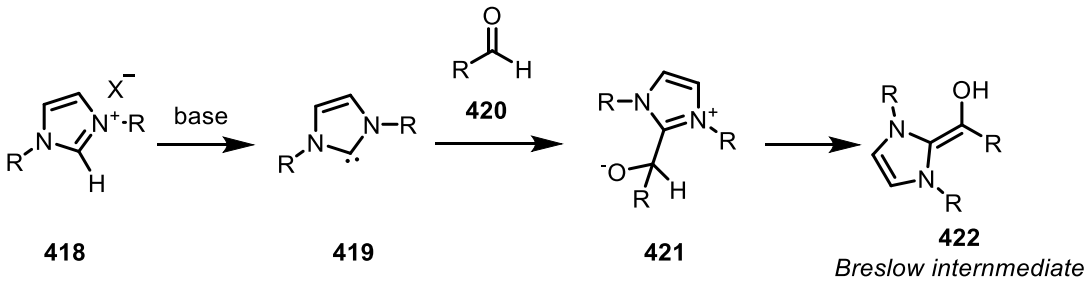
Scheme 138 A general depiction of the VNS reaction

There are limitations in the substrates used for this transformation and the reaction conditions employed. The use of organocatalytic strategies to generate carbanions presented an interesting opportunity to extend this chemistry into new areas, and potentially identify novel transformations.

2. Results

2.1. *N*-Heterocyclic carbene catalysis

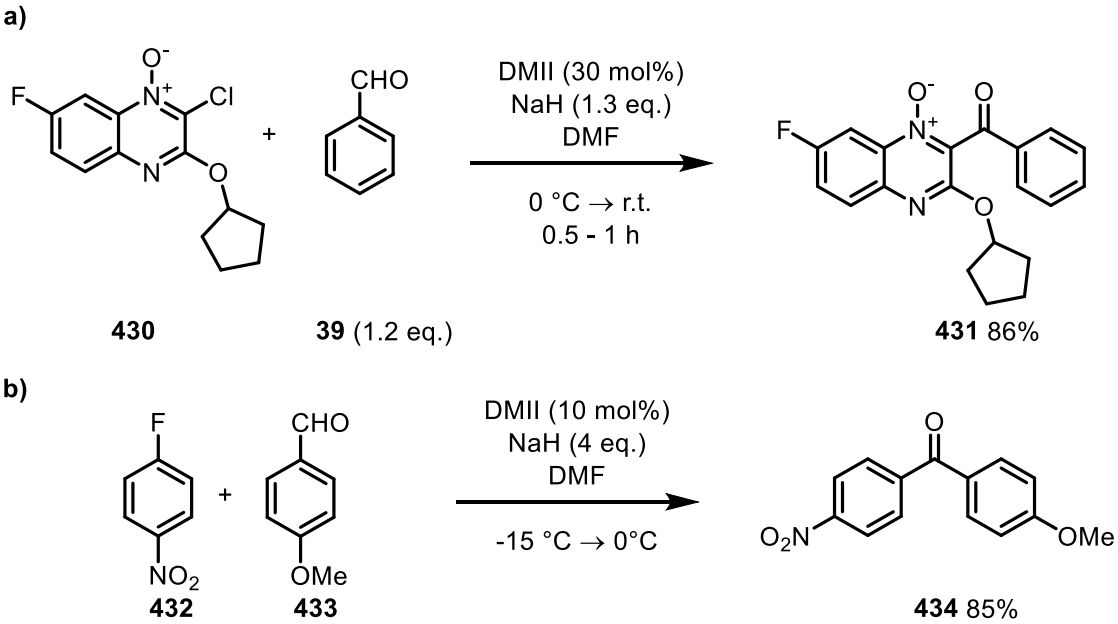
N-heterocyclic carbenes **419** (NHCs) have been developed as catalysts for the generation of acyl anion equivalents. This mode of reactivity is based on the cyanide-catalysed benzoin condensation,[362-363] and the biochemical generation of acyl anion equivalents by the enzyme co-factor thiamine.[364] The catalyst is formed through deprotonation of an azolium salt precatalyst **418**. Condensation of the *N*-heterocyclic carbene **419** results in the formation of a Breslow intermediate **422** (Scheme 139),[365] which can then act as an acyl anion equivalent. If the NHC condenses with α,β−unsaturated aldehydes, homoenolates are formed. Azolium enolates and acyl azoliums can be prepared with other electrophiles. The role of *N*-heterocyclic carbenes in organocatalysis has been reviewed.[366]



Scheme 139 The condensation of an *N*-heterocyclic carbene with an aldehyde to form the Breslow intermediate

The NHC-catalysed reaction of benzaldehydes **39** with heteroaromatic chlorides **430** had been reported by Miyashita,[367-368] and later by Kaufman (Scheme 140, a).[369] Suzuki then reported the NHC mediated reaction of aryl fluorides **432** with benzaldehydes **39** (Scheme 140, b).[370-371] Both transformations used dimethylimidazolium iodide (DMII), or a similar NHC precatalysts. The mechanism of these reactions is proposed to proceed *via* condensation of benzaldehyde with the NHC to form the Breslow intermediate which then undergoes a nucleophilic

aromatic substitution reaction with the aryl halide. The resultant intermediate then eliminates to regenerate the NHC and form the diaryl ketone products **431** or **434**. This precedence, coupled with the extensive comparisons of S_NAr with VNS, prompted us to investigate the potential for an NHC mediated VNS reaction.



Scheme 140 a) NHC catalysed reaction of aldehydes with heteroaryl chlorides b) the NHC catalysed reaction of aldehydes with aryl fluorides

The mechanism of an NHC mediated VNS (Figure 10) is proposed to proceed *via* initial formation of the Breslow intermediate from the NHC **419** and aldehyde **39** (**I**), then nucleophilic attack onto the electron deficient arene **412** (**II**), followed by deprotonation and elimination to regenerate the NHC (**III**). The elimination product **437** is then quenched with an electrophile (**IV**), such as a proton, to afford the final diaryl methanol product **438**. Unproductive side reactions, such as the Canizzaro reaction and benzoin condensations, were anticipated. Through optimisation of the reaction conditions, these pathways could potentially be minimised.

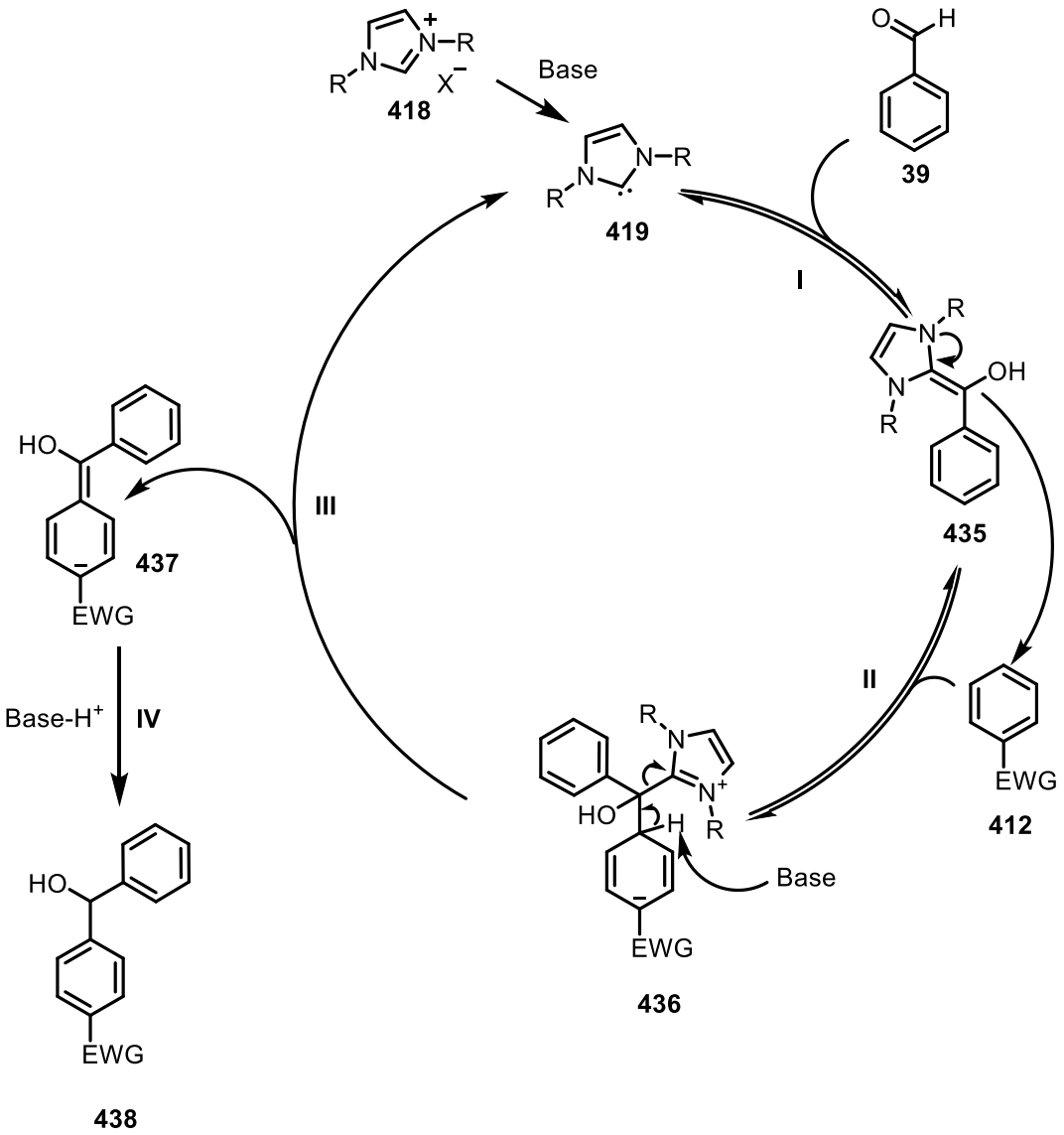


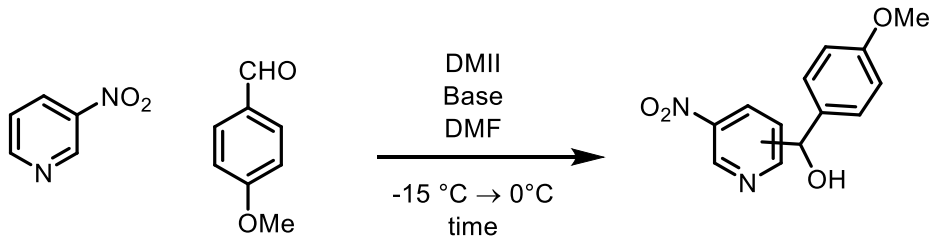
Figure 10 The proposed mechanism of NHC catalysed VNS reaction of aldehydes with nitroarenes

3-Nitropyridine **439** was selected as a substrate for initial investigations, as it has been established as one of the most reactive partners in the VNS reaction, superseded only by 2-chloro-3-nitrobenzene, which would be susceptible to nucleophilic aromatic substitution.[372] As no competing S_NAr reaction was possible with the selected substrate, initial reaction conditions between **439** and **433** were modelled on those reported by Suzuki for NHC mediated S_NAr.[370-371, 373]

Various reactions conditions were screened and, in most cases, decomposition of **439** was observed (Table 29, entries 1 and 2). This was characterised by the formation of

highly coloured products and an absence of returned starting material. Control experiments (Table 29, entries 3, 4, 5) were conducted and confirmed the decomposition of 3-nitropyridine. No decomposition of the nitropyridine occurred in the presence of milder bases that are capable of deprotonating DMII to form the active catalyst, but the only substances identified were those associated with unproductive reactions of the NHC catalyst (Table 29, entries 7 and 8).

Table 29 Screening conditions for the DMII catalysed VNS reaction between 439 and 433



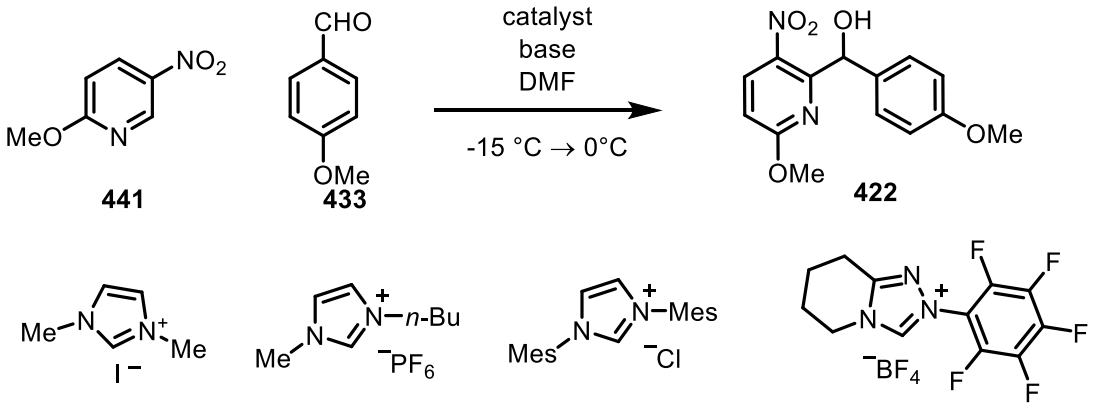
439 **433** **440**

Entry[a]	Base	Result
1[b]	NaH (4.0 eq.)	decomposition
2	NaH (1.3 eq.)	decomposition
3[c,d]	NaH (1.0 eq.)	decomposition
4[d,e]	NaH (1.0 eq.)	**433** recovered
5[c,f]	NaH (2.0 eq.)	decomposition
6	KO*t*-Bu (1.3 eq.)	**433** recovered + **439** decomposition
7	DBU (1.3 eq.)	**439** recovered
8	K_3PO_4 (1.3 eq.)	**439** recovered

[a]Conditions 3-nitropyridine (1 eq.), *p*-anisaldehyde (1.2 eq.), DMII (30 mol%), DMF, 0 °C, 1 h; [b] 10 mol%, 2h; [c]no aldehyde; [d]no catalyst; [e]no pyridine; [f]1.0 eq. catalyst

The reaction substrate was changed to the slightly less electrophilic 2-methoxy-5-nitropyridine **441**, and reactions were performed at −15 °C to avoid decomposition of the nitropyridine (Table 30). No reaction was observed with DMII (Table 30, entry 1) nor with catalysts **433** or **444** (Table 30, entries 2 and 4). IMes gave only undesired side products derived from the aldehyde, and some nucleophilic substitution of the methoxy group by the *tert*-butoxy (Table 30, entries 3 and 5).

Table 30 Screening NHC pre-catalysts for the VNS reaction between 411 and 433

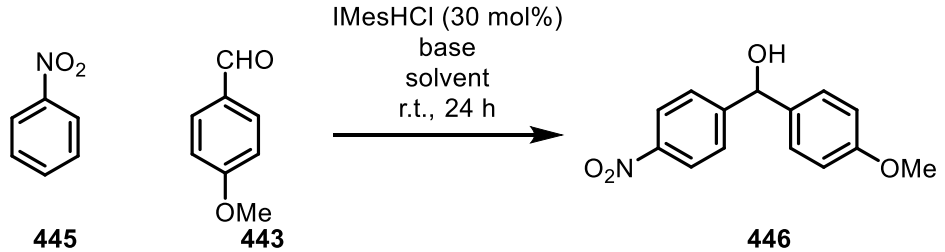


Entry[a]	Catalyst	Base	Result
1	DMII	NaH	No reaction
2	Cat A	KO*t*-Bu	No reaction
3	Cat B	KO*t*-Bu	S_NAr and **443** by-products
4	Cat C	KO*t*-Bu	No reaction
5	Cat B	KO*t*-Bu	Complex mixture

Conditions: 2-methoxyl-5-nitropyridine (1.0 eq.), *p*-anisaldehyde (1.1 eq.), base (1.3 eq.) precatalyst (30 mol%), DMF, −15 to 0 °C, 2 h; [b]6 h

Nitrobenzene **445** was also investigated as a reaction partner in the transformation of interest. The proposed product **446** of the transformation was also prepared independently to aid analysis. The IMesHCl was first investigated (Table 31), with DBU and KO*t*-Bu acting as bases both for the generation of the NHC and the key elimination step. However, no product was detected whilst using DBU under cryogenic conditions (Table 31, entries 1 and 2), with either THF or nitrobenzene as the reaction medium. Similarly, with KO*t*-Bu at ambient temperature, none of the desired product was detected in a range of solvents (Table 31, entries 3 – 6).

Table 31 Screening conditions for the IMes catalysed VNS reaction of 445 and 433



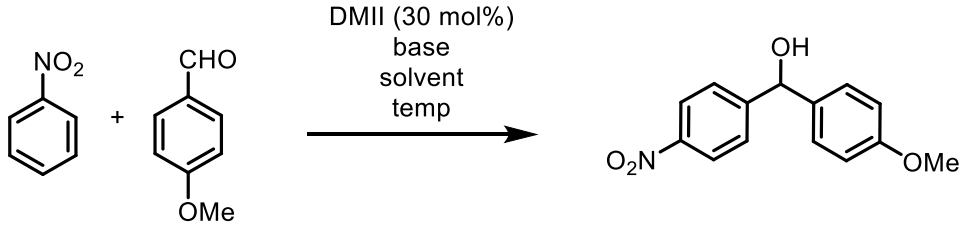
445 **443** **446**

Entry[a]	Base	Solvent	Result
1[b]	DBU (2.0 eq.)	THF (0.5 M)	No product
2[b,c]	DBU (1.3 eq.)	$PhNO_2$ (0.5 M)	No reaction
3	KO*t*-Bu (1.3 eq.)	DMF (0.3 M)	No product
4	KO*t*-Bu (1.3 eq.)	MeCN (0.3 M)	No product
5	KO*t*-Bu (0.3 eq.)	DCE (0.3 M)	No reaction
6	KO*t*-Bu (0.3 eq.)	1,4-Dioxane (0.3 M)	No product

[a]Conditions: nitrobenzene (1.0 eq.), *p*-anisaldehyde (1.0 eq.) CatB (30 mol%), r.t., 24 h; [b]From −78 °C to r.t., 18 h; [c] Nitrobenzene as reaction medium

DMII was then investigated as a precatalyst for the reaction of nitrobenzene **445** (Table 32). At ambient temperature, **443** was consumed but none of the desired product **446** formed (Table 32 entries 1 – 3). Increasing the reaction temperature to 80 °C formed a small quantity of benzamide when DMF was used as the solvent (Table 32, entry 4), and only products of unproductive aldehyde reactions were obtained in other solvents (Table 32, entry 5 and 6). Changing the base from NaH to KO*t*-Bu, at both ambient temperature and −40 °C gave a possible trace of the product, as detected by ^{1}H NMR, but nothing of significance could be isolated (Table 32, entry 7 and 10). K_3PO_4 afforded unproductive aldehyde condensation products with unconsumed nitrobenzene (Table 32, entry 8), and DBU gave only returned starting materials (Table 32, entry 9).

Table 32 Screening conditions for the DMII catalysed VNS reaction between 445 and 443



445 **443** **446**

Entry[a]	Base	Solvent	Temp	Result
1	NaH	DMF	r.t.	No product
2	NaH	THF	r.t.	No product
3	NaH	PhMe	r.t.	No product
4	NaH	DMF	80 °C	benzamide (6%)
5	NaH	THF	80 °C	No product
6	NaH	PhMe	80 °C	No product
7	KO*t*-Bu	DMF	r.t.	No product
8	K_3PO_4	DMF	r.t.	No product
9	DBU	DMF	r.t.	No reaction
10[b]	KO*t*-Bu	DMF	−40 °C to r.t	No product

[a]Conditions: nitrobenzene (1.0 eq.) *p*-anisaldehyde (1.0 eq.), base (1.3 eq.) DMII (30 mol%), 18 h;
[b] KO*t*-Bu (5.0 eq.)

Rajan-Babu had reported that, in the presence of TASF, silyl enol ethers could add to nitrobenzene in an oxidative variant of the vicarious nucleophilic substitution reaction.[374-375] Models of the Breslow intermediate have been studied by Mayr to determine their nucleophilicity by determining the rate constant for the reaction with benzyhydrylium ions at 20 °C.[376] Benzyhydrilium ions are used as reference electrophiles in Mayr's studies of nucleophiles, and standard parameters of nucleophilicity have been determined from these experiments using equation 1, where k is the rate constant, E is the solvent-independent electrophilicity parameter, and s_N and N are solvent-dependent parameters.

$$\log k = s_N(N + E) \quad (1)$$

The deoxy-Breslow intermediate **447** and **448**, formed from benzyl bromide and IMes, was determined to have a nucleophilicity parameter (*N*) of 17.41 in DMSO and 17.21 in THF and the *O*-methylated intermediate **450** has a value of 16.61 in THF (Figure 11). Comparatively, "naked" enolates, such as those derived from aryl ethyl acetates **449**, are calculated to have nucleophilicity parameters which are significantly higher.[377] Therefore, the Breslow intermediate may not be sufficiently nucleophilic to form the σ^H-adduct, particularly in light of the alternative reaction pathways available to the intermediate.

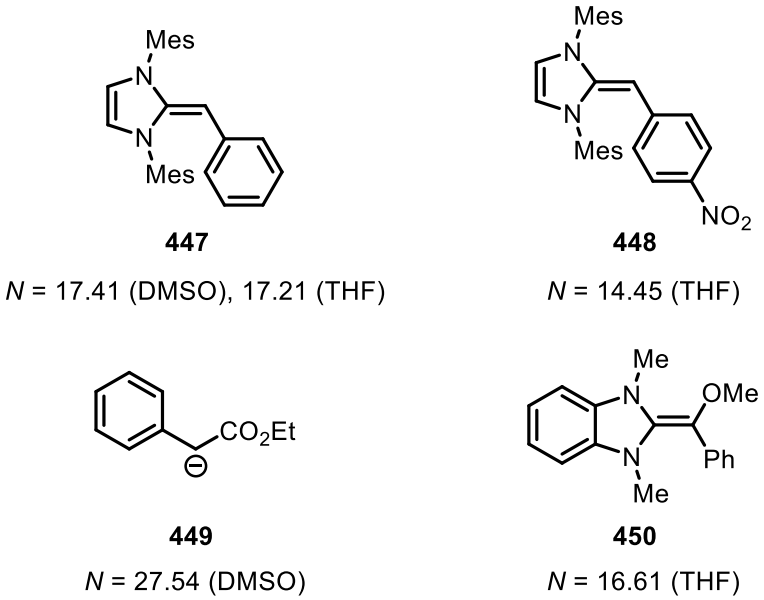
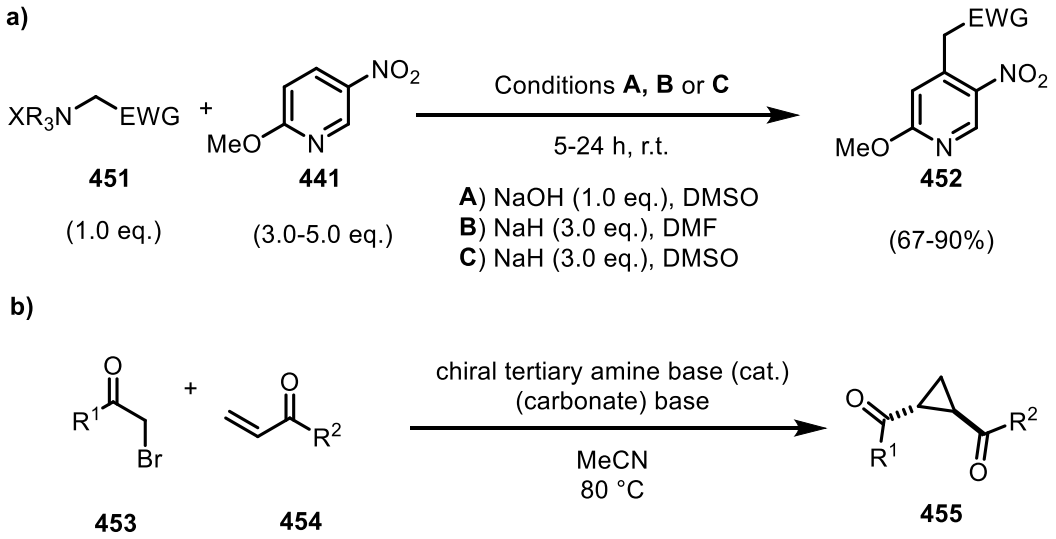


Figure 11 Nucleophilicity parameters

2.2. Tertiary amine catalysis

The role of tertiary amine catalysis in VNS was next investigated. Jończyk had demonstrated that preformed quaternary ammonium salts **451** were suitable substrates for VNS with activated pyridines **441** (Scheme 141, a).[378] This transformation could potentially be combined with the *in-situ* formation of ammonium salts from α-halo carbonyls **453**, like in the formation of cyclopropanes **455** from Michael acceptors **454** (Scheme 141, b).



Scheme 141 a) VNS reaction of ammonium ylides with nitropyridines b) Catalytic formation of ammonium ylides with a tertiary amine and carbonate bases to make cyclopropanes.

Thus, the merging of *in situ* ammonium ylide formation with the VNS reaction was proposed (Figure 12). The substitution of the α-nucleofuge by a tertiary amine **456** would lead to the *in-situ* formation of a quaternary ammonium salt **458** (**I**). This intermediate would then be deprotonated (**II**) to form an ammonium ylide **458**. This ylide would then undergo nucleophilic addition with an electro-deficient arene **445** (**III**) to form the intermediate σ^H-adduct **459**, followed by elimination of the tertiary amine (**IV**), and finally, an acidic quench (**V**) to afford the α-arylated product **461**.

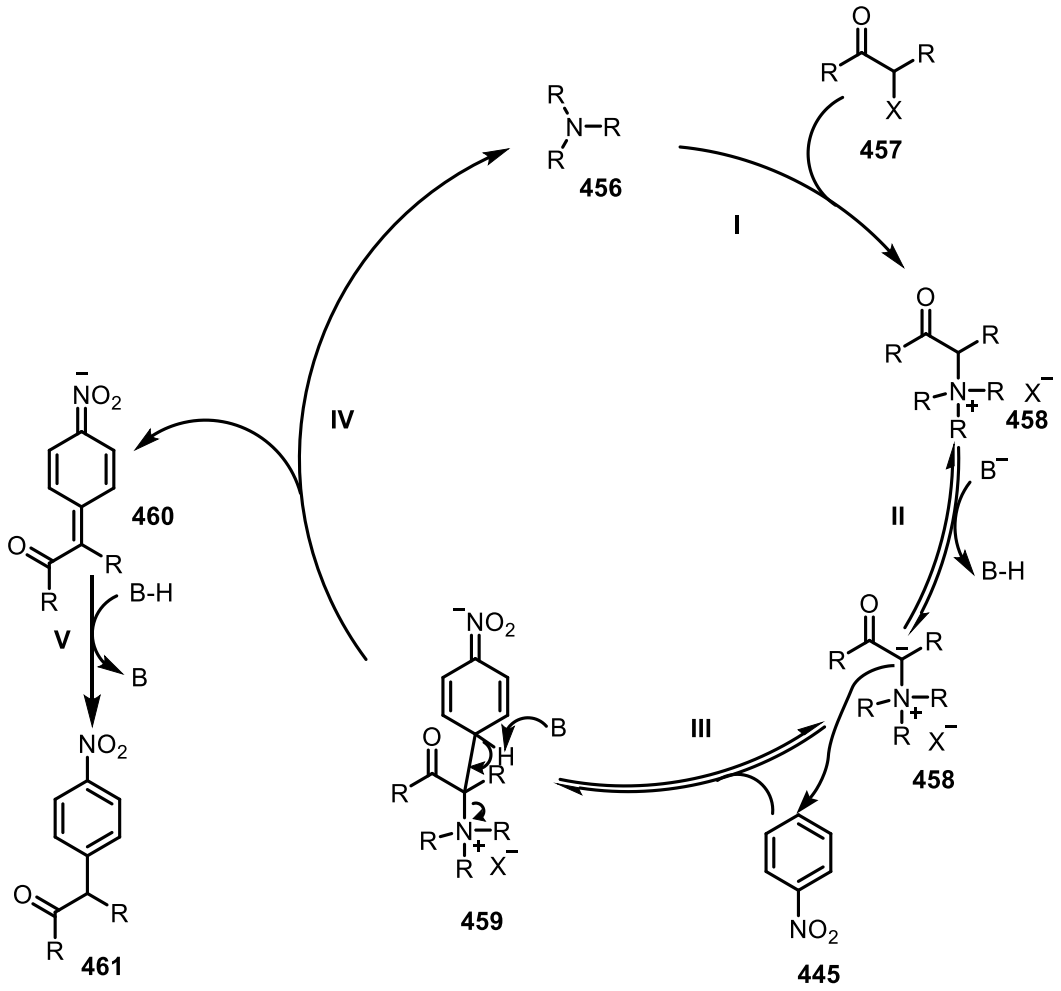
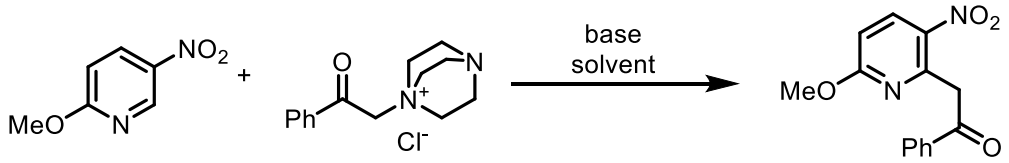


Figure 12 The mechanism of the postulated tertiary amine catalysed VNS reaction

The quaternary ammonium salt of 2-chloroacetophenone **462** was prepared with DABCO and tested for VNS reactivity with 2-methoxy-5-nitropyridine **441** (Table 33). With ground, dried NaOH in DMSO, DMF or MeCN at room temperature, no product was detected by ^{1}H NMR nor by GCMS of the crude reaction material (Table 33, entries 1 – 3). Decomposition of the quaternary ammonium salt occurred and the pyridine was recovered with NaH in DMF, both with rigorous exclusion of oxygen and water, or standard experimental set up (Table 33, entries 4 and 5). The major product resulted from demethylation of the methoxy group with KO*t*-Bu as a base at −40 °C, (Table 33, entry 6). Finally, a strong non-nucleophilic base DBU gave no reaction (Table 33, entry 7). With no desired reactivity observed, this substrate combination was set aside.

Table 33 Screening conditions of the VNS reaction between 441 and 462



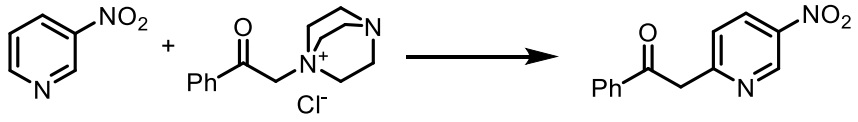
441 462 463

Entry[a]	Base	Solvent	Result
1	NaOH[b]	DMSO	0%
2	NaOH[b]	DMF	0%
3	NaOH[b]	MeCN	0%
4[c,d]	NaH (9.0 eq.)	DMF	**441** returned
5[c,f]	NaH (3.0 eq.)	DMF	**441** returned
6[g]	KO*t*-Bu (1.0 then 4.0 eq.)	DMF	**441** demethylation
7[c]	DBU (10 eq.)	DMF	0%

[a]Conditions: 2-methoxy-5-nitropyridine (1.0 eq.), quaternary ammonium salt (1.0 eq.), solvent (0.1 M) 18 hours, r.t..; [b]Ground, dried [c]2-methoxy-5-nitropyridine (3.0 eq.); [d]Schlenk technique [e]2-methoxy-5-nitropyridine (8.0 eq.); [f]DMF (0.03 M) [g]–40 °C

Next, the VNS reaction between the **462** and the more reactive 3-nitropyridine **439** was investigated (Table 34). With three equivalents of NaOH at 80 °C, a trace amount of the product **464** was observed by ^{1}H NMR (through comparison with literature data), however, nothing could be isolated (Table 34, entry 1). Less than 0.5% of the product of substitution at the 6-position was isolated when the reaction was conducted at ambient temperature. In addition, a possible isomer was observed and other impurities including benzoic acid (Table 34, entry 2). The isolated yield improved slightly (Table 34, entry 3 and 4) with more polar solvents (DMF and DMSO). Although it remained an insubstantial quantity, particularly when compared to the work of Jończyk. One possible explanation for this is that the ketone-enolate, which is formed in this instance, is less reactive than those formed through deprotonation of an ester, amide, or nitrile.

Table 34 Screening conditions for the VNS reaction of 439 and 462



439 **462** **464**
(plus regioisomers & tautomers)

Entry[a]	Base	Solvent	Result
1[b,c]	NaOH	MeCN	Trace by ^{1}H NMR
2	NaOH	MeCN	trace **464**
3	NaOH	MeCN	trace **464** with benzoic acid
4	NaOH	DMF	trace **464** + 2 unidentified products
5	NaOH	DMSO	trace **464**
6	KO*t*-Bu	DMF	decomposition
7	KO*t*-Bu	DMSO	decomposition

[a]Conditions 3-nitropyridine (1.0 eq.), quaternary ammonium salt **462** (1.0 eq.), base (3.0 eq.), r.t., 24 h; [b] 80 °C [c]2 h;

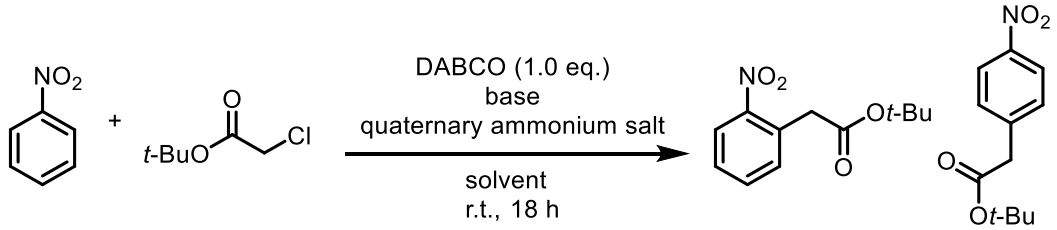
Employing KO*t*-Bu as base primarily lead to decomposition, but it was found that different methods of quenching the reaction had a noticeable effect. No product could be detected if HCl (1.0 M) was added to the reaction, whereas, if the crude reaction mixture was added to HCl (1.0 M) then a characteristic peak of the VNS product could be observed in the ^{1}H NMR spectrum. This peak was also observed when the VNS reaction was quenched with TFA (neat), but not TfOH (neat) or sat. aqueous NH_4Cl. Unfortunately, no significant products were isolated by column chromatography.

Studies of the reaction mixture of **439** and **462** by ^{1}H NMR spectroscopy revealed that the mixing of **439** with NaOH in DMSO leads to a significant line broadening of the pyridine proton signals, to the point where they become barely visible. A deep red colouration and some precipitate formation is also observed. Quenching with acid reforms **439**, but the amount was not quantified. This phenomenon is also observed by Rajan-Babu in the VNS reaction silyl enol ethers with nitroarenes, at −60 °C sharp peaks in the ^{1}H NMR spectrum, which broaden at 0 °C, and are barely

visible at ambient temperature.[374] The line broadening was proposed to be a consequence of the formation of a paramagnetic intermediate, similar to those formed in the addition of thiolate to nitrotoluenes.[379]

Makosza reported that in the oxidative VNS of silyl enol ethers with nitropyridines, the countercation of the fluoride source, tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF), rather than the silicate was responsible for stabilisation of the σ^H-adduct.[380] They also demonstrated that the oxidative VNS reaction was catalysed by tetra-alkyl ammonium salts. Therefore, some simple reactions of 2-chloro *tert*-butyl acetate with nitrobenzene, DABCO (for ylide formation) and a tetra-alkyl ammonium salt were performed with a range of bases (Table 35). Ylide formation was confirmed by ^{1}H NMR with carbonate bases, but no VNS product was detected. With $CsOH{\cdot}H_2O$ an initial deep purple colour was observed (which is characteristic of a σ-adduct), and some trace peaks corresponding to the product were present in the ^{1}H NMR spectrum of the crude reaction mixture, but no product could be isolated or identified by GCMS analysis (Table 35).

Table 35 Tetra-alkylammonium salts for the catalysis of VNS between 455 and 465



455 **465** **466** **467**

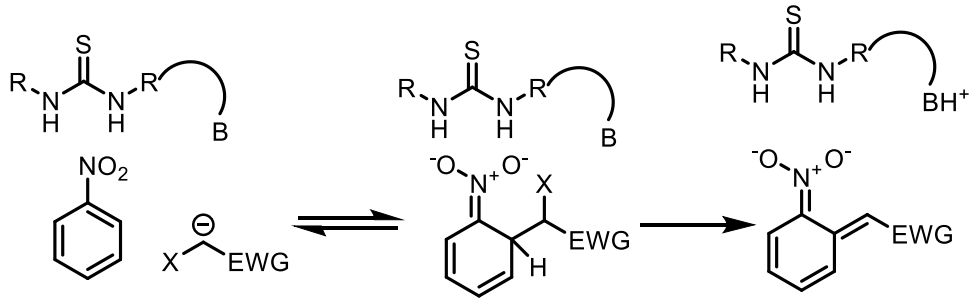
Entry[a]	Base	Solvent	Additive	Results
1	K_2CO_3 (2.0 eq.)	MeCN	TBACl (1.0 eq.)	No reaction
2	K_2CO_3 (2.0 eq.)	THF	TBACl (1.0 eq.)	No reaction
3	K_2CO_3 (2.0 eq.)	PhMe	TBACl (1.0 eq.)	No reaction
4	K_2CO_3 (2.0 eq.)	MeCN	Et_3BnNCl (1.0 eq.)	No reaction
5	K_2CO_3 (2.0 eq.)	THF	Et_3BnNCl (1.0 eq.)	No reaction
6	K_2CO_3 (2.0 eq.)	PhMe	Et_3BnNCl (1.0 eq.)	No reaction
7	NaOH[b]	PhMe (1:1)	Et_3BnNCl (0.1 eq.)	No reaction
8	NaOH[b] (10 eq.)	PhMe	Et_3BnNCl (0.1 eq.)	No reaction
9	KOH[b] (10 eq.)	PhMe	Et_3BnNCl (0.1 eq.)	No reaction
10	$LiOH·H_2O$ (10 eq.)	PhMe	Et_3BnNCl (0.1 eq.)	No reaction
11	$CsOH·H_2O$ (10 eq.)	PhMe	Et_3BnNCl (0.1 eq.)	No product
12	$CsOH.H_2O$ (2.0 eq.)	PhMe	Et_3BnNCl (0.1 eq.)	No product
13	Cs_2CO_3 (2.0 eq.)	PhMe	Et_3BnNCl (0.1 eq.)	No reaction

[a]Conditions: nitrobenzene (1.0 eq.) *tert*-butyl chloroacetate (1.0 eq.) DABCO (1.0 eq,), r.t. o/n; [b](50% *w/w*)

Ultimately, the large excess of the base, required to achieve the product-determining elimination step of the reaction, was detrimental to the other reagents.

2.3. Bifunctional superbase/H-bonding catalysis

It had become apparent that to expand the scope of the VNS reaction, identification of a catalyst for either the addition or elimination steps would be beneficial. One approach was to use a bifunctional superbase catalyst, which could co-ordinate to the nitro functionality and potentially assist the product determining elimination step (Scheme 142).



Scheme 142 The proposed use of a bifunctional hydrogen bonding and Brønstead base catalyst in the VNS reaction

Initially, a study of the bistrifluromethyl thiourea **468** with nitrobenzene **455** was performed. When the thiourea is added to nitrobenzene in deuterated toluene a shift in the ^{1}H NMR was observed, indicating an intermolecular interaction between the two substances (Figure 13).[381]

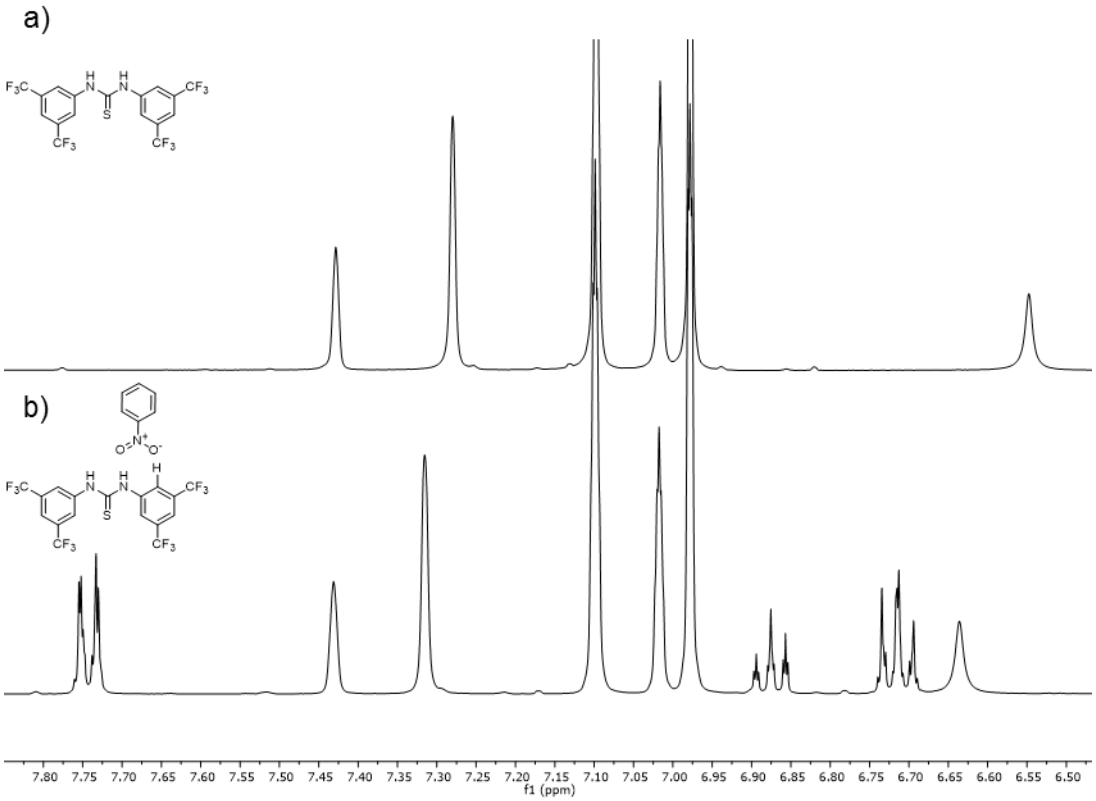
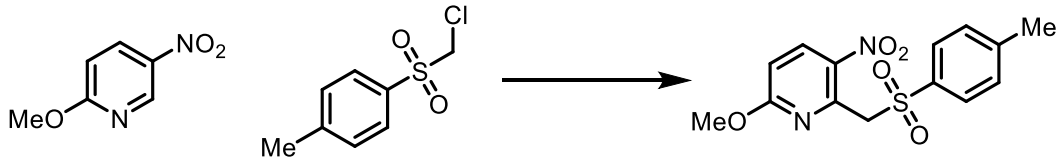


Figure 13 a) ^{1}H NMR of 468 in *d8*-toluene δ 6.50 – 7.80 b) ^{1}H NMR of 468 and 455 in *d8*-toluene δ 6.50 – 7.80

An established VNS reaction of 2-methoxy-5-nitropyridine **441**, with chloromethyl *p*-tolylsulfone **469**, afforded the VNS product **470** in 5% yield (Table 36, entry 1) with excess DBU compared to 62% with the literature conditions (Table 35, entry 2). The use of a substochiometric quantity of the thiourea **468** with two equivalents of TMG did not give any conversion from the starting materials (Table 35, entry 3).

Table 36 Establishing a VNS reaction with an organic base

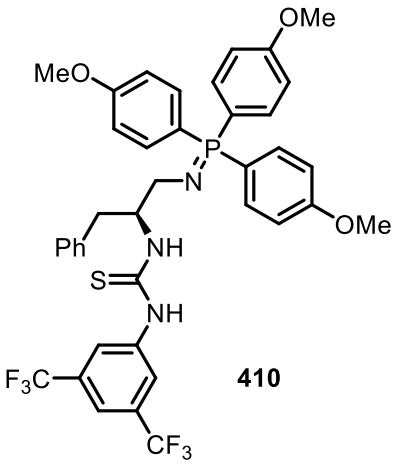


411 469 470

Entry[a]	Conditions	470 / %[b]
1	DBU (5.0 eq.), DCM, r.t., 24 h	5
2	KO*t*-Bu (2.0 eq., 1.0 M in THF), DMF, <10 °C, 5 h	62
3	TMG (2.0 eq.) PhMe, r.t., **468**, 48 h	0

[a]Conditions: 2-methoxy-5-nitropyridine (1.0 eq.), chloromethyl *p*-tolylsulfone (1.0 eq.); [b]Isolated yields

A bifunctional iminophospharane catalyst **410** was selected (Figure 14) which was designed by Dixon.[349] This catalyst has a high pK_{BH+} (25.0 in MeCN), yet is comparatively easy to prepare, due to the formation of the basic motif through the condensation of an azide with a triaryl phosphine.

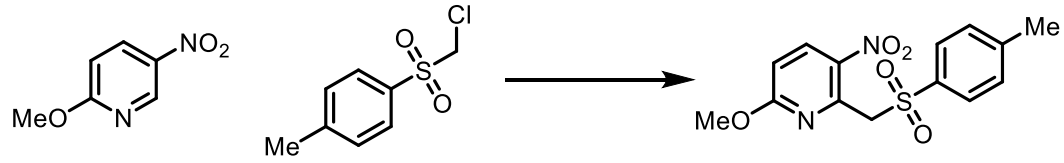


410

Figure 14 Dixon's bifunctional hydrogen bonding iminophosphorane Brønsted base catalyst

Initial investigations, which tested one equivalent of the **410** with 2-methoxy-5-nitro pyridine **441** and the chloromethyl *p*-tolylsulfone **469** were unsuccessful (Table 37, entry 1). A promising 25% yield was obtained from addition of the preformed σ^H-adduct to the **410** under cryogenic conditions (Table 36, entry 2). However, a control reaction in the absence of **410** gave a 37% yield (Table 36, entry 3), indicating that the product had formed independently of the proposed catalyst.

Table 37 Investigating the use of bifunctional catalyst 210 in the VNS reaction of 411 and 469



411 **469** **470**

Entry[a]	**Conditions**	**470 / %**[b]
1	**410** (1.0 eq.), PhMe, r.t., 72 h	0
2	i) 18-c-6 (1.0 eq.), KO*t*-Bu (1.0 eq.), THF, −78 °C ii) add to **410** (1.0 eq.) at −78 °C to r.t., 24 h	25
3	i) 18-c-6 (1.0 eq.), KO*t*-Bu (1.0 eq.), THF, −78 °C, to r.t., 24 h	37

[a]Conditions: 2-methoxy-5-nitropyridine (1.0 eq.), chloromethyl *p*-tolylsulofone (1.0 eq.); [b]Isolated yield

3. Conclusions and future work

These results collectively indicate that, as was indicated by the previous work in this field, a very strong base is required to achieve the product determining elimination step of vicarious nucleophilic substitution. As such, a limited selection of substrates is compatible with the conditions. Attempts to circumvent the use of a strong base through using a hydrogen-bonding bifunctional catalyst was unsuccessful.

Potential avenues of future work would involve investigating oxidative VNS, as opposed to base mediated VNS. Alternatively, the development of a betaine-type catalyst,[382] which contains an alkoxide base motif may be capable of performing the requisite elimination.

Experimental Data

1. General Information

Nuclear Magnetic Resonance (NMR) spectra were recorded on 300, 400 or 500 MHz Bruker NMR spectrometers at 298 K (unless stated otherwise). All chemical shift values are reported in parts per million (ppm) with coupling constant (*J*) values reported in Hz. All spectra were referenced to a residual solvent peak.[383] The notation of signals is: Proton: δ chemical shift in ppm (number of hydrogens, multiplicity, *J* value(s), hydrogen assignment). Carbon: δ chemical shift in ppm (carbon assignment). Fluorine: δ chemical shift in ppm (fluorine assignment). Phosphorous: chemical shift in ppm (phosphorous assignment). Splitting patterns are assigned s = single, d = doublet, t = triplet, q = quartet, p = pentet, h = heptet, sep. = septet, m = multiplet.

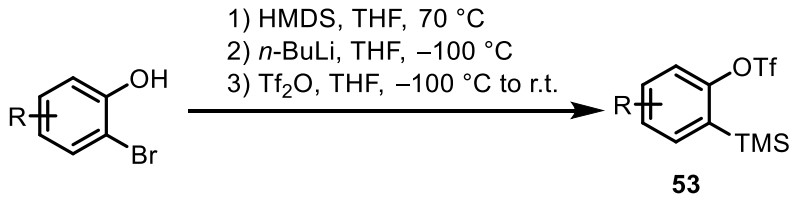
Low resolution and high resolution mass spectra were obtained using either positive and/or negative electrospray ionisation (ES), electron impact ionisation (EI) or chemical ionisation (CI) techniques. Melting points were measured on a various heater apparatus and are uncorrected. IR spectra were recorded on an ATR FTIR spectrometer as evaporated films or neat. Chiral stationary phase HPLC analysis was performed with an Agilent 1200 Series HPLC. LCMS analysis was performed with an Agilent 1200 series fitted with a 3.0 x 20 mm, C18, 3.0 μm column, and mass analysis by single quadrupole Agilent 6100 with an ES source. Gas chromatography mass spectrometry (GCMS) was performed with an Agilent Technologies 7890A GC system with a 5975C inert XL EI/CI MSD Triple Axis Detector using a BP5 – 30m X 0.25 mmx 0.25 μm column

Routine TLC analysis was carried out on aluminium sheets coated with silica gel 60 Å F_{254}, 0.2 mm thickness. Visualization was performed using UV light (285 nm) and treatment with an appropriate stain. Flash chromatography was performed using silica gel (Sigma Aldrich, 40 – 63 μ, 60 Å) or a Biotage® Isolera™ equipped with Biotage® SNAP Ultra cartridges.

Tetrahydrofuran (THF) was distilled over sodium wire and benzophenone. Dichloromethane (CH_2Cl_2), toluene, di-*iso*-propylamine (DIPA) and triethylamine were distilled over calcium hydride, diethyl ether was dried using a solvent purification system. All other solvents and reagents were purchased from commercial sources and used as supplied, including anhydrous solvents in sure seal bottles, unless otherwise stated. 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.

2. General Procedures:

2.1. General Procedure A



53

The appropriate 2-bromophenol (1.0 eq.) and hexamethyldisilazane (1.5 eq.) were heated to 70 °C in THF (0.3 M) for 2 hours. Residual hexamethyldisilazane and ammonia were removed under reduced pressure to give a (2-bromophenoxy)trimethylsilane, which was used without further purification.
The (2-bromophenoxy)trimethylsilane (1.0 eq.) was dissolved in THF (0.05 M) and cooled to −100 °C with a diethyl ether-liquid nitrogen cold bath. *n*-BuLi (1.6 M, 1.1 eq.) was then added dropwise, and the reaction was stirred for 30 minutes (reaching a maximum of −80 °C). Whilst maintaining a temperature of less than −80 °C, trifluoromethanesulfonic anhydride (1.2 eq.) was added dropwise, and the reaction was stirred for a further 30 minutes at −100 °C. After which time, it was warmed to ambient temperature over 2 hours and quenched with cold, sat. $NaHCO_3$. The aqueous phase was extracted with ether, and the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was purified by column chromatography.

2.2. General Procedure B

A solution of the aryne precursor (1.0 eq.) in acetonitrile:toluene mixtures (0.5 M) was added to dried cesium fluoride (3.0 eq.). The reaction mixture was stirred at ambient temperature for 4 to 24 hours. The reaction was then diluted with water and diethyl ether, and the aqueous phase was extracted with diethyl ether. Combined

organics were washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness. The crude material was purified by column chromatography.

2.3. General procedure C

The sulfonyl chloride (1.0 eq.) was dissolved in ethanol (0.5 M) and the respective aniline (2.0 eq.) was added. The reaction mixture was stirred and monitored by TLC analysis (1:3 *v/v* EtOAc:hexane). Upon completion, the reaction mixture was acidified with HCl (1.0 M) and stirred at 0 °C for 5 minutes, and then was then diluted with EtOAc and water. The aqueous phase was washed with EtOAc, then the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was purified by column chromatography.

2.4. General procedure D

A solution of sulfonyl chloride (1.0 eq.) in dry CH_2Cl_2 (0.7 M) was added over 15 minutes to a solution of amine (1.1 eq.) and pyridine (1.1 eq.) in dry CH_2Cl_2 (0.7 M). The reaction was stirred at ambient temperature for 2 – 3 hours and the progress of the reaction was monitored by TLC (1:3 *v/v* EtOAc:hexane). Upon completion, the reaction mixture was acidified with HCl (1.0 M, pH 2.0), the aqueous phase was separated and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to dryness. The crude material was purified by column chromatography.

2.5. General procedure E

A solution of the sulfonyl chloride (1.0 eq.) in dry CH_2Cl_2 (0.2 M) was added dropwise to a solution of the amine (1.1 eq.) and triethylamine (1.2 eq.) in CH_2Cl_2

(0.1 M). The reaction was stirred at ambient temperature for 18 hours, and then acidified with HCl (1.0 M, pH 2.0), the aqueous phase was separated and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated to dryness. The crude material was purified by column chromatography.

2.6. General procedure F

The sulfonyl chloride (1.0 eq.) was dissolved in THF (0.2 M) and appropriate amine (3.0 eq.) was added to the reaction mixture. The reaction was stirred for 30 minutes at ambient temperature until completion was indicated by TLC (1:3 *v/v* EtOAc:hexane). The reaction mixture as acidified with HCl (1.0 M, pH 2) at 0 °C, then diluted with EtOAc and water. The aqueous phase was washed twice with EtOAc and the combined organics were washed with saturated brine and dried over $MgSO_4$, filtered and concentrated under vacuum. The crude material was purified by column chromatography.

2.7. General Procedure G

The sulfonamide (1.0 eq.), potassium fluoride (3.0 eq.) and 18-crown-6 (3.0 eq.) were measured into a microwave vial and then THF (0.1 M) and the aryne precursor (1.0 eq.) were added. The vial was sealed with a cap, and the solution was then stirred at reflux for 24 hours. The reaction was the cooled, and diluted with EtOAc and water. The aqueous phase was separated and extracted twice with EtOAc. The combined organics were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude material was purified by column chromatography (SiO_2 gel, 0:1 to 1:9 *v/v* EtOAc:hexanes).

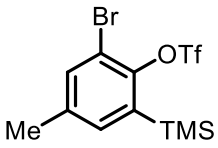
2.8. General Procedure H

The sulfonamide (1.0 eq.), potassium fluoride (6.0 eq.) and 18-crown-6 (6.0 eq.) were measured into a microwave vial and then THF (0.1 M) and the aryne precursor (2.0 eq.) were added. The vial was sealed with a cap and the solution was then stirred at reflux for 24 hours. The reaction was then cooled, and then diluted with EtOAc and water. The aqueous phase was separated and extracted twice with EtOAc. The combined organics were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude material was purified by column chromatography (SiO_2 gel, 0:1 to 1:9 *v/v* EtOAc:hexanes).

3. Data for Chapter 1

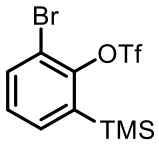
3.1. Benzyne precursor synthesis

Various 2-(trimethylsilyl)aryl trifluoromethanesulfonates are commercially available. The other arynes used in the study were prepared according to modified literature procedures.[384]



Chemical Formula: $C_{11}H_{14}BrF_3O_3SSi$
Molecular Weight: 391.27

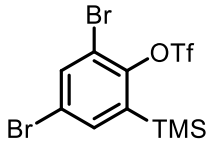
2-Bromo-4-methyl-6-(trimethylsilyl)phenyl trifluoromethanesulfonate 255 was synthesised according to general procedure A from 2-bromo-4-methylphenol (9.6 mmol), and isolated as a colourless oil (2.96 g, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 2.3, 0.9 Hz, 1H, ArH), 7.27 – 7.25 (m, 1H, ArH), 2.35 (app. t, *J* = 0.7 Hz, 3H, CH_3), 0.39 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8 (C), 139.5 (C), 137.2 (C), 136.4 (CH), 136.3 (CH), 118.7 (d, *J* = 321 Hz, CF_3); 116.2 (C), 20.7 (CH_3), 0.2 ($Si(CH_3)_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ −71.7 (CF_3); *m/z* (EI^+) 377 (80%, $[M - CH_3]^+$), 244 (100%, $[M - OSO_2CF_3]^+$). The physical data are consistent with the values reported in the literature.[384]



Chemical Formula: $C_{10}H_{12}BrF_3O_3SSi$
Molecular Weight: 377.25

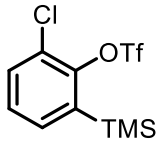
2-Bromo-6-(trimethylsilyl)phenyl trifluoromethanesulfonate 254 was synthesised according to general procedure A from 2-bromophenol (9.3 mmol), and isolated as a colourless oil (2.35 g, 67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.8, 1.7 Hz,

1H, ArH), 7.50 (dd, *J* = 7.4, 1.7 Hz, 1H, ArH), 7.23 (app. t, *J* = 7.6 Hz, 1H, ArH), 0.40 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9 (C), 137.9 (C), 135.9 (CH), 135.9 (CH), 129.2 (CH), 119.0 (q, *J* = 320.8 Hz, CF_3), 116.7 (C), 0.2 ($Si(CH_3)_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ −71.7 (CF_3); *m/z* (EI^+) 363 (80% [*M* − CH_3]$^+$), 230 (100% [*M* − OSO_2CF_3]$^+$). The physical data are consistent with the values reported in the literature.[385]



Chemical Formula: $C_{10}H_{11}Br_2F_3O_3SSi$
Molecular Weight: 456.14

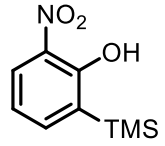
2,4-Dibromo-(trimethylsilyl)phenyl trifluoromethanesulfonate was synthesised according to general procedure A from 2,4-dibromo-phenol (5.9 mmol), and was isolated as a colourless oil (1.60 g, 59% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 2.4 Hz, 1H, ArH), 7.57 (d, *J* = 2.4 Hz, 1H, ArH), 0.41 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9 (C), 140.2 (C), 138.4 (CH), 138.0 (CH), 122.6 (C), 118.7 (q, *J* = 320.9 Hz, CF_3), 117.7 (C), 0.1 ($Si(CH_3)_3$); ^{19}F NMR (377 MHz, $CDCl_3$) −71.5 (CF_3); *m/z* (EI^+) 440.9 (40% [M − CH_3]), 307.9 (100% [M − OSO_2CF_3]); ν_{max} (neat)/cm^{-1} 2956, 1539, 1409, 1362, 1254, 1211, 1166, 1135, 1059.



Chemical Formula: $C_{10}H_{12}ClF_3O_3SSi$
Molecular Weight: 332.79

2-Chloro-6-(trimethylsilyl)phenyl trifluoromethanesulfonate was synthesised according to general procedure A from 2-bromo-6-chlorophenol (9.5 mmol), and isolated as a colourless oil (1.17g, 37%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, *J* =

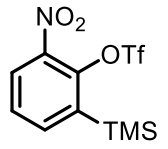
7.8, 1.7 Hz, 1H, ArH), 7.46 (dd, *J* = 7.4, 1.7 Hz, 1H, ArH), 7.31 (app. t, *J* = 7.6 Hz, 1H, ArH), 0.40 (s, 9H, 3 x CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3 (C), 137.7 (C), 135.0 (CH), 132.6 (CH), 129.0 (CH), 127.6 (C), 118.9 (q, *J* = 320.8 Hz, CF_3), 0.4 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) −71.6 (CF_3); *m/z* (EI^+) 317.0 (75% $[M - CH_3]^+$), 184.0 (100% $[M - OSO_2CF_3]^+$); ν_{max} (neat/cm^{-1}) 2959, 2904, 1401, 1209, 1175, 1135, 1086, 1062, 843.



Chemical Formula: $C_9H_{13}NO_3Si$
Molecular Weight: 211.29

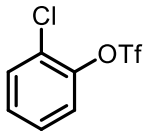
2-Nitro-6-(trimethylsilyl)phenol was synthesised according to a modified literature procedure.[384] 2-Bromo-6-nitrophenol (1.5 g, 7.0 mmol, 1.0 eq.) and hexamethyldisilazane (2.2 mL, 10.5 mmol, 1.5 eq.) were heated to 70 °C in THF (0.3 M) for 2 hours. Residual hexamethyldisilazane and ammonia were removed under reduced pressure to give (2-bromo-6-nitrophenoxy)trimethylsilane, which was used without further purification. The (2-bromo-6-nitrophenoxy)trimethylsilane was dissolved in THF (0.05 M) and cooled to −100 °C. *n*-BuLi (3.08 mL, 1.6 M in hexanes, 7.7 mmol, 1.1 eq.) was added dropwise, and the reaction was stirred for 30 minutes (reaching a maximum of −80 °C. The crude reaction mixture was purified by column chromatography and pure fractions were isolated to afford an amorphous yellow solid (239 mg, 16%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.01 (s, 1H, OH), 8.10 (dd, *J* = 8.4, 1.7 Hz, 1H, ArH), 7.66 (dd, *J* = 7.0, 1.7 Hz, 1H, ArH), 6.97 (dd, *J* = 8.4, 7.0 Hz, 1H), 0.34 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2 (C), 143.3 (CH), 133.2 (C), 131.9 (C), 126.2 (C), 120.2 (CH), −1.1 (CH_3); *m/z* (ES^-) 210.0 ([*M* − H]$^-$, 100%); HRMS ($APCI^+$) *m/*z calculated for $C_9H_{14}NO_3Si$ 212.0737 [*M* + H]$^+$,

found 212.0736; ν_{max} (neat)/cm^{-1} 3186, 2956, 2899, 1592, 1532, 1456, 1425, 1324, 1293, 1246, 1166, 1121, 1089, 1066.



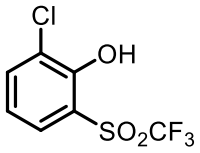
Chemical Formula: $C_{10}H_{12}F_3NO_5SSi$
Molecular Weight: 343.35

2-Nitro-6-(trimethylsilyl)phenyl trifluoromethanesulfonate was synthesised from 2-nitro-6-(trimethylsilyl)phenol according to a modified literature procedure.[264] Trifluoromethanesulfonic anhydride (0.17 mL, 0.98 mmol, 1.1 eq.) was added dropwise to a solution of 2-nitro-6-(trimethylsilyl)phenol (190 mg, 0.9 mmol, 1.0 eq.) in anhydrous pyridine (0.3 mL) at 0 °C, and then allowed to warm to ambient temperature over 22 hours. The crude reaction mixture was quenched with HCl (1.0 M, 1.0 mL) and extracted with CH_2Cl_2 (2 x 5.0 mL). The organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude reaction mixture was purified by column chromatography afford a yellow oil (220 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 7.9, 1.8 Hz, 1H, ArH), 7.82 (dd, J = 7.5, 1.8 Hz, 1H, ArH), 7.58 – 7.50 (m, 1H, ArH), 0.44 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6 (C), 142.0 (C), 141.0 (CH), 139.2 (C), 128.8 (CH), 127.4 (CH), 118.3 (q, J = 320.4 Hz, CF_3), –0.12 (CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ −72.9 (CF_3); *m/z* (ES^+) 366.01 ([M + Na]$^+$, 100%); HRMS ($APCI^+$) *m/z* calculated for $C_{10}H_{13}F_3NO_5SSi$ 344.0236 [M + H]$^+$, found 344.0230; ν_{max} (neat)/cm^{-1} 2956, 2899, 1594, 1567, 1537, 1405, 1351, 1293, 1254, 1210, 1180, 1131, 1107, 1071.



Chemical Formula: $C_7H_4ClF_3O_3S$
Molecular Weight: 260.61

2-Cholorophenyl trifluoromethylsulfonate was synthesised according to a modified literature procedure.[264] Trifluromethanesulfonic anhydride (1.5 mL, 8.9 mmol, 1.1 eq.) was added dropwise to a solution of 2-chlorophenol (0.84 mL, 8.1 mmol, 1.0 eq.) in anhydrous pyridine (3.0 mL) at 0 °C. The reaction was left to warm to ambient temperature over 24 hours, then quenched with HCl (1.0 M, 5.0 mL) and extracted with dichloromethane (2 x 10 mL). The organic phases were combined, washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude reaction mixture was purified by column chromatography to afford a colourless oil (2.09 g, 99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.48 (m, 1H, ArH), 7.39 – 7.30 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7 (C), 131.3 (CH), 129.2 (CH), 128.3 (CH), 127.3 (C), 123.0 (CH), 118.6 (q, J = 320.6 Hz, CF_3); ^{19}F NMR (471 MHz, $CDCl_3$) δ −73.5 (CF_3). The physical data are consistent with the values reported in the literature.[264]

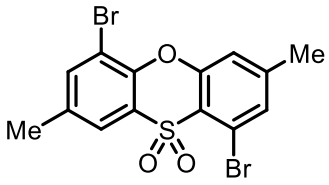


Chemical Formula: $C_7H_4ClF_3O_3S$
Molecular Weight: 260.61

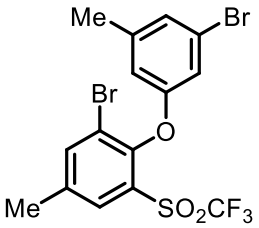
2-Chloro-6-trifluoromethanesulfonylphenol 266 was synthesised according to a modified literature procedure.[264] A solution of DIPA (0.56 mL, 4.0 mmol, 1.05 eq.) in THF (4.0 mL, 1.0 M) under nitrogen was cooled to −78 °C. *n*-BuLi (1.72 mL, 2.33 M in hexanes, 4.0 mmol, 1.05 eq.) was added, and the solution was transferred to an

ice bath for 30 minutes. The LDA solution was then cooled to −78 °C and 2-chlorophenyl trifluoromethylsulfonate **9** (1.0 g, 3.8 mmol, 1.0 eq.) in THF (20 mL, 0.19 M) was added dropwise. The reaction mixture was stirred for 5 hours at −78 °C, after which time the reaction was transferred to an ice bath and quenched with HCl (1.0 M, 5.0 mL) at 0 °C. The acidic phase was extracted with hexane:ethyl acetate 20:1 solution (3 x 10 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$, and then concentrated under vacuum. The crude was purified by column chromatography to afford a yellow solid (189 mg, 19%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (br. s, 1H, OH), 7.80 (dd, *J* = 7.9, 1.7 Hz, 1H, ArH), 7.71 (dd, *J* = 8.0, 1.6 Hz, 1H, ArH), 7.11 (t, *J* = 8.0 Hz, 1H, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5 (C), 139.7 (CH), 130.4 (CH), 124.6 (C), 121.5 (CH), 119.8 (q, *J* = 325.7 Hz, CF_3), 115.2 (d, *J* = 1.8 Hz, C); ^{19}F NMR (471 MHz, $CDCl_3$) δ −73.5 (CF_3); *m/*z (ES^-) 258.8 ([*M* − H]$^-$, 100%). The physical data are consistent with the values reported in the literature.[264]

3.2. *Fries rearrangement – Cyclisation Studies*

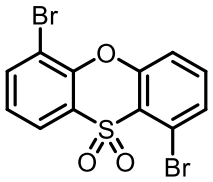


Chemical Formula: $C_{14}H_{10}Br_2O_3S$
Molecular Weight: 418.10



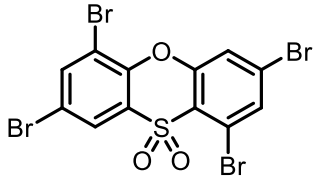
Chemical Formula: $C_{15}H_{11}Br_2F_3O_3S$
Molecular Weight: 488.11

Phenoxathiin dioxide 241 and **triflone 263** were synthesised according to general procedure B from 2-bromo-4-methyl-6-(trimethylsilyl)phenyl trifluoromethanesulfonate **240** (419 mg, 1.1 mmol). Triflone **263** was isolated as a white solid (22 mg, 9%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 2.1, 0.9 Hz, 1H, ArH), 7.73 (dd, *J* = 2.1, 0.8 Hz, 1H, ArH), 6.90 (td, *J* = 1.5, 0.7 Hz, 1H, ArH), 6.54 (ddd, *J* = 2.4, 1.7, 0.7 Hz, 1H, ArH), 6.40 (ddd, *J* = 2.3, 1.4, 0.7 Hz, 1H, ArH), 2.36 (t, *J* = 0.7 Hz, 3H, CH_3), 2.14 (app. q, *J* = 0.6 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (C), 149.1 (C), 143.2 (CH), 141.5 (C), 138.3 (C), 133.1 (CH), 127.1 (CH), 122.5 (C), 116.1 (CH), 115.4 (CH), 112.8 (C), 21.4 (CH_3), 20.8 (CH_3) *CF_3 carbon not observed*; *m/z* (ES^+) 510.9 ([*M* + Na]$^+$, 100%); HRMS (TOF MS APCI$^+$) *m/z* calculated for $C_{15}H_{12}Br_2F_3O_3S$ 486.8821 [*M* + H]$^+$, Found 486.8819; mp: 101 – 109 °C; and phenoxathiin-dioxide **241** as a white crystalline solid (98 mg, 44%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 1.9, 0.9 Hz, 1H, ArH), 7.72 – 7.66 (m, 1H, ArH), 7.43 (dd, *J* = 1.6, 0.7 Hz, 1H, ArH), 7.26 (d, *J* = 1.5 Hz, 1H, ArH), 2.44 (app s, 6H, 2 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7 (C), 145.7 (C), 144.2 (C), 138.4 (CH), 136.1 (CH), 132.1 (CH), 125.8 (C), 122.6 (CH), 121.1 (C), 118.9 (CH), 117.2 (C), 111.3 (C), 21.3 (CH_3), 20.7 (CH_3); *m/z* (ES^+) 419 ([*M* + H]$^+$, 100%); HRMS (ESI^+) *m/z* Calculated for $C_{14}H_{10}O_3Br_2SNa^+$ 438.8610 [*M* + Na]$^+$, found 438.8612; mp: 230 – 234 °C.



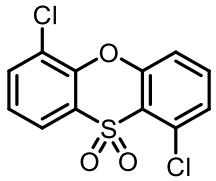
Chemical Formula: $C_{12}H_6Br_2O_3S$
Molecular Weight: 390.05

1,6-Dibromophenoxathiine 10,10-dioxide 255 was synthesised according to general procedure B from 2-bromo-6-(trimethylsilyl)phenyl trifluoromethanesulfonate (378 mg, 1.0 mmol), an isolated as a white crystalline solid (43 mg, 29%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.0, 1.5 Hz, 1H, ArH), 7.89 (dd, *J* = 7.9, 1.6 Hz, 1H, ArH), 7.62 (dd, *J* = 5.3, 3.7 Hz, 1H, ArH), 7.52 – 7.45 (m, 2H, ArH), 7.30 (*app.* t, *J* = 8.0 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9 (C), 146.4 (C), 137.8 (CH), 134.0 (CH), 131.4 (CH), 126.4 (C), 125.6 (CH), 124.1 (C), 123.1 (CH), 118.9 (CH), 117.6 (C), 111.9 (C); *m/z* (ES^+) 391.0 ($[M + H]^+$, 100%); HRMS (ESI^+) *m/z* calculated for $C_{12}H_6O_3SNa^+$ 410.8297 $[M + Na]^+$, found 410.8282; mp: 205 – 207 °C.



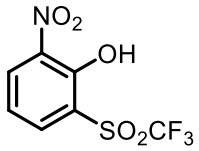
Chemical Formula: $C_{12}H_4Br_4O_3S$
Molecular Weight: 547.84

1,3,6,8-tetrabromophenoxathiine 10,10-dioxide 259 was synthesised according to general procedure B from 2,4-bromo-6-(trimethylsilyl)phenyl trifluromethanesulfonate (136 mg, 0.3 mmol), and was isolated as a white crystalline solid (16 mg, 20%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 2.2 Hz, 1H, ArH), 8.02 (d, *J* = 2.2 Hz, 1H, ArH), 7.79 (d, *J* = 1.8 Hz, 1H, ArH), 7.68 (d, *J* = 1.8 Hz, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9 (C), 145.6 (C), 140.4 (CH), 134.4 (CH), 128.1 (C), 127.6 (C), 125.8 (CH), 123.4 (C), 122.2 (CH), 118.8 (C), 118.0 (C), 113.3 (C); *m/z* (ES^+) 570.7 ([*M* + Na]$^+$, 100%); HRMS ($APCI^+$) *m/z* calculated for $C_{12}H_4Br_4O_3$ 544.6687 [*M* + H]$^+$, found 544.9976; mp: 259 – 265 °C.



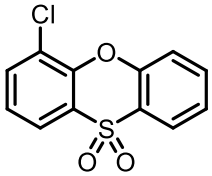
Chemical Formula: $C_{12}H_6Cl_2O_3S$
Molecular Weight: 301.14

1,6-Dichlorophenoxathiine 10,10-dioxide 258 was synthesised according to general procedure B from 2-chloro-6-(trimethylsilyl)phenyl trifluromethanesulfonate (49.9 mg, 0.15 mmol), and isolated as a white crystalline solid (10 mg, 45%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.1, 1.5 Hz, 1H, ArH), 7.73 (dd, *J* = 7.9, 1.5 Hz, 1H, ArH), 7.58 (dd, *J* = 8.6, 7.9 Hz, 1H, ArH), 7.45 – 7.40 (m, 2H, ArH), 7.37 (t, *J* = 8.0 Hz, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7 (C), 145.6 (C), 134.6, (CH) 133.8 (CH), 131.4 (C), 127.8 (CH), 126.7 (C), 125.2 (CH), 123.2 (C), 122.8 (C), 122.2 (CH), 118.3 (CH); *m/z* (ES^+) 301 ([*M* + H]$^+$, 100%); HRMS (ESI^+) *m/z* calculated for $C_{12}H_{10}O_3N_1Cl_2S_1$ 317.9753 [*M* + NH_4]$^+$, found 317.9750; mp: 182 – 189 °C.

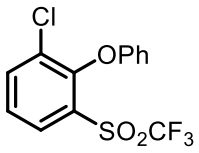


Chemical Formula: $C_7H_4F_3NO_5S$
Molecular Weight: 271.17

2-Nitro-6-((trifluoromethyl)sulfonyl)phenol 261 was synthesised according to general procedure B from 2-nitro-6-(trimethylsilyl)phenyl trifluoromethanesulfonate **1i** (90 mg, 0.26 mmol), and isolated as a yellow solid (48 mg, 68%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 7.33 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 5.87 (app. t, *J* = 8.0 Hz, 1H, ArH), 4.29 (s, 1H, OH); ^{13}C (101 MHz, CD_3OD) δ 165.9 (C), 142.2 (C), 141.2 (CH), 136.5 (CH), 128.3 (C), 121.8 (app. d, *J* = 326.4 Hz, CF_3), 110.6 (CH); ^{19}F (377 MHz, $CDCl_3$) −73.32 (CF_3); *m/z* (ES^-) 270.0 (100%, $[M - H]^-$); HRMS (ES^+) *m/z* calculated for $C_7H_4O_5NF_3NaS$ 293.9654 $[M + Na]^+$, found 293.9640; mp: decomposition.



Chemical Formula: $C_{12}H_7ClO_3S$
Molecular Weight: 266.70

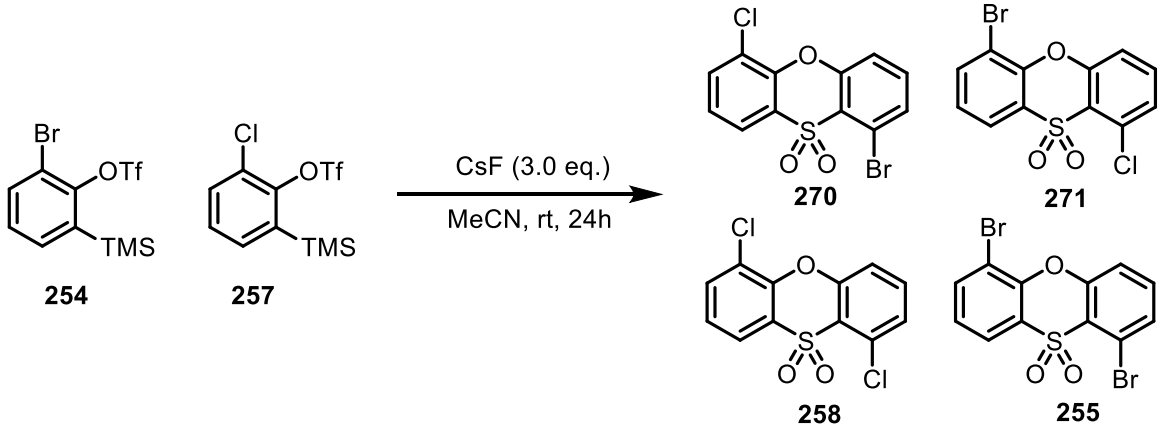


Chemical Formula: $C_{13}H_8ClF_3O_3S$
Molecular Weight: 336.71

4-Chlorophenoxathiine 10,10-dioxide 268 and **1-chloro-2-phenoxy-3-((trifluoromethyl)sulfonyl)benzene 269** were synthesised according to general procedure B, from 2-chloro-6-((trifluomethyl)sulfonyl)phenol (78.2 mg, 0.3 mmol) and 2-(trimethylsilyl)phenyl trifuloromethylsulfonate (98.5mg, 0.33 mmol). The triflone **269** was isolated as a yellow oil (17 mg, 16%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.1, 1.6 Hz, 1H, ArH), 7.89 (dt, *J* = 8.1, 1.1 Hz, 1H, ArH), 7.48 (*app*. dt, *J* = 8.1, 0.7 Hz, 1H, ArH), 7.36 – 7.28 (m, 2H, ArH), 7.13 – 7.05 (m, 1H, ArH),

6.85 – 6.77 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1 (C), 151.0 (C), 139.4 (CH), 131.8 (CH), 131.0 (C), 130.4 (C) 129.6 (CH), 126.4 (CH), 123.3 (CH), 115.6 (CH), *CF_3 carbon not observed*; *m/z* (ES^+) 359.0 (100%, $[M + Na]^+$); HRMS (ES^+) *m/z* calculated for $C_{13}H_{12}O_3NClF_3S$ 354.0173 $[M + NH_4]^+$, found 354.0173; ν_{max} (neat)/cm^{-1} 3082, 2973, 2359, 1592, 1571, 1490, 1446, 1436, 1369, 1251, 1208, 1189, 1161, 1131, 1085, 1024; and **268** as a white crystalline solid (24 mg, 27%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 8.0, 1.7 Hz, 1H, ArH), 7.97 (dd, *J* = 8.0, 1.6 Hz, 1H, ArH), 7.76 – 7.64 (m, 2H, ArH), 7.52 (dd, *J* = 8.5, 1.1 Hz, 1H, ArH), 7.48 – 7.43 (m, 1H, ArH), 7.35 (t, *J* = 8.0 Hz, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (C), 147.7 (C), 134.7 (CH), 134.5 (CH) 126.7 (C), 125.6 (CH), 125.1 (CH), 124.8 (C), 123.9 (C), 123.5 (CH), 121.9 (CH), 119.4 (CH); *m/z* (ES^+) 267.0 (100%, $[M + H]^+$); HRMS ($APCI^+$) *m/z* Calculated for $C_{12}H_7ClO_3S$ 299.9877 $[M + H]^+$, Found 266.9875; mp: 148 – 152 °C.

3.3. Crossover reaction



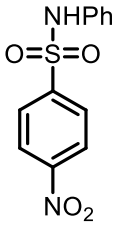
2-Bromo-6-(trimethylsilyl)phenyl trifluoromethanesulfonate **254** (0.25 mmol) and 2-chloro-6-(trimethylsilyl)phenyl trifluromethanesulfonate **257** (0.25 mmol) were subjected to the conditions outlined in general procedure B. The products were

isolated as an inseparable mixture by column chromatography (31 mg) and determined to have a relative ratio of **258**:**270**+**271**:**255** 28:49:23 by GCMS analysis. Back injector temperature set to 300 °C with 20:1 split ratio, and helium carrier gas at 1.0 mL per minute. Initial temperature of 50 °C with a 3-minute hold followed by an increase of 25 °C per minute to 300 °C and then a 5-minute hold at 300 °C. The auxiliary heater to MS set to 300 °C. **258** (t_R = 14.6 minutes, *m/z* 299.9), **270**+**271** (t_R =15.2 minutes, *m/z* 345.9) and **255** (t_R = 15.9, *m/z* 389.8)

4. Data for Chapter 2

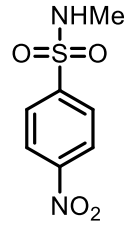
Data for compounds prepared solely by S. M. A. Sohel can be located in the supporting information of the associated publication.[269]

4.1. Characterisation data for sulfonamides



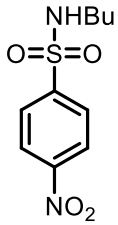
Chemical Formula: $C_{12}H_{10}N_2O_4S$
Molecular Weight: 278.28

4-Nitro-*N*-phenylbenzenesulfonamide 281 was synthesised according to general procedure C (1.0 mmol), and isolated as a pale yellow crystalline solid (218 mg, 78%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.61 (s, 1H, NH), 8.37 (d, *J* = 8.9 Hz, 2H, ArH), 7.99 (d, *J* = 8.9 Hz, 2H, ArH), 7.27 (d, *J* = 7.2 Hz, 1H, ArH), 7.25 (d, *J* = 7.2 Hz, 1H, ArH), 7.13 – 7.04 (m, 3H, ArH); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 149.8 (C), 144.9 (C), 136.9 (C), 129.4 (CH), 128.3 (CH), 124.8 (CH), 124.7 (CH), 120.7 (CH); *m/z* (ES^-) 277 ($[M - H]^-$, 100%). The physical data are consistent with the values reported in the literature.[386]



Chemical Formula: $C_7H_8N_2O_4S$
Molecular Weight: 216.21

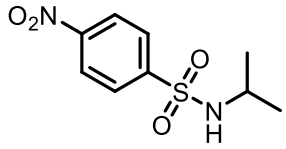
***N*-Methyl-4-nitrobenzenesulfonamide 407** was synthesised according to general procedure F (1.0 mmol), and isolated as a white crystalline solid (182 mg, 84%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.43 (d, *J* = 8.8 Hz, 2H, ArH), 8.02 (d, *J* = 8.8 Hz, 2H, ArH), 7.84 (s, 1H, NH), 2.46 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 149.6 (C), 144.9 (C), 128.3 (CH), 124.7 (CH), 28.6 (CH_3); *m/z* (ES^-) 215 ($[M - H]^-$, 100%). The physical data are consistent with the values reported in the literature.[386]



Chemical Formula: $C_{10}H_{14}N_2O_4S$
Molecular Weight: 258.29

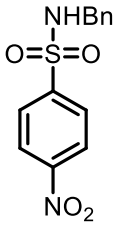
***N*-Butyl-4-nitrobenzenesulfonamide** was synthesised according to general procedure F (1.0 mmol), and isolated as a white crystalline solid (181 mg, 70%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.41 (d, *J* = 8.7 Hz, 2H, ArH), 8.03 (d, *J* = 8.7 Hz, 2H, ArH), 7.96 (t, *J* = 5.9 Hz, 1H, NH), 2.78 (q, *J* = 6.6 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 1.34 (p, *J* = 6.9 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 1.22 (h, *J* = 7.2 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 0.79 (t, *J* = 7.3 Hz, 3H, $NCH_2CH_2CH_2CH_3$); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 149.5 (C), 146.2 (C), 128.0 (CH), 124.6 (CH), 42.2 ($NCH_2CH_2CH_2CH_3$), 31.1 ($NCH_2CH_2CH_2CH_3$), 19.2 ($NCH_2CH_2CH_2CH_3$), 13.4

($NCH_2CH_2CH_2CH_3$); *m/z* (ES^-) 257 ([*M* − H]$^-$, 100%). The physical data are consistent with the values reported in the literature.[387]



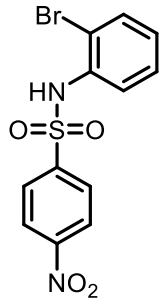
Chemical Formula: $C_9H_{12}N_2O_4S$
Molecular Weight: 244.27

***N*-Isopropyl-4-nitrobenzenesulfonamide** was synthesised according to general procedure F to afford a white crystalline solid (176 mg, 72%).; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.41 (d, *J* = 8.8 Hz, 2H, ArH), 8.06 (d, *J* = 8.9 Hz, 2H, ArH), 8.01 (d, *J* = 6.5 Hz, 1H, NH), 3.39 – 3.21 (m, 1H, CH), 0.96 (d, *J* = 6.5 Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 149.4 (C), 147.6 (C), 127.9 (CH), 124.6 (CH), 45.6 (CH), 23.2 (CH_3); *m/z* (ES^-) 243 [M − H]$^-$. The physical data are consistent with the values reported in the literature.[4]



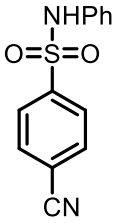
Chemical Formula: $C_{13}H_{12}N_2O_4S$
Molecular Weight: 292.31

***N*-Benzyl-4-nitrobenzenesulfonamide 387** was synthesised according to general procedure F to afford a white crystalline solid (225 mg, 77%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.57 (t, *J* = 6.2 Hz, 1H, NH), 8.36 (d, *J* = 8.9 Hz, 2H, ArH), 8.00 (d, *J* = 8.9 Hz, 2H, ArH), 7.30 – 7.16 (m, 5H, ArH), 4.06 (d, *J* = 6.2 Hz, 2H, CH_2); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 149.4 (C), 146.4 (C), 137.1 (C), 128.3 (CH), 128.1 (CH), 127.7 (CH), 127.3 (CH), 124.5 (CH), 46.2 (CH_2); *m/z* (ES^-) 291 ([*M* − H]$^-$, 100%). The physical data are consistent with the values reported in the literature.[388]



Chemical Formula: $C_{12}H_9BrN_2O_4S$
Molecular Weight: 357.18

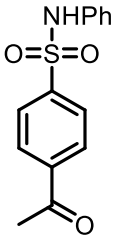
***N*-(2-Bromophenyl)-4-nitrobenzenesulfonamide** was synthesised according to general procedure C (1.0 mmol), and isolated as a pink solid (191 mg, 54%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.40 (s, 1H, NH), 8.40 (d, *J* = 8.9 Hz, 2H, ArH), 7.94 (d, *J* = 8.9 Hz, 2H, ArH), 7.61 (dd, *J* = 8.4, 1.5 Hz, 1H, ArH), 7.35 (td, *J* = 7.6, 1.5 Hz, 1H, ArH), 7.23 – 7.16 (m, 2H, ArH); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 149.8 (C), 146.0 (C), 134.2 (C), 133.4 (CH), 128.9 (CH), 128.9 (CH), 128.6 (CH), 128.3 (CH), 124.7 (CH), 120.9 (C); HRMS (ES^-) *m/z* calculated for $C_{12}H_8BrN_2O_4S$ 354.9388 [*M* − H]$^-$, found 354.9379; mp: 136 – 138 °C.



Chemical Formula: $C_{13}H_{10}N_2O_2S$
Molecular Weight: 258.30

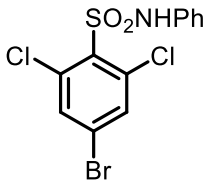
4-Cyano-*N*-phenylbenzenesulfonamide was synthesised according to general procedure C (1.0 mmol), and isolated as a white solid (240 mg, 93%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H, ArH), 7.76 (d, J = 8.3 Hz, 2H, ArH), 7.34 (s, 1H, NH), 7.18 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0 (C), 135.5 (C), 133.0 (CH), 129.7 (CH), 128.0 (CH), 126.3 (CH), 122.1 (CH), 117.3 (C), 116.7 (C); HRMS (ES^-) *m/z* calculated for

$C_{13}H_9N_2SO_2$ 257.0385 $[M - H]^+$, found 257.0390. The physical data are consistent with the values reported in the literature.[389]



Chemical Formula: $C_{14}H_{13}NO_3S$
Molecular Weight: 275.32

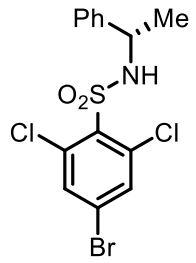
4-Acetyl-*N*-phenylbenzenesulfonamide was synthesised according to general procedure C (1.0 mmol), and isolated as a pale brown solid (246 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.5 Hz, 2H, ArH), 7.95 (d, J = 8.5 Hz, 2H, ArH), 7.54 (s, 1H), 7.23 (t, J = 7.7 Hz, 2H, ArH), 7.14 – 7.07 (m, 3H), 2.70 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2 (C=O), 142.8 (C), 140.2 (C), 136.0 (C), 129.6 (CH), 129.0 (CH), 127.7 (CH), 126.0 (CH), 122.1 (CH), 27.04 (CH_3). The physical data are consistent with the values reported in the literature.[390]



Chemical Formula: $C_{12}H_8BrCl_2NO_2S$
Molecular Weight: 381.07

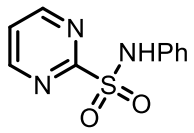
4-Bromo-2,6-dichloro-*N*-phenylbenzenesulfonamide was synthesized according to general procedure C (1.0 mmol), and isolated as a white crystalline solid (248 mg, 70%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.90 (s, 1H, NH), 7.96 (s, 2H, ArH), 7.28 – 7.24 (m, 2H, ArH), 7.10 –7.08 (m, 2H, ArH), 7.06 – 7.02 (m, 1H, ArH); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 136.6 (C), 135.3 (C), 134.1 (CH), 133.4 (C), 129.4 (CH),

126.6 (CH), 124.2 (CH), 118.8 (CH); HRMS (ES^-) *m/z* calculated for $C_{12}H_7NO_2SCl_2Br$ 377.8758 [$M - H^+$], found 377.8765; mp: 108 °C.



Chemical Formula: $C_{14}H_{12}BrCl_2NO_2S$
Molecular Weight: 409.12

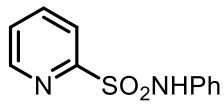
(*S*)-4-Bromo-2,6-dichloro-*N*-(1-phenylethyl)benzenesulfonamide was synthesised according to general procedure D (4.0 mmol), and isolated as a white crystalline solid (1.26 g, 78%); ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 2H, ArH), 7.15 – 7.07 (m, 5H, ArH), 5.78 (d, *J* = 8.5 Hz, 1H, NH), 4.55 (dq, *J* = 8.5, 7.0 Hz, 1H, CH), 1.52 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.4 (C), 135.3 (C), 135.2 (C), 133.6 (C), 128.5 (CH), 127.8 (CH), 125.9 (CH), 125.5 (CH), 54.7 (CH), 22.9 (CH_3); *m/z* (ES^-) 408 (100%, [M − H]$^-$); HRMS (ES^+) calculated for $C_{14}H_{11}Br_1Cl_2NO_2S$ 409.9026 [M]$^+$, found 409.9025, mp: 129 – 131 °C.



Chemical Formula: $C_{10}H_9N_3O_2S$
Molecular Weight: 235.26

***N*-Phenylpyrimidine-2-sulfonamide** was synthesised according to a modified literature procedure.[391] HCl (2.0 M, 25 mL) and CH_2Cl_2 (25 mL) were cooled to −5 °C and, with rapid stirring, cold NaOCl (10 %, 18 mmol, 1.1 mL) was added at a rate such that the internal temperature does not exceed 0 °C. The 2-mercaptanpyrimidine (560 mg, 5 mmol, 1.0 eq.) was added in small portions and an

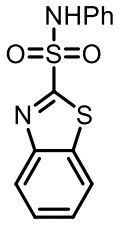
internal temperature of −5 °C to −10 °C was maintained. The reaction was left to stir rapidly for 20 minutes, after which time the excess chlorine was quenched by adding sat. $Na_2S_2O_3$. The crude reaction was transferred to a cold separating funnel, and the organic phase was quickly extracted with cold CH_2Cl_2 (50 mL). The organic phase was cooled to 0 °C and aniline (1.4 mL, 15 mmol, 3.0 eq.) was added. The reaction was warmed to ambient temperature over 40 minutes (conversion monitored by TLC 1:19 *v/v* Et_2O:CH_2Cl_2). The crude reaction mixture was purified by column chromatography to afford a pale yellow solid (200 mg, 17%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, *J* = 4.9 Hz, 2H, ArH), 7.58 (s, 1H, NH), 7.48 (t, *J* = 4.9 Hz, 1H, ArH), 7.30 – 7.21 (m, 4H, ArH), 7.13 (tt, *J* = 7.4, 1.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0 (C), 158.6 (2 x CH), 136.0 (C), 129.3 (CH), 125.7 (CH), 123.6 (CH), 122.1 (CH); *m/z* (ES^-) 234 ($[M - H]^-$); HRMS (ES^+) calculated for $C_{10}H_9N_3O_2SNa$ $[M + Na]^+$ 258.0308, found 258.0306; mp: 142 – 145 °C.



Chemical Formula: $C_{11}H_{10}N_2O_2S$
Molecular Weight: 234.27

***N*-Phenylpyridine-2-sulfonamide** was synthesised according to a modified literature procedure.[391] HCl (2.0 M, 25 mL) and CH_2Cl_2 (25 mL) were cooled to −5 °C. With rapid stirring cold NaOCl (10 %, 18 mmol, 1.1 mL) was added at such a rate than the internal temperature does not exceed 0 °C. The 2-mercaptanpyridine (555 mg, 5 mmol, 1 eq.) was added in small portions, and internal temperature of −5 to −10 °C was maintained. The reaction was left to stir rapidly for 20 minutes after which time the excess chlorine was quenched by adding sat. $Na_2S_2O_3$. The crude reaction was transferred to a cold separating funnel, and the organic phase was

quickly extracted with cold CH_2Cl_2 (50 mL). The organic phase was cooled to 0 °C and aniline (1.4 mL, 15 mmol, 3.0 eq.) was added. The reaction was warmed to ambient temperature over 40 minutes (conversion monitored by TLC 1:19 *v/v* Et_2O:CH_2Cl_2). The crude reaction mixture was purified by column chromatography to afford a pale yellow solid (820 mg, 70%); ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 9.22 (s, 1H, NH), 8.65 (ddd, *J* = 4.7, 1.7, 1.1 Hz, 1H, ArH), 7.98 (ddd, *J* = 7.8, 7.4, 1.7 Hz, 1H), 7.93 (ddd, *J* = 7.8, 1.4, 1.1 Hz, 1H), 7.55 (ddd, *J* = 7.4, 4.7, 1.4 Hz, 1H, ArH), 7.28 – 7.13 (m, 4H, ArH), 7.06 (tt, *J* = 6.8, 1.3 Hz, 2H); ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 157.9 (C), 150.9 (CH), 139.1 (CH), 138.6 (C), 129.8 (CH), 127.9 (CH), 125.2 (CH), 123.5 (CH), 121.8 (CH); *m/z* (ES^-) 233 ([*M* – H]$^-$, 100%). The physical data are consistent with the values reported in the literature.[392]

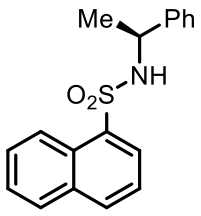


Chemical Formula: $C_{13}H_{10}N_2O_2S_2$
Molecular Weight: 290.36

***N*-Phenylbenzo[*d*]thiazole-2-sulfonamide** was synthesised according to modified literature procedure.[393] A stirred suspension of 2-mercaptobenzothiazole (2.0 g, 12 mmol, 1.0 eq.) in HCl (1.0 M, 30 mL) and CH_2Cl_2 (0.2 M, 60 mL) was cooled in a salt ice bath and sodium hypochlorite (~10%, 36 mL, 36 mmol, 3.0 eq.) was slowly added. The solution continued to be stirred for 1 hour. The reaction mixture was then separated in a pre-cooled separating funnel, and the aqueous layer was extracted with cold CH_2Cl_2 (10 mL). The organic layers were quickly washed with cold sat. $NaHCO_3$ (10 mL) and brine (10 mL), and dried over $MgSO_4$ for 30 minutes at −78 °C under a nitrogen atmosphere, then filtered and concentrated under vacuum. Ice

cold, dry diethyl ether was added (5.0 mL), then the mixture cooled to −78 °C, filtered and then the solid washed with cold (−78 °C) dry Et_2O and dried for 30 minutes. The resulting cream solid was stored under nitrogen at −18 °C.

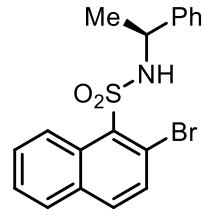
A portion of the cream solid (500 mg, 2.1 mmol) was then dissolved in ethanol at 0 °C and aniline (0.4 mL, 4.2 mmol) was added. The mixture was warmed to ambient temperature, by which time the reaction appeared complete by TLC. The crude reaction mixture was recrystallized from ethanol. However, some aniline remained, and so column chromatography was performed (SiO_2 gel, 0:1 to 1:1 EtOAc:hexane) to afford a white crystalline solid (207 mg, 35%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 11.24 (s, 1H, NH), 8.25 (dd, *J* = 7.4, 1.7 Hz, 1H), 8.19 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.68 (td, *J* = 8.0, 7.5, 1.7 Hz, 1H), 7.64 (td, *J* = 8.0, 7.4, 1.7 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.11 (t, *J* = 7.3 Hz, 1H, ArH); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 165.6 (C), 151.6 (C), 136.4 (C), 135.9 (C), 129.3 (CH), 127.9 (CH), 127.8 (CH), 125.1 (CH), 124.6 (CH), 123.3 (CH), 121.1 (CH); HRMS (ES^+) *m/z* calculated for 313.0081 $[M + Na]^+$, found 313.0089. The physical data are consistent with the values reported in the literature.[394]



Chemical Formula: $C_{18}H_{17}NO_2S$
Molecular Weight: 311.40

(*S*)-*N*-(1-phenylethyl)naphthalene-1-sulfonamide was prepared according to the following procedure. (*S*)-(−)-α-Methylbenzylamine (0.71 mL, 5.5 mmol, 1.1 eq.) in CH_2Cl_2 (55 mL, 0.1 M) was added dropwise to 1-naphthalenesulfonyl chloride (1.13 g, 5.0 mmol, 1.0 eq.) and Et_3N (0.8 mL, 6.0 mmol, 1.2 eq.) in CH_2Cl_2 (25 mL, 0.2

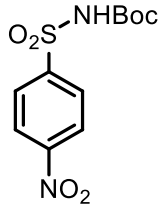
M). The solution was stirred at ambient temperature until the starting material had been consumed (TLC, 1:3 EtOAc:hex). The crude reaction mixture was concentrated and loaded directly onto silica gel for flash chromatography (SiO_2 gel, 1:5 *v/v* EtOAc:petrol). The pure product was isolated as a white crystalline solid (1.45 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 – 8.68 (m, 1H, ArH), 8.14 (dd, *J* = 7.5, 1.3 Hz, 1H, ArH), 7.93 (d, *J* = 8.2 Hz, 1H, ArH), 7.88 – 7.83 (m, 1H, ArH), 7.61 (ddd, *J* = 8.6, 6.9, 1.5 Hz, 1H, ArH), 7.54 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, ArH), 7.36 (dd, *J* = 8.3, 7.3 Hz, 1H, ArH), 7.00 – 6.93 (m, 1H, ArH), 6.92 (d, *J* = 4.4 Hz, 4H, ArH), 5.91 – 5.82 (m, 1H), NH), 4.51 (p, *J* = 7.0 Hz, 1H, CH), 1.36 (d, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5 (C), 135.1 (C), 134.1 (CH), 134.1 (C), 129.7 (CH), 129.0 (C), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.2 (CH), 126.7 (CH), 125.9 (CH), 124.5 (CH), 124.1 (CH), 54.0 (CH), 23.6 (CH_3); *m/z* (ES^+) 105 (100%, $[M - 206]^+$), 223 (90%, $[M - 88]^+$), 334 (80%, $[M + Na]^+$).



Chemical Formula: $C_{18}H_{16}BrNO_2S$
Molecular Weight: 390.30

(*S*)-2-bromo-N-(1-phenylethyl)naphthalene-1-sulfonamide 337 was prepared according to the following procedure. *Sec*-Butyl lithium (1.3 M, hexane, 6.15 mL, 8.0 mmol, 2.0 eq.) was added drop wise to a solution of (*S*)-*N*-(1-phenylethyl)naphthalene-1-sulfonamide (1.2 g, 4.0 mmol, 1.0 eq.) in THF (40 mL, 0.1 M) at −78°C. The reaction mixture was stirred at −78 °C for 30 minutes. Bromine (0.3 mL, 6.0 mmol, 1.5 eq.) was added to the reaction mixture over 30 minutes and then it was warmed to ambient temperature, with stirring, over 30

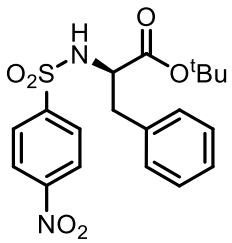
minutes. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL) at 0 °C. The reaction mixture was diluted with ethyl acetate (20 mL), aqueous phase was separated and washed with ethyl acetate (20 mL x 2). The combined organics were washed with brine and dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude reaction mixture was purified by flash chromatography (SiO_2 gel, 1:9 *v/v* EtOAc:petrol) to afford a white crystalline solid (1.2 g, 76 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, *J* = 8.9 Hz, 1H, ArH), 7.77 (dd, *J* = 7.9, 1.8 Hz, 1H, ArH), 7.68 (d, *J* = 8.8 Hz, 1H, ArH), 7.65 – 7.50 (m, 3H, ArH), 6.93 (s, 5H, ArH), 5.92 (d, *J* = 7.8 Hz, 1H, NH), 4.55 (p, *J* = 7.1 Hz, 1H, CH), 1.45 (dd, *J* = 7.1, 1.7 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 (C), 135.9 (C), 133.8 (CH), 133.2 (C), 132.0 (C), 131.7 (CH), 128.7 (CH), 128.7 (CH), 128.3 (CH), 127.6 (CH), 126.9 (CH), 126.0 (CH), 125.7 (CH), 122.9 (C), 54.5 (CH), 23. (CH_3); *m/z* (ES^-) 112 (100%, $[TFA]^-$), 224 (80%, $[2TFA]^-$), 390 (70%, $[M]^-$); HRMS (ES^+) *m/z* calculated for $C_{18}H_{16}NO_2NaSBr$ 411.9983, found 411.9991.



Chemical Formula: $C_{11}H_{14}N_2O_6S$
Molecular Weight: 302.30

***tert*-Butyl ((4-nitrophenyl)sulfonyl)carbamate** was prepared according to a modified literature procedure.[395] Et_3N (0.19 mL, 1.36 mmol, 1.1 eq.), DMAP (16 mg, 0.13 mmol, 0.1 eq.) were added sequentially to a solution of 4-nitrobenzene sulfonamide (250 mg, 1.24 mmol, 1.0 eq.) in CH_2Cl_2 (2.0 mL) at ambient temperature under an atmosphere of nitrogen. Then Boc_2O (311 mg, 1.43 mmol, 1.15 eq.) was added over 15 minutes, as a solution in CH_2Cl_2 (3 mL). The reaction

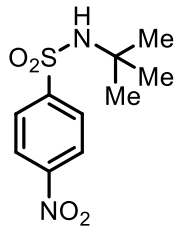
mixture was stirred for 3 hours and then concentrated under vacuum. The residue dissolved in EtOAc (20 mL), and this solution was successively washed with HCl (1.0 M, 10 mL), water (10 mL) and brine (10 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a white solid (293 mg, 0.98 mmol, 79%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.10 (s, 1H, NH), 8.46 (d, *J* = 8.9 Hz, 2H), 8.12 (d, *J* = 8.9 Hz, 2H), 1.30 (s, 9H, $(C(CH_3)_3)$; ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 150.2 (C=O), 149. (C), 144.7 (C), 129.0 (CH), 124.7 (CH), 82.9 ($C(CH_3)_3$, 27.5 ($C(CH_3)_3$); *m/z* (ES^-) 301 (100%, $[M - H]^+$); HRMS *m/z* (ESI^-) calculated for $C_{11}H_{13}N_2O_6S$ 301.0500, found 301.0494; mp: decomposition at 127 °C.



Chemical Formula: $C_{19}H_{22}N_2O_6S$
Molecular Weight: 406.45

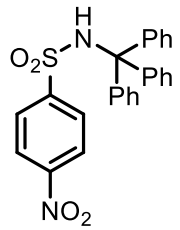
***tert*-Butyl ((4-nitrophenyl)sulfonyl)-D-phenylalaninate 335** was prepared according to a literature procedure.[230] The hydrochloride salt of *L*-phenylaniline *tert*-butyl ester (260 mg, 1.0 mmol, 1.0 eq.), 4-nitrobenzenesulfonyl chloride (220 mg, 1.0 mmol, 1.0 eq.) and Et_3N (0.42 mL, 3.0 mmol, 3.0 eq.) were dissolved in CH_2Cl_2 (10 mL) and stirred at ambient temperature for 18 hours. The reaction mixture was then acidified with HCl (1.0 M, 10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were washed with sat. brine (30 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude material was purified by column chromatography (SiO_2 gel, 1:3 *v/v* EtOAc:hexanes) to afford the product as a white solid (372 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.0 Hz, 2H), 7.87 (d, *J* = 9.0 Hz, 2H), 7.26 – 7.19 (m, 5H), 7.15 – 7.05 (m, 2H, ArH), 5.37 (d, *J* = 9.5

Hz, 1H, NH), 4.13 (ddd, *J* = 9.5, 6.9, 5.7 Hz, 1H, CH), 3.06 (dd, *J* = 13.9, 5.7 Hz, 1H, CH_aH$_b$), 2.97 (dd, *J* = 13.9, 6.9 Hz, 1H, CH$_a$$H_b$), 1.27 (s, 9H (C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 169.8 (C=O), 145.8 (C), 145.0 (C), 135.1 (C), 129.7 (CH), 128.7 (CH), 128.5 (CH), 127.5 (CH), 124.3 (CH), 83.4 (*C*(CH$_3$)$_3$), 57.4 (CH), 39.5 (CH$_2$), 27.9 (C(*C*H$_3$)$_3$); *m/z* (ES$^-$) 405 (100%, [*M* −H]$^-$). The physical data are consistent with the values reported in the literature.[230]



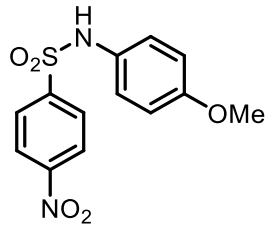
Chemical Formula: $C_{10}H_{14}N_2O_4S$
Molecular Weight: 258.29

***N*-(*tert*-butyl)-4-nitrobenzenesulfonamide** was prepared according to general procedure E (5.0 mmol), and was isolated as a pale yellow solid (1.1 g, 4.2 mmol, 84%); ^{1}H NMR (400 MHz, (CD$_3$)$_2$SO) δ 8.37 (d, *J* = 9.0 Hz, 2H), 8.04 (d, *J* = 9.0 Hz, 2H), 7.97 (s, 1H, NH), 1.11 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, (CD$_3$)$_2$SO) δ 149.9 (C), 149.2 (C), 127.8 (CH), 124.6 (CH), 53.8 (*C*(CH$_3$)$_3$), 29.8 (C(*C*H$_3$)$_3$); *m/z* (ES$^-$) 257 (100%, [*M* − H]$^-$). The physical data are consistent with the values reported in the literature.[396]



Chemical Formula: $C_{25}H_{20}N_2O_4S$
Molecular Weight: 444.51

4-Nitro-*N*-tritylbenzenesulfonamide was prepared by the following procedure. 4-Nitrobenzene sulfonamide (260 mg, 1.3 mmol, 1.0 eq.) was heated to reflux with trityl chloride (530 mg, 1.9 mmol, 1.5 eq.) and Et_3N (0.19 mL, 1.4 mmol, 1.1 eq.), in MeCN (26.0 mL, 0.05 M) for 24 hours. The reaction was then cooled and the volatile components were removed under vacuum. The residue was dissolved in EtOAc (25 mL) and HCl (1.0 M, 25 mL), and then the aqueous phase was washed with EtOAc (3 x 25 mL). The combined organics were washed with water (50 mL) and sat. brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by column chromatography to afford a white solid (373 mg, 64%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.10 (s, 1H, NH), 7.98 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 9.0 Hz, 2H), 7.33 – 7.23 (m, 6H, ArH), 7.24 – 7.08 (m, 9H, ArH); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 148.4 (C), 147.8 (C), 143.4 (C), 128.9 (CH), 127.6 (CH), 127.50 (CH), 126.8 (CH), 123.3 (CH), 71.8 (C); *m/z* (ES^-) 443 (100%, $[M - H]^-$). The physical data are consistent with the values reported in the literature.[396]

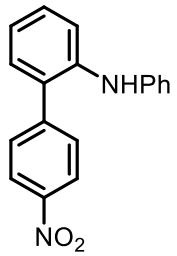


Chemical Formula: $C_{13}H_{12}N_2O_5S$
Molecular Weight: 308.31

***N*-(4-methoxyphenyl)-4-nitrobenzenesulfonamide** was synthesised by general procedure E (1.0 mmol), and isolated as a pale yellow solid (200 mg, 0.65 mmol, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.9 Hz, 2H), 7.85 (d, *J* = 8.9 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.79 (d, *J* = 8.9 Hz, 2H), 6.51 (s, 1H), 3.77 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (C), 150.3 (C), 144.8 (C), 128.7 (CH),

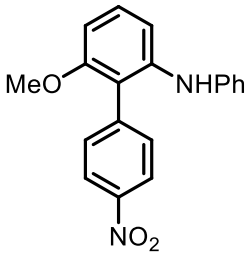
127.5 (C), 126.4 (CH), 124.3 (CH), 114.9 (CH), 55.6 (OCH_3); *m/z* (ES^-) 307 (100%, $[M - H]^-$). The physical data is consistent with literature values.[386, 397]

4.2. Characterisation data for biaryls



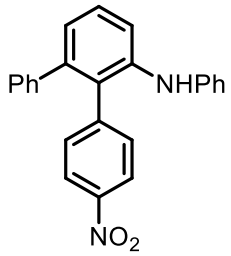
Chemical Formula: $C_{18}H_{14}N_2O_2$
Molecular Weight: 290.32

4'-Nitro-*N*-phenyl-[1,1'-biphenyl]-2-amine 280 was synthesised by general procedure G (0.25 mmol), and isolated as a red crystalline solid (40 mg, 56%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.8 Hz, 2H, ArH), 7.65 (d, *J* = 8.8 Hz, 2H, ArH), 7.40 (d, *J* = 8.1 Hz, 1H, ArH), 7.28 (td, *J* = 7.5, 1.1 Hz, 1H), 7.30 – 7.21 (m, 3H, ArH), 7.07 (td, *J* = 7.5, 1.3 Hz, 1H, ArH), 7.00 (d, *J* = 7.7 Hz, 2H), 6.95 (t, *J* = 7.4 Hz, 1H), 5.44 (s, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1 (C), 146.3 (C), 143.1 (C), 140.3 (C), 130.9 (CH), 130.3 (CH), 129.8 (C), 129.7 (CH), 129.6 (CH), 124.2 (CH), 122.1 (CH), 121.6 (CH), 119.0 (CH), 118.3 (CH); HRMS (ES^+) *m/z* calculated for $C_{18}H_{13}N_2O_2$ 289.0977 $[M - H]^-$, found 289.0991; mp: 93 – 98 °C.



Chemical Formula: $C_{19}H_{16}N_2O_3$
Molecular Weight: 320.35

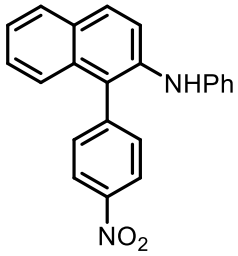
6-Methoxy-4'-nitro-*N*-phenyl-[1,1'-biphenyl]-2-amine 282 was synthesised according to general procedure G (0.25 mmol), and was isolated as an orange crystalline solid (52 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.6 Hz, 2H, ArH), 7.54 (d, *J* = 8.6 Hz, 2H, ArH), 7.31 – 7.19 (m, 3H, ArH), 7.01 (td, *J* = 8.7, 1.0 Hz, 3H, ArH), 6.95 (tt, *J* = 7.4, 1.0 Hz, 1H, ArH), 6.60 (dd, *J* = 8.3, 0.5 Hz, 1H, ArH), 5.16 (br s, 1H, NH), 3.74 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5 (C), 147.2 (C), 142.7 (C), 142.3 (C), 141.9 (C), 132.2 (CH), 129.9 (CH), 129.5 (CH), 124.0 (CH), 121.9 (CH), 119.1 (CH), 117.8 (C), 110.4 (CH), 103.6 (CH), 55.8 (OCH_3); HRMS (ES^+) *m/z* calculated for $C_{19}H_{16}N_2O_3Na$ 343.1059 $[M + Na]^+$, found 343.1075; mp: 153 – 156 °C.



Chemical Formula: $C_{24}H_{18}N_2O_2$
Molecular Weight: 366.42

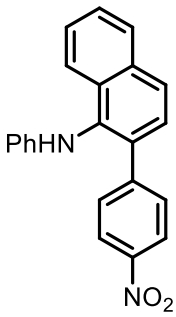
4''-Nitro-*N*-phenyl-[1,1':2',1''-terphenyl]-3'-amine 283 was synthesised by general procedure G (0.25 mmol), and isolated as an orange solid (65 mg, 71%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.8 Hz, 2H, ArH), 7.38 (dd, *J* = 8.2, 1.3 Hz, 1H, ArH), 7.34 (d, *J* = 7.4 Hz, 1H, ArH), 7.30 (dt, *J* = 9.1, 2.5 Hz, 2H, ArH), 7.25 (dd, *J* = 8.5, 7.4 Hz, 2H, ArH), 7.14 (dt, *J* = 4.1, 1.6 Hz, 2H, ArH), 7.04 – 6.98 (m, 6H, ArH), 6.95 (t, *J* = 7.4 Hz, 1H, ArH), 5.17 (s, 1H, NH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.9 (C), 144.9 (C), 142.9 (C), 142.8 (C), 140.9 (C), 132.3 (CH), 129.7 (CH), 129.6 (CH), 129.2 (CH), 128.0 (CH), 127.9 (C), 126.9 (CH), 123.8 (CH), 123.3 (CH), 121.9 (CH), 119.0 (CH), 116.7 (C), *one C not observed*; HRMS

(APCI$^+$) *m/z* calculated for $C_{24}H_{19}N_2O_2$ 367.1447 [*M* + H]$^+$, found 367.1429; mp: 147 – 149 °C.



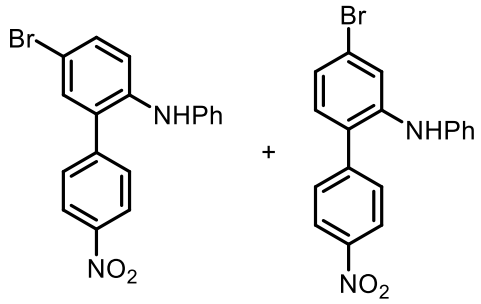
Chemical Formula: $C_{22}H_{16}N_2O_2$
Molecular Weight: 340.38

1-(4-Nitrophenyl)-*N*-phenylnaphthalen-2-amine 284 was synthesised according to general procedure G (0.25 mmol), and was isolated as a red crystalline solid (43 mg, 51%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 – 8.36 (m, 2H, ArH), 7.86 – 7.79 (m, 2H, ArH), 7.63 – 7.55 (m, 3H, ArH), 7.36 (ddd, *J* = 6.7, 4.8, 3.3 Hz, 2H, ArH), 7.32 – 7.22 (m, 3H, ArH), 7.05 – 6.92 (m, 3H, ArH), 5.34 (br s, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7 (C), 144.4 (C), 143.1 (C), 138.1 (C), 133.1 (C), 132.4 (CH), 129.7 (CH), 129.6 (CH), 129.5 (C), 128.4 (CH), 127.1 (CH), 124.6 (CH), 124.2 (CH), 124.0 (CH), 123.3 (C), 122.0 (CH), 119.4 (CH), 118.8 (CH); *m/z* (EI$^+$) 340 ([*M*]$^+$, 100%); HRMS (ES$^+$) *m/z* calculated for $C_{22}H_{16}O_2N_2$ 340.1206 [*M*]$^+$, found 340.1197; mp: 162 – 164 °C.



Chemical Formula: $C_{22}H_{16}N_2O_2$
Molecular Weight: 340.38

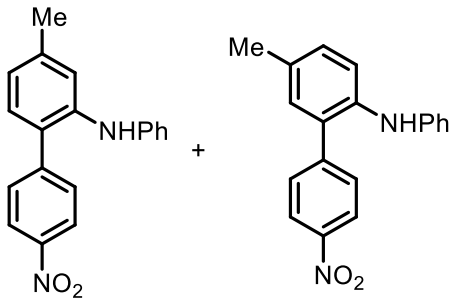
2-(4-Nitrophenyl)-*N*-phenylnaphthalen-1-amine 285 was synthesised according to general procedure G (0.25 mmol), and was isolated as a yellow solid (14 mg, 17%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.5 Hz, 2H, ArH), 8.02 (d, *J* = 8.4 Hz, 1H, ArH), 7.93 (d, *J* = 8.1 Hz, 1H, ArH), 7.84 (d, *J* = 8.5 Hz, 1H, ArH), 7.56 (dd, *J* = 9.2, 2.6 Hz, 3H, ArH), 7.54 – 7.43 (m, 2H, ArH), 7.15 (dd, *J* = 8.4, 7.1 Hz, 2H, ArH), 6.81 (t, *J* = 7.3 Hz, 1H, ArH), 6.61 – 6.49 (m, 2H, ArH), 5.52 (s, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.3 (C), 147.2 (C), 146.8 (C), 134.8 (C), 134.7 (C), 132.6 (C), 130.7 (C), 130.2 (CH), 129.5 (CH), 128.5 (CH), 127.7 (CH), 127.0 (CH), 126.9 (CH), 126.5 (CH), 125.0 (CH), 123.9 (CH), 119.7 (CH), 114.9 (CH); HRMS (TOF MS ES$^+$) *m/z* Calculated for $C_{22}H_{16}O_2N_2$ 340.1206 $[M]^+$, found 340.1214; mp: decomposition at 202 °C.



Chemical Formula: $C_{18}H_{13}BrN_2O_2$
Molecular Weight: 369.22

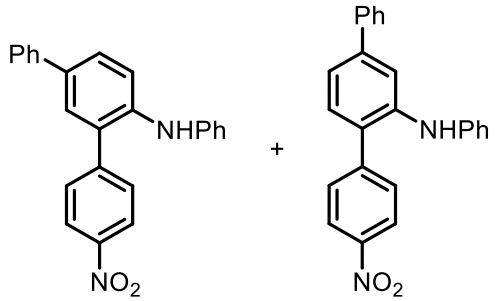
5-Bromo-4'-nitro-*N*-phenyl-[1,1'-biphenyl]-2-amine 286 and **4-bromo-4'-nitro-*N*-phenyl-[1,1'-biphenyl]-2-amine 287** were synthesised according to general procedure G (0.25 mmol), and were isolated unseparated as red solid (38 mg, 63%, 2.1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.3 Hz, 6H), 7.64 (d, *J* = 8.8, Hz, 6H), 7.49 (d, *J* = 1.9 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.38 (s, 3H), 7.36 – 7.22 (m, 10H), 7.18 – 6.94 (m, 13H), 5.51 (s, 1H), 5.43 (s, 2H) *sum of integration expect 43, total 43*; ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2 (C), 147.1 (C), 145.0 (C), 144.6 (C), 142.1 (C), 141.9 (C), 141.4 (C), 139.5 (C), 133.1 (CH), 132.3 (CH), 131.9 (CH),

130.9 (CH), 130.1 (CH), 130.1 (CH), 129.6 (CH), 129.58 (CH), 129.56 (CH), 127.3 (C), 124.3 (CH), 124.2 (CH), 124.1 (CH), 123.6 (C), 122.7 (C), 122.1 (CH), 119.7 (CH), 119.5 (CH), 118.6 (CH), 113.5 (C); *m/z* (APCI$^+$) 369 ([*M* + H]$^+$, 100%), 371 ([*M* + H]$^+$, 100%); HRMS (APCI$^+$) *m/z* calculated for $C_{18}H_{14}N_2O_2Br$ 369.0239 [*M* + H]$^+$ found 369.0251.



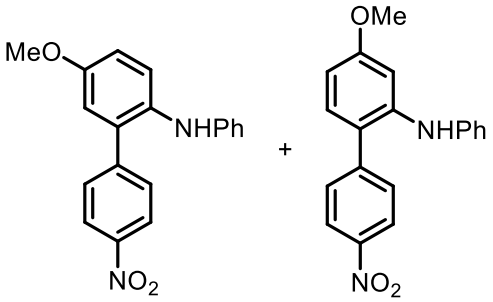
Chemical Formula: $C_{19}H_{16}N_2O_2$
Molecular Weight: 304.35

4-Methyl-4'-nitro-*N*-phenyl-[1,1'-biphenyl]-2-amine 288 and **5-methyl-4'-nitro-*N*-phenyl-[1,1'-biphenyl]-2-amine 289** were synthesised according to general procedure G (0.46 mmol), and were isolated unseparated as a red crystalline solid (89 mg, 64%, 1:1.1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.20 (m, 4H, ArH), 7.68 – 7.56 (m, 4H, ArH), 7.35 – 7.28 (m, 1H, ArH), 7.26 – 7.19 (m, 7H, ArH), 7.17 (dd, *J* = 8.1, 5.4 Hz, 2H, ArH), 7.11 (s, 1H, ArH), 7.03 – 6.85 (m, 7H), 5.38 (s, 1H, NH), 5.28 (s, 1H, NH), 2.37 (s, 3H, CH_3), 2.35 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9 (C), 146.8 (C), 146.3 (C), 146.2 (C), 143.8 (C), 143.0 (C), 139.9 (C), 139.9 (C), 137.2 (C), 132.1 (CH), 131.2 (CH), 130.7 (C), 130.6 (CH), 130.3 (CH), 130.1 (CH), 130.1 (CH), 129.4 (CH), 129.4 (CH), 127.0 (C), 124.0 (CH), 123.9 (CH), 122.9 (CH), 121.4 (CH), 120.7 (CH), 120.5 (CH), 119.4 (CH), 118.1 (CH), 117.0 (CH), 21.4 (CH_3), 20.7 (CH_3); HRMS (ES$^+$) calculated for $C_{19}H_{17}N_2O_2$ 305.1290 [*M* + H]$^+$, found 305.1298.



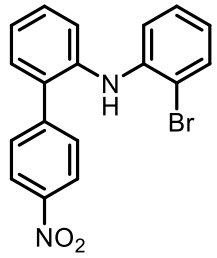
Chemical Formula: $C_{24}H_{18}N_2O_2$
Molecular Weight: 366.42

4''-Nitro-*N*-phenyl-[1,1':3',1''-terphenyl]-4'-amine 290 and **4-nitro-*N*-phenyl-[1,1':4',1''-terphenyl]-2'-amine 291** were synthesised according to general procedure G (0.48 mmol), and were isolated unseparated as a red crystalline solid (111 mg, 66%, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.23 (m, 4H, ArH), 7.77 – 7.67 (m, 4H, ArH), 7.63 (d, *J* = 1.7 Hz, 1H, ArH), 7.62 – 7.53 (m, 6H, ArH), 7.52 – 7.42 (m, 6H, ArH), 7.41 – 7.33 (m, 3H, ArH), 7.33 – 7.21 (m, 3H, ArH), 7.09 – 7.02 (m, 5H), 7.02 – 6.91 (m, 2H, ArH), 5.50 (s, 1H, NH), 5.47 (s, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1 (C), 147.0 (C), 146.0 (C), 145.8 (C), 142.8 (C), 142.7 (C), 142.6 (C), 140.5 (C), 140.3 (C), 140.1 (C), 139.5 (C), 134.7 (C), 131.2 (CH), 130.3 (CH), 130.1 (CH), 129.7 (C), 129.6 (CH), 129.5 (CH), 129.3 (C), 128.9 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 127.7 (CH), 127.1 (CH), 126.6 (CH), 124.2 (CH), 124.2 (CH), 121.7 (CH), 121.6 (CH), 120.7 (CH), 118.7 (CH), 118.5 (CH), 118.2 (CH), 117.3 (CH), *one CH unobserved*; HRMS (ES^-) calculated for $C_{24}H_{17}N_2O_2$ 365.1290 $[M - H]^-$, found 365.1273.



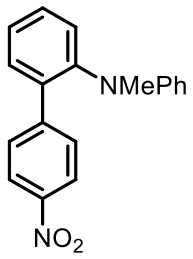
Chemical Formula: $C_{19}H_{16}N_2O_3$
Molecular Weight: 320.35

5-Methoxy-4'-nitro-*N*-phenyl-[1,1'-biphenyl]-2-amine 292 and **4-methoxy-4'-nitro-*N*-phenyl-[1,1'-biphenyl]-2-amine 293** were synthesised according to general procedure G (0.48 mmol), and were isolated unseparated as a red solid (77 mg, 67%, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.8 Hz, 2H), 8.23 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.23 – 7.15 (m, 3H), 7.04 (d, *J* = 7.7 Hz, 2H), 7.00 – 6.95 (m, 2H), 6.94 (d, *J* = 3.0 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 2.9 Hz, 1H), 6.86 – 6.78 (m, 4H), 6.62 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.47 (s, 1H), 5.11 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9 (C), 155.9 (C), 147.0 (C), 146.7 (C), 146.1 (C), 146.0 (C), 145.2 (C), 142.5 (C), 141.5 (C), 133.9 (C), 132.5 (C), 131.7 (C), 130.1 (C), 130.0 (CH), 129.5 (CH), 129.4 (CH), 124.7 (CH), 124.1 (CH), 123.8 (CH), 122.0 (C), 121.8 (CH), 119.8 (C), 118.7 (CH), 115.7 (CH), 115.5 (CH), 115.2 (CH), 107.4 (CH), 103.6 (C), 55.7 (OCH_3), 55.4 (OCH_3); HRMS (ES^+) calculated for $C_{19}H_{16}N_2O_3Na$ 343.1059 $[M + Na]^+$, found 343.1074.



Chemical Formula: $C_{18}H_{13}BrN_2O_2$
Molecular Weight: 369.22

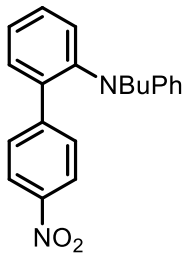
***N*-(2-Bromophenyl)-4'-nitro-[1,1'-biphenyl]-2-amine 294** was synthesised according to general procedure G (0.25 mmol), and was isolated as a yellow crystalline solid (68 mg, 73%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.51 – 7.45 (m, 1H, ArH), 7.41 – 7.36 (m, 2H, ArH), 7.34 (dt, *J* = 7.4, 1.1 Hz, 1H, ArH), 7.18 (ddd, *J* = 7.8, 5.3, 3.4 Hz, 2H), 7.15 – 7.13 (m, 3H), 6.74 (ddd, *J* = 8.1, 5.5, 3.4 Hz, 1H), 5.90 (s, 1H, NH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.3 (C), 146.0 (C), 141.2 (C), 138.9 (C), 133.2 (CH), 132.0 (C), 131.0 (CH), 130.1 (CH), 129.9 (CH), 128.3 (CH), 124.1 (CH), 123.7 (CH), 121.6 (CH), 121.5 (CH), 116.3 (CH), 112.8 (C); HRMS (APCI$^+$) *m/z* calculated for $C_{18}H_{14}N_2O_2Br$ 369.0239 $[M + H]^+$, found 369.0241; mp: 109 – 112 °C.



Chemical Formula: $C_{19}H_{16}N_2O_2$
Molecular Weight: 304.35

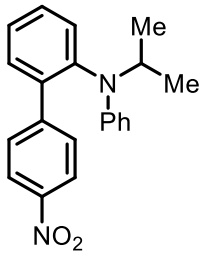
***N*-Methyl-4'-nitro-*N*-phenyl-[1,1'-biphenyl]-2-amine 298** was synthesised according to general procedure H (0.25 mmol), and was isolated as a yellow solid (44 mg, 58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.7 Hz, 2H, ArH), 7.54 (d, *J* = 8.7 Hz, 2H, ArH), 7.45 (t, *J* = 8.4 Hz, 2H, ArH), 7.38 – 7.31 (m, 2H, ArH), 7.18

(t, *J* = 8.0 Hz, 2H, ArH), 6.76 (t, *J* = 7.3 Hz, 1H, ArH), 6.67 (d, *J* = 8.0 Hz, 2H, ArH), 2.90 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.1 (C), 147.1 (C), 146.8 (C), 146.5 (C), 137.7 (C), 131.3 (CH), 130.4 (CH), 129.5 (CH), 129.2 (CH), 129.1 (CH), 126.6 (CH), 123.7 (CH), 118.1 (CH), 114.1 (CH), 39.6 (CH_3); HRMS (EI^+) *m/z* Calculated for $C_{19}H_{16}O_2N_2$ 304.1206 $[M]^+$, found 304.1198; mp: 126 – 130 °C.



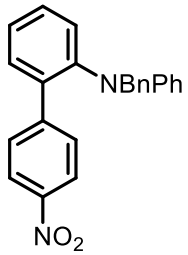
Chemical Formula: $C_{22}H_{22}N_2O_2$
Molecular Weight: 346.43

***N*-Butyl-4'-nitro-N-phenyl-[1,1'-biphenyl]-2-amine 299** was synthesised according to general procedure H (0.25 mmol) and was isolated as a yellow solid (36 mg, 42%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.8 Hz, 2H, ArH), 7.50 (d, *J* = 8.8 Hz, 2H, ArH), 7.45 (t, *J* = 7.9 Hz, 2H, ArH), 7.38 (d, *J* = 7.4 Hz, 1H, ArH), 7.32 (d, *J* = 7.9 Hz, 1H, ArH), 7.17 (t, *J* = 7.9 Hz, 2H, ArH), 6.74 (t, *J* = 7.4 Hz, 1H, ArH), 6.64 (d, *J* = 7.9 Hz, 2H, ArH), 3.11 (t, *J* = 8.0 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 1.53 – 1.41 (p, *J* = 7.5 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 1.17 (h, *J* = 7.4 Hz, 2H, $NCH_2CH_2CH_2CH_3$), 0.81 (t, *J* = 7.3 Hz, 3H, $NCH_2CH_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9 (C), 147.1 (C), 146.9 (C), 145.0 (C), 138.2 (C), 131.5 (CH), 130.7 (CH), 130.2 (CH), 129.6 (CH), 129.3 (CH), 126.7 (CH), 123.7 (CH), 117.7 (CH), 114.2 (CH), 51.4 ($NCH_2CH_2CH_2CH_3$), 28.8 ($NCH_2CH_2CH_2CH_3$), 20.3 ($NCH_2CH_2CH_2CH_3$), 14.0 ($NCH_2CH_2CH_2CH_3$); HRMS (TOF MS EI^+) *m/z* Calculated for $C_{22}H_{22}O_2N_2$ 346.1676 $[M]^+$, found 346.1667; mp 89 – 95 °C.



Chemical Formula: $C_{21}H_{20}N_2O_2$
Molecular Weight: 332.40

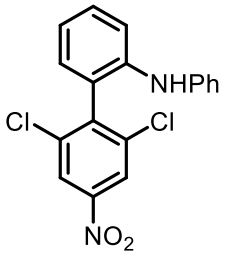
***N*-Isopropyl-4'-nitro-*N*-phenyl-[1,1'-biphenyl]-2-amine 300** was synthesised according to general procedure H (0.25 mmol) and was isolated as a yellow solid (28 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.8 Hz, 2H, ArH), 7.53 – 7.38 (m, 5H, ArH), 7.22 (dd, *J* = 7.5, 1.6 Hz, 3H, ArH), 7.20 – 7.14 (m, 2H, ArH), 6.73 (tt, *J* = 7.5, 1.1 Hz, 1H, ArH), 6.58 (d, *J* = 8.0 Hz, 2H, ArH), 4.05 (p, *J* = 6.6 Hz, 1H, CH), 0.88 (dd, *J* = 6.5, 1.2 Hz, 6H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5 (C), 147.6 (C), 147.0 (C), 142.1 (C), 141.1 (C), 132.9 (C), 131.3 (CH), 130.2 (CH), 123.0 (CH), 129.2 (CH), 127.5 (CH), 123.4 (CH), 117.4 (CH), 115.1 (CH), 49.5 (CH), 20.4 (CH_3); HRMS (TOF MS ES$^+$) *m/z* Calculated for $C_{21}H_{20}O_2N_2$ 332.1519, found 332.1521; mp 146 – 154 °C.



Chemical Formula: $C_{25}H_{20}N_2O_2$
Molecular Weight: 380.45

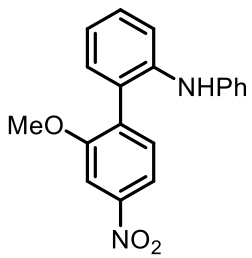
***N*-Benzyl-4'-nitro-*N*-phenyl-[1,1'-biphenyl]-2-amine 301** was synthesised according to general procedure H (0.25 mmol), and was isolated as a yellow solid (43 mg, 45%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.8 Hz, 2H, ArH), 7.50 – 7.41 (m, 5H, ArH) 7.38 – 7.32 (m, 1H, ArH), 7.22 – 7.17 (m, 2H), 7.17 – 7.09 (m, 4H), 6.75 (tt, *J* = 7.3, 1.1 Hz, 1H, ArH), 6.70 – 6.60 (m, 2H, ArH), 4.39 (s, 2H, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2 (C), 147.2 (C), 146.9 (C), 145.2 (C), 138.4 (C), 138.2 (C), 131.7 (CH), 130.6 (CH), 130.3 (CH), 129.7 (CH), 129.3 (CH),

128.5 (CH), 127.0 (CH), 126.9 (CH), 126.8 (CH), 123.8 (CH), 118.4 (CH), 114.6 (CH), 56.2 (CH_2); HRMS (EI^+) *m/z* calculated for $C_{25}H_{20}O_2N_2$ 380.1519 $[M]^+$, found 380.1506; mp: 132 – 136 °C.



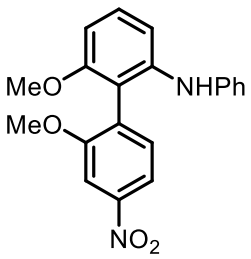
Chemical Formula: $C_{18}H_{12}Cl_2N_2O_2$
Molecular Weight: 359.21

2',6'-Dichloro-4'-nitro-*N*-phenyl-[1,1'-biphenyl]-2-amine 302 was synthesised according to general procedure G (0.25 mmol), and was isolated as a deep red crystalline solid (72 mg, 81%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.37 (s, 2H, ArH), 7.34 – 7.26 (m, 2H, ArH), 7.21 (brs, 1H, NH), 7.13 (t, *J* = 7.8 Hz, 2H, ArH), 7.09 – 7.06 (m, 1H, ArH), 7.02 – 6.97 (m, 1H, ArH), 6.95 (d, *J* = 7.8 Hz, 2H, ArH), 6.76 (t, *J* = 7.3 Hz, 1H, ArH); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 147.3 (C), 143.7 (C), 143.6 (C), 141.5 (C), 136.5 (C), 130.4 (CH), 130.0 (CH), 129.0 (CH), 125.4 (CH), 123.4 (CH), 120.8 (C), 120.3 (CH), 118.5 (CH), 117.9 (CH); HRMS ($APCI^+$) *m/z* calculated for $C_{18}H_{13}N_2O_2Cl_2$ 359.0354 $[M + H]^+$, found 359.0346; mp: 172 – 174 °C.



Chemical Formula: $C_{19}H_{16}N_2O_3$
Molecular Weight: 320.35

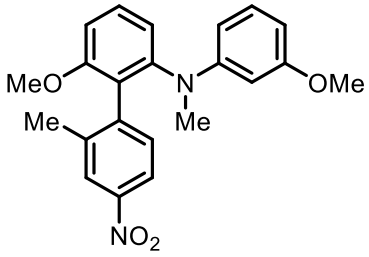
2'-Methoxy-4'-nitro-*N*-phenyl-[1,1'-biphenyl]-2-amine 304 was synthesised according to general procedure G (0.46 mmol), and was isolated as bright red solid (120 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.3, 2.0 Hz, 1H, ArH), 7.83 (d, *J* = 2.0 Hz, 1H, ArH), 7.45 (d, *J* = 8.3 Hz, 1H, ArH), 7.40 (dd, *J* = 8.3, 1.3 Hz, 1H, ArH), 7.35 – 7.31 (m, 1H, ArH), 7.23 – 7.20 (m, 3H, ArH), 7.06 (dt, *J* = 7.4, 1.5 Hz, 1H, ArH), 6.96 – 6.93 (m, 2H, ArH), 6.90 – 6.87 (m, 1H, ArH), 5.54 (brs, 1H, NH), 3.85 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.9 (C), 148.3 (C), 143.4 (C), 141.0 (C), 135.3 (C), 132.2 (CH), 131.2 (CH), 129.3 (CH), 129.2 (CH), 127.4 (C), 121.5 (CH), 120.8 (CH), 118.8 (CH), 117.6 (CH), 116.3 (CH), 105.9 (CH), 56.1 (OCH_3); HRMS (ES^+) *m/z* calculated for $C_{19}H_{16}N_2O_3Na$ 343.1059 [*M* + Na]$^+$, found 343.1071; mp: 81 – 84 °C.



Chemical Formula: $C_{20}H_{18}N_2O_4$
Molecular Weight: 350.37

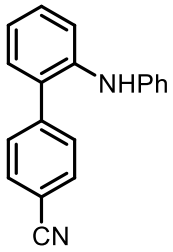
2',6-Dimethoxy-4'-nitro-*N*-phenyl-[1,1'-biphenyl]-2-amine 309 was synthesised according to general procedure G (0.46 mmol), and was isolated as red crystalline solid (99 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 1H, ArH), 7.75 (s, 1H, ArH), 7.33 (d, *J* = 8.3 Hz, 1H, ArH), 7.21 – 7.11 (m, 3H, ArH), 6.94 (d, *J* = 8.2 Hz, 1H, ArH), 6.88 (d, *J* = 7.9 Hz, 2H, ArH), 6.82 (t, *J* = 7.4 Hz, 1H, ArH), 6.54 (d, *J* = 8.2 Hz, 1H, ArH), 5.16 (brs, 1H, NH), 3.72 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (C), 157.6 (C), 148.4 (C), 143.1 (C), 142.1 (C), 133.2 (CH), 131.0 (C), 129.5 (CH), 129.2 (CH), 121.2 (CH), 118.4 (CH),

116.0 (CH), 114.9 (C), 110.7 (CH), 106.2 (CH), 103.7 (CH), 56.1 (OCH_3), 55.7 (OCH_3); HRMS (ES^+) *m/z* calculated for $C_{20}H_{18}N_2O_4Na$ 373.1164 [*M* + Na]$^+$, found 373.1179; mp: 160 – 163 °C; HPLC CHIRALPAK® IB 4.6 × 250 mm column, 1% IPA in hexanes, 30 min, 1 mL/min, λ = 254 nm, t_R = 16.2 and 17.4.



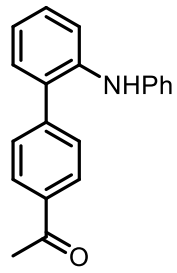
Chemical Formula: $C_{22}H_{22}N_2O_4$
Molecular Weight: 378.43

6-Methoxy-*N*-(3-methoxyphenyl)-*N*,2'-dimethyl-4'nitro-[1,1'-biphenyl]-2-amine 308 was synthesised according to general procedure H (0.46 mmol), and was isolated as an amorphous yellow solid (82 mg, 48%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 2.5 Hz, 1H, ArH), 7.90 (dd, *J* = 8.5, 2.5 Hz, 1H, ArH), 7.40 (t, *J* = 8.2 Hz, 1H, ArH), 7.16 (d, *J* = 8.5, Hz, 1H, ArH), 7.02 (t, *J* = 8.2, Hz, 1H, ArH), 6.97 (d, *J* = 8.0, Hz, 1H, ArH), 6.89 (d, *J* = 8.4 Hz, 1H, ArH), 6.29 (dd, *J* = 8.0, 2.4 Hz, 1H, ArH), 6.17 (dd, *J* = 8.4, 2.4 Hz, 1H, ArH), 6.11 (t, *J* = 2.4 Hz, 1H, ArH), 3.77 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 2.78 (s, 3H, NCH_3), 2.22 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3 (C), 157.2 (C), 150.5 (C), 147.6 (C), 146.9 (C), 142.7 (C), 139.1 (C), 131.1 (CH), 130.2 (CH), 129.4 (CH), 126.8 (C), 124.3 (CH), 120.8 (CH), 120.3 (CH), 108.2 (CH), 107.4 (CH), 102.3 (CH), 100.9 (CH), 55.7 (OCH_3), 55.0 (OCH_3), 39.3 (NCH_3), 19.9 (CH_3); HRMS (ES^+) calculated for $C_{22}H_{22}N_2O_4Na$ 401.1477 [*M* + Na]$^+$, found 401.1477; HPLC CHIRALPAK® IB 4.6 × 250 mm column, 1% IPA in hexanes, 30 min, 1 mL/min, λ = 254 nm, t_R = 13.19 and 14.46.



Chemical Formula: $C_{19}H_{14}N_2$
Molecular Weight: 270.34

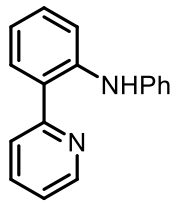
2'-(Phenylamino)-[1,1'-biphenyl]-4-carbonitrile 310 was synthesised according to general procedure G (0.25 mmol), and was isolated as a yellow oil (34 mg, 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.38 (dd, *J* = 8.4, 1.3 Hz, 1H, ArH), 7.29 (td, *J* = 8.4, 8.0, 1.9 Hz, 1H, ArH), 7.25 – 7.19 (m, 3H, ArH), 7.03 (td, *J* = 7.4, 1.3 Hz, 1H, ArH), 7.01 – 6.96 (m, 2H, ArH), 6.93 (t, *J* = 7.4 Hz, 1H, ArH), 5.41 (s, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2 (C), 143.0 (C), 140.1 (C), 132.7 (CH), 130.8 (CH), 130.2 (CH), 130.0 (C), 129.5 (CH), 129.5 (CH), 121.9 (CH), 121.5 (CH), 118.9 (CN), 118.7 (CH), 118.7 (CH), 111.2 (C); HRMS (TOF MS AP$^+$) *m/z* Calculated for $C_{19}H_{15}N_2$ 271.1235 $[M + H]^+$, found 271.1245.



Chemical Formula: $C_{20}H_{17}NO$
Molecular Weight: 287.36

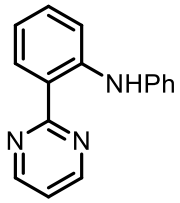
1-(2'-(Phenylamino)-[1,1'-biphenyl]-4-yl)ethan-1-one 311 was synthesised according to general procedure G (0.25 mmol), and was isolated as a white solid (50 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.24 (m, 4H, ArH), 7.11 – 7.03 (m, 3H,

ArH), 7.00 – 6.98 (t, *J* = 7.3 Hz, 1H), 5.58 (s, 1H, NH), 2.66 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.8 (C=O), 144.2 (C), 143.1 (C), 140.1 (C), 136.0 (C), 130.8 (CH), 130.6 (C), 129.6 (CH), 129.5 (CH), 129.1 (CH), 129.0 (CH), 121.6 (CH), 121.3 (CH), 118.2 (CH), 118.2 (CH), 26.81 (CH_3); HRMS (ES^+) *m/z* calculated for $C_{20}H_{17}NONa$ 310.1208 $[M + Na]^+$, found 310.12136; mp: 137 – 140 °C.



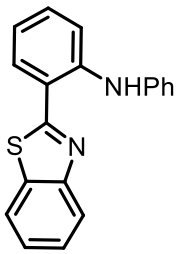
Chemical Formula: $C_{17}H_{14}N_2$
Molecular Weight: 246.31

***N*-Phenyl-2-(pyridin-2-yl)aniline 315** was synthesised according to general procedure G (0.25 mmol), and was isolated as a pale yellow solid (29 mg, 42%); ^1H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H, NH), 8.55 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 7.70 (td, *J* = 7.8, 1.7 Hz, 1H, ArH), 7.63 (dt, *J* = 8.1, 1.0 Hz, 1H, ArH), 7.53 (dd, *J* = 7.8, 1.7 Hz, 1H, ArH), 7.39 (dd, *J* = 8.3, 1.0 Hz, 1H, ArH), 7.18 (dtd, *J* = 8.5, 6.9, 1.8 Hz, 3H, ArH), 7.15 – 7.09 (m, 3H, ArH), 6.88 – 6.81 (m, 2H, ArH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2 (C), 147.6 (CH), 143.1 (C), 142.9 (C), 137.2 (CH), 130.0 (CH), 129.8 (CH), 129.4 (CH), 124.9 (C), 122.9 (CH), 121.4 (CH), 121.3 (CH), 119.6 (CH), 119.4 (CH), 116.8 (CH); HRMS (ESI^+) calculated for $C_{17}H_{15}N_2$ 247.1230 $[M + H]^+$, found 247.1234. The physical data are consistent with the values reported in the literature.[14]



Chemical Formula: $C_{16}H_{13}N_3$
Molecular Weight: 247.30

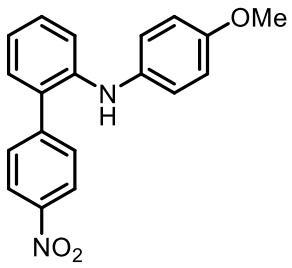
***N*-Phenyl-2-(pyrimidin-2-yl)aniline 316** was synthesised according to general procedure G (0.35 mmol), and was isolated as a yellow oil (48 mg, 55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H, NH), 8.69 (d, *J* = 4.9 Hz, 2H, ArH), 8.44 (dd, *J* = 8.0, 1.6 Hz, 1H, ArH), 7.32 (dd, *J* = 8.5, 1.3 Hz, 1H, ArH), 7.28 – 7.13 (m, 5H, ArH), 7.03 (t, *J* = 4.9 Hz, 1H, ArH), 6.93 (tt, *J* = 7.0, 1.6 Hz, 1H, ArH), 6.81 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8 (C), 156.3 (CH), 145.7 (C), 142.2 (C), 131.7 (CH), 131.4 (CH), 129.4 (CH), 122.4 (CH), 121.4 (CH), 120.8 (C), 118.4 (CH), 117.7 (CH), 115.5 (CH); HRMS (APCI$^+$) calculated for $C_{16}H_{14}N_3$ 248.1188 [*M* + H]$^+$, found 248.1181.



Chemical Formula: $C_{19}H_{14}N_2S$
Molecular Weight: 302.40

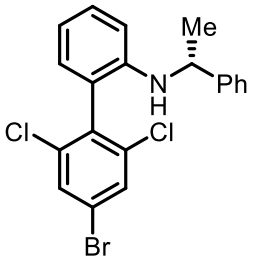
2-(Benzo[d]thiazol-2-yl)-*N*-phenylaniline 314 was synthesised according to general procedure G (0.25 mmol) and was isolated as a yellow solid (22 mg, 74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.83 (s, 1H, NH), 7.99 (d, *J* = 8.0 Hz, 1H, ArH), 7.90 (d, *J* = 8.0 Hz, 1H, ArH), 7.82 (d, *J* = 8.0 Hz, 1H, ArH), 7.48 (t, *J* = 7.5 Hz, 1H), 7.44 – 7.34 (m, 6H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.11 (t, *J* = 6.6 Hz, 1H, ArH), 6.85 (t, *J* = 7.5 Hz, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1 (C), 153.5 (C),

144.2 (C), 141.5 (C), 133.4 (C), 131.6 (CH), 130.9 (CH), 129.5 (CH), 126.3 (CH), 125.2 (CH), 123.3 (CH), 122.6 (CH), 122.4 (CH), 121.3 (CH), 118.0 (CH), 116.7 (C), 114.6 (CH); HRMS (APCI$^+$) *m/z* Calculated for $C_{19}H_{15}N_2S$ 303.0956 $[M + H]^+$, found 303.0948; mp: 125 – 128 °C



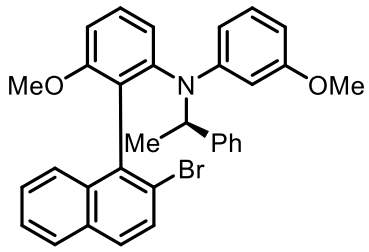
Chemical Formula: $C_{19}H_{16}N_2O_3$
Molecular Weight: 320.35

***N*-(4-methoxyphenyl)-4'-nitro-[1,1'-biphenyl]-2-amine 328** was synthesised according to general procedure G (0.5 mmol), and was isolated as a red solid (63 mg, 39%,); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.26 (m, 2H, ArH), 7.76 – 7.67 (m, 2H, ArH), 7.35 – 7.13 (m, 3H, ArH), 7.10 – 6.93 (m, 3H, ArH), 6.93 – 6.83 (m, 2H, ArH), 5.42 (s, 1H, NH), 3.83 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (C), 146.9 (C), 146.4 (C), 142.2 (C), 135.2 (C), 130.7 (CH), 130.3 (CH), 129.7 (CH), 127.4 (C), 124.2 (CH), 122.8 (CH), 120.2 (CH), 115.8 (CH), 114.8 (CH), 55.6 (OCH_3); *m/z* (ESI$^-$) 319 (100%, $[M – H]^+$); HRMS (ES$^+$) *m/z* calculated for $C_{19}H_{15}N_2O_3$ 320.1122 $[M]^+$, found 320.1120; mp 97 – 99 °C.



Chemical Formula: $C_{20}H_{16}BrCl_2N$
Molecular Weight: 421.16

(*R*)-4'-Bromo-2',6'-dichloro-*N*-(1-phenylethyl)-[1,1'-biphenyl]-2-amine 322 was synthesised according to general procedure H (0.25 mmol), and was isolated as a pale yellow oil (66 mg, 63%); R_f = 0.63 (EtOAc:hexanes, 1:9); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 1.9 Hz, 1H, ArH), 7.66 (d, *J* = 1.9 Hz, 1H, ArH), 7.37 – 7.26 (m, 5H, ArH), 7.25 – 7.20 (m, 1H, ArH), 7.15 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 1H, ArH), 6.92 (dd, *J* = 7.4, 1.7 Hz, 1H, ArH), 6.76 (td, *J* = 7.4, 1.1 Hz, 1H, ArH), 6.51 – 6.45 (m, 1H, ArH), 4.58 – 4.48 (m, 1H, NHC*H*), 3.52 (brs, 1H, N*H*CH), 1.41 (d, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1 (C), 144.0 (C), 137.5 (C), 137.1 (C), 135.9 (C), 131.5 (CH), 131.3 (CH), 129.9 (CH), 129.7 (CH), 128.7 (CH), 127.0 (CH), 125.9 (CH), 122.1 (C), 121.5 (C), 117.1 (CH), 112.2 (CH), 53.4 (NCH), 25.3 (CH_3); HRMS (APCI$^+$) *m/z* calculated for $C_{20}H_{17}BrCl_2N$ 419.9916 [*M* + H]$^+$, found 419.9917.

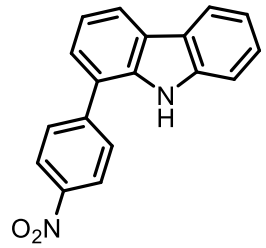


Chemical Formula: $C_{32}H_{28}BrNO_2$
Molecular Weight: 538.49

2-(2-Bromonaphthalen-1-yl)-3-methoxy-*N*-(3-methoxyphenyl)-*N*-((*S*)-1-phenylethyl)aniline 388 was synthesised according to general procedure H (0.25 mmol scale) as a 1:1.4 mixture of diastereoisomers and was isolated as a brown oil (26 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.1 Hz, 2H, ArH), 7.58 (d, *J* = 8.3 Hz, 1H, ArH), 7.53 – 7.47 (m, 3H, ArH), 7.45 (d, *J* = 8.8 Hz, 2H, ArH), 7.40 (d, *J* = 8.2 Hz, 1H, ArH), 7.37 (d, *J* = 5.0 Hz, 1H, ArH), 7.35 (d, *J* = 5.1 Hz, 1H, ArH), 7.33 – 7.29 (m, 2H, ArH), 7.24 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H, ArH), 7.22 – 7.16 (m, 2H, ArH), 7.11 (dd, *J* = 8.2, 1.0 Hz, 1H, ArH), 7.11 (dd, *J* = 8.3, 0.9 Hz,

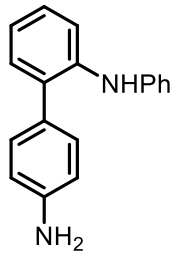
1H, ArH), 7.00 – 6.93 (m, 3H, ArH), 6.92 – 6.75 (m, 9H, ArH), 6.68 (t, *J* = 8.2 Hz, 1H, ArH), 6.62 (t, *J* = 8.2 Hz, 1H, ArH), 6.47 (dt, *J* = 8.4, 1.2 Hz, 3H, ArH), 6.45 – 6.38 (m, 2H, ArH), 6.16 – 6.09 (m, 1H, ArH), 6.08 – 5.99 (m, 4H, ArH), 5.92 (t, *J* = 2.3 Hz, 1H, ArH), 5.79 (t, *J* = 2.3 Hz, 1H, ArH), 4.80 (q, *J* = 6.9 Hz, 1H, CH), 4.69 (q, *J* = 7.0 Hz, 1H, CH), 3.62 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 1.40 (d, *J* = 7.0 Hz, 3H, CH_3), 1.13 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (C), 159.05 (C), 159.0 (C), 159.0 (C), 150.2 (C), 149.8 (C), 147.3 (C), 147.3 (C), 143.2 (C), 142.6 (C), 135.0 (C), 134.8 (C), 134.3 (C), 133.8 (C), 132.4 (C), 132.4 (C), 130.0 (CH), 130.0 (CH), 129.9 (CH), 129.5 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 127.94 (CH), 127.8 (CH), 126.8 (CH), 126.5 (CH), 126.46 (CH), 126.42 (CH), 126.3 (CH), 126.2 (CH), 126.2 (CH), 126.1 (CH), 126.02 (C) 125.9 (CH), 125.8 (CH), 124.5 (C), 124.2 (C), 123.6 (C), 121.6 (CH), 120.0 (CH), 115.4 (CH), 113.7 (CH), 108.1 (CH), 107.8 (CH), 107.1 (CH), 106.8 (CH), 106.77 (CH), 106.4 (CH), 106.0 (CH), 104.5 (CH), 60.08 (CH), 60.05 (CH), 56.3 (OCH_3), 56.3 (OCH_3), 54.9 (OCH_3), 54.9 (OCH_3), 16.2 (CH_3), 15.7 (CH_3); *m/z* (ES^+) 538 $[M + H]^+$, HRMS (FTMS, $APCI^+$) Calculated for $C_{32}H_{28}BrNO_2$ 537.1303 $[M]^+$, found 537.1302.

4.3. Characterisation data for biaryl derivatives



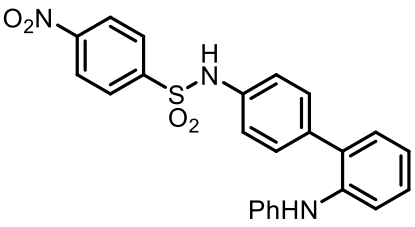
Chemical Formula: $C_{18}H_{12}N_2O_2$
Molecular Weight: 288.31

1-(4-Nitrophenyl)-9*H*-carbazole 322 was synthesised according to a modified literature procedure.[289] The *N*-(2-bromophenyl)-4'-nitro-[1,1'-biphenyl]-2-amine **294** (50 mg, 0.13 mmol, 1.0 eq.), palladium acetate (2.2 mg, 0.01 mmol, 10 mol%), PCy_3HBF_4 (7.4 mg, 0.02 mmol, 20 mol%), oven dried potassium carbonate (37 mg, 0.27 mmol, 2.0 eq.) were dissolved in degassed DMA (0.65 mL, 0.2 M) and heated to reflux for 24 hours. The crude reaction mixture was filtered through a pad of Celite© and then purified by column chromatography (SiO_2, 0 – 10% EtOAc:hexanes) to afford the title compound as a yellow solid (33 mg, 86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.7 Hz, 2H), 8.27 (s, 1H, NH), 8.16 (d, *J* = 7.9 Hz, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 8.7 Hz, 2H), 7.53 – 7.43 (m, 3H, ArH), 7.37 (t, *J* = 7.6 Hz, 1H, ArH), 7.29 (ddd, *J* = 8.1, 4.7, 3.5 Hz, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2 (C), 146.1 (C), 139.7 (C), 137.0 (C), 129.2 (CH), 126.6 (CH), 126.1 (CH), 124.8 (CH), 124.5 (C), 123.5 (C), 122.7 (C), 121.2 (CH), 120.7 (CH), 120.3 (CH), 120.2 (CH), 111.0 (CH) *m/z* (ES^-) 287 ($[M - H]^-$, 100%). The physical data are consistent with the values reported in the literature.[398]



Chemical Formula: $C_{18}H_{16}N_2$
Molecular Weight: 260.34

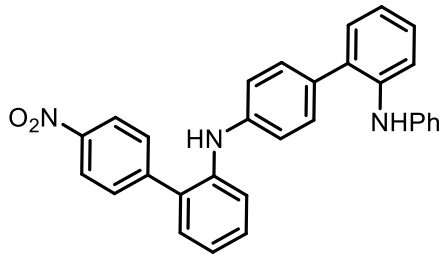
***N*^{2}-phenyl-[1,1'-biphenyl]-2,4'-diamine 280** (145 mg, 0.5 mmol) was dissolved in EtOH (25 mL), and was reduced using a Thales Nano H-Cube flow reactor with a 10% Pd/C cartridge at ambient temperature (30 bar, 1 mL/min). The crude reaction mixture was purified by column chromatography (SiO_2 gel, 0 – 1:1 *v/v* EtOAc:hexanes) to afford **323** as a light brown oil (113 mg, 86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.3 Hz, 1H, ArH), 7.17 – 7.05 (m, 6H, ArH), 6.92 (d, *J* = 7.4Hz, 2H), 6.86 (t, *J* = 6.9 Hz, 1H), 6.79 (t, *J* = 7.4 Hz, 1H, ArH), 6.59 (d, *J* = 8.3 Hz, 2H, ArH), 5.56 (s, 1H, NH), 3.54 (s, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9 (C), 143.7 (C), 140.2 (C), 131.8 (C), 130.9 (CH), 130.4 (CH), 129.4 (CH), 128.9 (C), 127.6 (CH), 121.1 (CH), 120.9 (CH), 118.0 (CH), 117.4 (CH), 115.4 (CH); HRMS (ES^+) *m/*z Calculated for $C_{18}H_{17}N_2$ 261.1392 $[M + H]^+$, found 261.1399.



Chemical Formula: $C_{24}H_{19}N_3O_4S$
Molecular Weight: 445.49

The sulfonamide **324** was prepared from *N*^{2}-phenyl-[1,1'-biphenyl]-2,4'-diamine **323** though the following procedure. 4-Nitrobezenesulfonyl chloride (94 mg, 0.42 mmol)

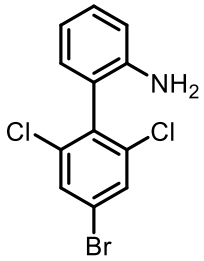
was dissolved in dry CH_2Cl_2 (7.0 mL) and added to **323** (110 mg, 0.42 mmol) and dry pyridine (34 μL, 0.46 mmol, 1.1 eq.) in dry CH_2Cl_2 (7.0 mL). The reaction mixture was stirred at ambient temperature for 4 hours and then acidified with HCl (0.1 M, 5.0 mL). The aqueous phase was extracted with CH_2Cl_2 (2.0 mL x 3); the combined organics were washed with brine (10 mL) and dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude reaction mixture was purified by column chromatography (SiO_2, 10 – 40% *v/v* EtOAc:hexanes) to afford **324** as a yellow solid (82 mg, 44%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.38 (d, *J* = 8.5 Hz, 2H, ArH), 7.00 (d, *J* = 8.5 Hz, 2H, ArH), 6.34 (d, *J* = 8.2 Hz, 2H, ArH), 6.29 – 6.24 (m, 3H, ArH), 6.22 (d, *J* = 7.8 Hz, 1H, ArH), 6.11 – 6.03 (m, 5H), 5.76 (d, *J* = 7.8 Hz, 1H, CH), 5.66 (t, *J* = 7.3 Hz, 1H, CH) *two NH not observed*; ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 149.9 (C), 145.3 (C), 145.2 (C), 139.8 (C), 136.0 (C), 135.9 (C), 133.5 (CH), 131.0 (CH), 129.8 (CH), 129.0 (CH), 128.4 (CH), 124.8 (CH), 123.1 (CH), 122.4 (C), 120.5 (CH), 118.6 (CH), 115.4 (CH); HRMS (ES^-) *m/z* calculated for $C_{24}H_{18}N_3OS$ 444.1018 [*M* – H]$^-$, found 444.1003; mp: 218 – 220°C.



Chemical Formula: $C_{30}H_{23}N_3O_2$
Molecular Weight: 457.53

The extended biaryl **325** was prepared according to General Procedure H from **325** (0.54 mmol scale). The product was isolated as a red solid (55 mg, 67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.7 Hz, 2H, ArH), 7.65 (d, *J* = 8.7 Hz, 2H, ArH), 7.47 (d, *J* = 8.1 Hz, 1H, ArH), 7.36 (d, *J* = 7.7 Hz, 2H, ArH), 7.32 (d, *J* = 8.4 Hz, 2H,

ArH), 7.30 – 7.19 (m, 5H, ArH), 7.09 (t, *J* = 7.4 Hz, 1H, ArH), 7.06 – 7.02 (m, 4H, ArH), 6.98 (t, *J* = 7.4 Hz, 1H, ArH), 6.92 (t, *J* = 7.3 Hz, 1H, ArH), 5.63 (s, 1H, NH), 5.49 (s, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2 (C), 146.2 (C), 143.6 (C), 142.5 (C), 140.3 (C), 139.8 (C), 131.8 (C), 131.4 (C), 131.0 (C), 130.9 (CH), 130.5 (CH), 130.4 (CH), 130.2 (CH), 129.8 (CH), 129.5 (CH), 128.0 (CH), 124.3 (CH), 122.5 (CH), 121.3 (CH), 121.1 (CH), 119.5 (CH), 118.2 (CH), 118.0 (CH), 117.7 (CH); HRMS (ES^+) *m/z* calculated for $C_{30}H_{24}N_3O_2$ 458.1869 $[M + H]^+$, found 458.1865; mp: 214 – 216 °C.

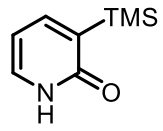


Chemical Formula: $C_{12}H_8BrCl_2N$
Molecular Weight: 317.01

4'-Bromo-2',6'-dichloro-[1,1'-biphenyl]-2-amine 334 was synthesised according to modified literature procedure.[399] Conc. HCl (4.0 mL) was added to (*S*)-4'-bromo-2',6'-dichloro-*N*-(1-phenylethyl)-[1,1'-biphenyl]-2-amine **332** (122 mg, 0.29 mmol) in a microwave vial and sealed, then the mixture was heated to 100 °C for 24 hours. The reaction was cooled to 0 °C, quenched with sat. $NaHCO_3$ (10 mL), and then diluted with EtOAc (20 mL). The aqueous phase was washed with EtOAc (2 x 10 mL) and then the combined organics were washed with sat. brine (20 mL) and dried over $MgSO_4$, filtered and concentrated under vacuum. The crude reaction mixture was purified by column chromatography (SiO_2, 10% EtOAc:hexane) to afford a white solid (65%, 64 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 2H), 7.26 (td, *J* = 8.2, 7.5, 1.5 Hz, 2H), 6.95 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.87 (td, *J* = 7.6, 1.1 Hz, 1H),

6.82 (dd, *J* = 8.2, 1.1 Hz, 2H). 3.32 (brs, 2H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (C), 136.9 (C), 135.8 (C), 131.3 (CH), 130.1 (CH), 130.0 (CH), 122.0 (C), 121.9 (C), 118.8 (CH), 115.9 (CH); HRMS (ESI^+) calculated for $C_{12}H_8BrCl_2N$ $[M + H]^+$ 315.9290, found 315.9195; mp: 106 – 108 °C.

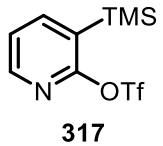
4.4. Hetaryne precursor synthesis



471

Chemical Formula: $C_8H_{13}NOSi$
Molecular Weight: 167.28

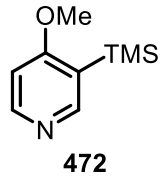
The **471** was prepared according to a literature procedure.[400] A freshly prepared solution of LDA (1.9 mL, 10 mmol, 2.0 eq.) was added to 2-hydroxy pyridine (500 mg, 5.0 mmol, 1.0 eq.) in THF (20 mL, 0.1 M) at −78 °C. The solution was stirred at −78 °C for 5 minutes, after which time TMSCl was added and then stirred at −78 °C for a further 15 minutes. The reaction was then warmed to ambient temperature and stirred for another hour, then filtered and concentrated under vacuum. The residue was dissolved in EtOAc and stirred with SiO_2 gel for 20 minutes to afford 3-trimethylsilyl-2-pyridone **471** (560 mg, 61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 6.5 Hz, 1H, ArH), 7.36 (d, *J* = 6.5, Hz, 1H, ArH), 6.27 (t, *J* = 6.5 Hz, 1H, ArH), 0.28 (s, 9H, $Si(CH_3)_3$). The physical data are consistent with literature values.[400]



317

Chemical Formula: $C_9H_{12}F_3NO_3SSi$
Molecular Weight: 299.34

The **371** was prepared according to a literature procedure.[400] 3-Trimethylsilyl-2-pyridone **471** (530 mg, 3.3 mmol, 1.0 eq.) and 2,6-di-*tert*-butyl pyridine (0.8 mL, 3.6 mmol, 1.1 eq.) were dissolved in CH_2Cl_2 (15 mL, 0.25 M). The solution was then added dropwise to trifluoromethanesulfonic anhydride (0.6 mL, 3.6 mmol, 1.1 eq.) at −78 °C. Upon complete addition, the solution was warmed to ambient temperature and stirred for 1 hour. Then the solvent was removed under vacuum, and the residue was washed with dry pentane (5.0 mL x 3). The combined organics were concentrated and then purified by column chromatography (SiO_2 gel, 1:20 *v/v* EtOAc:hexane) to afford the product as a colourless oil (260 mg, 30%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 4.8, 2.1 Hz, 1H, ArH), 7.92 (dd, *J* = 7.2, 2.1 Hz, 1H, ArH), 7.30 (dd, *J* = 7.2, 4.8 Hz, 1H, ArH), 0.37 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0 (C), 148.9 (CH), 147.1 (CH), 125.3 (C), 123.3 (CH), 118.6 (*app.* d, *J* = 320.5 Hz, CF_3), −1.45 ($Si(CH_3)_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ −72.95 (OSO_2CF_3); *m/z* (ES^+) 300 (100%, $[M + H]^+$). The physical data are consistent with those reported in the literature.[400]

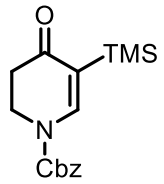


472

Chemical Formula: $C_9H_{15}NOSi$
Molecular Weight: 181.31

472 was prepared according to a literature procedure.[401] 4-Methoxypyridine (546 mg, 5.0 mmol, 0.9 eq.) in THF (5.0 mL), was added to freshly prepared LDA (5.5 mmol, 1.0 eq.) in THF (5.0 mL) at −78 °C, and was stirred at this temperature for 15 minutes. TMSCl (0.82 mL, 6.5 mmol, 1.1 eq.) was added and stirred at −78 °C for 15 minutes, and then at ambient temperature for 1 hour. Water (10 mL) was added and

the aqueous phase was extracted with Et_2O (10 mL x 3). The combined organics were washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. Purification by column chromatography (SiO_2 gel, 3:7 *v/v* EtOAc:petrol) afforded the product as a colourless oil (430 mg, 47%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.8 Hz, 1H, ArH), 8.38 (s, 1H, ArH), 6.72 (d, *J* = 5.8 Hz, 1H, ArH), 3.84 (s, 3H, OCH_3), 0.28 (s, 9H, $Si(CH_3)_3$). The physical data are consistent with the values reported in the literature.[401]

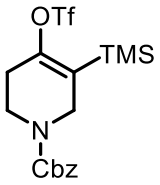


473

Chemical Formula: $C_{16}H_{21}NO_3Si$
Molecular Weight: 303.43

473 was prepared according to a literature procedure.[402] To a solution of 4-methoxy-3-(trimethylsilyl)pyridine **472** (3.20 mg, 1.8 mmol, 1.0 eq.) in MeOH (3.6 mL, 0.5 M) was added $NaBH_4$ (75 mg, 2.0 mmol, 1.1 eq.) at −78 °C. After stirring at this temperature for 20 minutes, benzyl chloroformate (0.28 mL, 2.0 mmol, 1.1 eq.) in THF (3.6 mL) was added over 15 minutes. After stirring for 1 hour at −78 °C, H_2O (3.6 mL) was added and the reaction was warmed to room temperature. After 1.5 hours, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The resulting crude product was purified by column chromatography (SiO_2, 9:1 *v/v* hexanes:EtOAc) to afford the product as a colourless oil (380 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H, C=C*H*), 7.49 – 7.34 (m, 5H, ArH), 5.27 (s, 2H, OC*H*$_2$Ph), 4.00 (dd, *J* = 7.9, 6.8 Hz, 2H, CH_2), 2.53 (dd, *J* = 7.9, 6.8 Hz, 2H, CH_2),

0.15 (s, 9H, $Si(CH_3)_3$). The physical data are consistent with that reported in the literature.[402]

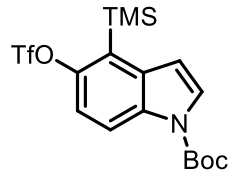


318

Chemical Formula: $C_{17}H_{22}F_3NO_5SSi$
Molecular Weight: 437.51

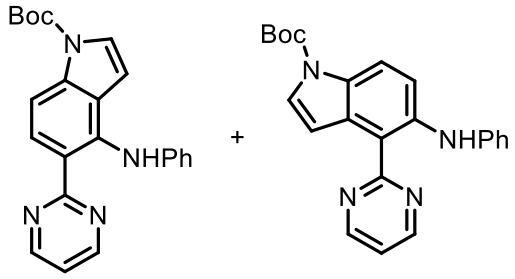
The **318** was prepared according to a literature procedure.[402] To a stirred solution of vinylogous amide **473** (378 mg, 1.25 mmol, 1.0 eq.) in THF (10 mL) was added L-selectride (1.0 M in THF, 1.4 mL, 1.4 mmol, 1.1 eq.) at −78 °C. After stirring for 15 min, Tf_2O (0.24 mL, 1.4 mmol, 1.1 eq.) was added dropwise over 15 min. The reaction was stirred for 20 minutes at −78 °C, and then a saturated aqueous solution of $NaHCO_3$ (10 mL) was added and the reaction was warmed to ambient temperature. After stirring for 2 hours, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organics were washed with brine (1 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The resulting crude product was purified by flash chromatography with basic Brockman Grade I 58 Å alumina (hexanes), followed by a silica gel column (3:2 *v/v* hexanes:EtOAc) to give the product (130 mg, 24% yield) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C) δ 7.41 – 7.29 (m, 5H, ArH), 5.17 (s, 2H, OCH_2Ph), 4.11 (t, *J* = 2.6 Hz, 2H, NCH_2), 3.67 (t, *J* = 5.8 Hz, 2H, NCH_2CH_2), 2.54 (tt, *J* = 5.7, 2.7 Hz, 2H, NCH_2CH_2), 0.24 (d, *J* = 1.1 Hz, 9H, $Si(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$, 55 °C) δ 155.1 (C=O), 136.7 (C), 128.7 (CH), 128.3 (CH), 128.1 (CH), 118.5 (app. d, *J* = 320.0 Hz, CF_3), 67.9 (OCH_2Ph), 45.4 (NCH_2), 40.9 (NCH_2CH_2), 28.8 (NCH_2CH_2), −1.29 (3 x CH_3), *quaternary alkene peaks not observed*; *m/z* (ES^+) 438

([*M* + H]$^+$, 100%). The physical data are consistent with that reported in the literature.[402]



Chemical Formula: $C_{17}H_{22}F_3NO_5SSi$
Molecular Weight: 437.51

319 was prepared according to a literature procedure.[403] DMAP (2.0 mg, 0.015 mmol, 0.1 eq.) was added to a solution of 4-(trimethylsilyl)-1*H*-indol-5-yl trifluoromethanesulfonate (51 mg, 0.15 mmol) in THF (1.5 mL). The resulting solution was stirred at ambient temperature for 5 min, then Boc_2O (33 mg, 0.15 mmol, 1.0 eq.) added. The resulting mixture was stirred for 15 h, then filtered over silica gel with Et_2O. Evaporation under reduced pressure afforded the product (66 mg, quantitative yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.1 Hz, 1H, ArH), 7.71 (d, *J* = 3.8 Hz, 1H, ArH), 7.29 – 7.19 (m, 2H, ArH), 6.76 (dd, *J* = 3.8, 0.8 Hz, 1H, ArH), 1.67 (s, 9H, $C(CH_3)_3$), 0.49 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4 (C), 149.3 (C=O), 136.0 (C), 133.5 (C), 127.7 (C), 124.8 (CH), 118.7 (q, *J* = 320.5 Hz, CF_3), 117.4 (CH), 116.4 (CH), 108.6 (CH), 85.2 ($C(CH_3)_3$), 27.5 ($C(CH_3)_3$), 1.24 ($Si(CH_3)_3$). The physical data are consistent with that reported in the literature.[403]



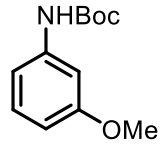
maj min

Chemical Formula: $C_{23}H_{22}N_4O_2$
Molecular Weight: 386.46

***Tert*-butyl 4-(phenylamino)-5-(pyrimidin-2-yl)-1*H*-indole-1-carboxylate 320** and **tert-butyl 5-(phenylamino)-4-(pyrimidin-2-yl)-1*H*-indole-1-carboxylate 321** were according to general procedure G (0.15 mmol) and were isolated, unseparated as a yellow oil (11 mg, 19%, 1:8.3); *major isomer* **320** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H, NH), 8.81 (d, *J* = 4.9 Hz, 2H, ArH), 8.08 (d, *J* = 9.1 Hz, 1H, ArH), 7.55 (d, *J* = 3.8 Hz, 1H, ArH), 7.39 (d, *J* = 9.2 Hz, 1H, ArH), 7.31 (dd, *J* = 3.8, 0.8 Hz, 1H, ArH), 7.22 – 7.08 (m, 6H, ArH), 6.84 (tt, *J* = 7.2, 1.3 Hz, 1H, ArH), 1.60 (s, 9H, $C(CH)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9 (C), 155.3 (CH), 148.7 (C=O), 142.6 (C), 138.9 (C), 128.2 (CH), 127.8 (C), 125.5 (CH), 119.8 (CH), 118.7 (C), 117.9 (CH), 117.0 (CH), 116.5 (CH), 114.8 (CH), 114.7 (C) 107.7 (CH), 82.5 ($C(CH_3)_3$), 27.2 ($C(CH_3)_3$; *m/z* (ES^+) 387 ($[M + H]^+$, 80%), 103 ($[C_5H_{10}O_2]^+$, 100%); HRMS (ES^+) calculated for $C_{23}H_{23}N_4O_2$ 387.1821 $[M + H]^+$, found 387.1804.

Minor isomer **321** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1H, NH), 8.72 (d, *J* = 4.9 Hz, 2H, ArH), 8.37 (d, *J* = 9.0 Hz, 1H, ArH), 7.81 (d, *J* = 9.0 Hz, 1H, ArH), 7.05 (t, *J* = 4.9 Hz, 1H, ArH), 6.96 – 6.92 (m, 2H, ArH), 6.09 (dd, *J* = 3.8, 0.8 Hz, 1H,, ArH), 1.18 (s, 9H, $C(CH)_3$) *18/23 observed*.

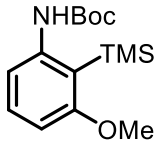
4.5. Preparation of 340



474

Chemical Formula: $C_{12}H_{17}NO_3$
Molecular Weight: 223.27

***Tert*-Butyl 3-methoxyphenylcarbamate 474** was prepared according to a modified literature procedure.[404] To 3-aminoanisole (0.56 mL, 5.0 mmol, 1.0 eq.) in THF (20 mL, 0.25 M), was added Boc_2O (1.4 g, 6.0 mmol, 1.2 eq.) as a solution in THF (6.0 mL, 1.0 M). The solution was heated to reflux for 18 hours and then the solvent was removed under vacuum. The residue was taken up in EtOAc (20 mL), and was washed with water (20 mL), sat. $NaHCO_3$ (20 mL) and sat. brine (20 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was used without further purification (100%, 1.1 g,); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 8.2 Hz, 1H, ArH), 7.10 (s, 1H, ArH), 6.86 – 6.78 (m, 1H, ArH), 6.58 (ddd, *J* = 8.2, 2.4, 1.0 Hz, 1H, ArH), 6.47 (s, 1H, NH), 3.80 (d, *J* = 1.3 Hz, 3H, OCH_3), 1.51 (d, *J* = 1.2 Hz, 9H, $C(CH_3)_3$); *m/z* (ES^+) 168 (100%, $[M - C(CH_3)_3 + H]^+$), 246 (20%, $[M + Na]^+$). The physical data are consistent with the values reported in the literature.[404]

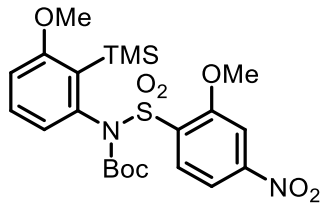


475

Chemical Formula: $C_{15}H_{25}NO_3Si$
Molecular Weight: 295.45

The **475** was prepared according to a literature procedure.[405] At −78 °C, DIPA (0.73 mL, 10 mmol, 2.0 eq.), **474** (1.13 g, 5.0 mmol, 1.0 eq.), and TMSCl (0.76 mL, 6.0 mmol, 1.1 eq.) were added consecutively to *n*-butyl lithium (1.3 M in hexanes, 13.1 mL, 10 mmol, 2.0 eq.) in THF (15 mL). When the mixture had attained ambient

temperature, the volatile components were removed under vacuum. The crude reaction mixture was purified by column chromatography (SiO_2 gel, 1:9 *v/v* EtOAc:hexanes) to afford a colourless solid (654 mg, 2.2 mmol, 44%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.2 Hz, 1H, ArH), 7.20 (t, *J* = 8.1 Hz, 1H, ArH), 6.68 (s, 1H, NH), 6.51 (dd, *J* = 8.2, 0.9 Hz, 1H, ArH), 3.68 (s, 3H, OCH_3), 1.44 (s, 9H ($C(CH_3)_3$), 0.29 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8 (C), 153.3 (C=O), 143.4 (C), 131.0 (CH), 115.1 (C), 105.8 (CH), 79.9 ($C(CH_3)_3$), 39.0 (OCH_3), 28.3 ($C(CH_3)_3$), 1.6 ($Si(CH_3)_3$); *m/z* (ES^-) 294 (100%, $[M - H]^+$).

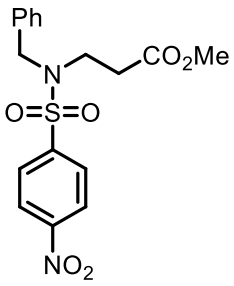


Chemical Formula: $C_{22}H_{30}N_2O_8SSi$
Molecular Weight: 510.63

340 was prepared according to a modified literature procedure.[406] To a solution of sodium hydride (dispersion in mineral oil 60%, 110 mg, 2.7 mmol, 1.2 eq.) in DMF (22 mL, 0.1 M) at 0 °C, carbamate **475** (650 mg, 2.2 mmol, 1.0 eq.) was added. After 30 minutes, 2-methoxyl-4-nitrobenzenesulfonyl chloride (680 mg, 2.7 mmol, 1.2 eq.) was added, and then the reaction mixture was stirred at this temperature for 1 hour. After this time, the reaction was diluted with iced water (10 mL), filtered and concentrated under vacuum. The crude material was purified by column chromatography (Biotage Isolera 25 g SNAP column, 0:1 to 1:4 EtOAc:hexanes) to afford a white solid (190 mg, 17%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.6 Hz, 1H, ArH), 7.97 – 7.88 (m, 2H, ArH), 7.26 (d, *J* = 8.0 Hz, 1H, ArH), 6.89 (dd, *J* = 8.3, 0.9 Hz, 1H, ArH), 6.59 (dd, *J* = 7.9, 0.9 Hz, 1H, ArH), 4.02 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 1.37 (s, 9H, ($C(CH_3)_3$), 0.42 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 165.1 (C=O), 157.3 (C), 151.8 (C), 150.5 (C), 141.0 (C), 134.5 (C), 133.5 (CH), 130.7 (C), 129.8 (CH), 122.8 (CH), 114.9 (CH), 110.5 (CH), 107.5 (CH), 84.5 ($C(CH_3)_3$), 56.6 (OCH_3), 55.4 (OCH_3), 28.0 ($C(CH_3)_3$), 0.82 ($Si(CH_3)_3$); *m/z* (ES^+) 454 (100%, $[M - (CH_3)_3 + H)]^+$), 533 (60%, $[M + Na]^+$); HRMS (ESI^+) *m/z* calculated for $C_{22}H_{31}O_8N_2SSi$ 511.1565 $[M + H]^+$, found 511.1542.

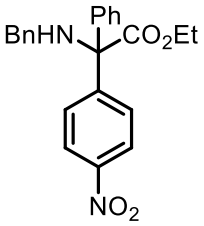
5. Data for Chapter 3



Chemical Formula: $C_{17}H_{18}N_2O_6S$
Molecular Weight: 378.40

Methyl acrylate (0.9 mL, 10 mmol, 1.0 eq.) was added dropwise to a solution of benzylamine (1.6 mL, 10 mmol, 1.0 eq.) in methanol (10 mL). The reaction was stirred at ambient temperature for 18 hours, and then concentrated under vacuum. The crude reaction material was dissolved in CH_2Cl_2 (10 mL) and Et_3N (1.5 mL, 11 mmol, 1.1 eq.) was added. A solution of 4-nitrobenzenesulfonyl chloride (2.9 g, 10 mmol, 1.0 eq.) was then added dropwise, and the resulting reaction was stirred at ambient temperature until complete consumption of the intermediate methyl 3-(benzylamino)propanoate was observed by TLC analysis. The reaction was then quenched with 1.0 M HCl at 0 °C; the organic phase was separated and washed with water and brine, dried over $MgSO_4$, filtered and then concentrated under vacuum. The crude material was then purified by column chromatography to afford **388** as a cream solid (2.13 g, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.7 Hz, 2H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.37 – 7.30 (m, 3H, ArH), 7.28 – 7.23 (m, 2H, ArH), 4.40 (s, 2H NCH_2Ph), 3.58 (s, 3H, OCH_3), 3.45 (t, *J* = 7.5 Hz, 2H, NCH_2CH_2), 2.44 (t, *J* = 7.5 Hz, 2H, NCH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C=O), 150.1 (C), 145.6 (C), 135.3 (C), 129.0 (CH), 128.5 (CH), 128.5 (CH), 128.4 (CH), 124.6 (CH), 53.0 (NCH_2Ph), 52.0 (OCH_3), 44.3 (NCH_2CH_2), 34.0 (NCH_2CH_2); *m/z* (ES^+) 379 (100%, $[M + H]^+$); HRMS *m/z* ($FTMS^+$) calculated for $C_{17}H_{19}O_6N_2S$ 379.0958 [*M* +

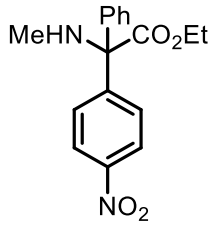
H^+], found 379.0958; *v*/cm^{-1} (solid) 3098 (ArH), 3064 (ArH), 2951 (CH), 2928 (CH), 2858 (CH), 1735 (s, C=O), 1520 (s, NO_2), 1350 (s, NO_2), 1346 (s, S=O), 1164 (s, S=O); mp 88 – 92 °C.



Chemical Formula: $C_{23}H_{22}N_2O_4$
Molecular Weight: 390.44

N-Benzyl-4-nitrobenzenesulfonamide (161 mg, 0.5 mmol, 1.0 eq.) and ethyl 2-bromo-2-phenylacetate (88 µL, 0.5 mmol, 1.0 eq.) were dissolved in CH_2Cl_2 (5 mL, 0.1 M), then DBU (150 µL, 1.0 mmol, 2.0 eq.) was added and the reaction mixture stirred at ambient temperature for 48 hours. After this time, HCl (1.0 M, 5.0 mL) was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude reaction mixture was purified, by column chromatography, to afford **402** as a light brown oil (52 mg, 26%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.6 Hz, 2H, ArH), 7.83 (d, *J* = 8.6 Hz, 2H, ArH), 7.47 (d, *J* = 7.6 Hz, 2H, ArH), 7.40 – 7.27 (m, 8H, ArH), 4.23 (*app.* qd, *J* = 7.1, 2.4 Hz, 1H), 3.46 (s, 2H, NC*H*$_2$Ph), 2.61 (s, 1H, NH), 1.25 (t, *J* = 7.1 Hz, 3H, $CH_aH_bCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3 (C=O), 148.7 (C), 147.0 (C), 140.8 (C), 139.6 (C) 129.4 (CH), 128.53 (CH), 128.48 (CH), 128.1 (CH), 128.0 (CH), 127.6 (CH), 127.3 (CH), 123.1 (CH), 72.6 (C), 62.1 (CH_2CH_3), 48.5 (NCH_2Ph), 14.1 (CH_2CH_3); *m/z* (ES$^+$) 177 ([M – 231]$^+$, 100%), 391 ([*M* + H]$^+$, 75%); HRMS *m/z* (ESI$^+$) calculated for $C_{23}H_{23}O_4N_2$ 391.1625 [*M* + H]$^+$, measured 391.1650; *v*/cm^{-1} ($CDCl_3$) 3335 (w, NH), 3062 (w, ArH), 3026 (w, ArH), 2981 (w, CH), 2851 (w, CH), 1728

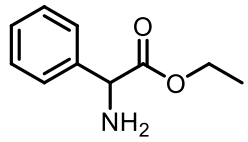
(s, C=O), 1519 (s, NO_2), 1346 (s, NO_2), 1216 (m, C–N); HPLC Lux® 5 µm AMYLOSE-1 4.6 × 250 mm column, 1% IPA in hexanes, 50 min, 1 mL/min, λ = 254 nm, t_R = 40.02 and 43.80.



Chemical Formula: $C_{17}H_{18}N_2O_4$
Molecular Weight: 314.34

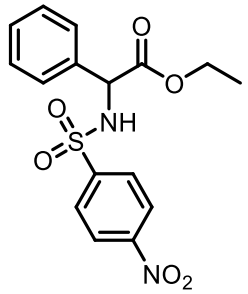
409 (70 mg, 0.185 mmol, 1.0 eq.) and the *N*-[4-trifluoromethyl)benzyl]cinchoninium bromide (11 mg, 0.02 mmol, 10 mol%) were dissolved in CH_2Cl_2 (1.0 mL, 0.2 M), and then Cs_2CO_3 (121 mg, 0.37 mmol, 2.0 eq.) was added and the reaction was stirred at ambient temperature for 48 hours. After this time, HCl (1.0 M, 5.0 mL) was added, the phases were separated and the aqueous phase was washed with CH_2Cl_2 (3 x 5 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was purified by column chromatography (5:95 *v/v* acetone:toluene) to afford **408** as a brown oil (41 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.9 Hz, 1H), 7.66 (d, *J* = 8.9 Hz, 1H), 7.32 – 7.11 (m, 5H, ArH), 4.17 (qd, *J* = 7.1, 2.2 Hz, 2H, C*H*$_a$*H*$_b$CH$_3$), 2.35 – 2.11 (br s, 1H, NH), 2.09 (s, 3H, NHC*H*$_3$), 1.13 (t, *J* = 7.1 Hz, 3H, CH$_a$H$_b$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5 (C=O), 148.5 (C), 147.1 (C), 140.6 (C), 129.7 (CH), 128.5 (CH), 128.0 (CH), 127.9 (CH), 123.1 (CH), 73.3 (C), 62.2 (C*H*$_2$CH$_3$), 30.9 (NCH$_3$), 14.2 (CH$_2$C*H*$_3$); *m/z* (ES$^+$) 284 (90%, [*M* – NHMe]$^+$), 315 (40%, [*M* + H]$^+$); HRMS *m/z* (ESI$^+$) calculated for $C_{17}H_{19}O_4N_2$ 315.1339, found 315.1333; *v*/cm^{-1} ($CDCl_3$) 3350 (w, NH), 3056 (w, ArH), 2983 (w, CH), 2805 (w, CH), 1729 (s, C=O), 1520 (s, NO_2), 1348 (s, NO_2), 1264 (m, C–N); HPLC Lux® 5 µm

AMYLOSE-1 4.6 × 250 mm column, 1% IPA in hexanes, 50 min, 1 mL/min, λ = 254 nm, t_R = 24.71 and 28.22.



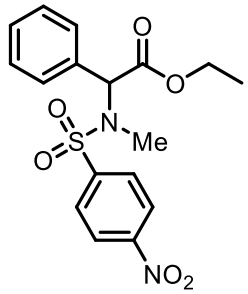
Chemical Formula: $C_{10}H_{13}NO_2$
Molecular Weight: 179.22

Phenylglycine ethyl ester was prepared via a modified literature procedure.[407] Phenyl glycine (1.5 g, 10 mmol, 1.0 eq.) was dissolved in absolute ethanol (10 mL, 1.0 M) and the solution was cooled to 0 °C, after which $SOCl_2$ (1.8 mL, 25 mmol, 2.5 eq.) was added dropwise. After addition was completed, the reaction mixture was heated at reflux for approximately 10 minutes, to dissolve the white precipitate, then allowed to cool to ambient temperature and stirred under N_2 overnight. The ethanol was removed under vacuum to give a white solid, the residue was taken up in diethyl ether (20 mL), filtered and dried under reduced pressure to afford the hydrochloride salt of the phenylglycine ethyl ester (1.42 g, 95%). The free amine was isolated immediately before use by dissolving the salt in sat. $NaHCO_3$, and extracting twice with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4 before concentrating under vacuum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H, ArH), 4.59 (s, 1H, CH), 4.24 – 4.08 (m, 2H, C*H*$_2$CH$_3$), 1.91 (s, 2H, NH_2), 1.21 (t, *J* = 7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1 (C=O), 140.5 (C), 128.9 (CH), 128.1 (C), 126.9 (CH), 61.5 (*C*H_2CH$_3$), 59.0 (CH), 14.2 (CH_2*C*H$_3$); *m/z* (ES$^+$) 163 (100%, [*M* – NH_2]$^+$), 180 (90%, [*M* + H]$^+$). The physical data are consistent with the values reported in the literature.[407]



Chemical Formula: $C_{16}H_{16}N_2O_6S$
Molecular Weight: 364.37

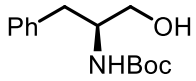
4-Nitrobenzenesulfonyl chloride (1.0 g, 4.5 mmol, 0.7 eq.) was added in one portion to a solution of phenyl glycine ethyl ester (1.15 g, 6.4 mmol, 1.0 eq.) and pyridine (1.5 mL, 4.5 mmol, 0.7 eq.) in CH_2Cl_2 (60 mL, 0.1 M). The resulting solution was stirred at ambient temperature for 5 hours (monitored by TLC, 8:2 *v/*v chloroform:diethyl ether). Aqueous HCl (1.0 M) was then added, and the acidified solution (pH = 2) was extracted with CH_2Cl_2 (3 x 30 mL). The organic phase was carefully shaken with sat. $NaHCO_3$ (3 x 30 mL), then dried over $MgSO_4$, filtered and dried under vacuum to afford ethyl 2-((4-nitrophenyl)sulfonamido)-2-phenylacetate **476** as a yellow crystalline solid (1.50 g, 93%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.7 Hz, 2H, ArH), 7.78 (d, *J* = 8.7 Hz, 2H, ArH), 7.24 (d, *J* = 7.3 Hz, 2H, ArH), 7.20 (t, *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 7.3 Hz, 2H, ArH), 5.92 (d, *J* = 6.9 Hz, 1H), 5.15 (d, *J* = 6.9 Hz, 1H), 4.14 (dq, *J* = 10.8, 7.1 Hz, 1H, C*H*$_a$H$_b$), 4.06 (dq, *J* = 10.8, 7.1 Hz, 1H, CH$_a$*H*$_b$), 1.14 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7 (C=O), 149.9 (C), 146.3 (C), 134.8 (C), 129.1 (CH), 129.0 (CH), 128.4 (CH), 127.5 (CH), 124.0 (CH), 62.9 (CH_2), 59.7 (CH), 14.0 (CH_3); *m/z* (ES^+) 387 (100%, $[M + Na]^+$); HRMS (ESI^+) *m/z* calculated for $C_{16}H_{16}O_6N_2NaS$ 387.0621 $[M + Na]^+$, found 387.0641. The physical data are consistent with literature values.[408]



Chemical Formula: $C_{17}H_{18}N_2O_6S$
Molecular Weight: 378.40

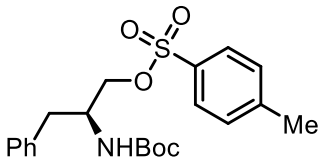
Ethyl 2-((N-methyl-4-nitrophenyl)sulfonamido)-2-phenylacetate 409 was prepared according to a modified literature procedure.[409] **476** (364 mg, 1.0 mmol, 1.0 eq.) was dissolved in acetone (14 mL, 0.07 M), and then K_2CO_3 (156 mg, 1.15 mmol, 1.15 eq.) and iodomethane (0.07 mL, 1.15 mmol, 1.15 eq.) were added sequentially. The resulting mixture was stirred at ambient temperature for 24 hours, and then the volatile components were removed under vacuum. The crude mass was taken up in ether (50 mL), washed with 10% aq. HCl (50 mL), $NaHCO_3$ (50 mL), $Na_2S_2O_3$ (50 mL) and sat. brine (50 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude reaction mixture was purified by column chromatography (SiO_2 gel, 1:4 EtOAc:hexane) and pure fractions were isolated to afford a white solid (79 mg, 21%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.7 Hz, 2H, ArH), 7.95 (d, *J* = 8.7 Hz, 2H, ArH), 7.34 – 7.26 (m, 3H, ArH), 7.18 – 7.12 (m, 2H, ArH), 5.82 (s, 1H, CH), 4.08 – 3.94 (m, 2H, CH_aH_bCH$_3$), 2.71 (s, 3H, NCH$_3$), 1.10 (t, *J* = 7.1 Hz, 3H, CH$_a$H$_b$CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3 (C=O), 150.1 (C), 144.9 (C), 133.2 (C), 129.07 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 124.3 (CH), 62.8 (CH), 61.7 (CH_2), 31.1 (NCH$_3$), 14.1 (CH$_3$); *m/z* (ES$^+$) 401 (100%, [*M* + Na]$^+$; HRMS (ESI$^+$) *m/z* calculated for $C_{17}H_{18}O_6N_2NaS$ 401.0778 [*M* + Na]$^+$, found 401.0770; mp: 121 – 123 °C; *ν*/cm^{-1} (solid) 3096 (w, ArH), 3065 (w, ArH), 3034 (w, ArH), 3007 (w, ArH), 2985 (w,

CH), 2963 (w, CH), 2940 (w, CH), 2869 (w, CH), 1745 (s , C=O), 1528 (s, NO_2), 1347 (s, NO_2), 1319 (s, S=O), 1171 (s, S=O).



Chemical Formula: $C_{14}H_{21}NO_3$
Molecular Weight: 251.33

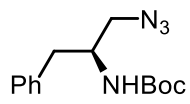
(*S*)-*tert*-Butyl 1-hydroxy-3-phenylpropan-2-ylcarbamate 477 was synthesised by a modified literature procedure.[410] (*S*)-2-(*tert*-Butoxycarbonylamino)-3-phenylpropanoic acid (2.65 g, 10 mmol) was dissolved in THF (20 ml), under a nitrogen atmosphere, and cooled to 0 °C. Then Et_3N (1.42 mL, 11 mmol, 1.1 eq.) and ethyl chloroformate (1.04 mL, 11 mmol, 1.1 eq.) were then added, resulting in the formation of a white precipitate. The solution was filtered after 15 minutes, and then the filtrate was added dropwise to a solution of sodium borohydride (0.62 g, 1.5 eq.) in water (8.0 mL) at 0 °C. After 0.5 h, the reaction mixture was warmed to room temperature and allowed to stir for a further 2 h. The reaction mixture was then acidified to pH 2 with hydrochloric acid (2 M), and extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$ (sat, 20 mL), dried over $MgSO_4$, filtered, and evaporated to dryness to afford a white solid (1.89 g, 7.5 mmol, 75%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.14 (m, 2H), 7.17 - 7.20 (m, 2H), 7.14 – 7.05 (m, 3H), 4.81 (s, 1H, OH), 3.79 (br s, 1H, CH), 3.56 (dd, *J* = 11.0, 3.7 Hz, 1H, CH_aH$_b$), 3.46 (dd, *J* = 11.0, 5.0 Hz, 1H, CH$_a$$H_b$), 3.02 (br s, 1H, NH) 2.76 (d, *J* = 6.7 Hz, 2H, CH_2), 1.33 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2 (C=O), 138.0 (C), 129.4 (CH), 128.6 (CH), 126.5 (CH), 79.7 (*C*CH_3), 64.0 (CH_2OH), 53.7 (CH), 37.5 (Ph*C*H_2), 28.4 (CH_3); *m/z* (ES$^+$) 152 (100%), 274 (90%, [*M* + Na]$^+$). The physical data are consistent with the values reported in the literature.[410]



Chemical Formula: $C_{21}H_{27}NO_5S$
Molecular Weight: 405.51

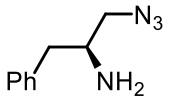
(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-phenylpropyl 4-methylbenzenesulfonate

478 was synthesised according to a literature procedure.[411] **477** (1.0 eq.) was dissolved in dry CH_2Cl_2 (20 mL, 0.35 M) and then cooled to 0 °C, followed by addition of Et_3N (2.0 eq.) and *p*-toluene sulfonyl chloride (1.2 eq.). The reaction was stirred for 3 hours at ambient temperature and then diluted with water (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the crude product was then purified by column chromatography (1:4 *v/v* hexane:EtOAc, SiO_2) to afford a white crystalline solid (1.50g, 54%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.15 – 7.08 (m, 3H), 6.98 (dd, *J* = 7.7, 1.8 Hz, 2H), 4.73 (d, *J* = 8.5 Hz, 1H, NH), 3.98 – 3.85 (m, 2H, CH and TsOCH_aH_b), 3.80 (dd, *J* = 9.4, 2.9 Hz, 1H, TsOCH$_a$*H$_b$*), 2.76 (dd, *J* = 13.5, 6.4 Hz, 1H, PhCH_aH$_b$), 2.68 (dd, *J* = 13.5, 8.1 Hz, 1H, PhCH$_a$*H$_b$*), 2.36 (s, 3H, CH_3), 1.29 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0 (C=O), 145.1 (C), 136.8 (C), 132.4 (C), 130.0 (CH), 129.3 (CH), 128.6 (CH), 128.1 (CH), 126.8 (CH), 79.8 ($C(CH_3)_3$), 70.1 (OCH_2), 50.8 (NCH), 37.2 (CH_2), 28.3 ($C(CH_3)_3$), 21.8 (CH_3); *m/z* (ES^+) 306 ([*M* – $C_5H_9O_2$ + H]$^+$, 100%), 428 ([*M*]$^+$, 60%). The physical data are consistent with the values reported in the literature.[411]



Chemical Formula: $C_{14}H_{20}N_4O_2$
Molecular Weight: 276.34

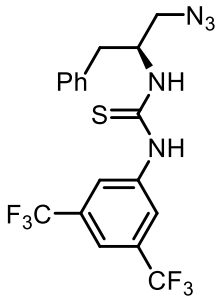
(*S*)-*tert*-Butyl(1-azido-3-phenylpropan-2-yl)carbamate 479 was prepared according to a modified literature procedure.[349] Sodium azide (338 mg, 5.2 mmol, 1.1 eq.) was added to a solution of **478** (1.9 g, 4.7 mmol, 1.0 eq.) in DMF (16 mL, 0.3 M) ambient temperature, and the resulting suspension was stirred at 45 °C for 6 hours. The reaction was cooled to ambient temperature, H_2O (15 ml) was added, and the aqueous phase was extracted with Et_2O (3 x 40 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated. The resulting crude was purified by flash column chromatography (petrol:Et_2O 7:3, SiO_2 gel) **(Caution: Behind a blast blast-shield)** to afford the product as a colourless solid (608 mg, 47%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.16 (m, 5H, ArH), 4.74 (d, *J* = 8.0 Hz, 1H, NH), 3.97 (br s, 1H, CH), 3.41 (dd, *J* = 12.4, 4.4 Hz, 1H, PhCH_aH$_b$), 3.29 (dd, *J* = 12.4, 4.5 Hz, 1H, PhCH$_a$$H_b$), 2.87 (dd, *J* = 13.6, 6.5 Hz, 1H, CH_aH$_b$N$_3$), 2.78 (dd, *J* = 13.6, 7.9 Hz, 1H, CH$_a$$H_bN_3$), 1.43 (s, 9H, $(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2 (C=O), 137.3 (C), 129.4 (CH), 128.8 (CH), 126.9 (CH), 79.9 (*C*$(CH_3)_3$, 53.3 (CH), 51.5 (CH_2), 38.3 (CH_2), 28.5 (C(*C*H_3)$_3$; *m/z* (ES$^+$) 177 ([*M* – $C_5H_9O_2$ + H]$^+$, 100%), 299 ([*M* + Na]$^+$, 40%). The physical data are consistent with the values reported in the literature.[349]



Chemical Formula: $C_9H_{12}N_4$
Molecular Weight: 176.22

An ice-cooled round-bottom flask containing **479** (360 mg, 1.29 mmol, 1.0 eq.) under inert atmosphere was placed behind a blast-shield. TFA (1.58 mL, 21 mmol, 16 eq.) was added carefully in a dropwise manner, and the solution was stirred at ambient temperature for 3 hours. The remaining TFA was removed under a stream of nitrogen, then the residue was dissolved in diethyl ether (5.0 mL) and aq. 2.0 M

NaOH was added until the solution reached pH 14. The aqueous phase was extracted with Et_2O (2.0 x 5 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated under a steam of nitrogen **(CAUTION: Behind a blast-shield).** (*S*)-1-Azido-3-phenylpropan-2-amine was isolated **480** as colourless solid was used without further purification (207 mg, 1.17 mmol, 91%); ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.37 – 7.16 (m, 5H, ArH), 3.41 – 3.33 (m, 1H, CH), 3.27 – 3.14 (m, 2H, CH_2), 2.78 (dd, *J* = 13.4, 5.3 Hz, 1H, C*H*$_a$H$_b$), 2.59 (dd, *J* = 13.4, 7.7 Hz, 1H, CH$_a$*H*$_b$), 1.40 (s, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1 (C), 129.2 (CH), 128.6 (CH), 126.5 (CH), 57.3 (CH_2), 52.4 (CH), 41.4 (CH_2); *m/z* (ES^+) 177 ([*M* + H]$^+$, 80%), 208 ([*M* + MeOH]$^+$, 100%).

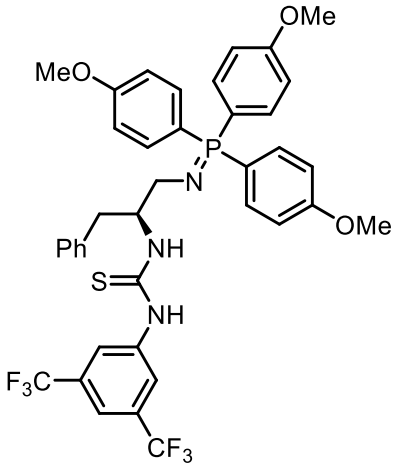


481

Chemical Formula: $C_{18}H_{15}F_6N_5S$
Molecular Weight: 447.40

The crude **480** (207 mg, 1.18 mmol, 1.0 eq.) was dissolved in dry THF (5.0 mL, 0.24 M), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (215 µL, 1.18 mmol, 1.0 eq.) was added and the solution was stirred at ambient temperature for 12 hours. Volatiles were removed under vacuum and the crude product was purified by flash column chromatography (20 – 30% *v/v* petrol:Et_2O) to obtain **481** as a colourless solid (360 mg, 0.81 mmol, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H, NH), 7.79 (br s, 2H, ArH), 7.73 (s, 1H, ArH), 7.34 (tt, *J* = 6.9, 1.2 Hz, 2H, ArH), 7.31 – 7.22 (m, 3H, ArH), 6.51 (br s, 1H, NH), 4.91 (br s, 1H, CH), 3.72 (dd, *J* = 12.4, 4.2 Hz, 1H,

PhCH_aH$_b$), 3.48 (dd, J = 12.4, 3.6 Hz, 1H, PhCH$_a$$H_b$), 3.08 (dd, J = 13.8, 6.4 Hz, 1H, CH_aH$_b$N$_3$), 2.88 (dd, J = 13.8, 8.3 Hz, 1H, CH$_a$$H_bN_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.0 (C=S), 138.5 (C), 136.4 (C), 133.2 (q, J = 34.0 Hz, C-CF_3), 129.2 (CH), 129.1 (CH), 127.3 (CH), 124.12 (q, J = 3.7 Hz, CH), 122.81 (q, J = 273.2 Hz, CF_3) 119.9 (*app.* t, J = 3.4 Hz, CH), 55.5 (CH), 52.4 (CH_2N_3), 37.5 (CH_2); *m/z* (ES^-) 446 ([M]$^-$, 100%). The physical data are consistent with the values reported in the literature.[349]

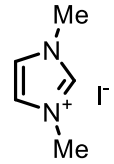


Chemical Formula: $C_{39}H_{36}F_6N_3O_3PS$
Molecular Weight: 771.76

The **410** was synthesised according to a literature procedure.[412] To **481** (8.9 mg, 0.02 mmol, 1.0 eq.) in anhydrous Et_2O (0.1 mL, 0.2 M), under an argon atmosphere, was added tris(4-methoxyphenyl)phosphine (7 mg, 0.02 mmol 1.0 eq.). Stirring was maintained at ambient temperature for 24 hours, and then the reaction mixture was concentrated under a stream of N_2 and then under vacuum until a white crystalline sold was formed. The iminophosphorane product was confirmed by MS and TLC, and the volatiles were removed by a N_2 stream to yield the crude **410**, which was used as a catalyst without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.41 (m, 2H, ArH), 7.39 (d, J = 8.9 Hz, 3H, ArH), 7.36 (d, J = 8.9 Hz, 3H, ArH),

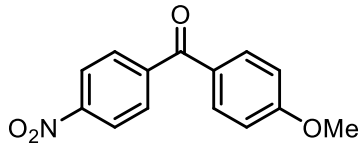
7.18 – 7.12 (m, 3H, ArH), 7.10 (d, *J* = 6.9 Hz, 1H, ArH), 7.04 (d, *J* = 7.1 Hz, 2H, ArH), 6.83 (dd, *J* = 8.9, 2.5 Hz, 6H, ArH), 4.44 (s, 1H, NH), 3.74 (s, 9H, 3 x OCH_3), 3.06 (t, *J* = 9.2 Hz, 1H, NCH_aH_b), 3.02 – 2.86 (m, 2H, *overlapping* NCH_aH_b and $PhCH_aH_b$), 2.57 (t, *J* = 10.8 Hz, 1H, $PhCH_aH_b$), *ArNH not observed*; ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8 (d, *J* = 2.8 Hz, *C*OCH_3), 137.7 (C), 134.7 (d, *J* = 11.8 Hz, CH), 133.9 (dd, *J* = 13.4, 11.9 Hz, CH) 130.5 (q, *J* = 32.6 Hz, *C*(CF_3)), 129.1 (CH), 128.7 (CH), 126.6 (CH), 125.1 (C), 123.7 (q, *J* = 272.7 Hz, CF_3) 122.4 (C), 115.06 (d, *J* = 13.7 Hz, CH), 113.9 (d, *J* = 13.3 Hz, CH) 68.0 (CH), 55.5 (OCH_3), 41.9 (CH_2), 39.8 (CH_2) *C=S not observed*; ^{31}P (202 MHz) δ 27.0 (br s), ^{19}F NMR (471 MHz, $CDCl_3$) δ −62.63; *m/z* 772 ($[M + H]^+$, 100%).

6. Data for Chapter 4



Chemical Formula: $C_5H_9IN_2$
Molecular Weight: 224.05

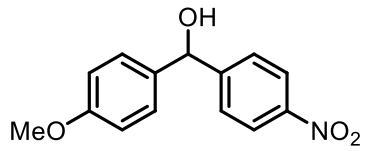
1,3-Dimethyl-1*H*-imidazol-3-ium iodide (DMII) was prepared according to a modified literature procedure.[413] Iodomethane (1.9 mL, 30 mmol, 1.5 eq.) was added to *N*-methyl imidazole (1.6 mL, 20 mmol, 1 eq.) was dissolved in dry toluene (7.5 mL, 4.0 M). The mixture was stirred in a capped vial, at ambient temperature, until a precipitate formed. The resulting precipitate was filtered, washed with anhydrous diethyl ether (2.0 mL), and dried under vacuum to afford the product as a cream solid (4.4 g, 99%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.05 (s, 1H, Ar*H*), 7.69 (d, *J* = 1.6 Hz, 2H, Ar*H*), 3.85 (s, 6H, CH_3); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 136.9 (CH), 123.3 (CH), 35.8 (CH_3); *m/z* (ES^+) 321 (100%, $[M + C_5H_9N_2]^+$). The physical data are consistent with the values reported in the literature.[413]



Chemical Formula: $C_{14}H_{11}NO_4$
Molecular Weight: 257.25

4-Methoxyl-4'-nitrobenzophenone 434 was synthesised according to a literature procedure.[370] 4-Fluoronitrobenzene (141 mg, 1.0 mmol, 1.0 eq.), *p*-anisaldehyde (121 µL, 1.0 mmol, 1.0 eq.) and DMII (22 mg, 0.1 mmol, 10 mol%) were added, under a flow of nitrogen, to DMF (7 mL, 0.14 M) in a Schlenk tube, and the mixture was cooled to −15 °C. Also under a flow of nitrogen, sodium hydride (160 mg, 4.0

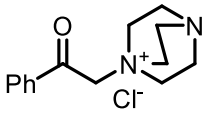
mmol, 4.0 eq.) was then carefully added at −15 °C and stirred for 15 minutes. The reaction mixture was allowed to warm to −5 °C, and was stirred at this temperature for 2 hours to afford a yellow solid (210 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.9 Hz, 2H), 7.88 (d, *J* = 8.9 Hz, 2H), 7.81 (d, *J* = 9.0 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6 (C=O), 164.1 (C), 149.6 (C), 143.9 (C), 132.8 (CH), 130.5 (CH), 129.0 (C), 123.6 (CH), 114.1 (CH), 55.8 (OCH_3); *m/z* (ES^+) 258 ($[M + H]^+$, 80%), 121 ($[M - C_8H_7O_2]^+$, 100%). The physical data are consistent with the values reported in the literature.[371]



Chemical Formula: $C_{14}H_{13}NO_4$
Molecular Weight: 259.26

(4-Methoxyphenyl)(4-nitrophenyl)methanol 446 was synthesised according to a modified literature procedure.[414] 4-Nitrobenzaldehyde (151 mg, 1.0 mmol, 1.0 eq.) and 4-methoxyboronic acid (227 mg, 1.5 mmol, 1.5 eq.) were added to a 10-dram vial and dissolved in THF (4.0 mL, 0.25 M). The chloro(1,5-cyclooctadiene)rhodium(I) dimer (12 mg, 0.025 mmol, 2.5 mol%) and K_3PO_4 (636 mg, 3.0 mmol, 3.0 eq.) were then added. The reaction mixture was stirred at ambient temperature for 15 minutes, after which time water (5.0 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 5.0 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The crude reaction mixture was purified by column chromatography (EtOAc:hexane, SiO_2 gel, 0 – 40 %) to afford the product as a yellow solid (173 mg, 67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.8 Hz, 2H, ArH), 7.52 (d, *J* = 8.4 Hz, 1H, ArH), 7.22 (d, *J* = 8.4 Hz, 2H, ArH), 6.85 (d, *J* = 8.8 Hz, 2H, ArH), 5.82 (s, 1H, CH), 3.77 (s, 3H, OCH_3), 2.81 (s, 1H, OH); ^{13}C NMR

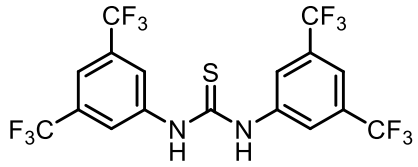
(101 MHz, $CDCl_3$) δ 159.6 (C), 151.3 (C), 147.1 (C), 135.1 (C), 128.2 (CH), 127.0 (CH), 123.6 (CH), 114.3 (CH), 75.1 (CH), 55.4 (OCH_3); *m/z* (ES^-) 258 [(*M* − H]$^-$, 100%). The physical data are consistent with the values reported in the literature.[414]



Chemical Formula: $C_{14}H_{19}ClN_2O$
Molecular Weight: 266.77

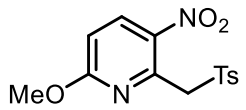
1-(2-Oxo-2-phenylethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride 462

prepared by a modified literature procedure.[415] 2-Chloroacetophenone (2.9 g, 24 mmol, 1.0 eq.) and DABCO (2.7 g, 24 mmol, 10 eq.) were added to THF (100 mL, 0.24 M) and stirred at ambient temperature for 30 minutes. The THF was then removed by evaporation and the residue was washed with petrol. The residue was then taken up in a methanol, benzene mixture (1:1) which was subsequently removed under vacuum to afford a white solid (4.8 g, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 8.0, 7.4 Hz, 2H), 6.00 (s, 2H, CH_2), 4.15 (t, *J* = 7.6 Hz, 6H, CH_2), 3.20 (t, *J* = 7.6 Hz, 6H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1 (C=O), 134.9 (CH), 134.8 (C), 129.2 (CH), 128.6 (CH), 65.9 (CH_2), 52.7 (CH_2), 45.5 (CH_2); *m/z* (ES^+) 231 ([*M* – Cl]$^+$, 100%). The physical data are consistent with the values reported in the literature.[415]



Chemical Formula: $C_{17}H_8F_{12}N_2S$
Molecular Weight: 500.31

1,3-Bis(3,5-bis(trifluoromethyl)phenyl)thiourea 470 was prepared according to a modified literature procedure.[381] To a mixture of 1,1'-thiocarbonyldiimidazole (175 mg, 1.0 mmol, 1.0 eq.) in dried CH_2Cl_2 (1.0 mL, 1.0 M), under an argon atmosphere, was added carefully 3,5-bistrifluoromethylaniline (0.33 mL, 2.1 mmol, 2.1 eq.) and the resulting solution was stirred for 24 h at ambient temperature. The solvent was evaporated, and diethyl ether (5.0 mL) was added to the pale-yellow oil. The organic phase was extracted with HCl (1.0 M, 3 x 5 mL), aqueous sat. $NaHCO_3$ (3 x 5.0 mL), and sat. brine (3 x 5.0 mL). The organic phase was dried with Na_2SO_4, filtered an evaporated to dryness, then the light-yellow solid was recrystallized from $CHCl_3$. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from $CHCl_3$ again. The white solid was dried under vacuum in a desiccator over P_2O_5 to afford a white solid (360 mg, 72%); ^{1}H NMR (500 MHz, CD_3OD) δ 8.22 (s, 2H), 7.73 (s, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 181.1 (C=S), 141.2 (C), 131.5 (q, J = 33.4 Hz, CCF$_3$), 123.4 (d, J = 5.0 Hz, CH), 123.3 (q, J = 271.8 Hz, CF_3), 117.5 (*app* p, J = 3.7 Hz, CH); *m/z* (ES$^-$) 499 ([M − H]$^-$, 100%). The physical data are consistent with the values reported in the literature.[381]



Chemical Formula: $C_{14}H_{14}N_2O_5S$
Molecular Weight: 322.34

6-Methoxy-3-nitro-2-(tosylmethyl)pyridine 470 was synthesised according to a modified literature procedure.[416] A mixture of 6-methoxy-3-nitropyridine (77 mg, 0.5 mmol, 1.0 eq.) and 1-chloromethane-sulfony4-methybenzene (102 mg, 0.5 mmol 1.0 eq.) was dissolved in DMF (0.5 mL) and cooled to 5 °C. To this solution, KO*t*-Bu (1.0 M in THF, 1.0 mL, 2.0 eq.) was added dropwise, maintaining a temperature of ≤ 10 °C, the dark reaction mixture is stirred for 5 hours at room temperature. Evaporation removed the volatile components, and water (50 mL) was added to the remaining solution. A dark brown precipitate formed which was collected by filtration. The residue was purified by column chromatography (3:7 *v/v* EtOAc:hexane, SiO_2) to afford a pale brown solid (99 mg, 62%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 9.0 Hz, 1H, ArH), 7.58 (d, *J* = 8.2 Hz, 2H, ArH), 7.27 (d, *J* = 8.2 Hz, 2H, ArH), 6.77 (d, *J* = 9.0 Hz, 1H, ArH), 5.13 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3), 2.42 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8 (C), 145.1 (C), 143.7 (C), 141.0 (C), 136.5 (CH), 136.1 (C), 129.8 (CH), 128.5 (CH), 111.8 (CH), 61.8 (CH_2), 54.7 (OCH_3), 21.7 (CH_3); *m/z* (ES^+) 323 (100%, $[M + H]^+$); HRMS *m/z* (FTMS ESI^+) calculated for $C_{14}H_{15}N_2O_5S$ 323.0696 $[M + H]^+$, found 323.0685. The physical data are consistent with the values reported in the literature.[417]

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